NGF activation of NF-κB through $p75^{NTR}$ may up-regulate the expression of such extracellular matrix proteins in Schwann cells, thereby influencing their migration during nerve regeneration (*7*).

The NGF–$p75^{NTR}$–NF-κB signaling pathway may also play a role in other pathophysiological states. NGF is, so far, unique among the neurotrophins in acting as a link between inflammation and the peripheral nervous system (*20*). NGF levels are up-regulated in inflamed tissue (*21*), and it has been shown that NGF is released by cells of the immune system (*20*), as are cytokines, which act through NF-κB. NGF is also known to be required for the hyperalgesia accompanying tissue damage, and it exerts its effects on nociceptive sensory neurons (*22*). Thus, it can be envisaged that NGF activates the $p75^{NTR}$–NF-κB pathway in a context relevant to the generation of hyperalgesia.

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Cerebellum Implicated in Sensory Acquisition and Discrimination Rather Than Motor Control

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Recent evidence that the cerebellum is involved in perception and cognition challenges the prevailing view that its primary function is fine motor control. A new alternative hypothesis is that the lateral cerebellum is not activated by the control of movement per se, but is strongly engaged during the acquisition and discrimination of sensory information. Magnetic resonance imaging of the lateral cerebellar output (dentate) nucleus during passive and active sensory tasks confirmed this hypothesis. These findings suggest that the lateral cerebellum may be active during motor, perceptual, and cognitive performances specifically because of the requirement to process sensory data.

For a century, the cerebellum has been regarded as a motor organ (*1*). Lesions to the cerebellum cause incoordinated movement (*2*), and the cerebellum is activated during movement (*3*, *4*). Recent studies of brain-injured humans revealed that the cerebellum is instrumental in nonmotor behaviors such as judging the timing of events, solving perceptual and spatial reasoning problems, and generating words according to a semantic rule (*5*). Very recently, cerebellar activity has been detected during these perceptual and cognitive behaviors (*6*) and during the mental rotation of abstract objects (*7*). Such findings challenge classical motor theories of cerebellar function. Although the cerebellum receives input from virtually every sensory system (*8*, *9*) and is activated by tactile stimulation alone (without movement) (*3*), it has not been considered a sensory organ because cerebellar lesions do not cause gross sensory deficits (*2*). However, ascertaining whether neural tissue has a motor or sensory function is a subtle problem because motor behavior is guided by ongoing sensory acquisition of object information, and motor efficiency (the accuracy, coordination, and smoothness of motor behavior) depends on continuously updated sensory data.

To dissociate sensory acquisition and discrimination from motor performance per se, we imaged blood oxygenation change, a correlate of neural activity, in the lateral (dentate) nucleus of humans as they performed tasks involving passive and active sensory discriminations. The dentate nucleus is the sole output for the large lateral hemispheres of the primate cerebellum, and its activation has usually been linked to finger movements (*10*). We tested the hypothesis (*11*) that dentate activation is more closely associated with sensory discriminations made through the fingers than with finger-movement control per se.

Six healthy volunteers performed four tasks (*12*). In the Cutaneous Stimulation (CS) task (*13*), they passively experienced sandpaper rubbed against the immobilized pads of the second, third, and fourth fingers of each hand. In the Cutaneous Discrimination (CD) task (*13*), they were asked to actively compare (without responding) whether the coarseness of the sandpaper on the two hands matched. The coarseness of the sandpaper changed randomly every 3 s. In the Grasp Objects (GO) task (*14*), they used each hand to repeatedly reach for, grasp, raise, and then drop an object. In the Grasped Objects Discrimination (GOD) task (*14*), they grasped one object with one hand while using the

