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RESEARCH ARTICLE

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Activation of the cerebellum in co-ordinated eye and hand tracking movements: an fMRI study

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Abstract Dysfunction of the cerebellum leads to significant deterioration of movements performed under visual guidance and of co-ordinated eye and hand movement. Visually guided tracking tasks combine both of these control features, as the eyes and hand together track a visual target. To better understand the involvement of the cerebellum in tracking tasks, we used functional magnetic-resonance imaging to study the activation of cerebellar structures in visually guided tracking movements of the eye and hand. Subjects were tested performing ocular tracking, manual tracking without eye movement or combined eye and hand tracking of a smoothly moving visual target. Three areas were activated in the cerebellum: a bilateral region in the ansiform lobule of the lateral hemisphere, a region in the ipsilateral paramedian lobule and a region in the oculomotor vermis. The ansiform and paramedian areas were most strongly activated by hand movement, although the vermal site was also active. The reverse was found for ocular tracking, with predominantly vermal activation. Activation of these cerebellar cortical areas related to movement of eyes or hand alone was significantly enhanced when the subjects performed co-ordinated eye and hand tracking of a visual target. These results provide the first direct evidence from a functional-imaging study for cerebellar activation in eye and hand co-ordination.

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Introduction

In this paper, we aim to address the question, does the cerebellum have a particular role in the integration of oculomotor and limb control? The cerebellum is already suspected to play an important role in the co-ordination of movement, since it is clear that the effects of cerebellar dysfunction are pronounced in two circumstances. First, in multi-joint movement of the arm more than in single-joint control. Holmes (1939) originally reported that cerebellar patients show deficits in single-joint movements, and, while single-joint deficits have been confirmed by Beppu et al. (1987), Hore et al. (1991) and others, there are specific problems of multi-joint control seen in cerebellar disorders (Bastian et al. 1996). Thach and his colleagues (Bastian et al. 1996; Thach et al. 1992) have argued that a specific role of the cerebellar cortex may be to assist in co-ordination of whole-limb or whole-body movements.

Second, visually guided movements are more markedly disrupted than movements without visual control, and cerebellar patients have a specific difficulty in using visual information to control their arm and hand movements (Beppu et al. 1987; Haggard et al. 1995; Holmes 1939). Visual feedback is likely to be problematic for cerebellar patients because the visual feedback signals are out of date with respect to the motor commands, mainly due to visual processing delays (Miall et al. 1986), and visual errors cannot be mapped directly onto the errors in the motor command that must be corrected. Hence, the cerebellum may contribute to motor control by providing a forward estimate of the consequences of movement (Jordan 1994; Miall and Wolpert 1996; Wolpert et al. 1995).

In fact, visually guided tracking tasks, in which subjects use some form of hand-held control to guide a cur-

sor onto a target, appear to be particularly sensitive to cerebellar dysfunction as they provide challenges for co-ordination within the limb (i.e. between different limb segments), for co-ordination between the eye and hand and for the integration of visual feedback signals into ongoing movement. The interaction between eye and hand is likely to be bi-directional. It is known that visual-tracking performance is improved if both eye and hand track the same target motion (Brown et al. 1993; Van Donkelaar 1997; Vercher and Gauthier 1988; Vercher et al. 1996), and it seems that an important contribution to control of the hand motion comes from the ocular-motor system (Blouin et al. 1996; Van Donkelaar et al. 1994; Van Donkelaar et al. 1996). Likewise, oculomotion is more accurate, with higher smooth-pursuit gain and reduced lag, if the hand is also used (Abrams et al. 1990; Biguer et al. 1984; Koken and Erkelens 1992; Steinbach and Held 1968; Vercher et al. 1994). Thus, at some level, information about motion of either the eye or hand is available to both control systems. It is already known that the cerebellum is important for this interaction: Vercher and Gauthier (1988) demonstrated that the short-latency ocular following of a handcontrolled cursor is lost after dentate lesions; Van Donkelaar and Lee (1994) showed that cerebellar patients were more disabled in combined hand and eye tasks than when performing without conjoint eye and hand movement.

In this paper, we report functional magnetic-resonance imaging experiments that address these two roles of the cerebellum, looking at the cerebellar activation during co-ordinated eye and hand movement in a tracking task. There have been several reports of cerebral activation in visually guided or visually driven movement (Culham et al. 1998; Ellerman et al. 1998; Flament et al. 1996; Grafton et al. 1992; Jueptner et al. 1996; Tamada et al. 1999; Turner et al. 1998), but only a few have concentrated upon, or even fully imaged, the cerebellum. Hence, we have localised those areas of the human cerebellar cortex that are activated during movements of eyes or the hand, or both, to follow movement of a visual target.

Materials and methods

We tested subjects in two related visual-movement experiments. Three subjects were used in each experiment. All subjects gave their informed consent in accordance with the declaration of Helsinki, and the experiments were approved by the local ethical committee. One of the authors (RCM) was a subject; all other subjects were na to the tasks, but were given instructions before scanning and several minutes practice at each task once in position on the scanner bed. RCM performed both experiments; two other subjects performed experiment 1 only, and two subjects took part in experiment 2 only.

Imaging paradigm

Axial slices were taken spanning the vertical extent of the cerebellum, but excluding the cerebral sensory and motor areas. Functional images were collected using an EPI sequence on a 1.5T MRI Siemens Magnetom Vision scanner. A standard whole-head coil and an echo-planar imaging (EPI) booster was used for all image acquisitions. Functional images with apparent transverse relaxation time (T^*_2) were obtained with an EPI sequence (repetition time TR =4.4 s; echo time TE =66 ms; flip angle FA =90°). Ten axial slices (7 mm thick, 2.1 mm inter-slice separation; 128×128 pixels with a field of view of 240×240 mm) were acquired. Voxel sizes were thus 1.88×1.88×9.1 mm. A total of 128 multi-slice images were acquired during performance of the tracking task.

A T_1-weighted structural image was next acquired (ten axial slices co-registered with the functional slices, using a conventional sequence; TR =350 ms, TE =6 ms, FA =90°, FoV =240×240 mm). Slices were 256×256 voxels of 0.98×0.98×9.1 mm. Immediately following the structural sequence, a second sequence of 128 functional images were collected, using the same EPI parameters described above, but with the slices shifted axially by 4.6 mm to cover the inter-slice separation.

Data analysis

Data were analysed with SPM-96 statistical parametric mapping software from the Wellcome Dept. of Cognitive Neurology, London, UK; (Friston et al. 1995a); implemented in Matlab (Mathworks, Sherborn Mass., USA).

