Activation of Cerebellar Hemispheres in Spatial Memorization of Saccadic Eye Movements: An fMRI Study

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Abstract: What mechanisms allow us to direct a precise saccade to a remembered target position in space? The cerebellum has been proposed to be involved not only in motor and oculomotor control, but also in perceptual and cognitive functions. We used functional MRI (Echoplanar imaging at 1.5 T) to investigate the role of the cerebellum in the control of externally triggered and internally generated saccadic eye movements of high and low memory impact, in six healthy volunteers. Memory-guided saccades to remembered locations of 3 targets (triple-step saccades) in contrast to either central fixation or to visually guided saccades activated the cerebellar hemispheres predominantly within lobuli VI-crus I. The same areas were activated when an analogous visuospatial working memory task was contrasted to the triple-step saccades. Visually guided saccades activated the posterior vermis and the triple-step saccades, contrasted to the working memory task, activated predominantly the posterior vermis and paravermal regions. Our data confirm the primary involvement of the posterior vermis for visually-triggered saccadic eye movements and present novel evidence for a role of the cerebellar hemispheres in the mnemonic and visuospatial control of memory-guided saccades. *Hum. Brain Mapp. 22:155–164, 2004.*
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Key words: cerebellum; visually-guided; memory-guided; saccades; fMRI

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INTRODUCTION

Once an object has captured our attention, even if briefly and inadvertently, we are able to perform quite precise memory-guided saccadic eye movements toward it. What are the mechanisms that allow for such precise transformation of the spatial information held in our memory into precise eye movements towards remembered targets? Anatomical and electrophysiological experiments in primates as well as clinical data demonstrate a role especially of the posterior vermis and the fastigial nucleus in controlling the accuracy and timing of saccades [Büttner, 1999; Fuchs et al., 1993; Kase et al., 1980; Suzuki and Keller, 1988; Thier et al., 2000]. PET studies demonstrate activation of the vermis during saccades [Dejardin et al., 1998; Desmurget et al., 1998; Sweeney et al., 1996] and of the cerebellar hemispheres during motor learning [Seitz et al., 1990; Thach, 1996]. In addition to motor or oculomotor tasks, cerebellar hemispheric activation was demonstrated using cognitive tasks

such as sensory discrimination, problem solving, or a pure attention task [Allen et al., 1997; Gao et al., 1996; Kim et al., 1994]. But the involvement of the cerebellum in higher cognitive functions is still a matter of controversy [Leiner et al., 1993; Schmahmann and Sherman, 1998]. Anatomical data in the monkey propose a functional segregation within the cerebellar hemispheres, as the motor cortical areas project to the anterior lobe, prefrontal areas to lobuli VI–VII, and parietal areas to lobuli VII–VIII [Brodal and Bjaalie, 1992] (see Fig. 5). The purpose of this study was to use fMRI to explore the role of the human cerebellum for the performance of saccadic eye movements with different cognitive demands. We investigated the functional significance of the postulated cerebro-cerebellar connections by looking for saccade-specific activation in the vermis and for memory-related activation for the hemispheres especially lobuli VI–VIII, which are connected with the parieto-prefrontal network for spatial working memory. In a task with no memory load, subjects had to perform externally triggered visually-guided reflexive saccades. In a task with a moderate memory load, they had to generate a sequence of saccades to the remembered locations of three peripheral targets that had been flashed in rapid succession. In this task, cognitive demands included suppression of reflexive saccades towards the target flashes, cueing of spatial attention to target location, spatial working memory of three target locations, internal triggering of the saccadic sequence, and spatial transformations. The latter are necessary because the second and third saccade of each trial do not start from the central fixation point, from where the three targets had been seen, but had disappeared before the first saccade. This requires updating of the second and third target's retinal coordinates by subtracting extraretinal information (e.g., efference copy) about the motor vectors of the previous saccades [Heide et al., 1995]. To further enhance the memory load and to dissociate the saccade-related components of this task from its cognitive components (e.g., working memory), we compared the triple-step task with a pure visuospatial working memory task that required memorization of the same sequence of three targets for at least 2.5 sec, but without actually performing saccades. We expected saccade-specific activation in the posterior vermis and activation of the hemispheres in the memory conditions.

SUBJECTS AND METHODS

Subjects

Six right-handed subjects (4 men, 2 women; age range 25–35 years) were studied. None of the subjects had a current or past history of neurological or ophthalmological disorders and all were normal on examination. The study was approved by the local Ethics Committee. All subjects gave written informed consent prior to examination after the nature of the experimental procedures was explained.

Imaging and Data Analysis

We performed functional MR images of cerebral blood oxygen level-dependent signal changes (BOLD) at 1.5-T (Siemens Vision, Erlangen, Germany; standard headcoil) using echoplanar sequences (TR/TE/flip angle = 5 sec/66 msec/90 degrees, slice thickness 4 mm) of the brain in 30 contiguous horizontal slices parallel to the intercommissural line covering the whole brain. The field of view was 200 × 200 mm in a 64 × 64 matrix, voxel size was 3.12 × 3.12 × 4 mm³. Analysis was focussed onto the cerebellum.

Image analysis was performed on a Ultrasparc Sun workstation (Sun Microsystems, Palo Alto, CA) using MATLAB (Mathworks, Natick, MA) and the statistical parametric mapping package (SPM96b, Wellcome Department of Cognitive Neurology, London, UK) [Friston et al. 1995, 1997]. The imaging data were corrected for head movements and signal intensity variation and transformed into a standard stereotactic space [Tailarach and Tournoux, 1988]. During spatial normalization, pixels were smoothed with a 4-mm isotropic Gaussian kernel. The effects of global volume activity and time were removed as confounds, using linear regression and sine/cosine functions. Removing the latter confounds corresponds to high-pass filtering of the time series to remove low-frequency artefacts, which can arise due to aliased cardiac and other cyclical components. The contrast between task and control conditions was thresholded at $P < 0.05$ (uncorrected) for each voxel using the delayed box-car reference function of the SPM96b software. For visualization, color-coded quantitative maps of positive contrasts were superimposed on corresponding T1-weighted templates. The anatomical nomenclature was based on the three-dimensional atlas of the human cerebellum in proportional stereotactic space by Schmahmann et al. [1999] (see Table II for a summary of the Talairach coordinates, converted from the MNI-brain).

