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# Functional MRI localizing in the cerebellum

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The cerebellum contains approximately half of the brain's neurons, but its particular nerve cells are so small that the cerebellum constitutes only 10% to 15% of the entire brain weight, approximately 140 g in human beings. It is composed of a highly convoluted cerebellar cortex and a core of white matter with three nuclei are embedded on each side (Fig. 1). It is located dorsal to the brain stem in the posterior fossa, inferior to the tentorium cerebelli, and internal to the occipital bone. It overlies the pons and medulla, connecting with these structures and with the mesencephalon through three peduncles on each side. The cerebellum has a superior surface apposed to the tentorium and a convex inferior surface that abuts the inner surface of the occipital bone.

There are three major lobes, the anterior, posterior, and flocculonodular, and these can be further subdivided into a series of lobules. The lobules have been given proper names, but this nomenclature has largely been replaced by the numbering system introduced by Larsell [1], which consists of a Roman numeral applied to each of the folia of the vermis (Fig. 2). On the basis of phylogenetic and embryologic studies, the lobules have been grouped into three components: the archicerebellum, paleocerebellum, and neocerebellum. The archicerebellum consists of the flocculonodular lobe, and the paleocerebellum comprises the vermis of the anterior lobe (culmen and lobulus centralis) plus the lower vermis with the pyramis, uvula, and paraflocculus. The neocerebellum comprises both hemispheres and has developed together with the telencephalon as the latest phylogenetic structure and is thus most prominent in mammals, especially in hominids [2].

All inputs to the cerebellar cortex are mediated by two sorts of afferents: mossy fibers and climbing fibers. It is now well established that all climbing fibers emerge from the inferior olivary nucleus, whereas all other afferent fiber systems originate from the spinal cord, the vestibular nuclei, and the pons terminate as mossy fibers with synapse on dendrites of granule cells [3]. With respect to their origin, the three cerebellar components are also called the vestibulocerebellum, spinocerebellum, and ponto- or cerebrocerebellum. The archicerebellum receives its major input from the vestibular system (Fig. 3). Fibers from the spinal cord ascend within the spinocerebellar tract and terminate in the paleocerebellum, mainly in the anterior lobe. The human neocerebellum receives its major input from large masses of cells in the pons and from the inferior olivary nucleus in the medulla. All output fibers leave the cerebellar cortex via Purkinje cells and project to a set of deep cerebellar nuclei. The fastigial nucleus receives fibers from the midline vermal zone and projects to the lateral vestibular nucleus. The interposed nuclei comprising the nucleus globosus and emboliformis receive fibers from the paravermal zone and project via the superior cerebellar peduncle to the contralateral red nucleus. The dentate nucleus is by far the largest nucleus; it receives output fibers of the cerebellar hemisphere and projects contralateral to the ventrolateral nucleus of the thalamus.

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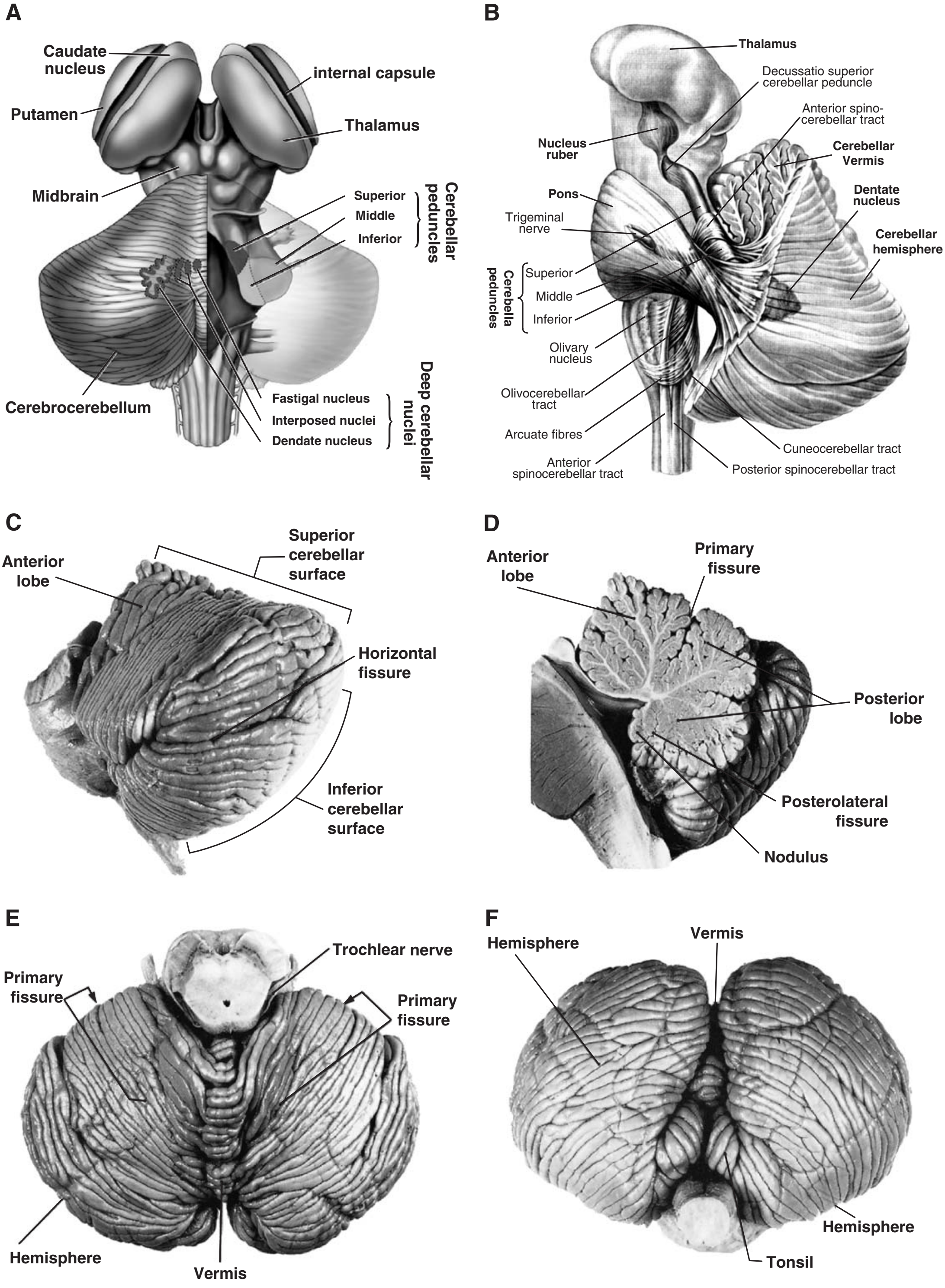
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Dendate nucleus
Deep cerebellar nuclei
B
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Anterior spino-cerebellar tract
Nucleus ruber
Cerebellar Vermis
Pons
Dentate nucleus
Trigeminal nerve
Cerebellar hemisphere
Superior
Middle
Inferior
Cerebella peduncles
Olivary nucleus
Olivocerebellar tract
Arcuate fibres
Cuneocerebellar tract
Anterior spinocerebellar tract
Posterior spinocerebellar tract
C
Anterior lobe
Superior cerebellar surface
Horizontal fissure
Inferior cerebellar surface
D
Anterior lobe
Primary fissure
Posterior lobe
Posterolateral fissure
Nodulus
E
Primary fissure
Trochlear nerve
Primary fissure
Hemisphere
Vermis
F
Hemisphere
Vermis
Hemisphere
Tonsil

## Brief history of functional assignment in the cerebellum

The existence of functional assignment within the cerebellum was first recognized almost two centuries ago by comparative anatomic and physiologic studies. Careful analyses of the motor disturbances led Flourens [4] to conclude in 1824 that the cerebellum is neither an initiator nor an actuator but instead serves as a coordinator of movements. An animal with a damaged cerebellum still initiates and executes movements but only in a clumsy manner. From that time on, most investigators recognized the specifically motor role of the cerebellum. In 1991, more than 60 years later, Luciani [5] observed that cerebellar lesions did not impair coordinated movement as such but were caused by more elemental deficits, which he called atonia, asthenia, and astasia. Atonia is the loss of muscle tone, asthenia is weakness of muscles, and astasia is a deficit in the regularity and stability of muscle contraction. He also recognized that motor disturbances caused in an animal by a partial lesion of the cerebellum were gradually compensated for because of the functional plasticity of cerebellar tissues.

In 1904, Bolk [6] introduced his scheme of functional organization after he had examined the cerebella of more than 60 different mammalian species. He reasoned that the cerebellum is probably made up of a number of centers, each of which controls the actions of a different group of muscles. He suggested that movements can be subdivided into two basic types: one group of movements that require a muscular collaboration across the midline of the body and being represented in an unpaired structure of the cerebellum like the vermis and a second group of unilateral movements which can perform independently and are controlled by lateral structures. He concluded that the midline vermis controls bilaterally synchronized movements, whereas the cerebellar hemispheres direct unilateral movements. He also proposed sagittal continuity of the cerebellar cortex across the folia of the vermis and hemispheres and transverse continuity between the vermis and hemispheres. According to his subdivision, the sulcus primarius anterior or fissura prima splits the cerebellum into an anterior lobe and a posterior lobe (Fig. 4).

In 1910, Comolli [7] introduced the concept of paleo- and neocerebellum to differentiate the oldest and youngest cerebellar regions, respectively. According to this concept, the vermis and the flocculus represent the paleocerebellum and the hemispheres represent the neocerebellum. The cerebellar hemispheres are prominent in mammals but are barely discernible in birds [8]. Furthermore, in the superior mammals, most strikingly in hominids, the vermis is progressively reduced in size, whereas the cerebellar hemispheres are markedly enlarged, [2]. Because the hemispheres are widely connected with the cerebral cortex through the pontine nuclei, their progressive development is related to the concurrent development of the pons.

In 1934, Larsell [1] proposed a further subdivision of the cerebellar areas. His research extending over more than 30 years was posthumously was published in 1971 in a book by Larsell and Jansen [9]. His work provided a comparative anatomic basis of cerebellar localization and served as the basis for our present concepts of cerebellar morphology. He started from the observation that the fissure that appears most precociously in ontogeny as well as in phylogeny is the posterolateral fissure. This fissure splits the cerebellum into two lobes, the flocculonodular lobe and the corpus cerebelli, which encompass the whole remaining cerebellum. The corpus cerebelli is further subdivided into two lobes, anterior and posterior, by the fissura prima. According to Larsell [1], the craniocaudal course from the lingula to the nodulus is divided into 10 lobuli (vermis: I–X, hemisphere: HI–X). These are subdivided into up to six lamellae (a–f; see Fig. 2). Larsell's subdivision constituted the final step in a series of the classifications of cerebellum anatomy.

