ANATOMICAL AND PHYSIOLOGICAL FOUNDATIONS OF CEREBELLAR INFORMATION PROCESSING

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Abstract | A coordinated movement is easy to recognize, but we know little about how it is achieved. In search of the neural basis of coordination, we present a model of spinocerebellar interactions in which the structure–functional organizing principle is a division of the cerebellum into discrete microcomplexes. Each microcomplex is the recipient of a specific motor error signal — that is, a signal that conveys information about an inappropriate movement. These signals are encoded by spinal reflex circuits and conveyed to the cerebellar cortex through climbing fibre afferents. This organization reveals salient features of cerebellar information processing, but also highlights the importance of systems level analysis for a fuller understanding of the neural mechanisms that underlie behaviour.

PARAVERMIS
A region on either side of the midline of the cerebellum that lies lateral to the vermis and medial to the hemisphere. It contains the cerebellar cortical zones C1, C2 and C3 and receives climbing fibre input from the inferior olive and projects to the nucleus interpositus. Here, the term is used to denote the functionally related C1, C3 and Y (but not the C2) zones.

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One of the major challenges of systems neuroscience is to understand the neural basis of perception and behaviour. Considerable progress has been made, for instance, with regard to the analysis of the neural mechanisms that underlie visual perception. In large part, this has been achieved by using a combination of anatomical tract tracing and physiological characterization of neuronal receptive fields[1]. By comparison, our understanding of movement control remains rather less complete. Nevertheless, over the past decade or two, a similar combination of systems level anatomical and physiological approaches has been used to unravel some of the intricacies of an important sensorimotor control system, namely the cerebellum.

Fundamental to the operation of any CNS structure is the information processing that it accomplishes. The cerebellum receives a wide variety of sensory inputs and generates motor-related outputs according to internal rules of computation. These rules are determined by the internal connectivity of cerebellar neuronal networks and the intrinsic properties of cerebellar neurons. Consequently, the information content of its inputs together with the structural organization of the internal circuitry of the cerebellum imposes constraints on theoretical models of cerebellar function. Effective communication between anatomists, physiologists and modellers is therefore essential for understanding how the cerebellum contributes to the control of movement and other processes.

With this outlook in mind, the aim of the present review is to summarize recent advances in our understanding of the anatomy and physiology of an important region of the cerebellum — the PARAVERMIS — and its influence on voluntary limb movements. The paravermis has abundant connections with the spinal cord, and we present evidence to indicate that a key organizing principle is its subdivision into an array of multizonal microcomplexes (MZMCs). The functional organization of these microcomplexes is thought to reflect spinal withdrawal reflex organization. As a result, individual cerebellar microcomplexes could be kept informed about inappropriate movements — that is, 'MOTOR ERRORS' — that are related to elementary movements of a limb, such as those that result from contractions of single muscles. By incorporating recent findings on intrinsic cerebellar cortical connectivity, we also speculate on how this modular arrangement might have a role in cerebellar contributions to movement control. It is important to emphasize, however, that the model presented here is derived mainly from studies of the
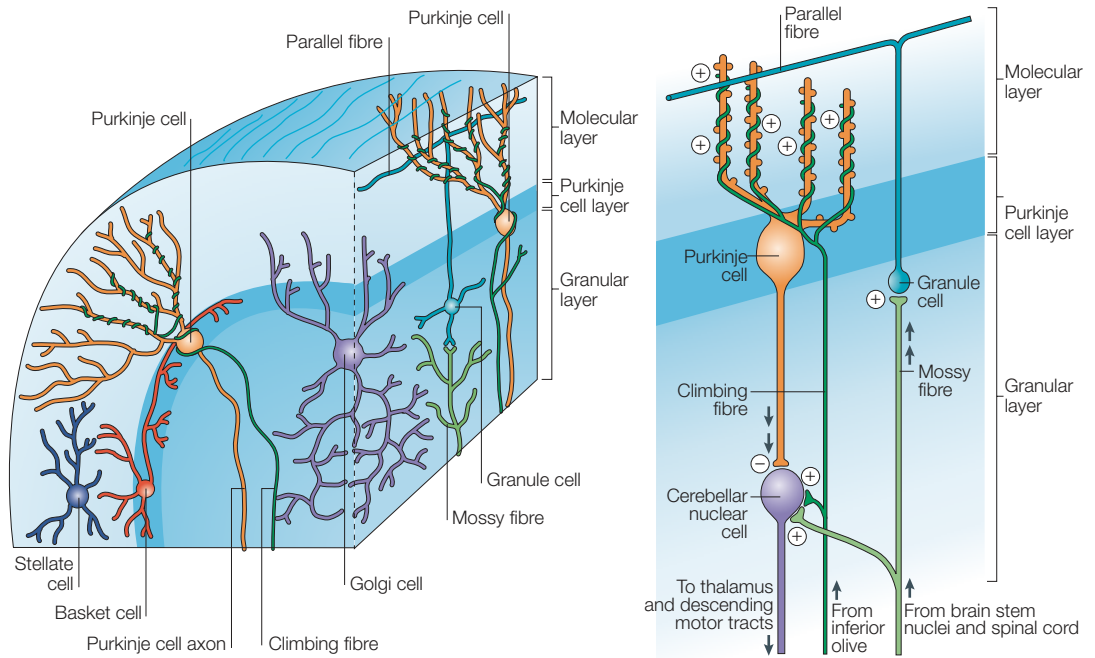
Figure 1 | **Basic structure of the cerebellar cortex.** There are two main afferents to the cerebellar cortex: climbing fibres, which make direct excitatory contact with the Purkinje cells, and mossy fibres, which terminate in the granular layer and make excitatory synaptic contacts mainly with granule cells, but also with Golgi cells. In some cases, the stem axons of climbing and mossy fibres also provide collaterals to the cerebellar nuclei en route to the cerebellar cortex. The ascending axons of the granule cells branch in a T-shaped manner to form the parallel fibres, which, in turn, make excitatory synaptic contacts with Purkinje cells and molecular layer interneurons — that is, stellate cells and basket cells. Typically, parallel fibres extend for several millimetres along the length of individual cerebellar folia[134,135]. With the exception of granule cells, all cerebellar cortical neurons, including the Purkinje cells, make inhibitory synaptic connections with their target neurons. Modified, with permission, from REF. 1 © (2004) Sinauer Associates.

MOTOR ERROR
In the case of motor commands, the difference between the actual motor command and the correct command, or between the intended and achieved movement. A simple example is the retinal slip signal, in which this difference is detected directly at the sensory surface by specialized retinal ganglion cells.

GAIN
The amplification factor that regulates the relationship between input and output, for instance, in a reflex circuit.

TIMING THEORY
Here, the term refers to Braitenberg's idea that parallel fibres provide delay lines for converting spatial patterns into temporal patterns.

LEARNED PATTERN RECOGNITION THEORIES
Here, the term refers to the theories of Marr and Albus, in which the cerebellum is viewed as a spatial pattern recognition device with learning capacity.

CONTROL THEORY
Here, the term refers to a conceptual framework wherein engineering control principles are applied to the modelling of CNS functions.

paravermal cerebellum and its connectivity with the spinal cord. The manner in which cerebellar control systems are connected to other structures in the CNS might vary, and this, in turn, might influence the role of any given cerebellar region[2]. Nevertheless, it is generally accepted (for reasons given below) that findings based on the investigation of one particular region of the cerebellum should be applicable to the cerebellum as a whole.

Concepts and models of cerebellar function

The importance of the cerebellum in the coordination of movement is undisputed[3–8], and a growing body of evidence indicates that it might also be involved in certain cognitive processes[9,10]. Cerebellar networks show long-term synaptic plasticity[11–14], which indicates that experience-dependent adaptive and learning processes are also a salient feature of cerebellar function[15–17]. Such adaptive capacity is a key feature of many current theories of cerebellar function.

Indeed, modelling has a long tradition in cerebellar studies and models differ in many respects (see REF. 18 for a review). Some models address the involvement of the cerebellum in specific reflex behaviours, such as the adaptive regulation of GAIN in the vestibulo–ocular reflex (see REF. 19 for a recent review), or the role of the cerebellum in classical conditioning of eye-blink reflexes (see REF. 20 for a recent review). More general cerebellar models range from those inspired chiefly by cerebellar cytoarchitecture and the physiological properties of its constituent

neurons (historically starting with the TIMING THEORY[21] and the LEARNED PATTERN RECOGNITION THEORIES[22,23]) to those motivated more by CONTROL THEORY[24–26]. The model presented here builds on a specific tradition that emphasizes the division of the cerebellum into a collection of 'modules' defined by structure–function relationships. These modules are thought to form the basis for information processing performed by the cerebellum[2,27,28].

Basic structure of the cerebellar cortex

Throughout its highly convoluted extent, the cerebellum can be divided into three cortical layers with the same basic neuronal circuitry everywhere, which involves five main cell types (FIG. 1). The most conspicuous of these are the Purkinje cells, which form an orderly monolayer interposed between the granular and molecular layers, extending their planar dendritic trees into the molecular layer above. As these cells are the sole output neurons of the cerebellar cortex they are central to cerebellar cortical information processing.

The granular layer below the Purkinje cells derives its name from the small, densely packed granule cells that send their axons into the molecular layer, where they bifurcate to become parallel fibres (FIG. 1). These course parallel to the long axis of each folium and as a result they intersect the fan-like dendritic trees of many Purkinje cells. Mossy fibre afferents target granule cells and, therefore, excite the Purkinje cells indirectly through the granule cell–parallel fibre pathway, which causes the
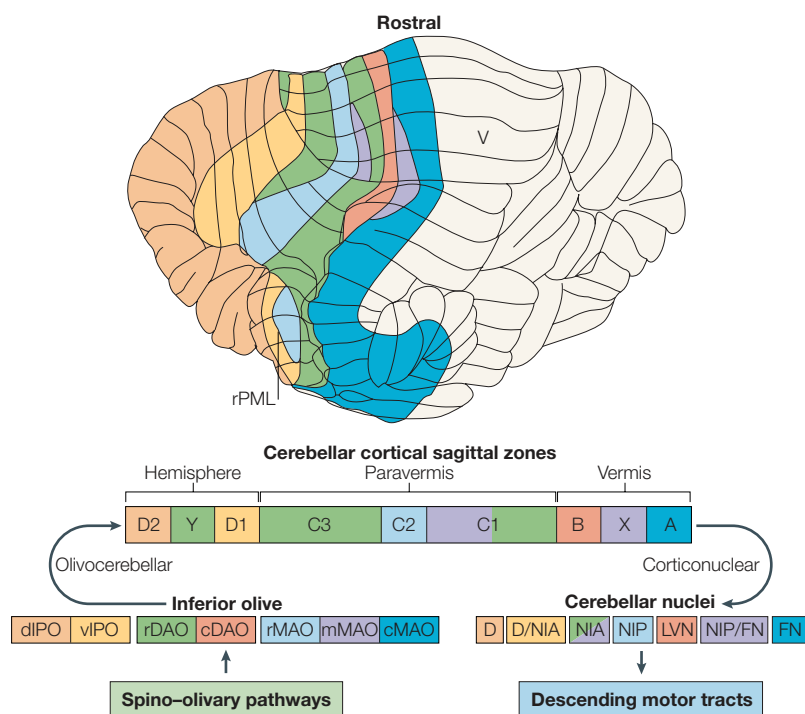
Figure 2 | **Connectivity of the cerebellum.** The top panel shows a dorsal view of the cat cerebellum, indicating the approximate location of different sagittal zones on the cerebellar surface. In the simplified block diagrams below, matching colours show, for individual cerebellar cortical zones, the sites of origin of climbing fibres in the contralateral inferior olive, and the corresponding corticonuclear output targets in the ipsilateral cerebellar nuclei. Different regions of the inferior olive receive signals from the spinal cord through an array of spino–olivary pathways, and individual cerebellar nuclei influence descending motor pathways with different responsibilities in motor control. As a result, zones located in different regions of the cerebellar cortex are thought to be associated with different aspects of motor control. For example, the C1, C3 and Y zones receive input from the postsynaptic dorsal column pathway[58] through the rostral part of the dorsal accessory olive and output through the nucleus interpositus anterior (NIA) to the rubrospinal and corticospinal tracts. These tracts are especially concerned with the control of voluntary limb movements, such as walking and goal-directed reaching[136,137]. Lesions in experimental animals indicate that the paravermis is important for precision limb movements such as skilled walking[7,138] and goal-directed reaching[139–143]. An important principle seems to be that coordination is achieved by anticipatory control and compensation of inter-joint interactions characteristic of multi-joint limb movements[141]. A diminished capacity to generate such compensatory activity in a predictive manner seems to be a cardinal cerebellar symptom in all species studied, including man[144,145]. Conspicuously, cerebellar lesions result in deficits both of isolated reach and isolated grasp, and of the coupling between these two components of a goal-directed movement[146]. cDAO, caudal part of dorsal accessory olive; cMAO, medial accessory olive; D, dentate nucleus; dIPO, dorsal lamella of the principal olive; FN, fastigial nucleus; LVN, lateral vestibular nucleus; mMAO, middle part of medial accessory olive; NIP, nucleus interpositus posterior; rDAO, rostral part of dorsal accessory olive; rMAO, rostral medial accessory olive; rPML, rostral folia of the paramedian lobule of the posterior lobe; V, lobule Va–c of the anterior lobe; vIPO, ventral lamella of the principal olive.

Purkinje cells to discharge 'simple spikes' (conventional action potentials). They also contact various types of interneuron in the cerebellar cortex, both directly and indirectly through the parallel fibres (not shown in FIG. 1).

