Differential neural correlates of reciprocal activation and cocontraction in dorsal and ventral premotor cortices

Masahiko Haruno, Gowrishankar Ganesh, Etienne Burdet, and Mitsuo Kawato

ATR Computational Neuroscience Laboratory, Kyoto; Center for Information and Neural Networks, National Institute of Information and Communications Technology, Kobe Hyogo; PRESTO, Japan Science and Technology Agency; Tamagawa University Brain Science Institute, Tokyo, Japan; and Department of Bioengineering, Imperial College of Science, Technology and Medicine, South Kensington Campus, London, United Kingdom

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METHODS

Subjects and setup. Two females and 10 males, all right-handed, healthy adults between 23 and 40 years old, participated in the study. The Institutional Ethics Committee of ATR Computational Neuroscience Laboratory (Kyoto, Japan) approved the experiments, and subjects gave informed consent prior to participation. A fMRI-compatible robotic interface (Gassert et al. 2006) was used to restrain the subject’s wrist to an isometric posture with straps and a plastic splint (Fig. 1A) while the subject contracted his or her muscles. This device has a custom-made torque sensor that was used to collect wrist joint torque during the experiment. All of the subjects used their right hand to conduct the task.

Address for reprint requests and other correspondence: M. Haruno, Center for Information and Neural Networks, National Institute of Information and Communications Technology, 588-2 Iwaoka-cho Nishiku, Kobe Hyogo 651-2492, Japan (e-mail: mharuno@nict.go.jp).
During fMRI experiments, EMG was recorded from two muscles acting at the wrist [flexor carpi radialis (FCR) and extensor carpi radialis brevis (ECRB) or extensor carpi radialis longus (ECR)] because they are the dominant muscles actuating wrist flexion-extension. In the isometric torque condition, subjects increased their wrist torque (red bar) to match a visual target, shown randomly to the left (i.e., flexion) or right (i.e., extension) of the fixation. In the cocontraction condition, subjects held the cocontraction level (blue bar) of the wrist muscles at a target corresponding to average rectified EMG from the previous torque block, displayed randomly to the left or right of the fixation point. 

After electrode placements for each muscle were determined using functional movements, the area was cleansed with alcohol and abrasive gel (Nuprep, Weaver and Company, Aurora, CA). EMG electrodes designed for MRI environments (NE-706A, Nihon Kohden, Tokyo, Japan) were filled with EMG electrode paste (Biotech, GE Marquette Medical Systems, Japan) and firmly taped to the subject's skin. Two electrodes were positioned on the belly of each muscle, separated by 1 cm. An elastic cloth sleeve was placed over the electrodes and wires, fixing them against the subject’s forearm to avoid any accidental electrode removal and to minimize the movements of the electrode wires during scanning. Once the subject was positioned in the scanner, the long, braided electrode wires were firmly fixed to prevent movement in the magnetic field of the scanner. To avoid external noise being carried into the shielded MRI room, the electrode wires were passed through multiple ferrite filters before passing through waveguides in the penetration panel of the MRI room. 

EMG signals were cleaned online during scanning and used to provide EMG feedback. The details of EMG processing are described in Ganesh et al. (2007).

In a separate session performed outside of the MRI scanner, the EMG signals from four wrist muscles—FCR, ECR, flexor carpi ulnaris (FCU), and extensor carpi ulnaris (ECU)—and four upper-arm muscles—biceps brachii, triceps brachii lateral head, pectoralis major, and posterior deltoid—were recorded from two separate groups of subjects (n = 8 and 4, respectively). These supplementary behavioral data were obtained using a mock MRI. EMGs were rectified and band-pass filtered (20–200 Hz), and the average throughout the task was subtracted. A subject’s EMGs from FCR, ECR, FCU, and ECU during the first set of the five [torques 1 and 2 (t1 and t2), cocontractions 1 and 2 (c1 and c2), and rest (r)] conditions are displayed in Fig. 2A.