At the beginning of the 1940s, new functional assignments emerged from electrophysiologic investigations. Adrian [10] recorded cerebellar unitary discharges during joint displacements, muscle stretching, or tactile stimulation in anesthetized cats and monkeys as well as in decerebrate cats. He demonstrated that proprioceptive and exteroceptive information is somatotopically arranged

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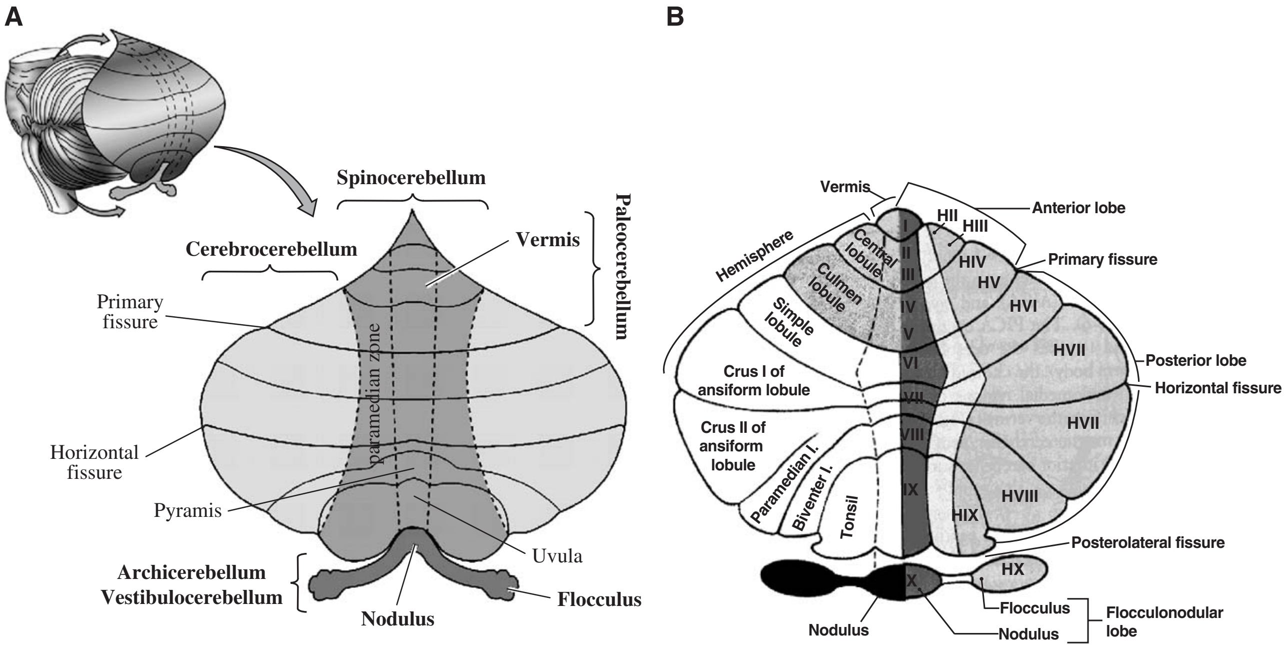
Fig. 1. Anatomy of the cerebellum. Dorsal (*A*) and lateral (*B*) views of the cerebellum with depiction of the cerebellar nuclei and peduncles and the course of the cerebellar peduncles as well as the other major input tract. (*Adapted from* Nieuwenhuys R, Voogd J, Huijzen C. The human central nervous system. 3rd edition. New York: Springer; 1988.) Depiction of cerebellar lateral (*C*), midsagittal (*D*), superior (*E*), and inferior (*F*) surfaces. (*Adapted from* Haines DE. Fundamental neuroscience. New York, Churchill Livingstone; 1997.)



Grodd: fMRI of the cerebellum

Fig. 2. Anatomic assignments of the cerebellum. (*A*) Unfolded cerebellar surface with display of major compartments and anatomic nomenclature. (*B*) Assignment of major lobules according to Larsell [1].

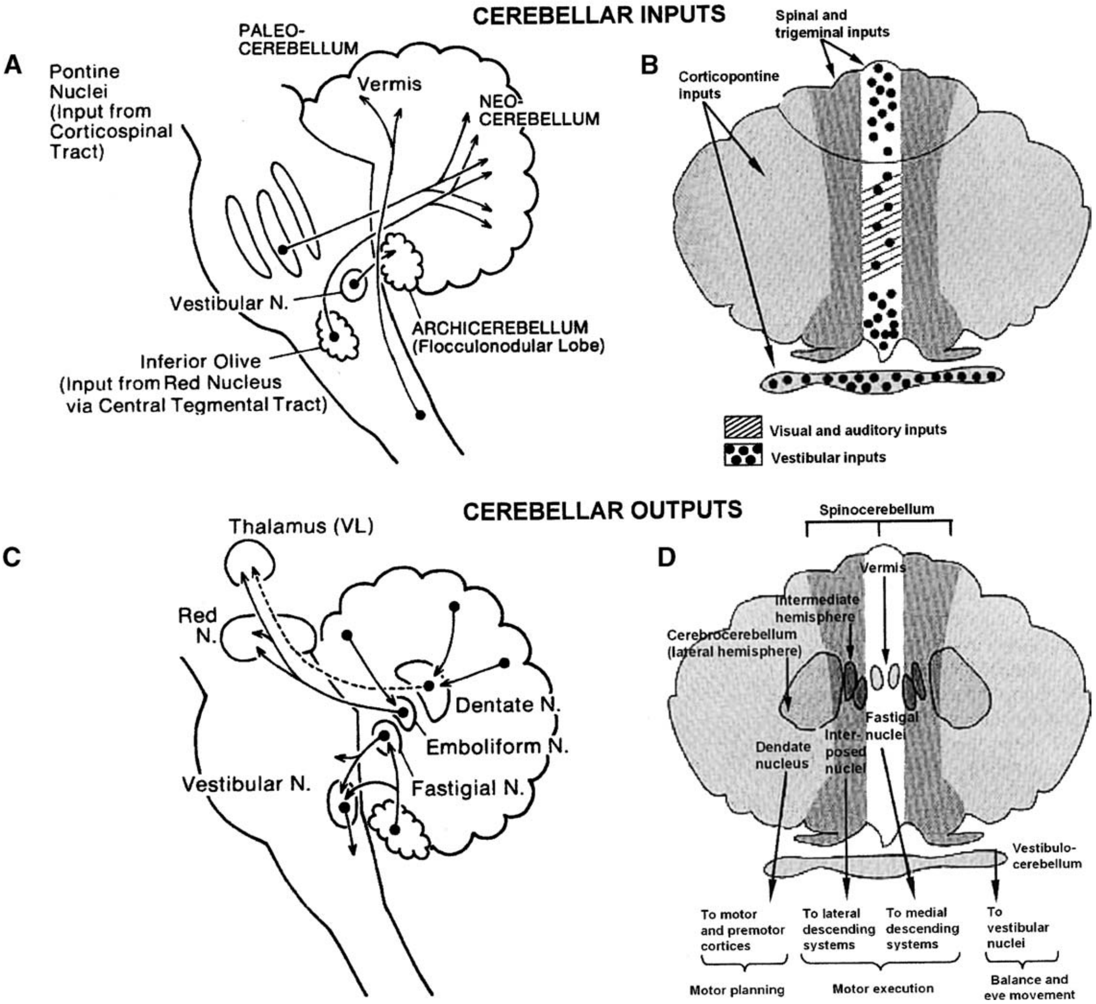


Fig. 3. Cerebellar input and output channels. Overview of the major cerebellar input (*A, B*) and output (*C, D*) pathways with their corresponding cerebellar compartments (*B, D*).

in the anterior lobe. Specifically, hind limb afferents project to vermian and hemispheric regions of the lobulus centralis (Larsell's lobules III and HIII), forelimb afferents project to the culmen (lobules IV, V, HIV, and HV), and face afferents project to the lobulus simplex (lobules VI and HVI).

Similarly, in 1944, Snider and Stowell [11] revealed two inverted somatotopic maps in the anterior lobe and paramedian lobule in anesthetized cats and monkeys, where exteroceptive information from hair or vibrissae is projected (see Fig. 4). Their mapping was based on recordings of surface potentials, which reflect the predominant cerebellar input. The body map in the anterior lobe has the hind limbs oriented forward, whereas the face extends backward into the first lobule of the posterior lobe. The map in the paramedian lobule has the head forward and the limbs represented on either side of the midline. Arms and legs are represented adjacent to the vermis over the intermediate cortex of the hemispheres. The projections to the anterior lobe are strictly ipsilateral, whereas the afferents to the paramedian lobule are bilateral, although with a slight bias toward the ipsilateral projection. In addition, these investigators described slightly overlapping auditory and visual inputs to the vermis (lobulus simplex, folium, and tuber vermis), probably reaching the cerebellum through the colliculi and the tectocerebellar tract. The somatotopic representation demonstrated for exteroceptive and proprioceptive

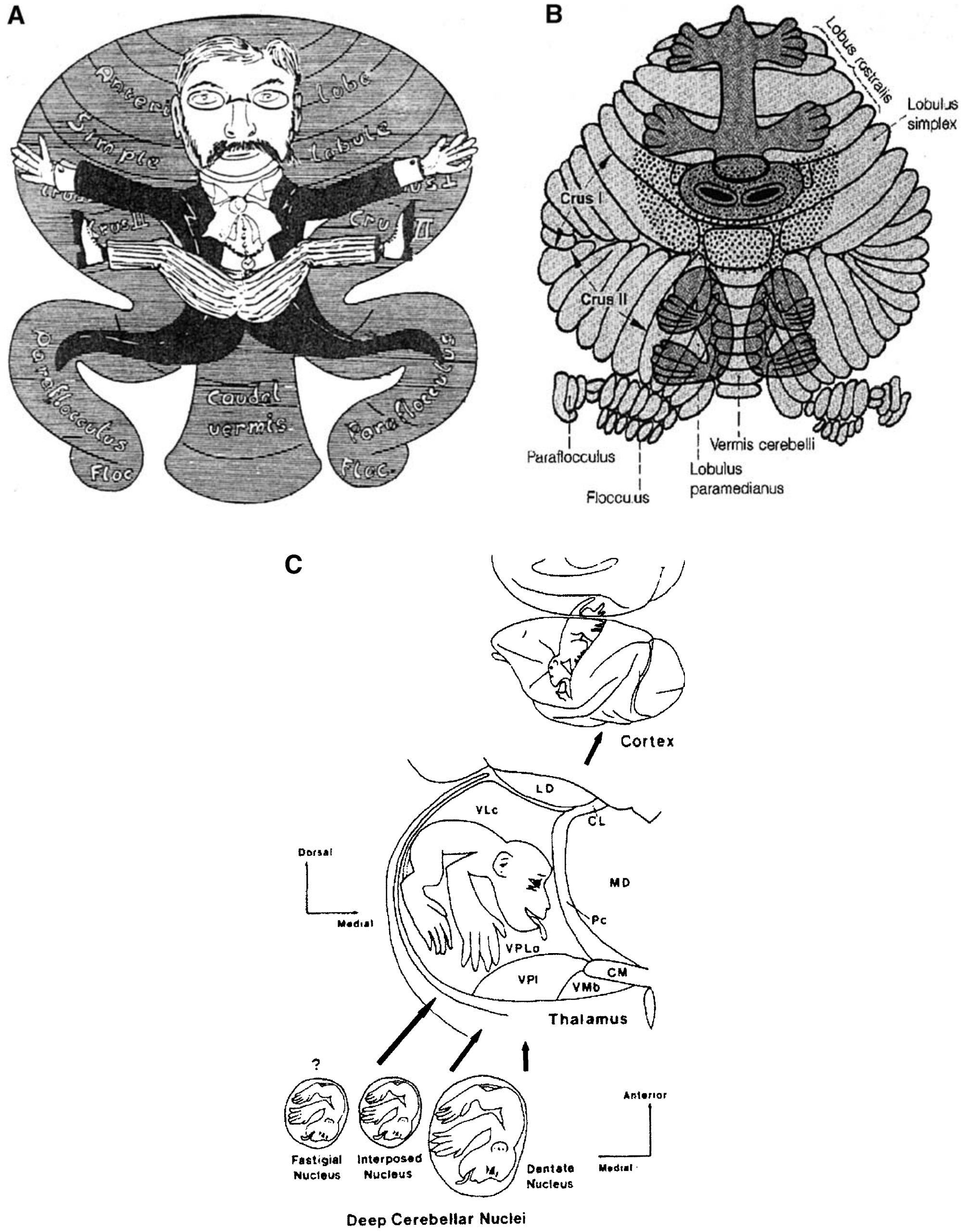


Fig. 4. Cerebellar somatotopy. Cortical arrangement of body parts as seen by Bolk (*A*) and Snider and Eldred (*B*) and somatotopic organization of the deep cerebellar nuclei as predicted by Asanuma (*C*). (*A: From* Glickstein M, Yeo C. The cerebellum and motor learning. J Cogn Neurosci 1990;2:69–80; with permission. *B: From* Snider R, Stowell A. Receiving areas of the tactile, auditory and visual systems in the cerebellum. J Neurophysiol 1944;7:331–57; with permission. *C: Adapted from* Asanuma C, Thach WT, Jones EG. Brain stem and spinal projections of the deep cerebellar nuclei in the monkey, with observations on the brain stem projections of the dorsal column nuclei. Brain Res Rev 1983;5:299–322.)

