From Movement to Thought: Anatomic Substrates of the Cerebellar Contribution to Cognitive Processing

Jeremy D. Schmahmann

*Department of Neurology, Massachusetts General Hospital and Harvard Medical School,
Boston, Massachusetts 02114*

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Abstract: The cerebellar contribution to cognitive operations and emotional behavior is critically dependent upon the existence of plausible anatomic substrates. This paper explores these anatomic substrates, namely, the incorporation of the associative and paralimbic cerebral areas into the cerebrocerebellar circuitry in nonhuman primates. Using the novel information that has emerged concerning this system, proposed rules are derived and specific hypotheses offered concerning cerebellar function and the relationship between cerebellum and nonmotor behavior, as follow. (1) The associative and paralimbic incorporation into the cerebrocerebellar circuit is the anatomic underpinning of the cerebellar contribution to cognition and emotion. (2) There is topographic organization of cognitive and behavioral functions within the cerebellum. The archicerebellum, vermis, and fastigial nucleus are principally concerned with affective and autonomic regulation and emotionally relevant memory. The cerebellar hemispheres and dentate nucleus are concerned with executive, visual-spatial, language, and other mnemonic functions. (3) The convergence of inputs from multiple associative cerebral regions to common areas within the cerebellum facilitates cerebellar regulation of supramodal functions. (4) The cerebellar contribution to cognition is one of modulation rather than generation. Dysmetria of (or ataxic) thought and emotion are the clinical manifestations of a cerebellar lesion in the cognitive domain. (5) The cerebellum performs the same computations for associative and paralimbic functions as it does for the sensorimotor system. These proposed rules and the general and specific hypotheses offered in this paper are testable using functional neuroimaging techniques. Neuroanatomy and functional neuroimaging may thus be mutually advantageous in predicting and explaining new concepts of cerebellar function.   © 1996 Wiley-Liss, Inc.

Key words: cerebellum, cerebellar nuclei, cerebral cortex, association areas, paralimbic cortices, pons, thalamus, neural circuit, cognition, behavior, affect, emotion

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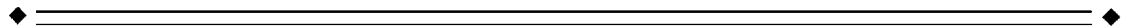
INTRODUCTION

It has become well-established in clinical neurology and neuroscience that the cerebellum is essential for the coordination of movement. Less attention has been directed to observations which date back almost as long as the recognition of motor disability that behavioral anomalies may occur in association with cerebellar disorders [Dow and Moruzzi, 1958; Schmahmann, 1991]. These earlier reports have been mostly anecdotal, and usually substantiated by only minimal pathologic verification. In addition, bedside clinical examination and cognitive screening tests have not consistently revealed deficits beyond motor incoordi-

nation in patients with even advanced cerebellar disorders. Consequently, earlier suggestions that there may be a cerebellar contribution to nonmotor function [Dow and Moruzzi, 1958; Berntson et al., 1973; Dow, 1974; Martner, 1975; Snider and Maiti, 1976; Heath, 1977; Watson, 1978] have been largely dismissed, and this relationship considered as an epiphenomenon, i.e., cognitive changes in patients with cerebellar diseases have been viewed as a reflection of concomitant cerebral disease.

Snider remarked in 1950 [in Henneman et al., 1952] that one of the problems he saw with the physiologic and anatomic investigations of the cerebellum was that one could "remove considerable masses of cerebellar tissue without producing any apparent deficits. Now how are we going to explain that fact?" he wondered. "One cannot help but feel that these intricate relay systems exert very subtle influences which, when withdrawn, produce no very obvious disturbances. But, if more critical studies were made, it perhaps might be easy, in some instances at least, to pick up the subtle differences that must distinguish these cerebellar cases from the normal. It is tempting, for example, to believe ... that there is some subtle influence exerted on the threshold activity of the cortical areas. Whether this influence is exerted by simple reverberation or by some not yet understood physico-chemical phenomenon is not known. I believe that these results may lead to the development of clinical tests which will reveal disorders of the cerebellum that are now undetected." Snider's comments were made at a time when the existence of somatotopically organized cutaneous and kinesthetic input to the cerebellum was being established [Snider and Stowell, 1942; Snider, 1950, 1952; Hampson et al., 1952; Henneman et al., 1952; Woolsey, 1952]. Sensory maps of the cerebellum were being derived from electrical studies of the cerebral cortex, cerebellum, and periphery (mediated by spinocerebellar pathways), and they included primary and secondary sensory areas. The cerebellum was being parcellated into functional regions using approaches similar to those adopted for the cerebral cortex. A primary sensory homunculus was present in the anterior lobe; rerepresentations were situated independently and bilaterally in the posterior lobes; and the visual, auditory, and head and neck sensory inputs were located at the junction of these two regions in the cerebellar vermal lobule named the tuber vermis (Fig. 1). Physiologists further determined that the pattern of motor responses of the limbs or head and neck that could be elicited by cerebellar stimulation closely reflected the sensory topography. Early physiologic studies additionally

showed interactions between the cerebellum and "autonomic parts" of the cingulate gyrus, observations bolstered already at that time by demonstrations of autonomic influences of cerebellar stimulation (change in bowel motility, and effects on pupil dilatation, among others). These observations regarding primary and secondary sensory representations, animal behavioral phenomena, and clinical-pathologic correlations documented over the last 50–100 years, were all but ignored by clinical neurologists and generally minimized by cerebellar physiologists in favor of hypotheses about the cerebellar role in motor coordination.

Almost half a century after the comments by Snider [1950, 1952] and the extensive review by Dow and Moruzzi [1958] and their reminder to readers to consider the relationship of the cerebellum to sensory and autonomic phenomena, the notion that cerebellar function may extend beyond motor control is again gathering momentum, and being further developed and defined. This has been precipitated in part by anatomic studies and derivative functional hypotheses concerning the associative and paralimbic contributions to the cerebrocerebellar circuit [Schmahmann and Pandya, 1987, 1989; Schmahmann, 1991, 1994; Middleton and Strick, 1994], by the wider dissemination and conceptual reevaluation [Leiner et al., 1986, 1993] of detailed observations by Dow [1942, 1974] related to the evolutionary changes of the dentate nucleus and the predicted significance of those findings, by the demonstration of a cerebellar role in classical conditioning [Thompson, 1988], and by reports correlating disturbances of higher function with cerebellar disease in patients [Bauman and Kemper, 1985; Botez et al., 1985, 1989; Courchesne et al., 1988; Bracke-Tolkmitt et al., 1989]. Additionally, a powerful catalyst for this renewed interest in, and ability to address, these issues is the fact that investigators in functional neuroimaging have been impressed for some years by the range of tasks that are associated with activation of the cerebellum. Although initially only noted incidentally with some interest, a number of recent studies have specifically addressed the issue of cerebellar activation by nonmotor and specifically cognitive tasks. The interpretation of the results of these functional studies in humans is influenced in large part by neuroanatomic information derived from investigations in nonhuman primates. This paper explores the anatomic organization of the cerebrocerebellar system in the monkey, and presents specific hypotheses and proposed rules governing human cerebellar functions in nonmotor and cognitive opera-

A

Anterior Lobe

Anterior Lobe

Lobulus Simplex

Primary fissure

Crus I

Crus I

Crus II

Vermis

Crus II

Paramedian Lobule

Spinal Cord

Paramedian Lobule

B

Anterior lobe

Lobulus Simplex

Crus I

Crus II

Vermis

Paraflocculus Flocculus

Spinal Cord

C

CEREBRUM

MOTOR   SENSORY

CEREBELLUM

PUPIL

LEG I

EYES

ARM I

VISUAL I

VISUAL II

FACE I

AUD I

F II

AUD II

AT II

INSULA

LING

CENT   LEG

CUL   ARM

SIMP

DECL

TUB

PY

UV

NOD

I

II

Figure 1.

Diagrams summarizing the somatotopic organization of the cerebellum as determined by functional studies performed in the 1940s. **A:** Tactile projections to the cerebellum. Anterior area encompasses lobulus simplex and anterior lobe and is an ipsilateral projection. Posterior area is located primarily in the paramedian lobules bilaterally but may extend into crus I and II and medially into the pyramis. Note double sensory area, i.e., the ipsilateral anterior lobe-lobulus simplex region and bilateral paramedian lobule region. Note also the face, arm, and leg subdivisions of these tactile areas. Proprioceptive areas were felt to be coextensive with these tactile areas. **B:** Schematic drawing of the cerebellum shows that auditory and visual areas, as determined by click and photic stimulation, are coextensive. This so-called audio-visual area lies primarily in the lobulus simplex, folium, and tuber vermis but extends into crus I and II. **C:** Conception by Woolsey [1952] of the relationship between primary and secondary sensory areas of the cerebral cortex and those in the cerebellum. These diagrams do not depict early demonstrations of vestibular projections to the flocculonodular lobe, the point-to-point relationship between the olivary nuclei and all aspects of the cerebellum, and between the external cuneate nuclei and the anterior lobe and posterior vermis. The relationship between parietal cortex and lateral cerebellum was determined by later physiological studies [Allen and Tsukuhara, 1974; Sasaki et al., 1975], and between the cerebral visual cortical areas and the dorsal paraflocculus in contemporary anatomical investigations [see Stein and Glickstein, 1992]. Discontinuity in somatotopic representation in the cerebellum ("fractured maps") was relatively recently described [Kassel et al., 1984; Bower and Kassel, 1990] and is not depicted in these original illustrations. Adapted from Snider [1952] (A and B), and Woolsey [1952] (C).

tions and affective states. Functional neuroimaging, and the experimental psychology that refines it, are in a position to test these hypotheses, and they may help "explain" the previously undetermined "facts" of cerebellar function.

CEREBROCEREBELLAR CIRCUITRY

Consistent with the notion that in the nervous system, function is dependent on structure, if there is a cerebellar contribution to cognitive function then there must be a corresponding anatomic substrate that supports it. Systems neuroanatomy, derived largely from work in nonhuman primates, has been important in developing the concept of distributed neural circuits. This concept holds that cognitive function is distributed among multiple cortical and subcortical nodes, each of which functions in concert but in a unique manner to produce an ultimate behavior pattern [Pandya and Kuypers, 1969; Jones and Powell, 1970; Mesulam, 1981, 1990; Pandya and Yeterian, 1985; Goldman-Rakic, 1988; Posner et al., 1988; Alexander and Crutcher, 1990]. This notion is central to the consideration of the cerebellum in the context of nonmotor behavior. The association areas and paralimbic cortices have been extensively demonstrated as anatomic regions necessary to support a variety of cognitive operations [reviewed in Pandya and Yeterian, 1985]. There is now substantial and detailed evidence documenting that the cerebellum is linked to these higher-order regions through the cerebrocerebellar circuit.

