Cerebellum and Nonmotor Function

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Abstract

Does the cerebellum influence nonmotor behavior? Recent anatomical studies demonstrate that the output of the cerebellum targets multiple nonmotor areas in the prefrontal and posterior parietal cortex, as well as the cortical motor areas. The projections to different cortical areas originate from distinct output channels within the cerebellar nuclei. The cerebral cortical area that is the main target of each output channel is a major source of input to the channel. Thus, a closed-loop circuit represents the major architectural unit of cerebro-cerebellar interactions. The outputs of these loops provide the cerebellum with the anatomical substrate to influence the control of movement and cognition. Neuroimaging and neuropsychological data supply compelling support for this view. The range of tasks associated with cerebellar activation is remarkable and includes tasks designed to assess attention, executive control, language, working memory, learning, pain, emotion, and addiction. These data, along with the revelations about cerebro-cerebellar circuitry, provide a new framework for exploring the contribution of the cerebellum to diverse aspects of behavior.

Contents

> "In biology, if seeking to understand function, it is usually a good idea to study structure." (Crick & Koch 2005, p. 6)

This statement by Crick & Koch is especially applicable to the functions of the cerebellum. We believe that important insights into cerebellar function can be gained from an anatomical analysis of cerebellar output. Indeed, recent results indicate that a major component of cerebellar output targets nonmotor areas of the cerebral cortex. This feature of cerebellar structure suggests the cerebellum influences not only the generation and control of movement but also nonmotor aspects of behavior.

In this chapter we review new evidence about the areas of the cerebral cortex that are the target of cerebellar output. We describe the functional map that has recently been discovered within one of the major output nuclei of the cerebellum, the dentate nucleus. We present evidence that the fundamental unit of cerebro-cerebellar operations is a closed-loop circuit. Finally, we provide clear examples from imaging and lesion studies that the cerebellum has a nonmotor function.

The cerebellum is massively interconnected with the cerebral cortex. The classical view of these interconnections is that the cerebellum receives information from widespread cortical areas, including portions of the frontal, parietal, temporal, and occipital lobes (**Figure 1**) (Glickstein et al. 1985, Schmahmann 1996). This information was then thought to be funneled through cerebellar circuits where it ultimately converged on the ventrolateral nucleus of the thalamus (e.g., Allen & Tsukahara 1974, Brooks & Thach 1981). The ventrolateral nucleus was believed to project to a single cortical area, the primary motor cortex (M1). Thus, cerebellar connections with the cerebral cortex were viewed as a means of collecting information from widespread regions of the cerebral cortex. The cerebellum was thought to perform a sensorimotor transformation on its inputs and convey the results to M1 for the generation and control of movement. According to this view, cerebellar output was entirely within the domain of motor control, and abnormal activity in this circuit would lead to purely motor deficits.

Our continuing analysis of cerebellar output and function has led us to challenge this view (e.g., Akkal et al. 2007; Ben-Yehudah & Fiez 2008; Ben-Yehudah et al. 2007; Clower et al. 2001, 2005; Dum & Strick 2003; Fiez 1996; Hoover & Strick 1999; Kelly & Strick 2003; Middleton & Strick 1994, 1996a, b, 2001; Schell & Strick 1984). It is now clear that efferents from the cerebellar nuclei project to

M1: primary motor cortex

multiple subdivisions of the ventrolateral thalamus (for a review, see Percheron et al. 1996), which, in turn, project to a myriad of cortical areas, including regions of frontal, prefrontal, and posterior parietal cortex (Jones 1985). Thus, the outputs from the cerebellum influence more widespread regions of the cerebral cortex than previously recognized. This change in perspective is important because it provides the anatomical substrate for the output of the cerebellum to influence nonmotor as well as motor areas of the cerebral cortex. As a consequence, abnormal activity in these circuits could lead not only to motor deficits but also to cognitive, attentional, and affective impairments. Below, we provide additional support for this new perspective based on the analysis of focal lesions of the cerebellum and activation of the cerebellum during nonmotor tasks.

Prior neuroanatomical approaches for examining cerebro-cerebellar circuits have been hindered by a number of technical limitations. Chief among these is the multisynaptic nature of these pathways and the general inability of conventional tracers to label more than the direct inputs and outputs of an area. To overcome these and other problems, we developed the use of neurotropic viruses as transneuronal tracers in the central nervous system of primates (for references and a review, see Kelly & Strick 2000, 2003; Strick & Card 1992). Selected strains of virus move transneuronally in either the retrograde or anterograde direction (Kelly & Strick 2003, Zemanick et al. 1991). Thus, one can examine either the inputs to or the outputs from a site. The viruses we use as tracers move from neuron to neuron exclusively at synapses, and the transneuronal transport occurs in a time-dependent fashion. By careful adjustment of the survival time after a virus injection, we were able to study neural circuits composed of two or even three synaptically connected neurons. We used virus tracing to examine cerebello-thalamocortical pathways to a wide variety of cortical areas (Akkal et al. 2007; Clower et al. 2001, 2005; Hoover & Strick 1999; Kelly & Strick 2003; Lynch et al. 1994; Middleton & Strick 1994, 1996a, b, 2001) (**Figure 2**).

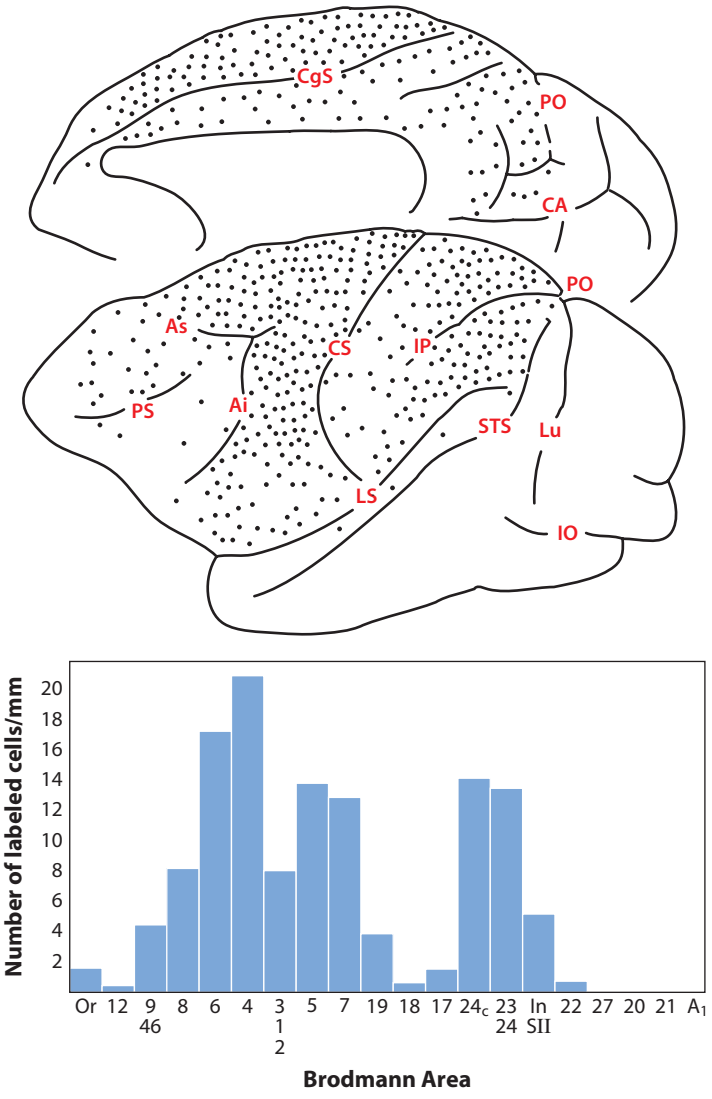

Figure 1

Origin of projections from the cerebral cortex to the cerebellum. (*Top*) The relative density of corticopontine neurons is indicated by the dots on lateral and medial views of the macaque brain. (*Bottom*) Histogram of relative density of corticopontine cells in different cytoarchitectonic areas of the monkey. Ai, As, inferior and superior limbs of arcuate sulcus, respectively; CA, calcarine fissure; CgS, cingulate sulcus; CS, central sulcus; IP, intraparietal sulcus; LS, lateral sulcus; Lu, lunate sulcus; IO, inferior occipital sulcus; PO, parietal-occipital sulcus; PS, principal sulcus; STS, superior temporal sulcus. Adapted from Glickstein et al. 1985, published in *The Journal of Comparative Neurology*, Vol. 235, No. 3, 1985, pp. 343–59. Copyright © 1985. Alan R. Liss, Inc. Reprinted with permission of John Wiley & Sons, Inc.

