Dynamic Modulation of Mossy Fiber System Throughput by Inferior Olive Synchrony: A Multielectrode Study of Cerebellar Cortex Activated by Motor Cortex

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Schwarz, Cornelius and John P. Welsh. Dynamic modulation of mossy fiber system throughput by inferior olive synchrony: a multielectrode study of cerebellar cortex activated by motor cortex. J Neurophysiol 86: 2489–2504, 2001. We investigated the effects of climbing fiber synchrony on the temporal dynamics of mossy fiber system throughput in populations of cerebellar Purkinje cells (PCs). A multielectrode technique was used in ketamine-anesthetized rats that allowed both complex and simple spikes (CSs and SSs) to be recorded from multiple PCs simultaneously in lobule crus IIA. Stimulation of the tongue area of the primary motor cortex (TM1) was used to evoke cerebro-cerebellar interaction. At the single PC level, robust short-term interactions of CSs and SSs were observed after TM1 stimulation that typically consisted of an immediate depression and subsequent enhancement of SS firing after the occurrence of a CS. Such modulations of SS rate in a given PC were as robustly correlated to the synchronous CSs of other PCs as they were to the CS on its own membrane—and did not require a CS on its own membrane—indicating a network basis for the interaction. Analyses of simultaneously recorded PCs demonstrated that CS and SS firing were dynamically correlated after TM1 stimulation in a manner that indicated strong control of mossy fiber system throughput by CS synchrony. For ≤300 ms after TM1 stimulation, most PCs showed episodic modulations in SS rate that appeared to be entrained by the population rhythm of climbing fiber synchrony. SS rhythmicity also was modulated dynamically by CSs, such that it was depressed by CSs and facilitated by their absence. The modulations in SS rate, a given PC’s modulation in SS rhythmicity did not require it to fire a CS but was, on those instances, equally correlated to the synchronous CSs of other PCs. The data indicate that the climbing fiber system controls the temporal dynamics of SS firing in populations of PCs by using synchrony to engage intracerebellar circuitry and modulate mossy fiber system throughput.

INTRODUCTION

How the two major afferent systems of the cerebellum—the climbing fiber and mossy fiber systems—might interact to produce functionally meaningful cerebellar output remains an unresolved and compelling question. If the two systems ever function concertedly, it is not through a direct influence of one on the other. The two systems are anatomically separate and independent at the brain stem level. The climbing fibers originate solely from the inferior olive, a nucleus that projects only to the cerebellum (Desclin 1974; Szentágothai and Rajkowsit 1959). The mossy fibers originate from a variety of brain stem nuclei, the plurality of which originates from the pontine nuclei that also project only to the cerebellum (Brodal 1981). Neither system can directly influence the other’s throughput within the cerebellar cortex. Mossy fibers innervate granule cells whose parallel fiber axons synapse onto Purkinje cells (PCs). Climbing fibers bypass the granule cells altogether and do not make axo-axonic synapses with the parallel or mossy fibers. Neither the mossy nor the parallel fibers interact with climbing fibers and none of the three fiber types projects out of the cerebellum to innervate the brain stem. Thus opportunities for direct interaction do not exist.

Nevertheless, the climbing fiber and mossy fiber systems share two elements of the cerebellum that may permit functional interaction. First, both systems use PCs as their sole output element, so the PC membrane could be a site where one system might modulate the synaptic efficacy, and thus throughput, of the other. Second, both systems innervate components of intracerebellar circuitry that can modulate throughput either at or before the level of the PC. For instance, collaterals of climbing fibers innervate the inhibitory Golgi (Hámori and Szentágothai 1966; Schulman and Bloom 1981) and basket cells (Lemkey-Johnston and Larramendi 1968; Scheibel and Scheibel 1954), providing a means whereby the climbing fiber system could decrease mossy fiber system throughput by di-synaptically inhibiting granule cells and PCs, respectively. Moreover, collaterals of climbing and mossy fibers innervate neurons of the deep cerebellar nuclei, which, in turn, issue mossy fibers that project to granule cells (Provini et al. 1998) and project to mossy fiber somata in the brain stem (Schwarz and Schmitz 1997). Such circuitry could allow climbing and mossy fiber activity to increase the throughput of the mossy fiber system. Last, recurrent collaterals of PCs innervate interneurons of the cerebellar cortex that inhibit granule cells and other PCs (Hámori and Szentágothai 1968; McCrea et al. 1976; Ramón y Cajal 1995). Because PC output is inhibitory (Ito and Yoshida 1964), activation of the PC, thus could disinhibit both granule cell and PCs. In sum, there are a few circuit possibil-
ities within cerebellar cortex that might allow the two afferent systems to modulate each other’s throughput.

The present study employed multiple microelectrode technology to investigate whether and how the climbing fiber system might modulate the throughput of the mossy fiber system. The experiments were designed to determine whether the propensity of the climbing fiber system to fire synchronously might engage the intracerebellar circuitry to functionally link the mossy fiber system to the climbing fiber system. We combined multielectrode neurophysiology with on-line digital signal processing to record both complex and simple spikes (CSs and SSs) from multiple PCs simultaneously to measure the ensemble activity of the climbing fiber and mossy fiber systems at the same time, respectively. We used electrical microstimulation of the tongue representation of the primary motor cortex (TM1) to trigger both CSs and SSs in the PCs of crus IIA, a lobe that has been implicated in the control of oro-facial-lingual movement (Bower et al. 1981; Welsh 1998; Welsh et al. 1995). The normalized joint perievent time histogram (nJPETH) cross-correlation technique was used to assess the dynamics of CS-SS interaction within and among PCs at high temporal resolution (Aertsen et al. 1989). The experiments demonstrated robust modulation of mossy fiber system throughput by synchrony within the climbing fiber system. The experiments also demonstrated a unique control of the rhythmicity of mossy fiber system throughput by climbing fiber synchrony. A preliminary report of this work has been published in abstract form (Schwarz and Welsh 1997).

