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Frontal Lobe and Posterior Parietal Contributions to the Cortico-cerebellar System

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Abstract Our growing understanding of how cerebral cortical areas communicate with the cerebellum in primates has enriched our understanding of the data that cerebellar circuits can access, and the neocortical areas that cerebellar activity can influence. The cerebellum is part of some large-scale networks involving several parts of the neocortex including association areas in the frontal lobe and the posterior parietal cortex that are known for their contributions to higher cognitive function. Understanding their connections with the cerebellum informs the debates around the role of the cerebellum in higher cognitive functions because they provide mechanisms through which association areas and the cerebellum can influence each others' operations. In recent years, evidence from connectional anatomy and human neuroimaging have comprehensively overturned the view that the cerebellum contributes only to motor control. The aim of this review is to examine our changing perspectives on the nature of cortico-cerebellar anatomy and the ways in which it continues to shape our views on its contributions to function. The review considers the anatomical connectivity of the cerebellar cortex with frontal lobe areas and the posterior parietal cortex. It will first focus on the anatomical organisation of these circuits in non-human primates before discussing new findings about this system in the human brain. It has been suggested that in non-human primates "although there is a modest input from medial prefrontal cortex, there is very little or none from the more lateral prefrontal areas" [33]. This review discusses anatomical investigations that challenge this claim. It also attempts to dispel the misconception that prefrontal projections to the cerebellum are from areas concerned only with the kinematic control of eye movements. Finally, I argue that our revised understanding of anatomy compels us to reconsider conventional views of how these systems operate in the human brain.

Keywords Prefrontal cortex · Frontal lobe · Posterior parietal cortex · Evolution · Cognitive · Motor control

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The Frontal Lobe and Posterior Parietal Cortex

Although neuronal activity during motor control can relate to the details of movement such as movement kinematics, muscle activations and joint angles, there are areas in which neuronal activity codes the abstract properties of actions and does not relate to such details. It could, for example, relate to the goals of actions and to the rules that govern actions without reflecting such details. Neuronal activity could even remain indifferent to the effectors that might be used to execute these actions. The primate frontal lobe and posterior parietal cortex contain such neurons. Many authors [9, 46, 62, 74] have argued that the functional organisation of the frontal lobe is based on a rostro-caudal gradient, such that neurons that lie increasingly anteriorly to the primary motor cortex tend to code increasingly abstract information. For instance, while the firing properties of neurons in the premotor cortex (adjacent to the primary motor cortex) reflect the processes associated with the planning of movements [19, 96], neurons in the prefrontal cortex, located more rostrally in sulcus principalis (area 46; Fig. 1a), can code information in terms of the rules by which actions are governed [18, 63], and their response characteristics are not related to the details of the

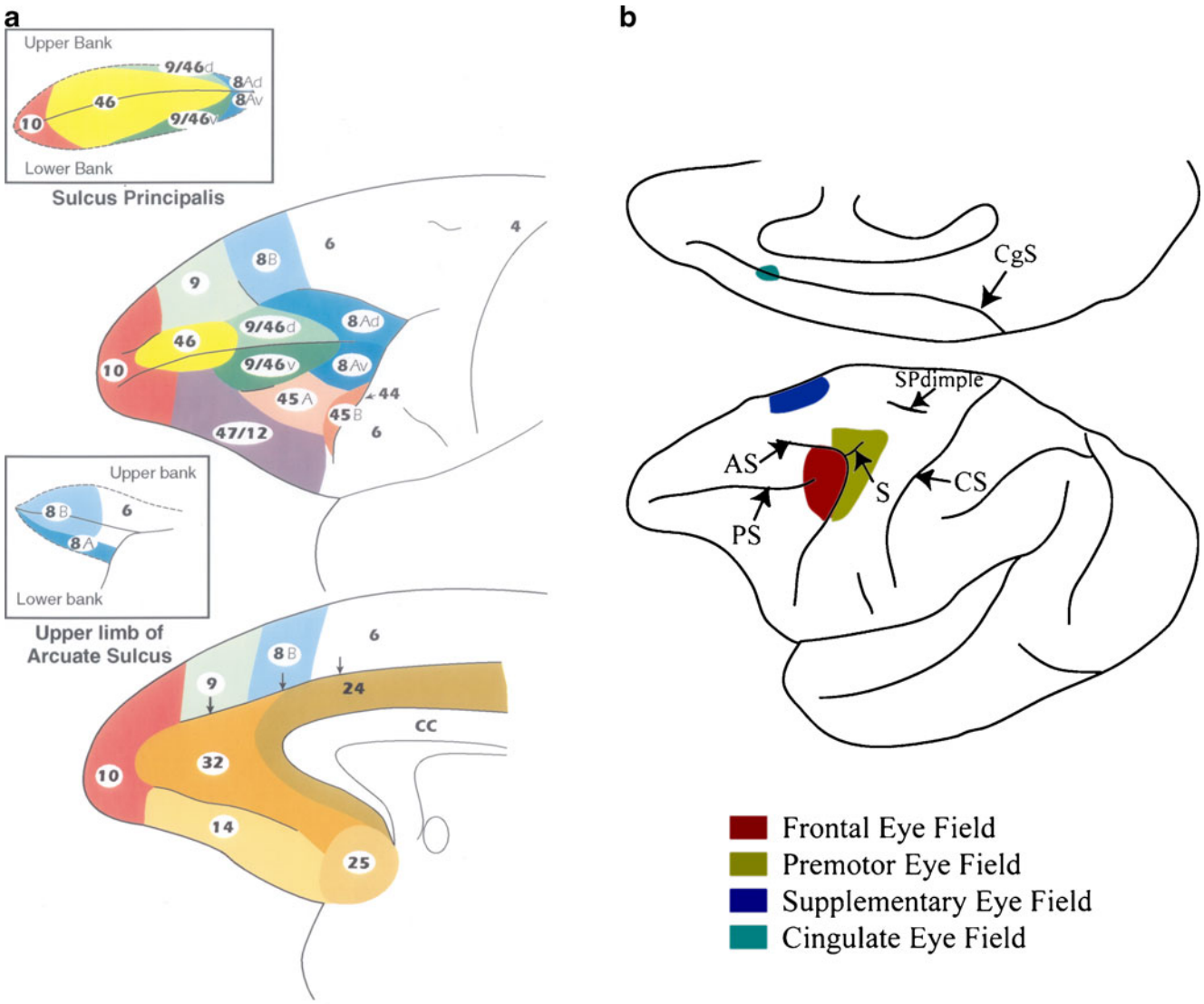


Fig. 1 **a** Frontal lobe organisation in monkeys. **b** The location of the frontal lobe eye fields in monkeys. The frontal eye fields occupy areas 8A, and the supplementary eye field occupies area 8B.With the exception of a small area in the cingulate gyrus, according to Amiez and Petrides [2], there are no eye fields in other parts of the prefrontal cortex. *CS* central sulcus, *PS* principalis sulcus, *AS* arcuate sulcus, *SPdimple* superior precentral dimple, *CgS* cingulate sulcus, *S* spur. Adapted from Amiez and Petrides [2]

movements themselves. These rules can be represented in a manner that is independent of the effectors with which they can be executed. A sequence of movements could be executed with either the left or the right hand, but the sequence itself is coded by prefrontal neurons independently of the various combinations of effectors that might execute it. The importance of this to the present discussion is that there are connections between such prefrontal areas and areas and the cerebellar cortex. These suggest a role for the cerebellum in the processing of abstract, "non-motor" or "cognitive" information.

The frontal eye field (FEF) also has connections with the cerebellum and contributes importantly to the control of eye movements. The locations of the eye fields in the frontal lobes in humans and non-human primates has been the subject of some debate [91]. However, Amiez and Petrides [2] concluded that in monkeys, the FEF lies "in the depth of the anterior bank of the arcuate sulcus, the rostral border being at the transition with area 46 and the caudal border being premotor area 6" (see Fig. 1b). The activity of neurons in this area relates not only to the kinematics of eye movements, but also to a range of variables that are unrelated to motor control. These include shifts in decision criteria [31], response selection [77] and other forms of executive control. The connections between the FEF and the cerebellum imply that these areas can exchange information related to both motor and executive control of eye movements. The claim has been made that some of the inputs from the cerebral cortex to the cerebellum that appear to contribute to cognitive control may be in fact be primarily involved in

"eye movement control" [26, 34]. The anatomical and physiological basis of this claim is not clear but it is made in the context of area 46 projections. If the suggestion is that area 46 has been mistaken for the parts of the frontal eye field that encroach upon sulcus principalis, I argue below that this is not likely. I also argue that there are a number of prefrontal areas involved in higher cognitive function which project to the cerebellum, but have no known role in the control of eye movements.

Like the frontal lobe, the primate PPC is also well known for its contributions to visuomotor control and to the cognitive control of action [3, 23]. In both humans and monkeys, the PPC is subdivided by the intraparietal sulcus into the superior and inferior parietal lobules (SPL and IPL, respectively) in both humans and monkeys. Brodmann subdivided the PPC into two distinct areas in monkeys (areas 5 and 7), the former occupying the SPL and the latter the IPL. The relationship between gross anatomy and cytoarchitecture appears to be quite different in the human brain, in which areas 5 and 7 both occupy the SPL, and the IPL is occupied by areas 39 and 40 (neither appears to have homologues in monkeys according to Brodmann). This makes homologies between humans and monkeys difficult. The parietal extension of the cingulate cortex on the medial convexity is also considered to be a part of the posterior parietal cortex and is occupied by area 23. The intraparietal sulcus in monkeys is subdivided into three main areas, these being the anterior intraparietal sulcus (AIP), the lateral intraparietal sulcus (LIP) and the medial intraparietal sulcus (MIP). Each can be further subdivided (see Lewis and Van Essen [54]), and the human intraparietal sulcus is thought to contain homologous areas. Area MIP is considered to be a part of the "parietal reach region" (PRR) by Andersen and Buneo [3].