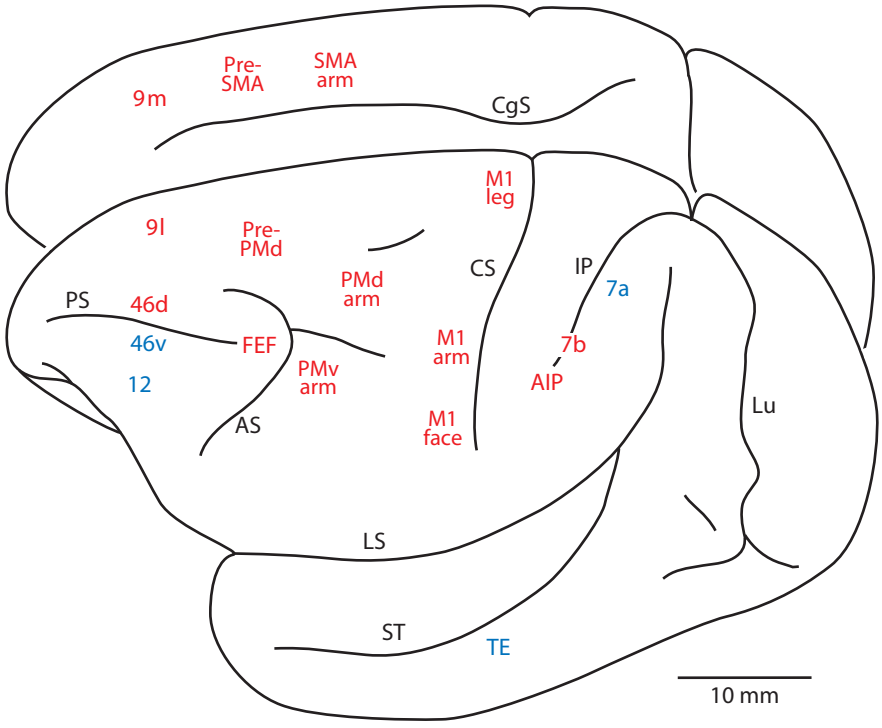

Figure 2

Targets of cerebellar output. Red labels indicate areas of the cerebral cortex that are the target of cerebellar output. Blue labels indicate areas that are not the target of cerebellar output. These areas are indicated on lateral and medial views of the cebus monkey brain. The numbers refer to cytoarchitectonic areas. AIP, anterior intraparietal area; AS, arcuate sulcus; CgS, cingulate sulcus; FEF, frontal eye field; IP, intraparietal sulcus; LS, lateral sulcus; Lu, lunate sulcus; M1, face, arm, and leg areas of the primary motor cortex; PMd arm, arm area of the dorsal premotor area; PMv arm, arm area of the ventral premotor area; PrePMd, predorsal premotor area; PreSMA, presupplementary motor area; PS, principal sulcus; SMA arm, arm area of the supplementary motor area; ST, superior temporal sulcus; TE, area of inferotemporal cortex.

CEREBELLAR OUTPUT CHANNELS

In our initial studies, we injected virus into physiologically defined portions of M1 and set the survival time to label second-order neurons in the deep cerebellar nuclei (Hoover & Strick 1999). In general, cerebellar projections to M1 originate largely from neurons in the dentate nucleus (75%), although a smaller component also originates from interpositus (25%). Our description focuses on the organization of the dentate. The dentate nucleus is a complex three-dimensional structure (**Figure 3**). Therefore, we created an unfolded map of the nucleus to display observations from different experiments in a common framework (**Figure 4**) (Dum & Strick 2003).

Virus transport following injections into the arm representation of M1 labeled a compact cluster of neurons in the dorsal portion of the dentate at mid-rostro-caudal levels (**Figure 2**; **Figure 3**, far right panel; **Figure 4**, top center panel). Virus transport from the leg representation of M1 labeled neurons in the rostral pole of the dorsal dentate (**Figure 2**; **4**, top left panel), whereas virus transport from the face representation labeled neurons at caudal levels of the dorsal dentate (**Figures 2**; **Figure 4**, top right panel). Clearly, each cortical area receives input from a spatially separate set of neurons in the

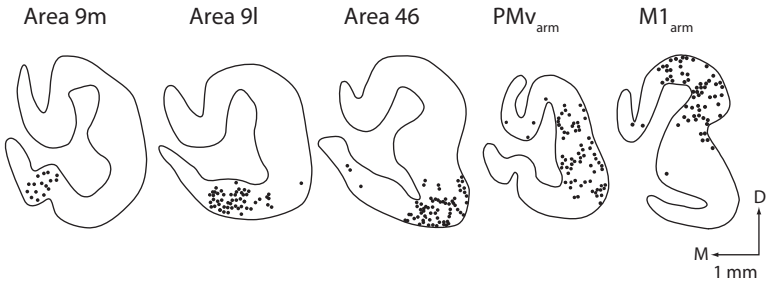

Figure 3

Output channels in the dentate. The dots on representative coronal sections show the location of dentate neurons that project to a specific area of the cerebral cortex in the cebus monkey. The cortical target is indicated above each section. [Abbreviations are according to **Figure 2** (M1, primary motor cortex; PMv, ventral premotor area)]. D, dorsal; M, medial. Adapted from Middleton & Strick 1996b.

dentate, which we have termed an output channel (Middleton & Strick 1997). The rostral to caudal sequence of output channels to the leg, arm, and face representations in M1 (**Figure 4**, top panels; **Figure 5**) corresponds well with the somatotopic organization of the dentate previously proposed on the basis of physiological studies (e.g., Allen et al. 1978, Stanton 1980, Rispal-Padel et al. 1982, Asanuma et al. 1983, Thach et al. 1993).

The region of the dentate that contains neurons that project to M1 occupies only 30% of the nucleus (Dum & Strick 2003, Hoover & Strick 1999). This implies that a substantial portion of the dentate projects to cortical targets other than M1. To test this proposal and define the cortical targets of the unlabeled regions of the dentate, we injected virus into selected premotor, prefrontal, and posterior parietal areas of the cortex (**Figure 2**).

Virus transport from the arm representations of the ventral premotor area (PMv) and the supplementary motor area (SMA) demonstrated that both cortical areas are the target of cerebellar output (**Figure 2**) (Akkal et al. 2007, Middleton & Strick 1997). The output channels to these premotor areas are located in the same region of the dentate that contains the output channel to arm M1 (**Figures 3**, **5**). We have speculated that the clustering of output channels to M1 and the premotor areas in the dorsal region of the dentate creates a motor domain within the nucleus (**Figure 5**) (Dum & Strick 2003). Furthermore, the output channels to the arm representations of these motor areas appear to be in register within the dentate. This raises the possibility that the nucleus contains a single integrated map of the body within the motor domain.