Experimental Protocol

The protocols consisted of 6 cycles of an activation (25 sec) and a control condition (25 sec) resulting in 60 images per session in block design (63 images were measured, but the first three images were discarded to avoid technical artefacts). Visual stimuli were presented with a red laserpoint (diameter 0.5 degrees, luminance 23.1 cd/m², background luminance <0.02 cd/m²) projected onto a screen in front of the scanner and visualized by a mirror attached to the headcoil. An external computer controlled the stimulation protocol and movements of the laser point that were driven by a mirror galvanometer (General Scanning). The task designs (A,B, and C) were measured in all 6 volunteers and the task sequence was pseudorandomized to counterbalance possible task specific influences. Task D was added to the task protocol for 3 volunteers.

Task Design (see Fig. 1)

A. Visually-guided saccades (VG) vs. central fixation (Fix): Peripheral targets with different horizontal eccentricities
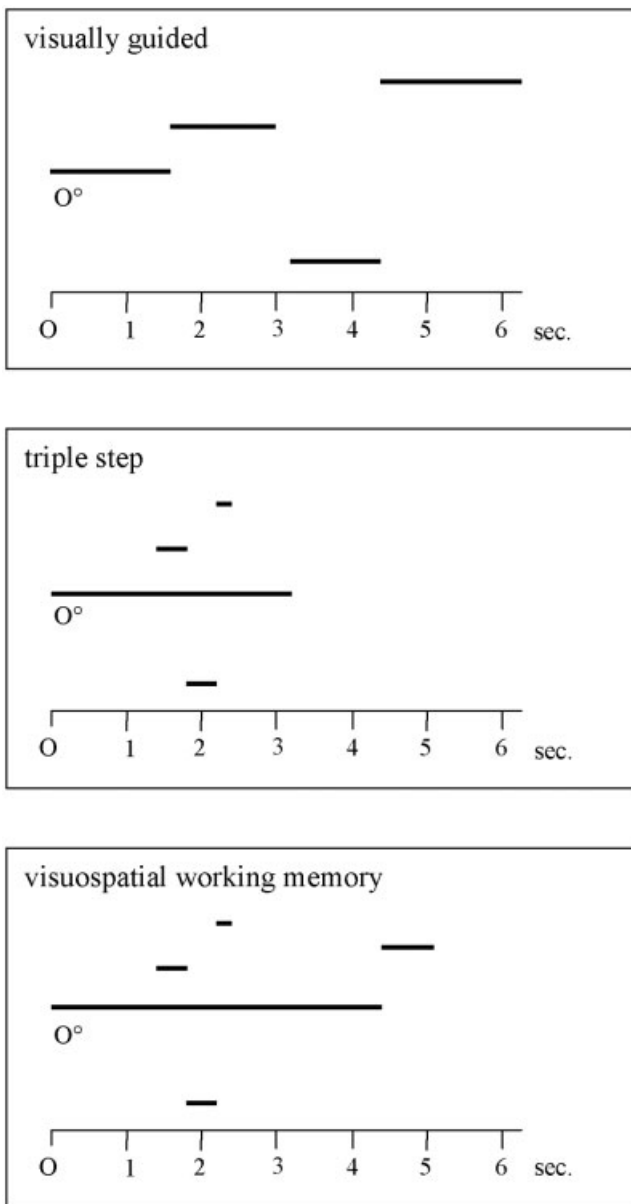
Figure 1.

Schematic plots of the tested saccade tasks (visually-guided saccades, triple-step saccades, and a test for visuospatial working memory). Upward deflection means rightward deviation, ranging between 0 degrees and 10 degrees of visual eccentricity, downward deflection means leftward deviation, respectively. On the abscissa, time is plotted in seconds. After 6.25 sec, the central fixation point reappears to start the next sequence. During the triple-step task, the 3 targets had to be memorized while subjects kept on fixating the central fixation point. After a delay of 750 msec (memorization time), the fixation point disappeared as the go-signal to perform saccades to the memorized locations of the three targets in the presented order. For the visuospatial working memory task, the target had to be acquired by a single visually-guided saccade only when its location was identical to one of the three targets presented before, which happened randomly in 50% of the trials.

(5–10 degrees) were presented successively for a pseudo-randomized time interval of 1,200–1,800 msec to trigger 16 saccades balanced throughout one activation period (25 sec). The fixation point alternated between the left and the right visual hemifield, equally distributed within the whole sample of trials in a pseudorandomized order. The instruction was to continuously track the target. The control condition (Fix) was fixation of the stationary laserpoint positioned in the center of the field of view.

B. Triple-step saccades (TR) vs. Fix: After the presentation of a central fixation point for 1,500 msec, 3 successively flashed laser targets were presented with different horizontal eccentricities (5–10 degrees) alternating between the left and the right visual hemifield analogous to A in a pseudorandomized order. Presentation times were 400, 300, and 200 msec for the three targets that had to be memorized while subjects kept on fixating the central fixation point. After a delay of 750 msec (memorization time), the fixation point disappeared as the go-signal to perform saccades to the memorized locations of the three targets in the presented order in darkness. After 3,100 msec, the central fixation point reappeared to start the next trial. Altogether, one triple-step trial lasted for 6,250 msec with 16 saccades in one activation period (25 sec, 4 triple-step trials).

C. TR as the active condition was contrasted with VG as the high baseline condition.

D. TR was contrasted with a visuospatial working memory task (WM). WM consisted of the flashed presentation and memorization of visual targets in TR sequence. After 1,500 msec of central fixation, the triple-step sequence was presented and the volunteers had to memorize the target positions. After another 2,000 msec of central fixation (memorization time), a new target was presented that had to be compared with the 3 targets presented before. This target had to be acquired by a single visually-guided saccade only when its location was identical to one of the 3 targets, which happened randomly in 50% of the trials. Four of these trials were performed during one activation period (25 sec).

In all these tasks, each activation or control condition lasted for 25 sec and was composed of four blocks of trials each lasting 6.25 sec. Before each measurement, at least one cycle of the respective task was presented for practice. Performance was controlled by infrared reflection oculography outside the scanner prior to the experiments. In addition, a qualitative assessment of the subjects' global eye movement performance (presence and direction of saccades) was obtained by electro-oculographic recordings during an fMRI measurement. For further control of subjects' fixation behaviour inside the MRI scanner, we performed an additional fMRI experiment where the active condition consisted of central fixation and the control condition of rest in darkness. As there was no significant activation of any of the cortical saccade areas, not even of the frontal eye fields, we took this as a confirmation that fixation must have been fairly stable.

