

# Relation Between Muscle and Brain Activity During Isometric Contractions of the First Dorsal Interosseus Muscle

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**Abstract:** We studied the relationship between muscle activity (electromyography, EMG), force, and brain activity during isometric contractions of the index finger, on a group and individual level. Ten subjects contracted their right or left index finger at 5, 15, 30, 50, and 70% of their maximal force. Subjects received visual feedback of the produced force. We focused our analysis on brain activation that correlated with EMG. Brain activity of specific anatomical areas (region-of-interest analysis, ROI) was quantified and correlated with EMG activity. Furthermore, we tried to distinguish between brain areas in which activity was modulated by the amount of EMG and areas that were active during the task but in which the activity was not modulated. Therefore, we used two regressors simultaneously: (1) the produced EMG and (2) the task (a categorical regressor). As expected, activity in the motor areas (contralateral sensorimotor cortex, premotor areas, and ipsilateral cerebellum) strongly correlated with the amount of EMG. In contrast, activity in frontal and parietal areas (inferior part of the right precentral sulcus, ipsilateral supramarginal gyrus, bilateral inferior parietal lobule, bilateral putamen, and insular cortex) correlated with activation per se, independently of the amount of EMG. Activity in these areas was equal during contractions of the right or left index finger. We suppose that these areas are more involved in higher order motor processes during the preparatory phase or monitoring feedback mechanisms. Furthermore, our ROI analysis showed that muscle and brain activity strongly correlate in traditional motor areas, both at group and at subject level. *Hum Brain Mapp* 29:281–299, 2008. © 2007 Wiley-Liss, Inc.

**Key words:** force; EMG; fMRI; regression analysis

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## INTRODUCTION

Functional magnetic resonance imaging (fMRI) has become increasingly popular for studying motor control, and hand tasks are often used in these experiments. Hand movements are preferred because of the large cortical representation of hand muscles, and hand muscles can be activated without associated head movements.

A few studies have investigated the relationship between brain activation and force production during iso-

metric (Dai et al., 2001; Thickbroom et al., 1998; Ward and Frackowiak, 2003), short-lasting near-isometric (Dettmers et al., 1995), or dynamic contractions (Ludman et al., 1996).

Only one study has addressed the relation between brain activation and muscle activity (electromyography, EMG) at different force levels (Dai et al., 2001). As EMG gives an indication of the output from the central nervous system to the muscle it is extremely interesting to determine in which brain areas activity correlates with EMG. Dai et al. (2001) recorded muscle activity during periods of nonscanning. They sampled EMG during very short time periods (200 ms) and did not use EMG directly to assess areas in which brain activity correlate with muscle activation. Furthermore, their data (Dai et al., 2001) only referred to group analyses; up till now no data is available on the relation between muscle and brain activity at an individual subject level.

Patients often have a lateralized motor impairment, and during experiments patients often perform the task with one side. It depends on the questions being asked if the healthy control side or the affected side is tested. Unfortunately, no control data is available on the relation between muscle activation (EMG) and brain activity during force production with the nondominant limb.

A recent experiment in monkeys showed that the relation between activation of various muscles (EMG) and activity in the primary motor cortex and cerebellum can best be described as being linear (Townsend et al., 2006). In the present experiment, we used EMG of the prime mover (the first dorsal interosseus muscle) to reveal brain areas in which the activity correlated linearly with muscle activity. Furthermore, we tried to distinguish between human brain areas showing activity linearly correlated with modulation of muscle activity and areas showing activity correlated with muscle activity per se; that is, areas that showed similar activity during all contractions independently of the amount of force. Additionally we established a quantitative relation between index finger abduction force, activity of the first dorsal interosseus muscle (EMG), and level of brain activity in several motor areas. Right-handed individuals performed contractions with both the dominant and the nondominant hand, and data were analyzed both on a group and individual level.

Part of this data was presented in abstract form (Van Duinen et al., 2004).

## METHODS

### Subjects

Ten right-handed subjects (mean age:  $25.4 \pm 2.5$  years) participated in this study. All subjects signed an informed consent prior to participation in the experiment. All experimental procedures were undertaken with the approval of the medical ethical board of the UMCG, conform the standards set out in the Declaration of Helsinki (2000).

## Measurements

### Force

We measured index finger abduction force with a custom-made MR compatible strain gauge force transducer (see Fig. 1). The force transducer was adjusted to the hand size of the subject by positioning the index finger parallel to a laminated bar with a connection between this bar and the proximal interphalangeal joint of the index finger. The force recordings were stored at a PC using Spike2 via an A/D converter (sampling frequency: 500 Hz; Cambridge Electronic Design, Cambridge, UK).

### Electromyography

We used sintered silver/silver-chloride electrodes (Easycap, Herrsching-Breitbrunn, Germany) in combination with the BrainAmp MR plus amplifier (Brain Products GmbH, Munich, Germany) for EMG recordings of the right and left first dorsal interosseus muscle (FDI). For that purpose, a pair of electrodes was placed on the belly of the FDI and the metacarpophalangeal joint, after cleaning and scrubbing the skin. The wires of the electrodes were twisted per muscle to equalize the effect of the magnetic field on the EMG recordings (Van Duinen et al., 2005). A reference and a ground electrode were positioned on the processus styloideus ulnaris of the right and left arm, respectively. The electrodes were connected to the BrainAmp amplifier, which was connected via an optical cable to a PC, equipped with Brain Vision Recorder software, outside the MR room (sampling frequency: 5,000 Hz).

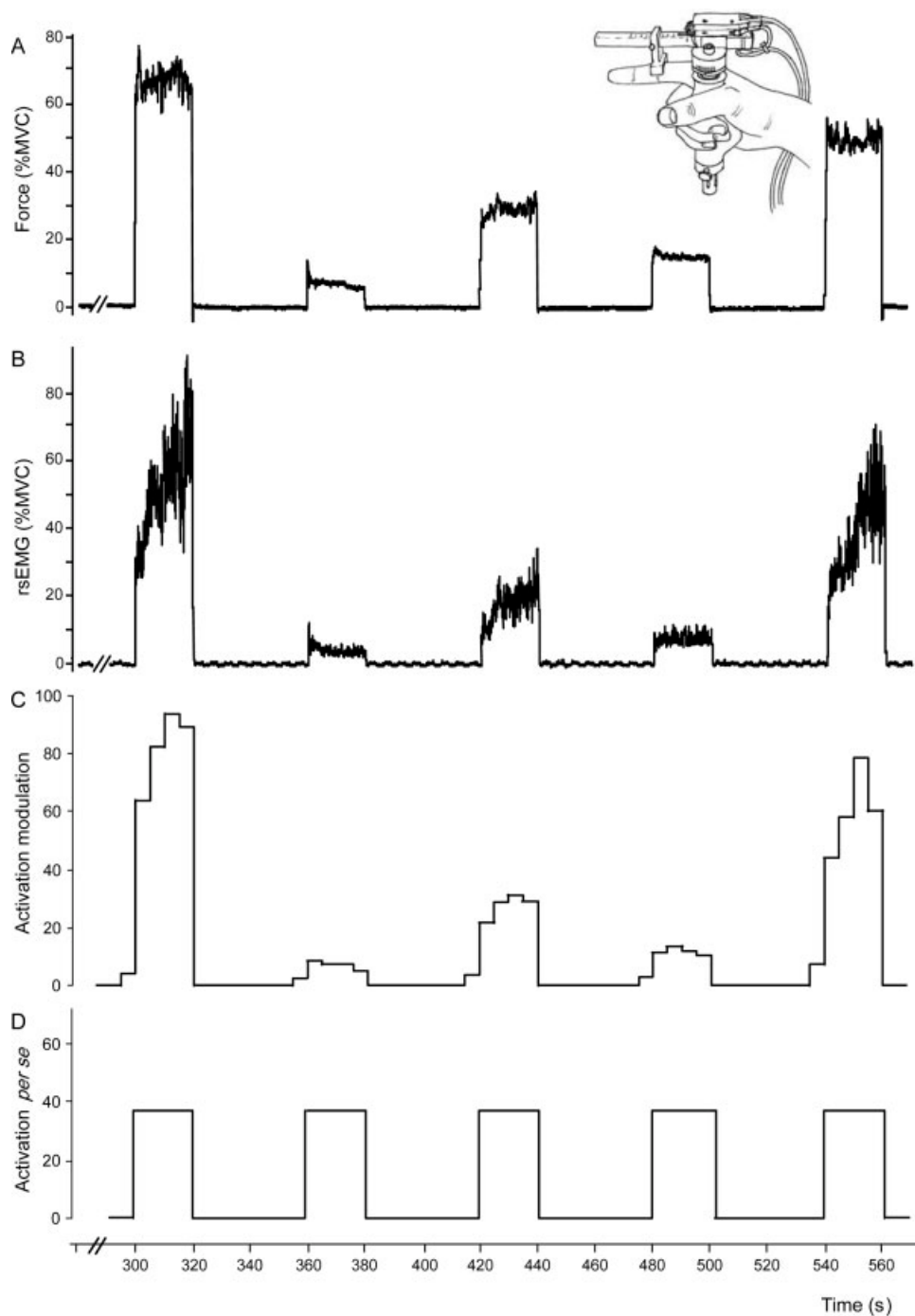
### Magnetic resonance imaging

Functional images were acquired using a 3T MRI scanner (Philips, Best, Netherlands), which was equipped with echo planar imaging (EPI) capability and a standard transmit/receive (TR) head coil. The following pulse sequence parameters were used: FFE single shot EPI; 46 slices, slice thickness 3.5 mm, no gap; field of view 224 mm; scanning matrix  $64 \times 64$ ; transverse slice orientation; repetition time (TR) = 5 s; echo time (TE) = 35 ms; minimal temporal slice timing: 2,884 ms; flip angle  $90^\circ$ . The repetition time (5 s) consisted of 3-s scanning and 2-s nonscanning periods (sparse sampling). We used this sparse sampling protocol to check whether force and EMG measurements were influenced by MR-scanning. In the remainder of this study, the acquisition of 46 slices will be referred to as one scan.

In addition, T1-weighted anatomical images of the entire brain were obtained with the following pulse sequence parameters: 160 slices, slice thickness 1 mm; field of view 256 mm; scanning matrix  $256 \times 256$ ; transverse slice orientation; TE = 4.6 ms; TR = 25 ms; flip angle  $30^\circ$ .

