

Responses of Sagittally Aligned Purkinje Cells During Perturbed Locomotion: Synchronous Activation of Climbing Fiber Inputs

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SUMMARY AND CONCLUSIONS

1. These experiments were performed to test the hypothesis that climbing fiber inputs to sagittally aligned Purkinje cells located in a single folium are activated synchronously in response to a perturbation of the step cycle that interrupts the trajectory of the ipsilateral forelimb.

2. The experiments were performed in acutely decerebrate ferrets capable of walking spontaneously on a moving treadmill. A multiple single-unit recording technique was employed utilizing a fixed array of five sagittally oriented electrodes with electrode tips $\sim 200 \mu\text{m}$ apart.

3. The extent to which the climbing fiber inputs to the recorded Purkinje cells were activated synchronously by the perturbation was calculated for individual trials by determining the synchrony index, a measure of the fraction of the cells responding to each perturbation.

4. The data indicate that there was a statistically significant increase in the synchronous activation of climbing fiber inputs at times immediately after the perturbation. No comparable complex spike modulation was found at the same phase of the unperturbed step cycle.

5. The specific combinations of climbing fiber inputs to neighboring Purkinje cells activated by successive perturbations varied from trial to trial.

6. The implications of these observations are discussed in the context of the nature of the inputs encoded by climbing fiber activation and the role of this afferent system in cerebellar cortical information processing.

INTRODUCTION

Anatomic and physiological studies have shown that both the olivocerebellar projection and the cerebellar corticonuclear projection are organized in parasagittal strips of comparable dimensions (Armstrong et al. 1973a-c; Haines et al. 1982; Voogd and Bigare 1980). Each longitudinal zone not only receives climbing fiber projections from different sites within the inferior olive (Brodal and Kawamura 1980; Groenewegen and Voogd 1977; Voogd and Bigare 1980) but also contains Purkinje cells whose axons collect in parasagittal sheets and project to corresponding, relatively nonoverlapping regions in the deep cerebellar nuclei (Dietrichs 1981; Dietrichs and Walberg 1979, 1980; Haines et al. 1982). Collectively, these studies indicate that each half of the anterior lobe can be divided into at least seven adjacent narrow longitudinal zones (A, B, C₁, C₂, C₃, D₁, and D₂). Although in some species the number of zones differ, the characteristics of the existing zones are similar

across most mammals. Olivary neurons also send collaterals to deep cerebellar and vestibular nuclei (Groenewegen and Voogd 1977; Van der Want et al. 1989). These collaterals terminate in the particular region of the cerebellar or vestibular nuclei receiving a corticonuclear projection from the same sagittal zone to which the parent climbing fibers project (Houk and Gibson 1986). Despite these intriguing organizational features of the sagittal zones, to date there is no generally accepted view regarding their functional significance.

Several investigators have approached the function of this system by examining the temporal relationship among climbing fiber inputs to simultaneously recorded Purkinje cells oriented in different anterior-posterior and medial-lateral directions relative to each other. Most studies determined the cross correlation of spontaneously occurring climbing fiber inputs (Bell and Kawasaki 1972; Dupont and Crepel 1979; Sasaki et al. 1989) and climbing fiber inputs evoked either by passive stimuli or by the administration of pharmacological agents (Bloedel et al. 1983; Llinas and Sasaki 1989; Sasaki et al. 1989). It is generally agreed that the climbing fiber inputs to neighboring Purkinje cells aligned in parasagittal strips are temporally correlated under these conditions. However, the extent to which these correlations vary during specific behavioral conditions remains uninvestigated.

Modifications in the correlation among climbing fiber inputs to nearby Purkinje cells can be expected, because the electrotonic coupling among olivary neurons (Sotelo et al. 1974) can vary as a result of interactions occurring in this structure (Llinas et al. 1974; Llinas and Sasaki 1989). The recent studies of Armstrong and colleagues (Amos et al. 1987; Andersson and Armstrong 1987; Armstrong and Edgley 1984; Armstrong et al. 1988) employed behavioral paradigms together with single-cell recording techniques to examine the complex spike responses of Purkinje cells localized to identified sagittal zones during modified and unmodified locomotion. Together these studies provide a clear indication that the sagittal distribution of climbing fiber inputs is an important functional property of this system.

This manuscript is the first of a series from this laboratory reporting experiments that utilize a multiple single-unit recording approach to examine the function of the climbing fiber system in the context of its termination patterns within the cerebellar sagittal zones. This experiment was designed to compare the temporal relationship of the

climbing fiber inputs with simultaneously recorded, sagittally aligned Purkinje cells under two conditions: perturbed and unperturbed locomotion. The study employs decerebrate ambulating ferrets to test the hypothesis that the climbing fiber inputs to neighboring, sagittally aligned Purkinje cells are activated synchronously when an ongoing step cycle is interrupted by a perturbation that alters the trajectory of the forelimb.

In these experiments the responses of up to six Purkinje cells aligned in parasagittal strips and separated by $\sim 200 \mu\text{m}$ in the paravermal regions of lobules V and VI were recorded simultaneously during perturbed and unperturbed locomotion. The data analysis in this paper is designed to quantify the simple and complex spike activity of the recorded Purkinje cells on the basis of their responses in individual trials rather than over several cumulative trials, as required when using histogram or correlogram techniques. In assessing the complex spike responses of simultaneously recorded cells, the analysis of single trials is particularly important because of the probabilistic nature of their activation (Bloedel and Ebner 1984). Consequently, histograms obtained from several cells across successive trials do not necessarily reflect the degree to which the climbing fiber inputs are synchronously activated in individual trials.

It will be shown that a perturbation interrupting the trajectory of swing phase can evoke synchronized climbing fiber inputs to sagittally aligned Purkinje cells and that the combination of climbing fiber inputs comprising these responses is quite variable over successive trials. A brief report from the initial series of experiments has been presented previously (Lou and Bloedel 1986).

METHODS

Animal preparation

Ferrets weighing between 1,000 and 1,400 g were used in the experiments. After a subcutaneous injection of atropine (0.3 mg/kg), a tracheostomy was performed under halothane anesthesia, and the animal was artificially respired. The body temperature was maintained at 38–39°C with the use of a heating pad, and the expired CO_2 concentration was maintained at 4–5% throughout the surgical procedure. After the animal was placed in a stereotaxic frame, a glue cap was created on the frontal bone to secure the animal's head during locomotion.

Decerebration at the precollicular, premammillary level was then performed. Because there is no stereotaxic atlas available for the ferret, the colliculi were exposed by aspirating the parietal and occipital lobes following the craniectomy. The two electrodes used for the electrocoagulation were inserted at a 22° angle from vertical at the rostral level of the superior colliculi. Eighty-four lesions were separated from each other by 1.5 mm in a grid across the brain stem. Histological assessment of the tissue taken from the initial series of experiments indicated that this method ensured that there was no viable tissue between the lesion sites, and the anterior-posterior extent of the lesion was consistent over the entire lesioned area. Next, a posterior fossa craniectomy was performed to expose lobules V and VI of the right cerebellum under a 38.5°C saline drip. A thin layer of agar was placed on the cerebellar cortex after removal of the dura.

