Review

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Timing and plasticity in the cerebellum: focus on the granular layer

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Two of the most striking properties of the cerebellum are its control in timing of motor operations and its ability to adapt behavior to new sensorimotor associations. Here, we propose a 'time-window matching' hypothesis for granular layer processing. Our hypothesis states that mossy fiber inputs to the granular layer are transformed into well-timed spike bursts by intrinsic granule cell processing, that feedforward Golgi cell inhibition sets a limit to the duration of such bursts and that these activities are spread over particular fields in the granular layer so as to generate ongoing time-windows for proper control of interacting motor domains. The role of synaptic plasticity would be that of fine-tuning pre-wired circuits favoring activation of specific granule cell groups in relation to particular time windows. This concept has wide implications for processing in the olivo-cerebellar system as a whole.

The cerebellum and timing of movements

The cerebellum is a brain structure of crucial importance for sensorimotor control, and its disruption causes a dramatic neurological syndrome called ataxia (the paradigmatic symptoms were first outlined by L. Luciani in 1891 [1] and then extended by clinicians such as J.F.F. Babinski, P. Marie and G. Holmes; for a review including a historical recollection see Ref. [2]). Over the last decades the cerebellum has also been suggested to be involved in cognitive and emotional functions [3–5], which is in line with the possibility that cerebellar lesions contribute to pathological syndromes such as autism and schizophrenia [2,6,7].

The various cerebellar functions, ranging from relatively simple control of proximal musculature and autonomic processing to more complicated issues such as control of multi-joint arm movements and cognitive processing, are carried out by specific cerebellar modules [8]. The fact that all modules have the same circuit architecture [9–11] indicates a common scheme for signal processing (Figure 1). Such common olivo-cerebellar computations could perform general operations such as comparing expected and actual discharge patterns, revealing differences between them and applying the appropriate corrections on a long-term basis [5,12–14]. Thus, the general system mechanisms involved are likely to exploit internal representations that can be learned and stored within the cerebellar cortical network and/or its target neurons in the deep cerebellar nuclei (DCN) and vestibular nuclei (VN).

During ataxia, motor sequences are usually characterized by abnormal timing with delayed muscle activations and sudden interruptions of movements followed by exaggerated corrections (hypermetria), which, in turn, contribute to tremor and failure of ongoing motor coordination. These aberrations in both timing and coordination are often due to inadequate control of the interplay between agonist and antagonist muscles as can be readily observed during for example control of limb movements [15]. Still, separate dysfunctions in timing and coordination of movements might well be observed as they can be experimentally identified as two different processes, the former being the delay and duration of movements and the latter being the control of state-dependent representations of the elementary movement components [16]. Ultimately, deficits in the timing of movements must be reflected in abnormal activities of neurons in the DCN or VN, which, at least partly, encode the relative phase of muscle contractions [17]. As such, the cerebellum can be seen as a phase-modulating device [18].

Although interruptions in the cerebellar cortical circuitry usually lead to some form of ataxia, more subtle (often genetically induced) abnormalities that do not directly interfere with the structure of this circuitry usually do not lead to obvious deficits in motor performance but to isolated impairments in motor learning instead [19–21] (Box 1). Such limited learning impairments after cerebellar cortical manipulation are well documented in eyeblink conditioning and adaptation of the vestibulo-ocular reflex, which are relatively simple and tractable forms of behavior [21]. Interestingly, reversible, relatively subtle manipulations of the DCN can also have distinct effects on performance and learning parameters during eyeblink conditioning, but here the performance deficits dominate [22]. Thus, timing and adaptation of sensorimotor activities emerge as two fundamental functions of cerebellar processing, and abnormalities in both of them can be used to estimate the level and location of cerebellar dysfunction.

Presumably, acute motor timing and long-term adaptation of movements both require fast signal processing in the cerebellum. Finger tapping in humans can proceed as fast as ~10 repetitions sec^{-1} [23–25] and its regularity is severely disturbed by cerebellar damage (a symptom called dysdiadochokinesia). Accurate measurements of response

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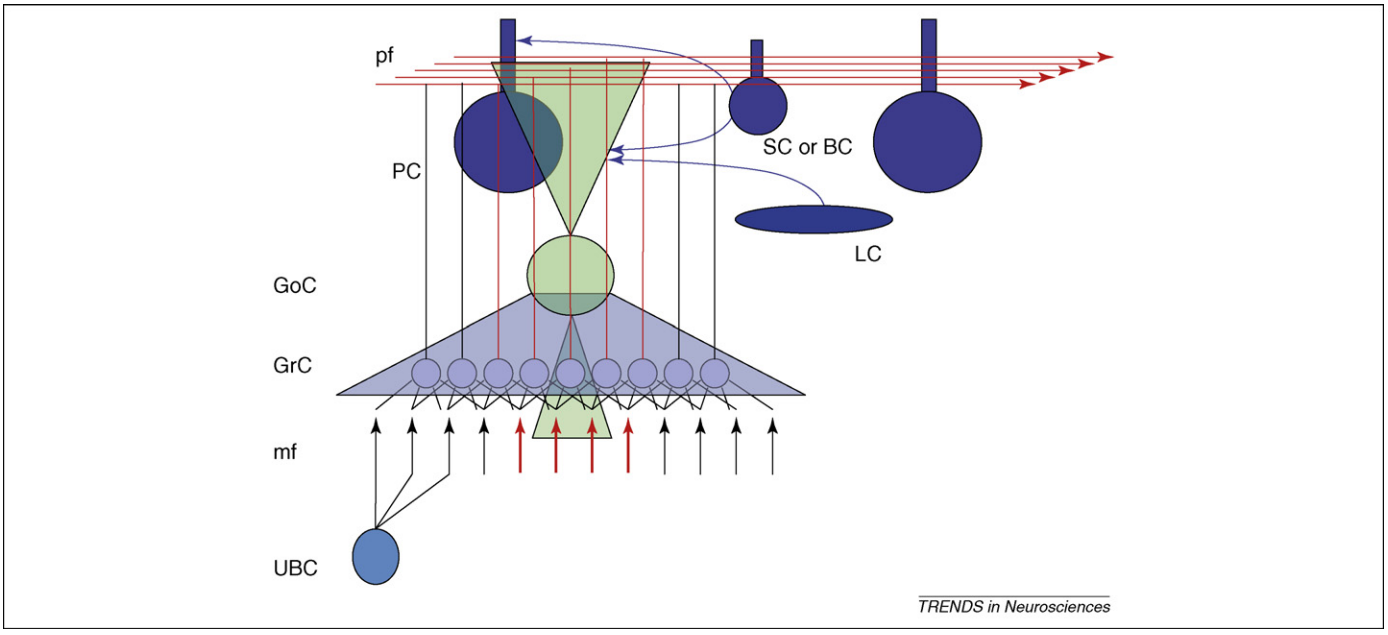

