

Parallel Fibers Synchronize Spontaneous Activity in Cerebellar Golgi Cells

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Cerebellar Golgi cells inhibit their afferent interneurons, the excitatory granule cells. Such a feedback inhibition causes both inhibitory and excitatory neurons in the circuit to synchronize. Our modeling work predicts that the long granule cell axons, the parallel fibers, entrain many Golgi cells and their afferent granule cells in a single synchronous rhythm. Spontaneous activity of 42 pairs of putative Golgi cells was recorded in anesthetized rats to test these predictions. In 25 of 26 pairs of Golgi cells that were positioned along the transverse axis, and presumed to receive common parallel fiber input, spontaneous activity showed a high level of coherence (mean Z score > 6). Conversely, 12 of 16 Golgi cell pairs positioned along the

parasagittal axis (no common parallel fiber input) were not synchronized; 4 of 16 of them showed only low levels of synchronicity (mean Z score < 4). For transverse pairs the accuracy of the coherence, measured as the width at half-height of the central peak of the cross-correlogram, was rather low (29.8 ± 12.5 msec) but increased with Golgi cell firing rate, as predicted by the model. These results suggest that in addition to their role as gain controllers, cerebellar Golgi cells may control the timing of granule cell spiking.

Key words: cerebellum; coherence; computer models; cross-correlation; Crus II; rat

Golgi cells play an important role in cerebellar function, because they are the only element within the circuit that regulates granule cell activity (Eccles et al., 1964) (Fig. 1A). Feedback inhibition exerted by Golgi cells may set the activation threshold for granule cell firing, thus retaining neuronal activity in the granular layer within operational bounds (Marr, 1969; Albus, 1971; Ito, 1984). This negative gain control is considered essential because of the massive excitatory projection to Purkinje cells, which, in rat, receive $\sim 150,000$ parallel fiber inputs (Harvey and Napper, 1991).

The granule cell–Golgi cell circuit has certain properties that make it unique in the nervous system. Granule cells do not have synaptic contacts with other granule cells; there are no synaptic connections within the Golgi cell population either (Ito, 1984; Voogd and Glickstein, 1998). The granule cell–Golgi cell connection thus constitutes a pure feedback circuit. It is known from other systems that feedback inhibition causes both inhibitory and excitatory neurons in the circuit to synchronize (Cobb et al., 1995; Traub et al., 1996; Buzsáki, 1997). A computer model study (Maex and De Schutter, 1998a,b) revealed that the connective properties of the granule cell–Golgi cell circuit contribute to the emergence of rhythmic synchronous firing of both cell populations once they are activated by random mossy fiber input. This synchronization depends on the feedback inhibition that entrains Golgi cells and granule cells in a common rhythm, with granule

cells firing just before Golgi cells, as well as on the long parallel fibers (up to 4.7 mm; Pichitpornchai et al., 1994) that couple all these oscillators together in a global synchronization.

The classic view of Golgi cell function implies that they control the amplitude of granule cell activation only (Marr, 1969; Albus, 1971; Ito, 1984). Our modeling results suggest that Golgi cells also affect the timing of granule cell spikes. The model predicts that Golgi cells positioned along the transverse axis fire synchronously as a result of their common parallel fiber input (Fig. 1B). Golgi cells positioned along the sagittal axis are not presumed to receive common parallel fiber input if they are separated by more than the average size of their dendritic trees (~ 200 μm ; Dieu-donné, 1998b) and are therefore expected to show uncorrelated firing. Cells that are very close to each other may also receive common mossy fiber input (Fig. 1B), independent of their respective orientation.

To test the model predictions, spontaneous activity of pairs or trios of Golgi cells was recorded simultaneously in the cerebellar hemisphere of anesthetized rats (Vos et al., 1999).

