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*J Neurophysiol* 97:1342-1352, 2007. First published Aug 16, 2006; doi:10.1152/jn.01253.2005

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# Holding an Object: Neural Activity Associated With Fingertip Force Adjustments to External Perturbations

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Submitted 30 November 2006; accepted in final form 22 July 2006

**Ehrsson HH, Fagergren A, Ehrsson GO, Forssberg H.** Holding an object: neural activity associated with fingertip force adjustments to external perturbations. *J Neurophysiol* 97: 1342–1352, 2007. First published August 16, 2006; doi:10.1152/jn.01253.2005. When you hold an object, a sudden unexpected perturbation can threaten the stability of your grasp. In such situations grasp stability is maintained by fast reflexive-like grip-force responses triggered by the somatosensory feedback. Here we use functional magnetic resonance imaging (fMRI) to investigate the neural mechanisms involved in the grip-force responses associated with unexpected increases (loading) and decreases (unloading) in the load force. Healthy right-handed subjects held an instrumented object (of mass 200 g) between the tips of right index finger and thumb. At some time during an interval of 8 to 45 s the weight of the object was suddenly increased or decreased by 90 g. We analyzed the transient increases in the fMRI signal that corresponded precisely in time to these grip-force responses. Activity in the left primary motor cortex was associated with the loading response, but not with unloading, suggesting that sensorimotor processing in this area mediates the sensory-triggered reflexive increase in grip force during loading. Both the loading and the unloading events activated the cingulate motor area and the medial cerebellum. We suggest that these regions could participate in the updating of the sensorimotor representations of the fingertip forces. Finally, the supplementary somatosensory area located on the medial wall of the parietal lobe showed an increase in activity only during unloading, indicating that this area is involved in the sensorimotor processing generating the unloading response. Taken together, our findings suggest different central mechanisms for the grip-force responses during loading and unloading.

## INTRODUCTION

When holding an object between the fingertips the stability of the grasp depends on the application of adequate forces. The grip forces applied normal to the contact surfaces produce a frictional force that opposes the tangential load force (Johansson and Westling 1984; Westling and Johansson 1984). The stability of the grasp is threatened if the load force suddenly and unexpectedly increases, such as when a dog pulls its leash or when holding a basket into which someone unexpectedly puts a bottle of milk when shopping at the supermarket. During such “loading events,” there is an unpredictable increase in the load force, which means that the frictional force becomes too low and a small slip, or microslip, occurs. This slip activates sensory receptors in the skin of the fingertips, which in turn results in an automatic increase in the grip force, with a latency

of about 40–60 ms (Johansson and Westling 1988; Johansson et al. 1992a,b,c, 1994; Macefield and Johansson 2003; Macefield et al. 1996), which has been called a reactive or a catch-up response. This latency is longer than most spinal reflexes in intrinsic hand muscles (about 35 ms), which suggests that the reactive grip-force response is mediated by supraspinal centers.

One view is that the primary motor cortex (M1) is responsible for the generation of the grip-force response during loading. The main motivation for this hypothesis is that the latency of the grip-force response is similar to the “long-latency” reflexes that can be elicited by muscle stretch (Marsden et al. 1976; Matthews 1991) or electrical stimulation of the digital nerves (Evans et al. 1989; Garnett and Stephens 1980; Stephens et al. 1978), both of which are considered to involve the M1 (Matthews 1991; Palmer and Ashby 1992). However, unlike the long-latency muscle stretch reflexes, the reactive grip-force responses during loading depend mainly on cutaneous afferents from the fingertips (Johansson et al. 1992a,b,c; Macefield et al. 1996). Furthermore, it is possible that subcortical structures, the most likely of which is probably the cerebellum, could contribute to the reactive grip-force responses. The supposition is substantiated by the knowledge that tactile information from the upper limbs reaches the cerebellum through several different pathways (Bloedel and Courville 1981; Ito 1984) and that neurons in the cerebellar cortex of monkeys respond to load perturbations when performing a precision grip (Dugas and Smith 1992). Further, a human study using magnetoencephalography showed that the cerebellar responses to median nerve stimulation can precede the activity evoked in the primary sensorimotor cortex (Tesche and Karhu 2000). Thus although the exact neuronal mechanisms producing the reactive grip-force responses in the normal brain remain uncertain, both the M1 and the cerebellum are key candidates.

When we hold an object and the load force is unexpectedly reduced, there is an upward perturbation of the partially relieved hand (Hugon et al. 1982) and another type of grip-force response is triggered (an “unloading event”). During these unexpected decreases in load force, the grip force is reduced smoothly over a period of several hundred milliseconds, until the grip force once again matches the weight of the object and the surface friction (Johansson et al. 1992a,b,c). No rapid reactive “catch-up” response is observed. Although there is no risk of a slip occurring, the initial excessive force level is inappropriate because it potentially could cause muscle fatigue

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and physical damage to fragile objects, and thus it is reduced by the CNS. The primary mechanism responsible for the grip force the reduction in the grip force during unloading is not known, although the difference in the speed at which the grip responses are modulated during loading and unloading indicates that the underlying neural substrates are likely to differ.

The aim of the research reported here was to identify the neuronal correlates of the grip-force modulations associated with loading and unloading events. We scanned the brains of six healthy subjects using functional magnetic resonance imaging (fMRI). The participants held an instrumented test object (200 g) between the tips of right index finger and thumb (precision grip). Every so often, the weight of the object was suddenly increased or decreased by 90 g, with the interval between these changes being between 8 and 45 s to ensure that the changes were not anticipated. This perturbation elicited loading or unloading grip-force modulations. We analyzed the transient increases in the fMRI signal that were time-locked to these grip-force responses using statistical parametric mapping with an event-related design (Friston et al. 2004). We hypothesized that the primary motor cortex (Johansson et al. 1994; Picard and Smith 1992) and subcortical structures (Harrison et al. 2000), probably the cerebellum (Dugas and Smith 1992), would reflect the grip-force response during loading. In contrast, we predicted that activity in nonprimary sensory and motor areas would be associated with the unloading response because of the relatively slow time course of the force reduction.

## METHODS

### *Subjects, general procedure, and apparatus*

Six right-handed healthy male subjects with no history of neurological disease participated in the study (20–32 yr of age). They were naive with respect to the specific purposes of the experiments. The participants had given their written consent and the Ethical Committee of the Karolinska Hospital had approved the study, which was performed in accordance with the guidelines of the Declaration of Helsinki 1975.

