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## Involvement of multiple functionally distinct cerebellar regions in visual discrimination: a human functional imaging study

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### Abstract

We investigated the contribution of the human cerebellum to cerebral function during visual discrimination using PET and fMRI. The cognitive task was a successive discrimination of shades of brown with a parametric variation of the stimulus presentation rate and a constant task difficulty. The successive color discrimination task was contrasted to a dimming detection control task, with identical retinal input but with double the number of motor responses. Three sets of activated cerebellar and cerebral regions were observed: rate-dependent and rate-independent color discrimination networks and a motor-and-detection network. The rate-dependent color discrimination network included both an anterior and a posterior activation site in lobule-VI of the two lateral cerebellar hemispheres, whereas the rate-independent network involved a bilateral activation site in lateral Crus-I. Cerebellar sites of the motor-and-detection network were located in medial lobule-V bilaterally, in the vermis, and in posterior left Crus-I and right Crus-II. An additional fMRI study was performed to control for differences in motor output and response timing between the tasks. In this control study, the cerebellar activation sites of the rate-dependent and rate-independent color discrimination networks remained unaltered. The motor-and-detection network included cerebellar activations in posterior left Crus-I and right Crus-II, but none in lobule-V or the vermis. Thus, cerebellar activation sites of the motor-and-detection network could be subdivided into those related to a motor network and those belonging to a dimming detection network. We conclude that successive color discrimination activates multiple, functionally distinct cerebellar regions.

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### Introduction

The cerebellum is classically assumed to primarily serve motor control (Evarts and Thach, 1969; Ito, 1984; Houk and Wise, 1995) and motor learning functions (Marr, 1969; Albus, 1971; Lisberger, 1988; Thach, 1996). Recent studies, however, suggest that the lateral cerebellum is involved in higher brain functions such as tactile sensory discrimination (Gao et al., 1996; Liu et al., 2000), semantic discrimination (Xiang et al., 2003), attention (Allen et al., 1997), and cognition (Petersen et al., 1989; Kim et al., 1994; Schmahmann, 1997; Schmahmann and Sherman, 1998; Andreasen

et al., 1999; Mandolesi et al., 2001; Bischoff-Grethe et al., 2002; Vokaer et al., 2002). Other studies suggest that the cerebellum may be involved primarily in timing (Ivry and Keele, 1989; Jueptner et al., 1995; Tesche and Karhu, 2000; Dreher and Grafman, 2002; Ivry et al., 2002), a function that could subservise motor and sensory as well as cognitive tasks. However, the specific contribution of the cerebellum in these distinct functions and in the processing of sensory stimuli in particular remains unclear (De Schutter and Maex, 1996; Medina and Mauk, 2000).

Knowledge concerning cerebellar anatomical connections has evolved in a similar fashion. The traditional view was that cerebrocerebellar input provided the cerebellum with information from widespread cortical areas (Brodal, 1978; Glickstein et al., 1985; Schmahmann, 1997), and the

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cerebellar output was thought to be directed exclusively to the primary motor cortex (M1). Consequently, these cerebrocerebellar loops were believed to function primarily in motor control (Evarts and Thach, 1969; Allen and Tsukahara, 1974; Asanuma et al., 1983). Recent studies, however, show that the cerebellar efferents also extensively innervate nonmotor areas of the cerebral cortex (Middleton and Strick, 1994, 1997, 2001; Clower et al., 2001). Furthermore, Middleton and Strick (1997, 2001) have suggested that the cerebrocerebellar circuitry is organized as multiple, topographically closed loops.

In previous human positron emission tomography (PET) studies, we have found lateral cerebellar activation sites during several visual discrimination tasks (Orban et al., 1997; Dupont et al., 1998; Cornette et al., 1999), suggesting a role for the cerebellum in these tasks. Because it remained unclear exactly what the cerebellum contributes to cerebral function in this context, we investigated its activation during visual discrimination in more detail. In the present PET and functional magnetic resonance imaging (fMRI) studies of the human brain, we used the successive color discrimination task or temporal same different task (TSD; Orban et al., 1997; Cornette et al., 2001), with a parametric variation of the stimulus presentation rate. Several studies (Rees et al., 1997; Cornette et al., 1999) have shown that stimulus presentation rate has a strong modulating effect on cerebellar activation. An innovation to our study design is that we kept task difficulty constant, independent of presentation rate. The parametric variation also allowed us to disambiguate phasic from tonic modulatory effects in the activated brain regions (Rees et al., 1997), and to identify those cerebellar and cerebral regions that were similarly modulated. Furthermore, we performed an fMRI control study in which motor output and response timing were carefully matched between the experimental and control conditions.

## Materials and methods

### Subjects

Twelve (mean age, 23.3 years) and four (mean age, 26.5 years) male, right-handed volunteers participated in the PET and fMRI study, respectively. Two of the latter four subjects also participated in the fMRI control study. All subjects had normal or corrected (contact lenses) to normal vision and normal color vision, which was tested with the Ishihara plates (Kanohara, Tokyo, Japan). They had no neuropsychiatric disease or history and were drug-free. The studies were approved by the ethical committees of the U.A. and of the K.U.Leuven Medical School. Subjects gave written informed consent, in accordance with the Declaration of Helsinki.

### Experimental design of PET and main fMRI study

#### Stimuli

Stimuli were generated with a PC using a TIGA-diamond (Salient AT3000) graphics card. In the PET experiment, stimuli were displayed on a high resolution color monitor (Philips Brilliance 201B), which was mounted above the scanner bed at an angle of 52° relative to the horizontal, at a distance of 114 cm. In the fMRI experiments, stimuli were projected by means of a LCD projector (Barco Reality 6300) onto a translucent screen positioned in the bore of the magnet at 30 cm from the subject's eyes. A small white fixation point was continuously present at the center of the screen.

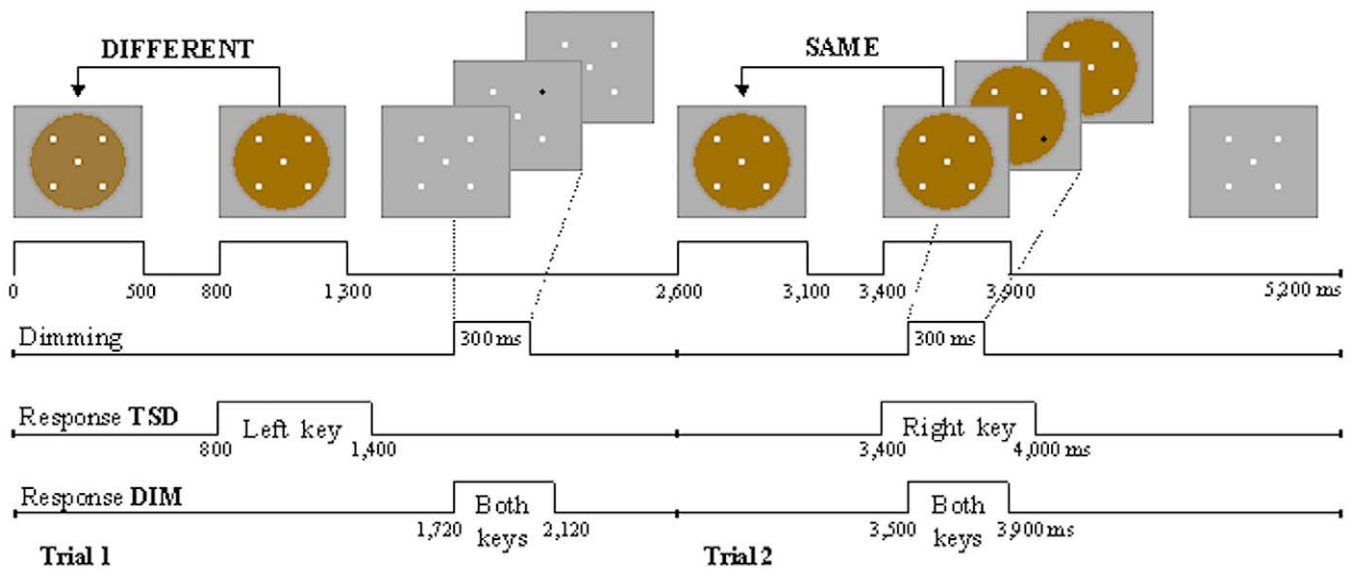
The stimulus was a central, circular, colored patch of 4° diameter presented on a gray background. The stimuli were colored different shades of brown, to avoid subjects using verbal labels (Boynton and Olson, 1987). Equiluminant stimuli were obtained by heterochromatic flicker photometry (15 Hz; Wagner and Boynton, 1972) in the scanner for each subject. The stimulus contained four white points surrounding the central fixation point (all 0.15° diameter) at a distance of 1.3°, and positioned at angles of 45, 135, 225, and 315° with respect to the horizontal. The luminance of these four points was decreased (dimming) at random times.