MATERIALS AND METHODS

Multielectrode extracellular recordings. Recordings (Vos et al., 1999) were made in the cerebellar cortex (Crus I and II) of anesthetized (ketamine,

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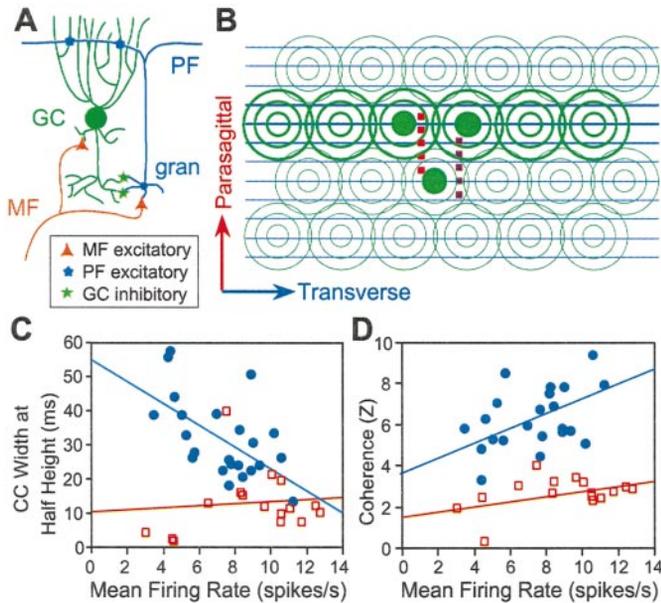


Figure 1. Effect of firing rate on coherence depends on orientation of cells. *A*, Connectivity in the granular layer. Granule cells (*gran*, blue) receive excitation from mossy fibers (*MF*, orange) and send their output along their parallel fiber (*PF*, blue). Golgi cells (*GC*, green) receive both *MF* (orange triangles) and *PF* (blue pentagons) excitation and reciprocally inhibit (green stars) granule cells. *B*, Top view of cerebellum demonstrating the two potential sources of common excitatory input to Golgi cells (green concentric circles represent dendritic arbor). Long *PFs* (thick blue lines) can couple *GCs* (thick circles) together for large distances along the transverse axis, and/or *MFs* (colored squares; difference in color denotes different *MFs*) can directly excite only a few closely *GCs* (filled circles). *C*, *D*, Scattergrams with the mean average firing rate and the width (milliseconds) of the central peak of the normalized cross-correlogram (*C*) or the strength (*Z* score) of the correlation (*D*) plotted for each Golgi cell pair. Only for cells positioned in the same transverse plane (blue dots) were significant correlations found.

75 mg/kg, i.p.; xylazine, 3.9 mg/kg, i.p.; hourly supplements, one-third initial dose, i.m.) rats (male, Sprague Dawley or Wistar, 350–500 gm) with tungsten (2 M Ω) microelectrodes. Signals were filtered and amplified (bandpass = 400–20,000 Hz; gain = 5000–15,000) using a multichannel neuronal acquisition processor (Plexon Inc., Austin, TX). Spike waveforms were discriminated with a real-time hardware-implemented combined time–voltage window discriminator (Nicoletis and Chapin, 1994). Up to three separate records of activity at rest (>300 sec each) were concatenated so that at least 2800 spikes (per unit) were used for further analysis. Electrolytic lesions (15 μ A, 12 sec, cathodal DC current) were made to mark the location of the electrode tips.

Identification of Golgi cells. Putative Golgi cells were recognized by the distinctive rhythm of their activity at rest (Atkins et al., 1997); spikes appeared as pronounced “pops” at a slow cadence with appreciable intervals (no bursting). Golgi cells were identified using quantitative criteria of others (Eccles et al., 1966; Miles et al., 1980; Edgley and Lidiert, 1987; Van Kan et al., 1993; Atkins et al., 1997): low discharge rates at rest (interspike intervals >20 msec), long duration (>0.8 msec) diphasic (negative–positive or positive–negative) wave shapes, long tuning distances, no complex spikes, and location in the granular layer. Additional criteria were used to differentiate other cerebellar units; complex spikes typified Purkinje cells, and mossy fibers were distinguished by a double peak on the interspike interval histogram (Vos et al., 1999). The small-amplitude, short-duration waveforms that were recorded everywhere in the granule cell layer, but that could not be isolated to single units, were presumably granule cell spikes. Categorization of isolated units as Golgi cells was further confirmed by histological proof that the electrolytic lesion was in the granule cell layer.