The other main class of cerebellar afferent is the climbing fibres, which arise exclusively from the inferior olive, a well-defined complex of sub-nuclei in the ventral part of the caudal brain stem (for further details, see REFS 29–31). In marked contrast to the indirect influence of mossy fibres, the climbing fibres make direct synaptic contact with Purkinje cells (FIG. 1). Moreover, each Purkinje cell receives input from just one climbing fibre,

but the contact is so extensive that climbing fibres generate the largest depolarizing event seen in any neuron: a highly characteristic burst of impulses known as a climbing fibre response[32] or complex spike[33].

Functional microanatomy of cerebellar circuitry

Given the uniform structure of the cerebellar cortex, the basic neural computation performed is assumed to be similar throughout, whether used for the control of autonomic functions, limb movements or higher functions such as language. Notwithstanding regional differences in chemoarchitecture (for example, in the cerebellar cortical distribution of molecular markers such as zebrin[34–36]), it follows that functional differences between various parts of the cerebellar cortex must arise primarily, if not exclusively, from local differences in input and output connectivity. It is, therefore, understandable that considerable emphasis has been placed on the study of cerebellar cortical input and output pathways (for 'historical' references, see REFS 37,38). Levels of resolution have been gradually refined, and the modern key organizing principle, on the basis of detailed studies mainly in cats and rats, is a division of the cerebellar cortex into a series of longitudinally oriented strips or 'sagittal zones'. Individual zones are typically 1–2 mm in width, running across the cerebellar lobules for many millimetres in the rostro-caudal plane[28,37,39,40] (FIG. 2). The Purkinje cells in each zone receive climbing fibre input from a circumscribed region of the inferior olive and, in turn, send output to a circumscribed region in the cerebellar nuclei, thereby forming discrete olivo–cortico–nuclear complexes[2] (FIG. 2).

For the olivocerebellar climbing fibre input to each cerebellar cortical zone, there is a corresponding detailed topography. In brief, rostral and caudal subdivisions of the contralateral inferior olive map onto zones located in the lateral (paravermal and hemispheral) and medial (vermal) parts of the ipsilateral cerebellar cortex. More detailed anatomical tract tracing studies in rats and cats indicate that a given cerebellar cortical zone receives climbing fibre input from a discrete cluster of olive cells that often form a rostrocaudally elongated column in the olive[41–46]. Also, olivocerebellar axons branch preferentially in the rostrocaudal axis so that individual olive cells typically provide a single climbing fibre to each of several Purkinje cells at different points along the length of a single cerebellar cortical zone[47]. Climbing fibres therefore impose a very precise order on cerebellar cortical organization, which presumably has important implications for function. Therefore, it is perhaps not surprising that the integrity of the climbing fibre projection is vital to normal cerebellar contributions to movement control. If the cerebellum is deprived of its climbing fibre input, severe disorders to movement result that are similar in many respects to those that arise after damage to the cerebellum itself[48–50]. So, understanding the functional organization of climbing fibres is likely to be essential to establishing how the cerebellum accomplishes its various roles.
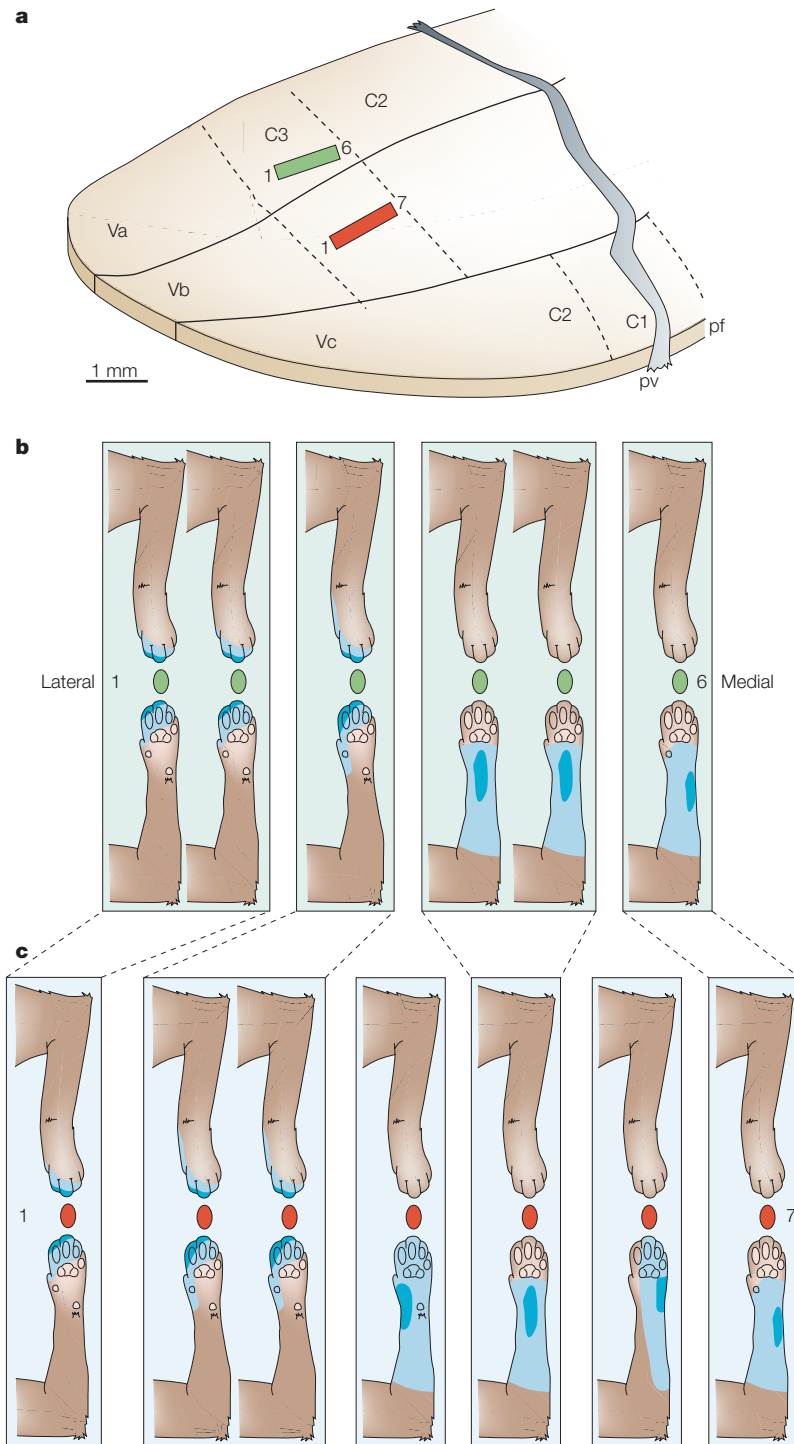
Figure 3 | **Mapping of cerebellar cortical microzones. a** | A dorsal view of the cat paravermal cerebellum in the region of lobules Va–c. The boundaries of individual zones are delimited by dashed lines. A mediolateral sequence of Purkinje cell recordings was made at two different rostrocaudal levels in the C3 zone, and the climbing fibre receptive fields on the ipsilateral forelimb were mapped using quantifiable nociceptive input. **b,c** | Each set of figurines of the dorsal and ventral aspects of the ipsilateral forelimb shows the receptive fields on the skin obtained from the two corresponding colour-coded sequences of recording tracks. Dark blue areas denote regions of skin that generated maximal response; light blue areas denote total extent of receptive field. Note the transition of receptive fields within each mediolateral sequence, defining the boundary between adjacent microzones (boxed), and that individual microzones that are present at both rostrocaudal levels are arranged in the same mediolateral order (linked by dashed lines). See main text for further details. pv; paravermal vein; pf, primary fissure. Data from REF. 54.

MZMCs are fundamental cerebellar processing units. In terms of functional organization, different parts of the olive convey information from one or several specific spino–olivo–cerebellar pathways and, consequently, each zone can be readily identified with electrophysiological mapping techniques[39,40,51]. Within each zone, smaller units known as 'microzones' can also be readily identified electrophysiologically[52–55]. These are defined by the specific functional characteristics of their climbing fibre input. Therefore, a microzone is a narrow longitudinal strip of cerebellar cortex within which all Purkinje cells receive climbing fibre-mediated input with similar receptive field identity. In the case of the paravermal cerebellum, each climbing fibre has a particular receptive field on the skin, usually located on one of the ipsilateral limbs (FIG. 3). This results in an intricate but highly reproducible map within the cerebellar cortex that is particularly well studied in the forelimb area of the paravermal C3 zone of the cat[54,56–58]. Microzones are also the defining components of olivo–cortico–nuclear microcomplexes[2,27], which might be thought of as the cerebellar counterparts of cerebral cortical columns.
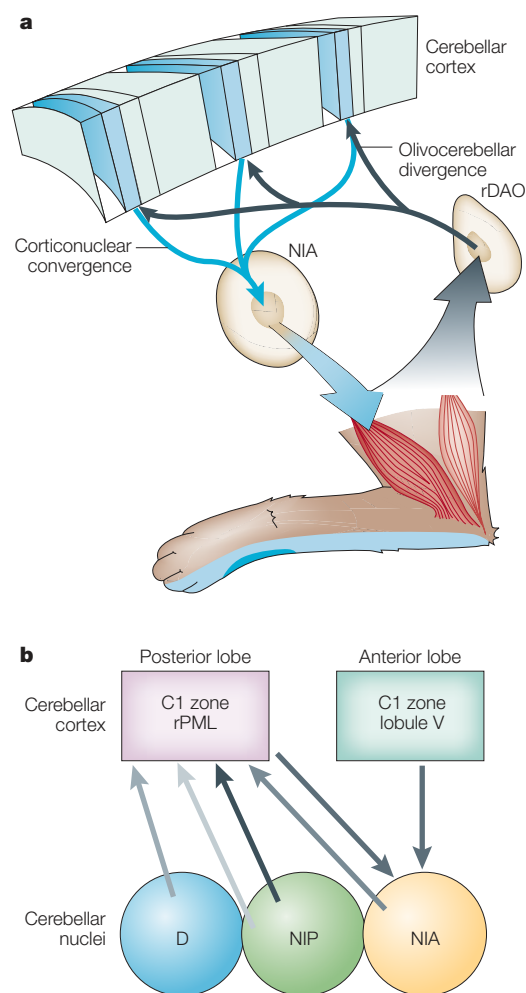
Both electrophysiological and anatomical studies in cats have shown that the stem axons of olive cells can branch to innervate microzones in different cerebellar cortical zones and/or in different parts of the same zone[57,59]. For example, some axons branch widely to innervate microzones located in the anterior and posterior lobes[45,60]. This olivocerebellar divergence has two important implications. First, it provides a structural basis for a functional linkage of two or more microzones with the same climbing fibre receptive field, but with an independent cerebellar cortical location. Second, it indicates that the map related to the ipsilateral body surface generated by climbing fibre input that terminates in the C3 zone is at least partly repeated in the cerebellar cortical C1 and Y zones (FIG. 2). The functional organization of climbing fibre input to the C1 zone supports this assumption[61].

An important additional finding is that the multiple paravermal cerebellar cortical representations defined by climbing fibre input to the C1, C3 and Y zones appear to converge onto a single representation in one of the paravermal output nuclei: the anterior division of nucleus interpositus (NIA)[62]. This convergence seems to occur between parts of zones with common climbing fibre input, regardless of whether they are separated mediolaterally or rostrocaudally in the expanse of the cerebellar cortical sheet. Taken together, these observations led to the hypothesis that many, if not all, of the basic structural–functional units of the paravermal cerebellum are multizonal microcomplexes (MZMCs)[62,63]. Such an arrangement, whereby a strict correspondence is maintained between input and output in spatially separate microzones, is an extension of the ideas originally put forward by Oscarsson[27] and elaborated by Ito[2]. The modification here is that there is a specific convergence of information to the same region of a cerebellar nucleus that arises from multiple similar microzones in the cerebellar cortex.

More specifically, each MZMC can be defined as two or more microzones located in different parts of the paravermal cerebellar cortex that receive climbing fibre input with similar receptive field characteristics (olivocerebellar divergence), and that provide cerebellar corticonuclear output to a common group of cerebellar nuclear neurons (cerebellar corticonuclear convergence; FIG. 4a). The most direct evidence to support this arrangement so far has been obtained from cats by using electrophysiological techniques in combination with a bidirectional double-tracer method[64]. Injections of tracer were made into two cerebellar cortical regions in the paravermal C1 and C3 zones with similar climbing fibre receptive field characteristics. The degree of overlap in NIA between the two territories occupied by anterogradely labelled cerebellar cortico-nuclear terminals was in strict proportion to the number of olive cells that were double-labelled with retrograde tracer. This shows a close correspondence between olivocerebellar divergence and cerebellar corticonuclear convergence from functionally similar but spatially separate cerebellar cortical areas, which is entirely in agreement with the proposed MZMC organization of the paravermis.

MZMC structure allows parallel information processing. What is the functional significance of the distributed nature of the MZMCs? Besides climbing fibres, the other main input to the cerebellum is the mossy fibre projection (FIG. 1), which arises from a wide variety of sources, including the spinal cord[65], numerous brain stem nuclei (especially the pons; see REF. 66 for a review) and the cerebellum itself [67–70]. The organization of mossy fibres in relation to cerebellar cortical micro-zones is of particular interest with regard to the spatial distribution of individual paravermal MZMCs. At least hypothetically, microzones in different parts of the cerebellar cortex that are associated with an individual MZMC could process in parallel and integrate infor-mation derived from mossy fibre inputs that arise from different origins. But is there any evidence for such an arrangement?