#### Tasks

During each trial of the successive color discrimination task or Temporal Same Different task (TSD; Orban et al., 1997; Cornette et al., 2001; Fig. 1a), two stimuli were presented successively, each lasting 500 ms with a fixed interstimulus interval of 300 ms. The color of the first stimulus was chosen pseudorandomly; that of the second one was the same in half of the trials. Subjects were asked to press, within 600 ms of the onset of each second stimulus presentation, the right-hand key if the second stimulus had the same color as the previous one of that trial, or the left-hand key if it had a different color. The control task was a dimming detection task (DIM; Fig. 1a) in which subjects were presented with the same display as in TSD, but had to attend to a change in luminance (300 ms) of one of the four points. They had to press both keys within 400 ms after the onset of a dimming event. Dimming randomly occurred once during every trial or during the ensuing intertrial interval. The retinal input was identical in TSD and DIM, but the motor output in DIM was double that in TSD in the main studies. Both tasks were performed at different stimulus presentation rates (PET: 10, 22, 34, 46, 58, 70 stimuli per minute; fMRI: 10, 25, 40, 55, 70 stim/min), resulting in a  $2 \times 6$  (PET) or  $2 \times 5$  (fMRI) factorial-parametric design. The mean intertrial interval varied from 10,700 ms during the slowest rate to 414 ms during the fastest rate. The intertrial interval varied randomly, but equaled at least half the corresponding mean intertrial interval. A fixation-only condition (FIX) was used as a baseline task.

During two 2.5 h training sessions, the differences be-

## a Main studies (PET and fMRI)



## b Control study (fMRI)

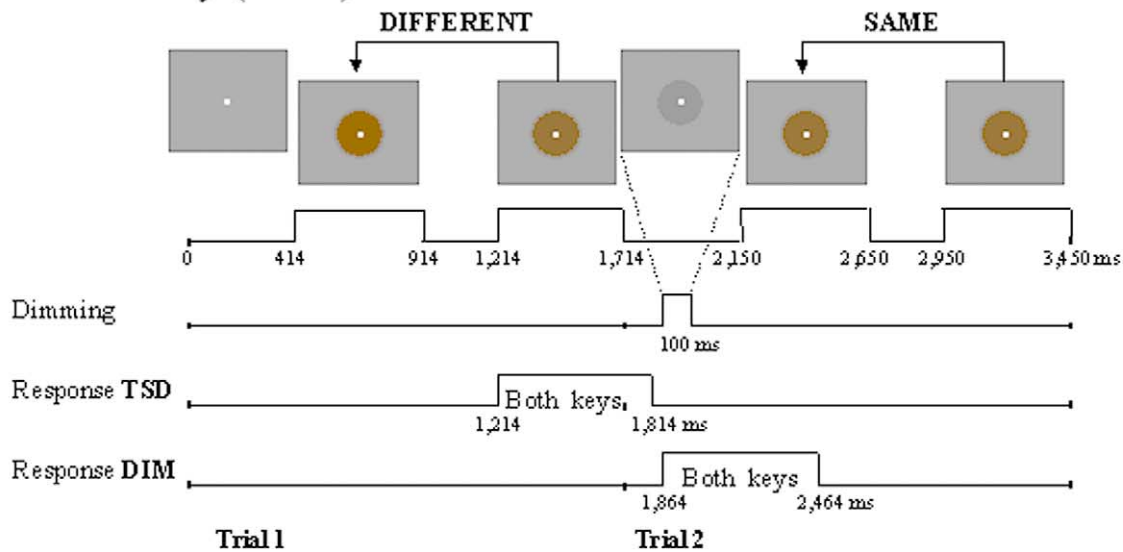


Fig. 1. Task and stimulus configuration in the main (a) and control studies (b). (a) Two trials are illustrated for both tasks at a presentation rate of 46 stimuli/min for the main studies. Colored stimuli were successively presented during 500 ms with a fixed interstimulus interval of 300 ms. Arrows point to the stimulus with which the color of the subsequent stimulus of that trial had to be compared in the Temporal Same Different (TSD) or successive color discrimination task. The response window included 600 ms after the onset of every second stimulus presentation. The left-hand key or right-hand key had to be pressed in case of a different or same color, respectively. In the dimming detection control task (DIM), a change in luminance of one of the four points surrounding the central fixation point had to be detected. Dimming occurred randomly once during every trial or during the ensuing intertrial interval, and lasted 300 ms. The response window comprised 400 ms after the onset of a dimming, and both keys had to be pressed. The number of dimming events and the number of paired stimuli were exactly the same in both tasks, but motor output in DIM was double that in TSD because subjects had to press both keys in DIM. (b) Two trials are shown for both TSD and DIM at a presentation rate of 70 stimuli/min for the control study, in which the number, type (both keys in all conditions), and timing of motor responses (600 ms in both tasks) were carefully matched between tasks.

tween the colors (TSD) and the changes in luminance (DIM) were individually adapted for each condition, until a stable performance level of 82% was obtained for all experimental and control conditions. These parameters were then used in the following scanning sessions to obtain equal performance levels for every subject over all tasks.

### Image acquisition

#### PET study

Images were acquired with a high resolution PET scanner (Siemens-CTI, ECAT Exact HR+, 3D mode), using the  $H_2^{15}O$  method (Fox et al., 1986). Subjects were immobi-

lized using a foam head holder (Smither Medical Products, Akron, OH, USA). A transmission scan was obtained to correct for attenuation. At the beginning of each task, subjects received an injection of 300 MBq  $H_2^{15}O$  over 20 s. The emission scan was started when radioactivity reached the brain (around 40 s after injection) and lasted 60 s. In all subjects, 14 emission scans (TSD and DIM each at six different rates and FIX repeated once) were taken. The order of the conditions was randomized between subjects.

#### *fMRI main study*

This experiment complemented the PET study by providing more anatomical detail with its higher spatial resolution, and by allowing more scans and single subject analyses. Each functional time series consisted of 190 gradient-echo echoplanar imaging (EPI) whole-brain scans (repetition time (TR)/echo time (TE) = 3060/40 ms, flip angle 90°, field of view (FOV) = 200 × 200 mm, 64 × 64 matrix, 4 mm slice thickness, 0.5 mm slice gap, 32 sagittal slices), acquired in block design, using a 1.5 Tesla MR scanner (Siemens Vision). Within one time series, the five TSD and DIM conditions were each presented twice in blocks of 21.4 s (seven scans), and were interleaved every two blocks with the FIX condition for 15.3 s (five scans). At the beginning of each epoch, the subjects were given verbal instructions about what task they had to perform. In every subject, these time series were repeated 14 times in two scanning sessions, with the conditions in different order, yielding a total of 196 images per TSD and DIM condition. The subject's head was immobilized using a bite-bar. Sagittal anatomical images were acquired before each functional imaging session (3D Magnetization Prepared Rapid Gradient Echo, TR/TE = 11.4/4.4 ms, inversion time (TI) = 300 ms, FOV = 256 × 256 mm, 256 × 256 matrix, 160 mm slab thickness, 128 sagittal partitions). Subjects were required to maintain fixation on the central fixation point throughout the entire experiments. Eye movements were monitored during scanning using electrooculography in the PET camera and the OBER2 device (Permobil Meditech, Timra, Sweden) in the MR scanner. Except for pressing the keys with their hands, the subjects were instructed not to make any movements during scanning.

#### *Data analysis*

The PET and fMRI data were analyzed using Statistical Parametric Mapping version SPM99 (Wellcome Department of Cognitive Neurology, London, UK). The functional scans were realigned and coregistered with the anatomical images, stereotactically normalized to the Montreal Neurologic Institute template in Talairach space (Talairach and Tournoux, 1988), and spatially smoothed with an isotropic Gaussian Kernel (PET: 16 mm full width at half maximum, fMRI-group: 9 mm, fMRI-single subject: 6 mm). ANCOVA was used to remove global changes in cerebral blood flow for PET and in blood oxygenation level dependent contrast

for fMRI. Low frequency drifts in the fMRI data were removed using an appropriate high-pass filter. Condition effects were tested by applying appropriate linear contrasts to the parameter estimates for each condition, resulting in a *t* statistic for every voxel, which constituted the statistical parametric maps (SPM). Both a fixed-effect and a random-effect group analysis, the latter allowing population inferences (Holmes and Friston, 1998), were performed on the PET data. A fixed-effect group analysis and single subject analyses were done on the fMRI data. Unless stated otherwise, the threshold was set at  $P < 0.05$  corrected for multiple comparisons. Because of the a priori information, a threshold of  $P < 0.001$  uncorrected was used for the single subject analyses and for the fMRI control experiment.