The cerebrocerebellar circuit consists of a feedforward, or afferent limb, and a feedback, or efferent limb. The feedforward limb is comprised of the corticopontine and pontocerebellar mossy fiber projections; the feedback loop is the cerebellothalamic and thalamocortical pathways (Fig. 2). A second major feedforward system links the cerebral cortex with the red nucleus, from where the central tegmental tract leads to the inferior olivary nucleus and then through the climbing fiber system to the cerebellar cortex. It transpires that this second afferent arc may have limited relevance for discussion of the relationship between the cerebellum and cognition, as addressed later. Input from serotonin-, norepinephrine-, and dopamine containing-brain stem structures constitutes another substantial source of cerebellar afferents. Spinal and other brain stem inputs to the cerebellum are not part of the cerebrocerebellar system and will not be discussed here.

The interpretation of functional neuroimaging is heavily dependent upon an understanding of neuro-anatomic structures and their connectivity within distributed systems. For this reason, the anatomic underpinnings which appear to be the substrate of the cerebellar contribution to cognition are discussed in some detail. Both the feedforward and the feedback limbs of the cerebrocerebellar circuit are elaborated upon. This is necessary because our conceptual approach [Schmahmann, 1991] holds that the cerebellum modifies behaviorally relevant information that it has received from the cerebral cortex via the corticopontine pathway, and it then redistributes this now "cerebellar-processed" information back to the cerebral hemispheres. In this manner the cerebellum is an integral component of the distributed neural circuitry subserving multiple domains of cognitive processing.

Feedforward limb of the cerebrocerebellar system

The corticopontine pathway originates in neurons in layer Vb of the cerebral cortex, the axons of which enter the internal capsule, descend into the cerebral peduncle, and terminate around neurons that occupy the ventral half of the pons. Motor, premotor, and supplementary motor regions as well as primary somatosensory cortices send their efferents to the cerebellum via this route [Nyby and Jansen, 1951; Brodal P, 1978; Brodal A, 1981; Glickstein et al., 1985; Shook et al., 1990; Schmahmann and Pandya, 1995b].

The origins of the corticopontine pathway are not limited to these sensorimotor cortices. The posterior parietal areas contribute to this feedforward system with a good deal of topographic ordering (Figs. 3C, 4). The posterior parietal association cortices are critical for directed attention, visual-spatial analysis, and vigilance in the contralateral hemispace. When lesioned, these areas are associated with complex behavioral manifestations. This includes trimodal neglect in which patients are unaware of the contralateral side of space including their own body parts, and alien hand syndrome in which the contralateral extremities appear to take on a life of their own, moving seemingly at will without the patient's instruction or knowledge until the extremity by chance appears in the preserved visual hemifield [Critchley, 1953; Denny-Brown and Chambers, 1958; Mountcastle et al., 1977; Lynch, 1980; Hyvarinen, 1982]. The superior parietal lobule, more concerned with intramodality associative functions (multiple joint position sense, touch, and proprioceptive impulses from similar regions), projects throughout the rostrocaudal extent of the pons, focusing mostly on the nuclei in the central and lateral region of the basilar pons. The inferior parietal lobule, especially the most caudal region, is strongly implicated in
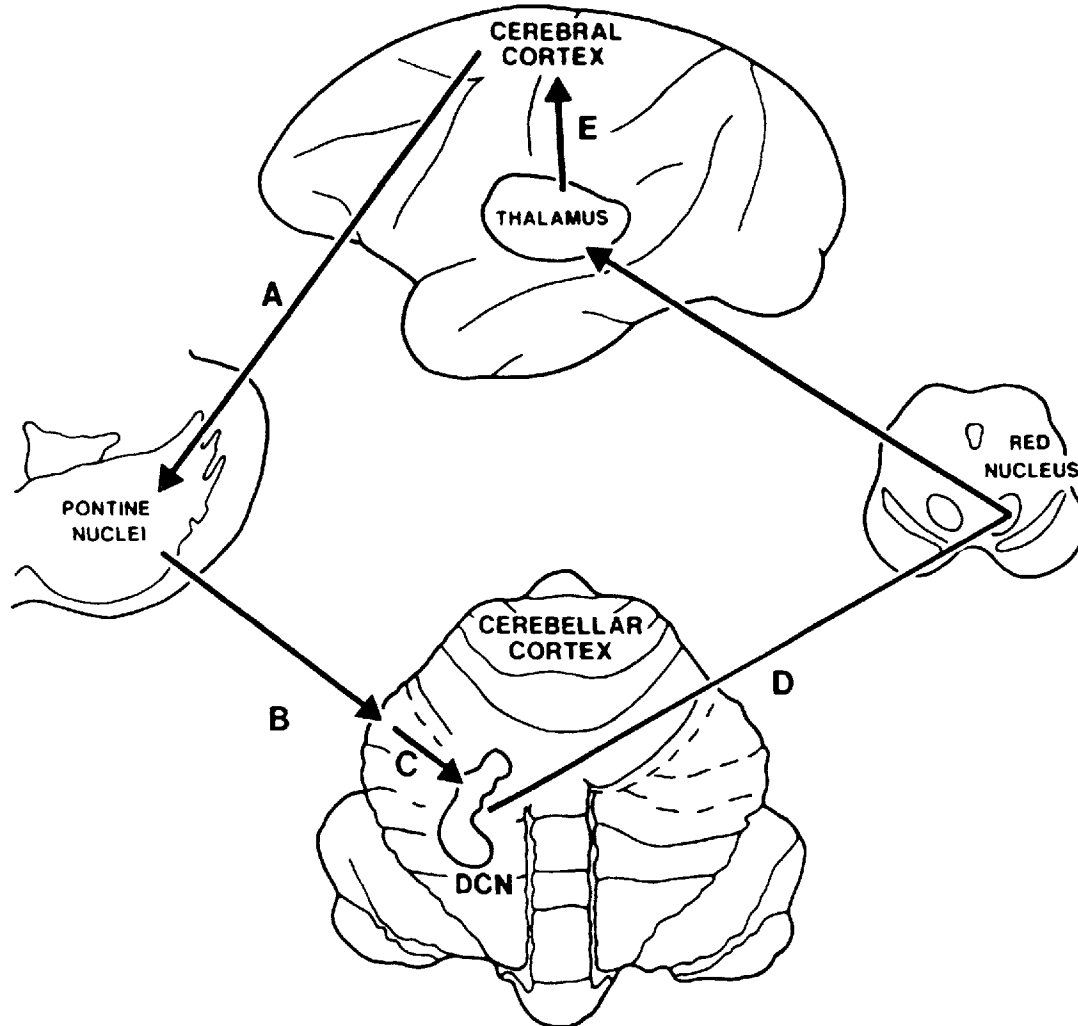
Figure 2.

Diagrammatic representation of anatomical circuitry linking association areas and paralimbic cortices of cerebral hemispheres with the cerebellum. The feedforward limb of the cerebrocerebellar circuit consists of the corticopontine projection (**A**) which carries this higher-order information (as well as sensorimotor inputs) from the cerebral cortex to the nuclei situated in the gray matter of the ventral pons, and the axons of the pontine neurons which convey this information via the pontocerebellar pathway (**B**) to the cerebellar cortex. The feedback limb of the cerebrocerebellar system originates in the cerebellar corticonuclear projection (**C**), and continues in a rostral direction as the deep cerebellar nuclei (DCN) send their axons to the thalamus (the cerebello-thalamic projection, (**D**) via the red nucleus, to which en passant terminals are distributed. Thalamic projections back to the association cortices (**E**) complete the feedback circuit. The corticopontine projection is over-whelmingly ipsilateral, so that, for example, the right cerebral hemisphere projects to the right pons. Brain stem connections with the cerebellum cross twice: once on the way to, and once when returning from, the cerebellum. The pontocerebellar projection is mostly crossed (70–80%), so that the right pons is connected more strongly with the left cerebellum. The left cerebellum sends a predominantly crossed projection (through the decussation of the superior cerebellar peduncle, or brachium conjunctivum) to the right thalamus. The ipsilateral thalamocortical projection then terminates in the cerebral hemisphere of origin. This schematic view of the cerebro-cerebellar link does not imply a closed-loop system, and multiple details of each of the projection systems discussed in detail in the text are not shown in this illustration (reprinted from Schmahmann, 1994).

the neglect syndrome, and is anatomically interconnected with other cortical association areas as well as with paralimbic cortical regions and limbic thalamic nuclei [Pandya and Yeterian, 1985; Cavada and Goldman-Rakic, 1989a,b; Schmahmann and Pandya, 1990]. The projections from the inferior parietal lobule favor the rostral half of the pons, terminations being located more at the lateral and dorsolateral pontine regions

[Brodal P, 1978; Glickstein et al., 1985; May and Andersen, 1986; Schmahmann and Pandya, 1989]. The pattern of connections observed in the parietopontine projection reflects what appears to be a general rule of organization of this system. Each cortical area is interconnected with a corresponding unique subset of neurons distributed within the pontine nuclei. This is reminiscent also of other cortico-subcortical systems, including the reciprocal thalamocortical [Weber and Yin, 1984; Yeterian and Pandya, 1985; Giguere and Goldman-Rakic, 1988; Schmahmann and Pandya, 1990; Barbas et al., 1991; Siwek and Pandya, 1991] and corticostriatal [Yeterian and Pandya, 1991, 1993; Eblen and Graybiel, 1995] projections.

There is an anatomic principle that cortical regions that are interconnected tend to share common subcortical projections [Yeterian and Van Hoesen, 1978]. The multimodal posterior parietal regions are interconnected in a precisely ordered manner, with association areas in the superior bank of the superior temporal sulcus, the parastriate visual association areas in the dorsal and medial prelunate regions, and the prefrontal cortices, and with the parahippocampal and cingulate gyri, which form part of the paralimbic circuitry [Pandya and Kuypers, 1969; Jones and Powell, 1970; Seltzer and Pandya, 1978; Van Hoesen, 1982; Petrides and Pandya, 1984; Vogt and Pandya, 1987; Cavada and Goldman-Rakic, 1989a,b]. It is therefore novel information, although not necessarily unexpected, that pontine projections are derived from each of these associative cortices. The superior temporal gyrus and supratemporal plane, which are auditory association areas, are connected with the lateral and dorsolateral basilar pons (Figs. 3B, 4). The cortex in the upper bank of the superior temporal sulcus has neurons that are activated during face recognition tasks, and they are further selectively activated depending on the direction of gaze of the presented face [Perrett et al., 1987]. The lateral, dorsolateral, and extreme dorsolateral pontine nuclei receive most of the terminations from these temporal lobe regions [Schmahmann and Pandya, 1991]. Other temporal lobe cortices that are responsive to motion and direction of movement (areas MT, FST, and MST) also have pontine connections [Ungerleider et al., 1984], but the inferotemporal cortex, including the rostral lower bank of the superior temporal sulcus, which is relevant for feature discrimination [Desimone and Ungerleider, 1989; Felleman and Van Essen, 1991], has no pontine efferents [Brodal P, 1978; Glickstein et al., 1985; Schmahmann and Pandya, 1991, 1993]. This apparent dichotomy in the temporal lobe pontine connectivity between visual motion (where) vs. visual feature discrimination (what)

systems [Ungerleider and Mishkin, 1982] is observed also in the parastriate pontine system. That is, the medial and dorsal prelunate regions project to the pons (lateral nucleus and lateral aspect of the peripeduncular nucleus most heavily), but the ventral prelunate cortices and the inferotemporal regions do not [Glickstein et al., 1985; Fries, 1990; Schmahmann and Pandya, 1993]. The dorsal visual stream concerned with motion analysis and visual-spatial attributes of motion therefore participates in cerebrocerebellar interaction, but the ventral visual stream governing visual object identification does not. The posterior parahippocampal gyrus, which is responsive to visual stimuli in the peripheral lower quadrant [Boussaoud et al., 1991] and which has been identified as part of the substrate for spatial attributes of memory [Nadel, 1991], also has pontine connections, mostly to the lateral, dorsolateral, and lateral aspect of the peripeduncular nuclei [Schmahmann and Pandya, 1993].