So far, the most detailed anatomical tracer studies that address this possibility have been confined to investigating differences in mossy fibre inputs at the zonal level of resolution. For example, the C1 and C3 zones in cats have been found to have significant quan-titative differences in the density of their mossy fibre projections from the basilar pontine nuclei, the lateral reticular nucleus and the nucleus reticularis tegmenti pontis[71,72]. This indicates that different mossy fibre-mediated information might be processed in these two zones, potentially by microzones that belong to the same MZMC. However, perhaps the most striking dis-tinction found so far is that all of the paravermal zones differ in the extent to which they are targets for corti-cally directed axons of cerebellar nuclear cells, which probably terminate as mossy fibres in the granular layer. The nucleus interpositus posterior (NIP) seems to be the most important source of these nucleocortical pro-jections, and there is a degree of non-reciprocity in the

Figure 4 | **Parallel processing in cerebellar microcomplexes. a** | The basic structural design of a paravermal multizonal microcomplex (MZMC) as deduced from electrophysiological mapping studies[62] and supported by neuroanatomical tract tracing experiments[64,147]. Each paravermal MZMC is defined by divergence of information in the olivocerebellar projection and convergence of information in the corresponding corticonuclear projection (see text for further details). **b** | Schematic diagram summarizing the cerebellar corticonuclear and nucleocortical connections of the C1 zone in the forelimb-receiving parts of the anterior and posterior lobes of the cat cerebellum. Downward arrows indicate the corticonuclear projections that target the cerebellar nuclei. Upward arrows indicate the corresponding nucleocortical projections. For the latter, the depth of shading of each arrow indicates the density of the projection from each of the cerebellar nuclei; darker arrows indicates greater density. Note that the C1 zone in the forelimb-receiving part of the anterior lobe (lobule V) receives no nucleocortical projection, whereas the same zone in the homologous part of the posterior lobe receives an extensive nucleocortical projection. This is consistent with the possibility that individual microzones that belong to the same MZMC, but are located in different parts of the cerebellar cortex, receive distinct patterns of mossy fibre inputs (see text for further details). D, Dentate nucleus; NIA, nucleus interpositus anterior; NIP, nucleus interpositus posterior; rDAO, rostral part of the dorsal accessory olive; rPML, rostral folia of paramedian lobule; lobule V, lobule Va–c. Panel **a** modified, with permission, from REF. 148 © (1998) American Physiological Society. Panel **b** data from REFS 68–70.
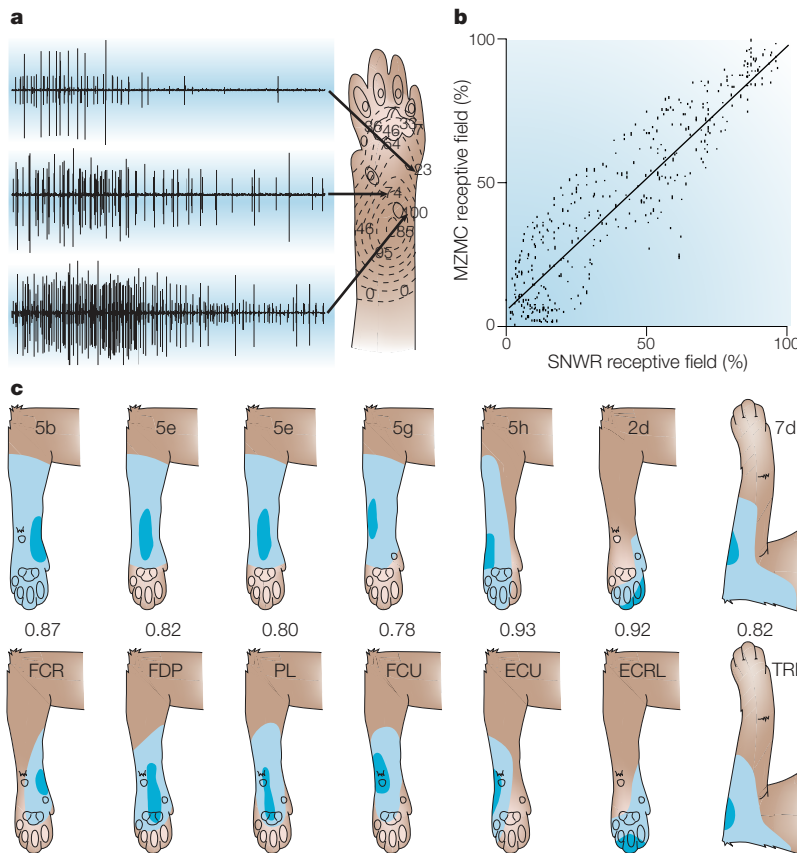
Figure 5 | **Quantitative comparison of receptive fields. a** | Samples of electromyographic (EMG) activity evoked by noxious mechanical stimulation of skin sites with different sensitivity (left). A sample receptive field map of a single palmar flexor muscle constructed by quantification of EMG responses shown on the ventral side of the left forelimb of the cat (right). Numbers indicate response magnitude as a percentage of maximal response. Dashed lines indicate mathematically derived iso-response levels. This procedure was used to determine the receptive fields that are shown in a simplified form in **c** (bottom row) such that dark blue areas denote the receptive field areas with maximal response and light blue areas denote the total extent of receptive fields. **b** | Example graph plotting the quantitative data on receptive field sensitivity (expressed as a percentage of maximal response) of climbing fibre input to a paravermal multizonal microcomplex (MZMC) as a function of the equivalent data for the corresponding spinal nociceptive withdrawal reflex (SNWR). The correlation coefficient obtained provides an objective measure of the degree of similarity between receptive fields in the two systems. **c** | Sample nociceptive climbing fibre receptive fields of individual Purkinje cells (top, based on complex spike activity) and individual forelimb muscles (bottom, based on EMG activity) both using the method described in **a**. Correlation coefficients for the examples shown were, on average, 0.85. The close correspondence indicates that individual climbing fibre afferents convey information about the skin surface representing an imprint of withdrawal efficacy of a single muscle. In addition, the same climbing fibre receives convergent input from group II muscle afferents, originating mainly in the same muscle[84]. Therefore, an individual climbing fibre monitors both the input and the output element of an individual SNWR module (compare with FIG. 10). The functional significance of the muscle afferent input is not known, as cutaneous and muscle afferent input interactions have not been investigated. However, the convergence emphasizes the integrated sensorimotor nature of the paravermal climbing fibre input. 5b, e, g, h, 2d and 7d, denote classification of different climbing fibre microzones (see REF. 54 for details). ECRL, extensor carpi radialis longus; ECU, extensor carpi ulnaris; FCR, flexor carpi radialis; FCU, flexor carpi ulnaris; FDP, flexor digitorum profundus; PL, palmaris longus; TRI, triceps. Panels **a** and **c** modified, with permission, from REF. 84 © (2002) Blackwell Publishing Ltd.

topography of the projection[68–70]. For example, in the anterior lobe of the cat cerebellum, the C1 zone receives little or no such projection, whereas in the posterior lobe, the same zone has an appreciable nucleocortical projection, mainly from NIP, but also, to a lesser extent, from NIA and dentate nucleus (FIG. 4b).

This implies that output from different cerebellar cortical zones (the C2 zone and also the C1 and D zones to some extent; see FIG. 2) is fed back to the granular layer of one portion of the C1 zone, but not to another. Such findings are consistent with the notion that the structural organization of the paravermal cerebellar cortex allows similar climbing fibre inputs to integrate with mossy fibre signals that arise from different sources.

Functional significance of climbing fibres

Many different functions have been suggested for climbing fibres (see REF. 73 for a review), but two concepts remain central in the context of movement control. First, that climbing fibres mediate motor error signals[2] and, second, that climbing fibre activity is instrumental in the induction of synaptic plasticity underlying motor adaptation and motor learning[74]. These concepts are often linked to one another, and both are supported, and were, in fact, inspired, by theoretical considerations of cerebellar cortical infrastructure[22,23].

Types of information mediated by climbing fibres. Experimentally, more or less straightforward relationships between the occurrence of climbing fibre signals and various types of unexpected perturbation of movement have been described[74–77] (however, see REF. 78 for an alternative view). Although these and similar findings have been taken as support for the ERROR-DETECTION HYPOTHESIS, theorists have raised concerns as to the plausibility and physiological origin of a true motor error signal. In particular, the nature of such a signal does not seem compatible with the 'sensory' characteristics of climbing fibre responses[24,79]. A key issue, therefore, concerns whether climbing fibre signals should instead be thought to signal sensory errors (defined as the sensory consequences of a motor error), and, if so, how these might be transformed into motor error signals. According to some theories of cerebellar function, such a transformation is a prerequisite for the use of sensory information to form and update internal cerebellar models of movements or movement components[25,26] (but see REFS 79,80 for an alternative view).

As a possible solution to this motor error problem, it has been proposed that climbing fibre signals encode sensory information in a motor frame of reference[24,81,82]. If this were the case, then it might be expected that climbing fibre responses would have both sensory and motor characteristics. Experimental evidence consistent with this possibility has been obtained in the cerebellar ventral PARAFLOCCULUS[83]. In this system, patterns of climbing fibre activity during the ocular following response indicate not only that climbing fibre signals represent sensory input (visual stimuli associated with RETINAL SLIP), but also that their activation seems to relate to the direction of eye movements, and in particular, to the axis of contraction of individual eye muscles. This indicates that the climbing fibre input to the cerebellar ventral paraflocculus is conveyed by a sensorimotor brain stem system that
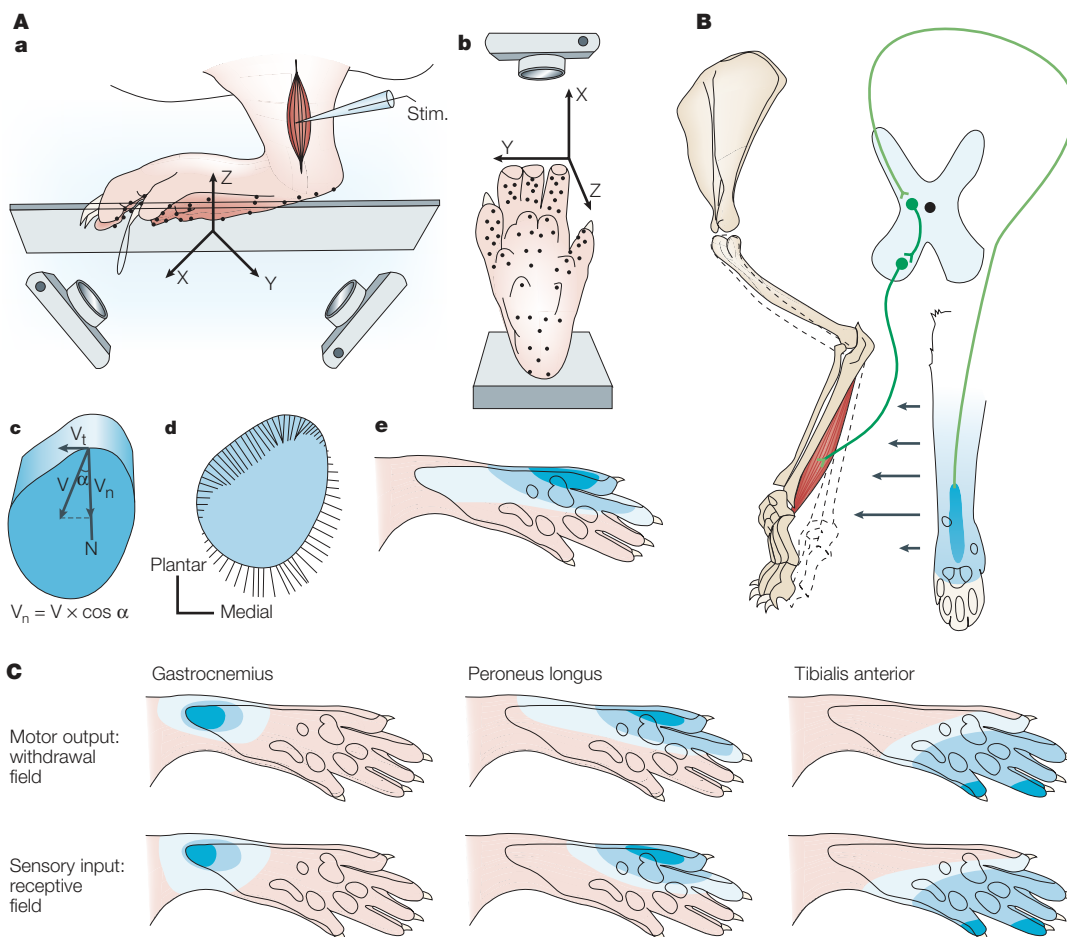
Figure 6 | **Sensorimotor transformations in spinal nociceptive withdrawal reflex modules. A** | A method to document and analyse how movements caused by the contraction of single muscles move a skin surface in three dimensions. **a** | Movements of the right hind paw of the rat were elicited by intra-muscular stimulation (stim.) of individual muscles and documented with two cameras placed at right angles to each other. Dots indicate the points on the skin that were traced by motion analysis. **b** | The shape of each paw segment was determined by photographing sections of a hardened wax model of the entire paw. **c** | Cross-section of a digit segment: the movement of the skin surface was decomposed to determine the actual withdrawal of the skin surface, defined as the inward vector indicated by V_n. N, normal; V_t, tangential vector. **d** | Sample of withdrawal vectors V_n along the skin surface of the proximal phalanx of digit V on contraction of a given muscle. **e** | Distribution of V_n on the whole hind paw on contraction of the same muscle. Shading indicates areas of low (light blue), medium (mid blue) and high (dark blue) degrees of withdrawal. **B** | Simplified diagram of a spinal nociceptive withdrawal reflex module in the cat. The skin receptive field on the left forelimb — as determined by recording and quantification of the electromyographic response in a single muscle on nociceptive stimulation of the skin (see FIG. 5) — is shown on the right (dark blue area denotes the receptive field area with maximal response and light blue area denotes the total extent of the receptive field). Arrows indicate schematically the magnitude of withdrawal of the different parts of the receptive field on contraction of the muscle depicted to the left. **C** | Comparison of quantified withdrawal fields (as in **A**) and quantified skin receptive fields (as in **B**) for three muscles in the rat hindlimb shows high levels of similarity (correlation coefficients ranging 0.81–0.88). Panels **A** and **C** modified, with permission, from REF. 86 © (1994) Springer. Panel **B** data from REF. 132.

