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The Role of the Cerebellum in Cognition and Emotion: Personal Reflections Since 1982 on the Dysmetria of Thought Hypothesis, and Its Historical Evolution from Theory to Therapy

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Abstract The cognitive neuroscience of the cerebellum is now an established multidisciplinary field of investigation. This essay traces the historical evolution of this line of inquiry from an emerging field to its current status, with personal reflections over almost three decades on this journey of discovery. It pays tribute to early investigators who recognized the wider role of the cerebellum beyond motor control, traces the origins of new terms and concepts including the dysmetria of thought theory, the universal cerebellar transform, and the cerebellar cognitive affective syndrome, and places these developments within the broader context of the scientific efforts of a growing community of cerebellar cognitive neuroscientists. This account considers the converging evidence from theoretical, anatomical, physiological, clinical, and functional neuroimaging approaches that have resulted in the transition from recognizing the cerebellar incorporation into the distributed neural circuits subserving cognition and emotion, to a hopeful new era of treatment of neurocognitive and neuropsychiatric manifestations of cerebellar diseases, and to cerebellar-based interventions for psychiatric disorders.

Keywords Cerebrocerebellar system · Cerebellar cognitive affective syndrome · Ataxia · Behavior · Psychosis · Schizophrenia · Autism · History

I am grateful for the invitation by the editor of this Special Issue to contribute personal reflections concerning the historical evolution of the role of the cerebellum in cognition and affect. In my lectures and discussions on this topic over almost three decades, I am often asked how it is that I came to this notion, and what were the challenges I faced when proposing these ideas in the face of conventional wisdom to the contrary. I will use this opportunity to tell the story, both personal and academic, of the transformation of our understanding of cerebellum from a purely motor control device to one which is more widely relevant in cognitive neurology and neuropsychiatry.

I hope that readers will find this narrative useful, and recognize that whereas I independently came to these ideas early on, the elaboration of these ideas and their evolution into the new field of neuroscience of the cerebellum and cognition is built upon the shoulders of the giants who preceded us, and interwoven with important discoveries of other contemporary investigators.

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Coming to the Question

My medical education at the University of Cape Town and my residency in the Neurological Unit of the Boston City Hospital (BCH) between 1982 and 1985 were heavily clinical, focused on the history and examination of the patient in order to arrive at an accurate clinical diagnosis and develop a strategy for management. From 1946 to 1967 the Neurological Unit was led by Derek Denny-Brown (1901–1981), the James Jackson Putnam Professor of Neurology at Harvard Medical School

and a major figure in American neurology in the twentieth century (Locke 1969). I recall as a medical student having read some of his papers on the cerebral consequences of closed head trauma (Denny-Brown 1942), and it was thrilling to be immersed in the academic environment at BCH that he had developed and fostered (Denny-Brown 1964). My fellow neurology residents and I were regularly regaled with stories about Dr. Denny-Brown by my teachers, principally Tom Sabin, our chief of neurology and a master clinician himself. Denny-Brown's comprehensive investigations and authoritative writings elaborated upon the importance of the basal ganglia as subcortical elements in the motor system (Denny-Brown 1962). Against this background, I met two patients in 1982–83 whose presentations were puzzling, and who led me to ask the question about the role of the cerebellum in cognition that would define my career going forward.

One was a 56-year-old man with a small stroke in the genu of the right internal capsule that presented clinically as a neglect syndrome. He was not aware of left hemispace, he neglected the left side of the page when interpreting diagrams and in his own drawings, and he had loss of visual spatial orientation which was apparent in his disorganized rendition and placement of cities on a map of the eastern United States where he had driven a truck for the past three decades. The second patient was a 63-year-old executive whom I met while on rotation at the Lahey Clinic in Burlington, MA, with a left hemineglect syndrome that resulted from a focal infarct in the head of the right caudate nucleus (Caplan et al. 1990).

The legacy of behavioral neurology at the Neurological Unit was strong. Denny-Brown had discussed the clinical consequences of frontal and parietal lobe lesions (Denny-Brown and Banker 1954; Denny-Brown and Chambers 1958; Denny-Brown et al. 1952), and Norman Geschwind (1926–1984), widely regarded as the father of behavioral neurology and chief of neurology at the Beth Israel Hospital in Boston, had been chief at BCH prior to Tom Sabin. Dr. Geschwind still gave Saturday morning rounds at BCH as well as in the Aphasia Unit of the Boston Veterans Hospital. We were influenced by the clinical studies of Ken Heilman at the University of Florida in Gainesville, another BCH alumnus who together with colleagues including Ed Valenstein and Bob Watson addressed the neural substrates and clinical phenomenology of attention (Heilman et al. 1986; Heilman and Van Den Abell 1980; Watson et al. 1981), and of particular note for me at the time, the finding of thalamic neglect—a parietal type syndrome in patients with lesions in the thalamus (Valenstein et al. 1982). I remember sitting in the medical library at the Lahey Clinic reading the paper by Marsel Mesulam, also a BCH alumnus then at the Beth Israel Hospital in Boston, on the distributed neural networks subserving attention (Mesulam 1981). My two patients with