inputs mediated by spinocerebellar pathways was also valid for neocortical afferents, which reach cerebellar regions via the pontine nuclei. Subdivisions of the primary motor cortex (M1) that represent the face, arms, and legs project within the cerebellum into the same areas as the spinocerebellar projections from the face, arms, and legs, respectively, demonstrating an elegant somatotopic arrangement of inputs, regardless of the site of origin.

Soon after the discovery of the somatotopic organization of cerebellar afferents, experiments were performed to elucidate the efferent projections of the cerebellum. In the absence of anesthesia, stimulation of the cerebellar cortex evokes localized movements. As for the anterior lobe, stimulation of the lobule simplex evokes head movements of the face and jaw, stimulation of the culmen evokes forelimb movements, stimulation of the centralis evokes hind limb movements, and stimulation of the lingula evokes tail movements. Trunk muscles are represented medially, whereas limb muscles are represented laterally. This scheme, which was first disclosed in the decerebrate animal, was confirmed in intact animals by means of chronically implanted electrodes. Hampson et al [12] reported that in the decerebrate cat, dog, and monkey, electrical stimulation of the anterior lobe provoked inhibition of hypertonus in the ipsilateral limbs and increased hypertonus in the contralateral limbs.

More recent studies have revealed that in the mammalian cerebellum, the main afferent and efferent projections have a parasagittal band-like topographic organization [13,14]. This somatotopic organization was demonstrated for climbing and mossy fiber afferents as well as for efferent Purkinje cell projections to cerebellar and lateral vestibular nuclei. In the pars intermedia of the anterior lobe, as far as the climbing fibers are concerned, the hind limb is represented in the lobus centralis and the forelimb is represented in the culmen. Similarly, in the vermian portion of the anterior lobe, a sagittal organization was found, with the forelimb and hind limb represented medially and laterally, respectively [15,16]. Electrophysiologic studies in primates show that deep cerebellar nuclei are also somatotopically organized (see Fig. 4). They are arranged to receive projections from the two maps on the dorsal and ventral surfaces of the intermediate and lateral zones of the cerebellar cortex and project contralateral to the red nucleus and M1 through the thalamus [17].

At a finer level of resolution, experimental studies based on single-cell recordings in mammals have shown that body parts are not represented continuously over larger areas of the cerebellar cortex but are broken down into smaller discontinuous patches. A small area that receives sensory input from the arm (by way of mossy fiber–granule cell connections) might be located adjacent to an area that receives input from a noncontiguous region of the same upper extremity. In addition, each body part is represented in several locations. This spatial pattern of representation is referred as fractured somatotopy [18].

On the basis of numerous experimental findings, similar somatotopic maps have been hypothesized in human beings, but a relative uncertainty exists as to what extent the spino- and neocerebellum serve sensorimotor functions and which part serves other brain functions, especially sensory and cognitive processing [19]. The existing clinical topodiagnostic scheme in human beings still attributes motor deficits only to the lateral, intermediate, and vermal zones. In general, this notion is consistent with the experimental findings [11] in that (1) lateral cerebellar damage predominantly results in a delay of movement initiation and decomposition of multijoint movements, which are invariably more pronounced in the arm; (2) paramedian lesions often cause dysarthria; and (3) lesions to the vermis yield ataxia of stance and gait [20].

## Functional imaging of the cerebellum

Detailed functional mapping of the human cerebellum first became possible with the advent of positron emission tomography (PET) and functional MRI (fMRI) in the 1980s. Although both neuroimaging techniques are of an indirect nature because they are coupled via a hemodynamic response function to the underlying neuronal events, they have nevertheless opened a wide range of cerebellar investigations. As a result, a steadily increasing number of imaging studies have been published regarding functional localization in the cerebellum. In this article, we summarize some of the major results in assigning sensorimotor, language, and other sensory and cognition functions to the cerebellum.

### *Spatial normalization of the cerebellum*

Because functional mapping shows considerable differences in individual brain anatomy, PET and fMRI of the cerebrum are usually subjected to a group statistic. The latter is accomplished within a normalization procedure using a defined reference space to achieve probabilistic mapping. The most applied normalization procedure refers to the Talairach space, originally developed for stereotactic procedures to the thalamus, which thus does not include the cerebellum [21]. Nevertheless, this normalization approach is still commonly applied in human neuroimaging studies and implemented in a number of evaluation programs [22,23]. Meanwhile, a three-dimensional MRI atlas of the human cerebellum in a proportional stereotaxic space has been introduced by Schmahmann et al [24], in which the Talairach space is simply modified by extending the coordinate system caudally. In addition, on the basis of this extended reference frame, a first MRI atlas with detailed coordinates of the cerebellar nuclei has been published [25].

Nevertheless, better reduction of variance caused by differences in individual anatomy is achieved by applying a transformation procedure specific for the cerebellum, because this approach accounts for variations in the medullopontine angulation. Such a transformation can easily be realized analogous to the Talairach normalization by introducing an appropriate reference frame and specific anatomic landmarks for the cerebellum. By defining three orthogonal planes centered on the floor of the fourth ventricle and introducing seven predefined landmarks, one can achieve spatial normalization by adjusting the individual landmarks to the determined values by means of linear expansion or compression along these three axes [26]. The superiority of this approach compared with Talairach normalization is especially pronounced for the inferior cerebellar surface (Fig. 5).

## *Sensorimotor functions*

### *Cortical topography*

By applying such cerebellar-centered normalization procedure, Grodd et al [26] have recently determined the areas of activation in the cerebellar cortex in 46 human subjects during a series of motor tasks with fMRI (Fig. 6). The representation areas for movements of the lips, tongue, hands, and feet were found to be sharply confined to lobules, sublobules, and the sagittal zones in the rostral and caudal spinocerebellar cortex. There was a mirror-like symmetry aligned to the midline. The activation maps separate into two distinct homunculoid representations: one, a more extended representation, was located upside down in the superior cerebellum, and a second one, doubled and smaller, was located in the inferior cerebellum. The two representations were remarkably similar to those proposed by Snider and Eldred [27] five decades ago (Fig. 7). In the upper representation, intralimb somatotopy for the right elbow, wrist, and fingers was likewise revealed. The maps seem to confirm earlier electrophysiologic findings of sagittal zones in animals. They differed, however, from micromapping reports on fractured somatotopy in the cerebellar cortex and most likely reflect the input integration of afferent peripheral and central information in the cerebellar cortex.

### *Active versus passive movement*

The former study was restricted to active movements and did not investigate the patterns of activation during passive limb excursions, and it is still unknown whether a similar dual representation for afferent inputs to the cerebellum exists, as reported in the cat and monkey. If this would be the case, the question arises whether the two areas have comparable roles in motor and sensory processing or whether there are differences in these areas during voluntary movement and passive kinesthetic sensory stimulation. The aim of the cerebellar fMRI study by Thickbroom et al [28] was thus to determine whether a dual representation can also be demonstrated with passive movement and to compare the patterns and degree of cerebellar activation with kinematically comparable active and passive limb movement. They compared differences between active and passive index finger movement and detected activation ipsilateral in the anterior and posterior lobes during both tasks (Fig. 8). During passive movement, dual activation was detected in the ipsilateral cerebellum, in the anterior lobe, and in the posterior lobe. A similar pattern of activation was observed during voluntary movement; however, the overall magnitude was approximately doubled in both areas. They conclude that the rostral representation is the dominant one but that both areas may be involved in kinesthetic sensory and motor processing.

### *Executed versus imagined movement*

The question as to what extent imagery and perception share the same neuronal substrates or whether they are based on completely different neuronal mechanisms, such as abstract

