The cerebrocerebellar system: anatomic substrates of the cerebellar contribution to cognition and emotion

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Abstract
The contribution of the cerebellum to the modulation of cognition and emotion is facilitated by the connections between the cerebellum and brain structures known to be associated with a wide array of non-motor behaviors. The cerebellum has interconnections with brainstem and thalamic reticular systems that subserve arousal. Autonomic activity is supported by the reciprocal interconnections with the hypothalamus. Limbic and paralimbic connections include the hypothalamus, septal region, hippocampus, and cingulate gyrus. Associative connections consist of both feedforward and feedback limbs. The basilar pons receives inputs from the prefrontal, posterior parietal, superior temporal, parahippocampal, and cingulate cortices, as well as from the sensorimotor cortices. This information is conveyed from the pons to cerebellum, before it is relayed back via thalamus to the associative and paralimbic regions of the cerebral cortex. The anatomical arrangement of segregated loops of cerebral cortical connections stands in contrast to the cerebellar cortical architecture that is essentially uniform. This has theoretical and clinical ramifications. It is the anatomical basis for the dysmetria of thought hypothesis that postulates a universal cerebellar transform, in which the cerebellum performs its unique computation in a topographically precise manner on diverse streams of information relating to almost all aspects of behavior including cognition and emotion. It provides an anatomic basis for the observations of cerebellar activation by cognitive and affective paradigms in functional neuroimaging experiments. It helps explain the clinical phenomena that characterize the cerebellar cognitive affective syndrome, and it provides an anatomic basis for a causal relationship between cerebellar pathology and psychiatric and neurobehavioral conditions. Knowledge of these anatomical pathways is critical to the further development of hypotheses, experimental approaches, and clinical questions that can advance the understanding of the contribution of the cerebellum to cognition and to disorders of intellect and emotion.

Introduction
The cerebellar cortex is characterized by a repeating cytoarchitecture that, with a few exceptions, is essentially constant throughout the structure (Voogd & Glickstein, 1998). A repeating sequence is also seen in the chemoarchitectonic divisions within the cerebellar cortex that are identified by alternating bands of neuronal staining induced by monoclonal antibodies (Hawkes et al., 1985). This pattern of organization has led to the development of a number of models in which the cerebellum performs a uniform computation. Clinical, experimental, and functional neuroimaging studies demonstrate that the cerebellum is involved in multiple different functions from arousal, to sensorimotor function and higher order processing (see Schmahmann, 1997), and preliminary evidence suggests that there is a topographic arrangement of these functions within the cerebellum (Schmahmann, 1991; Desmond & Fiez, 1998; Schmahmann et al., 1998).

The evolving understanding of this broader role of the cerebellum has been facilitated and substantiated by new insights into the cerebellar connections with other brain regions. Given the uniformity of cerebellar cortical architecture, the connectional specificity of the cerebrolincerebellar pathways confers on the cerebellum the ability to modulate the wide array of behaviors attributed to it. The anatomic systems that support the cerebellar contribution to cognition and affect are important in understanding the cerebellar role in nervous system organization, and consequently in the neurologic and psychiatric manifestations of systemic and focal brain pathology. This paper therefore provides a brief overview of the afferent and efferent cerebellar interconnections with other brain areas, and emphasizes the connectional specificity of the different aspects of the cerebrolincerebellar circuit.

There are cerebellar connections with the reticular system that support arousal; the hypothalamus, important for autonomic function; the limbic system that subserves the experience and expression of emotion; and the paralimbic and neocortical association areas crucial for cognitive processes and the cognitive dimensions of affect.

Reticular system
The vermis at the cerebellar midline and the fastigial nucleus are anatomically tightly linked and
functionally related (Haines, 1981). Reticular projections to the vermal-fastigial region arise from the pontine raphe and pontine reticular tegmental nucleus, and from the mesencephalic and medullary reticular formation (Noda et al., 1990). The lateral reticular nucleus sends projections to all the cerebellar nuclei (Qvist, 1989; Gonzalo-Ruiz & Leichnetz 1990).

Fastigial nucleus projections to the reticular formation are directed to the medial, lateral and paramedian reticular nuclei, the vestibular nuclei, nucleus tractus solitarius, nucleus gigantocellularis, and to the nucleus pontis caudalis (Andrezik et al., 1984). The physiological significance of this projection is underscored by the fact that blood pressure and heart rate are increased following fastigial stimulation (Andrezik et al., 1984). The fastigial nucleus also sends efferents to the central mesencephalic reticular formation, the periaqueductal gray and the lateral reticular nucleus (Qvist, 1989).