Virus transport following injections into prefrontal cortex revealed that some subfields are the target of dentate output, whereas others are not (Middleton & Strick 1994, 2001). Dentate output channels project to areas 9m, 9l, and 46d, but not to areas 12 and 46v (**Figures 2–5**). Importantly, the extent of the dentate that is occupied by an output channel to a specific area of prefrontal cortex is comparable to that occupied by an output channel to a cortical motor area (**Figure 4**). Thus, it is likely that the signal from the dentate to prefrontal cortex is as important as its signal to one of the cortical motor areas. In addition, dentate output channels to areas of prefrontal cortex are located in a different region of the nucleus than the output channels to the cortical motor areas. The output channels to prefrontal cortex are clustered together in a ventral region of the nucleus that is entirely outside the motor domain. The output channels to prefrontal cortex are also rostral to the output channel that targets the frontal eye field (Lynch et al. 1994).

Although the presupplementary motor area (PreSMA) has traditionally been included with

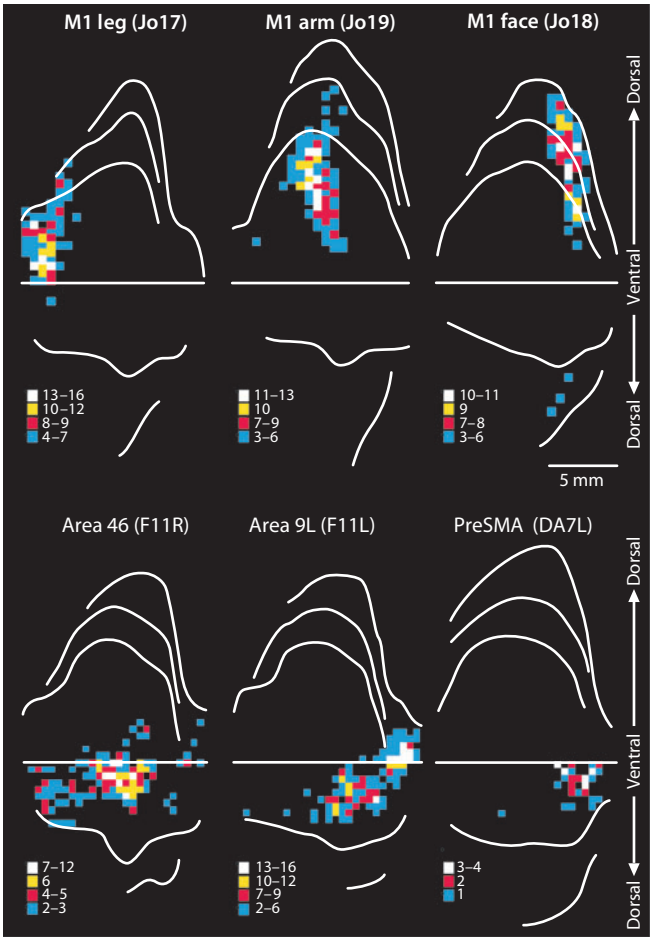

Figure 4

Unfolded maps of the dentate: output channels to different areas of the cerebral cortex in the cebus monkey. (*Top panels*) Somatotopic organization of output channels to leg, arm, and face M1 in the dorsal dentate. (*Bottom panels*) Ventral location of output channels to prefrontal cortex. The key below each diagram indicates the density of neurons in bins through the nucleus. Rostral is to the left. [Abbreviations are according to **Figure 1** (M1, primary motor cortex; PreSMA, presupplementary motor area)]. Adapted from Dum & Strick 2003 (which includes a detailed description of the unfolding method).

the motor areas of the frontal lobe, we argue that it should be considered a region of prefrontal cortex (for reviews, see Akkal et al. 2007, Picard & Strick 2001). In support of this proposal, virus transport from the PreSMA labeled an output channel in the ventral dentate where the output channels to areas 9 and 46 are located (**Figure 2**; **Figure 4**, bottom; **Figure 5**). This result illustrates that the topographic arrangement of output channels in the dentate does not mirror the arrangement of their targets in the cerebral cortex. For example, the PreSMA is adjacent to the SMA on the medial surface of the hemisphere (**Figure 2**), but the output channels to the two cortical areas are spatially separated from one another in the dentate (**Figure 5**). Thus, the topographic arrangement of output channels in the dentate appears to reflect functional relationships between cortical areas rather than the spatial relationships among them.

Virus transport from regions of posterior parietal cortex demonstrated that some of its subfields are also the target of output channels located in the dentate (**Figures 2**, **5**) (Clower et al. 2001, 2005). For example, area 7b, which in the cebus monkey is located laterally in the intraparietal sulcus, is the target of an output channel located ventrally in the caudal pole of the dentate (**Figure 5**). A second region of posterior parietal cortex, the anterior intraparietal area (AIP), receives a focal projection from a small cluster of neurons that is located dorsally in the dentate at mid-rostro-caudal levels. In addition, the AIP receives a broadly distributed projection from neurons that are scattered in dentate regions that contain output channels to M1, the PMv, and perhaps other premotor areas. This creates a unique situation in which AIP may receive a sample of the dentate output that is streaming to motor areas in the frontal lobe, as well as input from its own separate output channel. There is additional preliminary evidence that regions of the medial and lateral banks of the intraparietal sulcus are the target of cerebellar output (Ugolini et al. 2006). However, area 7a, which is located on the inferior parietal lobule (**Figure 2**), does not receive substantial input from the dentate or other cerebellar nuclei (Clower et al. 2001). Currently, the information about cerebellar projections to areas in posterior parietal cortex is complex and incomplete. It is clear, however, that several areas in this cortical region are the target of output channels from the ventral dentate.

TOPOGRAPHY OF FUNCTION WITHIN THE DENTATE

We coalesced the unfolded maps from individual experiments into a single summary diagram where the average location of each output channel is indicated (**Figure 5**). This summary diagram emphasizes several notable features about the topographic organization of the dentate. A sizeable portion of the nucleus projects to parts of the prefrontal and posterior parietal cortex. The output channels to prefrontal and posterior parietal areas are clustered in a ventral and caudal region of the nucleus. Consequently, these output channels are spatially segregated from those in the dorsal dentate that target motor areas of the cortex. Thus, the dentate appears to be spatially subdivided into separate motor and nonmotor domains that focus on functionally distinct cortical systems. Another feature emphasized by the summary diagram is that the cortical targets for large portions of the dentate remain to be determined.