TABLE I. Behavioural data: latencies and accuracies of the saccades during the oculomotor performance tasks*

	VG	TR
Latencies (msec)		
1st saccade	162 ± 40	372 ± 192
2nd saccade[a]	160 ± 25	422 ± 196
3rd saccade[a]	152 ± 28	412 ± 102
Amplitude gain		
1st saccade	0.88 ± 0.04	0.96 ± 0.12
2nd saccade	0.90 ± 0.03	0.90 ± 0.11
3rd saccade	0.89 ± 0.04	0.92 ± 0.12
Error of final eye position (degrees)		
1st saccade	0.3 ± 0.1	1.8 ± 1.5
2nd saccade	0.2 ± 0.2	3.6 ± 2.8
3rd saccade	0.4 ± 0.2	2.9 ± 1.3

*Data are presented as means ± SD. VG, visually guided; TR, triple-step. Data were collected outside the scanner prior to the fMRI experiments. [a]For TR, intersaccadic interval.

RESULTS

Behavioural Data

The latencies and accuracies of the oculomotor performance during visually guided or triple-step saccades outside the scanner are summarized in Table I. Visually-guided saccades had a latency around 160 msec with a considerable amount of reflexive saccades (latencies below 150 msec, 39% on average). Target undershot was around 11% with a gain being 0.89 on average. The target position was reached by means of a corrective saccade so that the error of final position was around 0.3 degrees. In contrast, the latencies of the triple-step saccades were around 300 msec with intersaccadic intervals above 400 msec. Due to the generation of the saccades without visual feedback, the accuracy was lower with respect to a higher error in the final eye position and higher standard deviation of their gain.

FMRI Results

All the tasks activated regions within the cerebellum in each of the six volunteers. Group analysis (exp. A) of visually-guided saccades (VG) compared to fixation (Fix) revealed activation within the posterior vermal and paravermal regions predominantly within the vermal lobuli VI–VII (Fig. 2A,B). Group analysis (exp. B) of the contrast between the triple-step task (TR) and fixation resulted in the predominant activation of the left cerebellar hemisphere corresponding to lobuli VI-crus I (Fig. 2C, one volunteer had to be excluded from analysis of this task performance because of movement artefacts). The study was centered on cerebellar activation, but to demonstrate the differential prefrontal and parietal activations during the TR-task, we added a comparison of the cerebral activation maps for visually-guided and triple-step saccades (Fig. 2D).

In addition to experiment A+B, where central fixation served as control, we used a differential task design with TR as active condition and VG or WM as control. The intention was to control for different oculomotor and cognitive components of the triple-step task (Fig. 3). VG implied the same oculomotor output as TR, i.e., the same sequence of saccades. The contrast between TR and VG (Fig. 3, left column) revealed activation of both cerebellar hemispheres within the lobuli VI-crus I (z coordinates of −26 to −30), identical to the area activated during TR with central fixation as control. Another area was activated within the lower part of the left cerebellar hemisphere located within the lobule VIIB-VIII (z −48). To further separate the oculomotor from the visuospatial, attentional, and working memory components of the triple-step task, we compared the triple-step task with the visuospatial working memory task (WM) in three volunteers. Visual stimulation in WM was identical to TR, the working memory load was higher as the memorization time was longer. TR as contrasted to WM demonstrated predominant activation within the posterior vermis. The reverse comparison (WM as active condition, TR as control) activated areas within the hemispheric lobuli VI-crus I and the lower part of the left cerebellar hemispheres lobuli VIIB-VIII (Fig. 3, middle and right columns), close to the activation foci of the triple-step task (Fig. 3A,C, left column). Table II summarizes the x,y,z coordinates and the Z-scores of the peak activations corresponding to the stereotactic brain atlas by Talairach and Tournoux [1988].

The concomitant cerebral and cerebellar activated regions are surveyed in Table III to demonstrate the activation of the typical network of the frontal eye field (FEF), supplementary eye field (SEF), and parietal cortex by visually guided saccades and additional prefrontal activations due to the additional mnemonic components in the TR task or the differential task designs. Oculomotor tasks activated the network of FEF, SEF, parietal cortex, and Vermis, whereas mnemonic tasks additionally involve the prefrontal cortex and the cerebellar hemispheres.

Figure 4 schematically displays the activation foci within the Talairach space and overlaid onto a flattened surface of the cerebellum. The tasks with a dominant oculomotor component (visually guided saccades, triple-step vs. visuospatial working memory) are preferentially oriented along the midline, whereas the tasks with a cognitive preload localize within the lateral hemispheres.

DISCUSSION

In accordance with previous studies, the conditions of our study that tested the execution of saccades (VG-Fix and TR-WM) activated the posterior vermis within lobuli VI–VII and adjacent paravermal areas. Electrophysiological experiments and clinical data have presented evidence that the posterior vermis in lobule VI/VII is involved in the direction selective control of saccade metrics [Fuchs et al., 1993; Kase et al., 1980; Suzuki and Keller, 1988] and of saccadic adaptation [Barash et al., 1999; Desmurget et al., 1998]. Lesion data demonstrate similar results. Unilateral lesions of the oculomotor vermis result in hypometric ipsilateral and hypermetric contralateral saccades [Aschoff and Cohen, 1971;
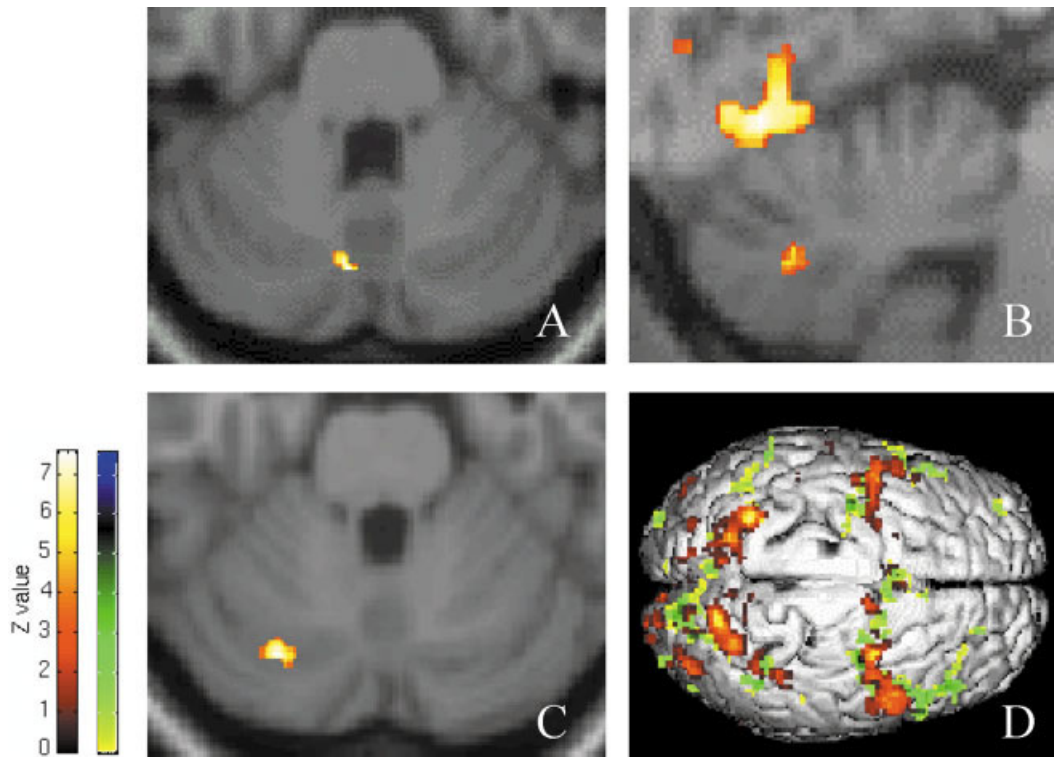
Figure 2.