Efferent projections are also directed through the superior cerebellar peduncle to the non-specific intralaminar thalamic nuclei, notably the central lateral, paracentral, paraventricular and parafascicular nuclei (Miller & Strominger, 1977; Person et al., 1986; Qvist, 1989; Gonzalo-Ruiz & Leichnetz, 1990; Aumann & Horne, 1996) that project widely throughout the cerebral hemispheres and may play a role in arousal as well as in nociception.

Catecholaminergic and monoaminergic systems

Brainstem neurotransmitter systems in the raphe (serotonin), locus ceruleus (norepinephrine), ventral tegmental area (dopamine) and possibly histaminergic structures receive diffuse cerebral cortical input and in turn convey their efferents to widespread cerebellar regions (Snider, 1975; Dempsey et al., 1983; Marcinkiewicz et al., 1989). This may confer a background tone upon which the mossy fiber and climbing fiber systems in the cerebellum exert their more specific and topographically precise influence.

Autonomic system

The influence of cerebellar stimulation on the autonomic nervous system in cats was one of the earliest demonstrations of a cerebellar role in non-motor activity. These autonomic phenomena included inhibition of respiratory and vasomotor carotid sinus reflexes by stimulation of the anterior vermis (Moruzzi, 1940), and bradycardia, hypotension, mydriasis, altered gastrointestinal motility, length of gestational period and piloerection induced by anterior lobe cortex or fastigial nucleus stimulation (Rasheed et al., 1970; Doba & Reis, 1972; Martner, 1975). More recent studies of cerebellar influences on vasomotor tone (Andrezik et al., 1984; Paton & Spyer 1990; Reis & Golanov, 1997) and on vagally mediated respiratory reflexes (Xu & Frazier, 1997) confirm and extend the earlier observations. Functional imaging studies that reveal cerebellar activation during painful stimulation (Coghill et al., 1999; Ploghaus et al., 1999), thirst (Parsons et al., 2000), and hunger (Tataranni et al., 1999) also implicate the cerebellum in these autonomic-limbic behaviors.

The anatomic basis of these physiological demonstrations was examined by investigations into the anatomic links between the cerebellum and these brain regions important for autonomic function. These are the hypothalamus, certain brainstem nuclei including those that subservce taste (the nucleus tractus solitarius), and structures concerned with pain modulation such as the periaqueductal gray, and the central lateral and paracentral intralaminar thalamic nuclei. Dietrichs (1984) and Haines & Dietrichs (1984) demonstrated that projections arise from multiple hypothalamic nuclei and terminate in all layers of the cerebellar cortex and in the deep cerebellar nuclei (Figure 1).

Further, all the cerebellar nuclei send efferents back to the hypothalamus (Haines et al., 1997). The nucleus tractus solitarius receives heavy projections from the fastigial nucleus (Andrezik et al., 1984), and the fastigial projections to the intralaminar thalamic nuclei have been referred to above.

Limbic system

The evidence for cerebellar limbic interactions is presently derived from behavioral and physiologic studies, and from a smaller amount of direct anatomic evidence. The phenomenon of sham rage that is produced in cats by hypothalamic stimulation (Bard, 1928) was shown to be altered by stimulation of the anterior cerebellum Moruzzi (1947), and specifically by the vermis and fastigial nucleus (Zanchetti & Zoccoli, 1954). Berntson et al. (1973) showed eating and grooming responses in cats by stimulation of fastigial nucleus and superior cerebellar peduncle. Complex oral behaviors were elicited in the rat by fastigial nucleus stimulation (Ball et al., 1974), and self-stimulation (previously thought to be regulated by the amygdala) was induced by stimulation of the rostral anterior lobe and the fastigial nucleus (Micco, 1974). Reis et al. (1973) showed that low intensities of fastigial nucleus stimulation produced grooming and ingestive behaviors, but at higher intensities of stimulation, predatory attack, and sham rage were elicited.