subcortical neglect, and the medical literature they prompted me to explore thus led me, as a first year neurology resident, to two inter-related lines of thought. First, it was apparent that subcortical lesions produced complex behavioral impairments similar to those resulting from lesions in association areas engaged in attention, notably the parietal lobe. The basal ganglia, head of the caudate nucleus in particular, was thus apparently not engaged solely in motor control, but in behavioral matters as well. Second, to understand these cases it was necessary to consider the anatomical interactions between subcortical structures and the cerebral cortex. Using the Geschwind model (Geschwind 1965a,b), the likely mechanism of neglect from the genu lesion was disconnection of the association areas in the prefrontal cortex (PFC) engaged in directed attention from the prefrontal-projecting medial thalamic nucleus (and limbic related anterior thalamic nuclei). The caudate nucleus neglect case may have resulted from disruption of its interactions with parietal lobe regions engaged in attention. The spark of the new idea that occurred to me at this time was that the corollary of this line of thinking was i) if the basal ganglia are not only motor but cognitive as well, what about the big motor machine at the base of the brain—could the cerebellum be involved in cognition as well?; and ii) the most immediate way to investigate the possibility of this cognitive-cerebellum idea would be to determine if there were anatomical pathways to support such a relationship. In other words, if there were no highways linking cerebellum with cerebral association areas, then the relationship would not be feasible and the idea would be moot.

Pursuing the Notion in the Early Literature

My first course of action in the winter of 1983–4 was to investigate whether this idea had been proposed previously. What I discovered was something akin to a subterranean counterculture of cerebellum and cognition with contributions by eminent scientists, studies and ideas buried beneath the prevailing wisdom of the day, unknown by almost all, and hidden from curricula for medical students or neuroscience undergraduates. The wall of opposition I ran into early on as my own work evolved made it clear to me what some of these earlier investigators must have faced. As I came to know the literature further through the years, it has also become clear that most of the ideas currently taking hold have solid basis in anatomical and physiological studies that commenced over seven decades ago, and in clinical reports that date back almost 200 years. It was a great joy to rummage through these old papers and journals in the basement stacks and in the rare book collection of the Countway Library of Medicine at Harvard Medical School.

Apparently provoked by Franz Joseph Gall's (1758–1828) cortical localization theory and phrenology, and

Gall's suggestion that the cerebellum was the seat of "physical love"—sexual proclivity and the like (Gall et al. 1838; Neuburger 1897/1981), Marie Jean Pierre Flourens (1794–1867) studied the behavior of pigeons subject to cerebellectomy to reach his famous conclusion (Flourens 1824) that the cerebellum was critical for the *coordination* of movement rather than the *generation* of movement as Luigi Rolando (1773–1831) had suggested (Rolando 1810, in Clarke and O'Malley 1996). Flourens also ascribed to an idea proposed earlier by Albrecht von Haller (1708–1777), namely, the functional omnivalence (equivalence) of the cerebrum and cerebellum such that the entire cerebral hemisphere was uniformly organized with homogeneous function throughout, all parts capable of being engaged in all behaviors (Clarke and O'Malley 1996). Flourens was correct regarding cerebellum being engaged in coordination of motor control, but he did not predict that there is more to cerebellum than motor control. He was correct also, I believe, that cerebellum is "equipotential" in that all parts of cerebellum essentially perform the same *computation*, but incorrect in regarding cerebral cortex as equipotential, and in concluding that the entire cerebellum is dedicated to motor coordination. I return to these ideas later.

The opposing view of cerebellum was already apparent, it transpired, within a few years of Flourens' publication of his findings. There may be reports prior to Combette's (1831) description of intellectual deficits in a patient with cerebellar agenesis, but that was the first I could find. This and other descriptions of patients with cerebellar disorders in whom intellectual, psychological, and "sociopathic" impairments were noted provided a rich and early introduction to the possibility that cerebellum has a role in non-motor function.