### Tasks

Subjects were positioned supine in the scanner, holding the force transducers in their hands, and their arms were



**Figure 1.**

Schematic illustration of the force transducer in combination with records of index finger abduction force (**A**), and the rectified and smoothed EMG of the first dorsal interosseus (rsEMG; **B**). The duration of each contraction is ~20 s, followed by 40 s

rest. The order of the force levels in this example is 70, 5, 30, 15, and 50% MVC. **C**, **D**. Schematic illustrations of the regressors “activation modulation” (**C**) and “activation per se” (**D**).

supported by pillows. Subjects received continuous visual feedback of the task, the target force, and their force production via a beamer on a screen, which they were able to

see in a mirror. The visual feedback of the task was a stimulus line; when this line went up, subjects had to produce force; when this line went down, subjects were allowed to

relax. A second and a third line showed the target force and the actual produced force.

In the first run, the subjects produced three maximal voluntary contractions (MVCs) per hand. The maximal contractions were maintained for 10 s, followed by 50 s rest and were alternated between the right and left index finger. The strongest contraction was designated as the control MVC (determined for the right and left hand separately).

In the second run, the subjects had to perform submaximal isometric contractions with their right index finger. The subjects matched their force with a target force for 20 s, followed by 40 s rest. The target line was set at 5, 15, 30, 50, or 70% MVC. All force levels were repeated three times, resulting in 12 scans per force level; the order of the force levels was pseudo-random. To prevent effects of fatigue, the pseudo-random order prevented immediate repetition of relatively high force levels; furthermore, the contractions were followed by relatively long resting periods.

In the third run, this submaximal isometric contraction task was repeated for the left index finger.

## Analyses

### Force

Offline, the data were analyzed using Spike2. To be able to express all forces in the percentage of the MVC force, we determined the peak amplitude of the maximal contractions. Next, we determined the mean amplitudes and the coefficients of variation (standard deviation of the force divided by the mean force) for each submaximal contraction (20 s). Furthermore, the “mean force per scan” (the acquisition of one volume of the entire brain; 5 s) was calculated.

### Electromyography

Offline, we used Brain Vision Analyzer software (version 1.05.0001) to preprocess the data (see also Van Duinen et al., 2005). Bipolar derivations were calculated for each muscle, followed by high-pass filtering (10 Hz) to remove possible movement artifacts. Thereafter the data were corrected for scanner artifacts (Allen et al., 2000; Van Duinen et al., 2005), followed by low-pass filtering (400 Hz) and down sampling (by a factor 2). Subsequently, the data were exported (in ASCII format) to be imported in Spike2 for further analysis.

In Spike2, we determined the maximum amplitude of the rectified and smoothed (100 ms) EMG signal during the maximal contractions, and the mean amplitudes of the rectified EMG signals during each submaximal contraction (20 s). Furthermore, we calculated the mean amplitude of the EMG per scan (5 s).

Linear regression analysis was performed to determine the correlation between mean force and mean EMG amplitudes during the contractions.

### Magnetic resonance imaging

We used SPM2 software (<http://www.fil.ion.ucl.ac.uk/spm>, Wellcome Department of Imaging Neuroscience; Friston et al., 1995) to preprocess the images. The functional images were (1) realigned to remove head motion artifacts; (2) coregistered with the anatomical image for a more accurate localization of the origin of the signals; (3) normalized to a T1 template to perform the group analyses; and (4) smoothed with a Gaussian Kernel of 8 mm full width at half maximum to increase the signal-to-noise ratio.

We performed two statistical analyses in SPM2. In both analyses, we included head movement parameters, resulting from the realignment procedure (Friston et al., 1996). In the first analysis, EMG or force (mean amplitude per scan) was used as a regressor. To correct for the slow onset of the haemodynamic response, the values of these regressors were shifted one scan (5 s). This analysis reveals anatomical regions in which the activity correlates with the produced EMG or force during the task. As expected from the strong correlation between EMG and force, the analysis based on the force and the analysis based on EMG measurements were almost identical. Therefore, we only report the results for the EMG analysis.

In the second analysis, we aimed to distinguish anatomical areas in which the activity correlated with activation per se from areas that are involved in the activation modulation. Here we used two regressors simultaneously: (1) the amount of EMG produced during the submaximal contractions (the same regressor as in the first analysis; see Fig. 1C) and (2) a conventional box-car regressor (on/off; see Fig. 1D). Instead of using “zero” for rest and “one” for the contraction, we used “zero” for rest and “the mean EMG over all the contractions” for the contractions. This procedure allows a direct comparison between the activation patterns for the two regressors. Note that by adding a regressor in analysis 2, the activation patterns that correlate with the amount of EMG differ in analyses 1 and 2. Although the two regressors in analysis 2 are mathematically not independent, the determinants are larger than zero, and therefore it is possible to use them within the same analysis (see also Discussion).

These two analyses resulted in three contrasts per subject: (1) EMG-level (first analysis), (2) activation modulation (second analysis), and (3) activation per se (second analysis). These contrasts were used as input for second level group analyses (one sample *t* tests; uncorrected  $P < 0.001$ ; clustersize  $\geq 10$  voxels). The activated areas were defined with a probabilistic cytoarchitectonic map (Eickhoff et al., 2005). For the motor and premotor cortices, we used data from the meta-analysis by Mayka et al. (2006), and for the pars opercularis of the inferior frontal gyrus we used Tomaiuolo et al. (1999).

To quantify the relationship between muscle and brain activity in individual subjects, we performed a region of interest (ROI) analysis, using Marsbar (Brett et al., 2002).

**TABLE I. Mean amplitudes of force, force variability, and EMG ( $\pm$  standard deviation) during the levels of right and left index finger abduction force**

Target force (%)	Mean force (% MVC; target hand)	Mean force variability (target hand)	Mean EMG (% MVC; target hand)	Mean force (% MVC; contra-lateral side)	Mean EMG (% MVC; contra-lateral side)
Right-hand contractions					
5	9.2 $\pm$ 3.4	0.14 $\pm$ 0.06	6.1 $\pm$ 1.5	0.10 $\pm$ 0.71	0.47 $\pm$ 0.22
15	17.0 $\pm$ 2.3 <sup>a,b</sup>	0.10 $\pm$ 0.05 <sup>a</sup>	10.8 $\pm$ 1.4 <sup>a,b</sup>	0.14 $\pm$ 0.64	0.75 $\pm$ 0.27
30	32.1 $\pm$ 2.3 <sup>a,b</sup>	0.08 $\pm$ 0.04 <sup>a</sup>	25.9 $\pm$ 6.0 <sup>a,b</sup>	0.44 $\pm$ 0.88	0.66 $\pm$ 0.10
50	52.5 $\pm$ 2.3 <sup>a,b</sup>	0.08 $\pm$ 0.009 <sup>a</sup>	51.6 $\pm$ 9.0 <sup>a,b</sup>	0.78 $\pm$ 0.89 <sup>a</sup>	0.98 $\pm$ 0.85
70	70.3 $\pm$ 4.2 <sup>a,b</sup>	0.08 $\pm$ 0.02 <sup>a</sup>	72.2 $\pm$ 11.7 <sup>a,b</sup>	1.91 $\pm$ 2.61 <sup>a</sup>	2.52 $\pm$ 2.66 <sup>a,b</sup>
Left-hand contractions					
5	8.7 $\pm$ 1.8	0.17 $\pm$ 0.15	7.4 $\pm$ 2.5	0.17 $\pm$ 0.82	0.11 $\pm$ 0.56
15	18.0 $\pm$ 2.5 <sup>a,b</sup>	0.09 $\pm$ 0.09 <sup>a</sup>	13.0 $\pm$ 3.8 <sup>a,b</sup>	0.17 $\pm$ 0.64	0.17 $\pm$ 0.79
30	32.5 $\pm$ 1.9 <sup>a,b</sup>	0.08 $\pm$ 0.05 <sup>a</sup>	23.1 $\pm$ 4.2 <sup>a,b</sup>	0.24 $\pm$ 0.57	0.14 $\pm$ 0.88
50	53.7 $\pm$ 3.4 <sup>a,b</sup>	0.08 $\pm$ 0.03 <sup>a</sup>	45.6 $\pm$ 9.1 <sup>a,b</sup>	0.75 $\pm$ 1.10	0.72 $\pm$ 1.16
70	73.4 $\pm$ 2.5 <sup>a,b</sup>	0.07 $\pm$ 0.02 <sup>a</sup>	67.2 $\pm$ 12.9 <sup>a,b</sup>	2.93 $\pm$ 03.12 <sup>a,b</sup>	2.75 $\pm$ 2.47 <sup>a,b</sup>

<sup>a</sup>Significantly different from the 5% MVC target force ( $P < 0.05$ ).

<sup>b</sup>Significantly different from the previous target force ( $P < 0.05$ ).

First, we defined ROIs based on a model including all contractions (comparable with the activity of Fig. 3A,B); this procedure ensures including all areas that were involved in force production. Thereafter, the large activated cluster in the sensorimotor cortex was masked with anatomical ROIs to separate different regions; precentral gyrus, postcentral gyrus, and supplementary motor area (SMA), respectively (automated anatomical labeled; Tzourio-Mazoyer et al., 2002). Second, we obtained the mean effect size (contrast value minus baseline) of all voxels included in the ROI for each force level. For comparison with previous literature we expressed the effect size as a percentage signal change (effect size divided by the baseline and multiplied by 100%).

To test whether the contrast values differed significantly between the five force levels (within-subject factor: target force level; five levels) an ANOVA for repeated measures was used (SPSS). When the main analysis indicated a significant effect for “force,” post-hoc analyses were performed (least significant difference). The same statistical procedures were performed for the force and EMG data.

## RESULTS

Two subjects showed head movements during one of the tasks. The data from these subjects during this task were excluded from the brain activity analysis. The first subject showed one large movement (>5 mm in one scan) during the right contractions. This single movement apparently resulted in an artifact that was not totally removed by the realignment or the inclusion of motion parameters. The data from the left contractions of this subject were used for further analysis. The other subject showed small head movements during contractions with the left index finger that correlated strongly with the task, at the start and end of each contraction. No significant movements were observed during right-hand contractions, therefore the data from these contractions were included in the analysis.