The experimental task in our study involved discrimination of color. This attribute is known to activate several regions in the ventral occipitotemporal visual cortex, which is located directly adjacent to some cerebellar regions, particularly the posterior part of lobule-VI. Due to distortion of the EPI-images by magnetic susceptibility artifacts, activation in the superior cerebellum might be confused with activation in ventral temporal cortex. Therefore, we projected fMRI activations for the different contrasts not only onto the high-resolution anatomical scans but also onto the individual EPI-dataset of each subject (see two examples in Fig. 2). This procedure confirmed the cerebellar location of all activation sites listed in Tables 1 and 2, which were identified according to the human cerebellar atlas of Schmahmann (Schmahmann et al., 2000).

#### *Planned contrasts*

First, we studied all cerebellar regions that were activated in the TSD and DIM tasks, by using a contrast of all TSD and DIM conditions relative to the baseline fixation condition (TSD + DIM)-2FIX. This contrast was performed to explore the entire volume of cerebellar activity during these tasks. Then, within the active cerebellar regions, sites showing preferential activity for one or the other task effect, i.e., TSD-DIM or DIM-TSD, were delineated. The main effect of task (TSD-DIM) revealed activity in regions involved in color discrimination, whereas in the reverse main effect of task (DIM-TSD), activity was observed in sites related to dimming detection and motor execution, because the number of motor responses in DIM was double that in TSD in the main experiment.

Second, we further disentangled and characterized the cerebellar activation sites by using conjunction and masking analyses. We performed two conjunction analyses: one between the main effect of task, given by the subtraction TSD-DIM, and the parametrically increasing rate effect, and another between the reverse main effect of task (DIM-TSD) and the increasing rate effect. We used conjunction analyses because a significant effect in the conjunction implies the effect to be significant in each of its two elements, i.e., task effect and rate effect (Price and Friston, 1997). Conse-

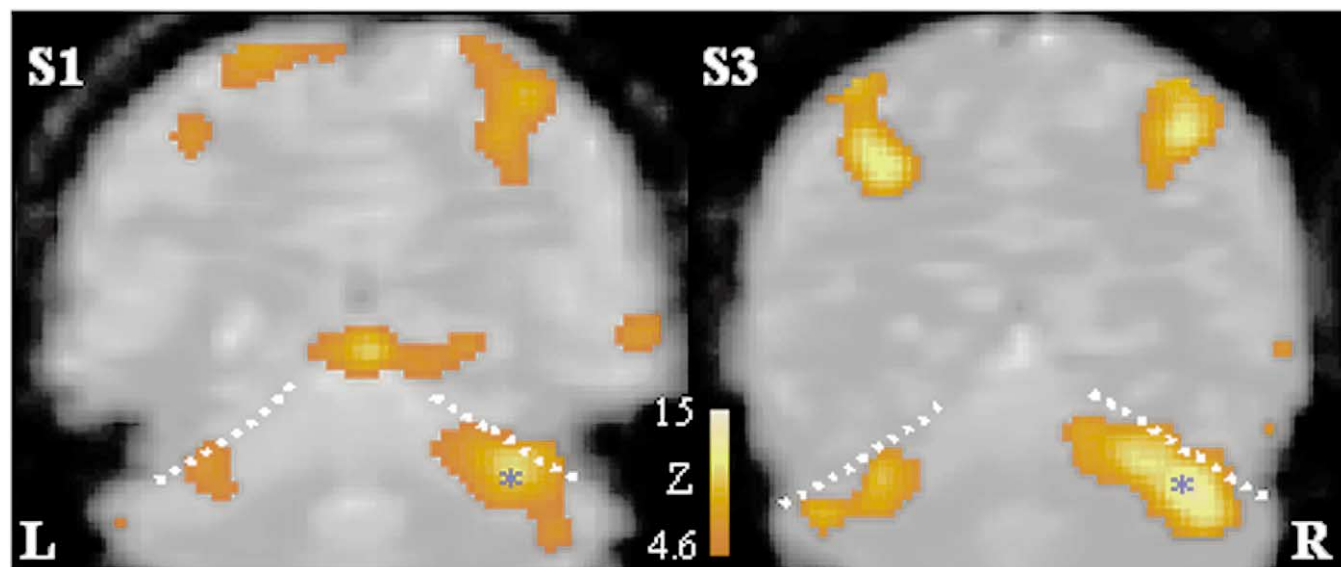


Fig. 2. Statistical parametric maps (SPMs) showing voxels significant ( $P < 0.05$  corrected for multiple comparisons) in the single subject fMRI analysis of two subjects (S1 and S3) for the subtraction TSD-FIX in the original experiment, rendered on their normalized first EPI-image. The white dashed line indicates the border between cerebrum and cerebellum. The blue asterisk represents the local maximum of the right posterior lobule-VI activation site on these coronal sections of the two subjects. Also part of the left-sided posterior lobule-VI activation site can be observed. The color bar indicates Z scores.

quently, these conjunctions could characterize both rate-dependent cerebellar activation sites involved in the main effect and reverse main effect of task. Furthermore, in the main effect of task (TSD-DIM) and in the reverse main effect of task (DIM-TSD), we used an exclusive mask that consisted of both the increasing and decreasing rate effects. These contrasts were performed in order to identify sites that were significantly activated by the task effect but did not show any rate effect (either increasing or decreasing). In this manner, we were able to characterize rate-independent cerebellar activation sites. Third, the parametric variation of

the stimulus presentation rate also allowed us to disambiguate phasic from tonic modulatory effects in the activated brain regions (Rees et al., 1997), and to identify those cerebellar and cerebral regions that were similarly modulated. A phasic modulatory effect increases the neuronal response within each trial of a task period (PET) or epoch (fMRI), without changing the baseline neuronal activity. With increasing stimulus presentation rate, more trials and thus more neuronal responses will be included in each task period/epoch. This results in an increase of the differential PET/MR activity in TSD relative to DIM with increasing rate, and thus in an increase in both the intercept and the slope of the PET/MR activity–rate relationship in TSD. Thus, phasic modulation reflects a change in the correlation between brain activity and stimulus presentation rate in TSD relative to DIM. In brain regions that are phasically modulated, task and rate will therefore interact. A tonic modulatory effect increases the neuronal activity in TSD relative to DIM equally across the entire task period/epoch, resulting in a differential PET/MR activity independent of the stimulus presentation rate; the intercept of the linear PET/MR activity–rate function is changed but the slope remains constant. Thus, tonic modulation reflects an increase in baseline activity without a change in the correlation between activity and rate, and here task and rate do not interact.

To differentiate between tonic and phasic task modulations, regions that showed an interaction between the factors task and rate were identified (Rees et al., 1997). The level of significance in the interaction analysis ( $Z_{\text{int}}$ ) was calculated for all regions resulting from the conjunction and masking

Table 1  
fMRI main study: entire volume of active cerebellum

Cerebellar region	fMRI group			
	x	y	z	Z score
a R lobule-VI	33	-42	-30	>8
b L lobule-VI	-30	-54	-27	>8
c R lobule-V	18	-51	-21	>8
d L lobule-V	-18	-51	-24	7.19
e Vermis lobule-VI	3	-78	-21	>8
f Vermis lobule-VIIAt	9	-87	-36	>8
g Vermis lobule-VIIB	3	-78	-42	>8
h R Crus-I	48	-75	-36	>8
i L Crus-I	-42	-78	-36	>8
j L Crus-I	-27	-87	-27	6.32
k R Crus-II	21	-87	-45	>8
l R Crus-II	30	-87	-39	>8
m R Crus-II	12	-87	-42	>8
n L Crus-II	-12	-84	-48	5.31

Note. All cerebellar activation sites reaching  $P_{\text{corr}} < 0.05$  in group fMRI main study for the contrast (TSD + DIM)-2FIX. R, Right; L, left.

