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Human brain activity in the control of fine static precision grip forces: an fMRI study

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Abstract

Dexterous manipulation of delicate objects requires exquisite control of fingertip forces. We have used functional magnetic resonance imaging to identify brain regions involved in the skilful scaling of these forces when normal human subjects (n = 8) held with precision grip a small object (weight 200 g) in the dominant right hand. In one condition, they used their normal, automatically scaled grip force. The object was held gently in a second condition; the isometric grip force was maintained just above the critical level at which the object would have slipped. In a third condition, the force was increased to hold the object with a more firm grip. The supplementary and cingulate motor areas were significantly more active during the gentle force condition than during either of the other conditions in all subjects, despite weaker contractions of the hand muscles. In addition, the left primary sensorimotor cortex, the ventral premotor cortex and the left posterior parietal cortex were more strongly activated during gentle than during normal grasping. These novel results suggest that these regions are specifically involved in dexterous scaling of fingertip forces during object manipulation.

Introduction

The dexterity of the human hand is based on the ability to control movement and force of the fingertips precisely in relation to a given task. When we hold an object between the thumb and index finger, the isometric grip force is adjusted automatically to the object's weight and surface characteristics (roughness, curvature). This grip force is a certain safety margin greater than the critical threshold at which the object would slip out of the fingers (Johansson, 1996). The safety margin is reduced when we cautiously loosen the grip in order to hold an object gently, with the least possible grip force, e.g. while carefully manipulating readily deformable or fragile items. A balance between grasp stability and force reduction has to be established, because the grip force is lowered, yet kept high enough to avoid unintentional slips of the object. Which brain areas are active during such skilful scaling of the isometric fingertip force?

Graded contractions of intrinsic and extrinsic hand muscles, controlled by the corticospinal system, play a crucial role in the scaling of the precision grip force (Hepp-Reymond *et al*., 1996). Cortico-motoneuronal connections project from the primary motor cortex directly to spinal motoneurons of finger muscles (Lemon, 1993). Other corticospinal pathways originate from the supplementary and cingulate motor areas, and the premotor cortex (Dum & Strick, 1991). Previous imaging studies have demonstrated activation of these primary and secondary motor areas during both simple and complex hand movements (Colebatch *et al*., 1991; Shibasaki *et al*., 1993). Activity of the primary and supplementary motor cortex became stronger and more widespread when finger movements (e.g. key-press tasks) were performed at increasing levels of force (Dettmers *et al*., 1995, 1996; Thickbroom *et al*., 1998, 1999). However, Ehrsson *et al*. (2000) found stronger activity of secondary motor and parietal areas during a precision grip than during a power grip task, although the latter task involved more force with more extensive contractions of hand muscles.

Hence, cortical activity during hand motor tasks seems not only to depend on the amount of muscular force but also changes with demands on dexterous control. Activation of sensorimotor areas by the skilful scaling of fine manipulative forces has not yet been studied. We used functional magnetic resonance imaging (fMRI) to compare human brain activity during three precision grip tasks, corresponding to three force conditions. In the first condition, adult subjects simply held an object between the thumb and index finger and thereby let the motor system automatically adapt the grip force to the pertinent frictional conditions. In the second, the key condition, they reduced the grip force skilfully with the intention of holding the same object gently, without allowing it to slip between the fingers. In a third condition, the subjects intentionally increased their grip force to hold the object more firmly between the thumb and index finger. We expected that those brain areas which are specifically involved in skilful force reduction, controlling grasp stability close to the slip threshold, would be most active during gentle holding.

Materials and methods

Subjects

Eight healthy male volunteers (aged 22–33, mean age 28.5 years) took part in the present study. All were right-handed, and none of them had a previous history of any neurological disorder. All gave

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informed consent before the experiments, which had been approved by the Ethical Committee of the Karolinska Hospital (Stockholm, Sweden).

Behavioural paradigm

The paradigm was practiced one week before the image acquisition for ≈ 1 h, and again for ≈ 30 min before magnetic resonance (MR) imaging. This training ensured stable performance and avoided confounding effects of motor learning during image acquisition. Subjects wore headphones and lay supine, with their arms extended comfortably. The right hand and forearm rested on a moulded wooden support covered with thin soft foam. The elbow was nearly extended and the wrist was abducted (ulnar abduction) by ≈ 20°. The forearm was in a relaxed semiprone posture, and the hand rested on the support. A grip object (weight 200 g) was placed close to the hand, with its lower edges 1–2 cm above the tips of the thumb and index finger. Upon an acoustic cue, the object was grasped between the thumb and index finger, lifted with a radial adduction movement (amplitude ≈ 25°) of the wrist, and then held steadily at a height of 3–5 cm (Fig. 1). Forty seconds later, a second cue signaled that the object should be put down and released, and the hand relaxed. The object had two flat vertical grip surfaces (35 × 35 mm, spaced 30 mm apart) covered with sandpaper (grit size 600) and was equipped with nonmagnetic force transducers. The grip force, applied perpendicular to the surfaces, and the load force (tangential to the surfaces) were sampled with a time resolution of 400 Hz during both training and image acquisition. Signals were stored and analysed using the computer-based SC/ZOOM data acquisition system (Department of Physiology, Umeå University, Sweden).