During the experiments the participants rested in a supine position in an MR scanner. A bite bar was used to restrict head movements. Each participant's arms were extended and oriented parallel to his trunk and supported from the elbow to the radial side of the hand. The subjects used their right hand to perform a radial flexion of the wrist to lift and hold a nonmagnetic object between the tips of the thumb and the index finger (Fig. 1). The object was lifted about 5 cm up from the support and was held still at that height. The object had vertical flat and parallel contact surfaces (spaced 30 mm apart; 35 × 35 mm) covered with sandpaper (grit: 180). The handle of the object was connected by a taut string to a receptacle located outside the MR scanner. Onto this receptacle, an extra weight of 90 g could easily be added and removed between trials by the experimenter. This weight was chosen because pilot experiments previously showed that it produced robust grip-force responses during loading but without any accidental slips of the object. This extra weight was attached to a string that was held by the experimenter. The weight of the object before adding the additional weight was 200 g. The object was equipped with optometric transducers that measured the mean forces normal to the contact surfaces (the grip force) and the sum of the vertical (load) forces. An optometric position sensor captured the lifting movement by measuring the position of the string. The participants were blindfolded throughout the experiments. They wore headphones to receive auditory instructions and to reduce the noise from the MR scanner.

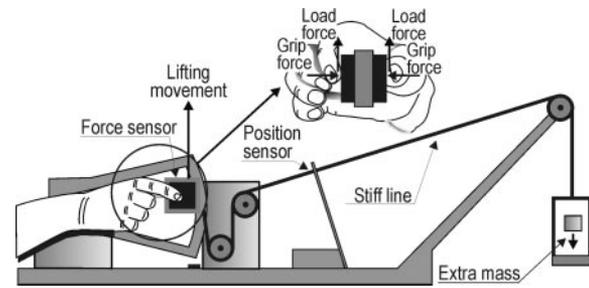


FIG. 1. Grip apparatus and the precision grip lift task. Participants grasped the test object between their right index finger and thumb, lifted it, and held it steady above the support surface. Lower arm and wrist were supported to avoid any movements of the arm. Grip forces and load forces applied to the object and the position of the object were recorded and analyzed off-line. Object was connected by a stiff line to a receptacle outside the scanner where we could drop, or rapidly remove, an extra mass of 90 g. (We acknowledge the help of Dr. Per Jenmalm in creating this figure.)

### *Task and stimuli*

The participants lifted the object and held it still for 3 min and 15 s, and then put it down and released it. After a 45-s rest period, to avoid muscle fatigue, they repeated the lift for another 3 min and 15 s. The subjects were instructed not to apply an excessive grip force or to make any movements when holding the object. During the holding period, sudden changes in the weight of the object occurred, at random intervals of between 8 and 45 s, intended to eliminate any anticipatory grip-force responses and learning-related effects. Two different types of changes in the weight occurred (loading and unloading). During the loading trials the changes were performed by dropping the 90 g weight onto the receptacle (see Fig. 1). This extra weight was dropped from a height of about 2 cm. This generated a transient increase in the load force. In contrast, during the unloading events, the weight was lifted from the receptacle with a brisk movement, almost instantaneously reducing the load force. The experimenter, seated beside the end of the scanner bed, received computer-generated visual instructions that were projected onto the surface of the scanner about when to drop or raise the weight. Before the scanning, the subjects trained at lifting the object and were presented with loading and unloading stimuli.

### *Behavioral analysis*

During the scanning, a data acquisition and analysis system (SC/ZOOM, Department of Physiology Section, IMB, University of Umeå, Sweden) was used to sample the signals from the force transducers and the position sensors. The SC/ZOOM system also recorded the time of acquisition of each MR image so that we knew the exact relative timing of the force and fMRI data. The force and position signals were displayed on-line and stored at 400 Hz with 14-bit resolution. All data were manually inspected and confirmed before further analysis. The timing of all load/unload events was registered and used in the analysis of the MR images (see following text). Each participant was asked to perform between 52 and 55 load events and between 50 and 54 unload events. We picked 10 load and 10 unload events at random per participant for detailed behavioral analysis. For each event, five measurements were made, as follows: 1) *position change*, reflecting the movement of the hand by measuring the maximum vertical change in fingertip position; 2) *reaction onset*, the latency between the onset of the event and the increase or decrease in the reactive grip force (defined as the maximum of the second derivative of the force data); 3) *reaction peak*, the latency between the onset of the event and the peak reactive grip force (there was no corresponding negative peak for the unloading events); 4) *peak grip force increase/decrease*, the amplitude of the difference between the grip force applied at the reaction peak and the grip force at the onset

of the event; and 5) *new steady state*, the time taken to reach the new steady state measured as the time to have elapsed between the onset of the event and the point in time where the grip force had stopped changing and had settled to the appropriate level for the new load force. (This time point was defined as the first time that the force reached a value that was within  $\pm 2$  SD of the baseline force.) The results are presented for each subject in Table 1. Values are presented as group mean  $\pm$  SD unless otherwise stated. All differences between the load and the unload events were tested for their statistical significance. First we analyzed the data for the subjects individually (the asterisks show the level of significance), then mean values were compared across subjects; the latter are reported with the resulting *P* values.

### Brain scanning

Functional MRI was conducted on a 1.5-T scanner (Signa Horizon Echospeed, General Electric Medical Systems, Milwaukee, WI) equipped with a head coil. We collected gradient-echo, echo-planar (EPI) T2\*-weighted image volumes with blood oxygenation level-dependent (BOLD) contrast. The imaging parameters were: echo time (TE) = 50 ms; field of view (FOV) = 22 cm; matrix size = 64  $\times$  64; pixel size = 3.4  $\times$  3.4 mm; and flip angle = 90°. Twenty-four contiguous axial slices of 6 mm thickness were collected in each volume to cover the whole brain.

Functional-image volumes were collected in six separate runs. In each run, 110 volumes were acquired continuously, with one volume being collected every 5,000 ms (TR = 5.00 s). By jittering the grip-force events and the acquisition of the MRI scans, an effective temporal resolution of about 1 s was achieved. To allow for T1 equilibration effects, we started each experiment by recording four "dummy" volumes that were not stored. A total of 660 volumes were collected for each participant.