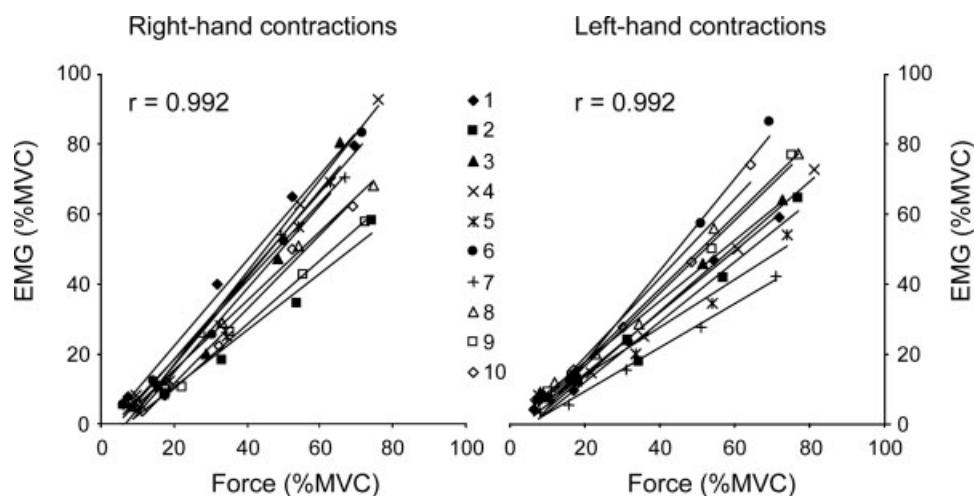
## Force and EMG

Our EMG and force recordings were not significantly affected by the scanning procedures (see also Van Duinen et al., 2005). Figure 1 shows an example of force and EMG recordings during submaximal contractions. The maximal voluntary force ranged from 21.99 to 65.64 N. For most force levels, subjects performed the force task according to the instructions. However, at the lowest force level (5% MVC) subjects produced significantly more force (right hand: 9.2% MVC; left hand: 8.7% MVC). The absolute variability in the force was smaller at low than at high force levels. Yet, the coefficient of variation, defined as the standard deviation of the force divided by the mean force, was larger during the contractions at 5% MVC force than during the other force levels ( $F_{(4,36)} = 11.68$ ;  $P < 0.0001$ ; post-hoc analysis: 5% MVC versus all force levels:  $P < 0.01$ ). Table I describes the mean values for force, force variability, and EMG amplitude for both right and left submaximal contractions for the group of subjects ( $n = 10$ ). At the highest target force level (70% MVC), there was also a significant activation of the contralateral, nontarget muscle during both right-hand and left-hand contractions (Table I).

Since we measured both force and EMG in the MR scanner, we were able to determine the correlation between muscle activity (EMG) and muscle output (force; Fig. 2). Both for the group as well as for the individual subjects, these correlations were highly significant for both right and left index finger abductions ( $r^2 > 0.95$ ). There were no significant differences in these correlations between the right and left index finger.

## Brain Activity

The relation between EMG and brain activation was almost identical to the relation between force and brain ac-



**Figure 2.**

The correlation between force and EMG during right-hand and left-hand contractions. The mean amplitude of the three contractions at each force level (%MVC) is plotted against the mean amplitude of the accompanying rsEMG (%MVC), for each individual subject. For both hands the mean correlation coefficient is 0.992.

tivity, therefore, we only present the EMG data. At first, we determined brain areas that were activated during the submaximal contractions, using EMG activity as a regressor. For contractions with the right or the left index finger, the analysis showed strong activation of the contralateral sensorimotor cortex extending into premotor areas, medial areas (including SMA and cingulate cortex), bilateral cerebellum, and parietal areas (Fig. 3A,B, Table II).

To compare brain activity that was associated with muscle activation per se versus activity that correlated with modulation of muscle activity, we used two regressors simultaneously in the same model (see Methods and Fig. 1C,D). The areas showing a significant correlation with the regressor “activation modulation” are visible in Figure 3C,D ( $T > 4.5$ , uncorrected  $P < 0.001$ ; Table III), whereas the areas showing a significant correlation with the regressor “activation per se” are plotted in Figure 3E,F ( $T > 4.5$ ; uncorrected  $P < 0.001$ ; Table IV). Some areas showed activation that correlated with both regressors.

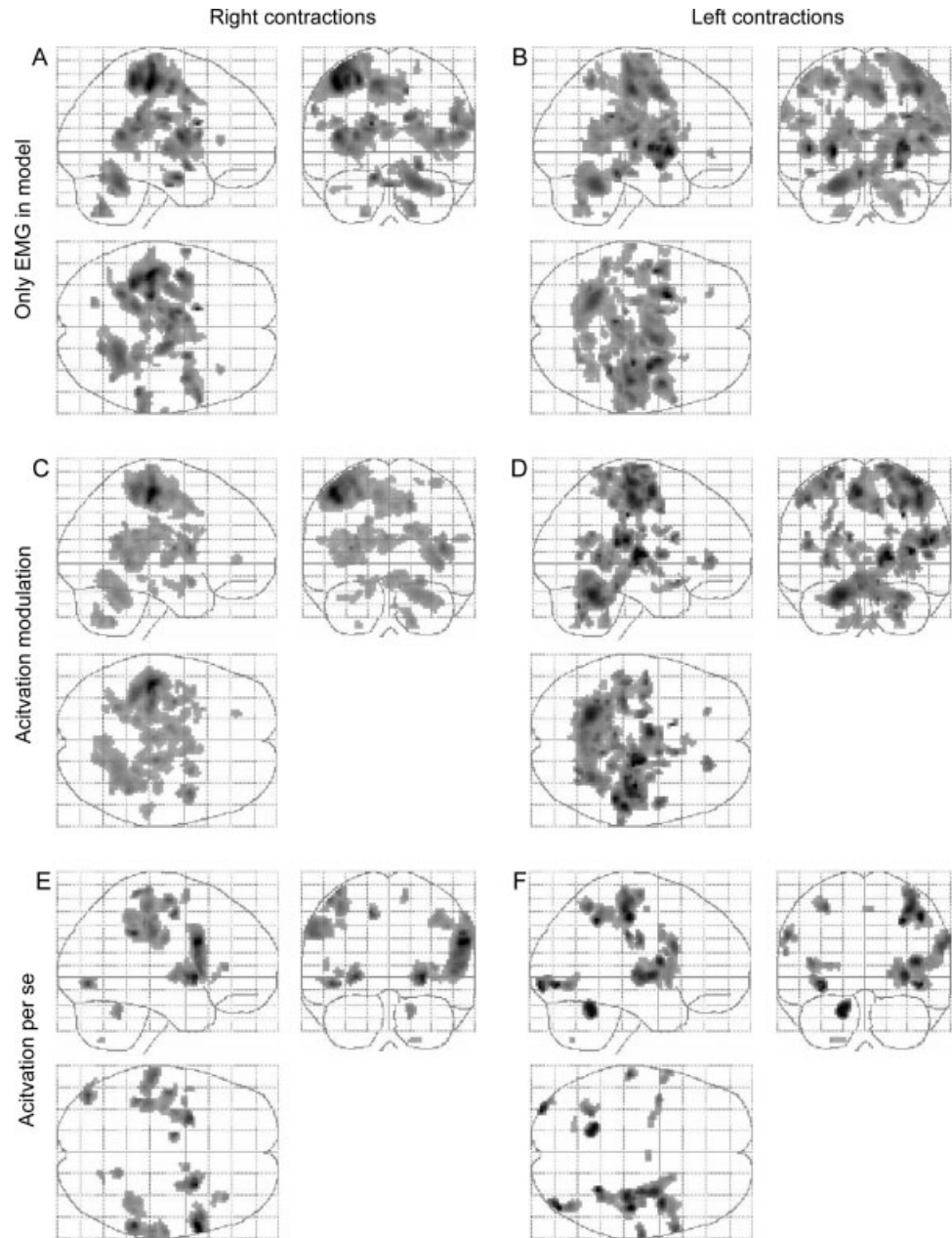
The regressor “activation modulation” revealed activity in areas that strongly correlated with force gradation. This was found, as expected, in the contralateral sensorimotor cortex—this cluster extended into the SMA—, bilateral premotor areas (including the Rolandic operculum and dorsal premotor areas), and the bilateral cerebellum with the strongest activation foci in the ipsilateral hemisphere. Furthermore, an activation cluster was observed bilaterally in the parietal operculum. In the right hemisphere, this cluster included the superior temporal gyrus. During left-hand contractions, this cluster extended into the right supramarginal gyrus and posterior part of the putamen. During contractions with the left index finger, strong activation was

seen in the right thalamus. Additionally, there was activation in the ipsilateral motor cortex, especially during left index finger contractions.

To compare brain activity during contractions of the left and right index finger we plotted brain activity on the same brain slices (Fig. 4A). Figure 4 shows that during contractions with the left or right index finger, activation clusters in the left sensorimotor cortex are observed; less overlap in activity is seen in the right sensorimotor cortex. Furthermore, activation in the SMA, parietal operculum bilaterally, and in a small part of the cerebellum overlap, while most other motor area were more lateralized (see also Table III).

The regressor “activation per se” revealed activation predominantly in frontal and parietal areas. A large activation cluster was observed around the right inferior part of the precentral sulcus. This area included the inferior frontal operculum (BA 44; Eickhoff et al., 2005) at the border of the Rolandic operculum, ventral premotor areas, and the lateral part of the insular cortex. A second cluster contained the bilateral inferior parietal lobule and the (ipsilateral) supramarginal gyrus. Furthermore, there was activation in the contralateral precentral gyrus, bilateral putamen, (left) inferior occipital gyrus. Most activation clusters were comparable when using EMG or force parameters in the model. However, when using EMG parameters, there was additional activation of ipsilateral cerebellum (border lobulus IV/V and VI, and lobule VIII), which was absent when using force parameters.

Figure 4B (see also Table IV) shows activation clusters in which the activity during contractions with the left and right index finger overlap. Areas that are active during both contractions are found in the right postcentral gyrus,



**Figure 3.**

Brain activity during right-hand and left-hand contractions. Left column shows activity during contractions with the right hand (A, C, E); right column shows activity during contractions with the left hand (B, D, F). Top panel (A, B): brain activity correlating with mean EMG amplitude per scan (only muscle activity and movement parameters in the model). Middle panel (C, D): brain activity correlating with the regressor “activation modulation” (see Fig. 1C). Bottom panel (E, F): brain activity correlating with “activation per se” (see Fig. 1D). All activity results from a random effects analysis of nine subjects (for right-hand contractions subject 7 excluded; for left-hand contractions subject 8 excluded);  $P < 0.001$  uncorrected, cluster size  $\geq 10$ .

left supramarginal gyrus, inferior parietal lobule (bilateral), occipital gyrus, and bilaterally in the insula and putamen.

