

Coding in the Granular Layer of the Cerebellum

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Abstract

In this paper we formulate a new theory of how information is coded along the parallel fibers in the cerebellar cortex. A question which may arise is why such a new theory is needed at all. Previously we have argued that the dominant theory of cerebellar coding, i.e. the perceptron learning theory formulated by Marr (1969) and Albus (1971) that was extended by Ito (1982; 1984) and more recently by Mauk and colleagues (Raymond et al., 1996; Mauk, 1997), does not comply with current experimental data. The basic assumption of these theories, that long-term depression (LTD) is the mechanism by which memory traces are coded at the parallel fiber to Purkinje cell synapse and that LTD induction is controlled by the climbing fiber input, is not beyond doubt (De Schutter, 1995; 1997). For example, recent data showing that LTD can be induced by pure parallel fiber excitation without any conjunctive signal (Hartell, 1996; Eilers et al., 1997; Finch and Augustine, 1998) does not conform to the theory proposed by Marr, Albus and Ito. Instead these findings indicate that the climbing fiber signal is not required to induce learning at the parallel fiber synapse and that, in fact, LTD may have quite a different function. Moreover, studies using transgenic mice in which LTD induction was blocked have raised serious doubts about a link between LTD and cerebellar motor control (e.g. De Zeeuw et al., 1998) and about the necessity of cerebellar LTD for eyeblink reflex conditioning (reviewed in De Schutter and Maex, 1996). As we have discussed this issue extensively elsewhere (De Schutter, 1995; De Schutter and Maex, 1996; De Schutter, 1997), we will not further address it here.

Instead we will focus on the function of the input layer of the cerebellar cortex, the granular layer, and the mossy fiber projections to it. As this layer processes the mossy fiber input it makes sense to first try to understand how it transforms inputs to the cerebellum into parallel fiber signals before considering in more detail the role of LTD at the parallel fiber synapse. Such a study is necessary, especially now that recent experimental data have raised doubts about the effectiveness of parallel fiber input in exciting Purkinje cells (Cohen and Yarom, 1998; Gundappa-Sulur et al., 1999). Most of the data presented and reasoning developed in this chapter concern the hemispheres of the rat cerebellum and the corticopontine somatosensory projections to this region. This emphasis reflects both our own work and the wealth of data available on these parts of the cerebellum. Considering the conserved cytoarchitecture from archi- to neocerebellum (Palay and Chan-Palay, 1974; Ito, 1984) it seems reasonable to expect that our conclusions about the neocerebellum will also apply to the rest of the cerebellum.

A short review of the anatomy and physiology of the granular layer

In this section we briefly introduce the reader to both well known facts and more recent data on the granular layer of the cerebellar cortex. As mentioned before we focus on the mossy fiber system which is numerically the most important input to the cerebellum (Murphy and Sabah, 1971; Brodal and Bjaalie, 1992). For the processing of mossy fiber input the anatomy of cerebellar cortex can be approximated by a two-layered network. The granule cell input layer encodes the incoming mossy fiber signals and transmits them through the parallel fiber system to the output layer, consisting mainly of the Purkinje cells. In both layers neural activity is controlled by inhibitory neurons, the Golgi cells in the input layer, and the basket and stellate cells in the output layer.

Because of the large number of granule cells (about 101 billion in man;

Andersen et al., 1992), the granule cell to Golgi cell ratio is very high. Recent estimates of a ratio of 400 (Korbo et al., 1993) are lower than those used previously (Ito, 1984), but all these studies have probably underestimated the ratio as they assumed that all large neurons in the granular layer are Golgi cells which is not the case (Dieudonné and Dumoulin, 2000; Geurts et al., 2000). Mossy fibers activate both the excitatory granule cells and the inhibitory Golgi cells in the granular layer (Fig. 1).

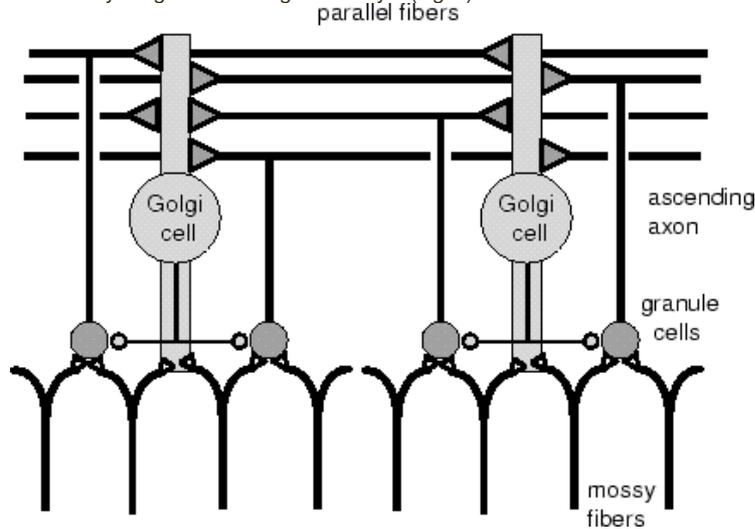


Figure 1

Schematic representation of the organization of the granular layer of the cerebellum, transverse view. Mossy fibers originating external to the cerebellum excite both granule and Golgi cells, granule cells excite by their long parallel fibers Golgi cells, and Golgi cells inhibit granule cells. Each granule cell receives about 4 mossy fiber inputs and about 10 inhibitory contacts but it is unclear whether these come from different Golgi cells or not. The number of parallel fiber contacts onto Golgi cells is not known.

Each granule cell receives input from multiple mossy fibers, but physiological recordings suggest that mossy fibers projecting to a particular region code similar information (see below and Bower et al., 1981). The granule cell axon has an ascending part (Gundappa-Sulur et al., 1999) which may have a strong excitatory influence on overlying Purkinje cells (Bower and Woolston, 1983; Cohen and Yarom, 1998) and then splits into two parallel fiber segments. The parallel fibers do not only transmit information to the Purkinje cell output layer, but also provide additional excitatory input to Golgi cells. Each Golgi cell in turn inhibits the many granule cells present within the range of its axonal arbor (Eccles et al., 1966). Unique to the granular layer circuit is the absence of inhibitory connections between Golgi cells and of excitatory connections between granule cells. Combined with the parallel fiber excitation of Golgi cells and their inhibition of granule cells, this means that it contains pure feedback inhibition loops. In addition the direct excitation of Golgi cells by mossy fibers forms a feed-forward inhibition connection.

