

The primate cortico-cerebellar system: anatomy and function

Narender Ramnani

Abstract | Evidence has been accumulating that the primate cerebellum contributes not only to motor control, but also to higher ‘cognitive’ function. However, there is no consensus about how the cerebellum processes such information. The answer to this puzzle can be found in the nature of cerebellar connections to areas of the cerebral cortex (particularly the prefrontal cortex) and in the uniformity of its intrinsic cellular organization, which implies uniformity in information processing regardless of the area of origin in the cerebral cortex. With this in mind, the relatively well-developed models of how the cerebellum processes information from the motor cortex might be extended to explain how it could also process information from the prefrontal cortex.

Traditional views of the cerebellum hold that this structure is engaged exclusively in the control of action, with a specific role in the acquisition of motor skills^{1–4}. This has been substantiated by an impressive body of evidence accumulated over several decades^{5–7}. However, with the advent of functional neuroimaging methods, it soon became clear that cerebellar activity could be commonly evoked by a variety of conditions that are far removed from the domain of motor control^{8–11}. Numerous reports also suggest associations between cerebellar pathology and disorders of higher function that cannot easily be explained by impairments in motor control^{12–14}. Despite the fact that we know so much about the cerebellum and its involvement in behaviour, there is now a plethora of (often contradictory) views about its functions.

The aim of this review is to consider what information is processed in the cerebellum and how this information is processed in cerebellar circuitry. These issues can be re-framed by asking which areas of the brain (particularly the various divisions in the cerebral cortex) project to the cerebellum and by considering how cerebellar circuitry itself is organized. Therefore, I first discuss the architecture of the cerebellum and its intrinsic and extrinsic connections, and then go on to cover cerebellar function.

Existing ideas about cerebellar contributions to motor control that date back to the 1960s have substantial empirical support^{15–18}. However, they remain incomplete in the light of evidence for cerebellar involvement in information processing beyond the domain of motor control. This review does not aim to present a complete

theoretical account of cerebellar information processing, but it does suggest ways in which existing theoretical frameworks can be adapted to accommodate these findings.

Anatomical architecture and connections

There are three aspects of cerebellar anatomy that make it a remarkable structure. First, the beautifully regular and simple cellular organization in the cerebellar cortex is repeated in a crystalline manner across the entire cortex. Second, there is the global nature of its connectivity with other areas of the brain, in particular its connections with the cerebral cortex^{19,20}. Finally, the human cerebellum contains ~50 billion neurons²¹ — roughly half of the total number of neurons in the brain. The impressive orders of magnitude suggest extremely powerful mechanisms for processing information.

Intrinsic cerebellar organization. Like the forebrain, the cerebellum has its own cortex — a three-layer sheet of highly organized cells and fibres (comprehensively reviewed in REF. 22). These neurons project to the cerebellar nuclei (subcortical structures buried deep inside cerebellar white matter), which form the outputs from the cerebellum to other brain areas (FIG. 1a). Larsell^{23,24} provided the most comprehensive description of cerebellar cortical morphology, describing ten ‘lobules’ that can be identified in all mammalian species (FIG. 1b).

The fundamental information processing unit of the cerebellar cortex is the Purkinje cell, which integrates information from two main precerebellar

Cognitive Neuroscience
Laboratory, Department of
Psychology, Royal Holloway,
University of London, Egham,
Surrey TW20 0EX, UK.
e-mail: n.ramnani@rhul.ac.uk
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Climbing fibres

Axons of inferior olive neurons that extend into the cerebellar cortex and exert a powerful influence on Purkinje cells. One of two main inputs into the cerebellum.

relay stations: the pontine nuclei and the inferior olive (FIG. 1c). Each Purkinje cell can receive inputs from up to ~200,000 parallel fibres²⁵ that convey information from the pontine nuclei. By contrast, climbing fibres convey information from the inferior olive, and each fibre forms multiple synapses with a single Purkinje cell (FIG. 1c). Specific segments in the inferior olive project to functionally distinct, parasagittally aligned Purkinje cells (microzones²²). One feature of this cellular organization that has an important bearing on our understanding of cerebellar function is that it is invariant across the entire

cerebellar cortex^{19,20}, which implies uniformity in the way that information is processed across the cerebellar cortex. Although there is some variation across the cortex, this is minor in relation to the scale of the uniformity²⁰. It can therefore be argued that the diverse information processing in the cerebellar cortex arises not from differences in local circuitry, but from the diverse nature of the inputs to the cerebellum, and in particular from the cerebral cortex.

Cerebellar connections with the cerebral cortex.

Knowledge of the connections between the cerebral cortex and the cerebellum is particularly important when considering the role of the cerebellum in processing different forms of information that vary in their levels of abstraction²⁶. This section focuses on the anatomical routes through which the cerebellum can communicate with cortical areas of the frontal lobe. Although we know a great deal about ascending inputs to the cerebellum, the organization of descending projections is becoming increasingly studied. Cortico-pontine projections have been studied thoroughly, but information about cortico-olivary projections remains sparse²⁷ and will not be considered here.

Cortico-ponto-cerebellar projections form part of a closed loop system with the cerebral cortex, in which the cerebellum returns projections to the cerebral cortex via the thalamus²⁸⁻³¹. In non-human primates, the densest cortico-pontine projections arise in the precentral cortex (area 4, primary motor cortex; area 6, premotor cortex), and there are also less prominent projections from dorsal areas of the prefrontal cortex³²⁻³⁶ (Walker's area 46 (REF. 37)) (see also FIG.2). The precise organization of these loops has only recently become clear. Strick and colleagues^{38,39} used trans-synaptic tracers that harness the ability of genetically altered viruses to cross synapses. They revealed projections from dorsal areas 9 and 46 of the prefrontal cortex to the ventral cerebellar dentate nucleus³⁹. A further study³⁸ showed the afferent and efferent connections of areas 4 and 46 with the cerebellum. The motor cortex connects with lobules V, VI, HVIIB and HVIII of the cerebellar cortex (FIG. 3a,b), and with dorsal parts of the dentate nucleus (the 'motor' module). The prefrontal cortex was shown to connect mainly with lateral Crus II and vermal lobules VII and IX of the cerebellar cortex (FIG. 3c,d), and with the ventral portions of the dentate nucleus (the 'prefrontal' module). So far, this is the only study in primates to have mapped the trans-synaptic projections from the cerebral cortex to sites of termination in the cerebellar cortex.

