NeuroReport 9, 2359–2363 (1998)

Separate cerebellar areas for motor control

Katsuyuki Sakai,[1,2] Ryouske Takino,[3] Okihide Hikosaka,[1,CA] Satoru Miyauchi,[4] Yuka Sasaki,[4] Benno Pütz[5] and Norio Fujimaki[4]

[1]Department of Physiology, Juntendo University School of Medicine, 2-1-1 Hongio, Bunkyo-ku, Tokyo, 113; [2]Department of Neurology, Division of Neuroscience, Graduate School of Medicine, University of Tokyo, Tokyo 113; [3]Shiaume Gakuen College, Tokyo 187; [4]Communications Research Laboratory, Tokyo 184; [5]Exploratory Research for Advanced Technology, Japan Science and Technology Corporation, Kyoto 619-02, Japan

[CA]Corresponding Author

CEREBELLAR activation was measured using functional magnetic resonance imaging, while seven normal subjects tapped their fingers paced by tone sequences with or without tone omission. The cerebellar anterior lobe (Larsell's H IV-V) ipsilateral to the movement was activated to a similar degree irrespective of the presence or absence of the tone omission. In contrast, the lateral part of the bilateral posterior lobe (H VIIa) was significantly highly activated for the tone sequence with random omission, compared with either that without omission or that with regular omission. The result suggests that the H IV-V is involved in motor execution, while the lateral part of H VIIa is involved in online motor adjustment to unpredictable sensory stimuli. *NeuroReport* 9: 2359–2362 © 1998 Rapid Science Ltd.

Key words: Anterior lobe; Cerebellum; Functional magnetic resonance imaging; Motor control; Posterior lobe; Tone sequence

Introduction

The cerebellum is composed of functional modules arranged in the medio-lateral direction; the medial part being responsible for the control of equilibrium and posture, while the lateral neocerebellar regions being responsible for coordination of rapid movements of the extremities.[1,2] On the other hand, the cerebellum is anatomically divided along the rostro-caudal axis; the anterior lobe and the posterior lobe, each of them further divided into several lobules.[3] For the anterior lobe, there is strong evidence that movement is represented somatotopically on the ipsilateral side.[5,6] In contrast, the posterior lobe is thought to be related to higher order functions such as language,[7,8] motor imagery[9] and motor learning.[10] These findings would suggest the functional separation of the cerebellum in the rostro-caudal axis.[4] However, confirmation of this idea was required because only few studies to date have tested the differential activation of the two lobes using the same paradigm. Furthermore, precise location of the posterior lobe activation has not been clarified.

In the present study, we hypothesized that these two lobes were differently involved in motor control. To test this hypothesis, we measured the cerebellar activation using functional magnetic resonance imaging (fMRI) while the subject made tone-paced finger tapping and withheld tapping on tone omission.

Materials and Methods

Subjects: Seven normal right-handed subjects (five males and two females, 23–49 years old) participated in the study. Informed consent was obtained from all the subjects prior to the study. The protocol of the present study was in accordance with the ethical guideline of the institute.

Task procedures: Three different kinds of tone sequences were presented with interstimulus intervals of 300 ms (each tone had a frequency of 1 kHz, rise-fall time 5 ms, plateau 20 ms, intensity 95 dB): (1) a tone sequence with a constant interval (constant tone); (2) a tone sequence with omissions occurring after 3–9 tones (random omission), and (3) a tone sequence with omissions occurring after every 6 tones (regular omission). The tones were delivered to a headphone through a pair of plastic tubes (length 180 cm), which successfully reduced the scan noise. The subjects, lying supine in the MRI scanner, were asked to tap their right index fingers against their

thumbs paced by the tone sequence, and withhold tapping on omissions. In the base-line (rest) condition, no tone was presented and the subjects were asked not to move. In experiment 1, constant tone, random omission and rest conditions were repeated four times each, while in experiment 2, random omission, regular omission and rest conditions were repeated four times each. Each condition lasted 40 s, therefore, the total number of finger tapping was 144 for each constant tone condition, and 124 for random omission and for regular omission. The order of the two test conditions was counterbalanced across the four repetitions in each experiment. The subjects saw a screen through a mirror, and were asked to fixate at the center throughout the experiment. The type of the ongoing task condition was indicated on the screen.