Electrical stimulation of the cerebellum influences the physiology of limbic system structures, producing evoked responses in hippocampus and amygdala (Whiteside & Snider, 1953; Heath & Harper, 1974), and altered and/or arrested abnormal or epileptiform discharges in the hippocampus (Mutani, 1967; Babb et al., 1974). Heath et al. (1978) demonstrated facilitation in the septal region, inhibition in the hippocampus, and a mixed pattern of responses in the
Figure 1. Diagram of efferent projections of hypothalamic nuclei to cerebellum, pontine nuclei, and lateral reticular nucleus. Cells number 1, 2 and 3 are indicative of (1) hypothalamic cells that project only to the cortex, (2) hypothalamic cells that project to the cortex and send collaterals into the cerebellar nuclei, and (3) hypothalamic cells that project only to the cerebellar nuclei. Hypothalamic nuclei listed in parenthesis give rise to relatively fewer projections. All cerebellar nuclei project back to hypothalamus (not shown) and terminate in lateral, posterior, and dorsal hypothalamic areas, and in dorsomedial and paraventricular hypothalamic nuclei. (DHAr, dorsal hypothalamic area; DMNu, dorsomedial hypothalamic nucleus; DNu, dentate nucleus; ENu, emboliform nucleus; FNu, fastigial nucleus; GnHu, globose nucleus; LHAr, lateral hypothalamic area; LMNu, lateral mammillary nucleus; MNu, medial mammillary nucleus; PHAr, posterior hypothalamic area; PVZo, periventricular zone; SMNu, supramammillary nucleus; SupChN, suprachiasmatic nucleus; SupOpNu, supraoptic nucleus; TMMu, tuberomammillary nucleus; TubCm, tuber cinereum; VMNu, ventromedial nucleus.) (From Haines et al., 1997, with modified legend.) Reprinted with kind permission of Harcourt Inc.

amygdala in cats and rats following stimulation of the rostral vermis, fastigial nucleus, and intervening midline folia, but not following stimulation of the lateral cerebellar hemispheres and dentate nucleus.

Anatomic studies reveal projections from the fastigial nucleus of cat to the ventral tegmental area (VTA), interpeduncular nucleus, periaqueductal gray and locus ceruleus that are themselves interconnected with limbic regions (Snider & Maiti, 1976). The mesothalambic component of the VTA also has a reciprocal projection back to the cerebellum (Oades & Halliday, 1987). The medial mammillary bodies are closely linked with the limbic anterior thalamic nuclei through the mammillothalamic tract, and they are also in communication with the cerebellum by way of their projections to the nuclei of the basilar pons (Haines & Dietrichs, 1984; Aas & Brodal, 1988). The hypothalamocerebellar connections discussed above are relevant in the consideration of the limbic cerebellum particularly in light of the phenomenon of sham rage produced originally by hypothalamic stimulation.

Finally, the cingulate gyrus implicated in depression (Ebert & Ebmeier, 1996) and in obsessive compulsive disorder (Rauch et al., 1994) has direct projections into the feedforward limb of the cerebrocerebellar circuits through the basilar pons (Vilensky & Van Hoesen, 1981; Brodal et al., 1991). The rostral cingulate projects to pontine nuclei, the caudal cingulate to more lateral regions.

These studies together reveal that cerebellum is interconnected with multiple different elements of the limbic circuits that subserve emotion, although considerable detail is still missing from the understanding of these pathways.

**Association and paralimbic cortices**

The cerebral cortex is linked with the cerebellum via a two-stage feedforward limb in which the pontine nuclei serve as the obligatory synaptic step between the corticopontine pathway and the mossy fiber-mediated pontocerebellar pathway. The two-stage feedback system from cerebellum to cerebral cortex
has the thalamus as the obligatory synaptic step, between the cerebellothalamic pathway traveling in the superior cerebellar peduncle and the thalamocortical pathway (Figure 2).

Both the feedforward and feedback limbs are critical components of this circuit because of the specific information carried to the cerebellum by the inputs, and the cerebral regions that are the recipients of the cerebellar feedback. In the discussion concerning the role of the cerebellum in higher function, there are no pathways more critical than those linking the associative and paralimbic regions of the cerebral hemispheres with the cerebellum. These pathways provide the anatomic substrates that subserve the cerebellar involvement in cognitive operations.

**Feedforward limb**

It has long been known that neurons in layer Vb of the motor, premotor, and supplementary motor regions as well as primary somatosensory cortices and the rostral parietal lobe send their efferents to the cerebellum via the corticopontine pathway (Sunderland, 1940; Nyby & Jansen 1951; Brodal, 1978). Recent evidence, however, indicates that the corticopontine projections arise not only from these sensorimotor related regions, but considerable projections to pons are derived also from the prefrontal cortex, from multimodal regions of the posterior parietal and temporal lobes, from paralimbic cortices in the cingulate and posterior parahippocampal gyrus, and from the visual association cortices in the parastriate region as well.