Table 2  
PET and fMRI main study: overview of the cerebellar activation sites

Cerebellar region	fMRI group				#ss	$Z_{\text{int}}$	Control Y/N	PET group					T/P/U
	<i>x</i>	<i>y</i>	<i>z</i>	Z score				<i>x</i>	<i>y</i>	<i>z</i>	Z score	RFX	
Rate-dependent color discrimination network													
1 R anterior lobule-VI	36	-42	-33	>8	3	1.63	Y	34	-42	-26	4.53	**	T
2 L anterior lobule-VI	-33	-42	-33	>8	4	1.60	Y	-38	-44	-32	3.29	*	T
3 R posterior lobule-VI	39	-54	-30	>8	4	3.41	Y	42	-60	-32	<b>5.52</b>	**	U
4 L posterior lobule-VI	-36	-60	-30	>8	4	3.47	Y	-44	-62	-30	<b>5.35</b>	**	U
Rate-independent color discrimination network													
5 R Crus-I	33	-66	-36	>8	4	1.70	Y	32	-72	-30	3.15	*	T
6 L Crus-I	-39	-63	-36	>8	4	1.94	Y	-50	-54	-36	3.11	*	T
Motor-and-detection network													
7 R lobule-V	18	-51	-21	>8	4	2.29	N	20	-58	-16	2.41	*	U
8 L lobule-V	-15	-51	-21	>8	4	2.98	N	-14	-52	-22	4.00	**	U
9 Vermis lobule-VI	0	-72	-12	5.32	3	1.96	N						T
10 Vermis lobule-VI	-3	-63	-21	6.74	3	0.64	N						T
11 R vermis lobule-VIIAt	6	-87	-33	>8	4	3.64	N						U
12 L vermis lobule-VIIAt	-6	-87	-30	>8	2	2.04	N						U
13 Vermis lobule-VIIB	3	-78	-42	>8	3	2.53	N						U
14 L Crus-I	-27	-87	-27	>8	2	1.07	Y						T
15 R Crus-II	18	-87	-45	>8	3	1.69	Y						T

Note. All cerebellar activation sites reaching  $P_{\text{corr}} < 0.05$  in fMRI main study. Cerebellar sites in PET fixed-effect analysis at  $P_{\text{corr}} < 0.05$  (bold), at  $P_{\text{uncorr}} < 0.001$  (normal), and at  $P_{\text{uncorr}} < 0.01$  (*italic*). R, Right; L, Left; RFX, random-effect analysis (PET study); #ss, frequency of occurrence in fMRI single subjects;  $Z_{\text{int}}$ , Z score in interaction analysis of fMRI main study; Y/N, activation site present (Yes) or absent (No) in both subjects of fMRI control study at  $P_{\text{uncorr}} < 0.001$ ; \*\*, activation site in PET-RFX at  $P_{\text{uncorr}} < 0.001$  and (\*) at  $P_{\text{uncorr}} < 0.01$ ; T, tonic; P, phasic; U, undifferentiated (T/P/U refers to both PET and fMRI main study).

analyses in the PET and fMRI main study. Task modulation was defined as tonic (T) for  $Z_{\text{int}} \leq 1.96$  ( $P_{\text{uncorr}} > 0.025$ ), phasic (P) for  $Z_{\text{int}} \geq 4.51$  ( $P_{\text{corr}} < 0.05$ ) or undifferentiated (U) for  $1.96 < Z_{\text{int}} < 4.51$ .

### fMRI control study

The control experiment was designed to eliminate two possible confounds in the main study: differences in motor output (pressing one key in TSD vs both keys in DIM) and in response timing (600 ms in TSD vs 400 ms in DIM) between the experimental and control conditions.

In the control study, two of the original four fMRI subjects participated. In TSD, they pressed both keys if the second stimulus had a different color from the first, and no key if it had the same color (Fig. 1b). In DIM, subjects pressed both keys in the case of a change in luminance of the stimulus. In the control study, the number of key presses was equalized in TSD and DIM by halving the number of dimming events. Dimming occurred randomly once every two trials and lasted 100 ms. The response window in DIM was 600 ms and thus equaled that in TSD. Thus, in the control study, the number, type, and timing of the motor responses were equal between the TSD and DIM conditions. The visual stimulus in the control experiment was a small 1° radius color disc with a central white fixation point, but without the presence of the four dimming points (Fig. 1b).

Instead, dimming occurred over the entire 1° radius stimulus. Consequently, in the control study, visuospatial attention was carefully matched between tasks. In the fMRI control experiment, only two stimulus presentation rates (10 and 70 color stimuli/min) were used for both tasks. The acquisition of the images and the data analysis were identical to those in the original experiment.

### Results

In the current PET and fMRI studies, two tasks (Fig. 1) were compared: a successive color discrimination task (TSD) and a dimming detection control task (DIM). In TSD, the color of every second stimulus of two successively presented stimuli had to be compared with that of the preceding stimulus, followed by a single key press in the main studies (right-hand if same color, left-hand if different color). In DIM, a change in luminance had to be detected, followed by a double key press (both hands). TSD was used to study nonmotor and cognitive aspects of visual discrimination, whereas in DIM the motor component dominated. In the fMRI control study, the motor component was eliminated by equalizing the number, type, and timing of the motor responses between PET TSD and DIM conditions.

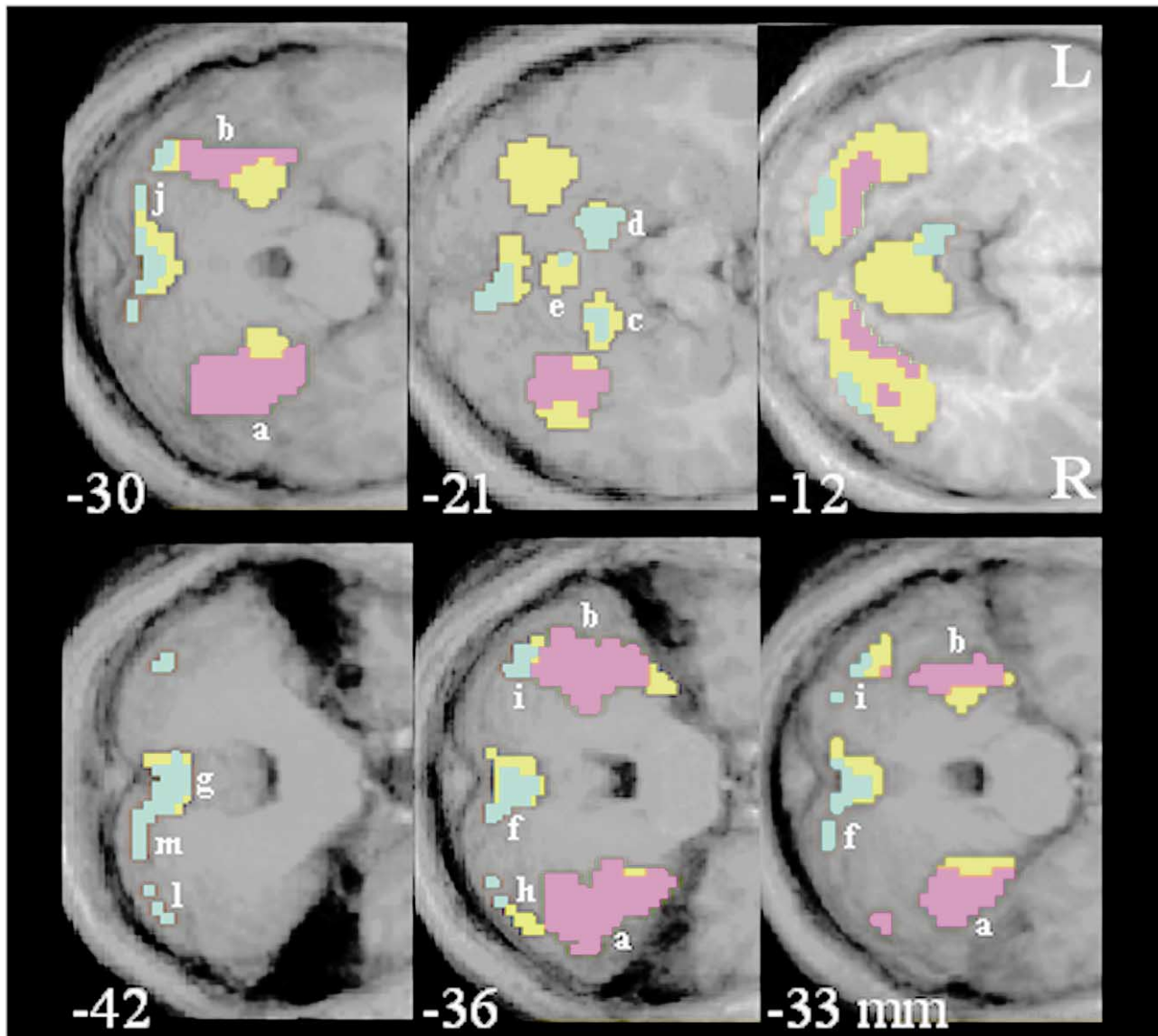


Fig. 3. Entire volume of active cerebellum. Statistical parametric maps (SPMs) showing voxels significant ( $P < 0.05$  corrected for multiple comparisons) in the group fMRI main study for the contrast (TSD+DIM)-2FIX (all colors), superimposed onto transversal sections through the cerebellum of the average ( $n = 4$ ) anatomical MRI scan. Sites with a preferential activity for the main effect of task (TSD-DIM) are presented in pink, and for the reverse main effect of task (DIM-TSD) are indicated in turquoise. Active significant voxels that did not show a preferential activity for either task effect are shown in yellow. The right side of the brain is located at the lower side of the images. The values in mm refer to the distance below the anteroposterior intercommissural line. Letters correspond to regions listed in Table 1.