Spatial realignment and normalisation

The scans from each session were realigned to correct for motion using the first as a reference (Woods et al. 1992). The six parameters of this rigid body transformation were estimated using a least-squares approach (Friston et al. 1995b), based on an approximate linear relationship between the images and their partial derivatives with respect to parameters of the transformation. Following realignment, all images from each subject were transformed into a standard space. This normalising spatial transformation matched each scan (in a least-squares sense) to a template image using 12 parameter affine (linear) and quadratic (non-linear) three-dimensional transformations. Attempts to register the functional or structural images to the spatial co-ordinates of the standard SPM brain templates (Talairach and Tournoux 1988) were unsuccessful; while some whole-brain images could be registered, images centred on the cerebellum could not. Hence, the functional images from six sessions (three subjects, each repeated twice) were normalised to a template generated from the structural image from one subject smoothed with a 5 mm FWHM Gaussian filter. Again the parameters were estimated using standard least squares after linearising the problem. As a final pre-processing step, the images were smoothed using an (5 mm FWHM) isotropic Gaussian kernel.

Statistical analysis

The condition, subject and co-variate effects were estimated according to the general linear model at each and every voxel (see Friston et al. 1995a). The design matrix included global activity as a confounding co-variate, and this analysis can therefore be regarded as an ANCOVA (Friston et al. 1990). To test hypotheses about regionally specific condition or co-variate effects, the estimates were compared using linear compounds or contrasts. The resulting set of voxel values for each contrast constitute a statistical parametric map of the *t* statistic, SPM{t}.

Statistical inference

The SPM{t} were transformed to the unit normal distribution (SPM{Z}) with a threshold set at P=0.001, uncorrected. The resulting foci were then characterised in terms of spatial extent (k) and peak height (u). The significance of each region was estimated

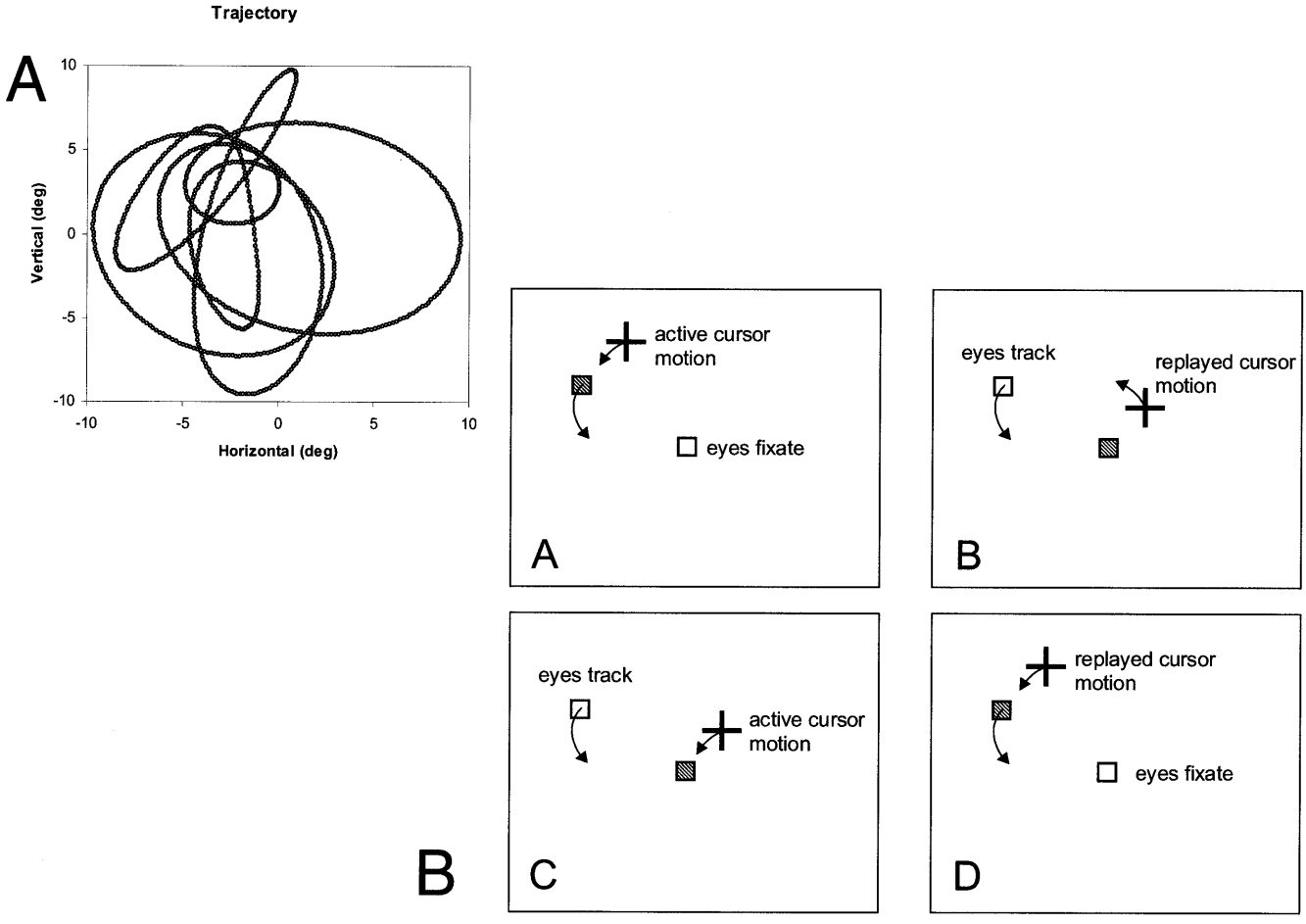

Fig. 1A, B Target motion and display conditions. **A** The trajectory of the target across the display screen, each *dot* representing one frame of the motion. The axes are approximately the visual angles subtended at the subject's eye. **B** The four conditions used in experiment 1, as displayed to the subject. The subjects were always to follow the white target (*hollow square*) with their eyes, and the red square (*shown hatched*) was always the target for the cursor (*large cross*). The cursor was actively moved by the subject in tasks A and C, or it was passively moved in tasks B and D, following the previously recorded trajectory to maintain approximately similar retinal inputs

using distribution approximations from the theory of Gaussian Fields. This characterisation is in terms of the probability that a region of the observed number of voxels (or bigger) could have occurred by chance [$P(\text{nmax}>k)$], or that the peak height observed (or higher) could have occurred by chance [$P(\text{Zmax}>u)$] over the entire volume analysed (i.e. a corrected *P*-value).

Behavioural tasks

Experiment one. Cerebellar activation during co-ordinated eye and hand tracking

Subjects lay on the scanner bed with head restraint achieved by Velcro straps across their forehead and by an individually moulded bite bar covered with a vinyl polysiloxane dental plastic compound (Exafine, GC Intl., Tokyo, Japan). They viewed a back projection screen set across the scanner opening and positioned just above the subjects' legs. A front-silvered mirror within the head coil allowed vision of the screen, and the distance from eye to screen was about 1.5 m. A colour LCD VGA-projector (Sony VPH-12720 J) was used to display images on the screen and also to project text cues to the subjects between different tracking conditions: a single, large font word ("REST", "MOVE" etc.) was displayed at the bottom centre of the screen for 4.4 s, indicating the changes between each tracking condition. In addition, the operator gave a verbal instruction to the subjects via pneumatic head-phones at the same time as the visual instruction was displayed.