Group analysis data (6 volunteers) demonstrating the activation of the posterior vermal lobules VI–VII by visually guided saccades (VG) in transversal (**A**) and sagittal projection (**B**). **C:** The triple-step task (TR) predominantly activates the left lobuli VI-crus I (5 volunteers, one excluded because of movement artefacts). **D:** Cerebral activation foci by visually-guided saccades (red) including the network comprising of the frontal eye field, supplementary eye field, parietal cortex, and visual areas. The activations of the cerebellar hemispheres, lobuli VI–VII, during the triple-step task are accompanied by prefrontal activations (green). The activation pattern by visually-guided saccades is plotted on top of the triple-step saccades. The color bars represent the corresponding Z-values (left for a–c, right including the overlay map in d).

Büttner and Straube, 1995; Büttner, 1999]. Compared to previous functional MRI and PET data that also demonstrated activation of the vermis during the performance of saccades [Dejardin et al., 1998; Fox et al., 1985; Petit et al., 1997; Sweeney et al., 1996], our data locate saccade-related activation more precisely to the vermal lobuli VI/VII corresponding to more recent fMRI studies that also located visually-guided saccade activity within these lobuli [Hayakawa et al., 2002; Stephan et al., 2002]. However, there was a relative lack of vermal activation in the TR-Fix task in the group analysis and in relation to the TR-WM task. As saccadic burst neurons of the oculomotor vermis are silent during periods of fixation [Ohtsuka and Noda, 1995], it is improbable that fixation during this task led to a strong vermal activation so that the contrast between active and baseline results in extinction of this focus. However, vermal Purkinje cells have been shown to be more active during saccades in light than in darkness [Helmchen and Büttner, 1995]. Furthermore, there are at least two pieces of evidence that the oculomotor vermis is more involved in controlling the metrics of externally triggered visually-guided saccades than of internally generated saccades: First, cerebellar lesions caused dysmetria of visually-triggered saccades, leaving self-generated saccades intact [Straube et al., 1995]. Second, the adaptation of saccadic amplitude to a repeated intrasaccadic target displacement, which is predominantly controlled by the posterior vermis [Barash et al., 1999; Desmurget et al., 1998], does not transfer from visually-guided to memory-guided or self-generated saccades [Deubel, 1995]. These data might explain our finding that the posterior vermis was activated more during visually-guided saccades than during triple-step saccades performed in darkness. Obviously, neither the activation of the cerebellar vermis nor that of the hemispheres was specific for the triple-step task. So there was no cerebellar activation reflecting the spatial updating of retinotopic target locations by the use of efference copy signals, which is needed to perform the triple-step task accurately. According to previous studies, this function is controlled more upstream, in the posterior parietal cortex [Heide et al., 1995, 2001].

Moreover, a novel finding of this study is the demonstration of activation of the cerebellar hemispheres within the lobuli VI-crus I and VIIB-VIII during sequences of memory-guided saccades in the triple-step task and during the visuo-
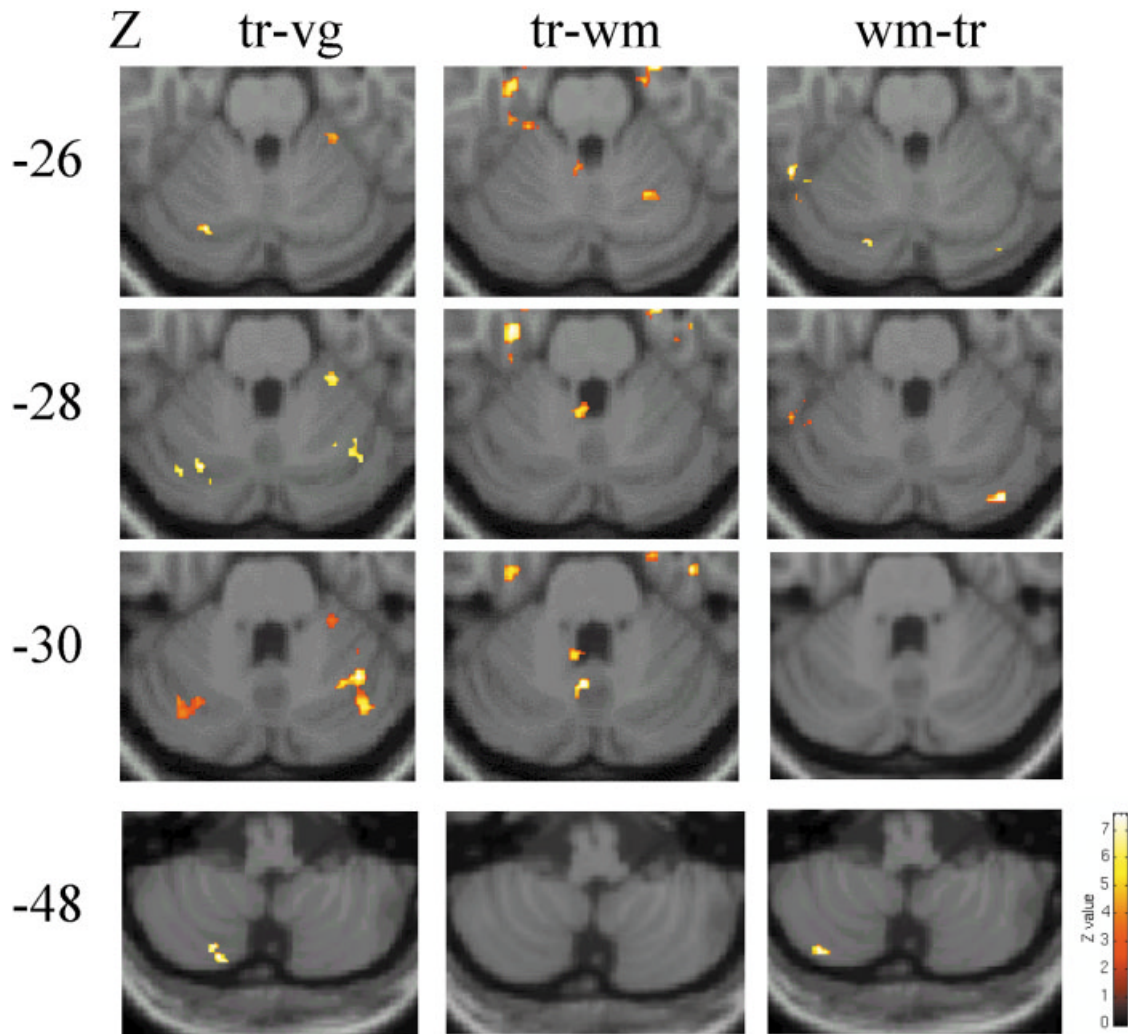
Figure 3.