On completion of the surgical procedure, the ear bars and mouthpiece were removed, and the halothane was discontinued. The head of the animal was held securely to the stereotaxic frame

using only the contacts on the glue cap. The responsiveness of the animal was frequently assessed to ensure that the animal did not show any signs of distress or discomfort, indicating the decerebration was incomplete. Perhaps because of the extensive lesioning procedure detailed above, this problem was never encountered. On resumption of spontaneous breathing, the respirator was disconnected, and the animal was suspended over the treadmill with a broad towel band supporting its abdomen (Fig. 1). Usually the animal was capable of walking on the treadmill within 1 h after discontinuing the halothane. Given the location of the midbrain lesion, the animal walked spontaneously on the moving treadmill.

Recording methods

An array of five epoxy-coated tungsten electrodes (5–10 M Ω) aligned in a sagittal row with tips $\sim 200 \mu\text{m}$ apart was used for extracellular recording of Purkinje cells, identified on the basis of their climbing fiber responses (Eccles et al. 1966). The electrodes in the array were held in place with hardened molten sucrose and consequently could not be moved individually. Up to six Purkinje cells (2 with 1 electrode) in a sagittal row in the surface layer of lobule V or VI could be isolated simultaneously with the use of this array.

Once the cells were isolated, receptive fields of the complex spike responses were not determined systematically because of the problems associated with stopping the locomotor behavior. Cessation of motion for a period long enough to assess the receptive fields of all the isolated neurons usually jeopardized the quality of the locomotion when stepping was resumed. Consequently, the practice of testing receptive fields was discontinued early in the experiments. However, as indicated by the nature of the results, all sets of neurons reported here received climbing fiber inputs activated when the paw dorsum contacted the perturbation bar. For evaluating the hypothesis for which these experiments were designed, this was considered sufficient. Consequently, the relationship between response properties and differences in receptive-field characteristics was not assessed.

This recording system was capable of maintaining the stability of the unitary recordings for a period long enough to evaluate all of the sets of cells reported in this manuscript. This was accomplished principally through slight adjustments in the manipulator during an initial 3- to 5-min recording period while the animal walked on the treadmill. Usually a 10- to 12-min period was sufficient for the acquisition of one full set of data. Once the initial isolation was complete, there was virtually no difficulty in maintaining stable recordings over this relatively brief period. At the time of the off-line analysis, stability again was checked as the activity of a cell was discriminated. Each cell's discrimination was consistently checked to ensure that the waveform was not modified. In the few cases in which a slight modification did occur, the unit was rediscriminated before subsequent trials were analyzed.

Experimental paradigm

The experimental paradigm is illustrated in Fig. 1. The position of the right front leg was monitored by a potentiometer attached by a string either just below the elbow joint or just above the wrist. The output signal of the potentiometer was fed into a threshold detector that produced a pulse when a critical limb position was attained. These pulses were gated by a foot pedal and served as the triggers for the perturbations and for timing pulses for the computer-based off-line analysis. The speed of the treadmill could be varied over an appropriate range of walking speeds.

The perturbation was produced by a bar that extended into the trajectory of the right forelimb at a specific phase of the step cycle. The perturbation was applied pseudorandomly once every 7–10

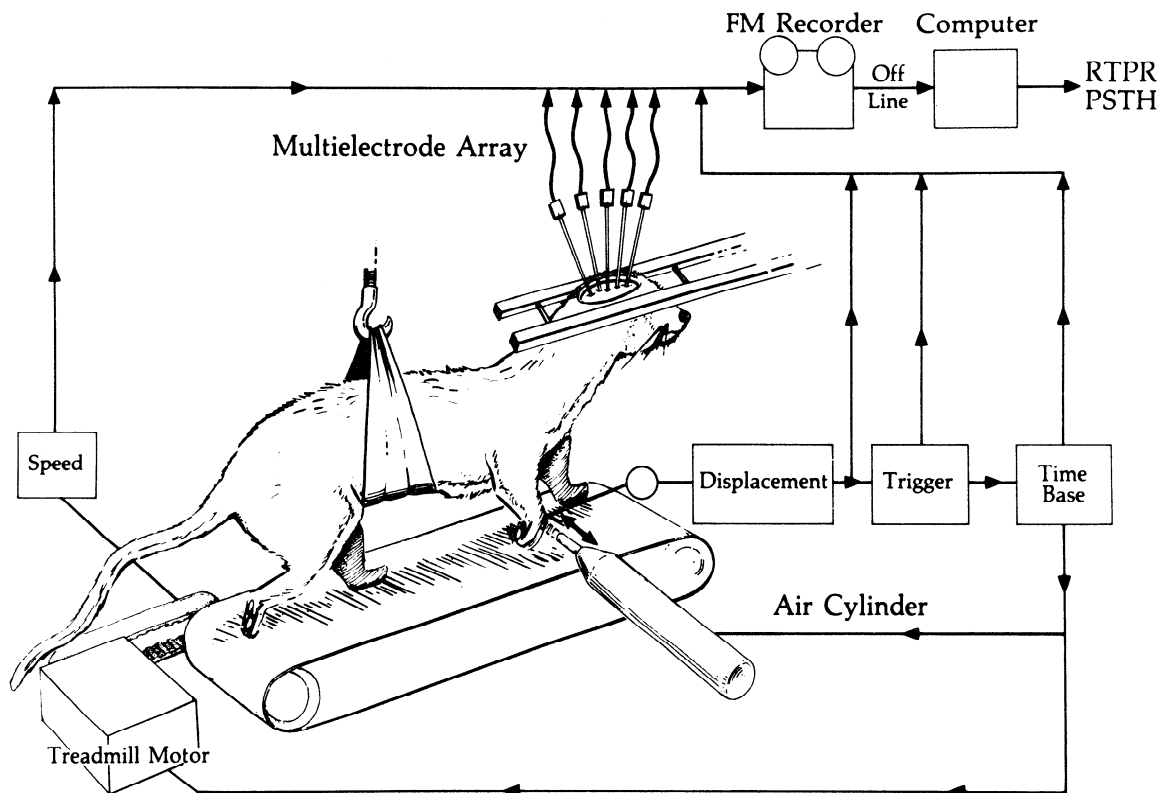


FIG. 1. Experimental setup. The ferret is suspended over the treadmill with a towel supporting the abdomen and a Kopf semichronic head holder stabilizing and securing the head. Recordings from the 5 microelectrodes of the array are led directly into a Honeywell tape recorder without any signal conditioning. In addition, the signal from the potentiometer monitoring the protraction and retraction of the forelimb ipsilateral to the recording site, the treadmill speed, and the various trigger pulses described in the text are also recorded on the tape. Modifications in treadmill speed or the activation of the air cylinder can be triggered at specified voltages recorded from the potentiometer. All computer-based analysis is performed off-line.

step cycles. The position of the perturbation bar was monitored by the use of a mechanically coupled potentiometer, and the time of contact was determined from the record of the forelimb movement obtained by the use of either the potentiometer system described above or the Watscope-Watsmart system, a camera-based system for detecting the position of infrared-emitting diodes placed on the forepaw and over the wrist, elbow, and shoulder joints. In some later experiments the time the right forelimb contacted the perturbation bar was directly monitored by the use of a contact sensor mounted on the bar. Unitary data, limb displacement, perturbation triggers, treadmill speed, and either the position of the perturbation rod or the time the right forelimb contacted the perturbation bar were stored on magnetic tape (Honeywell 5600C) for off-line data processing using a PDP-11/34 or 11/73 computer.