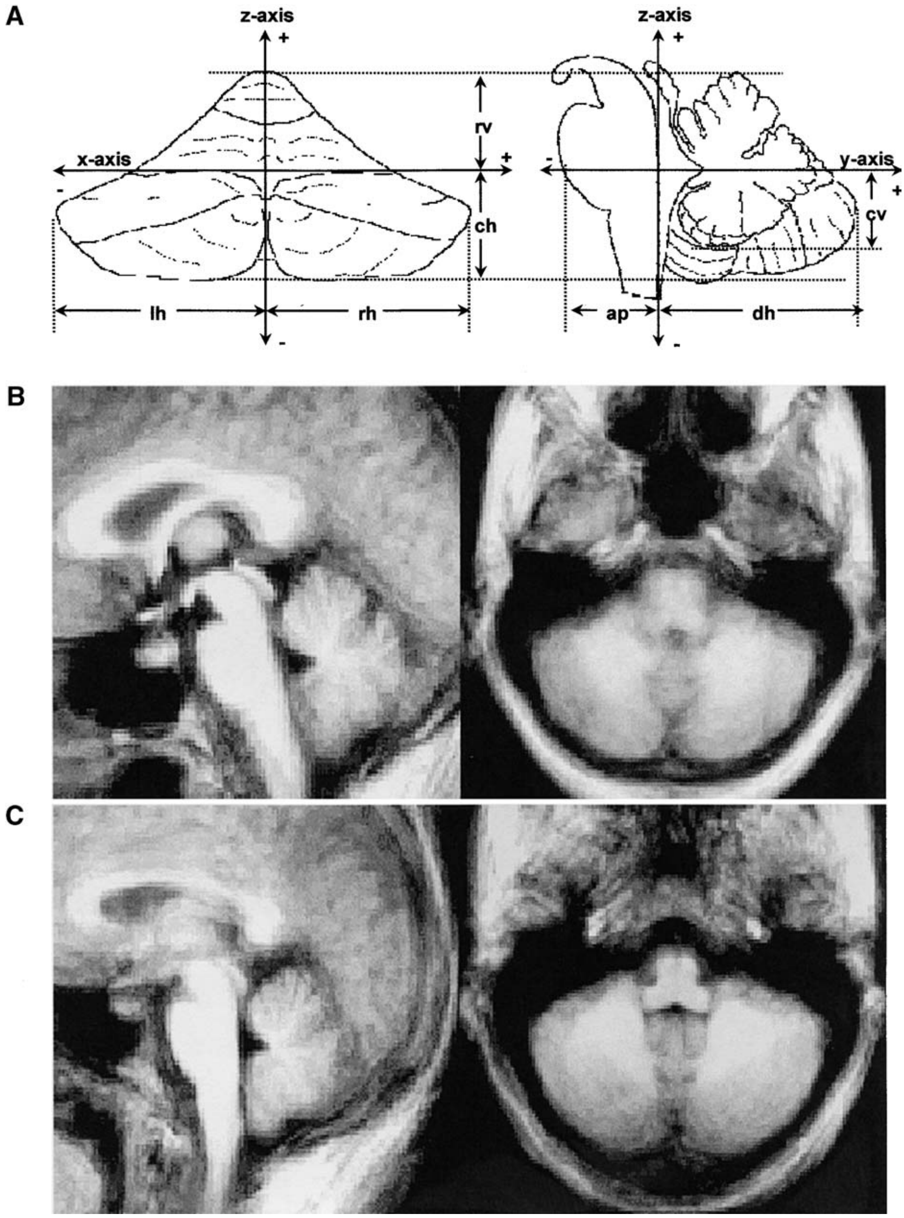


Fig. 5. Cerebellar transformation. (*A*) Linear transformation of the cerebellum. Three perpendicular planes (midsagittal x-plane, y-plane along the floor of the fourth ventricle, and z-plane through the apex of the fourth ventricle) centered at the dorsal pons with definition of seven anatomic landmarks (ap, anterior pons; ch, caudal hemisphere; cv, caudal vermis; dh, dorsal hemisphere; lh, left hemisphere; rh, right hemisphere; rv, rostral vermis) used for cerebellar transformation. (*B, C*) Results of two transformation procedures on the averaged cerebellar anatomy of 10 subjects in a midsagittal view (*left*) and axial view (*right*) on the inferior cerebellar surface. Talairach transformation (*B*) and cerebellum-centered transformation (*C*) according to Grodd et al [26]. Note the superior outline of the spinal cord and cerebellar tonsils in *C*.

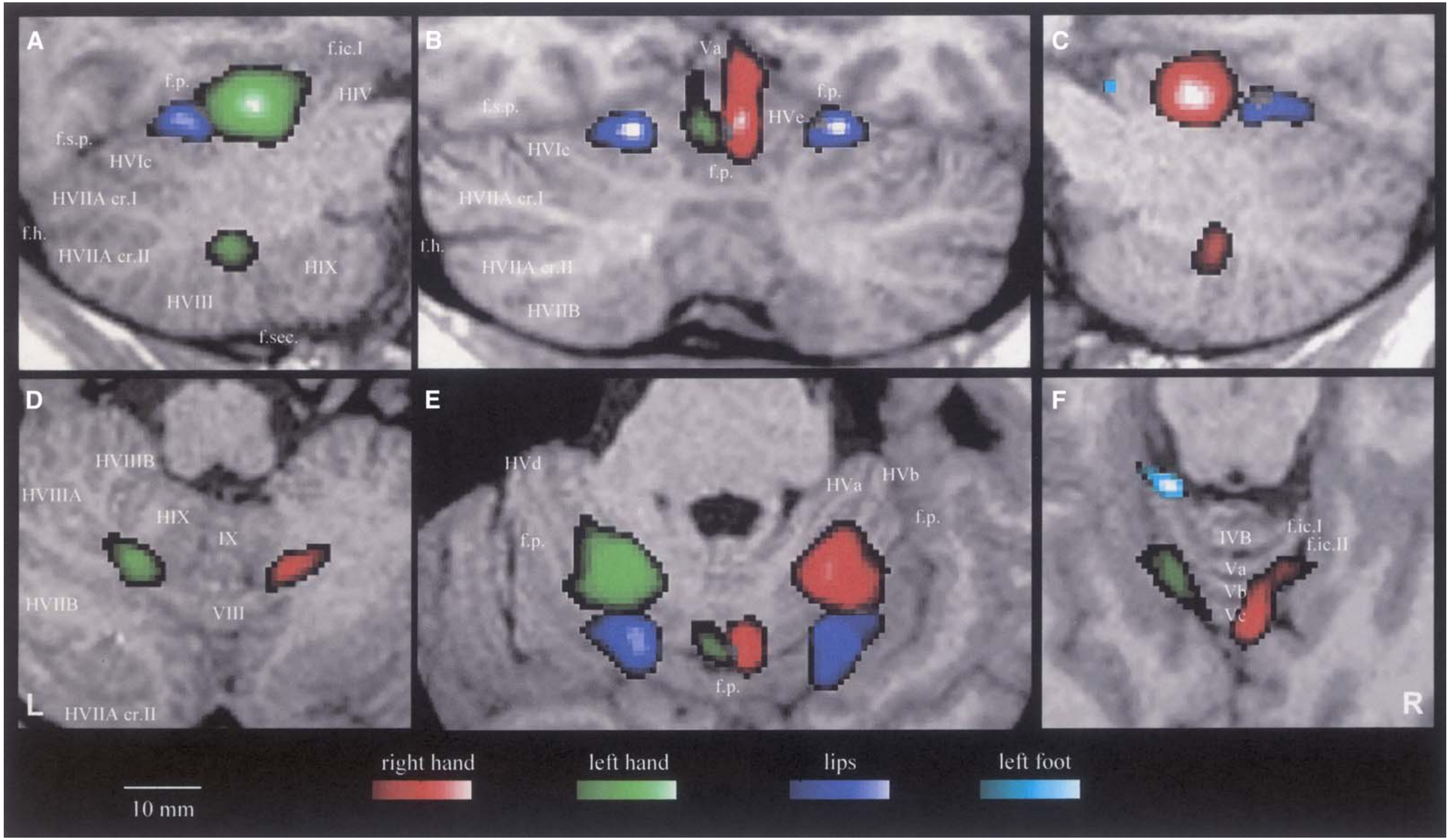


Fig. 6. Topography of cerebellar activation. Functional MRI activation displayed on an individual cerebellar template for movements of the hands (*right* [red], *left* [green]), the lips (blue), and the feet (cyan) ($P < 0.01$). Left parasagittal (*A*), coronal (*B*), right parasagittal (*C*), inferior axial (*D*), medioaxial (*E*), and superior axial (*F*) sections. f.h., fissura horizontalis; f.p., fissura prima; f.sec., fissura secunda; f.s.p., fissura superior posterior; L, left; R, right. (*From* Grodd W, Hülsmann E, Lotze M, Wildgruber D, Erb M. Sensorimotor mapping of the human cerebellum: fMRI evidence of somatotopic organization. Hum Brain Mapp 2001;13:55–73; with permission.)

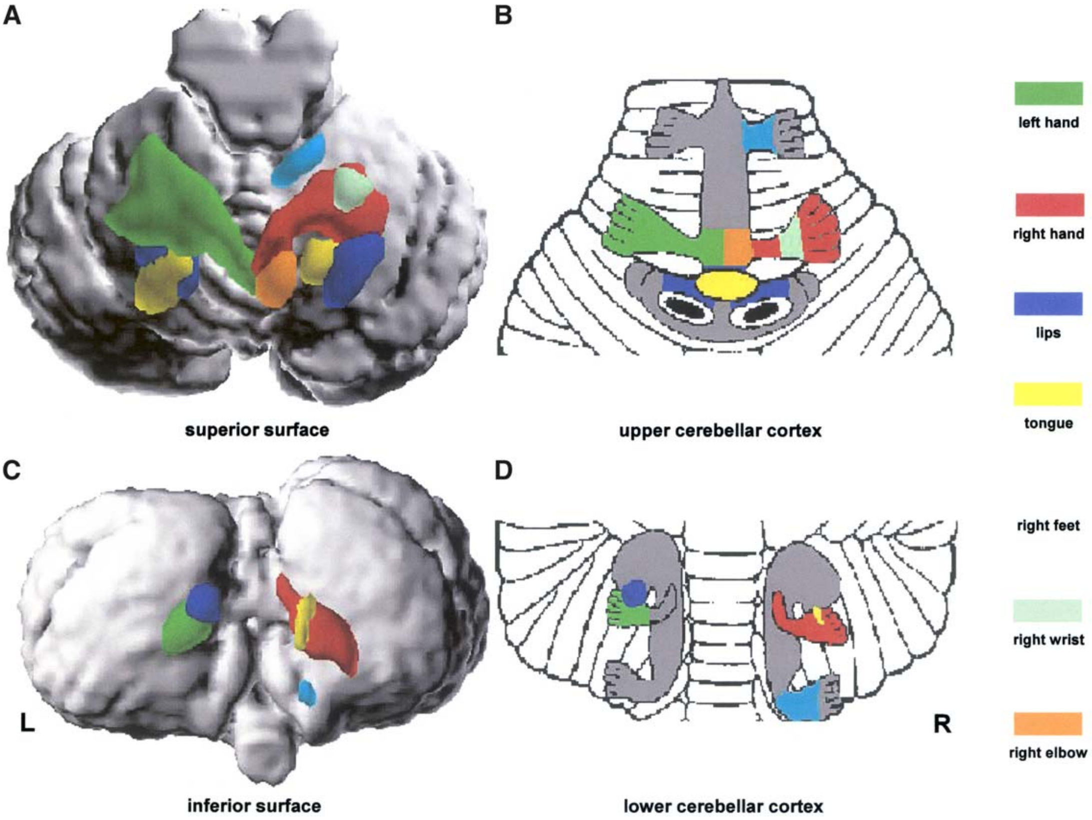


Fig. 7. Functional somatotopy of the cerebellum. Display of cerebellar surface with superimposed color-coded functional MRI activation volumes on the superior (*A*) and inferior (*C*) cerebellar surface with corresponding display of the cerebellar homunculi (*B, D*) as represented by Snider and Eldred. (*Data from* Brain Innovation B.V. Web site. http://www.brainvoyager.com. Accessed September 27, 2004.)

postperceptual representations, is an ongoing debate in the neurosciences. The discussion has mainly focused on visual imagery; evidence from neuroimaging and neuropsychologic testing suggests that imagery and perception use the same brain areas. Motor imagery may have different characteristics, in which it is not the virtual environment that is imagined but introspective kinesthetic feelings of moving the limb [29]. Movement imagery as an internal process may be compared with movement preparation, two processes that might be functionally equivalent. Lotze et al [30] have studied fMRI brain activation during executed movement (EM) and imagined movement (IM) of both hands. In conjunction with electromyographic control of the musculi flexor digitorum superficialis and training of high vividness of IM before image acquisition, they determined regional cerebral activation for EM and IM compared with rest in selected regions. In all subjects, the supplementary motor area (SMA), premotor cortex, and primary motor cortex M1 showed significant activation during both conditions, but only the somatosensory cortex (S1) was significantly more highly activated during EM. The prefrontal and parietal regions revealed no significant changes during both conditions, but in the cerebellum, ipsilateral activation was decreased during IM compared with EM (Fig. 9). In addition, the foci of maximal cerebellar activation between IM and EM differed significantly. High ipsilateral activation was observed in the anterior lobe (lobule HIV-HV) during EM, whereas during IM, a smaller activation area was found distant approximately 2 cm dorsolateral in lobule HVII. Although the cortical results support the hypothesis that motor imagery and motor performance possess similar neural substrates, the activation in the cerebellum during EM and IM may be in accordance with the assumption that the posterior cerebellum is involved in the inhibition of movement execution during imagination.

