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Functional organization of the primary motor cortex characterized by event-related fMRI during movement preparation and execution

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Abstract

Neuronal recording and neuroimaging studies have shown that the primary motor area (M1) not only participates in motor execution, but is also engaged during movement preparation. The purpose of the present study was to map the distribution of the preparation- and execution-related activity within the contralateral M1 using functional magnetic resonance imaging. Eleven subjects performed a delayed sequential finger movement task, in which a CUE signal indicated a movement sequence in advance of an imperative GO signal. The hemodynamic response related to the CUE and GO signals decreased in a linear fashion across the central sulcus, with activity greater along the lateral extent compared to the medial extent. This decrease was especially evident in the epoch following the CUE. Our data reveal a pattern of functional organization within M1 related to the preparation and execution of movement sequences.

Keywords: Primary motor cortex; Supplementary motor area; Preparation; Execution; Sequential movement; Functional magnetic resonance imaging; Event-related procedure

Neuronal recording in non-human primates and neuroimaging studies in the humans suggest a hierarchical organization across the cortical areas involved in motor control. The primary motor area (M1) is thought to constitute one of the lower levels of the hierarchy, primarily involved in the initiation and execution of movements that follows processing in higher cortical areas related to response selection and preparation. This simple model has undergone refinement and revision over the years [18]. Preparation-related activity can be observed in motor neurons within M1 of the monkey [1,5], although the majority of M1 neurons are not influenced by the behavioral context [15]. Moreover, some functional neuroimaging studies in humans have indicated that M1 participates in motor preparation as well as execution [6,11,16], although other studies have failed to detect preparation-related activity in M1 [13,19].

Using event-related functional magnetic resonance imaging (fMRI), we have recently reported that the hemodynamic response in M1 increases, albeit weakly, during an extended preparatory interval prior to the production of sequential finger movements [4]. To extend this finding, the present study was designed, to replicate the involvement of M1 in sequence preparation and to map hemodynamic changes over the course of movement preparation and execution. We used event-related fMRI to explore M1 while subjects performed a delayed sequential movement task.

Eleven right-handed volunteers (six male and five female, aged 20–30) participated in the experiment. None reported significant neurological or psychiatric disorders. Informed written consent was obtained from all subjects and approved by the Institutional Review Board at the Institute of Psychology, Chinese Academy of Sciences.

The methods were similar to those reported in our previous study [4]. During scanning, subjects performed a delayed sequential finger movement task with the right hand. The stimuli were presented on a rear-projection screen. Initially, a row of four vertical gray rectangle boxes was illuminated (Fig. 1a). The boxes, from left to

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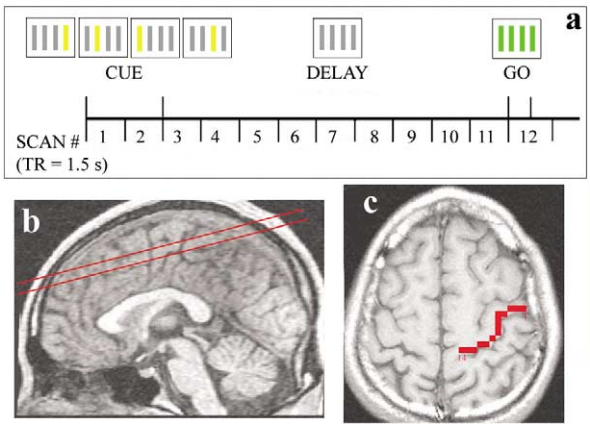

Fig. 1. (a) Illustration of the task. The stimulus sequence was cued by the successive change every 750 ms of the four boxes from gray to yellow. After 13.5 s, all of the boxes turned green, signaling movement initiation. Scans were obtained every 1.5 s. (b) Position of the two oblique slices providing coverage of the hand area with M1. (c) Composite voxels numbered in the anterior lip of the left central sulcus from the lateral to medial.

right, were mapped to responses associated with the index, middle, ring, and little fingers respectively. A trial began when one of the boxes changed from gray to yellow for 750 ms. Immediately after this interval, another box turned yellow and so on until all four boxes had changed color. The order of the color changes was randomized from trial to trial and served as the CUE signal, indicating the required sequence of responses for that trial. After a delay of 13.5 s, all four boxes simultaneously turned green for 750 ms. This change served as the GO signal. The subjects were required to produce the prescribed sequence with their right hand as quickly as possible. The onset of the next CUE epoch began 16.5 s after the previous GO signal. Thus, each trial lasted 33 s and each subject completed 11 trials.