**Prefrontal cortex**

The prefrontal cortex is essential for such higher functions as planning, foresight, judgment, attention, language, and working memory (Milner, 1964; Luria, 1966; Fuster, 1980; Stuss & Benson, 1986). Anterograde tract tracing studies using tritiated amino acids (Schmahmann & Pandya, 1995, 1997a) reveal that prefrontal corticopontine 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), 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 & Akert, 1977; Glickstein et al., 1985; Stanton et al., 1988; Goldman-Rakic & Friedman, 1991; Pandya & Yeterian, 1991; Petrides & Pandya, 1994; Petrides, 1995). The terminations in the pons are distributed in a topographically precise manner, favoring the median, paramedian, dorsomedial and medial part of the peripeduncular pontine nuclei (Schmahmann & Pandya, 1997a) (see Figure 3).

**Posterior parietal cortex**

The posterior parietal association cortices are critical for directed attention, visual-spatial analysis, and vigilance in the contralateral hemisphere. When lesioned these areas are associated with complex behavioral manifestations (Critchley, 1953; Denny-Brown & 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 (Schmahmann & Pandya, 1989) [see Figure 3(right)]. The inferior parietal lobule, especially the most caudal region, is strongly implicated in the neglect syndrome, and is anatomically interconnected with other cortical association areas as well as with paralimbic cortical regions and limbic thalamic nuclei (Pandya & Yeterian, 1985; Cavada & Goldman-Rakic, 1989a, 1989b; Schmahmann & 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, 1978; Glickstein et al., 1985; May & Andersen, 1986; Schmahmann & Pandya, 1989).
Figure 3. (Left) Shows the distribution within the basilar pons of the rhesus monkey of projections derived from the prefrontal cortices. Injections of anterograde tracers in the medial (A) and lateral (B) surfaces of the cerebral hemisphere result in terminations (color-coded) in rostrocaudal levels of the pons I–IX. The plane of section through the basilar pons for both left and right figures is at the bottom of the diagram. The prefrontopontine projection is characterized by a complex mosaic of terminations. Each cerebral cortical region has preferential sites of pontine terminations. There is considerable interdigitation of the terminations from some of the different cortical sites, but almost no overlap. (From Schmahmann & Pandya, 1997a.) © 1997 Society for Neuroscience. Reprinted with kind permission of the Journal of Neuroscience.

(Right) This figure is a color-coded summary diagram illustrating the distribution within the basilar pons (levels I–IX) of the rhesus monkey of projections derived from association and paralimbic cortices in the prefrontal (purple), posterior parietal (blue), temporal (red), and parastriate and parahippocampal regions (orange), and from motor, premotor and supplementary motor areas (green). The medial (A), lateral (B) and ventral (C) surfaces of the cerebral hemisphere are shown above. Cerebral areas that have been shown to project to the pons by other investigators using either anterograde or retrograde tracers are depicted in white. Areas that have no pontine projections (according to anterograde and retrograde studies) are shown in yellow; those with no pontine projections according to retrograde studies are in gray. Dashed lines on the hemispheres represent sulcal cortices. Dashed lines in the pons represent pontine nuclei, and solid lines demarcate corticospinal fibers. (From Schmahmann, 1996.) Reprinted with kind permission of Human Brain Mapping.
Temporal lobe

The superior temporal gyrus and supratemporal plane, which are auditory association areas, are connected with the lateral and dorsolateral pontine nuclei. 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 & Pandya, 1991) [Figure 3(right)]. 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 & Ungerleider, 1989; Felleman & Van Essen, 1991) has no pontine efferents (Brodal, 1978; Glickstein et al., 1985; Schmahmann & Pandya, 1991, 1993). There is thus a dichotomy in the temporal lobe pontine connections between visual motion (where) versus visual feature discrimination (what) systems (Ungerleider & Mishkin, 1982). The temporal lobe is known to be important for linguistic processing, and these temporopontine connections, along with those from the monkey homologue of Broca’s area, are interesting in the light of cerebellar activation during functional neuroimaging studies of cerebellum (Fiez & Raichle, 1997) and in disorders of language in individuals with cerebellar lesions (Silveri et al., 1994; Pollack et al., 1995; Schmahmann & Sherman, 1998; Leggio et al., 2000).