The three force conditions were signaled by different auditory cues. In the first condition, the object was lifted and held with the self-selected, natural grip force (normal hold) at constant height before it was put down again after 40 s. In the second condition, the subjects lifted the object and then reduced their grip force to hold it gently, but without slipping (gentle hold). In the third condition (firm hold), the object was held with a moderately elevated (≈ 4 N) grip force. The subjects reported that they could maintain this force level for 40 s without fatigue. Feedback from a computer screen was provided during the initial 20 min of the training, until the subjects grasped the object correctly, adjusted the forces appropriately, and consistently lifted the object to the desired height. For the rest of the experiments, the subjects were blindfolded and had to rely on their fingertip sensation when adjusting force. After training, the subjects were asked to slowly release the object until it slipped, and we determined the grip force of the slip threshold for each individual. The maximum voluntary force of a pinch between thumb and index finger was also measured. Before fMRI scanning, we also recorded and inspected the electromyographic activity (emg) of the first dorsal interosseus muscle of the right hand during the three force conditions. Bipolar surface electrodes with an interelectrode distance of 15 mm were used (MYO 115, Liberty Technology, Hopkinton, MA, USA) were used. In three subjects, we also checked emg activity of the biceps and triceps.

During fMRI scanning, each subject performed six experimental runs of 520 s duration. In each run, the subjects alternated between rest periods and precision grip-hold periods, as signaled by auditory cues that were given every 40 s. Each of the three conditions (normal, gentle, firm force) was performed twice during a run, and the order of the conditions was counterbalanced across the different runs. Each subject thus performed 12 trials of each force condition in six runs, so we collected in total 96 trials of each condition. The static grip force of each trial was averaged from holding periods of 30 s duration,

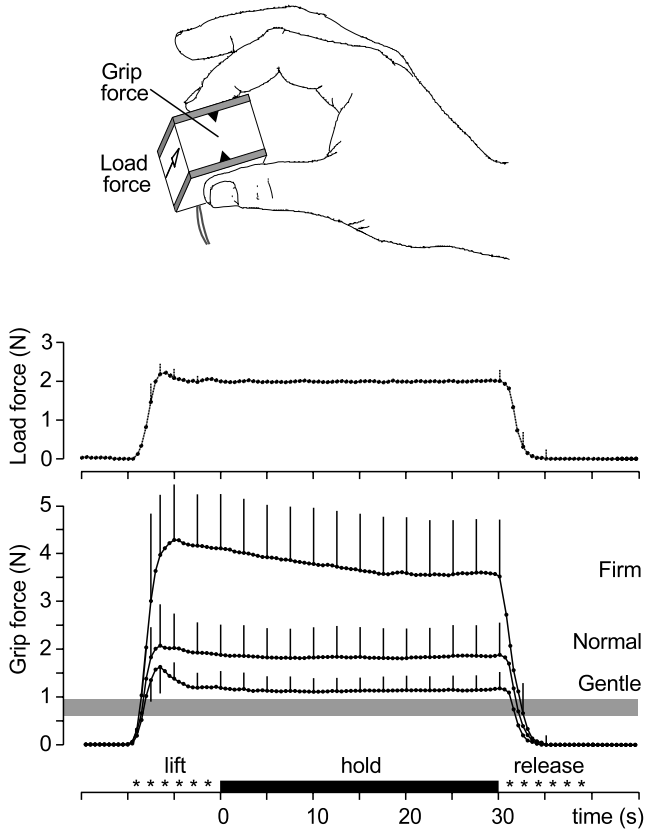

FIG. 1. (Top) Posture of the hand while holding the object; view from above. The directions of the grip force (black arrowheads) and the load force (open arrow) are indicated. (Middle and bottom) Load and grip force profiles of the three force conditions (gentle, normal, firm). Mean values from 96 trials (12 per subject) per condition. Error bars indicate SD. The range of grip forces at slip is shown as a horizontal grey bar. The dynamic transitional phases (lift, release) are marked with asterisks; the holding period is labelled with a black bar.

when the object was held steadily (Fig. 1). Fluctuations of the grip force during this static holding period (within-trial variations) were measured as the total (integrated) deviation of the recorded values from the mean. For each condition (normal, gentle, firm hold), we calculated the mean static force, the mean variability from trial to trial, and the mean within-trial variability. Data of the three force conditions were compared using analysis of variance followed by paired *t*-tests. The dynamic transitional phases (lifting, releasing the object) were excluded from the analysis. These phases were characterized by hand movements and rapid changes in force (Fig. 1), whose slope was somewhat variable from subject to subject. All hand movements were videotaped.

Image acquisition

A 1.5-Tesla MR system (Echospeed, General Electrics Medical Systems, Milwaukee, Wisconsin, USA) with a standard radio-frequency head coil was used. For anatomical images of the whole brain, a three-dimensional gradient echo sequence [flip angle 50°, signal (echo)-gathering time (TE) = 4 ms, sequence repetition time (TR) = 13 ms] generated 124 coronal slices (2 mm thick) with a matrix size of 256 × 128 and a 24 × 24 cm field of view. For fMRI imaging, 21 contiguous axial slices (3.4 mm thick) were selected; these covered the frontal and parietal lobes. The basal ganglia and cerebellum were outside the field of view. Functional images with

blood oxygenation level-dependent (BOLD) contrast were acquired by gradient echo planar imaging (flip angle 90°, TE = 60 ms, TR = 5000 ms, a matrix size of 64 × 64, a field of view of 22 × 22 cm and a voxel size of 3.4 × 3.4 × 3.4 mm). Image volumes were continuously acquired every 5 s; one run (520 s) consisted of 104 image volumes. Four volumes preceding each run were discarded to allow signal equilibration. A plastic bite bar, which had been fitted to the teeth before scanning started, restricted head movements. To avoid confounding effects of jaw muscle contractions, we instructed the subjects not to bite strongly but just to keep their teeth in the imprints of the plastic.