### Brain Activity Versus EMG/Force

We performed ROI analyses to quantify the relation between EMG or force and brain activity. EMG and force data correlated strongly and therefore the correlation between EMG or force and brain activation showed similar results. Therefore, only EMG data are presented (Figs. 5–8). The brain activity (percentage signal change) was plotted against EMG values for the most important motor

areas: the contralateral precentral gyrus (including M1 and PMd), contralateral postcentral gyrus (S1), SMA, and lobule VI of the ipsilateral cerebellum (CBL VI). On basis of the results found with the second analysis, we also included ROI analyses for the ipsilateral precentral gyrus (M1 and PMd) and the inferior part of the right precentral sulcus (including the inferior frontal operculum and ventral premotor areas). To determine the relation between EMG and brain activity in the aforementioned areas for individual subjects we performed linear regression analysis. Figures 5 and 6 show the relation and correlation coefficients during right and left index finger abductions,

**TABLE II. Brain areas activated during index finger abduction, the activity was based on EMG activity (Fig. 3A,B)**

Anatomical region (functional area)	BA	Right contractions				Left contractions				
		x	y	z	Peak T value	BA	x	y	z	Peak T value
Central region										
L Postcentral gyrus (S1)	2: 70%	-34	-40	56	11.49	2: 40%	-34	-46	56	6.06
L Pre/postcentral gyrus (SMC)	2: 50%; 4p: 40%	-40	-28	52	14.18					
L Pre/postcentral gyrus (SMC)						6: 70%	-38	-12	66	6.17
L Precentral gyrus (M1)	4p: 40%; 6: 20%	-24	-26	56	11.74	3a: 70%; 4p: 40%	-26	-30	48	5.22
L Precentral gyrus							-46	-12	60	7.77
L Precentral gyrus (M1, PMd)						4a: 50%	-42	-12	44	6.17
L Precentral gyrus (PMd, PMv)						6: 80%	-48	-8	48	8.70
L Inferior precentral gyrus (PMv)	6: 50%	-60	2	34	7.45					
L Precentral gyrus (PMd, M1)	6: 70%	-20	-20	76	6.66	6: 70%	-20	-18	70	7.48
R Postcentral gyrus (S1, M1)							54	-16	54	7.39
R Precentral gyrus (PMd, M1)	6: 70%	22	-10	68	5.35	6: 70%; 4a: 40%	38	-24	64	9.90
R Precentral gyrus (PMd, M1)						4p: 60%; 3b: 20%	32	-26	50	10.01
R Precentral gyrus (PMd, M1)						6: 90%	40	-12	62	9.41
R Precentral gyrus (PMd, M1)							18	-22	74	5.96
R Postcentral gyrus (S1)	1: 30%	66	-16	32	5.46					
R Postcentral gyrus (S1)						3b: 100%	42	-22	48	12.75
L Rolandic operculum							-44	-2	2	14.09
R Rolandic operculum		40	2	16	8.23					
Medial region										
L Superior frontal gyrus (SMA)	6: 60%	-10	-10	54	8.96	6: 70%	-6	-6	54	8.06
R Superior frontal gyrus (MPMC)	6: 20%	14	-12	48	8.45	6: 50%	8	-4	50	11.15
R Superior frontal gyrus (MPMC)						6: 100%	12	-14	76	8.27
L Middle cingulate cortex		-12	-26	44	5.22		-12	-26	44	8.35
R Middle cingulate cortex							12	0	44	9.91
Frontal lobe										
R Inferior frontal gyrus, pars opercularis	44: 70%	56	12	14	8.14	44: 70%	56	12	20	7.73
R Inferior frontal gyrus, pars opercularis						44: 30%; 6: 20%	58	10	32	4.96
Parietal lobe										
L Supramarginal gyrus	OP1: 30%	-42	-36	24	6.87		-50	-42	24	8.33
R Supramarginal gyrus	hIP1: 10%	52	-36	26	8.68					
L Operculum 1	40%	-54	-30	22	5.80	60%	-52	-26	20	5.66
R Operculum 1						80%	54	-22	18	9.68
L Parietal operculum						OP1: 30%	-64	-20	28	7.16
R Parietal operculum						OP1: 50%	56	-20	20	10.00
L Superior parietal lobule						2: 20%	-30	-54	56	9.31
R Superior parietal lobule							38	-48	64	5.26
Temporal lobe										
L Superior temporal gyrus							-48	-40	14	5.34
R Superior temporal gyrus		66	-34	22	7.23		66	-30	18	7.63
L Insular lobe		-40	-2	12	10.25					
R Insular lobe		40	2	10	7.98		44	2	10	12.25
R Insular lobe (anterior)		34	28	8	5.87					
Subcortical nuclei										
L Pallidum							-16	-2	6	6.51
R Pallidum							26	-2	2	12.68
L Putamen							-24	6	0	18.40
R Putamen		30	4	12	5.29		32	-8	4	14.62
L Caudate nucleus		-14	10	22	11.22		-12	2	16	9.51
R Caudate nucleus							18	0	24	7.00
L Thalamus		-14	-22	6	4.95					
L Amygdala		-22	0	-10	4.85					
R Amygdala							26	0	-10	14.13
L Hippocampus						CA: 30%	-40	-18	-18	5.65
L Hippocampus						CA: 80%	-28	-42	2	6.54
R Hippocampus						CA: 10%	12	-34	16	5.74
Occipital lobe										
L Precuneus							-22	-48	10	8.02
Cerebellum										
R Cerebellum (lobule IV-V)		12	-56	-12	6.16					
L Cerebellum (lobule VI)							-4	-62	-16	6.86

TABLE II. (continued)

Anatomical region (functional area)	BA	Right contractions				Left contractions				
		x	y	z	Peak T value	BA	x	y	z	Peak T value
L Cerebellum (lobule VI)		-34	-58	-28	4.75		-20	-52	-26	11.49
R Cerebellum (lobule VI)		22	-52	-24	8.79		30	-54	-26	6.56
L Cerebellum (lobule VIII)		-18	-72	-50	6.09		-20	-64	-50	6.12
R Cerebellum (lobule VIII)		18	-66	-44	7.31					
L Cerebellum (crus 1)		-44	-60	-30	5.05					
R Cerebellum (crus 1)		40	-56	-32	6.90					

BA: Brodmann area; CA: cornu Ammonis (Ammon's horn of hippocampus); hIP: human inferior parietal area; M1: primary motor cortex; MPMC: medial premotor cortex; OP: operculum (parietal); PMd: dorsal premotor area; PMv: ventral premotor area; S1: sensory motor cortex; SMA: supplementary motor area; SMC: sensorimotor cortex; SUB: subiculum.

The anatomical and functional names plus the probability values of the Brodmann areas are based on the Anatomy Toolbox (Eickhoff et al., 2005);  $x$ ,  $y$ , and  $z$  are MNI coordinates. Furthermore, to specify motor areas we used the Mayka et al. (2006) and to specify the pars opercularis of the inferior frontal gyrus Tomaiuolo et al. (1999).

respectively. Both figures show clear positive linear correlations for all subjects in most brain areas, except for the inferior part of the right precentral gyrus.

Figures 7 and 8 show the group results for right and left index finger abductions, respectively. For the group data, we determined whether the percentage signal change differed significantly between consecutive force levels. Indeed, these values differed in all areas except the inferior part of the right precentral gyrus. Post-hoc analyses revealed that most consecutive force levels were accompanied by a significant increase in brain activation (see Figs. 7 and 8). Only for the low force levels (EMG: from 6% MVC to 10% MVC), the increases in brain activity were not significant. Furthermore, in the ipsilateral precentral gyrus, the increases in brain activity were only significant for the highest force levels.

## DISCUSSION

During index finger abduction, linear correlations were found between muscle activity, force, and activity in brain areas related to motor control. We demonstrated this correlation, both at a group and at an individual level. Furthermore, we found that brain areas were differentially involved in muscle contractions: "activation per se" revealed activity mainly in the inferior part of the right precentral sulcus (including the inferior frontal operculum, ventral premotor areas, and extending into the insula) and bilateral parietal areas. In contrast, "activation modulation" revealed activity mainly in the contralateral sensorimotor areas, including SMA, the dorsal premotor areas, and bilateral cerebellum.

Our data shows a similar activation pattern as described by Dettmers et al. (1995) during a positron emission tomography (PET) study. In this study, the authors searched for brain areas that were involved in force modulation during rhythmic index finger flexion (1 Hz) at different force levels. They showed a logarithmic relationship between force and brain activation, whereas we found a linear relationship. At high

force levels, the relative increase in brain activity was lower in their study, although they used lower forces and less force steps (5, 10, 20, 60% MVC). As rhythmic contractions at high frequencies tend to enhance blood flow changes (Rao et al., 1996), it is possible that in the study by Dettmers et al. (1995) low force levels already induced relatively high levels of brain activity and that this activity tends to level off at high forces.

## Relation Between Force, EMG, and Brain Activity

The strong correlation during isometric contractions between the mean amplitudes of force and rectified surface EMG confirms previous studies (Bigland and Lippold, 1954; Edwards and Lippold, 1956; Lippold, 1952), and this corroborates the validity of our EMG and force recordings during MR scanning. This observation does not automatically imply that the relation between force and EMG is always so simple, in large muscles often a nonlinear relation is found (Lawrence and De Luca, 1983). In addition, in fatiguing contractions, force and EMG are affected differently. For instance, in a submaximal fatiguing contraction, force stays constant while EMG can increase or decrease (Zijdewind et al., 1995).

During index finger abductions, several brain areas were activated. Most of these areas are known to be involved in a network controlling motor output and were expected to correlate with muscle activity (Dai et al., 2001; Dettmers et al., 1995; Thickbroom et al., 1998). Indeed, the ROI analysis of the contralateral precentral gyrus, postcentral gyrus, the SMA, the ipsilateral precentral gyrus, and lobule VI of the ipsilateral cerebellum showed a linear correlation between EMG or force and brain activity. Our data extends previous results by showing a strong correlation between brain activity and muscle output at an individual level as well. This finding strengthens previous data, as regression analysis performed on data obtained in different subjects does not necessarily imply a linear correlation within a single subject.