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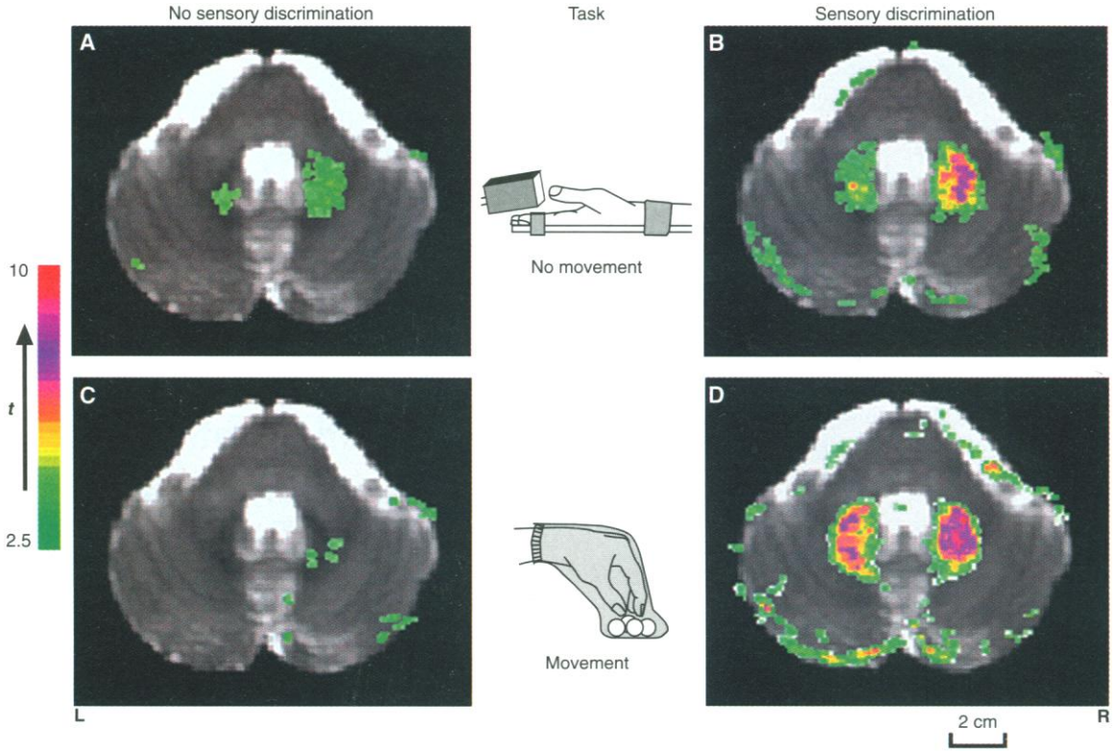

Fig. 1. Functional MRI (color) overlaid on anatomical MRI (gray), showing dentate activations for (**A**) CS, (**B**) CD, (**C**) GO, and (**D**) GOD tasks. The dentate nuclei are the two dark crescent-shaped structures on either side of the cerebellar midline. Functional and anatomical images were coregistered for each task by performing rotation, translation, and scaling on each participant's images and then averaging images across participants. A group t test, comparing task-induced changes relative to rest, was performed on these images for each task. Activation was detected with a threshold defined by t = 2.5 and a cluster of five adjacent pixels. The detected activations are statistically significant ($P < 0.05$) relative to the whole cerebellar plane sampled.

other hand to grasp another object, and they noticed covertly whether the shapes of the two objects matched. In no task did the participants see the stimuli. During each task, participants lay supine in a 1.9-T magnetic resonance imaging (MRI) instrument (*15*). An axial plane through the dentate nuclei was identified with a T_2 scout image and was then functionally mapped with T_2* gradient-echo images (*16*, *17*). Task-induced changes (task minus rest) were detected by a pixel-clustering analysis of response intensity and spatial extent (*18*).

The cerebellar output nuclei showed significant task-induced increases in blood flow (Figs. 1 to 3) during the CS task. Thus, dentate nuclei are activated by purely sensory stimuli; this finding confirms positron-emission tomography results that show cerebellar activation during hand vibration (*3*). This activation was equally strong in the left and right dentate but tended to be more extensive in the right dentate, probably reflecting the left cerebral dominance of the right-handed participants. Known anatomical connections (*8*, *19*) may enable cerebellar participation in such sensory processing.

When the same stimuli were presented under identical conditions and a discrimination was required (CD task), dentate nuclei were more than twice as active ($P < 0.05$) (Figs. 1 to 3). This activation was bilateral but was stronger in the right dentate. The enhanced activity could reflect the anatomical connections between these cerebellar regions and the prefrontal cortex that supports working memory processes (*20*) that are possibly necessary for discrimination.