Data analysis

Images were analysed using the SPM (statistical parametric mapping) 96 software (Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm), and calculations and image matrix manipulations were performed in Matlab (Mathworks, Sherborn, MA, USA) on a Sun Sparc Ultra 10 workstation (Sun Microsystems, Mountain View, CA, USA). To correct the effect of head motion across scans, the time series of functional image volumes were spatially realigned, using a least sum of squares method with three-dimensional interpolation (Friston *et al*., 1996). The realigned data volumes were coregistered with the anatomical images, transformed into a stereotactic space (Talairach & Tournoux, 1988; Friston *et al*., 1995a) as defined by the standard brain of the Montreal Neurological Institute, and resampled with a voxel size of 4 × 4 × 4 mm. Image volumes were then smoothed spatially with a Gaussian filter of 8 mm full width at half maximum (to accommodate anatomical variations between subjects), and the time series were smoothed with a Gaussian kernel of 2.83 s width. Proportional scaling was applied to remove global (whole volume) changes of signal intensity, i.e. each scan was adjusted by scaling to the same global intensity value. To disclose activity that was robust across subjects objectively and to increase the sensitivity of the analysis, we analysed the fMRI data from the eight subjects as a group (fixed-effects model). We also examined statistical contrasts for individual subjects using the same data sets as before; they were, however, spatially smoothed with a 4-mm Gaussian filter, i.e. less than in the group analysis. The other procedures were the same as for the group.

The fMRI data were modelled and statistically analysed using the 'General Linear Model' approach (Friston *et al*., 1995b). To assess brain activation during static force production, we compared periods of static holding and of rest, which each corresponded to six image volumes (30 s). Four conditions of interest were defined: normal hold, gentle hold, firm hold and rest. Condition-dependent activations during these periods were modelled with a delayed boxcar waveform. The fMRI signals of the interspersed dynamic transitional phases (lift, release; two image volumes each) were biased by effects of hand movements and auditory cues. Hence these phases were treated as conditions of no interest, excluding their effects (which were also modelled with a delayed boxcar waveform) from the relevant comparisons of the static hold periods. A design matrix was defined

TABLE 1. Static grip forces of the different conditions

Condition	Interindividual averages		Variability from trial to trial† (N)	Grip force fluctuations‡ (N × s)
	Absolute force (N)	Relative force (%)*		
Gentle hold	1.15 ± 0.20	1.7 ± 0.4	0.21 ± 0.08	2.28 ± 0.73
Normal hold	1.83 ± 0.49	2.8 ± 0.8	0.39 ± 0.18	3.43 ± 1.60
Firm hold	3.72 ± 0.89	5.5 ± 1.2	0.75 ± 0.31	7.97 ± 3.02

Values are mean ± SD. All conditions differ significantly from each other (ANOVA, *post hoc t*-tests, $P < 0.05$). *Percentage of the maximum voluntary grip force; †SD of 12 trials per subject and condition; ‡within-trial variability of the grip force, integrated over 30 s of static holding. N, Newton.

TABLE 2. Brain activity during gentle, normal and firm holding

Brain region	Area	Coordinates of foci			*Z*-scores of foci*	Volumes of activation†
		x	*y*	*z*		
Contrast (Gentle – Rest)						
L. central sulcus	M1/S1	–44	–28	52	7.35	296
L. precentral gyrus	M1/PMD	–36	–24	60	6.85	(same cluster)
L. inf. parietal cortex	BA 40	–64	–36	36	7.48	(same cluster)
L. intraparietal sulcus	BA 7/40	–56	–40	52	7.54	(same cluster)
L. inf. precentral gyrus	PMV	–56	4	36	6.18	37
Superior frontal gyrus	SMA/CMA	–4	–8	56	7.82	257
R. inf. parietal cortex	BA 40	44	–44	44	4.85	81
R. intraparietal sulcus	BA 7/40	52	–40	52	5.17	(same cluster)
Contrast (Normal – Rest)						
L. central sulcus	M1/S1	–40	–24	52	4.79	114
L. intraparietal sulcus	BA 7/40	–52	–44	52	5.81	(same cluster)
R. inf. parietal cortex	BA 40	44	–48	44	4.57	13
Contrast (Firm – Rest)						
L. central sulcus	M1/S1	–44	–28	52	6.73	319
L. precentral gyrus	M1/PMD	–36	–20	60	5.25	(same cluster)
L. inf. parietal cortex	BA 40	–60	–40	44	6.87	(same cluster)
L. intraparietal sulcus	BA 7/40	–52	–44	56	6.85	(same cluster)
L. inf. precentral gyrus	PMV	–56	4	36	5.03	23
R. inf. parietal cortex	BA 40	48	–60	44	5.27	87

L, left; R, right; inf, inferior; M1/S1, primary sensorimotor cortex; PMD, dorsal premotor cortex; PMV, ventral premotor cortex; SMA, supplementary motor area; CMA, cingulate motor area; BA, Brodmann area. *Significant peaks of fMRI signal ($P < 0.05$ after correction for multiple comparisons). †Number of supratheshold ($Z > 3.09$) voxels of the clusters; voxel size is 4 × 4 × 4 mm.

TABLE 3. Differences in brain activation between force conditions

Brain region	Area	Coordinates of foci			Z-scores of foci*	Volumes of activation‡
		x	*y*	*z*		
Contrast (Gentle – Normal)						
L. central sulcus	M1/S1	–52	–24	48	5.01	52
L. precentral gyrus	M1/PMD	–36	–24	60	4.96	(same cluster)
L. inf. precentral gyrus	PMV	–60	4	36	4.51	13
Superior frontal gyrus	SMA	–4	–4	56	7.11	140
Cingulate sulcus	CMA	–4	0	44	7.04	(same cluster)
L. inf. parietal cortex (supramarginal gyrus)	BA 40	–64	–36	36	5.77	56
Contrast (Gentle – Firm)						
L. central sulcus	M1/S1	–52	–20	48	(3.21)†	14
Superior frontal gyrus	SMA	–4	–4	56	6.85	134
Cingulate sulcus	CMA	0	–4	48	6.29	(same cluster)
L. inf. parietal cortex	BA 40	–64	–36	32	5.13	21
Contrast (Firm – Normal)						
L. central sulcus	M1/S1	–48	–24	48	(3.27)†	9
L. precentral gyrus	M1/PMD	–36	–20	64	(3.47)†	8
L. inf. precentral gyrus	PMV	–60	8	32	(4.35)†	11