The projections to the pons from the posterior parahippocampal gyrus (Figs. 3C, 4) are relevant also because of its role in memory, and its position in the paralimbic circuitry [Pandya and Yeterian, 1985]. The cingulate gyrus, also part of the paralimbic circuit, and implicated in motivational behavior, has previously been shown to have topographically organized pontine projections. Rostral cingulate regions project to more medial pons, while more caudal cingulate projections are directed to the lateral pons [Vilensky and Van Hoesen, 1981].

In addition to these cortically-derived projections, the cerebellum has direct and reciprocal connections with the posterior and lateral nuclei of the hypothalamus [Haines and Dietrichs, 1984], and with the noradrenergic locus coeruleus, serotoninergic raphe nuclei, and dopaminergic systems in the brain stem [Snider, 1975; Dempsey et al., 1983; Marcinkiewicz et al., 1989]. Furthermore, the pons receives inputs from the hypothalamus [Aas and Brodal, 1988], from polymodal deep layers of the superior colliculus which are implicated in attention [Frankfurter et al., 1977], and from the medial mammillary bodies implicated in memory systems [Aas and Brodal, 1988]. Some earlier physiologic and anatomic studies further suggested that there are connections linking the archicerebellum (flocculonodular lobe), fastigial nucleus, and anterior vermis with parts of the limbic system, including the septal nuclei, hippocampus, and amygdala [Anand et al., 1959; Harper and Heath, 1973; Snider and Maiti, 1976].

The prefrontal cortex is essential for such higher functions as planning, foresight, judgment, attention, language, and working memory, to mention some
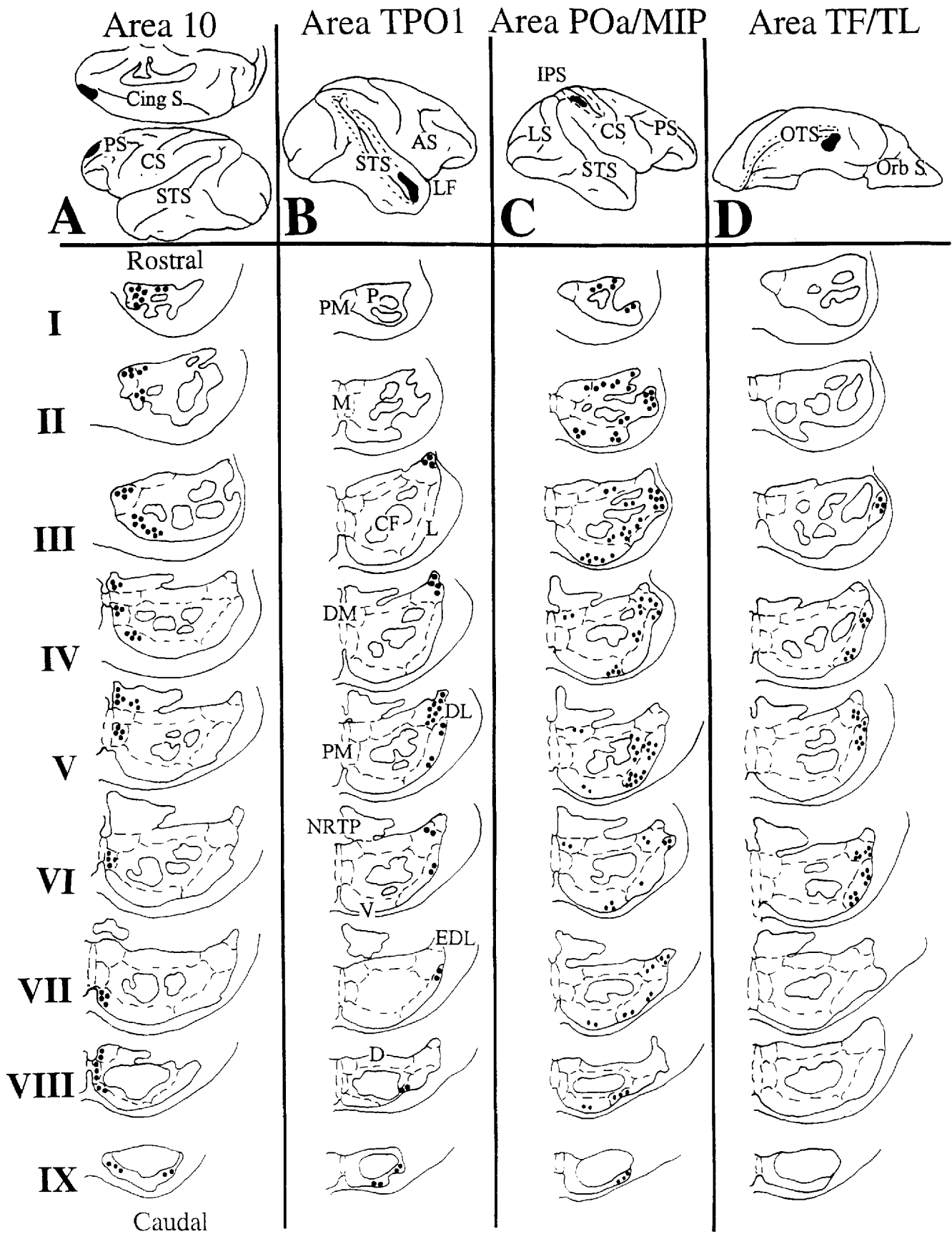
Figure 3.

[Milner, 1964; Luria, 1966; Fuster, 1980; Stuss and Benson, 1986]. This region should be a contributing element to a distributed neural circuit that is postulated to support cognitive operations. There is indeed an organized and consistent projection from the prefrontal cortices of the rhesus monkey into the feedforward limb of the cerebrocerebellar circuit, with terminations in the pons distributed in a topographically precise manner, favoring the median, paramedian, dorsomedial, and medial parts of the peripeduncular pontine nuclei [Schmahmann and Pandya, 1995a, 1996] (Figs. 3A, 4). The projections arise most prominently from the dorsolateral and dorsomedial convexities, from areas concerned with attention as well as with conjugate eye movements (area 8), the spatial attributes of memory and working memory (area 9/46d), planning, foresight, and judgment (area 10), and motivational behavior and decision-making capabilities (areas 9 and 32), and from areas considered to

be homologous to the language area in human (areas 44 and 45) [Brodmann, 1909; Astruc, 1971; Künzle and Akert, 1977; Glickstein et al., 1985; Stanton et al., 1988; Goldman-Rakic and Friedman, 1991; Pandya and Yeterian, 1991; Petrides and Pandya, 1994; Petrides, 1995; Schmahmann and Pandya, 1995a, 1996].

These observations indicate that the first critical stage of the feedforward limb of the cerebrocerebellar circuit is derived not only from sensorimotor cortical areas but, to a substantial degree, from associative and paralimbic cortices as well. The origins of this corticopontine system are not haphazard, but are predictable from architectonic and functional principles. Each cortical locus is connected with a unique subset of neurons within the basilar pontine nuclei (Fig. 3). Further, the organization of terminations in the basilar pons forms a highly patterned, complex mosaic of interdigitating terminations, determined by the site of origin of the projection (Fig. 4).

There is a further degree of detail in the corticopontine projection worthy of consideration here. The origin and termination of each projection are linked, predictably, by a fiber pathway that connects them. It transpires that the trajectories of the corticopontine fiber systems are highly organized. There is a topographic arrangement within the white matter of the cerebral hemispheres of the fiber systems derived from different cortical sites. Whereas, for example, all the post-Rolandic corticopontine fibers are obliged to descend abruptly into the cerebral peduncle at the level above the midpoint of the lateral geniculate nucleus, they adopt a unique course both as they move (rostrally or caudally) towards the lateral geniculate nucleus, and as they hover above it prior to their precipitous descent [Schmahmann and Pandya, 1992]. A different arrangement but with similar organizing principles applies to the prefrontopontine fibers, which either gently descend or sharply dive down at the anterior limb of the internal capsule en route to the cerebral peduncle [Schmahmann and Pandya, 1994]. Thus, the corticopontine projection is distinguishable at each point, from origin through trajectory to termination, and appears to be organized in parallel, each cortical locus having a unique complement of pontine neurons to which it directs its efferent volleys. In this sense, the organization of the cerebrocerebellar system bears some resemblance to the multiple parallel loops that characterize the cortico-subcortical interactions with the basal ganglia [Goldman-Rakic and Selemon, 1990].

There is only limited information available regarding the pontocerebellar projection in the nonhuman primate. Anatomic and physiologic studies indicate

