# Precise spike timing of tactile-evoked cerebellar Golgi cell responses: a reflection of combined mossy fiber and parallel fiber activation?

Progress in Brain Researchx

De Zeeuw C.I., Ruigrok T.J.H. and N.M. Gerrits N.M. editors
124: 95-105 (2000)
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## Abstract

In recent years a number of papers emerged with tales of ventures in what J.I. Simpson (this Volume) named "the *terra incognita* in the cerebellar cortex": the gray zone (granular layer) between input (mossy fibers) and output (Purkinje cells). This gray zone holds feedforward and feedback circuits which pre-process afferent information before it reaches the Purkinje cells.
Some of these recent publications specifically focused on the Golgi cell, the primary inhibitory interneuron of the granular layer circuitry (Dieudonné 1998ab; Maex and De Schutter, 1998a,b; Watanabe *et al*., 1998; Vos *et al*. 1999a,b). They univocally concluded that Golgi cells do more than control the gain of parallel fiber input to Purkinje cells (see also De Schutter *et al*. this Volume), which was suggested to be their only function in the classic cerebellar theories of Marr (1969), Albus (1971) and Ito (1984).

## Introduction

Figure 1 shows a schematic drawing of the anatomical connections of Golgi cells. Golgi cells receive direct excitatory input from mossy fibers (Hámori and Szentágothai, 1966). They are also contacted by parallel fibers (Fox *et al*., 1967), which excite Golgi cells after activation of granule cells by mossy fibers. In addition, Golgi cells do not contact each other (nor do granule cells) (Palay and Chan-Palay, 1974). Being inhibitory, Golgi cells exert both a feedback (Eccles *et al*., 1966b) and a feed-forward (Precht and Llinás, 1969) inhibition of granule cell activity. The classic view of Golgi cells as local controllers of granule cell activity was inspired by descriptions of these anatomical connections.

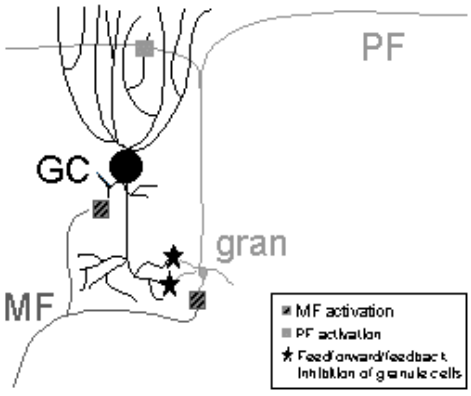


**Figure 1**
Connectivity in the granular layer. Granule cells (gran; light gray) receive excitation from mossy fibers (MF; darker gray) and send their output along their parallel fiber (PF). Golgi cells (GC; black) receive both MF (dark squares) and PF (light squares) excitation and reciprocally inhibit (stars) granule cells.

Despite the rather straightforward afferent "wiring" scheme, the characterization of the response properties of Golgi cells appeared rather

difficult in paradigms of vestibulo-ocular reflex adaptation (Miles *et al*., 1980; Atkins *et al*., 1997), locomotion (Edgley and Lidierth, 1987) or limb movement (Van Kan *et al*., 1993). We recently conducted a series of experiments to further assess firing and response properties of Golgi cells in anesthetized rats (Vos *et al*., 1999a,b). In the present chapter we give a brief account of our observations on discharge patterns of cerebellar Golgi cells in Crus I-II, evoked by punctate, tactile stimulation of the face.

## Methods

***Multi-electrode extracellular recordings***

Recordings (for full description of the recording procedure see Vos *et Al*., 1999ab) were made in the cerebellar cortex (Crus I - II) of ketamine-xylazine anesthetized, male Sprague-Dawley rats (350-500g, N=38) with tungsten microelectrodes (2 MOhm).

Signals were filtered and amplified (bandpass = 400-20,000 Hz; gain = 5,000-15,000) using a Multi-channel Neuronal Acquisition Processor (Plexon Inc., Austin, TX, USA). Spike waveforms were discriminated with a real-time hardware-implemented combined time/voltage window discriminator (Nicolelis and Chapin, 1994). Electrolytic lesions (15 micro A, 12 s, cathodal DC current) were made to mark the location of the electrode tips.