*Significant differences (peaks with $P < 0.05$ after correction for multiple comparisons). †Uncorrected $P < 0.001$ ($Z > 3.09$), but not significant after correction for multiple comparisons. ‡Number of supratheshold ($Z > 3.09$) voxels in the cluster; voxel size is $4 \times 4 \times 4$ mm.

that comprised linear contrasts testing for significant activation during the holding periods compared to rest [comparing categories: (normal hold – rest), (gentle hold – rest), (firm hold – rest)]. Voxels were identified as activated if their transformed *t*-values passed the threshold of $Z = 3.09$ (uncorrected $P < 0.001$). From these thresholded statistical images, we report peaks of activations (Table 2) whose height, after correction for multiple comparisons, passed a significance level of $P < 0.05$ (corrected). The activation volumes, i.e. the numbers of significantly activated voxels ($Z > 3.09$) of the clusters, are also reported.

Differences in activation between force conditions were statistically evaluated with the contrasts [gentle vs. normal hold], [firm vs. normal hold], [gentle vs. firm hold]. From these differences between force conditions, we only report activity of voxels that were also significantly active as compared with rest. By this means, we focus on brain areas that were active during the grip–hold task, and exclude the possibility that the differences between conditions merely reflect different degrees of deactivation. We used a significance threshold of $P < 0.001$ at each voxel (corresponding to $Z > 3.09$) for the activation (difference) maps, and report peaks of activations (Table 3) whose height corresponded to a significance level of $P < 0.05$ after correction for multiple comparisons. Areas, which showed differences in activation corresponding to $P < 0.001$ (uncorrected) at each voxel but whose peaks did not pass the threshold of $P < 0.05$ after correction for multiple comparisons, are furthermore reported as statistical trends (clearly marked in Table 3).

Talairach coordinates (x = left–right; y = posterior–anterior; z = ventral–dorsal) of the local foci of activity were determined (Talairach & Tournoux, 1988). Prominent sulcal landmarks (central, precentral sulci, etc.) from an averaged normalized image volume of the eight subjects were used in the group analysis to assign clusters of activated voxels to anatomical locations (Duvernoy, 1991; Roland & Zilles, 1996). For display purposes, activated regions were projected on high-resolution scans of a standard (Montreal Neurological Institute) brain.

We furthermore obtained the time course of the fMRI signal (Figs 5a and 6a) of selected foci of activation. For each run, the signal changes of the respective voxels were calculated as percentages. The baseline value of the run, which was set to zero (see Figs 5a and b, and 6a and b), was the average of all conditions including rest. Such data from all subjects were then used to calculate the mean fMRI signal profiles of the three (gentle, normal, firm) force conditions. Hence the resulting curves are based on 96 trials of each condition, which had been collected from six runs per subject (total of 48 runs). For each of these trials, we also averaged the fMRI signal of the six scans that had been gathered during 30 s of static holding. This value was then plotted against the corresponding static grip force of the respective trial. The resulting scatterplots (Figs 5b and 6b) show, for each trial ($n = 288$), the relationship between the force of the fingertips and the corresponding fMRI signal of the focus of activity during static holding.

Results

Task performance

The posture of the hand during the precision grip and the mean force profiles (pooled across subjects) of the three conditions are given in Fig. 1. Different time intervals could be established on the basis of the force curves. During the static holding periods (duration 30 s), the grip and load forces and the position of the object were almost constant. Conversely, the dynamic transitional phases (duration 10 s) were characterized by rapid changes during which the object was gripped and lifted or put down and released. The mean grip forces of static holding with a normal, gentle or firm precision grip (Table 1) differed significantly ($F_{2,21} = 39.8$, $P < 0.001$). Corresponding to the weight of the object, the load force was always identical (2 N). The critical threshold at which the object began to slip out of the fingers was, on average, at a grip force of 0.75 N (range 0.69–0.85 N; hatched segment in Fig. 1). In gentle holding, the static grip force was only 0.4 N above this critical threshold. The safety margin was larger (1.1 N) during normal and firm (3.0 N) holding. Hence the gentle but nevertheless secure holding required a precise and steady adjustment. Accordingly, the trial-to-trial variability of the static grip force was

significantly lower during gentle holding than in the other conditions ($F_{2,21}$ = 12.8, P < 0.001, Table 1). Moreover, the fluctuations of the static grip force (within-trial variations) differed significantly between conditions ($F_{2,21}$ = 14.7, P < 0.001). The grip force was kept most constant during gentle holding, and fluctuations were larger during normal and firm holding (Table 1). No slips were observed. The subjects' performance remained stable throughout the course of the experiments, and the posture of the fingers (Fig. 1) was the same in all force conditions. Overall, the grip forces used were low (< 7%, see Table 1) in relation to the maximum voluntary force. The electromyogram (emg) activity of the first dorsal interosseus muscle increased in parallel with grip force in all subjects. Elbow and shoulder joints did not move during the grip–lift task, and there was no discernible emg activity of the biceps and triceps muscles.