The target(s) were provided by a small light-coloured square moving in a slow, smooth and unpredictable trajectory against a black background (Fig. 1A). In all instances, the target for the eyes was a filled white square 5×5 pixels, subtending about 0.73° at the subject's eye, and moving within a frame subtending approximately 23×20° at the eye. The target waveform was the sum of four non-harmonically related sinusoids (0.125–0.55 Hz), chosen to satisfy approximately the 2/3 law for speed and curvature (Lacquaniti et al. 1983); average target velocity was 21.3°/s.

Movement of the subject's hand was recorded by a modified computer mouse (PocketEgg, ELECOM, Japan), moved across a 20×20 cm urethane board and displayed on the screen as a light green cross 10×10 pixels in size. Hence, subjects performed a visual tracking task in which they attempted to track the target waveform with the cursor as accurately as possible. As explained in more detail below, there were actually two separate targets displayed on screen: one was a white "ocular" target to be followed with the eyes; the second was a hollow, light red square of 7×7 pixels, which was the target for the mouse-controlled cursor (Fig. 1B).

To monitor tracking performance in the manual tracking condition, we recorded the absolute spatial error between the cursor and the target accumulated over each 4.4 s, and also the total distance the mouse was moved every 4.4 s. Movement of the eyes could

Table 1 Experimental conditions and visual stimuli. The *white target* was the target for all eye movements. The *red target* was the target for the green cursor, which was either controlled by the subject using a computer mouse or was driven by the trajectory followed by the subject in a previous trial, which was stored and replayed

Experiment	Condition	White target	Red target	Green cursor	Eye motion	Limb motion
1	A: hand only	Still	Moving	Active	Fixation	Pursuit tracking
	B: eye only	Moving	Still	Replayed	Tracking	At rest
	C: eye and hand	Moving	Moving	Active	Tracking	Compensatory tracking
	D: rest	Still	Moving	Replayed	Fixation	At rest
2	A: rest	Still	–	–	Fixation	At rest
	B: eyes only	Moving	–	–	Tracking	At rest

not be monitored during scanning, but was recorded in subject RCM and in other subjects outside the scanner during the same tracking tasks using the ASL 501 infrared reflectometry eye-tracking system, monitoring left eye position in two dimensions.

Subjects alternated every 17.6 s between four tasks in an ABCD CBAD sequence. A 2×2 factorial design was used, with main factors of hand tracking and eye tracking. Thus, task A involved pursuit manual tracking ("hand-only"), using the mouse to superimpose the green cursor on the moving red target while the eyes remained fixed on the stationary, central, white target (Fig. 1B). Task B involved ocular tracking of the moving white target ("eyes-only"); subjects held the mouse still, but followed the smoothly moving ocular target with their eyes. Task C was to pursue the moving white target with the eyes, while also tracking the moving green cursor using the mouse ("eye and hand"). The baseline task D was ocular and hand fixation ("fixation"); the white ocular target was displayed stationary at the centre of the screen, and the subjects held the mouse still.

While a 2×2 factorial design is relatively common, we used pursuit manual tracking in the hand-only (task A) condition, but used "compensatory manual tracking" (Poulton 1974) in the eye and hand condition (task C). In the latter case, the cursor was displaced from the central, stationary red target by the same pseudo-random waveform used to move the ocular target, and the subject was required to make compensatory movements with the computer mouse to return the cursor to the stationary target.

This difference in tracking modalities can be justified as follows. The factorial design requires a condition in which the eyes move without hand movement, which is straightforward, a condition in which there is combined eye and eye tracking, which could have been achieved with normal pursuit of a moving target, and a condition in which there is hand movement without eye movement. A standard method to achieve this last condition is to use a "compensatory tracking" mode. Here, the eye can be shown to fixate the stationary target, while compensatory hand movements are used to control the cursor (Weir et al. 1989). However, normal pursuit tracking is markedly easier than compensatory tracking (Poulton 1974; Weir et al. 1989), and thus one could not simply compare the two. The difference in difficulty is largely because a compensatory display does not allow the subject to assess the position and velocity of the target waveform, but only the instantaneous tracking error and error velocity; in pursuit, one has access to target position and velocity cues (Weir et al. 1989)

Thus, we needed two comparable tasks involving hand tracking, one with and one without eye tracking, in which cues about target velocity and position were equally available, in which equivalent retinal inputs were provided in each condition by equal spatial separation of the eye and hand targets on the screen in both conditions, and in which the manual tracking was of approximately equal difficulty. Our design achieved all three of these aims (Fig. 1B): we used pursuit tracking with the hand while the eye was fixating a stationary target (task A, Table 1), so that the position and velocity of the target motion was available to the subject, albeit on the peripheral retina. Second, we used compensatory tracking with the hand whilst the eye was pursuing the target (task C), so that again target position and velocity cues were available from the ocular-motor system, while keeping the targets of the eye and hand spatially separated on the retina. Third, we recorded tracking errors and the path-length of the hand movement in the two conditions, and these were not significantly different.

Finally, to maintain equivalent retinal input in the four conditions, we used a "record and playback" technique to move the cursor on the screen during tasks without active hand movement (Table 1). Thus, the movement of the cursor was stored during task A and replayed in task B. The cursor movement was stored in task C and replayed in task D, etc. In this way, the movement of red target and the green cursor across the retina were approximately similar in all tasks, while the white target was foveated in all tasks.

Note that, during successful performance of the combined eye-hand tracking task, the spatial and temporal trajectories of the eye and hand were the same (see Figs. 1B and 2C). In other words, knowledge that the eye was moving at a particular speed in a particular direction, say to the left, could be used to guide the motion of the hand to the left: there was therefore the possibility of using eye and hand inter-communication to improve performance. It is this spatially and temporally consistent movement of hand and eye that we are considering to be the principal element of co-ordination within these experiments. Even in the other tasks, there may still be co-ordination, for example within the multiple joints of the arm, but this should be equivalent across the different tasks and, thus, not be expected to contribute to the functional activation observed.

Experiment two. Cerebellar activation during visually guided eye movements

Ocular tracking responses detected in experiment 1 proved to be only just above statistical threshold (P=0.01). Hence, in a second experiment, we contrasted activation within the cerebellum during only two conditions, ocular tracking of the moving target and ocular fixation. As in experiment 1, ten axial slices were taken spanning the vertical extent of the cerebellum, excluding the dorsal cerebral areas. Repetition rate was 4.4 s, and 128 images were acquired per session. This allowed us to double the number of statistical comparisons from 32 images per condition (experiment 1) to 64 per condition.

In this experiment, subjects followed the same target waveform used in experiment 1, tracking the moving white ocular target for 17.6 s and alternating with fixation of the stationary central target. Each task lasted 17.6 s and ran in an ABAB sequence. The same imaging parameters, slice locations etc. were used as before.

Results

Experiment one. Cerebellar activation during co-ordinated eye and hand tracking

Tracking was performed under three conditions, either manual tracking alone, ocular tracking alone, or combined manual and ocular tracking.