***Identification of Golgi cells***

Typically, 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). A total of 87 units were categorized as Golgi cells based on the same criteria as those used by others ( Eccles *et al*., 1966b; Miles *et al*., 1980; Edgley and Lidierth, 1987; Van Kan *et al*., 1993; Atkins *et al*., 1997): low discharge rates at rest (interspike intervals > 20 ms), long duration (> 0.8 ms) di-phasic (negative-positive or positive-negative) wave shapes, long tuning distances, no complex-spike discharges and location of the electrolytic lesion in the granular layer (e.g. Fig. 2ABC).

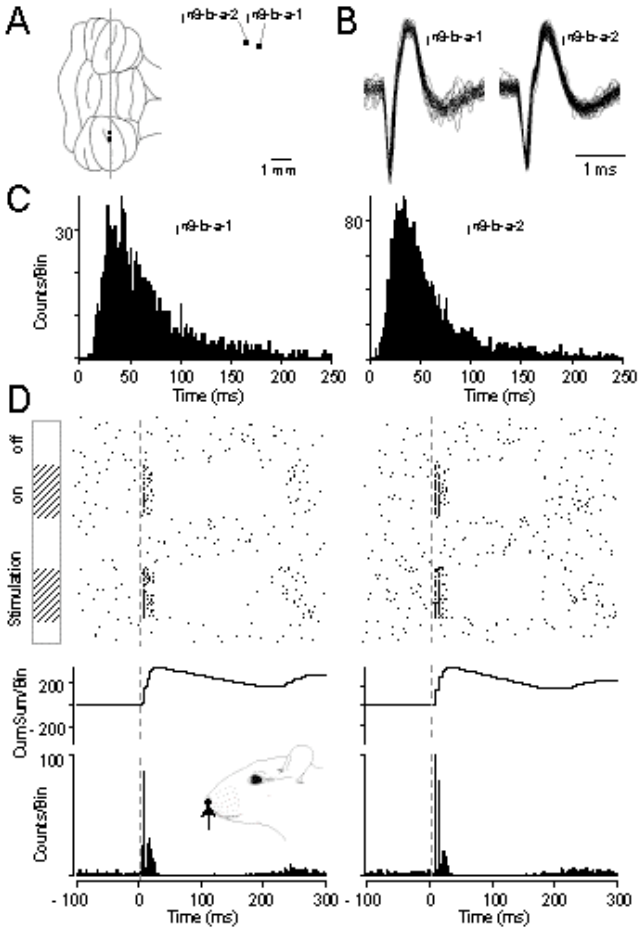

**Figure 2**
Firing and response characteristics of two simultaneously recorded Golgi cells in Crus II of a ketamine-xylazine anesthetized rat.
**A.** Schematic representation of the position of the electrodes in Crus IIa and line drawing of the transverse section with the location of the electrolytic lesions in the granular layer.
**B**. Superimposed records of 100 spikes from both units (jn8-b-a-1, jn8-b-a-2).
**C**. Interspike interval histograms (1 ms bins) based on 2040 spikes (jn8-b-a-1) and 4540 spikes (jn8-b-a-2) captured during a 400 s recording of activity at rest. Average firing rates of the cells were respectively 5.08 and 11.32 spikes/s. Median ISIs were 61 ms and 48 ms.
**D**. The rhinarium was mechanically stimulated at 1 Hz (1 mm probe, 10 ms duration). For both units, rasterized traces of recorded spikes captured on 450 successive trials are shown (-100/+300 ms from stimulus onset, indicated by dashed line; hatched bars on left of rasters indicate two periods of 100 successive trials with stimulation). Below the rasters the cumulative frequency distributions are shown for the 200 trials with stimulation (cumulative sum of spikes/bin, 1 ms bins, pre-stimulus spike counts are used as zero-offset). The lower panels show the peri-event histograms for both units (-100/+300 ms from stimulus onset, 1 ms bins; dashed line indicates stimulus onset) with the number of spikes/bin over 200 trials with stimulation. Firing rates at rest (30 ms epoch before stimulation) were respectively 5.16 and 8.51 spikes/s. Post stimulus firing rates were 58.6 and 63.6 spikes/s (30 ms epoch). The spike pattern evoked by the same stimulus is different in both simultaneously recorded units. Both units show a silent period.