#### Behavioral data during scanning

Mean performance for all TSD and DIM conditions was 84.5% correct (SD 7.1%) and 84.2% correct (SD 7.2%), respectively in the PET experiment, and 81.3% correct (SD 4.5%) and 79.1% correct (SD 6.2%) in the fMRI experiment. There were no significant differences in mean performance within or between the different TSD and DIM conditions (ANOVA;  $P > 0.2$ ) in either experiment. The frequency of saccades averaged one per minute in the PET experiment and one per condition for every single time series in the fMRI study. The frequency of eye movements

did not differ significantly among conditions in either experiment (Friedman ANOVA;  $P > 0.2$ ).

#### Imaging data

##### Entire volume of active cerebellum

First, we studied all the cerebellar regions that were activated in the TSD and DIM tasks for both the PET and fMRI main study, by using a contrast of the TSD and DIM conditions relative to the baseline fixation condition (TSD+DIM)-2FIX. Local maxima of cerebellar activation sites were observed in lobule-VI of the two lateral hemi-

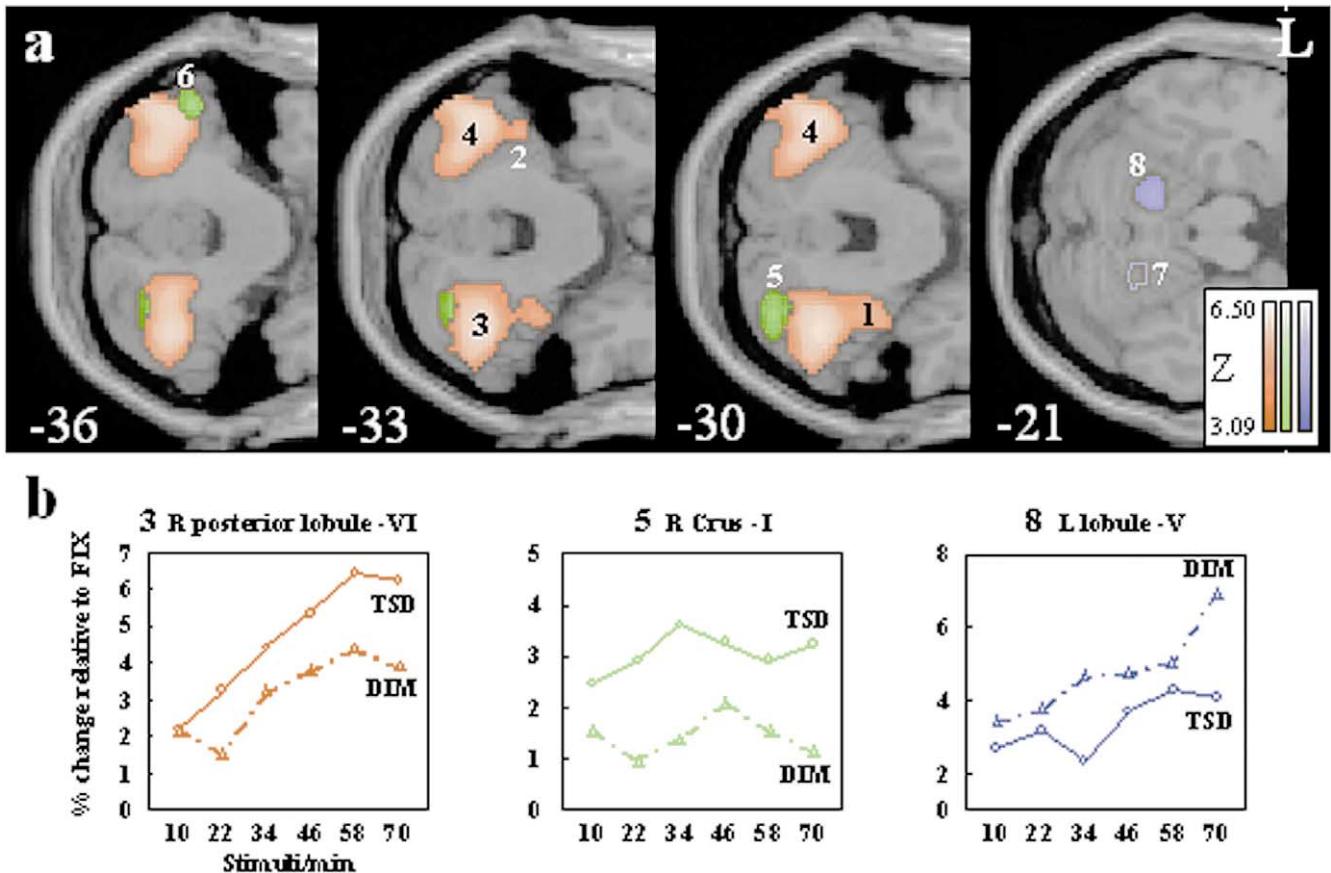


Fig. 4. PET study: Cerebellar activation sites belonging to the different networks. (a) SPMs showing cerebellar voxels significant ( $P < 0.001$  uncorrected for multiple comparisons, fixed-effect analysis) in the PET study, of the rate-dependent (conjunction analysis between TSD-DIM and increasing rate; red) and rate-independent color discrimination network (TSD-DIM with exclusive mask of both increasing and decreasing rate effect; green), and of the motor-and-detection network (conjunction analysis between DIM-TSD and increasing rate; blue). The blue outline indicates an activation site at a lower threshold of  $P < 0.01$  uncorrected. Activation sites are projected onto transversal sections through the cerebellum of the standard single subject anatomical MRI scan. The colored bars refer to the corresponding colored activity blobs and indicate the Z scores. For other conventions, see Fig. 3. (b) For each network, the activity profile of a representative cerebellar activation site is shown. In these profiles, the percent change relative to the baseline fixation condition is plotted for all TSD and DIM conditions. The solid line indicates the TSD conditions and the dashed line represents the DIM conditions. Numbers correspond to regions listed in Table 2.

spheres, in medial lobule-V bilaterally, vermis lobules-VI, VIIAt, VIIB, and in bilateral Crus-I and Crus-II in the fMRI main study (Fig. 3 and Table 1). Except for right Crus-II (Table 2, k and l), these cerebellar activation sites were also present in the PET study ( $P < 0.001$  uncorrected). Fig. 3 gives an overview of all significantly ( $P < 0.05$  corrected for multiple comparisons) activated cerebellar voxels involved in our tasks for the group fMRI main study (Fig. 3, all colors).

Next, within the previously identified active cerebellar regions, sites that showed preferential activity for the main effect of task (TSD-DIM; Fig. 3, pink), or for the reverse main effect of task (DIM-TSD; Fig. 3, turquoise) were delineated in both main studies. Bilateral lobule-VI showed preferential activity for TSD-DIM, whereas the other cerebellar sites were preferentially activated in DIM-TSD in both the PET and fMRI main study.

We next further disentangled and characterized the different cerebellar activation sites resulting from the overall

task effect in both PET and fMRI main studies. By using conjunction and masking analyses, three networks of activated cerebellar and cerebral regions were characterized and will be further described: the rate-dependent and rate-independent color discrimination networks and the motor-and-detection network. The cerebellar regions belonging to these three networks are shown in Figs. 4 (PET) and 5 (fMRI). The PET and fMRI coordinates of the cerebral activation sites and aspects of the study related to the visual cortex including retinotopic mapping are described elsewhere (K. Claeys, P. Dupont, L. Cornette, S. Sunaert, P. Van Hecke, E. De Schutter, and G. A. Orban, unpublished observations).