Quantification of coherence of firing. Simultaneously recorded spike trains of two different units, A and B, represented as binary time series, were cross-correlated to calculate the number of times (y_n) that unit B fired within a time interval $[n\Delta t, (n + 1)\Delta t]$ from spikes fired by the

reference unit A (y_n = counts/bin; bin width, Δt = 1 msec; $-1000 \leq n < 1000$) (Melsen and Epping, 1987). The cross-correlogram y_n was smoothed four times with a three-point averaging filter $\{1/3, 1/3, 1/3\}$, normalized, and expressed in standard scores $[Z = (y_n - \gamma_E)/s_y]$, with $\gamma_E = fr_A fr_B T \Delta t$ ($fr_{A,B}$, average firing rate of A and B; T , recording time), which is the expected value of y_n in case of uncorrelated firing between units (i.e., null hypothesis); and $s_y = SD$ of y_n . Normalization guaranteed cross-correlogram peak height and width to be independent of T . A Z score > 3 within $[-20 \leq n < 20]$ was defined as a significant central cross-correlogram peak. Strength of coherence was determined as the central peak height, i.e., the highest Z score. Peak width (in milliseconds) was determined at half-height and was defined between the n values, on either side, marking the first of three successive entries below half-height. Spike train analyses and cross-correlations were performed with STRANGER (Biographics Inc., Austin, TX) and MATLAB (The MathWorks, Inc., Natick, MA).

Statistical analysis. Pearson correlation coefficients were calculated to test the relation between the average firing rate of a Golgi cell pair and the strength of the coherence (Z score). A χ^2 test of independence was performed to determine whether the frequency of pairs with a significant level of coherent firing was different between distance and transversely oriented pairs. The relation between distance and peak parameters was determined by calculating Spearman’s rank correlations (ρ). Differences between groups for peak parameters were tested using unpaired, two-tailed t tests.

Ethical considerations. Animals were treated and cared for according to the ethical standards and the guidelines for the use of animals in research of the National Research Committee on Pain and Distress in Laboratory Animals (National Research Council, 1992). Testing procedures were approved by the Ethical Committee of the University of Antwerp, in accordance with federal laws.

RESULTS

We recorded 42 putative Golgi cell pairs (24 pairs and 6 trios) in 38 ketamine–xylazine-anesthetized rats. Of these, 26 pairs were positioned along the transverse axis, and 16 were positioned along the sagittal axis. Synchronization was measured as the height of the central peak in the normalized cross-correlogram.

Almost all transverse pairs (25 of 26) showed high levels of coherent firing (Table 1). Distances between these pairs varied from 300 to 2100 μ m, and no significant relationships between distance and parameters describing the central peak were found ($-0.326 < \text{Spearman’s } \rho < 0.052$; $p \geq 0.2227$). An example of a transverse trio of Golgi cells is shown in Figure 2. The coherence between these cells was highly significant, with Z scores from 7.6 to 8.5. Central peaks were rather broad, with half-height widths of 23–25 msec.

The majority of sagittal pairs (12 of 16) did not fire coherently (distances were between 150 and 1500 μ m). An example of a sagittal trio with flat cross-correlograms is shown in Figure 3. Of the four sagittal pairs that did show coherent firing, the level of coherence was significantly lower (Z scores < 4) than the level of coherence found in transverse pairs (Table 1). Subsequent histological analysis revealed that in each of these four pairs the distance between the recording sites was <200 μ m.

These findings confirm the prediction generated by our network simulations, i.e., that Golgi cells that receive common parallel fiber input are synchronized, whereas others are not, unless they are so close to each other that they may receive common mossy fiber input. The results were independent of the type of anesthetic used, because similar patterns were found for five pairs of Golgi cells recorded in three α -chloralose-anesthetized rats (results not shown).