Parastriate cortices

The dorsal-ventral dichotomy seen in the temporopontine connections is also seen in the projections arising from the parastriate cortices in the occipitotemporal and occipitoparietal regions. The medial and dorsal prelunate regions project to the pons (dorsolateral nucleus, 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; May & Andersen, 1986; Fries, 1990; Schmahmann & Pandya, 1993). The dorsal visual stream concerned with motion analysis and visual-spatial attributes of motion therefore participates in the cerebrocerebellar interaction, but the ventral visual stream governing visual object identification does not.

Paralimbic cortices

The posterior parahippocampal gyrus is responsive to visual stimuli in the peripheral lower quadrant (Boussaoud et al., 1991) and has been identified as part of the substrate for spatial attributes of memory (Nadel, 1991). Pontine connections arising from this region are directed to the lateral, dorsolateral, and lateral aspects of the peripeduncular pontine nuclei (Schmahmann & Pandya, 1993). The cingulate cortex projections to the pons have been mentioned above, and these arise not only from the motor related areas in the depth of the cingulate sulcus (Picard & Strick, 1996), but also from regions of the cingulate gyrus thought to be concerned with motivation and drive (Devinsky et al., 1995; Paus, 2001). The anterior insular cortex, an important cortical component of autonomic and pain modulation systems (Mesulam & Mufson, 1985) has been shown in retrograde anatomical studies to have pontine connections (Glickstein et al., 1985), although the precise ordering of the projections from this region in the basilar pons is not yet established.

Specificity of connections

It is apparent from the foregoing discussion that the corticopontine projections are highly organized within the basilar pons. The associative and paralimbic projections together constitute a considerable extent of the pontine nuclear territory. Quantitative comparisons have not yet been performed, but these higher order anatomic connections are not at all overwhelmed but the motor corticopontine projections. The motor terminations have their own separate and distinct location, mostly in the caudal half of the pons, whereas the associative projections are found throughout the pons, with a rostral predominance (Schmahmann, 1996) [Figure 3(right)].

Each cortical area also has its own focus of predilection within the basilar pons. Thus, for example, the prefrontopontine terminations are present mostly in the medially situated nuclei within the rostral half of the pons (Schmahmann, 1996; Schmahmann & Pandya, 1997a) [see Figure 3(right)]. Moreover, each prefrontal area projects to a unique set of terminations within this general ‘prefrontal’ pontine territory (Schmahmann & Pandya, 1997a) [see Figure 3(left)]. The corticopontine terminations thus comprise a patchwork mosaic of interdigitating but highly specific terminations.

The trajectories of the corticopontine fiber systems are also discretely organized within the cerebral white matter. Whereas, for example, all the post-Rolandic corticopontine fibers descend abruptly into the cerebral peduncle above the mid-point 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 descent (Schmahmann & Pandya, 1992). Similar organizing principles apply to the prefrontopontine fibers that traverse the anterior limb of the internal capsule en route to the cerebral peduncle (Schmahmann & Pandya, 1994). Thus the corticopontine projections are distinguishable at each
point, from origin, though trajectory, to termination, and appear to be organized in parallel. Each cortical locus has a unique complement of pontine neurons to which it directs its efferent volleys. In this sense the organization of the cerebrocerebellar system resembles the multiple parallel loops that characterize the cortico-subcortical interactions with the basal ganglia (Goldman-Rakic & Selemon, 1990).

**Climbing fibers**

The interaction between the pontine mossy fiber system input to the cerebellum, and the climbing fibers derived exclusively from the inferior olivary nucleus, has served as the substrate for hypotheses concerning the cerebellar role in both motor and non-motor behaviors (Marr, 1969; Albus, 1971; Ito, 1993; Thach, 1997). The inferior olive receives little, if any, direct input from the cerebral cortex. Its major source of descending afferents arises from the red nucleus that carries mostly sensorimotor information (Kuypers & Lawrence, 1967; Humphrey et al., 1984; Kennedy et al., 1986). It does, however, also receive some associative cortical input indirectly from brainstem reticular nuclei and from the zona incerta (ZI) (Saint-Cyr & Courville, 1980). The ZI receives input from the rostral cingulate cortex (area 24); the prefrontal cortex (areas 9/46d at the dorsolateral convexity and area 9 at the medial convexity); the posterior parietal cortex (areas PF and PG in the inferior parietal lobule, and area PGm at the medial convexity of the superior parietal lobule); and from the medial prefrontal cortex (Shah et al., 1997). The detection of associative projections to the zona incerta, that in turn projects to the inferior olivary nucleus, maintains the possibility that interaction between the mossy-fiber and climbing fiber systems may be relevant for higher function, in addition to tasks related to motor performance and motor learning.

