Human Cerebellum Plays an Important Role in Memory-Timed Finger Movement: An fMRI Study

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1Institute of Development, Aging and Cancer, Tohoku University; 2Aoba Brain Imaging Research Center, Telecommunication Advancement Organization; 3Tohoku University Graduate School of Medicine; 4Division of Radiology, Tohoku University Hospital; and 5The Japan Society for the Promotion of Science, Sendai 980-8575, Japan

Kawashima, Ryuta, Jiro Okuda, Atsushi Umetsu, Motoaki Sugiiura, Kentaro Inoue, Kyoko Suzuki, Michio Tabuchi, Takashi Tsukiura, Singh L. Narayan, Tatsuo Nagasaka, Isao Yanagawa, Toshikatsu Fujii, Shoki Takahashi, Hiroshi Fukuda, and Atsushi Yamadori. Human cerebellum plays an important role in memory-timed finger movement: an fMRI study. J. Neurophysiol. 83: 1079–1087, 2000. The purpose of this study was to determine, by using functional magnetic resonance imaging, the areas of the brain activated during a memory-timed finger movement task and compare these with those activated during a visually cued movement task. Because it is likely that subjects engage in subvocalization associated with chronometric counting to achieve accurate timing during memory-timed movements, the authors sought to determine the areas of the brain activated during a silent articulation task in which the subjects were instructed to reproduce the same timing as for the memory-timed movement task without any lip movements or vocalization. The memory-timed finger movement task induced activation of the anterior lobe of the cerebellum (lobules IV and V) bilaterally, the contralateral primary motor area, the supplementary motor area (SMA), the premotor area (PMA), the prefrontal cortex, and the posterior parietal cortex bilaterally. The corresponding areas in the SMA and left prefrontal cortex were specifically activated during the silent articulation task compared with the resting condition. The anterior lobe of the cerebellum on both sides was also activated during the silent articulation task compared with the resting condition, but these activities did not reach statistical significance (P < 0.05 corrected). In addition, the anterior cerebellum on both sides showed significant activation during the memory-timed movement task when compared with the visually cued finger movement task. The visually cued finger movement task specifically activated the ipsilateral PMA and the intraparietal cortex bilaterally. The results indicate that the anterior lobe of the cerebellum of both sides, the SMA, and the left prefrontal cortex were probably involved in the generation of accurate timing, functioning as a clock within the CNS, and that the dorsal visual pathway may be involved in the generation of visually cued movements.

INTRODUCTION

The generation of rhythmic self-paced movements has recently been the subject of several neuroimaging studies. To perform rhythmic self-paced movements, the capacity to time the movements precisely is important. However, the neural substrates for the explicit timing of movements remain unclear. Some human neuroimaging studies have investigated this subject by comparing brain activity during memory-timed movements with that during externally triggered movements (Larsen et al. 1996; Remy et al. 1994). However, these studies focused on the activation of cortical primary and nonprimary motor areas, but not of other brain areas involved in the control of voluntary movement. Recently, Rao et al. (1997), by using whole brain functional magnetic resonance imaging (fMRI), compared the brain areas activated during memory-timed finger tapping and during auditorily cued movements. They reported that the supplementary motor area (SMA), the putamen, the thalamus, and the inferior frontal cortex were specifically involved in the memory-timed movements. Nevertheless, they used a series of tones separated by a constant interval as a control condition for the auditorily cued movements. It is likely that subjects predict the timing of the movements when sensory cues are presented at consistent intervals. Thus, the brain areas involved in the timing of movements are also probably activated in this condition.