MOLECULAR GRADIENTS IN THE DENTATE

The division of the dentate into separate motor and nonmotor domains is reinforced by underlying molecular gradients within the nucleus (Akkal et al. 2007, Dum et al. 2002, Fortin et al. 1998, Pimenta et al. 2001). Fortin et al. (1998) reported that immuno-staining for two calcium binding proteins, calretinin and parvalbumin, is greatest in ventral regions of the squirrel monkey dentate. A monoclonal antibody, 8B3, which recognizes a chondroitin sulfate proteoglycan on subpopulations of neurons, also differentially stains the dentate in cebus monkeys and macaques (Akkal et al. 2007, Dum et al. 2002, Pimenta et al. 2001). Immunoreactivity for 8B3 is most intense in ventral regions of the dentate that project to prefrontal and posterior parietal areas of cortex. In contrast, antibody staining is least intense in the dorsal regions of the nucleus that project to the cortical motor areas. These observations suggest that 8B3 recognizes a significant portion of the nonmotor domain within the dentate. Our measurements indicate that approximately 40% of the nucleus is intensely stained by 8B3. This analysis does not include the caudal portion of the dentate,

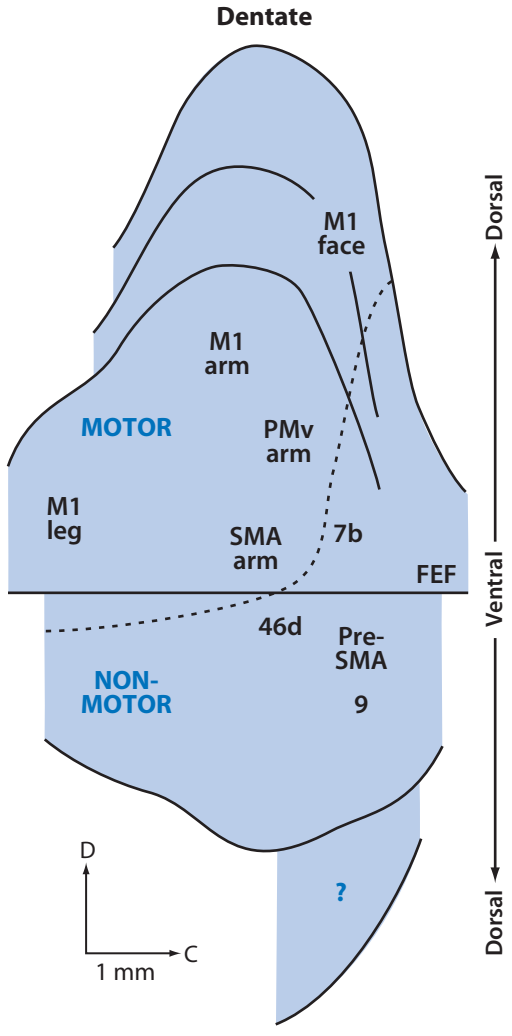

Figure 5

Summary map of dentate topography. The lettering on the unfolded map indicates the cortical target of different output channels in the cebus monkey. The location of different output channels divides the dentate into motor and nonmotor domains. Staining for monoclonal antibody 8B3 is most intense in the nonmotor domain. The dashed line marks the limits of intense staining for this antibody. The designation of the region marked by "?" is unclear. [Abbreviations as in **Figure 2** (FEF, frontal eye field; M1, primary motor cortex; PMv, ventral premotor area; Pre-SMA, presupplementary motor area; SMA, supplementary motor area)]. Adapted from Dum & Strick 2003 and Akkal et al. 2007.

(marked by a "?" in **Figure 5**) because this region does not stain intensely for 8B3 and we have yet to determine its cortical target. However, based on its location, we suspect that this caudal region projects to a nonmotor area of the cerebral cortex. If this is the case, then the nonmotor domain of the dentate may represent as much as 50% of the nucleus in the cebus monkey.

HUMAN DENTATE

It has long been recognized that the human dentate is composed of a dorsal, microgyric portion and a ventral, macrogyric portion (for references and illustration, see Voogd 2003). Compared with the microgyric dentate, the macrogyric dentate is reported to (*a*) develop later, (*b*) have smaller cells, (*c*) display a selective vulnerability in cases of neocerebellar atrophy, and (*d*) have a higher iron content. This last observation suggests that molecular gradients may exist within the human dentate as they do in the monkey dentate; however, this possibility remains to be tested. Comparative studies suggest that the dentate has expanded in great apes and humans relative to the other cerebellar nuclei (Matano et al. 1985). Furthermore, most of this increase appears to be due to an expansion in the relative size of the ventral half of the dentate (Matano 2001). This observation implies that the nonmotor functions of the dentate grow in importance in great apes and humans.

MACRO-ARCHITECTURE OF CEREBRO-CEREBELLAR LOOPS

The cortical areas that are the target of cerebellar output also project via the pons to the cerebellar cortex (Glickstein et al. 1985, Schmahmann 1996). This observation suggests that cerebro-cerebellar connections may form a closed-loop circuit. We have tested this concept for a representative motor area (the arm area of M1) and a nonmotor area (area 46 in the prefrontal cortex) (Kelly & Strick 2003). In essence, we examined whether a specific region of the cerebellar cortex both receives input from and projects to the same area of the cerebral cortex.

We used retrograde transneuronal transport of rabies virus to define the Purkinje cells in cerebellar cortex that project to M1 or to area 46. The arm area of M1 receives input from Purkinje cells located mainly in lobules IV–VI of the cerebellar cortex (**Figure 6**, left panel). In contrast, area 46 receives input from Purkinje cells located mainly in Crus II of the ansiform lobule (**Figure 6**, right panel). We saw no evidence of overlap between the two systems. Thus, the two areas of the cerebral cortex are the target of output from Purkinje cells that are located in separate regions of the cerebellar cortex. Clearly, the separation of motor and nonmotor functions seen in the dentate nucleus extends to the level of the cerebellar cortex.

In separate experiments, we used anterograde transneuronal transport of a herpes virus to define the granule cells in cerebellar cortex that receive input from M1 or from area 46. The arm area of M1 projects to granule cells located mainly in lobules IV–VI, whereas area 46 projects to granule cells mainly in Crus II. Again, each cerebral cortical area projects to granule cells that are located in a separate region of the cerebellar cortex. Moreover, these findings indicate that the regions of the cerebellar cortex that receive input from M1 are the same as those that project to M1. Similarly, the regions of the cerebellar cortex that receive input from area 46 are the same as those that project to area 46. Thus, M1 and area 46 form separate, closed-loop circuits with different regions of the cerebellar cortex (**Figure 7**). Altogether, these observations suggest that multiple closed-loop circuits represent a fundamental architectural feature of cerebro-cerebellar interactions.

There are a number of important functional implications to these results. They suggest that the cerebellar cortex is not functionally homogeneous. Instead, our results imply that cerebellar cortex contains localized regions that are interconnected with specific motor or nonmotor areas of the cerebral cortex. In fact, we have argued that the map of function in the cerebellar