Figure 1. Schematic representation of the granular layer network. The basic granular layer network is formed by the mossy fiber (mf) input, granule cells (GrCs), Golgi cells (GoCs) and their connections [9,11,32]. In the scheme, three organizing principles are emphasized, namely the lateral inhibition exerted by Golgi cells [47], the vertical organization of the mossy fiber input [88] and the inhibitory feedback from molecular layer interneurons. When a group of mf discharges (red arrows), both GrC and GoC are activated. GrCs emit ascending axons, which bifurcate in the molecular layer into parallel fibers (pfs) activating GoC, stellate and basket cells (SCs and BCs) and Purkinje cells (PCs). The extension and efficiency of connections between the ascending branch and overlying PC apical dendrites provides the substrate for the vertical organization. SC and BC, in turn, inhibit the GoC generating molecular layer feedback. The GoC provides axons in the granular layer that extend over an area that is wider than their basal and apical dendrites (green triangles), thereby causing lateral inhibition (light blue area) [47]. In addition to this basic circuitry, several other elements have a role in granular layer functions. These include Lugaro cells (LCs), which inhibit the GoC, unipolar brush cells (UBCs), which are predominantly contacting granule cells in the vestibulocerebellum expanding their excitation fields, and several inputs such as those of the sparse climbing fiber input to the Golgi cells and the monoaminergic and serotonergic fibers terminating blindly in the granular neuropil (not shown in the diagram; see Ref. [32]).

times in a ball-release test during throwing have also revealed that the cerebellum controls finger movements with millisecond precision and that this precision in timing increases with learning and is impaired in cerebellar patients [26]. Similarly, in eyeblink conditioning the cerebellum can detect and adapt temporal correlations in the order of tens of milliseconds [21,27]. These marvellous performances raise the questions as to how fast peripheral inputs can reach the cerebellar cortex, how fast the cerebellar computational network processes this information and how fast, in turn, then the cerebellar cortex can exert its effects at the motor output level. It is well established for all sorts of sensory inputs including optokinetic, vestibular, auditory and somatosensory inputs that they can reach the cerebellum within tens of milliseconds with a variability in the millisecond range [28–30]; whereas it is also clear that stimulation of the cerebellar cortex can elicit, for example, eye and head movements within the same time range [20,31]. However, it remains to be elucidated how exactly the cerebellar cortex is transforming the sensory information into a motor control signal that can be used at a millisecond scale. Here, we present a hypothesis as to how neuronal computations in the granular layer might contribute to this process.

Box 1. Motor-learning impairment in cerebellar mutants

There are numerous examples of selective impairment of learning in cerebellar cortical mutants that do not show overt ataxic behavior or motor impairment. Neither Purkinje-cell-specific inhibition of protein kinase C nor ablation of fragile X mental retardation protein affects either timing or amplitude of the unconditioned reflex; they merely lead to deficits in learning-dependent timing of the conditioned eyeblink response [31,100]. Similarly, inhibition of protein kinase C or elimination of α-Ca^{2+}-calmodulin-dependent protein kinase II and protein kinase G in Purkinje cells, which all impair parallel fiber LTD, hardly affects the motor performance of compensatory eye movements, whereas they clearly impair adaptation of the vestibulo-ocular reflex [101–103]). Recently, these examples can also be extended to the more complicated limb-movement control. Locomotion tests on the Erasmus ladder show that some spontaneous genetic modifications of Purkinje cells, such as those in *lurcher* mutants that ultimately lead to Purkinje cell death, result in direct timing deficits during motor performance, whereas just altering the timing of climbing fiber activities such as in Cx36-deficient animals leads to mainly an impairment in learning-dependent timing on the ladder [87]. Similarly, global mutants in which the granular layer is affected, such as the spontaneous *weaver* mutant [104], *FHF1–FHF4* [105], *EPS8* [106] or *PrP* [107] knockout mice, can also show a mix of performance and learning deficits, whereas more subtle mutations such as those of the mossy fiber LTP-deficient *NR2A–NR2C* knockout or C-terminal-deletion mutants only show deficits in cerebellar motor learning [63] (C. Andreescu *et al.*, unpublished). Thus, together, studies in cerebellar mouse mutants indicate that plasticity and timing processing in the granular layer are just as essential for cerebellar function as those in the molecular layer.

Principles of granular layer processing: highlights and problems

The perspective that we will take in this review is to consider cerebellar processing starting from the granular layer circuit. Understanding how the granular layer processes incoming information is crucial because its sole output, the granule cell axon (parallel fiber system), forms one of the main inputs to the Purkinje cell, which, in turn, forms the sole output unit of the cerebellar cortex as a whole (Figure 1). The granular layer receives many sorts of converging information originating from many different

brain regions through the mossy fibers [9–11]. These fibers activate both the granule cells, which are the smallest (~5 μm diameter) and most numerous neurons in the brain (~10^{11} in humans), and the Golgi cells, which are the sole inhibitors of the granule cells themselves [32]. The inhibition of Golgi cells onto granule cells results from both a feedback and a feedforward loop because Golgi cells are not only innervated by their output, that is the granule cell axon–parallel fiber system (feedback loop), but also by the input to the granule cells, that is the mossy fiber system (feedforward loop).