Figure 3.
Diagram of projections to the basis pontis from selected regions within cerebral association areas. Diagram illustrates that each cerebral area is connected with a unique and distributed subset of pontine neurons. Projections appear to be arranged in an interdigitating but not overlapping manner. **A:** Anterograde tracer (radiolabeled amino acids, represented by shaded black area in cerebral hemispheres) was injected into medial and lateral parts of the rostral prefrontal cortex (area 10). **B:** Injection into the cortex buried within the rostral upper bank of the superior temporal sulcus (area TPO_1, with encroachment on the adjacent areas TS_1, TAa, and Pro). **C:** Injection into cortex buried within the lower bank of the intraparietal sulcus (area POa, or LIP). **D:** Injection into parahippocampal gyrus (areas TF/TL). Terminations of the anterogradely transported label are represented by black dots in the ipsilateral half of the basis pontis. The pons is depicted from rostral level I to caudal level IX, according to Nyby and Jansen [1951], and as modified by Schmahmann and Pandya [1988, 1989]. Cases were derived from (A) Schmahmann and Pandya [1995a], case 5; (B) Schmahmann and Pandya [1991], case 1; (C) Schmahmann and Pandya [1989], case 11; and (D) Schmahmann and Pandya [1993], case 11. Area 10 is according to Brodmann [1909]; POa is the designation of Pandya and Seltzer [1982]; LIP of May and Andersen [1986]; TF of von Bonin and Bailey [1947]; TL of Rosene and Pandya [1983]; TPO_1, TS_1, TAa, and Pro of Seltzer and Pandya [1978] and Galaburda and Pandya [1983]. Abbreviations for cerebral cortex: AS, arcuate sulcus; Cing S, cingulate sulcus; CS, central sulcus; IPS, intraparietal sulcus; LF, lateral (sylvian) fissure; LS, lunate sulcus; Orb S, orbital sulcus; OTS, occipitotemporal sulcus; PS, principalis sulcus; STS, superior temporal sulcus. Abbreviations for pontine nuclei: CF, corticofugal fibers; D, dorsal; DL, dorsolateral; DM, dorsomedial; EDL, extreme dorsolateral; L, lateral; M, median; NRTP, nucleus reticularis tegmenti pontis; PM, paramedian; P, peduncular; V, ventral.
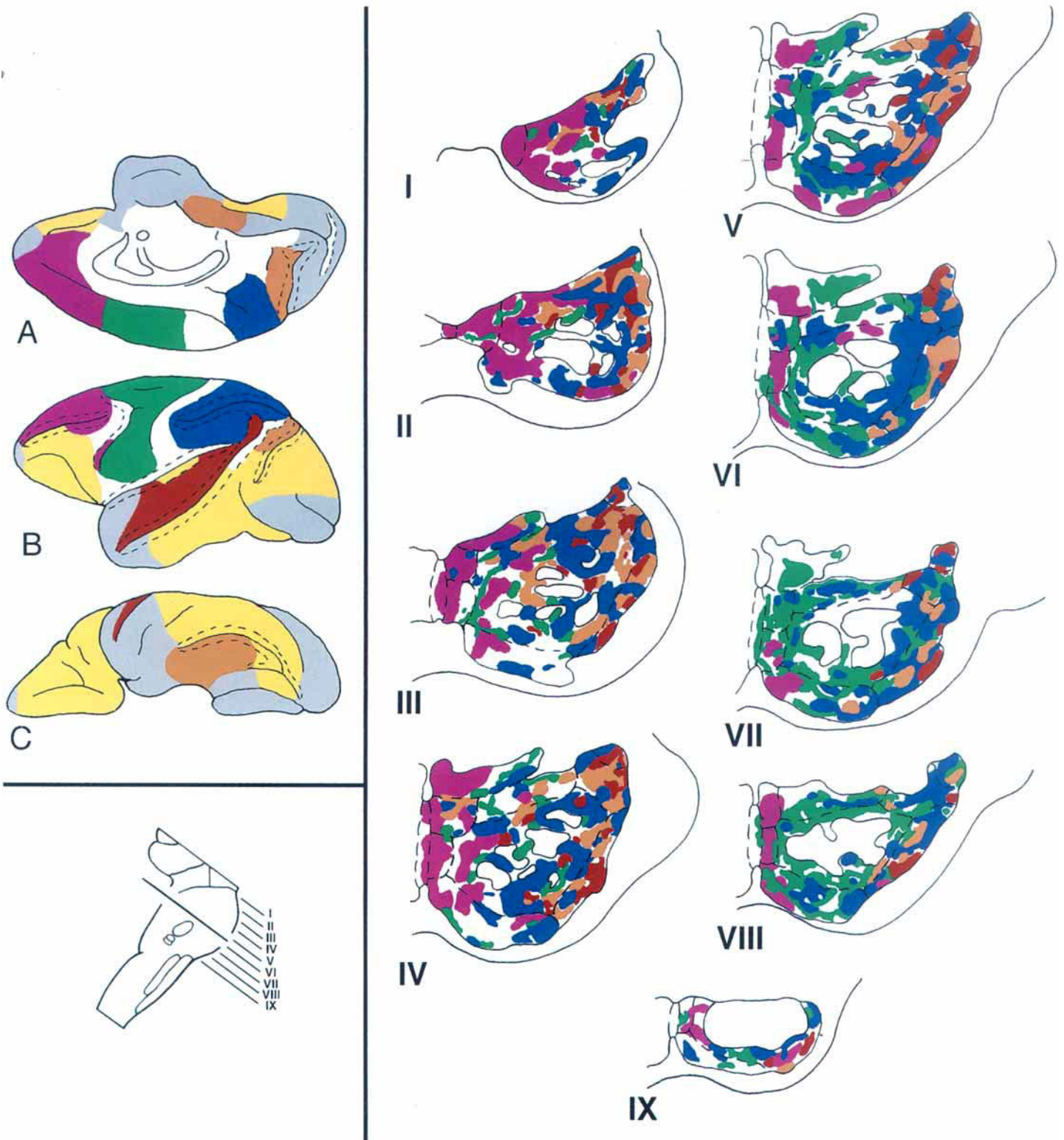
Figure 4.

that the dorsal paraflocculus, uvula, and the vermal visual area (vermal lobule VII of Larsell [1970]) receive information from visually responsive neurons in the dorsolateral pontine region and the nucleus reticularis tegmenti pontis, which is situated immediately dorsal to the basilar pontine nuclei [Brodal P, 1979, 1980; Stein and Glickstein, 1992; Glickstein et al., 1994]. The clustering of labeled cells that Brodal [1979] discerned in his horseradish peroxidase (HRP) study of the pontocerebellar projection in the monkey suggested a high degree of order, with each cerebellar subdivision receiving input at least partly from its own pontine territory. One small part of the cerebellum would also receive input from several discrete pontine cell groups situated far apart (Fig. 5). The anterior lobe (mainly lobule V of Larsell [1970]) received input from medial parts of the caudal pons; vermal lobules VII–VIIIA from two cell groups located in the dorsomedial and dorsolateral pons; vermal lobule VIIIB from the intrapeduncular nucleus; crus I of the ansoparamedian lobule from medial parts of the rostral pons; and crus II from the lateral pons. The hemispheres had relatively greater pontine input than the rostral vermis. These findings led Brodal [1979] to conclude that the corticopontocerebellar pathway in the monkey was organized in a precise manner, and it allowed for the possibility of a small cell group in the cerebral cortex to influence several discrete parts of the cerebellar cortex. He thus concluded that the anterior lobe and lobulus simplex

(Larsell [1970], lobes I–VI) receive afferents from the motor and premotor cortices and to a small extent from the parietal lobe. In the ansoparamedian lobule (Larsell [1970], lobules VII–VIII), the premotor and prefrontal cerebral regions were linked with cerebellar crus I, the motor cortex with crus II, and (in agreement with earlier physiological work of Allen and Tsukuhara [1974] and Sasaki et al. [1975]), the somatosensory and parietal association areas are linked with the paramedian lobule (Fig. 6).

These general organizational principles notwithstanding, detailed understanding of the pontocerebellar system is still not available with the kind of precision now at hand for the corticopontine component of the feedforward limb. Much remains to be elucidated regarding the details of the pontine afferents to defined regions of the cerebellum, and with respect to the cerebral and cerebellar connections of individual basilar pontine regions. There is essentially no information available, for example, concerning the transfer of associative information from the pons to cerebellum. Whereas it appears that higher-order information is distributed in complex but specific patterns throughout the basilar pons, the manner in which this information is conveyed to the cerebellum, and the corresponding topographic organization within the cerebellum, have not yet been studied. Furthermore, the fractured somatotopy that has been discerned in the sensory afferents to the cerebellum [Kassel et al.,

Figure 4.

Composite color-coded summary diagram illustrating distribution within the basilar pons of the rhesus monkey of projections derived from associative cortices in prefrontal (purple), posterior parietal (blue), temporal (red), and parastriate and parahippocampal regions (orange), and from motor, premotor, and supplementary motor areas (green). Medial (**A**), lateral (**B**), and ventral (**C**) surfaces of the cerebral hemisphere are shown at upper left. The plane of section through the basilar pons is at lower left, and rostrocaudal levels of pons I–IX are shown at right. Cerebral areas that have been shown to project to the pons by other investigators using either anterograde or retrograde tracers are depicted in white; those areas studied with both anterograde and retrograde studies and found to have no pontine projections are shown on the hemispheres in yellow; and those with no pontine projections according to retrograde studies by other investigators are shaded in gray. Dashed lines in hemisphere diagrams represent sulcal cortices. In the pons diagrams, dashed lines represent pontine nuclei, and solid lines depict the traversing corticofugal fibers. Pontine projections are presented as a whole, and this diagram does not illustrate the finding that each architectonic area has its own unique pattern of pontine terminations. Associative corticopontine projections are substantial and are not overshadowed by the motor corticopontine system. It is apparent that there is a complex mosaic of terminations in the pons.

Each cerebralcortical region has preferential sites of pontine terminations. There is considerable interdigitation of terminations from some different cortical sites, but almost no overlap. This pattern is reminiscent of the fractured somatotopy shown in the sensory projections to the cerebellum (Fig. 7). This figure was derived from a review of 80 cases previously reported in Schmahmann and Pandya [1989, 1991, 1993, 1995a, 1996], and in abstract form in Schmahmann and Pandya [1995b]. All cases were studied using the same experimental technique. Pontine terminations were mapped manually onto a standard outline of the pons. Inherent inaccuracies in this method are readily acknowledged, largely on the basis of between-case comparison. There are also unavoidable inaccuracies in the attempted precise transformation of the data from an actual transverse section of the pons to an idealized version. Open areas in the pons are likely to represent sites of termination of projections from cortices not studied by these investigators. Comparison with published data from other laboratories [Künzle and Akert, 1977; Brodal, 1978; Vilensky and Van Hoesen, 1981; Ungerleider et al., 1984; Glickstein et al., 1985; Fries, 1990] provides support for this conclusion. Data from those studies were not included in this diagram, however, as the tracer substances, methodology, and/or planes of section employed in those experiments were different, rendering direct comparison of pontine terminations too unreliable.
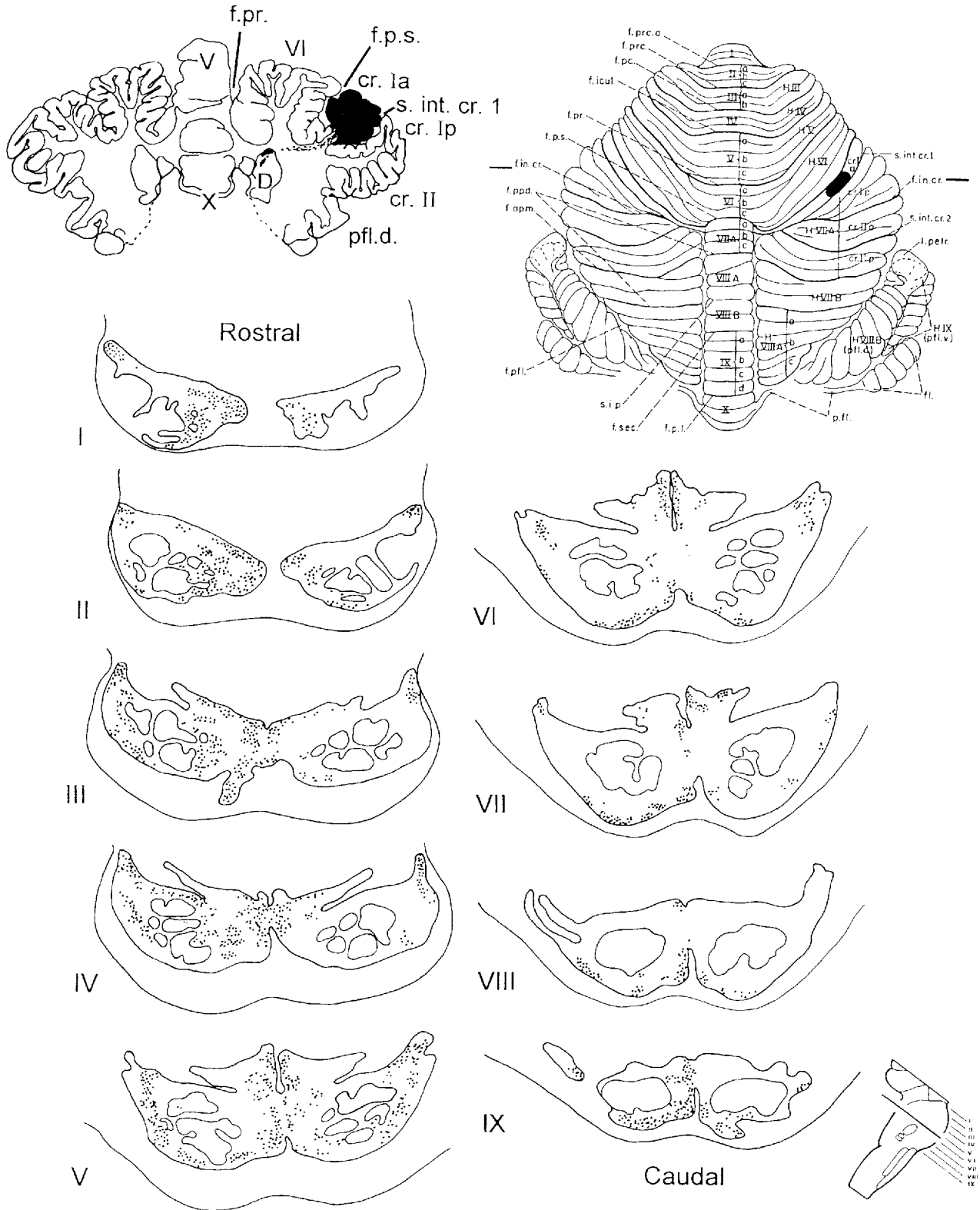
Figure 5.