Subjects were instructed to prepare the response sequence during the CUE epoch and to keep their fingers stationary before the GO signal appeared. All of the subjects were given extensive practice outside the scanner. During this practice session, the experimenter monitored performance to ensure that the participants were not generating any visible movements prior to the onset of the GO signal. They were also debriefed after the scanning session and none of the subjects reported having made movements during the CUE epoch.

All MR images were collected in a 1.5 T whole-body scanner (GE, Echo Speed). From the sagittal localizer image, two oblique axial slices were chosen at approximately 45–60 mm above the anterior commissure, with an angle of 15° to the AC–PC plane (Fig. 1b). These slices were selected to cover the hand representation in M1 [8,21]. T2* weighted images were collected with a gradient echo EPI (echo planner imaging) pulse sequence sensitive to blood oxygenation level dependent contrast (TR = 1.5 s, TE = 60 ms, FOV = 24 cm, flip angle = 90°, in-plane resolution = 3.75 mm, thickness = 5 mm, gap = 2.5 mm) For each of the 11 trials, 22 functional MR images per slice were obtained (total block duration = 363 s). A total of 242 functional scans were obtained for each slice, with four scans obtained prior to the start of the first trial and four scans obtained after the end of the last trial.

Two slices of T1-weighted anatomic images were collected in the same position with spin echo pulse sequence (TR = 440 ms and TE = 11 ms). Finally, a fast SPGR sequence (TR = 11.1 ms, TE = 4.2 ms, flip angle = 45°, FOV = 22, NEX = 2) was used to scan the whole brain for structural 3D reconstruction and spatial normalization.

The imaging data were analyzed with AFNI software [3]. The initial and final four scans were not included in the event-related analyses. After head motion correction, the image data were spatially normalized [17] and re-sampled at 3 mm cubed. This resulted in 5–7 (depending on the angle of initial imaging) horizontal slices for each subject. To correct for anatomical differences between subjects, the data were spatially smoothed, using a conservative smoothing kernel (full width at half maximum = 5 mm). The middle 4–5 spatially normalized and re-sampled horizontal slices were selected for further analysis. These covered the central sulcus (CS) from the most anterior-lateral to the most posterior-medial part. To minimize the potential contribution of premotor cortex [10], M1 was defined anatomically as a single line of voxels in the anterior lip of the left CS (Fig. 1c). A multiple linear regression procedure (by Douglas Ward in version 2.6 of AFNI) [3] was used to identify activated voxels in M1, with the procedure performed separately for the analysis time-locked to the CUE and GO signals.

Across the 11 participants, 474 voxels were localized to M1. Of these 474 voxels, 34 showed a significant response during the interval between CUE onset and the GO signal. 202 voxels were activated after the GO signal ($F > 6.360$,

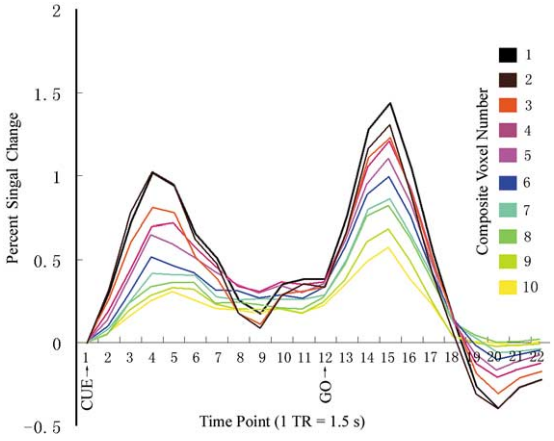

Fig. 2. Percent change from baseline in the hemodynamic response of each composite voxel in M1 as a function of scan number. Voxels are numbered 1–10 from anterior-lateral to posterior-medial and scans were obtained every 1.5 s. Note that the first CUE appeared at Scan 1 and the GO signal appeared at Scan 12.

$P < 1.0 \times 10^{-8}$, uncorrected). Significantly more voxels within M1 responded to the GO signal compared to the CUE signal ($\chi^2 = 7316$, $P < 0.0001$). When a less strict level of significance was adopted ($P < 0.05$), this difference persisted, although the absolute number of activated voxels increased dramatically (preparation/execution: 214/401).