**TABLE III. Brain activity correlating with “activation modulation” (Fig. 3C,D)**

Anatomical region (functional area)	BA	Right contractions				Left contractions				
		x	y	z	Peak T value	BA	x	y	z	Peak T value
Central region										
L Postcentral gyrus (S1)	1: 70%	-44	-26	56	20.06					
L Pre/postcentral gyrus (SMC)						4a: 40%	-32	-28	60	10.21
R Pre/postcentral gyrus (SMC)	2: 50%; 4p: 50%	-40	-28	50	16.38					
R Pre/postcentral gyrus (SMC)						3b: 50%	44	-16	48	11.44
L Precentral gyrus (M1)	6: 60%; 4a: 40%	-30	-26	64	11.11	3b: 70%	42	-22	52	13.00
R Pre/postcentral gyrus (M1)						3a: 40%; 4p: 40%	30	-24	48	10.91
L Precentral gyrus (PMd, M1)						6: 70%; 4a: 30%	-46	-10	50	10.09
L Precentral gyrus (PMd, SMC)	6: 50%	-38	-24	62	11.43	6: 30%	-28	-28	72	9.34
L Precentral gyrus (M1, PMd)						6: 50%; 4a: 30%	-30	-26	72	8.87
R Precentral gyrus (PMd, SMC)	6: 90%	38	-22	64	6.05	6: 90%	38	-24	64	12.81
R Precentral gyrus (PMd)	6: 70%	24	-14	64	5.20					
L Rolandic operculum	OP4: 10%	-44	-4	10	6.16					
R Rolandic operculum		42	4	12	10.59	OP4: 20%	50	0	6	9.97
Medial region										
L Superior frontal gyrus (SMA-proper)	6: 50%	-10	-12	56	7.82	6: 80%	-6	-6	56	13.25
L Superior frontal gyrus (MPMC)						6: 30%	-4	2	46	7.63
R Superior frontal gyrus (MPMC)						6: 60%; 4a: 20%	8	-20	48	8.11
R Superior frontal gyrus (MPMC)	6: 10%	12	-2	52	6.20					
R Middle cingulate cortex		16	-22	48	9.44					
R Middle cingulate cortex						6: 20%	10	0	42	9.32
R Anterior cingulate cortex							14	38	2	7.22
R. Paracentral lobule	3a: 20%	16	-30	50	6.16					
Frontal lobe										
R Rectal gyrus/olfactory cortex							10	14	-14	9.35
Parietal lobe										
R Supramarginal gyrus						hIP1: 10%	48	-34	26	8.83
L Parietal operculum	OP2: 20%	-34	-28	24	6.15					
L Parietal operculum	OP1: 90%	-44	-24	18	5.36	OP1: 90%	-44	-24	16	9.12
R Parietal operculum						OP2: 60%	36	-26	22	7.47
R Parietal operculum	OP1: 80%	50	-26	18	4.60	OP1: 60%	52	-28	18	14.17
Temporal lobe										
R Superior temporal gyrus	OP1: 20%	58	-30	20	5.51	OP1: 10%	46	-34	16	13.40
L Insular lobe (posterior)	OP3: 10%	-32	-16	8	5.67					
L Insular lobe (anterior)	44: 10%	-38	6	6	6.32					
R Insular lobe (posterior)						OP2: 20%	36	-18	10	14.95
Subcortical nuclei										
R Pallidum							28	-6	-2	7.45
L Putamen		-26	-10	10	6.61					
R Putamen							30	-8	0	7.78
R Putamen							30	-20	6	7.65
L Caudate nucleus							-12	10	20	9.89
R Caudate nucleus							18	0	24	7.10
L Amygdala		-16	-4	-18	5.56					
R Thalamus							18	-16	8	16.01
L Hippocampus	EC: 60%; Amyg: 50%	-16	-2	-24	5.73					
L Hippocampus	SUB: 90%	-18	-26	-20	4.97					
L Hippocampus						CA: 80%	-30	-40	0	8.23
R Hippocampus	SUB: 50%	16	-36	-10	5.03					
R Hippocampus						CA: 30%	38	-28	-10	5.47
Cerebellum										
L Cerebellum (lobule IV-V)		-10	-34	-12	5.19					
R Cerebellum (lobule IV-V)		8	-64	-8	5.92					
R Cerebellar vermis (4-5)		2	-62	-14	6.40					
L Cerebellum (lobule VI)		-24	-52	-24	5.18		-20	-54	-24	13.19
R Cerebellum (lobule VI)		22	-52	-24	8.01		30	-52	-26	10.21
L Cerebellum (lobule VIII)		-24	-62	-48	5.14		-16	-66	-46	6.07
R Cerebellum (lobule VIII)		18	-56	-46	7.54					
L Cerebellum (lobule IX)							-6	-42	-42	6.57
R Cerebellum (lobule IX)							6	-44	-48	5.49
R Cerebellar vermis (8)		4	-70	-34	4.89					
L Cerebellum (crus 1)		-36	-60	-28	5.08					
R Cerebellum (crus 1)		40	-58	-30	6.15					

Amyg: amygdala; BA: Brodmann area; CA: cornu Ammonis (Ammon’s horn of hippocampus); EC: entorhinal cortex (hippocampus); hIP: human inferior parietal area; M1: primary motor cortex; MPMC: medial premotor cortex; OP: operculum (parietal); PMd: dorsal premotor area; S1: sensory motor cortex; SMA: supplementary motor area; SMC: sensorimotor cortex; SUB: subiculum.

The anatomical and functional names plus the probability values of the Brodman areas are based on the Anatomy Toolbox (Eickhoff et al., 2005); x, y, and z are MNI coordinates. Furthermore, to specify motor areas we used the Mayka et al. (2006) and to specify the pars opercularis of the inferior frontal gyrus Tomaiuolo et al. (1999).

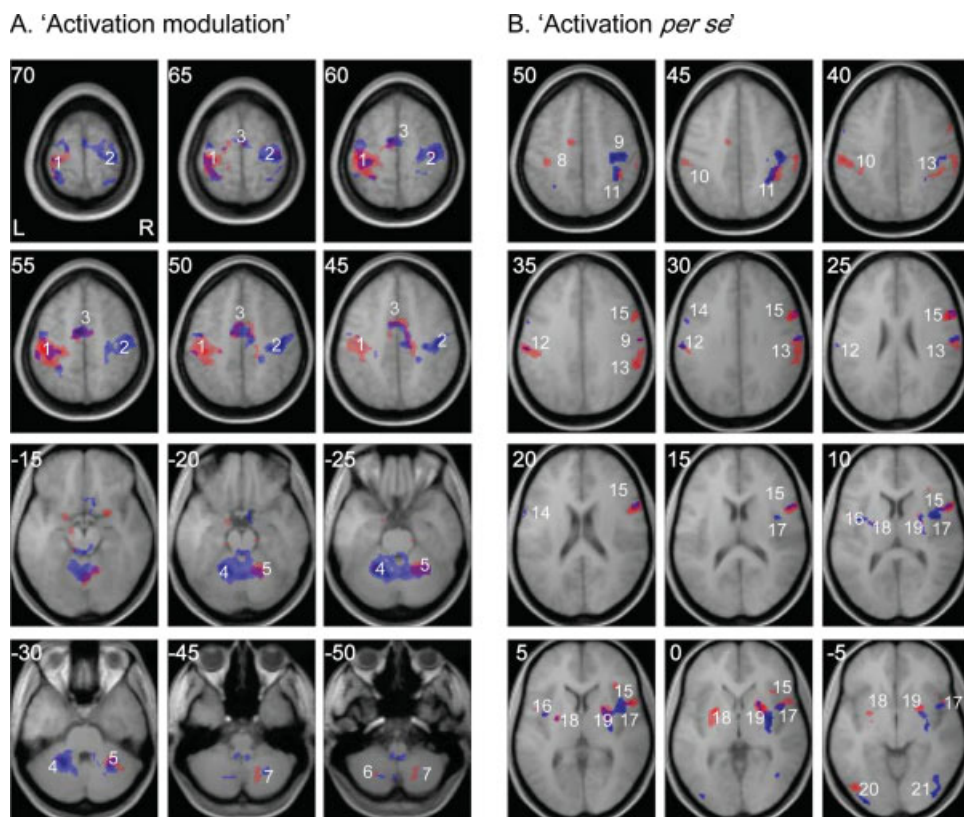
TABLE IV. Brain activity correlating with “activation per se” (Fig. 3E,F)

Anatomical region (functional area)	BA	Right contractions				Left contractions				
		<i>x</i>	<i>y</i>	<i>z</i>	Peak <i>T</i> value	BA	<i>x</i>	<i>y</i>	<i>z</i>	Peak <i>T</i> value
Central region										
L Postcentral gyrus (S1)	1: 70%	-40	-38	66	8.51					
R Postcentral gyrus (S1)						3b: 80%	42	-22	46	10.11
R Postcentral gyrus (S1)	1: 20%	62	-16	30	7.55	1: 20%	66	-14	28	7.14
L Pre/postcentral gyrus (SMC)	4p: 50%	-38	-30	54	8.10					
L Pre/postcentral gyrus (SMC)	4a: 60%	-38	-30	68	7.71					
R Precentral gyrus (M1)						4p: 60%	34	-26	52	8.69
L Precentral gyrus (M1, PMd)		-46	-14	60	9.30					
L Precentral gyrus (PMd, M1)	6: 60%	-36	-16	56	6.36					
R Precentral gyrus (M1, PMd)						4a: 70%	38	-24	58	7.74
R Precentral gyrus (PMd, M1)						6: 60%	36	-22	60	7.39
L Precentral gyrus (PMv)							-62	6	20	5.91
L Precentral gyrus (PMv)						6: 40%	-56	4	32	5.45
L Precentral gyrus (PMv)						6: 70%	-56	2	40	4.86
L Rolandic operculum	44: 30%	-48	4	8	5.63					
Medial region										
R Superior frontal gyrus (SMA)						6: 80%	4	-8	52	5.10
L Superior frontal gyrus (MPMC)	6: 30%	-14	-8	50	9.81					
R Superior frontal gyrus (MPMC)	6: 40%	14	0	62	6.24					
Frontal lobe										
R Inferior frontal gyrus, pars opercularis	44: 40%	58	10	28	16.31	44: 60%	62	12	24	7.24
R Inferior frontal gyrus, pars opercularis	44: 50%	52	12	4	9.64					
R Inferior frontal gyrus, pars triangularis		36	30	8	6.62					
Parietal lobe										
L Supramarginal gyrus		-60	-24	34	8.93	OP4: 10%	-60	-24	32	7.34
R Supramarginal gyrus		58	-40	34	12.24					
R Supramarginal gyrus		62	-24	46	7.36					
R Parietal operculum	OP1: 20%	64	-28	38	6.09					
L Superior parietal lobule						2: 20%	-36	-56	62	4.93
L Inferior parietal lobule	hIP2: 20%	-38	-40	42	5.49		-34	-54	54	6.92
R Inferior parietal lobule	hIP1: 30%	38	-44	46	6.51	2: 20%	36	-46	50	6.28
Temporal lobe										
R Inferior temporal gyrus							42	-70	-6	6.48
Occipital lobe										
L Inferior occipital gyrus		-44	-76	-6	10.32		-32	-92	-8	9.12
R Inferior occipital gyrus							44	-78	-6	9.56
L Middle occipital gyrus		-52	-74	-2	5.96		-40	-86	0	5.88
R Middle occipital gyrus							40	-64	2	4.97
R Insular lobe (anterior)		36	22	-2	5.66					
L Insular lobe		-38	0	4	6.08		-40	0	10	6.34
R Insular lobe	44: 30%	42	6	0	4.94	OP3: 10%	40	2	12	8.70
Subcortical nuclei										
L Putamen		-26	4	0	10.95					
L Putamen		-30	-8	0	7.47		-26	-6	10	5.41
R Putamen		26	8	0	13.67					
R Putamen		26	-6	4	6.98		32	-4	2	8.35
Cerebellum										
L Cerebellum (border lobule IV/V-VI)							-18	-52	-24	9.22
R Cerebellum (border lobule IV/V-VI)		16	-52	-26	7.05					
L Cerebellum (lobule VIII)							-26	-66	-50	5.13
R Cerebellum (lobule VIII)		18	-66	-50	5.44					

BA: Brodmann area; CA: cornu Ammonis (Ammon’s horn of hippocampus); hIP: human inferior parietal area; M1: primary motor cortex; MPMC: medial premotor cortex; OP: operculum (parietal); PMd: dorsal premotor area; PMv: ventral premotor area; S1: sensory motor cortex; SMA: supplementary motor area; SMC: sensorimotor cortex; SUB: subiculum.