Recently cerebellar slice recordings have provided additional insights in granule and Golgi cell physiology. Granule cells are regularly firing neurons which do not show adaptation (D'Angelo et al. 1995; Brickley et al. 1996). In rat cerebellar slices they have a rather high threshold, requiring co-activation of two or more mossy fiber inputs to fire the cell (D'Angelo et al. 1995). The mossy fiber to granule cell synapse can undergo long-term potentiation (LTP; D'Angelo et al., 1999) and under particular conditions granule cells may show burst firing (D'Angelo et al., 1998).

Golgi cells are spontaneously active in slice (3-5 Hz; Dieudonné, 1998) and show firing rate adaptation upon current injection. This firing rate adaptation plays an important role in how these cells synchronize in vivo (see below and Maex et al., 2000).

The fractured somatotopy of mossy fiber projections

The response characteristics of the granular layer to tactile stimulation have been studied extensively in the cerebellar hemispheres of the anesthetized rat. At the level of field potentials which probably reflect the activation of mossy fiber synapses, one finds a fractured somatotopy of the tactile receptive fields (Shambes et al., 1978; Welker, 1987; Bower and Kassel, 1990). This means that the receptive field map is a mosaic of small patches

(on the order of a few 100 μ m diameter), each representing a different part of the body surface (Fig. 2).

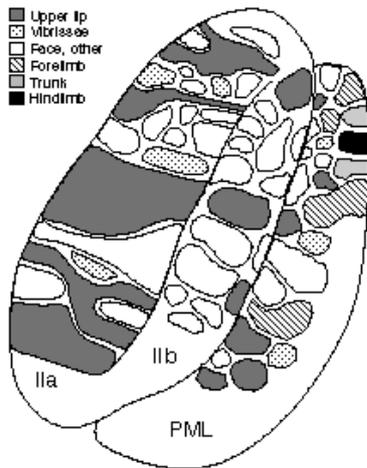


Figure 2

The tactile receptive field map of the cerebellar folia crusIIa, crusIIb, and the paramedian lobule (PML). Each patch represents either ipsilateral, contralateral or bilateral responses. The patch-like mosaic representation of different body parts, with adjacent patches often receiving projections from non-adjacent body parts, has been termed fractured somatotopy. The schematic map shown in this figure emphasizes the multiple representations of the upper lip. Modified from Welker (1987) and Bower and Kassel (1990).

Furthermore, each particular input location, e.g. the upper lip region, is represented multiple times, but always surrounded by different neighboring patches. This particular arrangement of the receptive fields, combined with the dominance of the ascending component of the granule cell axon (Bower and Woolston, 1983; Gundappa-Sulur et al., 1999), has led Bower (1997) to propose that the parallel fibers may have a role different from the ascending component. The parallel fiber would carry context signals from distant patches to the Purkinje cells which integrate these signals with the dominant local mossy fiber input from the underlying patch.

The field potentials recorded in each of the patches in response to tactile stimulation contain two components. The early one (8-10 ms delay) is caused by a direct pathway from the trigeminal nuclei, while the late one (16-22 ms delay) reflects mossy fiber activation through a thalamo-cortico-ponto-cerebellar loop (Morissette and Bower, 1996). The two separate mossy fiber pathways project to the same patches in cerebellar cortex (Bower et al., 1981), though the pontocerebellar mossy fibers tend to have a more diffuse projection and carry more often bilateral signals than the trigeminal ones (Morissette and Bower, 1996).

Recently we have started recording the responses of inhibitory Golgi cells in these areas to tactile stimulation (Fig. 3) (Vos et al., 1999b; 2000).

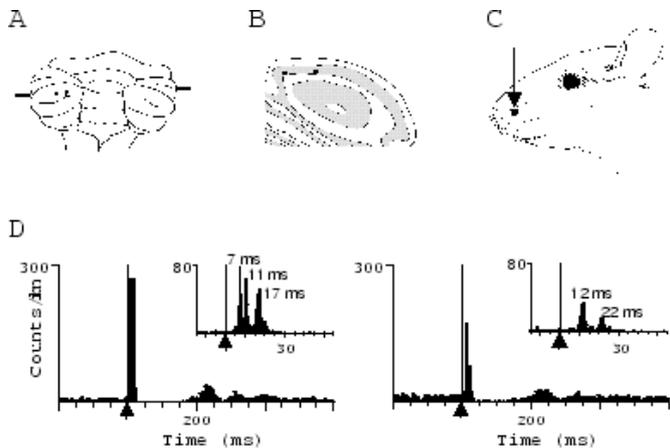


Figure 3

Response of two Golgi cells to tactile stimulation. A: Recording sites in crus II marked on top view of the cerebellum. B: Same on a transverse section. C: Location of the tactile stimulus. D: Responses of the two cells, in both cases the complete response

over 600 ms following the stimulus (notice the long silent period) and a blow up of the initial response (first 50 ms) are shown. Because of the double early peak (7 and 11 ms) the cell to the left is presumed to receive direct trigeminal mossy fiber input, the one to the right is activated through parallel fiber synapses. Both cells show an early trigeminal (< 15 ms) and late corticopontine component. Modified from Vos et al. (1999b).

In contrast to the fractured somatotopy observed in field potential recordings, Golgi cell receptive fields are very large and often bilateral. They usually also reflect the consecutive activation of the two different mossy fiber pathways, with delays of the respective peak responses which are similar to those observed in the field potential recordings. The large receptive fields observed in Golgi cell recordings are probably due to the activation of each Golgi cell by parallel fibers originating from patches with different input representations. In addition, for most Golgi cells it is possible to find a particular response pattern which has a trigeminal component consisting of two or more sharp and highly accurate peaks (Fig. 3). This specific response pattern can be evoked from only one location on the rat's face and presumably reflects the direct activation of the Golgi cell by mossy fibers in the local patch (Vos et al., 1999b; 2000).

Another intriguing property of the Golgi cell responses is the long silent period following the initial excitatory response (Fig. 3; Vos et al., 1999b; De Schutter et al., 2000). As Golgi cells are spontaneously active this silent period is quite noticeable. Similar silent periods are also found in other parts of the somatosensory system (Mountcastle et al., 1957; Mihailoff et al., 1992; Nicoletis and Chapin, 1994), where they are assumed to be the consequence of local feedforward inhibition (Dykes et al., 1984). Note, however, that in somatosensory cortex such silent periods are observed in excitatory neurons while inhibitory neurons remain active (Brumberg et al., 1996). This is clearly not the case in the granular layer where a silent period is observed in the inhibitory Golgi cell.