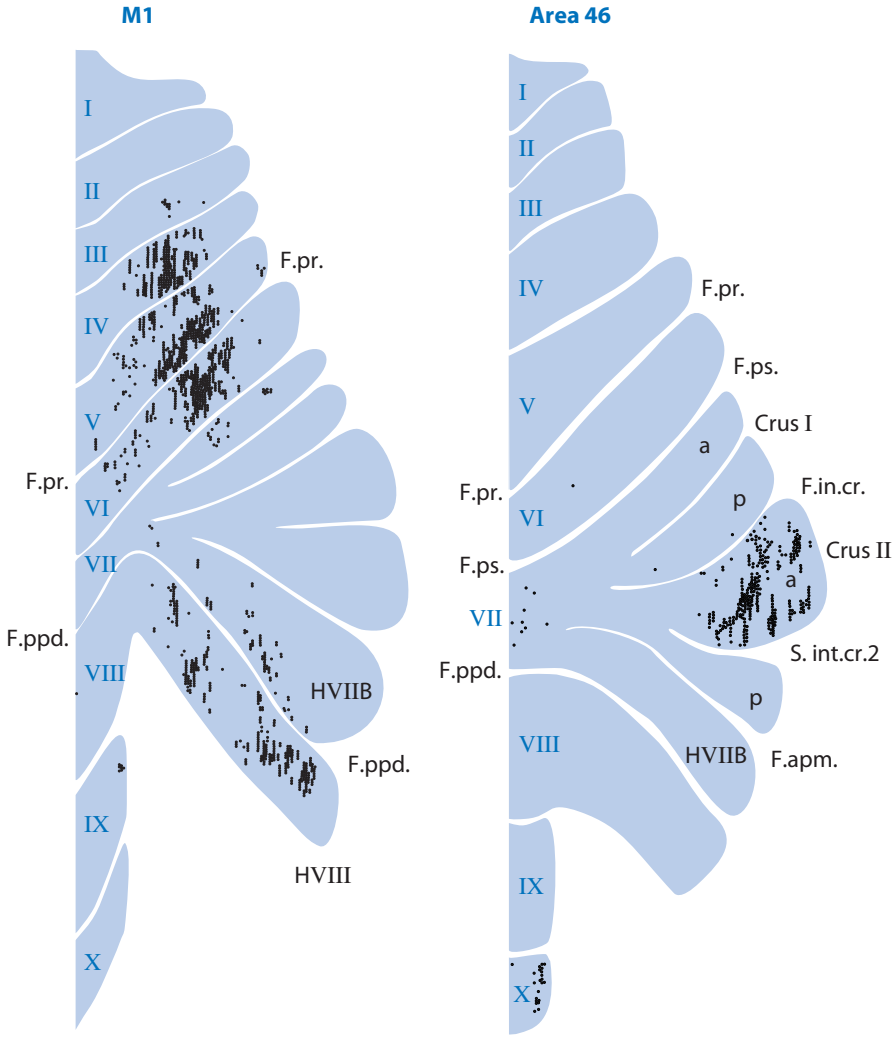

Figure 6

Regions of cerebellar cortex that project to areas of cerebral cortex. The black dots on the flattened surface maps of the cerebellar cortex indicate the location of Purkinje cells that project to the arm area of M1 (*left panel*) or to area 46 (*right panel*) in the cebus monkey. The Purkinje cells that project to M1 are located in lobules that are separate from those that project to area 46. Nomenclature and abbreviations are according to Larsell (1970). Adapted from Kelly & Strick 2003.

cortex is likely to be as rich and complex as that in the cerebral cortex (Kelly & Strick 2003). As a consequence, global dysfunction of the cerebellar cortex can cause wide-ranging effects on behavior (e.g., Schmahmann 2004). However, localized dysfunction of a portion of the cerebellar cortex can lead to more limited deficits, which may be motor or nonmotor depending on the specific site of the cerebellar abnormality (e.g., Allen & Courchesne 2003, Fiez et al. 1992, Gottwald et al. 2004, Schmahmann & Sherman 1998). Thus, precisely defining the location of a lesion, a site of activation, or a recording site is as important for studies of the cerebellum as it is for studies of the cerebral cortex.

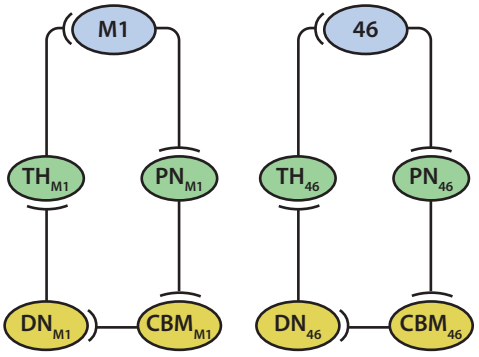

Figure 7

Closed-loop circuits link the cerebellum with the cerebral cortex. We illustrate two topographically separate closed-loop circuits. One interconnects the cerebellum with M1 and the other interconnects the cerebellum with area 46. In each loop, the cortical area projects to a specific site in the pontine nuclei (PN), which then innervates a distinct region of the cerebellar cortex (CBM). Similarly, a portion of the dentate nucleus (DN) projects to a distinct region of the thalamus, which then innervates a specific cortical area. Note that the cortical area, which is the major source of input to a circuit, is the major target of output from the circuit. CBM, cerebellar cortex; DN, dentate; PN, pontine nucleus; TH, subdivisions of the thalamus.

WHAT IS THE FULL EXTENT OF THE CEREBELLAR INFLUENCE OVER NONMOTOR AREAS OF THE CEREBRAL CORTEX?

As noted above, the cortical targets for substantial portions of the dentate remain unidentified. In addition, fastigial and interpositus nuclei send efferents to the thalamus (Asanuma et al. 1983, Batton et al. 1977, Kalil 1981, Stanton 1980), and the cortical targets of these deep nuclei remain to be fully determined. The closed-loop architecture described above enables us to make some predictions about additional cortical targets of cerebellar output (Dum & Strick 2003, Kelly & Strick 2003, Middleton & Strick 1998). If closed-loop circuits reflect a general rule, then all of the areas of cerebral cortex that project to the cerebellum are the target of cerebellar output. In addition to the cortical areas we have already studied, the cerebellum receives input from a wide variety of higher-order, nonmotor areas. This includes areas of extrastriate cortex, posterior parietal cortex, cingulate cortex, and the parahippocampal gyrus on the medial surface of the hemisphere (**Figure 1**) (Brodal 1978; Glickstein et al. 1985; Leichnetz et al. 1984; Schmahmann & Pandya 1991, 1993, 1997; Vilensky & van Hoesen 1981; Wiesendanger et al. 1979). If some or all of these areas turn out to be cerebellar targets, then the full extent of cerebellar influence over nonmotor areas of the cerebral cortex is remarkable and much larger than previously suspected.

Some have challenged the concept that a major component of cerebellar output targets cognitive areas of the cerebral cortex. For example, Glickstein & Doron (2008) argue that the regions of prefrontal cortex that are the target of dentate output are concerned with the control of eye movements. They point out that a portion of area 46 in the cebus monkey is included in a "prefrontal eye field" (Lynch & Tian 2006). However, our injection sites into area 46 display little or no overlap with the prefrontal eye field (compare figure 2 in Middleton & Strick 2001 with figure 2 in Tian & Lynch 1996). Our injection sites into areas 9l and 9m also display little or no overlap with known eye fields. Furthermore, the output channels to prefrontal cortex are located in dentate regions that are largely rostral to the output channel that targets the frontal eye field (**Figure 5**). Indeed, the output channel to the frontal eye field is located in the caudal pole of the dentate (Lynch et al. 1994). This region of the dentate is likely to lie outside of the nonmotor domain because it does not stain intensely for 8B3. Thus, there is considerable evidence that the cerebellar output to prefrontal cortex is distinct from the cerebellar control of eye movements.

CEREBELLO-LIMBIC CIRCUIT

In discussing the neural substrate for a cerebellar influence over nonmotor functions, it is important to note the longstanding notion

that the cerebellum is interconnected with the limbic system. Cerebellar stimulation can alter limbic function and elicit behaviors like sham rage, predatory attack, grooming, and eating (e.g., Berntson et al. 1973, Reis et al. 1973, Zanchetti & Zoccolini 1954). Cerebellar lesions can tame aggressive monkeys independent of gross motor abnormalities (Berman 1997, Peters & Monjan 1971). Classic electrophysiological evidence suggests that cerebellar stimulation, especially in portions of the fastigial nucleus and associated regions of vermal cortex, can evoke responses at limbic sites, including the cingulate cortex and amygdala (e.g., Anand et al. 1959, Snider & Maiti 1976).

The major weakness in the cerebello-limbic hypothesis is the absence of a clear anatomical substrate that links the output of the cerebellum, and especially the fastigial nucleus, with limbic sites such as the amygdala. Although neuroanatomical evidence indicates that the deep cerebellar nuclei are interconnected with the hypothalamus (Haines et al. 1990), these connections do not appear sufficient to mediate all of the behavioral effects evoked by cerebellar stimulation. Thus, the circuits that link the output of the cerebellar nuclei with regions of the limbic system need to be explored using modern neuroanatomical methods.