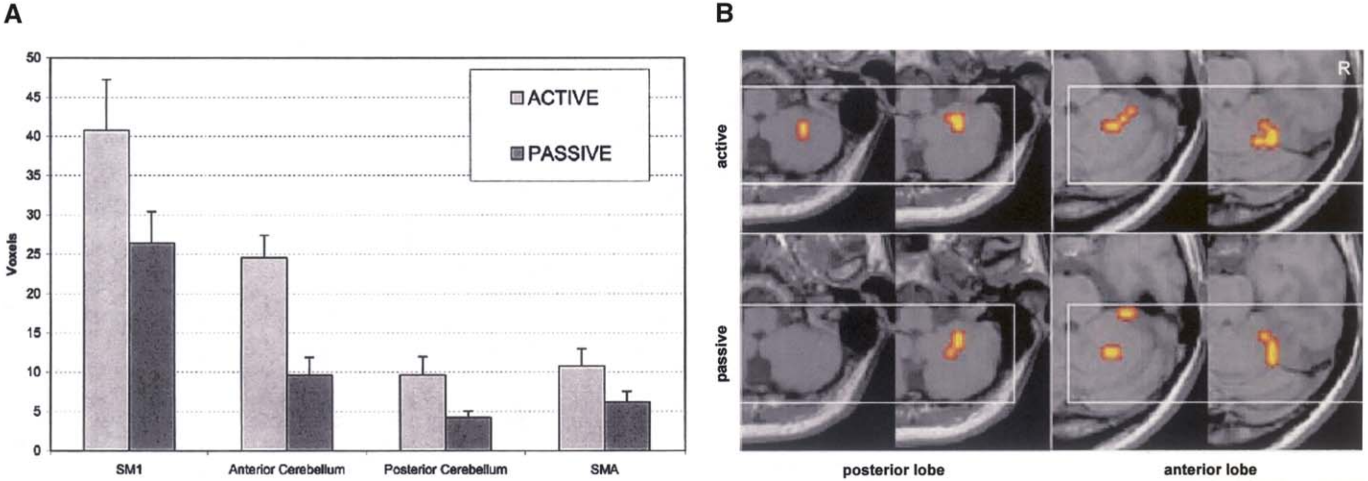


Fig. 8. Comparison of active and passive movement. (*A*) Group data comparing the number of activated voxels in the contralateral sensorimotor cortex (SM1), supplementary motor area (SMA), and anterior and posterior ipsilateral cerebellar hemispheres during voluntary and passive movement (mean and standard error). (*B*) Cerebellar activation during voluntary right index finger movement of one subject in axial planes of two contiguous slices in the anterior (*left*) and posterior (*right*) lobes for active (*top*) and passive movement (*bottom*). (*From* Thickbroom GW, Byrnes ML, Mastaglia FL. Dual representation of the hand in the cerebellum: activation with voluntary and passive finger movement. Neuroimage 2003;18:670–4; with permission.)

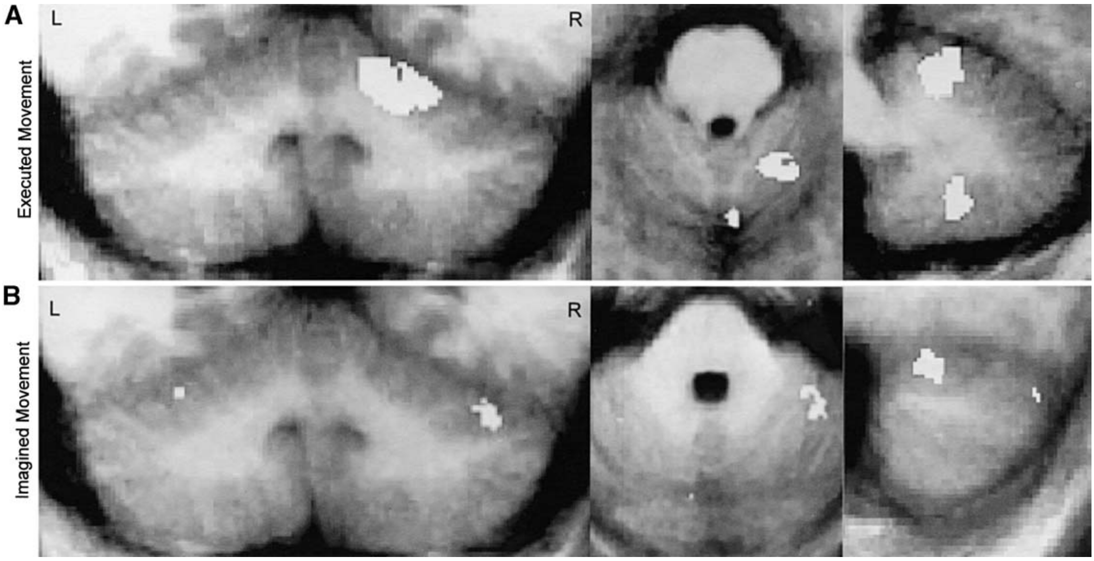


Fig. 9. Comparison of executed movement (EM) and imagined movement (IM). Cerebellar activation during EM (A) and IM (B) of the hand projected on normalized cerebellum of 10 subjects in coronal (*left*), axial (*middle*), and parasagittal views (*right*). Note that the activation maximum for EM is ipsilateral in the anterior hemisphere (lobule HIV-V) and that the activated maximum for IM is smaller and in the posterior hemisphere (lobule HVII) located 2.2 cm lateral and 1 cm dorsal to EM. (*Adapted from* Lotze M, Montoya P, Erb M, Hülsmann E, Flor H, Klose U, et al. Activation of cortical and cerebellar motor areas during executed and imagined hand movements: an fMRI study. J Cogn Neurosci 1999;11:491–501.)

*Frequency of voluntary movements*

For voluntary movements, a number of functional imaging studies have indicated a mass activation effect within the hand representation area of the sensorimotor cortex during finger-tapping or finger-to-thumb opposition tasks in terms of a stepwise or linear function between movement rate and hemodynamic response. With respect to subcortical structures of the sensorimotor system, there is, by contrast, only preliminary evidence for nonlinear rate/response functions within the basal ganglia and cerebellum. Therefore, Riecker et al [31] performed an fMRI study with externally paced finger tapping of six frequencies: 2, 2.5, 3, 4, 5, and 6 Hz. Parametric analysis revealed the expected increase of the hemodynamic response within the left mesiofrontal cortex and sensorimotor cortex in parallel to the movement rate (with the plateau phase at the sensorimotor cortex for frequencies greater than 4 Hz) (Fig. 10). By contrast, the left caudate nucleus, putamen, and external pallidum showed a negative linear rate/response relation.

Interestingly, two hemodynamic responses emerged ipsilateral in the anterior and posterior lobes of the cerebellum, which both exhibited a stepwise rate/response function. In accordance with clinical findings, these data indicate that the cerebellum responds different to movement frequencies less than or greater than approximately 3 Hz, respectively.

*Timing of voluntary movements*

Timing is essential for the execution of skilled movement, but our knowledge of the neuronal systems underlying timekeeping operations is limited. A number of studies suggested that the internal generation of precisely timed movement is dependent on at least three interrelated neural systems: one that is involved in explicit timing (basal ganglia and SMA) [32], one that mediates sensory memory, and one that is involved in sensorimotor processing (sensorimotor cortex and cerebellum) [33]. In an intriguing experiment, Hülsmann et al [34] monitored the time scale of corticocerebellar interaction during a delayed motor response by event-related fMRI. They assumed that the cerebellum has to be consulted within a limited window of time prior to a planned action and that cerebellar activation should thus occur in a time-dependent manner with respect to the corresponding telencephalic areas.

They evaluated the activation for simple thumb movement with a time-shifted

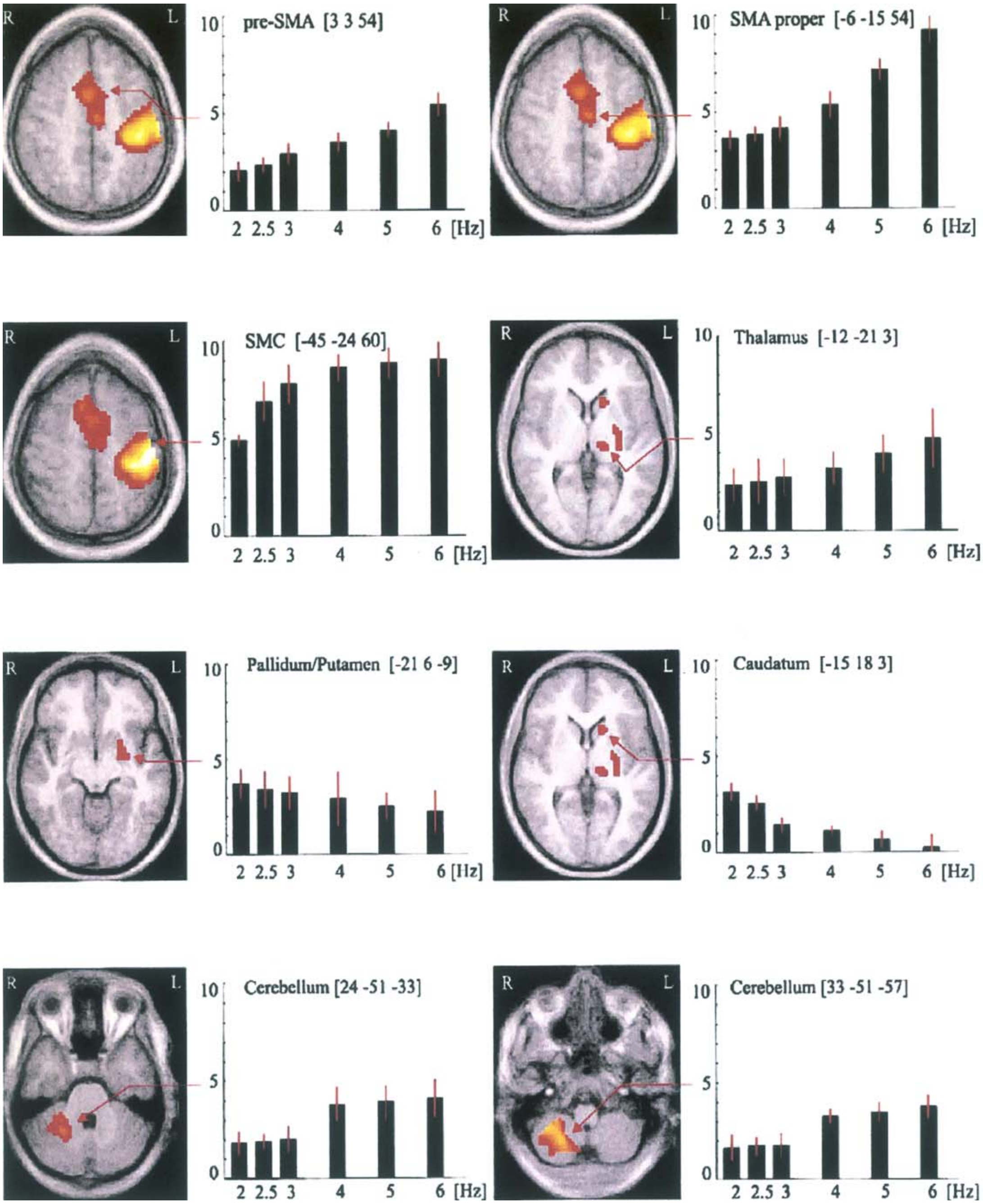


Fig. 10. Frequency dependence of voluntary movement. Parametric analysis of hemodynamic activation of group data ($n = 8$). The different rate/response functions (size of effect and variance of signal intensity calculated in arbitrary units by Statistical Parameter Mapping [SPM]) within the respective activated clusters (displayed on transverse sections of the averaged anatomic reference images) across all six different rates. SPM coordinates are given in square brackets. L, left; R, right; SMA, supplementary motor area; SMC, sensorimotor cortex. (*From* Riecker A, Wildgruber D, Mathiak K, Grodd W, Ackermann H. Parametric analysis of rate dependent hemodynamic response functions of cortical and subcortical brain structures during auditorily cued finger tapping: an fMRI study. Neuroimage 2003;18:731–9; with permission.)