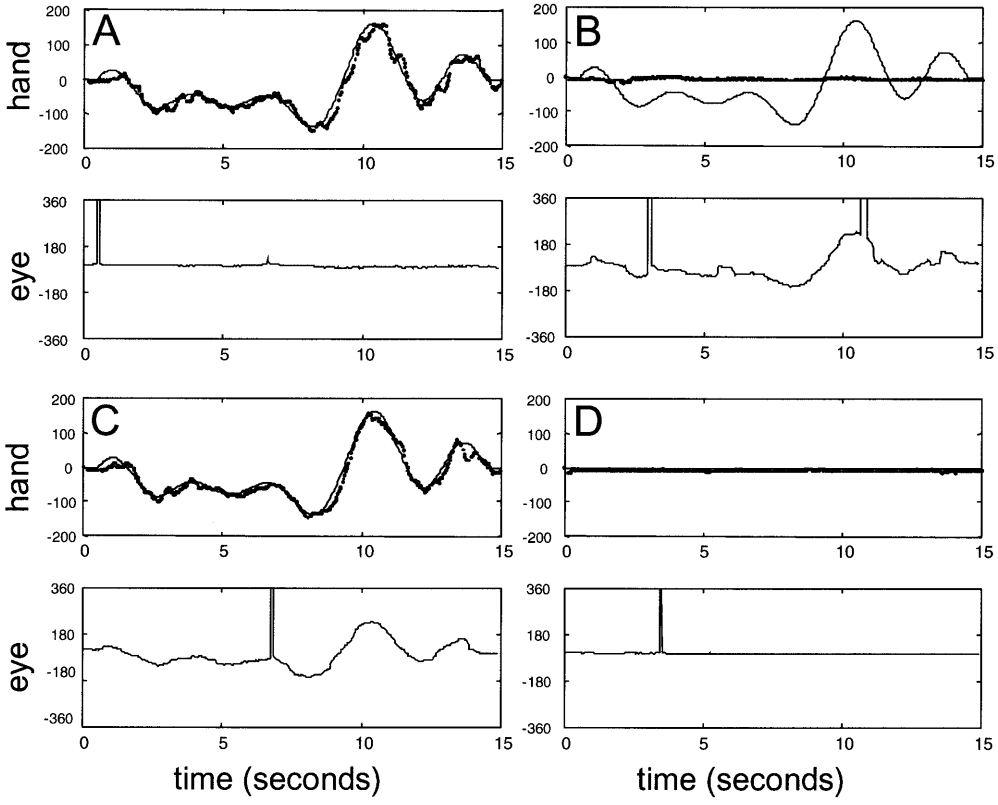

Fig. 2 Typical hand and eye recordings from subject RCM during the four different conditions (*A–D*) used in experiment 1. The *upper panels* show the horizontal component of the target trajectory (*fine line*) and the cursor trajectory (*thick line*); the *lower panels* show the horizontal eye movements. The large upward deflections in these traces represent blinks. Units of horizontal motion are in screen pixels

Ocular tracking

Recordings of eye movements were made outside the scanner, using the same target waveform and with the same angular deviation and velocities of target; the targets were displayed and viewed directly on a VGA computer monitor, although intensity and contrast were set approximately equal. Tracking was performed with a mixture of smooth pursuit and frequent small saccades. There were no gross differences between the eye-movement traces in the eye-only and eye-hand conditions (Fig. 2A, C).

Manual tracking

The subjects' manual tracking errors and mouse path-length were recorded during the scanning sessions and demonstrated that approximately equal tracking performance was achieved in the hand-only and the eye-hand conditions. We recorded the total movement of the cursor every 4.4 s (Fig. 3A) and also the positional distance of the cursor from the target. The distance moved by the mouse was 4% greater in the hand only condition than in the eye-hand condition ($F_{1,10}$=2.84, P=0.12, ANOVA). Due to a programming mistake, we saved the positional distance between the cursor and the ocular target in the eye-hand tracking conditions and the error between the cursor and the manual target in the hand-only condition. However, we were able to reconstruct the cursor-to-ocular target "fixation error" for both conditions by measuring the errors in the record and playback conditions, and this allowed another comparison of the manual performance in the two manual tracking conditions (Fig. 3B). Again, there were no significant differences between the two tasks (fixation errors were 8% lower in the hand only condition than in the eye-hand condition, but this was not statistically significant: $F_{1,10}$=3.40, P=0.09, ANOVA).

There is a strong periodic pattern to the path-length and tracking-error data in Fig. 3 because the pseudorandom target waveform varied in its speed and direction. The target trajectory was reset to the start of the waveform every 17.6 s; the waveform repeat rate was 15 s, so that the waveform and scan acquisition would, unless reset, synchronise only once every 100 s. By resetting the waveform, all functional scans were performed under similar task-difficulty conditions. However, it was then possible that the subjects might have improved their performance over time, as they could have acquired knowledge of this repeated target function. This did not appear to be the case; Fig. 3 indicates similar scatter of the errors and mouse path-length across the 128 scans (duration 9.4 min); the slopes of regression lines through these data sets were not significantly different from zero (P>0.6).

Functional activation

Visual tracking using the hand-held computer mouse activated with very high significance cerebellar regions

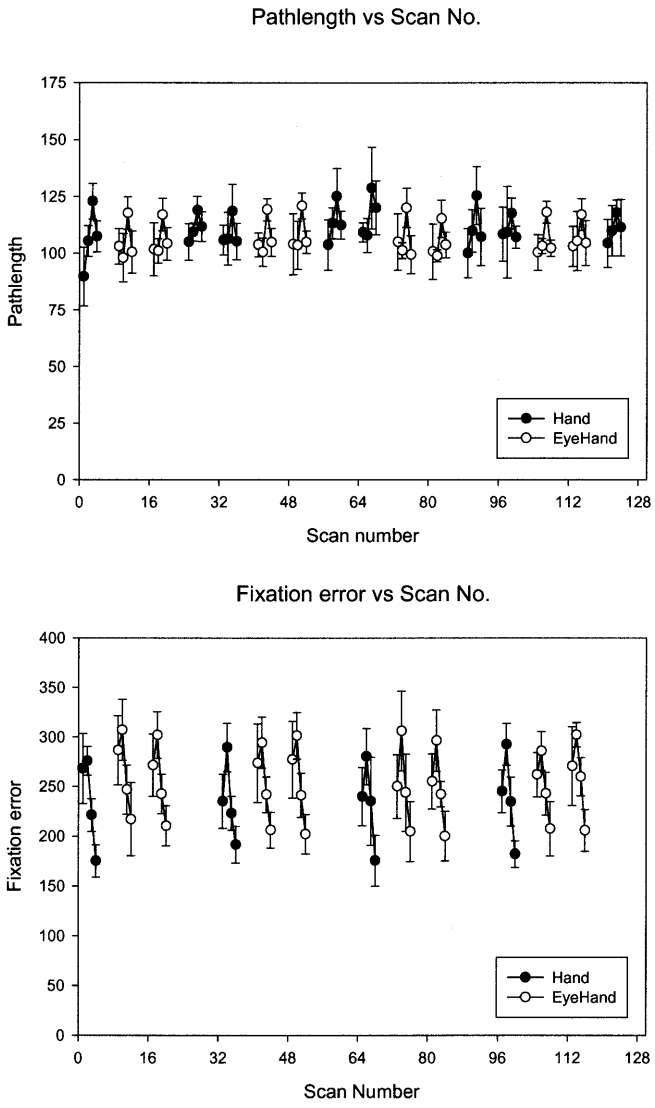

Fig. 3 Mean and standard deviation of the manual tracking performance scores for all subjects (three subjects, two repetitions). The *upper panel* indicates the total movement of the cursor in each 4.4-s period (*pathlength*), while the *lower panel* indicates the "fixation error" – the average distance between the cursor and the fixation point. The data was not recoverable in every other hand-tracking condition