The cerebellum seems to be composed of multiple, independent anatomical modules, each forming a component in a closed anatomical loop that sends and receives projections from a specific area of the cerebral cortex (FIG. 3e). In macaque monkeys, there is little disagreement that the motor loop is much more prominent than the prefrontal loop^{2,35,36}. The efferent projections from the prefrontal cortex to the cerebellum arise predominantly from dorsal prefrontal regions (area 9/46 of Petrides and Pandya^{40,41}, or 46 of Walker³⁷), which arguably constitutes the apex of the hierarchically organized

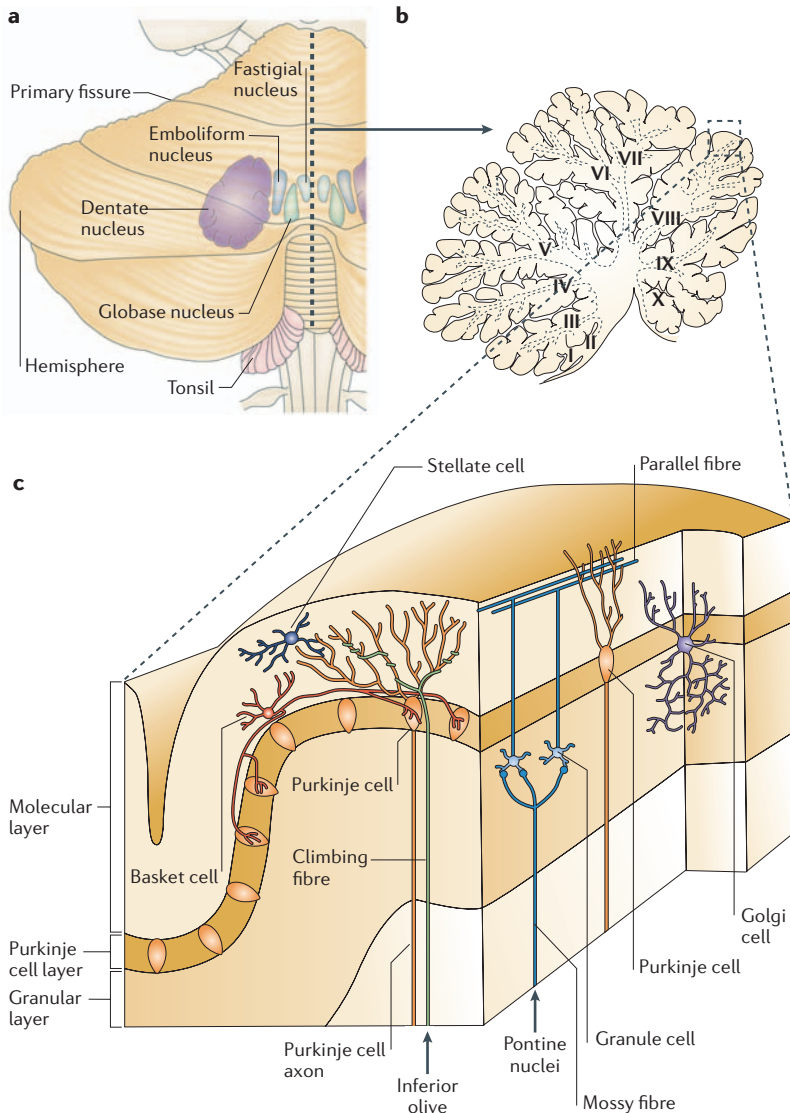


Figure 1 | Anatomical architecture of the cerebellum. **a** | Posterior view of the human cerebellum, showing the cerebellar nuclei embedded below the cerebellar cortex. **b** | Drawing of midsagittal cross-section through the human cerebellum (dotted line indicates the plane of section), showing lobular organization. Each of the ten lobules is demarcated by a Roman numeral (I–X). **c** | The microstructural organization of the cerebellar cortex. Cut-away illustration of an individual cerebellar cortical lobule, indicating the presence of three layers. The figure shows the relative positions of Purkinje cells and their main inputs (parallel and climbing fibres). Panel **a** modified, with permission, from REF. 149 © (1991) Elsevier Science. Panel **b** modified, with permission, from REF. 23 © (1972) University of Minnesota Press. Panel **c** modified, with permission, from REF. 150 © (1989) Oxford Univ. Press.

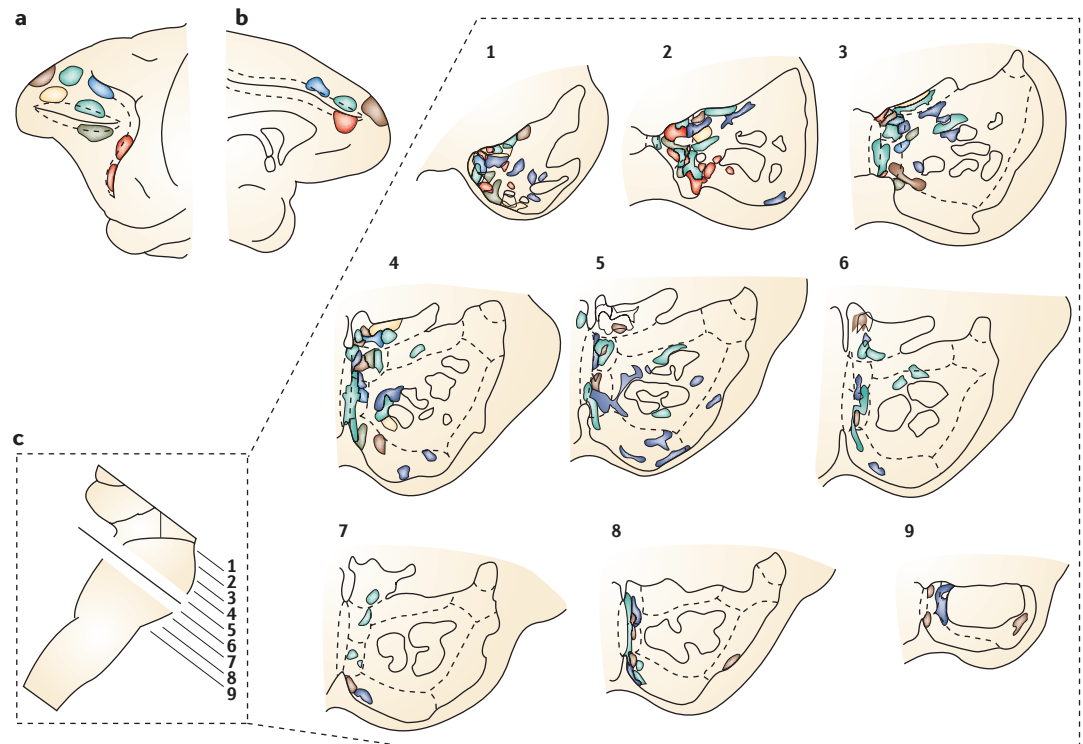


Figure 2 | Prefrontal projections to the pontine nuclei. Colour-coded injection sites in lateral (a) and medial (b) convexities of the macaque monkey prefrontal cortex. Panel c, areas with terminal label in the pontine nuclei to which these cortical sites project. Modified, with permission, from REF. 33 © (1997) Society for Neuroscience.

cortical motor system⁴². Of all prefrontal areas, Walker's area 46 has the most significant projections to the premotor system^{43,44}. Although it is not as directly engaged in the control of movement as the premotor cortex, it is thought to specifically encode action-related information in abstract terms (for example, the goals of actions)⁴⁵. Therefore, it might even be argued that projections between the dorsal prefrontal cortex and cerebellar cortical area Crus II also subserve motor functions.