It has been argued that the cerebellum is preferentially involved in controlling complex movements, multijoint movements, and movements that require visuomotor coordination or learned automatic movements (Stein and Glikstein 1992; Thach et al. 1992), although one of the important functional roles of the cerebellum is the control of motor timing (Ivry et al. 1988; see also Thach 1996). A very robust finding reported by Ivry and colleagues (1998), based on a series of experiments in patients and normal control subjects, is that the lateral cerebellum participates in temporal processing (Ivry et al. 1988; Ivry and Keele 1989 Keele et al. 1985). The results of the functional imaging studies using single-photon emission computed tomography (SPECT) indicate the involvement of the lateral cerebellum in silent mental counting, which requires chronometric counting (Decety et al. 1990; Ryding et al. 1993). In recent neuroimaging studies, activation of the anterior lobe of the cerebellum of both sides was noted, when subjects estimated time differences by comparing a test time with a standard interval (Jueptner et al. 1995), and when subjects reproduced rhythms of increasing complexity (Penhune et al. 1998), indicating the involvement of the cerebellum in motor timing and perceptual timing, respectively.
In the present study, we investigated the question of whether the human cerebellum is involved in memory-timed finger movements. Therefore, we measured regional cerebral hemodynamic responses using whole brain fMRI during a memory-timed finger movement task and compared these with those activated during visually cued movements in which the visual cues were presented at random intervals. In addition, because it is likely that the subjects engage in subvocalization associated with chronometric counting to achieve accurate timing during memory-timed movements, we also measured brain activity during a silent articulation task, in which the subjects were asked to reproduce the same timing as during memory-timed movement without any lip movements or vocalization.

METHODS

Subjects

Eight right-handed male volunteers (aged 19–27 yr) participated in the present study. Written informed consent was obtained from each subject on forms approved by the Tohoku University and the Declaration of Helsinki (1975). All the subjects were healthy, with no history of psychiatric or neurological illness, and none of them were taking any medication. For determination of brain anatomy, MRI of the brain was performed on a separate occasion on each subject using a spoiled gradient-echo sequence (echo time [TE] = 12 ms, recovery time [TR] = 50 ms, flip angle [FA] = 45°) with a 0.5-T scanner (Yokogawa Medical, Tokyo) consisting of 96 slices with a voxel size of 1 × 1 × 1.5 mm.

Task procedure

All the subjects performed the following four tasks: 1) memory-timed finger movement (task A), 2) visually cued finger movement (task B), 3) silent articulation (task C), and 4) resting as baseline control (task D). A fixation point on which the subjects were instructed to fix their gaze was continually displayed at the center of the visual field during the performance of each task. The subjects lay supine in the MRI scanner and focused on the eye fixation point through a mirror. In the memory-timed finger movement task, the subjects were instructed to click a mouse with the index finger of the right hand once every 1,500 ms (2/3 Hz) without any preceding cue. In the visually cued finger movements tasks, the brightness of the eye fixation point was changed alternately for random durations (mean ± SD: 1,500 ms; range 500–2,500 ms), and the subjects were instructed to click the mouse when they detected a change in the brightness level of the eye fixation point. All the subjects detected changes in brightness during fMRI measurements. During the silent articulation task, the subjects were instructed to say “pi” silently once every 1,500 ms without any preceding cue. They were instructed to avoid moving their fingers and lips. During the resting state, the subjects were instructed not to move at all and not to focus on anything in particular. The brightness of the eye fixation point was not changed at any time except during the visually cued finger movement task. A brief verbal instruction was given to cue subjects from one condition to the next through headphones at the beginning of each condition. The reaction times for clicking the button were measured during the fMRI measurements.

Before the fMRI experiments, all subjects were trained to tap the index finger of the right hand once every 1,500 ms (2/3 Hz) in time with a metronome. The training was continued until the subjects thought, and reported, that they had an idea of the specific pace and that they could reproduce the same pace without any preceding cue.

fMRI data acquisition

All the subjects were scanned using the head coil of a 1.5-T whole-body scanner (Siemens, Erlangen, Germany). Individual bite fixation bars were prepared to reduce movements of the head. The subject’s head was fixed using straps and ear fixation blocks. A time series of 128 scans was performed with an interscan interval of 4.0 s. In each scan, 15 horizontal slices of T2-weighted gradient-echo echoplanar images (TR = 4,000 ms, TE = 66 ms, FA = 90°) were collected with a voxel size of 2 × 2 × 8 mm. The interslice interval was 2 mm.

