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Neuronal Activity Related to the Visual Representation of Arm Movements in the Lateral Cerebellar Cortex

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Liu, Xuguang, Edwin Robertson, and R. Christopher Miall. Neuronal activity related to the visual representation of arm movements in the lateral cerebellar cortex. *J Neurophysiol* 89: 1223–1237, 2003. First published November 20, 2002; 10.1152/jn.00817.2002. Testing the hypothesis that the lateral cerebellum forms a sensory representation of arm movements, we investigated cortical neuronal activity in two monkeys performing visually guided step-tracking movements with a manipulandum. A virtual target and cursor image were viewed co-planar with the manipulandum. In the normal task, manipulandum and cursor moved in the same direction; in the mirror task, the cursor was left-right reversed. In one monkey, 70- and 200-ms time delays were introduced on cursor movement. Significant task-related activity was recorded in 31 cells in one animal and 142 cells in the second: 10.2% increased activity before arm movements onset, 77.1% during arm movement, and 12.7% after the new position was reached. To test for neural representation of the visual outcome of movement, firing rate modulation was compared in normal and mirror step-tracking. Most task-related neurons (68%) showed no significant directional modulation. Of 70 directionally sensitive cells, almost one-half (n = 34, 48%) modulated firing with a consistent cursor movement direction, many fewer responding to the manipulandum direction (n = 9, 13%). For those "cursor-related" cells tested with delayed cursor movement, increased activity onset was time-locked to arm movement and not cursor movement, but activation duration was extended by an amount similar to the applied delay. Hence, activity returned to baseline about when the delayed cursor reached the target. We conclude that many cells in the lateral cerebellar cortex signaled the direction of cursor movement during active step-tracking. Such a predictive representation of the arm movement could be used in the guidance of visuo-motor actions.

INTRODUCTION

The purpose of this study was to examine the functional specificity of the lateral cerebellar cortex in its visual representation of arm movements. Different regions in the cerebellar cortex make separate contributions to visually guided limb movements. Lateral cerebellar activity appears to be more closely related to teleceptive sensory inputs for guiding limb movements than to the limb movements per se (for review, see Stein and Glickstein 1992). The lateral cerebellum also provides a heavy ascending projection to the motor cortical areas via the motor thalamus, in comparison with the intermediate, paravermal, and vermal regions of the cerebellar cortex that output mainly to the red nucleus, brain stem nuclei, and descending pathways. Neurons in the lateral cerebellar cortex respond to visual inputs during guided limb movements (Glickstein et al. 1980; Marple-Horvat et al. 1998; Stein 1986). Noda and Mikami (1986) and Marple-Horvat and Stein (1990) suggested that the visual responses in the dorsal paraflocculus and in those parts of the dentate and interpositus nuclei receiving from the paraflocculus play a role in the guidance of monkeys' movements. Chapman et al. (1986) also reported that dentate nucleus cells showed responses to teleceptive sensory cues. The responses are often conditional on the correct visually guided response (Chapman et al. 1986; Marple-Horvat and Stein 1990; Strick 1983).

There is also some serial order to the neural responses within the cerebellum, motor cortex, and muscles, although by no means absolute. Chapman et al. (1986) found that 91% of dentate neurons showed a clear modulation before the onset of movement, while interpositus cells were active at or after movement onset. Thach (1975) revealed that dentate neurons discharge on average approximately 20 ms before those in the precentral motor cortex; the latter in turn precede those in interpositus nucleus. Cooling (Vilis et al. 1976) or ablation (Spidalieri et al. 1983) of the dentate nucleus delays the discharge of precentral neurons, and this is associated with prolongation of visually triggered reaction times. Thus it seems that visual trigger signals originating in the parieto-occipital cortex may first activate the lateral cerebellum and dentate nucleus whose output is fed to the motor cortex. The motor commands generated by the motor cortex (and presumably influenced by this lateral cerebellar signal) are then projected to brain stem and spinal cord, as well as back to the paravermal and paramedian cerebellar cortex and interpositus nuclei via the reciprocal cerebro-cerebellar connections.

Accordingly, when the lateral cerebellar cortex or the interposed or dentate nuclei are inactivated, reaching movements are decomposed into jerky, intermittent movements, and impairments appear in visually guided tracking (Brooks et al. 1973; Miall et al. 1987). These impairments may arise because the inactivated cerebellum fails to make sufficient use of visual information about the direction, range, and speed with which the target and the arm move (Stein and Glickstein 1992). Hence cerebellar target neurons in the motor cortex are not modulated appropriately, and a correctly sequenced motor program is not generated. Cerebellar deficits are especially pronounced during visually guided movement, however, and

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tracking movements are more intermittent when vision of the moving limb is used than when no vision is available (Beppu et al. 1987; Haggard et al. 1995). We have argued from such data that the cerebellum allows processing of the visual *reafference* (visual feedback) from on-going movement (Liu et al. 1997; Miall 1998; Miall et al. 1993). Others (e.g., Bower 1997) have stressed its role in sensory processing.

Human functional imaging data suggests that lateral areas of the cerebellar cortex are activated during visually guided tasks (Ellerman et al. 1998; Grafton et al. 1992; Jueptner and Weiller 1998; Jueptner et al. 1996), with differential activation in visually guided conditions versus movements without visual guidance (Jueptner et al. 1996), although others report that the difference to be more medial, in the vermis (Ellerman et al. 1997; Inoue et al. 1998).

The lateral cerebellum, therefore, seems to be heavily involved in the sensory guidance of movement. We have cited mainly literature on visual guidance above, but the involvement in lateral cerebellum in single joint movements and in proprioception means that nonvisual guidance should also be involved (Bastian et al. 1996; Holmes 1939; Rubia and Kolb 1978; Smith et al. 1993; Thach et al. 1986, 1992).

There are several physiological models of cerebellar control of limb movements. One closely related to the hypothesis of the present experiment is that the cerebellum forms a *forward internal model*. It is proposed (Ito 1972, 1990; Kawato and Gomi 1992; Kawato et al. 1987; Miall et al. 1993) that the lateral cerebellar hemisphere holds a forward internal representation of the arm. This internal representation is hypothesized to be in a sensory coordinate frame and used to predict the sensory reafferent signals caused by movement (Miall et al. 1993). Thus we aimed to test the hypothesis that cells in the lateral cerebellar cortex would code for sensory consequences of actions.

We investigated first how lateral cerebellar cortical cells respond to sequential events during visually guided step-tracking tasks. Next, by reversing the directional relationship between movement of the arm and movement of the visual cursor representing the arm and by introducing time delays between movements of the arm and of the cursor, we also investigate how lateral cerebellar activity correlates with the visual representation of arm movements. Some of this data were described in a preliminary report (Miall 1998). Our hypothesis is that cells coding for a visual representation of an ongoing arm movement would display an activity pattern consistent with the movement of the visually displayed cursor, with or without the mirror reversal of arm movement to cursor movement. We further hypothesize that this internal neural representation of the visual outcome of arm movement should be time-locked to the arm movement itself, because of the causal relationship between movement and reafference.