consistent with the active use of eye and right hand, as well as areas in striate and pre-striate cortex consistent with visual processing of the target and cursor motion. Because of the slice locations, we cannot report cerebral activation sites above the level of the basal ganglia (approximately above z=16 mm, Talairach and Tournoux 1988); however, below this axial level, we did not observe any areas of significant activation outside the cerebellar, posterior parietal and occipital cortical areas.

Contrasting all tracking movement versus fixation

Comparing all the three tracking tasks (tasks A–C) versus the baseline condition (task D), there was a broad area of significant activation across the anterior lobe and anterior vermis of the cerebellum (Fig. 4B–D), with peak activation in the intermediate cortex of the ansiform lobule (Duvernoy 1995) ipsilateral to the tracking hand (Fig. 4C). There was also a significant activation site in the contralateral anterior lobe (Fig. 4C) and a strong activation site in the ipsilateral posterior lobe of the cerebellum, in what we have identified as the ipsilateral paramedian lobe, but which may also include parts of the dorsal paraflocculus (biventer lobule, Fig. 4F, G). There was a very small corresponding area of contralateral paramedian activation (Fig. 4F). There was also strong activation of visual cortical areas (Fig. 4A, B). There were no activated loci that could be unambiguously located in the cerebellar nuclei; this is not unexpected with functional imaging at 1.5T.

Activation during hand movement

Testing the main effect of hand movement (tasks A and C, both with hand movement, against tasks B and D, both without hand movement) demonstrated significant activation of the same cerebellar areas as shown in Fig. 4 (data not shown, see Table 2). Peak significance levels were slightly higher, and the extent of the activated areas slightly larger. Thus, the major contributing factor to the contrast shown in Fig. 4 was that due to hand tracking movement. Contrasting just the hand-only condition with the fixation condition (task A vs D) confirmed this; the same set of areas shown in Fig. 4 were activated, with comparable levels of significance (Table 2).

Activation during eye movement

Testing the main effect of eye movement (tasks B and C, both with eye movement, against tasks A and D, both with ocular fixation) resulted in no significant activation sites except in occipital areas. Primary visual cortex and an area corresponding in MT/V5 were activated, as they had been in other contrasts (e.g. Fig. 4). Contrasting the eyes-only condition against the fixation condition (task B vs. D) showed a small area of vermal activation just below the standard statistical thresholds used for all other analysis (reduced from P=0.001, k=2 to P=0.01, k=1) in the same location as activated in Fig. 4D.

Activation during co-ordinated eye and hand movement

To examine activation due specifically to co-ordinated eye movement, we contrasted the eye-hand condition with hand-only condition (task C vs. A). This showed weak activation of the visual areas seen in Fig. 4, but no significant activation in the cerebellum. Thus, as before, the contribution of eye movement to the cerebellar activation was negligible in this experiment.

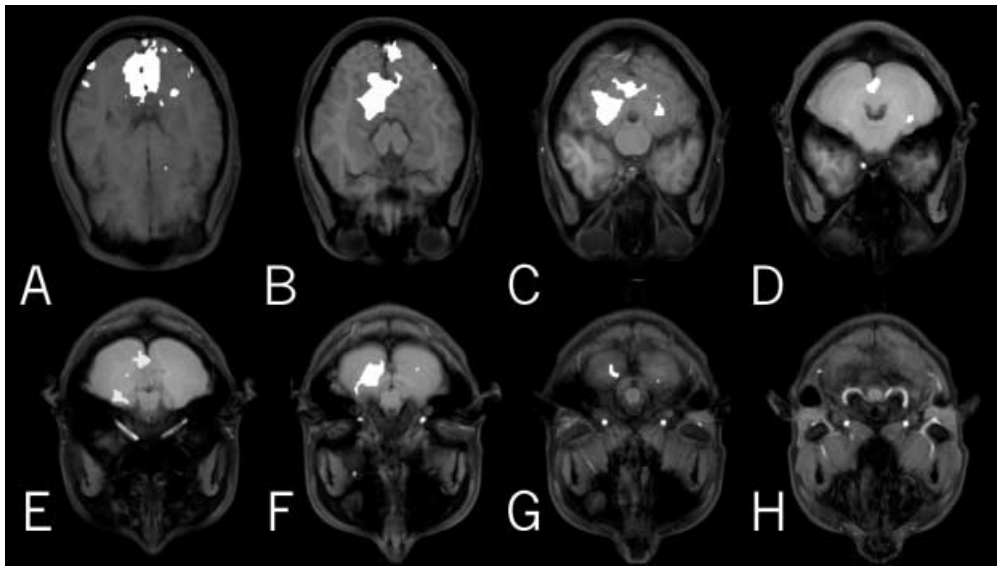

Fig. 4A–H Contrast of all tracking conditions versus rest (tasks A, B, C vs. D; experiment 1). Strong activation was observed in visual cortical areas (**A, B**) and very significant activation seen in the ipsilateral hemisphere (ansiform lobule) of the cerebellum (**C**), vermis (**D–E**) and paramedian lobule (**F, G**)

Table 2 Functional activation of cerebellar sites during eye and hand tasks: regional activation clusters characterised by the volume of each region (*k*), its significance based on spatial extent *P*(*n*max>*k*), the highest *Z* value (*u*), its corrected significance *P* based on *P*(*Z*max>*u*) and the location of this primary maximum. Up to three secondary maxima (*light font*) are included for each major region (*bold font*) with their associated significance based on the corrected *P* values. The co-ordinates given are in millimetres, calculated from the voxel location of the peak; these are approximately equivalent to Talairach and Tournoux (1988) co-ordinates, following a rigid body rotation and translation of the normalised images shown in the figures. *Ansi.* Ansiform lobule, *Post Ansi.* posterior ansiform lobule, *Paramedian* paramedian lobule with possible involvement of biventer lobule