Trials were divided into perturbed and unperturbed trials. Each trial consisted of approximately three steps. In perturbed trials the trigger and data collection system were set so that the perturbation was usually applied in the second step of the trial (see Figs. 3, 4, and 6). Unperturbed trials were taken sequentially using the same step-evoked trigger. As a result, the time courses of the perturbed and unperturbed trials were comparable because the same treadmill speed was used for both. Epochs of perturbed and unperturbed trials were alternated until the recording of the neurons in the set deteriorated.

Off-line data analysis

The complex and simple spikes of each Purkinje cell were discriminated separately with the use of time-amplitude discrimina-

tion techniques. For each trial the gated pulses generated by limb position were used to trigger the computer to sample spike trains, limb position, and perturbation data. Data were sampled for 1,600 ms after the trigger with the use of a binwidth of 1 ms for the spike data. Note that a trial length (1,600 ms) was chosen to include approximately three steps. Usually 10–20 trials of both perturbed and unperturbed runs were analyzed. Ten trials of each type constituted a completed study. The characteristics of the complex spike responses are reported in this paper. The simple spike responses and their relation to the evoked climbing fiber inputs will be reported in a subsequent manuscript.

The synchronous firing of the climbing fiber inputs to the sagittally aligned Purkinje cells first was evaluated by plotting the time of occurrence of the complex spikes for each cell in the simultaneously recorded set on the same time axis for each trial (see Fig. 4A for an example). Next, a window was chosen during which the degree of synchrony among the complex spikes evoked by the perturbation would be quantitatively assessed. For this reason the phase of the step cycle at which synchrony was measured in both perturbed and unperturbed trials was always selected from the perturbed trials. A window of 80 ms was chosen on the basis of experimental data demonstrating that harmaline-induced rhythmic discharge of inferior olivary neurons occurs at frequencies of 8–12 Hz (De Montigny and Lamarre 1973; Llinas and Volkind 1973) and that natural forepaw stimuli evoke complex spike responses having a periodicity between 100 and 160 ms time-locked to the peripheral stimulus (Bloedel and Ebner 1984). Consequently, it is unlikely that the same climbing fiber would discharge twice within an 80-ms window. For the purpose of this analysis, synchrony was defined as the occurrence of complex spikes of

different Purkinje cells within this 80-ms window. In this context, synchronous complex spike responses need not be simultaneous; namely, they need not occur precisely at the same time. This distinction was necessary because the evoked complex spikes did not always occur simultaneously even though they were evoked within the response window.

Once the window was selected, the synchronous firing of the simultaneously recorded complex spike responses was quantified by calculating the synchrony index (SI), defined as the fraction of Purkinje cells responding with a complex spike during the response window for each trial. For example, if four of five cells were activated by their climbing fiber input within the window in a single step cycle, the synchrony index would equal 0.8. This calculation was done for the perturbed step in each perturbed trial and the corresponding phase of the corresponding step in each unperturbed trial.

For each set of cells the data from the perturbation and nonperturbation trials were analyzed separately. The average SI was calculated for both types of trials. The statistical significance of the increased synchrony index in the perturbation trials compared with that of the nonperturbation trials was then determined with the use of a Student's *t* test.

RESULTS

In these experiments the responses of 122 cells comprising 45 sets of 2 or more neurons were studied and analyzed. As shown in Fig. 2, the sets included 6 neuron pairs, 11 triplets, 11 4-cell sets, 10 5-cell sets, and 7 6-cell sets. Because only five electrodes were used in the recording electrode arrays, two cells were recorded from the same electrode in the sets that contained six cells. Among these 45 sets, 32 were completely analyzed; the other 13 sets were analyzed partially up to the time when the experiment was interrupted, usually because of cessation of locomotion or loss of the isolated neurons. Recording sites were limited to the area just lateral to the paravermal vein in lobules V or VI.

The characteristics of the two types of behavioral responses to the perturbation evoking the responses described below are shown in Fig. 3. The swing phase in an unperturbed step is shown in *A*. In *B* the perturbation bar, the end

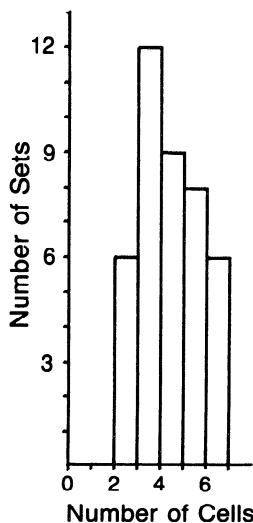


FIG. 2. Bar histogram illustrating the number of sets comprised of 3–6 cells.

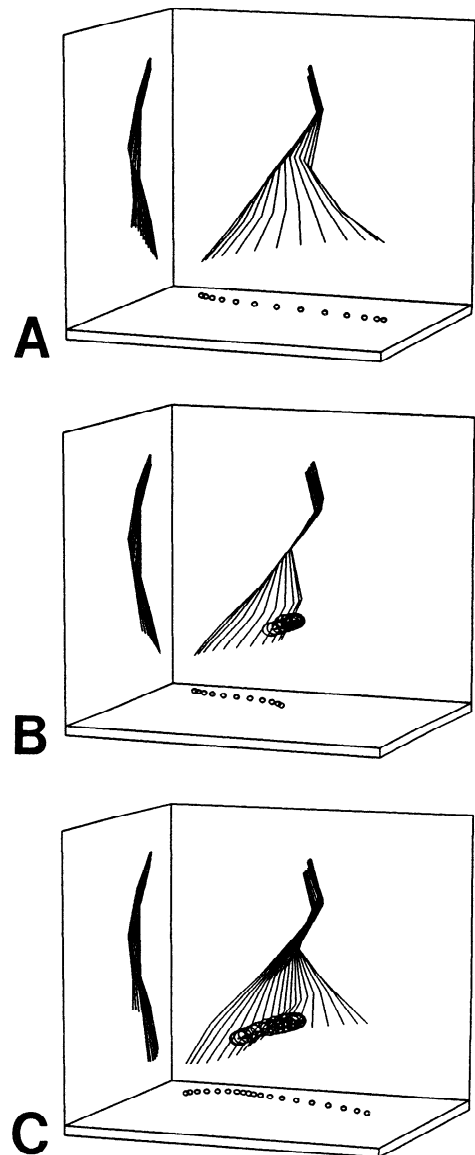


FIG. 3. Stick figure diagram illustrating the effect of the perturbation on the protraction of the forelimb. Figures were drawn by joining successively the infrared-emitting diodes located over the scapular spine, shoulder, elbow, wrist, and base of the lateral toe. A projection of the stick figures also is shown in a posterior projection, and the toe position is shown on a ventral projection. Anterior is to the right. *A*: unperturbed protraction of the forelimb. *B*: one step cycle in which the bar interrupted the forward movement of the limb. *C*: a different step cycle in which the limb was lifted over the bar after contact. In *B* and *C* the open circles in the vicinity of the lower leg indicate the location of the end of the perturbation bar.