1984; Bower and Kassel, 1990] (Fig. 7) may apply to the associative system as well, but this possibility has not been evaluated.

Feedback limb of the cerebrocerebellar system

The feedback loop of the cerebrocerebellar system is comprised of the cerebellar corticonuclear projection, the efferents from deep cerebellar nuclei *en passant* through the red nucleus to the thalamus, and the thalamocortical relay.

The intricacies of the cerebellar cortex itself are beyond the scope of this discussion, except to state that elegant models of cerebellar function [Marr, 1969; Albus, 1971; Ito, 1982] have been based on the structural consistency of the cortex and its physiologic behavior [Eccles et al., 1967; Thach, 1968; Palay and Chan-Palay, 1974]. Neurotransmitter/modulator/peptide differences in neuronal subtypes of cerebellar cortex are increasingly being identified [Oertel, 1993], and a mediolateral zonal pattern of organization of the cortex has been defined [Voogd, 1967; Oscarsson, 1979; Dore et al., 1990] that correlates with connectional specificity in the olivary projections to the cerebellum [Voogd and Bigaré, 1980]. These chemical-morphological variations provide some hope that the otherwise homogeneous-appearing cortex can be sub-

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Figure 5.
Diagram illustrating the distribution of labeled neurons (shown as black dots) in the basilar pons following injection of a tracer substance (wheat germ agglutinin-horseradish peroxidase (WGA-HRP), shown here in black shading) into crus I anterior of hemisphere lobule VIIA of a rhesus monkey cerebellum [Schmahmann and Pandya, unpublished]. The plane of the transverse section of the cerebellum (top left) showing the injection site is marked on the flattened map of the cerebellum (top right) according to Larsell [1970]. The plane of section of the rostrocaudal levels of the pons from I–IX is depicted in the diagram at lower right. Pontine nuclear subdivisions are not shown. Labeled neurons are seen bilaterally in the pons, but with a contralateral predominance. Neurons are distributed in multiple but distinct regions of the basilar pons following the injection in this single folium. This arrangement seems to allow for multiple cerebral cortical areas to communicate with the cerebellar folium via the distributed pontine neurons, as suggested in Figure 4. Pontine projections to subdivisions of each cerebellar folium are likely to be more restricted. Incidentally noted is anterograde transport of label from the injection site to a restricted site within the dentate nucleus of the ipsilateral cerebellum. Abbreviations for top left: cr. Ia, crus I anterior; cr. Ip, crus I posterior; cr. II, crus II; D, dentate nucleus; f.pr., primary fissure; f.p.s., superior posterior fissure; s.int.cr. I, internal sulcus of crus I. Roman numerals V, VI, and X refer to cerebellar lobules according to Larsell [1970].

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divided by methods other than gross anatomic descriptions and topographically organized connectional relationships.
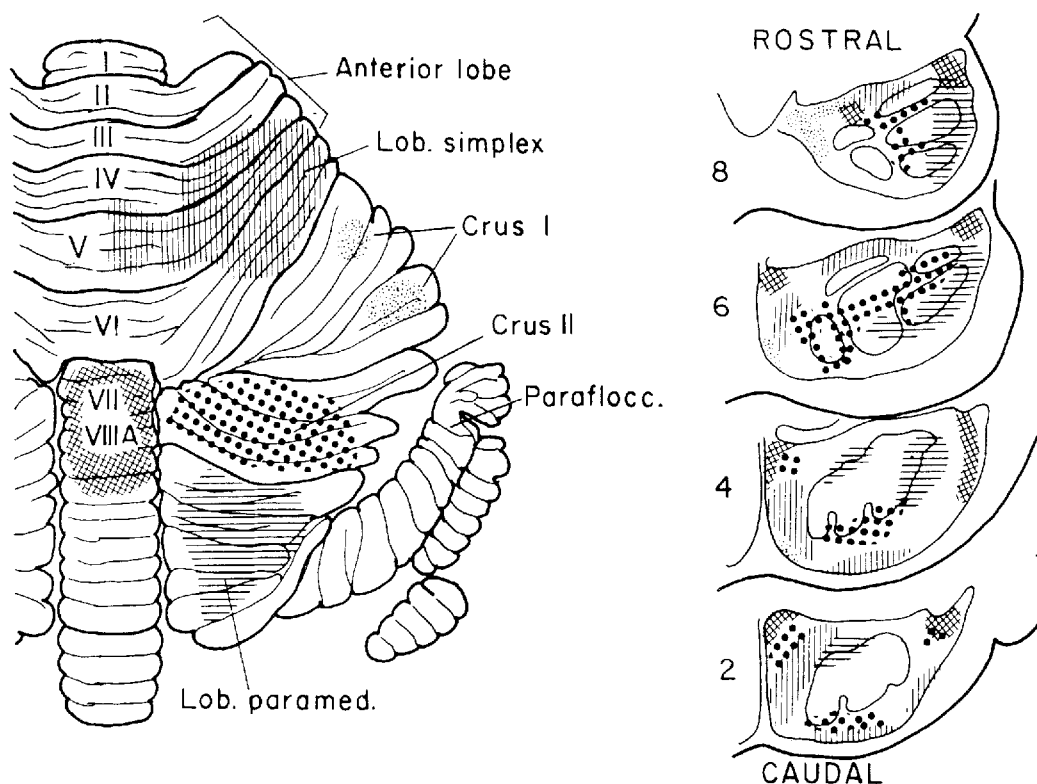
The corticonuclear projection consists of the axons of the cerebellar Purkinje cells, the only neuron responsible for efferents from the cerebellar cortex, that traverse the cerebellar white matter and terminate in the deep cerebellar nuclei. These nuclei in the nonhuman primate are the fastigial, interpositus anterior and posterior (equivalent to the globose and emboliform in the human), and lateral or dentate nucleus, as one moves from medial to lateral. The term "deep nuclei," seemingly redundant, is used to distinguish these nuclei from precerebellar nuclei, including the lateral reticular, inferior olivary, vestibular, and basilar pontine nuclei, among others, that have connections (often reciprocal) with the cerebellum. The topographic arrangement of the corticonuclear projection appears to be reasonably simple. The midline cortex projects to medial nuclear regions (fastigial nucleus), the lateral hemisphere projects to the dentate, and the intervening cortex corresponds with the nuclei in a predictable mediolateral pattern. The flocculonodular lobe additionally has direct connections with the vestibular nuclei, and the anterior interpositus with the red nucleus [Brodal A, 1981]. Ito [1982] utilized the repeating sequence of cortical organization and the predictable corticonuclear arrangement to postulate the concept of a corticonuclear microcomplex acting as the essential functional unit of the cerebellum.

Dow [1942] drew attention to the differential organization of the dentate nucleus in man and anthropoid apes as compared to that of lower primates and subprimate species. Referencing earlier work in the field, he noted [Dow, 1974] that the dentate nucleus "in man and anthropoid apes consists of two parts, a dorsomedial microgyric, magnocellular older part, which is homologous to the dentate nucleus of lower forms, and a very much expanded new part which comprises the bulk of the dentate nucleus in man and higher apes, the ventro-lateral macrogyric parvicellular part." Dow expanded further on how these two parts of the dentate differ with respect to a number of morphologic and embryologic properties, and then postulated, marshaling some early physiology and degeneration studies in humans, that the newer part of the dentate (the "neodentate") expanded in concert with, and was connected to, the frontal, temporal, and parietal association areas of the higher primates and man.