PARAFLOCCULUS
In experimental animals, the dorsal and ventral paraflocculus are the two most caudal lobules of the cerebellar hemisphere.

RETINAL SLIP
An unwanted movement of the visual image on the retina that occurs, for instance, when the movement of the eyes is inadequate to follow a moving object.

'pre-processes' the sensory input, thereby generating climbing fibre signals with properties that are transitional between sensory and motor information.

Spinal reflex and climbing fibre relations. Despite their explanatory value for the regulation of eye movements, the findings on the ventral paraflocculus are not easily extrapolated to other parts of the motor system. This is because eye movements are relatively simple: they are limited to motion in two dimensions and involve movement of a constant mass. Recently, however, progress has been made with regard to understanding the nature and origin of climbing fibre signals that are relevant to the more complex issue of limb movement control. Quantitative techniques have been used to compare the spatial encoding of sensory information mediated by climbing fibres that terminate in the paravermal cerebellum with sensory encoding in a previously well-characterized sensorimotor system that mediates spinal nociceptive withdrawal reflexes (SNWR; FIG. 5). In brief, correlation analysis of quantified receptive field maps[84] showed that the skin receptive fields of climbing fibres that terminate in individual microzones in the paravermal cerebellar cortex[54] and the receptive fields of individual modules of the SNWR system[85]

were highly similar. Therefore, climbing fibre signals that arise from the spinal cord might be pre-processed by SNWRs. The latter system consists of 35–40 separate modules, each comprising a specific skin receptive field, a segmental multi-synaptic reflex arc and a specific output muscle[85]. Each module performs a detailed sensorimotor transformation that results in a graded withdrawal of the limb (or part of the limb), such that its particular receptive field on the skin is moved away from the stimulus. For any given SNWR module, the input strength has a characteristic pattern on the skin that mimics the pattern of 'WITHDRAWAL EFFICACY' when the output muscle of the module contracts[86] (FIG. 6).

The similarity between the receptive fields of climbing fibres and SNWRs might explain why the cerebellar paravermis is divided into microzones in the first place — that is, why it is modular in functional organization. An action-based representation of sensory information should yield a highly processed (computational) map in the cerebellar cortex rather than a faithful representation of the body surface with an orderly sequence of receptive fields, as in a conventional sensory map that is 'somatotopical' in the strict sense of the word[87]. In fact, skin areas displaced by the action of single muscles do not necessarily form a continuum on the body surface. On the contrary, a system organized on the basis of a movement-related representation of the skin is inherently modular if such a system operates through an array of individual muscles. The implications of this organization for cerebellar information processing are considered below.

However, before returning to this issue, it is of interest to note that the close correspondence between SNWR modules and paravermal climbing fibres might also be relevant to the observation that climbing fibre pathways that arise from the spinal cord are subject to substantial central control, especially during active movements such as walking[88–91] or reaching for an object[92,93]. The 'gating' of transmission occurs only at certain times, specific to the particular movement. During locomotion, for instance, skin afferents from the ipsilateral forepaw are most likely to transmit information through ascending climbing fibre pathways to the C1 and C3 zones in lobule V of the cerebellar cortex in the swing phase of the step cycle[88–90]. Although gating and its temporal pattern seem to be fundamental characteristics of climbing fibre pathways in general, its mechanisms and functional significance are not well understood[94,95]. Notably, however, a similar phenomenon has been reported for spinal reflex pathways: the swing phase of the step cycle is also the time when activation of the same skin afferents is most likely to elicit reflex withdrawal of the limb[96]. This similarity in the pattern of modulation provides additional evidence for the possibility of a close functional link between ascending climbing fibre pathways and spinal reflex circuits, and indicates that the movement-related gating might have a common origin, presumably at the level of the spinal cord.

Both SNWRs and climbing fibres signal motor errors. To better understand the action-based nature of sensory encoding in SNWR modules, it is useful to consider their postnatal development[97–99]. The sensorimotor transformations performed in each module are not innate but instead are functionally adapted by a postnatal learning process that occurs during active sleep. Specifically, as individual muscles are brought to twitch by spontaneous activity in spinal sensorimotor circuits, the ensuing tactile feedback is used to tune the connection strengths in individual SNWR modules[100]. The change of tactile input from the withdrawn skin area that occurs in conjunction with the spontaneous single muscle movements has an adaptive effect on the reflex module[101]. By this process, each skin receptive field becomes a sensory IMPRINT of the withdrawal efficacy of an individual muscle (FIG. 7).

In individual SNWR modules, the precise sensorimotor relationship between the distribution of sensitivity on the skin of noxious (or tactile[102]) inputs and the withdrawal efficacy of the muscle[86] provides a theoretical foundation for the detection of motor errors. First, the probability that the skin receptive field of a particular reflex module will be stimulated (for example, by hitting an external object), and therefore be activated at a given point in time, is inversely proportional to the level of contraction of the muscle of that module (as muscle contraction will tend to withdraw the relevant skin area from the stimulus). Second, if a point in the receptive field does encounter a noxious stimulus, the degree of activation of the module for a given stimulus intensity is in direct proportion to the extent to which the muscle has the capacity to withdraw the stimulated point from the stimulus. Therefore, the more inadequate the contraction of a muscle is — that is, the larger the motor error of that specific muscle — the stronger the receptive field activation will be. In other words, the degree to which the sensory receptive field is activated during movement provides precise information about the extent to which an elemental part of the motor system has made an error.

By analogy to input to individual SNWR modules, signals conveyed to the paravermal MZMCs through ascending climbing fibre pathways[84] would seem to be encoded in a way that is directly related to motor output[86]. The information contained in climbing fibre signals arising from the spinal cord does not represent an error signal in sensory coordinates that must be converted from a sensory into a motor error. That conversion has already taken place in the spinal cord. As a result, climbing fibres that terminate in individual paravermal MZMCs seem to provide information about motor errors that relate to the action of single muscles. Overall, the action-based features of climbing fibre sensory signals seem to be broadly consistent with those stated by the CEREBELLAR FEEDBACK-ERROR-LEARNING MODEL[24,81,82]. Despite differences with respect to phylogenetic age and the complexity of motor control carried out, both limb and eye movement[83] cerebellar control systems seem to involve similar principles of sensory encoding, which indicates that these principles might apply more generally.

WITHDRAWAL EFFICACY
The motor effect of a muscle in terms of its movement away from an external reference point, which can be represented as a quantitative topographical map based on an analysis of the displacement of many points on the skin during the contraction of a single limb muscle.

IMPRINT
In the SNWR system there is, for each individual muscle, a close relationship between the distribution of sensitivity in the receptive field on the skin and the pattern of skin withdrawal caused by muscle contraction. Therefore, the output of the single muscle reflex component appears to be 'imprinted' on the spinal reflex circuitry that carries out the input–output transformation.

CEREBELLAR FEEDBACK-ERROR-LEARNING MODEL
A cerebellar model proposed by Kawato and colleagues that specifically addresses the issue of how sensory errors might be transformed into motor errors.
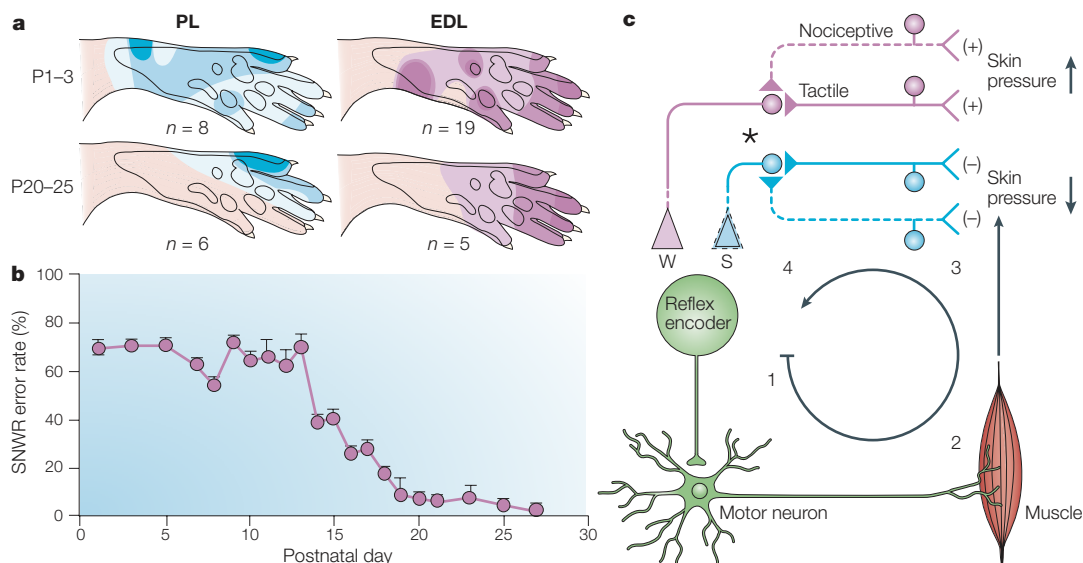
Figure 7 | **Postnatal developmental tuning of sensorimotor transformations in rat spinal nociceptive withdrawal reflex modules. a** | Quantified receptive fields of two hindlimb muscles at postnatal days (P) 1–3 (top) and 20–25 (bottom) show developmental tuning of sensorimotor transformations. The number of individual receptive fields used to create the average is shown below each figurine. EDL, extensor digitorum longus; PL, peroneus longus. **b** | Developmental tuning curves of tail withdrawal on nociceptive stimulation of the skin in one litter of rat pups. Error rates (defined as inappropriate tail movements towards a noxious stimulus) are around chance level (50%) or worse during the first two postnatal weeks and then decrease rapidly to reach adult level by the end of the third postnatal week. **c** | A proposed self-organizing circuitry that uses tactile information related to withdrawal efficacy to adjust the strength of nociceptive connections. One 'learning' cycle consists of the following chain of events: spontaneous bursts in 'reflex encoders' (that is, neurons that encode the magnitude of the reflex response) (1); motor neuron activation by the reflex encoder leads to a muscle twitch (2); the twitch produces either an increase or a decrease in non-noxious skin pressure on the tail (3), resulting in altered sensory input to pre-reflex encoder interneurons (asterisk). Pink and blue lines represent afferents from skin areas on the tail from where an increase (+) or a decrease (–), respectively, in low-threshold mechanoreceptor (tactile) input would occur. Dashed lines symbolize the rare occurrence of nociceptive input. Finally, the strength of erroneous connections (receiving increased tactile input) between pre-reflex-encoder interneurons and the reflex encoder is weakened (W) and that of appropriate ones (receiving reduced tactile input) is strengthened (S) (4). Once the tuning is established, activation of the skin receptive field of the muscle will lead to that particular skin area being moved away from the stimulus. Panel **a** modified, with permission, from REF. 97 © (1996) Blackwell Publishing Ltd. Panels **b** and **c** modified, with permission, from REF. 101 © (2003) Society for Neuroscience.

## Information processing in paravermal MZMCs

From the point of view of information processing, a fundamental issue to understanding the function of the paravermal cerebellum is the way in which input and output in individual MZMCs is modified over time. Indeed, the importance of the cerebellum as a storage site of internal models of the motor apparatus[25,26] depends entirely on its capacity to adaptively change input–output transformations. The neuronal mechanisms that underlie this adaptive capacity include synaptic plasticity influencing transmission from parallel fibres to Purkinje cells and also from parallel fibres to cerebellar cortical interneurons. An important factor in regulating cerebellar synaptic plasticity seems to be the interactions between climbing fibre and mossy fibre–parallel fibre inputs[103]. Patterns of convergence between the climbing fibre and mossy fibre afferent systems are thought to be fundamental to these interactions (FIG. 8).

Climbing and mossy fibre relationships are specific.

With regard to functional organization, there are both similarities and differences between climbing fibre and mossy fibre–parallel fibre inputs to the paravermal cerebellum. This issue can be broken down into two levels that correspond to two stages of information processing. The first level is the relationship between climbing fibre receptive fields that define a given cerebellar cortical microzone and receptive fields of individual mossy fibres in the underlying granular layer. Mossy fibres with a given peripheral receptive field have wider areas of termination than climbing fibre microzones, with a certain degree of overlap between neighbouring areas[104]. As a result, each microzone receives input from several mossy fibre receptive fields. Nevertheless, the overall mossy fibre input is similar to the climbing fibre input (FIG. 8c; complex spike in FIG. 8a), and is a feature that seems to be conserved across species and other parts of the cerebellar cortex (for example, crus II in the rat[105]).