METHODS

Experiments were performed on 16 Sprague-Dawley albino rats (Taconic Farms, Germantown, NY) in accordance with applicable guidelines. The rats were anesthetized with a mixture of ketamine (175 mg/kg) and atropine (1 mg/kg) administered intraperitoneally. Anesthesia depth was maintained to ensure the absence of limb withdrawal and corneal reflexes. Additional injections of 25 mg/kg ketamine were given when needed. In three rats, a bipolar wire electrode was wrapped around the medial branch of the left hypoglossal nerve before the skull was prepared for cerebellar neurophysiology. The nerve electrode was fabricated from two 25-μm, platinum-iridium wires (7750, A-M Systems, Carlsborg, WA), insulated with Teflon except for the last 5 mm. The uninsulated portion was wrapped around the nerve and the wrapping was covered with silicon to insulate it from the surrounding muscle before the incision was sutured. The nerve potentials were differentially amplified using a gain of 1,000. After mounting the head in a stereotactic frame, the scalp was incised and small holes were drilled in the skull over TM1 on the right (Donoghue and Wise 1982) and the left crus IIa folium of the cerebellar cortex (Welsh et al. 1995). The multineuronal data were analyzed with the normalized joint peri-event time histogram (nJPETH), first described by Aertsen et al. (1989). We chose this type of analysis as it yields a measure of correlated activity of two spike trains through time with respect to a trigger event. For most of our analyses, the trigger event was stimulation of TM1 while other analyses were performed using CSs as trigger events. Our use of the nJPETH for the analysis of cerebellar multineuron data provided high-resolution time maps of the cross-correlation of two PCs’ SSs and/or CSs at any given time relative to a TM1 stimulus or a third PC’s CS and the correlation dynamics of two PCs’ spike trains relative to a TM1 stimulus or a CS. Each bin of the nJPETH can be interpreted as the correlated activity at a particular time delay at a moment along peri-event time. The normal-
ization of the JPETH allowed us to reach a quantitative level of analysis by comparing correlation between different pairs of spike trains recorded in different experiments. One important feature of this method is that it subtracts a periepisode time histogram (PETH) based predictor to remove correlation due to changes in firing rate. The comparability to JPETHs of other pairs of spike trains is then accomplished by the next step which involves dividing the JPETH (bin by bin) by the vector product of the standard deviation of the periepisode time histogram. The procedure transforms the values of the periepisode joint histograms to normalized units ranging from -1 to 1 (Aertsen et al. 1989).

For presentation purposes, we rotated the nJPETHs clockwise by 45° so that periepisode time was represented on the horizontal axis and delay time was represented on the vertical axis. After rotating the nJPETH, averaging along the horizontal axis yielded a normalized cross-correlogram (nCC), identical to the well-known cross-correlogram (Perkel et al. 1967) but in normalized values to allow for comparison across spike trains and experiments. Integration along the vertical axis, in a narrow window of time delay, yielded a normalized periepisode time coincidence histogram (nPETCH), which plotted the strength of two spike trains’ correlation at a particular time delay through periepisode time. Note that in contrast to the nCC, the nPETCH was computed by summing the respective bins (instead of averaging) which allows for the intuitive interpretation of the nPETH as the temporal dynamics of the area under a peak in the cross-correlogram. An important instance of the nPETCH was taken at a delay of 0 ms to allow the dynamics of two PCs’ spike synchrony to be studied through periepisode time. Population data were computed by averaging nCCs and nPETCHs of all pairs in the sample. The time limits (time delays for nPETCHs and PST time for nCCs) were adjusted for each pair to extract features in the nJPETHs optimally. Figures 5 and 7 give the ranges of limits used to extract the histograms in single pairs.

To study anatomical relations between TM1 and crus Ila, lipophilic dyes were injected into both the stimulating and recording sites at the end of six experiments. The anterograde tracer 1,1’-dioctadecyl-3,3,3’,3’-tetramethylindocarbocyanine perchlorate (DiI, Molecular Probes, Eugene, OR) was injected into TM1 and the retrograde tracer 4-(4-didecylaminostyryl)-N-methylpyridinium iodide (DiAsp, Molecular Probes) was injected into crus Ila. The injections were made through glass pipettes (tip diameters, ~25 μm) using a Picospritzer pressure injection system (General Valve, Fairfield, NJ) calibrated to ensure injection diameters < 500 μm. DiI was injected 1.2 mm below the surface of TM1 while DiAsp was injected 300 μm below the surface of crus Ila. After 4 days of survival, the rats were killed by an overdose of pentobarbital sodium (>100 mg/kg ip) and sequential transcardiac perfusions of 100 ml phosphate buffer (0.1 mM, pH 7.4) and 500 ml of 4% phosphate-buffered paraformaldehyde. The brain stem, blocks of cerebrum containing TM1, and the cerebellum were postfixed in 4% paraformaldehyde for 1–2 h and 30% sucrose phosphate-buffer for 12 h. Sections (60 μm) were taken in the parasagittal plane on a freezing microtome. The sections were mounted on glycerin-covered microslides, coverslipped, and visualized with an epifluorescence microscope (Zeiss Axioskop, Thornwood, NY). The only cases examined were those in which the injections were confined to the cerebral and cerebellar gray matters. Sections containing the pontine nuclei and inferior olive were inspected to locate overlapping sites of anterogradely labeled terminals from TM1 and retrogradely labeled neurons projecting to crus Ila.

**RESULTS**

**Motor cortex stimulation evokes time-modulated spike trains in PCs**

Under ketamine anesthesia, stimulation of TM1 with trains of current pulses evoked large movements of the tongue, and, in some cases, stimulation with single current pulses evoked discrete tongue twitches. In three rats, we verified that the stimulus was delivered to TM1 (Fig. 1A) by recording directly from the hypoglossal nerve, which showed a 10.4 ± 1.4 (SD) ms activation latency (as measured by the peak of the short-latency response in PETHs, Fig. 1B). Overall 196 PC recordings (of 234 obtained) showed CS and/or SS trains that were triggered by TM1 stimulation. Single 300-μs pulses were always sufficient to evoke 200- to 300-ms trains of both SSs and CSs in ensembles of simultaneously recorded PCs (Fig. 1B). Of the 196 spike trains, 92% showed a short (< 20 ms)-latency spike to 100-μA stimulation of TM1. The mean latencies of the short-latency SS (11.5 ± 2.5 ms) and CS (10.0 ± 3.1 ms) were in the same range as that of the hypoglossal nerve. The minimum current required to evoke SSs, CSs, and hypoglossal nerve responses was 15 μA. Our multiple electrode experiments allowed 324 CS-CS and 146 CS-SS pairwise interactions to be analyzed.