In view of the fact that so little is known about the connective anatomy of the human brain, one of the most pressing dilemmas in evolutionary neurobiology is whether we are justified in assuming that knowledge of structure and function from non-human primates can be extrapolated to humans. It would not be unreasonable to assume that the dominance of cerebellar connections to the motor system has been phylogenetically preserved, but important findings from evolutionary neurobiology prompt us to reconsider this position.

It is thought that the evolution of areas in the cerebral cortex has been non-uniform, such that some areas have evolved more rapidly than others⁴⁶. The prefrontal cortex is thought by some to have evolved particularly rapidly, being enlarged in humans compared with other primates. The 'Mosaic' hypothesis⁴⁷ suggests that the selectional pressures that drive brain evolution act not on single brain areas but on interconnected systems. Have the areas that are interconnected with the prefrontal cortex also evolved rapidly? One

recent study would suggest so. Its findings indicate that the expansion of the prefrontal cortex is explained not by changes in the grey matter, but by changes in the white matter that connects the prefrontal cortex with its efferent and afferent targets⁴⁸. If this idea is extended to the cortico-cerebellar system, the hypothesis would predict the selective expansion of all components of the prefrontal loop. Matano⁴⁹ has used volumetric analyses in post-mortem histological cerebellar tissue to show that, in humans, the ventral dentate (interconnected with the prefrontal cortex) is indeed disproportionately larger than the dorsal dentate (interconnected with the motor cortex) when compared with the dorsal and ventral dentate in the great apes.

To what extent have prefrontal-cerebellar projections specifically evolved? Cortico-pontine fibres converge in the cerebral peduncle before terminating in the pontine nuclei. Early post-mortem degeneration studies of the human cerebral peduncle^{50–52} categorized three fibre segments, the largest of which was thought to originate in the primary motor cortex and occupy two-thirds of the cerebral peduncle. This methodology revealed a general topography, but the commonly presented diagrammatic representation of the boundaries between segments (FIG. 4d) was at best a rough estimate.

Recent developments in diffusion tensor MRI (DT-MRI)^{53–56} have enabled the segmentation of cerebral peduncle fibres on the basis of their origins in the cerebral cortex, in both human and macaque brains⁵⁷ (FIG. 4). The topographic organization was broadly consistent

Crus II

This is the area of the macaque monkey cerebellar cortex that is most heavily interconnected with the area 46 of the prefrontal cortex.

Cerebral peduncle

All cortical projections that send fibres to the pontine nuclei converge into this white matter fibre bundle before synapsing with pontine neurons. This is a convenient location at which to study the organization of cortico-pontine projections using diffusion tensor imaging.