Group analysis data of the differential task design. TR with VG as control (tr-vg, 6 volunteers) predominantly activated areas within the lobules VI-crus I and the lower part of the left cerebellar hemisphere (**left**) corresponding to the lobule VIIB-VIII. TR with WM as control (tr-wm) revealed activation within the vermal/left paravermal region (**middle**), whereas the reverse condition (wm-tr, 3 volunteers) demonstrated predominant hemispheric activation of areas within lobule crus I (**right**). The color bar represents the corresponding Z-values.

spatial working memory task, which included the cueing of visuospatial attention in both visual hemifields, the voluntary suppression of visual reflexive saccades, and the use of visuospatial working memory. Although we have to consider that we did not measure the oculomotor performance during the scanning, the volunteers accurately performed the tasks outside the scanner without significant saccades during the memorization conditions. The statistical power was limited due to a sample of six volunteers demonstrating only the "peak of the iceberg," but the hemispherical activations were confirmed and became even more evident from the two comparisons (TR-VG and WM-TR), whereby the first condition had always a higher memory load than the second. The notion that the cerebellar hemispheric activation is bound to the mnemonic control of saccades is derived from the following arguments: (1) In the WM condition, memorization intervals were longer than in TR and no generation of a saccadic sequence or updating of retinotopic target locations had to be executed. As saccade-related activity at least in cortical areas depends on the frequency of executed saccades [Kimmig et al., 2001], the activation in WM is unlikely caused by the 2 saccades executed during an activation cycle of 25 sec. (2) Since the necessity to suppress visually-triggered saccades was similar in WM and TR, the suppression-related activity was most likely cancelled out by subtraction. These results correspond to some extent to a recent fMRI study testing spatial working memory in autistic patients and normal volunteers, in which performance of

TABLE II. Foci of activation within the cerebellum*

Task Activ.-Cont.	Probands tested (group analysis)	Foci of activation		
		(x,y,z coordinates)	Z-score	Hemisphere (H), Vermis/Paraver (Vs)
tr-fix	1–4, 6	−26 −74 −28	5.61	VI-Crus I (H)
		−6 −44 −44	4.38	IX (H)
vg-fix	1–6	−6 −72 −28	7.9	VI–VII (Vs)
		−12 −76 −42	5.01	VIIB (H)
tr-vg	1–6	40 −70 −30	5.64	VI-Crus I (H)
		26 −34 −28	5.09	V (H)
		−26 −70 −30	5.49	VI-Crus I (H)
		−24 −74 −48	4.37	VIIB-VIII (H)
tr-wm	1, 2, 4	−4 −60 −30	3.74	VI–VII (Vs)
		8 −70 −38	3.33	VII–VIII (Vs)
		24 −58 −24	4.9	VI (H)
wm-tr	1, 2, 4	−20 −70 −26	4.76	VI-Crus I (H)
		34 −84 −28	4.69	VI-Crus I (H)
		−36 −76 −48	4.91	VIIB-VIII (H)

*Summary of the x,y,z-coordinates and Z-scores of the peak activations corresponding to the stereotactic atlas of Tailarach and Tournoux [1988] and the anatomical description based on Schmahmann [1999]. tr: triple-step saccades; vg: visually guided saccades; wm: visuospatial working memory task; fix: fixation.

an oculomotor delayed response task demonstrated activation of the lateral cerebellum. However, activation within the cerebellum was not very well defined, as it was not in the scope of the study, and in some volunteers only the upper part of the cerebellum was scanned [Luna et al., 2002].

These findings are in accordance with the postulated anatomical patterns of connections between cerebellar structures with corresponding cortical areas. These cortical areas comprise prefrontal areas 46 and 9 that play an important role in spatial working memory [Middleton and Strick, 1994, 1997; Schmahmann and Pandya, 1997]. Additional cerebello-cerebral connections in the monkey that included the parietal cortex were summarized by Brodal and Bjaalie [1992] (Fig. 5). The projections from the prefrontal cortex to the lobuli VI-crus I and especially from the parietal regions to

TABLE III. Qualitative survey of cerebro-cerebellar areas showing significant activation during the different task-control conditions*

Location	VG	TR	TR-VG	TR-WM	WM-TR
Vermis	+	+		+	
FEF	+	+	+	+	
SEF	+	+	+		
IPS/IPL	+	+	+	+	+
Cereb. Hemis.		+L	+	+R	+
PFC		+	+		+