We observed that the short-latency activation of the cerebellum by TM1 stimulation was always followed by a relatively long-lasting modulation of both CS and SS firing that
had interesting properties. Figure 2 presents perievent time histograms of well-discriminated SSs and CSs obtained from the same PC. Both SSs and CSs showed a period of inhibition immediately following the short-latency responses. The inhibition was the most common event triggered by TM1 stimulation, had the lowest stimulation threshold, and was even observed in the small percentage of PCs that did not fire a short-latency SS and CS. In many cases, 15 μA stimulation of TM1 inhibited both CS and SS firing for ≤100 ms without triggering a short-latency activation (Fig. 2A). Irrespective of TM1 stimulation amplitude, the duration of the SS depression (50–75 ms) was always briefer than the inhibition of the CS (≤150 ms). Notably, the CS inhibition was consistently followed by a rhythmic CS response. Up to three oscillatory CSs having a frequency of 14.9 ± 2.4 Hz could be recorded beginning 180 ± 17 ms after 300 μs of 100 μA TM1 stimulation. Coincident with the oscillatory CSs, periods of depressed SS firing were typically observed in each recorded PC. The moments of SS depression occurred periodically and were clearly phase-locked to the rhythmic CSs (Fig. 2A, ⋅⋅⋅). To summarize, the modulation of PC firing rate by TM1 stimulation occurred in three distinct phases: a short-latency activation carried by both afferent systems, a subsequent phase of deep inhibition in both CS and SS firing, and a final, oscillatory phase in which CS and SS rate were modulated concertedly but in opposite directions.

Two characteristics of the evoked CS and SS trains suggested that the rate control of CSs and SSs were functionally related and were executed by a common mechanism. First, the peaks of CS oscillation and the correlated decreases in SS rate showed the identical stimulus threshold (Fig. 2A). Second, the latencies of the peaks and troughs in the perievent histograms for both the CSs and the SSs were the same for single PCs (Fig. 2A) and across the entire sample of PCs (Fig. 2B). The latencies calculated for the entire sample (Fig. 2B) were computed from peaks and troughs in PETHs that exceeded the 0.9 confidence limit, as described by Abeles (1982). Within the total sample, the latencies of the first and second peaks and troughs in the oscillatory CS and SS firing were not significantly different. The first CS peak (n = 101) and SS trough (n = 24) occurred at 180 ± 17 and 175 ± 21 ms, respectively (t-test, P > 0.05). The second CS peak (n = 64) and SS trough (n = 17) occurred at 247 ± 16 and 253 ± 14 ms, respectively (P > 0.05). One possible basis for the interaction between CS and SS trains could have been the often-described inhibitory effect that the CS has on SS firing (Fig. 2C) (for review see Simpson et al. 1996). However, our use of multineuron recording indicated that the interactions involved a more complex and interesting mechanism.

**Distributed CS modulation of SS rate**

We wanted to determine whether the concerted and inverse modulation of CS and SS rate could be explained by a distributed action of the climbing fiber system on the SS-generating circuitry of the cerebellar cortex. Such a hypothesis could be plausible given the collateral projections of climbing fibers to inhibitory interneurons within the cerebellum that synapse either onto the granule cells or PCs. As a first step, we analyzed PC recordings to determine whether the SS rate modulations after TM1 stimulation required the PC to fire a CS. If the decreases in SS rate were due to a direct, biophysical effect of the CS on the excitability of the PC membrane, the SS rate decrease would be expected to be absent on the trials in which TM1 stimulation did not trigger a CS. For this analysis, only the highest-fidelity recordings were examined (signal to noise ratio >10 for both spike types) as its power depended on being able to reliably detect CSs and discriminate them from SSs. Figure 3 shows an example that represented the major effect seen in all PCs investigated in this manner (n = 11). Here, raw records from two types of trials are shown for the same PC—a trial in which TM1 stimulation did (Fig. 3A) and did not (Fig.
and modulations in SS firing depended on CSs. C. rally related to the pauses in SS firing in responsible for the modulation of SS rate (compare Fig. 3, climbing fiber and the CS that it triggered was not directly was as robust (Fig. 3 D). This result indicated that the PC’s on the 965 of 1376 of trials when the PC did not fire a CS in related to the short- and long-latency CSs (Fig. 3 C). D, the SS rate modulation on all trials. E: identical plot as in C, but trials were selected in which no CSs were evoked. F: PETH of CSs for the trials depicted in C. Note the occurrence of a short (●) and long-latency CS (■) evoked by TM1 stimulation, both of which were temporally related to the pauses in SS firing in C. G: peri-event time histogram of CSs for the trials depicted in D and E. Here, trials were selected for the absence of CSs within 250 ms after TM1 stimulation. Neither the early nor the late modulations in SS firing depended on CSs. 3B) trigger a CS. A sum of all stimulation trials (n = 1376) in this paper indicated that the long-latency CS response consisted of only one additional CS (Fig. 3F, ■), such that an oscillation was not observed even with a TM1 stimulus of 100 μA. The PC fired SSs with two distinct pauses that were temporally related to the short- and long-latency CSs (Fig. 3C). However, on the 965 of 1376 of trials when the PC did not fire a CS in response to TM1 stimulation (Fig. 3G), the SS rate modulation was as robust (Fig. 3D). This result indicated that the PC’s climbing fiber and the CS that it triggered was not directly responsible for the modulation of SS rate (compare Fig. 3, C and D).

To test for the possibility that the SS rate modulation was due to strong activation of the mossy fiber/parallel fiber system, we further selected those CS-negative trials in which short-latency SSs (0–50 ms after TM1 stimulation) were absent (Fig. 3E). Here, on 319 of 1,376 trials in which TM1 stimulation triggered neither any CS activity nor a short-latency SS in the example PC, the long-latency rate modulation in SSs was clearly present (Fig. 3E). This result demonstrated that long evoked activity in the mossy fiber/parallel fiber system, as indicated by a short-latency SS, was not necessary for the later SS rate modulation. Thus in view of the closely related modulation of SSs and CSs, the data pointed to the possibility that the decrease in SS firing was related to a distributed, ensemble property of the climbing fiber system. Because synchrony is a well-recognized attribute of ensemble olivocerebellar activity, we proceeded to characterize CS synchrony in response to TM1 stimulation.

Figure 4 demonstrates the degree and temporal structure of CS synchrony after TM1 stimulation in normalized joint PETHs (nPETHs in Fig. 4A) for one multielectrode experiment in which the CSs of six PCs were simultaneously recorded. Each of the two-dimensional plots shown in Fig. 4A demonstrates the time-related occurrence of CSs from two PCs. Matrices were formed that showed the relative occurrence of the CSs of two PCs (vertical axis) as a function of time before and after TM1 stimulation (horizontal axis) as described in METHODS. A vertical section through each matrix provided an instantaneous cross-correlogram in normalized values (nCC in Fig. 4, C and D) of the two PCs’ CSs at a moment in time relative to TM1 stimulation. Importantly for our experiments, a horizontal section through the matrices at time 0 of the vertical axis provided a histogram of the degree of CS synchrony between two PCs as a function of time before and after TM1 stimulation (nPETHs in Fig. 4A).

