Both sides of human cerebellum involved in preparation and execution of sequential movements

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Using an event-related fMRI procedure, we investigated the role of the human cerebellum in sequential finger movements. Subjects performed a delayed sequential finger movement task in which an instructive cue preceded the imperative signal by 16.5 s. Bilateral activation was observed in the cerebellum following both the cue and imperative signals. The activated regions overlapped within the cerebellum, extending across intermediate and lateral regions corresponding to lobules HV-HVII. In contrast, activation in primary motor cortex was primarily restricted to the execution phase and most prominent in the contralateral hemisphere. These results indicate that the cerebellum is bilaterally recruited for the preparation and execution of sequential movements. *NeuroReport* 11:1–5 © 2000 Lippincott Williams & Wilkins.

Key words: Cerebellum; Event-related procedure; Functional magnetic resonance imaging; Sequential movements

INTRODUCTION

Voluntary movements are generally decomposed into two basic processes, motor preparation (planning and programming) and motor execution. Anatomical, physiological, and neuropsychological studies point to a role of the cerebellum in both aspects of motor control. Within this structure, it has been suggested that the lateral zone of cerebellum is primarily involved in motor preparation while the intermediate zone is closely related to ongoing motor control [1].

The neural substrates of voluntary movements in humans have been examined with non-invasive brain mapping techniques such as PET and fMRI. This work has helped identify a distributed network of structures involved in sequential movements, including the cerebellum [2]. However, this literature has revealed an inconsistency in that, while most authors report only ipsilateral cerebellar activation during voluntary movements [3–5], others have observed contralateral activation [6]. In addition, most imaging studies have relied on block design procedures [3–7], in which subjects are asked to do the same task continually and activation is measured across an extended period. With this procedure, one is neither able to detect metabolic changes associated with a single trial, nor is it possible to separate activation associated with the preparation and execution of movements.

In contrast to the block design procedure, event-related fMRI can measure the hemodynamic response on a trial by trial basis [8–10]. By combining event-related fMRI with a delayed response motor task [11], one should be able to temporally separate the hemodynamic events, and presumably the neural correlates associated with motor preparation and execution. We apply this logic in the present study to explore the role of the human cerebellum in voluntary movement. A sequential movement task was used in which an advance cue indicated the target sequence to be performed following an imperative response signal.

MATERIALS AND METHODS

Subjects: Ten healthy volunteers (five males and five females, range 18–29 years, mean 23 years) without any history of psychiatric and neurological problems participated in the study. All were right handed as determined by a Chinese version of a standardized inventory [12].

MRI equipment and scan pattern: A 1.5 T GE Signa Horizon magnetic resonance imaging system was used. During the experiment, subjects lay supine with their hands comfortably positioned at their side. Conventional anatomic images were collected with T1-weighted spin echo sequence (TR = 440 ms, TE = 11 ms, FOV = 22 × 22 cm, slice thickness = 5 mm, skip = 2.5 mm, matrix = 256 × 256, NEX = 2). Functional images were acquired with gradient-

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echo echo planar imaging (TR = 1500 ms, TE = 60 ms, FOV = 22 × 22 cm, slice thickness = 5 mm, skip = 2.5 mm, matrix = 256 × 256, NEX = 1). Two slices were selected for the cerebellar analysis, parallel to the anterior commissure and the superior cerebellar peduncle. Considering the important role of primary motor cortex (M1) in movement initiation and movement control, we obtained data from two additional axial slices that spanned M1 in four of the subjects.

Delayed sequential finger movement task: Stimulus signals were generated by a personal computer. An LCD projector was used to present the stimuli on a screen visible from inside the scanner. Initially, a row of four vertical white rectangle boxes was presented on a black background. The subjects were instructed that illumination of the boxes would indicate the target response. A compatible stimulus–response mapping was used in which, from left to right, the boxes corresponded to movements with index, middle, ring, and little fingers respectively. At the start of each trial, the color of one of the four boxes changed to yellow. After a delay of 200 ms, another box turned yellow. This procedure was repeated until all four boxes had changed color. The order of the color changes was randomized from trial to trial and served as the cue signals, indicating the required sequence of responses for that trial. Subjects were instructed to prepare the sequence in advance of an imperative go signal. After a delay of 16.5 s, the four boxes simultaneously turned green for 200 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 for 33 s, divided into two stages. The motor preparation stage began with the onset of the cue signal and the motor execution stage began with the onset of the go signal. Twenty-two fMR images per slice were collected during the 33 s trial. There were 11 trials in each 363 s run, providing a total of 242 functional MR images per slice.