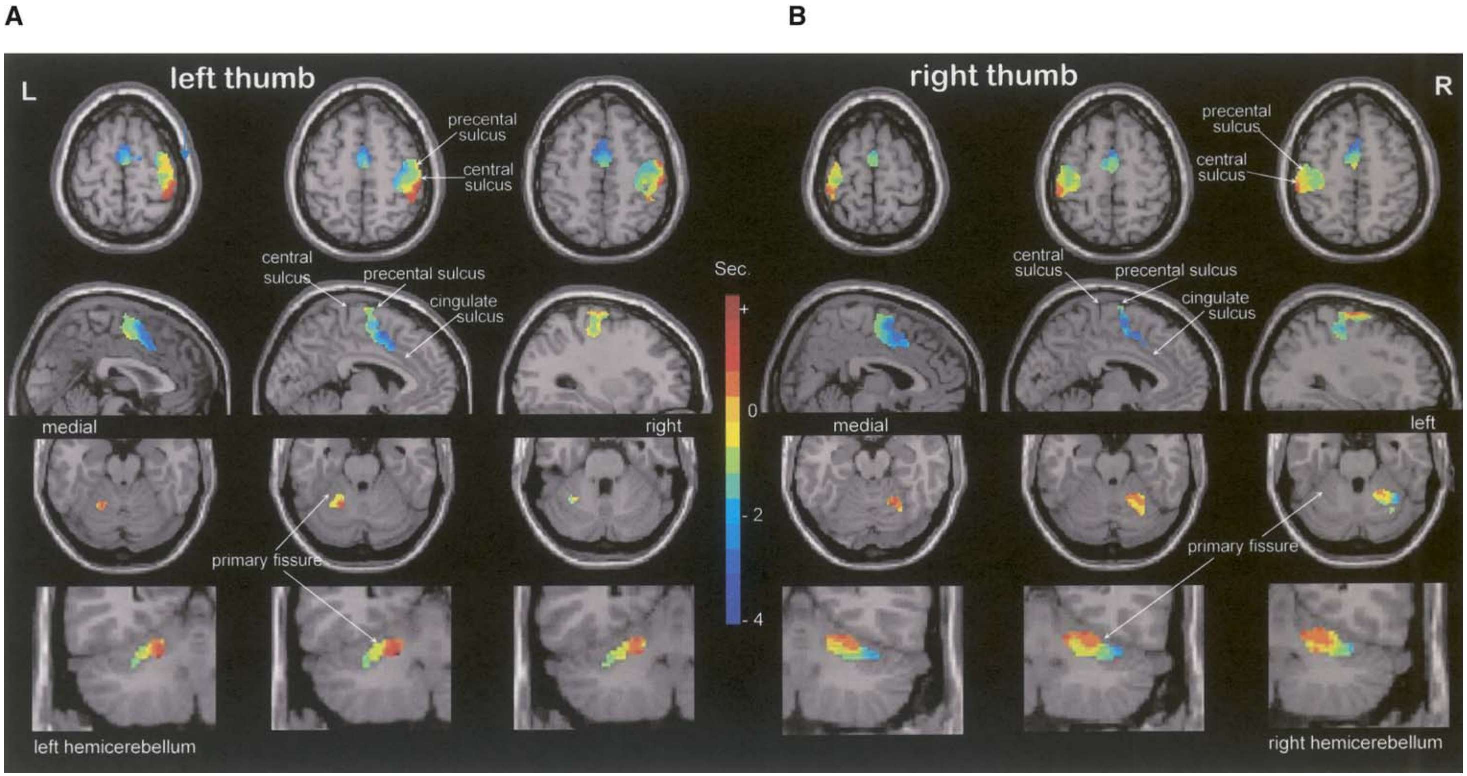


Fig. 11. Time course of cortical and cerebellar activation for thumb movement. Color-coded delay map depicting the time points of maximal *t* values of single voxels in the contralateral medial prefrontal cortex, the sensorimotor cortex, and the ipsilateral hemicerebellum superimposed on anatomic axial (running from top to bottom), sagittal (running from medial to outside), and coronal (running from posterior to anterior) slices of a single subject brain (MNI) for left (*A*) and right (*B*) thumb movement. Cingulate motor areas on both sides of the cingulate sulcus showed the earliest activation, followed by the presupplementary motor area and supplementary motor area (SMA) proper. The premotor activation occurred 2 seconds before movement onset, and anterior to the precentral sulcus in the sensorimotor cortex, it occurred 0.5 to 1 second before movement onset and proceeded toward the central sulcus. In the cerebellum, early activation located in lobule HVI, caudal to the primary fissure, was in time with the late anterior cingulate and SMA, whereas late cerebellar activation was located in spinocerebellar lobule HV, rostral to the primary fissure, in time with the sensorimotor cortex. (*From* Hülsmann E, Erb M, Grodd W. From will to action: sequential cerebellar contribution to voluntary movements. Neuroimage 2003;20:1485–92; with permission.)

hemodynamic response and found spatially and temporally separated cerebral and cerebellar activations, which accompanied the entire process, from conscious planning to final motor output, within a time frame of 6 seconds (Fig. 11). The cerebral activations spread from the anterior cingulate cortex through the SMA and premotor area to the primary motor and sensory cortices. This cascade was temporally in parallel with cerebellar activations propagating from the neocerebellum to the spinocerebellum. An early lateral cerebellar recruitment of 3 seconds prior to movement onset confirms its involvement in early motor planning (Fig. 12). A later medial activation occurring close to movement onset most probably reflects spinocerebellar kinesthetic feedback. Between these two points, a striking lateromedial succession was found, which is in line with the hypothesis of the existence of multiple internal models residing in the cerebellum, with each communicating with its own corresponding telencephalic region.

### *Somatosensory cancellation*

In an elegant fMRI study, Blakemore et al [35] investigated how the cerebellum uses a signaled efference copy for the prediction of central motor commands. They compared the responses when subjects experienced a tactile stimulus that was self-produced or externally applied. More activity was found in S1 when the stimulus was externally produced. In the cerebellum, less activation was associated with a movement that generated a tactile stimulus than with a movement that did not (Fig. 13). The reduction in S1 to self-produced tactile stimuli is likely to be the physiologic correlate of the reduced perception associated with this type of stimulation, whereas the selective deactivation in the right anterior lobe by self-produced tactile stimulus suggests that the cerebellum differentiates between movements depending on their specific sensory consequences. This reasoning is consistent with the theory that the cerebellum is a component of a system that provides (via an internal forward model [36]) precise prediction of the sensory consequences of motor commands, which, when congruent with the actual sensory consequences, are used to cancel the perception of a tactile stimulus.

## *Language and cognitive processing*

PET and fMRI studies have consistently reported on cerebellar activation associated with mental operations, such as memory retrieval, verbal fluency, language comprehension, and control of attention [37,38]. Neuropsychologic studies have shown that patients with focal or diffuse cerebellar pathologic findings are impaired on a wide range of cognitive tasks, especially those associated with higher executive control [39].

### *Speech production*

Although the cortical areas like the left inferior frontal lobe (Broca's area), left superior temporal lobe (Wernicke's area), and M1 bilaterally are well known to be involved in language production and comprehension, the localization and extent of cerebellum participation are less secure. fMRI investigations of speech production and singing [40] have revealed that the superior cerebellum is activated reciprocally to the concomitant cortical areas of the dominant hemisphere (ie, right-sided activation for speech and left-sided activation for singing) (Fig. 14).

Because a variety of data indicate that the cerebellum participates in speech tasks that require precise representation of temporal information, Wildgruber et al [41] have determined whether the cerebellum is prone to differences in syllable speed. Therefore, fMRI was performed during silent repetitions of the syllable "ta" at three different rates (2.5, 4.0, and 5.5 Hz). Again, as for finger tapping [31], the spatial extent and magnitude of hemodynamic responses at the level of the motor cortex showed a positive correlation to production frequencies, whereas the lower rates (2.5 and 4.0 Hz) gave rise to higher magnitudes of activation within the left putamen as compared with the 5.5-Hz condition (Fig. 15). In contrast, cerebellar responses were rather restricted to fast performance (4.0 and 5.5 Hz) and exhibited a shift in a caudal direction during 5.5 Hz as compared with 4.0 Hz. These findings corroborate the suggestion of a differential role of various cortical and subcortical areas depending on speech motor speed, and the data are closely parallel to clinical findings: extensive acoustic analyses of syllable repetition tasks in cerebellar patients found slowed maximum repetition rates that do not seem to fall below 3 Hz [42]. Presumably, these effects must be considered a characteristic sign of cerebellar dysfunction.

### *Language perception and temporal discrimination*

Access to the word form of a lexical item requires, among other functions, the processing of durational parameters of verbal utterances. Assuming the cerebellum to participate in explicit