Task. The subjects performed in five conditions: r, t1, c1, t2, and c2. Throughout the experiment, they received visual feedback of the applied torque and total muscle activation in the form of two bars (Fig. 1B). While the torque sensor reading was used as the visual feedback of torque, the visual feedback of total muscle activation was calculated...
Fig. 2. Behavioral data and analysis. A: raw EMG data from a subject’s wrist muscles—FCR, ECR, flexor carpi ulnaris (FCU), and extensor carpi ulnaris (ECU)—during the r, t1, c1, t2, and c2 conditions. The color marker below the condition indicates trial types (blue: flexion; red: extension; and gray: cocontraction). B: the EMG ratio (FCR + ECR)/(FCR + ECR + FCU + ECU) throughout the task was plotted for each condition. C: EMG data from upper-arm (biceps, triceps) and shoulder (pectoralis major and posterior deltoid) muscles plotted after normalizing with the activity during the t1 condition. These muscles did not show any significant change in activity across conditions. D: torque and integrated EMG of a typical subject show stable values over the task. Horizontal lines represent targets (0.5 Nm for t1 and 1.0 Nm for t2). Each point represents an average over 10 trials in 1 condition. E: mean torque and SD calculated across subjects show that torque was very small in the rest and cocontraction conditions. F: the ratios of EMG amplitude. c1 to t1 and c2 to t2 were not different from 1.0, and ratio t2 to t1 and c2 to c1 was significantly larger than 1.0.

The condition blocks (of r, t1, c1, t2, and c2) lasted for [30 s (rest) + 4 (conditions) × 10 (trials) × 4 s = 190 s] and were repeated eight times for a total experiment time of 1,520 s for each subject (Fig. 1C). All subjects had a practice session before the fMRI experiment to familiarize themselves with the paradigm and visual feedback and to avoid any learning-related effects during the scanning (see also RESULTS).

fMRI. A 1.5-T MRI scanner (Shimadzu-Marconi Eclipse 1.5T Power Drive 250) was used to obtain BOLD contrast functional images, which when weighted with the apparent transverse relaxation time, were obtained with a gradient echo echoplanar imaging (EPI) sequence. Data were collected from the whole brain. For each subject, 768 scans of BOLD images [repetition time 5.0 s, echo time 49 ms, flip angle 80°, field of view (FOV) 192 mm, resolution 3 × 3 × 3 mm, gap 1 mm, 64 × 64 in-plane voxels (in-plane FOV 224 mm²)] were acquired. In addition to these experimental trials, each session contained six preliminary dummy scans to allow for T1 (short TR and short TE) equilibration effects. A custom-made bite bar was used in all experiments to reduce head movement, which resulted in head motion amplitude below 1 mm and 1° for all subjects. With these acquisition parameters, the parietal cortex was on the edge of the scope for several subjects; thus activity in the parietal cortex was excluded from subsequent fMRI analysis. However, data on the whole cerebellum, SMA, and PMd used for the analysis were available fully for all subjects.

fMRI analysis. EPI time series were preprocessed using a standard procedure in Statistical Parametric Mapping (SPM2) (Friston et al. 1995). The first six dummy volumes were discarded, and the remaining volumes were realigned to the first volume and unwarped. EPI and structural images were spatially normalized to the Montreal Neurological Institute (MNI) template embedded in SPM2. The normalized images were resliced into 2 × 2 × 2-mm voxels using the T2 (long TR and long TE) template of SPM and smoothed using an 8-mm full-width, half-maximum Gaussian kernel. The preprocessed data...
were analyzed using random effect models (i.e., one-sample t-test) in SPM2 (Friston et al. 1995).

If neural activity specific to reciprocal activation were present, we hypothesize that it would increase with the torque amplitude in the torque conditions (Fig. 1D) and take similar low values in both the rest and cocontraction conditions. In contrast, neural activity specific to cocontraction control is expected to change with the amplitude of cocontraction in cocontraction conditions, with the rest and torque conditions taking similar low values (Fig. 1D).

The absolute value of torque averaged over each torque condition was used to create a parameterized block regressor for reciprocal activation conditions, while the r, c1, and c2 conditions were set to zero (Fig. 1D). Similarly, the average of two EMGs over each cocontraction condition was used to create a parametric block regressor for cocontraction conditions, while r, t1, and t2 were set to zero (Fig. 1D). These regressors were simultaneously fed to SPM with six dimensional movement parameters to isolate the neural correlates of reciprocal activation and cocontraction.

A parametric approach of fMRI data analysis (Haruno and Kawato 2006; Haruno et al. 2004) was preferred for identifying torque or cocontraction control-specific voxels over the conventional subtraction between torque and cocontraction conditions, since it also considers the amplitude of torque or cocontraction in the correlation analysis.