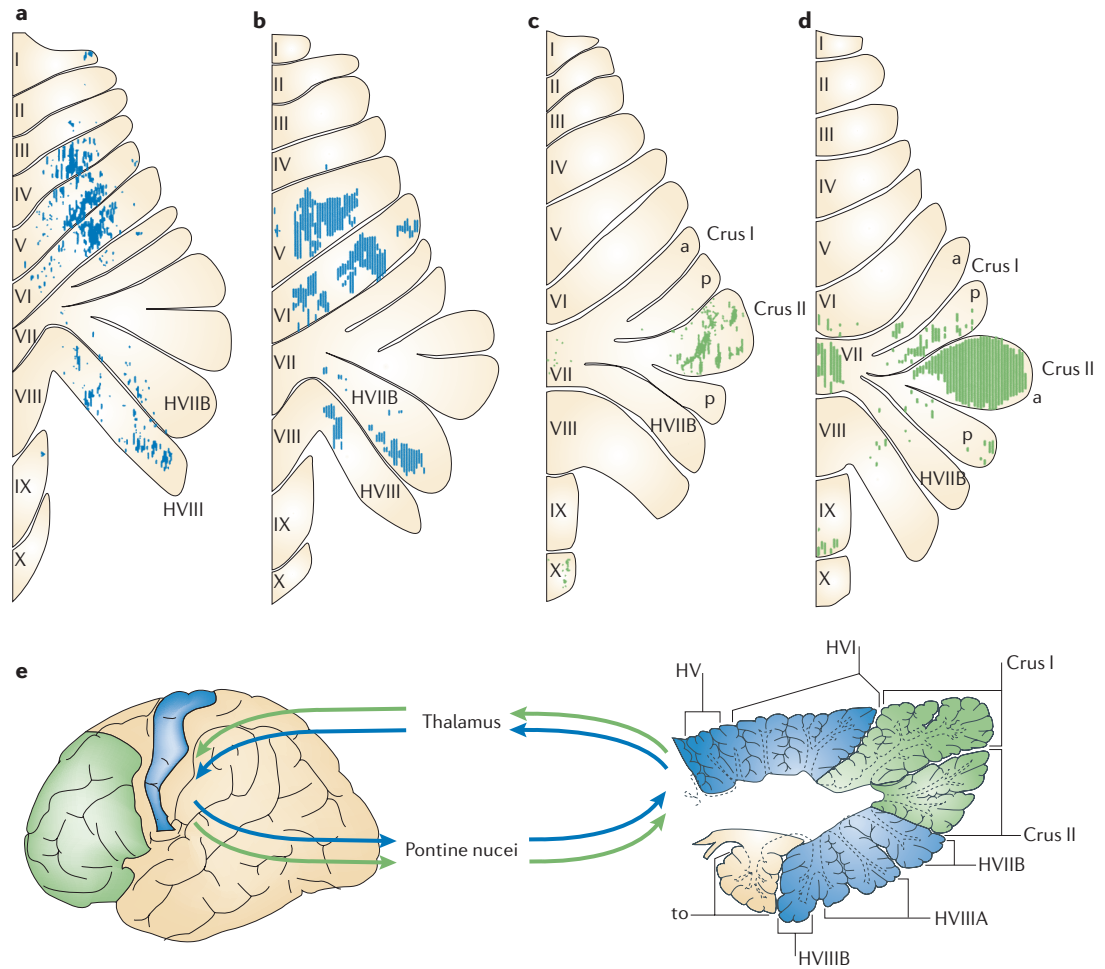


Figure 3 | Motor and prefrontal modules in the primate cerebellar cortex. In the macaque monkey, transneuronal tracers were injected into the arm area of the primary motor cortex (area 4) and prefrontal area 46 (REF. 38). Results show the sites of cerebellar cortical terminal label after the injections of retrograde and anterograde tracers (area 4, blue; area 46, green). **a** | Retrograde projections from area 4. **b** | Anterograde projections from area 4 to granule cells. **c** | Retrograde projections from area 46 to Purkinje cells (a, anterior; p, posterior). **d** | Anterograde projections from area 46 to granule cells. **e** | Homologous areas in the human cerebellar cortex and a schematic illustration of how they are interconnected with the human cerebral cortex (to, cerebellar tonsil). Panels **a–d** modified, with permission, from REF. 38 © (2003) Society for Neuroscience. Panel **e** (left) modified, with permission, from REF. 152 © (1999) Springer. Panel **e** (right) modified, with permission, from REF. 23 © (1972) University of Minnesota Press.

with that shown by the degeneration studies, and was preserved across the two species. In macaque brains, fibres from the cortical motor system occupied the largest proportion of the cerebral peduncle as expected (FIG. 4f,g), and a comparatively small proportion was occupied by fibres from the prefrontal cortex. By contrast, in the human brain, the largest contribution came not from the cortical motor areas but from the prefrontal cortex (FIG. 4e), which supports the view that in humans the cerebellum has a more important role than in macaques in processing information from the prefrontal cortex — an area in which neurons code information at a more abstract level than in the cortical motor areas. This lends support to the view that the human cerebellum is not merely involved in the control of action, but is also actively engaged in processing more abstract information from the prefrontal cortex.

Functional implications

Cerebellar interactions with the cortical motor system.

The focus of theoretical work on cerebellar function has been on its role in the control of action and the acquisition of motor memory⁵⁸. The architecture of the cerebellar cortex has inspired several theoretical models of its functions. Brindley⁵⁹ proposed that new actions are initially under ‘conscious’ control by cerebral cortical mechanisms, and that cerebellar circuits learn links between these actions and the contexts in which they are executed. So, the context itself comes to evoke the action, facilitating the automatic, unconscious cerebellar control of the same action. Marr¹⁸ formalized this process in a model based on the experience-dependent acquisition and storage of motor memory. It suggests that the strength of Hebb-like synapses between parallel fibres and Purkinje cell dendrites could encode these representations. It also proposes that these synaptic

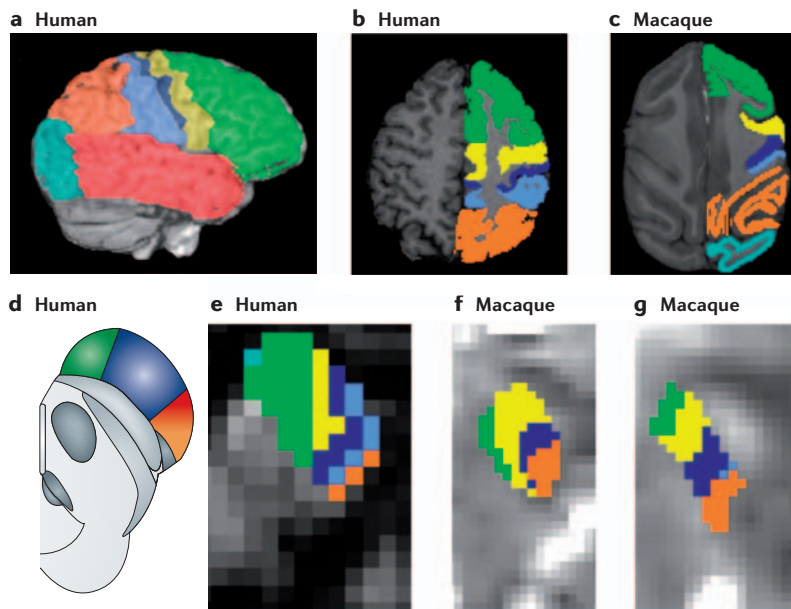


Figure 4 | The organizational origins of cortico-cerebellar fibres in the cerebral peduncle. Diffusion tensor imaging (DTI) was used to determine the contributions of several distinct zones in the cerebral cortex to fibres in the cerebral peduncle on their way to the pontine nuclei in humans and macaque monkeys⁵⁷. Areas shown are the prefrontal cortex (green), premotor cortex (yellow), primary motor cortex (dark blue), primary somatosensory cortex (light blue), temporal lobe (red), parietal cortex (orange) and occipital lobe (turquoise). Subdivisions of the cerebral cortex represented on a rendered surface (a) and an axial section (b) of the human brain and an axial section of the macaque brain (c). **d** | An early schematic view of the organization of cortico-cerebellar fibres through the cerebral peduncle, taken from REF. 153 (derived from early degeneration studies). Fibres in the cerebral peduncle were previously thought to be organized topographically in three main segments, the largest originating in the motor cortex and others from the prefrontal cortex and the temporal lobe and parietal cortex. However, this is inconsistent with more reliable evidence from DTI. Although the largest segment originates in the cortical motor areas (blue and yellow) in the macaque monkey (f and g), the largest segment in the human cerebral peduncle arises in the prefrontal cortex (e). Panels a–c, e–g modified, with permission, from REF. 57 © (2006) Oxford University Press. Panel d modified, with permission, from REF. 153 © (1994) Elsevier Science.

modifications occur under the guidance of error signals conveyed by climbing fibres — complex spikes evoked by climbing fibres would effectively cause a change in synaptic strength between Purkinje cell dendrites and activated parallel fibres. Purkinje cells could therefore learn to acquire the ability to respond to signals conveyed by parallel fibres, under the guidance of a teaching signal from climbing fibres. The cellular and molecular mechanisms of parallel fibre–Purkinje cell plasticity have been studied extensively *in vitro*^{60–62}, and evidence from *in vivo* studies in animal models shows that similar mechanisms might form the basis of cerebellar plasticity during learning⁶³. Although some electrophysiological investigations in animal models have shown that complex spikes can be evoked in response to errors^{64–66}, this relationship is highly controversial and not universally accepted^{67,68}.