Experiment	Conditions (contrast)	Lobule	Cluster *P**	Voxels	Voxel *P***	Max *Z*	*X*	*Y*	*Z*
1	All movement (tasks A, B, C vs. D)	Ansiform	**<0.001**	**1581**	**<0.001**	**7.90**	**–20**	**–45**	**–17**
		Ansi./Vermis	–	–	<0.001	7.82	–9	–49	–5
1	Main effect: hand (tasks A, C vs. B, D) s002210000489	**Vermis**	**<0.001**	**1466**	**<0.001**	**8.98**	**–9**	**–49**	**–5**
		Vermis	–	–	<0.001	8.67	–2	–62	–12
		Ansiform	–	–	<0.001	8.88	–20	–45	–17
		Contra Ansi.	–	–	<0.001	7.76	25	–46	–17
		Paramedian	–	–	<0.001	8.55	–17	–63	–40
1	Main effect: eye (tasks B, C vs. A, D)	**Occipital**	**<0.001**	**970**	**<0.001**	**8.42**	**–11**	**–65**	**8**
1	Hand movement alone (task A vs. D)	**Vermis**	**<0.001**	**1137**	**<0.001**	8.43	**–9**	**–49**	**–5**
		Vermis	–	–	<0.0001	7.26	–2	–70	–19
		Ansiform	–	–	<0.001	8.41	–20	–45	–17
		Paramedian	–	–	0.001	8.20	–17	–63	–40
		Contra Ansi.	**0.001**	**115**	**<0.001**	**6.68**	**29**	**–41**	**–27**
		Contra Ansi.	–	–	<0.001	6.64	25	–46	–17
1	Co-ordinated hand movement (task C vs. B)	Ansiform	**<0.001**	**1258**	**<0.001**	**8.53**	**–9**	**–49**	**–5**
		Ansiform	–	–	<0.001	8.32	–20	–45	–17
		Vermis	–	–	<0.001	8.15	–2	–62	–12
		Paramedian	–	–	<0.001	8.00	–17	–63	–40
1	Coordinated eye and hand movement (task C vs. A, B)	**Ansiform**	**<0.001**	**500**	**<0.001**	**6.26**	**–15**	**–47**	**–6**
		Vermis	**<0.002**	**52**	**<0.001**	**5.91**	**–3**	**–67**	**–20**
		Vermis			<0.001	3.79	4	–63	8
		Ansiform	–	–	0.003	5.26	–15	–45	–17
2	Eye movement (task B vs. A)	**Paramedian**	**0.021**	**35**	**0.001**	**5.54**	**–15**	**–49**	**–44**
					0.002	5.35	–3	–67	–30
					0.225	4.30	15	–61	–41
		Post. Ansi.	–	–	0.290	4.22	–18	–33	–39
					0.429	4.08	–11	–38	–37
		Ansiform			**0.000**	**6.26**	**–30**	**–51**	**–25**
		Vermis	–	–	0.000	6.48	6	–61	–22
		Paramedian	**0.033**	**19**	**0.003**	**5.33**	**19**	**–33**	**–39**

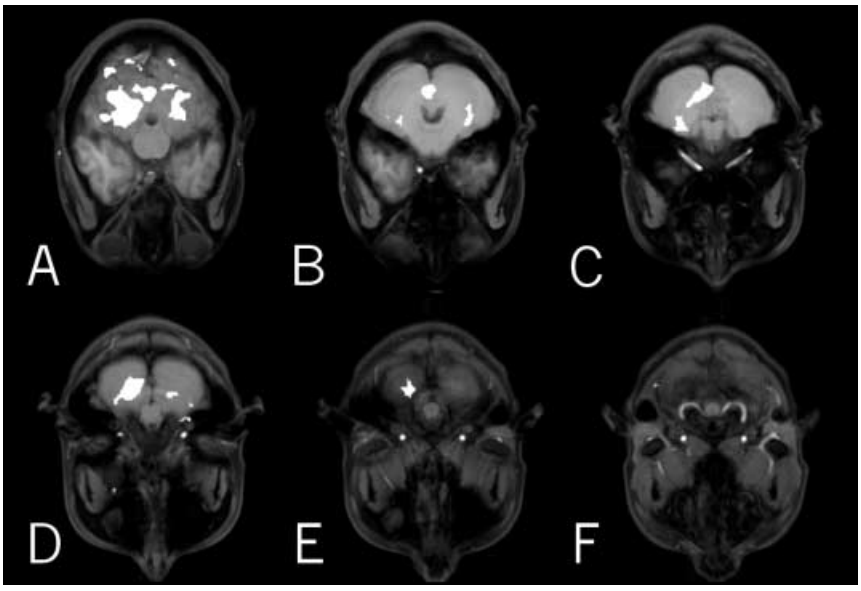

Fig. 5A–F Comparison of the eye-hand versus eye-only conditions (task C vs. B; experiment 1). These consecutive axial slices correspond to panels **C–H** of Fig. 4

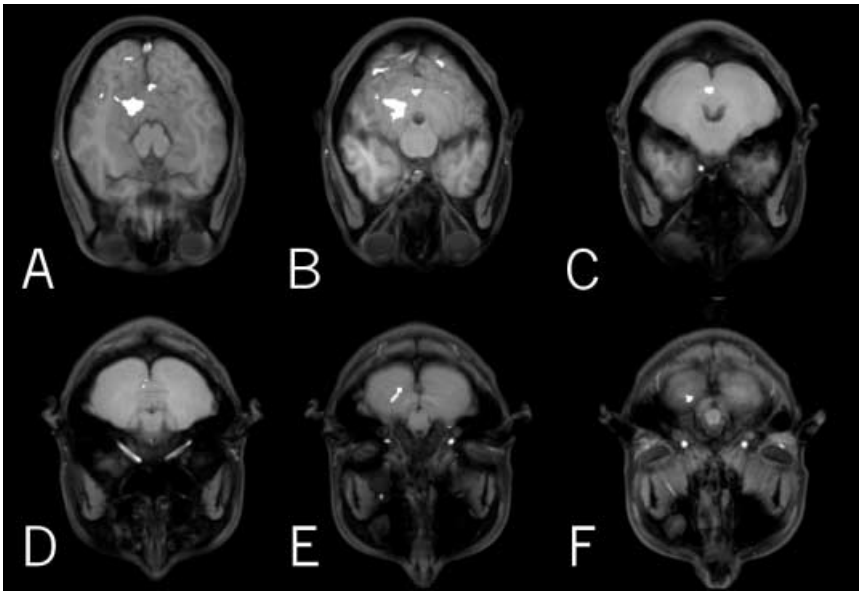

Fig. 6A–F Comparison of the eye-hand versus eye or hand (task C vs. A and B; experiment 1) conditions, showing increased activation during co-ordinated eye and hand tracking tasks. Areas of significance were more activated in the eye and hand condition. Notice also the vermal area activated in **B**. These consecutive axial slices correspond to **B–G** of Fig. 4.

To examine activation specifically due to co-ordinated hand movement, we contrasted the eye-hand condition with eyes-alone (task C vs. task B). The hand-movement related areas seen in Fig. 4 were again activated (Fig. 5), which was of course expected in this contrast because of the addition of the hand movement to the common eye tracking. However, the vermal area was also significantly activated (Fig. 5A, B). Thus, despite there being similar eye movement in both tasks, this area was significantly more activated when the hand was used in co-ordination with the eyes.