The analysis was performed on well-discriminated CSs of six PCs simultaneously recorded from a linear eight-electrode array oriented as shown in Fig. 4B. As can be seen in Fig. 4A, each of the pairwise comparisons showed a positive (red) band of correlation at 0 ms on the vertical axis, indicating that all pairs of PCs fired CSs synchronously. Closer inspection of the 0-ms bands (bracketed in Fig. 4A and plotted above as nPETHs) revealed that the synchrony was not constant but occurred episodically after TM1 stimulation. This result indicated that CS synchrony was not uniform through time but was concentrated in discrete time windows in the 400 ms after TM1 stimulation. Specifically, the time 0 nPETHs demonstrated, for all cases, that CS synchrony was nearly absent in the first 100 ms after TM1 stimulation but grew to a maximum 180–300 ms after the stimulus before it thereafter returned to baseline levels. It should be noted that the synchrony during the short-latency responses to TM1 stimulation was present in the raw PETHs (at 10–15 ms) but was removed by the normalization procedure and did not appear in the nPETHs. This was generally observed in all nPETHs obtained in this study, indicating that the changes in firing rate during the short latency response fully accounted for the synchrony observed in the raw correlograms in most cases (see population data in Figs. 5 and 7).

Normalized cross-correlation histograms taken as vertical sections through the nPETHs demonstrated that the moments of highest CS synchrony occurred when the climbing fiber system was firing in an oscillatory mode. Thus a display of all of the cross-correlograms indicated that CS firing was arrhythmic during moderate CS synchrony before TM1 stimulation (Fig. 4C). In contrast, the time 0 peaks on the cross-correlograms were significantly larger 200 ms after TM1 stimulation when they also showed a series of well-defined peaks and troughs indicating rhythmic firing (Fig. 4D). In summary, the analysis indicated that TM1 stimulation triggered delayed synchrony among the CS firing of PC populations that reached a maximum when the system went into a transient period of robust oscillation. Importantly, the analysis reflected true neuronal interaction, because modulations in firing rates as sources
A  nJPETHs / nPETCHs

B

C  nCCs

D  nCCs

200 ms before stimulus

200 ms after stimulus (marked by ___ in A)
of correlation were removed by normalizing the JPETHs (Aertsen et al. 1989).

Analysis of the entire sample of PCs in the study confirmed the generality of the result shown in Fig. 4. Figure 5A shows the time-varying occurrence of CS rhythmicity relative to TM1 stimulation. The analysis plots the average magnitude of the peaks ~70 ms on either side of time 0 (bracketed region in Fig. 5A) from each PC’s CS autocorrelogram over time (n = 109). In so doing, the final histogram indicated the strength of 15-Hz CS firing as a function of time before and after TM1 stimulation (Fig. 5B, nPETCH). The analysis indicated a highly defined window of time, 180–250 ms after TM1 stimulation, in which oscillatory CSs occurred. Figure 5, C and D, shows a similar analysis but for the mean correlation magnitude of the CS firing of 324 PC pairs. Here, the time-varying magnitude of synchronous (○) and phase-advanced (●) CSs is presented relative to TM1 stimulation. As can be seen (Fig. 5D), there was a significant degree of CS synchrony prior to TM1 stimulation. Activation of TM1 rapidly but transiently decreased the amount of correlation within the climbing fiber system for ~150 ms but thereafter greatly enhanced CS synchrony (150–275 ms after TM1 stimulation) as compared with baseline. It is important to note that the width at half-peak centered on 0 ms in the nCCs was only 8 ms, indicating the presence of precise synchrony within the climbing fiber system. More strikingly, a similar analysis of phase-advanced CS firing showed a discrete window, 175–250 ms after TM1 stimulation, in which a CS in one PC predicted a CS in another PC 75 ms later. The growth in such phase-locked activity indicated the development of a population, 15-Hz oscillation within the climbing fiber system. In summary, the ensemble analysis indicated that a brief activation of the motor cortex induced a long-lasting and highly dynamic modulation of CS synchrony and rhythmicity.

Dynamic modulation of CS-SS interactions by CS synchrony

The finding of a dynamic modulation of synchronous oscillation in the climbing fiber system after TM1 stimulation allowed us to examine whether CS-SS interactions changed in parallel with the changes in the functional state of the climbing fiber system. The specific issue to be addressed was whether the modulation of SS rate that has been correlated with the occurrence of a CS is static, unique, and fixed for each PC (e.g., Fig. 2C) or whether it is a controlled variable that dynamically changes through time.

Figure 6 shows multielectrode data from an experiment in which three of four PCs showed SSs (PC1, -3, and -5) and the fourth (PC6) showed robust CSs in response to TM1 stimulation. The data allowed CS-SS interactions between different PCs to be quantified with the nPETCH analysis. The analysis was performed as described for Fig. 4 with the exception that a second PC’s SSs were plotted along the vertical axis before and after TM1 stimulation. Vertical sections taken from the resultant two-dimensional matrices (single asterisked brackets, Fig. 6B) provided normalized cross-correlograms of the SSs of one PC relative to the CSs of another PC (nCCs in Fig. 6A). Horizontal sections taken from the two-dimensional matrix (double asterisked brackets in Fig. 6B) provided normalized histograms of the correlation between CSs and SSs as a function of time before and after TM1 stimulation (nPETCHs in Fig. 6C). The resulting histogram indicated the normalized probability of SSs occurring in one PC within 15 ms before or after TM1 stimulation.
after the moment when the referent PC fired a CS. In addition, firing rates for the SS-firing PC and the CS-firing PC are presented in standard peri-event time histograms in register with the correlation histograms (Fig. 6D).