Data analysis: Two software packages, WCM AFNI (analysis of functional neuro-images) [13] and SPSS (statistical package for the social science) were used for image display and data analysis. fMR images were co-registered to remove head-motion artifacts and normalized according to the standard coordination defined by Talairach and Tournoux atlas [14]. The images were then re-sampled and smoothed with an isotropic Gaussian kernel (FWHM = 5 mm) to enhance the signal-to-noise ratio. The voxel size for this procedure was 3 × 3 × 3 mm.

The signal change within a voxel was calculated with a deconvolution procedure and multiple linear regression. Voxels for which the change in the hemodynamic response produced a F ratio >2.35 ($p<0.001$), were defined as activation points. To elevate the reliability further, regions of interest (ROIs) were defined as regions in which there were at least six adjoining activated points [15]. The region of activation was then superimposed on the anatomic image to produce individual and group mean activation maps (Fig. 1).

The signal change in each voxel within the ROI was averaged according to the onset of the stimulus signals (cue and go). These changes provide a measure of the fractional signal intensity change over time (transformation computation, see legend of Fig. 2). Finally, these data were averaged over voxels within each ROI and then averaged over subjects (Fig. 2).

RESULTS

Location and volume of activation during performance of delayed sequential finger movements: The brain activation maps projected on to an anatomic image are shown in Fig. 1 (a and b show the activation during preparation and execution,respectively, in one subject; c shows the activation in all subjects during the 33 s trial period). For all 10 subjects, both cerebellar hemispheres were significantly activated when planning and producing sequential finger movements with the right hand. Regions activated following the cue signal essentially overlapped with those activated following the go signal (Fig. 1a,b). We did not observe a functional dissociation between areas associated with motor preparation and motor execution in the cerebellum. The area of activation extended across the intermediate and lateral zones of the cerebellum. Considered in terms of the anterior–posterior axis, activation was observed in lobules HV–HVII. Based on the Talairach and Tournoux atlas, the center of activation within the ipsilateral, right cerebellar cortex was at coordinates (x,y,z) -28.41 ± 5.31, 56.18 ± 3.26, -19.15 ± 1.95 (mean ± s.d., $n = 10$). The corresponding values for the left, contralateral cerebellar cortex was 30.27 ± 4.10, 57.35 ± 4.11, -20.47 ± 2.28 ($n = 10$). Thus, the centers of activation within the two halves of the cerebellum are roughly symmetrical. The mean volumes of the ipsilateral and contralateral activated areas are $10.66 \pm 2.58\,cm^3$ ($n = 10$), $8.10 \pm 2.88\ cm^3$ ($n = 10$), suggesting a trend for greater activation in the ipsilateral side ($p = 0.06$). Note that unlike M1, the primary direct and indirect projections of the cerebellum influence the ipsilateral side of the body.

Bilateral activation was also observed in M1 for delayed sequential finger movements with the right hand. In contrast to that observed for the cerebellum, the volume of the activated area in contralateral M1 was much larger than that in ipsilateral M1. Indeed, no activation was detected in the ipsilateral M1 for one of the four subjects. The mean volume of the activated area in contralateral M1 was $2.73 \pm 0.52\,cm^3$ ($n = 4$); for ipsilateral M1, the value falls to $0.93 \pm 0.33\,cm^3$ ($n = 3$).

Time course of signal intensity change during performance of delayed sequential finger movements: Figure 2 shows the time course of the fractional signal intensity change for each activated brain area while subjects performed the delayed sequential finger movement task. The signal reached its peak intensity ~6 s after each stimulus event (cue or go). The activity in the contralateral M1 was significantly stronger during the execution stage than during preparation stage ($p < 0.05$), although this region was active following either the cue or the go signals. Activation within ipsilateral MI was weak, but significant, and restricted to the execution epoch.

In contrast to M1, the activation functions for both halves of the cerebellum were very similar. Salient peaks