### Data analysis and image processing

We used the Statistical Parametric Mapping software to process and analyze the images (SPM99; <http://www.fil.ion.ucl.ac.uk/spm>; Wellcome Department of Cognitive Neurology, London, UK). The volumes were realigned, coregistered to each individual anatomical T1-weighted image (3D-SPGR), and normalized to the stereotaxic coordinate system defined by Talarach and Tournoux using the standard brain space of SPM99 and the Montreal Neurological Institute (MNI). Thus the coordinates used to report the location of the activations are all in MNI space. In all subjects, the estimated head movements were <3 mm, which is considered to be good and is not

too great for the realignment process to deal with appropriately. The image volumes were subsequently spatially smoothed with an isotropic Gaussian filter of 10 mm full width at half-maximum (FWHM) and smoothed temporally with a Gaussian kernel of 4-s width to increase the signal-to-noise ratio and to satisfy the Gaussian assumptions made in SPM99. The data were modeled using the general linear model (GLM). We fitted a linear regression model (the GLM) to the data of all subjects together. For each subject, the static holding periods and the rest periods were modeled as boxcar functions and the loading and unloading responses were modeled as brief events. We time-locked these modeled events to the first change in load force during the perturbation trials and we used the standard SPM hemodynamic response function to filter the boxcar waveform that defined the different experimental conditions. The head movement parameters were entered in the GLM to remove, by regression, any residual head-movement-related activity that had not been compensated for by the realignment process described above (six parameters defining rigid body movement). Importantly, because the neural responses associated with the loading/unloading events are delayed by 6 s as a consequence of the hemodynamic response, whereas potential artifacts arising from head movement are not, the latter cannot influence our results. A high-pass filter (with cutoff at 100 s) was used to remove low-frequency drift and fluctuations in the signal. Proportional scaling was applied to compensate for global changes in the signal.

Because we had only six subjects, we used conjunction analysis to identify areas that are consistently activated across subjects (Friston 1999a, 2005). By estimating the task-specific effects using linear contrasts in the GLM for each subject, we created statistical images [i.e., statistical parametric maps (SPMs)] with a t-distribution (SPM |t|) that we transformed, subsequently, to the Z-distribution (SPM |Z|). For the conjunction analyses, the SPM |t| resulting from the six contrasts obtained for each of the six subjects are combined to generate a new SPM |t<sub>min</sub>| that describes the minimum t-value detected in the contrasts. The minimum t-statistic can be related to the population prevalence of individuals showing activation (Friston et al. 1999a). We used the threshold of *P* < 0.05 (corrected), which corresponds to a prevalence of 60% (i.e., 60% of the population will be expected to show activation). This approach is similar to a random-effects analysis in the sense that the results are generalized to the general population (Friston et al. 1999a, 2005; Nichols 2005). We used the threshold *P* < 0.05 after a correction of the number of multiple comparisons in the whole brain volume (false discovery rate correction in SPM99). In the contralateral primary motor cortex, the ipsilateral cerebellum (both discussed in the INTRODUCTION) and the cingulate and the supplementary motor areas (as discussed by Cadoret

TABLE 1. Behavioral data

Subject	Position Change, mm		Grip force timing, s					Grip Force Peak Increase/Decrease, N	
	Load	Unload	Reaction onset		Reaction Peak Load	New steady state		Load	Unload
			Load	Unload		Load	Unload		
5045	—	—	0.07 (0.02)	0.61 (0.50)**	0.26 (0.14)	1.06 (0.38)	1.85 (0.68)**	1.4 (1.8)	-0.4 (0.6)**
5046	—	—	0.08 (0.02)	0.35 (0.18)***	0.30 (0.03)	1.42 (0.81)	2.39 (1.03)*	1.6 (0.6)	-0.5 (0.4)***
5049	-5 (1)	4 (2)***	0.08 (0.00)	0.20 (0.05)***	0.22 (0.05)	1.52 (0.53)	1.71 (0.65)	2.4 (0.7)	-1.1 (0.7)***
5052	-5 (2)	4 (1)***	0.08 (0.01)	0.24 (0.10)***	0.25 (0.11)	1.31 (0.48)	1.55 (0.90)	2.0 (1.2)	-0.5 (0.3)***
5063	-4 (1)	3 (1)***	0.08 (0.02)	0.29 (0.17)**	0.39 (0.14)	1.92 (0.40)	2.51 (0.97)	1.5 (1.4)	-0.3 (0.3)**
5055	-4 (2)	2 (1)***	0.07 (0.02)	0.23 (0.10)***	0.20 (0.06)	1.30 (0.47)	1.97 (1.13)	1.1 (0.4)	-0.6 (0.2)***
Mean	-5 (2)	3 (2)	0.08 (0.02)	0.31 (0.25)	0.27 (0.11)	1.42 (0.57)	2.00 (0.95)	1.4 (0.6)	-0.6 (0.5)
<i>P</i>	<0.001		<0.001			ns		<0.01	

Values are means with SD in parentheses; *N* = 10 per subject. For two subjects the position was not measured. Position change indicates the maximum change in fingertip position resulting from an unload or load event. Grip force timing is specified in relation to the start of the event. The terms reaction onset, reaction peak, and new steady state are defined in METHODS. Grip force peak increase/decrease is the maximum change in grip force amplitude before the grip force settled at a new steady state after the perturbation. The mean is the group mean. The *P* value results from a second-level fixed-effect analysis using a least-square fit of the subjects' mean values.

and Smith 1997), where we had an a priori hypothesis that there would be activation during loading, we used a small volume correction (a sphere with a 15-mm radius) and a threshold of  $P < 0.05$ , corrected, taking the coordinates from a previous study (Ehrsson et al. 2000b).

Our experimental design, with a sparse presentation of events, was optimized to detect neuronal responses evoked by the loading and unloading events relative to the baseline (Friston et al. 1999b), although this design is inefficient when it comes to making a direct contrast between the perturbations events. Thus in this paper, the main analysis consists of the contrasts identifying activity associated with the loading and unloading events compared with the baseline, respectively, and for this we use the threshold of  $P < 0.05$ , corrected. The contrasts between the loading and unloading events represent a supplementary analysis for which we used the threshold of  $P < 0.001$ , uncorrected. This analysis was restricted to areas that were significantly active (i.e.,  $P < 0.05$ , corrected) during the loading/unloading events.

Finally, in previous precision grip studies we pooled all data across subjects and performed a fixed-effects analysis (Ehrsson et al. 2000a, 2001; Kuitz-Buschbeck et al. 2001); we also ran this type of analysis on the present data to enable comparisons to be made. All the areas in the results presented here were significantly activated when we performed the fixed-effects analysis ( $P < 0.05$ , corrected using the whole brain as the search space).

The anatomical localization of the activation was related to the major sulci and gyri (Duvernoy 1991) distinguishable in a mean standardized anatomical MRI obtained from the six subjects.

## RESULTS

### Task performance

The results of the analysis of the force and position data from all subjects are summarized in Table 1. Load reactions were characterized by a grip-force peak ( $1.40 \pm 0.60$  N; mean  $\pm$  SD across subjects) at  $0.27 \pm 0.11$  s (Fig. 2A). The earliest onset of the grip-force response was observed after  $0.08 \pm 0.02$  s. This is in agreement with similar studies (Johansson and Westling 1988). The load impact perturbed the hand position slightly downward ( $-5 \pm 2$  mm). The grip force slowly settled to a new steady-state level that was appropriate for the new load, some  $1.42 \pm 0.57$  s after the load impact.