Finally, contrasting the eye-hand condition against both eye-only and hand-only (task C vs. tasks A and B) activated restricted regions in the cerebellum similar to those observed in hand-only tracking (compare Fig. 6B, C with Fig. 4C, D), with activation of ipsilateral ansiform lobule and the vermis. However, in this contrast, there was greatly reduced activation within the posterior cerebellar regions (Fig. 6E, F). Thus, the ansiform and vermal cerebellar areas activated by hand tracking alone were significantly more activated during co-ordinated eye and hand tracking. The paramedian/biventer lobule activity was only marginally more activated in the combined eye-hand task than in the hand-only task.

Experiment two. Cerebellar activation during visually guided eye movements

To improve the statistical significance of the activation during ocular tracking, we doubled the number of comparisons between ocular tracking and fixation. There was

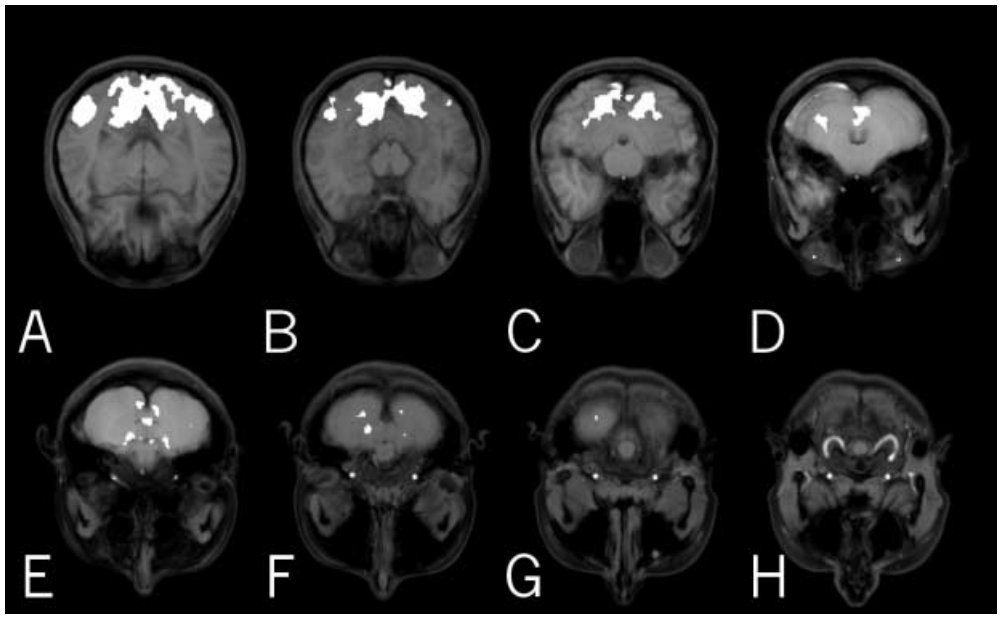

Fig. 7A–H Functional activation during ocular tracking (experiment 2). Strong activation is seen in visual cortical areas (**A–C**), including extrastriate motion-sensitive areas MT/V5 (**A**). The most pronounced cerebellar-activation cluster was in the vermis (**D**), although there were small activation sites in bilateral areas of intermediate cortex (**E**) and paramedian and/or biventer lobules (**F**). These consecutive axial slices correspond to those of Fig. 4, spatially normalised onto the brain of a different subject

no hand-tracking component to this task, and the only target displayed on the screen was the white square, which either followed the same trajectory as used in the other experiments, or remained stationary at the screen centre. The ocular tracking condition most strongly activated the primary visual cortex (Fig. 7), and the two extra-striate areas weakly activated in the other tracking conditions (compare Fig. 7A with Fig. 4A). There was also significant activation at the same site in the oculomotor vermis (Fig. 7D, E) as previously seen at a low significance level. Restricted parts of the sites in the ansiform, paramedian and biventer lobules of the cerebellum that had been activated by hand movement without eye movement (Table 2) were also significantly activated (Fig. 7D, F, G).

Discussion

There are three main points for discussion from these results. First, there were two activated areas in the lateral ansiform and paramedian lobules of the cerebellum concerned with visually guided hand movements. Second, there was also significant vermal activation seen with ocular tracking. Third, the lateral site in the ansiform lobule and the vermal site were strongly activated by hand and eye movement, respectively, but were each significantly more activated in co-ordinated eye and hand tracking than the summed activity in hand-alone or eye-alone tracking.

Together, these results support the hypothesis that the cerebellum makes a particularly important contribution to movements under direct visual control. We suggest that the last result provides support for a role of the cerebellum in the co-ordination of eye and hand movements.

First, the two main areas in cerebellar cortex concerned with visually guided hand movements, in the lateral ansiform lobule and paramedian lobule, have now been documented several times in different movement tasks (Ellerman et al. 1998; Flament et al. 1996; Jueptner et al. 1997a, 1997b). The ansiform activation areas are also consistent with sites explored electro-physiologically in monkeys performing visuo-motor tracking tasks (Ebner and Fu 1997; Marple-Horvat and Stein 1987, 1990; Miall 1998; Ojakangas and Ebner 1992; Thach et al. 1992), while inactivation of this area in monkeys leads to ataxic movement of the ipsilateral arm and wrist (Miall et al. 1987). The paramedian site has not often been explored electro-physiologically. However, it is not clear from the current experiments whether this activation site lies only within the paramedian lobule or if it includes activation of the adjacent biventer lobule. This is the human analogue of the dorsal paraflocculus in the monkey and is known to have many cells responsive to visual motion (Glickstein et al. 1989; Stein and Glickstein 1992) or both arm movement and visual motion (Marple-Horvat and Stein 1990).

Second, it seems that there is a selective activation of the cerebellar vermis in these visuomotor tracking tasks. Inoue et al. (1998) found in a comparison of reaching movements to visual targets with and without visual feedback that the vermis was the only cerebellar site associated with the visual-feedback condition. Ellerman et al. (1998) then contrasted a similar step-tracking task with non-visually guided eye or hand movements (movement in complete darkness) and showed that the vermal activation in their visually guided condition was not seen in the non-visual arm movement condition. Jueptner et al. (1996) found lateral cerebellar cortical and posterior lobe vermal activation in a PET study comparing a line-re-tracing task with a new line-drawing task, indicating again that the vermis is particularly activated in the visual feedback controlled condition. Interestingly, Jueptner et al. (1997a) suggest that the majority of cerebellar acti-

vation in their tasks was related to sensory input, rather than motor output. Therefore, with regard to the activation reported in this paper, we would suggest that the ansiform lobule activity is related to active movement of the ipsilateral arm and hand; the paramedian/biventer activity is likely to be concerned with integration of sensory (visual and proprioceptive) input into the visually guided movement, while the activity in the vermis is particularly concerned with visual feedback control in our task.