Activity during static holding

Brain activation was rather weak during normal holding, i.e. when the static fingertip forces were scaled automatically (Fig. 2, middle column). Compared with the resting period, only the left primary sensorimotor cortex (M1/S1), left intraparietal regions and a small right posterior parietal area (Table 2) were active. The local peak of M1/S1 activity was in the central sulcus, but the limited spatial resolution of the statistical maps did not allow distinction between primary motor and primary somatosensory cortical activation. In firm holding (Fig. 2, right column) the activated area of M1/S1 extended further rostral to the dorsal premotor cortex (PMD). Here an additional local peak of activity was present (Table 2). A further focus of activity was located in the left inferior precentral gyrus (Fig. 2, right column, no. 2), i.e. in the putative ventral premotor cortex (PMV; Roland & Zilles, 1996). Moreover, the left inferior parietal cortex and right parietal regions were active during firm holding (Table 2). The peaks of posterior parietal activity [Brodmann areas (BA) 7, 40] were, however, somewhat variable from subject to subject. The most pronounced brain activity was measured during gentle holding, when the grip force was skilfully reduced (Fig. 2, left column). In addition to the specified areas (left M1/S1, left PMV, bilateral posterior parietal cortex) of the brain, which were strongly activated, there was conspicuous activation of medial wall areas, as shown in the left column of Fig. 2. The activation peak was located caudal to a vertical line through the anterior commissure (AC-line), and its coordinate (x, y, z = –4, –8, 56) most probably corresponds to the left supplementary motor area (SMA) proper according to Picard & Strick (1996). However, the activated volume extended beyond the midline into the right SMA, rostrally into the putative pre-SMA and ventrally to the cingulate sulcus. Therefore both the ventral part of the SMA and the caudal cingulate motor area (CMA) were involved. The volume of the cluster (Table 2) confirms the widespread activation of the medial wall during the gentle force condition.

Comparison of the force conditions

Statistically significant differences between the gentle, normal and firm force conditions were identified by contrasts of the respective brain activation patterns (Table 3). Four regions of the brain were activated to a significantly greater extent in gentle holding than during holding with automated, normal force, namely the primary sensorimotor (M1/S1) cortex, the left PMV, the left inferior parietal cortex (BA 40), and the cortex on the medial surface of the frontal lobes (SMA/CMA). Figure 3 gives a view of these regions, which were particularly active during the skilful reduction of grip force. The motor areas of the medial wall (SMA/CMA) and the left inferior parietal cortex (BA 40) were even significantly more active during gentle than during firm holding with increased force, and the same trend was observed for M1/S1. The respective foci and the volumes of enhanced activation are listed in Table 3. The moderate increase of the grip force (firm hold) beyond the normal level had much less effects on brain activity than controlled force reduction. Compared with normal holding, the fMRI signal in the left PMV, in M1/S1 and in the precentral gyrus tended to increase (Table 3). No brain regions were significantly more active during firm than during gentle holding.

Results of individual subjects, which provide more anatomical details of the medial wall, are shown with parasagittal sections of the left hemisphere (Fig. 4). Voxels which were more active (uncorrected P < 0.001; Z > 3.09) during the gentle than during the normal force condition are highlighted in this descriptive analysis. The regions of enhanced activity extend from the cingulate sulcus into the superior frontal gyrus, involving the caudal CMA and mainly ventral parts of the SMA. The active areas are mostly located posterior to the AC-line, but in five subjects (Fig. 4A–C, F and G), they stretch out anteriorly beyond this line. These individual data confirm the consistent activation of the left hemispheric medial wall during skilful reduction of the grip force.

To further illustrate the differences in activity between the three force conditions, we show mean time courses of the fMRI signal, which were obtained from the data of all subjects (Figs 5 and 6). Figure 5a displays the signal profiles of the activation peak in the SMA (xyz coordinates: –4, –8, 56; see Table 2). Similar curves were found in the CMA (not shown). Differences in activity between the conditions are evident during the static holding periods. Lowering the grip force to 1.2 N (mean value of gentle hold) raised the fMRI signal of the SMA by ≈ 0.5%, above the values of the other two conditions and of rest (Fig. 5a). This is also illustrated with data of all single trials, where the static grip force values are plotted against the corresponding fMRI signal (Fig. 5b). The signal profiles of the activation focus in the primary sensorimotor cortex (x, y, z = –44, –28, 52) are given in Fig. 6. Regional activity of M1/S1 was lower during holding with normal, automatically adjusted force than during both gentle and firm holding (Fig. 6a and b). Both in the SMA and in M1/S1, there were similar temporary increases of the fMRI signal in all force conditions during the phases of dynamic transition, i.e. while the object was lifted or put down. These dynamic phases had been excluded from the aforementioned comparisons of the static periods.

Discussion

The main finding in the present study is the strong activation of primary and secondary sensorimotor areas when the subjects reduced the fingertip forces and held the object with a gentle grip just above the slip threshold. The most important difference between this (gentle) task and the other two conditions (normal and firm) was that subjects were forced to exert a precise control of the grip force in order not to drop the object. In both the firm and gentle conditions the subjects voluntarily adjusted the force level. In both conditions the brain activation increased in comparison with the automatic scaling of force during the normal holding task (see Fig. 2, Table 2). Partly, the change from automatic to voluntary control may explain the difference between gentle and normal, but the stronger activation during the gentle task remained also in a direct comparison with the voluntary firm hold condition.