fMRI data acquisition: fMRI was conducted on a 1.5T whole body scanner equipped with a circular-polarized head coil (Siemens Vision, Germany). In each experiment a time series of 123 scans was performed with an inter-scan interval of 4 s. In each single scan 10 slices of T2*-weighted gradient-echo echo-planar images (TR/TE 120/66 ms, FA 90°, thickness 7 mm, FOV 220 × 220 mm, matrix 128 × 128) were obtained to encompass the entire cerebellum. The anterior portion of each slice plane was tilted upward from the AC-PC line by 10°. The images for the first three scans were removed from the subsequent analysis to allow the MR signal to reach steady-state and the delay of hemodynamic response. The above mentioned task procedure was started from the third scan and ended at the second to the last scan. The last scan was additionally performed to account for the delay of hemodynamic response and the subjects were asked to keep rest during the last scan. After obtaining functional images, we collected T1 weighted anatomical images (TR/TE: 150/6 ms, FA 90°, FOV 256 × 256, matrix 256 × 256, thickness 7 mm, NEX 6) for the same slice position. In addition on a separate session, we obtained a series of high resolution T1-weighted whole brain anatomical images (FLASH; TR/TE/TI 2800/4/300, FA 15°, matrix 256 × 256, FOV 230 × 230 thickness 1 mm) in contiguous sagittal sections which served as the dataset for the determination of the contour of the cerebellar sulci.

fMRI data analysis: After application of a motion correction program (AIR 3.0[11]) to the functional image datasets cross-correlation of the signal intensity (SI) data with a box-car reference function derived from the task sequence was calculated between each of the test conditions and rest. The reference function was shifted for one datapoint to account for the delay of the rise time of the blood oxygenation level. Activation foci were determined as pixels with correlation coefficient above 0.3, which corresponds to $p < 0.005$. Pixels shown to be active in isolation were eliminated. The location of activation foci was described anatomically, which gave us an a priori information about the location of the regions relevant for the task.

For the next step, we analysed the SI data from the anatomically defined region of interest (ROI). We determined three ROIs, one within the cerebellar anterior lobe and the others within the posterior lobe, based on the anatomical landmarks with reference to the T1-weighted co-planar anatomical images. The cerebellar sulci were examined with the use of the orthogonal images obtained from the high resolution T1-weighted anatomical image dataset and were identified according to the atlas of the human cerebellum.[12] The ROI for the anterior lobe was placed in the lateral half of the right H IV-V,[3] which was identified as the lobule between the preculminate fissure and the primary fissure (Fig. 2a). The other two ROIs for the posterior lobe were bilaterally placed in the lateral one third of the crus I of the ansiform lobule (Larsell's H VIIa). The H VIIa was determined as the lobule surrounded by the superior posterior fissure anteriorly and the horizontal fissure posteromedially. For each of the three ROIs, the SI data were compared between the two test conditions (40 data points for each condition) using an unpaired *t*-test. In addition, the relative SI increase from the base-line condition was calculated for each ROI.

Results

Location of activation foci: In experiment 1, comparison of constant tone with rest revealed a single area of activation within the anterior lobe of the cerebellum, which was located within Larsell's H IV-V, ipsilateral to the finger movement (Fig. 1a; red circle). The activated pixels were distributed in oblique bands following the contour of individual folia. On the other hand, comparison of random omission with rest disclosed two additional activation foci symmetrically located within the lateral part of the cerebellar posterior lobe, which was determined as Larsell's H VIIa (Fig. 1a; green circles). To see whether this posterior lobe activation was related to the withholding of tapping or the unpredictable timing of tapping omission, we conducted experiment 2 (Fig. 1b). The anterior lobe was shown to be similarly activated in random omission and regular omission (Fig. 1b; red circles). However, the posterior lobe activation markedly decreased in regular

Table 1. The signal intensity data from the ROIs in the H IV-V and H VIIa for experiment 1. The relative SI increase from the baseline rest condition and *p* values for comparison of the SI data between constant tone and random omission are shown individually for each subject.

	Anterior lobe (H IV-V)			Posterior lobe (H VIIa)		
Subject	Constant (%)	Random (%)	*p*	Constant (%)	Random (%)	*p*
1	1.97	1.86	0.81	0.23	1.40	< 0.0001
2	1.53	1.27	0.59	0.46	1.60	0.0015
3	1.21	1.26	0.65	0.75	2.20	< 0.0001
4	0.88	1.04	0.09	0.51	2.32	< 0.0001
5	1.13	0.859	0.14	0.87	1.90	0.0090
6	1.50	1.63	0.36	0.63	1.46	< 0.0001
7	1.44	1.64	0.15	0.46	1.26	0.0007
All	1.38	1.37	0.81	0.56	1.73	< 0.0001

Table 2. The signal intensity data for experiment 2. The SI data for random omission and regular omission were compared.