In all conditions, an extensive cerebellar and cerebral network was revealed. The networks revealed by the PET study, in which in addition a more stringent random-effect analysis was performed, were similar to the corresponding networks observed in the fMRI study. This and the large number of images (196 per condition) for each

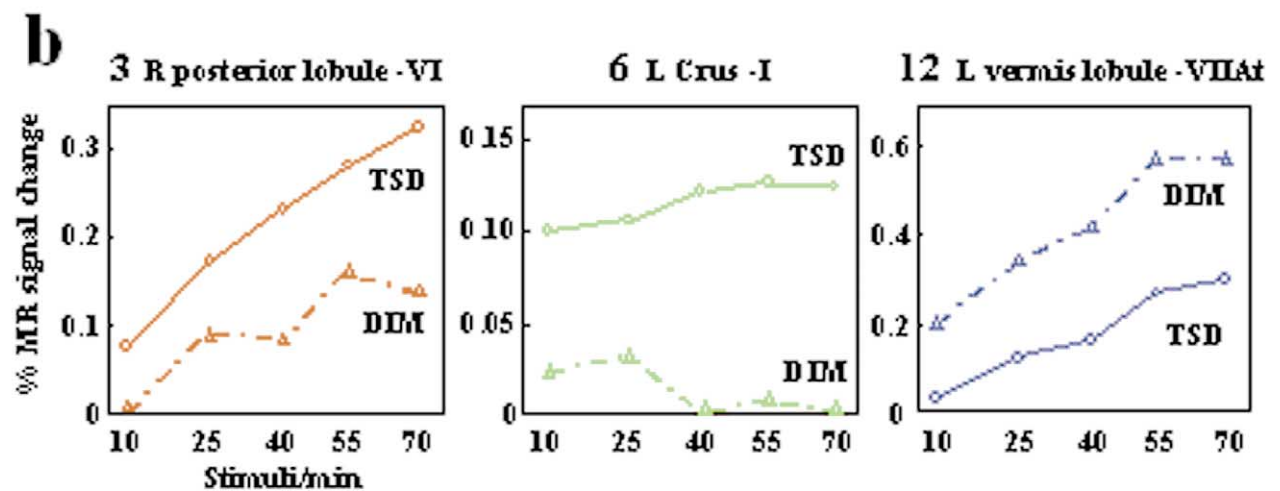
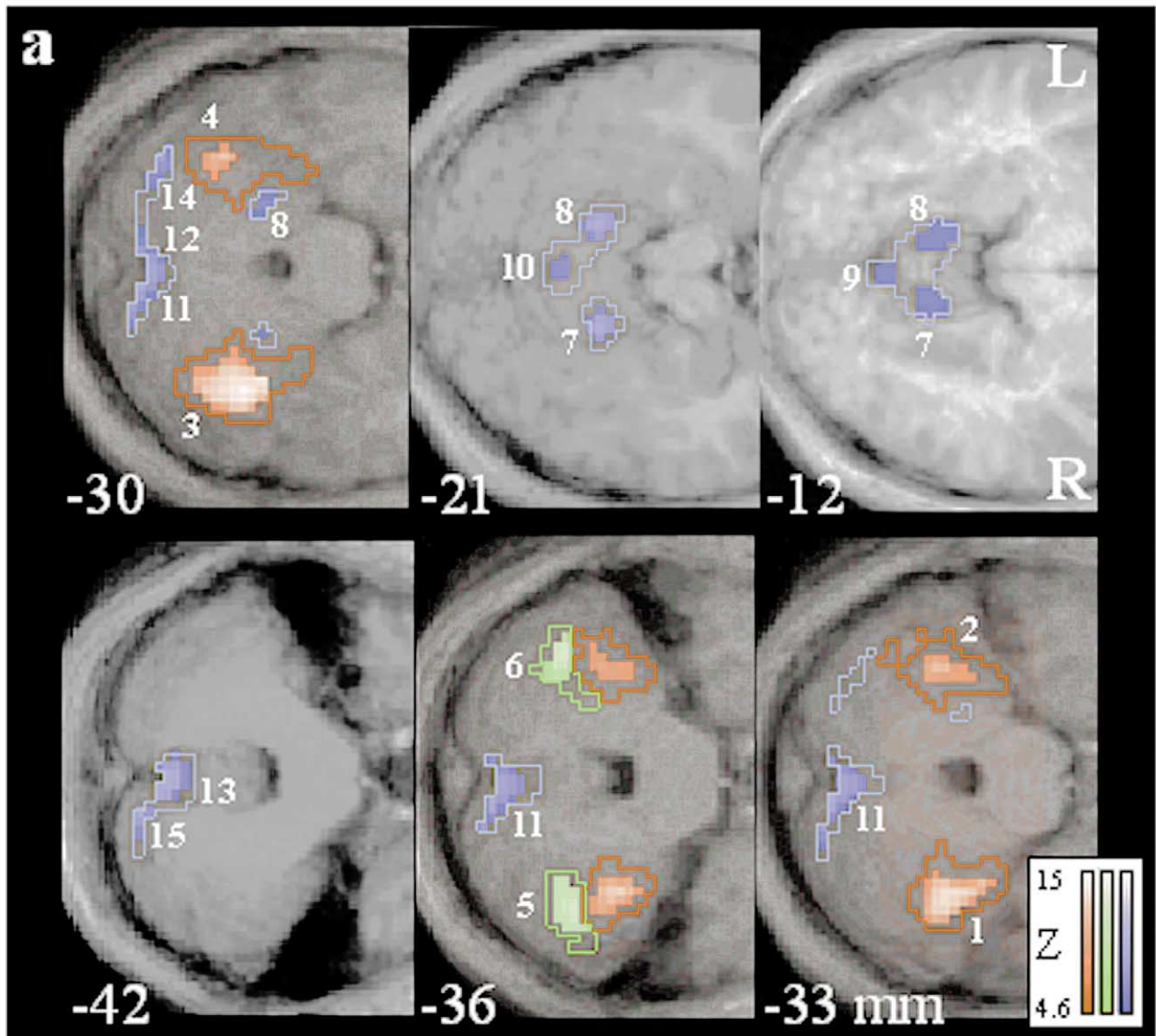


Fig. 5. fMRI main study: Cerebellar activation sites belonging to the different networks. (a) SPMs showing significant cerebellar voxels at  $P < 0.05$  corrected for multiple comparisons (colored blobs) and voxels activated at a lower threshold ( $P < 0.001$  uncorrected for multiple comparisons, colored outlines) in the group fMRI main study, in the rate-dependent (red) and rate-independent color discrimination network (green), and in the motor-and-detection network (blue). Activation sites are shown on transversal sections through the cerebellum of the average ( $n = 4$ ) anatomical MRI scan. For other conventions, see Fig. 3 and 4. (b) For each network, the activity profile of a representative cerebellar activation site is shown. In these profiles, the percent adjusted MR signal change relative to the baseline fixation condition is plotted for all conditions. Error bars (SEM) are smaller than the symbols used and are therefore not shown. The corresponding Z scores in the interaction analysis between task and rate ( $Z_{int}$ ) for the different cerebellar sites are shown in Table 2 for the group fMRI main study. Same conventions as in Fig. 4b.

subject in the fMRI experiment confirms and consolidates the results obtained from the four subjects included in the fMRI study.

#### *Rate-dependent color discrimination network*

The conjunction between the main effect of task (TSD-DIM) and the increasing rate effect reveals the rate-dependent network involved in the successive color discrimination task. It included an anterior and a posterior activation site bilaterally in lobule-VI of the lateral cerebellar hemispheres in both main studies (Table 2; red in Figs. 4 and 5). These regions were located 12 to 18 mm (fMRI) and 18 mm (PET) apart anteroposteriorly, with the posterior region lying close to the superior posterior fissure. Many cerebral regions were also activated, such as bilateral dorsal premotor cortex (dPMC; BA 6), superior frontal sulcus (BA 6), inferior frontal gyrus (BA 44), and medial presupplementary motor area (pre-SMA; BA 8/6). In occipitotemporal cortex, activation sites were seen in right calcarine sulcus (BA 17), in bilateral lingual (BA 18) and fusiform gyrus (BA 19), and in left inferior temporal gyrus (BA 37). Furthermore, activation sites were observed in right inferior parietal lobule (BA 40), in bilateral anterior and middle dorsal intraparietal sulcus and postcentral gyrus (BA 1,2) bilaterally. The cerebellar activation sites observed in the PET study and fMRI main study corresponded well. However, the separation between the anterior and posterior lobule-VI sites was less clear in the PET study due to the lower resolution (Fig. 4a). There was a very good agreement between the cerebellar sites observed in the fMRI group and single subject analyses (Table 2).

By studying the interaction between the factors task and rate, tonically and phasically modulated cerebellar and cerebral regions could be characterized in both PET and fMRI main study. Overall, half of the activated regions showed clear tonic or phasic modulation. Only these regions will be further described. The  $Z$  scores of the interaction analysis between task and rate ( $Z_{\text{int}}$ ) are indicated for each cerebellar activation site for the group fMRI main study in Table 2. The anteriorly located cerebellar activation sites in the rate-dependent color discrimination network showed tonic modulation (Table 2). None of the activated cerebellar regions showed phasic modulation in this study. Cerebral regions that were tonically modulated were right lingual gyrus, right intraparietal sulcus, and right postcentral gyrus. Except for dPMC which showed an undifferentiated modulation, all the frontal areas were phasically modulated as were the right calcarine sulcus and the right fusiform gyrus.