We also compared cerebellar activation in a sensory discrimination task that required rapid coordinated finger movements (GOD) to that in a control task that required similar movements but did not require discrimination (GO). The GO task produced very slight, statistically insignificant activation (Figs. 1 to 3). The slight activation likely reflected cutaneous stimulation of the fingers that touched the stimuli (*14*). The lack of activation in the GO task confirmed that rapid, coordinated, fine finger movements, in the absence of a sensory discrimination, do not engage the dentate nucleus. This response matches the slight dentate activity recorded in another fine motor behavior (visually guided reaching and grasping of a peg) (*21*). The fact that active finger movements do not alone significantly activate the dentate nuclei indicates that, even if participants made finger movements during either cutaneous task that were too slight to be detected by the experimenters (*13*), those

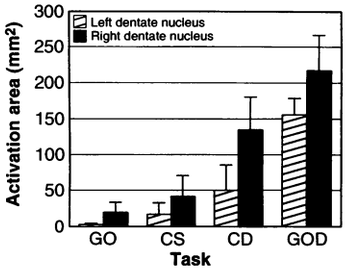

Fig. 2. Activation area in the dentate nuclei for each task. A group t test was applied to each participant's data for each task compared with rest. Then, for each participant, activation foci were detected by selecting areas with $t > 2.5$ and at least five adjacent pixels (corresponding in combination to $P < 0.05$). The mean (±SEM) of these activated foci was calculated for each task across participants.

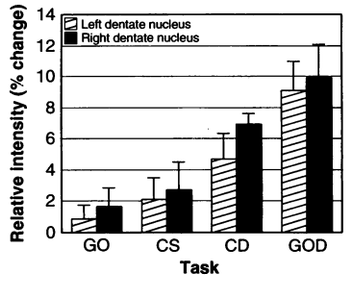

Fig. 3. Intrinsic relative signal changes at the activation area in the dentate nuclei for each task. A group t test was applied to each participant's data for each task compared with rest. Then, for each participant, activation foci were detected by selecting areas with $t > 2.5$ and at least five adjacent pixels (corresponding in combination to $P < 0.05$). For each participant, the relative signal change was calculated in the above-threshold activation areas by subtracting the average signal value during rest from that during the task and dividing by the average signal value during rest. The mean relative signal change (±SEM) was calculated for each task across participants.

movements per se would not cause the significant activations.

By far the strongest activation (Figs. 1 to 3) occurred during the GOD task. Again, the right dentate was slightly more active than the left. The extreme contrast ($P < 0.005$) between the degree of dentate activation in the two grasping tasks provides evidence of strong cerebellar support for sensory discrimination.

Together, these data rule out the conclusion that the greater cerebellar activity in the GOD task may reflect fine motor control. The GO task, which requires similarly fine motor control, produces no significant dentate activation. Thus, fine movement control per se does not engage the dentate, in contrast to sensory stimulation per se. The massive increase in activity in the GOD task relative to that in the GO task is entirely out of proportion to the subtle differences that may exist between the two tasks' very similar movements. The chief difference in movements—that the GOD task was performed at a slightly slower pace—would wrongly predict a decrease in activation because motor performance rate and activation strength are positively correlated (*22*).

Thus, our results implicate the dentate nucleus of the human cerebellum in sensory acquisition and discrimination. Activation occurred during sensory stimulation, when there were no accompanying overt finger movements or discrimination. Substantial finger movements, when not associated with tactile discrimination, did not induce significant activation. Dentate activation was greatly enhanced when a sensory discrimination was required, with or without overt finger movements. However, the strongest activation occurred when sensory discrimination was paired with finger movements.

Although these findings implicate the lateral cerebellum in sensory discrimination rather than in movement per se, they do not identify its specific role. For example, the greater increase in dentate activity for the GOD task may simply result from the multidimensional complexity of this sensory processing task compared with the unidimensional nature of the CD task. Nevertheless, the interpretation closest to our hypothesis (*11*) is that greater cerebellar activation during active manipulation reflects a direct role of the cerebellum in modulating the motor control system to reposition the tactile sensory surfaces of the fingers. This coordination may be based on the cerebellar analysis of the sensory information actually being acquired, and it may serve to ensure that the highest quality data about object shape are being obtained in a coordinated fashion from all finger surfaces.