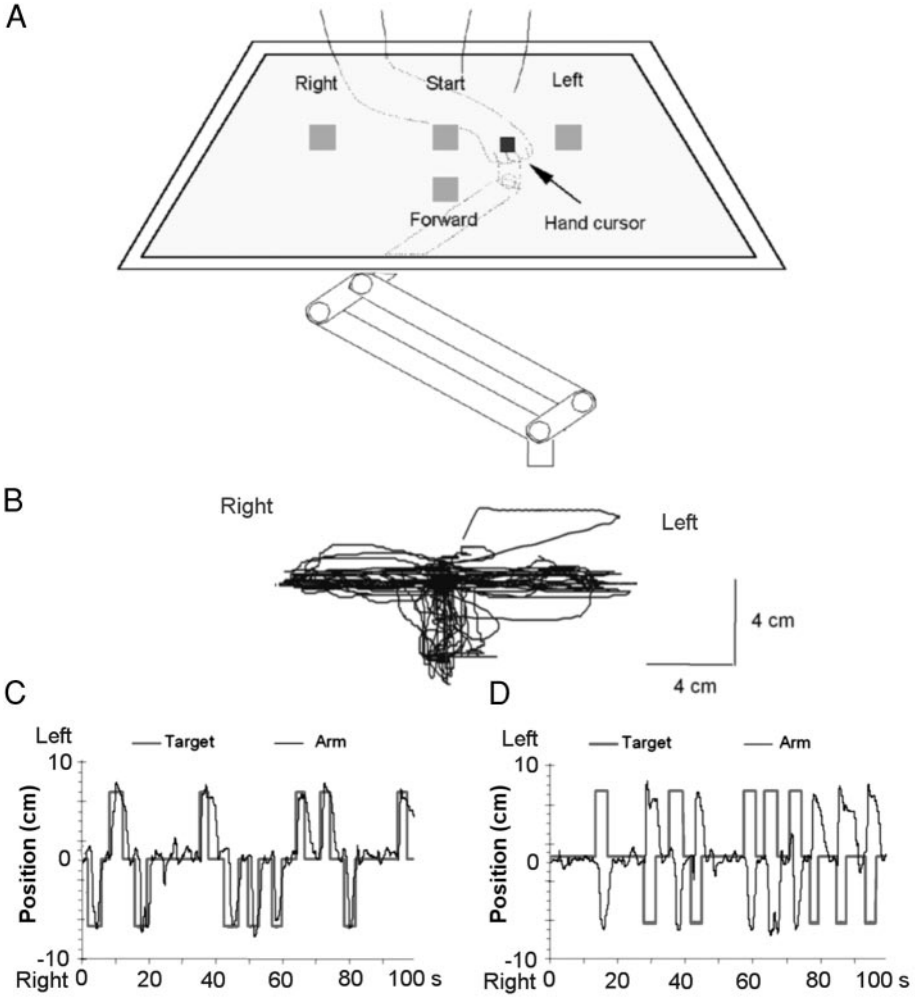


FIG. 1. The visually guided step-tracking tasks. *A*: target positions and hand and cursor motion. A mirror blocked direct vision of the animal's forearm and provided a virtual image of the target and cursor co-planar with the manipulandum. In each trial, after the monkey placed the cursor onto the target at the starting point (Start), the target jumped to a new position left, right, or forward. The monkey was required to track the target with the cursor for reward. *B*: example of traces of cursor movement in a block of 36 trials (12 in each direction). *C*: an example of the horizontal component of target and arm movements plotted against time for the normal task, in which the arm (and the cursor) moved in the same direction as the target. *D*: the mirror task: to track the target with the cursor, the arm moved in the reversed direction.

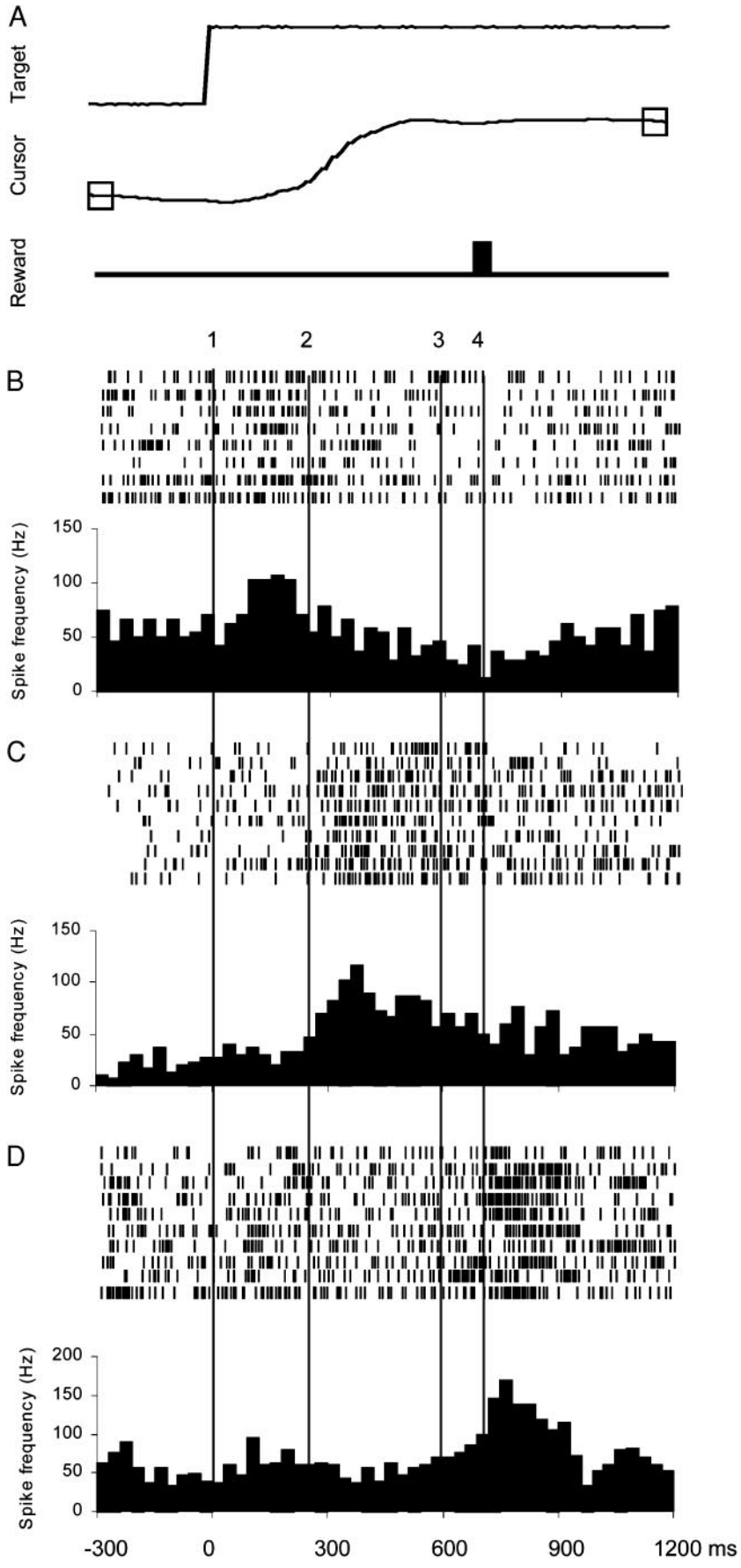


FIG. 2. Examples of 3 different groups of task-related neurons in the lateral cerebellar cortex. *A*: time course of target movement (*top*), cursor movement (*middle*), and reward delivery (*bottom*) in a typical single trial. All rasters are aligned to the onset of target motion. *B*: example of a premovement cell displaying an increase in discharge rate following the onset of target movement (marked by the vertical line 1) and before the typical onset of cursor movement (line 2). *C*: example of a perimovement cell displaying an increase in discharge rate during movement and until the new target position was acquired (line 3). *D*: example of a postmovement cell displaying an increase in discharge rate after the target was acquired in its new position (line 3) and during reward delivery (line 4). In *B–D*, the rasterplots of individual trials and averaged spike frequency histograms in 30-ms bins are aligned on the onset of target movement (line 1). Cells have been selected to show typical activity patterns from blocks of trials with approximately equal time courses; hence the vertical lines show the typical timepoints of movement onset, target acquisition and reward, which vary trial-by-trial from target movement onset.

METHODS

Animals and apparatus

Two juvenile rhesus monkeys (*Macaca mulatta*), weighing between 6.2 and 7.8 kg, served as subjects in the present experiments. All procedures for animal care and use were in accord with the "Guiding Principles for animal Care and Use of Animals". Each monkey was trained to perform visually guided step-tracking movements with the right arm by grasping and moving a manipulandum that allowed multi-joint responses in a two-dimensional workspace. After training, recording chambers were implanted above the ipsilateral cerebellum under full surgical anesthesia. Standard electrophysiological techniques were used to record single cell activity through tungsten-in-glass microelectrodes (impedance, 0.75–1.5 MΩ).

Visually guided step-tracking tasks

Two visually guided step-tracking tasks were used. In both, the monkey was required to track a visual target (8 × 8 mm) with a cursor (8 × 8 mm). A jointed manipulandum was positioned underneath an angled semi-silvered mirror. Target and cursor were projected onto a rear projection screen (VGA resolution) and viewed in the mirror. The position of the handle held by the monkey was measured in two dimensions with precision potentiometers, and was spatially aligned with the visual cursor. Prior to recording, the displayed cursor position was calibrated to the manipulandum handle by fitting quadratic regression equations between cursor *x* and *y* positions and the two voltage signals available form the potentiometers on each arm of the jointed manipulandum (Fig. 1*A*), over a 9-point grid of calibration positions. Hence, we recorded cursor position signals in terms of horizontal and anterior-posterior components. Calibration was within 5 mm across the entire workspace, assessed by visual inspection of cursor and manipulandum through the semi-silvered mirror. The target was initially displayed in the midline, 3 cm from the bottom of the display window, and approximately 20 cm directly in front of the animal's torso, as the starting point for each trial. After the monkey placed and held the cursor onto the target for a random interval (100–300 ms), the target jumped to a new position 7 cm left or right or 5 cm forward (Fig. 1*A*). Target direction was randomized across trials. The monkey was then required to accurately reach the target within 750 ms and to hold the cursor there for ≥150 ms before reward with liquid food. The target subsequently returned back to the starting position and the monkey moved back at a self-paced speed to initiate the next trial. In the *normal* form of the task (Fig. 1*C*), the manipulandum and cursor were spatially co-registered, and moved in the same direction; in the *mirror* task (Fig. 1*D*), the manipulandum and cursor moved in left-right reversed directions. Forward movement was not affected.