The analysis indicated that the occurrence of a CS in one PC predicted a period of deep inhibition in the SSs of other simultaneously recorded PCs. For the three SS-firing PCs shown in Fig. 6 (PC1, -3, and -5), the nPETEs indicated a period of SS inhibition around the time that PC6 fired a CS (black bands bounded by the double asterisked frames). How-ever, as indicated by the nPETEs, the inhibition was dynamic because its magnitude changed rapidly over time. Thus after a period of weak inhibition in the first 100 ms after TM1 stimulation, the inhibition quickly grew to a robust maximum at ~200 ms after TM1 activation. Notably, the SS inhibition by CS activity was maximal during the time of CS oscillation (dotted lines, Fig. 6). Moreover, the central band of SS inhibition was also flanked by deep peaks and troughs in SS rate during the period of CS synchrony (Fig. 6; single asterisked brackets). The analysis provided two important findings. First, the nature of the CS-SS interaction was not fixed because SSs could be depressed or enhanced at different times after the CS. Second, and more intriguingly, the analysis indicated that the strength of CS-SS interactions was not the same at all times but was time varying and appeared to be controlled by the strength of CS synchrony and oscillation—an ensemble characteristic of the climbing fiber system.

To determine the generality of the phenomenon shown in Fig. 6, we analyzed 111 CS-SS pairs by correlating the CS firing and SS firing of different PCs simultaneously recorded in all of our multielectrode experiments (Fig. 7). It is important to emphasize that the analysis shown in Fig. 7 specifically excluded CS-SS interactions recorded from the same PC. In this way, the magnitude of SS inhibition (Fig. 7A) and SS facilitation (Fig. 7B) relative to a CS in another PC could be determined. As a preanalysis, the center of maximal SS inhibition...
plots the mean magnitude of SS inhibition over time relative to TM1 stimulation. Here, it can be seen CSs exerted an inhibitory effect on SSs before TM1 stimulation, had no significant effect on SSs in the first 150 ms after TM1 stimulation, and produced a profound inhibition 200–300 ms after TM1 stimulation. Figure 7B shows a similar dynamism for SS facilitation, with CS facilitation being maximal at 200–300 ms after TM1 stimulation. For purposes of direct comparison, Fig. 7C replots the strength of CS synchrony relative to TM1 simulation for the entire dataset. Comparing Fig. 7, A–C, clearly reveals that the dynamic modulation of CS-SS interaction was tightly locked in time to the dynamics of CS synchrony.

Modulation of SS time structure by CS synchrony

We next determined whether the time structure of SS trains was modulated in conjunction with the level of CS synchrony. We found, replicating Ebner and Bloedel (1981a), that a large percentage of PCs fired SSs rhythmically at a frequency of 75 ± 18 Hz. Side peaks in normalized autocorrelograms reflected this rhythmicity in 33 of 42 PCs. The number of clearly discernible side peaks in the SS autocorrelograms varied from 1 to 4 (Fig. 8A), indicating variability in the strength of SS rhythmicity. In addition to rhythmic firing, some PCs showed bursts of SSs with varying internal structure that produced a broad positive offset in the normalized autocorrelograms (e.g., PC5 in Fig. 9).

We found that the strength of the SS rhythm varied dynamically as a function of time after TM1 stimulation. Figure 8B shows nJPETHs for the SSs of three PCs. In these plots, nJPETH matrices were computed by correlating a PC’s SSs to themselves, for every 2 ms in time relative to TM1 stimulation, to yield a normalized auto-PETH. As such, the internal organization of these plots represented the time structure of a given PC’s SSs as a function of time after TM1 stimulation. Vertical sections through these matrices provided normalized autocorrelograms (nACs) for a PC’s SSs at specific perievent times (nACs in Fig. 8A) and horizontal sections (nPETCHs in Fig. 8C) provided time-varying plots of the strength of specific components of the SS autocorrelograms. Figure 8C clearly shows that the strength of SS rhythmicity varied significantly and rapidly as a function of time after TM1 stimulation. The strength of the SS rhythm was maximal ~80 ms after the short-latency CS but declined to nearly zero at the time of oscillatory CSs in a different PC (Fig. 8C). Figure 8, E and F, shows, in average data, that the rhythmicity within SS trains (n = 42) changed dynamically over time relative to TM1 stimulation. The average plots indicated that SS rhythmicity was greatest 50–100 ms after TM1 stimulation but was virtually absent 200 ms after the event—the time when CS oscillations began (Fig. 8E). Note that the positive offset in the average nJPETHs and nACs originate from a positive offset in the autocorrelogram which corresponds to a broad positive peak due to nonrhythmic burst firing. These positive offsets were observed to dynamically change their thickness and slope over time, indicating variability in the internal spike structure of the SS bursts (Fig. 8F).

To directly show that the reduction in SS rhythmicity was related to an ensemble property of climbing fiber activity, we used CSs as trigger events for auto-PETHs of SSs. Figure 9
shows an experiment in which the SSs of three PCs (PC3, -5, and -6) were correlated to the CSs of a fourth PC (PC4). As expected from the analysis shown in Fig. 8, the firing rate and rhythmicity of SSs in the three PCs was transiently reduced for ~50 ms immediately after the occurrence of a CS in PC4 (Fig. 9A). More intriguingly, we repeated the analysis for data taken from two PCs whose recordings yielded the best discriminations of CSs from SSs (PC3 and -6 in Fig. 9B). In this last analysis, we only analyzed those trials in which these two PCs did not fire a CS after TM1 stimulation and correlated their SS activity to the evoked CSs of PC4. As can be seen in Fig. 9B, triggering the auto-perievent time histograms of two PCs’ SSs to another PC’s CSs, in the absence of CSs on their own membrane, revealed an identical modulation in SS rhythmicity. This result strongly indicated that synchrony within the climbing fiber system was responsible for the modulation of SS rhythmicity.

**Fig. 8.** Dynamics of SS rhythmicity after TM1 stimulation and its relation to CS oscillation. A: nACs of SSs in 3 simultaneously recorded PCs calculated at 4 different times after TM1 stimulation. B: normalized “auto”-PETHs of SSs relative to TM1 stimulation in the 3 PCs. C: nPETHs showing the temporal dynamics of the magnitude of SS rhythmicity relative to TM1 stimulation. The plots show the area under the 2nd side peak indicated by the horizontal bracket in the corresponding nPETH. D: PETHs of the 3 PCs’ SS rate (top) and the CS rate of a fourth simultaneously recorded PC (bottom), relative to TM1 stimulation. Dotted lines indicate the times from which the nACs in A were calculated and demonstrate that SS rhythmicity was maximal during CS pauses. The time base is identical in B–D. E and F: population data of SS rhythmicity calculated from 33 PCs. The mean nPETH in F was calculated using the 1st side band of each PC’s auto-PETH and shows that SS rhythmicity was strongest during the recovery from the SS depression produced by TM1 stimulation. SS rhythmicity in the population decreased during the CS oscillation at 170–280 ms. The mean nACs in F show that SS rhythmicity (75 ± 18 Hz at 100-μA TM1 stimulation) was sharpest during recovery from the depression. The mean nACs also showed a broad positive offset, probably related to nonrhythmic SS patterns seen in a subset of the spike trains. The analysis used the same experiment shown in Fig. 6.
Convergence of motor cortex efferents and cerebellar afferents

To demonstrate the anatomical pathways by which TM1 influenced crus IIa, we performed a double label tract-tracing study using fluorescent dyes in six rats. DiI was used to anterogradely trace axons that emanated from the stimulation site in TM1. DiAsp was used to retrogradely label the somata of neurons that innervated the recording sites in crus IIa. Figure 10 shows a representative example of the pattern of label found in the two major interfaces of signal throughput from the superior cerebellar peduncle.