of which is shown at successive times with an open circle, arrested the forward movement of the limb. In a subsequent trial (*C*) the bar interrupted the trajectory, and the paw slid up and over the bar as the step cycle continued. In this example the bar began to retract just as the limb was elevated and began to continue forward. Although not studied systematically, the type of response to the perturbation did not appear to increase or decrease the probability of activating the climbing fiber inputs in the 80-ms window after the perturbation.

The most striking observation in this study was the dramatic, synchronous activation of the climbing fiber inputs

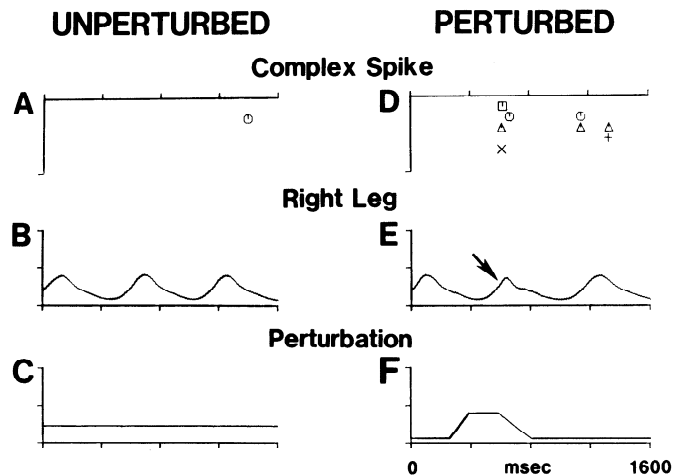


FIG. 4. Comparison of the complex spike activity in an unperturbed (*A–C*) and perturbed (*D–F*) trial while recording from the same set of 5 sagittally distributed Purkinje cells. Complex spike activity for each of the 5 recorded neurons is shown on separate lines in *A* (unperturbed trial) and *D* (perturbed trial). In this and all other figures in which single-trial data are shown, the following relationship between symbols and recorded neurons will be followed: *cell 1*, square; *cell 2*, circle; *cell 3*, triangle; *cell 4*, plus sign; *cell 5*, X; *cell 6* (not present in this set), open diamond. The protraction (increasing values on ordinate) and retraction (decreasing values on ordinate) of the ipsilateral forelimb are shown in *B* and *E* for the 2 trials. *F*: time course of the perturbation rod as it is interjected into the trajectory of swing phase. Arrow in *E* indicates the time at which the foot contacted the perturbation bar.

to the sagittally aligned Purkinje cells in response to the perturbation of the step cycle. This is illustrated in Fig. 4, which shows one unperturbed trial (*A–C*) and one perturbed trial (*D–F*) obtained from a five-cell set. The complex spike activity for each cell in the unperturbed and perturbed trial is shown in *A* and *D*, respectively, with the time of occurrence of each cell's complex spikes plotted in different rows with the use of different symbols. The perturbing rod started to extend into the trajectory of the right forelimb at ~280 ms and remained maximally extended until ~600 ms. While extended, it was contacted by the limb at the

time indicated by the arrow in *E*. The effect of bar contact on the record characterizing the forward-backward movement of the forelimb (*E*) was not dramatic because the potentiometer was attached at the animal's elbow to ensure that the connecting string did not contact the bar.

The plot in *D* shows that the climbing fiber inputs to *cells 1, 2, 3,* and *5* were synchronously activated in response to the perturbation. As indicated in METHODS, synchronous firing was defined as the occurrence of complex spikes in two or more Purkinje cells of the set within an 80-ms interval. Notice also that *cells 2* and *3* as well as *3* and *4* were activated simultaneously as pairs later in the trial. The periodicity of each cell's complex spike responses was not systematically evaluated in these experiments. However, in some sets a second group of complex spikes was evoked time-locked to the perturbation. In the set in Fig. 4, two pairs of neurons were simultaneously activated later in the trial. This likely reflects the oscillatory behavior of olivary neurons (Llinas and Yarom 1981a,b) and the tendency of this behavior to be reset by peripheral stimuli (Bloedel and Ebner 1984).

A comparison of Fig. 4, *A* and *D*, demonstrates the remarkable difference in the synchronous activation of climbing fiber inputs evoked at a fixed, specific phase of the step cycle in perturbed and unperturbed step cycles. The presence of synchronous complex spike responses in the perturbation trials was as dramatic as their absence in unperturbed trials. Although Fig. 4 shows only one nonperturbation and one perturbation trial, this difference characterized all of the experimental data, as indicated in the statistical analysis presented below. No matter how dramatic the synchronous response to the perturbation, no set of neurons displayed phase-locked synchronous activation of climbing fiber inputs discernible over several successive nonperturbation trials.

Some of the characteristics of the climbing fiber activity in unperturbed trials is shown in Fig. 5. The plots related to set 1 were obtained from two unperturbed trials while recording from a set of six neurons. In this particular set the