In our network simulations (Maex and De Schutter, 1998b) synchronicity of firing usually occurs in the context of rhythmic oscillations, except when Golgi cells fire at very low rates, such as those found in our recordings (average, 7.7 spikes/sec; median

Table 1. Strength and width of coherence of firing: effect of orientation

Orientation	No. of pairs		Strength as Z score [mean (SD)]		Width (msec) [mean (SD)]
	Total	CC Z >3	All pairs	CC Z >3	CC Z >3
Sagittal	16	4	2.655 (0.813)	3.423 (0.357)	21.7 (12.4)
Transverse	26	25	6.006 (1.588)	6.101 (1.494)	29.8 (12.5)
Statistic	$\chi^2 = 23.464$		$t_{\text{diff}} = -7.806$	$t_{\text{diff}} = -2.689$	$t_{\text{diff}} = -1.197$
<i>p</i>	<0.0001		<0.0001	<0.005	0.2417

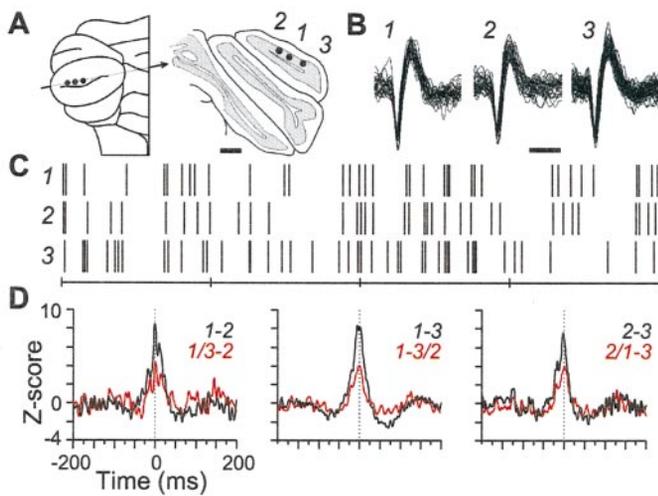


Figure 2. Three Golgi cells simultaneously recorded in Crus IIa and positioned along the transverse axis. *A*, Schematic representation of the localization of the recorded units. Scale bar, 1 mm. *B*, Superimposed records of 100 waveforms. Calibration, 1 msec. *C*, Raster plots of simultaneously recorded spike trains (4 sec sample). *D*, Cross-correlograms (1 msec bin) based on 5124 spikes of cell 1, 2862 spikes of cell 2, and 3538 spikes of cell 3, fired at rest (500 sec recording). The maximum Z scores in each of the cross-correlograms were, respectively, 8.25, 8.32, and 7.94. The red line in each graph represents the cross-correlogram between spikes of one neuron (2, 1, 3) with all spikes that were fired coherently between the other two (1/3, 3/2, 2/1); the maximal Z scores were, respectively, 4.28, 3.95, and 4.16.

interspike interval, 100 msec; Vos et al., 1999). We did observe small side peaks (Z score < 3.5) in 17 of 26 cross-correlograms of transverse pairs (e.g., Fig. 2*D*, center, right). The absence of more obvious rhythmicity could be related to the Golgi cells not firing at constant rates (Figs. 2*C*, 3*C*), and this would imply that even at rest mossy fiber input is modulated. Because particularly the rhythmicity appeared very sensitive to mossy fiber firing rate in the model (Maex and De Schutter, 1998b), fluctuating activation levels could obscure the detection of distinct side peaks in the cross-correlogram (Eggermont and Smith, 1996). In fact, oscillations at frequencies corresponding to periods at which most side peaks occurred in the present study (100–200 msec) have been observed in the granular layer of awake, behaving rats (Hartmann and Bower, 1998) and monkeys (Pellerin and Lamarre, 1997).

The model also predicted that synchronization is more accurate at higher Golgi cell firing rates (Maex and De Schutter, 1998b), such as those observed in awake animals (Edgley and Lidieth, 1987; Van Kan et al., 1993). In transverse pairs we did find a significant reverse correlation between average firing rate and the accuracy of coherence (width of central peak at half height; $r = -0.582$; $p < 0.005$) (Fig. 1*C*) and a significant positive