We found the strongest activation in M1/S1, CMA, SMA, PMV and parietal (BA 7, 40) areas during the gentle holding. Dynamic fluctuations of the force, which would have enhanced the fMRI signal (Thickbroom *et al.*, 1999), could be excluded as an underlying cause (see Table 1). It is furthermore unlikely that the strong brain activity

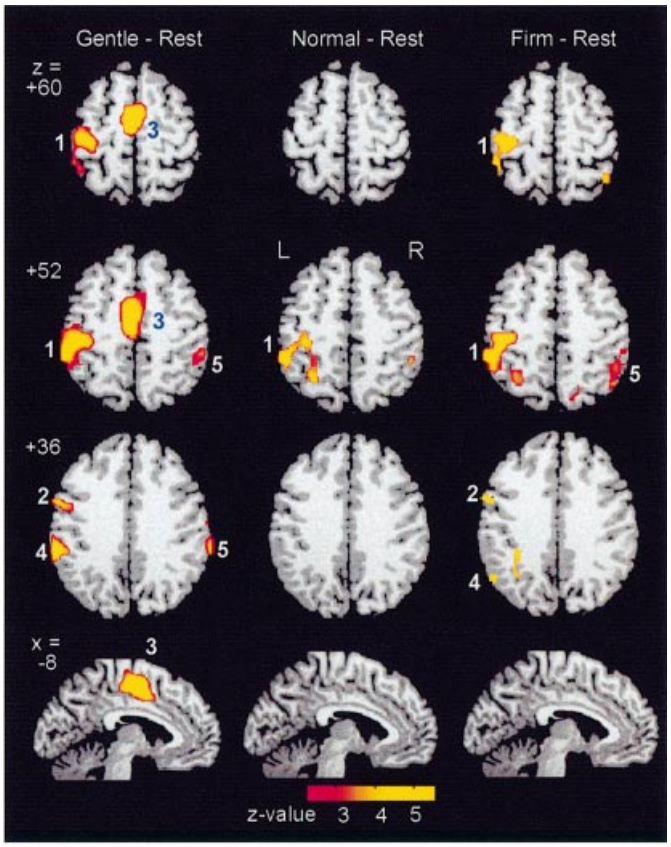

Fig.2

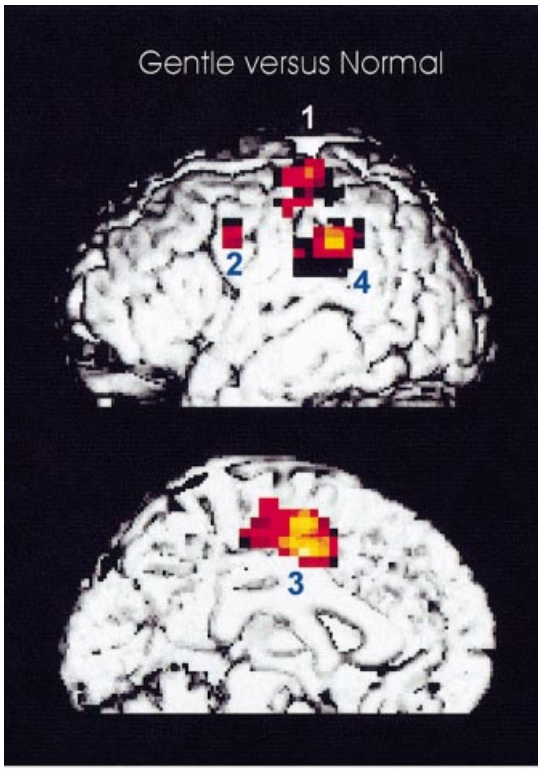

Fig.3

FIG. 2. Activation maps for static holding. The images show regions that were activated ($Z > 3.09$ compared with rest) during holding with gentle (left column), normal (middle column) and firm (right column) grip force. (1) Primary sensorimotor cortex; the activated area extends to the intraparietal region; (2) ventral premotor cortex; (3) supplementary and cingulate motor area; (4) left and (5) right inferior parietal cortex. Results from the group analysis were overlaid on a reference template (MNI standard brain). The Talairach z coordinates of the axial slices, and (bottom row) the y coordinate of the left parasagittal slices are indicated in the left margin. L, left hemisphere; R, right hemisphere.

FIG. 3. Difference maps of gentle vs. normal condition (group analysis). Surface rendering of brain regions that were more active ($Z > 3.09$) during static holding with a reduced grip force than during normal holding with automatic scaling of force. Left hemisphere: (1) primary sensorimotor cortex; (2) ventral premotor cortex; (3) supplementary and cingulate motor areas and (4) inferior parietal cortex.

FIG. 4. Results of individual subjects. Parasagittal sections ($x = -4$) of the medial wall of the left hemisphere. Voxels that were more active ($Z > 3.09$) during holding with gentle force than normal force are labelled. The blue vertical line is the AC-line; anterior is on the right side. Red arrows indicate location of the central sulcus.