The anatomical and functional names plus the probability values of the Brodmann areas are based on the Anatomy Toolbox (Eickhoff et al., 2005); *x*, *y*, and *z* are MNI coordinates. Furthermore, to specify motor areas we used the Mayka et al. (2006) and to specify the pars opercularis of the inferior frontal gyrus Tomaiuolo et al. (1999).

In the group analysis, we demonstrated that increments in muscle activation of 15% MVC are accompanied by a significant increase in brain activation (Figs. 7 and 8) in most motor areas (contralateral precentral gyrus, postcentral gyrus, the SMA, and lobule VI of the ipsilateral cerebellum). The increase in EMG from 5 to 15% MVC (only



**Figure 4.**

Brain activation during right and left index finger abductions. Activity related to right index finger abductions are presented in red, to left in blue; the overlap in activity between right and left resulted in purple. In the upper left corner, the z coordinate is presented (in MNI space). **A.** Brain activation related to modulation of muscle activation. During right abductions there is mainly activity in the contralateral sensorimotor cortex and ipsilateral cerebellum, during left abductions too, but there is also activity in the ipsilateral sensorimotor cortex and contralateral cerebellum. **B.** Brain activation related to muscle activation per se, independently

of the amount of muscle activity. Instead of opposite activity between right and left index finger abduction, this leads to parallel activity. The numbers in the brains refer to the following areas: 1 = L SMC; 2 = R SMC; 3 = SMA; 4 = L CBL VI; 5 = R CBL VI; 6 = L CBL VIII; 7 = L CBL VIII; 8 = L postcentral gyrus; 9 = R postcentral gyrus; 10 = L parietal inferior; 11 = R parietal inferior; 12 = L supramarginal gyrus; 13 = R supramarginal gyrus; 14 = L inferior precentral sulcus; 15 = R inferior precentral sulcus; 16 = L insula; 17 = R insula; 18 = L putamen; 19 = R putamen; 20 = L occipital inferior; 21 = R occipital inferior.

10% increase) was not accompanied by a significant increase in brain activity, whereas all other increments (15% or higher) were accompanied by increases in brain activity. This implies that it is important to control the levels of muscle activation during an fMRI task. For instance, when the absolute force levels between groups differ significantly (e.g. patients and control subjects), it is important to use relative force levels during motor tasks instead of using the same task for the two groups.

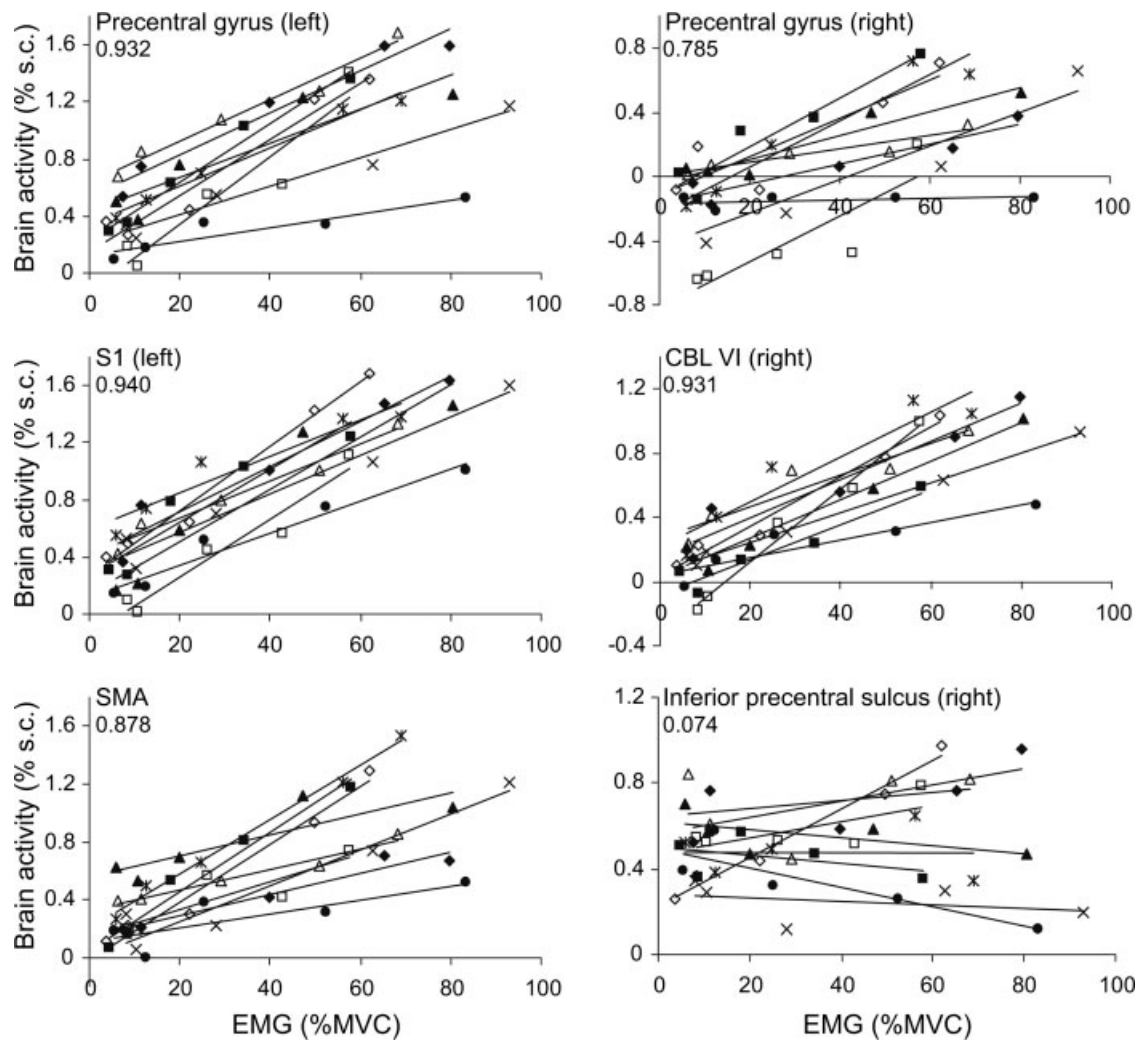
### Brain Activation

Using two regressors simultaneously, “activation modulation” and “activation per se,” we could distinguish brain activity correlated with the amount of muscle activation from brain activity correlated with muscle activation per

se. In the latter model, we expected to reveal activity in areas involved in motor planning, preparation, attention, and monitoring (visual) feedback that was not modulated by the amount of force that the subject had to produce. It is unclear whether motor planning or preparation or even attention is modulated by the required amount of force.

### Activation per se

The regressor “activation per se” revealed a large activation cluster around the right inferior part of the precentral sulcus. This area included the inferior frontal gyrus, pars opercularis (anterior and lateral of the Rolandic operculum; probably BA 44; Eickhoff et al., 2005), ventral premotor areas, and the lateral part of the insular cortex. A second cluster contained the bilateral inferior parietal lobule and



**Figure 5.**

The correlation between force and the activity in several brain areas of individual subjects during right-hand contractions. For each subject, the mean amplitude of the three contractions at each force level (%MVC) is plotted against the signal change (%) per contraction level for several ROIs. For each region of interest the mean correlation

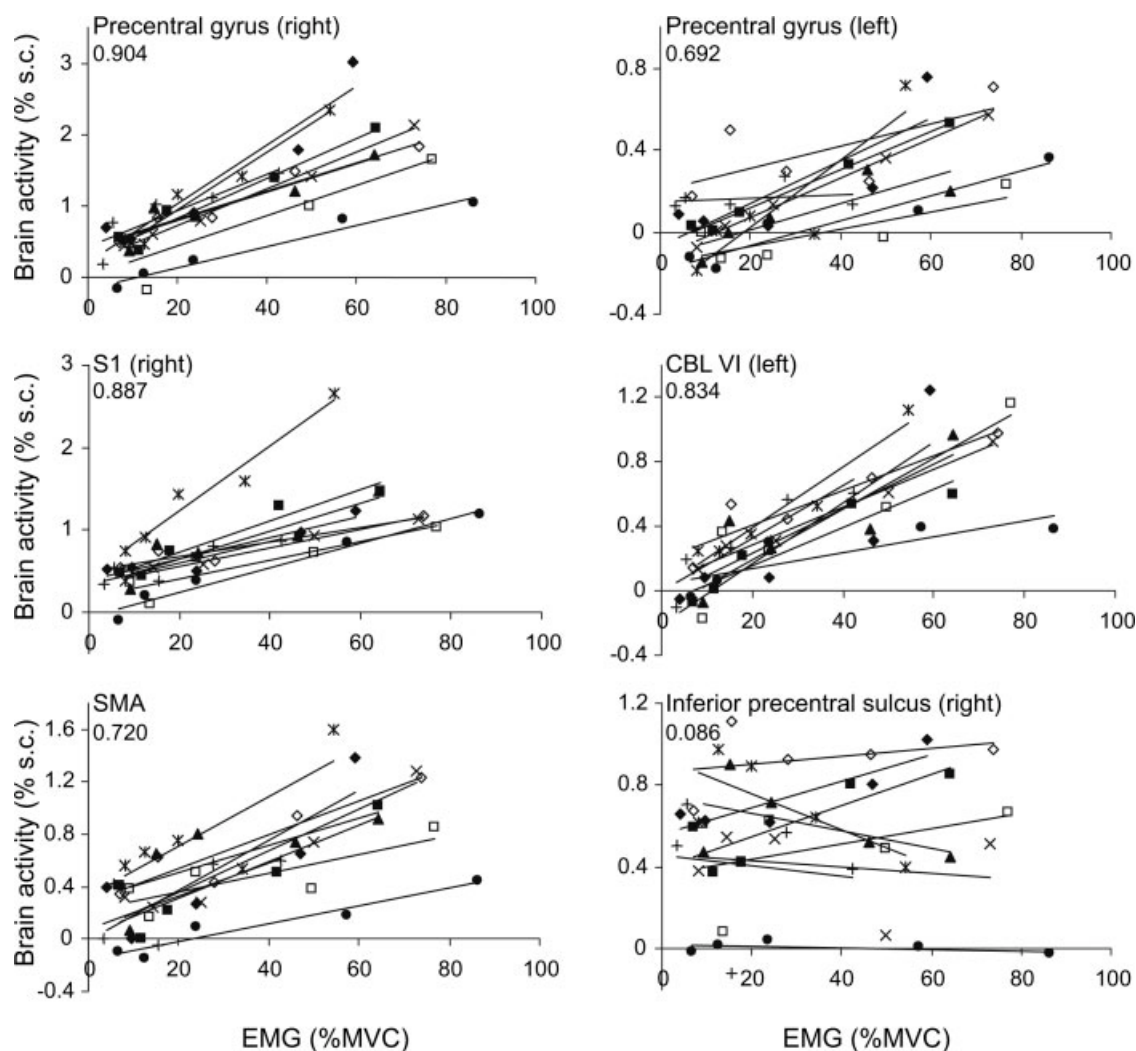
coefficient ( $n = 9$ ) is given. These ROIs consisted of activated clusters in the contralateral precentral gyrus (MI and PMd; left) and postcentral gyrus (S1; left), supplementary motor area (SMA), lobule VI of the ipsilateral cerebellum (CBL VI; right), ipsilateral precentral gyrus (MI and PMd right), and the inferior precentral sulcus.