My review of the early studies revealed a wealth of information consistent with the view that the integrative role of the cerebellum appeared not to be limited to motor control and programming. I highlighted aspects of this early literature in a series of (unsuccessful) grant applications in 1984 and introduced the results of this historical research in the subsequent anatomical papers and theoretical formulations. What stood out for me was the amount of clinical material, both observational and experimental that made it clear there were effects of cerebellar manipulation or disease that could not be explained by the motor hypothesis.

Clinical observers dating back to the 1800's reported intellectual, psychiatric, and social-emotional dysfunction in patients with cerebellar degeneration and agenesis (Schmahmann 1991), although it is not possible to know whether the pathology was indeed confined to cerebellum in those cases. Physiological studies complemented the clinical reports, showing autonomic (Zanchetti and Zoccolini 1954; Martner 1975; Watson 1978) and complex behavioral consequences (Berntson et al. 1973; Ball et al. 1974) of cerebellar stimulation including grooming, sham rage, and

predatory attack, usually evoked by stimulation of the midline fastigial nucleus and vermis.

The results of the physiological studies of Ray S. Snider and his colleagues in the 1940's showing cerebellar somatotopy (Fig. 1) were, and still are, extremely important (Snider and Stowell 1944; Snider and Eldred 1948; Snider 1950, 1952; Henneman et al. 1952). Dispelling the equipotentiality notion definitively, these physiological studies revealed what Clinton Woolsey (1904–1993) (Woolsey 1952) regarded as primary and secondary somatosensory areas of the cerebellum, and they also showed visual and auditory areas of the cerebellar vermis (lobules VI and VII). What is just as striking about this diagram were the large areas of cerebellum that were silent in these sensorimotor mapping studies. It was as though there was a large "silent frontal lobe" equivalent in the cerebellum, residing in the more recently evolved lateral hemispheres. This dichotomy of cerebellar areas shown by physiology to be relevant for sensorimotor function on the one hand, as opposed to areas devoid of sensorimotor involvement on the other, set up the topography hypothesis that I would address going forward. Snider would later demonstrate physiological interactions between the cerebellar vermis and limbic related structures in the brainstem and cerebral hemispheres—the Papez circuit (Snider and Maiti 1976), leading him to suggest that the cerebellum is relevant not only to neurology but also to psychiatry.

In the late 1960s, James W. Prescott, health scientist administrator at the National Institutes of Child Health and Human Development from 1966 to 1980, developed a remarkable hypothesis (Prescott 1971; Heath 1997). Based in part on his observations of Harry Harlow's (1905–1981) monkeys (Harlow and Harlow 1962) he regarded somatosensory input, particularly movement stimulation, to be important in the development of emotional behavior. He identified somatosensory deprivation as the primary etiological factor in the development of social-emotional disorders, particularly pathological violent behaviors, and he drew on the notion of denervation supersensitivity (Cannon 1939) to postulate that the cerebellum becomes supersensitive and hyperexcitable due to insufficient somatosensory stimulation. He proposed a major role for the cerebellum in emotional processes: "In considering the cerebellum as a master regulatory system for sensory, emotional and motor processes, a neuronal model involving the cerebellum, frontal orbital cortex, limbic and reticular structures has been evolved to account for both autistic withdrawn and violent-aggressive behaviors resulting from isolation rearing" (Prescott 1971, p370). In Prescott's view, emotional-behavioral pathologies (withdrawn, apathetic, autistic, hyperactive, stereotypical and stimulus-seeking behaviors) could thus be attributable to dysfunction of the cerebellar regulatory system.