Coding in the corticopontine pathway

Knowing the properties of the corticopontine pathway is important as this may provide clues to what type of information the cerebellum wants to receive. Compared to the situation in the cerebellar hemispheres the mapping from the neocortex to the pontine nuclei (PN) is relatively simple. In the developing rat, axons originating in restricted cortical regions grow into widespread but specific lamellar subspaces in the PN (Leergaard et al., 1995, Fig. 4A).

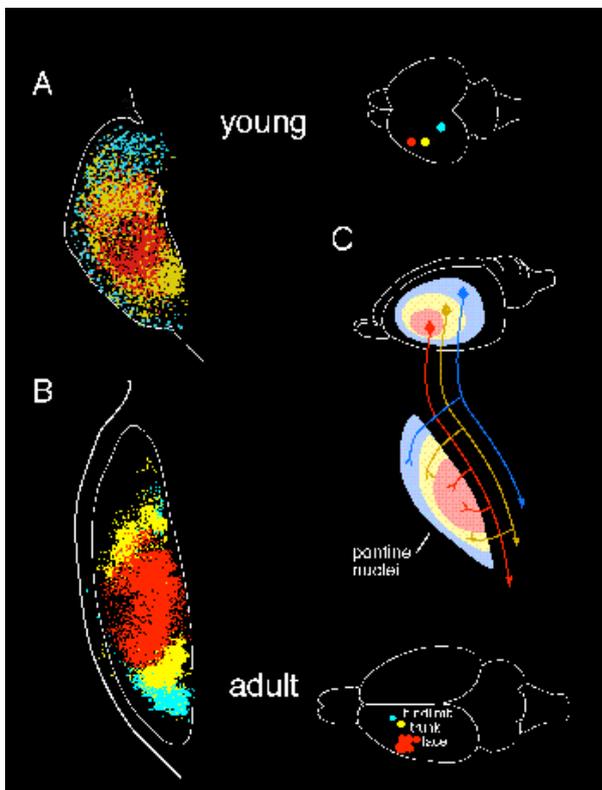


Figure 4

The orderly topographic mapping of the cerebral cortex onto the pontine nuclei in developing and adult rats. A: Projections in the developing rat. Sagittal clip plane, 200 μ m thick, from a 3-D computerized reconstruction of the PN. Rostral is upwards and ventral to the left. Data from multiple single-tracing experiments (injection sites shown on inset drawing of the cerebral hemisphere) are superimposed in one model. Dots represent the distribution of labelled axons in the PN. A shift in cortical site of origin (red - yellow - blue) corresponds to an internal-to-external shift of distribution in the PN, largely preserving neighbouring relationships. B: Adult rat projections from three major adjacent SI body representations. Presentation as in A. Note that the representations of the trunk (yellow) and hindlimb (blue) surround the representation of the face (red). The adult PN contains multiple representations for each body parts, but overall neighbouring relationships of the SI map are preserved. C: Cartoon of the Leergaard et al. (1995) hypothesis explaining the establishment of general topographic organisation in the rat corticopontine system. Temporal gradients, from early to late, are illustrated by the colours red-yellow-blue. Early arriving corticopontine fibres innervate the early established central core of the PN, whereas later arriving fibres innervate progressively more external volumes. (A) and (C) are modified from Leergaard et al. (1995) and (B) from Leergaard et al. (2000).

There is an orderly topographic relationship between cortical sites of origin and the PN lamellar target regions, possibly related to temporal gradients operative within the cortex and PN (Fig. 4C). The anterolateral part of the cortex projects to an internal, central core of the PN, ventral to the descending fiber tract. Cortical sites at increasing distance from this anterolateral region innervate progressively more external lamellar subvolumes. This 3-D pontine topographical arrangement observed in young animals preserves the overall neighboring relationships of the cortical map.

Corticopontine projections in adult animals have classically been described as topographically organized (for review, see Brodal and Bjaalie, 1992). Compared to the initially widespread projections in the young animal, adult projections are more restricted and the continuous lamellar pattern is broken into pieces, described as patches or clusters within lamellar regions (Bjaalie et al., 1997; Leergaard and Bjaalie, 1998; Leergaard et al., 2000a). In single sections these separated patches may be interpreted as the substrate for the fractured map in cerebellar cortex. But, as neighbor relationships among the multiple patches or clusters of terminal fields in the PN largely reproduce those found in the neocortex (Leergaard and Bjaalie, 1998; Leergaard et al., 2000a), the overall mapping of the cortex onto the PN is primarily continuous, and not fractured. An example is shown in Figure 4B. With the use of anterograde axonal tracing, a sequence of electrophysiologically defined cortical primary somatosensory (SI) body representations (face - trunk - hindlimb) is here seen to project onto the PN in an orderly inside-out fashion. The face projection occupies a central core region of the PN, whereas the projection from the adjacent trunk representation surrounds this central core. The SI hindlimb projection is located further away, in a more external location of the PN. There is no mixing of the projections from these SI body representations in the pontine map. What then happens at a smaller scale? For example, could there be a fractured projection from smaller regions of SI onto the PN? We are currently studying the detailed organization of the projection from the SI face area with double anterograde tracing from individual whisker barrels and 3-D computerized reconstruction (Leergaard et al., 2000b). Again, we observe a primarily organized projection pattern.

Furthermore, we have started recording the responses in the PN to peripheral stimulation (Eycken et al., 2000). When the recording electrode is advanced in steps of a few micrometers through the PN, locations of tactile receptive fields change gradually. We have so far not observed any abrupt transitions or major jumps from one body region to another, as would be expected from a fractured map.

While the mapping of the neocortex onto the PN may be relatively simple in terms of cartography, it becomes more complicated if one considers one of the stimulus attributes being transmitted, i.e. the representation of different receptive fields. This issue has been studied in the somatosensory and the visual system. Thus, the projection from SI cortex to PN contains a more even distribution of distal versus proximal body representations than SI itself (Øverby et al., 1989; Vassbø et al., 1999). Similarly, the corticopontine projection from several visual cortical areas has a more even distribution of foveal versus extrafoveal representations than the neocortex (Bjaalie and Brodal, 1983; Bjaalie, 1985, 1986).