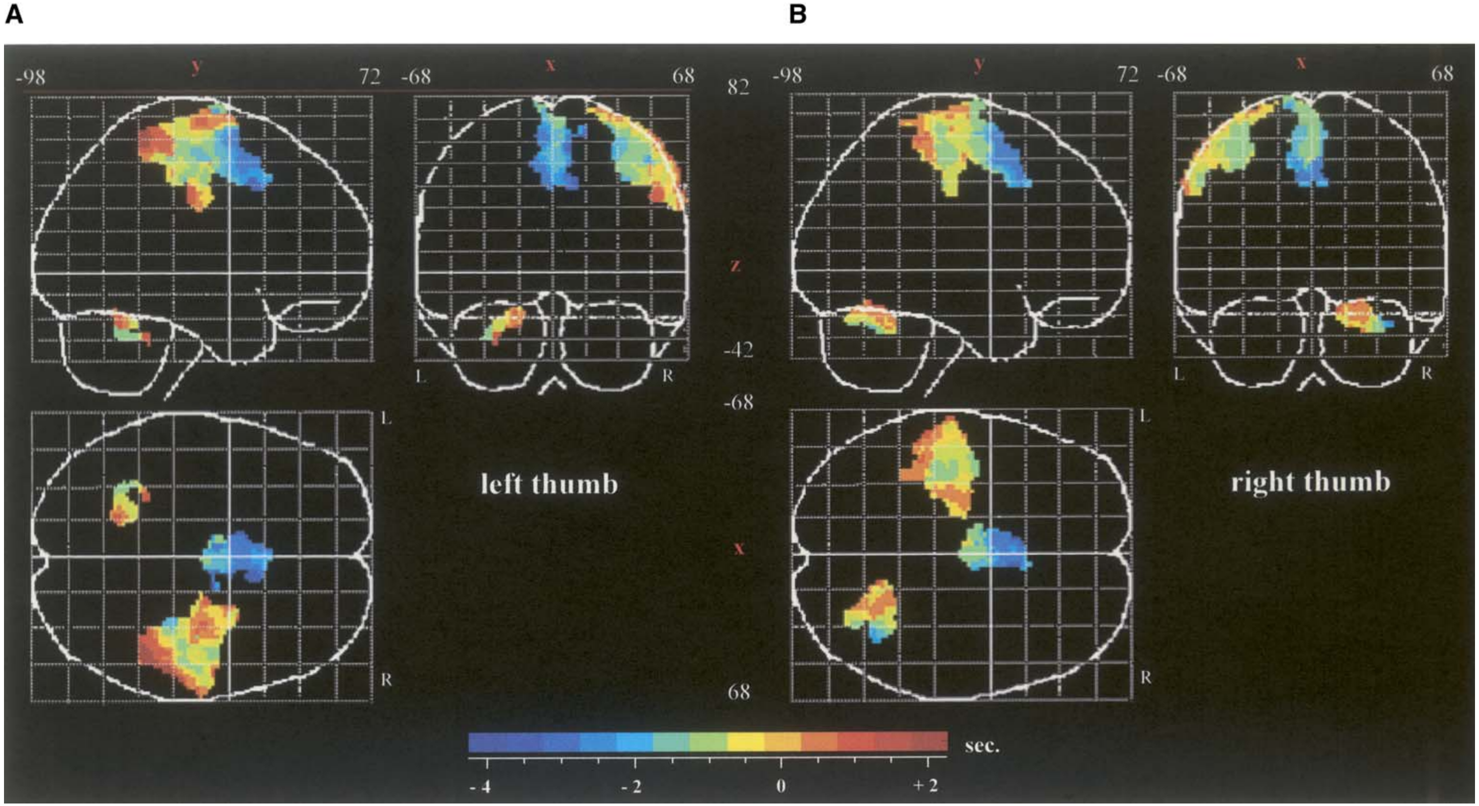


Fig. 12. Delay maps of activation during voluntary movement. Maps of single-voxel hemodynamic response function projected on axial, coronal, and sagittal planes (coordinates in millimeters; L, left; R, right) for left (*A*) and right (*B*) thumb movement as a maximum intensity projection of the time point when the projected voxels reached their maximal *t* value (for scaling, see colored bar). Note the sequential delay within the medial prefrontal cortex, the sensorimotor cortex, and the cerebellum. The progress of the cortical activation accounts for approximately 5 mm/s. (*From* Hülsmann E, Erb M, Grodd W. From will to action: sequential cerebellar contribution to voluntary movements. Neuroimage 2003;20:1485–92; with permission.)

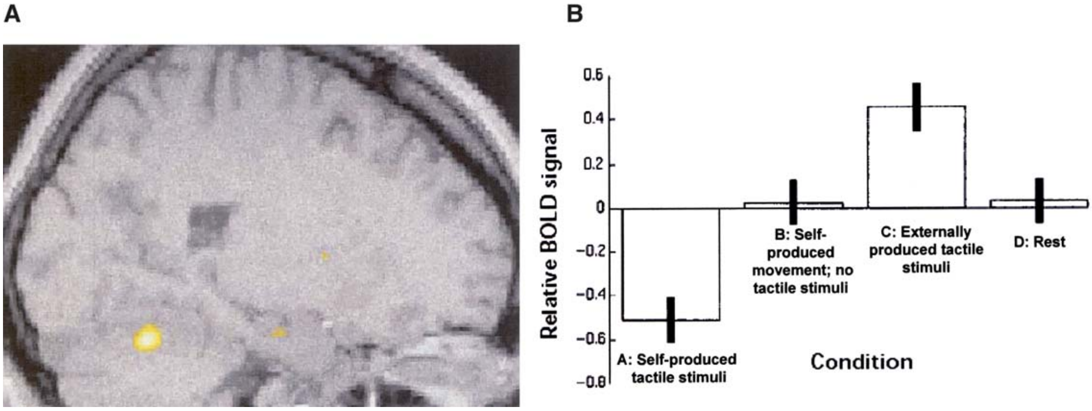


Fig. 13. Cerebellum and tickling cancellation. Significantly decreased activity in the right anterior cerebellar cortex associated with the interaction between the effects of self-generated movement and tactile stimulation for a single subject (*A*) and condition-specific parameter estimates (*B*), which reflect the adjusted blood oxygen level–dependent signal relative to the fitted mean and are expressed as a percentage of whole-brain mean activity. (*From* Blakemore SJ, Wolpert DM, Frith CD. Central cancellation of self-produced tickle sensation. Nat Neurosci 1998;1:635–40; with permission.)

timing functions, cerebellar dysfunctions should therefore impair word recognition. To specify the topography of the assumed cerebellar speech perception mechanism, an fMRI study was performed using the German lexical items "Boden" ([bodn], "floor" in English) and "Boten" ([botn], "messengers" in English) as test materials [43]. The contrast in the sound structure of these two lexical items can be signaled by the length of the wordmedial pause (closure time [CLT], an exclusively temporal measure) or by the aspiration noise of wordmedial "d" or "t" (voice onset time [VOT], an intrasegmental cue). The subjects had to identify both words by analysis of the durational parameter CLT or the VOT aspiration segment. In a subtraction design, CLT categorization as compared with VOT identification yielded a significant hemodynamic response in the right cerebellar hemisphere (neocerebellum Crus I) and in the left frontal lobe inferior to Broca's area (Fig. 16). These findings provide the first evidence for a distinct contribution of the right cerebellar hemisphere to speech perception in terms of encoding of durational parameters of verbal utterances. Verbal working memory tasks, lexical response selection, and auditory imagery of word strings have been reported to elicit activation clusters of a similar location. Conceivably, representation of the temporal structure of speech sound sequences represents the common denominator of cerebellar participation in cognitive tasks acting on a phonetic code.

Recently, Keele and Ivry [44] proposed that the cerebellum may subserve time estimation within the perceptual domain. In accordance with this suggestion, speech perception requiring minute differentiation of time intervals was found to be compromised by cerebellar pathologic findings, because patients performed significantly worse than controls when asked to compare the duration of two successive time intervals (approximately 400 milliseconds), with each bound by pairs of auditory clicks. In a rather recent fMRI study, Mathiak et al [45] suggested that the storage of precise temporal structures relies on a cerebellar-prefrontal loop. They have tested this assumption using a nonspeech task involving duration storage and comparison. The subjects performed two tasks: identifying pauses between tones as "short" or "long" (range: 30–130 milliseconds) and deciding which of two successive pauses was longer. At the level of the cerebellum, the main contrast (discrimination – identification blocks) yielded a single cluster of activation rostral to the horizontal fissure (lateral Crus l) within the right hemisphere (see Fig. 16). The pattern matches the responses found during the encoding of specific temporal aspects of speech sounds [43] and documents cerebellar involvement during an auditory duration short-term memory and comparison task. A distinct right hemisphere cerebellar activation cluster superior to the horizontal fissure emerges when identification was compared with discrimination of pause durations. These findings are in accord with clinical data demonstrating deficient perception of temporal speech cues in subjects with cerebellar atrophy. The comparison to previous findings on speech perception and

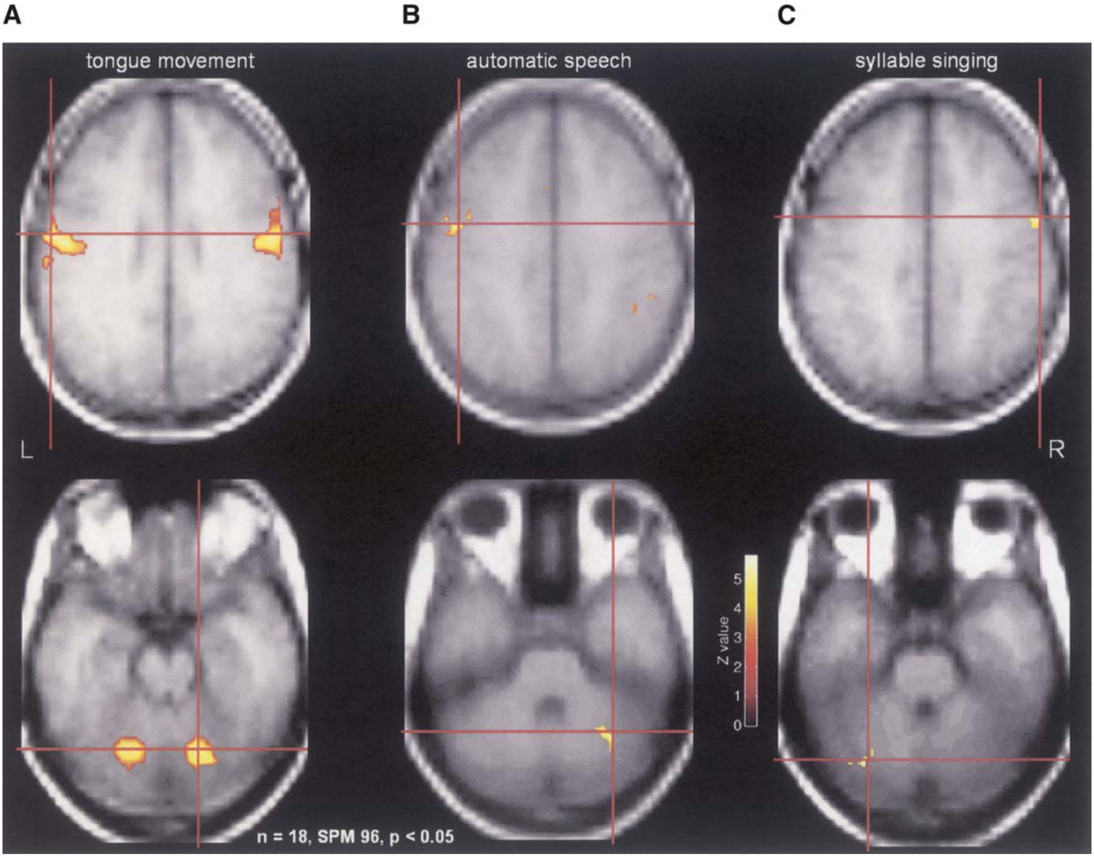


Fig. 14. Cerebellar activation during speech and singing. Functional MRI activation maps (n = 18, Statistical Parameter Mapping = 96; $P < 0.05$) at the level of the primary motor areas (*top row*) and the superior cerebellum (*bottom row*) during tongue movement (*A*), automatic speech (recitation of the name of the month) (*B*), and syllable singing (*C*). Note the shift of cerebellar activation from the right side during speech to the left side during singing. (*From* Ackermann H, Wildgruber D, Daum I, Grodd W. Does the cerebellum contribute to cognitive aspects of speech production? A functional magnetic resonance imaging (fMRI) study in humans. Neurosci Lett 1998;247:187–90; with permission.)

verbal working memory suggests that this operation on intervals is an essential component of language processing.

### *Clinical perspective and summary*

All fMRI findings reported here result exclusively from studies in healthy human subjects and can only be transferred to clinical findings in patients with cerebellar disorders with caution. Nevertheless, mapping of cerebellar function by fMRI now enables us not only to re-establish older anatomic findings of somatotopic representations but to gain new insights in the function of the cerebellum and its intimate relations to cerebral regions serving sensorimotor function, sensory discrimination, and cognitive processing. Consequently, it will change our understanding of neurologic and psychologic failures in patients with inborn errors or neurodegenerative diseases or after neurosurgical procedures.