**RESULTS**

**Behavioral data.** Figure 2A shows the raw EMGs of a typical subject recorded in a mock MRI. EMGs of FCR, ECR, FCU, and ECU are displayed for one set of conditions. We can see that both flexors and extensors were more active in t2 and c2 than in t1 and c1. Furthermore, flexors and extensors increased activity only in either flexion or extension trials, respectively, but coactivated in cocontraction conditions. These observations indicate that the subjects accurately maintained activity of each muscle with negligible cocontraction in torque conditions. It is also noteworthy that FCR and ECR were not the only muscles involved in the task, but flexors (FCR and FCU) and extensors (ECR and ECU) exhibited synchronized activity in torque and cocontraction conditions, although a level of noise was seen in the FCU. Note that the synchronized activity in torque and cocontraction conditions, (FCR and FCU) and extensors (ECR and ECU) exhibited were not the only muscles involved in the task, but flexors (Humphrey and Reed 1983), for low-strength isometric contractions, as in the current study, the muscle moment arms remain approximately constant (Winter 1990). Therefore, the upper-arm and shoulder muscles were predicted to be similarly activated between the torque and cocontraction conditions. This was confirmed by the similar muscle activity across various conditions of the experiment (Fig. 2C).

Figure 2D shows the average torque and average total EMG (FCR + ECR) over blocks of a typical subject performing a series of condition sequences in the fMRI scanner: r, t1, c1, t2, and c2. The averaged torque (Fig. 2F) and cocontraction (Fig. 2F) over all of the subjects exhibited four important characteristics. First, the torque in the rest condition was not different from zero (P > 0.76). Second, the torques in t1 and t2 conditions were not different from the target values of 0.5 Nm (P = 0.30) and 1.0 Nm (P = 0.81), respectively, and did not change over time (Fig. 2D). Third, the torque in the two cocontraction conditions was almost zero. Fourth, EMG amplitude was similar in t1 and c1 conditions (i.e., their ratio was not significantly different from 1.0; P = 0.21) and also in t2 and c2 (P = 0.067), but it was substantially different between t1 and t2 and c1 and c2 (Fig. 2F; P < 0.002).

**Neural correlates of total muscle activity.** We asked the subjects to exert torque in the two opposite directions (flexion and extension). Therefore, even though the different conditions in the experiment required torque or cocontraction control, the same set of muscles was used as actuators in different combinations to achieve both. To investigate the neural correlates of these commonly activated muscles, a block-design correlation analysis of the fMRI data was carried out with a regressor parameterized by the total mean EMG in each block [Fig. 2D; P < 0.001, uncorrected; voxel cluster size >10 voxels included; SPM random effect model (Friston et al. 1995)].

Activity was observed in the left M1 (Fig. 3A). The average of the BOLD activity from the peak coordinates (−42, −18, 54) of all subjects (Fig. 3B) illustrates that this location in M1 was not activated at rest and was similarly active in t1 and c1 (P > 0.45, t-test), as well as in t2 and c2 (P > 0.33, t-test). Furthermore, the activity was very different between these two torque-cocontraction sets; i.e., the activity ratio during t2 and c2 was significantly different from the activity during t1 and c1 (P < 0.001): almost twice as large. In addition, at least 10 consecutive voxels around the peaks showed substantial similarity to the peak activity. This suggests that our setup was able to detect functionally correct motor areas.

**Brain regions selectively involved in reciprocal muscle control.** To analyze the fMRI activity specific to reciprocal activation, we conducted a linear regression of BOLD signal (P < 0.001, uncorrected; voxel cluster size >10; SPM2 random effect model) (Friston et al. 1995) with each subject’s torque regressor (Fig. 1D). Activity-correlated torque was detected in the boundary between the posterior part of the left PMd (peak voxel) and left M1 (Fig. 4A) in the anterior cerebellum (Fig. 4C). The MNI coordinates of the peak voxels were (−26, −8, 54) and (14, −46, −22), respectively.

Figure 4, B and D, summarizes the across-subject results, displaying the BOLD signal increase of the same peak voxels [(−26, −8, 54) and (14, −46, −22)], averaged over trials and subjects. BOLD signals were significantly larger in t2 than in t1 (P < 0.001 for the PMd in Fig. 4B, and P < 0.01 for the cerebellum in Fig. 4D), and the values of rest and cocontraction conditions were much smaller than in t1 (P < 0.05 for Fig. 4B, t-test). Additionally, Fig. 4, B and D, indicates that the BOLD difference between t1 and t2 was more prominent in the PMd than in the cerebellum. This may reflect functional differences between these two regions. When we made the statistical threshold lower (P < 0.005, uncorrected; voxel cluster size >10), correlation in the PMd and cerebellum became bilateral, and the SMA also appeared (Table 1).