It is known that distal body parts are emphasized in the somatosensory

cortical areas, in the sense that they occupy disproportionately larger cortical volumes (Nelson et al., 1980). If this emphasis were maintained in the pathway from somatosensory areas to the cerebellum, one would expect even densities of corticopontine neurons within each somatosensory area. With the use of retrograde axonal tracing and cortical map reconstruction, we have found uneven densities of corticopontine neurons in SI of the cat (Øverby et al., 1989) and SI (area 3b) and areas 1 and 2 of the monkey (Vassbø et al., 1999). In these areas and species, the body parts with the largest cortical magnification factors always contain the lowest densities of corticopontine neurons. Figure 5 exemplifies this principle in monkey area 3b.

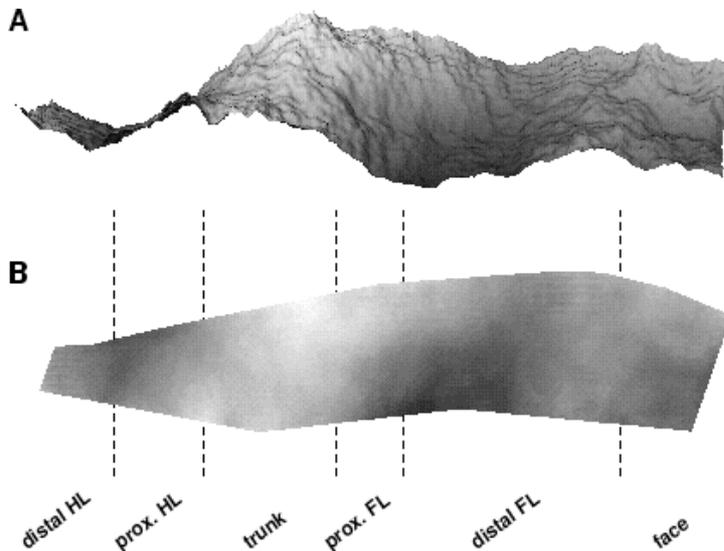


Figure 5

Flattened map of the cynomolgus monkey area 3b, showing density gradients of corticopontine cells in shades of grey. White indicates high density; dark grey low density. The PN was injected with large amounts of wheat germ agglutinin horseradish peroxidase and the retrogradely labelled neurons in the cortex were quantitatively mapped. A: Three-dimensional landscape presentation of the density distribution. B: Two-dimensional density map. Dashed lines indicate the approximate boundaries of the major body representations in area 3b, as outlined by Nelson et al., (1980). Note that the highest densities of corticopontine neurons are found in the representations of the trunk, proximal hindlimb (HL), and proximal forelimb (FL). The same pattern is found in other postcentral somatosensory areas. Modified from Vassbø et al. (1999).

It can be seen that regions representing the trunk and proximal limbs contain higher densities of corticopontine neurons than regions representing distal limbs. The lower densities are particularly evident in the distal forelimb representation. Thus, the distal forelimb representation, which is known to be strongly emphasized in terms of cortical volume, appears to be de-emphasized in the corticopontine projection, or not emphasized to the same extent as in the cortex.

The distribution of corticopontine neurons in visual areas of the cat follows the same principles. Similar cortical map reconstructions (Bjaalie and Brodal, 1983; Bjaalie, 1985, 1986) show that regions representing the central visual field (analogous to distal forelimb) contain lower densities of corticopontine neurons than regions representing the peripheral visual field (analogous to proximal body regions). But in terms of the number of corticopontine neurons devoted to equally sized visual field blocks, central vision was still moderately over-represented compared to peripheral vision (due to high cortical magnification factors for central vision). Fig. 6 shows corticopontine density distribution in the cat visual area 18.

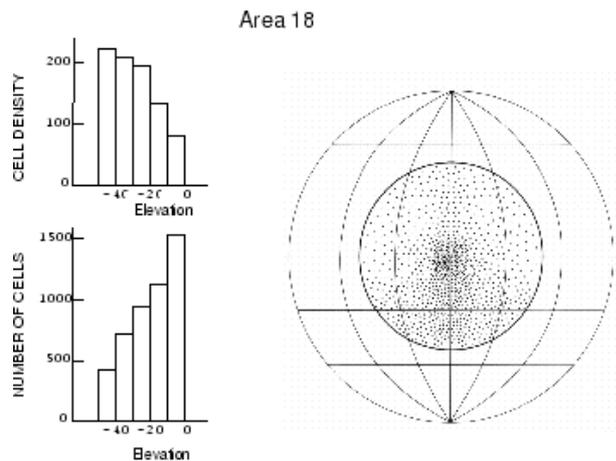


Figure 6

Distribution of corticopontine neurons in cat visual area 18. The PN was injected with large amounts of wheat germ agglutinin horseradish peroxidase and the retrogradely labelled neurons in the cortex were quantitatively mapped. The histograms show the distribution of corticopontine neurons in equally sized blocks of the lower visual field close to the vertical meridian (azimuth 0(- 20)). Upper left: Densities of corticopontine neurons (cells/mm² cortex) decrease from the representation of the lower peripheral visual field (elevation -50) to the central visual field representation (elevation 0). Lower left: The number of corticopontine neurons devoted to each equally sized block of the visual field (cells/mm² cortex x mm² cortex/visual field block) is higher for blocks close to the central visual field representation. The perimeter chart shows the relative strength of the corticopontine projection from different parts of the visual field represented in area 18, based on quantitative data exemplified in the lower right histogram. Modified from Bjaalie (1985).

The findings summarized in Figs. 5 and 6 have important implications as they suggest that cortical information is rescaled and partially renormalized before being transmitted to the cerebellum. While maps in the cortex typically overrepresent functionally important parts of the input map, like the fovea for the visual system, the hand for the monkey somatosensory system or the vibrissae for the rat somatosensory system, this may not be the case to the same extent for input to the cerebellum. As far as the map of somatosensory projections to the rat cerebellar hemisphere is known (one should realize that only the crowns of the folia have been mapped in detail, e.g. Fig. 2) it seems that vibrissal input is represented to a smaller extent than in somatosensory cortex (Chapin and Lin, 1990; Voogd and Glickstein, 1998).

We can conclude that the corticopontine projections transmit another subset of the input space than is represented in the cerebral cortex. Furthermore, it seems likely that the transformation from a continuous map in SI to a fractured somatotopic map in the cerebellum takes place primarily in the pontocerebellar projection given that the corticopontine projection is not basically fractured, but the pontocerebellar pathway needs further study. Finally, it is well known that the corticopontine projections are among the fastest pathways in the human nervous system (Allen and Tsukahara, 1974).