In addition, Golgi cells could also be quantitatively differentiated from other cells with a non-parametric coefficient of variation (nCV) that was calculated based on the ratio between the median interspike interval and its median absolute deviation (MAD)(see Figure 2 of Vos *et al*., 1999b). Golgi cell firing at rest (average 8.4 spikes/s) appeared not more regular than simple-spike firing of Purkinje cells (n=38; average 27.9 spikes/s), but more regular than the bursting firing pattern of presumed mossy fibers (n=30; 8.75 spikes/s).

***Tactile stimulation***
Once a unit was categorized as a putative Golgi cell, and spontaneous activity was recorded, mechanical taps with a hand-held cotton-tipped wooden probe were used to explore its receptive field (RF). In addition, somatic responses were quantitatively tested in half of the rats, with controlled mechanical stimuli. A stainless steel probe (1 mm, cylindrical, flat surface, maximal excursion 2.5 mm) mounted on an electromagnetic activator (12V solenoid) and driven by a digital stimulator was precisely positioned at (at least 4) different facial loci ipsi-and/or contralateral to the recording site to deliver innocuous mechanical stimuli (<10ms). In some rats one specific locus was stimulated at different frequencies (0.5-6Hz). For each stimulus configuration the same stimulation paradigm consisting of (at least) 100 trials without stimulation, followed by (at least) 100 trials with stimulation, was repeated twice (Fig. 2D).

## Golgi cell response properties

***Golgi cell receptive fields are large***
Of all Golgi cells tested (N=87), most responded to tactile stimulation (84 %). Responsive Golgi cells had facial receptive fields, which is consistent with previously described trigeminal-evoked responses of granule and Purkinje cells in Crus I and II (e.g. Shambes *et al*., 1978; Bower *et al*., 1981). In contrast to the patchy organization of mossy fiber projections to Crus I and II (Glickstein *et al*., 1994), and the fractured somatotopic maps found for granular layer field potentials (Shambes *et al*., 1978; Bower *et al*., 1981) or Purkinje cells (Bower and Woolston, 1983) in these lobules, most Golgi cells recorded in our study (Vos *et al*., 1999b) had rather large RFs. In 67% of the Golgi cells tested, the RF covered the entire territory of the maxillary branch of the trigeminal nerve (including vibrissal pad, furry buccal pad, rhinarium and upper lip) ipsilateral to the recording site. Sometimes the RF extended to territories of the other trigeminal nerve branches (14%), or included contralateral parts (35%) (e.g. Fig. 4).
Extended Golgi cell RFs have also been reported by others. Edgley and

Lidierth (1987) found 85/87 Golgi cells to respond to tactile stimulation in the awake cat, the majority of which had large and bilateral RFs. Also in halothane-anesthetized rats, an unspecified proportion of Golgi cells responded to peripheral stimulation (Schulman and Bloom, 1981). In barbiturate-anesthetized animals (7 monkeys, 11 cats) only few Golgi cells (3/18) responded to somatosensory stimulation (Van Kan *et al*. 1993). In awake monkeys however, all of the Golgi cells tested (5/5) responded to passive joint manipulation, though they lacked directional specificity (van Kan *et al*., 1993). For Golgi cells recorded in the cerebellar flocculus of the awake rabbit and the awake monkey a great diversity of modulation patterns was found (Miles *et al*., 1980; Atkins *et al*., 1997). The latter two findings are, like the presence of large tactile RFs observed by others and in the present study, an indication of an enormous convergence of excitatory inputs onto single Golgi cells.

***Excitatory responses are followed by a silent period***

All tactile-evoked responses were typified by a long silent period (duration: 13-200ms) that followed the initial "excitatory" response (latency: 28-69 ms; e.g. Fig. 2D, Fig 5D). This silent period was quite noticeable because all cells were spontaneously active before stimulus onset. The duration of this silent period appeared to be related to the amplitude of the excitatory component (Vos *et al*., 1999b, Figure 8). Sometimes a "rebound" increase in activity was observed at the end of the silent period (e.g. Fig. 3D).

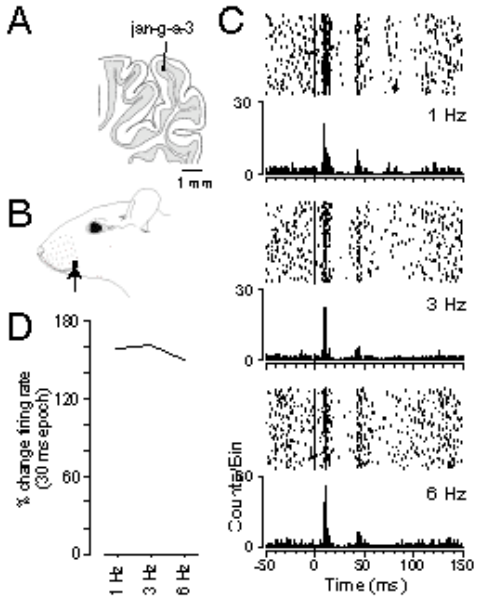


**Figure 3**

Effect of stimulation frequency on a Golgi cell response.