Each subject performed two runs. For each run, the data from the first four scans were discarded to eliminate transients’ arising before the achievement of dynamic equilibrium, and the last four scans were blank scans. The remaining 120 runs were divided into two trial groups (the first four trials and the second four trials), and each task occurred randomly once within each half. The total duration per run was 8 min 32 s.

Data analysis

Individual fMRI images of the 240 brain volumes were realigned to remove movement-related artifacts and coregistered to each subject’s anatomic brain image with the help of statistical parametric mapping software (SPM96, Wellcome Department of Cognitive Neurology, London, UK). The anatomic images were spatially normalized using both linear and nonlinear parameters by the human brain atlas (HBA) system (Roland et al. 1994), and the same parameters were used for spatial normalization of the functional images. Then, the functional images were smoothed with a Gaussian filter with a full width at half maximum of 8 mm. The Talairach coordinates and z scores of the peak activation for the group-averaged results are shown in Table 1.

TABLE 1. Talairach coordinates and z scores of the peak activation for the group-averaged results

<table>
<thead>
<tr>
<th>Activation</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>z Score</th>
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<td>28</td>
<td>−52</td>
<td>−32</td>
<td>5.24</td>
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</tbody>
</table>

Silent articulation – Rest   |     |     |     |         |
| Supplementary motor         | 2   | 2   | 58  | 4.13    |
| Inferior Frontal (L)        | −50 | 8   | 2   | 4.31    |

Stereotaxic coordinates (in mm) identify the location of the maxima of hemodynamic responses corresponding to the atlas of Talairach and Tournoux (1988). L, left hemisphere; R, right hemisphere.
half-maximum of 12 mm. A mean image was created for each condition in each run for each subject, allowing for the hemodynamic lag between conditions (delay 6 s; dispersion 8 s) (Friston et al. 1995a; Worsley and Friston 1995), globally scaling image intensity to a grand mean of 1,000. After specifying the appropriate design matrix (8 subjects, 4 conditions, 2 functional images for each condition), the hemodynamic responses produced by the different experimental conditions were assessed at each voxel using a general linear model and a theory of Gaussian fields (Friston et al. 1995b), which constituted the SPM. The resultant set of voxel values for each contrast constitutes the SPM\(t\) \(SPM(t)\). These \(t\) values constitute the SPM\(t\), which is transformed to the normal distribution to obtain SPM\(z\), which was thresholded at \(P < 0.05\) (corrected for multiple comparisons). Finally, each area of activation was superimposed onto the standard brain anatomy of the HBA to define the anatomic localization.

In this study, we undertook the following comparisons for the main experiment: 1) memory-timed finger movement task versus resting (task A vs. task D), 2) visually cued movement task versus resting (B vs. D), and 3) silent articulation task versus resting (C vs. D). In addition, to reveal which areas of the brain were relatively more strongly activated during memory-timed and visually cued movements, we performed the conjunction analyses (Price and Friston 1996) of (A-B with A-D) and (B-A with B-D), respectively. In this study, the conjunction analysis was applied by masking, whereby the second subtraction was tested only in pixels that reached significance \((P < 0.001)\) in the first subtraction. Masking was performed in two directions (i.e., the first subtraction was performed with the second and vice versa. For each comparison, voxels with \(P < 0.05\) (corrected for multiple comparisons) were considered to represent regions with significantly changed regional cerebral blood flow (rCBF).

**RESULTS**

The mean ± SD frequency of the memory-timed finger movements during the fMRI measurements was 0.59 ± 0.11 Hz, which is lower than that noted during visually cued movements (0.67 Hz). The mean ± SD reaction time for the visually cued finger movements during the fMRI measurements was 358.5 ± 68.4 ms.