#### *Rate-independent color discrimination network*

In the previous conjunction analysis, brain regions that showed a rate-independent activity over the different stimulus presentation rates were not included. To identify rate-independent regions, an additional analysis using an exclusive mask of both the increasing and decreasing rate effects on the main effect of task (TSD-DIM) was performed (see

methods). This smaller, symmetrical rate-independent color discrimination network included bilateral Crus-I of the lateral cerebellar hemispheres (Table 2; green in Figs. 4 and 5) and the dorsolateral prefrontal cortex bilaterally (DLPFC; BA 9/46; (42,39,3); (-39,33,18); (-48,27,24); all  $Z > 8.0$ ) in both PET and fMRI main studies. The localization of the activation site in right Crus-I was very similar in both studies. The site in left Crus-I, however, was located more laterally and anteriorly in the PET study. There was a strong conformity between the cerebellar sites observed in the group and single subject fMRI analyses. Cerebellar and cerebral regions belonging to this rate-independent network showed tonic modulation (Table 2).

#### *Motor-and-detection network*

The conjunction between the reverse main effect of task (DIM-TSD) and the increasing rate effect was used to investigate the motor network, because there were twice the number of motor responses in DIM compared to TSD. Because some of the activated regions might also be related to the dimming detection (see further), this network was named motor-and-detection network. An extensive network with many cerebellar and cerebral activated regions was revealed. Cerebellar activation sites were observed in bilateral lobule-V in both PET and fMRI main study (Table 2; blue in Figs. 4 and 5). In the latter study, sites in vermis lobules-VI, VIIAt, VIIB, and posterior left Crus-I and right Crus-II were also revealed. Activated cerebral regions included bilateral primary motor cortex (M1; BA 4), precentral gyrus (BA 6), and medial supplementary motor area (SMA; BA 6), bilateral middle (BA 19) and inferior occipital gyrus (BA 18), and bilateral inferior and right middle temporal gyrus (BA 37) and bilateral posterior intraparietal sulcus (BA 7). Excellent conformity between the group and single subject fMRI results was seen in cerebellar lobule-V bilaterally and in right lobule-VIIAt of the vermis (Table 2). Activation in the other cerebellar sites showed more variability between the group and single subject fMRI results. Cerebellar and cerebral activation sites included in the motor-and-detection network showed an exclusively tonic or undifferentiated modulation, contrary to the combined phasic and tonic modulations that were observed in the color discrimination network.

Similar to the additional masking analysis performed on the main effect of task (see rate-independent color discrimination network), we used an exclusive mask of both the increasing and decreasing rate effects on the reverse main effect of task (DIM-TSD). This analysis failed to reveal any rate-independent components within the motor-and-detection network.

#### *fMRI control study*

The control experiment was performed to eliminate differences in motor output (pressing one key or both keys)

and in response timing (600 ms or 400 ms) between the experimental and control conditions.

The cerebellar activation sites belonging to the rate-dependent and rate-independent color discrimination networks remained unaltered in both subjects of the control study (Fig. 6 and Table 2), confirming our original results. In the motor-and-detection network, activation sites in bilateral lobule-V and the vermis were no longer observed in the control experiment, whereas sites in posterior left Crus-I and right Crus-II were unchanged in both subjects (Fig. 6 and Table 2). Thus, as a consequence of equalizing the motor component between tasks in the control experiment, the cerebellar activation sites of the motor-and-detection network could be further subdivided. Lobule-V and the vermis are related to the motor component of the task, whereas posterior left Crus-I and right Crus-II might be related to the dimming detection.

## Discussion

In the present study we have demonstrated that a successive color discrimination task activates multiple, functionally distinct regions in the cerebellum. Before discussing the implications of our findings, we will first consider some methodological issues of the study.

### *Methodological considerations*

The stimulus attribute color was used because it is a simple, purely sensorial quality that is not associated with any classical cerebellar function. In contrast to other imaging studies (Thach, 1996) where it was argued that the task contained a hidden motor component such as silent counting, we are confident that the cerebellar sites activated during color discrimination are related exclusively to non-motor and cognitive components of the task.

In the main experiments, the motor response in TSD was unilateral, whereas in DIM a bilateral motor response was required. Consequently, some activation sites in our main study may be related to the bimanual coordination component of the DIM task (see further). In our control study, however, this component was carefully matched between tasks, as were the motor output and response timing. Because task difficulty was kept constant across all tasks at the different rates, cerebellar activations could not be attributed to a difference in task difficulty (Sunaert et al., 2000; Xiang et al., 2003), nor to an additional learning effect during scanning (Imamizu et al., 2000).

As expected, the parametrically varying stimulus presentation rate allowed us to identify many rate-dependent cerebellar activations (Rees et al., 1997; Cornette et al., 1999). Interestingly, our cerebellar activation sites showed exclusively tonic modulation. This is in contrast to the findings of Rees et al. (1997) who reported both tonic and phasic modulatory effects in the cerebellum. This could be ex-

plained by the fact that, unlike the study of Rees et al. (1997), difficulty in our study task was kept constant, resulting in a constant amount of attentional modulation at all stimulus presentation rates. Another factor may be our more stringent criteria for tonic and phasic modulation, which resulted in half the cerebellar sites being categorized as undifferentiated activations.

In general, there was a good conformity between the PET and fMRI results. However, the segregation between the anterior and posterior lobule-VI activation sites was less clear in the PET study. The activation site in left Crus-I of the rate-independent network was located more laterally and anteriorly in the PET experiment. Furthermore, activation sites in the posterior vermis of the motor-and-detection network were observed in the fMRI study but not in the PET experiment. These differences are apparently due to variability among individual subjects, as indicated by the fMRI single subject analyses. The otherwise good agreement between our PET and fMRI results generalizes the results obtained from four extensively studied subjects included in the fMRI study.

### *Role of the distinct cerebellar activation sites*

The cerebellar activation sites in the rate-dependent color discrimination network were located bilaterally in lobule-VI of the lateral hemispheres. Orban et al. (1997) used a successive discrimination of grating orientation in a PET study, which revealed a similar region in the right lateral lobule-VI. Our posterior activation in left lobule-VI corresponds to the site observed by Allen et al. (1997) in a visual attention task. Using a visual object categorization task, Rees et al. (1997) observed bilateral activation sites in lobule-VI, similar to our posterior activations, in which activity also increased with stimulus presentation rate. In these studies it was concluded that the cerebellar regions were activated by visual attention. Participation by cerebellar lobule-VI in visuospatial attention is very unlikely in our study because spatial differences in the stimulus between the tasks were carefully matched in the control study. However, in our study, selective attention for the feature of the stimulus is different in TSD and DIM, so that a cerebellar participation in a visual featural attention network might be possible. The cerebellar activation sites in lobule-VI were coactivated with pre-SMA and dPMC, as were the previously mentioned sites observed by Rees et al. (1997). Anatomical connections between the cerebellum and dPMC and pre-SMA have been demonstrated in monkeys (Wiesendanger and Wiesendanger, 1985; Matelli and Luppino, 1996). Dorsal PMC and pre-SMA are involved in higher-order aspects of motor planning, and particularly the human dPMC has been shown to be involved in decision processes that precede motor output (Leonards et al., 2000; Peuskens et al., 2001). Consequently, another hypothesis about the role of cerebellar lobule-VI of the rate-dependent color discrimination network is that it might subserve a network involved in