One consideration concerning the cerebellum that may deserve greater recall than the well-acknowledged differences in size, cellular anatomy, and neuronal organization is the simple fact that the cerebrum is a structure of midline origin. Although connected to bilaterally organized inputs and outputs, the cerebellum possesses complete transverse tissue continuity, which permits unrestricted information flow across the

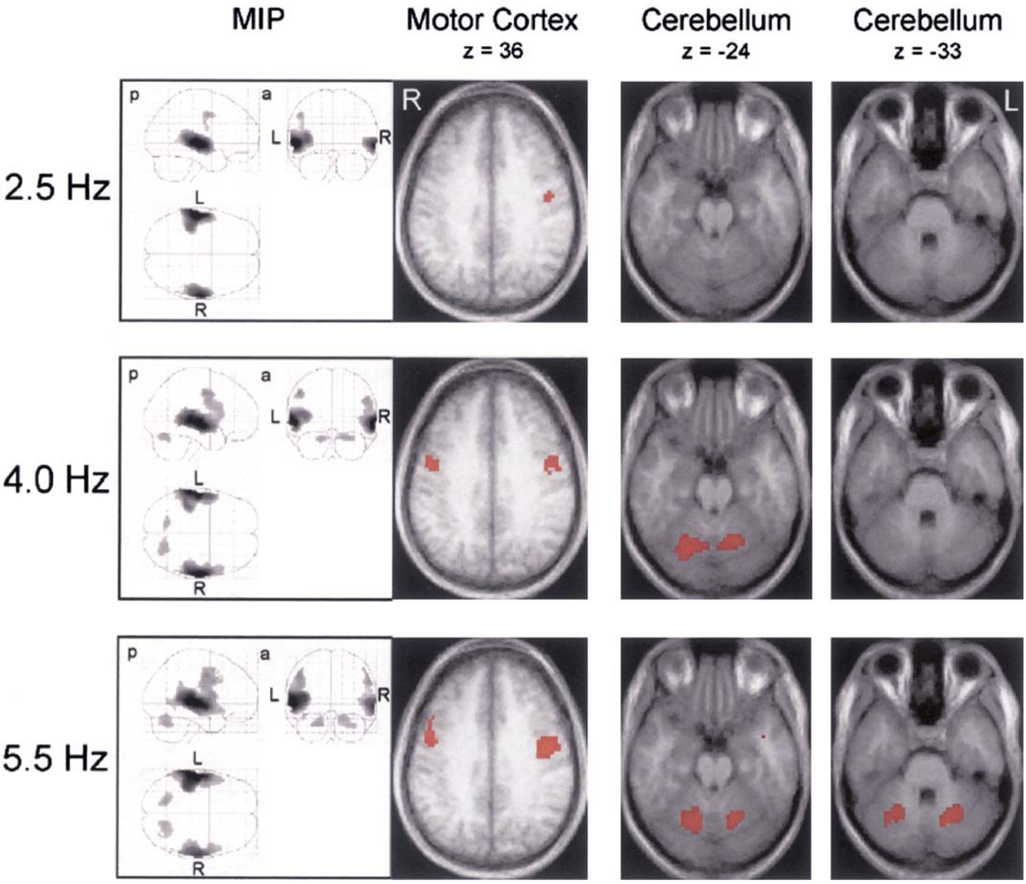


Fig. 15. Cerebellar activation and syllable repetition. Functional MRI activation during covert syllable repetitions at three different frequencies displayed as a maximum intensity projection into a glass brain (*left column*) and superimposed on three transversal planes. The distance to the intercommissural plane is given above the respective columns. Averaged anatomic images across all subjects are used as an anatomic reference (n = 10; $P < 0.05$, corrected). Note the appearance of cerebellar activation at 4 Hz and higher. (*From* Wildgruber D, Ackermann H, Grodd W. Differential contributions of motor cortex, basal ganglia, and cerebellum to speech motor control: effects of syllable repetition rate evaluated by fMRI. Neuroimage 2001;13:101–9; with permission.)

hemispheres on all levels. This is important for the functional interpretation of the cerebellum as well as for the judgment of causes for clinical symptoms in cerebellar patients and one reason for the plasticity of symptoms and their fast recovery. In this context, we finally discuss two clinical syndromes of midline cerebellar pathologic change: the posterior vermal split syndrome and the Joubert syndrome.

Bastian et al [46] first described the posterior vermal split syndrome after surgery for removal of fourth ventricle tumors in children. The immediate postoperative clinical symptoms comprise deficits of balance and stepping in tandem gait but only mild abnormalities in self-paced gait, whereas voluntary movement of the fingers, arms, and legs remains normal. All signs resolve within 3 to 4 weeks. These findings are the result of a neurosurgical procedure in which tumor access is achieved by a midline approach through lobules VI through X. Because lobules VI through X receive mainly vestibular and only sparse somatosensory and corticopontine inputs and project to the fastigial nucleus, a splitting of the median region causes a transverse disconnection syndrome across the midline, which results in a disturbance of balance and bilateral coordination of the legs.

Similar underlying pathophysiology could account for the symptomatology of the Joubert

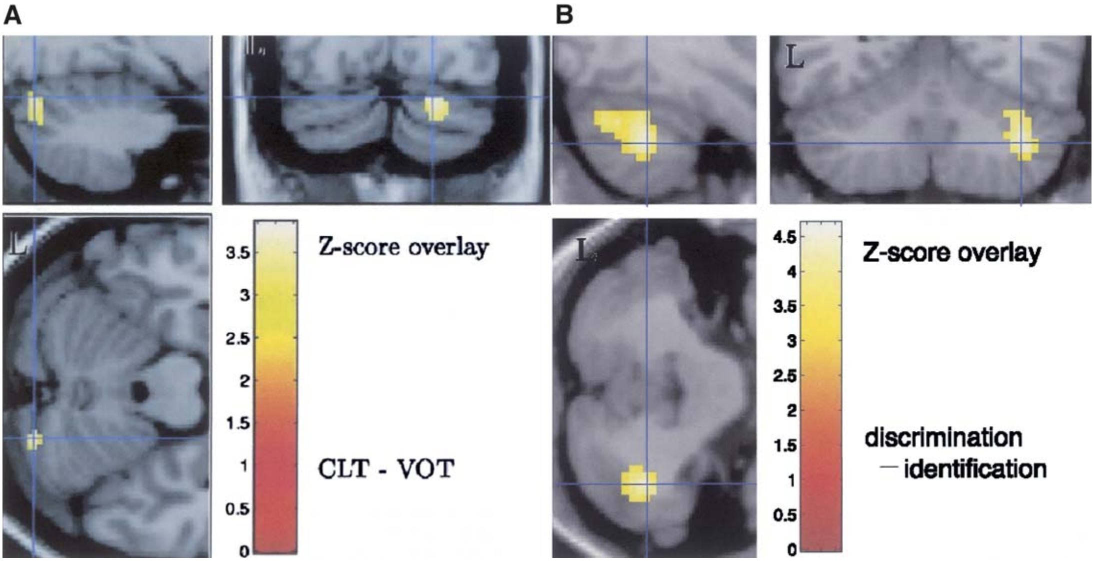


Fig. 16. Cerebellar activation in syllable and temporal discrimination. Syllable discrimination (*A*) and temporal discrimination (*B*) depicted in parasagittal, coronal, and axial views (Z-score overlay on normalized anatomic images with a threshold at $Z > 3.1$ corresponds to $P < 0.001$, uncorrected) both yield right cerebellar activation (lateral aspect of Crus I). (*A*) Decoding of the intersegmental closure time (CLT) versus the voice onset time (VOT). (*B*) Discrimination of pause durations (short versus long) versus stimulus categorization. (*A*: *From*: Mathiak K, Hertrich I, Grodd W, Ackermann H. Cerebellum and speech perception: a functional magnetic resonance imaging study. J Cogn Neurosci 2002;14:902–12; with permission. *B*: *From* Mathiak K, Hertrich I, Grodd W, Ackermann H. Discrimination of temporal information at the cerebellum: functional magnetic resonance imaging of nonverbal auditory memory. Neuroimage 2004;21:154–62; with permission.)

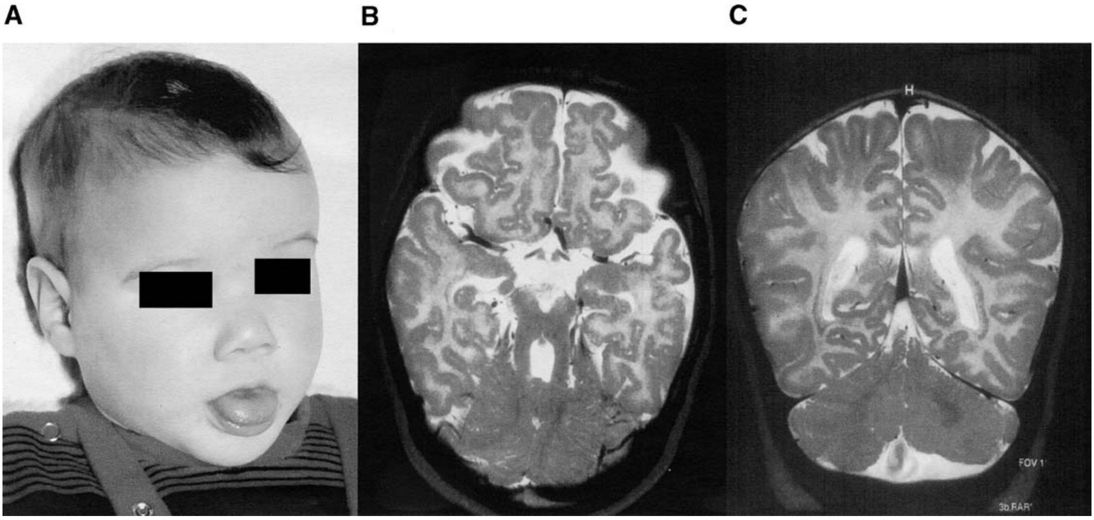


Fig. 17. Joubert syndrome. (*A*) Photograph of a 3-year-old boy with Joubert syndrome. Note the medial rotation of the eyes and the tongue protrusion. T2-weighted MRI scans in axial (*B*) and coronal (*C*) projections depicting the typical "molar tooth sign" in *B* and the missing fusion of the hemispheres because of aplasia of the vermis in *C*. (Courtesy of Prof. E. Boltshauser, Zürich, Switzerland.)

syndrome [47], a rare autosomal recessive brain malformation that is anatomically characterized by the absence or underdevelopment of the cerebellar vermis. Recent observations suggest an absence of the decussatio of the superior cerebellar peduncle and central pontine tracts as well [48]. The most common clinical features in infants include abnormally rapid breathing (hyperpnea), jerky eye movements, mental retardation, and the inability to coordinate voluntary muscle movements. MRI reveals typical features like the "molar tooth sign" in the axial plane, consisting of a deepening of the posterior interpeduncular fossa, thick and straight superior cerebellar peduncles, and vermal hypoplasia or dysplasia (Fig. 17). Knowing that the lips and mouth are represented bilaterally in lobules HVI and HVIII (see Fig. 7), the jerky eye movements and tongue protrusion accompanying the syndrome most likely reflect a lack of transverse continuity in the medial zone of lobules VI through X. Again, one can hypothesize that parallel fiber inputs to Purkinje cells across the midline are a necessary condition for bilateral coordination and for sufficient control of orofacial musculature, a consideration that was suggested by Bolk a century ago [6].

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