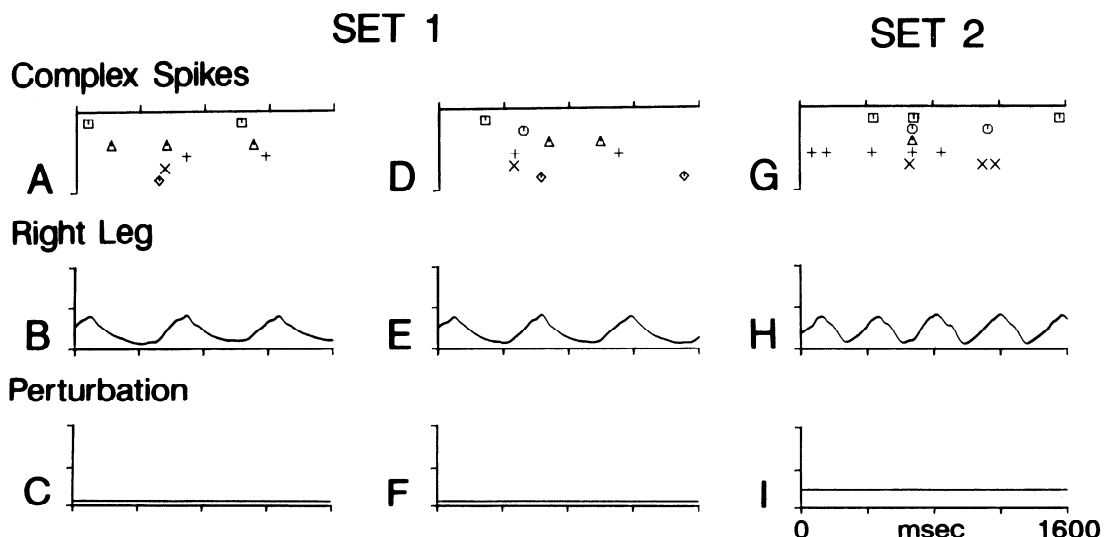


FIG. 5. Data from 2 sets of neurons in unperturbed trials (*A–F* and *G–I*, respectively). Purkinje cells in set 1 had an unusually high mean rate of climbing fiber activity across the cells of the set. The format of the data presentation is the same as Fig. 4. Set 1 consists of 6 neurons, and set 2 consists of 5 cells.

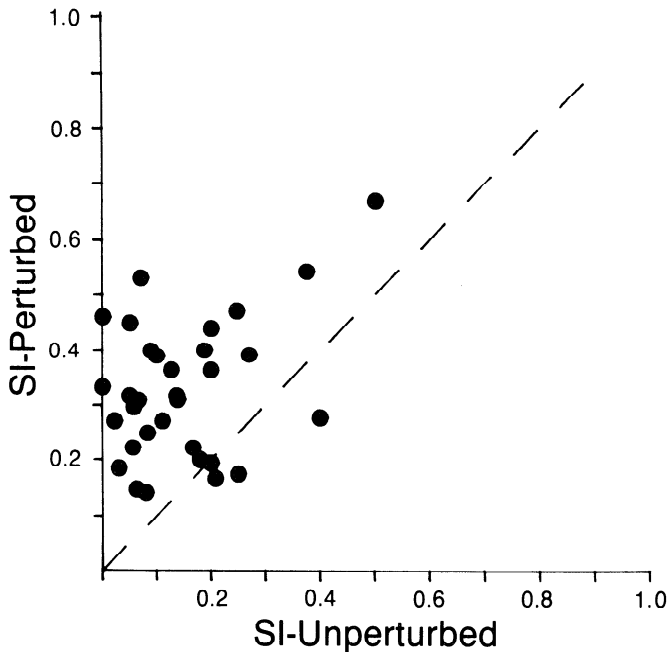


FIG. 6. Relationship between the synchrony index (SI) in perturbed trials and SI in unperturbed trials for the same sets of neurons. Dashed line indicates the relationship expected if the SIs were identical in perturbed and unperturbed trials.

average discharge rate of each cell's complex spikes was reasonably high. Despite this fact, no consistent phase-specific synchronous activation of the complex spikes occurred throughout the six step cycles shown. In *A* there was a synchronous activation of *cells* 3, 5, and 6 at ~ 550 ms. Similarly, in the next trial there was a synchronous activation of *cells* 4 and 5 in *D* shortly after 400 ms. However, these synchronous responses were not phase specific, occurring at different phases of the step cycles in the two trials.

The trial shown for set 2 (*G-I*) consisting of five cells was chosen to illustrate that the synchronous activation of most of the cells in the set occasionally occurred during unper-

turbed locomotion. In this trial all five cells of the set were synchronously activated at ~ 700 ms into the trial. However, correlated with this synchronous activity is a small alteration during protraction (*H*). The relationship of the synchronous responses to modifications of the step cycle due to factors other than the perturbation bar (e.g., postural sway, slip) in unperturbed trials was not investigated. However, on the basis of the consistency of the responses to perturbations, the occurrence of synchrony in unperturbed trials may be related to other types of alterations in gait. Whatever its basis, synchronous activity clearly can occur in unperturbed trials. However, the statistical evaluation of the data presented below emphasizes that the complex spike responses time-locked to the perturbation are not likely due to the phase locking of these responses to some consistent feature of the unperturbed locomotor cycle.

As described in METHODS, the SI, defined as the number of complex spikes/cell/trial, was calculated to quantify the degree of synchrony among the climbing fiber inputs evoked by the perturbation. A comparison of the SIs of the perturbed and unperturbed trials for each individual set is shown in Fig. 6. In this figure the SI of the unperturbed trials (horizontal axis) in each individual set is plotted against that of the perturbed trials (vertical axis). Each individual set is represented by one solid circle. The dashed line indicates the expected values if the SI were the same in both perturbed and unperturbed trials for all sets. In all but four sets, the SI for the perturbed trials is greater than that for the unperturbed trials. Furthermore, the difference between the average SI for the perturbed trials (0.327) and the unperturbed trials (0.147) across all the sets is statistically significant at $P < 0.001$.

One of the interesting features of the synchronously activated complex spike responses was that the combination of Purkinje cells responding synchronously to the perturbation and the relative response latencies varied over successive perturbation trials. This is illustrated in Fig. 7 for three successive perturbation trials from a five-cell set. Conventions are the same as in the previous figure. Again the poten-

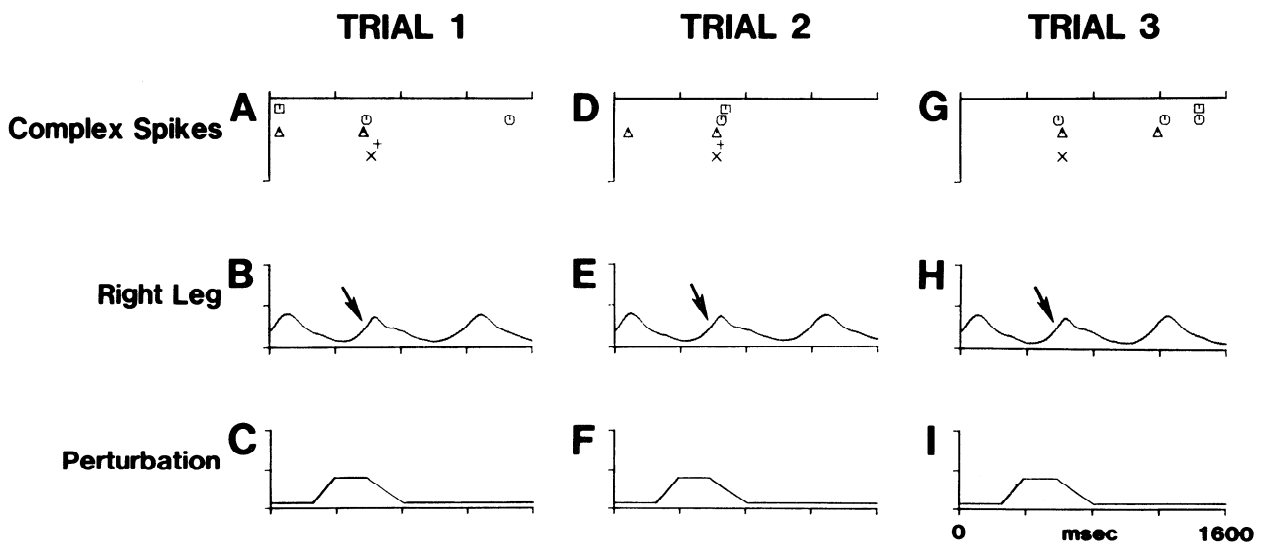


FIG. 7. Variability of the complex spike responses recorded from a set of 5 Purkinje cells over 3 successive perturbation trials. The format of the figure is identical to that used in Fig. 4.