The apparent simplicity of this arrangement, supported by electrophysiological data and a precise anatomical quantification of the convergence:divergence ratios of its neuronal connections [9], has inspired Marr [33] to propose his motor learning theory and Albus [34] and Ito [5,10,35] to elaborate on this hypothesis. In principle, the Marr–Albus–Ito concepts advocate that climbing fibers can alter the efficacies of parallel fiber synapses onto Purkinje cells. The granular layer should generate a sparse representation and perform spatial-pattern separation of the mossy fiber inputs with consequent expansion recoding of their patterns [36]. This redistribution means that signals coming from mossy fibers are assigned to much larger (expanded) granule cell groups for subsequent elaboration. In this view, a randomly distributed inhibition from the Golgi cells is predicted to enhance sparseness and spatial-pattern separation. Moreover, based on the assumption that incoming signals are rate coded, the mossy-fiber–granule-cell–Golgi-cell circuit could control input gain of the mossy fiber to granule cell transmission [33,34]. This view has been recently supported by the discovery that a form of tonic inhibition in the glomerulus could indeed regulate the gain of this transmission [37].

Although the basic circuitry and some physiological properties of the granular layer network offer an adequate design for redistributing incoming information, things become much more interesting as temporal dynamics and plasticity are taken into account. This aspect is particularly important because frequency coding, which underlies the gain control theory, might not be fully effective over the restricted periods of time during which the cerebellum has to operate. A simple calculation helps in understanding the issue for the control of the initiation of a movement. Because granule cells respond with 100–200 Hz bursts to punctuate stimulation [38,39], over 10 ms (the time-scale of behavioral cerebellar control [21,27]; see earlier) there would be time for 1 or 2 spikes per granule cell at most. In this scenario, information cannot be efficiently conveyed through average frequency but needs to be largely carried by first-spike delay instead. Actually, as seen from the transmitter side, first-spike delays modulated over 5–10 ms along afferent sensory pathways provide a plausible coding strategy [40,41]. And, as seen from the main receiver (the Purkinje cell), spike-time modulation on a similar time range might provide an effective code [42,43]. Thus, the cellular and network mechanisms that control timing in the granular layer network are likely to operate, at least in part, by first-spike delay determination.

The impact of inhibition on timing in the granular layer

It wasn't until the potential roles of the Golgi cells were considered in detail that the granular layer was proposed to process input temporal patterns [44,45]. In fact, systematic analysis of the potential effects of Golgi cell inhibition enables the identification of the fundamental properties of inhibition that can influence temporal aspects of network properties [46], namely feedforward inhibition, feedback inhibition and lateral inhibition. In addition, by controlling the level of granule cell depolarization, Golgi cell inhibition should be able to regulate NMDA-channel unblock and thereby the induction of long-term synaptic plasticity (i.e. inhibition controlled plasticity).

Recently, we have indeed shown that various forms of inhibition with different sorts of effects occur in the granule cell layer; these include feedforward inhibition, which causes a time-windowing effect, lateral inhibition, which determines a center-surround organization of the granular layer response, and local control of the excitatory–inhibitory balance, which determines what regions will undergo long-term potentiation (LTP) or long-term depression (LTD) [47,48]. The time-window induced by feedforward inhibition is typically of ~5 ms and enables the granule cells to fire 1–2 spikes in response to a single mossy fiber stimulus. Moreover, the time window can be expected to be synchronized over large granular layer fields owing to both the extension of the Golgi cell axon and the spread of feedback inhibition through the parallel-fiber–Golgi-cell–granule-cell loop.

Our experimental investigations are in line with several modeling studies, which predicted that the Golgi cell system can indeed produce time windowing and that it can be entrained into activity cycles involving large numbers of synchronized granule cells [49–51]. In these spiking cerebellar networks the granule cells might generate a variety of temporal dynamics under inhibitory control of the Golgi cells [52]. Thus, one can conclude that, from a network point of view, there is ample experimental and modeling evidence that the granular layer circuit is well designed to operate as a timing control system.

The impact of neuronal electroresponsiveness on timing in the granular layer

Together with circuit organization, neuronal electroresponsiveness can also have a profound impact on timing. A main consequence of the intrinsic properties of granule cells and Golgi cells is to enhance burst generation. The importance of this mechanism could be that of generating reliable and strong responses to the high-frequency bursts of impulses entering the granular layer through the mossy fibers [29,38,39,53]. Bursts are intensified by specific ionic mechanisms including the resurgent Na^+ current and the NMDA current, the contributions of which become particularly efficient when cell excitation is intense [54–56]. As a consequence, the response of those granule cells that are intensely activated will be the generation of a burst, the duration of which is limited by a brisk feedforward inhibition caused by a similar burst in the Golgi cell. On this basis, it might be anticipated that erratic spikes in the mossy fibers will not be efficiently transmitted so that the burst–burst mechanism would, indeed, increase the signal