Many interrelated theoretical accounts have been developed that attempt to explain cerebellar contributions to motor control (for a review, see REF. 69). Gordon Holmes, one of the pioneers of cerebellar theory,

suggested a possible role for the cerebellum in controlling rate and regularity of movement through indirect influence on motor control structures⁶. A later set of theories proposed a role for the cerebellum in learning and applying the parameters of movements so that they can be executed without the need for feedback control⁷⁰. A third group of theories suggest that the properties of cerebellar circuits can explain a role for the cerebellum in the temporal organization of coordinated action^{71–73}. Although these attempt to explain cerebellar involvement in motor control, they do not systematically explain how common cerebellar mechanisms might contribute to both motor control and cognitive function. One alternative set of accounts might be more successful in this respect. Its major strength is that it borrows ideas from control theory^{58,69,74–77} (an important field of engineering), and in doing so imports a set of well-developed theoretical principles. Control theoretic accounts of motor control are computationally explicit in providing systematic explanations of how specific forms of information are processed. Not only does control theory draw from ideas relating to small-scale cerebellar microcircuitry^{16–18,61}, it also integrates our understanding of the large-scale connectivity of the cerebellum with the cerebral cortex more specifically than previous work⁷⁸.

Control theory and the cerebellum: motor control.

The process of motor control can be theoretically described in terms of lower motor control centres (such as those in the spinal cord) translating motor commands from higher centres (such as the cerebral cortical motor areas) into muscle movements. The resulting movement is accompanied by a set of sensory consequences; for example, proprioceptive feedback from the muscles and sensory feedback from body contact with the environment. However, before such feedback can be usefully implemented in motor control, three problems have to be resolved. First, inherent delays in the transmission of this data back to the brain mean that the sensory feedback arrives when it is too late to influence the ongoing movement. Second, the sensory consequences of action indicate only the extent to which movement deviates from ideal performance if compared with an appropriate reference signal. Third, the sensory information that is fed back to the brain cannot be directly understood by systems that normally code information in terms understood by the motor system.

Control theory provides an elegant solution to these problems. The central concept in control theory is the ‘internal model’. Essentially, internal models are neural representations acquired through learning that can simulate natural processes such as body movements⁷⁷. Through experience-dependent learning, they encode and continuously refine input–output relationships between motor commands and their consequences. Two important classes of internal model, ‘inverse’ and ‘forward’ models, have been used as a basis for discussing cerebellar information processing⁷⁹. The forward model (FIG. 5a), which is relevant to this review, contains representations of correct input–output mappings learned with error feedback in real world situations⁷⁷. Inputs to

forward models consist of efference copies of motor commands that are normally used by the motor system to generate movements. Outputs consist of the predicted sensory consequences of ideally executed movement. The direct stream of information processing that converts motor commands into actions is supplemented by an additional parallel stream of processing (a side loop) that mimics the information processing in the direct stream. Efference copies of the motor commands are used by a forward dynamic model to predict the ideal new state of the body after the movement, and a forward output model predicts the ideal sensory consequences (corollary discharge) for successfully applied motor commands. Of course, to participate in error correction, some part of the system must also engage in error detection. A comparator identifies discrepancies between the actual and predicted sensory consequences, and signals errors in the accuracy of the forward models. This error signal is used to alter input–output mappings in forward models so that subsequent predictions for the same situation can be made more accurately.

This theoretical scheme resolves the problems outlined earlier, because the results of feedback are stored in internal models through learning and are applied on subsequent trials. This information is used to influence motor control even in advance of movement. Also, the sensory consequences of movement can be compared directly with a reference signal that indicates predicted outcome for an ideal movement. Finally, there is no requirement to code error in motoric terms, as reafferent sensory signals from the body and corollary discharge signals from forward output models are coded in a common language, and so can be directly compared.

The idea that internal models are powerful theoretical tools for explaining motor control has acquired considerable support^{58,80–82}. But can this theoretical architecture be instantiated within the networks of the brain? The architecture of direct and side-loop information processing streams seems to have close anatomical parallels with the direct supraspinal control of the motor apparatus and the parallel cerebellar circuits that are attached to this direct pathway (FIG. 5b). It has been suggested that the cerebellar cortex is a likely location for the storage of motor memory, perhaps in the form of forward models^{15,16,18}, and there are several molecular and cellular^{15,62,83} studies that seem consistent with the idea that the cerebellar cortex is important for motor learning, and might be an important site of learning-related plasticity. Motor commands generated in the primary motor cortex are sent to lower motor control centres in the brainstem and spinal cord^{184–87}. If cerebellar cortical circuitry was to receive efference copies of these motor commands, there would have to be a pathway that carried the same information from the primary motor cortex to the cerebellar cortex. The cortico-ponto-cerebellar system serves this purpose well. Fibres on their way to the spinal cord collateralize, and the collateral projections synapse onto neurons in the pontine nuclei⁸⁸. Motor commands might also be conveyed via direct cortico-pontine projections that arise in the motor cortex.

How can outputs from cerebellar cortical forward models influence motor control? Outputs from the motor modules of the cerebellum project back to the primary motor cortex via the thalamus to influence motor control at a relatively high level, perhaps directly influencing motor commands^{89–91}. There are also mechanisms through which lower centres can be influenced. The rubrospinal tract, a major descending pathway, begins in the red nucleus and terminates on the motoneurons of the spinal cord^{92,93}. Projections from the cerebellar nuclei to the red nucleus⁹⁴ allow cerebellar output to influence spinal mechanisms involved in motor control.

Evidence suggests that the inferior olive could serve as a comparator^{64–66}. It seems ideally placed in anatomical terms because it receives direct reafferent sensory and proprioceptive signals via the spinal cord^{95–98}. There are also pathways that can convey corollary discharge information from the cerebellum to the inferior olive either directly⁹⁹, or via the red nucleus^{94,100}. Electrophysiological evidence also shows that complex spikes in Purkinje cells are evoked by the unexpected sensory consequences of movement^{101–103}.

The notion of forward models supports the idea that there are two systems working in parallel, with one learning from and simulating the operations of the other. What is the advantage of a neural system that effectively mimics information processing in other parts of the nervous system? The direct stream of information processing involves the cerebral cortex. Information processing architectures of the cerebral cortex are considered to be flexible (for example, representations are sufficiently flexible to generalize), but they are also slow. It would be an advantage to use 'side loop' cerebellar forward models in situations in which such flexibility is not required (for example, when representations are effector-specific), and when the rapid, stereotypical information processing used for routine operations is more efficient. This must also be a significant advantage when flexible and routine information processing need to take place simultaneously. In these instances, routine background information processing in cerebellar circuitry and flexible operations in the cerebral cortex can take place in parallel without interrupting each other.