*VG: visually guided; TR: triple-step; WM: working memory; FEF: frontal eye field; SEF: supplementary eye field; IPS/IPL: intraparietal sulcus/lobule; PFC: prefrontal cortex; R/L: only right-/left-sided activation.
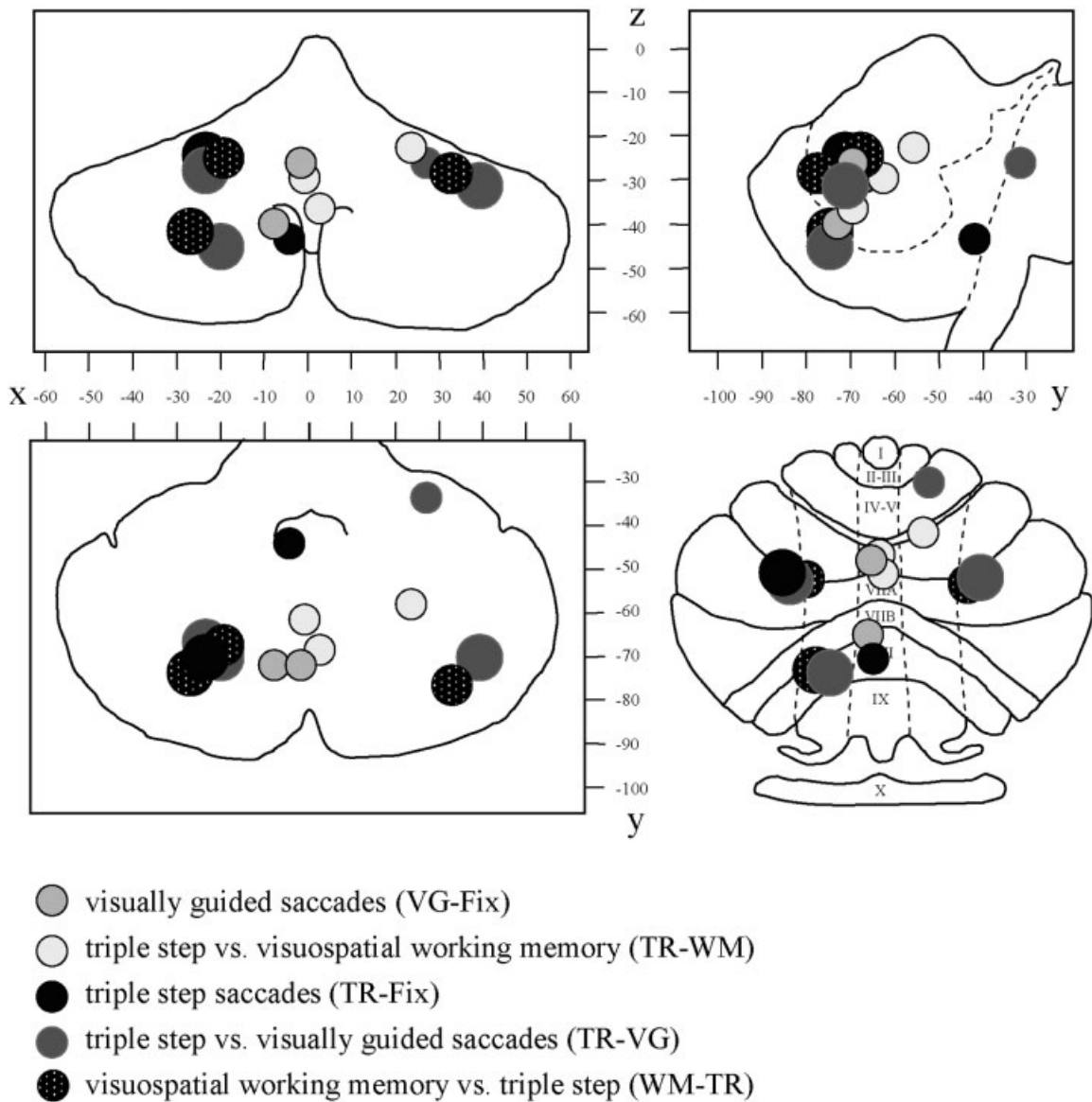
the lobuli VIIB–VIII would nicely explain our activations within the cerebellar hemispheres related to visuospatial working memory.

A role of the cerebellar hemispheres in cognitive processes like learning is in accordance with earlier neuroimaging evidence [Friston et al., 1992; Roland, 1987; Seitz et al., 1990]. Nevertheless, a number of cognitive processes have recently been mapped to the cerebellum substantiating the notion that the cerebellum subserves cognition in a multifold manner. However, up to now no functional imaging studies looked explicitly at the cerebellum during visuospatial working memory tasks. Nevertheless, some other oculomotor studies demonstrated activation of the cerebellar hemispheres. A PET and a recent functional MRI study on the performance of self-initiated saccades demonstrated vermal, paramedian, and hemispherical activation foci [Ellermann et al., 1998; Law et al., 1998; Leigh and Zee, 1999]. A more detailed differentiation between oculomotor and cognitive aspects of these tasks was not performed, but they interpreted the hemispheric activation as information processing during the initiation of saccades. Another study by Dieterich et al. [2000] demonstrated hemispheric and vermal activation foci by optokinetic stimulation and saccades, whereas fixation suppression of the horizontal optokinetic stimulation revealed only hemispheric activation. They interpreted activation of the vermis as reflecting oculomotor performance and activation of the cerebellar hemispheres as reflecting the processing of visuospatial attention. However, their task design did not allow a clear separation of these different components and the fMRI-activation maps with small activation foci within many parts of the cerebellar hemispheres did not allow a clear distinction of task relevant

Figure 4.

Summary of the activation foci of the different tasks after group analysis. The foci are schematically displayed within the Talairach space for the coronal (**top left**), sagittal (**top right**), and axial (**bottom left**) orientation. **Bottom right:** The foci overlaid onto a flattened surface of the cerebellum. Larsell lobules are marked. The tasks with a dominant oculomotor component (visually-guided saccades, triple-step vs. visuospatial working memory; light grey) are preferentially oriented along the midline, whereas the tasks with a cognitive preload localize within the lateral hemispheres (black/dark grey).

regions. It seems more likely that particularly the areas within the lobuli VI-crus I and VIIB+VIII that were activated in our study correspond to processing of visuospatial working memory and attention. For the latter, this is in line with another study by Allen et al. [1997] who examined activation by hand movements and selective attention and demonstrated attentional activation within an area corresponding to the regions defined in our study in lobuli VI-crus I. Another more recent study by Stephan et al. [2002] demonstrated activation within the lobuli VI and VIII by visually-guided saccades modified by repeated performance of the same task that also could be interpreted as a result of attentional modulation.