Neurons in the PPC are known for their contributions to sensory and motor processes but are now also well-known for their contributions to coding higher level information related to the autonomous selection of actions and environmental targets [4, 22, 86] and decisions based on reward [69]. Activity in parts of the PPC is well-known to reflect the intention to act, such that the goals of actions can be represented in the absence of the details relating to motor control [3, 4, 86]. While the contributions of PPC-cerebellar connections to visuomotor control are frequently acknowledged, their contributions to higher level representations tend to be overlooked. The fact that they project to the cerebellum adds to the weight of evidence that the cerebellum processes abstract information.

The Cortico-cerebellar System in Non-Human Primates

Although neuroimaging studies make important contributions to our understanding of the human cortico-cerebellar system (see below), they currently suffer from the limitation that they don't reveal details of "point-to-point" synaptic connectivity. To date, such information has only come from the use of neuroanatomical tracers in non-human primates.

The primate cortico-cerebellar system consists of layer V neurons in the cerebral cortex which connect with the cerebellar cortex via relays in the pontine nuclei [17, 93]. These areas of the cerebellar cortex return projections to the cerebral cortex via relays in the cerebellar nuclei and the thalamus [8, 60]. The review considers the anatomical connectivity of the cerebellar cortex with frontal areas and the posterior parietal cortex through the corticopontine mossy fibre system and cerebello-thalamo-cortical pathways. Cerebro-cerebellar climbing fibre paths are not considered. Our understanding of how this system is organised in primates has changed radically in the last few years, and this understanding, in turn, compels us to think differently about the contributions of the cerebellum to behaviour in primates. A range of approaches have been employed. Some have used conventional anatomical tracers to identify point-to-point monosynaptic connections, while others have used recently developed viral tracers [48]. The advantage of the latter is that they can trace polysynaptic connections because they can cross the synaptic cleft and have been able to describe all of the connections between specific parts of the cerebral and cerebellar cortices in a given case. These have been particularly useful in charting the topographic organisation of the cerebellar cortex.

Frontal Lobe Connections with the Cerebellum

The connections from the cerebral cortex to the pontine nuclei are the principal routes through which the cerebral cortex supplies the cerebellum with information. It is important to note that there are alternative routes through which neocortical information arrives at the cerebellum. However, given that much more is understood about pathways via the pontine nuclei, only these will be considered here. Most would agree that of all of the cortical areas that project to the pontine nuclei in non-human primates, the cortical motor areas have the densest projections. Brodal [16] investigated the brains of adult rhesus monkeys in which lesions had been placed in several localised areas of the cerebral cortex in 38 cases, including areas of the prefrontal cortex. He characterised degenerating fibres to the pontine nuclei using three different staining methods and noted that the most projections arose from the primary motor cortex. He also noted that, with the possible exception of area 9, "little or no degeneration was found" for cases in which lesions were placed in the prefrontal cortex (areas anterior to premotor area 6). He concluded that projections from the prefrontal cortex were negligible. Similarly, in a seminal paper by Glickstein et al.

[36], the question was addressed by filling the pontine nuclei with the retrograde tracer horseradish peroxidase into the pontine nuclei in eight macaque monkeys. The advantage of this technique is that it has the potential to reveal all of the cortical areas that project to the injection site in each monkey. The densest projections were found to arise in the cortical motor areas. Unlike Brodal [16], they found that the projections from area 6 were as dense as those from area 4. The authors reported the existence of some projections to the prefrontal cortex but argued that they were weak. The implication for function is that the primate cerebellar cortex and the prefrontal cortex exert little influence over each other and that the cerebellum is unlikely to make a significant contribution to higher cognitive function [34]. Reconstructions in the paper nevertheless indicate the presence of cells in the dorsal bank of sulcus principalis (see Fig. 2) in Brodmann's area 9 which is homologous to Walker's area 46.[1]

The work of Glickstein et al. [36] has been influential in constructing the case against cerebellar involvement in higher function. It has attempted to quantify the projections from various parts of the neocortex to the pontine nuclei and has sometimes been used to argue that the density of prefrontal projections is low. A re-examination of the work finds evidence that seems to contradict this view (although some caution is needed because their quantitative analysis is derived from only two cases). The density of cells containing retrogradely transported tracer is reported in a number of neocortical areas including a range of frontal lobe and posterior parietal areas. Their analysis showed that after the primary and premotor cortex, the cell densities in cingulate areas 24 and 25, which are both prefrontal areas, and cingulate area 23 in the posterior parietal cortex, were found to be about 70% as high as that in area 4. The cell densities are comparable with posterior parietal areas 5 and 7. Area 24 is well known for its role in decision-making, and area 25 (subgenual cingulate cortex) is known to play important roles in the regulation of mood [25, 40, 58]. Their connections are with each other, with areas 11, 12, 13, and 14 in obitofrontal cortex, with area 46 on the lateral prefrontal convexity, with the hippocampal system and the amygdala (Vogt and Pandya 94). Their projections to the pontine nuclei must be important because the cell counts are high, but this network of areas is concerned with higher cognitive functions, not with motor control. Although the cingulate cortex does contain three small cingulate motor areas, these are restricted to small areas within the cingulate sulcus [41] and cannot account for the high cell density seen in areas of the cingulate cortex in which there are no motor areas. Glickstein et al. [36] therefore provides evidence that medial parts of the prefrontal cortex project substantially to the pontine nuclei. The cell densities in other prefrontal areas are reported as being low (areas 10, 11, 13 and 14). Other work is not consistent with this finding (for example, Schmahmann and Pandya [83] report dense projections from area 10 to the parmedian parts of the pontine nuclei; see below, and Fig. 3). Glickstein et al. [36] have mentioned that studies using very much higher concentrations of HRP have resulted in higher cell counts. The cell counts might therefore have been higher in these areas if higher concentrations of tracer had been used.

Perhaps some of the clearest and most convincing results have come from a series of papers by Schmahmann and Pandya [78–84] in which they injected anterograde tracers into several areas of the cortex in macaque monkeys. Small localised injections were made in several parts of frontal lobe cortex [83]. They reported the presence of terminal label in areas of the pontine nuclei following injections in areas 8, 9, 10, the dorsal and ventral banks of sulcus principalis (9/46d and 9/46v), and area 45B. Interestingly, such projections were not found if tracers were injected into tissue below the ventral bank of sulcus principalis or the orbital surface of the prefrontal cortex (areas 47/12, 46v, 11 or 14). These areas are not as well integrated with the cortical motor system as the more dorsal parts of the prefrontal cortex (area 46d sends its outputs directly to the premotor cortex—these ventral areas do not). One could speculate that projections from dorsal parts of the prefrontal cortex to the pontine nuclei are restricted to those conveying to the cerebellum higher-order information related to the cognitive control of action. In fact, Glickstein and colleagues recently claimed that much of the input from areas designated by others to be prefrontal, could in fact be oculomotor in character [26, 37]. The argument is not sustainable in light of the evidence. Figure 3 summarises the findings of Schmahmann and Pandya [83]. Some of these areas do play a role in the kinematic and cognitive control of eye movements, including the FEF that includes area 8 and the most posterior parts of sulcus principalis, but other areas more anterior than these lie outside areas 4 and 6, and do not have roles in the kinematic control of eye movement. For instance, the frontal pole (area 10) is an area

[1] The tissue in and around sulcus principalis in the prefrontal cortex is important to this debate because its projections to the cerebellum have recently been studied using trans-synaptic tracers (see below). Glickstein et al. [36] do indeed report the presence of label in this area (see Fig. 2), and as mentioned above, it has an important role in the processing of abstract information. In the nomenclature of Brodmann (1905), used by Glickstein et al. [36], area 9 encompasses the sulcus principalis extending onto the medial convexity to the upper bank of the cingulate sulcus. Others have used the nomenclature of Walker [95] and make a distinction between areas 9 and 46. Area 46 includes both banks of the sulcus principalis, and area extends from the upper bank of sulcus principalis. It is important to note that when Glickstein refers to area 9, this includes the tissue in sulcus principalis that other authors have called area 46. Glickstein et al. [36] show that this area sends projections to the pontine nuclei (see Fig. 2).