Table 1 summarizes the data on Talairach coordinates (Talairach and Tournoux 1988) and the \(z\) score of peak activation in each task versus rest. Memory-timed movements significantly activated the anterior lobe of the cerebellum on both sides (lobules IV and V), the contralateral primary motor area (M1), the dorsal premotor areas (PMA) bilaterally, the SMA, the inferior frontal cortex bilaterally, the left intraparietal cortex, and the right inferior parietal lobe compared with the control resting condition (Fig. 1).
The same area in the ipsilateral (right) anterior cerebellum, the contralateral M1, the bilateral dorsal PMA, the left intraparietal cortex, and the right inferior parietal cortex were also significantly activated during the visually cued movement task. The SMA was also significantly activated, but the location of the peak activation was more posterior to that during the memory-timed movements. In addition, the visually cued movements activated the ipsilateral ventral PMA, the right middle frontal cortex, the left inferior parietal cortex, the right superior temporal cortex, the left insula, and the right thalamus (Fig. 1B). The contralateral (left) anterior cerebellum showed slight increases in activity (P < 0.01: uncorrected; Fig. 2). The silent articulation task activated the SMA and the left inferior frontal cortex compared with the control resting condition (Fig. 1C). These two areas were the same as those activated during the memory-timed movement task. The anterior lobe of the cerebellum was activated bilaterally during the silent articulation task compared with the resting condition. However, these activations did not reach statistical significance (P < 0.05: corrected), although an uncorrected significance level of P < 0.001 was observed (Fig. 2).

The conjunction of memory-timed movement minus visually cued movement with memory-timed movement minus rest (A-B with A-D) revealed significant activation in the anterior lobe of the cerebellum (lobules IV and V) bilaterally (Fig. 3), the left middle frontal cortex (Fig. 4A), and the left inferior frontal cortex (Fig. 4B). Activation in an area of the left middle frontal cortex did not reach statistical significance (P < 0.05 corrected) in the memory-timed movement versus rest comparison, although an uncorrected significance level of P < 0.0001 was observed. The conjunction of visually cued movement minus memory-timed movement with visually cued movement minus rest (B-A with B-D) showed significant activation in the ipsilateral PMA (Fig. 5C) and the intraparietal cortex bilaterally (Fig. 5, A and B). The Talairach coordinates (Talairach and Tournoux 1998) and z score of peak activation are summarized in Table 2.

**DISCUSSION**

Our results demonstrate that memory-timed finger movements activated the anterior lobe of the cerebellum bilaterally, the contralateral M1, the PMA bilaterally, the SMA, and the parietal cortex and the prefrontal cortex bilaterally. Among these structures, the anterior lobe of the cerebellum of both sides, the SMA and the left prefrontal cortex were probably involved in the generation of accurate timing, functioning as a clock of the CNS.

**Cerebellum**

In the present study, the anterior lobe of the cerebellum of the ipsilateral hemisphere was activated during both memory-timed and visually cued movement tasks. The results support the traditional role of the cerebellum in the control of movement and the findings of anatomic and neurophysiological studies as well as recent human neuroimaging studies that movement is represented somatotopically on the ipsilateral side (Allen et al. 1997; Colebatch et al. 1991; Deiber et al. 1996; Fox et al. 1985; Grafton et al. 1993; Stephan et al. 1995; Thach 1996; Van Mier et al. 1998). In addition, we found that the anterior lobes of the cerebellum of both sides were activated to a greater extent during memory-timed movements than that during visually cued movements, the silent articulation task, and the control resting condition (Figs. 2 and 3). It is of interest...
to note that the self-paced finger movements in association with rapidly alternating movements of flexion and extension of the fingers activated only the ipsilateral anterior cerebellum (Fox et al. 1985), although, in this study, self-paced finger movements timed by memory activated the anterior cerebellum bilaterally. These bilateral activations cannot be related to the execution of movements, because the number of movements during the measurement was higher in the visually cued movement task than in the memory-timed movement task in this study. The silent articulation task in this study, in which the subjects engaged in subvocalization associated with chronometric counting to achieve accurate timing, activated the anterior cerebellum bilaterally ($P < 0.001$), although this activation did not reach statistical significance ($P < 0.05$ corrected). The results are consistent with those reported by previous neuroimaging studies using SPECT showing the involvement of the cerebellum in silent mental counting, which requires chronometric counting (Decety et al. 1990; Ryding et al. 1993). However, they used region-of-interest–based analysis, and further, analyzed only the inferolateral parts of the cerebellar hemisphere. Therefore, to summarize, our results suggest that the ipsilateral anterior cerebellum is involved in the control of finger movements, and the anterior cerebellum of both sides is involved in chronometric counting to achieve accurate timing, and that these areas are more strongly activated to control the timing of the actual movements.