	Anterior lobe (H IV-V)			Posterior lobe (H VIIa)		
Subject	Constant (%)	Random (%)	*p*	Constant (%)	Random (%)	*p*
1	1.71	1.62	0.77	0.90	2.35	0.0002
2	1.44	1.39	0.89	0.87	1.91	0.0022
3	1.81	1.81	0.98	1.14	2.40	< 0.0001
4	1.64	1.37	0.18	0.62	2.06	< 0.0001
5	1.99	2.11	0.54	0.03	1.41	0.0017
6	1.52	1.91	0.19	1.13	2.63	0.0003
7	1.38	1.33	0.78	1.05	1.63	0.0064
All	1.64	1.65	0.96	0.82	2.06	< 0.0001

and regular omission, while comparison of the SI data within the H VIIa showed a significant difference between the two conditions in all the subjects ($p < 0.01$; Table 2).

Discussion

Our results have suggested that the cerebellum is constituted with different functional areas for motor control. Specifically, we have identified that three regions in the cerebellar cortex, the H IV-V ipsilateral to the movement and the lateral portion of the H VIIa bilaterally, participate in motor control for the tone-paced tapping. Because the total number of finger tapping was matched closely across all the conditions, similar activation of the H IV-V across the three conditions suggests that this area is related to the movement execution per se. The location and the pattern of activation were consistent with previous findings.[6,13,14]

In contrast, activation of the bilateral H VIIa was higher in random omission than in constant tone. This raised the possibility that the activation was related to the withholding of tapping. However, in experiment 2, activation of this area significantly decreased in regular omission compared to that in random omission, although the number of omissions was closely matched between the two conditions (20 omissions for each condition). Thus the H VIIa activation was not related to the withholding of tapping, but was related to the unpredictable timing of tapping omissions. These results lead to the following interpretation. Under the constant tone condition, the subjects' finger tapping would, for the most part, be dependent on the internal time-keeping system that does not require sensory feedback mechanisms.[15] In other words, the movement would be nearly automatic and processed off-line. Likewise, in regular omission, the movement can be automatic, because the subjects can perform the task by repeating the six presses and rest almost independently from the sensory stimuli. By contrast, in random omission the timing of withholding tapping is unpredictable and therefore the subjects had to abruptly stop the tapping sequence and then restart it. Since the condition does not allow the subjects to preprogram the tapping sequence, the subjects had to make on-line adjustment of the tapping to the randomly missing tone sequence. Thus we would like to suggest that H VIIa is involved in on-line motor adjustment to unpredictable auditory stimuli.

An important aspect of our finding is the cerebellar functional separation along the rostro-caudal axis. Similar functional separation has recently been

shown by Allen *et al.*[16] They have shown that the attention ROI including the superior semilunar lobule, which is identical to the H VIIa, was activated during a visual attention task. They also showed that the Motor ROI including the anterior quadrangular lobule, which is identical to HIV-V, was activated only when the movement execution was required. Although our H VIIa activation in the random condition might reflect the increased demand on attention, we consider that the activation reflects motor control mechanism. Indeed, silent counting of the number of omissions instead of withholding tapping caused little activation in this area (Sakai *et al.*, unpublished observation). Also relevant to our finding is a recent study by Imamizu *et al.*[17] which showed that a similar region in the H VIIa was activated only during the early phase of visuomotor learning, while the anterior lobe remained to be active throughout learning. Their finding might suggest that the H VIIa is also related to on-line motor adjustment to visual stimuli.

Timing processes might also play an important role in the posterior lobe activation. A number of studies have shown that the cerebellum is involved in the timing process.[15,18,19] Jueptner *et al.*[20,21] have shown bilateral cerebellar activation similar to ours under a timing discrimination task. Furthermore, the finding from cerebellar patients seemed to support the existence of separate neural correlates for the motor implementation and the timing process.[22] Although Ivry *et al.*[22] assigned the finding to the medio-lateral functional separation within the cerebellum, their medial cerebellar lesion preferentially involved the anterior lobe, while the lateral lesion involved the posterior lobe. Thus we consider that their data also support our rostro-caudal functional separation.