**The pontocerebellar pathway**

Comprehensive anatomical details now exist for the corticopontine projections, but the details of the pontocerebellar system remain unclear, beyond some general organizing principles.

Information derived from physiological and anatomical studies indicates that both central and peripheral auditory and visual inputs are received in vermal lobules VI and VII, conveyed mostly via the dorsolateral pons and the nucleus reticularis tegmenti pontis (Snider, 1950; Allen & Tsukahara, 1974; Brodal, 1979, 1980; Stein & Glickstein, 1992; Glickstein et al., 1985). The dorsal paraflocculus also receives visual input from the dorsolateral pontine nucleus (Glickstein et al., 1994).

The parietal and prefrontal cortices are functionally related mainly to crus I, crus II and the paramedian lobule in the neocerebellar hemispheres, according to physiological studies (Allen & Tsukahara, 1974; Sasaki et al., 1975). The pontocerebellar studies of Brodal (1979) revealed that the anterior lobe receives input from medial parts of the caudal pons; the vermal visual area from the dorsomedial and dorsolateral pons; vermal lobule VIIIB from the intrapenduncular nucleus; crus I of the ansiform lobule from medial parts of the rostral pons, and crus II from the medial, ventral, and lateral pons. These studies, taken together with the investigations of the corticopontine pathways (Brodal, 1978; Schmahmann & Pandya 1997b), suggest the following. The anterior lobe in particular receives afferents from motor, premotor, and rostral parietal cortices. Prefrontal cortices are linked with crus I of the ansiform lobule, and with crus II to a lesser extent. Parietal association cortices are linked with crus I, crus II and lobule VIIIB. A more complete exploration of the pontocerebellar pathways is still needed in order to better understand the relationship between cerebral cortex and cerebellum.

There is a high degree of order in the pontocerebellar projection. Each cerebellar folium receives input from a unique complement of pontine cell groups, some of which are widely separated (Brodal, 1979; Schmahmann, 1996) (Figure 4).

The pattern of diverging corticopontine projections, and converging pontocerebellar projections has led to the suggestion that information from one cerebral cortical area is distributed to numerous sites in the cerebellar cortex (Brodal, 1979). Preliminary trans-synaptic anterograde tracer experiments in the prefrontal cortex, however (Strick, 1999), reveal that the anterograde projections through the medial pons are directed to focal areas in crus I and crus II, and are not widely distributed. This is an important detail that needs further clarification as it relates directly to the issue of connectional and functional topography in the cerebellum.

**Feedback limb**

The cerebellar cortical feedback to the cerebral cortex originates in the projection from the Purkinje cell layer to the deep cerebellar nuclei (the fastigial, globose, emboliform, and dentate). These projections are arranged in an orderly manner with medial cortical areas committing efferents mostly to the midline nuclei fastigial nucleus, and lateral cerebellar cortices projecting to the lateral, or dentate, nucleus (Jansen & Brodal, 1940; Chambers and Sprague, 1955; Haines, 1989) (see Figure 4). The dentate nucleus itself has for some time been recognized to be architectonically heterogeneous, and Dow (1942) elaborated upon this by defining a dorsomedial part with minimal gyration and large neurons, and a ventrolateral part that is heavily folded and contains small neurons. This distinction is readily apparent on light microscopy. Dow recognized that the dorsomedial part was phylogenetically older, whereas the ventrolateral part...
was more recently evolved. Leiner et al. (1986) later postulated that the newer ventrolateral dentate developed along with the expanded neocerebellar hemispheres, and evolved in concert with the cerebral association areas (prefrontal cortex in particular), thus facilitating a cerebellar role in language processing. This prediction has been supported by subsequent clinical (e.g. Leggio et al., 2000; Levisohn et al., 2000) and functional imaging studies (see Desmond & Fiez, 1998).

The conventional understanding has been that the cerebellar dentate nucleus projects via motor thalamic nuclei back to the motor related cortices. However, the cerebellar nuclear projections to thalamus arise not only from the dentate nucleus but from the fastigial and the interpositus nuclei as well (Brodal, 1981). Further, the thalamic input is directed not only to the classic cerebellar recipient ‘motor’ thalamic nuclei [subdivisions of VL, VPL and nucleus X of Olszewski (1952)], but the ‘non-motor’ thalamic nuclei have considerable cerebellar input as well. These include the intralaminar nuclei, particularly centralis lateralis (CL), as well as the paracentralis (Pcn) and centromedian-parafascicular (CM-PF) complex, and the medial dorsal nucleus (Strick, 1976; Batton et al., 1977; Thach & Jones, 1979; Stanton, 1980; Kalil, 1981; Wiesendanger & Wiesendanger, 1985; Ilinsky & Kultas-Ilinsky, 1987; Orioli & 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