It has been argued that one of the important functional roles of the cerebellum is the control of motor timing (Thach 1996). A finding reported by Ivry and colleagues (1998), based on a series of very robust experiments in patients and normal control subjects, is that the lateral cerebellum participates in nonmotor temporal processing (Ivry and Keele 1989; Ivry et al.
1988; Keele et al. 1985). In recent neuroimaging studies, the activation of the anterior lobe of the cerebellum of both sides was noted, when the subjects estimated time differences by comparing a test time with a standard interval (Jueptner et al. 1995) and when subjects reproduced rhythms of increasing complexity (Penhune et al. 1998), indicating the involvement of the cerebellum in motor timing and perceptual timing, respectively. Van Mier et al. (1998) also suggested that the anterior cerebellum might relate to movement timing at a muscle-specific level. In this study, during the memory-timed movement task, the subjects were instructed to reproduce accurately the timing of the movements from their working memory.

Therefore our results, combined with the results of previous studies, support the hypothesis that the cerebellum is a clock within the CNS, either because of its own intrinsic circuitry (Ivry et al. 1988) or in combination with its extrinsic motor and premotor connections (Thach 1996) that may time many activities independently and in addition to actual movements.

Prefrontal cortex

An area in the left middle frontal gyrus was specifically activated during the memory-timed movement task (Fig. 4A). Activation of this area, located in the dorsolateral prefrontal cortex, has also been reported in other positron emission tomography (PET) studies of memory-timed finger movements (Kawashima et al. 1996a; Larsen et al. 1996). Frith et al. (1991) reported the activation of an area in the vicinity of the aforementioned area in relation to the willed component of movement. Because memory-timed movement is a voluntary act requiring repeated decision to move (Larsen et al. 1996), our results support the argument of Frith et al. (1991) in favor of the functional role of the dorsolateral prefrontal cortex in the generation of self-determined finger movements. Although the generation of memory-timed movements requires the maintenance of information regarding movement timing in working memory, another possible explanation for the left dorsolateral prefrontal activation is the working memory load imposed during the performance of self-paced movement (Petrides et al. 1993).

The left inferior frontal cortex was activated during the silent articulation task, as well as during the memory-timed movement task in this study (Fig. 4B). Our results indicate that this area may be involved in subvocalization associated with chronometric counting. Recent neuroimaging studies have indicated that the left inferior frontal cortex is involved in language processing, in terms of perception, production, and memory, in normal subjects (Demonet et al. 1993; Kelley et al. 1998; Petersen et al. 1989, 1990; Posner and Carr 1992; Wagner et al. 1998). Our results are in agreement with results of these studies.