In contrast, the reaction to an unload event was characterized by a slow decrease in the grip force ( $-0.6 \pm 0.5$  N), starting  $0.31 \pm 0.25$  s and settling  $2.00 \pm 0.95$  s after the unloading ceased (Fig. 2B). The unload event perturbed the hand position slightly upward ( $3 \pm 2$  mm).

### Brain activation

**NEURAL RESPONSES ASSOCIATED WITH LOADING.** We first searched for areas associated with loading events. In the cortex these were associated with significant activation of the left primary motor cortex and primary somatosensory cortex (with the peak being in the anterior bank of the central sulcus), the left dorsal premotor cortex (PMD), and the left cingulate motor area. Subcortically, we found activity in the right lateral cerebellum and the medial cerebellum (vermis) ( $P < 0.05$ , corrected; see Table 2 and Fig. 3).

Because it is textbook knowledge that somatosensory afferent signals reach the primary somatosensory cortex by the ventral posterolateral nucleus (VPL) of the thalamus, and that the right lateral cerebellum is reciprocally anatomically connected to the primary motor cortex by the ventral lateral

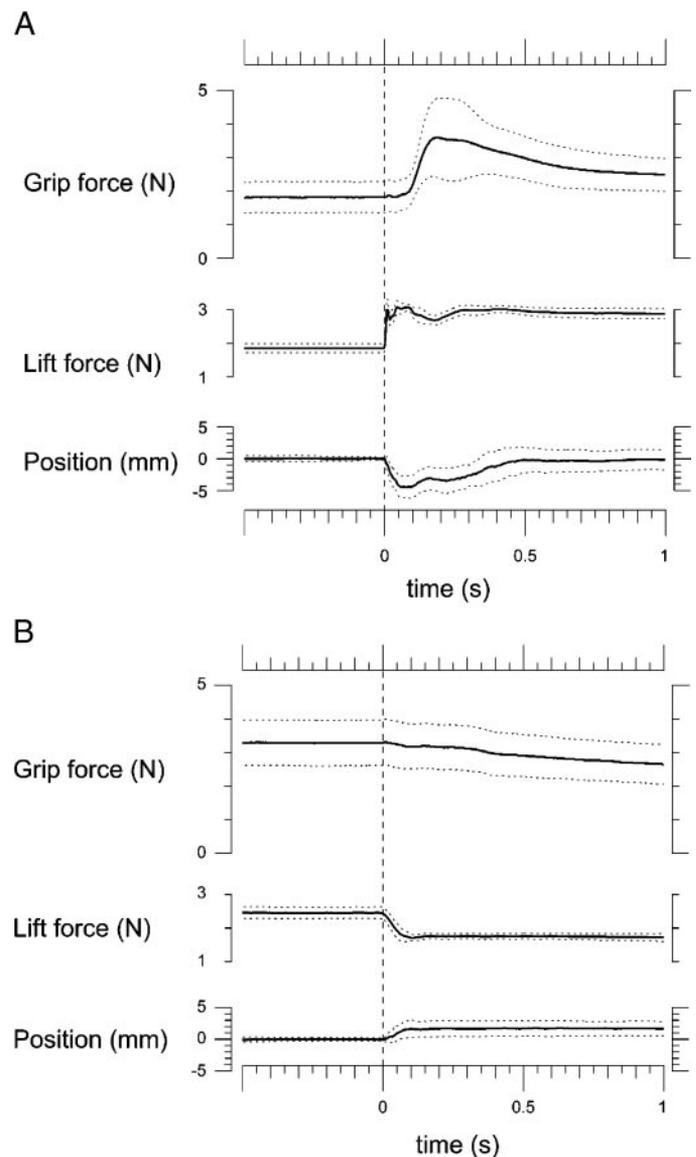


FIG. 2. Average force recordings for a representative participant from loading (A) and unloading (B) trials. Mean grip forces, load forces, and position are plotted over time (dark lines). Dotted lines indicate the SD of the forces and the data with respect to position. During the loading events (A) the rapid increase in lift force was followed by a reflexive-like increase in the grip force after about 70 ms. During the reduction in lift force (shown in B, corresponding to the unloading) the decrease in grip force was slower and typically continued for several hundred milliseconds.

thalamic nucleus (VL) and the pons, we lowered the statistical threshold ( $P < 0.01$ , uncorrected) in a purely descriptive approach to see whether there was any activity in these regions. As a result, we observed such relatively weak activity, in the left VPL ( $x = -12$ ,  $y = -24$ ,  $z = -4$ , Z-score = 2.42,  $P = 0.008$ ), the left VL ( $x = -12$ ,  $y = -16$ ,  $z = 0$ , Z-score = 2.42,  $P = 0.008$ , uncorrected), and in the left pons ( $x = -8$ ,  $y = -28$ ,  $z = -12$ , Z-score = 3.50,  $P < 0.001$ ). No other activity was observed in the thalamus or pons.

**NEURAL RESPONSES ASSOCIATED WITH UNLOADING.** Next we examined the areas that were active during the unloading events (Table 3 and Fig. 4). Significant cortical activation ( $P < 0.05$ , corrected) was observed in the left supplementary motor area, the left cingulate motor area, the left pre-SMA, the bilateral

TABLE 2. Loading responses

Anatomical Structure	Z-Score	Corrected P-Value <sup>†</sup>	Coordinates (MNI)		
			X	Y	Z
L. CMA	4.70	0.02	-8	4	44
L. central sulcus (M1/S1)	4.51	<0.01 <sup>‡</sup>	-40	-24	56
L. PMD	4.22	0.02	-28	-8	52
Med. cerebellum (vermis; Lobule VI)	3.86	0.05	0	-72	-24
R. lat cerebellum (Lobule V)	3.77	<0.02 <sup>‡</sup>	8	-60	-16

Only clusters of five voxels or more are reported. <sup>†</sup> $P < 0.01$  after correction for all voxels in the brain. <sup>‡</sup> $P < 0.05$  after small volume correction based on a priori hypothesis.

superior temporal cortex, and the medial wall of the left posterior parietal cortex (the precuneus and SSA). Subcortically, activity was detected in the left ventral lateral thalamus and the medial cerebellum (vermis). No activity was observed in the primary motor cortex, the primary somatosensory cortex, or in the ventral posterolateral thalamic nucleus during the unloading events, even when we lowered the statistical threshold ( $P > 0.001$ , uncorrected).