Finally, Fig. 5 contrasts M1 peak activity correlated with total EMG (Fig. 3A) and PMd peak activity correlated with torque with a stringent statistical threshold (P < 0.0005,
uncorrected; voxel cluster size >10). The peak voxel with torque is located more anterior in the PMd, whereas the peak voxel with total EMG is located more posterior in the M1.

**Brain regions selectively involved in cocontraction control.**

To detect the neural correlates of cocontraction control, a regressor focusing on cocontraction periods was built using the mean EMG of the major extensor ECR and flexor FCR and by setting zero during the rest and reciprocal activation conditions (Fig. 1D and METHODS). BOLD activity that correlated with this cocontraction regressor ($P < 0.001$, uncorrected; voxel cluster size >10; SPM random effect model) was found on the left PMv (Fig. 6A), with the peak voxel at (−60, 6, 12) in the MNI coordinates. Correlation was also found in the left putamen and M1 but was less significant than that of the PMv (Table 1).

Figure 6B summarizes the across-subject results of the BOLD signal increase of the same peak voxel (−60, 6, 12) averaged over trials and subjects. BOLD signal was significantly ($P < 0.05$, t-test) larger in c2 than in c1, and the values in the torque conditions were significantly ($P < 0.01$ between c1 and t2, t-test) smaller than in the cocontraction conditions and not different between these two conditions ($P > 0.09$ between t1 and t2, t-test).

When the statistical threshold was lowered to $P < 0.005$, uncorrected; voxel cluster size >10, activity in the SMA became visible for both torque and cocontraction conditions, similar to M1 (Table 1). This activity was found to be posterior to the anterior commissure and confined in the SMA proper.

**DISCUSSION**

This study examined the neural substrates for the voluntary control of reciprocal activation and the cocontraction of muscles using fMRI with a MRI-compatible manipulandum and real-time feedback of EMG. Activity in the caudo-PMd and the anterior cerebellum was found to be correlated with torque, and the PMv activity was modulated by the cocontraction level. These findings reveal the key role of the premotor cortices in the voluntary control of reciprocal activation and the cocontraction of muscles.

We also found that the M1 and SMA were involved in both tasks (Table 1), consistent with previous studies (Dai et al. 2001; Dettmers et al. 1995; Pope et al. 2005; Vaillancourt et al. 2003). In addition, activity in the cerebellum and putamen was differentially correlated with torque and cocontraction level, respectively. This dissociation of the subcortical areas was consistent with the reported inability to control cocontraction in dystonia patients, which is believed to be caused by deficits in the putamen.

The PMd has been reported to be involved in force generation (Dai et al. 2001; Dettmers et al. 1995; Pope et al. 2005; Vaillancourt et al. 2003) and the spatial representation of task goals (Hallsband and Passingham 1985; Jackson and Husain 1996; Kurata and Hoffman 1994; Majdandzic et al. 2009; Pesaran et al. 2006). Our results agree with these previous findings. However, since we contrasted activity with the cocontraction condition, which specifies muscle activity but no direction, the PMd differences in our study might reflect some higher-level mapping between motor output and direction (Hoshi and Tanji 2007). However, this is improbable, because the activity in the PMd was correlated with the amplitude of torque, which would not be expected in higher-level mechanisms.

On the other hand, the PMv is known to be active, specifically during precision grip tasks (Davare et al. 2006), which are expected to require cocontraction control for precise interaction with external objects (Majdandzic et al. 2009). A fMRI study of reaching movements with a joystick (Seidler et al. 2004) reported that the PMv is one of the areas that showed a negative correlation to target size, whereas activity in the PMd increased with target size. This observation could be explained by the involvement of the PMv in control of impedance [which is directly related to cocontraction and known to be negatively correlated with target size in goal-directed reaching (Osu et al. 2004; Selen et al. 2006)].