![Diagram showing the convergence of motor cortex efferents and cerebellar afferents.](image-url)
cerebrum to the cerebellum. In the inferior olive, TM1 terminals were identified in patches isolated to the medial accessory and principal subnuclei of the inferior olive, as reported by Saint-Cyr (1983) and Swenson et al. (1989). These patches of TM1 efferents overlapped with crus IIa projecting neurons in three of four rats in at least one site within the inferior olive. In the two other rats, the anterograde label was too weak to make a clear determination. In the pontine nuclei, TM1 terminals were localized to ventral subnuclei. Terminal label was dense and was organized in patches as reported by Mihailoff et al. (1985). Retrogradely labeled afferents of crus IIa were found in a large area of the pontine nuclei that exceeded the extent of the TM1 terminals. In four of six rats, at least one pontine site could be identified where anterograde and retrograde label overlapped. The data showed that the evoked SS and CS responses of crus IIa PCs were mediated most likely by cerebrospinal projections to the pontine nuclei and inferior olive, respectively.

**Discussion**

Using a multielectrode approach to record both SSs and CSs in multiple PCs simultaneously, the present study demonstrated that the firing rate and temporal patterns in SS trains are modulated by the ensemble activity of the climbing fiber system. Normalized JPETH analysis revealed that this modulation varies in strength and sign over time after activation of the motor cortex and thus is highly dynamic. It was shown that motor cortex stimulation evoking synchrony and oscillation within the climbing fiber system is most effective in dynamically influencing SS firing.

**Motor cortex engagement of coordinated CS and SS firing**

Motor cortex stimulation triggered both CSs and SSs in PCs with latencies compatible with disynaptic throughput via the inferior olive or trisynaptic throughput via the pontine nuclei and granule cells. Anatomical experiments showed convergence of TM1 efferent terminals on clusters of olivary and pontine nuclei neurons that projected to crus IIa. In a minority of cases, short-latency CSs and SSs occurred without demonstrable overlap of TM1 terminals and projection neurons in the brain stem. However, the few negative outcomes did not allow the conclusion that the short-latency responses were not mediated by the direct olivary and pontine pathways for three reasons. First, short horizontal fibers connecting adjacent sites of motor cortex may be a component of the circuit that triggers the responses observed in both direct pathways (Weiss and Keller 1994). Second, the absence of tracer overlap within the pontine nuclei may be explained by the remote origin of the parallel fiber inputs to the recorded PCs; the distance of parallel fiber terminals from their parent somata and mossy fiber afferents can be 2 mm (Pichitpornchai et al. 1994)—well beyond the 250 μm radius of the tracer injections. Third, electrotonic coupling among neuronal ensembles in the inferior olive (Llinàs et al. 1974; Sotelo et al. 1974) may lead to a short-latency CS that is triggered by olivary neurons not directly innervated by the TM1 efferents. Thus the most parsimonious conclusion was that TM1 stimulation triggered CSs and SSs in PCs by direct corticobulbar projections to the inferior olive and pontine nuclei, respectively.

A fundamental finding was that activation of the motor cortex induced highly structured trains of CS and SS firing that far outlasted the duration of the stimulus. Although the duration of TM1 stimulation was only 300 μs in our experiment, the evoked activity patterns in cerebellar cortex lasted for 300 ms. The issue to be addressed was how the stimulus-evoked modulation of CS and SS activity could persist for 1,000 times longer than the triggering stimulus. The temporal structure of the rate modulations strongly suggested that regenerative firing within the inferior olive was the responsible agent.
clusion that TM1 stimulation triggered regenerative firing within the inferior olive was based on three observations. First, the trains of CS firing after TM1 stimulation had timing indicative of rebound excitation within the inferior olive. For virtually all PCs studied, TM1 stimulation triggered a short-latency CS that was followed by a 180-ms pause and up to two or three rhythmic CSs at ~15 Hz. Intracellular stimulation of olivary neurons in vitro also triggered an action potential that was followed by a 155-ms pause and a train of three rhythmic action potentials at ~9–12 Hz (Llinás and Yarom 1981a,b, 1986). As shown biophysically, the long pause after the first action potential is produced by a calcium-dependent hyperpolarization that, on release, triggers rebound excitation and regenerative firing with shorter interspike intervals (Bal and McCormick 1997; Llinás and Yarom 1981a,b, 1986). Second, the TM1-evoked trains of CSs occurred synchronously with high precision across PCs, indicating the operation of a coupling mechanism. It is well known that olivary neurons are electrotonically coupled (Llinás et al. 1974; Sotelo et al. 1974) and that this property forms the basis for synchronous and regenerative CS firing in vivo (Lang et al. 1996). Third, the temporal and spatial characteristics of the CS trains triggered by TM1 stimulation were nearly identical to those evoked by somatosensory stimulation (Ebner and Bloedel 1981b; Llinás and Sasaki 1989), which have been attributed to regenerative firing conferred by the membrane and coupling properties of olivary neurons. Those three parallels indicated that TM1 stimulation triggered regenerative firing within the inferior olive that allowed the evoked cerebellar activity to continue well beyond the duration of the descending volley from the cerebrum. The extremely tight time-relation between the regenerative CS firing and the modulation in SS rate strongly suggested that the latter was induced by the climbing fiber system.

**Network bases of climbing fiber-mossy fiber system interaction**

The present study provided three novel findings that indicated that interactions between the climbing and mossy fiber systems are mediated by the cerebellar network rather than by a direct interaction of the two systems on individual PCs. First, the SS rate modulation in any given PC did not require it to fire a CS but was nonetheless temporally related to the CSs in one or more PCs as far away as 2 mm. Second, the strength of rhythmic synchrony within climbing fiber ensembles—not firing rate in individual climbing fibers—was the most definitive variable for modulating SS firing. Third, SS inhibition and SS facilitation induced by climbing fiber activity occurred independently as separate functional events.