**A.** Schematic representation of the position of the electrode in Crus IIa and line drawing of the sagittal section with the location of the electrolytic lesion in the granular layer.

**B.** The same stimulus (1 mm probe, 10 ms duration) was applied to the hairy skin between the gamma vibrissa and vibrissa E1 at 1, 3 and 6 Hz.

**C.** Rasterized traces and PSTHs (-50/+150 ms from stimulus onset; 1 ms bins) with the responses (average spikes/s) to each stimulus frequency (200 trials each).

**D.** Line graph representing the percent increase in firing rate (30 ms epochs) evoked by each stimulus frequency. Response amplitudes did not differ between the stimulation frequencies.

Similar silent periods have been observed in other Golgi cell preparations, e.g. in anesthetized cats in response to parallel and mossy fiber stimulation but not to inferior olive stimulation (Eccles *et al*., 1966b), in awake cats in response to peripheral stimulation (Armstrong and Drew, 1979), and in anesthetized rats in response to inferior olive stimulation (Schulman and Bloom, 1981).

The cause and function of this silent period remain unclear. Silent periods have been observed in visual and somatosensory pathways and this suggests that a lack of mossy fiber activation underlies the silent period. In

fact, Eccles *et al*. (1971) reported that discharges of presumed mossy fibers could be silenced for almost 100 ms, even in the absence of any initial excitation.
However, factors intrinsic to Golgi cells or to the cerebellar circuitry may contribute to the appearance of the silent period. In a study of cerebellar interneurons, Eccles *et al*. (1966a) observed that parallel fiber stimulation initially facilitates responses of presumed inhibitory interneurons to subsequent parallel fiber excitation. The initial facilitation gives way to a marked depression of the responses to new parallel fiber input that arrives 50-500 ms after the conditioning stimulus. Such a post-activation depression could also underlie the observed silencing of the Golgi cell, although we did not test whether the cells were actually non-responsive during the silent period.
In cerebellar slice preparations, a strong tonic form of granule cell inhibition was recently observed (Brickley *et al*., 1996; Wall and Usowicz, 1997). This tonic inhibition was postulated to be caused by Golgi cell activity resulting in spillover of GABA which activates high affinity receptors (Rossi and Hamann, 1998), and its duration should thus be correlated with the amplitude of the Golgi cell response. Since tonic granule cell inhibition causes an interruption of parallel fiber excitation to the Golgi cell, the effect of diminished or absent mossy fiber input could be enhanced. Other evidence that supports this hypothetical scenario is the strong on-beam inhibition evoked by short bursts of parallel fiber excitation, and observed in an isolated guinea pig cerebellum (Cohen and Yarom, 1998).
A last possibility is that the stimulus-induced mossy fiber activation evokes a (damped) oscillation in the granular circuit, as predicted by Maex and De Schutter (1998). In the raster plots shown in Figure 3C (especially for 1 Hz stimulation), oscillatory "ripples" in the Golgi cell response can be discerned.