the (ipsilateral) supramarginal gyrus. Furthermore, significant activation was found in the contralateral precentral gyrus, putamen (bilateral), left inferior occipital gyrus, and ipsilateral cerebellum (border lobulus IV/V and VI, and lobule VIII). Most of these areas were activated equally during contractions with the left or contractions with right index finger, underlining the hypothesis that these areas are involved in higher order motor processing. We will discuss the activity of some of these areas in more detail later.

### Frontal areas

Both right and left contractions induced activation at the inferior part of the right precentral sulcus (including infe-

rior frontal gyrus, pars opercularis). Previous experiments showed activity in this area during motor preparation (Simon et al., 2002; Toni et al., 2002). Activity in this area was also seen during precise finger movements with tactile feedback (Ehrsson et al., 2000), manipulation of hand-held objects (Binkosfski et al., 1999), tasks in which subjects were exposed to unpredictable changes in finger pinch forces that they had to produce (Schmitz et al., 2005), and handgrip force tasks with visual feedback (Ward and Frackowiak, 2003). These results suggest that this area is not involved in a dedicated hand task but rather in monitoring feedback and guiding hand performance on basis of this feedback. In our study, subjects performed contractions at different force levels by matching their force with



**Figure 6.**

The correlation between force and the activity in several brain areas of individual subjects during left-hand contractions. For each subject, the mean amplitude of the three contractions at each force level (%MVC) is plotted against the signal change (%) per contraction level for several ROIs. For each region of interest the mean correlation coefficient ( $n = 9$ ) is given. These ROIs

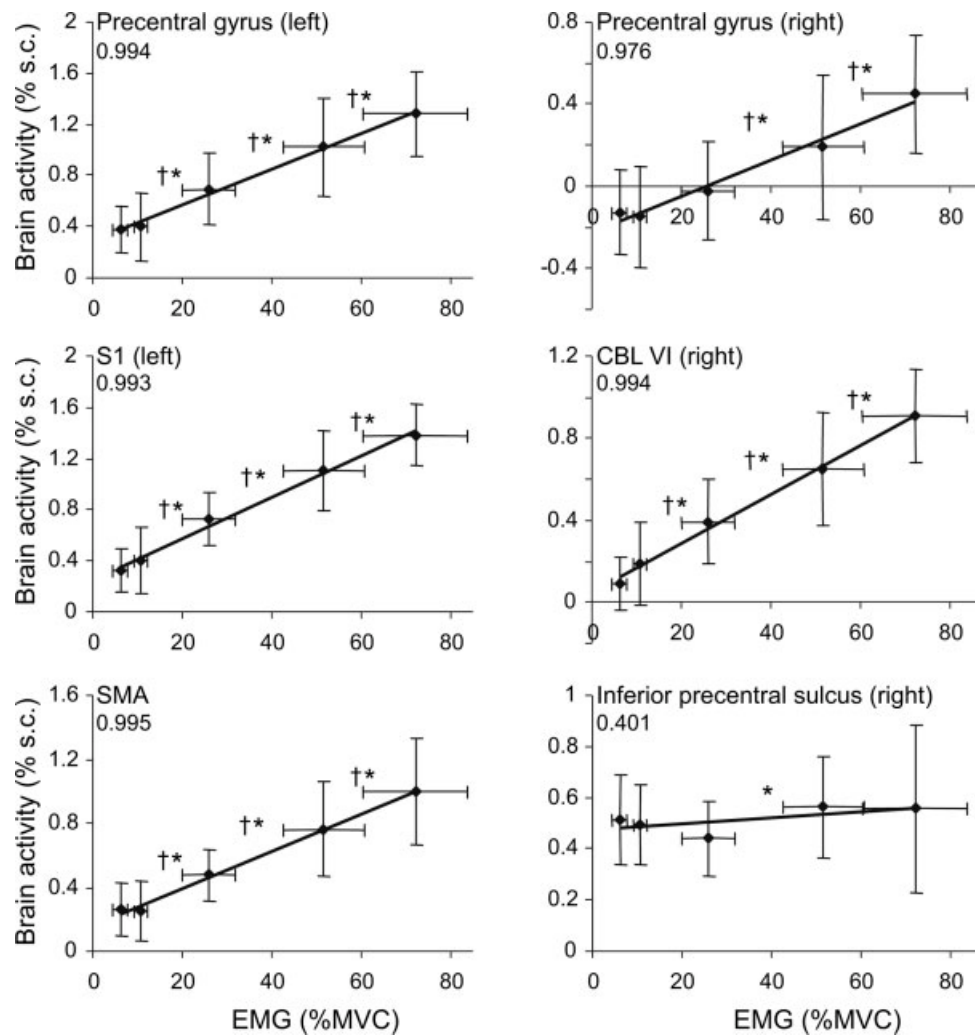
consisted of activated clusters in the contralateral precentral gyrus (MI and PMd; right) and postcentral gyrus (S1; right), supplementary motor area (SMA), lobule VI of the ipsilateral cerebellum (CBL VI; left), ipsilateral precentral gyrus (MI and PMd left), and the inferior precentral sulcus.

a visual cue of the target force level. Subjects needed to adjust their force continuously to maintain the target force level. The process of force matching was equal for all force levels, as was also shown by a comparably coefficient of variation (only during 5% MVC the coefficient of variation was higher, but the absolute force error was lower during 5% MVC).

**Parietal areas**

The activity in the supramarginal gyrus and the inferior parietal lobule also correlated stronger with muscle activa-

tion per se than with activation modulation. The parietal cortex is known to be a critical link between sensory input and action. On-line corrections of hand movements and hand aperture are disrupted after TMS-induced lesions (Rushworth and Taylor, 2006). The (left) supramarginal gyrus is known to be active during motor preparation, especially during motor attention (Deiber et al., 1996; Krams et al., 1998; Rushworth et al., 1997). For instance, when subjects were informed about the direction of a movement but had to wait before they were allowed to perform the movement (Decety et al., 1992). Furthermore, strong activation in the inferior parietal lobule was found



**Figure 7.**

The mean correlation between force and the activity in several brain areas during right-hand contractions. The mean amplitude of the force levels of all subjects plotted against the mean signal change (%) of these force levels for the same ROIs as Fig. 5. An asterisk (\*) denotes a significant increase in brain activity ( $P < 0.05$ ) between two successive force levels; a dagger (†) denotes a significant increase in brain activity compared with the activity at 5% MVC ( $P < 0.05$ ). For each region of interest the correlation coefficient is given.

during visuomotor tasks, suggesting an important role of these areas during visually guided movements (Vaillancourt et al., 2003). The (right) supramarginal gyrus was activated when the predicted and actual weights that subjects had to lift were mismatched (Jenmalm et al., 2006). These results suggest that the supramarginal gyrus plays a role in monitoring sensory input and updating sensorimotor memories. As mentioned earlier, in our experiment, processing of visual feedback and adjusting force output was necessary at all force levels. Furthermore, subjects were informed about the magnitude of their contraction and the hand with which they had to contract before they performed the actual movement. These task-characteristics probably induced a similar level of activity in the inferior and superior parietal areas for all force levels.