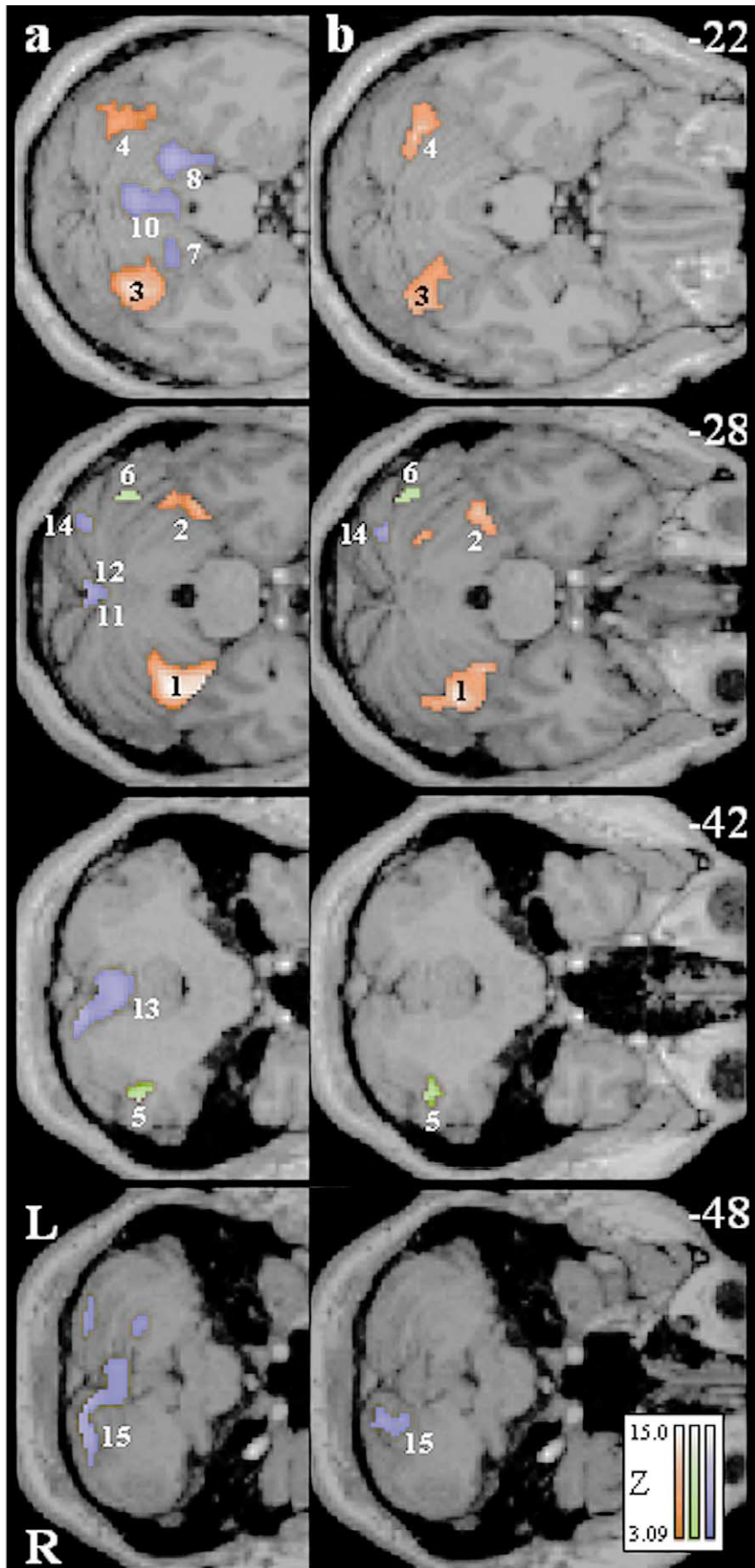


Fig. 6. fMRI control study: Matched motor output and response timing. SPMs showing voxels significant ( $P < 0.001$  uncorrected) in the single subject analysis (S1) for the three networks as in Figs. 4 and 5 in the original (a) and control (b) fMRI studies. Activation sites are superimposed onto transversal sections through the cerebellum of the individual anatomical MRI scan of S1. Numbers correspond to regions listed in Table 2. Same conventions as in Figs. 3, 4a, and 5a.

decision processes or in response reassignment (Bischoff-Grethe et al., 2002). An alternative interpretation is that the cerebellum supports the increased sensory processing necessary at higher stimulus presentation rates (Gao et al., 1996; Bower, 1997; Hartmann and Bower, 2001).

The bilateral cerebellar activation sites in lateral Crus-I belonging to the rate-independent color discrimination network were coactivated with the dorsolateral prefrontal cortex (areas 9 and 46) bilaterally. In monkeys, prefrontal areas 9 and 46 have been shown to project to regions of the pontine nuclei (Brodal, 1978; Glickstein et al., 1985; Schmähmann, 1997), which in turn further project to the cerebellum. Conversely, Middleton and Strick (1994, 1997, 2001) have shown that areas 46 and 9 of the DLPFC in monkeys are extensively innervated by cerebellar efferents. Clinical data from cerebellar patients also suggest connections between the cerebellum and the DLPFC (Fiez et al., 1992; Schmähmann and Sherman, 1998), which is involved in diverse cognitive functions (for review see: Duncan and Owen, 2000; Miller and Cohen, 2001). One of the extensively studied roles of the DLPFC is related to working memory functions (Goldman-Rakic, 1987; Petrides, 1994; Courtney et al., 1996; D'Esposito et al., 1998; Smith and Jonides, 1999; Cornette et al., 2001). Cornette et al. (2001), however, have shown that in a successive orientation discrimination task, with a delay of only 300 ms between two successive stimuli, an ultra-short-term memory component is involved. This ultra-short-term mnemonic component engaged the occipitotemporal cortex. Because the current study used exactly the same task, but with color as attribute, it is unlikely that the DLPFC activation is related to working memory. Another function assigned to the DLPFC is establishing the rules, i.e., appropriate mappings between inputs, internal states, and outputs, needed to perform a given task (Miller and Cohen, 2001), a cognitive role that seems more plausible in the context of our study. Thus, the cerebellar activation sites in Crus-I of the lateral cerebellar hemispheres might be related to this cognitive aspect of the task, and could subserve such a cognitive network.

The activated cerebellar regions of the motor-and-detection network could be subdivided into a motor and a detection component, based on the results of the fMRI control study. In the motor network, activation sites were located bilaterally in medial lobule-V of the cerebellar anterior lobe and in lobules-VI, VIIAt, and VIIB of the vermis. These sites were no longer observed in the control study in which motor output was equalized between tasks. In a recent sensorimotor mapping fMRI study of the human cerebellum, Grodd et al. (2001) have shown that motor activity of the hand activates ipsi- and contralateral lobule-V at a distance of 15–30 mm from the midline, corresponding with our data. Cerebellar arm areas in lobule-V of the vermis and hemispheres have been identified in monkeys (Middleton and Strick, 1997). Tracy et al., (2001) have shown in humans that bimanual coordination activates lobule-VI of the vermis. This fits with our results because we observed a

similar activation site in vermal lobule-VI in the original study. This site was no longer seen in the control study, in which bimanual coordination was matched between tasks. The motor cerebellar regions in our study were coactivated with M1 and SMA. A significant correlation between activity in the dentate nucleus and SMA was similarly found by Liu and co-workers (1999) using a tactile discrimination task. Both M1 and SMA in monkeys have been shown to project to the cerebellum and to be the target of its thalamic outputs (Rouiller et al., 1994; Matelli and Luppino, 1996; Hoover and Strick, 1999).

The activation sites in posterior left Crus-I and right Crus-II of the motor-and-detection network were unaltered after equalizing the motor component in the control study. Furthermore, these sites were coactivated with visual cortical regions in both the original and control studies, and might thus be related to the detection of the dimming event. Therefore, posterior Crus-I and Crus-II might subserve a dimming detection network. These cerebellar activation sites also did not correspond to the posterior regions involved in hand movement in the mapping experiment of Grodd et al. (2001).

In summary, our results suggest that lobule-VI of the lateral cerebellar hemispheres is involved in a network related to visual attention or to decision processes. Lateral cerebellar Crus-I is part of a rate-independent network that could be involved in establishing the rules needed to perform the task. Lobule-V and the vermis are involved in motor execution and vermal lobule-VI specifically in bimanual motor coordination, together constituting a motor network. Finally, posterior Crus-I and Crus-II might play a role in dimming detection.

#### *Role and organization of the cerebellum*

The rate dependency of most of the cerebellar activation sites in our study suggests that cerebellar participation is critical whenever a task has to be performed rapidly. This fits the clinical finding that mainly rapid movements are impaired in patients with cerebellar lesions (Hore et al., 1991; Berardelli et al., 1996). Several authors (Ivry and Keele, 1989; Jueptner et al., 1995; Tesche and Karhu, 2000; Dreher and Grafman, 2002; Ivry et al., 2002) have suggested a timing function for the cerebellum. The rate dependency of most activations in our study could favor a cerebellar function in timing, but the large number of different activation sites is rather at odds with a simple clock hypothesis.

Middleton and Strick (1997, 2001) suggested that the cerebrocerebellar interaction is organized as multiple, topographically closed loops. Because functional imaging does not allow us to establish causal relations between the activated regions, no solid conclusions about the closed loop hypothesis can be made. However, the rate-independent color discrimination network involving only a single cere-

bellar and cerebral activation site in each hemisphere might support this hypothesis.

In conclusion, we have demonstrated for the first time the joint involvement of multiple, spatially discrete, and functionally distinct cerebellar regions using functional imaging. Lobule-VI and lateral Crus-I seem to be involved with nonmotor and cognitive components of the color discrimination task, lobule-V and the vermis with the motor components of the task, and posterior Crus-I and Crus-II with the detection of the dimming event. These findings suggest the participation of the cerebellum, which is mainly rate dependent, in a variety of different motor and nonmotor task components. Because of the uniform and relatively simple cytoarchitecture of the cerebellum, it is generally assumed that its function, in the sense of its local operations, is everywhere identical (Ito, 1993; Braitenberg et al., 1997). If so, it is a challenge to elucidate this common cerebellar function.

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