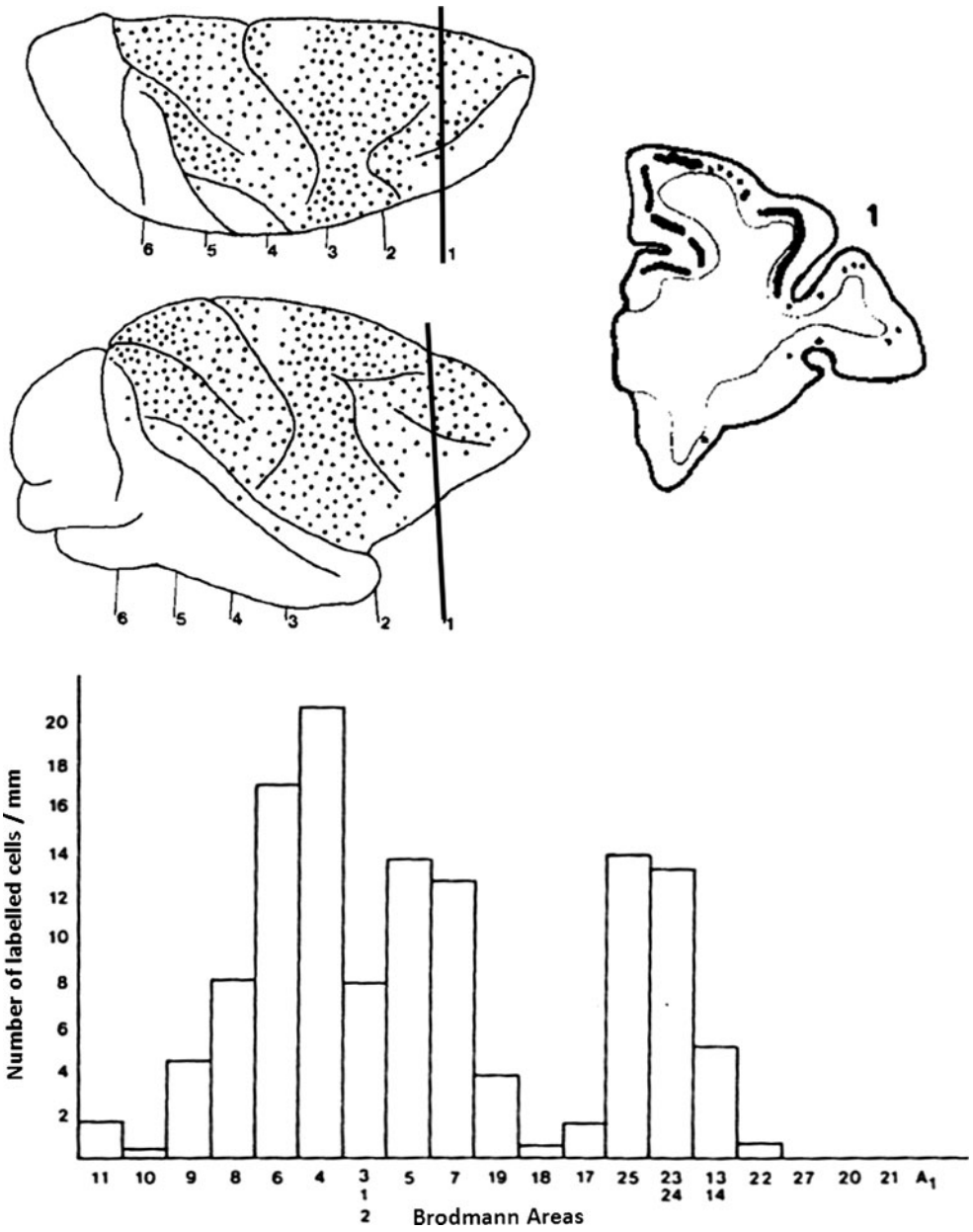
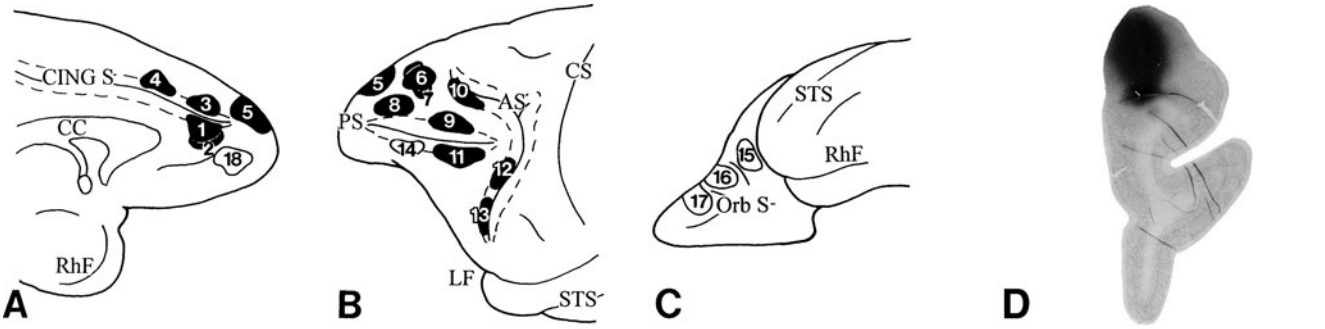


Fig. 2 From [36]. Copyright, John Wiley & Sons, Inc. 1985. The cortex of the macaque monkey (superior and lateral views), in which stippling indicates the presence of label after an injection of retrograde tracer into the pontine nuclei. The coronal section through the prefrontal cortex shows the presence of labelled cells in the dorsal bank of sulcus principalis. The graph is reproduced from Fig. 3 of this paper and shows the average number of labelled cells per millimetre in different Brodmann areas. This material is reproduced with permission of John Wiley & Sons, Inc.

which is too far rostral to be mistaken for a part of the frontal eye field or a part of the premotor cortex, but nevertheless densely projects to the pontine nuclei (see Fig. 3d, e). Such areas are better known for their contributions to higher cognitive function than the kinematic properties of eye movements [61, 74, 92].

Understanding the outputs from the cerebellum to the cerebral cortex can determine which areas of the cerebral cortex are susceptible to cerebellar influence via the thalamus. All three cerebellar nuclei send their outputs to various areas of the cerebral cortex. Here, the focus is on dentate nucleus outputs to the frontal lobe. Strick and colleagues have used transneuronal retrograde tracers to show that that the dentate can be broadly subdivided into sets of motor and non-motor "output channels", through which cerebellar activity cannot only influence cortical motor areas, but also areas of the prefrontal cortex [88].

The *dorsal* parts of the dentate nucleus are connected with the primary motor cortex, caudal parts of the dorsal premotor cortex, ventral parts of the premotor cortex and the supplementary motor cortex. In contrast, the *ventral* portions of the dentate nucleus are connected with prefrontal areas 46 (dorsal), 9, and the pre-SMA [1, 59]. Strick and colleagues have argued that the outputs from the cerebellum are segregated into separate motor and non-motor output channels, where the dorsal parts of the dentate send projections to motor areas, while ventral parts sends outputs to non-motor areas [1, 28, 29].



Case Number	Area	Rostro-caudal level	Median	Paramedian	Peri-peduncular	Dorso-medial	Intra-peduncular	Ventral	Lateral	NRTP	Dorsal	Dorso-lateral	Extreme Dorso-lateral
1,2	32	I - III	-	++	+	-	-	-	-	-	-	-	-
3	9(med)	I - VII	++	+	+	+	-	-	-	++	-	-	-
4	8B	I-IV	-	++	+	-	-	-	-	+	-	-	-
5,8	10	I - IX	-	+++	++	-	-	+	+	++	-	-	-
6,7,8	9(lat)	I - IX	-	+++	+	++	-	+	-	-	-	-	-
9	9/46d	I - VIII	-	++	++	++	+	+	-	++	-	-	-
10	8Ad	I - IX	-	+++	++	+	-	+	+	+	-	-	-
11	9/46v	I - V	-	+	+	+	-	-	-	-	-	-	-
12,13	45B	I - III	-	+	+	-	-	-	-	-	-	-	-
14	46(vent)	-	-	-	-	-	-	-	-	-	-	-	-
15	47/12	-	-	-	-	-	-	-	-	-	-	-	-
16	47/12	-	-	-	-	-	-	-	-	-	-	-	-
17	11	-	-	-	-	-	-	-	-	-	-	-	-
18	14	-	-	-	-	-	-	-	-	-	-	-	-

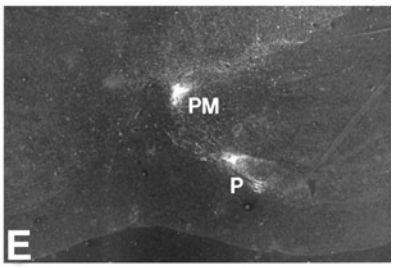


Fig. 3 Anterograde projections from frontal lobe areas to the pontine nuclei (from [83]. Schematic figure of macaque monkey frontal lobe areas depicting injection sites in each case (**A** medial; **B** lateral; **C** orbital; injection sites which resulted in pontine label are filled). Anterior prefrontal cortex was injected in case 5 (**D** histology for injection site; **E** dark field photomicrograph depicting areas of label in the pontine nuclei). The table indicates the extent of label in the pontine nuclei for each area of the cerebral cortex

Neurophysiological experiments on the cerebral cortex in monkeys can be interpreted in rich anatomical context: these have tended to attribute functional properties to distinct cortical "areas" defined by their unique cytoarchitectonic properties. Since their neuronal organisation differs across these areas, it is reasonable to assume that they also differ in their contributions to function. In recent years, there has been an increasing emphasis on characterising the properties of these cerebral cortical areas in terms of their connections. Their unique patterns of connectivity ("connectional fingerprints" [68]) supplement cytoarchitectonic data and help to explain the functional properties determined through lesion analysis and electrophysiology. Can this approach be applied to the cerebellar cortex? It is generally agreed that the cytoarchitecture of the cerebellar cortex is relatively uniform and does not vary substantially in the way that the cerebral cortex does. However, it is clear that the cerebellar cortex can be segregated into distinct zones on the basis of its connectivity (see below).

Interpreting task-related activity in particular areas of the cerebellar cortex imposes a requirement to understand the topographic organisation of cerebellar cortical connections with other parts of the brain, particularly with functionally diverse areas such as the cerebral cortex. This requires a direct characterisation of polysynaptic pathways between the two cortices that is most efficiently achieved using transynaptic viral tracers [48]. There are very few studies that inform our understanding in this way, but these lay the groundwork for understanding the architecture of the human cortico-cerebellar system using neuroimaging methods (see below). One of these focuses on frontal lobe projections [44] and much more recently, another on projections from the posterior parietal cortex [71] which is discussed in the following section.