tiometer was attached above the elbow. In these three successive trials (*A-C*, *D-F*, and *G-I*) the perturbation synchronously activated slightly different combinations of climbing fiber inputs. In trial 1 (*A*) cells 2–5 were activated synchronously by the perturbation, in trial 2 (*D*) the climbing fiber inputs to cells 1–5 responded synchronously, whereas in trial 3 (*G*) cells 2, 3, and 5 were synchronously activated. Typical of most sets, the relative latencies of the complex spike responses recorded from these cells also varied from trial to trial. For example, in trial 1, cell 3 responded first, and no cells were activated simultaneously. In contrast, in trial 2, cells 3 and 5 were activated simultaneously and responded with the shortest latency. Cells 3 and 5 were also activated simultaneously in trial 3, but cell 2 responded to the perturbation with the shortest latency.

The different combinations with which the climbing fiber inputs can be evoked within the response window over several successive perturbations for a different five-cell set are emphasized further in Fig. 8. Five different markers are used to represent each of the five cells' complex spikes. Characteristic of all sets studied, the combinations of climbing fiber inputs to these parasagittally aligned Purkinje cells varied considerably. For example, cells 4 and 5 are activated synchronously in trial 1, and cells 1, 3, 4, and 5 are activated synchronously in trial 2. In trial 7 the climbing fiber inputs to all five Purkinje cells in the set are activated synchronously by the perturbation. In this set the most frequent combinations of synchronously activated climbing fiber inputs were among cells 1, 3, 4, and 5 (trials 2, 8, 11, and 17) and among cells 1–4 (trials 9, 13, and 16). Other combinations were also observed: cells 1, 3, and 5 (trial 4 and 5); cells 1, 2, 3, and 5 (trial 6). Across all the trials, cell 2 was activated less frequently by the perturbation than cells 1, 3, 4, and 5. However, it was always activated synchronously with cell 1 and cell 3. In all, there were 11 combinations of activated climbing fiber inputs evoked over the 17 trials.

A similar study performed in another set of five Purkinje cells is shown in Fig. 9. Again many combinations of climbing fiber inputs were activated over several perturbation trials. In this set, 11 different combinations of climbing fiber inputs were evoked over these 13 perturbed trials. In the most frequently observed combinations, cells 2, 3, and 5 were activated synchronously in trials 5 and 9; cells 1, 2, 3, and 5 in trials 12 and 13. The climbing fiber inputs to

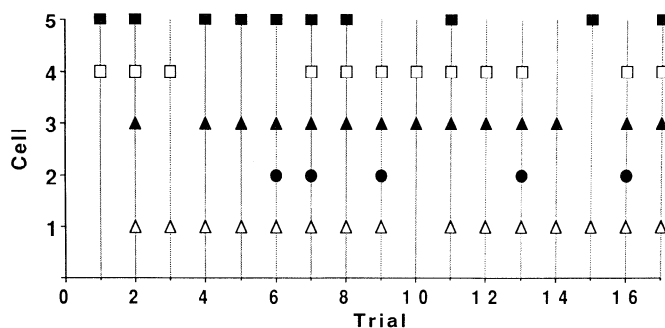


FIG. 8. Relationship between the coupling of the climbing fiber inputs to a set of 5 neurons across 17 successive perturbation trials. For clarity the symbols pertaining to each trial are connected by a dashed line.

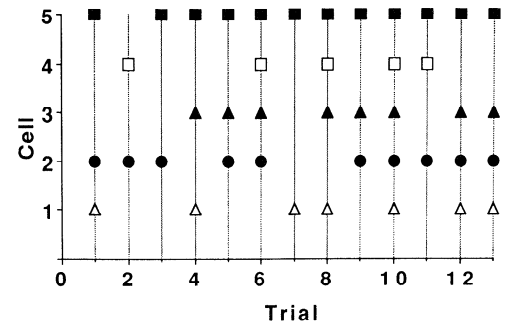


FIG. 9. Relationship of the coupling between the climbing fiber responses across 13 consecutive perturbation trials for a set of 5 neurons.

all of the cells in the set were activated synchronously in trial 10.

To obtain some initial insights into whether the various combinations of climbing fiber inputs are related to electrotonic interactions among olivary neurons (Llinas and Yarom 1981a,b; Llinas et al. 1974) or to other factors possibly related to the temporal properties of olivary afferent activity, the probability with which specific combinations of climbing fiber inputs occur synchronously across several perturbation trials was compared with the probability that the combination would occur based only on each cell's probability of responding to the perturbation across the same trials. Four sets of data were selected for this analysis on the basis of the characteristics of their complex spike responses (comparatively high SI). For the two sets shown in Figs. 8 and 9, a comparison of the probabilities for some of the combinations are shown in Table 1. Unexpectedly, the observed probability of occurrence of each combination of climbing fiber inputs (actual) was very similar to that predicted based only on the probability of each cell's climbing fiber input responding to the perturbation (calculated). This is particularly apparent for the set in Fig. 9. Notice the

TABLE 1. Comparison of the actual and calculated probabilities for specific combinations of climbing fiber inputs responding to forelimb perturbation

Combinations	Probabilities	
	Actual	Calculated
17-Trial set, Fig. 8		
1, 3, 5	0.47	0.43
1, 3, 4, 5	0.29	0.30
1, 2, 3	0.29	0.20
1, 2, 3, 4	0.24	0.14
2, 3, 4	0.24	0.17
3, 4, 5	0.29	0.33
13-Trial set, Fig. 9		
1, 2, 3	0.23	0.26
3, 4, 5	0.23	0.31
1, 3, 5	0.31	0.31
2, 3, 5	0.46	0.43

As explained in the text, the *actual* probability reflects the observed probability of the various combinations of complex spike responses. The *calculated* probability is the probability expected if the specified combinations reflected only the frequency of occurrence of each cell's response to the perturbations. Calculations are made for the sets of neurons shown in Figs. 8 and 9.

similarity between the actual probability of occurrence of the response combinations and the calculated probabilities based on frequency of occurrence. For the set shown in Fig. 8, the actual probability of occurrence was consistently higher than the calculated value when *cells 2 and 3* were included in the analyzed group. This relationship may reflect a contribution of coupling to the observed rate of occurrence in this set. Thus, although factors such as coupling may play some role in determining these probabilities, the synchrony cannot be completely ascribed to this mechanism.