There are four circuits within the cerebellum that may allow the climbing fiber system to influence mossy fiber system throughput. Although physiological knowledge about how the intracerebellar circuitry modulates cerebellar throughput is incomplete, certain conclusions can be drawn from available information. First, the inhibitory action of climbing fiber activity on SS rate may involve connections of climbing fiber collaterals to the inhibitory Golgi and basket interneurons (Hámori and Szentágothai 1966; Lemkey-Johston and Larramendi 1968; Scheibel and Scheibel 1954; Schulman and Bloom 1981). These interneurons powerfully inhibit granule cells and PCs, respectively (Eccles et al. 1966a,b) and are optimally positioned to reduce mossy fiber system throughput. Second, inhibitory collaterals of PC axons onto these same interneurons may disinhibit granule cells and PCs and, thereby, allow climbing fiber activity to boost SS rate (Hámori and Szentágothai 1968; McCrea et al. 1976; Ramón y Cajal 1995). This mechanism is the converse of the first and may be a way for the climbing fiber system to disengage the inhibitory interneuronal circuitry. Third, SS facilitation may be produced by the circuit consisting of climbing fiber collaterals to the cerebellar nuclei and the excitatory connections that they make onto the granule cells in the cerebellar cortex (Provini et al. 1998) or to precerebellar nuclei in the brain stem (Schwarz and Schmitz 1997; Schwarz and Thier 1999). Through this mechanism, the collaterals of climbing fibers might monosynaptically recruit mossy fibers originating in the deep nuclei or disynaptically recruit those originating in the pontine nuclei. The fourth possibility involves Lugaro cells (Laine and Axellrad 1996, 1998) and is suggested by the fact that CS-SS interactions were observed among PCs offset in the mediolateral plane. Lugaro cells are known to project mediolaterally and to synapse onto Golgi cells (Dieudonné and Dumoulin 2000). This unique class of inhibitory interneuron may form a circuit whereby climbing fiber collaterals could influence Golgi cells that are offset in the mediolateral plane. Working together, a Lugaro-Golgi network could add to local climbing fiber-Golgi circuits to extend effects on the mossy fiber system into the mediolateral axis. A fifth possibility is that recurrent pathways through the brain stem mediated by climbing fiber collaterals to the deep cerebellar nuclei may contribute to the observed interactions (Schwarz and Schmitz 1997).

The present data show that the functional coupling of the mossy and climbing fiber system is fixed neither in strength nor sign. This implies that a dynamic interplay of many intracerebellar circuits mediates climbing fiber effects on mossy fiber system throughput. For the first 150 ms after TM1 activation, CS synchrony is low and climbing fiber activity does not modulate SSs; at this early time the two systems act as independent entities. Thereafter CS synchrony grows rapidly and mossy fiber system throughput becomes entrained to the climbing fiber system. SS inhibition dominates immediately after an episode of synchronous CSs, suggesting an early recruitment of intracerebellar inhibition by basket and Golgi interneurons. By some 40 ms later, SS inhibition dissipates and SS facilitation becomes apparent, an effect that may result from activation of PC collateral circuitry, activation of mossy fiber somata in the deep nuclei by climbing fiber collaterals, and/or by engagement of cerebellar-brain stem loops that recruit additional mossy fiber input to cerebellum. By recording multiple PCs in the mediolateral plane, we observed CS-SS interactions that were orthogonal to the tendency of CSs to fire synchronously in the rostrocaudal plane (Lang et al. 1999; Llinás and Sasaki 1989). The finding that TM1 stimulation triggered CS synchrony in the mediolateral plane indicated that the spatial dynamics of mossy-fiber system throughput may be critically determined by the spatial organization of CS synchrony. Such mediolateral CS synchrony may be a means to coordinate SS firing across narrow parasagittal microzones by engaging local interneuronal circuitry.

The present experiments indicate that the spatial dynamics of SS rate modulation by the climbing fiber system are bound
to be very complex and only fully resolvable by large-scale neuronal ensemble recordings. The spatial distribution of SS rate modulations at any given time will be determined by the spatial organization of concurrent synchronous climbing fiber activity, by the distribution of those climbing fibers’ collaterals onto cerebellar interneurons, and by the distribution of the mediating intrinsic cerebellocortical fibers. Thus the spatial details of the modulation-map will be determined by a matrix of interneuronal connections whose spatial pattern of physiological effect will only be loosely related to the concurrent pattern of CS synchrony. Spatial patterns of CS synchrony change rapidly during skilled movement with a time constant in the tens of milliseconds (Welsh et al. 1995). This implies that the spatial structure of SS rate modulation changes equally fast—a level of spatiotemporal complexity that adds to the temporal dynamics as reflected in the changes in strength and sign over time after a single bout of high CS synchrony.

**Ensemble nature of CS-SS interactions**

The present study helps to resolve a number of discrepancies in the literature regarding the interaction of climbing and mossy fiber systems. Current understanding of CS-SS interactions has originated mostly from studies investigating the interaction of CS and SS firing in a single PC. The results reported by these studies have been inconsistent, as some reported an inhibitory effect of a CS on SS rate (Bell and Grimm 1969; Bloedel and Roberts 1971; Latham and Paul 1971; Murphy and Sabah 1970, 1971; Rubia and Henneman 1978) while others reported an enhancing effect (Ebner and Bloedel 1981c; McDevitt et al. 1982). Moreover, the mechanism of CS inhibition on SS firing was argued by several research groups to result from the interaction of CSs and SSs on the membrane of the PC (Bell and Grimm 1969; Colón et al. 1980). Yet, others concluded that such inhibition was mediated by cerebellar interneurons (Bloedel and Roberts 1971; Eccles et al. 1971; Latham and Paul 1971; Montarolo et al. 1982; Rubia and Henneman 1978). The few reports that studied CS and SS trains recorded simultaneously from more than one PC diverged also. Bell and Grimm (1969) did not find CS-SS interactions between pairs of simultaneously recorded PCs, while Bloedel et al. (1983) and Lou and Bloedel (1992a,b) found a facilitation of SS rate time locked to the occurrence of a CS in a neighboring PC. Our study helps to clarify these inconsistencies by demonstrating that CS-SS interactions exist on both the single PC and on the population level, that such interactions can be observed even after removing trials in which the PC fired a CS—indicating a network basis for the interaction, and that the sign of the interaction depends on the time delay with respect to the synchronous firing of the climbing fibers. The latter observation was supported by the latencies given by earlier studies for the depressing (Simpson et al. 1996) and the facilitating (Ebner and Bloedel 1981a) effects of CSs on SS firing as observed in single PCs. Moreover, the sequence of depression-facilitation has been supported by the findings of Sato et al. (1992) in single PCs which demonstrated that two-thirds of PCs show a sequence of SS depression-facilitation after the occurrence of a CS.