It is generally agreed that in monkeys, the densest projections from the cerebral cortex to the pontine nuclei arise from neurons in the primary motor cortex [16, 17, 36]. These convey information to Purkinje cells located in lobules HIV, HV, HVI HVIIB and HVIII [44], which return their outputs to the cortex via relays in the dorsal parts of the dentate nucleus and "motor" thalamus. Strick et al. [88] argue that cortico-cerebellar projections are probably organised as a set of closed loops, so that Purkinje cells that receive inputs from the motor cortex could send outputs back to the motor cortex. Efferent copies of signals from the motor cortex that are destined for the spinal cord are "copied" to these Purkinje cells. The same lobules also receive limb proprioceptive inputs via the spino-cerebellar tracts (see [15]) and are therefore in a good position to interpret the sensory consequences of movement in the context of the motor commands that generated them—a process important for motor learning [72, 97].

In many ways the "prefrontal loop" is more interesting because it adds new information about the organisation of this system in primates and supports the notion that the cerebellum plays a part in higher cognitive function. Following injections of anterograde transynaptic tracer into both banks of sulcus principalis in prefrontal area 46, the densest label was found mostly in granule cells of Crus IIa of lobule HVIIA, and less in Crus Ip and Crus IIp. Cells in

lobule X and vermal lobule VII were also labelled. Retrograde tracer into the same prefrontal area labelled ventral parts of the dentate nucleus and also cerebellar cortical Crus IIa [44]. The afferent and efferent connections of the motor and prefrontal cortex therefore appear to be completely segregated in the cerebellar cortex, suggesting that diverse cortical areas occupy distinct, topographically organised territories in the cerebellar cortex. Activity reported in these territories in functional neuroimaging studies can therefore be meaningfully interpreted in the context of their connectivity. For example, on the basis of the anatomical connectivity of Crus I and Crus II, one could reasonably infer that tasks with high cognitive demands that activate Crus I and Crus II may do so because of the ways in which these areas interact with the prefrontal cortex. It has been suggested that if plasticity in cerebellar parts of the motor loop supports the acquisition of motor skills, then similarly, plasticity in cerebellar components of the prefrontal loop may be engaged in the acquisition of cognitive skills [52, 72]. Recent work has shown some evidence in support of this view [11, 12].

Glickstein and Doron [34] have suggested that the prefrontal connections with the cerebellar cortex reported by Kelly and Strick [44] "may be part of an eye movements' circuit" concerned with kinematic rather than cognitive control. This is unlikely because the injection sites in their study do not correspond with any of the eye fields in the frontal lobes. Lynch et al. [56] investigated the connections of the FEF to the cerebellar nuclei in cebus monkeys. They mapped the location of the FEF in the anterior bank of the arcuate sulcus, in an area corresponding to area 8A (Petrides and Pandya [70]). This study reported the presence of label in the caudal pole of the ventral dentate. Interestingly, Strick and colleagues suggest that the caudal pole is distinct from both the motor and non-motor areas of the dentate nucleus (see [88]). The injection sites in the two studies were therefore different. The circuits that were investigated by Kelly and Strick [44] were therefore separate from those related to the frontal eye fields and are probably not part of any eye movement circuits.

It is important to note that there have been no reports of systematic attempts to map the connections between the cerebellar cortex and the premotor cortex (area 6). The premotor cortex lies between the prefrontal cortex and primary motor cortex. The connections of these areas with the cerebellar dentate appear to be topographic because dentate neurons connected to the premotor cortex are spatially intermediate to those connected with the prefrontal and primary motor cortex [67]. It is possible that connections with the cerebellar cortex might be similarly topographic. Kelly and Strick [44] showed that neurons in the superior portions of Crus I (Crus Ia) contain little, if any, label, following injections of tracer into either the primary motor cortex or the prefrontal cortex. This part of the cerebellar cortex, which lies in between the prefrontal- and motor-projecting lobules, might be connected with the premotor cortex. Lu et al. [55] injected retrograde trans-synaptic tracer (rabies virus) injections into areas of the precentral cortex. They labelled the same regions of the cerebellar cortex as those reported in Kelly and Strick [44], but additionally found label in Crus I when injections were made in proximal and distal forelimb areas of the primary motor cortex. Lu et al. [55] have not reported how they identified the boundary between area 4 and area 6 in their studies, so one could speculate that tracer may have been injected not only into the primary motor cortex, but also into premotor cortex.

Posterior Parietal Connections with the Cerebellum

A number of studies have mapped projections from the PPC to the pontine nuclei, and the outputs from the cerebellar dentate to the PPC. Glickstein et al. [35] injected WGA-HRP into the dorsolateral pons and studied the cerebral cortical retrograde projections to the pons and the orthograde projections to the cerebellar cortex. The area of the cerebellar cortex containing the densest label was the dorsal paraflocculus, suggesting that the injection site targeted regions of the pontine nuclei that conveyed visual inputs. Reconstructions (Fig. 7 in their paper) indicate that neocortical label was confined largely to the tissue ventral to the intraparietal sulcus in the IPL (Brodmann area 7). The absence of label in other areas could be due to incomplete filling of critical areas of the pontine nuclei, and this could therefore represent an incomplete picture. Glickstein et al. [36] filled the pontine nuclei completely in four cases. The strength of this study for the present review is that it demonstrated all of the parietal areas that projected to the pontine nuclei and revealed that both Brodmann areas 5 and 7 project substantially to it.

Schmahmann and Pandya [78, 80] studied projections of both the IPL and SPL in monkeys in some detail. Injections of anterograde tracers were made into cortical tissue on the medial and lateral convexities, and into the intraparietal sulcus. In general, their findings indicate that both the SPL and the IPL send relatively heavy projections to peripeduncular and lateral nuclei. The IPL rather than the SPL send projections to the intrapedunclular, dorsal and dorsolateral nuclei (a finding consistent with [36]).

Studies using trans-synaptic tracers have been able to map the relationships between the posterior parietal cortex and the cerebellum more directly. Strick and colleagues injected retrograde tracer into anterior parts of the intraparietal sulcus (AIP) in cebus monkeys. A strength of this study was that it defined AIP on the basis of connections with the hand area of the ventral premotor cortex, which

itself was mapped using microstimulation. The AIP was found to receive projections from broadly distributed areas of the dentate, with a focal cluster in its dorsal part, considered by Strick and colleagues to be dominated by motor rather than non-motor projections. The inferior parietal lobule can be subdivided into cytoarchitectonic areas 7a (anterior) and 7b (posterior). Using similar methods, Clower et al. [20] reported that parietal area 7b was found to be a target of the ventral dentate, but area 7a and LIP (probably a dorsal part) found not to receive projections from the dentate. Prevosto et al. [71] used transneuronal tracer injections into MIP and ventral parts of LIP (LIPv). MIP and LIPv injections resulted in label occupying a ventral part of the dentate. LIPv in particular received projections from the caudal pole, close to parts of the dentate that that project to the FEF [56].

Transneuronal tracers have recently also been used to map the polysynaptic connections between the posterior parietal cortex and the cerebellar cortex. Interestingly, Prevosto et al. [71] (Fig. 4) report that Purkinje cells that send trisynaptic outputs to MIP were organised into translobular "bands". This is a characteristic feature of the organisation of olivo-cortico-nuclear modules [6, 7] and highlights the need to understand cortico-cerebellar organisation in the context of these modules. MIP receives inputs from such bands that extend across Crus IIp of lobule HVIIA (30.9%) and the adjacent paramedian lobule (HVIIB; 19.7%). Cells were also present in longitudinal bands in paravermal parts of lobules V and lobule VI (26.1%). No cells were present in the oculomotor vermis (vermal lobule VII).

How do these results relate to the motor and non-motor output channels in the cerebellar dentate? While the dorsal,