These findings are not inconsistent with the principal effects of cerebellar damage on human movement. Cerebellar deficits in voluntary movement, such as incoordination and ataxia, may reflect disruption of the sensory data (from the medial cerebellum–controlled muscle spindle system) on which the motor system depends, rather than disruption of cerebellar computations of smooth motor performance per se (*11*). Our results are also not inconsistent with data from neurophysiological studies of awake animals that have been interpreted to implicate the cerebellum in motor behavior, because the sensory and motor components of task performance have not been well dissociated.

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12. Participants in the CS and CD tasks were males, ages 32 to 44 (mean, 38). Five members of this group and a female (age 30) did the GO and GOD tasks. All participants gave informed consent and practiced each task for 10 min. In one session, they performed three cycles of rest control, CS, and CD; in another, they performed three cycles of rest control, GO, and GOD.
13. In the CS and CD tasks, movements were prevented by immobilization and instruction. The arm was immobilized by straps encircling the body. The wrist, hand, and fingers were immobilized by a rigid wooden surface affixed to the dorsum of the hand by tape encircling the wrist and fingers. During stimulation, participants were instructed to allow the hand to remain flaccidly immobile, resting in the restraints. Sandpaper was applied to the finger pads by a continuous oscillation uncoordinated between hands. Four grades of sandpaper were used: 60, 100, 150, or 400 (U.S.A. Standard Grading system; maximal packing of grains of sand of 268, 141, 33, and 23.6 μm size, respectively). As the sandpaper was mildly aversive, involuntary movements toward the stimuli were unlikely. Involuntary movements away from the stimuli were prevented by the rigid surface to which the fingers were attached. Because electromyography cannot be performed within the MRI bore, participants were visually monitored for movement throughout each trial. No movements were observed.
14. In the two grasping tasks, each (unrestrained) hand was enclosed in its own tightly woven cotton sock; each sock contained an identical set of four different stimuli. Each stimulus was a smooth wooden sphere 2.5 cm in diameter; the stimuli were differentiated by one, two, or three additional planar surfaces. In the GO task, participants reached and grasped, in pincer fashion, a stimulus at random and then raised and dropped it. This sequence was repeated continuously and was performed independently by each hand. In the GOD task, participants grasped a stimulus with the left hand, felt its shape while using the right hand to grasp and feel another stimulus, and noticed whether the two objects were identical in shape. If the objects were different, the object in the right hand was dropped and another object was grasped and compared with the object in the left hand. If the objects matched, participants released both stimuli and immediately began a new cycle, using the opposite hand to grasp the reference object.
15. The MRI images were made with a whole-body MRI system operating at 81 MHz (Gyrex; Elscint, Haifa, Israel). The participant's head was immobilized with a facial mask. A body coil was used for the radiofrequency transmission. The signal was received by a quadrature surface coil (US Asia Instruments, Highland Heights, OH).
16. High-resolution multiple T_2-weighted spin-echo images in the transverse plane covering the cerebellum were acquired to locate the dentate nucleus. A single (6 mm) slice through the dentate was selected. Typically, the T_2*-weighted images were collected by a conventional gradient-echo sequence with three cycles of rest control and each of two tasks. Twenty images were acquired for each task within each cycle (7.8 s per image). Imaging parameters were as follows: echo time, 40 ms; repetition time, 60 ms; flip angle, 20°. Images were acquired with 256 complex pairs in the readout direction and 128 phase-encoding steps in a field of view 25.6 cm by 25.6 cm, with an in-plane spatial resolution of 1 mm by 2 mm.
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18. The acquired 128 × 256 functional MRI data were zero-filled to 256 × 256 and were then Fourier-transformed. Maps of functional activation were calculated by comparison of T_2*-weighted images acquired during rest control with those acquired during tasks [J. Xiong, J.-H. Gao, J. L. Lancaster, P. T. Fox, *Hum. Brain Mapp.* **3**, 287 (1995)]. Activation (Figs. 2 and 3) was defined by the combination of two criteria to afford a 0.05 level of statistical significance. A *t* test was used to compare the resting baseline with task activation, and only pixels with a significant activation ($t > 2.5$) were included in the functional map. Regions with less than five contiguous activated pixels were then excluded. The resulting functional map was laid over a T_2*-weighted image to determine activation sites. The area of activation used for comparisons was the number of activated pixels within the dentate nuclei. Omnibus statistics and planned comparisons were made with separate analyses of variance and Newman-Keuls tests of participants' activation area values and intensity values for left and right dentate nuclei.
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