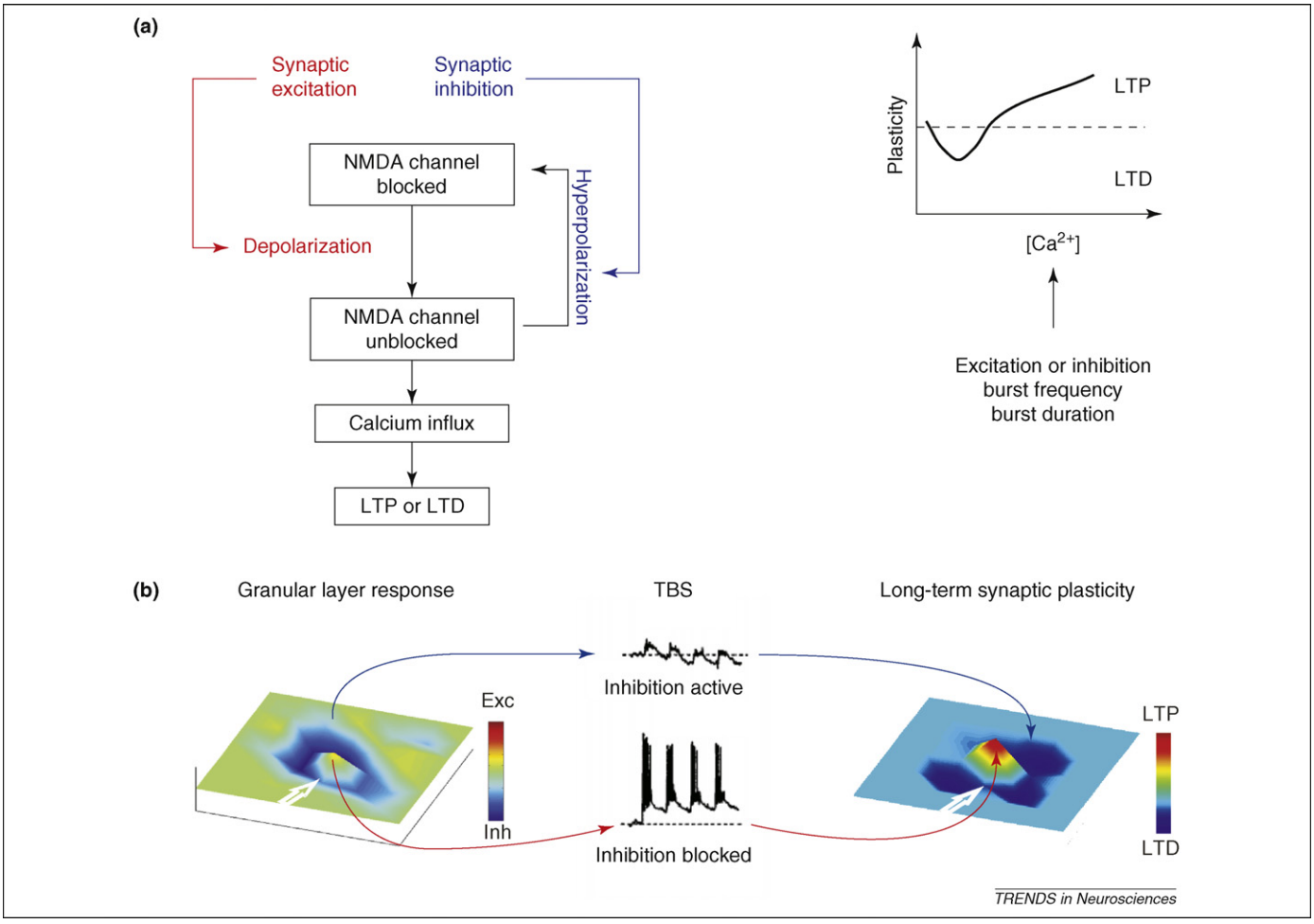

Figure 2. Long-term synaptic plasticity in the granular layer. **(a)** Among several forms of long-term synaptic plasticity in the cerebellar cortex and nuclei [58], LTP and LTD have been demonstrated at the mossy-fiber–granule-cell synapse [60]. This plasticity follows a bidirectional Bienenstock–Cooper–Munro-like rule and is Hebbian in nature in that it depends on simultaneous repetitive mossy fiber activity and postsynaptic depolarization. The NMDA receptor acts as the main coincidence detector and operates through a regulation of calcium influx [63,65]. NMDA-channel unblock, which can be regulated by the duration and frequency of mossy fiber bursts, makes the induction process highly sensitive to the inhibitory Golgi cell control. **(b)** The electrical responses of the granular layer are organized in center-surround (left). The lateral distribution of inhibition determines much stronger depolarization in the center than in the surround during the repetitive synaptic activation used to induce long-term synaptic plasticity (middle panel is taken, with permission, from Ref. [61]). Eventually, this process causes LTP in the center and LTD in the surround (adapted from Ref. [47]). Abbreviations: Exc, excitation; Inh, inhibition; TBS, theta-burst stimulation.

to noise ratio [53] and enable secure transmission along the mossy fiber pathway [39].

The impact of plasticity on temporal processing in the granular layer: the 'window-matching' hypothesis

The cerebellum has several forms of synaptic plasticity and intrinsic excitable mechanisms that might fine-tune its temporal control, the most renown of which is LTD at the parallel fiber–Purkinje cell synapse [57–59]. To date, in the granular layer, the most robust form is the bidirectional NMDA-receptor-dependent plasticity that has been described at the mossy fiber to granule cell synapse [47,60–65] (Figure 2). At this synapse, both LTP and also, probably, LTD are expressed presynaptically (A. D'Errico *et al.*, unpublished), and, as such, they might have a prominent and integrated impact on the time of occurrence of the first spike in response to an input burst of the mossy fibers [66] (Box 2). More specifically, by controlling first-spike delay, LTP would enable spikes to fall inside the window set by the Golgi cells, whereas LTD would drive the granule cells response beyond the window limit (Figure 3a): we call this effect 'window matching'. Such fine-tuning of timing can enhance the more direct control that is exerted by altering the number, frequency and synchrony of active mossy fibers in addition to the rate of action potential generation in the granule cell [61,67]. Thus, the duration of a time-window of a granule cell is set by the feedforward inhibition provided by the Golgi cells, whereas the number of spikes that occur within this window is not only determined by the instantaneous mossy fiber discharge or postsynaptic responsiveness but also by the sign of synaptic plasticity. Thus, this plasticity could continuously modify the spike discharge of a group of granule cells operating within a particular time-window or it could be even more dominant in that it might determine which neurons will emit spikes in a certain time window. Interestingly, given the ample and partially overlapping distribution of Golgi cell axonal fields [68] and the variable number of active mossy fibers per granule cell, there is a large number of potential combinations regulating spike coding and the window-matching effect (Figure 3b). In summary, the window-matching effect is expected to depend on one or more of the following factors:

Box 2. Why is presynaptic LTP expression suitable for the window-matching mechanism?