At the time that Dow [1974] formulated these hypotheses, it was the understanding that cerebellar-thalamic projections arose exclusively from the den-
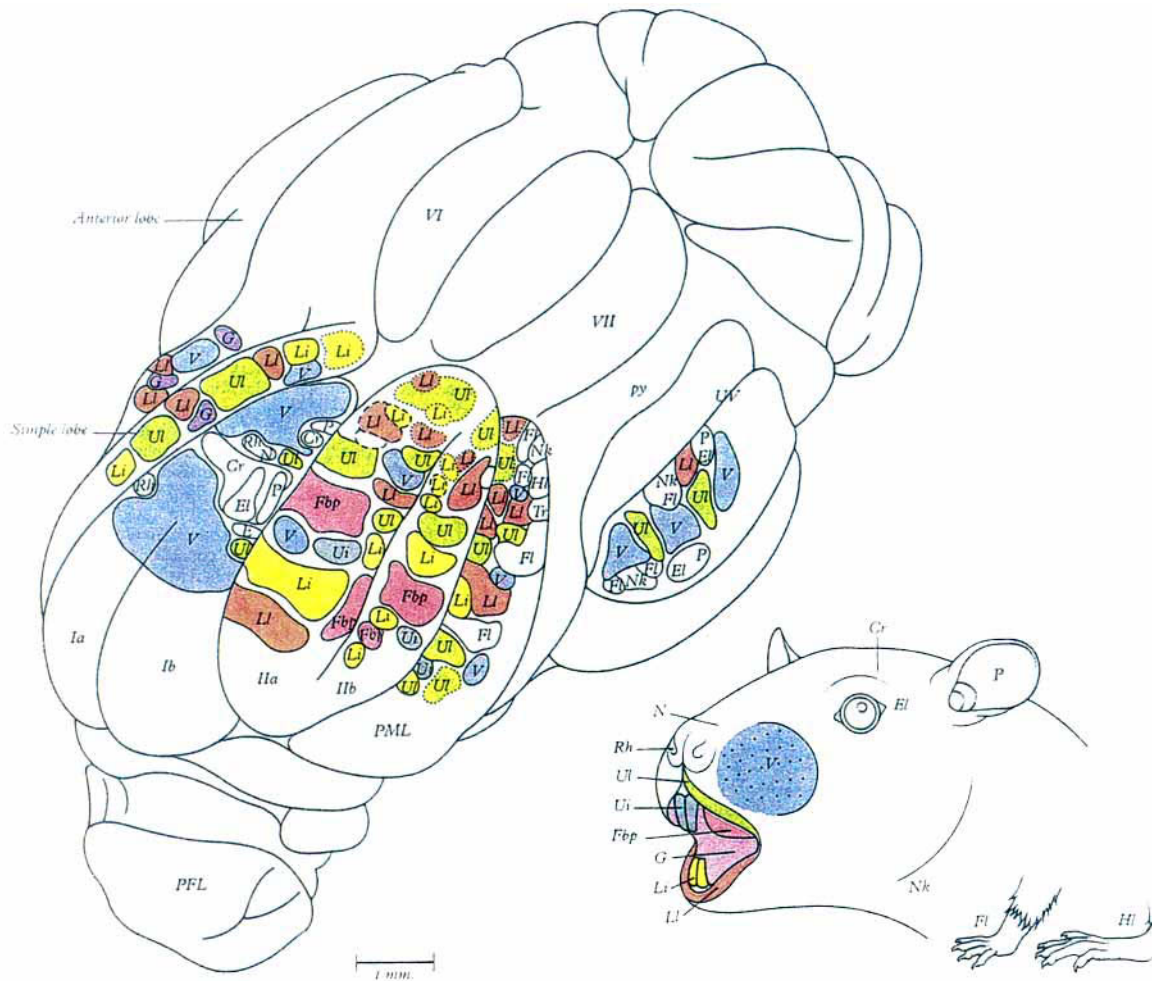
Figure 6.

Diagram summarizing the main features of the topographical arrangement of pontocerebellar connections as revealed in the WGA-HRP study of Brodal [1979]. In that study, tracer was injected into various parts of the cerebellar cortex, and the distribution of labeled neurons in the pons was noted. See text for details (reprinted from Further observations on the cerebellar projections from the pontine nuclei and the nucleus reticularis tegmenti pontis in the rhesus monkey, P Brodal, J Comp Neurol, Copyright © 1982 John Wiley & Sons, Inc.). The general organization as presented by Brodal appears to be accurate, although details seem somewhat more complex than depicted here [Schmahmann and Pandya, unpublished. See Fig. 5]. A compilation of various sources has led to the notion, not yet sufficiently evaluated by newer techniques, that the relationship between the cerebral cortex and the cerebellar cortex, as discussed in the text, is loosely as follows. The anterior lobe and lobulus simplex receive afferents from the motor and premotor cortices and to a small extent from the parietal lobe. The premotor and prefrontal cerebral regions are linked with cerebellar crus I, the motor cortex is linked with crus II, and the somatosensory and parietal association areas are linked with the paramedian lobule. Visual association cortices appear to be related to the paraflocculus [Brodal P, 1979; reviewed in Brodal A, 1981; Stein and Glickstein, 1992]. This currently incomplete and sketchy understanding of the important pontocerebellar pathway and the relationship between the cerebellar cortex and the associative and paralimbic regions of the cerebral hemispheres is in need of update and revision.

tate nucleus and were conveyed through the ventrolateral thalamic nucleus to the motor cortex [Henneman et al., 1952]. Subsequent anatomic studies employing newer techniques demonstrated that the dentate is assisted in this role by thalamic efferents which arise from other cerebellar nuclei, namely the fastigial and the interpositus [Batton et al, 1977; Stanton, 1980; Kalil, 1981]. Additionally, it transpires that the classic cerebellar recipient motor thalamic nuclei (the pars oralis of the ventral posterolateral nucleus, or VPLo, the caudal and pars postrema aspects of the ventrolateral nucleus, or VLc and VLps, and nucleus X, in the terminology of Olszewski [1952]) are not alone in receiving input from the cerebellum. There are nonmotor thalamic nuclei that have a considerable cerebellar input as well. These include the intralaminar nuclei, particularly the centralis lateralis (CL), as well as the paracentralis (Pcn) and centromedian (CM), and the medial dorsal nucleus [Thach and Jones, 1979; Stanton, 1980; Kalil, 1981; Ilinsky and Kultas-Ilinsky, 1987; Orioli and Strick, 1989]. The CL nucleus, like other intralaminar nuclei, has widespread cortical connections, including the posterior parietal cortex, the multimodal regions of the upper bank of the superior temporal sulcus, the prefrontal cortex, the cingulate gyrus, and the primary motor cortex [Kievit and
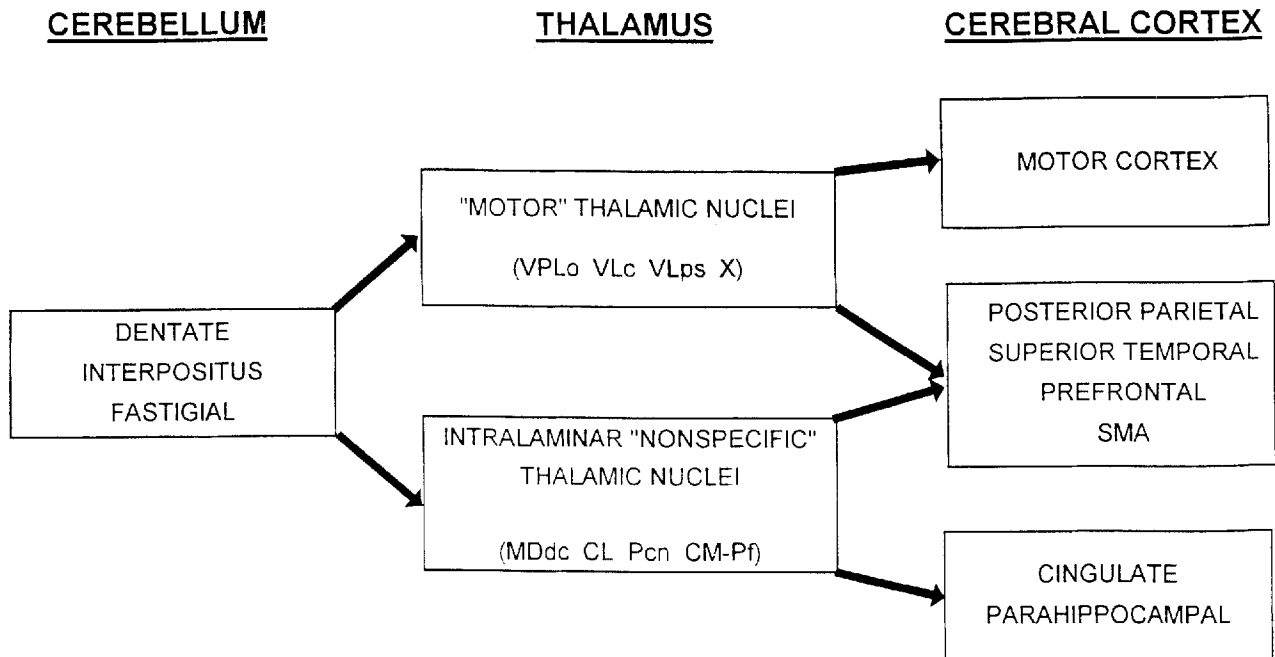
Figure 7.

Diagram illustrating the fractured somatotopic distribution of patches of mossy fibers sharing the same receptive fields in the posterior lobe of the rat cerebellum. Fractured somatotopy results in interdigitation in the cerebellum of afferents from geographically separated peripheral regions. There appear to be features in common between this arrangement and that described for associative (and sensorimotor) corticopontine pathways (see Figs. 3, 4). These patterns of organization are consistent with the notion that there is convergence of inputs from multiple associative cerebral regions to common areas within the cerebellum. This diagram is a redrawing of that from Shambes et al. [1978] and Welker [1987]. It is reproduced from *Gray's Anatomy*, 38th edition, 1995, p. 1056 (with permission). Cr, crown; El, eyelids; Fbp, furry buccal pad; Fl, foot and forelimb; G, gingiva; Hl, hindlimb; Ia, c, crus I of ansiform lobule, folium a,b; IIa,b, crus II of ansiform lobule, folium a,b; Li, lower incisor; Ll, lower lip; N, nose; Nk, neck; P, pinna; PFL, paraflocculus; PML, paramedian lobule; py, pyramis; Rh, rhinarium; Ui, upper incisor; uv, uvula; VI, VII, lobules VI, VII of Larsell [1970].

Kuypers, 1977; Yeterian and Pandya, 1985, 1989; Vogt and Pandya, 1987; Schmahmann and Pandya, 1990; Siwek and Pandya, 1991]. The Pcn nucleus projections include the parahippocampal gyrus [Blatt et al., 1991, personal communication] (Fig. 8).

The cerebellar nuclei project to the medial dorsal (MD) thalamic nucleus, which has generally been regarded as the major site of thalamic connections with the frontal lobe. The MD receives projections from the cerebellum mainly in its paralaminar parts,

i.e., in the laterally-situated pars multiformis (MDmf), and more caudally in the pars densocellularis (MDdc) [Stanton, 1980; Ilinsky and Kultas-Ilinsky, 1987]. The cerebellar-recipient paralaminar MDmf and MDdc have reciprocal connections with area 8, area 46 at both banks of the principal sulcus, and area 9 in the frontal lobe [Giguere and Goldman-Rakic, 1988; Barbas et al., 1991; Siwek and Pandya, 1991], but also with the cingulate gyrus, posterior parietal cortex, and multimodal parts of the superior temporal sulcus

Figure 8.

Summary diagram of cerebello-thalamo-cortical pathways that may be relevant in redirecting information from the cerebellum back to higher-order areas of the cerebral cortex. The traditionally motor cerebellar-recipient thalamic nuclei (VPLo, VLc, VLps, and X of Olszewski [1952]) project not only to the motor and premotor cortex, but in varying degrees of strength they are also connected with the supplementary motor area (SMA), and the prefrontal (areas 8 and 46), posterior parietal (superior and inferior parietal lobules), and multimodal temporal regions (area TPO in the upper bank of the superior temporal sulcus) as well. Furthermore, the intralaminar (CL, Pcn, CM-Pf) and medial dorsal (MDdc) thalamic nuclei, that are known to project in varying combinations to the association and limbic cortices, have been shown to receive projections from the deep cerebellar nuclei. CL nucleus projections, in particular, are widespread and include the primary motor cortex (projection not shown). Topographic organization of the cerebellothalamic projection and the thalamocortical projection is not represented here. See text for references (reprinted from Schmahmann [1994]). CL, centralis lateralis; CM, centromedian; MDdc, medial dorsal nucleus, pars densocellularis; Pcn, paracentralis; Pf, parafascicularis; VLc, ventral lateral, pars caudalis; VLo, ventral lateral, pars oralis; VLps, ventral lateral, pars postrema; X, nucleus X.