In *monkey 2*, recordings were also carried out while a short delay of 70 ms was introduced between movements of the manipulandum and cursor (Miall et al. 1985) in both normal or mirror task. We found that 70 ms was the maximal delay with which the monkey was able to maintain higher than 90% success rate without further training. After several weeks of training with gradually increasing delays, additional recordings were made with a delay of 200 ms in the normal task, again at >90% success rate. These delays were used to differentiate the onset of cursor movement from hand movement. Whenever possible, blocks of normal and mirror tasks, with or without delay, were employed in a random sequence while spike activity was recorded from the same cell. A total of 24–30 trials (8–10 trials in each movement direction, Fig. 1*B*) were recorded for each cell for each task. In addition, spike activity was also recorded during 20 recording sessions from task-related neurons when the experimenter performed the normal task; the monkey attended to the display and was rewarded but did not perform the step-tracking movements.

Data analysis

STEP-TRACKING BEHAVIOR. Movement durations (from leaving starting zone to reaching new target zone) and peak velocities were calculated for all trials performed by *monkey 1* during the cell recordings. In *monkey 2*, movement times and peak velocities were analyzed in more detail. Because of the smooth onset of many movements (e.g., Fig. 2*A*), movement times are presented measured from target movement onset to peak manipulandum velocity time. Values were averaged over 200–250 trials from 20 representative sessions spanning the early, middle, and later stages of recording and compared between normal and mirror tasks, with and without feedback delay in three movement directions. Statistical tests were separately carried out for horizontal and vertical movements. For horizontal movement, in which direction of the arm and cursor were reversed in the mirror task, results were tested using a three-factor ANOVA (factors of direction, task, and 70-ms delay, with a significance level of $P < 0.05$). For the forward direction, in which movement of the arm and cursor were unchanged between the normal and mirror tasks, a two-factor ANOVA was used (task and 70-ms delay). Only limited sessions were collected in the mirror task with a 200-ms delay, so no statistical analysis of the behavior is presented for this condition in this paper.

STATISTICAL TESTS OF MODULATION IN FIRING RATE. *Task-related activity.* Each trial was divided into three 500-ms time segments. *1*) Premovement, 500 ms before the onset of movement (the moment the cursor moved from the initial target zone); *2*) perimovement, 500 ms after onset of movement; and *3*) postmovement, 500–1,000 ms after onset of movement. Spikes were counted over 8–10 movements in the same direction into 30-ms bins across the three 500-ms periods. Task-related changes in activity were determined by significant differences across the three 500-ms periods (1-way repeated measures ANOVA, with significance level of $P < 0.05$). Similarly, directional activity of cells was determined by significant ANOVA across three movement directions (2-way direction × time period ANOVA). For those cells showing statistically significant direction responses ($P < 0.05$: main effect of direction or direction × time interaction), a comparison between normal and mirror tasks then identified activity related to either the cursor movement or the arm movement.

Modulation of firing rates. The mean premovement firing rate and modulation of neuronal activity was calculated for each neuron in each target direction, after alignment to the peak movement velocity,

TABLE 1. *Comparison of movement performance in different conditions*

	Normal Task		Mirror Task	
	Movement time (s)	Peak velocity (m/s)	Movement time (s)	Peak velocity (m/s)
No delay				
Right	0.38 ± 0.08	0.46 ± 0.10	0.40 ± 0.09	0.33 ± 0.08
Left	0.38 ± 0.13	0.27 ± 0.06	0.53 ± 0.14	0.31 ± 0.07
Forward	0.40 ± 0.12	0.40 ± 0.09	0.41 ± 0.10	0.35 ± 0.09
70-ms delay				
Right	0.37 ± 0.08	0.50 ± 0.11	0.43 ± 0.12	0.35 ± 0.10
Left	0.48 ± 0.14	0.30 ± 0.08	0.54 ± 0.13	0.32 ± 0.07
Forward	0.40 ± 0.10	0.42 ± 0.09	0.42 ± 0.14	0.39 ± 0.09
200-ms delay				
Right	0.24 ± 0.08	0.28 ± 0.06		
Left	0.24 ± 0.10	0.12 ± 0.03		
Forward	0.23 ± 0.12	0.26 ± 0.09		

Data was averaged from 20 sessions of 200–250 trials, *monkey 2*. Movement times were measured from target motion onset to time of peak manipulandum velocity. "Left, right, and forward" refer to the direction of the cursor movement; the arm and manipulandum movements would be left-right reversed with respect to the cursor in the mirror task condition.

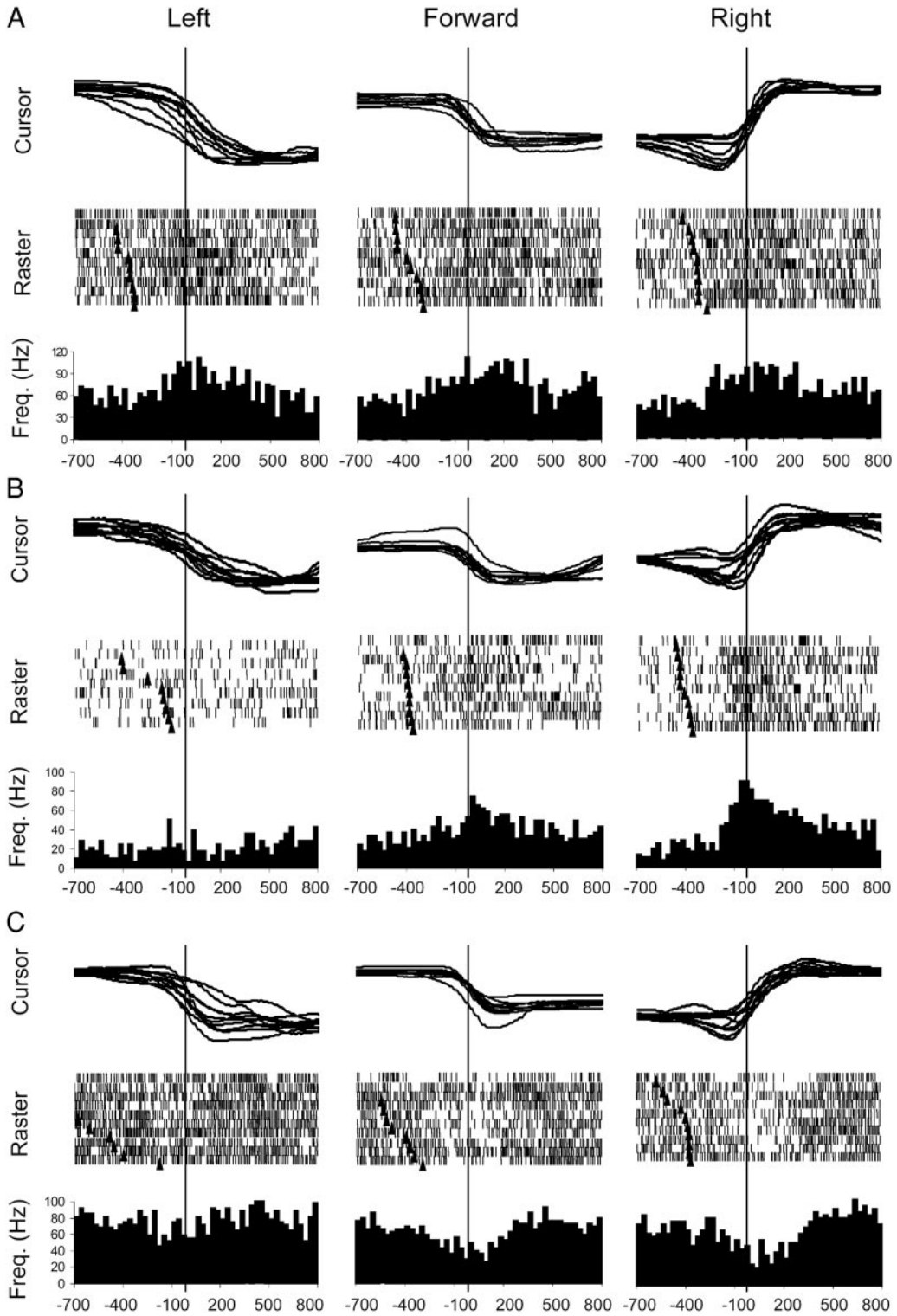
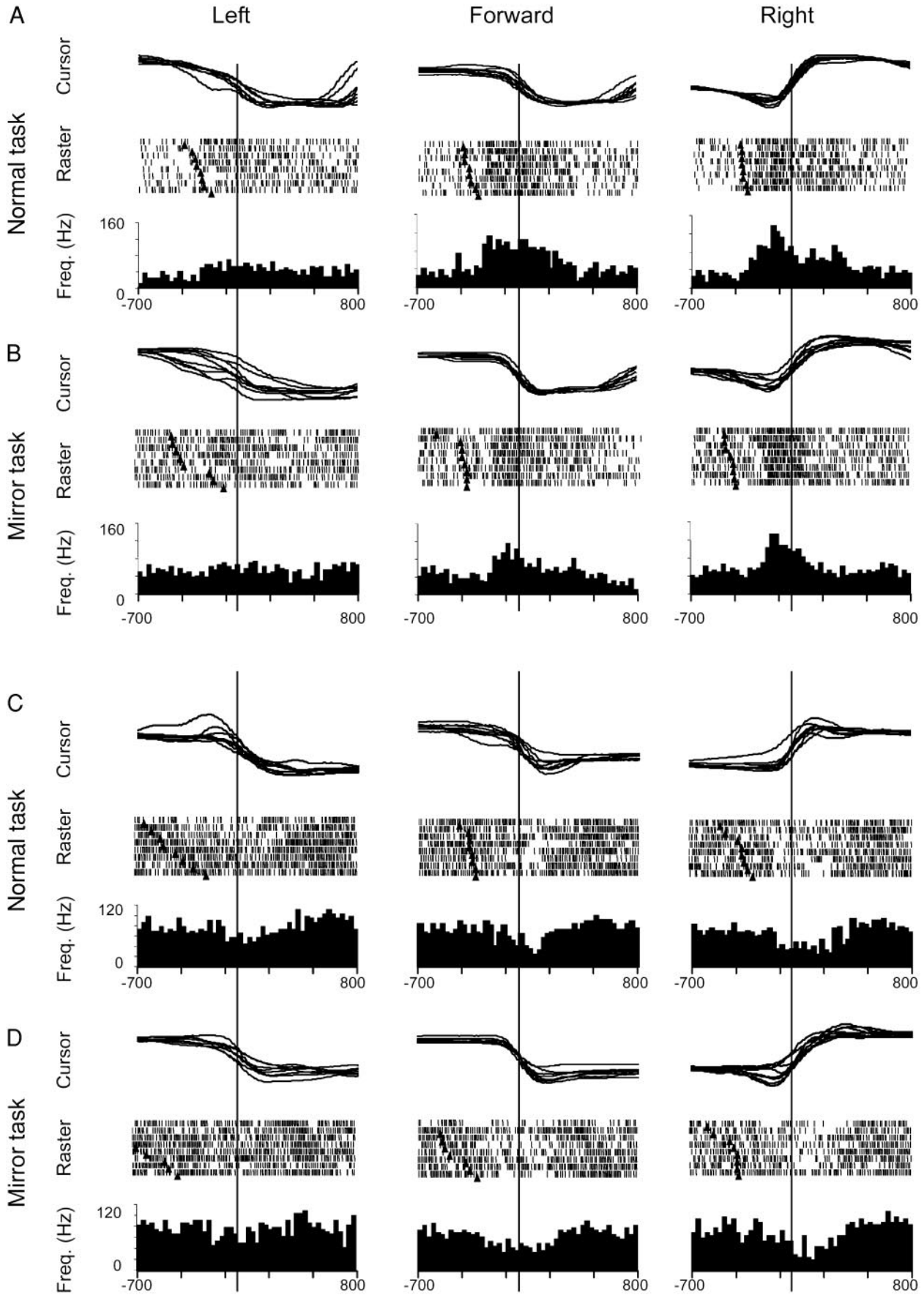