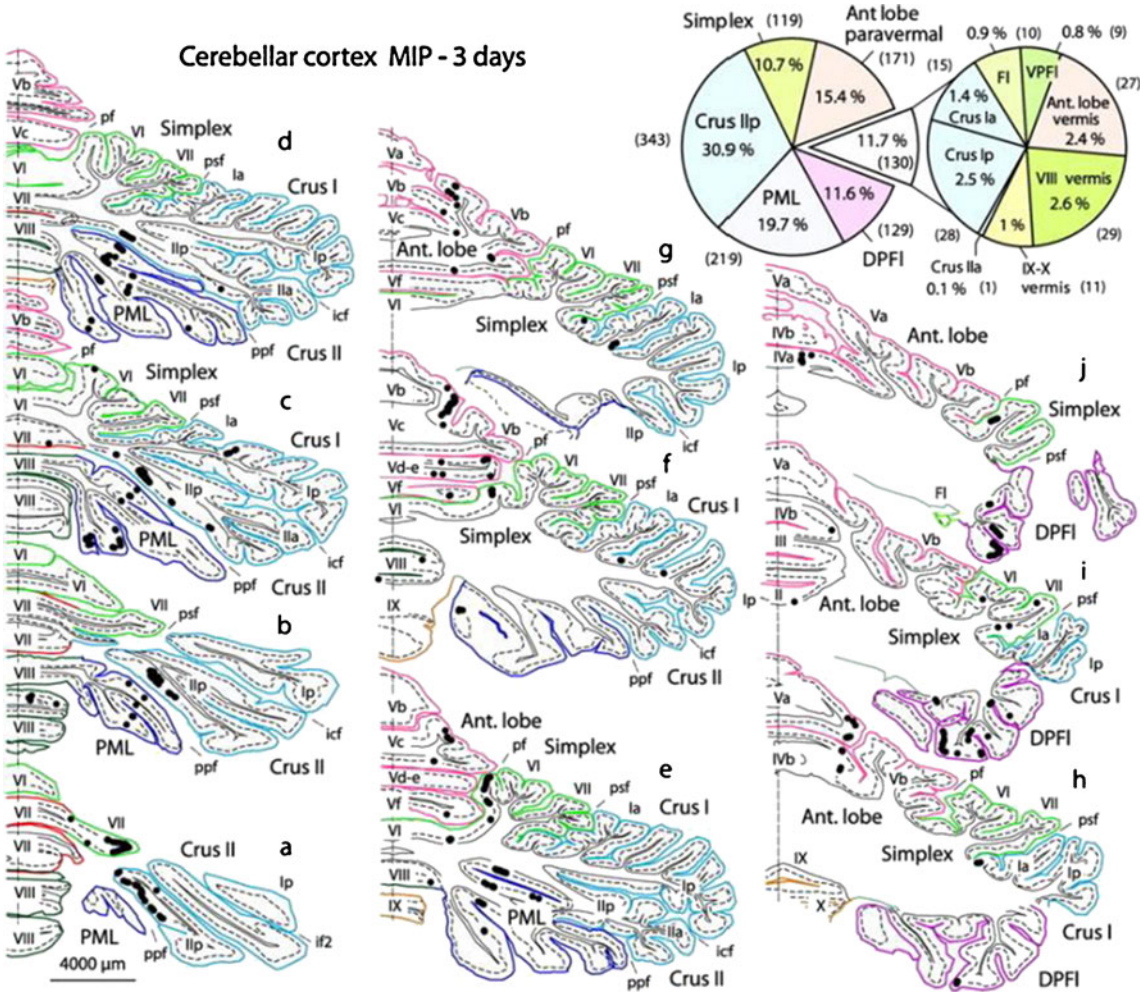


Fig. 4 Transneuronal projections from medial intraparietal cortex (MIP) to the cerebellar cortex. From [71]. Distribution of Purkinje cells with trisynaptic inputs to the left MIP area, labelled transneuronally at 3 days with rabies virus. Cross-section levels (**a**–**j**): from caudal to rostral. Cerebellar lobules are named and color coded; fissures are named and indicated by a *mark*. Most labelled PCs are found in three main groups: obliquely oriented bands in the depth of Crus IIp and PML, multiple bands in DPFl, longitudinal bands in paravermal AL and simplex. Pie chart (*top right*): percentages and absolute numbers (*in brackets*) of labelled PCs in the different cerebellar subdivisions. *Fl* flocculus, *VPFl* ventral paraflocculus. Fissures (*f*): *icf* intercrural f, *if2* intracrural f 2, *pf* primary f, *ppf* prepyramidal f, *psf* posterior superior f. Legend and figure reproduced from Fig. 7 in Prevosto et al. [71] by permission of Oxford University Press

motor parts of the dentate send projections to AIP, the ventral, non-motor parts send outputs to MIP, the ventral portions of LIP and area 7b. It is well known that activity in these areas relates not only to visuomotor control, but in some areas, this relates specifically to the rules that guide actions. For instance, there is a wealth of evidence that demonstrates the involvement of LIP in decision-making based on the outcomes of actions [21, 38, 45, 75, 85]. One prominent example includes the study of Platt and Glimcher [69] who showed that activity in LIP is sensitive to the rewarding outcomes that monkeys can expect as a result of choosing a particular action. Importantly, this effect was "separable from the effects of the immediate visual environment and from the neural events that govern movement dynamics". MIP is considered to be a part of the "parietal reach region" (PRR). Apart from its roles in directing reaching movements on the basis of target location, the activity of neurons in this area is known to reflect cognitive decisions about reaching movements. As with neurons in LIP, neurons in PRR reflect intentions for actions specified at highly abstract levels (see [3]). Although there is no doubt that the cerebellum can influence visuomotor information from the PPC, it should also be acknowledged that higher level information related to intentions and decisions are also subject to cerebellar influence through the same routes. If, as is likely, the PPC connections with the cerebellum form closed loops, then the influence between these areas of the PPC and the cerebellum must be reciprocal.

MIP and area 46 share certain anatomical and functional relationships: they are both engaged in the processing of abstract information and are influenced by outputs from ventral rather than dorsal parts of the dentate. MIP and area 46 are also both trans-synaptically connected with Crus II. However, they are probably not connected with the same cortico-nuclear cerebellar circuits. Purkinje cells that connect with MIP originate in Crus IIp and those that connect with prefrontal area 46 originate in Crus IIa (see Larsell and Jansen [50], page 53 for a discussion of the anatomical distinctions between Crus IIa and Crus IIp in the human brain). Neuroimaging studies that test hypotheses about the involvement of Crus II in the human brain could draw more detailed conclusions if they were able to localise at spatial scales that resolve between these adjacent anatomical regions.

It is tempting to accept the view that the cortico-cerebellar system is organised as a series of closed loops [88]. The evidence shows that broadly speaking, the lobules that receive inputs from particular areas of the cerebral cortex via the pontine nuclei tend to send outputs back to those areas. This supports the closed loop view as a general principle of organisation, but it is important to note that there is still little in the way of firm evidence that directly demonstrates point-to-point connectivity in such a system. In other words, there are no studies that show, in the same animal, that cerebral cortical neurons which form polysynaptic afferent connections with particular cerebellar Purkinje cells via the pontine nuclei, receive efferent connections from the same Purkinje cells via the cerebellar nuclei and the thalamus. Kelly and Strick [44] showed that cerebellar cortical inputs from the primary motor cortex in one animal included lobule HIV, but cerebellar cortical outputs to the same area in another animal did not. It is of course entirely possible that the differences can be accounted for by differences in tracer uptake and transport in different cases, but nevertheless, a positive demonstration of point-to-point connectivity remains to be demonstrated. The future use of dual trans-synaptic tracers may prove promising in this regard [65]. Also, the general principle of closed loop organisation can only be substantiated if it can be demonstrated in a number of systems, but to date, we only have an understanding of both efferent and afferent connections of a few cerebral cortical areas with the cerebellar cortex. The majority of projections are yet to be mapped.

How Does Neuroimaging Contribute to our Understanding of the Human Cortico-cerebellar System?

In recent years, the case for the involvement of the cerebellar cortex in higher cognitive function has been supported by studies showing that cerebellar cortical lesions result in cognitive deficits, and that often, activity in the cerebellar cortex can only be explained by the cognitive rather than motor task demands. The locations of lesions and activations in such studies matters because they provide an understanding of the connectivity of these cerebellar cortical areas. Non-human primate studies of connectional anatomy provide valuable insights, but in drawing conclusions about the topography in the *human* cerebellar cortex, it becomes necessary to assume anatomical homologies between the non-human primates in which connectivity is well understood, and humans, in which it has never been investigated. How sound are these assumptions?

While many agree that the template for cortico-cerebellar organisation is the same across all primates, there are certainly good reasons to believe that this system has not scaled uniformly during the course of human evolution: some parts appear to have grown faster than others and could play more important roles in the human brain. This is true of the prefrontal cortex, which I have argued is an integral part of the cortico-cerebellar system. The term "concerted evolution" (see [87]) refers to the idea that the elements of an anatomically interconnected system which act as a functional unit are subjected to the same selection pressures. These

components therefore evolve similarly in concert with each other. By this argument (see [72]), the rapid growth of the prefrontal cortex should have been accompanied by comparable growth to the cerebellar structures and the pathways that connect the cerebellum and prefrontal cortex. The human posterior parietal cortex has also expanded considerably relative to other hominids [42, 66]. The growth of the motor loop should not be as pronounced because the cortical motor system has grown less than the prefrontal cortex. In line with this hypothesis, Matano [57] demonstrated that the macrogyric (ventral) portion of the cerebellar dentate nucleus is significantly enlarged in the human brain compared with its microgyric (dorsal) portion. In monkeys, the dorsal portion connects with the motor cortex, whereas the ventral portion connects with prefrontal area 46. Sultan et al. [89] dispute the distinction between dorsal and ventral portions of the dentate. They compared the morphology of the dentate nucleus in humans and a macaque monkey. While the distinction appeared to be clear in the monkey dentate, the authors report that the regions are also recognised in humans, and that the ventral portion is larger than the dorsal portion, although not to the extent that one would expect on the basis of previous studies. However, the actual sizes of the dorsal and ventral portions are not reported in either species, so a direct comparison is not possible.

Neuroimaging methods have been used to test this hypothesis in the cerebellar cortex and in the corticopontine system. Measuring the volumes of gross anatomical structures in the brain can be achieved more accurately in vivo with MRI than post-mortem with conventional methods in which histological processing could cause brain tissue to distort and shrink. Balsters et al. [10] recently employed this approach using structural MRI scans of the cerebellum in capuchin monkeys, chimpanzees and humans. The cerebellar cortex was parcellated into its constituent lobules, and the volumes in each species were compared. Crus I and Crus II occupied a significantly larger proportion of the cerebellum in humans compared with chimpanzees and capuchin monkeys. In contrast, the lobules interconnected with the cortical motor system occupied similar proportions in these three species. The results are consistent with the view that areas of the cerebellar cortex that connect with the prefrontal cortex have expanded significantly and in concert with the prefrontal cortex, over the timecourse of human evolution.