The function of the cerebellar granular layer

Most cerebellar theories give little consideration to the function of the granular layer; they focus instead on the interaction between parallel fibers and Purkinje cells (Ito, 1982; Braitenberg et al., 1997) and, more recently, also on that between Purkinje cells and neurons in the deep cerebellar nuclei (Raymond et al., 1996). This focus on the output side of the cerebellar circuitry may be misconceived, considering that the granular layer contains 98% of the cerebellar neurons (Palay and Chan-Palay, 1974). In fact, Marr (1969) and Albus (1971) did consider the function of the granular layer in detail in their original papers. They contribute it an important function in recoding the mossy fiber input so that the simple perceptron learning rule, which they propose for the parallel fiber to Purkinje cell synapse, can be applied to complex input patterns. Without such a recoding scheme perceptrons cannot learn to distinguish patterns that are not linearly separable (Minsky and Papert, 1969). Albus' paper contains a nice example where he shows how the recoding of mossy fiber input by the granular layer, which is in effect a combinatorial expansion by about two orders of

magnitude, can circumvent this problem. In these theories the inhibitory Golgi cells control the activation threshold of granule cells, thereby keeping the number of active parallel fibers relatively small and constant over large variations in the number of active mossy fibers (Marr, 1969). This control over the number of active parallel fibers enhances the performance of the perceptron learning rule. Albus (1971) used the word "automatic gain control" to describe the role of the feedback inhibition by Golgi cells. Overall this would restrain the number of active parallel fibers contacting a single Purkinje cell to 1 % (Albus, 1971) or 0.3 to 6 % (Marr, 1969).

We have recently criticized the proposed gain control function of Golgi cells (De Schutter et al., 2000) and will not repeat our arguments in detail here. Instead we will focus on our recent modeling and experimental work, which suggests another function for cerebellar Golgi cells: the control over the timing of granule cell spikes (Maex and De Schutter, 1998; Vos et al., 1999a). Golgi cells fire synchronously along the parallel fiber beam. Our modeling studies of cerebellar cortex indicate that the cerebellar granular layer is highly prone to synchronous oscillations (Maex and De Schutter, 1998b). A typical example is shown in Fig. 7.

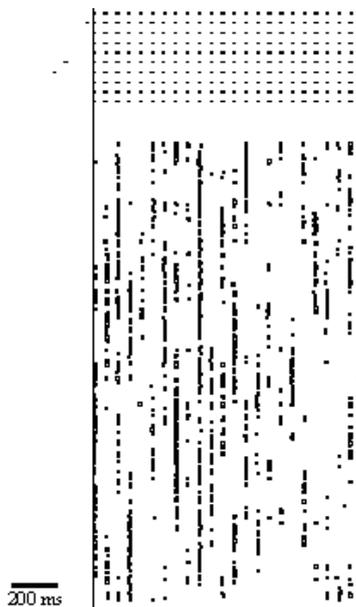


Figure 7

Raster plot showing spike timing of 10 Golgi cells (upper part) and 300 granule cells (lower part). Initially the network is not activated and only the Golgi cells fire occasionally. At the time indicated by the vertical line homogeneous 40 Hz mossy fiber input is applied and the complete circuit starts firing synchronously at a regular rhythm of about 20 Hz. Simulation of the standard network configuration described in Maex and De Schutter (1998b) but with a more dense packing of the units (30 Golgi cells, 21555 granule cells and 2160 mossy fibers).

The raster plots show the activity in a large one-dimensional network simulation, where all units are positioned along the parallel fiber axis. Initially, no mossy fiber input is provided and the spontaneous activity of Golgi cells results in a low rate of desynchronized firing. When the simulated mossy fibers are activated, however, all Golgi cells synchronize immediately and start firing rhythmically. In comparison, the granule cells show more complicated behavior. While they are also entrained in the synchronous oscillation, they fire less precisely and often skip cycles. The differences in behavior of individual granule cells in Fig. 7 can be explained by the randomization of connectivity and intrinsic excitability parameters (Maex and De Schutter, 1998b), indicating that such relative small sources of variability can generate complex activity patterns within the overall regular oscillation. The appearance of synchronous oscillations is explained by the intrinsic dynamics of the pure feedback inhibition circuit (Fig. 1). This can be easily understood by first considering the subcircuit consisting of a single Golgi cell and its many postsynaptic granule cells. Inhibitory neurons exert a strong influence on the timing of action potentials in their target neurons (Lyttton and Sejnowski, 1991; Cobb et al., 1995). The simulated granule cells will fire when inhibition is at its lowest, which is just before the next Golgi cell spike. Consequently the large population of granule cells postsynaptic to one Golgi cell will fire at about the same time. The loosely synchronous

granule cell activity then excites the same Golgi cell and causes it to fire immediately, leading to the establishment of a synchronized oscillation within this subcircuit, with granule spikes shortly preceding the Golgi cell spike. The long parallel fibers which are typical for the structure of the cerebellar cortex couple many of these oscillatory subcircuits together. Common parallel fiber input will cause Golgi and granule cells located along the same transverse axis to fire (almost) synchronously. This is a dynamic property of the cerebellar circuitry; once the granular layer is activated sufficiently the most stable form of spiking is a synchronous oscillation (Maex and De Schutter, 1998b). The accuracy of this synchronization increases with increased mossy fiber activity, which also leads to an increased Golgi cell firing rate (Maex and De Schutter, 1998b). Consequently we expect to find a firing-rate dependency of the synchronization (Maex et al., 2000). As seen in Fig. 7 the synchronization is immediate upon activation; there is no delay due to the slow parallel fiber conduction velocity (Maex and De Schutter, 1999). Finally, Golgi and granule cell populations are synchronized over the complete extent of the transverse axis where mossy fibers are activated, even if this is much longer than the mean parallel fiber length of 4.7 mm (Pichitpornchai et al., 1994). Because both cell populations fire in loose synchrony Golgi cell activity can be used to estimate the timing of granule cell spikes, though individual granule cells may skip cycles of the oscillation (Fig. 7). This is important as one cannot isolate single granule cells *in vivo*, while it is relatively easy to isolate Golgi cells (Edgley and Lidieth, 1987; Van Kan et al., 1993). These modeling predictions were confirmed using multi-single-unit recordings of spontaneous Golgi cell activity in the rat cerebellar hemispheres (Vos et al., 1999a). A total of 42 Golgi cell pairs in 38 ketamine-xylazine anesthetized rats were recorded. Of these, 26 pairs were positioned along the transverse axis (i.e. along the same parallel fiber beam), while the other 16 pairs were located along the sagittal axis (no common parallel fiber input). All transverse pairs except one showed a highly significant coherence measured as the height of the central peak in the normalized cross-correlogram. An example of such a cross-correlogram obtained from a pair of Golgi cells along the transverse axis is shown in Fig. 8.