DISCUSSION

Overview of findings

These data are among the first to demonstrate a behavioral condition in which climbing fiber inputs to sagittally aligned Purkinje cells are synchronously activated in a consistent manner. The use of multiple single-unit recording together with a method for analyzing data on a trial-by-trial basis was critical for obtaining these observations. The findings extend previous studies illustrating the existence of sagittally distributed climbing fiber inputs under spontaneous or pharmacologically induced conditions (Llinas and Sasaki 1989; Sasaki et al. 1989) by showing that up to six sagittally aligned Purkinje cells receive synchronously activated climbing fiber inputs after intermittent perturbation of the forelimb during the locomotor cycle. Although previous studies demonstrated that climbing fiber inputs of two or three neighboring Purkinje cells can be evoked synchronously following natural stimuli applied to the forelimb (Bloedel et al. 1983), this experiment illustrates that this synchronous activation can occur across sagittally distributed Purkinje cells in response to a perturbation applied during an ongoing movement.

The findings do not define the width of these sagittal zones. However, recent experiments comparing responses recorded from two five-electrode arrays show clear differences in the complex spike responses recorded from two different identified zones separated by only one other zone (e.g., B and C₂, C₁, and C₃) (Kelly et al. 1989). In addition, studies using single-cell recording techniques also indicate a zonal organization for the complex spike responses evoked by perturbations of locomotor behavior (Amos et al. 1987; Andersson and Armstrong 1987). The studies reported here indicate that the activated complex spikes actually occur in the same trials.

The remainder of this DISCUSSION will focus on the systems responsible for activating the climbing fiber input, the appropriate conditions under which the climbing fibers are activated, and the implications of these findings to the class of operations performed by the climbing fibers in the cerebellar cortex.

Mechanisms responsible for the synchronous activation of climbing fiber inputs to sagittally distributed Purkinje cells

The synchronous activation of these climbing fiber inputs could result from one or a combination of at least three factors. First, the synchrony could be due to the intrafolial

branching of climbing fibers within the cortex itself. The possibility that the Purkinje cells oriented in a sagittal strip may receive climbing fiber inputs from different branches of the same climbing fiber has been supported by both anatomic and electrophysiological studies. Anatomically climbing fibers having two or three branches in the upper portion of the granular layer likely supply two or three neighboring Purkinje cells in the same folium (Fox et al. 1969; Rosina and Provini 1985). Electrophysiological studies and multiple fluorescent tracing experiments also have suggested that climbing fiber axons branch before reaching the cerebellar cortex so that a single climbing fiber might activate Purkinje cells in different folia in a narrow parasagittal strip along the same zone (Armstrong et al. 1973a-c; Faber and Murphy 1969; Rosina and Provini 1983, 1985). Together these data indicate that a single inferior olivary neuron may supply climbing fiber collaterals not only to the Purkinje cells in different lobules within a parasagittal strip but also to two or three parasagittally organized Purkinje cells within a single folium.

Second, the electrotonic coupling of inferior olivary neurons could contribute significantly to the synchronous firing of complex spikes. Electrotonic coupling of these cells was first suggested by studies (De Montigny and Lamarre 1973; Llinas and Volkind 1973) demonstrating that the administration of harmaline could generate a synchronous activation of Purkinje cells via the climbing fiber system. Further anatomic and physiological studies have shown that the electrotonic coupling of inferior olivary neurons is mediated by dendrodendritic gap junctions within the inferior olivary glomerulus (Llinas et al. 1974; Sotelo et al. 1974). Most recently, the properties of the electrotonic coupling between these cells were further investigated by simultaneously recording 32 Purkinje cells in the rat (Llinas and Sasaki 1989; Sasaki et al. 1989). Cross-correlation analysis of Purkinje cells' complex spikes demonstrated that the synchronous firing occurred in rostrocaudal bands across the folium with mediolateral spans of only 250–500 μm . These investigators also showed that the spatial organization of the coupling between inferior olivary neurons could be modified by systemic application of picrotoxin, which blocks γ -aminobutyric acid inhibition, a possible inhibitory mechanism for regulating the functional extent of the coupling.

Third, the response properties of the inputs to the inferior olive could contribute to the synchronous activation of climbing fibers, assuming an appreciable temporal correlation in the activity of olivary inputs responding to the perturbation. This is quite feasible given the size of the receptive fields of some olivary neurons and the fact that cells with similar receptive fields project to specific strips in the cerebellar cortex (Andersson and Oscarsson 1978; Gibson et al. 1987; Oscarsson 1979). Because of the polysynaptic nature of some of the olivary inputs (Bloedel and Courville 1981), the climbing fiber responses evoked by this mechanism would be expected to show appreciably less simultaneity than those evoked by the first two proposed mechanisms.

If intracerebellar and intrafolial branching were responsible for the synchronous discharge of complex spikes in neighboring Purkinje cells, very comparable latencies

would be expected among their responses. Simultaneity would also be expected if the degree of electronic coupling and the coupling coefficient were high (see Sasaki et al. 1989 for examples). Clearly, the findings in Figs. 4, 5, and 7 emphasize that this is not always the case. These data as well as those illustrated in a previous manuscript (Lou and Bloedel 1986) indicate that climbing fiber inputs are not necessarily activated simultaneously in response to the perturbation. Although indicating that branching may not contribute to the combinations of synchronously activated climbing fiber inputs reported in this paper, the lack of simultaneity in some trials does not rule out the possible contribution of electronic coupling to this observation. Hypothetically, if the extent of the coupling were weak, the lower amplitude depolarizations evoked in neighboring olivary neurons could summate with the ongoing oscillations of the cell's membrane potential to evoke action potentials that were not simultaneous with the triggering neuron. The fact that the electronically evoked voltage changes can be >20 ms in duration (Llinas and Yarom 1981a) provides a further basis for some variability in the latencies among electrotonically coupled neurons.

The findings in Table 1 provide indirect evidence against a high degree of direct coupling between the recorded neurons in the selected examples. In the sets shown in Figs. 8 and 9, the specific neurons synchronously activated by the perturbation in successive trials varied more dramatically than would be expected for a system exclusively regulated by electrotonic coupling. It also is feasible that olivary neurons in the ferret are more loosely coupled than in the guinea pig and rat (Llinas and Sasaki 1989; Llinas and Yarom 1981a,b; Sasaki et al. 1989). Species variability in electrotonic coupling has been suggested by other investigators (Llinas and Yarom 1981a). This possibility also may explain the fact that initial experiments in the cat employing the same paradigm used in these experiments revealed the presence of simultaneous responses to forelimb perturbation in many of the initial neuronal sets examined (Kelly et al. 1989).

On the basis of these arguments, the lack of simultaneity and the degree of variability observed in the cell combinations could be due to either weak electrotonic coupling or the properties of the afferent systems responsible for activating the olivary neurons. Future studies will have to determine the precise mechanism for the observed synchrony and its temporal characteristics.