We next examined the functional organization of CUE- and GO-related activation within M1. For this analysis, the anatomically defined voxels in each horizontal slice were numbered sequentially in the anterior-lateral to posterior-medial direction. The activation across the horizontal slices was assumed to be similar; thus, the activation of all selected slices was pooled to form a single line of composite voxels. The number of composite voxels ranged from ten to 14 for different subjects, reflecting differences between individuals in the length of the CS. The analysis was restricted to voxels 1–10 since these were identified in all individuals. By restricting the analysis to voxels adjacent to the central sulcus and by using a conservative spatial smoothing procedure, it is unlikely that the activation functions would be contaminated by activation in premotor cortex.

The time course of activation for each of the remaining composite voxels was then averaged across trials and normalized to give a function based on the percent change in activation. As shown in Fig. 2, there is a near-linear decrease in the magnitudes of both CUE- and GO-related activities, moving from the anterior-lateral (n1) to the posterior-medial (n10) aspect of M1.

To quantitatively test the difference of the trends of CUE- and GO-related activity, a ratio was calculated based on the peak of the activation functions to these two events. The peak value of CUE-related activity was defined as the average of the third, fourth, and fifth scan number (4.5–7.5 s after the CUE) [12]. Similarly, the peak value of GO-related response was defined as the average of the 14th, 15th, and 16th scan number (4.5–7.5 s after the GO). Following Johnson et al. [10], these ratios were then used in a regression analysis to determine beta coefficients for the composite voxels, providing estimates of the distribution of CUE- and GO-related activity in contralateral M1. A one-sample *t*-test was used to evaluate the null hypothesis that the beta coefficients calculated across the eleven subjects were equal to zero, indicating that the organization of CUE- and GO-related activation was equivalent. The mean coefficient value across individuals is significantly less than zero (mean beta coefficient $= -0.50$, SD $= 0.44$, $t = -3.765$, $P = 0.004$, two-tailed). This decreasing trend indicates that CUE-related activity decreases more quickly than GO-related activity across the anterior-lateral to posterior medial extent of M1.

These results provide additional evidence for a role of M1 in motor preparation. Many voxels in M1 were activated during the epoch in which the participants were instructed to prepare a series of finger movements. This is consistent with previous neuronal recording studies in monkeys [1,10,15,20] and neuroimaging studies in humans [2,4,6,11,16]. It should be noted that Lee et al. [13] and Toni et al. [19] failed to detect preparation-related activity in the M1. We suspect that their null results may reflect the fact that they used a relatively simple task compared to the delayed sequential task used in the present study (see also Ref. [4]). Further work is needed to test if the requirement for sequential movements is the critical factor associated with activation of subregions of M1 during movement preparation.

A number of neurophysiological studies have investigated the functional organization of M1. For example, following a stimulus indicating the direction for a forthcoming movement, the activity was lower in the more caudal regions of M1 in the monkey [10,20]. Our results reveal a similar pattern of organization within human M1. CUE-related preparatory activity was greatest in the anterior-lateral region, although this area also showed stronger activation during the sequence execution phase. Within the posterior-medial region, activation was minimal during the preparatory period and high during the execution period. Kawashima et al. [11], using PET, described a somewhat different pattern of preparation and movement related activity in M1. Using a reaching task, they reported two distinct regions of activation within M1. One was related to preparation, localized in non-contiguous lateral and medial zones. The other was engaged during the execution phase and was localized in the middle of the preparation-related areas. The difference between our results and those of Kawashima et al. remains to be determined but may result from differences in the behavioral tasks and imaging modalities.

The functional role of M1 activation during movement preparation remains unclear. This activation could reflect processing related to the translation of an abstract sequence representation, defined as a series of spatial goals, into a specific sequence of finger movements [7]. As such, the CUE -related activity in M1 would constitute a form of motor imagery, as subjects rehearse a planned action [9,14]. Alternatively, the preparation of the response sequence may occur in upstream areas of the motor hierarchy, and this activation might automatically cascade onto motor cortex, similar to what is assumed to occur when actions are selected and executed without delay.

Future studies should allow more precise analysis of the role of motor cortex in movement preparation. First, the use of non-ferrous electromyogram (EMG) recording systems will be useful for evaluating the extent of level muscle activation during movement preparation. We expect that it is not existent, at least with the lengthy cue periods used in the current study, but EMG recordings would allow a more careful determination of whether planning processes induce subthreshold muscular activation. Second, and more important, by collecting larger data sets and/or using higher-field magnets, it should be possible to map out motor cortex on an individual basis rather than rely on methods that require spatial normalization and averaging procedures across individuals. This approach can be used to further explore the

functional organization of motor cortex and determine if the degree of inter-individual variation in this organization.

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