Long-term synaptic plasticity, although eventually regulating the size of the postsynaptic response, is characterized by a variety of mechanisms broadly classified as presynaptic or postsynaptic [108,109]. The implications of the different mechanisms are unclear when merely considering the response to a single synaptic stimulus. However, once repetitive neurotransmission dynamics are considered, an interesting scenario emerges [110] in which different mechanisms seem to satisfy different functional requirements. This issue has recently been investigated at the mossy-fiber–granule-cell relay by means of biophysically detailed mathematical modeling [66]. A presynaptic mechanism, in which neurotransmitter release probability is modulated, regulates short-term plasticity during repetitive neurotransmission. This, in turn, results in a precise regulation of the first-spike latency in the postsynaptic neuron. This effect occurs because release probability determines the amount of glutamate released in the synaptic cleft during a train of stimuli and subsequently regulates temporal integration through glutamate spillover and postsynaptic receptor desensitization. Thus, the presynaptic processes of the granule cells play a key part in adaptable time-window matching. Conversely, a postsynaptic mechanism provides a tight control over postsynaptic-response frequency without comparably affecting spike latency. In regulating the firing frequency this postsynaptic process might act together with the induction of long-term changes in intrinsic excitability, which can lead to the generation of burst activities rather than single spikes [61]. The segregated effects of these presynaptic and postsynaptic processes make it attractive to speculate, from an evolutionary point of view, that release probability at the mossy-fiber–granule-cell synapse has been selected as the target of plasticity in which a tight control on neurotransmission dynamics and first-spike latency is required, whereas postsynaptic modifications would be more important when the output frequency needs to be regulated. Similar co-operative presynaptic and postsynaptic mechanisms have not only been reported for other synapses of the cerebellum [58,111]) but also for synapses in other brain circuits [103,104].

(i) The efficiency of coincidence detection of mossy fiber activity in a given granule cell. In addition to the number of active fibers, the frequency and synchrony of discharge are probably important.
(ii) The efficiency of granule cell inhibition by Golgi cells. In addition to the number of active Golgi cells on a given granule cell, the rapidity of reaction and the number of spikes emitted by the Golgi cell are probably important.
(iii) The intensity of LTP or LTD at the mossy-fiber–granule-cell junctions. In addition to this, regulation of granule cell intrinsic excitability might favor spiking within the permissive window. Other yet undiscovered forms of long-term synaptic plasticity or modulation in the circuit (e.g. between mossy fibers and Golgi cells and between Golgi cells and granule cells) might further tune the window-matching mechanism.

These considerations indicate that, if the potential roles of mossy-fiber–granule-cell synaptic plasticity are fully exploited, the granular layer network is ideally designed to operate as a flexible device for redistributing information in the spatiotemporal domain. Figure 3c reports a mathematical simulation of the impact of the major mechanisms determining the window-matching effect and first-spike delay regulation.

Transferring temporal codes to Purkinje cells and molecular layer interneurons

To process the afferent signals generated during ongoing movements, the cerebellar network needs to be tuned toward the appropriate spike codes [69,41]. The temporal resolution of somatosensory processing in afferent pathways is typically in the range of ~5 ms, in that the latency to the first spikes shows such a level of variation [40]. Interestingly, this resolution matches the minimum time window that can be set by Golgi cells and the regulatory range of the LTP/LTD mechanism. The precision in the number, duration and timing of spikes emitted by the granule cells will probably each affect signal processing in the molecular layer in their own way. First, the number of spikes is relevant in that a single spike will probably merely activate high release probability synapses formed by the ascending branch of granule cell axons onto Purkinje cell dendrites, whereas activation of low-release-probability synapses between parallel fibers and Purkinje cells requires activities induced by multiple spikes [70,71]. Second, the duration of spike activities in granule cell axons is presumably important because bursts composed of 2–3 spikes and a duration of ~10 ms can generate a form of NMDA-receptor-dependent LTD at the parallel fiber–Purkinje cell synapse [72]. Third, the absolute timing in the granule cells might also be relevant in that Purkinje cells acting as perceptrons need to sample signals with high synchrony over their inputs so as to perform pattern detection [72–75].

Although feedforward inhibition and time windowing are not unique to the granular layer of the cerebellum (for general discussion see Ref. [46]), the advantage of these processes in this layer is that of regulating the probability of spikes in specific groups of neurons by the induction of LTP or LTD at the mossy-fiber–granule-cell synapses. Thus, pre-wired circuits can be fine-tuned to generate coherent and specific patterns that are conveyed to the molecular layer. In this respect it is important to note that computational modeling has revealed that presynaptic LTP and LTD expression mechanisms at the mossy-fiber–granule-cell relays are particularly efficient in regulating the timing of the granule cell activities as compared with a mere frequency relay mechanism [66] (Box 2). Taken together, we can conclude that ample evidence supports the notion that the spatiotemporal distribution of activities in the granule cell layer is readily modifiable and will profoundly affect various temporal aspects of signal processing in the molecular layer and, thereby, that of its final output, the Purkinje cells.

Temporal patterns in Purkinje cells and behavioural relevance

In the previous sections, we explained why cellular and network properties of the granular layer are well designed to control the distribution of temporally relevant mossy fiber signals. The question remains as to how this function of the granule cell layer might contribute to the overall function of the cerebellum. Because Purkinje cells form the sole output of the cerebellar cortex, it is parsimonious to also explain the role of the granule cell layer from the perspective of Purkinje cell encoding. If the way that the Purkinje cells encode information and control cerebellar