This account of cortico-cerebellar engagement in motor control derives empirical support from diverse approaches. First, an abundance of clinical evidence exists to show that the integrity of the human cerebellum is essential for the seamless integration of separate movements into a skillfully executed and coordinated whole^{6,104–106}. Important evidence also comes from studies in which permanent and reversible cerebellar lesions impair the acquisition and retention of motor memories in animal models. Simple, well characterized forms of motor learning have been abolished or impaired by permanent and reversible pharmacological inactivations^{66,107,108} of specific cerebellar modules. Such effects have also been shown in primates for more complex forms of learning. Lu and colleagues¹⁰⁹ reversibly inactivated the dorsal dentate nucleus (a component of

Efference copy

Information processing might require that information exchanged between two systems is monitored by a third system (as in the case of systems that incorporate control theoretic internal models). Therefore, whenever such information is exchanged, an exact copy (an efference copy) is additionally transmitted to the monitor.

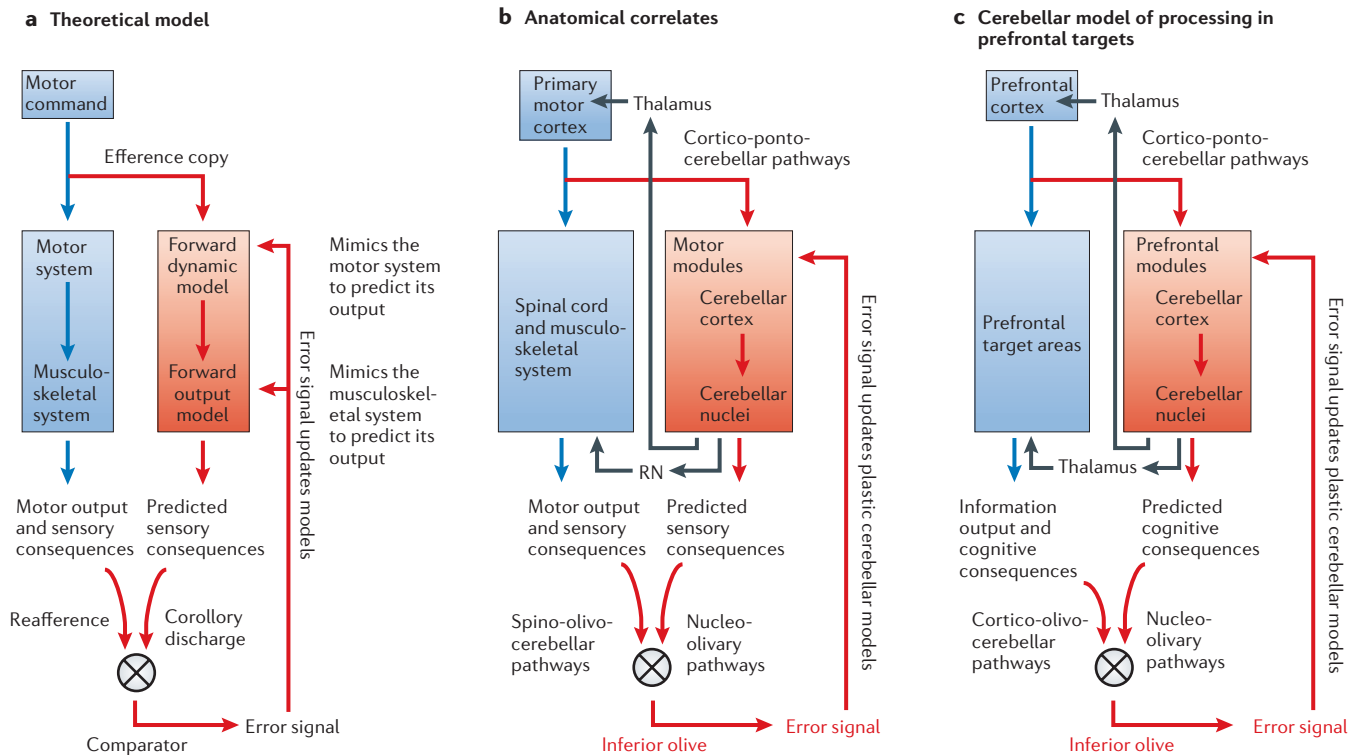


Figure 5 | Theoretical and neural organization of forward models. **a** | Theoretical organization of information processing streams that use forward models for motor control. Motor commands directed to systems that control movement are also copied to forward models that mimic input–output relationships exhibited by these systems (blue, direct route; red, side-loop). **b** | Anatomical correlates of this theoretical organization. Note that the anatomical model contains additional components that exert control over motor control systems (for example, by modulating rubrospinal circuits) (RN, red nucleus). **c** | Analogous anatomical model involving prefrontal interactions. The organization is the same as that in panel **b**. Information arising in the prefrontal cortex is copied to the cerebellum in the same way that motor commands are copied from the primary motor cortex to the spinal cord. In this scheme, cerebellar forward models mimic the input–output relationships of prefrontal targets (note that the target of a prefrontal neuron can be neurons outside the prefrontal cortex, but can also be another prefrontal neuron). Forward models might therefore be able to mimic information processing that is intrinsic to the prefrontal cortex. Modified, with permission, from REF. 77 © (1996) Elsevier Science.

the motor loop) in monkeys. The monkeys were unable to retrieve overlearned motor sequences, but were still able to learn new ones. The effect was specific to the cerebellar hemisphere ipsilateral to the paw with which learned sequences were executed. Therefore, the control of unfamiliar movements might not rely on the motor loop, but after motor learning the control of learned actions depends on effector-specific forward models of motor sequences that are stored in areas of the cerebellum interconnected with the cortical motor system. It is arguable that permanent and reversible effects of cerebellar lesions are not restricted to cerebellar circuits, but impair the physiology of interconnected areas (cortico-cerebellar diaschesis¹¹⁰). However, neuroimaging studies reveal the presence of activity in the human cerebellum related to error signals^{111–113}, and electrophysiological methods in animal models show that these can be manifested as complex spikes in Purkinje cell firing^{101–103} (although, as mentioned earlier, the role of complex spikes in error processing is controversial). Studies of cerebellar activity have also shown that cer-

ebellar activity specifically reflects the operations of internal models during motor control^{112,114–116}.