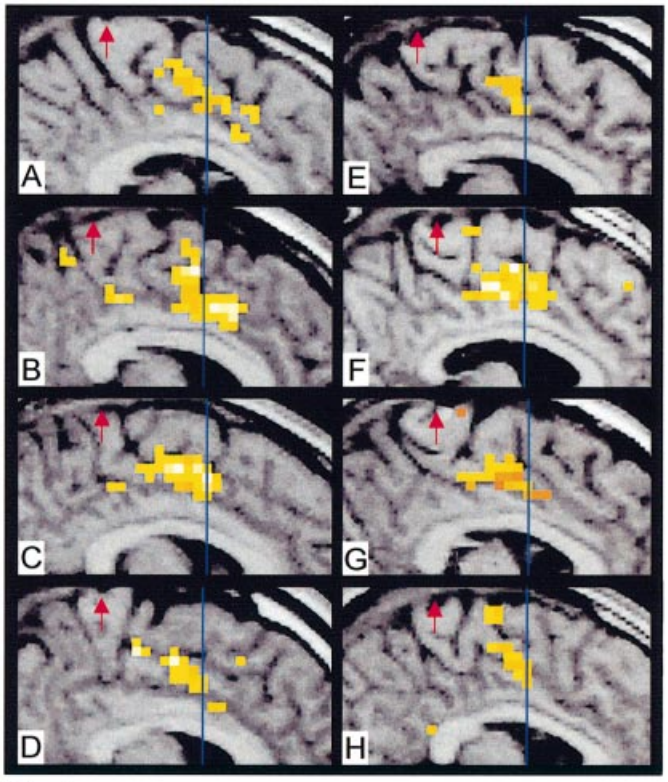

Fig.4

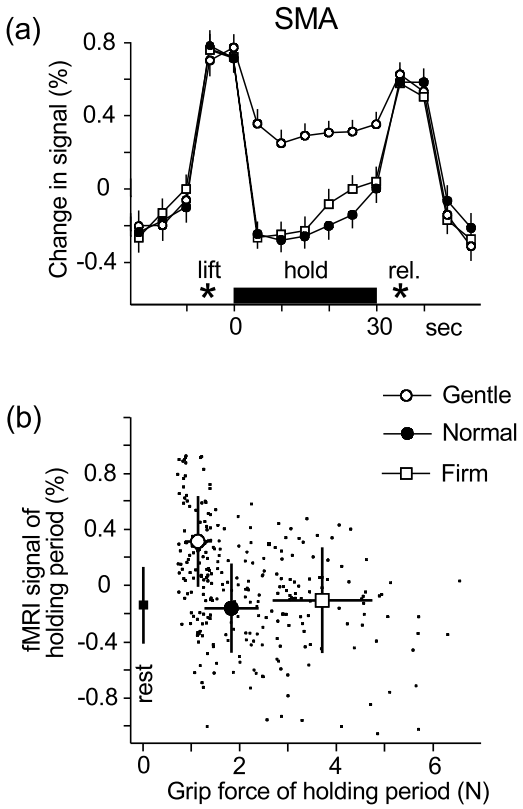

FIG. 5. fMRI signal profiles of the activation focus in the SMA (–4, –8, 56). (a) Average modulation of the signal during the gentle (open circles), normal (black circles) and firm (open squares) grip force conditions. The transitional dynamic phases (lift; rel., release) are marked with asterisks. The holding period is labelled with a black bar. Error bars indicate SEM. (b) The fMRI signal during the static holding period is plotted against the corresponding grip force. Dots show data from all trials ($n = 288$) of all subjects. Mean values of the gentle, normal and firm force conditions and of rest are indicated; error bars give SD.

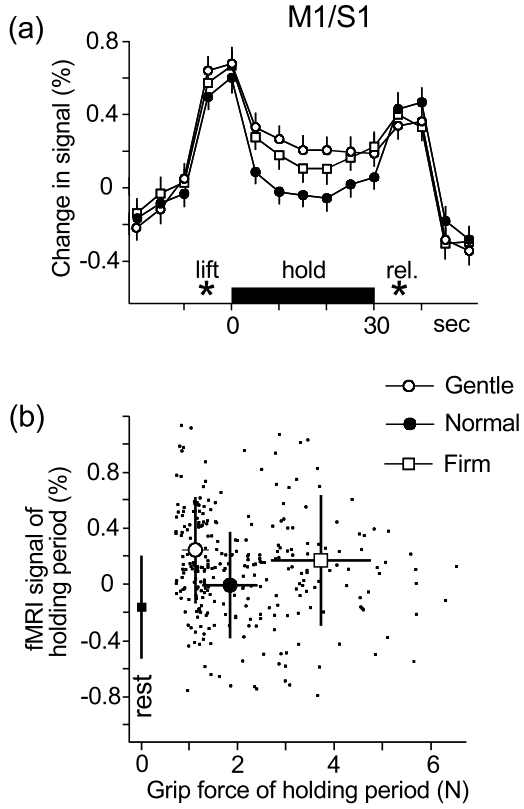

FIG. 6. fMRI signal profiles of the activation focus (–44, –28, 52) in the primary sensorimotor cortex. (a) Average modulation of the fMRI signal during the gentle, normal and firm grip force conditions. (b) The fMRI signal during static holding and the corresponding static grip forces. Otherwise as in Fig. 5.

was due to contractions of different muscle groups, or due to cocontractions, because such patterns were not reported by Hepp-Reymond *et al.* (1996). With intramuscular emg electrodes, these authors measured the activity of 15 hand muscles. When subjects heightened the isometric precision grip force from 1 to 3 N (comparable to our study), the emg activity of the prime movers (1st dorsal interosseus, adductor pollicis, flexor digitorum) clearly increased. Though less markedly, the activity of most other hand muscles increased, too (their fig. 6).

The stronger brain activity in the gentle force condition may rather be due to the difficulty of this task. When the object was held cautiously, the natural tendency to scale the grip force to a higher ('normal') level had to be suppressed. Fluctuations of the force had to be avoided in order to prevent unintentional slips. The attentive demands may have enhanced cortical activation, because watchful perception of cutaneous and proprioceptive information from the digital pulp and hand muscles is necessary for the precise scaling of force close to the slip threshold (Johansson & Westling, 1987). By gating mechanisms, this can influence the central processing of afferent signals and increase the excitability of the primary sensory areas, which are in turn closely linked to motor areas (Jones *et al.*, 1978; Hyvärinen *et al.*, 1980; Hsiao *et al.*, 1993).