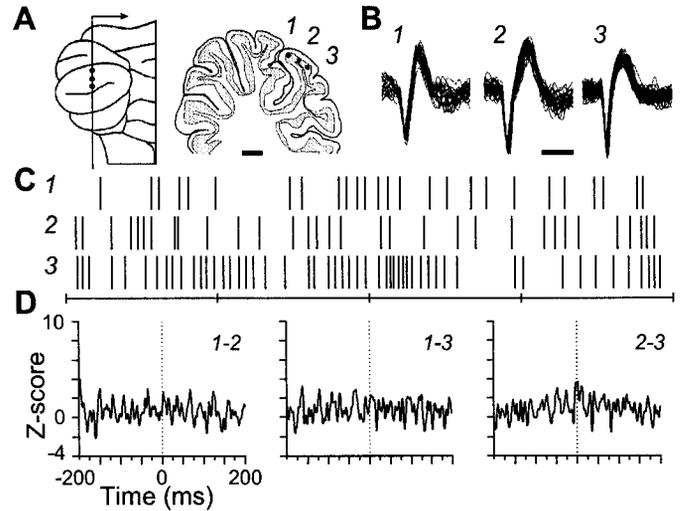


Figure 3. Three Golgi cells simultaneously recorded in Crus IIa and positioned along the parasagittal axis. See legend of Figure 2 for details and scales. Cross-correlograms were based on 3945 spikes of cell 1, 3857 spikes of cell 2, and 6531 spikes of cell 3, fired at rest (500 sec continuous recording). The maximal Z scores at ~ 0 msec (± 20 msec) were, respectively, 2.55, 1.82, and 3.83.

correlation between firing rate and coherence strength ($r = 0.497$; $p < 0.05$) (Fig. 1*D*). No significant correlations were found for the sagittal pairs (width, $r = 0.087$; $p = 0.7570$; strength, $r = 0.399$; $p = 0.1263$) (Fig. 1*C,D*).

Despite the strong correlation between firing rate and accuracy of coherence in transverse Golgi cell pairs, cross-correlogram peaks were relatively wide (Table 1). This can be attributed to two factors. First, the broad peaks could be an epiphenomenon of the lower spontaneous firing rates found in anesthetized preparations. Second, the lack of millisecond synchrony may be attributable to the low efficacy of parallel fiber synapses onto Golgi cells (Dieudonné, 1998b). The latter implies that many parallel fiber inputs have to summate to reach spiking threshold. We have recently found that this causes loose synchronization of Golgi cells in the model (Maex et al., 1998). Conversely, the sparser but stronger mossy fiber synapses (Dieudonné, 1998a) are expected to synchronize Golgi cells more tightly; there was a tendency for narrower cross-correlogram peaks for the four sagittal pairs showing weak correlations (Table 1).

The broad cross-correlogram peaks could also have resulted from nonsynchronous, phase-delayed activation of Golgi cells, the delay of which would depend on the location of the excited granule cells relative to the two Golgi cells. To uncover such nonsynchronous modes of activation, simultaneously recorded activity of transversely oriented Golgi cell trios was reanalyzed,

and cross-correlograms were generated between spikes of cell A and the spikes of cell B that were synchronous with those of cell C (time lag, ± 1 msec). If the central peak on these cross-correlograms would be systematically offset from 0 msec, this would imply a successive wave of Golgi cell activation traveling along the parallel fibers. However, for all transverse trios ($n = 4$), cross-correlograms between spikes of one cell and only the synchronous spikes between the other two had a peak centered at 0 msec (e.g., Fig. 2D, red lines). This implies that the broad central peaks were not attributable to nonsynchronous modes of activation. It suggests that the Golgi cell synchronization occurred as a rather global phenomenon along the parallel fiber axis, as in the model.

DISCUSSION

Our results confirmed two predictions of the model (Maex and De Schutter, 1998b): 1) Golgi cells that receive common parallel fiber input fire coherently, whereas activity of Golgi cells that do not receive common parallel fiber input is less coherent; and 2) the accuracy of the coherence increases with the level of network activity. Another model prediction, that granule cell activity along the parallel fiber axis is also synchronized, could not be investigated experimentally, because it is impossible to isolate single granule cell units using extracellular electrodes because of the dense packing of these very small neurons (Ito, 1984).