[Yeterian and Pandya, 1985, 1989; Vogt and Pandya, 1987; Schmahmann and Pandya, 1990].

A further relevant feature of the feedback circuit is that the traditionally motor thalamic nuclei have projections to regions of the cerebral cortex outside the primary and supplementary motor areas. The prefrontal periarcuate areas are also reciprocally interconnected with nucleus X [Kievit and Kuypers, 1977; Stanton et al., 1988], VLc [Kievit and Kuypers, 1977], and VPLo [Künzle and Akert, 1977]. This was confirmed more directly in a recent transsynaptic retrograde tracer study of area 46 of the prefrontal lobe (cerebral cortex injected with tracer, label followed back to neurons in thalamus and further back to cerebellar dentate neurons) [Middleton and Strick, 1994]. The temporal and posterior parietal lobes have also been shown to receive projections from these cerebellar-recipient thalamic nuclei. The upper bank of the superior temporal sulcus receives projections from the VLc and VLps nuclei [Yeterian and Pandya, 1989]. Widespread regions of the posterior parietal cortex receive projections from the VLps nucleus; the VLc projections to the parietal lobe are similar although less intense; nucleus X projects to both the upper and lower banks of the intraparietal sulcus, and VPLo projects to both the gyral and sulcal cortices of the superior parietal lobule at the lateral convexity of the hemisphere [Schmahmann and Pandya, 1990].

It remains to be shown using direct transneuronal techniques how much of the cerebellar input to the thalamus is conveyed to these different cortical areas. Nevertheless, it would appear from the available anatomic evidence that the cerebellar recipient "motor" thalamic nuclei project not only to the motor cortices, but also to the associative areas in the posterior parietal and superior temporal cortices, and to the

prefrontal cortex. Furthermore, the intralaminar nuclei, which are themselves recipient of cerebellar efferents, project widely throughout the cerebral cortex, to the motor, associative, and paralimbic cortices.

Details are not currently available regarding precise topographical relationships between each cerebellar nucleus and its corresponding complement of thalamic terminations. Some topographic patterns have been established, however, for the differential anterior or posterior dentate nucleus projections [Thach and Jones, 1979]. Additionally, these authors defined certain principals of organization of the cerebellothalamic projection. Thus, single cerebellar nuclear regions project to a few (between 3–7) rostrocaudally-oriented rod-like aggregates within a dorsoventral curved lamella in the thalamus.

Climbing fibers and cognition:
Is there an anatomic substrate?

Before leaving this anatomic discussion, it is necessary to visit the issue of the climbing fiber input to the cerebellum. The cerebral afferents of the pontine (mossy fiber) and olivary (climbing fiber) systems are markedly different. The existence of a direct corticoolivary pathway is questionable, and if present, has not been shown to arise from outside of motor areas. In the nonhuman primate, the inferior olive receives most of its descending input from the parvicellular red nucleus. The afferents of the parvicellular red nucleus are derived most heavily from motor, premotor, and supplementary motor cortices, and to some extent from the postcentral gyrus and area 5 in the superior parietal lobule. They are not derived to any convincing degree (at least in studies to date) from the associative or paralimbic cortices [Kuypers and Lawrence, 1967; Saint-Cyr and Courville, 1980; Humphrey et al., 1984; Kennedy et al., 1986]. Archambault [1914] reported rubral connections with the infratemporal cortices in humans. This improbable pathway has not been confirmed, however, and cannot reliably be used at this time. The zona incerta which projects to the inferior olive [Saint-Cyr and Courville, 1980; Cintas et al., 1980] receives projections from prefrontal cortices [Kuypers and Lawrence, 1967; Shammah-Lagnado et al., 1985], so there may be some indirect prefrontal input to the olivary system. Nevertheless, it appears that these two systems are quite different. The red nucleus-inferior olive system seems to convey predominantly motor and some sensory efferents from the cerebral cortex to the cerebellum. On the other hand, the pons (as discussed above) is relevant for motor and sensory as well as for associative and paralimbic information. This conclusion is bolstered by the finding of reciprocal connections between the red nucleus and the cerebellar anterior interpositus nucleus. This latter nucleus is the efferent channel of the intermediate region of the anterior lobe of the cerebellum, which appears to be truly a motor-related region [Brodal A, 1981; Seitz et al., 1991]. It thus seems to be the domain of the corticopontocerebellar (mossy fiber) pathway to convey associative and paralimbic information from the cerebral hemispheres to the cerebellum.

The overall picture that emerges is that the feedforward and feedback limbs of the cerebrocerebellar system include the associative and paralimbic cerebral cortices. This leads to the conclusion, based on anatomic grounds, that the cerebellum is an essential node in the distributed neural system that subserves cognitive operations.

THEORETICAL IMPLICATIONS

Perhaps it should not be surprising that the cerebellum may contribute to sensory, affective, autonomic, and cognitive functions as well as to motor control. John Hughlings Jackson wrote of the continuum from movement to thought [Jackson, 1887]. He agreed with Sir David Ferrier's statement that "mental operations, in the last analysis, must be merely the subjective side of sensory and motor substrata" [Ferrier, 1876]. In Jackson's view, movement was the externally visible manifestation of internal neuronal activity. Thought was as much a product of that neuronal activity, but the overt manifestations, he stated, were not readily detected by the observer. Thus, movement of a limb, and movement of an idea, occupy different positions on the same scale. "Before I put out my arm voluntarily I must have a 'dream' of the hand as being already put out. So too, before I can *think* of now putting it out I must have a like 'dream,' for the difference betwixt thinking of now doing and now actually doing is, like the difference betwixt internal speech and external speech, only one of degree; in one there is slight discharge of a certain series of nervous arrangements, in the other strong discharge of that series" [Jackson, 1879–1880]. The basal ganglia, also once regarded as quintessentially motor [Denny-Brown, 1966] are now strongly implicated in a variety of cognitive operations [Caplan et al., 1990], and it seems that the cerebellum is destined for similar treatment. In the view of Piaget [1977], movement is intricately bound with sensation, and with intellectual and emotional growth. Sensorimotor, cognitive, and affective systems all incorporate cerebellar input, and the evolving

understanding that these functions are likely to be influenced by the cerebellum is harmonious with this Piagetian concept.

It is not yet established by which precise mechanisms the cerebellar cortex and nuclei influence either motor or nonmotor activity (sensory, cognitive, autonomic, or emotional). Issues including mossy fiber-climbing fiber interaction [Marr, 1969; Albus, 1971], timing [Ivry and Keele, 1989], error detection [Fiez et al., 1992; Ito, 1993; Silveri et al., 1994], automatization [Jenkins et al., 1994; Doyon et al., 1995], shifting attention [Akshoomoff and Courchesne, 1992], dynamic state monitoring [Paulin, 1993a, b], and sensory preprocessing of information [Bower, 1995] have all been discussed in this context, and provide theoretical bases for further hypothesis testing. What is apparent, however, is that the anatomically-based concepts of cerebrocerebellar interaction discussed here in detail are compatible with many of the different hypotheses regarding cerebellar function. They also provide an anatomic framework within which to view these hypotheses. The associative and paralimbic cerebral cortices, as well as the motor and sensory areas, are incorporated into the cerebrocerebellar system in a topographically ordered manner. A further degree of specificity is added to this system by the cerebellar corticonuclear microcomplexes, and the differential organization of the cerebellar nuclei (including the neodentate). Moreover, each cerebellar nuclear region projects to "rods" of rostrocaudally oriented neurons within the thalamus, which in turn are connected with cerebral cortical columns [Asanuma et al., 1983]. These highly organized anatomic substrates facilitate cerebellar processing of a heterogeneous, sometimes overlapping, series of operations, be they motor or sensory perceptual tasks, cognitive manipulations, or affective states and autonomic reactions. These channels of communication in the cerebrocerebellar system are reminiscent of the multiple parallel but partially overlapping circuits described between the frontal lobe and the basal ganglia [Alexander and Crutcher, 1990; Goldman-Rakic, 1988]. Both of these major circuits (cerebral-cerebellar and cerebral-basal ganglia) appear to be discretely organized into *anatomical subsystems*. In addition, they both (as postulated here for the cerebellum) contribute to, and are integral components of, differentially-organized *functional subsystems* within the framework of distributed neural circuits. The proposed net effect of these multiple streams of diverse information reaching into and being sent back from the cerebellum is a cerebellar coordinate transformation integrating multiple internal representations with external stimuli and self-generated responses.

The cerebellar contribution to these different subsystems permits the ultimate production of harmonious motor, cognitive, and affective/autonomic behaviors.

It is useful to consider cognitive performance, affect, and autonomic function in light of the understanding of cerebellar motor deficits which are characterized by abnormalities of rate, rhythm, and force of movements. Intact cerebellar function facilitates actions harmonious with the goal, appropriate to context, and judged accurately and reliably according to the strategies mapped out prior to and during the behavior. When the cerebellar component of the distributed neural circuit is lost or disrupted, the oscillation dampener is removed, and there is no longer a smoothing out of behaviors around a homeostatic baseline. The consequence is "dysmetria of thought." With this concept, the approach to psychoses and other disorders of behavior enters a new phase of study, one that focuses on a possible aberration of the cerebellum.

Proposed rules governing the relationship between the cerebellum and cognitive processing

The theoretical notions derived from these anatomic studies suggest that there are central themes that help define the role of the cerebellum in its contribution to cognitive processing.

1. *The associative and paralimbic incorporation into the cerebrocerebellar circuit is the anatomic underpinning of the cerebellar contribution to cognition, emotion and autonomic function.* It is predicted that there are interactions between sensorimotor and cognitive/affective/autonomic afferents within the cerebellar cortex.

The aguments in favor of the various nonmotor behaviors of the cerebellum are outlined above. It should be noted that it is also possible to analyze the findings reported here more conservatively, and to draw rather different conclusions. A judicious approach may view the data, particularly the anatomic results, as follows. The cerebellum needs to know what intended trajectories are planned, and at what speed and in what direction objects are moving in space. With that information the cerebellum may facilitate a motor response that is rapid and efficient. This may well be a true functional correlate of the associative cerebrocerebellar circuit. This interpretation, however, appears too narrow and does not account for physiological, clinical, and functional neu-

roimaging observations. Another reasonable departure from the accepted notion of cerebellar motor function is more modest than the principles outlined so far in this paper. This view holds that associative and paralimbic connections may be viewed as facilitating a cerebellar influence on the cognitive or affective component of movement. In other words, perhaps this is a substrate for nonverbal communication, or "body language."

2. *There is topographic organization of cognitive and behavioral functions within the cerebellum. The archicerebellum, vermis, and fastigial nucleus are principally concerned with affective and autonomic regulation and emotionally relevant memory. The cerebellar hemispheres and dentate nucleus are concerned with executive, visual-spatial, language, and other mnemonic functions.*

The hypothesis that there is topographic organization of the behavior-related functions in the cerebellum is derived only in part from anatomic studes. This is in large measure because the data are presently sketchy concerning the cerebellar afferents (pons-to-cerebellum) and efferents (cerebellum-to-thalamus). Nevertheless, physiological, behavioral, and functional neuroimaging data show that nonmotor functions are not diffusely distributed throughout the cerebellum. This is in accord with the detailed anatomic organization of the associative and paralimbic corticopontine projection. It is also reminiscent of the topographic organization of the cerebellum with respect to the sensory and motor systems.