One may expect that differences in neural activity between the torque and cocontraction conditions originated from differences in arm-muscle activation or tactile feedback in the two conditions. We confirmed that external arm muscles do not...
contribute to the results (Fig. 2C) but are unable to confirm the same for inner arm muscles, which are difficult to measure in our setup. To check for possible tactile differences, we conducted a control experiment of passive wrist movement with the same fMRI-compatible device (Fig. 1A), where the brain received tactile feedback information but did not generate any motor commands. Under these conditions, brain activation was observed in the somatosensory area, the M1, and the anterior cerebellum but not in the premotor cortex. Conversely, we did not find any activity in the somatosensory area during regression with torque and during comparison of the torque and cocontraction conditions. These results suggest that tactile feedback was not the cause of the observed results.

What makes control of cocontraction distinct from reciprocal activation? Cocontraction in real life is usually accompanied by force control. This is evident, for example, in the precision grip of an egg, where a precise cocontraction level is used to enable precision control of the grip force. We tried to recreate a similar environment in our experiment, where in the cocontraction conditions, the subjects also had to maintain the torque bar at zero. It could be argued that cocontraction control is inherently more difficult than force control, and the reason behind the PMv activation is related to this. However, it is important to note that this “difficulty” is due to differences in the control requirements that are inherent to the cocontraction task, but not just due to differences in the involved muscles or their activation levels (which were equalized between the conditions). In this respect, the findings of this paper clarify that the antagonist muscles require a different or additional brain region when they are controlled simultaneously.

The table below summarizes the activity correlated with torque and cocontraction:

<table>
<thead>
<tr>
<th>Structure</th>
<th>Torque</th>
<th>Cocontraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>L PMd</td>
<td>(−26, −8, 54)</td>
<td></td>
</tr>
<tr>
<td>R PMd</td>
<td>(28, −4, 48)</td>
<td>(P &lt; 0.005)</td>
</tr>
<tr>
<td>L PMv</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R PMv</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L M1</td>
<td>(−38, −16, 62)</td>
<td>(−24, −20, 62)</td>
</tr>
<tr>
<td>R M1</td>
<td>(−28, −48, −32)</td>
<td>(P &lt; 0.005)</td>
</tr>
<tr>
<td>L CB</td>
<td>(14, −46, −22)</td>
<td></td>
</tr>
<tr>
<td>R CB</td>
<td>(−4, 0, 52)</td>
<td>(P &lt; 0.005)</td>
</tr>
<tr>
<td>SMA</td>
<td>(−2, −4, 62)</td>
<td>(P &lt; 0.005)</td>
</tr>
<tr>
<td>L Putamen</td>
<td>(−22, −2, −4)</td>
<td></td>
</tr>
</tbody>
</table>

The statistical threshold adopted was P < 0.001, uncorrected for multiple comparison, and cluster size >10, otherwise explicitly stated as P < 0.005. L, left; R, right; PMd, dorsal premotor cortex; PMv, ventral premotor cortex; M1, primary motor cortex; CB, cerebellum; and SMA, supplementary motor area.
of which controls a few similarly acting muscles (Umilta et al. 2007), whereas in reciprocal activation, the PMd may only control the smaller M1 neuronal pools, which project to a few target muscles (Fetz and Cheney 1980; Jackson et al. 2003; Rathelot and Strick 2006). Alternatively, the PMd and PMv may also regulate different subpopulations of M1 neurons in the current task, as reported previously for wrist-arm movements (Strick and Preston 1979). However, the presence of numerous intermingled neural circuits in M1 (Fetz and Cheney 1980; Graziano 2006; Jackson et al. 2003; Rathelot and Strick 2006) and limited spatial resolution of fMRI make it difficult to precisely identify the functional representation in M1 at present.

In summary, the results of our experiment indicate that the differential centers of the premotor cortex are related to the control of reciprocal activation and cocontraction. This suggests that distinct processes may be used by the CNS to control force and impedance, consistent with the specific inability to control cocontraction observed in dystonia patients (Berardelli et al. 1998). These findings provide a cohesive explanation for previous reports of premotor activation, as was detailed above. Precise information about the regulation of reciprocal activation and cocontraction performed by the premotor cortex could be gained through electrical recording in nonhuman primates and by performing the experiment analyzed in this paper with human patients.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: M.H. conception and design of research; M.H. and G.G. performed experiments; M.H. and G.G. analyzed data; M.H., G.G., E.B., and M.K. interpreted results of experiments; M.H. prepared figures; M.H. drafted manuscript; M.H., G.G., E.B., and M.K. edited and revised manuscript; M.H., G.G., E.B., and M.K. approved final version of manuscript.