DIFFERENTIAL NEURAL RESPONSES DURING LOADING AND UNLOADING. We then ran analysis in which we contrasted the loading and unloading events directly (i.e., we depicted areas that showed a differential response). Most notably, the left primary motor cortex and the left primary somatosensory cortex were significantly more active during loading than when unloading ( $P < 0.05$ , corrected; Fig. 5; see also Table 4).

In contrast, only one active cluster of voxels was found in the whole brain that was more active during unloading than loading ( $P < 0.001$ , uncorrected; cluster volume = 110 mm<sup>3</sup>; Table 5). This activation was located in the marginal segment of the cingulate sulcus, which corresponds to the supplementary somatosensory area (Fig. 6). The peak was located in the right hemisphere, but the active cluster was located in the midline and extended into the left hemisphere, where we had observed the strongest activation compared with the baseline. This fits nicely with the results presented above that showed that the SSA was significantly active compared with the baseline ( $P < 0.05$ , corrected) and not active at all during loading ( $P > 0.01$ , uncorrected). Recall from the METHODS section that our design had not been optimized for making direct contrasts between different events (because of the sparse presentation of events), so we used the threshold of  $P < 0.001$ , uncorrected for the SSA.

## DISCUSSION

Three main findings emerge from the first imaging study of the neural correlates of loading and unloading responses conducted while subjects were holding an object. First, we found increases in activity in the contralateral (left) primary motor cortex in response to loading, but not to unloading. In line with our hypothesis, this associates sensorimotor processing in the primary motor cortex with the reflexive grip-force response during loading. Second, we observed activity in the right lateral and medial cerebellum during the loading trials. This finding is consistent with the hypothesis that the cerebellum participates in the reflexive force responses during loading, but its specific

role remains to be ascertained because the medial cerebellum was also active during unloading. Third, unloading activated contralateral nonprimary sensorimotor areas rather than the primary sensorimotor cortex (M1 and S1). Both the loading and the unloading events were associated with activity in the left cingulate motor area and we suggest that the activity in this nonprimary motor area could reflect the change in the senso-

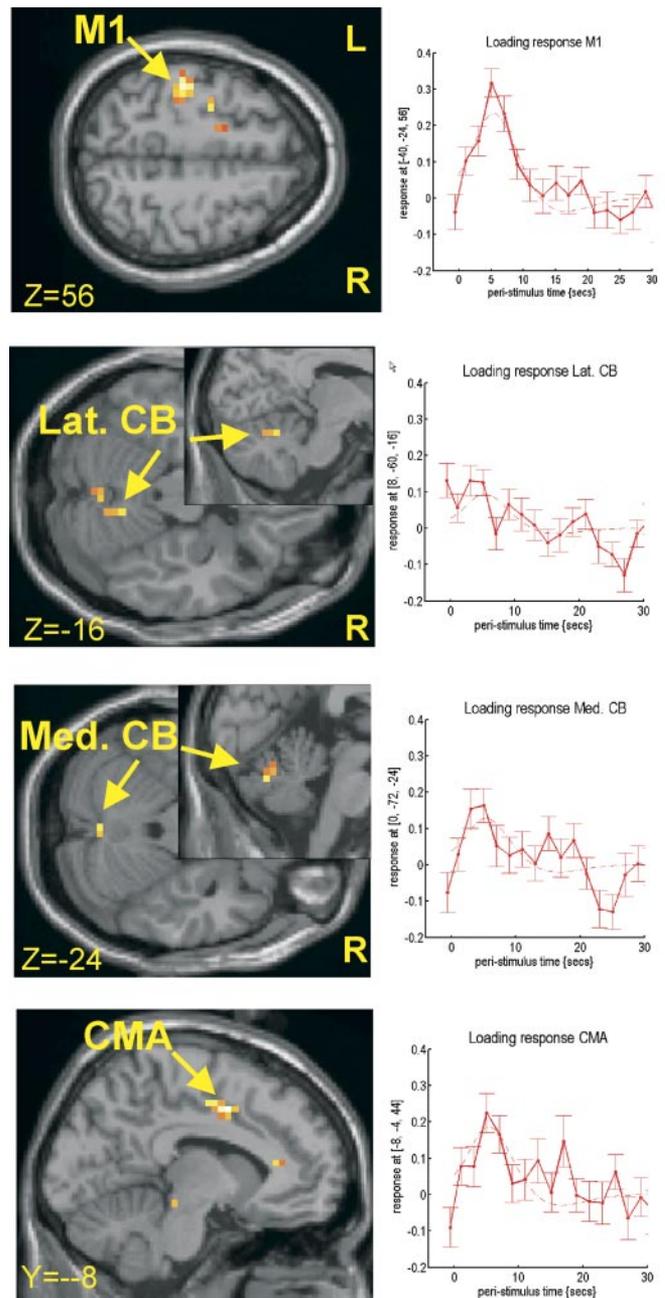


FIG. 3. Transient increases in the functional magnetic resonance image (fMRI) signal associated with the loading events. *Left images:* statistical parametric maps superimposed on the Montreal Neurological Institute (MNI) template brain obtained by comparing the loading events with the baseline (a red-yellow scale was used;  $P < 0.001$ , uncorrected). *Right:* plots of the fitted average fMRI response after the perturbations are displayed. Activation was observed in the primary motor cortex (M1; *top image and plot*), the lateral and medial cerebellum (*middle 2 images and plots*), and in the cingulate motor area (CMA) on the medial wall of the frontal cortex (*bottom image and plot*). R, right hemisphere. Coordinate in standard space for the slice is also indicated. Histogram is a peristimulus time histogram (PSTH).

TABLE 3. Unloading responses

Anatomical Structure	Z-Score	Corrected P-Value <sup>†</sup>	Coordinates (MNI)		
			X	Y	Z
L. CMA	4.73	0.01	-4	0	40
L. SMA	4.45	0.01	-4	-8	60
L. Pre-SMA <sup>‡</sup>	4.13	0.02	0	8	52
L. parietal operculum	4.25	0.02	-48	-24	12
L. SSA <sup>‡</sup>	4.41	0.01	0	-48	68
L. Precuneus <sup>‡</sup>	4.22	0.02	0	-56	56
R. sup. temporal g.	4.46	0.01	60	-16	0
L. sup. temporal g.	4.21	0.01	-64	-20	8
L. sup. temporal s.	3.68	0.02	-52	-20	-8
R. anterior cingulate cortex	3.44	0.04	4	24	24
R. ventral thalamus	4.06	0.02	4	-16	0
L. ventral lateral thalamus	4.18	0.02	-12	-12	0
M. cerebellum (Lobule III)	3.88	0.03	0	-44	-12

Only clusters of five voxels or more are reported. <sup>†</sup> $P < 0.01$  after correction for all voxels in the brain. <sup>‡</sup>Although the peak was located in the midline ( $x = 0$ ), the cluster of active voxels extended into the left hemisphere and therefore we label this activation as left-sided.

rimotor representation of the fingertip forces. The bilateral supplementary somatosensory area (SSA) was activated during unloading, but showed no response during loading (also see the BOLD plot in Fig. 5). This suggests that the SSA is involved in reduction of the grip force that occurs during unloading, although the exact mechanisms performed by this area remain uncertain.