The high level of similarity between individual mossy fibre and climbing fibre receptive fields[104] implies that at least some mossy fibre input, like climbing fibre input, is encoded in a motor frame of reference[106,107]. However, climbing fibre input from the periphery is multi-modal, with convergence between tactile and nociceptive skin afferents[108,109] and muscle afferents[110]. By contrast, input conveyed by at least some spinal pathways that terminate as mossy fibres is usually
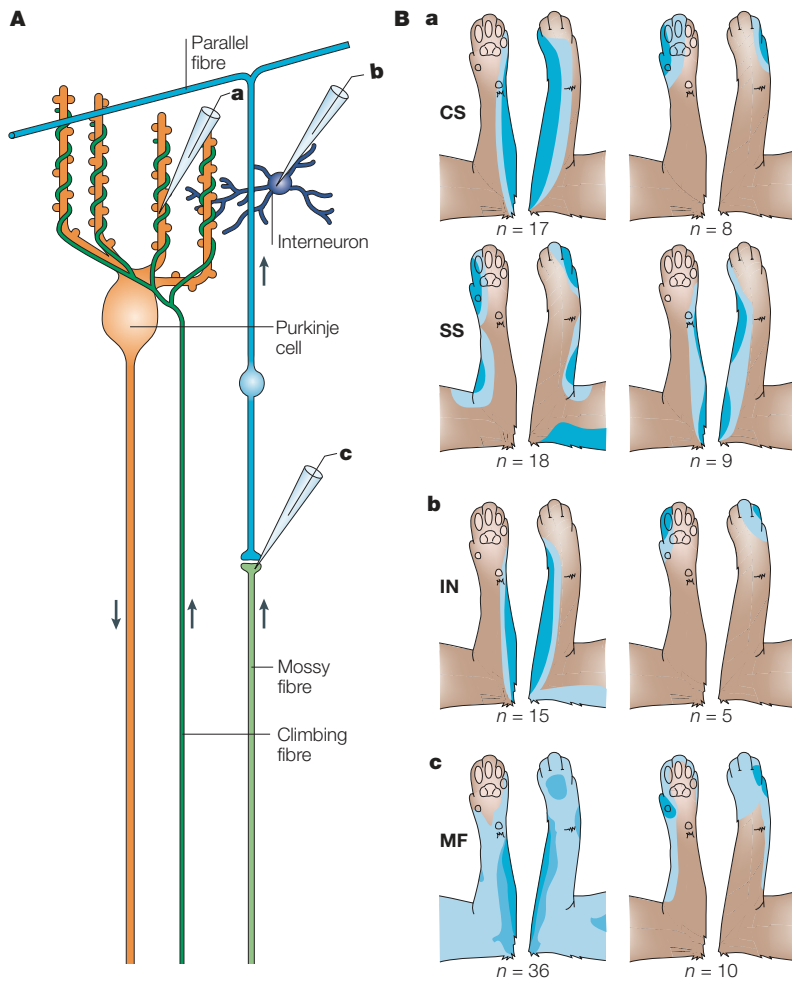
Figure 8 | **Receptive fields in the cerebellar cortex. A** | Schematic diagram of recording sites in Purkinje cells, interneurons (IN) and mossy fibres (MF) at right angles to the surface through the C3 zone in the paravermal cerebellar cortex. Mossy fibre input was provided by the external component of the cuneo–cerebellar tract[104,149]. **B** | Typical receptive field characteristics of neuronal elements in two microzones (left and right columns) are depicted on the ventral and dorsal surface of the left cat forelimb. **a** | Complex spike (CS) and simple spike (SS) receptive fields of Purkinje cells. **b** | Receptive fields of nearby interneurons. **c** | Receptive fields of mossy fibre terminals immediately below the Purkinje cell layer. Note that in each microzone, the CS response (due to climbing fibre activity) of individual Purkinje cells has a similar receptive field on the skin of the ipsilateral forelimb as local inhibitory interneurons and mossy fibre terminals in the subjacent granular layer. By contrast, the excitatory SS receptive field of the same Purkinje cells (due to mossy fibre–granule cell–parallel fibre input) is different. Values shown with each pair of limb figurines denote the numbers of units that contributed to producing the average receptive field map. Panel **B** modified, with permission, from REF. 112 © (2001) Blackwell Publishing Ltd and REF. 150 © (2003) Taylor and Francis.
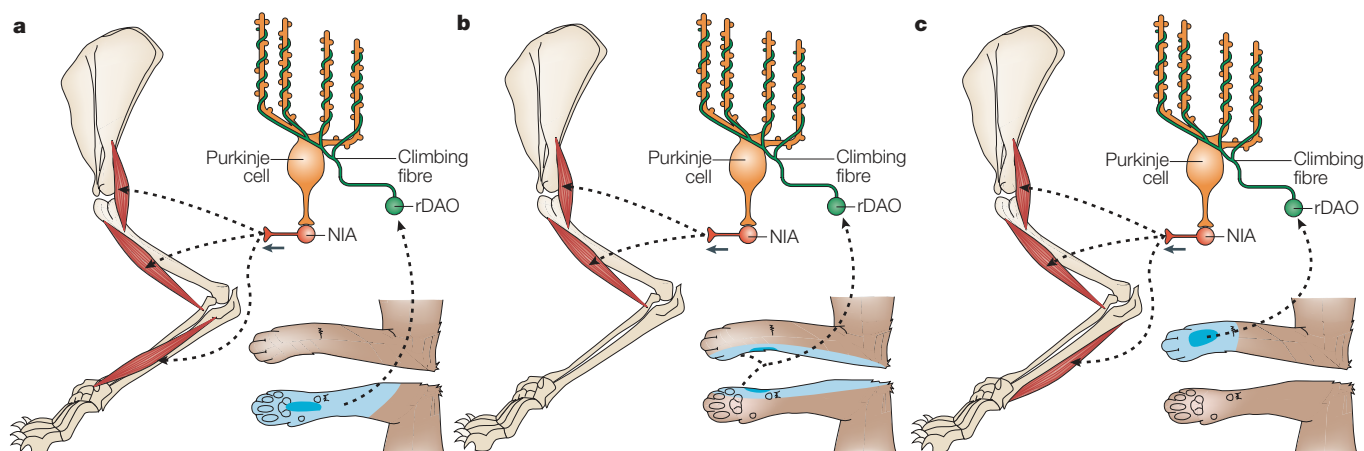
and cerebellar cortical interneurons. At present, opinion is divided as to whether the receptive fields of Purkinje cells generated by transmission in parallel fibres are primarily due to inputs from local or non-local granule cells. In the cerebellar paravermis, evidence from cats indicates that local mossy fibres do not, as might be expected, provide excitation to the Purkinje cells directly overlying them[112]. Instead, local interneurons have excitatory receptive fields similar to those of subjacent mossy fibres (FIG. 8b,c), implying that the ascending branch of individual granule cell axons and the most proximal parts of their parallel fibres primarily contact local inhibitory interneurons. As a result, the Purkinje cells in a given paravermal microzone have interneuron-mediated inhibitory receptive fields that are similar to those of the underlying mossy fibres. By contrast, the parallel fibre-mediated excitatory receptive fields of the same Purkinje cells are different and therefore seem to be derived from mossy fibres that terminate in non-local regions of cerebellar cortex (simple spike in FIG. 8a).

The latter finding contrasts, however, with earlier studies in rats that indicate that the ascending axons of granule cells make particularly powerful direct connections with Purkinje cells, which results in their parallel fibre-mediated receptive fields being similar to those of the underlying mossy fibres[113–115]. At present, it remains unclear how the discrepancy between these findings might be resolved, although differences between species (cat versus rat) and parts of the cerebellum studied (paravermis versus hemisphere) might be contributory factors. In the context of information processing in cerebellar circuits, this is an important issue to resolve, because if parallel fibre excitation of Purkinje cells arises from non-local mossy fibres, then parallel fibres could serve a central role in distributing information across several cerebellar cortical microzones. As discussed below, this, in turn, could provide a neuronal substrate for the control of muscle synergies based on spatial and/or temporal patterns of parallel fibre inputs to Purkinje cells.

Input–output relationships in MZMCs are specific. Microstimulation in different parts of NIA, relating to the output stage of different MZMCs, has been shown to evoke different limb movements that are mediated through the red nucleus and the rubrospinal tract[116–118]. In general, these movements usually involve two or three segments of an ipsilateral limb[116], indicative of control of multi-joint muscle synergies, such as retraction of the limb at the shoulder and flexion at the elbow (FIG. 9). Anatomical and physiological features of the rubrospinal[119,120] and corticospinal[121] tracts support the existence of such divergence. Looking at the system as a whole, an important consequence of this organization is that a significant number of limb muscles are likely to be controlled from several MZMCs. The functional overlap with regard to output implied by these patterns of connectivity is in stark contrast to the highly segregated microzonal climbing fibre input to individual MZMCs. The significance of this discrepancy is unclear, but it might relate to conflicting demands placed on the

modality specific — that is, it is either tactile or muscle afferent-related[104]. Consequently, although the spatial encoding of information is similar in the two systems, the information does not seem to be derived from the same spinal circuits. Rather, similarities between climbing and mossy fibres might indicate that action-based encoding of sensory information is a common principle of spinal networks[111].

The second level of climbing fibre and mossy fibre interactions concerns the relationship between climbing fibre and parallel fibre input to individual Purkinje cells

Figure 9 | **Input–output relationships.** Microstimulation of individual sites in nucleus interpositus anterior (NIA) relating to the output stage of different multizonal microcomplexes (MZMCs) results in distinct patterns of multi-joint movements in the ipsilateral limb of the cat. **a–c** | Relationships between climbing fibre input and nucleofugal output are shown for three example MZMCs. To the right of each panel is shown the skin climbing fibre receptive field of an individual MZMC, depicted on a dorsal and ventral view of the ipsilateral forelimb. Dark blue areas denote regions of skin that generated maximal response; light blue areas denote total extent of receptive field. To the left of each panel is a skeleton of the same forelimb showing schematically the groups of muscles activated on microstimulation of sites in NIA with receptive fields corresponding to the output stage of that particular MZMC. Wrist dorsiflexors and palmar flexors are shown on dorsal and ventral side of the forearm, respectively; elbow flexors and extensors on the upper arm; and shoulder flexors between the upper arm and scapula. Note that the experimental approach means that inhibitory influences on spinal segmental circuitry go undetected. In view of 'reciprocal' agonist/antagonist innervation by some rubrospinal neurons, it might be assumed that excitatory output to the antagonist muscle (see also FIG. 10) is, at least in some cases, associated with inhibitory output to the agonist (not shown). rDAO, rostral dorsal accessory olive. Data from REF. 116.

control system. Efficient learning, for instance, might be facilitated by modularity, which allows different components of a movement to be fine-tuned independently without interference from other components[122].

Overall, evoked movements usually also show a preferred direction that is in close correspondence with the climbing fibre receptive field of a given MZMC[116]. We argue above that the peripheral receptive field of the climbing fibre input to each paravermal MZMC encodes the withdrawal efficacy of a particular limb muscle. In terms of excitatory cerebellar output from the same MZMC (see also FIG. 9 legend), the distal-most muscle in the muscle synergy under control seems to have a roughly antagonistic action to the muscle associated with the input side of the circuit. For instance, in the cat, the paravermal MZMC receiving its climbing fibre input from the SNWR module that controls a palmar flexor of the wrist (palmaris longus) has a receptive field that has as its centre an area of skin on the ventral forepaw just proximal to the central footpad (FIG. 9a). When the limb is in a standing position, the action of this muscle is to withdraw this particular area of skin away from the stimulus[84] (FIG. 6B). By contrast, the muscle synergy that constitutes the excitatory cerebellar output from this specific MZMC seems to include the approximate antagonist of this muscle — probably the extensor digitorum communis, which is a dorsal flexor of the wrist[116] (FIG. 9a).

Implications for motor coordination
The previous sections draw attention to several features of the paravermal cerebellar system, which, taken together, could provide the basis for the control of single- and multi-joint movements (a hallmark of paravermal

contributions to motor control). First, the climbing fibre and the main mossy fibre input from the periphery to any particular MZMC have similar excitatory receptive fields[104] (FIG. 8). Second, the mossy fibre input seems to exert its effect primarily on the Purkinje cells in the same MZMC through local inhibitory interneurons, whereas the excitatory parallel fibre input to the same Purkinje cells seems to be derived mainly from non-local mossy fibres[112] that might encode the withdrawal efficacy of a different muscle (FIG. 8). As a consequence of these two patterns of interconnectivity, we speculate that each paravermal MZMC might participate in two types of interaction with the reflex circuitry of the spinal cord (FIG. 10).

On the one hand, mossy fibre input mediated through local granule cells and molecular layer interneurons in a particular MZMC might provide a neuronal substrate for regulating the timing of activity in two opposing muscles that are involved in single-joint movements (follow the path of signs in white circles in FIG. 10). In particular, peripheral feedback to the MZMC that is related to the action of a particular agonist muscle and mediated by mossy fibre afferents might act through the output of the MZMC as a cue to the termination of activity in that muscle (through inhibitory connections not indicated in FIG. 10; FIG. 9 legend) and influence the onset of antagonist muscle activity. In this respect, it is relevant to note that the correct timing of transitions between agonist and antagonist activity associated with single-joint movements[123] is disrupted following cerebellar damage[124].