FIG. 3. Examples of (*A*) a nondirectional neuron displaying an increase in firing rate during movements to all 3 directions; (*B*) a directional neuron displaying an increase in firing rate during movement to the right and forward; and (*C*) a directional neuron displaying a decrease in firing rate during forward movement and movement to the right but not to the left. Trial-by-trial records of cursor movement are shown, plotting movement in the appropriate dimension (horizontal cursor movement for left-right targets, forward movement for forward targets). Cursor records, rasters of individual trials, and averaged spike frequency histograms in *A–C* are aligned on peak manipulandum velocity, measured in 2 dimensions. The onset of target movement is marked with a small triangle in the raster for each trial, sorted by reaction time. Trials sorted by cursor movement directions to the left, forward, and right are presented in each column and labeled at the top.


A
Left
Forward
Right
Normal task
Cursor
Raster
Freq. (Hz)
160
0
-700
800
B
Mirror task
C
120
D

and averaged across all task-related neurons. Increases in activity in the 500-ms perimovement period above the premovement levels were presented as a percentage increase and ranked into the preferred, less preferred, and least preferred directions. Similar analysis was done for the inhibitory neurons. Mean modulation rates between the preferred and the opposite directions were compared across the normal and mirror tasks. For "cursor-related" cells (see *Histological procedure and construction of recording sites*; *monkey 2* only), the peak velocity was correlated to the increase in activity for both the preferred and the opposite directions, trial by trial.

To test the effect of feedback delay on the duration of neural responses, the start and endpoints of the modulated activity period were determined as the times where the level of activity in either the nondelayed or the delayed tasks changed more than 2 SD beyond the averaged premovement level.

Histological procedure and construction of recording sites

Small electrolytic marking lesions were made along tracks at known coordinates by passing DC current (20 μA, 30 s) via a microelectrode. Three days later the animals were killed with a lethal dose of pentobarbital sodium and subsequently perfused transcardially with saline, followed by 10% buffered formalin. Before the brain was removed from the cranium, a metal pin was inserted marking the recording chamber center. The brain was then removed and fixed. The cerebellum was dissected. After photographing its dorsal surface, the tissue was frozen and sectioned in the coronal plane at 50 μm. Every fifth section was stained with cresyl violet and mounted. The recording chamber was remapped onto the photograph of dorsal surface of the cerebellum by identifying its center mark. Finally, the micro-drive coordinates of the task-related neurons were plotted onto coronal sections covering the recording volume.

RESULTS

General patterns of step-tracking behavior

In *monkey 1*, movement durations did not differ between the normal and mirror tasks (ANOVA, $P > 0.05$, $n = 3174$), but peak velocities did significantly fall in this animal during mirror movements toward the right (mean drop of 17%; $P < 0.01$, ANOVA). For *monkey 2*, the averaged movement time and peak velocity in the normal and mirror tasks, with and without feedback delay, in each direction are given in Table 1. For left-right targets, the movement direction of the arm and cursor are reversed between the normal and mirror tasks. Results showed that the movement of the cursor to the left was slower than to the right in the normal task; this difference greatly reduced in the mirror task. Movement times were longer, and cursor movements to the right were of lower peak velocity in the mirror task compared with the normal task. The addition of 70-ms feedback delay had little effect on either performance indices. Addition of 200-ms feedback delay significantly reduced movement velocity (Table 1).

For movement in the forward direction, the display of the arm and cursor were essentially unchanged between the normal and mirror tasks. The peak movement velocity was slightly but significantly higher in the normal task (with or without feedback delay) than in the mirror task (again with or without delay), whereas the differences in reaction time among task conditions were insignificant.

General patterns of neuronal activity

A total of 173 cells (31 cells in *monkey 1*; 142 cells in *monkey 2*) that displayed significant changes in activity in relation to at least one of the tasks were recorded (ANOVA, $P < 0.05$). According to the timing of their firing patterns in relation to the sequential events of target movement, onset of manipulandum movement, target acquisition, and reward, the 142 task-related cells recorded from *monkey 2* fell into three groups. *Premovement cells* (13 cells, 9.2%, Fig. 2*B*) displayed increases in firing rate at early stage of the task, approximately 90–100 ms after the target moved into a new position, but clearly before the onset of arm motion. The monkey had an average movement time (measured to peak movement velocity) of 380 ms in these tasks; the time to initial manipulandum movement was typically about 200 ms. The majority of cells fell into the second group of *perimovementcells* (114 cells, 80.3%, Fig. 2*C*) and displayed changes in firing rate during arm movement. *Postmovement cells* (15 cells, 10.6%, Fig. 2*D*) increased firing rate at late stage as the target was reached at its new position and as the animal was being rewarded for successful movement. For *monkey 1*, the breakdown of the sample was similar: 17% premovement, 58% perimovement, and 25% postmovement modulated. Pre- and postmovement neurons did not show directional modulation, and no decreases in activity were found in our sample.