A potential confounder in the present study relates to changes in attention associated with the unpredictable sensorimotor events. Previous fMRI studies showed that areas in the prefrontal, posterior parietal, and temporal cortex are active in conjunction with unpredictable changes in sensory stimulation, even when these stimuli do not elicit a motor response (Downar et al. 2000). Thus it is possible that the activations we found in the superior temporal cortex, the anterior cingulate cortex, the pre-SMA, and the precuneus could be accounted for by "reflexive" shifts in attention to the hand during the unloading events. However, such attention-related processes could probably not explain the activation of the genuine motor areas that were found to be active (e.g., M1, the cerebellum, and posterior sections of the SMA and PMD). Furthermore, the activations in M1 and the SSA were found when we made direct comparisons between the activation associated with loading and unloading and, because these events were equally unexpected, the attentional factors could be expected to be matched.

In the present experiments the loading and unloading events were, respectively, achieved by dropping or rapidly lifting a weight onto or off a platform. This results in more rapid changes in the load force in the loading condition. However, these differences in the rate of the force change are probably insufficient to explain the characteristic force responses associated with loading and unloading or the qualitative differences in neural responses observed in the primary sensorimotor cortex and the SSA. The risk of dropping the object is present only when loading, thereby explaining why, in this case, the central control system responds with a rapid increase in the grip force. When decreasing the load, the response can be

understood only as the elimination of excessive grip forces and thereby minimizing energy consumption (see INTRODUCTION).

### Loading

An important question is whether the grip-force responses occurring during loading are mediated by the primary motor

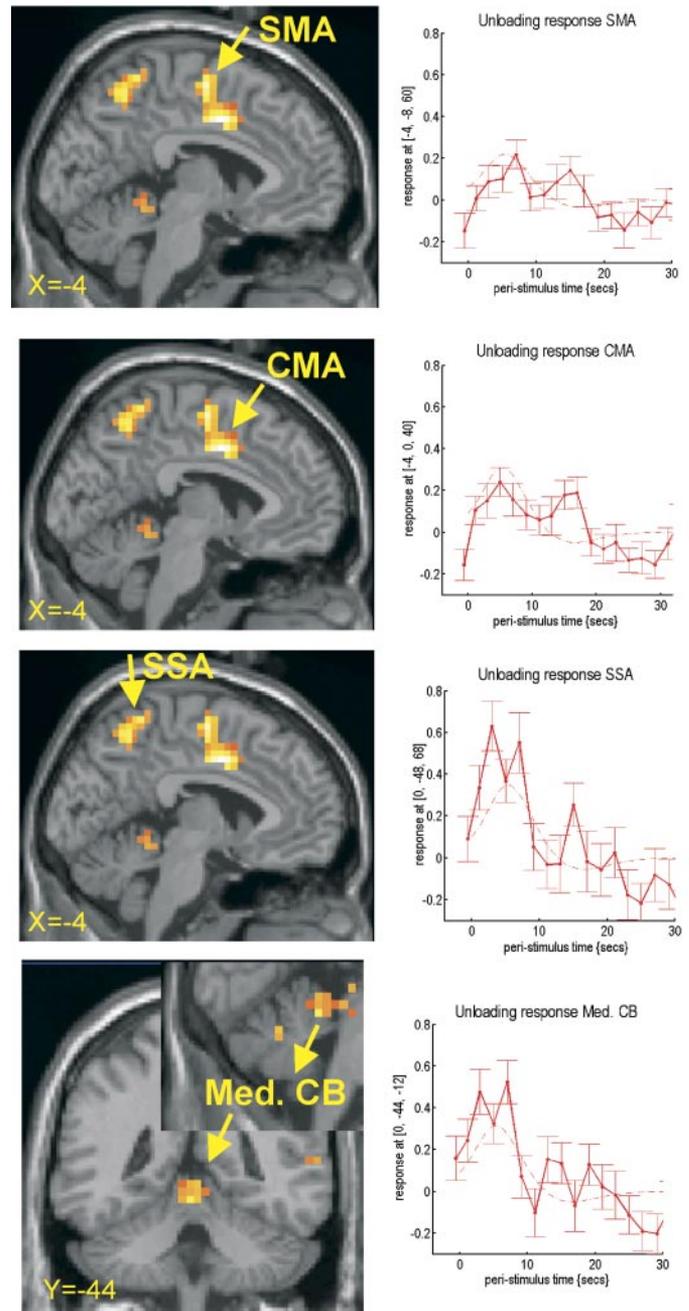


FIG. 4. Transient increases in the fMRI signal associated with the unloading events. *Left images:* statistical parametric maps for the unloading events compared with the baseline (red-yellow scale;  $P < 0.001$ , uncorrected), superimposed on the MNI template brain. *Right diagrams:* PSTH, which plots the fitted average fMRI response after the perturbations. Activation was observed on the medial wall of the frontal lobe in the supplementary motor area (SMA; *top image and plot*) and CMA (*2nd image from top*). Activation was also observed in the medial parietal lobe [precuneus and supplementary sensory area (SSA); *3rd image and plot from top*], and in the medial cerebellum (*bottom image and plot*). R, right hemisphere. Coordinate in standard space for the slice is also indicated.

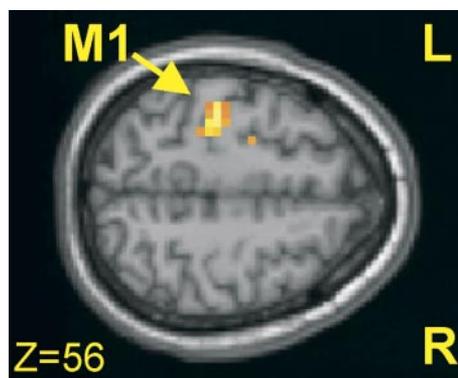


FIG. 5. Activity in the primary motor cortex (M1) was associated with loading, but not unloading. Cortices lining the central sulcus (primary motor cortex and primary somatosensory cortex) revealed significantly stronger activation during the loading events than the unloading ones. *Top picture*: statistical parametric maps (red-yellow scale;  $P < 0.001$ , uncorrected) superimposed on the MNI template brain. *Two bottom plots*: fitted average fMRI response in the M1 after the loading events (*middle plot*) and the unloading event (*bottom plot*). Note the clear M1 response associated with loading and compare this with the absence of any increase in activity during unloading. R, right hemisphere. Coordinate in standard space for the displayed slice is also indicated. PSTH, peristimuli time histogram.

cortex or by subcortical structures, of which the cerebellum is the foremost candidate. Our findings are consistent with either of these scenarios, but provide the strongest evidence in favor of the involvement of M1 because increases in M1 activity were observed only during loading. This is a finding that associates the M1 activity closely with the sensorimotor processes involved in the generation of the loading grip-force response.