Are such changes evident in the pathways that convey corticopontine fibres from the frontal lobe? It has long been known that corticopontine fibres in the primate brain, which pass through the cerebral peduncle, are topographically organised [32, 76, 90]. Levin [53] investigated these projections in monkeys using Marchi's degeneration method and reported that the cerebral peduncle could be divided into three segments, with the mid-portion containing fibres from areas 4 and 6 being the largest. This was flanked by smaller segments containing fibres from frontal lobe parts of the frontal lobe anteriorly, and parietal and temporal areas more posteriorly. Beck [13] conducted a similar study in using post-mortem fixed human brains. She concluded that prefrontal fibres occupy one sixth of the proportion of the human cerebral peduncle. The topographical findings were consistent with those of Levin [53] and were also confirmed by subsequent work. However, the quantitative aspects need to be treated with a measure of caution. Methods that rely on degeneration to trace fibres are probably too unreliable for quantitative work. For instance, in her study, Beck [13] reported a case in which there were very large lesions of the frontal lobe that included prefrontal and premotor areas, but no degeneration was detected in the cerebral peduncle in this case. The tissue was fixed and therefore subject to shrinkage and distortion, making rigorous quantitative approaches difficult. The conclusion that prefrontal inputs to the pontine nuclei occupy relatively small proportions of the cerebral peduncle cannot be drawn on the basis of such evidence and is not consistent with the evolutionary expansions observed in the structures that they connect.

Diffusion tensor imaging (DTI) allows investigators to use MRI to study the trajectories of fibre pathways in the living human brain [51]. It has been used to parcellate large fibre tracts into segments based on the cortical areas that contribute fibres to it [14]. Of course, it suffers from certain limitations. First, as with other MRI-related methods, the resolution is currently inadequate to establish point-to-point connectivity. It also does not allow one to distinguish efferent from afferent connectivity. Nevertheless, its great advantage is that it can be applied to humans and non-human primates, making it possible to take comparative approaches to connectional organisation. Ramnani et al. [73] used this approach to compare the anatomical organisation of corticopontine fibres in humans and macaque monkeys. Since fibres from the cerebral cortex converge in the cerebral peduncle before reaching the pontine nuclei, it serves as a convenient point at which to compare the relative contributions of different areas of the cerebral cortex to the pontine nuclei. The white matter fibres in cerebral peduncle were parcellated on the basis of their cortical sites of origin, in both humans and macaque monkeys. As in previous studies, results showed that the fibres were arranged topographically in both humans and monkeys (see Fig. 5). However, the proportion of the cerebral peduncle occupied by fibres from the prefrontal cortex was much larger in humans than in macaque monkeys. They report that about 15% of the cerebral peduncle receives fibres from the macaque monkey prefrontal cortex, whereas this figure increases to about

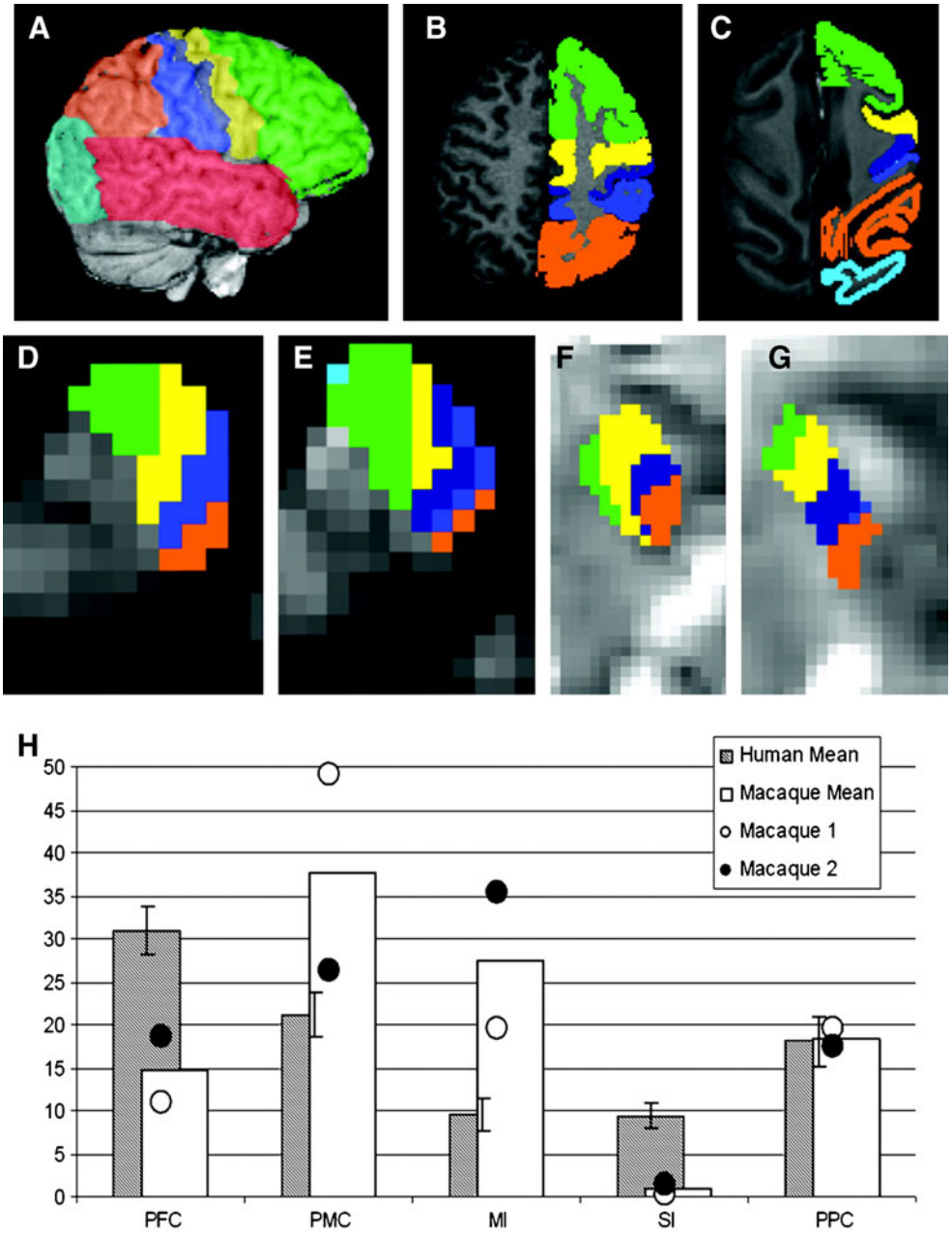


Fig. 5 Segmentation of the cerebral peduncle in humans and macaque monkeys based on diffusion tractography (reproduced from [73], by permission of Oxford University Press. Note the topographic distribution in both species, with fibres from anterior regions of the cortex passing through anteromedial portions of the cerebral peduncle, and those from posterior regions passing through posterolateral regions. **a**–**c** Anatomical masks in the cerebral cortex. **d**–**f** Representations of topographically organised fibre tracts in the cerebral peduncle. Note the enlarged representation from the human prefrontal cortex

30% in humans. By contrast, and consistent with Levin [53], the proportions occupied by fibres from the cortical motor areas were larger in macaque monkeys than in humans. This study provides further support for concerted evolution in the cortico-cerebellar system, and the important role that is likely to be played by the prefrontal loop in the human brain. Recently, Doron et al. [26] used diffusion imaging to investigate the same issue. Aspects of their findings are consistent with those of Ramnani et al. [73]. First, the topographic arrangement of corticopontine fibres observed in Ramnani et al. [73] was also seen in theirs. Also, fibre pathways from the most anterior prefrontal regions were found to "travel within the medial one third of the cerebral peduncle", and the densest projections appear to come from the superior frontal gyrus. They argue that the area of the superior frontal gyrus with the highest connection strengths might be the FEF. This locus was somewhat posterior to that reported in Ramnani et al. [73], who also found similar results even when a very anterior (the VCA line) boundary was used to excluded areas likely to be occupied by the premotor cortex or the frontal eye field. It should be noted that Doron et al. [26] did not take a comparative approach by applying the same analytical methods to data from humans and monkeys. It is therefore difficult to use their work to draw conclusions about differences between cortico-cerebellar organisation in

humans and non-human primates. They also omitted the analysis of anterior prefrontal cortex (including area 10). It has been argued above that this could be an important source of prefrontal projections to the pontine nuclei, so it is possible that their results may underestimate the true extent of prefrontal contributions.

As a method, tractography is at its best if it is used to study the trajectory of fibre pathways such as those in the corticopontine system that have relatively simple geometric organisation. However, existing methods cannot reliably track fibres through areas of significant geometric complexity (e.g., the pontine nuclei; [43]. They are also unable to resolve point-to-point synaptic connectivity, and so cannot provide information about forward connections from the cerebral cortex to the cerebellar cortex through the pontine nuclei, or about return pathways through the cerebellar nuclei and thalamus. Some recent studies have taken an alternative approach which relies on the physiology of the human cortico-cerebellar system rather than its anatomy. Essentially, they have used functional MRI to map the trans-synaptic physiological influences that the cerebral and cerebellar cortices exert over each other through their polysynaptic connections. The approach is broadly based on the principle that if two brain areas are closely interconnected, the fluctuations in their "resting state" background activity [24] will be statistically related. The approach is not new—it is related to an older one in which investigators used cerebral cortical stimulation and cerebellar recordings [30]. Studies as far back as the 1940s [27] recognised the importance of understanding the topographic organisation of cerebral cortical influences on cerebellar cortical activity.