![Diagram illustrating the distribution of labeled neurons (black dots) in the basilar pons following injection of tracer (WGA-HRP, black shading) into crus I anterior of rhesus monkey cerebellum [top left—transverse section; top right—flattened map (Larsell, 1970)]. Rostrocaudal levels of the pons I–IX are depicted in the diagram at lower right. Pontine nuclear subdivisions are not shown. Retrogradely labeled neurons are seen bilaterally in the pons, with a contralateral predominance, in multiple, distinct regions. Anterograde label is seen within the dentate nucleus. f.p. = crus I anterior; f.p. = crus I posterior; f.p. = crus II; D = dentate nucleus; f.p. = primary fissure; f.p.s. = superior posterior fissure; s.int.cr. = internal sulcus of crus I. Roman numerals VI and X refer to the cerebellar lobules according to Larsell (1970).] (Schmahmann & Pandya, from Schmahmann, 1996.) © 1997 Society for Neuroscience. Reprinted with kind permission of The Journal of Neuroscience.
prefrontal cortex, the cingulate gyrus, and the primary motor cortex (Kievet & Kuypers, 1977; Yeterian & Pandya, 1985, 1989; Vogt & Pandya, 1987; Schmahmann & Pandya, 1990; Siwek & Pandya, 1991), and the Pcn nucleus projections include the parahippocampal gyrus (G. Blatt, D.L. Rose, D.N. Pandya, 1991, personal communication). The medial dorsal (MD) thalamic nucleus receives projections from the cerebellum mainly in its paralaminar parts, that is, in the pars multiformis (MDmf), and pars densocellularis (MDdc) (Stanton, 1980; Ilinsky & Kultas-Illinsky, 1987). The MDmf and MDdc nuclei have reciprocal connections with the prefrontal cortex in area 8, area 46 at both banks of the principal sulcus, and area 9 (Giguere & Goldman-Rakic, 1988; Barbas et al., 1991; Siwek & Pandya, 1991), as well as with the cingulate gyrus, posterior parietal cortex, and multimodal parts of the superior temporal sulcus (Yeterian & Pandya, 1985, 1989; Vogt & Pandya, 1987; Schmahmann & Pandya, 1990). Furthermore, the traditionally motor thalamic nuclei are reciprocally interconnected with the prefrontal periaqueductal areas (Kievet & Kuypers, 1977; Stanton et al., 1988; Künzle & Akert, 1977), the multimodal cortex (area TPO) in the upper bank of the superior temporal sulcus (Yeterian & Pandya, 1989), and the posterior parietal cortex including both the upper and lower banks of the intraparietal sulcus (Schmahmann & Pandya, 1990).

These studies indicate that the cerebellum projects back to the higher order cerebral areas from which the inputs are derived (Schmahmann, 1991, 1996). This conclusion is supported and further clarified by more direct trans-synaptic retrograde tracer studies using attenuated herpes virus that replicates in synaptic neurons and amplifies the detectable signal at second order sites (Ugolini et al., 1987; Kuypers & Ugolini, 1990). Middleton & Strick (1994, 1997) demonstrated that the cerebellar dentate nucleus sends projections through thalamus to different areas of the frontal lobe in the monkey (Figure 5).

The dorsomedial part of the dentate nucleus sends its projections to the motor cortex, whereas the ventrolateral and ventromedial parts of the dentate nucleus are connected with the prefrontal cortex, including area 9/46. It is likely that this degree of organization in the feedback from the cerebellum to the cerebral hemispheres is reproduced throughout the cerebrocerebellar system, but this remains to be demonstrated.

**Clinical corroboration**

The reciprocal anatomic connections between the cerebral hemispheres and the cerebellum have been shown to be directly relevant in the experimental, clinical, and functional neuroimaging domains.