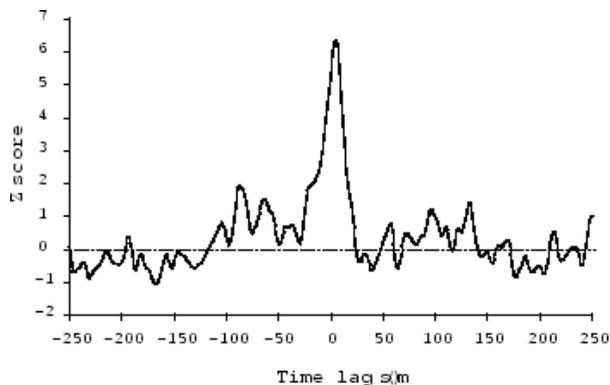


Figure 8

Cross-correlation of spontaneous activity of two Golgi cells receiving common parallel fiber input. The highly significant central peak (the cross-correlogram has been normalized for firing frequency) is indicative of synchronous firing which is not very accurate as the peak is wide. This is the same Golgi cell pair as of Fig. 4. See Vos et al. (1999a) for experimental and statistical procedures.

Conversely, in 12 out of 16 sagittal pairs no synchrony could be found. The remaining four sagittal pairs showed low levels of coherence, but in each of these pairs the Golgi cells were located within 200 μ m from each other. We assume that in these latter four pairs the cells were so close to each other that their dendritic trees overlapped (Dieudonné, 1998), allowing them to sample common mossy and/or parallel fiber input despite their parasagittal separation.

These findings confirmed the main prediction of the network simulations: Golgi cells along the parallel fiber beam fire indeed synchronously. Additionally, as predicted, the accuracy of synchronization, evidenced by higher and sharper central peaks in the cross-correlogram, increased with the Golgi cell firing rate (Fig. 1 of Vos et al., 1999a). This indicates that synchronization may be much more accurate in awake animals, compared to the loose synchrony observed in the anesthetized rat. The only data presently available from awake animals are field potential recordings (Pellerin

and Lamarre, 1997; Hartmann and Bower, 1998). These studies have also demonstrated the presence of oscillations in the granular layer that may correspond to those predicted by the model.

The effect of spatially localized mossy fiber input

In the previous section we considered the synchronization of Golgi cells in response to a spatially homogeneous mossy fiber input in the network simulations and compared this to experimental data obtained without any stimulation. This is of course a rather artificial assumption. Considering the patchy receptive fields in the granular layer (Fig. 2) one expects stimulation to cause spatially heterogeneous mossy fiber activation.

Recent modeling work in our laboratory demonstrates that a similar behavior can be observed when a patchy mossy fiber input is applied. Specifically, if two patches are activated by comparable levels of mossy fiber input they will synchronize immediately, even if separated by a few millimeters of only lowly activated granular layer (Franck et al., 2000). This can be observed in Fig. 9A, which shows the spike trains of the model Golgi cells and of a subset of granule cells in a one-dimensional model with strong feedback inhibition. Activation of two small patches (200 μ m diameter containing about 50 mossy fibers and 500 granule cells each, 1 mm separation) leads to the immediate synchronization of all Golgi cells along about 6 mm of the parallel fiber beam overlying the patches. As parallel fibers are 5 mm long in the network model, this means that all Golgi cells receiving input from the two patches become entrained in the rhythm, though the synchronization is clearly less robust than that evoked by homogeneous input (Fig. 7). The other Golgi cells in the network fire less than before or are hardly affected at all.

The picture looks somewhat different for granule cells. In Fig 9 only a small subset of granule cell traces can be shown, so the borders of the patches are not represented. It can nevertheless be seen that they are activated inside the patches only. Between the two patches and at the outer borders of the patches they are actively inhibited by the activated Golgi cells. The granule cell activity within and between the two patches is highly synchronized. Like for the fully activated network (Fig. 7) granule cells spike together with Golgi cells, but sometimes skip cycles.