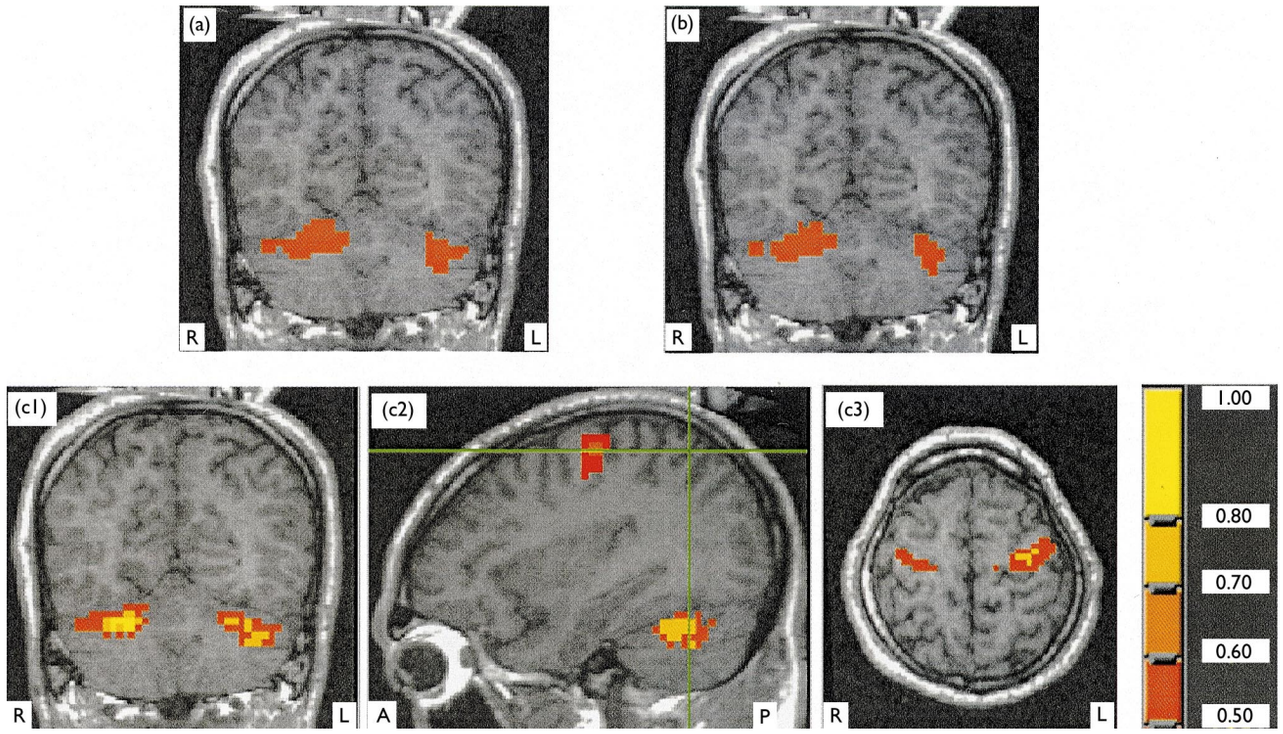

Fig. 1. The event-related fMRI activation maps during performance of the delayed sequential finger movement task. (**a**,**b**) fMRI activation maps of the cerebellum from one subject during the preparation and execution stages respectively; (**c1**–**c3**) event-related fMRI activation maps averaged over all subjects during the preparation and execution stages (bilateral cerebellum, $n=10$; left M1, $n=4$; right M1, $n=3$). The color bar on the right side represents activation probability. C1, C2 and C3 are coronal, sagittal and axial images respectively. The two green lines on the sagittal image (C2) indicate the location of the coronal and axial images respectively. R: right, L: left, A: anterior, P: posterior.

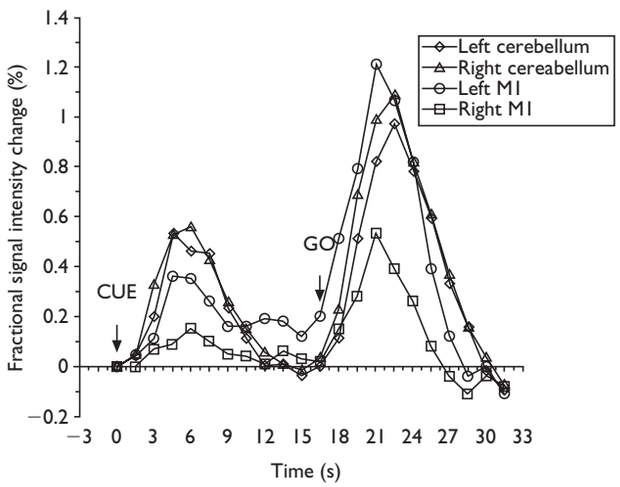

Fig. 2. Fractional signal intensity change within each activated brain area during performance of delayed sequential finger movements. The mean curve of fractional signal intensity change for all subjects within each activated brain area (bilateral cerebellum, $n=10$; left M1, $n=4$; right M1, $n=3$). Fractional signal intensity change $=(x-x_0)/x_0 \times 100\%$, corresponding to the percentage change in signal intensity for each individual point (x) relative to the initial signal level (x_0).

can be seen following both the cue and go signals and the magnitude of these peaks is similar in both epochs. Thus, the cerebellum was bilaterally activated during motor preparation and motor execution. The time of peak activation within the cerebellum during the motor execution phase occurred ~1.5 s later than in M1.