On the other hand, according to their firing pattern related to the direction of the movements, these cells fell into two general categories. Examples of these are illustrated in Fig. 3, *A* and *B*. The first group of cells (*nondirectional neurons*, 134 cells in total, 114 or 65.9% of the sample recorded from *monkey 2*) showed significant task-related change in firing rate during the movement (Fig. 3*A*) but showed no significant effect of movement direction or interaction between movement direction and task (normal and mirror-tracking, ANOVA, $P > 0.05$). The averaged premovement firing across all nondirectional cells was 72.0 ± 38.4 Hz. The mean increases in firing rate during the tracking movements were 35.2 ± 18.6%, 25.7 ± 16.6%, and 15.9 ± 15.6%, respectively, to the best, middle, and least modulated directions. The second group of cells (*directional neurons*, 70 cells in total, 59 cells or 34.1%of the sample recorded in *monkey 2*) showed significant modulation in firing rate between movement directions (Fig. 3*B*). In this group of cells, the averaged premovement firing rate was 64.0 ± 34.1 Hz, and the average increases in firing rate during movement were 90.3 ± 134.9%, 60.6 ± 84.3%, and 29.6 ± 47.9%, respectively, for the preferred, less preferred, and least preferred directions. Nine directional cells showed significant decreases in firing rate during arm movement (Fig. 3*C*). Their

FIG. 4. Two examples of cursor-related neurons displaying greatest modulation in firing rate when the cursor moved to the right (*right column*) in both normal (*A* and *C*) and mirror tasks (*B* and *D*). The format of each panel is the same as in Fig. 3. Columns are sorted by direction of cursor movement; hence the manipulandum was moved to the left during mirror trials shown in the *right column* of *B* and *D*. Two-way ANOVA of the perimovement activity modulation rate during the normal and mirror tasks showed significant differences between left and right tracking directions ($P < 0.05$), but no difference between tasks or an interaction ($P > 0.05$). As a control condition, no significant difference was seen in firing rate modulation when the arm and cursor moved forward under normal and mirror tasks (*middle column*).

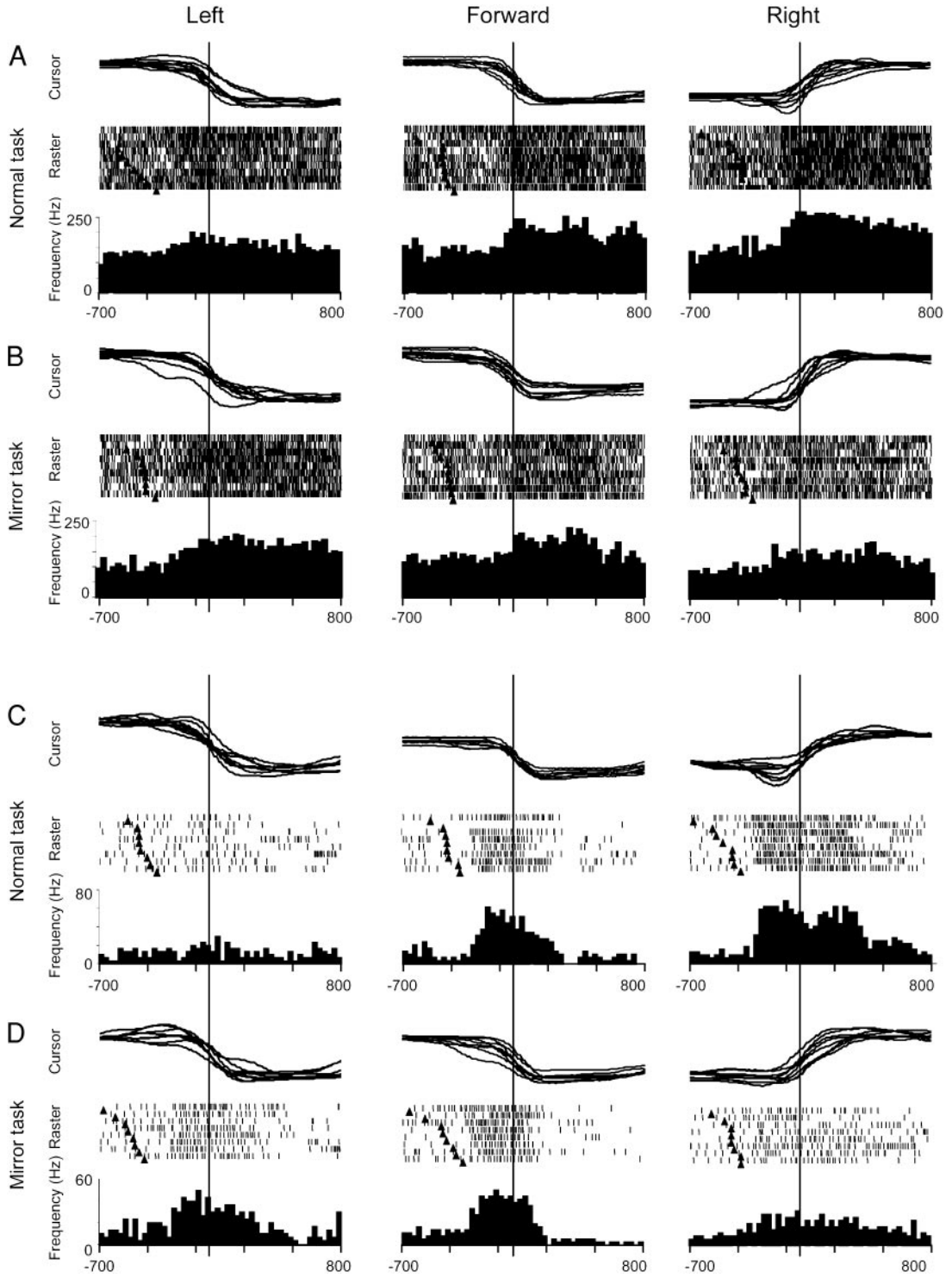


FIG. 5. Two examples of arm-related neurons displaying increases in firing rate when the arm moved to the right in both normal (*A* and *C*) and mirror tasks (*B* and *D*), whereas the cursor moved to the right in the normal task and to the left in the mirror task. The format is the same as in Fig. 4. Two-way ANOVA of the activity modulation rate during movement between the normal and mirror tasks showed significant differences between left and right directions and also a significant interaction, but no main difference between tasks. As a control condition, no significant difference was seen in firing rate modulation when the arm and cursor moved forward under normal and mirror tasks. A marked difference in baseline firing rate existed between these 2 neurons; the recorded location of this cell is indicated in Fig. 10.

averaged premovement firing rate was 70.8 ± 34.9 Hz, and the decrease in firing rate during movement was 33.0 ± 33.0%, 14.2 ± 12.8%, and 1.5 ± 8.5%, respectively. Twenty task-related neurons (comprising 12 nondirectional and 8 directional cells) were tested and showed no significant modulation during the monkey's observation of the task being performed

by the experimenter. For *monkey 1*, 11 of the 31 task-related cells (35.5%) were directionally modulated; another 5 cells (16%) showed significant directional modulation in only one of the two tasks (normal or mirror) and are thus ambiguously sensitive to direction.

Across 173 task-related cells recorded in both animals, 152 cells (87.9%) were provisionally classified as Purkinje cells. Of these, 84 featured complex and simple spikes; the other 68 cells (39.3%) had an averaged firing rate of 40–80 Hz. While not an absolute discriminating feature, a high and irregular firing rate is found frequently in Purkinje cells and less often in other cortical cells (Armstrong and Rawson 1979; Huang et al. 1993). The remaining 21 cells have lower average firing rates (<30 Hz). None of the 11 directional neurons recorded in *monkey 1* demonstrated clear complex spikes; 5 of these had firing rates of <40 Hz and may thus represent other cortical cells. All 59 directional neurons recorded from *monkey 2* showed simple and complex spikes.

Directional modulation in neuronal activity

Nearly one-half of the 70 directionally modulated neurons, comparing across the normal and mirror tasks to left and right directions, manifested statistically significant changes in firing rate more strongly related to the direction of the cursor movement rather than that of the manipulandum (for *monkey 1*: 4 cells, 36% of the 11 directional cells, 13% of all task-related neurons; for *monkey 2*: 30 cells, 51% of directional cells, 17.3% of total task-related neurons). All were classified as "perimovement" cells and we refer to these neurons as "cursor-related" (Fig. 4). Thus their directional modulation was consistent across the normal and mirror tasks with respect to the motion of the visual cursor (Fig. 4). Our use of the term "cursor-related" is not meant to imply that these cells respond to the visual display of the cursor image. Rather it implies that they respond to either the cursor image or some neural representation (potentially a predictive estimate) of the visual reafference of movement. We test this distinction later. In contrast, only nine cells (all from *monkey 2*; 13% of directional cells, 5.2% of the total) showed modulation in activity specifically related to arm movement direction rather than that of the cursor and were termed "arm-related" neurons (Fig. 5). The cell shown in Fig. 5, *C* and *D*, had a low spontaneous firing rate, reminiscent of cerebellar nuclear cell activity, but was confirmed to be in the cerebellar cortex (Fig. 10) and had complex spike activity. We were unable to fully classify the remaining 27 directional cells (15.6%) for several reasons. In some, activity was only modulated when the animal moved forward and the movement of the cursor and the arm were identical across the normal and mirror tasks in this direction; in others, the tuning was only apparent in one task; finally, several cells were lost or the animal stopped tracking before complete recording across the normal and mirror tasks was accomplished.