***Timing of tactile-evoked spikes is precise and location dependent***
Discharge patterns of cerebellar Golgi cells, evoked by punctate, tactile stimuli, showed a strict temporal patterning. The timing of the evoked spikes appeared very robust and precise over trials (e.g. Fig. 2D, 3D, 5D). In order to study the temporal characteristics of the evoked responses in more detail, distinct peaks on "high resolution" peri-stimulus time histograms (0.25 ms bins, 0-55 ms) were fitted with Gaussians (see Vos *et al*., 1999b; e.g. Fig. 4B). Each PSTH-peak represents the fact that in a substantial number of stimulus trials, a spike was fired at a specific, fixed latency from stimulus onset. The fitted PSTH-peaks were used to quantify the evoked response profiles. For each PSTH the number of "significant" peaks was determined, and for each peak, the latency (mean of the Gaussian), the accuracy of timing (standard deviation of the Gaussian) and the robustness (percent of trials contributing a spike to the peak) were deduced.
In agreement with known trigemino-cerebellar (e.g. Watson and Switser, 1978; Woolston *et al*., 1981; Jacquin *et al*., 1982; Huerta *et al*., 1983) and cortico-ponto-cerebellar (e.g. Welker, 1987; Brodal and Bjaalie, 1997) projections, Golgi cell responses showed an early (5-10 ms) and a late (13-26 ms) "excitatory" component (Fig.4B). In most instances, both the early and the late component appeared as a single peak on the PSTH (Fig. 4B). Sometimes, the first component consisted of two distinct PSTH-peaks with a short (< 4 ms) interval (e.g. Fig 2D: unit jn8-b-a-2; Fig 4B: stimulation between vibrissae ED-56). Other responses consisted of the early or the late component alone (Fig 4B: only late component: stimulation around the genal vibrissae; only early component: contralateral stimulus locations). Figures 3D and 4B demonstrate that not the stimulus frequency but the stimulus location determined the temporal pattern of the spikes (see also Vos *et al*., 1999b). The use of another anesthetic (alpha-chloralose) did not affect these response characteristics (Fig. 5D), although it slowed down the firing rate at rest considerably (Fig. 5E).

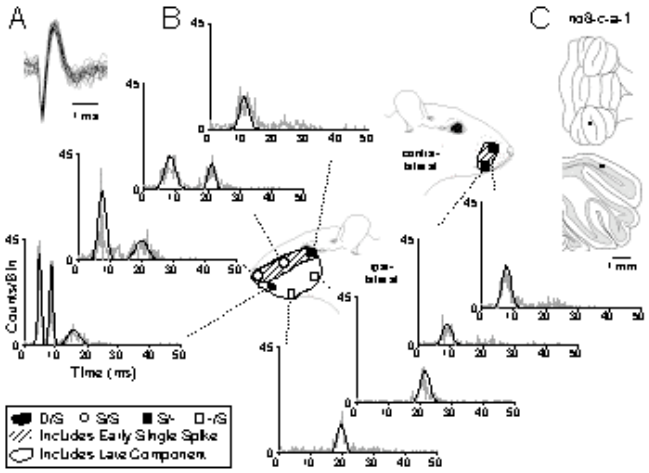


**Figure 4**

Large receptive fields of Golgi cells. A. Superimposed records of 100 spikes recorded from unit no8-c-a-1.

**B.** The same stimulus (1 mm probe, 1 Hz) was applied to nine different locations. High resolution PSTHs (0/50 ms from stimulus onset, 0.25 ms bins) based on stimulation of each of the locations (200 trials each) including the gaussian fit for each of the peaks are shown. The exact location from which each of the response profiles were evoked is indicated on graphical representations of the rat's face, contra- and ipsilateral to the recording site. The relation between the receptive field size and spike timing is illustrated: the facial field from which responses with an early double PSTH-peak response (black area), responses with an early single PSTH-peak response (shaded area), and responses that include a late component (white area) are drawn on the face-drawings.

**C.** Schematic representation of the position of the electrode in Crus IIa and line drawing of the transverse section with the location of the electrolytic lesion in the granular layer.

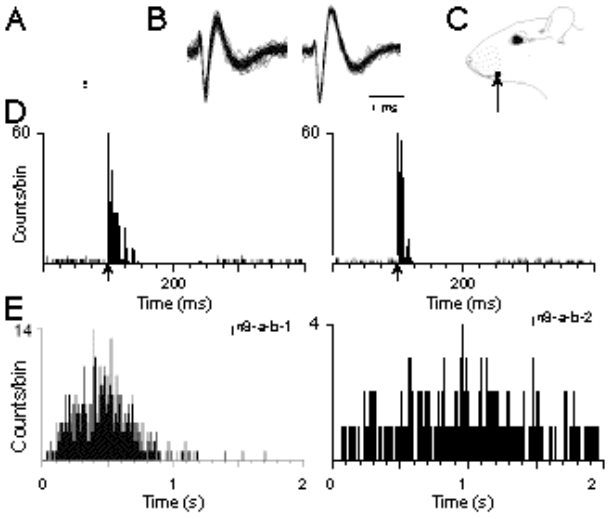


**Figure 5**

Responses of Golgi cells in alpha-chloralose-anesthetized rats.