On the other hand, similar peripheral feedback could be conveyed through the parallel fibres to influence the
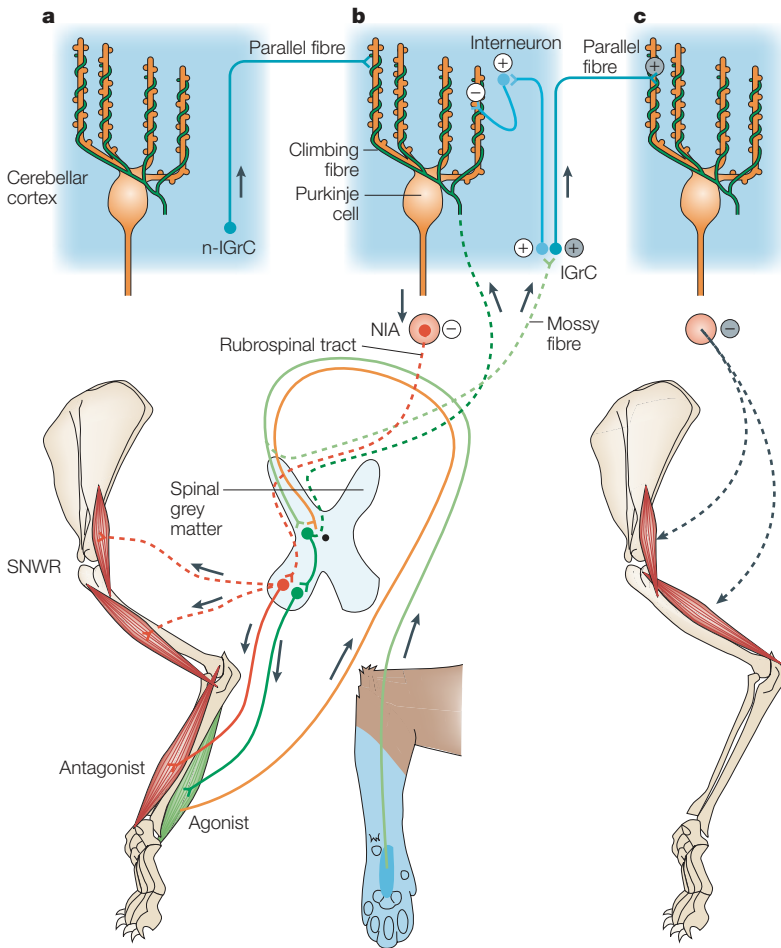
Figure 10 | **Spinocerebellar interactions and motor coordination.** Functional interrelationship between cerebellar microcomplexes and spinal reflex modules. Spinal nociceptive withdrawal reflex (SNWR) module (lower left panel): input–output characteristics of one example module. Skin input from a receptive field on the ventral side of the left forearm and paw (light green) and muscle input from a palmar flexor (orange; see FIG. 5 legend) converge in the spinal grey matter and send output to the muscle of the module (palmar flexor, agonist; green). Ascending pathways: skin information is relayed through mossy fibres (light green dashed line), and integrated skin and muscle afferent information is relayed through climbing fibres (dark green dashed line; inferior olive relay not shown). Cerebellar cortex (upper panel): input–output characteristics of one example microcomplex (**b**; not shown as multizonal for simplicity). Output from nucleus interpositus anterior (NIA) is mediated through the rubrospinal tract (red) to influence a group of muscles that act on several joints of the limb (lower left panel, shown in red, including antagonist). The Purkinje cells to the left (**a**) and right (**c**) illustrate non-local microcomplexes. Two hypothetical routes of signal flow within microcomplexes (**b**; signs in white circles) and between microcomplexes (**b**,**c**; signs in grey circles) are labelled as (+) and (–) signs to indicate excitation and inhibition respectively. In the microcomplex in part **b**, the local granule cell input (lGrC; see receptive field in lower panel) provides inhibitory input to the overlying Purkinje cells by way of a local interneuron input and also excitatory parallel fibre input to a non-local microcomplex (**c**). In a similar way, the excitatory parallel fibre input to the Purkinje cells in the microcomplex in part **b** originates in non-local granule cells (n-lGrC) located in a different microcomplex (**a**). Arrows show the direction of information flow (see text for further details). Interestingly, in classical conditioning of the eye-blink reflex[20], there is strong evidence that climbing fibres convey information to the cerebellar cortex about the unconditioned stimulus, which elicits a protective reflex (the eye-blink). Such a role is in keeping with the function of climbing fibres proposed in the present model.

Purkinje cells in a different MZMC (follow the path of signs in grey circles in FIG. 10). Therefore, with some delay relative to the effects on the local MZMC described above (because of the slow conduction time in the parallel fibres), the opposite effects on a non-local MZMC would

be caused by the mossy fibre input related to the action of a particular muscle (FIG. 10, lower right panel) As the output stage of the non-local MZMC would affect an altogether different muscle synergy, this kind of interaction could relate to the coordination of activity across multiple joints of the limb.

In the model in FIG. 10, climbing fibre-dependent and climbing fibre-independent plasticity could dynamically and adaptively regulate both the local MZMC and non-local MZMC interactions, in the former case by influencing synaptic transmission between the ascending axons of granule cells and local molecular layer interneurons, and in the latter by influencing synaptic transmission between parallel fibres and Purkinje cells[103]. In this respect, the gating of transmission in ascending climbing fibre pathways might allow only behaviourally relevant training signals to be forwarded to the cerebellum during movement[94]. Also at the behavioural level, information processing within and between MZMCs resembles, respectively, the non-associative and the associative learning used in cerebellar adaptation of gain in the vestibulo–ocular reflex and in classical conditioning of the eye-blink reflex. Conceptual similarities between our model and that of Kawato and co-workers (see above for references) have already been pointed out.

Note also that, from a historical perspective, the scheme in FIG. 10, by virtue of the two pathways — the one acting within the same MZMCs and the other across MZMCs — would seem to reconcile an important conceptual dichotomy in the early literature[125]. Holmes[5,6] (and before him Luciani[126]) emphasized the control by the cerebellum of individual movement elements and physical variables such that movement coordination as a whole equalled the sum of the regulation of many parts. On the other hand, Babinski[3,4] (and before him Flourens[127]) advocated a special organizing principle of coordination per se, by which the individual movement elements were coupled, the whole therefore being greater than the sum of the parts. These seemingly contradictory views are compatible with the pathways indicated in the present model (see signs in white and grey circles in FIG. 10). The interaction between MZMCs is also in keeping with a long-held view that the parallel fibres are an important substrate for the coordination of different body parts[125,128–131] (although see REFS 113–115 for a different point of view).

Concluding remarks

Although interpretations of how the networks outlined in FIG. 10 might operate during active movement are speculative, the model as such highlights the need for further anatomical and physiological data that are essential for a fuller understanding of this system. Uncharted territories include the organization of mossy fibre inputs from, for example, deep tissue receptors or cerebral cortical systems, and how during active movement, patterns of activity in these systems relate to the functional organization of MZMCs. The functional significance of the movement-related gating of transmission in climbing fibre pathways, and how this might influence cerebellar operation, also remains uncertain. There are also some

important conceptual shortcomings. For instance, by analogy to the SNWR system, encoding of sensory information in the paravermal MZMC system seems to have the standing position of the limb as a frame of reference. Displacement of the most distal skin surfaces by muscle contraction depends on whether the limb is making contact with the ground[86,132], and it remains unclear how the paravermal MZMC system operates when the limb is off the ground, during, for example, a reach-to-grasp movement. In this situation, the biomechanical effects of contraction of several limb muscles differ significantly from those during the standing position.

Despite these shortcomings, the findings indicate that climbing fibres that relay ascending signals convey information about motor errors. Such information could, without further processing, be used as training signals for the adaptive programming of cerebellar networks. This is supported by a comparison of our own data on climbing fibre input to the paravermal cerebellum with data on climbing fibre input to the ventral paraflocculus[83]. In addition, on the basis of detailed analyses of input conveyed by the dorsal spinocerebellar tract, Bosco and Poppele[106,107] have presented evidence that mossy fibre input might also be encoded in a motor frame of reference. Taken together, these findings imply that the encoding of sensory information in an action-based frame of reference might be a central organizing principle of ascending cerebellar afferent systems in general. In the model presented here, the encoding of afferent information is of direct relevance to the modular organization of cerebellar networks, which might be thought of as a consequence of the integrated sensorimotor role of the cerebellum. This role does not seem to conform to a clear distinction between 'sensory' and 'motor' processing (for an alternative view, see REF. 133). On the contrary, we believe that, to inform the debate about the complex nature of cerebellar topography[38], cerebellar afferent representations should be viewed as computational action-based maps rather than purely as sensory maps of the body surface.

Finally, it is also relevant to note that the precise but complex modular organization of cerebellar systems, exemplified by the paravermal MZMCs, highlights the importance of using an independent scheme to classify, as far as possible, the neurons recorded in behavioural studies. Differences with respect to input and output imply that each functional module contributes in a specific way to movement coordination. These different contributions might be expected to be associated with differences in neuronal firing patterns in relation to the performance of particular movements. Such relationships might well be obscured, or even lost, when pooling firing patterns from groups of neurons that do not belong to the same functional unit. One of the challenges for future cerebellar studies must be to relate neuronal spike trains in awake, behaving animals to functional localization.

1. Purves, D. *et al. Neuroscience* 3rd edn (Sinauer Associates, Sunderland, Massachusetts, 2004).
2. Ito, M. *The Cerebellum and Neural Control* (Raven, New York, 1984).
3. Babinski, J. De l'asynergie cerebelleuse. *Rev. Neurol.* **7**, 806–816 (1899).
4. Babinski, J. Asynergie et inertie cerebelleuses. *Rev. Neurol.* **14**, 685–686 (1906).
5. Holmes, G. The symptoms of acute cerebellar injuries due to gunshot injuries. *Brain* **40**, 461–535 (1917).
6. Holmes, G. The cerebellum of man. *Brain* **62**, 1–30 (1939).
7. Chambers, W. W. & Sprague, J. M. Functional localization in the cerebellum II: somatotopic organization in cortex and nuclei. *Arch. Neurol. Psychiatry* **74**, 653–680 (1955).
8. Dow, R. S. & Moruzzi, G. *The Physiology and Pathology of the Cerebellum* (Minnesota Univ. Press, Minneapolis, 1958).
9. Thach, W. T. On the specific role of the cerebellum in motor learning and cognition: clues from PET activation and lesion studies in man. *Behav. Brain Sci.* **19**, 411–431 (1996).
10. Schmahmann, J. D. *The Cerebellum and Cognition* (Academic, San Diego, 1997).
11. Ekerot, C.-F. & Kano, M. Long-term depression of parallel fibre synapses following stimulation of climbing fibres. *Brain Res.* **342**, 357–360 (1985).
12. Ito, M. Long-term depression. *Annu. Rev. Neurosci.* **12**, 85–102 (1989).
13. Ito, M. Cerebellar long-term depression: characterization, signal transduction, and functional roles. *Physiol. Rev.* **81**, 1143–1195 (2001).
14. Hansel, C., Linden, D. J. & D'Angelo, E. Beyond parallel fiber LTD: the diversity of synaptic and non-synaptic plasticity in the cerebellum. *Nature Neurosci.* **4**, 467–475 (2001).
15. Ito, M., Shiida, T., Yagi, N. & Yamamoto, M. Visual influence on rabbit horizontal vestibulo–ocular reflex presumably effected via the cerebellar flocculus. *Brain Res.* **65**, 170–174 (1974).
16. Robinson, D. A. Adaptive gain control of vestibuloocular reflex by the cerebellum. *J. Neurophysiol.* **39**, 954–969 (1976).
17. Thach, W. T. A role for the cerebellum in learning movement coordination. *Neurobiol. Learn. Mem.* **70**, 177–188 (1998).
18. Houk, J. C., Buckingham, J. T. & Barto, A. G. Models of the cerebellum and motor learning. *Behav. Brain Sci.* **19**, 368–383 (1996).

19. Boyden, E. S., Katoh, A. & Raymond, J. L. Cerebellum-dependent learning: the role of multiple plasticity mechanisms. *Annu. Rev. Neurosci.* **27**, 581–609 (2004).
20. Hesslow, G. & Yeo, C. H. in *A Neuroscientist's Guide to Classical Conditioning* (ed. Moore, J. W.) 86–146 (Springer, New York, Berlin, Heidelberg, 2002).
21. Braitenberg, V. & Atwood, R. P. Morphological observations on the cerebellar cortex. *J. Comp. Neurol.* **109**, 1–33 (1958).
22. Marr, D. A theory of cerebellar cortex. *J. Physiol. (Lond.)* **202**, 437–470 (1969).
23. Albus, J. S. A theory of cerebellar function. *Math. Biosci.* **10**, 25–61 (1971).
24. Kawato, M. & Gomi, H. A computational model of four regions of the cerebellum based on feedback-error learning. *Biol. Cybern.* **68**, 95–103 (1992).
25. Wolpert, D. M. & Kawato, M. Multiple paired forward and inverse models for motor control. *Neural Net.* **11**, 1317–1329 (1998).
26. Wolpert, D. M., Miall, R. C. & Kawato, M. Internal models in the cerebellum. *Trends Cogn. Sci.* **2**, 338–347 (1998).
27. Oscarsson, O. Functional units of the cerebellum — sagittal zones and microzones. *Trends Neurosci.* **2**, 143–145 (1979).
28. Voogd, J. & Bigaré, F. in *The Inferior Olivary Nucleus: Anatomy and Physiology* (eds Courville, J., de Montigny, C. & Lamarre, Y.) 207–234 (Raven, New York, 1980).
29. Armstrong, D. M. Functional significance of connections of the inferior olive. *Physiol. Rev.* **54**, 358–417 (1974).
30. Brodal, A. & Kawamura, K. Olivocerebellar projection: a review. *Adv. Anat. Embryol. Cell Biol.* **64**, 1–140 (1980).
31. Armstrong, D. M. Topographical localisation in the projections from the inferior olive to the paravermal cortex of the anterior lobe and paramedian lobule in the cerebellum of the cat. A brief review. *Arch. Ital. Biol.* **128**, 183–207 (1990).
32. Eccles, J. C., Llinas, R. & Sasaki, K. The excitatory synaptic action of climbing fibres on the Purkinje cells of the cerebellum. *J. Physiol. (Lond.)* **182**, 268–296 (1966).
33. Thach, W. T. Somatosensory receptive fields of single units in cat cerebellar cortex. *J. Neurophysiol.* **30**, 675–696 (1967).
34. Hawkes, R. An anatomical model of cerebellar modules. *Prog. Brain Res.* **114**, 39–52 (1997).
35. Herrup, K. & Kuemerle, B. The compartmentalization of the cerebellum. *Annu. Rev. Neurosci.* **20**, 61–90 (1997).