The mean modulation rates (premovement to perimovement period, see METHODS) between the preferred and the opposite directions in the cursor- and the arm-related neurons were compared between the normal and mirror tasks (Fig. 6). It can be seen that the cursor-related cells maintain their preferred direction with respect to the cursor between the normal and the mirror tasks, whereas the arm-related cells invert their preferred direction. In other words these arm-related cells maintain a preferred direction with respect to the manipulandum and not the cursor.

No significant correlation was found between the percentage modulation and the peak velocity among cursor-related directional neurons in movement toward both the preferred and the opposite directions.

Effects of time delay

To separate the timing of arm and cursor motion, time delays of 70 or 200 ms were introduced between movement of the maniplandum and the cursor. Initially, 34 task-related neurons

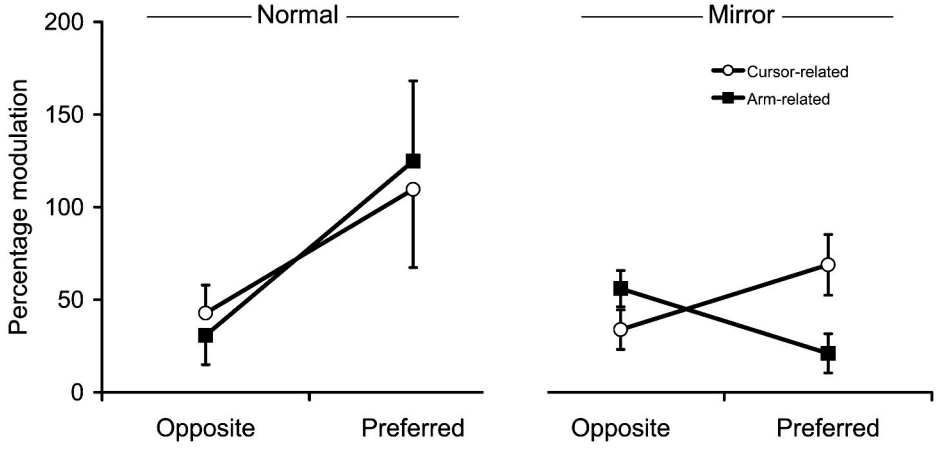


FIG. 6. Comparison of mean percentage modulation of firing rate during step-tracking in the preferred and opposite directions in the cursor- and arm-related neurons. The cells were classified by their firing pattern with respect to cursor movement in the normal and mirror tasks; the change in firing rate was then expressed as an absolute (unsigned) percentage of the baseline. Hence 0% represents no change while 50% represents a change of cell firing rate up or down by 50% of baseline. By definition, all neurons were more highly modulated in the preferred cursor direction than in the opposite direction in the normal task (*left panel*). The arm-related neurons ($n = 9$) manifested significantly lower modulation in activity when moving toward the preferred cursor direction than to the opposite direction. In contrast, the cursor-related neurons ($n = 34$) manifested significantly higher increase in activity when the cursor moved to the same preferred direction in the normal and the mirror tasks despite the reversal of the left-right relationship between the movements of the cursor and the arm. In other words, these cells were more related to the cursor direction than to the manipulandum direction.

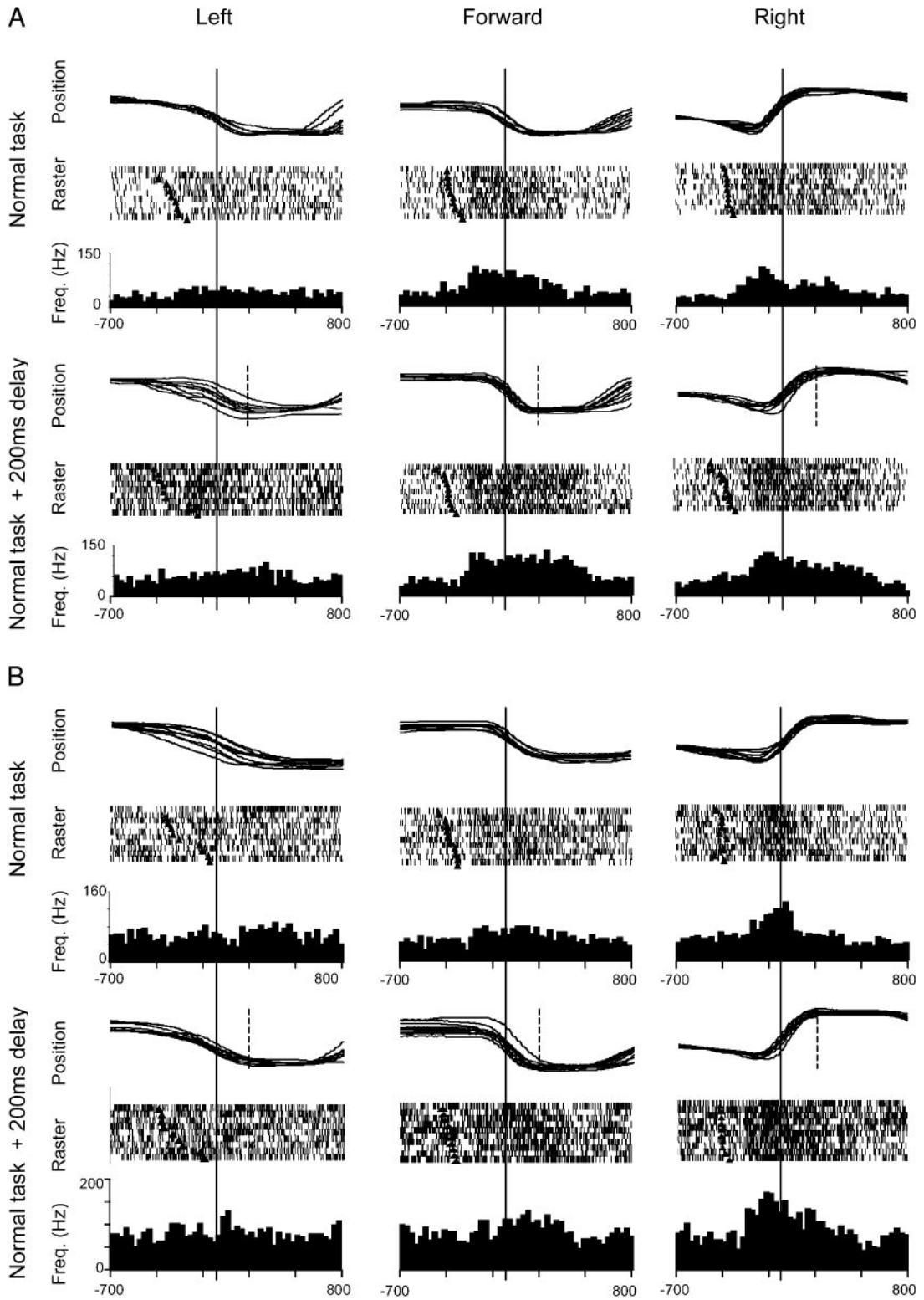


FIG. 7. Two examples of cursor-related neurons displaying an increase in firing rate during cursor movement to the right in both normal (*A* and *C*: normal task) and delayed feedback tasks (*B* and *D*: normal task, +200-ms delay). The format is the same as in Fig. 3; trials are aligned on peak manipulandum velocity (solid lines) and hence the peak velocity of cursor motion on the display screen would be delayed by 200 ms (i.e., rightward shifted, as indicated by the dotted lines). Compared with the normal task, the onset and amplitude of modulation of discharge during the delayed task was unchanged while its duration appears to be extended by an amount corresponding approximately to the delay.

(of which 4 were cursor-related) were tested with a 70-ms time delay, all from *monkey 2*. After further training in the same animal, 45 task-related neurons (of which 6 were cursor-related) were tested with a 200-ms delay.

The effects of delay of the cursor movement were examined for the different groups of cells. First, no overall significant effects were found on the magnitude of activity modulation in all 80 task-related neurons tested with delay, in comparison with tracking without delay in either normal or mirror task (3×2 time period $\times$ delay ANOVA, $P > 0.05$). Second, among the pre- and perimovement nondirectional neurons, no significant changes appeared in the onset of the increased activity of premovement ($n = 8$, Student's t-test, $P > 0.05$) or perimovement cells ($n = 66$) when tested with either a 70- or 200-ms delay. In other words, the delayed cursor movement did not affect the onset of activity in these cells, and therefore, their activity could be more directly related to other elements of the task such as target or hand movements than to the displayed movement of the cursor. In contrast, the onset of the increased activity in the postmovement cells ($n = 6$), modulated after the target was reached at its new position was postponed (63 ± 17 ms, $n = 4$) by the 70-ms delay and more markedly by the 200-ms delay (195 ± 14 ms, $n = 2$).