Although our recordings do not prove that the parallel fiber system was solely responsible for the coherence observed, the low level of coherence (Z score < 4) found for a few sagittal pairs puts an upper limit on the possible influence of mossy fibers in the synchronization process. Moreover, the parallel fibers and the poorly studied Lugaro axons (Lainé and Axelrad, 1996) are the only axons branching along the transverse axis; all other cerebellar afferents and axons branch completely (climbing fibers and inhibitory axons) or mostly (mossy fibers) along the sagittal axis (Ito, 1984; Voogd and Glickstein, 1998).

In the model (Maex and De Schutter, 1998b) synchrony is maintained over distances many times larger than the length of the parallel fiber. If common parallel fiber input to Golgi cells were the only cause of synchronization, synchrony should have decreased linearly to zero over a distance of ~ 4 mm (the length of a parallel fiber). We did not find such a relation between the strength of coherence and the transverse distance. This could be attributable to the limited sampling of "long"-distance (> 2 mm) pairs. Our recordings of Golgi cell trios (Fig. 2) suggested however that the coherence was rather global along the parallel fiber axis. And this implied that, as in the model, not only the common parallel fiber excitation but also the negative feedback of Golgi to granule cells contributed to the synchronization. Hartmann and Bower (1998) also reported widespread synchronous granular layer activity, even between two cerebellar hemispheres, but they proposed that the global synchrony in the cerebellum is of extracerebellar origin. However, a cross-hemispheric synchrony could be related to parallel fibers that cross the midline (Voogd, 1995). Furthermore, if synchronization would be of extracerebellar origin, Golgi cell pairs along the sagittal axis should have shown the same high levels of coherent firing.

The granular layer of the cerebellar cortex can be considered as an input layer, which preprocesses mossy fiber input before transmission over the parallel fibers to the output neurons, the Purkinje cells. In classic theories this input layer performs a combinatorial expansion of the input under gain control by Golgi cells (Marr, 1969; Albus, 1971). Our modeling data and the results

reported here suggest that this circuit performs, in addition, a tight control over the spike timing of both Golgi and granule cells. Although the central peaks on the cross-correlograms were relatively broad, we expect more accurate synchronization in awake animals in view of the reverse correlation between the average firing rate and the width of the cross-correlogram peak and under the assumption that firing rates will be higher without anesthesia. In addition, preliminary modeling and experimental data suggest that the coherent firing prevails with temporally and spatially modulated mossy fiber input.

In contrast to stimulus-evoked synchronous firing in cortex (Engel et al., 1997), which is thought to provide for dynamic binding of neuronal ensembles, the spontaneous synchronization of cerebellar Golgi cells may be instrumental to the transformation of spatial patterns encoded in mossy fiber input into temporal patterns on the parallel fiber system. Because of the patchy, fractured somatotopy of mossy fiber input to the granular layer (Bower and Kassel, 1990; Welker, 1987), this input shows complex spatial patterning. By synchronization of granule cell firing the spatial information encoded in mossy fiber activation patterns can be transformed into a temporal code (Hopfield, 1995). The Purkinje cells will thus receive a temporal spike pattern in which the relative position of coactivated patches is coded by the phase difference between the activity transmitted along parallel fibers originating from these different patches. These phase differences will change depending on the location along the transverse axis of the folium.

Recent optical imaging data by Cohen and Yarom (1998) suggest that the effect of parallel fiber synapses onto Purkinje cells is weak compared with that of synapses from the ascending part of the granule cell axon, because no beams of activation along the parallel fiber axis (Eccles et al., 1967) were found. Our study suggests that, in fact, such beam-like effects may instead exist at the level of synchronously activated Golgi cells. The parallel fiber spike patterns are not expected to directly activate the Purkinje cell: a coincidence detection such as the one proposed by Braitenberg et al. (1997) would not be very robust, considering the results of Cohen and Yarom (1998). As proposed in our modeling studies of Purkinje cells (De Schutter, 1995, 1998), the temporal spike patterns on the parallel fibers are thought to cause reproducible changes in the excitability of its active dendrite (Jaeger et al., 1997) and thus to affect the firing probability during subsequent input.

In conclusion, we propose that Golgi cells control the timing of granule cell spiking. The proposed role of the granular layer as a temporal encoder fits well with the general importance of timing in cerebellar function (Welsh et al., 1995; Raymond et al., 1996; Ivry, 1997; Thach, 1998).

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