WHAT IS THE FUNCTIONAL IMPACT OF NONMOTOR CEREBRO-CEREBELLAR LOOPS?

Anatomical evidence that the cerebellum exerts a significant influence over nonmotor cortical areas is complemented by neuroimaging and neuropsychological data, which indicate this influence is functionally important. Some of the first physiological data in humans came from a landmark neuroimaging study published by Petersen and colleagues (1989). This study used positron emission tomography (PET) imaging to identify localized changes in blood-flow associated with a hierarchy of simple language tasks. Each level of the task hierarchy was compared with the adjacent level to successively isolate areas involved in the perception, production, and high-level linguistic analysis of single words. The findings confirmed the importance of brain regions that had previously been implicated in perceptual, motor, and language processing. For instance, bilateral changes in blood flow that localized to the paravermal regions of the cerebellum were found when subjects read aloud or repeated words, as compared with when they passively viewed or listened to words; such activity during speech production was easily reconciled with evidence that damage to the cerebellum can produce motoric disturbances in speech (Holmes 1939). At the same time, there were several surprises, including the fact that a region in the right lateral cerebellar hemisphere showed greater blood flow when subjects performed a verb generation task (saying aloud an appropriate use for each noun), as compared with simply reading or repeating nouns. The response location differed from the paravermal activation observed during speech production and led the authors to favor a cognitive interpretation; however, they acknowledged that they were "unable to assign a specific candidate set of computations required by our generate task that might be related to cerebellar activation" (Petersen et al. 1989).

Since the Petersen et al. (1989) report, functional neuroimaging has become a widely employed method, with reports of cerebellar activation now commonplace. The range of tasks associated with activation in the cerebellum is dauntingly large, and includes tasks designed to probe the neural basis of attention, executive control, language, working memory, learning, pain, emotion, and addiction (for references and reviews, see Glickstein 2007, Timmann & Daum 2007). In considering this accrued data, one essential question is whether the identified cerebellar activations are indicative of important nonmotor functions or somehow incidental to cognition (Glickstein 2007). Although the tasks used in neuroimaging are often described in nonmotor terms (e.g., as a language task or an emotion task), they include motor components

(e.g., subjects may respond with a keypress on each trial, or be asked to maintain their gaze on presented stimuli). Thus, activation differences could reflect differences in motor planning or execution, which might occur as a task becomes more difficult and response times increase. If this is the case, then increased cerebellar engagement might alter motor output (e.g., keypresses could be emitted with more force) without impacting the cognitive aspects of task performance (e.g., the particular responses that are selected).

Principals of hemodynamic activation may differ between the cerebral and cerebellar cortices, and this also makes it difficult to interpret the functional significance of changes in cerebellar activation. In the cerebral cortex, hemodynamic responses are thought to reflect a complex integration and indirect measure of the active synaptic circuitry within a particular cortical area. Although there is still much to be understood, a rough correspondence can often be made between the functional characteristics of a particular cortical area as determined by single-unit recording studies in nonhuman primates, as compared with what has been learned through functional neuroimaging studies in humans (Logothetis 2008). The same correspondences between neuronal activity and changes in the hemodynamic state may not be true in the cerebellar cortex, which has a general cytoarchitecture that is clearly distinctive from that of the cerebral cortex. For instance, the sole output neurons of the cerebellum (Purkinje cells) are inhibitory, and the principal excitatory drive onto Purkinje cells comes from one system that provides a relatively tonic but weak influence, and another system that exerts a more phasic but extremely powerful influence.

Convergent data from human lesion studies speak to the functional relevance of the cerebellar activation observed in human neuroimaging studies. Schmahmann & Sherman (1998) were among the first to tackle this question through a clinical review of patients with cerebellar damage. They concluded that these patients exhibited a diverse set of symptoms, which they termed the cerebellar cognitive affective syndrome. Subsequent studies further documented the nonmotor effects of cerebellar damage, collectively providing evidence for impairments on standardized and experimental measures of attention and executive control, procedural memory, working memory, language, and visual-spatial processing (Timmann & Daum 2007). At the same time, a close examination of this neuropsychological literature reveals a high degree of inconsistency (Burk 2007, Frank et al. 2007, Glickstein 2007).

The factors that account for the variability between neuropsychological studies have yet to be determined. False positive findings might arise from failures to consider motor confounds that could affect cognitive task performance, and from the inclusion of participants whose deficits might reflect noncerebellar sources of dysfunction (Burk 2007, Frank et al. 2007, Glickstein 2007). False negative findings can also arise from several sources (Bellebaum & Daum 2007). The locus of cerebellar damage is likely to be a particularly important factor. Most of the studies have collapsed across subjects with different lesion sites within the cerebellum. Although this permits group-based statistical comparisons, it ignores evidence of functional topography within the cerebellum. As a consequence, the findings from a study are likely to be influenced by the particular mix of lesion sites represented within the subject group.

The results reviewed in earlier sections of this chapter suggest that the map of function in the cerebellar cortex is likely to be as rich and complex as that in the cerebral cortex. In this regard, we have previously questioned the use of descriptors such as cerebellar patient, which tend to de-emphasize the importance of the functional topography of the cerebellar cortex (Kelly & Strick 2003). For example, lesions that damage cerebellar tissue, which is interconnected with area 46, are unlikely to cause motor deficits, just as lesions that damage cerebellar tissue, which is interconnected with M1, are unlikely to result in cognitive deficits. Thus, precisely defining the location of a lesion, site of activation, or recording site is as important

for studies of the cerebellum as it is for studies of the cerebral cortex.

Finally, although most of the neuropsychological research has involved adult participants, it is important to acknowledge evidence that the cerebellum may be especially important for normal cognitive development. Within the neurosurgical literature, it has been recognized that children with a history of posterior fossa tumors are at risk for a variety of intellectual, emotional, and educational impairments (Cantelmi et al. 2008). It was thought that these disturbances were caused by radiation exposure that occurred as part of the tumor management strategy. However, more recent evidence suggests that these impairments are a side effect of the incidental cerebellar damage that frequently occurs during the tumor resection. A developmental perspective may also help to explain the associations that have been made between neuroanatomical and neurophysiological abnormalities in the cerebellum and disorders such as autism (Amaral et al. 2008), schizophrenia (Andreasen & Pierson 2008), and dyslexia (Nicolson et al. 2001).

In summary, the neuroimaging and neuropsychological literatures provide compelling, although not conclusive, evidence that the human cerebellum has important nonmotor functions. The precise nature of these functions remains poorly understood. There are still relatively few neuroimaging and neuropsychological studies that have specifically targeted the cerebellum for a priori investigation. Most of the neurophysiological work in nonhuman primates has utilized motor tasks that do not directly map onto the cognitive and affective tasks that have been employed in human research, and a large number of assumptions must be made about the coupling between neuronal firing and the neurovasculature in the cerebellum. Despite these limitations, a number of perspectives have been proposed that help to explain how the cerebellum may exert an important influence over human cognition and affect. In the sections below, we briefly review three such perspectives and discuss the role that anatomical information may play in advancing our understanding of the normal motor functions of the cerebellum.

HOW MIGHT THE CEREBELLUM INFLUENCE COGNITION AND AFFECT?

Speculations about the nonmotor functions of the cerebellum often begin by noting that the cytoarchitectonic structure of the cerebellum is uniform. This fact supports the overarching assumption that there are computational principles that apply to both the motor and nonmotor functions of the cerebellum. Accordingly, researchers have often turned to the motor literature for insights, as explained below.