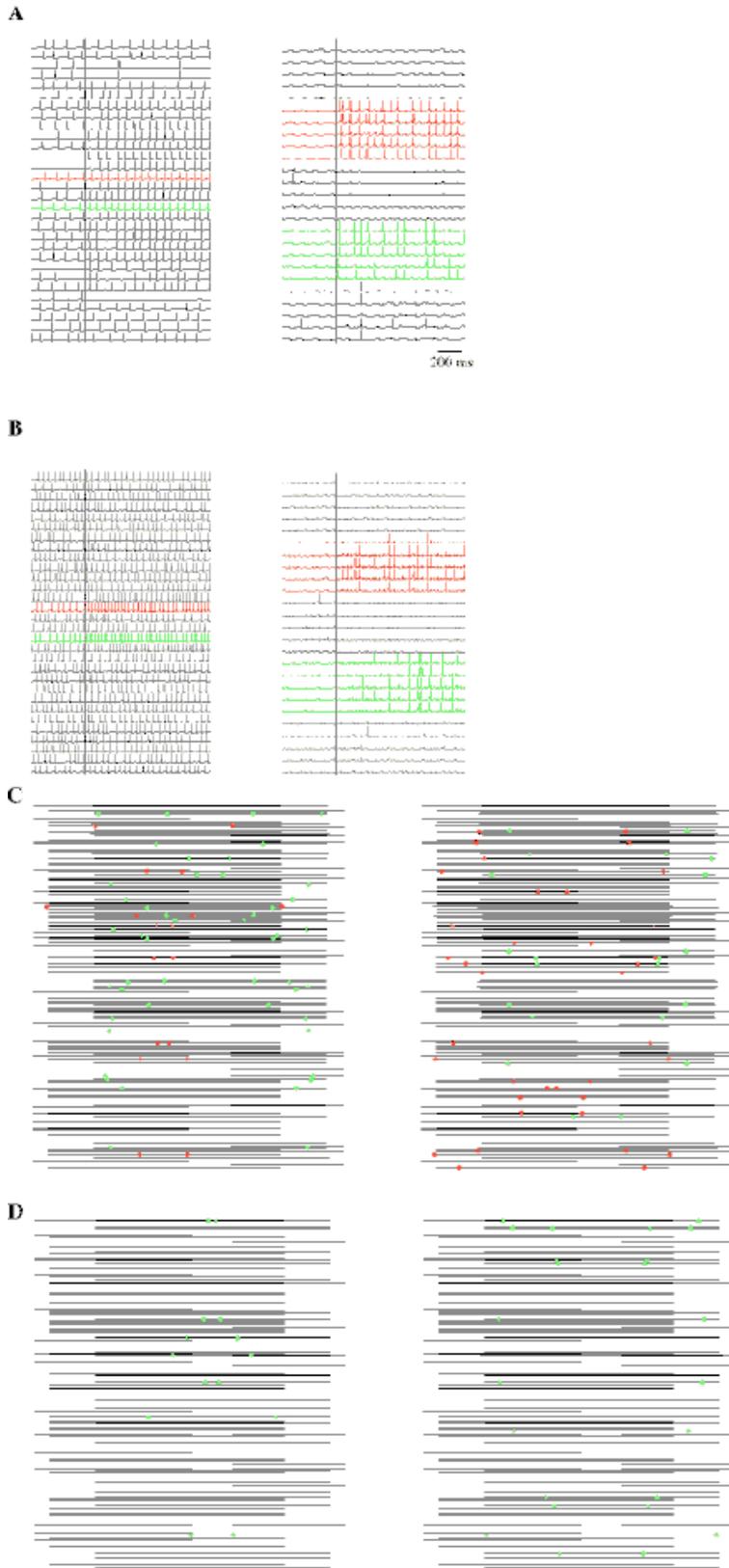


Figure 9

Comparison of firing patterns and parallel fiber activity in a network with strong feedback inhibition (A,C) and a network with strong feed-forward inhibition (B, D). A, B: Firing activity in all Golgi cells and a selection of granule cells. Initially the network is slightly activated by diffuse mossy fiber input (mean rate 5 Hz in A and 10 Hz in B). At the time indicated by the blue line two patches of 200 μ m diameter, separated by 1 mm, are activated (40 Hz mossy fiber input in A, 80 Hz in B). Spike trains from neurons in the patches are colored red and green. Because a random selection of granule cell

spike trains is shown their spatial position does not have a direct correspondence to that of the Golgi cells. C, D: Conduction of waves of spike activation along parallel fibers. The left and right panels shown are separated in time by 4 ms. Random sampling of parallel fibers originating within and outside the two patches. Spikes colored following patch of origin. See text for more details. In A, C GPF-AMPA is 80 nS and GGABA 50 nS; in B,D MF(GoC connection probability is 0.2 and GMF-AMPA 30 nS and GPF-AMPA is 4 nS, other parameters as in standard network configuration described in Maex and De Schutter (1998b) but with more dense packing of cells (see Fig. 7).

In addition granule cells sometimes fire bursts of two spikes. The latter behavior was even more pronounced when the network parameters from previous studies (Maex and De Schutter, 1998b) were used (to diminish bursting in Fig. 9A the synaptic strengths of parallel fiber and Golgi cell synapses have been raised, making the feedback inhibition loop stronger). The possible importance of granule cell bursting for induction of synaptic plasticity at the parallel fiber to Purkinje cell synapse (Linden and Connor, 1995; Finch and Augustine, 1998) has been discussed previously (De Schutter et al., 2000). It is interesting to note that bursting behavior is easier to evoke with spatially localized activation. At present we are evaluating the bursting behavior of the model further by introducing more accurate descriptions of the granule cell excitability (D'Angelo et al., 1998) into the network simulations.

In conclusion, the simulation of Fig. 9A demonstrates that, in a network model with strong feedback inhibition, activation of spatially separated patches can also couple the activity of Golgi cells. In their effect on granule cell firing Golgi cells seem to have both a discriminating and an integrating function: they increase the contrast in firing rate between activated and non-activated granule cells and they synchronize firing of activated granule cells. In contrast, if a similar input is applied to a network version with weak feedback inhibition and strong feed-forward inhibition the situation looks quite different (Fig. 9B). These networks show no synchronization of Golgi cell firing for homogenous mossy fiber input (Maex and De Schutter, 1998b). In Fig. 9B the Golgi cells are more active because of their direct excitation by mossy fibers. Only the Golgi cells receiving increased mossy fiber input in the patches (and a few of their immediate neighbors) show a response to the activation: they increase their firing rate without synchronizing. The granule cell activity is very heterogeneous: some fire at rates similar to those in 9A, others do not. While some of these spikes are clearly synchronized within a patch, there is almost no synchronization of activity between the two patches. The synchronization within patches is explained by common inhibition from one Golgi cell. As the parallel fiber activation of Golgi cells is very weak in these simulations, it is not sufficient to synchronize the Golgi cells.

Spatio-temporal coding along the parallel fiber beam

In the left panels of Fig. 9 we compare the granule cell spiking in a synchronized version (Fig. 9A) and desynchronized version (Fig. 9B) of the granular layer network model. In the right panels we compare the effect of synchronization on parallel fiber spike transmission by showing two snapshots for each network version.

Both simulations show waves of spikes traveling along the parallel fiber beam, but with an important distinction. In the feedback inhibition model the patches fire loosely synchronized so that the spikes originate in both patches, while in the feed-forward inhibition model all the spikes that can be observed at one time originate in only one of the patches. Only rarely did one observe spikes originating outside the patches or, in the case of Fig. 9D, a spike originating in the other patch. The comparison of these two simulations suggests that at the low firing rates present in the model granule cells the synchronization of the feedback inhibition model has an important effect on the patterns of parallel fiber spiking that are perceived by Purkinje cells. In particular, in the synchronized model the two patches activate Purkinje cells at roughly the same time (Fig. 9C) while without synchronization they will do so separately (Fig. 9D).

The spike waves of Fig. 9C-D are reminiscent of the tidal waves proposed by Braitenberg et al. (1997), with the important difference that their timing is generated inside the cerebellar cortex, not outside of it. But Braitenberg et al. (1997) proposed that only where all the spikes synchronize along the parallel fiber beam Purkinje cells would be activated. Because of the loose synchronization in the network model this is unlikely to occur. We assume that accurate synchronization may not be important, at least not along the

parallel fiber beam, because our Purkinje cell model (De Schutter and Bower, 1994a,b) is a very poor coincidence detector (De Schutter, 1998). This is to be expected as the Purkinje cell dendrite does not contain fast sodium channels (Stuart and Häusser, 1994). Instead its window of temporal integration is determined by much slower activating dendritic calcium channels (Regan, 1991; Usowicz et al., 1992).