This hypothesis is also in agreement with data derived from fastigial nucleus stimulation experiments in cats and ablation experiments in monkeys, from functional neuroimaging data regarding affective expression, and with anecdotal reports of clinical observations of psychotic behavior in patients with vermis or midline lesions [Heath et al., 1979]. It also is consistent with early physiologic observations, contemporary functional neuroimaging, and preliminary clinical work implicating the lateral cerebellar hemispheres in language, memory, executive, and visual-spatial disturbances. Precisely how these associative functions are distributed in the cerebellar hemispheres remains to be shown.

The cerebellum is not privy to information from all areas of the cerebral cortex. As discussed above, there appears to be a dichotomy in the feedforward, and probably in the feedback, limb as well. The hallmark of this dichotomy is the existence of cerebellar connections with the dorsal visual stream but not with the ventral visual stream. This pattern is reflected in the occipital, parietal, and temporal lobe projections, and in interconnected regions of the prefrontal and paralimbic cortices. The possible functional implications of these anatomic observations have been alluded to, and include relevance for spatial vs. object memory, and the emotional valence of different stimulus properties. Not least important, they also include the role of the cerebellum in the guidance of movement in extrapersonal space.

It has been suggested that learning is a principal, or critical, feature of the cerebellar contribution to nonmotor function. Ample evidence is now available that the cerebellum is able to influence learning paradigms that include some form of motor efferent. This conclusion is derived from studies of classical conditioning and motor learning. Two considerations derive from this line of thought, and these are restated here. The concept of cerebellar incorporation into the distributed neural circuitry subserving higher-order behavior is not predicated on the necessity for the cerebellum to function as a learning machine. Learning may well be one distributed function that requires a cerebellar contribution. It seems unlikely, though, based on the experimental and clinical observations to date, that this is the sine qua non of the cerebellar contribution to nonmotor processing. A related consideration is the nature of the cerebral input to the climbing fiber system. Present understanding of the anatomy of the cortico-rubro-olivary system is that it does not include associative or paralimbic cortices. This may suggest that the learning to which the cerebellum contributes must have a demonstrable motor efferent. If it can be shown, however, that cerebellar incorporation into a learning paradigm is not dependent upon a motor efferent, then it may be necessary to revisit the current understanding of the motor cortical input to the climbing fiber system. Alternatively, theoretical formulations about the climbing fiber-mossy fiber interactions as the basis of learning in the cerebellum may need to be reevaluated.

3. *The convergence of inputs from different associative cerebral regions to common areas within the cerebellum facilitates cerebellar regulation of supramodal functions.*

Anatomic studies suggest that the cerebral hemispheres are connected with the pons and cerebellum by a pattern of diverging and converging circuits. Sensory afferents to the cerebellum terminate with a "fractured somatotopy" in which discontinuous body parts are represented in adjacent cerebellar folia. Is

there a "fracturing" in the cognitive realm as well? In other words, are the cerebellar cortical terminations arising from prefrontal areas adjacent to inputs from parietal or superior temporal polymodal areas, or to those from paralimbic cortices in the cingulate and posterior parahippocampal gyri? This is suggested by the dispersed nature of the cerebral cortical input to the pons from associative and paralimbic cortices, as well as from the sensorimotor cortices. The connections of specific cerebral areas with specific cerebellar regions, however, are not known, and therefore this remains an open question. A possible correlate of this complex anatomy is that cerebellar clinical syndromes may manifest traces of different "cerebral" behavioral syndromes. In accordance with proposed rule 2 above, though, it may be expected that there is a relative topographic ordering of major functional specializations.

4. *The cerebellar contribution to cognition is one of modulation rather than generation.*

This concept dates back to the observations of Flourens [1824] from his work on cerebellectomized pigeons. It has been comfortably applied to the sensory and motor systems, and it is suggested here that this concept also translates to the cognitive realm. What precisely is meant by the term "modulates" is a matter of debate. The concept offered here is that the cerebellar role in the cognitive, affective, and autonomic domain is similar to that which has long been recognized in the motor realm. That is, the cerebellum serves as an oscillation dampener, maintaining function steadily around a homeostatic baseline, and smoothing out performance. The prominent sensory afferents to the cerebellum may facilitate these other functions, but it is also possible that the cerebellum modulates sensory acquisition as well.

5. *The cerebellum performs the same computations for associative and paralimbic functions as it does for the sensorimotor system.*

The mechanisms of cerebellar transformation of motor or nonmotor information remain open to debate. Whatever the mechanism, however, behaviorally relevant information from the cerebral cortex is funneled through the cerebrocerebellar circuit within multiple parallel but partially overlapping loops in the corticopontine pathway. These channels of information converge with topographic ordering within the cerebellar cortex. They are manipulated by the cerebellar corticonuclear microcomplexes. They are then trans-

mitted via the deep cerebellar nuclei back to both specific and nonspecific thalamic nuclei, before returning to the cerebral cortex. The available cerebellar computational mechanisms remain constant. The information being computed is different.

SUPPORTIVE EVIDENCE

These anatomic observations are not isolated findings but are bolstered by reports from other areas of neuroscience investigation that converge upon the same conclusion. Much of this work has been summarized previously [Dow and Moruzzi, 1958; Martner, 1975; Watson, 1978; Schmahmann, 1991, 1994]. The role of the archicerebellum and fastigial nucleus in autonomic responses and complex emotional behaviors [Zanchetti and Zoccolini, 1954; Peters and Monjan, 1971; Berntson et al., 1973; Reis et al., 1973; Cooper et al., 1974; Heath, 1977; Berman et al., 1978], the critical incorporation of the anterior interpositus nucleus in classical conditioned learning [Thompson, 1988; Solomon et al., 1989; Woodruff-Pak et al., 1990; Topka et al., 1993], and the disruption of visual-spatial skills in cerebellar lesioned models [Lalonde et al., 1987; Molinari et al., 1991] have been early and consistent indicators of nonmotor cerebellar functions. Functional neuroimaging studies of the cerebellum, now increasing exponentially in number as methodology and hypotheses evolve, point to cerebellar activation in a number of conditions.

These include linguistic processing [Petersen et al., 1988; Klein et al., 1995], mental imagery [Ryding et al., 1993; Mellet et al., 1995; Parsons et al., 1995], cognitive flexibility [Kim et al., 1994], sensory discrimination [Gao et al., 1996], classical conditioning [Logan and Grafton, 1994], motor learning [Seitz and Roland, 1992; Jenkins et al., 1994; Rauch et al., 1995], verbal memory [Grasby et al., 1993; Andreasen et al., 1995], working memory [Klingberg et al., 1995], and emotional states [Reiman et al., 1989; Bench et al., 1992; Dolan et al., 1992; George et al., 1995; Mayberg et al., 1995]. Clinical reports dating back a century [see Dow and Moruzzi, 1958; Schmahmann, 1991] relating cerebellar pathology to altered behaviors have been strengthened by more recent analyses. Deficits in planning and executive functions [Botez et al., 1989; Bracke-Tolkmitt et al., 1989; Grafman et al., 1992; Appollonio et al., 1993], motor learning [Sanes et al., 1990; Molinari et al., 1995], visual spatial ability [Botez et al., 1989], linguistic processing [Fiez et al., 1992; Silveri et al., 1994; van Dongen et al., 1994], and affect [Heath et al., 1979; Bauman and Kemper, 1985; 1994; Murakami et al., 1989] have all been reported to date,

but the complete characterization of what we have termed the cerebellar cognitive-affective syndrome [Sherman and Schmahmann, 1995] continues to receive attention and is in the process of being further defined.

FURTHER IMPLICATIONS FOR FUNCTIONAL NEUROIMAGING

The ability to examine the cerebellar component of the distributed neural circuit subserving cognitive operations in the normal subject is a major advance. Functional neuroimaging experiments have been able to document multiple distributed interconnected cerebellar as well as cerebral regions that contribute to these cognitive operations. Results have been predicted and bolstered by connectional neuroanatomy in nonhuman primates. The observations support the major theses of this paper, and they have the potential to address intriguing questions regarding cerebellar function.

Some testable hypotheses that readily present themselves for analysis include the following:

1. There is a functional topography within the posterior and lateral cerebellum and within the dentate nucleus such that executive, visual-spatial, and mnemonic functions can be correlated with separate mediolateral and rostrocaudal coordinates.
2. The vermis, flocculonodular lobe, and fastigial nucleus are activated in tests of emotion and autonomic regulation, and in disorders of affect.
3. The cerebellum is activated during tasks requiring visual-spatial analysis, but not by those that assess visual object discrimination.
4. Interconnected cerebral association areas and cerebellar sites are activated in concert with each other. In patients with cognitive impairment following cerebellar injury, reversed cerebellar diaschisis involves the cerebral association areas corresponding most closely with the behavioral syndrome.
5. The red nucleus (and the olivocerebellar system) are not involved in cognitive tasks devoid of motor efferents.

In order to make more informed judgments about which cerebellar regions are activated by what process, we have developed [Schmahmann et al., 1996] a system of analysis of cerebellar structures for use with PET or MRI similar to that already in use for the cerebral hemispheres [Talairach and Tournoux, 1988;

Rademacher et al., 1992]. Such a system should facilitate accurate localization of sites of activation, and volumetric comparisons.

The following statements are informative: "If the cerebellum can act in both the sensory and the motor sphere, as is indicated, then many of the older concepts of cerebellar function must be greatly modified. For example, it becomes clear that the idea of cerebellar function as a whole must be withdrawn and the idea adopted that there are localized functional areas which may act interrelatedly. Another idea which must be discarded is that the cerebellum is an organ solely concerned with proprioception ... and an idea which must be considerably broadened is that the cerebellum acts only to coordinate muscular activity. As has been seen, this concept is entirely too limited in its scope. ... These newer contributions to knowledge of the cerebellum make it imperative that one adopt broader concepts of cerebellar function. Obviously such functional concepts must encompass cerebellar influences on the sensory and motor centers of the cerebrum, as well as related influences on diencephalic, mesencephalic and medullary centers. As previously indicated, it is highly probable that this influence is exerted in such a way as to alter the threshold of excitability of these centers, depending on the physiologic need. If, as seems likely, this action is exerted in a temporal sphere, either to potentiate or to dampen their activity, depending on their needs for proper function, then the cerebellum stands out as 'the great modulator of neurologic function' and new horizons of cerebellar action are introduced into neurology and psychiatry." We end this paper as we started it. These words of Snider [1992] are even more true today than when first published.

The field of cognitive neuroscience as applied to the cerebellum is no longer merely emerging [Schmahmann, 1991] but has come of age. Further specific attention to cerebellar activation by cognitive tasks will be invaluable in testing and challenging the conclusions and hypotheses presented here, and in particular, the proposed rules governing the relationship between the cerebellum and cognition.

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