**TABLE 2. Talairach coordinates and z scores of the peak activation revealed by conjunction analyses for the group-averaged results**

<table>
<thead>
<tr>
<th>Activation</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>z Score</th>
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</thead>
<tbody>
<tr>
<td>(Memory-timed − visually cued) with (memory-timed − rest)</td>
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<td></td>
<td></td>
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<td>Anterior cerebellum (L)</td>
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<td>Anterior cerebellum (R)</td>
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<td>−52</td>
<td>−24</td>
<td>5.31</td>
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<tr>
<td>(Visually cued − memory-timed) with (visually cued − rest)</td>
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Stereotaxic coordinates (in mm) identify the location of the maxima of hemodynamic responses corresponding to the atlas of Talairach and Tournoux (1988). L, left hemisphere; R, right hemisphere.
SMA

In this study, the SMA was activated during each task compared with the resting condition. The location of peak activation was slightly different between the visually cued movement task and the other two tasks. The SMA is segregated into two parts, the pre-SMA and SMA proper, corresponding to the anterior and posterior parts of the SMA, on the basis of physiological (Halsband et al. 1994; Matsuzaka et al. 1992; Tanji 1994) and anatomic (Luppino et al. 1993; Matelli et al. 1991; Rizzolatti et al. 1996) studies. In the human brain, a perpendicular line crossing the anterior commissure (Vca line) has been proposed as the approximate anatomic landmark separating the pre-SMA from the SMA on the basis of PET activation studies (Picard and Strick 1996). In this study, the focus of SMA activation during the memory-timed movement and silent articulation tasks was probably located in the pre-SMA and that during the visually cued movement task in the SMA proper. Because we found exactly the same area of the SMA activated during the memory-timed movement and silent articulation tasks, we think that the pre-SMA activation in this study may be related to subvocalization associated with chronometric counting for accurate timing. Consistent results were also reported in recent functional imaging studies that showed pre-SMA activation during memory-timed finger movements (Kawashima et al. 1997, 1999; Larsson et al. 1996; Rao et al. 1997) and activation of the SMA proper during simple sensory-cued movements (Dettmers et al. 1995; Kawashima et al. 1996b; Rao et al. 1993; Remy et al. 1994; Stephan et al. 1995; Zatorre et al. 1992). Previous cerebral DC potential (see Deecke and Lang 1996 for review) and magnetic and electric encephalographic (Lang et al. 1991; Libet et al. 1982) studies in humans also suggest that the SMA is activated long before the initiation of self-initiated simple digit movements. A lesion study in humans showed that the SMA is involved in the generation of sequences from memory that fit into a precise timing plan (Halsband et al. 1993). These findings prompt us to propose that the pre-SMA plays a role in the control of motor timing and that, on the other hand, the SMA proper plays a role in sensorially cued movements.

Other areas

The PMA was activated bilaterally during the two finger movement tasks. The right PMA was activated to a greater extent during visually cued movements. Consistent results were reported in other PET studies (Larsson et al. 1996; Roland et al. 1980). The PMA has been considered to play a role in the sensory guidance of movements (Mitz et al. 1991; Passingham 1985). Mushiake et al. (1991) demonstrated that the neuronal activity in the PMA is more involved in visually triggered than self-paced movement and vice versa for the SMA and that the difference is small and relative rather than absolute. Our results are in agreement with these results.

In the present study, the posterior part of the intraparietal cortex showed task-specific activation by visually cued movements. Although recent human neuroimaging studies have shown the involvement of the posterior part of the intraparietal cortex in visuospatial processing (Kawashima et al. 1996c, 1998; Paus et al. 1993; Petit et al. 1996), our results are in agreement with the results of neurophysiological studies in monkeys that indicate that the posterior parietal cortex is a sensorimotor association area where neurons are activated in relation to either sensory or motor inputs (Sakata et al. 1995), as well as with the results of a recent neuroimaging study in humans that indicate that an area in the intraparietal sulcus is activated during both spatial and nonspatial tasks (Coull and Frith 1998). The results may indicate that the cortex lining the posterior part of the intraparietal sulcus in humans is functionally heterogeneous.

Lesions of the basal ganglia produce well-known motor deficits. It has been suggested that one of the functional roles of the basal ganglia is the control of motor timing (O’Boyle et al. 1996; Rao et al. 1997). The absence of basal ganglia activation in this study can probably be ascribed to a few subjects’ showing susceptibility artifacts in the basal ganglia (see Ojemann et al. 1997 for review).

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