In the same vein, O'Reilly et al. [64] continuously recorded brain activity in healthy human subjects using fMRI while they were at rest (there was no requirement to perform a task). The aim was to determine the areas of the cerebellar cortex in which spontaneous fluctuations in BOLD activity were statistically related to such activity in various parts of the cerebral cortex. Time-series data from various cerebral cortical areas (including the prefrontal, premotor, primary motor and posterior parietal cortices) were each regressed against timecourses in all the voxels in the cerebellum (the process therefore segmented the cerebellum into anatomical zones on the basis of their coherence with timecourses in cerebral cortical areas). The analysis identified the particular parts of the cerebellum with which resting state activity was statistically related with that in each of these cerebral cortical areas (Fig. 6). An important aspect of this study is that it was able to validate its findings against the known anatomical connectivity in non-human primates. Consistent with these studies, resting state activity in the primary motor cortex was coherent with that in lobules HV, HVI and HVIII. The study also reported statistical relationships between resting state activity in the prefrontal cortex and HVIIA, Crus I and Crus II. The results demonstrate a correspondence between the known anatomical connectivity between frontal lobe areas and the cerebellar cortex in monkeys, and the physiological influences between cerebral and cerebellar cortical areas in the human brain. This consistency increases the confidence with which one can make inferences about the anatomical organisation of the cortico-cerebellar system in the human brain.

Similar results have been independently confirmed in two other laboratories. Krienen and Buckner [47] similarly investigated the statistical relationships between resting state activity in a set of cortical areas and the cerebellum in the human brain. Resting state data from seed voxels in the primary motor cortex was related to activity in cerebellar cortical lobule HV and HVIIIB. These authors also investigated the connectivity of three areas of the prefrontal cortex. They reported that activity in dorsolateral, medial and anterior portions of the prefrontal cortex was related to activity in different segments of lobules VI, VIIB, Crus I and Crus II (see Fig. 7). Again, these results are generally consistent with the connectional organisation of frontal lobe areas in monkeys.

O'Reilly et al. [64] also considered the connectivity of the cerebellar cortex with the posterior parietal cortex and reported that resting state activity in the PPC was related to activity in Crus II and adjacent paravermal parts of HVIIa (Fig. 8). Subsequent work by Prevosto et al. [71] discussed above reported trans-synaptic connections from parietal area MIP to Crus II in monkeys. This lends further confidence in the ability of the method to detect physiological influences that are mediated through trans-synaptic connectivity in the human brain.

The broad consistency between work in humans and non-human primates suggests that relationships between anatomical projections and lobular anatomy is generally conserved and that the physiology of interconnected systems can reveal something about the anatomical connectivity of these systems. Figure 9 schematically illustrates the topographical organisation of connectivity with the primary motor cortex, the prefrontal cortex and the posterior parietal cortex in humans (based on [64]) and in non-human primates.

Habas et al. [39] investigated cortico-cerebellar connectivity in the human brain using an alternative statistical approach. Whereas the previous authors targeted particular regions of interest, these authors applied independent components analysis to resting state data. The strength of this approach is that it is able to use the statistical properties of the data to determine the identities of functional networks without specifying regions of interest. These authors reported four networks (only two are described here). These included a sensorimotor network which included the sensorimotor cortex, medial and lateral premotor areas, and cerebellar cortical lobules HV and HVI. It also included networks comprising the lateral prefrontal cortex and inferior parietal

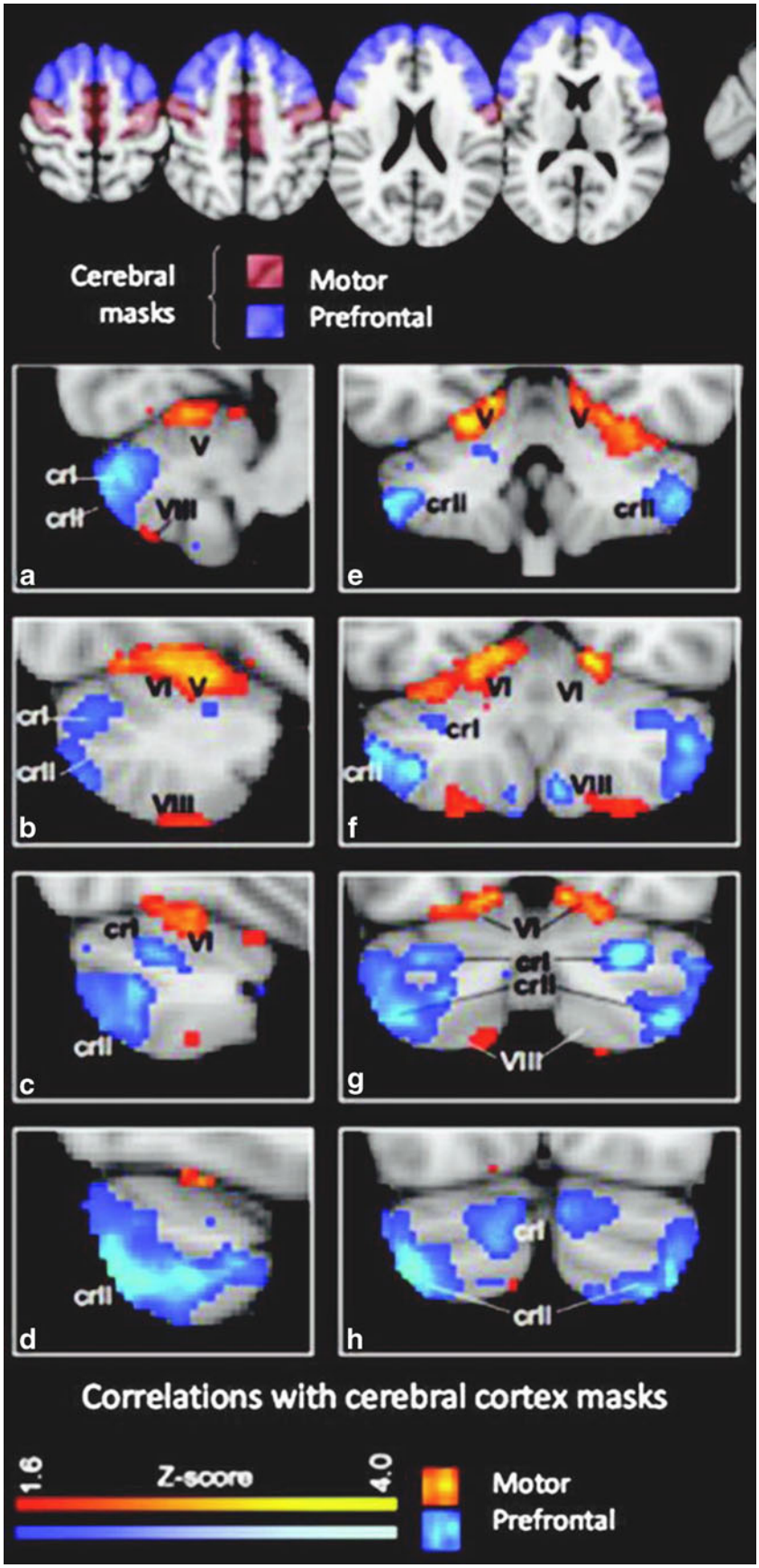


Fig. 6 Areas of the human cerebellar cortex in which resting state fluctuations in BOLD signal were statistically related to the motor cortex (*red-orange*), and prefrontal cortex (*blue*). Reproduced from [64], by permission of Oxford University Press