The least activation of sensorimotor areas was found when the subjects used their normal automatically scaled grip force. When they intentionally applied a higher static grip force (firm hold), activity of the premotor and primary sensorimotor cortex tended to increase (see Table 3). Previous studies have demonstrated force-dependent increases of activation in M1 during other static and dynamic hand motor tasks (i.e. pressing a key with the index finger, clenching the fist, precision grip task; Dettmers *et al.*, 1995, 1996; Thickbroom *et al.*, 1998; Ehrsson *et al.*, 2001). This corresponds to an enhanced descending neuronal drive, which intensifies muscle contraction by recruiting and raising the discharge frequency of motor units (Hennemann & Mendell, 1981). Increasing activity has also been reported for the SMA and CMA, and the primary somatosensory cortex (Dettmers *et al.*, 1995). These previous studies covered the range between 5 and 60% of the maximum voluntary force, sometimes with considerable irradiations of muscle activity at higher force levels (Dettmers *et al.*, 1995, 1996). The forces were adjusted to cued target values using external feedback, whereas the subjects in our study had to rely on their fingertip sensation. Furthermore, in the present paradigm they used < 7% of the maximum voluntary force. Comparably small precision grip forces between 1 and 3 N were studied by Crelier *et al.* (2000), who did not report any increase in the intensity of the activity in motor-related areas, but found that the volume tended to increase in parallel with force. Hence, in the present study we can not determine whether the increase in brain activity in the firm hold task compared with the normal task is due to the small increase of the exerted finger tip forces, or to the change from automatic to voluntary control.

Neuronal discharge patterns during grip tasks have been extensively studied in monkeys (overview in Lemon, 1993). Muir &

Lemon (1983) described corticomotoneuronal M1 cells facilitating hand muscles, which fired specifically during a precision grip. In the dynamic phases of grasping and releasing, such neurons show a temporary increase in the firing rate (Picard & Smith, 1992). The corticomotoneuronal activity during the static holding phase correlates with the isometric grip force (Maier *et al*., 1993; Hepp-Reymond *et al*., 1999). Interestingly, some neurons increase their firing rate when the grip force is decreased, i.e. they have a negative correlation with force. These cells can provide sensitive force control during the gradual release of objects from the grip, because they take over when other, positively covarying, neurons cease to be active (Lemon, 1993). In monkeys, neurons with a negative correlation between firing rate and force were also found in S1 and the premotor cortex (Wannier *et al*., 1991; Hepp-Reymond *et al*., 1994). If such neurons exist in human primary and secondary motor areas, they should be particularly active during the controlled reduction of the grip force.

The ventral premotor cortex is linked to the posterior parietal regions and to the primary motor cortex (Jeannerod *et al*., 1995; Rizzolatti *et al*., 1998). These areas, which were strongly activated during gentle holding, constitute a circuit which participates in grip formation and tactile exploration (Seitz *et al*., 1991; Sakata *et al*., 1995; Binkofski *et al*., 1999). A recent fMRI study demonstrated activation of bilateral ventral premotor and posterior parietal areas during a precision grip task (Ehrsson *et al*., 2000). This activity was stronger than during a power grip, although the power grip involved more force. The parietal activation may hence reflect the sensorimotor integration required for the dexterous control of fine fingertip forces applied to objects (Ehrsson *et al*., 2001).

The strong activation of the medial wall during gentle holding was particularly noticeable and consistent. Most likely both the ventral part of the SMA and the CMA were involved, although the border between these areas is not exactly known (Stephan *et al*., 1995, 1999; Picard & Strick, 1996). The SMA can control motoneurons of hand muscles via corticospinal links, but it also projects directly to the primary motor cortex (Dum & Strick, 1991; Tokuno & Tanji, 1993). Whereas its role in the preparation of movement, motor imagery and bimanual coordination is known (Roland *et al*., 1980; Tanji & Shima, 1994; Stephan *et al*., 1999), task-dependent activity of the human SMA in the control of low static precision grip forces has not yet been demonstrated. Selective ablation of an SMA in nonhuman primates led to an excessive increase in the grip force of the contralateral hand with persistent difficulties in releasing objects (Smith *et al*., 1981). This accords with the concept that the SMA modulates the activity of the primary motor cortex by suppressing excitatory afferent feedback loops (Hummelsheim *et al*., 1986), which in turn enables a reduction of the grip force and the release of objects. Gating of motor output might involve cortical neurons targeting spinal inhibitory interneurons, or activation of intracortical inhibitory interneurons (e.g. in M1; Davey *et al*., 1994), which reduce the excitatory corticospinal volley to spinal motoneurons. Congruent with this, Toma *et al*. (1999) reported activation of contralateral M1 and bilateral SMAs during the voluntary relaxation of forearm muscles. As in our study, the SMA activity was located near the midline and rather ventral (their table 2).

Caudal cingulate areas, close to the AC line, are usually active during complex motor tasks (Picard & Strick, 1996) and in precision grip tasks (Ehrsson *et al*., 2000, 2001). Dettmers *et al*. (1995) found a covariation of force and regional cerebral blood flow in the dorsal bank of the cingulate sulcus. Phase-specific modulations of neuronal activity in both the CMA and SMA during gripping with thumb and forefinger were reported by Cadoret & Smith (1997). The respective neurons receive afferent input from hand muscles and relay proprioceptive feedback during prehension. Enhanced processing of such feedback during the precise adjustment of small grip forces could underly the activity of the CMA during the gentle hold condition.

Taken together, brain activity did not merely increase in parallel with force. Indeed, motor-related regions were least active during automated behaviour, and most active during the demanding task which required skilful reduction of the fingertip force. These differences were significant, although static force conditions generally evoke less fMRI activity than dynamic tasks (Thickbroom *et al*., 1999; see also Ehrsson et al., 2000, 2001). The findings may be related to the pathophysiology of patients with motor cortical lesions who lose manual dexterity and often produce excessive grip forces (Eliasson *et al*., 1992; Hermsdörfer & Mai, 1996).

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Abbreviations

AC-line, vertical line through the anterior commissure; CMA, cingulate motor area; BA, Brodmann's area; BOLD, blood oxygen level-dependent signal; emg, electromyogram; fMRI, functional magnetic resonance imaging; M1, primary motor cortex; MR, magnetic resonance; PMD, dorsal premotor cortex; PMV, ventral premotor cortex; S1, primary somatosensory area; SMA, supplementary motor area; TE, signal (echo)-gathering time; TR, sequence repetition time.

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