36. Sugihara, I. & Shinoda, Y. Molecular, topographic, and functional organization of the cerebellar cortex: a study with combined aldolase C and olivocerebellar labeling. *J. Neurosci.* **24**, 8771–8785 (2004).
37. Voogd, J. & Glickstein, M. The anatomy of the cerebellum. *Trends Neurosci.* **21**, 370–375 (1998).
38. Manni, E. & Petrosini, L. A century of cerebellar somatotopy: a debated representation. *Nature Rev. Neurosci.* **5**, 241–249 (2004).
39. Oscarsson, O. in *The Inferior Olivary Nucleus: Anatomy and Physiology* (eds Courville, J., de Montigny, C. & Lamarre, Y.) 279–289 (Raven, New York, 1980).
40. Andersson, G., Ekerot, C.-F., Oscarsson, O. & Schouenborg, J. in *Cerebellum and Neuronal Plasticity* (eds Glickstein, M., Yeo, C. & Stein, J.) 165–173 (Plenum, New York, London, 1987).
41. Apps, R. Columnar organisation of the inferior olive projection to the posterior lobe of the rat cerebellum. *J. Comp. Neurol.* **302**, 236–254 (1990).
42. Trott, J. R. & Apps, R. Lateral and medial sub-divisions within the olivocerebellar zones of the paravermal cortex in lobule Vb/c of the cat anterior lobe. *Exp. Brain Res.* **87**, 126–140 (1991).
43. Trott, J. R. & Apps, R. Zonal organisation within the projection from the inferior olive to the rostral paramedian lobule of the cat cerebellum. *Eur. J. Neurosci.* **5**, 162–173 (1993).
44. Atkins, M. J. & Apps, R. Somatotopical organization within the climbing fibre projection to the paramedian lobule and copula pyramidis of the rat cerebellum. *J. Comp. Neurol.* **389**, 249–263 (1997).
45. Apps, R. Rostrocaudal branching within the climbing fibre projection to forelimb-receiving areas of the cerebellar cortical C1 zone. *J. Comp. Neurol.* **419**, 193–204 (2000).
46. Pardoe, J. & Apps, R Structure–function relations of two somatotopically corresponding regions of the rat cerebellar cortex: olivo–cortico–nuclear connections. *Cerebellum* **1**, 165–184 (2002).
47. Sugihara, I., Wu, H. S. & Shinoda, Y. The entire trajectories of single olivocerebellar axons in the cerebellar cortex and their contribution to cerebellar compartmentalization. *J. Neurosci.* **21**, 7715–7723 (2001).
48. Wilson, W. C. & Magoun, H. W. The functional significance of the inferior olive. *J. Comp. Neurol.* **83**, 69–77 (1945).

49. Murphy, M. G. & O'Leary, J. L. Neurological deficit in cats with lesions of the olivocerebellar system. *Arch. Neurol.* **24**, 145–157 (1971).

50. Llinas, R., Walton, K., Hillman, D. E. & Sotelo, C. Inferior olive: its role in motor learning. *Science* **190**, 1230–1231 (1975).

51. Garwicz, M., Ekerot, C.-F. & Schouenborg, J. Distribution of cutaneous nociceptive and tactile climbing fibre input to sagittal zones in cat cerebellar anterior lobe. *Eur. J. Neurosci.* **4**, 289–295 (1992).

52. Andersson, G. & Oscarsson, O. Climbing fiber microzones in cerebellar vermis and their projection to different groups of cells in the lateral vestibular nucleus. *Exp. Brain Res.* **32**, 565–579 (1978).

53. Andersson, G. & Oscarsson, O. Projections to lateral vestibular nucleus from cerebellar climbing fiber zones. *Exp. Brain Res.* **32**, 549–564 (1978).

54. Ekerot, C.-F., Garwicz, M. & Schouenborg, J. Topography and nociceptive receptive fields of climbing fibres projecting to the cerebellar anterior lobe in the cat. *J. Physiol. (Lond.)* **441**, 257–274 (1991).
An electrophysiological demonstration of a large number of microzones in the paravermal C3 zone, based on a detailed analysis of distributions of sensitivity in the nociceptive receptive fields of individual climbing fibres. Owing to the particular characteristics of the receptive fields, they are suggested to reflect movement rather than to relay sensory information from the periphery.

55. Hesslow, G. Correspondence between climbing fibre input and motor output in eyeblink related areas in cat cerebellar cortex. *J. Physiol. (Lond.)* **476**, 229–244 (1994).

56. Ekerot, C.-F. & Larson, B. The dorsal spino–olivocerebellar system in the cat. II. Somatotopical organization. *Exp. Brain Res.* **36**, 219–232 (1979).

57. Ekerot, C.-F. & Larson, B. Branching of olivary axons to innervate pairs of sagittal zones in the cerebellar anterior lobe of the cat. *Exp. Brain Res.* **48**, 185–198 (1982).

58. Ekerot, C.-F., Garwicz, M. & Schouenborg, J. The postsynaptic dorsal column pathway mediates cutaneous nociceptive information to cerebellar climbing fibres in the cat. *J. Physiol. (Lond.)* **441**, 275–284 (1991).

59. Armstrong, D. M., Harvey, R. J. & Schild, R. F. Cerebello–cerebellar responses mediated via climbing fibres. *Exp. Brain Res.* **18**, 19–39 (1973).

60. Rosina, A. & Provini, L. Somatotopy of climbing fiber branching to the cerebellar cortex in cat. *Brain Res.* **289**, 45–63 (1983).

61. Ekerot, C.-F. & Larson, B. The dorsal spino–olivocerebellar system in the cat. I. Functional organization and termination in the anterior lobe. *Exp. Brain Res.* **36**, 201–217 (1979).

62. Garwicz, M. & Ekerot, C.-F. Topographical organization of cerebellar cortical projection to nucleus interpositus anterior in the cat. *J. Physiol. (Lond.)* **474**, 245–260 (1994).
An electrophysiological study in anaesthetized cats in which MZMCs were first proposed. The topography of evoked field potentials in the NIA indicated that microzones in the C1, C3 and Y zones with similar climbing fibre input project to a common set of nuclear neurons.

63. Garwicz, M. *Cerebellar control of forelimb movements: modular organization revealed by nociceptive and tactile climbing fibre input*. Thesis, Lund Univ. (1992).

64. Apps, R. & Garwicz, M. Precise matching of olivo–cortical divergence and cortico–nuclear convergence between somatotopically corresponding areas in the medial C1 and medial C3 zones of the paravermal cerebellum. *Eur. J. Neurosci.* **12**, 205–214 (2000).
A combined electrophysiological mapping and bidirectional tracer study in cats showing that, consistent with the MZMC hypothesis, there was a close correlation between the incidence of double-labelled olive cells and the extent of overlap between corticonuclear terminal fields.

65. Oscarsson, O. in *Handbook of Sensory Physiology. Vol. II: Somatosensory System* (ed. Iggo, A.) 339–380 (Springer, New York, 1973).

66. Brodal, P. & Bjaalie, J. G. Salient anatomic features of the cortico–ponto–cerebellar pathway. *Prog. Brain Res.* **114**, 227–249 (1997).

67. Tolbert, D. L., Bantli, H. & Bloedel, J. R. Anatomical and physiological evidence for a cerebellar nucleo–cortical projection in the cat. *Neuroscience* **1**, 205–217 (1976).

68. Trott, J. R., Apps, R. & Armstrong, D. M. Topographical organisation within the cerebellar nucleocortical projection to the paravermal cortex of lobule Vb/c in the cat. *Exp. Brain Res.* **80**, 415–428 (1990).

69. Trott, J. R., Apps, R. & Armstrong, D. M. Zonal organization of cortico–nuclear and nucleo-cortical projections of the paramedian lobule of the cat cerebellum. I. The C1 zone. *Exp. Brain Res.* **118**, 298–315 (1998).
A combined electrophysiological and neuroanatomical tracing study in cats showing that, in marked contrast to the forelimb part of the C1 zone in the anterior lobe, the homologous part of the C1 zone in the posterior lobe has substantial nucleocortical projections. This is consistent with the idea that different parts of the same zone (possibly containing similar microzones) have different mossy fibre inputs.

70. Trott, J. R., Apps, R. & Armstrong, D. M. Zonal organization of cortico–nuclear and nucleo-cortical projections of the paramedian lobule of the cat cerebellum. II. The C2 zone. *Exp. Brain Res.* **118**, 316–330 (1998).

71. King, V., Armstrong, D. M., Apps, R. & Trott, J. R. Numerical aspects of pontine, lateral reticular and inferior olivary projections to two paravermal cortical zones of the cat cerebellum. *J. Comp. Neurol.* **390**, 537–551 (1998).

72. Herrero, L., Pardoe, J. & Apps, R. Pontine and lateral reticular projections to the c$_1$ zone in lobulus simplex and paramedian lobule of the rat cerebellar cortex. *Cerebellum* **1**, 185–199 (2000).

73. Simpson, J. I., Wylie, D. R. & De Zeeuw, C. I. On climbing fibre signals and their consequence(s). *Behav. Brain Sci.* **19**, 384–398 (1996).

74. Gilbert, P. F. C. & Thach, W. T. Purkinje cell activity during motor learning. *Brain Res.* **128**, 309–328 (1977).

75. Andersson, G. & Armstrong, D. M. Complex spikes in Purkinje cells in the lateral vermis (b zone) of the cat cerebellum during locomotion. *J. Physiol. (Lond.)* **385**, 107–134 (1987).

76. Ojakangas, C. L. & Ebner, T. J. Purkinje cell complex and simple spike changes during a voluntary arm movement learning task in the monkey. *J. Neurophysiol.* **68**, 2222–2236 (1992).

77. Kitazawa, S., Kimura, T. & Yin, P. B. Cerebellar complex spikes encode both destinations and errors in arm movements. *Nature* **392**, 494–497 (1998).

78. Horn, K. M., Pong, M. & Gibson, A. R. Discharge of inferior olive cells during reaching errors and perturbations. *Brain Res.* **1008**, 137–138 (2004).

79. Porrill, J., Dean, P. & Stone, J. V. Recurrent cerebellar architecture solves the motor-error problem. *Proc. R. Soc. Lond. B* **271**, 789–796 (2004).

80. Dean, P., Porrill, J. & Stone, J. V. Visual awareness and the cerebellum: possible role of decorrelation control. *Prog. Brain Res.* **144**, 61–75 (2004).

81. Kawato, M. & Wolpert, D. Internal models for motor control. *Novartis Found. Symp.* **218**, 291–304 (1998).

82. Kawato, M. Internal models for motor control and trajectory planning. *Curr. Opin. Neurobiol.* **9**, 718–727 (1999).

83. Kobayashi, Y. *et al.* Temporal firing patterns of Purkinje cells in the cerebellar ventral paraflocculus during ocular following responses in monkeys II. Complex spikes. *J. Neurophysiol.* **80**, 832–848 (1998).
A single-unit study in awake monkeys of climbing fibre and simple spike activity in the ventral paraflocculus during ocular following responses. Results indicate that climbing fibre signals have properties that are transitional between sensory and motor information.

84. Garwicz, M., Levinsson, A. & Schouenborg, J. Common principles of sensory encoding in spinal reflex modules and cerebellar climbing fibers. *J. Physiol. (Lond.)* **540**, 1061–1069 (2002).
Quantitative methods were used in anaesthetized cats to compare characteristics of individual SNWRs and signals carried by individual climbing fibres to cerebellar cortical microzones. High positive correlations between reflex input and climbing fibre skin receptive fields and between reflex output and climbing fibre muscle afferent input indicated that climbing fibre signals that arise from the spinal cord might be functionally linked to the SNWRs.

85. Schouenborg, J. & Kalliomäki, J. Functional organization of the nociceptive withdrawal reflexes. I. Activation of hindlimb muscles in the rat. *Exp. Brain Res.* **83**, 67–78 (1990).

86. Schouenborg, J. & Weng, H.-R. Sensorimotor transformation in a spinal motor system. *Exp. Brain Res.* **100**, 170–174 (1994).
A highly detailed three-dimensional analysis of the displacement of a large number of points on the skin during contractions caused by single limb muscles in the rat. By comparing the maps generated in this way with the nociceptive input from the skin mediated by spinal reflex pathways to single limb muscles, the precise relationships of an individual muscle and its sensory receptive field were revealed.

87. Kaas, J. H. Topographic maps are fundamental to sensory processing. *Brain Res. Bull.* **44**, 107–112 (1997).

88. Lidierth, M. & Apps, R. Gating in the spino–olivocerebellar pathways to the c$_1$ zone of the cerebellar cortex during locomotion in the cat. *J. Physiol. (Lond.)* **430**, 453–469 (1990).

89. Apps, R., Hartell, N. A & Armstrong D. M. Step phase-related excitability changes in spino–olivocerebellar paths to the c$_1$ and c$_3$ zones in cat cerebellum. *J. Physiol. (Lond.)* **483**, 687–702 (1995).