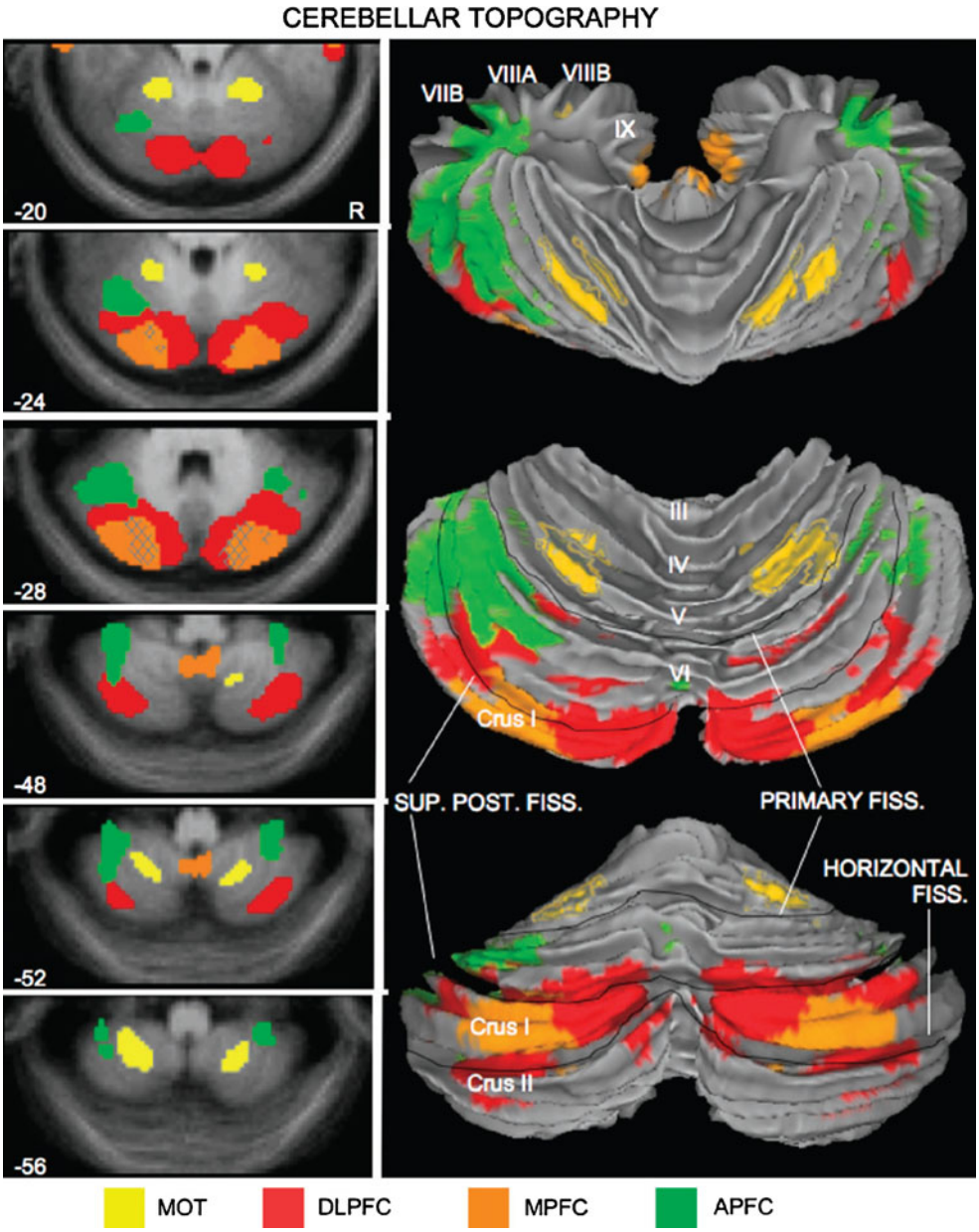


Fig. 7 Resting state BOLD activity in the human cerebellar cortex that related to the motor cortex and three sectors of the prefrontal cortex. *MOT* motor cortex, *DLPFC* lateral convexity of the prefrontal cortex, *MPFC* medial prefrontal cortex, *APFC* anterior prefrontal cortex. Reproduced from [47], by permission of Oxford University Press

lobule, along with cerebellar cortical Crus I and Crus II. Both of these results are consistent with the anatomical organisation in non-human primates and with the human neuroimaging studies reported above.

There is a correspondence between findings in humans and monkeys in some lobules, but also that there are inconsistencies in others. For instance, lobules HV, HVI, HVIIB and HVIIIA are related to the primary motor cortex in both

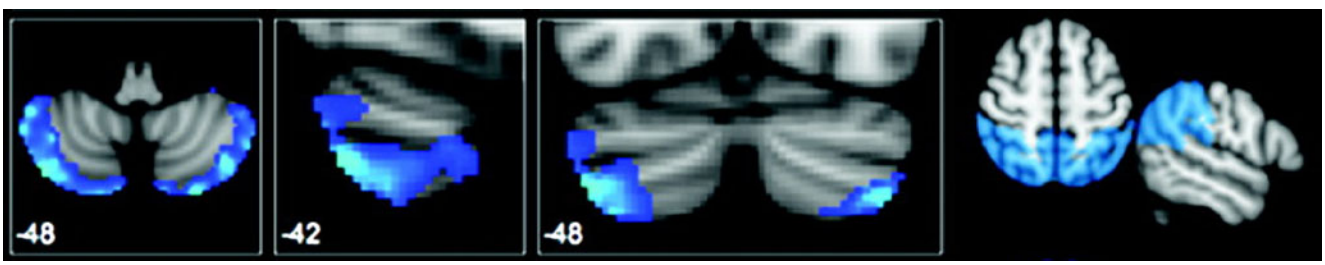


Fig. 8 Resting state activity in cerebellar cortical Crus II is statistically related to that in the posterior parietal cortex. Reproduced from [64], by permission of Oxford University Press

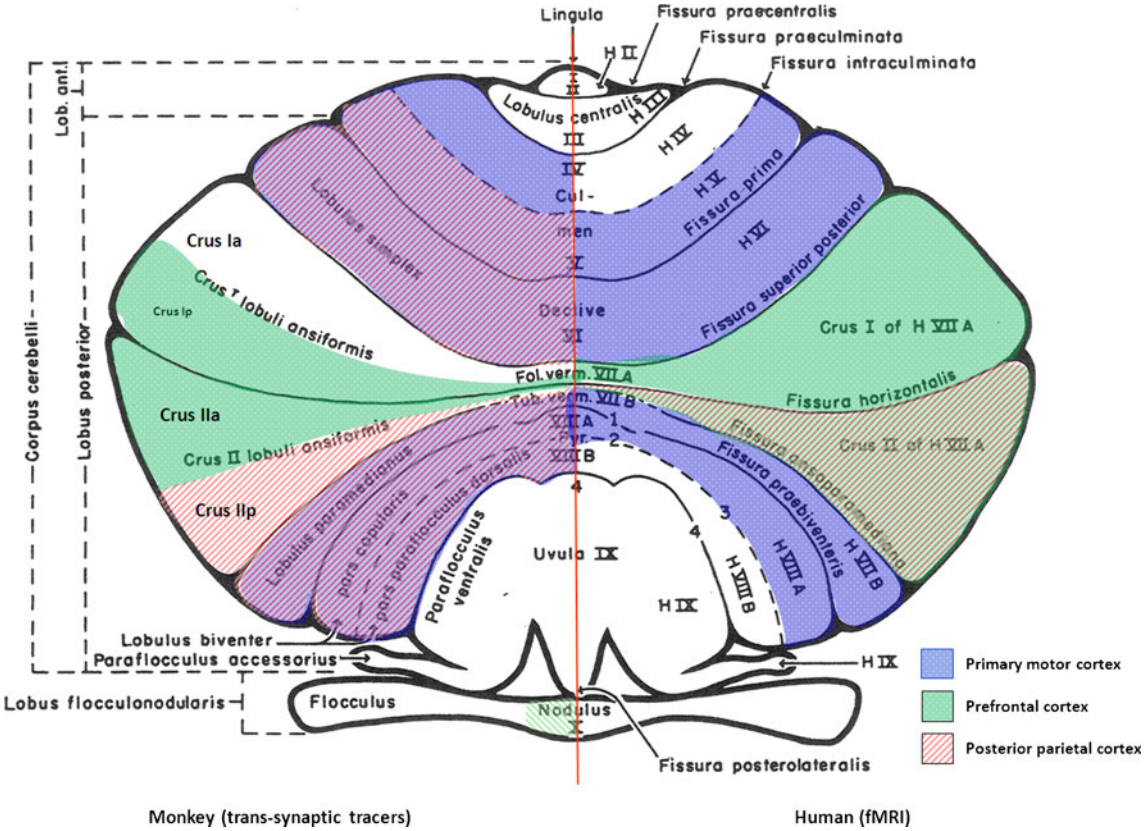


Fig. 9 Schematic generic figure of the cerebellar cortex from [5]. Connectivity of the monkey cerebellar cortex with the cerebral cortex (based on transsynaptic viral tracers) is depicted on the *left*. Connectivity of the human cerebellar cortex with the cerebral cortex (based on resting state BOLD activity) is depicted on the *right*. Lobular labels on the right are consistent with the nomenclature of Larsell ([49, 50]). Adapted from Angevine et al. [5]

humans and non-human primates, but data from monkeys additionally implicate lobules HIV and HVIIIB. Lobules interconnected with the prefrontal cortex in both humans and non-human primates include Crus I and Crus II. Whereas studies in non-human primates have been able to resolve label in sub-lobules Crus Ip and Crus IIa, imaging studies have not distinguished between them because they lack the spatial resolution to do so. The correspondence is much less clear in the case of the lobules connected with the posterior parietal cortex. Anatomical findings in monkeys and human neuroimaging both implicate Crus II. However, as with connectivity with the prefrontal cortex, the animal work implicates particular components (Crus IIp), whereas the human work refers more generally to Crus II. The animal work also implicates additional areas (HV, HVI, HVIIB and HVIII) which are not identified in the human work.

The inter-species similarities in the cerebellar cortical topography connectivity (particularly with frontal lobe areas) is striking, and suggests that "resting state" connectivity might be used to suggest the likely anatomical connectivity between the cerebral and cerebellar cortices in the human brain. It is also important to consider the reasons for differences. Subdivisions of the ansiform lobule appear to have different profiles of connectivity with areas of the cerebral cortex, so as our understanding of functional organisation grows, it will become increasingly important to ensure that functional studies are able to resolve these in order that activations in these areas can be interpreted properly. The spatial resolution of conventional functional MRI is currently too low to reveal these reliably. However, ultra-high field imaging (with field strengths of 7 T or more) has already demonstrated that it can be used to study the human brain at exquisitely fine scales in the human cerebral cortex [98]. There is every reason to expect that such an approach may be feasible for studying the fine scale functional organisation of the human cerebellum.

In conclusion, the outdated view of the cerebellum, in which its role is restricted to motor control, is inconsistent with new information about cerebellar connectivity from both humans and monkeys that conclusively demonstrates its relationships not only with the primary motor cortex, but also the prefrontal cortex, and posterior parietal cortex. Neuroimaging has played an important role in characterising the co-evolution of the prefrontal cortex and the parts of the cerebellar cortex to which it is connected. In humans, it seems likely that this system

plays important roles in monitoring and regulating the activity of the association cortex. The review emphasises that our understanding functional topography depends on our understanding of its connectional topography—it is not possible to interpret activity in the cerebellar cortex unless one can determine which areas of the cerebral cortex is driving this activity, or which areas it influences. Finally, most of the system still remains to be mapped: we do not have a comprehensive understanding how the cerebral cortex maps topographically onto the cerebellar cortex in the primate brain or how its organisation in humans differs from that of other primates.

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