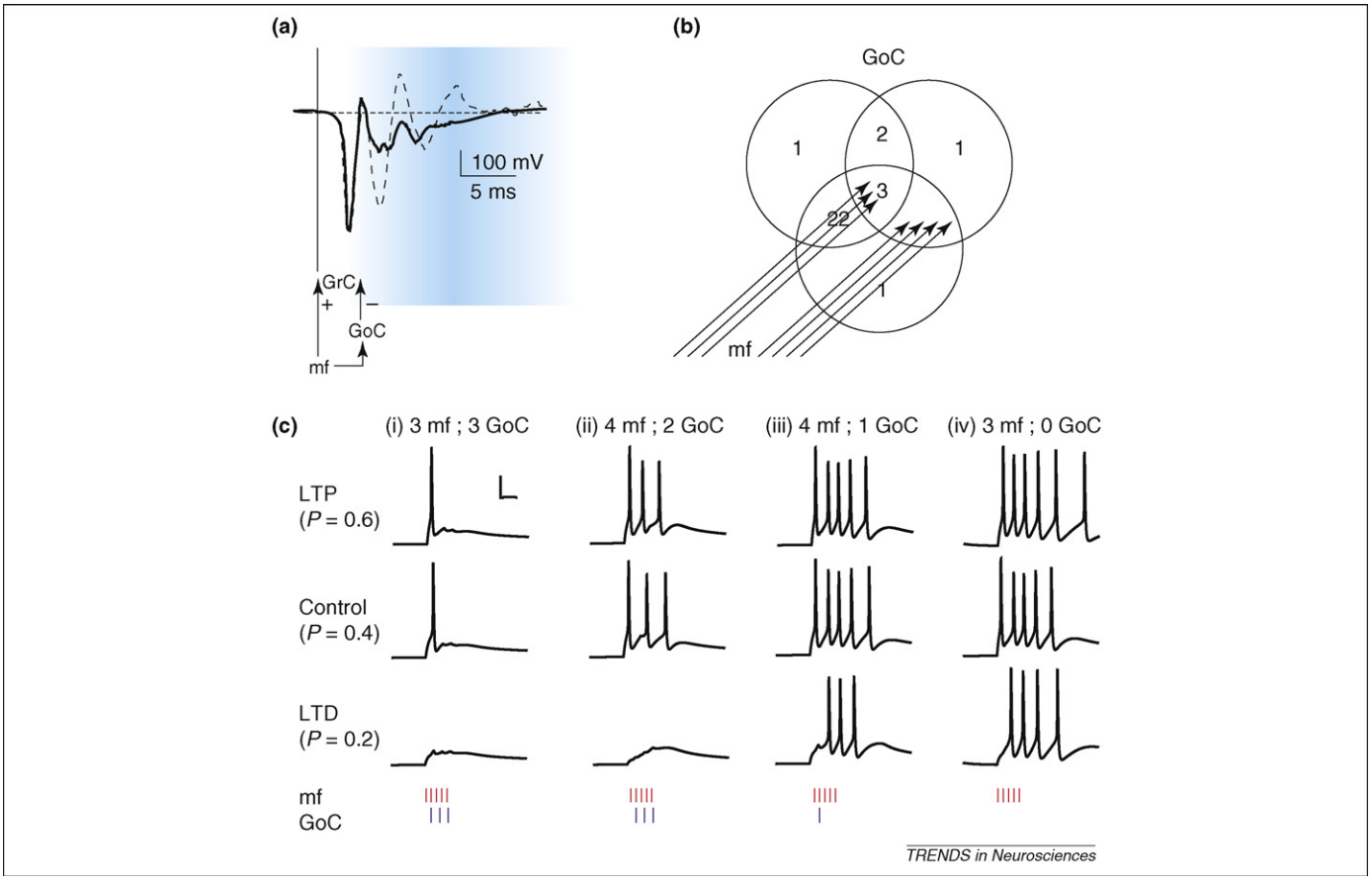

Figure 3. The 'window-matching' hypothesis. **(a)** When a group of mossy fibers (mfs) discharges, granule cells (GrCs) and Golgi cells (GoCs) are co-excited [28,29]. The Golgi cells, through feedforward inhibition, set a ~5 ms window for granule cell responsiveness. If the mossy-fiber–granule-cell synapse is in the LTP state (and coincident activity is high) then membrane potential rises rapidly and a spike or a short spike burst can pass through the permissive window. If the mossy-fiber–granule-cell synapse is in the LTD state (and coincident activity is low) then spike threshold is not attained until the arrival of inhibition, so that spikes can hardly be generated. The traces show that inhibition blocks the second (but not the first) spike in a field recording: inhibition is present in the continuous trace but is blocked by bicuculline in the dashed trace (adapted from Ref. [47]). The blue shadowing indicates the time course of granule cell inhibitory postsynaptic currents and represents the intensity of inhibition. **(b)** The mossy fibers and Golgi cells combined determine the efficiency of the window-matching mechanism. **(c)** Mathematical simulations of the window-matching hypothesis using the Nieus model of the granule cell [66] (further implemented by S. Diwakar and E. D'Angelo, unpublished). Various combinations of activity are shown following the arrangements shown in (b). The three rows represent release probability in mossy-fiber–granule-cell synapses in basal conditions ($P = 0.4$) and during LTD or LTP (either $P = 0.2$ or $P = 0.6$; [64]). Under physiological conditions (i and ii), mossy fibers [38,39] and Golgi cells [29,35,36] generate short high-frequency spike bursts (see also Refs [53,68]). The window-matching effect is evident when passing from low to high release probability (at $P = 0.2$ the granule cell does not respond). When inhibition is reduced below a certain threshold (the Golgi cell emits a single spike) (iii) the window effect is weaker, although regulation of first-spike delay remains (the delay is much longer at $P = 0.2$ than at higher release probabilities). The total absence of inhibition (as during experimental application of bicuculline) (iv) switches off the window control mechanism and further reduces the control over first-spike delay. The mossy fiber and Golgi cell impulses are indicated by red and blue marks, respectively. This simulation indicates that the variety of responses observed with whole-cell recordings *in vivo* [38,39] can reflect different combinations of excitation and inhibition in single granule cells.

motor output is understood, we might start to comprehend why the granular layer is well equipped to modify and distribute temporally relevant signals.

Recently, various studies indicated that the precise temporal patterns of the simple-spike activities of Purkinje cells are indeed relevant for cerebellar motor control. For example, an increase in irregularity of Purkinje cell firing, as can be observed in *tottering* mouse mutants, results in a reduced amplitude of compensatory eye movements [76] (Figure 4). Similarly, but in the opposite direction, an increase in the regularity of simple-spike activities, as can be observed after blockage of the molecular layer interneurons, results in reduced consolidation of motor learning and inability to adapt the phase of compensatory eye movements*. Importantly, both of these changes in regularity of firing occur without any obvious impact on the average firing frequency of the simple-spike activities during the movements, indicating that it must be the precise temporal pattern that is carrying the relevant coding. This notion is further supported by the fact that changes in behavioral state and tactile stimulation can affect the precision of Purkinje cell spiking patterns, as analyzed with the use of CV2 (coefficient of variation for consecutive interspike intervals) values [77]. The possibility that changes in temporal coding in the granule cell layer are also sufficient to induce changes in motor behavior is raised by the finding that cell-specific blockage of LTD at the parallel-fiber–Purkinje-cell synapse can lead to both the occurrence of interspike intervals with long durations and impaired motor learning, whereas the average firing frequency again is not affected [19,42,19,78,79].