We demonstrated that the amplitude of CS-SS interactions is not static but is related to the amount of rhythmic CS synchrony within the PC population. The dynamic range of the interaction extended from virtual independence during low CS synchrony to strong modulation during precisely synchronized CS oscillations. In the latter state, the sequence of inhibition and facilitation of SS firing appeared as a nearly symmetric pattern in the CS-SS cross-correlograms which showed facilitatory peaks on each side of the inhibitory trough (Fig. 5). It should be noted that the phase relation between CSs and SSs during oscillatory CS firing is difficult to interpret during CS oscillations, whereas CS-SS cross-correlations computed from data sets not containing CS rhythmicity showed unambiguous changes in SS rate after the occurrence of a CS.

In addition to climbing fiber control of SS rates, we showed that the temporal patterns in SS trains, such as 75-Hz rhythmic firing and arrhythmic bursting, were also modulated by synchrony in the climbing fiber system. Similar results were obtained by Ebner and Bloedel (1981a) during recording of CSs and SSs from single PCs. In that experiment, both arrhythmic SS clusters and fast rhythmic SSs were often found in the same PC, but in different states, as if the PC could switch firing mode. In our data, we often observed both rhythmic firing and arrhythmic cluster bursts at specific times after TM1 stimulation, indicating the absence of a clear separation between these two modes of SS firing. The changes in the autocorrelograms observed in the present study were graded, as the SS effect consisted of a reduction in either the rhythmicity or the clustering of SSs without producing a binary state-transition in firing mode. Nevertheless, our results extended the basic idea (Ebner and Bloedel 1981a) that patterns of CS firing control the temporal patterning of SS trains. Importantly, our results demonstrated that such control does not occur on the PC membrane but derives from the ensemble organization of the climbing fiber system and its distributed influence on intracortical processing.

**Functional implications**

The precise correlation of CS synchrony with SS rate modulation was consistent with a causal role of inferior olive synchrony in the modulation of mossy fiber system throughput. A large body of evidence has shown that synchrony, rather than firing rate, is used for coding in the climbing fiber system and thus may be used for the regulation of mossy fiber system throughput. That spike timing, but not rate, is the coding strategy of the olivocerebellar system was identified early on, when the activity of the climbing fibers was characterized as “phasic” (Llinàs 1970), “noncontinuous” (Llinàs 1991), or as being involved in movement initiation rather than continuous regulation (Mano et al. 1986, 1989). Evidence from multiple microelectrode neurophysiology demonstrated that episodic bouts of synchronous firing within the climbing fiber system are related to the real-time performance of skilled movement (Welsh and Llinàs 1997; Welsh and Schwarz 1998; Welsh et al. 1995, 2001). Such findings have given functional meaning to the low firing rates of olivary neurons and their high degree of electrotonic coupling. The existence of intense CS synchrony triggered by a descending volley from the motor cortex, and its tight temporal relation to SS rate modulation, indicates the importance of electrical coupling in the inferior olive for the global dynamics of cerebro-cerebellar interaction.

The present results help discriminate between two opposing views regarding the means whereby the climbing fiber system
controls movement. One view states that the climbing fiber and mossy fiber systems play important but noninteracting roles in the real-time control of movement as separate channels through the cerebellum (Llinás 1970; Welsh and Llinás 1997). A second view states that the climbing fiber system contributes little or nothing to the real-time control of movement but rather functions to modulate the activity of the mossy fiber system, either on a short-term (Bloedel and Kelly 1991) or a long-term basis (Ito 1972; Marr 1969). That the climbing fiber system has real-time effects on movement, independent of the mossy fiber system, is indicated by its collateral innervation of deep nuclear neurons (Brodal 1981) and ability to synchronously evoke trains of axonal spikes (Ito and Simpson 1971) in groups of PCs that strongly inhibit deep nuclear neurons. These two properties allow rhythmic sequences of excitation-inhibition-excitation to be produced in deep nuclear neurons by excitatory climbing fiber collaterals, synchronously firing inhibitory PC terminals, and rebound excitation (Llinás and Mühlethaler 1988), respectively. Current evidence, thus suggests a view that is much closer to the former, in which climbing fibers act as an independent, real-time control system that periodically has a strong entraining effect on the mossy fiber system. The question then becomes: what functionality does the episodic coupling of the two afferent systems add to the control of movement?

One hypothesis is that the episodic modulation of mossy fiber system throughput by climbing fibers is self-facilitative, such that it briefly co-opts the mossy fiber system to amplify its own effect on deep nuclear neurons. The idea originates from the observation that the duration of the hyperpolarizing current (Pedroarena and Schwarz 2000) or hyperpolarization (Llinás and Mühlethaler 1988) of cerebellar nuclear neurons induced by synchronous CSs was measured between 35 and 60 ms—a duration that is matched quite precisely by the SS depression accompanying a bout of climbing fiber synchrony. This implies that the duration of the climbing-fiber-evoked pause in SS firing is tuned to the membrane properties of the deep nuclear neurons, and reduces synaptic inhibition for the time required for the emergence of rebound excitation. The subsequent facilitation of SSs in groups of PCs would restore deep nuclear inhibition and could be used to shape rebound excitation triggered in groups of cerebellar nuclei neurons. Appropriation of mossy fiber function by climbing fibers, however, might only be useful if the inherent function of the mossy fiber system is not significantly compromised by the imprint of climbing fiber action or if the benefit gained outweighs the quench of mossy fiber system function. Although the coding strategy used by the mossy fiber system is not understood, we may assume that the dependence of the SS modulation on a high degree of synchrony in the climbing fibers together with climbing fibers’ low firing rate does not necessarily quench information conveyed by the mossy fiber system. Moreover, the remarkably divergent nature of the mossy fiber system suggests that distributed activation of PCs by large sets of granule cells could easily counteract the loss of functionality produced the transient takeover by the climbing fiber system of a small set of PCs’ simple spiking. Climbing fiber synchrony, by engaging intracerebellar circuitry, might extract subsets of PCs from conveying native mossy fiber system activity to sharpen its own action on movement, without impacting the overall functionality of mossy fiber system throughput.

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