**A.** Schematic representation of the position of the electrodes in Crus II.

**B.** Superimposed records of 100 spikes from both units.

**C.** The hairy skin between around the E1-vibrissa was mechanically stimulated at 1 Hz (1 mm probe, 10 ms duration). **D.** PSTHs for both units (-200/+600 ms from stimulus onset, 2 ms bins; arrows indicate stimulus onset) with the total number of spikes/bin over 200 stimulation trials. Post stimulus firing rates were 42 and 32 spikes/s (30 ms epoch). Like in ketamine-anesthetized rats, the spike pattern evoked by the same stimulus is different in both simultaneously recorded units. Both units show a silent period. **E.** ISIs (4 ms bins) based on 797 spikes (jn8-a-b-1) and 261 spikes (jn8-a-b-2) captured during a 360 s recording of activity at rest. Average firing rates of the cells were respectively 2.17 and 0.71 spikes/s. Median ISIs were 457 ms and 1106 ms. nCVs were 0.32 and 0.38.

***Golgi cell responses reflect trigemal and cortico-pontine input***

The latencies of the early and the late component of the Golgi cell response, match closely those of the early and late response component of granular layer field potential responses which were recorded in Crus II under similar experimental conditions (e.g. Morissette and Bower, 1996). This close match strongly suggests that the first component of the Golgi cell responses results from direct trigemino-cerebellar projections (e.g. Woolston *et al*., 1982), and the second component from cortico-pontine projections (e.g. Morissette and Bower, 1996)(Fig. 6 lower part).

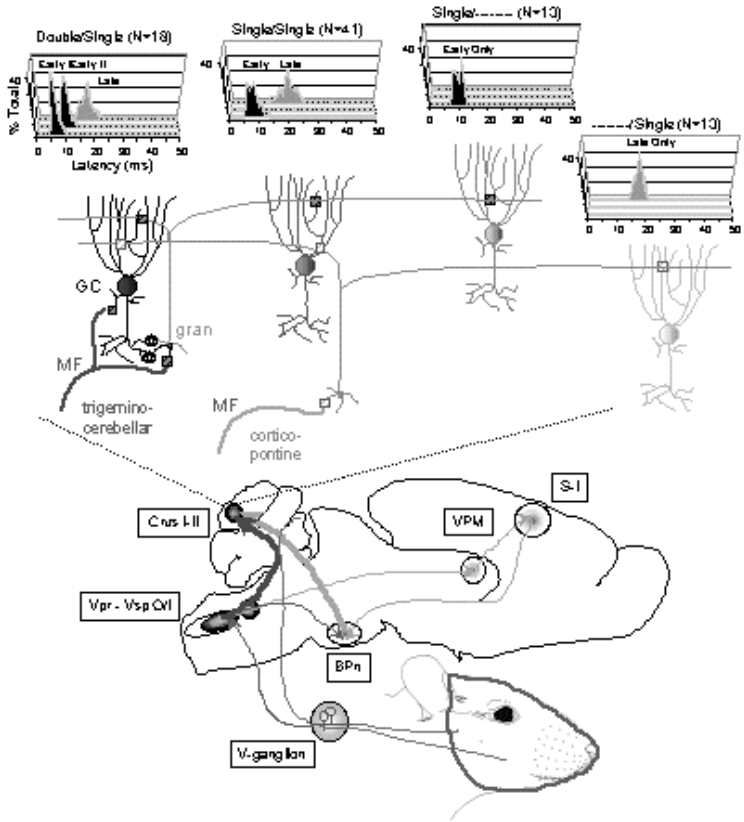


**Figure 6**

Hypothesis: temporal pattern of Golgi cell responses reflects combined mossy fiber and parallel fiber activation.

**Lower part:** Trigeminal information reaches the cerebellum directly via trigemino-cerebellar projections (dark arrows) and indirectly via cortico-pontine projections (light arrows) (trigeminal pathways to cerebellum are indicated: V-ganglion, trigeminal ganglion; BPn, Basilar Pontine nuclei; VPM, Ventral Posteromedial Thalamic nucleus; SI, somatosensory cortex; Vpr, Trigeminal nucleus Principalis; Vsp O/I, pars Oralis and Interpolaris of Trigeminal subnucleus Spinalis).