90. Apps, R. & Lee, S. Gating of transmission in climbing fibre paths to cerebellar cortical C1 and C3 zones in the rostral paramedian lobule during locomotion in the cat. *J. Physiol. (Lond.)* **516**, 875–883 (1999).

91. Pardoe, J., Edgley, S. A., Drew, T. & Apps, R. Changes in excitability of ascending and descending inputs to cerebellar climbing fibres during locomotion. *J. Neurosci.* **24**, 2656–2666 (2004).

92. Horn, K. M., Van Kan, P. L. & Gibson, A. R. Reduction of rostral dorsal accessory olive responses during reaching. *J. Neurophysiol.* **76**, 4140–4151 (1996).

93. Apps, R., Atkins, M. J. & Garwicz, M. Gating of cutaneous input to cerebellar climbing fibres during a reaching task in cat. *J. Physiol. (Lond.)* **502**, 203–214 (1997).

94. Apps, R. Movement-related gating of climbing fibre input to cerebellar cortical zones. *Prog. Neurobiol.* **57**, 537–562 (1999).

95. Apps, R. Gating of climbing fibre input to cerebellar cortical zones. *Prog. Brain Res.* **124**, 201–211 (2000).

96. Forssberg, H., Grillner, S. & Rossignol, S. Phase dependent reflex reversal during walking in chronic spinal cats. *Brain Res.* **85**, 103–107 (1975).

97. Holmberg, H. & Schouenborg, J. Postnatal development of the nociceptive withdrawal reflexes in the rat: a behavioural and electromyographic study. *J. Physiol. (Lond.)* **493**, 239–252 (1996).

98. Holmberg, H. & Schouenborg, J. Developmental adaptation of withdrawal reflexes to early alteration of peripheral innervation in the rat. *J. Physiol. (Lond.)* **495**, 399–409 (1996).

99. Holmberg, H., Schouenborg, J., Yu, Y. B. & Weng, H. R. Developmental adaptation of rat nociceptive withdrawal reflexes after neonatal tendon transfer. *J. Neurosci.* **17**, 2071–2078 (1997).

100. Petersson, P., Waldenström, A., Fahraeus, C. & Schouenborg, J. Spontaneous muscle twitches during sleep guide spinal self-organization. *Nature* **424**, 72–75 (2003).

101. Waldenström, A., Thelin, J., Thimansson, E., Levinsson, A. & Schouenborg, J. Developmental learning in a pain-related system: evidence for a cross-modality mechanism. *J. Neurosci.* **23**, 7719–7725 (2003).

102. Weng, H. R. & Schouenborg, J. On the sensory receptors contributing to withdrawal reflex pathways in the decerebrate spinal rat. *Exp. Brain Res.* **118**, 71–77 (1998).

103. Jörntell, H. & Ekerot C.-F. Reciprocal bi-directional plasticity of parallel fiber receptive fields in cerebellar Purkinje cells and their afferent interneurons. *Neuron* **34**, 797–806 (2002).

104. Garwicz, M., Jörntell, H. & Ekerot, C.-F. Cutaneous receptive fields and topography of mossy fibres and climbing fibres projecting to cat cerebellar C3 zone. *J. Physiol. (Lond.)* **512**, 277–293 (1998).

105. Brown, I. E. & Bower, J. M. Congruence of mossy fiber and climbing fiber tactile projections in the lateral hemispheres of the rat cerebellum. *J. Comp. Neurol.* **429**, 59–70 (2001).

106. Bosco, G. & Poppele, R. E. Reference frames for spinal proprioception: kinematics based or kinetics based? *J. Neurophysiol.* **83**, 2946–2955 (2000).

107. Bosco, G. & Poppele, R. E. Proprioception from a spinocerebellar perspective. *Physiol. Rev.* **81**, 539–568 (2001).
A review article that summarizes this group's important studies on the dorsal spinocerebellar tract (DSCT) system in the cat. A key conclusion is that mossy fibre inputs to the cerebellum conveyed by the DSCT system seem to encode whole-hindlimb kinematics.

108. Ekerot, C.-F., Gustavsson, P., Oscarsson, O. & Schouenborg, J. Climbing fibres projecting to cat cerebellar anterior lobe activated by cutaneous A and C fibres. *J. Physiol. (Lond.)* **386**, 529–538 (1987).

109. Ekerot, C.-F., Oscarsson, O. & Schouenborg, J. Stimulation of cat cutaneous nociceptive C fibres causing tonic and synchronous activity in climbing fibres. *J. Physiol. (Lond.)* **386**, 539–546 (1987).

110. Jörntell, H., Garwicz, M. & Ekerot, C.-F. Relation between cutaneous climbing fibre receptive fields and muscle afferent input to climbing fibres projecting to the cerebellar C3 zone in the cat. *Eur. J. Neurosci.* **8**, 1769–1779 (1996).

111. Levinsson, A., Holmberg, H., Broman, J., Zhang, M. & Schouenborg, J. Spinal sensorimotor transformation: relation between cutaneous somatotopy and a reflex network. *J. Neurosci.* **22**, 8170–8182 (2002).

112. Ekerot, C.-F. & Jörntell, H. Parallel fibre receptive fields of Purkinje cells and interneurons are climbing fibre-specific. *Eur. J. Neurosci.* **13**, 1303–1310 (2001).

A single-unit mapping study in decerebrate cats showing that skin receptive fields of climbing fibres and local interneurons in individual microzones are similar, whereas the parallel fibre receptive fields of the same Purkinje cells are different. An important conclusion is that excitatory input to Purkinje cells depends on input from non-local mossy fibres/granule cells and is mediated over some distance by parallel fibres.

113. Llinás, R. in *The Cerebellum, New Vistas (Experimental Brain Research Supplements 6)* (eds Palay, S. L. & Chan-Palay, V.) 189–194 (Springer, Berlin, Heidelberg, New York, 1982).

114. Bower, J. M. & Woolston, D. C. Congruence of spatial organization of granule cell and Purkinje cell layers of cerebellar hemispheres of the albino rat: vertical organization of cerebellar cortex. *J. Neurophysiol*. **49**, 745–766 (1983).

115. Cohen, D. & Yarom, Y. Patches of synchronized activity in the cerebellar cortex evoked by mossy-fiber stimulation: questioning the role of parallel fibers. *Proc. Natl Acad. Sci. USA* **95**, 15032–15036 (1998).

116. Ekerot, C.-F., Jörntell, H. & Garwicz, M. Functional relation between corticonuclear input and movements evoked on microstimulation in cerebellar nucleus interpositus anterior in the cat. *Exp. Brain Res*. **106**, 365–376 (1995).

117. Giuffrida, R. *et al*. Single muscle organization of interposito-rubral projections. *Exp. Brain Res*. **39**, 261–267 (1980).

118. Rispal-Padel, L., Cicirata, F. & Pons, C. Cerebellar nuclear topography of simple and synergistic movements in the alert baboon (*Papio papio*). *Exp. Brain Res*. **47**, 365–380 (1982).

119. Mewes, K. & Cheney, P. D. Facilitation and suppression of wrist and digit muscles from single rubromotoneuronal cells in the awake monkey. *J. Neurophysiol*. **66**, 1965–1977 (1991).

120. Belhaj-Saïf, A., Karrer, J. H. & Cheney, P. D. Distribution and characteristics of poststimulus effects in proximal and distal forelimb muscles from red nucleus in the monkey. *J. Neurophysiol*. **79**, 1777–1789 (1998).

121. Fetz, E. E., Cheney, P. D., Mewes, K. & Palmer, S. Control of forelimb muscle activity by populations of corticomotoneuronal and rubromotoneuronal cells. *Prog. Brain Res*. **80**, 437–449 (1989).

122. Mussa-Ivaldi, F. A. Modular features of motor control and learning. *Curr. Opin. Neurobiol*. **9**, 713–717 (1999).

123. Hallett, M., Shahani, B. T. & Young, R. R. EMG analysis of stereotyped voluntary movements in man. *J. Neurol. Neurosurg. Psychiatry* **38**, 1154–1162 (1975).

124. Hore, J., Wild, B. & Diener, H. C. Cerebellar dysmetria at the elbow, wrist and fingers. *J. Neurophysiol.* **65**, 563–571 (1991).

125. Thach, W. T., Goodkin, H. P. & Keating, J. G. The cerebellum and adaptive coordination of movement. *Annu. Rev. Neurosci*. **15**, 403–442 (1992).

126. Luciani, L. in *Human Physiology* Ch. 8, 467 (Macmillan, London, 1915). (Translated by F. A. Welby.)

127. Flourens, P. Recherches experimentales sur les propriétés et les fonctions du système nerveux, dans les animaux vertébres. (Crevot, Paris, 1824).

128. Eccles, J. C., Ito, M. & Szentágothai, J. *The Cerebellum as a Neuronal Machine* (Springer, Berlin, 1967).

129. Braitenberg, V., Heck, D. & Sultan, F. The detection and generation of sequences as a key to cerebellar function: experiments and theory. *Behav. Brain Sci.* **20**, 229–245 (1997).

130. Garwicz, M. & Andersson, G. Spread of synaptic activity along parallel fibres in cat cerebellar anterior lobe. *Exp. Brain Res*. **88**, 615–622 (1992).

131. Isope, P. & Barbour, B. Properties of unitary granule cell–Purkinje cell synapses in adult rat cerebellar slices. *J. Neurosci*. **22**, 9668–9678 (2002).

132. Levinsson, A., Garwicz, M. & Schouenborg, J. Sensorimotor transformation in cat nociceptive withdrawal reflex system. *Eur. J. Neurosci*. 4327–4332 (1999).

133. Bower, J. M. Is the cerebellum sensory for motor's sake, or motor for sensory's sake: the view from the whiskers of a rat? *Prog. Brain Res*. **114**, 463–496 (1997).

134. Brand, S., Dahl, A.-L. & Mugnaini, E. The length of the parallel fibres in the cat cerebellar cortex. An experimental light and electron microscopic study. *Brain Res*. **26**, 39–58 (1976).

135. Pichitpornchai, C., Rawson, J. A. & Rees, S. Morphology of parallel fibres in the cerebellar cortex of the rat: an experimental light and electron microscopic study with biocytin. *J. Comp. Neurol*. **342**, 206–220 (1994).

136. Lawrence, D. G. & Kuypers, H. G. J. M. The functional organization of the motor system in the monkey. I. The effects of bilateral pyramidal lesions. *Brain* **91**, 1–14 (1968).

137. Lawrence, D. G. & Kuypers, H. G. J. M. The functional organization of the motor system in the monkey. II. The effects of lesions of the brain-stem pathways. *Brain* **91**, 15–36 (1968).

138. Yu, J. & Eidelberg, E. Recovery of locomotor function on cats after localized cerebellar lesions. *Brain Res*. **273**, 121–131 (1983).

139. van Kan, P. L. E., Houk, J. C. & Gibson, A. R. Output organization of intermediate cerebellum of the monkey. *J. Neurophysiol*. **69**, 57–73 (1993).

140. Gibson, A. R., Horn, K. M., Stein, J. F. & van Kan, P. L. Activity of interpositus neurons during a visually guided reach. *Can. J. Physiol. Pharmacol*. **74**, 499–512 (1996). Recordings of individual neurons in the forelimb region of the NIA in awake, behaving monkeys supported the general idea that this cerebellar nucleus is important for the control of hand movements used in a reach-to-grasp movement.

141. Cooper, S. E., Martin, J. H. & Ghez, C. Effects of inactivation of the anterior interpositus nucleus on the kinematic and dynamic control of multijoint movement. *J. Neurophysiol*. **84**, 1988–2000 (2000).

Reversible lesions with muscimol of the NIA in awake cats showed that the cerebellar paravermal system is important in the anticipatory control of interactions between different limb segments involved in a reaching task.

142. Monzée, J. & Smith, A. M. Responses of cerebellar interpositus neurons to predictable perturbations applied to an object held in a precision grip. *J. Neurophysiol*. **91**, 1230–1239 (2004).

143. Monzée, J., Drew, T. & Smith, A. M. Effects of muscimol inactivation of the cerebellar nuclei on precision grip. *J. Neurophysiol*. **91**, 1240–1249 (2004).

144. Bastian, A. J., Martin, T. A., Keating, J. G. & Thach, W. T. Cerebellar ataxia: abnormal control of interaction torques across multiple joints. *J. Neurophysiol*. **76**, 492–509 (1996).

145. Bastian, A. J., Zackowski, K. M. & Thach, W. T. Cerebellar ataxia: torque deficiency or torque mismatch between joints? *J. Neurophysiol*. **83**, 3019–3030 (2000).

146. Zackowski, K. M., Thach, W. T. & Bastian, A. J. Cerebellar subjects show impaired coupling of reach and grasp movements. *Exp. Brain Res*. **146**, 511–522 (2002).

147. Garwicz, M., Apps, R. & Trott, J. R. Micro-organization of olivocerebellar and corticonuclear connections of the paravermal cerebellum in the cat. *Eur. J. Neurosci*. **8**, 2726–2738 (1996).

148. Garwicz, M., Ekerot, C.-F. & Jörntell, H. Organizational principles of cerebellar neuronal circuitry. *News Physiol. Sci*. **13**, 26–32 (1998).

149. Cooke, J. D., Larson, B., Oscarsson, O. & Sjölund, B. Origin and termination of cuneocerebellar tract. *Exp. Brain Res*. **13**, 339–358 (1971).

150. Ekerot, C.-F. & Jörntell, H. Parallel fiber receptive fields: a key to understanding cerebellar operation and learning. *Cerebellum* **2**, 101–109 (2003).

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Apps' Homepage:
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