Timing and the modular organization of cerebellar motor output

If it is indeed the precise temporal coding in Purkinje cells that plays an important part in controlling motor behavior,

* Schonewille, M. *et al.* (2007). Interneurons in the molecular layer of the cerebellum are required for consolidation of motor learning. Program No. 190.13. 2007 Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience, 2007 (www.sfn.org).

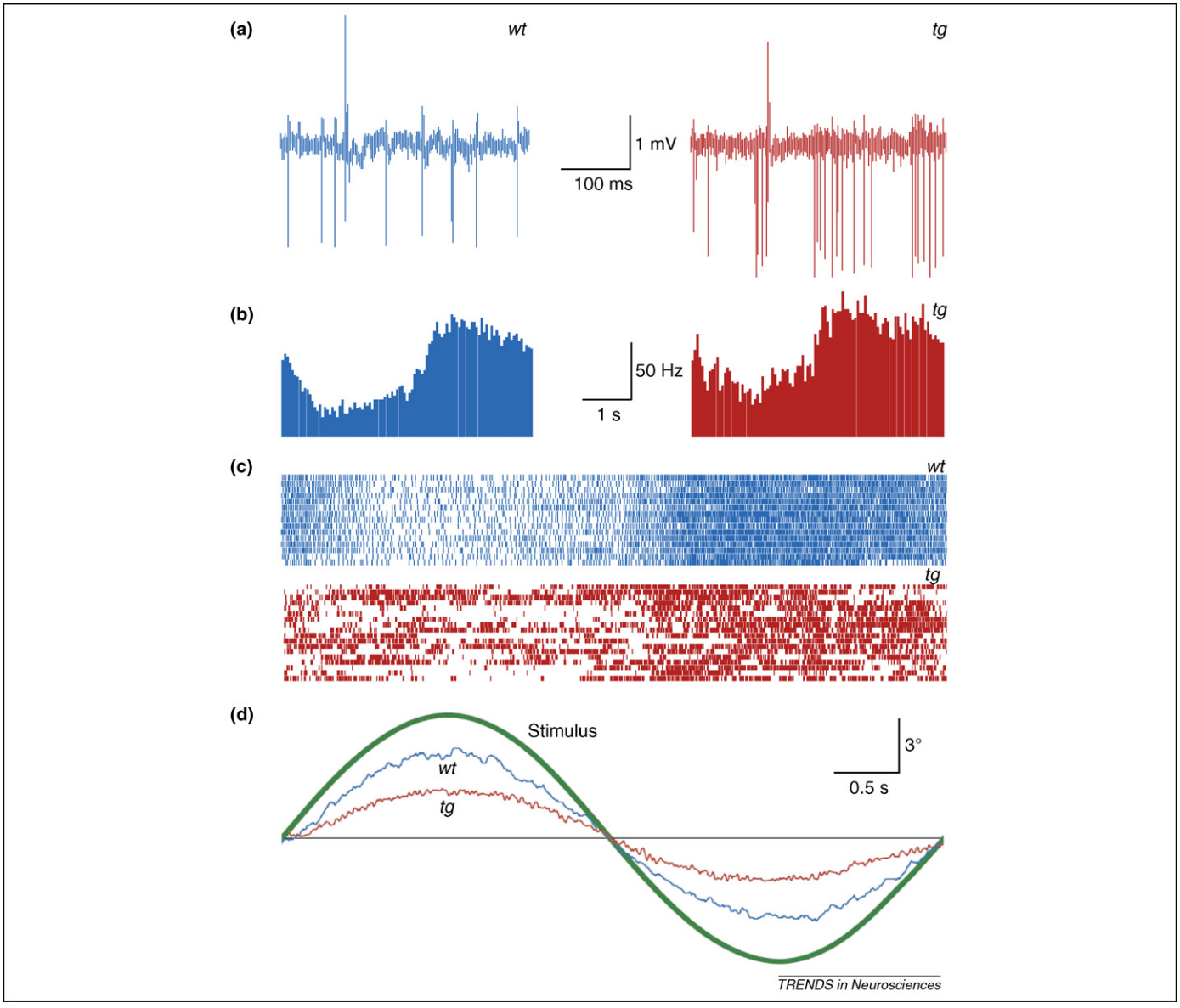

Figure 4. Impact of regularity of Purkinje cell firing on motor behavior. **(a)** Raw traces of simple-spike activities (spikes going down) show that those of *tottering* mouse mutants (*tg*, red) are much more irregular than those of wild-type littermates (*wt*, blue), whereas their complex-spike activities are normal (spikes going up). **(b)** Peri-stimulus histograms of Purkinje cells in the flocculus of the vestibulo-cerebellum of *tottering* mice show, on average, a normal simple-spike modulation during compensatory eye-movement responses to optokinetic stimulation (0.2 Hz at 6.3° amplitude). **(c)** However, raster plots show that their irregularity is greatly enhanced compared with that in wild types. **(d)** Eye-movement recordings during the same optokinetic stimulation (green) show that the amplitude of the eye movements in the *tottering* mice was significantly reduced. These data indicate that a normal average firing frequency of simple-spike activities is not sufficient for normal compensatory eye movements; the level of regularity also has to be optimal (for further explanation see Ref. [76]).

it becomes difficult to understand how Purkinje cells influence the DCN neurons unless they do so in a coherent fashion within a cerebellar module (we recall that modules assemble cortical microzones within specific extracerebellar circuits comprising the inferior olive and DCN; for anatomical and functional definitions see Refs [5,8,10]). In other words, if Purkinje cells act as independent units, it might be expected that the individual temporal patterns are averaged out at the DCN. However, if a sagittal stripe of Purkinje cells of a particular module, which all project to a particular DCN of the olivo-cerebellar system, acts coherently in that all Purkinje cells show the same or similar temporal pattern(s) of spikes and/or pauses within the same time windows, it seems much more likely that such patterns will indeed be recognized and will have a profound impact at their target neurons in the DCN. Yet, then the question arises as to how the different Purkinje cells within a module might create coherence in their simple-spike activities. There are at least three main possibilities that should be considered to explain this phenomenon, which apparently occurs in awake behaving animals [80].