Interestingly, in the cursor-related cells—which all showed perimovement activity—the delay demonstrated two separate effects on the neural activity patterns. First, no significant shift in the onset of the increased activity appeared even with 200-ms delay, suggesting the activity was consistently time-locked with the onset of the arm movement (Fig. 7). Second, the duration of the increased activity seemed to be proportionally prolonged following a 200-ms delay, from 380 ± 102 to 618 ± 212 ms ($n = 5$, $P < 0.05$, Fig. 7).

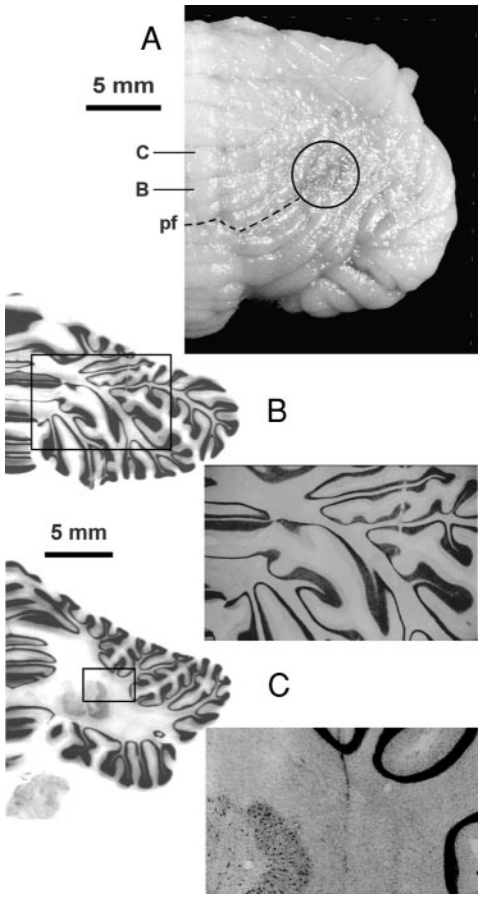


FIG. 8. Position of recording tracks from *monkey 1*: the majority of task related cells were recoded from a region bordering the primary fissure (pf) lateral to the dentate nucleus (*A*). The anterior-posterior positions of 2 slices (*B* and *C*) are indicated. In *C*, the most medial track is shown relative to the margin of the dentate.

Localization of the cursor-related neurons

The majority of all recorded task-related cells were in the lateral cortex, with only a few recording tracts medial to the lateral edge of the dentate nucleus (Figs. 8 and 10). In *monkey 1*, the task-related cells were mainly recorded from lobules V and VI bordering the primary fissure and a smaller number from the dorsal paraflocculus. Because only four cursor-related cells were found in this animal, no pattern of localization could be seen; these cells lay within lobules V and VI. For *monkey 2*, the location of the cursor-related neurons against other task-related neurons was plotted onto the dorsal surface of the cerebellum with various anatomical landmarks (Fig. 9) based on the recorded coordinates of the microdrive and lesion marks. Recording sites were within the lateral part of the anterior quadrangular lobule (17 cursor-related cells), the simple lobule (11 cells), and the ansiform lobule (2 cells), lying between approximately 4 mm anterior and 6 mm posterior to the primary fissure. Only a few recording tracks were into the intermediate, paravermal region of the cerebellar cortex. The distribution of neurons was also reconstructed onto eight selected coronal sections with 1-mm steps across the recording volume (Fig. 10, *1–8*). The majority of neurons recorded were located lateral to the lateral edge of the dentate nucleus. From our reconstructions, none of the task-related cells were located in the cerebellar nuclei; only two recording sites were reconstructed to nuclear zones and these were not directionally tuned cells. Comparing the cursor-related with other task-related neurons in the cerebellar cortex, no clear difference in anatomical distribution could be identified.

DISCUSSION

A paradigm used in many human movement studies requires a subject to perform visually guided actions while direct vision of the arm is blocked, and instead its position is represented—faithfully or with some experimental distortion—by a visual cursor. We applied this paradigm and attempted to disassociate the visual representation of the arm from movement of the arm itself. To achieve this, we used two perturbing features: *1*) left-right reversal of movement direction between the arm and its visual cursor to spatially separate the two, and *2*) introduction of a time delay on the movement of the cursor to temporally separate it from movement of the arm. Recording single unit activity from the lateral cerebellar cortex when pretrained monkeys performed these tasks, we were able to investigate how the simple spike activity of the Purkinje cells in the recording region was modulated in response to specific visuomotor elements of the task. Similar cursor/arm inversion tasks involving horizontal arm movements have previously been reported with recording in the motor cortical areas (Alexander and Crutcher 1990; Shen and Alexander 1997a,b) or the cere-

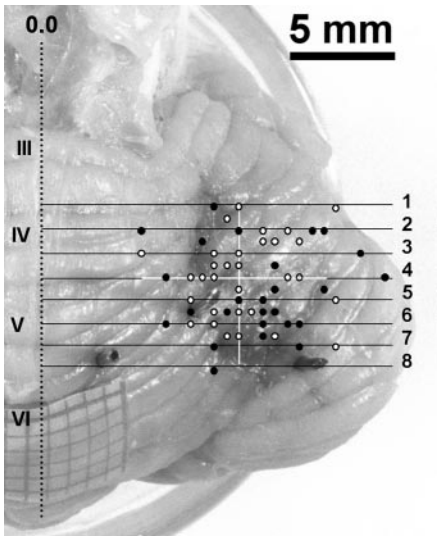


FIG. 9. Positions of the recording tracks on which any cursor-related (○) and other task-related (●) neurons were found are plotted on a photo of the dorsal surface of the cerebellum of *animal 2* with anatomical marks. Eight horizontal lines indicate position of 8 serial coronal sections in Fig. 10. The dotted vertical line indicates the midline of the cerebellum. A small grid of 1-mm spacing was placed on the cerebellar surface; a row of localizing pins inserted postmortem are aligned with horizontal section line 8. The vermis: lobules III, IV, V, VI and VII are marked.

bellum (Ebner and Fu 1997). Martin and Ghez (1985, 1991) used a related sensory-motor dissociation in cats, recording from red nucleus and motor cortex.

Our key findings were first that task-related cerebellar cortical activity was modulated either before arm movement, around the time of arm movement, or at the end of movement. Second, among the perimovement active cells (the largest category recorded), a large proportion of those in which we were able to determine significant directional modulation proved to be sensitive to the direction of motion of the cursor, and/or gaze position, and not of the arm itself. Third, in the subset of these cursor-related cells which we examined under delayed feedback conditions, delay of the on-screen cursor prolonged their activation but onset of increased activity remained time-locked to arm movement.

To expand on these findings, while the majority of neurons were modulated during arm movements, two small groups of neurons displayed changes in activity at either early or late stages of each trial. 17 cells (10.2% of total task-related neurons) displayed early increases in firing, at or even before the onset of the target movement, and none of these neurons were directionally modulated. This increase in activity might represent several events occurring at this early stage of the trial. First, the very early activity may represent a general preparation for movement, including changes in hand posture (wrist and fingers) while grasping the manipulandum (Van Kan et al. 1993, 1994). Both target duration and movement times were randomized; trials were aborted if the monkey moved outside the starting zone before the onset of the target movement, and trials were deselected if the monkey made a large movement in an anticipated or mirror-reversed direction rather than in the correct direction of target movement. Thus the early neural activity is unlikely to be anticipation of onset and direction of the target. Second, activity increase soon after the onset of target movement but before the onset of arm movement might represent the goal of the movement (Alexander and Crutcher 1992; Martin and Ghez 1985, 1991) or might be related to eye movement toward the target, which normally preceded the arm movement. Observation of the monkey's eye movements during recording in the task or during preselection of arm-movement related cells (e.g., during reaches for small feed items) suggested that none of the recorded cells were related to eye motion. Nor were these "premovement" cells directionally tuned, as we might expect for eye-movement related cells in the lateral cerebellum (Marple-Horvat and Stein 1990).

Another 21 cells (12.7% of total task-related neurons) displayed increases in firing rate at a late stage of the task at or after the moment the target was reached by the cursor. Again, these neurons were not directionally modulated. We suspect that their activity might relate to the reward process in which muscles in animal's neck, face, and mouth may be active in licking and swallowing. The remaining 128 cells (77.1% of all task-related neurons) displayed changes in firing around the time of arm movement.