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**Figure 5.** Lateral view of a cebus monkey brain (top) to show the location of injections of McIntyre-B strain of Herpes simplex virus type 1 in the arm representation of the primary motor cortex (M1arm), arm representation of the ventral premotor cortex (PMVarm), and areas 9 and 46 of the prefrontal cortex. The resulting retrogradely labeled neurons in the cerebellar dentate and interpositus nuclei (bottom) are indicated by solid dots. Relative anteroposterior locations of the labeled neurons within the dentate nucleus are indicated below each section. (Adapted from Middleton & Strick, 1997.) Reprinted with kind permission of Harcourt Inc.
The cerebrocerebellar interactions appear to be important in recovery from cerebellar injury. When sensory cortex is removed prior to an induced cerebellar lesion, the cerebellar deficits are exaggerated and recovery is limited (Mackel, 1987). When sensory cortex lesions are made subsequent to a cerebellar lesion, and after recovery from the cerebellar deficits, the initially recovered cerebellar deficits reappear. Furthermore, the effects of combined sequential cerebellar and sensory cortical lesions appear worse than expected if the two lesions were merely additive. These results indicate a functional interrelationship dependent upon the cerebrocerebellar system, which facilitates compensation following injury.

The phenomenon of cerebellar diaschisis—functional deactivation at a distance following damage to an interconnected region, has been documented following lesions of the cerebral hemispheres, including language related cortex in the frontal lobe (Metter et al., 1987). Conversely, reversed cerebellar diaschisis has also been observed. Lesions of cerebellum are associated with decreased activation in the contralateral cerebral hemisphere, in both sensorimotor as well as association cortices (Schmahmann, 1991; Botez-Marquard & Botez, 1997; Schmahmann & Sherman, 1998). These findings provide imaging support for the anatomic connections described here. They are also relevant in the genesis of the cerebellar cognitive affective syndrome (Schmahmann & Sherman, 1998) that results following focal cerebellar injury, and are consistent with the suggestion that the syndrome results from the removal of the cerebellar component of the distributed neural circuits responsible for cognition and affect (Schmahmann, 1991, 1996).

The cerebellar cognitive affective syndrome (CCAS) is most apparent when the lesion involves the posterior lobe of the cerebellum (Schmahmann & Sherman, 1998; Levisohn et al., 2000; Riva & Giorgi et al., 2000; Neau et al., 2000), whereas the motor phenomena typically ascribed to cerebellar dysfunction are more related to lesions of the anterior lobe. This is in agreement with the anatomic connections described above, where the rostral pons sends more associative input and projects to the posterior lobe, whereas the caudal pons receives more sensorimotor inputs and projects to the anterior lobe. The more detailed characterization of the anatomic correlates of the different elements of the CCAS (executive, visual spatial, linguistic) remain to be determined, although the midline location of the affective changes (Schmahmann & Sherman, 1998; Levisohn et al., 2000; Riva & Giorgi, 2000) is certainly consistent with the vermal-fastigial region interaction with the limbic system—giving rise to the notion of a limbic cerebellum (Heath, 1977; Schmahmann, 1991, 2000).

Initial attempts at characterization of the functional topography within cerebellum, consistent with the apparent specificity of the cerebrocerebellar loops, has been carried out in meta-analyses of functional neuroimaging studies (Desmond & Fiez, 1998; Schmahmann et al., 1998). The results are in agreement with the notion that the anterior lobe is the sensorimotor cerebellum, and the posterior lobe is the cognitive cerebellum. Executive and linguistic tasks activated lobule VI and crus I on the right, attentional modulation was more heavily concentrated in lobule VI on the left, and non-motor learning was focused particularly in crus I and crus II. The cerebellar vermis and paravermian regions are activated preferentially in studies of pain, hunger and thirst.

**Synthesis**

There is an evolving body of anatomic information that links the cerebellum with systems that subserve every level of behavior, from arousal to autonomic function, motivation, emotion, and the highest forms of cognitive processing. The cerebrocerebellar loops are topographically organized, linking specific cerebral areas with different regions of the cerebellum. The topographic arrangement in the cerebellar connections is superimposed upon an essentially constant pattern of intrinsic cerebellar cortical circuitry. This dichotomy provides support for the dysmetria of thought hypothesis (Schmahmann, 1991, 1996, 2000), predicated on the notion that the cerebellum performs its unique computations in a topographically precise manner on diverse streams of information relating to almost all aspects of behavior including cognition and emotion. The recognition of the anatomic, clinical and functional neuroimaging evidence suggesting a cerebellar role in higher order function has heralded a theoretical paradigm shift in clinical and cognitive neuroscience. It is necessary to explore the nature of cerebellar psychopathology, and to develop instruments to measure and further understand the cerebellar component of diseases that have traditionally fallen within the psychiatric domain. Knowledge of the anatomic underpinnings of the cerebro-cerebellar interaction will surely continue to be crucial.

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**References**


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