Origin of the climbing fiber responses evoked by forelimb perturbation

The complex spike responses evoked by the perturbation of the right forelimb most likely are mediated by one or a combination of previously described spinoolivocerebellar pathways (SOCs). However, the precise SOCP or SOCPs mediating these responses cannot be differentiated on the basis of the available data. This determination would require a careful segregation of each pathway during the course of the study, a procedure that cannot be satisfactorily performed without jeopardizing the locomotor capability of the animal. A number of SOCPs have been demonstrated with electrophysiological techniques (Ekerot and Larson 1979, 1980; Oscarsson 1969; Oscarsson and Sjo-

lund 1977a,b). Among the five SOCPs ascending through the ventral funiculus (VF-SOCPs) (Oscarsson and Sjolund 1977a,b), three pathways that terminate in zones a, c_1 , and c_3 of the cerebellar cortex are activated exclusively from nerves in the ipsilateral hindlimb and therefore cannot mediate the responses reported in this manuscript. Two other pathways, terminating in the b_1 and b_2 zones, are bilaterally activated from the forelimbs and hindlimbs. Other SOCPs ascending through the dorsal funiculus project to all the identified zones of the anterior lobe (Ekerot and Larson 1979, 1980). The Purkinje cells in zones c_1 , c_3 , d_1 , and d_2 receive ipsilateral inputs, whereas neurons in the c_2 zone can be activated from bilateral forelimb and hindlimb nerves, at least in the cat. Given the location of the recording sites and the site of the perturbation, the responses recorded in this study were likely mediated by these dorsal funicular pathways.

The peripheral receptors responsible for evoking the climbing fiber responses via the SOCPs also have been the subject of several investigations. Early studies (Oscarsson and Sjolund 1977a,b; Ekerot and Larson 1979, 1980) suggested that SOCPs generally require the activation of high-threshold afferents, because the reported responses are spatially diffuse and lack modality specificity. However, others (Ebner et al. 1983; Ebner and Bloedel 1981; Eccles et al. 1971; Gellman et al. 1985; Gibson et al. 1987; Robertson and Laxer 1981; Rushmer et al. 1976, 1980) showed that these pathways can be activated by low-threshold somatosensory stimuli. Many of the Purkinje cells responding to passive movement of the forepaw have been shown to be localized within a well-defined parasagittal strip very near the paravermal vein in lobule V, one of the primary recording sites in this study (Rubia and Kolb 1978; Rubia and Tandler 1981; Rushmer et al. 1976). Together these findings suggest that the climbing fiber responses observed in the present study are most likely evoked by the activation of low-threshold cutaneous receptors and possibly some joint proprioceptors responding to the forelimb perturbation.

Functional implications

The findings in this paper demonstrate one behavioral condition in which the climbing fiber inputs to the cerebellum are activated: an unexpected perturbation of swing phase during locomotion. The synchronous activation of the climbing fiber inputs to sagittally aligned groups of Purkinje cells in this study appear consistent with the event detector or error detector hypothesis (Rushmer et al. 1976). On the basis of the response characteristics of the climbing fiber system to passive forepaw movement in decerebrate cats, it was proposed that the climbing fiber inputs may serve as "event detectors" signaling to the cerebellum the precise timing of peripheral events. Consistent with this view, recordings from inferior olivary neurons in the awake cat (Gellman et al. 1985) showed that most of these cells respond to either passive cutaneous or proprioceptive stimulation or to "unexpected" contact of the receptive field during an active movement. In contrast, the neurons did not respond consistently when stimuli were encountered during the execution of an uninterrupted movement, e.g., when the stimulus resulted from contacting an object that was a target of the active movement. More recently,

Amos et al. (1987) and Andersson and Armstrong (1987) reported that unexpectedly removing the rung of a ladder from under a cat's paw effectively activated climbing fiber inputs to Purkinje cells.

Other studies indicate that the climbing fiber system may respond to specific features of the peripheral stimulus. The experimental studies of Simpson and colleagues strongly argue that the climbing fiber system can respond very precisely to stimulus direction (Graf et al. 1988). These investigations described a population of olivary neurons that respond specifically to the direction of visual stimuli moving across the retina, a stimulus that also activates climbing fibers during the execution of pursuit eye movements (Stone and Lisberger 1990). Robinson et al. (1988) found that climbing fibers can respond to specific features of a vestibular stimulus. Similarly, with the use of passive movements of the wrist joint, Kolb et al. (1987) demonstrated that the probability of activating climbing fiber inputs over several consecutive trials is dependent not only on the magnitude and rate of change of the joint angle but also on the absolute angle through which the limb is moved.

In addition to responding to unexpected perturbations and specific features of passive stimuli, climbing fibers are activated in association with the execution of limb movements. With the use of a perturbed locomotion paradigm, Kim et al. (1987, 1988) demonstrated that climbing fiber responses can be related to properties of the electromyographic activity in the extremity responding to the perturbation. Several recent studies also have illustrated that the climbing fiber system can be consistently activated during goal-directed limb movements in which no external perturbation has been applied. These include the initiation of a goal-directed arm movement (Mano et al. 1986; Wang et al. 1987) as well as the redirection of a volitional arm movement when a target's location is respecified during the movement's execution (Wang et al. 1987). These context-dependent and/or directionally specific responses would not necessarily be required of a system designed only for detecting that an event or error occurred. However, under some conditions, these may serve as adequate stimuli.

Together these data imply that there are likely several functional conditions under which the climbing fibers can be activated. These include critical phases of voluntary movements, specific characteristics of passive stimuli, and unexpected perturbations encountered during active movements. Thus the climbing fiber system's activation can reflect a variety of stimuli, including but not restricted to the occurrence of an error or an unexpected event.

In our experiments the climbing fibers clearly are activated by the occurrence of an unexpected perturbation. Given the sensitivity of the cerebellar afferents to exteroceptive and proprioceptive inputs from the extremities (Gellman et al. 1985; Gibson et al. 1987), the responses of sagittally aligned Purkinje cells may be evoked as a consequence of the afferents activated by the contact with the perturbation bar. Alternatively, these responses may be related to the movement performed to compensate for the perturbation. On the basis of the consistency of the complex spike response despite some fluctuations in the motor response to bar contact (see Fig. 3), we favor the first alternative. However, additional studies would be required to specifically resolve this issue.

On the basis of our findings together with those reviewed above, we propose that the context-dependent and/or stimulus-specific nature of the climbing fiber responses ensure that a spatially specific and functionally relevant distribution of sagittally distributed climbing fiber inputs are activated, not to encode a property of the stimulus or condition to which they respond, but to initiate a well-defined operation in the cerebellar cortex on the basis of critical patterns of convergence among olivary afferents.

The authors thank R. Ferguson for technical help during the experiments, M. Webster and J. McAlduff for help with the figures, and D. Janus and J. Carey for help with the manuscript.

The work was supported by National Institute of Neurological Disorders and Stroke Grant NS-21958.

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Received 1 July 1991; 27 March 1992.

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