DISCUSSION

Event-related fMRI is new functional imaging technique. While some of the initial reports with this method have examined the neural mechanisms of human voluntary movements, these studies have focused on the cerebral cortex [16,17]. In the current study, we used event-related fMRI technique to explore the role of the human cerebellum in the planning and production of sequential finger movements, comparing activation within this subcortical structure to that observed in primary motor cortex. Based on models of motor control, we had hypothesized that the lateral zone of cerebellum would be primarily involved in motor preparation and the intermediate zone would be primarily involved in motor execution. Similarly, we expected that M1 would exhibit a stronger signal during motor execution. We also expected that the activation for each neural regions would be lateralized, strongest within

the ipsilateral hemisphere for the cerebellum and contralateral hemisphere for M1.

Contrary to our expectations, the results showed that both cerebellar hemispheres were significantly activated during motor preparation and execution. Moreover, the extent of activation was similar during the two epochs (A and B in Fig. 1). Although we did not observe a functional dissociation of the lateral and more medial regions of the cerebellum during movement preparation and execution, our results do provide strong evidence of bilateral involvement of the cerebellum during both phases.

In accord with our predictions, M1 was weakly activated during motor preparation and significantly activated during motor execution. This activation was much stronger in the contralateral M1 (Fig. 2). These results are consistent with the hypothesis that M1 is primarily involved in motor execution, even when the required action involves a sequence of movements. However, we did observe some activation, albeit weak, within contralateral M1 during motor preparation [18]. Single-unit studies have demonstrated that firing within motor cortex neurons is predictive of the forthcoming movement during a delayed, instruction period [19]. The intensity of this activity during movement preparation is considerably lower than during movement execution, consistent with our results. It remains unclear whether the relatively low level of activity in M1, observed in single-cell studies or with fMRI in the current study, is an essential part of movement preparation or, alternatively, reflects priming from upstream motor areas that play a primary role in motor planning. Such areas may include the cerebellum.

Using event-related fMRI, we have provided further evidence implicating the cerebellum in movement preparation. Precuing techniques have not been widely used in imaging studies because the block designs used in PET and fMRI involve scanning epochs that include both preparation and execution (but see [20]). In correspondence with our results, neurophysiological studies with primates have found that cellular activity within the cerebellum change in advance of movement onset, consistent with a role in motor preparation [21]. However, these studies have not included delay periods making it difficult to separate movement planning and movement initiation.

The bilateral involvement of the cerebellum in both motor preparation and execution was unexpected given that most previous imaging studies have revealed only ipsilateral activation [3–5]. We can consider four possible accounts for this discrepancy. First, the event-related fMRI procedure used in this study may be more sensitive than the block design procedure. It may be that a block design procedure is not sufficiently sensitive to detect activation in the contralateral cerebellum (but see [7]). However, this hypothesis does not seem to mesh with the fact that the activation within both halves of the cerebellum was similar in the current study. A threshold problem would have predicted greater activation in the ipsilateral cerebellum.

Second, bilateral activation may require relatively complex movements. In many of the studies showing only ipsilateral cerebellar activation, the movements tended to be simpler, following a fixed pattern from trial to trial. We required a sequence of movements that changed on each trial. Perhaps the bilateral activation results from the additional coordination requirements involved in producing relatively unpracticed sequences. Studies with both human patients [22–24] and non-human primates [25] indicate that the acquisition and performance of movement sequences can be seriously impaired following cerebellar lesions. Third, we also required the subjects to produce the sequences as rapidly as possible. Under such conditions, the demands for precise timing of the sequential movements are likely to be quite high. The cerebellum has been hypothesized to play an important role in motor timing [26] and this control may engage bilateral regions.

Fourth, related to the last two points, the working memory and attentional demands are likely to be higher in our study compared to previous studies given the random variation in the sequences. The cerebellum has been hypothesized to contribute to these cognitive operations [27]. At present, we are unable to determine if the bilateral activity observed in the cerebellum during the CUE epoch is related to specific operations associated with motor sequence planning or reflect more generic operations associated with anticipating a forthcoming action.

CONCLUSION

We found that when subjects performed a delayed sequential finger movement task with their dominant hand, the cerebellum was bilaterally activated following both the instructive cue and the imperative go signals. This indicates that the cerebellum is bilaterally recruited for the preparation and execution of sequential movements.

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