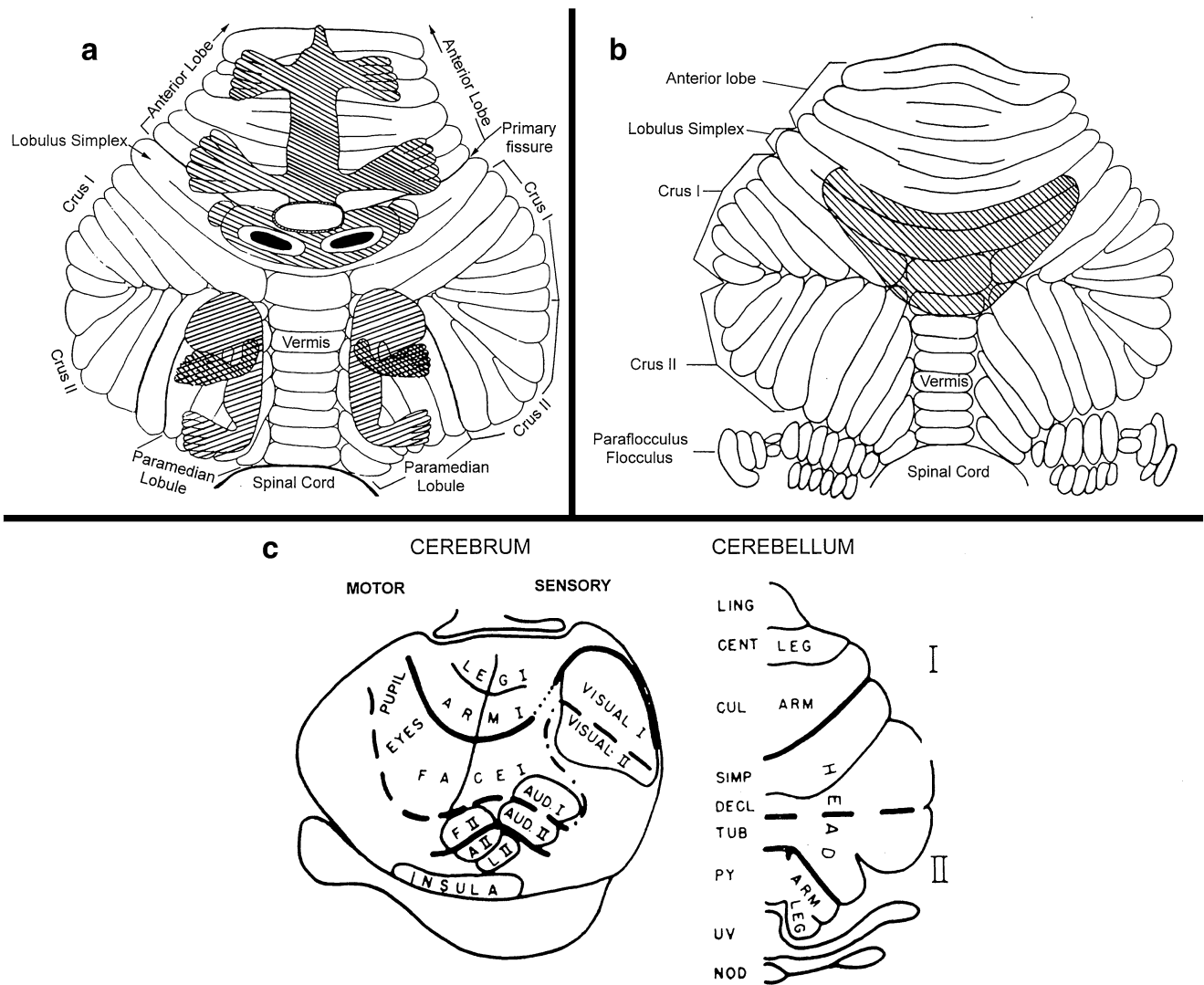


Fig. 1 Diagrams summarizing the somatotopic organization of the cerebellum determined by physiological mapping studies performed by Snider and colleagues in the 1940s. **a** Tactile and proprioceptive projections to the cerebellum. The anterior area encompasses the anterior lobe (lobules I–V) and lobulus simplex (lobule VI), and is an ipsilateral projection. The posterior area is located primarily in the paramedian lobules bilaterally (mostly lobule VIII) but may extend into crus I and II (the hemispheric components of lobules VIIA and VIIB respectively), and medially into the pyramis (part of lobule IX). Note this is a sensory map; there are face, arm, and leg subdivisions; there is

a double representation; and that most of the lateral hemisphere (crus I and crus II) has no sensory representations. **b** Schematic drawing of the cerebellum shows that auditory and visual areas, determined by click and photic stimulation, are coextensive in lobule VI, and in the vermal and medial hemispheric components of lobule VIIA (vermal VIIAf and crus I; and vermal VIIAt and crus II). **c** Conception by Woolsey (1952) of the relationship between primary and secondary sensory areas of the cerebral cortex and those in the cerebellum. **a** and **b** adapted from Snider (1952); **c** from Woolsey (1952). Reprinted with permission. Terminology from Schmammann et al. (2000)

Psychiatrist Robert G. Heath (1915–1999), founder and chair of the department of psychiatry and neurology at Tulane University in New Orleans, LA from 1949 through 1980, took note of Prescott’s hypothesis, and pursued an idea apparently prompted by William Mason (Mason and Berkson 1975) who had worked with Harlow, concerning the possible role for the cerebellum and the vestibular proprioceptive system in abnormal emotional behavior (Heath 1997). Heath’s studies were directed at demonstrating a functional neural system for

emotion, sensory perception, and memory, contending that this neural network could form a bridge for relating brain function to mental activity. He pointed to cerebellar midline involvement in autonomic and emotionally relevant behaviors (Heath et al. 1979), and on the basis of his physiological and behavioral experiments including cerebellar stimulation in patients with psychosis and aggression (Harper and Heath 1973; Heath and Harper 1974; Heath 1997; Heath et al. 1980), he proposed that the cerebellum, particularly the

vermis, was an emotional pacemaker (Heath 1977). This was the harbinger of the medial–lateral topographic arrangement of limbic versus cognitive territory in cerebellum.