However, the specific role of the cerebellum during mnemonic information processing and the mechanisms are still under debate [Thier et al., 1999]. Lesion data in monkeys showed that the cerebellum is not critical for spatial working memory, though it may contribute to the preparation of responses [Nixon and Passingham, 1999]. In contradiction, another study demonstrated cognitive impairment of set-
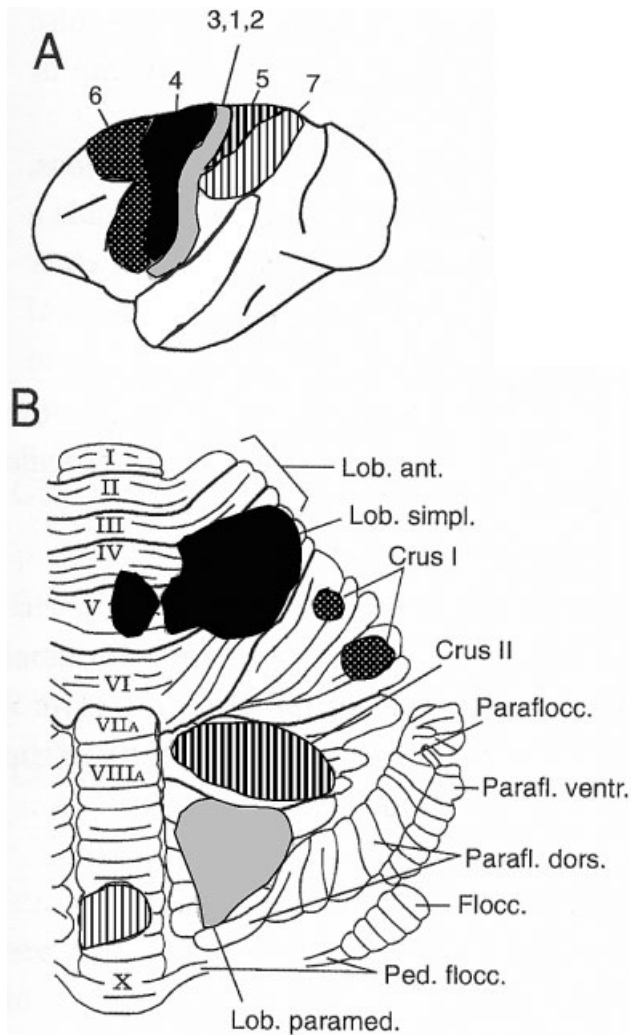
Figure 5.
Modified schematical drawing of cerebro-ponto-cerebellar connections in the monkey demonstrating a subspecification within the cerebellum. **A:** Numbers represent Brodmann areas. **B:** Cerebellar regions are matched to the cerebral areas. Reproduced from Colin et al. [2002] with permission of the publisher.

shifting and working memory in cerebellar patients with lesions within the posterior cerebellar hemispheres and the vermis [Schmahmann and Sherman, 1998]. In a recent fMRI study on attention and eye movements, the posterior vermis was exclusively activated by the execution of saccadic eye movements, whereas the cerebellar hemispheres were activated by covert shifts of attention to peripheral visual stimuli [Corbetta et al., 1998]. Accordingly, patients with damage to the posterior hemispheres and the vermis (lobuli VI+VII) are impaired in covertly orienting visuospatial attention [Townsend et al., 1999]. In our study, covert shifts of attention were crucial for performing the triple-step and visuo-spatial working memory tasks and, thus, may have contrib-

uted to activation of the cerebellar hemispheres, besides the influence of working memory.

In summary, the cerebellum participates in different cerebro-cerebellar networks controlling the processing of oculomotor as well as associated "cognitive" information. The posterior vermis lobuli VI–VII of the cerebellum play a predominant role in the control of any type of saccadic eye movements, but it appears to be more involved in externally triggered than in internally generated saccades. Internally generated sequences of memory-guided saccades, in addition, activate the cerebellar hemispheres, suggesting a role in mnemonic oculomotor control and in the covert shifting of visuo-spatial attention.

REFERENCES

Allen G, Buxton RB, Wong EC, Courchesne E (1997): Attentional activation of the cerebellum independent of motor involvement. Science 275:1940–1943.

Aschoff JC, Cohen B (1971): Changes in saccadic eye movements produced by cerebellar cortical lesions. Exp Neurol 32:123–133.

Barash S, Melikyan A, Sivakov A, Zhang M, Glickstein M, Thier P (1999): Saccadic dysmetria and adaptation after lesions of the cerebellar cortex. J Neurosci 19:10931–10939.

Brodal P, Bjaalie JG (1992): Organization of the pontine nuclei. Neurosci Res 13:83–118.

Büttner U (1999): Eye movements deficits in cerebellar disease. In: Becker U, Deubel H, Mergner T, editors. Current oculomotor research. New York: Plenum Press. p 383–389.

Büttner U, Straube A (1995): The effect of cerebellar midline lesions on eye movements. Neuroophthalmology 15:75–82.

Colin F, Ris L, Godeaux E (2002): Neuroanatomy of the cerebellum. In: Manto MU, Pandolfo M, editors. The cerebellum and its disorders. Cambridge, UK: Cambridge University Press. p 21.

Corbetta M, Akbudak E, Conturo TE, Snyder AZ, Ollinger JM, Drury HA, Linenweber MR, Petersen SE, Raichle ME, Van-Essen DC, Shulman GL (1998): A common network of functional areas for attention and eye movements. Neuron 21:761–773.

Dejardin S, Dubois S, Bodart JM, Schiltz C, Delinte A, Michel C, Roucoux A, Crommelinck M (1998): PET study of human voluntary saccadic eye movements in darkness: effect of task repetition on the activation pattern. Eur J Neurosci 10:2328–2336.

Desmurget M, Pelisson D, Urquizar C, Prablanc C, Alexander GE, Grafton ST (1998): Functional anatomy of saccadic adaptation in humans. Nat Neurosci 1:524–528.

Deubel H (1995): Separate adaptive mechanisms for the control of reactive and volitional saccadic eye movements. Vision Res 35:3529–3540.

Dieterich M, Bucher SF, Seelos KC, Brandt T (2000): Cerebellar activation during optokinetic stimulation and saccades. Neurology 54:148–155.

Ellermann JM, Siegal JD, Strupp JP, Ebner TJ, Ugurbil K (1998): Activation of visuomotor systems during visually guided movements: a functional MRI study. J Magn Reson 131:272–285.

Fox PT, Fox JM, Raichle ME, Burde RM (1985): The role of cerebral cortex in the generation of voluntary saccades: a positron emission tomography study. J Neurophysiol 54:348–369.

Friston KJ, Frith CD, Passingham RE, Liddle PF, Frackowiak RSJ (1992): Motor practice and neurophysiological adaptation in the cerebellum: a positron tomography study. Proc R Soc Lond B 248:223–228.