Cerebellar activity should change dynamically during learning. Control theory would predict the presence of error-related complex spike activity that declines during normal motor learning, because cerebellar forward models would incrementally acquire control over movements as they are learned. This should be reflected in increasing activity during motor control; indeed, neurophysiological methods in animal models have shown decreasing complex spike activity during motor learning¹⁰¹. Functional neuroimaging studies report both increases^{112,117–120} and decreases^{112,118,121,122} in cerebellar activity during motor learning, but it is not possible to unambiguously attribute such changes to either transitions in control or changes in error frequency when both change simultaneously. The inherent limits of functional neuroimaging methods also make it difficult to attribute these changes to specific neurophysiological causes, such as the presence of complex spikes in Purkinje cells. However, some experimental designs can be used to manipulate error independently

Diaschesis

A condition in which lesions not only impair information processing at the site of the lesion, but also adversely affect the information processing in connected downstream pathways. Therefore, the behavioural effects of lesions might at least in part be due to the impaired physiology of such areas rather than the direct effects of the lesion.

of other factors, and other researchers have reported the presence of error-specific cerebellar activity^{111,113}. This evidence seems consistent with the idea that cerebellar circuitry participates in motor learning by storing forward models.

Control theory and the cerebellum: beyond motor control.

It was suggested earlier that motor-related operations are likely to occupy only a small proportion of the cerebellar cortex. If this is the case, then what does the rest of the cerebellar cortex do?

The homogeneity of cerebellar cortical cytoarchitecture suggests that many other areas of the cerebellar cortex also acquire and store some kind of forward model that is unrelated to the information processing in the cortical motor areas. Here, I extend the idea of cerebellar cortical forward models from one that was specifically involved in simulating information processing in the targets of the motor cortex, to one that potentially simulates information processing in the targets of all cortical areas that project to the cerebellum through the cortico-ponto-cerebellar system. Ito⁷⁵ similarly suggests, for example, that in the early stages of learning, control signals arising in prefrontal areas act on representations in the temporal lobe and posterior parietal association areas. Through learning, these representations are effectively copied to the cerebellum, and the prefrontal cortex then acts on cerebellar forward models⁷⁵. Let us take the premotor cortex as another specific example. The premotor cortex occupies a strategic place in the hierarchically organized cortical motor system²⁶. Its connections allow it to re-code information from higher order areas of the prefrontal cortex (area 46 in particular)^{43,44} into code that can be understood by the primary motor cortex. For example, premotor areas are important in the generation of motor plans that are passed to the primary motor cortex for execution. If premotor efferents project to the primary motor cortex, then our analogy would suggest that it sends efference copies of this information to cerebellar cortical forward models, which simulate information processing in the primary motor cortex. Therefore, the cerebellar forward model receiving inputs from the premotor cortex would attempt to predict the outcomes of information processing in the primary motor cortex. Similarly, cerebellar forward models receiving efference copies from areas of the prefrontal cortex will model information processing in prefrontal target areas. The connectivity of the prefrontal cortex with other brain areas seems to have evolved selectively⁴⁸, and if cortico-pontine fibres copy this information to the cerebellum then it seems reasonable that the expansion of prefrontal connectivity should be mirrored by a selective expansion of cortico-cerebellar fibres. As discussed earlier, there is indeed anatomical evidence from diffusion tensor imaging to support this idea⁵⁷.

Cerebellar simulations of prefrontal processing?

Prefrontal territories each have their own unique connective 'fingerprint'¹²³. These areas are richly interconnected with one another and with other posterior cortical areas. If the instantiation of forward models in cerebellar cortical circuitry is a general principle rather

than one restricted to the control of movement, then it seems conceivable that the transmission of information from prefrontal areas to their targets could similarly represent the transmission of efference copies of prefrontal information to cerebellar cortical forward models that simulate information processing in prefrontal targets (FIG. 5c). As already discussed, in the human brain the prefrontal inputs to the cerebellum seem to be at least as significant (if not more so) than inputs from the motor cortex. This evidence strongly suggests that there are important interactions between the prefrontal cortex and the cerebellum in the human brain, and some authors have suggested that it forms the basis of cerebellar involvement in cognitive function^{124–126}.

Although many have suggested a role for the cerebellum in cognitive functions that are unrelated to motor control, exactly what is meant by 'cognitive' in operational terms has not always been clearly stated. I make a distinction between two interpretations. First, some studies have suggested that cerebellar circuits can participate in higher level information processing that is comparable to that found in the prefrontal cortex, which would enable the cerebellum to be directly involved in executive processes. These accounts can be taken to imply similar operations in prefrontal and cerebellar circuits that subserve flexible operations that allow us to achieve executive control (for example, the learning and application of rules and decision-making^{127,128}). Some authors even suggest that the anatomical architecture of the cerebellum and its connections can engage in the representation and manipulation of high-level symbolic information¹²⁹, but these accounts do not incorporate powerful, long-standing accounts of cerebellar cortical information processing that have been substantiated by theoretical and empirical support. Second, cerebellar circuits use much simpler operations to process the outputs of the prefrontal cortex, and do so in the same way that they process the outputs of other areas, including those that are situated in lower levels of the cortical motor hierarchy such as the primary motor cortex⁷⁷. This supports the idea that the cerebellar cortex applies the same algorithms uniformly to all of its inputs — a finding consistent with the uniform cytoarchitecture of the cerebellar cortex^{19,20}. It is also consistent with the idea that cerebellar cortical forward models work in the same way regardless of the nature of their inputs. Similar ideas have received consideration in the past. Ito⁶¹ proposed the idea of cerebellar 'microcomplexes' (modular olivo-cortico-nuclear circuits with anatomically distinct inputs and outputs). Although the algorithm instantiated in each microcomplex is proposed to be identical, these instantiate forward models of action as well as cognition because of cerebellar connectivity with cortical motor and prefrontal areas. A general principle of forward models is that the computational operations effect a simulation of information processing in other, less efficient systems. I suggest that, although the cerebellar cortex can simulate the way in which the outputs of prefrontal areas are processed, the operations instantiated in the cerebellar cortex are themselves fundamentally different to those applied in the targets of prefrontal outputs.

Control theory suggests that the behaviour of these simulations should differ in some important respects from the algorithms that they learn to mimic. Some models of cortico-cerebellar interactions make an explicit distinction between mechanisms in the cerebral cortex that rely on feedback control and so work flexibly (generalizing across contexts) but less efficiently, and cerebellar feedforward mechanisms that are relatively inflexible but work efficiently in particular contexts^{61,72,78}. Ito⁶¹, for example, suggests that cerebellar microcomplexes connected in parallel to the musculoskeletal system enable the feedforward control of action, and when the same microcomplexes are similarly connected to association cortices, they facilitate feedforward cognitive control.