There are two ways in which the synchronized spike waves may be decoded by Purkinje cells. The most simple one is to assume a population rate coding scheme (Rieke et al., 1997). Because both patches fire loosely synchronized (Fig. 9A) they cause short bursts of spiking activity along the parallel fiber beam (Fig. 9C) during their activation. Purkinje cells receiving synaptic input from those parallel fibers could simply integrate this input with a total excitation determined by the size and number of patches activated (for a particular mossy fiber input rate). Supportive for this hypothesis is that the conduction time needed for a spike to travel along one half of a parallel fiber (5-12 ms; Bernard and Axelrad, 1991; Vranesic et al., 1994) is in the same time range as the typical time window within which granule cells in both patches spike in the simulations of Fig. 9A (about 10 ms).

An alternative hypothesis is to assume a temporal code, captured in the relative timing of the granule cell spikes. It was Hopfield (1995) who first hypothesized that the nervous system can use relative phase lags between spikes to encode information. In the context of pattern recognition such a temporal code has the advantage of being much less sensitive to stimulus amplitude than standard rate codes (which are used by the perceptron learning rule of Marr and Albus). While Hopfield proposed that coincidence detection combined with different afferent delays would be used to decode such phase lags, one can imagine alternative schemes which decode the phase lags directly (Steuber and Willshaw, 1999).

Whichever hypothesis one prefers, the synchronization of firing of granule cells which are positioned along the same parallel fiber beam contributes to the transformation of spatial patterns present in the mossy fiber input into a temporal pattern that is transmitted along the parallel fiber system.

According to the population rate coding hypothesis it is the burst of synchronized spikes which associates the activity originating in two spatial locations; in the temporal coding the actual phase lags between spikes is the source of information. To distinguish between these two possibilities it would be helpful to know how accurate the timing is in awake animals, as the temporal coding hypothesis requires more accurate synchronization than that observed in anesthetized rats (Vos et al., 1999a; Maex et al., 2000). We are currently investigating this issue (Vos et al., 1999c).

Bringing it all together

Pontine sensory input to the cerebellum copies cortical activity, without any obvious mixing of signals. Furthermore, the output from the SI cortex to the cerebellum via the pontine nuclei is renormalized to represent different body parts more equally (Figs. 5-6). Because of the patchy, fractured somatotopy of mossy fiber input (Fig. 2), tactile input will generate specific spatial patterns consisting of several co-activated patches in the granular layer (see also Peeters et al., 1999). The complex spatial pattern of activation of patches may therefore be used to distinguish between different stimuli and/or activation patterns in neocortex. We propose that the Golgi cell feedback inhibition loosely synchronizes the activity of granule cells in co-activated patches and thereby supports the transformation of a spatially encoded mossy fiber signal into a temporal code of spike waves transmitted along the same parallel fiber beam. Without synchronization much higher granule cell firing rates are required to ensure loose coincidence of spikes originating in different patches (e.g. Fig. 9D).

The spatio-temporal transformation hypothesis accords with the properties of the synchronization described above. The immediate synchronization of Golgi cells (Fig. 7) allows for an efficient transformation, while the lack of accuracy fits with the variable conduction velocities of parallel fibers (Bernard and Axelrad, 1991; Vranesic et al., 1994) which will slowly desynchronize the signal anyway. We expect that in awake animals transient synchronous oscillations linking several different or identical receptive field patches rise and wane continuously, transforming the spatial pattern of input into short sequences of synchronous spike waves along the parallel fiber beam. The amplitude of the input pattern will determine the frequency of these oscillations (Maex and De Schutter, 1998b).

In principle this spatio-temporal code hypothesis is compatible with an additional combinatorial expansion of the mossy fiber signal, as suggested by Marr (1969) and Albus (1971). Nevertheless, alternative explanations for

the large number of granule cells are available. Our modeling studies show that a minimum number of parallel fiber contacts onto each Golgi cell must be activated to sustain the synchronous oscillations (Maex and De Schutter, 1998a). This is much more easily achieved in a sparsely activated network containing many granule cells.

In support of the spatio-temporal code hypothesis we have found that the most important stimulus aspect determining the fine temporal shape of Golgi cell responses is the part of the receptive field being activated, while stimulus amplitude has little or no effect (Volny-Luraghi et al., 1999; Vos et al., 1999b). In other words, the granular layer cares about the spatial pattern of mossy fiber input, which is determined by the stimulus location, not about stimulus amplitude. The renormalization of space in the corticopontine projection (Figs 5-6) also confirms the importance of spatial relations in this system.

Several questions remain. How do Purkinje cells decode these spike waves and what do the pontine nuclei contribute to this proposed scheme? At the level of the Purkinje cell many mechanisms are possible. The population rate coding scheme is compatible with the perceptron learning as proposed by Marr (1969) and Albus (1971), with the important addition of a spatio-temporal recoding not included in their theories. The phase coding scheme may require more specific learning rules (e.g. Steuber and Willshaw, 1999) or interactions between parallel fiber excitation and inhibition by stellate and basket cells (Jaeger et al., 1997; Jaeger and Bower, 1999).

Concerning the pontine nuclei an additional intriguing possibility is that they enhance the generation of synchronous oscillations in the granular layer. The synchronization of Golgi and granule cell spiking between patches assumes that the mossy fiber excitation of each patch is roughly equal (Franck et al., 2000). Therefore it would be useful to have a mechanism available which keeps mossy fiber excitation evenly distributed across activated fibers. How the pontine nuclei could achieve this with only very few interneurons (Brodal et al., 1988; Border and Mihailoff, 1990) remains unclear, though subcortical projections to the pontine nuclei (reviewed in Brodal and Bjaalie, 1992) and feedback projections from the cerebellum (Schwarz and Thier, 1999) might play a role. An alternative mechanism to keep activation by mossy fiber input in different patches roughly equal could be plasticity of the mossy fiber to granule cell synapse (D'Angelo et al., 1999). As LTP at this synapse is suppressed by Golgi cell inhibition it may preferentially enhance transmission at synapses which were not effective in activating the Golgi cell inhibitory feedback loop and thus boost mossy fiber transmission where it was relatively weak compared to elsewhere.

Conclusions

We propose that mossy fiber input to the cerebellum is coded primarily in spatial patterns, as reflected by the fractured somatotopy of the receptive fields in the granular layer. Feedback inhibition by Golgi cells loosely synchronizes granule cell firing along the parallel fiber beam. Simultaneous activation of granular layer patches causes synchronized firing of the activated granule cells and transforms the spatial code into a temporal code onto the parallel fiber beam. The corticopontine projection contributes by distributing a (partially) renormalized copy of cortical activity to multiple patches and possibly by equalizing activity across fibers.

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