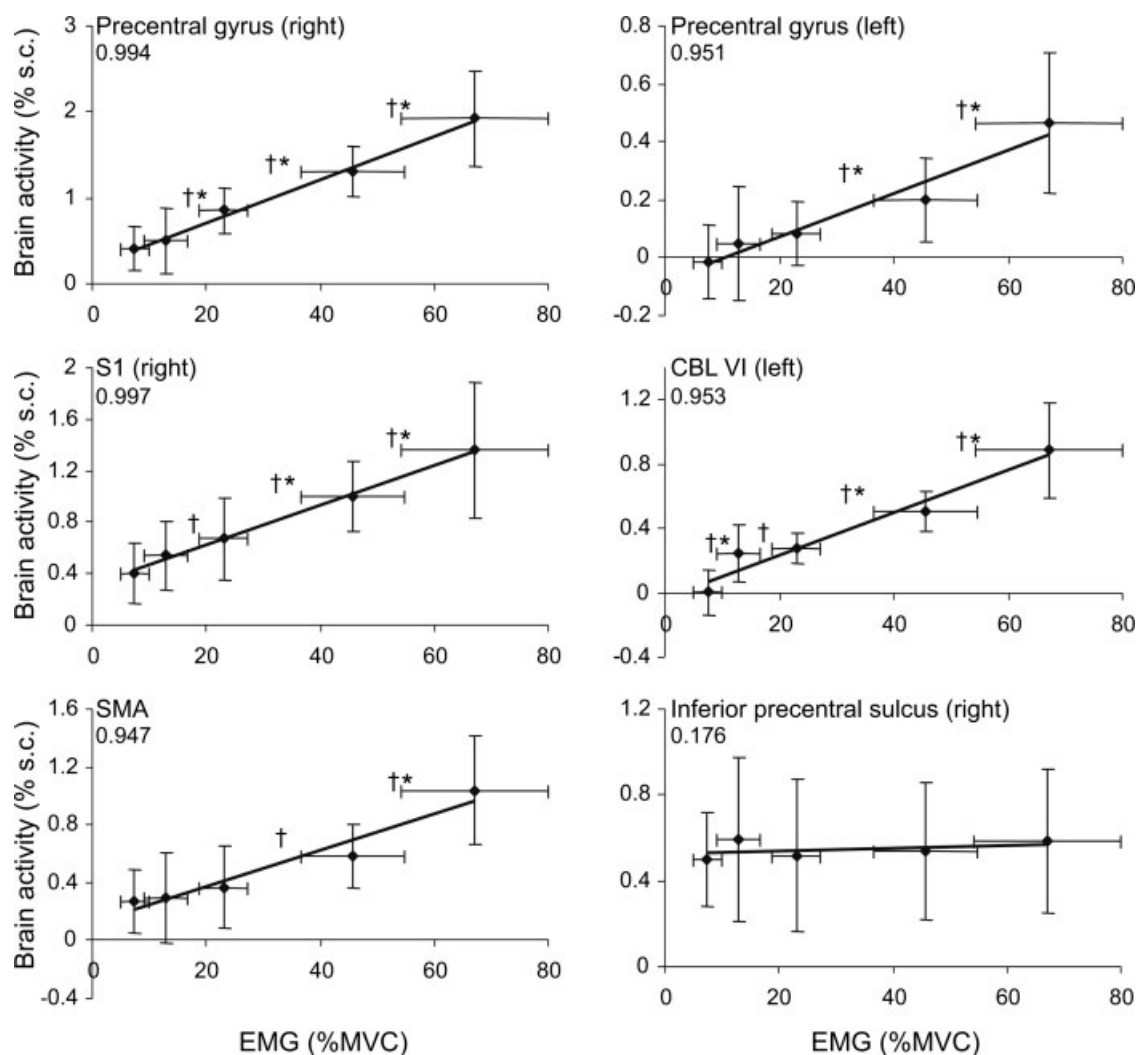
### Basal ganglia

In the basal ganglia, activation of the putamen was seen during “activation per se.” This result confirms data from Dettmers

et al. (1995), who found that the contralateral putamen was active during force production, but that the activity did not increase further at higher force levels. Evidence of a role of the putamen in visuomotor processing was also found when contrasting pinch grip task with force feedback versus the task without force feedback (Vaillancourt et al., 2003). Our result confirms the contribution of the putamen to visuomotor processing.

### Cerebellum (IV/IV-VI and VIII)

In the ipsilateral cerebellum, we found activation that was related to “activation modulation” and “activation per se.” Interestingly, none of these areas revealed activity in the “force per se” model (data not shown). If we looked in more detail into the activation of these areas, statistical analysis (regression analysis) showed that the activation in the cerebellum could be declared with the “activation modulation” regressor, but that the “activation per se” regressor also showed a significant but lower correlation. The “force modulation” regressor, however, could declare the activa-



**Figure 8.**

The mean correlation between force and the activity in several brain areas during left-hand contractions. The mean amplitude of the force levels of all subjects plotted against the mean signal change (%) of these force levels for the same ROIs as Fig. 6. An asterisk (\*) denotes

a significant increase in brain activity ( $P < 0.05$ ) between two successive force levels; a dagger (†) denotes a significant increase in brain activity compared with the activity at 5% MVC ( $P < 0.05$ ). For each region of interest the correlation coefficient is given.

tion in the cerebellum even better, thereby reducing the regression with the “force per se” model. The most striking difference between the force and the EMG regressors is the progressive increase in EMG activity during high force contractions (see Fig. 1B,C). Probably this pattern was not characteristic for the activation in the cerebellum.

Specific activation of the lateral part of the cerebellum is often found during visuomotor tasks, suggesting an important role in translating visual input to motor output (Vailancourt et al., 2003).

### Activation Modulation

The regressor “activation modulation” revealed activity in a network of cortical and subcortical regions known to

be part of the motor system (Dai et al., 2001; Dettmers et al., 1995, 1996a; Fink et al., 1997; Ward and Frackowiak, 2003). There was strong activation in the pre- and post-central gyrus, premotor areas (including the Rolandic operculum and the dorsal premotor areas), SMA, bilateral cerebellum, basal ganglia, and superior temporal gyrus. Due to the strong correlation between EMG and force, these results confirm and extend previous experiments investigating the relation between force and brain activity. Various contractions are used to study human brain activation: isometric contractions (no shortening of the muscle; hence no obvious movement) or concentric contractions (shortening of the muscle and obvious movements) in the static (long-lasting isometric contraction) or rhythmic

(short-lasting contractions either isometric or concentric) protocol. Most studies used rhythmic contractions at 1–2 Hz (Cramer et al., 2002; Dettmers et al., 1995, 1996a,b) and focused on the sensorimotor cortex and premotor areas. Using PET, Dettmers et al. (1995, 1996a) showed a logarithmic relation between activity in the contralateral primary motor cortex and force. However, when analyzing fMRI data with a correlation model, there was only weak activity in M1 and SMA (Dettmers et al., 1996a). Cramer et al. (2002) found a correlation between force and the number of active voxels in the sensorimotor cortex and a weak correlation between force and the number of active voxels in the SMA. In contrast, Ludman et al. (1996) did not find any correlation between force and BOLD activity.

During isometric contractions, a force-related increase in activation was seen in various areas, including contralateral sensorimotor areas (Dai et al., 2001; Thickbroom et al., 1998; Ward and Frackowiak, 2003), bilateral premotor areas, frontal and parietal areas, and part of the cerebellum (Dai et al., 2001; Ward and Frackowiak, 2003). The areas that were modulated by the amount of force in our study were comparable to the areas showing a linear or nonlinear relation with force in the study of Ward and Frackowiak (2003). In addition to their data, we found activity that correlated with force modulation in the SMA, premotor areas (rolandic operculum), contralateral cerebellum, superior temporal gyrus, and the hippocampus. A few areas will be discussed in more detail.

### Sensorimotor areas

Several PET and fMRI studies showed a strong correlation between activity within the sensorimotor cortex and force production (Dai et al., 2001; Dettmers et al., 1995, 1996a; Fink et al., 1997; Ward and Frackowiak, 2003). Animal experiments already showed correlations between activity within the primary motor cortex and force (Evarts, 1968; Evarts et al., 1983; Hepp-Reymond et al., 1978). Moreover, a recent experiment showed a linear relation between the combined activity of several muscles (EMG) and activation of M1 in monkeys (Townsend et al., 2006). A good correlation between activity in the postcentral gyrus and muscle activity is also expected, as several areas in the postcentral gyrus are activated by activity from receptors in muscles, tendons, joints, and skin (Kandel, 2000). Activity of these receptors is likely to increase with force increments (Matthews, 1981).

Contractions with the nondominant left index finger induced activation that correlated with force modulation in the ipsilateral sensorimotor areas as well (see also Fig. 4A). However, when we looked in more detail at this activity, the data showed that in right-hand contractions the activation level was below baseline at low force levels and also progressively increased at higher force levels. This pattern of activation in the ipsilateral cortex is consistent with data from previous experiments (Dettmers et al., 1995, 1996b) during rhythmic contractions. These authors

stress the analogy with data obtained with transcranial magnetic stimulation (TMS) (Dettmers et al., 1996b). TMS data also shows a decline in cortical excitability during low-force rhythmic contractions (Liepert et al., 2001). During isometric contractions, however, an increase in the ipsilateral corticospinal excitability is already seen at low force levels (Hess et al., 1986; Zijdwind et al., 2006) and it is therefore unclear what the decline in activation of the ipsilateral sensorimotor cortex demonstrates. Our EMG data show a significant increase in EMG activity during contractions at the highest target force level, suggesting that the activation in the “ipsilateral” sensorimotor cortex is due to activation of muscles contralateral to the target muscle (cf. Zijdwind and Kernell, 2001; Zijdwind et al., 2006).

### Cerebellum

Several foci of activity in the cerebellum correlated with muscle activity. A linear relation between activity in the cerebellum and muscle activity was also observed in the monkey (Townsend et al., 2006) and in humans (Dai et al., 2001; Ward and Frackowiak, 2003). This correlation could be due to an increase in sensory input as suggested by data from Jueptner et al. (1996, 1997; cf. Weiller et al., 1996; however Mima et al., 1999). They showed large overlapping activity during active and passive movements of the elbow, which suggest that the cerebellum is stronger involved in sensory information processing than in motor output. This result implies that the strong activation in the cerebellum in our study can be due to increased sensory input from proprioceptive and cutaneous receptors (visual feedback is equal for all tasks and this would not affect the activity during different force levels). Nevertheless, the cerebellum also is involved in motor output, as is shown ipsilateral activation of the cerebellum in spinal cord injured subjects (Cramer et al., 2005) and in patients suffering from a sensory neuropathy (Reddy et al., 2001). Jenmalm et al. (2006; see also Schmitz et al., 2005) showed activation in lobule VI when the weight of an object unexpectedly changed to a lighter weight. This result could indicate that our subjects overestimated the high force levels as EMG values were relatively high compared with the force levels (see Fig. 1), but this was only true for the contractions with the right hand.

### Statistical Models

We performed statistical analyses in which we used two regressors “activation per se” and “activation modulation.” A potential problem with this analysis is the (mathematical) dependence of the two regressors. In our setting, the general linear model was still well posed and MATLAB was capable of calculating the determinants. We checked the influence of the dependency of the regressors on the GLM solution by comparing the results with those of additional analyses in which Gram Schmidt orthogonalization was applied to the regressors. By orthogonalization the infor-

mation that is already present in the first regressor is subtracted, by subtracting the mathematical vector projection (see Feige et al., 2005; Van Rootselaar et al., 2007). The resultant vector is then used as a regressor. This analysis resulted in almost identical activation patterns and *T*-values. Therefore, we are confident that our analysis was correct. We chose to present our data without the orthogonalization, because this model is more direct and easier to comprehend.

### Intersubject Variability

Most subjects showed a strong correlation between muscle and brain activity in the contralateral precentral and postcentral gyrus, SMA and ipsilateral cerebellum. This gives an excellent starting point for investigating the relation between muscle and brain activity in patients or in control subjects during changing conditions (e.g. during the progressive disorders, functional recovery, or fatigue studies). It also stresses the importance of using relative force levels instead of absolute force levels when patients are followed over time. The load of a motor task must be adjusted to continuous changes in maximal force due to progression of the disease, recovery processes, or progression of fatigue.

### CONCLUSIONS

Overall, we showed a positive correlation between motor input (activity in motor regions in the brain) and motor output (muscle activity and contraction force), both at a group and at an individual level. These results are important for investigations for example on motor fatigue or investigations in patients. Besides the linear correlation between force and brain activity in some motor areas, other areas (the inferior frontal operculum, the bilateral inferior parietal lobules, and the supramarginal gyrus) showed a constant level of activation during muscle activation, independently of the amount of muscle activation.

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