However, it is important to note that the vermal site activated by visually guided hand tracking without ocular tracking (Table 2, task A vs. D) was the same site most strongly activated by the eye-tracking movements. Comparison of eye tracking versus fixation in experiment 1 produced almost no statistically significant activation ($P>0.01$); in experiment 2, we increased the power of the contrast between visual fixation and visual tracking, and were then able to demonstrate activation of the vermis (Fig. 7). There was no arm movement required in experiment 2 and so the vermal activation was clearly the result of the contrast in eye-movement conditions. This site is likely to lie within lobules VI and VII, the "oculomotor vermis". It is interconnected to the oculomotor nuclei via the fastigial nucleus and is clearly an important cerebellar region for oculomotor control (Carter and Zee 1997; Krauzlis and Miles 1998; Ohtsuka and Noda 1991; Takagi et al. 1998).

The third main discussion point is that, when looking at the areas more activated by the co-ordinated eye- and hand-tracking task in experiment 1, it was again the ansiform lobule and the vermal site that stood out (Fig. 6). There are two interpretations: that the increase reflects some new activation in the same or similar vicinity that is only seen in the co-ordinated task and is not seen in other tasks, or that it is the same areas which are activated by either eye or hand movement and that we have simply seen the combined activity when both were being used together. We would suggest that the former interpretation is more likely. First, the contrast used (–1, –1, +1, 0) tests for voxels with signal levels that are significantly greater than the sum of the signal level for the eye only and hand only conditions. This makes a less-stringent prediction than the conjoint analysis available in SPM, which would test for increases in activation level of equal magnitude from eye to eye-and-hand tracking as from hand to eye-and-hand tasks. Such a conjoint prediction is not justified for our data because of the greater activation observed in the hand task than in the eye task. However, our contrast could be confounded by an increase in activity in one task (e.g. hand) and a reduction in the other (eye), as the sum would then be smaller than the maximum. Testing the individual contrasts (hand vs. rest and eye vs. rest) showed that all the areas concerned were increased in activity in each condition, and so the use of this comparison is valid. Hence, the areas indicated in Fig. 6 are significantly more activated than expected from the linear sum of the activity in the individual eye or hand tracking conditions. Supra-linear summation does not exclude a passive additive process. However, functional activation recorded with PET or fMRI is usually a declining function of motor performance (Dettmers et al. 1995; Jenkins et al. 1997), so one might predict sub-linear, rather than supra-linear summation if there was only a passive combination of the two activation levels. We suggest that there is indeed extra neural activation seen in the co-ordinated movement task, over and above that seen in the two individual motor tasks.

Second, there is the behavioural evidence that co-ordinated eye and hand tracking is more effective than independent eye or hand tracking alone (Abrams et al. 1990; Biguer et al. 1984; Koken and Erkelens 1992; Van Donkelaar 1997; Vercher et al. 1994). We did not see significantly better manual tracking performance in the co-ordinated tracking condition (Fig. 3), although the total mouse movement was somewhat smaller, suggesting smaller or fewer intermittent corrective movements (Miall et al. 1986, 1987). However, our measures of tracking performance were relatively coarse. Furthermore, we deliberately chose tracking conditions to minimise differences in tracking performance, so that the resultant functional activity would not be simply confounded by overt changes in performance. This choice had been successful, as there were no statistically significant differences between the mouse-tracking errors or mouse-movement distances in the two comparable conditions. It is possible, of course, that some other uncontrolled difference between the two tracking modes used, compensatory and pursuit, may have affected the cerebellar activation levels. Further experiments will be needed to resolve this point.

Third, there is the evidence that the cerebellum is a key site in the co-ordinative process (Van Donkelaar and Lee 1994; Vercher and Gauthier 1988). Clearly, if the increase in functional activation in the cerebellum were simply the result of the addition of two independent processes, there would be no reason to expect lesions in this structure to specifically effect co-ordinated eye and hand movement, rather than effect both non-specifically.

There are many lines of evidence that suggest the cerebellum – particularly the lateral hemispheres – may have roles other than control of movement. Possible influences on functional activation in our tasks include attention (Allen et al. 1997; Coull and Nobre 1998), sensory processing (Gao et al. 1996; Jueptner et al. 1997a), error detection (Flament et al. 1996; Inoue et al. 1998) or motor learning (Flament et al. 1996; Jueptner et al. 1997b; Shadmehr and Holcomb 1997). These roles are not necessarily exclusive – we do not imply that, because the cerebellum is concerned with motor control, it cannot also be concerned with other processes (Miall and Wolpert 1996). However, Allen et al. (1997) showed that the area activated by a motor task was different from that activated by a cognitive (attention shift) task: the attention task activated most commonly the left superior posterior cerebellum, more lateral than the activation sites we observed in this study, while their motor task activat-

ed the anterior parts (the anterior portion of the quadrangular lobule), the same area strongly activated in the eye-hand task in our study.

We also took care to balance the visual inputs within the four conditions of experiment 1, and sensory inputs associated with eye or hand movement would not be expected to differ in these tasks. The spatial separation between ocular and manual targets on the screen (Fig. 1) is not expected to affect the cerebellum. Clower et al. (1996) reported only activity in area PEG of the posterior parietal lobe, and not cerebellum, due to the reintegration and alignment of visual and proprioceptive representations of the hand distorted by prism lenses.

The cerebellum has been proposed to be concerned with error detection or error processing, and in motor learning (see Clower et al. 1996; Cordo et al. 1997; Kitazawa et al. 1998). However, our subject's performance in these tasks was stable over time and similar across conditions (Fig. 3). Hence, there is no reason to suppose differential cerebellar activation because of tracking errors in the different conditions, nor significant motor learning during scanning. The equivalent performance across the tasks also suggests that the contrast between the conditions is not likely to be confounded by the increase in difficulty moving from single tasks to dual tasks. The final aspects of the task that would be expected to sensitively activate the cerebellum are tracking speed and velocity errors. We can estimate these from the total mouse movement and tracking errors (cumulatively measured every 4.4 s), which were not significantly different in the two tasks. In fact, the total mouse motion was smaller in the eye-hand condition than in the hand-only condition, and thus the difference in average speed is of the wrong sign to explain the increased cerebellar activity observed.

Thus, we argue that the cerebellum is particularly concerned with inter-communication between different motor effectors, to allow co-ordinated control. Visually guided control of the arm involves communication from oculomotor centres carrying information about the position and velocity of the eye motion, as these define the target's motion. Likewise, signals from the arm-control centres provide information that allows the eyes to accurately track the hand through visual space. So one might expect that the oculomotor site, active in eye tracking, would be more active in eye and hand tracking, if it then receives and processes information from the hand control site. The same would be expected for the hand-control areas. However, there are no direct connections between the cerebellar cortical regions shown to be activated by these experiments. Hence, the communication must involve extra-cerebellar relays, perhaps including areas in the premotor cortices or the cortical eye fields. It is our aim to now test cerebral areas in the same tasks to challenge this point.

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