First, Purkinje cells can be entrained in coherent molecular-layer oscillations at high-frequency ranges >80 Hz and emit spikes at the somewhat lower γ frequency that are still in phase with the beat of the high-frequency rhythm [81–83]. Thus, facilitated by gap junctional coupling and/or recurrent inhibition in the molecular layer, Purkinje cell outputs could, in principle, be emitted synchronously and in phase with the oscillation but at a lower frequency. However, these oscillations tend to weaken in

awake behaving animals, occur only in particular parts of the cerebellum and/or do not follow the sagittal modular distribution pattern (for commentary see Ref. [43]).

Second, simple-spike coherence might, in principle, be enhanced or even induced by synchronized climbing fiber activities [80,84–86], especially because simple-spike synchrony is enhanced when complex-spike synchrony is enhanced [13,80]. However, the synchronized simple-spike activities in a Purkinje cell pair do not follow directly in time that of their synchronized complex-spike activities [80] (C.I. De Zeeuw, unpublished). Moreover, the length of the pause in simple-spike activities directly after the complex spike, the so called climbing fiber pause, can also not be related to particular behavioral functions [30].

Third, induction of parallel fiber LTD or LTP by the presence or absence of climbing fiber activity might, in principle, induce traces of specific temporal patterns in simple-spike activities [42,57,87]. In fact, such patterns could even occur only during the training process and disappear once the learning process is finalized. However, in that scenario, a stronger correlation among simple-spike synchrony and complex-spike synchrony at the beginning of training paradigms such as continuous optokinetic stimulation in one direction would be expected [13,80]. Because such correlations have also not been found [13,80], it is parsimonious to conclude that coherence among simple-spike activities in different Purkinje cells is, for a substantial part, formed upstream (i.e. in the granular layer).

Several anatomical factors support the possibility that the formation of specific temporal patterns in the granular network of a cerebellar module contributes to the generation of specific temporal patterns of simple-spike activities in microzones of Purkinje cells. These include the fact that (i) compared with the parallel fibers, the ascending granule cell axons might exert a powerful activation of overlaying groups of Purkinje cells within the same microzone [70,88–90]; (ii) the modular oriented climbing fibers activate stellate and basket cells, which in turn inhibit both Purkinje and Golgi cells in the same microzone [68] (climbing fibers also probably provide excitatory collaterals to the Golgi cells [91]); (iii) individual Golgi cell axons in the granular layer are also focused on individual modules (R. Hawkes, personal commununication); (iv) recurrent collaterals of Purkinje cells also seem to be restricted to individual modules [92]; and (v) the feedback from the DCN to the granular layer is mostly also organized in the same modules [93,94]. Moreover, the temporal patterns generated in the granular layer might be further fine-tuned in the molecular layer because the axons of both stellate cells and basket cells are also mostly oriented in the sagittal plane of the modules [11]. It is, therefore, not only the cell physiological properties that are in line with the idea that the granular layer operates as modular temporal pattern generator but also, in fact, all connections that provide a direct or indirect feedback connection to the granular layer. Thus, we propose here that it is one of the main functions of the granular network to generate specific temporal patterns in the granule cell axons within a cerebellar module that will enable microzones of Purkinje cells to fire with specific temporal patterns of simple-spike activities in window ranges of ~5 ms.

Granular layer dynamics with tonic mossy fiber discharge

Although bursting is a characteristic modality of mossy fiber discharge evoked in isolation during punctuate stimulation, more complex sensory inputs can evoke a mixture of phasic, phasic-tonic and tonic patterns along different mossy fibers. This has been shown for various sensory pathways, including those originating from muscle spindles, skin and vestibular organs [59,95–98]. What will be the impact of tonic discharge on the window-matching mechanism? Computational modeling predicts that a continuous stimulation would evoke repetitive regular cycles of granule cell discharge enforced by feedback Golgi cell inhibition [32,49], and high-frequency activity has, indeed, been reported in the cerebellum [81,99]. Thus, continuous discharges would be fragmented by the granular layer circuit into short repetitive time windows. Intervening bursts, signaling transitions in stimulus intensity, could interact with such oscillation and, if strong enough, phase-reset the Golgi cells [48,55,56], which respond very rapidly to incoming inputs [9,28,29,88]. The window-matching mechanisms might, therefore, be embedded within a more organized system of oscillations (see Ref. [46] for similar consideration in the cerebral cortex), an aspect that deserves future experimental attention. Clearly, protracted mossy fiber activity has also the potential to enforce gain regulation [37], exploiting tonic inhibition [37,53,67]. Thus, gain regulation might coexist with the window-matching mechanism in the presence of tonic mossy fiber discharge.

A summary of concepts and conclusions

The granular layer has the potential to process incoming mossy fiber signals at the millisecond time scale generating an impressive number of spatio-temporal patterns through learning. Most remarkably, we propose that feed-forward Golgi cell inhibition generates a permissive time window of ~5 ms through which spikes can be optimally channeled to Purkinje cells. LTP and LTD at the mossy-fiber–granule-cell synapse would serve to determine whether excitatory postsynaptic potential temporal summation will enable spikes to be elicited in such a time window (hence the name of 'window-matching hypothesis'). The Golgi cells can extend this control over thousands of granule cells generating, therefore, a temporal frame for incoming signals. As a consequence the presentation of 5 ms patterns to Purkinje cells could enable a perceptron operation of these neurons. Clearly, these mechanisms could have a remarkable impact on cerebellar computation as a whole because these patterns will enable different Purkinje cells within individual modules to generate coherent simple-spike activities with specific interspike intervals over time.

There are ways to test the functional implications and the relative importance of the mechanisms reported here. The advances in voltage-sensitive dye imaging and multiple micro-wire recordings might be exploited to investigate spatio-temporal correlations in granular layer activities in response to specific stimulation and sensorimotor activity patterns. These patterns might then be reconstructed and analyzed by appropriate computational

models. Finally, specific mechanisms might be selectively manipulated in conditional genetic mutants enabling us to identify their impact on circuit functions and behaviors.

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