The most exciting finding of the present experiment was that 34 cells in the lateral cerebellar cortex manifested modulation in simple spike activity more strongly related to movement

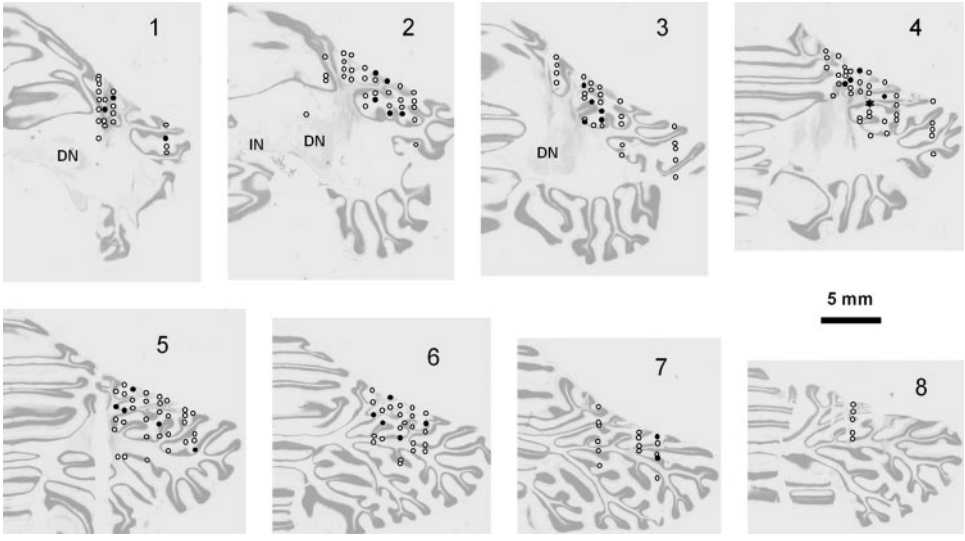


FIG. 10. Coronal sections through the recording sites of *animal 2* showing locations of the cursor-related neurons (○) and other task-related neurons (●). Positions of the sections are shown in Fig. 9. DN: dentate nucleus, IN: interpositus nucleus. The cell detailed in Fig. 5, *C* and *D* is marked by an asterisk in section 4.

direction of the cursor rather than that of the arm. This group represents only 19.6% of the total task-related neurons, but 48% of all directionally tuned cells and 79% of the sample in which we had sufficient data to fully specify activity in both normal and mirror tasks. Neurons specifically related to the direction of visual target motion have been recorded from many motor regions including the supplementary and primary motor areas, red nucleus, and putamen (e.g., Alexander and Crutcher 1992; Fu et al. 1995; Martin and Ghez 1985, 1991). The activity of those neurons, however, clearly began prior to the onset of the limb movement and thus represented the direction of the visual target or the visual goal of the limb movements. Bear in mind that the cursor and the target always move in the same direction during successful trials, so directional tuning measured without respect to movement time is ambiguous. Unlike neurons in motor cortical regions, the cerebellar cursor-related neurons identified in the present study were active during the on-going arm movement, and not at the onset of target motion.

Similar "cursor-related" activity was reported in the lateral cerebellar cortex by Ebner and Fu (1997) in a slightly different visuomotor task, in which the horizontal or vertical gain between movement of the arm and the cursor was modified. The neuronal discharge appeared to represent the movement of the cursor and not just the dynamics or kinematics of the hand position, because the "movement field" of these neurons shifted dramatically when the gain change caused cursor movement to shift away from arm movement.

To what extent are the responses of these cells visual or visuo-motor in origin? None of the cursor-related neurons was affected when the animal was exposed to flashlight stimulation or when the task was performed by the experimenter and observed by the animal. This implies that they are not driven simply by visual cues (Marple-Horvat and Stein 1990). Two further facts argue against the possibility that the cursor-related neurons were related to target and eye movements. First, in these over-trained animals (Marple-Horvat and Stein 1990 and unpublished data) and in human performing similar tasks (Miall et al. 2001; Weir et al. 1989), the eyes rarely fixate the cursor, and instead fixate the target position throughout active tracking. Activity related to movement of the target or the associated eye movement would be unaffected by the delay on the cursor movement, and yet the activity of the cursor-related neurons was affected. Second, if neuronal activity were directly related to the on-screen display, we would expect some response when the task was performed by the experimenter. This was clearly not the case in any of the cells in which we performed this test. However, we cannot exclude the possibilty that these neurons may code some combination of signals related to eye gaze or target position as well as to arm movement, and other studies have highlighted the cerebellar role in oculo-manual coordination (Marple-Horvat and Stein 1990; Miall et al. 2001; van Donkelaar and Lee 1994; Vercher and Gauthier 1988).

As another potential confound, one may argue that the arm movements were asymmetric in a body-centered frame of reference and may not have been completely reversed in terms of velocity, trajectory, etc., between the normal and mirror tasks, thus leading to the observed difference in modulation levels. However, across most recording sessions, the behavior of the animal actually reduced this potential confounding effect. Table 1 indicates that *monkey 2* (from which the majority of the neuronal data were taken) moved the manipulandum significantly faster to the right than to the left when performing the normal task. However, in the mirror task, the mean speeds were almost identical for these two directions. In Figs. 4 and 5, movement to the left was slower than movement forwards or right. However, in the mirror task the monkey was favoring lower *cursor* speed toward the left, even when moving the manipulandum to the right. We tested for but did not find significant trial-by-trial correlation between peak movement velocity and neuronal modulation levels for all cursor-related cells. Ebner and Fu (1997) and Fu et al. (1995) have previously reported such a relationship with movement velocity, but their task, unlike ours, forced a wide range of movement speeds. The third point is that we measured only hand position (via the jointed manipulandum), and this might not fully represent the complex, multi-joint hand and arm movement made by the animal (van Kan et al. 1993, 1994). Again, such movements were not obvious by visual inspection, but if present, they likely existed in both normal and mirror tasks. Moreover, lever or hand movement as an end-measure of whole arm movement does correlate well to neuronal activity in both motor and cerebellar cortices (Alexander and Crutcher 1990; Georgopulos et al. 1986; Ojakangas and Ebner 1992; Thach et al. 1992). So, while we do not claim in the present experiment that either the visual cursor projected on the screen or the neuronal activity recorded from the lateral cerebellar cortex are complete representations of the complex multi-joint arm movements, both are reasonable measures in a task in which only manipulandum and cursor positions determined the success of the animal.

If these 34 "cursor-related" cells do represent the visuomotor aspects of this step-tracking task, what of the other cells? We have seen a small percentage that were clearly coding for arm movement direction (9 cells, 13% of the directional cells or 21% of the sample fully tested). Most others (134 cells, 77% of total sample) could not be categorized because they displayed no clear directional bias. It is conceivable that a significant proportion of these cells might also be signaling visuomotor, but nondirectional, information. We can only speculate, but others, including the nine "arm-related" cells, might also be representing the movement in sensory terms, for example, coding for the proprioceptive consequences of the movement. Many cerebellar cells are responsive to proprioceptive inputs (Rubia and Kolb 1978; Smith et al. 1993; Thach et al. 1986). Hence, those cells we recorded that co-vary with arm direction and not cursor direction might actually code the nonvisual, proprioceptive signals. Without an experimental technique to separate proprioceptive and motor reference frames, we cannot be sure which is which. None of the neurons we have recorded could be unambiguously classified as *motor* rather than *sensory* related. In contrast, the largest group we did successfully classify (48% of the sample of 70 neurons) was found to be sensory (cursor)-related and not motor.

The second interesting aspect of these cursor-related neurons was the effect of time delayed visual feedback on these cells. Ebner and Fu (1997) tackled this question by applying a temporal regression technique to correlate the simple spike discharge of Purkinje cells with kinematics of the hand and cursor movements. Their results indicated that the simple spike discharge that correlated with movement kinematics actually

led the arm movement, whereas simple spike correlation with the visual cursor lagged behind, and thus reflected the visual reafference of the arm movement. In the present experiment, we used time delays to separate movement onset and duration from the cursor movement. Our results revealed that, without any dramatic change in the arm movements, the onset of simple spike discharge in the cursor-related neurons was unchanged by the visual feedback delay, and remained time-locked with the onset of arm movements (Fig. 7). However, the duration of discharge was extended by about the same duration of the delay imposed on the cursor. This suggested that simple spike discharge of the cursor-related neurons had two components. One may be generated in these neurons at the onset of the arm movement as a directionally specific prediction of the consequent cursor movement. The second component was affected by the delay and appeared at a late stage of the cursor motion, even after the actual arm movement was completed, suggesting that it may represent the delayed visual reafference of the on-going arm movement.

In bringing these two components together, we conclude that a significant proportion of the cells tested appear to code for the ongoing movement in a visual framework, and that this representation of the visual outcome of movement is time-locked to the motor commands generating the movement. We believe that these findings provide fresh evidence to suggest that the lateral cerebellum holds an internal "forward" representation of the arm movement. They appear to predictively code the sensory outcome of movement, and this prediction would form an integral part of the visuomotor control of arm movements.

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