Finally, the auditory areas would also play an important role in our task paradigm. Previously, Takino *et al.*[23] found that the STS was activated when the subjects listened attentively to the missing tone sequence, and suggested that this area, together with the primary auditory cortex, might play a role for perception and detection of the tone omission. The cerebellar H VIIa might receive the omission signal from the STS regions, and use it to withhold tapping. This idea would be supported by the anatomical findings that showed connections between the cerebellum and STS as well as other auditory areas.[24,25]

Conclusion

Using functional MRI, we have identified two cerebellar cortical areas involved differentially in motor control. The lateral half of the H IV-V ipsilateral to the movement was related to motor execution per se, while the lateral third of H VIIa bilaterally participated in on-line motor adjustment to unpredictable sensory stimuli. Although the mediolateral zonal pattern was proposed as the basic functional separation of the cerebellum, the present study has demonstrated the separation along the rostro-caudal axis.

References

1. Ito M. *The Cerebellum and Neural Control.* New York: Raven Press, 1984.
2. Ito M. *Trends Neurosci* **16**, 448–450 (1993).
3. Larsell O and Jansen J. *The Comparative Anatomy and Histology of the Cerebellum: The Human Cerebellum, Cerebellar Connections, and Cerebellar Cortex.* Minnesota: University of Minnesota Press, 1972.
4. Roland PE. *Can J Neurol Sci* **20**, S75–77 (1993).
5. Brooks VB and Thach WT. Cerebellar control of posture and movement. In: Brookhart JM, Mountcastle VB and Brooks VB. eds. *Handbook of Physiology. Section 1 vol II, Pt. 2.* Bethesda: American Physiological Society, 1981: 877–946.
6. Nitschke MF, Kleinschmidt A, Wessel K *et al. Brain* **119**, 1023–1029 (1996).
7. Roland PE, Eriksson L, Stone-Elander S *et al. J Neurosci* **7**, 2373–2389 (1987).
8. Petersen SE, Fox PT, Posner MI *et al. J Cogn Neurosci* **1**, 153–170 (1990).
9. Grafton ST, Arbib MA, Fadiga L *et al. Exp Brain Res* **112**, 103–111 (1996).
10. Flament D, Ellermann JM, Kim S-G *et al. Hum Brain Mapp* **4**, 210–226 (1996).
11. Woods RPW, Cherry SR and Mazziotta JC. *J Comput Assist Tomogr* **17**, 536–546 (1993).
12. Angevine Jr. JB, Mancall EL and Yakovlev PI. *The Human Cerebellum. An Atlas of Gross Topography in Serial Sections.* Boston: Little, Brown and Company, 1961.
13. Sadato N, Ibanez V, Deiber MP *et al. J Cerebr Blood Flow Metab* **16**, 23–33 (1996).
14. Rao SM. Harrington DL, Haaland KY *et al. J Neurosci* **17**, 5528–5535 (1997).
15. Ivry RI and Keele SW. *J Cogn Neurosci* **1**, 134–150 (1989).
16. Allen G, Buxton RB. Wong EC *et al. Science* **275**, 1940–1943 (1997).
17. Imamizu H, Miyauchi S, Sasaki Y *et al. NeuroImage* **5**, S598 (1997).
18. Keele SW and Ivry R. *Ann NY Acad Sci* **608**, 179–211 (1991).
19. Nitchelli P, Alway D and Grafman J. *Neuropsychologia* **34**, 863–871, (1996).
20. Jueptner M. Rijntjes M, Weiller C *et al. Neurology* **45**, 1540–1545 (1995).
21. Jueptner M, Flerich L, Weiller C *et al. NeuroReport* **7**, 2761–2765 (1996).
22. Ivry RI, Keele SW and Diener HC. *Exp Brain Res* **73**, 167–180 (1988).
23. Takino R, Pütz B, Sasaki Y *et al. NeuroImage* **3**, S319 (1996).
24. Schmahmann JD and Pandya DN. *J Comp Neurol* **308**, 224–248 (1991).
25. Yeterian EH and Pandya DN. *J Comp Neurol* **282**, 80–97 (1989).

ACKNOWLEDGEMENTS: This study was supported by JSPS Research for the Future program and Basic Research System Core.

Received 15 April 1998; accepted 3 May 1998