TABLE 4. Loading–unloading

Anatomical Structure	Z-Score	Corrected P-Value	Coordinates (MNI)		
			X	Y	Z
L. central sulcus (M1/S1)	4.07	<0.01†	–36	–24	56
L. postcentral g. (S1)	3.91	<0.02†	–32	–32	44
L. central sulcus (M1/S1)	3.77	<0.02†	–28	–28	60

Only clusters of five voxels or more are reported. † $P < 0.01$  after small volume correction based on a priori hypothesis.

We know from single-cell recordings that many cells in M1 are highly sensitive to tangential force perturbations (Picard and Smith 1992). Many of these cells have cutaneous receptive fields on the hand and respond in a reflexive-like manner to the perturbations, which suggests that the output from these cells mediates the grip-force responses (Picard and Strick 2003). Thus it is likely that the fMRI activation observed here corresponds to M1 cells involved in generating grip-force responses based on cutaneous inputs. The BOLD signal is generally considered to reflect the overall synaptic activity in an area (Logothetis et al. 2001). Thus the present M1 activation corresponds to synaptic input to interneurons and corticospinal neurons in a large population of M1 cells. Although fMRI activity cannot be equated with activation of the corticospinal tract, its engagement is likely because a previous transcranial magnetic resonance stimulation study reported enhancement of the motor cortical excitability during reactive grip-force responses to loading perturbations (Johansson et al. 1994). The corticospinal neurons are the most critical for mediating the grip-forces because they are monosynaptically connected to motor neurons in the ventral horn of the spinal cord, which in turn innervate the muscles of the fingers and hand (Lemon 1993).

The loading grip-force response critically depends on afferent tactile inputs from the fingertips (Johansson and Westling 1988; Johansson et al. 1992a,b,c; Picard and Smith 1992). The neuronal populations in M1 receive both tactile inputs from the skin of the fingertips and kinesthetic inputs from the finger muscles. These afferent signals are conveyed by cortico-cortical projections from S1 (Darian-Smith et al. 1993; Jones 1984; Jones et al. 1978; Stepniewska et al. 1993) and directly by connections from the spinal cord by the ventral posterolateral nucleus of the thalamus (Darian-Smith and Darian-Smith 1993; Jones 1984; Stepniewska et al. 1994). Thus the fact that we found significant activity in the S1 and M1 (area 3b;  $P < 0.05$ , corrected), in conjunction with weak activity in the ventral posterolateral thalamus ( $P = 0.008$ , uncorrected; see RESULTS), is consistent with both thalamocortical afferents and cortico-cortical transmission of tactile information from S1 to M1. We suggest that the M1 activation found in the present study could reflect an “M1 long loop reflex,” which produces a grip-force

TABLE 5. Unloading–loading

Anatomical Structure	Z-Score	Uncorrected P-Value	Coordinates (MNI)		
			X	Y	Z
R. SSA‡	3.51	<0.001	4	–48	64

Only clusters of five voxels or more are reported. ‡Cluster located in the midline.

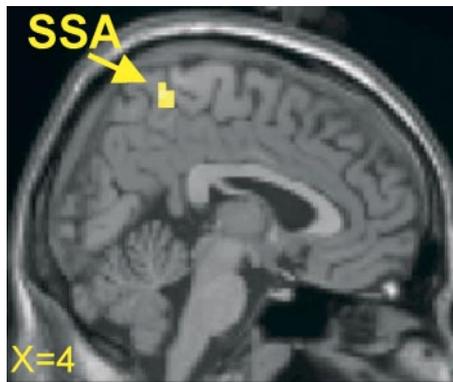


FIG. 6. Activity in the supplementary somatosensory area was associated with loading, but not unloading. At the top of the figure, the statistical parametric maps for the contrast unloading vs. loading are superimposed on the MNI template brain (red-yellow scale;  $P < 0.001$ , uncorrected). Two bottom figures plot the fitted average fMRI response in this area after the loading events (middle row) and the unloading event (bottom row). Coordinate in standard space is indicated. PSTH, peristimuli time histogram.

response during loading perturbations based on tactile inputs. Having made this suggestion, it should be stated that we cannot exclude the possibility that the M1 activation reflects the kinesthetic sensations associated with the loading events (Naito et al. 1999, 2002), rather than the sensorimotor transformations that are directly responsible for the force response. Thus the most reasonable interpretation of the present M1 activation is that it reflects both the processing of afferent cutaneous inputs and activity related to producing reactive grip forces.

The cerebellum is considered to be an important subcortical candidate for reactive grip-force control. We found two active cerebellar foci when we analyzed the fMRI data time-locked with the loading responses. One of these was located in the

right (ipsilateral) anterior cerebellar hemisphere. This part of the cerebellum receives inputs from the primary motor cortex and the premotor areas by the pons (Brodal 1979, 1980; Glickstein et al. 1985; Middleton and Strick 2000; Schmahmann and Pandya 1997). In turn, it influences the cortical motor output by its connections back to the motor cortex by the contralateral ventrolateral thalamus (Holsapple et al. 1991; Middleton and Strick 2000; Zemanick et al. 1991). In this way, the lateral cerebellum can play a supplementary role by fine-tuning the motor commands being formed in M1 in direct response to the perturbation. Weaker activity was found in the ventrolateral thalamus and pons during the loading trials ( $P < 0.008$ , uncorrected; see RESULTS), supporting this interpretation. The lateral cerebellar activity may also reflect the neural control of the exactly timed sequence of agonist and antagonist activation of the finger and hand muscles after the loading perturbation (Vilis and Hore 1977). There are also pathways from the cerebellar hemisphere to the spinal motor networks by connections through the interposed nuclei and the red nucleus (Asanuma et al. 1983; Courville 1966; Kennedy et al. 1986), although these structures are probably too small to be detected using our scanning protocol (no activity was observed) and therefore the involvement of this pathway is uncertain.