Friston KJ, Holmes AP, Poline JB, Grasby PJ, Williams SCR, Frackowiak RSJ, Turner R (1995): Analysis of fMRI time-series revisited. NeuroImage 2:5–53.

Friston KJ, Ashburner J, Poline JB, Frith CD, Heather JD, Frackowiak RSJ (1997): Spatial realignment and normalization of images. Hum Brain Mapp 2:165–189.

Fuchs AF, Robinson FR, Straube A (1993): Role of the caudal fastigial nucleus in saccade generation. I. Neuronal discharge patterns. J Neurophysiol 70:1723–1740.

Gao JH, Parsons LM, Bower JM, Xiong J, Li J, Fox PT (1996): Cerebellum implicated in sensory acqustion and discrimination rather than motor control. Science 272:545–547.

Hayakawa Y, Nakajima T, Takagi M, Fukuhara N, Abe H (2002): Human cerebellar activation in relation to saccadic eye movements: a functional magnetic resonance imaging study. Ophthalmologica 216:399–405.

Heide W, Blankenburg M, Zimmermann E, Kömpf D (1995): Cortical control of double-step saccades: implications for spatial orientation. Ann Neurol 38:739–748.

Heide W, Binkofski F, Seitz RJ, Posse S, Nitschke MF, Freund HJ, Kömpf D (2001): Activation of fronto-parietal cotrices during memorized triple-step sequences of saccadic eye movements: An fMRI study. Eur J Neurosci 13:1177–1189.

Helmchen C, Buttner U (1995): Saccade-related Purkinje cell activity in the oculomotor vermis during spontaneous eye movements in light and darkness. Exp Brain Res 103:198–208.

Kase M, Miller DC, Noda H (1980): Discharges of Purkinje cells and mossy fibers in the cerebellar vermis of the monkey during saccadic eye movements and fixation. J Physiol (Lond) 300:539–555.

Kim SG, Ugurbil K, Strick PL (1994): Activation of a cerebellar output nucleus during cognitive processing. Science 265:949–951.

Kimmig H, Greenlee MW, Gondan M, Schira M, Kassubek J, Mergner T (2001): Relationship between saccadic eye movements and cortical activity as measured by fMRI: quantitative and qualitative aspects. Exp Brain Res 141:184–194.

Law I, Svarer C, Rostrup E, Paulson OB (1998): Parieto-occipital cortex activation during self-generated eye movements in the dark. Brain 121:2189–2200.

Leigh JR, Zee DS (1999): The Neurology of eye movements, 3rd ed. New York: Oxford University Press. p 121.

Leiner HC, Leiner AL, Dow RS (1993): Cognitive and language functions of the human cerebellum. Trends Neurosci 16:444–447.

Luna B, Minshew NJ, Garver KE, Lazar NA, Thulborn KR, Eddy WF, Sweeney JA (2002): Neocortical system abnormalities in autism. An fMRI study of spatial working memory. Neurology 59:834–840.

Middleton FA, Strick PL (1994): Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. Science 266:458–461.

Middleton FA, Strick PL (1997): Dentate output channels: motor and cognitive components. Prog Brain Res 114:553–566.

Nixon PD, Passingham RE (1999): The cerebellum and cognition: cerebellar lesions do not impair spatial working memory or visual associative learning in monkeys. Eur J Neurosci 11:4070–4080.

Ohtsuka K, Noda H (1995): Discharge properties of Purkinje cells in the oculomotor vermis during visually guided saccades in the macaque monkey. J Neurophysiol 74:1828–1840.

Petit L, Clark VP, Ingeholm J, Haxby JV (1997): Dissociation of saccade-related and pursuit-related activation in human frontal eye fields as revealed by functional fMRI. J Neurophysiol 77:3386–3390.

Roland PE (1987): Metabolic mapping of sensorimotor integration in the human brain. In: Bock G, O'Connor M, Marsh J, editors. Motor areas of the cerebral cortex. Ciba Foundation Symposium 132. New York: Wiley.

Schmahmann JD, Pandya DN (1997): Anatomic organization of the basilar pontine projections from prefrontal cortices in rhesus monkey. J Neurosci 17:438–458.

Schmahmann JD, Sherman JC (1998): The cerebellar cognitive affective syndrome. Brain 121:561–579.

Schmahmann JD, Doyon J, McDonald D, Holmes C, Lavoie K, Hurwitz AS, Kabani N, Toga A, Evans A, Petrides M (1999): Three-dimensional MRI atlas of the human cerebellum in proportional stereotaxic space. NeuroImage 10:233–260.

Seitz RJ, Roland PE, Bohm C, Greitz T, Stone-Elanders S (1990): Motor learning in man: a positron emission tomographic study. NeuroReport 1:57–60.

Stephan T, Mascolo A, Yousry TA, Bense S, Brandt T, Dieterich M (2002): Changes in cerebellar activation pattern during two successive sequences of saccades. Hum Brain Mapp 16:63–70.

Straube A, Deubel H, Spuler A, Büttner U (1995): Differential effect of a deep bilateral cerebellar nuclei lesion on externally and internally triggered saccades. Neuroophthalmology 15:61–74.

Suzuki DA, Keller EL (1988): The role of the posterior vermis of monkey cerebellum in smooth pursuit eye movement control. II. Target velocity-related Purkinje cell activity. J Neurophysiol 59:19–40.

Sweeney JA, Mintun MA, Kwee S, Wiseman MB, Brown DL, Rosenberg DR, Carl JR (1996): Positron emission tomography study of voluntary saccadic eye movements and spatial working memory. J Neurophysiol 75:454–468.

Tailarach J, Tournoux P (1988): Co-planar stereotactic atlas of the human brain. New York: Thieme Medical Publishers.

Thach WT (1996): On the specific role on the cerebellum in motor learning and cognition: clues from PET activation and lesion studies in man. Behav Brain Sci 19:411–431.

Thier P, Haarmeier T, Treue S, Barash S (1999): Absence of a common functional denominator of visual disturbances in cerebellar disease. Brain 122:2133–2146.

Thier P, Dicke PW, Haas R, Barash S (2000): Encoding of movement time by populations of cerebellar Purkinje cells. Nature 405:72–76.

Townsend J, Courchesne E, Covington J, Westerfield M, Harris NS, Lyden P, Lowry TP, Press GA (1999): Spatial attention deficits in patients with acquired or developmental cerebellar abnormality. J Neurosci 19:5632–5643.