One perspective is that cerebellar activation often reflects its fundamental role in timing. The timing-related view has its roots in long-established clinical observations that motor coordination can be severely disrupted by cerebellar injury (Holmes 1939). Modern lesion studies have shown that patients with cerebellar damage have difficulties accurately producing and perceiving time intervals (Ivry & Keele 1989), and functional imaging studies have found effector-independent activation in the lateral cerebellum when subjects are asked to produce a complex rhythmic sequence (Bengtsson et al. 2005). Anatomically, it has been suggested that recurrent networks within the cerebellum permit fine discriminations among different spatiotemporal patterns of input to the cerebellar cortex (de Solages et al. 2008). With the loss of precise timing information and control, motor commands and internal cognitive states may no longer be appropriately selected and sequenced at a fine level. Thus, motorically, an individual may become less coordinated, and, cognitively, they may exhibit problems with task-shifting and other forms of executive control.

A second perspective is that cerebellar activation reflects the use of sensorimotor imagery, such as imagined speech. In the simplest version of this hypothesis, representations and processes that would be engaged during actual movement are co-opted to provide internal

representations that assist cognition. On the motor front, several studies have shown that the cerebellum is active when subjects imagine making a movement, such as a finger tap (Hanakawa et al. 2008). Similarly, the cerebellum is active when subjects are instructed to imagine producing simple speech utterances (Ackermann et al. 1998). These findings raise the possibility that the cerebellum will be recruited whenever subjects engage in inner speech—intuitively, the use of one's internal (imagined) voice to represent, maintain, and organize task-relevant information and conscious thoughts. Humans exhibit a strong tendency to engage in verbal coding and recoding, and thus internal speech-based representations may be important for a wide array of tasks that do not explicitly require speech or language processing. Beyond inner speech per se, recent findings suggest that conceptual knowledge of the world may rest, in part, upon internally driven activation of perceptual and motor representations (embodied cognition) (Barsalou 1999). For instance, when subjects view action words that are associated with the movements of particular body parts (e.g., kick, throw, and lick), somatotopically organized activation can be found in sensorimotor areas of the cerebral cortex (Hauk et al. 2004), and activation of a pain-related network has been found when individuals experience social rejection (Eisenberger & Lieberman 2004). Cortical areas associated with a putative mirror neuron system have garnered most of the attention in this area of research. However, there is some evidence that the cerebellum may be important as well (Fuentes & Bastian 2007, Leslie 2004).

A third view is that the cerebellum is a learning machine that supports the adaptive plasticity needed for the emergence of skilled behavior. This general idea has been captured in models of motor control, which typically contain three basic elements: (*a*) internal models that either predict the sensory input that should occur as a consequence of a motor output (forward models) or that predict the movements necessary to achieve a goal (inverse models), (*b*) a comparison process that detects errors in predicted versus actual outcomes, and (*c*) a learning process that uses error information to adaptively modify internal models so that movement execution can be fast and accurate. There is broad agreement that the cerebellum is crucial for the adaptive control of many different types of motor behavior, although as of yet there is little consensus on the nature of the computations it performs (e.g., which types of internal models are used, and whether they are simply passed from the cerebral cortex to the cerebellum or computed within the cerebellum) (Wolpert et al. 1998). Internal representations are also central to cognition. Consequently, it may be just as important to ensure the alignment of different types of cognitive representations as it is to ensure the alignment of sensory and motor representations. Cerebellar processing may help to adaptively modify internal representations so that the desired goals of cognition can be achieved in a skilled, and error-free, manner (Ito 2008).

Support for all three of these viewpoints can be found within the existing literature. This is partly because the ideas are to some extent interrelated, and thus they are not mutually exclusive. For instance, an internal model can be seen as a form of sensorimotor imagery (Fuentes & Bastian 2007), and the accurate detection of an error may rely on the coincident timing of input from two representational maps (de Solages et al. 2008). It is also true, however, that researchers have yet to evaluate these perspectives with a high degree of anatomical and theoretical specificity. In the section below, we return to the issue of topographic organization within the cerebellum, and we consider how such information may be used to advance our understanding of its nonmotor functions.

TOPOGRAPHICAL INFORMATION CAN BE USED TO ADVANCE THEORY

The benefits that should accrue from careful consideration of anatomical detail within the cerebellum are predicated on evidence that connections between the cerebellum and nonmotor

regions of the cerebral cortex are organized into anatomically and functionally dissociable loops. Unfortunately, topographic information has thus far played a modest role in functional interpretations of cerebellar activity. Too often, neuroimaging researchers simply refer to an activation focus as in the cerebellum, and those using neuropsychological methods analyze behavioral results without regard to the specific location of cerebellar damage.

The widespread use of the Talairach & Tournoux atlas system (Talairach & Tournoux 1988) accounts for some of the inattention to neuroanatomical detail. This atlas has provided a standard convention for reporting neuroimaging results, but it was developed for the cerebral cortex. The stereotactic procedures were not validated for the cerebellum, and the atlas does not even provide labels for its major hemispheric fissures. Newly developed tools, such as an atlas for the human cerebellum (Diedrichson 2006, Dimitrova et al. 2006, Makris et al. 2005, Schmahmann et al. 1999), can help to surmount the limitations of the Talairach & Tournoux atlas. However, some of the inattention to anatomical detail reflects a deeper issue. Namely, the correspondence between anatomical landmarks and functional areas is poorly understood within the cerebellum as compared with the cerebral cortex.

As information accrues about the correspondence between gross anatomical structure in the cerebellum and specific cortico-cerebellar loops, neuroimaging researchers will be in a better position to leverage knowledge about the precise locus of activation or site of damage to make inferences about function.

In principle, it is possible to make progress on delineating the functional topography of the cerebellum using neuroimaging data alone. For instance, in the motor domain, the loci of activation associated with lip, tongue, hand, and foot movements have been examined (e.g., Grodd et al. 2001). The results indicate that activation foci in the cerebellum are somatotopically organized, as predicted on the basis of prior findings from nonhuman research. To illustrate how this approach could be extended to the cognitive domain, consider the typical foci of activation reported in studies of reading and verbal working memory. Turkeltaub et al. (2002) used a voxelwise meta-analysis procedure to determine which regions of activation are consistently found when subjects read aloud a visually presented word, as compared with a simple baseline task (e.g., view a fixation cross). Across a set of 11 studies, they found evidence for reliable changes in the right and left paravermal cerebellar cortex. Chein et al. (2002) used a similar meta-analysis procedure to determine which regions of activation are consistently found when subjects perform a verbal working memory task (e.g., a two-back task with visually presented stimuli), as compared with a control task with similar perceptual-motor demands (e.g., a one-back task with visually presented stimuli). Across a set of 30 studies, they found evidence for reliable changes in the right lateral cerebellar cortex. The average foci of cerebellar activation found in these two meta-analyses are separated by more than 22 mm (see **Figure 8**), well beyond the typical 15+ mm range often associated with the functional differentiation of cortical foci (Xiong et al. 2000). Thus, it is likely that cerebellar activation foci found in the reading and verbal working memory meta-analyses reflect the engagement of different cortico-cerebellar loops.