The second cerebellar focus was located in the medial cerebellum (vermis). This part of the cerebellum receives prominent somatosensory inputs from the spinal cord by several direct and indirect pathways and has the capacity to control movements by directly influencing the spinal networks by connections through the fastigial nucleus and the lateral vestibular nuclei (Carleton and Carpenter 1983; Ruggiero et al. 1977). In addition to this, the vermis can influence the M1 by connections through the ventrolateral thalamus (Holsapple et al. 1991; Schmahmann and Pandya 1997). Thus the finding that the medial cerebellum was active in the present study, both during loading and unloading, is consistent with the view that this structure could be involved in the mediation of changes in grip forces as a consequence of changes in the sensory feedback from the fingertips.

We also observed increased activity in the nonprimary motor areas associated with the loading perturbations. Prominent activations were located in the cingulate sulcus, in the CMA near the border between this area and the SMA. A focus of activity was also observed in the left PMD. In macaque monkeys holding an object with a precision grip, "reflexive-like" excitation of neurons in the hand sections of ventral cingulate motor area and the SMA was evoked when the object was subjected to forceful perturbations (Cadoret and Smith 1997). However, these authors also indicated that the number of cells in these areas receiving cutaneous inputs was substantially lower than that in the M1 (Picard and Smith 1992), suggesting that these areas are less implicated in the modulation of the grip force based on cutaneous feedback. In addition to this, it is known that fewer cells in the SMA and CMA (Cadoret and Smith 1997) respond to force perturbations than in the M1 (Picard and Smith 1992). Thus although these nonprimary motor areas are activated during changes in the load when performing a precision grip, their relative importance for the mediation of the fast reactive grip-force response during loading remains somewhat uncertain.

## Unloading

The unloading response is characterized by the absence of a rapid reflexive-like grip-force modulation and a slower reduction in the grip force. There was a conspicuous lack of M1 activation (even when using a very liberal threshold of  $P < 0.05$ , uncorrected; as can be seen in Fig. 5). Thus the grip-force attenuation during unloading does not seem to be associated with significant increases in synaptic activity in the M1. Of course, negative findings in functional imaging studies should be interpreted with caution because fMRI is less sensitive than direct neuronal recordings (Logothetis et al. 2001). In the present experiments the unloading responses were relatively weak because the additional weight was quite light (only 90 g). Experiments conducted in the future should investigate removal of larger weights. However, our results do suggest that the nonprimary sensorimotor areas, including the SSA, are more important than the primary sensorimotor cortices for the control of the unloading response. A previous study reported activation of the M1 during voluntary relaxation of a contracted muscle (Toma et al. 1999). Major differences between this study and the present unloading responses are that the muscle relaxations were voluntary and involved proprioceptive muscle sensations. In contrast, the unloading events are automatic and the participants do not perceive any changes in the muscular force exhibited.

Unloading-related responses were observed in the medial wall motor areas (SMA, CMA), the medial posterior parietal cortex (precuneus and SSA), and the medial cerebellum (vermis). The strongest response was observed in the SMA and CMA, which are nonprimary motor areas. Because the CMA was also active during the loading response ( $P < 0.05$ , corrected) and the SMA showed a statistical trend for activation ( $P < 0.001$ , uncorrected), we propose that these phenomena reflect the change in the force output rather than the grip-force reduction per se. Thus the active neuronal populations in the CMA and SMA could be involved in processing information about the change in fingertip forces in the context of holding an object. This interpretation is consistent with an earlier study that showed that the activity on the medial wall of the frontal lobes (SMA) increases both during the initiation of muscle contraction and during the subsequent relaxation of the muscle (Toma et al. 1999).

An interesting observation was activation in the SSA that occurred only during unloading. This suggests that the SSA participates in the reduction in the grip force during unloading, although the exact mechanism remains uncertain. The SSA is considered to be a higher-order somatosensory area (Roland 1993; Seitz et al. 1991). In the monkey brain it is located in the posterior part of the cingulate sulcus and has a distinct somatosensory representation (Murray and Coulter 1981a,b). It is anatomically connected with sensorimotor areas, most notably the SMA, CMA, PMd, areas 4, 3, 1, and 2, the superior parietal cortex (area 5), and the secondary somatosensory cortex (Morecraft et al. 2004). Thus this area has the capacity both to analyze somatosensory information and to send this information to the frontal motor areas, including the M1. It is not likely that the SSA response reflected afferent tactile input because the tactile input was greater when the mass was dropped in the loading event. Furthermore, it is not likely to correspond to a somatic representation of the object weight or a change in the

forcefulness of the grip because, in that case, it would have been expected that the SSA would also have been activated during the loading events. Rather, our interpretation is based on the fact that one key feature of the unloading event is the inappropriately high grip force. The grip force is greater than required to avoid slip—that is, the slip margin is excessive. It is economic for the CNS to have a mechanism to adjust such excessive grip forces. Thus it is possible that the SSA activity reflects the somatic analysis of the excessive grip-load force ratio. This information could then be conveyed to other sensorimotor areas, supporting the reduction in the force output until the grip-load force ratio has been normalized. What may speak against this interpretation is that the loading responses include excessive grip forces after the initial increase in the reactive grip force, but no activation was seen in the SSA in association with this type of perturbation.

It could be argued that all that is needed to produce the grip-force responses seen during loading and unloading is a natural tendency to decrease the force over time, coupled with reactive grip-force increases triggered by microslips. However, this model cannot fully explain the normal stability of the grasp as seen when humans hold an object statically above a support surface. According to the simple model outlined above, one would expect cycles of reductions in the grip forces, coupled with reactive loading responses, and this certainly does not always occur. For example, in our data, such cyclical changes in force were not seen. In fact, the stability of the human grasp indicates that the brain contains central representations of the fingertip forces and the weight of the object and has access to information about the slip force.

In summary, our results reveal the neural correlates of loading and unloading grip-force responses. Earlier human studies described the active cortical networks associated with fingertip force control in various precision grip tasks when subjects voluntarily apply forces (Ehrsson et al. 2000a, 2001, 2003; Kinoshita et al. 2000; Kutz-Buschbeck et al. 2001; Schmitz et al. 2005). The study reported on here is the first to identify the neural correlates of automatic force adjustments to external perturbations. The loading and unloading responses are two important control mechanisms that are used by the CNS to maintain grasp stability. Thus the present findings contribute to our understanding of the neural substrates of manual dexterity in humans.

## ACKNOWLEDGMENTS

The authors especially thank Dr. Göran Westling (Physiology Section, IMB, Umeå University, Sweden) and C. Schmidt (Dept. of Woman and Child Health, Karolinska Institute, Stockholm) for technical support and S. Lidström for checking the English in the article.

## GRANTS

This study was supported by the Swedish Medical Research Council. H. H. Ehrsson received financial assistance from the Human Frontier Science Program and the Wennergren Foundation.

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