**Upper part:** In the cerebellar cortex, trigeminal activation of mossy fibers will excite Golgi cells either "mono-synaptically" or via the parallel fibers. In view of the shorter latency (see frequency histograms showing the number of "peaks" per 1 ms bin, on top), and other properties (see text) of responses with an early double peak, we hypothesize that these responses are the result of excitation by direct trigemino-cerebellar mossy fiber input. Single peaks are hypothesized to result from parallel fiber activation. The late response component is hypothesized to result from corticopontine input.

Although both projections arrive in the cerebellar cortex as mossy fibers, it is not very likely that the whole of each Golgi cell response was caused by direct mossy fiber input. Mossy fiber input to Crus I-II is fractured (Shambes *et al*., 1978; Bower *et al*., 1981; Bower and Kassel, 1990) and trigeminal and cortico-pontine mossy fiber projections largely overlap (e.g. Voogd and Glickstein, 1998). Thus if Golgi cell responses would result from pure mossy fiber excitation alone they should have had small RFs corresponding to one or, at most, a few patches (see Welker, 1987 for review). In contrast, Golgi

cells had very large RFs, which probably reflected an important excitation by parallel fibers.
Parallel fibers can, because of their length (Pichitpornchai *et al*., 1994) originate in many different patches. As such, they carry input from several parts of the rat's face outside the mossy fiber projection field, onto the same Golgi cell. Some patches in Crus II have contralateral or bilateral RFs (Welker, 1987) which could explain the bilateral RFs we observed in 41% of the Golgi cells.

***Double peak responses may result from "monosynaptic" mossy fiber activation***

In view of the observations that responses with an early double peak had (a) significantly shorter delays, (b) a significantly higher spike timing accuracy (i.e. less jitter), (c) a larger amplitude, and (d) a more restricted RF (e.g. Fig 4B), compared to other response components, we hypothesize that they resulted from a strong, direct mossy fiber input (see Vos *et al*., 1999b). For most "double peaks", the second peak was not much smaller than the first peak (e.g. Fig. 4B). This indicated that spikes were fired at both latencies in about the same number of trials. These "double spikes" may be a reflection of the presence of a doublet in the afferent mossy fiber input. It is also possible that the first spike results from mossy fiber activation and the second spike from subsequent parallel fiber activation. Least likely is the possibility that Golgi cells respond with "doublets" to single spike mossy fiber input.
We further hypothesize that early single peak components (Fig. 6) were produced by parallel fiber excitation which was delayed and less precise in timing because of the slow and variable parallel fiber conduction velocities (Bernard and Axelrad, 1991; Vranesic *et al*., 1994). It should be stressed that PSTH-profiles with and those without an early double peak were observed in the same individual Golgi cell (Fig. 4B). This rules out the possibility that all early double peak responses were in fact recorded directly from mossy fibers (and not from Golgi cells).
Since responses with only one component also had large RFs (e.g. Fig. 4B), it is most likely that they reflect a purely parallel fiber evoked event: either only the trigemino-cerebellar input (only early component), or only the cortico-pontine input (only late component). Single peaks also had significantly larger standard deviations (i.c. were less accurately timed; see Vos *et al*., 1999b). The latter is consistent with the assumption that the transmission over the parallel fibers weakens with increasing distance from the original mossy fiber input.

## Conclusions

The somatic receptive fields of Golgi cells recorded in Crus I and II of anesthetized rats were larger than expected based on known mossy fiber projection patterns in this region. The timing of the evoked Golgi cell discharges appeared remarkably precise and robust, and depended on the location of the stimulus within the RF. The presence of an early and a late component in the evoked responses probably reflected converging trigemino-cerebellar and cortico-ponto-cerebellar inputs. We also hypothesized that the early double-spike components resulted from direct mossy fiber activation, and that single spike components were evoked by parallel fiber inputs (Fig. 6).
The temporal and topographical characteristics of the somatic responses do not completely fit the traditional theories of cerebellar function which assume a pure gain control function of Golgi cells (Marr, 1969; Albus, 1971). Our results may necessitate a re-evaluation of their role in cerebellar function.

## Acknowledgements

The authors wish to thank Inge Bats for the photography, and Evelyne De Leenheir and Ursula Lubke for the histology. We gratefully acknowledge the technical wizardry of Mike Wijnants. We also like to thank the reviewers for their comments on an earlier version. This research was funded by EC

contract BIO4-CT98-0182, by IPA Belgium (P4/22) and by the Fund for Scientific Research - Flanders (FWO-Vl) (# 1.5.504.98). BPV and EDS are supported by the FWO-Vl.

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