Topographic distinctions between the activation patterns associated with two tasks can be used to constrain functional interpretations. For instance, behavioral data clearly indicate that an articulatory rehearsal (or inner speech) strategy is commonly used to help maintain verbal information in working memory (Baddeley 2003). Functional interpretations of cerebellar activation during verbal working memory have assumed that this activation reflected the use of the cerebellum to support articulatory rehearsal, perhaps through some form of motor speech imagery (Desmond & Fiez 1998). However, a simple motor imagery account fails to explain why the regions of the cerebellum that are engaged during articulatory rehearsal (e.g., during verbal working memory tasks) are not the same as those engaged during

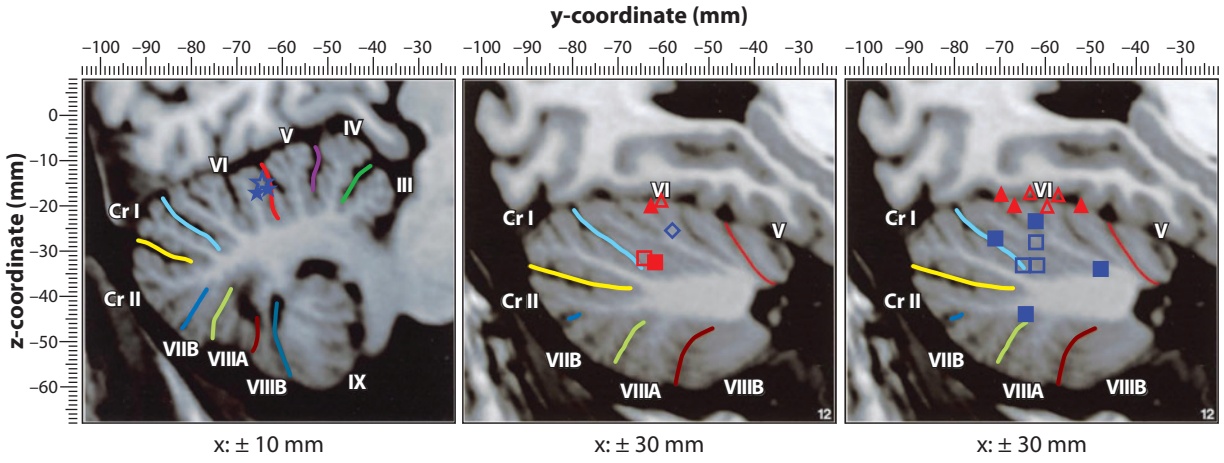

Figure 8

Topography of cerebellar activation reported in neuroimaging studies of reading, verbal working memory, cue-elicited craving, and pain processing. Foci are plotted on sagittal sections using the atlas sections and procedures developed by Schmahmann et al. (1999); left-lateralized foci are plotted using filled symbols and right-lateralized foci are plotted using open symbols. Vermal and bilateral paravermal foci (*filled* and *open stars*; *left section*) were reported in a meta-review of single-word reading (Turkeltaub et al. 2002), whereas a right-lateral focus (*open diamond*, *middle section*) was reported in a meta-review of verbal working memory (Chein et al. 2002). Bilateral responses have been found in studies of cue-elicited craving (*triangles*; Olbrich et al. 2006, Smolka et al. 2006, Wilson 2008, Xiao et al. 2006) and studies involving the presentation of pain-related visual stimuli (*squares*; Jackson et al. 2005, Moriguchi et al. 2007, Ogino et al. 2007, Singer et al. 2004, Ushida et al. 2008). The average locations of the responses are shown in the middle section, whereas the individual foci reported across studies are shown in the right section.

actual speech (e.g., during simple word reading tasks). Instead, a more complex account seems to be necessary. For instance, the differences in activation loci may reflect differences in the use of articulatory versus prearticulatory representations (Ackermann et al. 2007), internal versus external guidance of movement planning (Debaere et al. 2003), or the production of well-learned versus novel articulatory sequences (Ben-Yehudah & Fiez 2008, Rauschecker et al. 2008).

Outside of the motor and cognitive domains, cerebellar activation is frequently reported in task comparisons that involve affective processing. These include tasks used in studies of drug addiction and reward processing (Thoma et al. 2008), emotion appraisal and regulation (Schutter & van Honk 2005), and pain processing (Peyron et al. 2000). Such studies usually emphasize cerebral cortical areas, such as orbitofrontal cortex, ventromedial prefrontal cortex, and the amygdala. However, individuals with cerebellar damage can exhibit affective dysfunction (Schmahmann & Sherman 1998), and thus greater consideration of the functional contributions of the cerebellum may be warranted.

Careful consideration of the activation loci associated with different affective tasks may be a useful starting point for assessing the specificity of cerebellar involvement in emotional processing. To illustrate this point, we identified two groups of studies in which participants simply viewed images of affectively arousing stimuli, as compared with control conditions involving neutral stimuli. In one group, drug-dependent individuals viewed images containing drug-related stimuli (e.g., nicotine-dependent individuals saw an image of their hands holding a cigarette). Such stimuli can elicit significant increases in subjective craving for the drug (Wilson et al. 2005). In another group of studies, participants viewed images of injured body parts, or body parts experiencing painful stimulation (e.g., a picture of a hand being pierced by a needle). Such stimuli can elicit a subjective sense of pain, which may be associated with feelings of empathy toward an

injured person (Ushida et al. 2008). The foci of lateral cerebellar activation reported across these two groups of studies are shown in **Figure 8**.

Within each group, the activation foci tend to cluster together. This is encouraging because the studies were selected to be as homogenous as possible to optimize the likelihood that a similar network of brain regions would be recruited during the active and control tasks. At the same time, the typical locus of activation seems to differ across the two groups of studies. This observation suggests that the cerebellar activation is not simply a reflection of the motor imagery that is automatically triggered by the visual stimuli, because both types of stimuli are likely to engage similar motor effectors (e.g., hand and arm movements associated with smoking a cigarette, or withdrawing from a painful stimulation). If these results are confirmed, they would provide additional support for the concept that separate cerebrocerebellar circuits are engaged in response to the visual stimuli that induce internal states associated with craving versus pain.

SUMMARY AND CONCLUSIONS

The dominant view of cerebellar function over the past century has been that it is concerned with the coordination and control of motor activity (Brooks & Thach 1981). It is now apparent that a significant portion of the output of the cerebellum projects to nonmotor areas of the cerebral cortex, including regions of prefrontal and posterior parietal cortex. Thus, the anatomical substrate exists for cerebellar output to influence the cognitive and visuospatial computations performed in prefrontal and posterior parietal cortex (Clower et al. 2001, 2005; Middleton & Strick 2001). As a corollary, abnormalities in cerebellar structure and function have the potential to produce multiple motor and nonmotor deficits.

The output to nonmotor areas of the cerebral cortex originates specifically from a ventral portion of the dentate. This nonmotor region of the dentate is recognized by several molecular markers. Several authors have argued that ventral dentate and related regions of the cerebellar hemispheres are selectively enlarged in great apes and humans (Leiner et al. 1991, Matano 2001). Indeed, the enlargement of the ventral dentate in humans is thought to parallel the enlargement of prefrontal cortex. These observations have led to the proposal that the dentate's participation in nonmotor functions may be especially prominent in humans (e.g., Leiner et al. 1991, Schmahmann & Sherman 1998).

Anatomical evidence that the cerebellum exerts an influence over nonmotor regions of the cerebral cortex is complemented by data from neuroimaging and neuropsychology. These methodologies have provided compelling evidence that the cerebellum plays a functionally important role in human cognition and affect. The theoretical perspectives that have been used to explain how and why the cerebellum contributes to nonmotor tasks have drawn heavily upon the motor literature. Although these theoretical perspectives are useful, they are not computationally well-specified. As a result, they only loosely constrain the interpretation of cerebellar function in specific task contexts. Greater attention to anatomical information should help to significantly advance current understanding of cerebellar involvement in nonmotor function.

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Contents

Indexes

Errata

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