Cerebellar simulations should differ in two important dimensions from the cortical information processing that they mimic. First, cerebellar feedforward mechanisms should have an advantage over cortical mechanisms in terms of greater speed, accuracy and automaticity in relation to the slower cortical processes that they simulate (this is evidenced by the fact that the cerebellum responds to sensory input before even the primary sensory areas of the cerebral cortex^{130,131}). Second, cerebral cortical mechanisms should have the advantage of greater flexibility over cerebellar feedforward mechanisms. Ito⁷⁴ suggests that internal models in cerebellar circuits bestow the same advantages to thought as well as to action, making it both fast and accurate (these ideas echo the original ideas of Brindley⁵⁹). An important advantage of both systems working in parallel is that automatic information processing can take place in cerebellar circuits, leaving prefrontal circuits free to solve new problems with non-routine information processing. In contrast to prefrontal circuits, feedforward cerebellar models should be relatively inflexible because they fail to generalize beyond the context in which they are acquired. They would nevertheless work more efficiently when the particular rule always has to be applied in the same context. In summary, although anatomical evidence suggests that the primate cerebellum is important in processing information from the prefrontal cortex, it is unlikely that the algorithms implemented in cerebellar circuitry are comparable to those implemented in the prefrontal cortex. An important difference between prefrontal and cerebellar information processing might be that prefrontal circuits are able to abstract rules from the context in which they are learned, and so apply them flexibly in different contexts, whereas in cerebellar circuits the context and the rule are integrated in the same representation (an internal representation such as a forward model), such that it can only be efficiently applied in that context.

The idea that the cerebellum is involved in higher cognitive functions is controversial, but there is strong evidence to support this claim. Recent clinical, neuroimaging and neurophysiological evidence implicates the cerebellum in a range of cognitive and psychiatric deficits that cannot be explained purely in terms of motor control^{132,133}.

Neurophysiological evidence of cerebellar correlates of higher function is sparse, because such investigations in non-human primates are concerned mainly with

motor control. However, one study in macaque monkeys of visually guided reaching to a target shows that movement-related activity in the cerebellar cortical component of the prefrontal loop (Crus II) could be evoked by either limb, rather than just by the ipsilateral limb¹³⁴. This is consistent with the suggestion that these neurons were coding not for the limb-specific movement, but for the goal of the action, irrespective of the mechanism by which it could be achieved.

More convincingly, several neuroimaging studies in humans show that cerebellar activity in the healthy brain is evoked by the higher level cognitive demands, rather than the motor demands, of a task^{9,12,135–138}. Although these studies suggest that the cerebellum is engaged in processing abstract information, there is no consensus between them about its precise role. One of the most consistent findings in the functional neuroimaging literature is that verbal working memory reliably activates areas of the cerebellar cortex, including areas in the region of Crus II^{8,13,14,139–145}. This is complemented by the finding that patients with cerebellar lesions show selective deficits in verbal working memory^{146,147}. Desmond and colleagues¹⁴⁰ have suggested a control theoretic account of verbal working memory, based on cortico-cerebellar information processing. In common with the account presented here, they suggest that verbal working memory (acting as an articulatory control system) and motor skills are supported by common forms of processing in cortico-cerebellar circuitry, and that error correction signals enable the cerebellum to issue a feedforward command back to frontal lobe circuits via the thalamus. Earlier, it was mentioned that it is important to consider the changes in cerebellar activity that accompany learning. If control shifts from cortical to cerebellar areas during the process of learning, then one would expect corresponding decreases in prefrontal activity to take place as the task being learned comes to be controlled by systems that are specialized for automatic execution. Indeed, functional neuroimaging experiments of complex forms of motor learning (for example, motor sequence learning) show decreases in prefrontal activity^{45,120,148}.

This account of cortico-cerebellar interactions generates specific hypotheses that can be tested by future functional neuroimaging studies. It predicts that during the acquisition of cognitive skills that become increasingly stereotyped and automatic, a decline in prefrontal activity will be accompanied by increasing activity in connected areas (including Crus II). It further predicts that, if it were possible to experimentally dissociate learning-related and error-related activities, these would both occur in the same cerebellar cortical areas.

Conclusions, caveats and future directions

The iterative influences between theory and data generation have allowed general questions about the cortico-cerebellar system to evolve into increasingly specific ones. The most significant theoretical advances in our understanding of cortico-cerebellar contributions to motor control could not have been made on the basis of lesion studies, neurophysiology and neuroimaging alone — an understanding of cerebellar microstructure and

connectional anatomy has also been indispensable. But cerebellar contributions to motor control forms only a part of the overall picture; how can we develop a theoretical account of cortico-cerebellar function that also explains its engagement in higher cognitive function, without throwing away elegant and well-supported ideas about its involvement in motor control? In this review I have argued that this might be achieved by extending existing control theoretic accounts of motor control. Such an extension is predicated on the idea that, unlike the cerebral cortex, the microstructure of the cerebellar cortex seems to be relatively uniform. Algorithms that describe how the cerebellar cortex processes information from motor areas might also be applied to information from other areas of the cerebral cortex. Clues to the puzzle of cerebellar involvement in cognitive functions might therefore lie in its connections with the prefrontal cortex, just as its connections with the cortical motor system inform us about its role in motor control.

Progress in this field has depended on animal studies. The realization that monkey and human cortico-cerebellar systems can differ in important ways has meant that further progress in this field requires investigators to ask specific questions about anatomical organization and information processing in the human brain, the answers to which sometimes lie beyond the capabilities of current methods. For instance, which areas of the human cerebellar cortex are interconnected with the prefrontal and motor cortices? The importance of this question is highlighted by the fact that without the answer we cannot interpret functional neuroimaging studies with cerebellar activations, and must instead continue to rely on poten-

tially unsound extrapolations from our knowledge of neuroanatomy in non-human primates. Some fundamental issues related to the neurophysiology of this system (for example, neuronal coding of error signals) have not been fully answered in non-human primates, and have only been partially and indirectly addressed using functional neuroimaging methods in humans. It is difficult to test theories at the neuronal level in the human brain using current neuroimaging methods such as functional MRI, because activity cannot be ascribed to specific neuronal effects (for example, complex spikes in Purkinje cells).

Despite these technical obstacles, there is still ample scope to use functional neuroimaging to test specific hypotheses concerning cortico-cerebellar information processing. In this review I have suggested that cortico-cerebellar projections convey efference copies of information from cortical areas to modular cerebellar internal models so that they can efficiently mimic the information processing in the targets of those cortical areas. During the acquisition of motor skills, movements become increasingly controlled by cerebellar internal models rather than cerebral cortical circuitry, and are eventually executed automatically in a feed forward manner. Future neuroimaging studies (paralleling previous studies of motor learning) might be designed to systematically test the hypotheses that cerebellar components of the prefrontal loop acquire internal models to facilitate the skilled execution of routine cognitive operations. The presence of error signals might also be manipulated independently of motor learning to test the hypothesis that errors in the expected outcomes of cognitive operations trigger activity in these areas.

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Competing interests statement

The authors declare no competing financial interests.

FURTHER INFORMATION

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