In the 1970's, Irving S. Cooper (1922–1985) pioneered cerebellar stimulation for the treatment of cerebral palsy, spasticity and epilepsy, first at St. Barnabas Hospital and then Westchester County Medical Center and New York Medical College (Hornyak et al. 2001). Using a stimulator that he designed consisting of an array of electrodes placed over the surface of the cerebellum, he documented improvements in seizure control, but also in behaviors including alertness, depression, anger and aggression (Cooper et al. 1974; Cooper et al. 1978). Aaron J. (Joe) Berman (1919–2007) a neurosurgeon in New York, joined with Prescott to study aggression in the Harlow monkeys, and showed that violent behaviors improved in those that received midline cerebellar ablation, but aggression was unabated when the lateral cerebellar hemispheres were damaged but the midline regions were spared (Berman et al. 1978, republished 1997). This provided empirical support for the role of the cerebellar vermis in the modulation of emotion and social interaction. The enduring text (Dow and Moruzzi 1958) on the cerebellum by Robert S. Dow (1908–1995) and Giuseppe Moruzzi (1910–1986) included substantial discussion of nonmotor roles of the cerebellum. Dow (1974) later discussed this explicitly, noting that the lateral cerebellar hemispheres and the dentate nucleus expanded in concert with prefrontal and temporal association areas, suggesting that whatever the cerebellum does to motor control, so may it contribute to behaviors outside the motor domain.

My reading led me to reports of anatomical abnormalities in the cerebellum in diseases defined by their psychopathology, notably, various forms of psychosis (Heath et al. 1979; Joseph et al. 1985) and schizophrenia (Weinberger et al. 1980; Snider 1982), and the vestibulocerebellum had even found its way into psychoanalytic theory (Frick 1982). The findings in early infantile autism of depleted neuron counts in the midline cerebellar nuclei and loss of Purkinje cells in the cerebellar cortex by pediatric neurologist Margaret Bauman and my teacher and neuropathologist Tom Kemper at Boston City Hospital (Bauman and Kemper 1985) convinced them that the notion of cerebellum and cognition may indeed be real, and they were early supporters of investigations in this direction. The magnetic resonance imaging observations by Eric Courchesne and his colleagues at the University of California San Diego (Courchesne et al. 1988) of vermian changes on MRI in autism would provide further evidence in this regard. Based on their own observations the BCH team was not convinced that the pathology in autism was confined to the vermis, however.

Early on in my journey, Margaret Bauman alerted me to the work of Mihai Botez (1927–1998) in Montreal. Botez for some time had pondered the relationship of cerebellum to

nonmotor function, and with his wife Thérèse Marquard-Botez and colleagues including Robert Lalonde published on phenytoin toxicity producing ataxia as well as cognitive impairments (Botez et al. 1985), impaired spatial construction, conceptual perception and sequential organization in patients with Friedreich's ataxia (Botez-Marquard and Botez 1993), and navigational deficits in cerebellar mutant mice (Lalonde and Botez 1986). This led him to consider parietal-cerebellar loops subserving these relationships. The Botez's were gracious to me when I met them in Montreal in 1991 at the time of the International Brain Research Organization (IBRO) meeting, and whereas their contribution is not generally acknowledged, they were early proponents of this notion. Also beginning in the early 1980's, Duane Haines and Espen Dietrichs began to identify reciprocal connections between the cerebellum and the hypothalamus (Dietrichs and Haines 1984; Haines and Dietrichs 1984). Richard Thompson at the University of Southern California and his colleagues were defining the cerebellar role in the classically conditioned nictitating membrane response in the rabbit (Thompson 1983), extending the view of cerebellar motor learning (Albus 1971; Marr 1969) to the nonmotor domain of conditional associative learning. Work in the rat was providing support for a cerebellar role in habituation to the acoustic startle response (Leaton and Supple 1986), Richard Ivry at the University of California Berkeley was demonstrating that cerebellum is important for the perception, and not only the execution, of timed intervals (Ivry and Keele 1989), and Marco Molinari—one of a small number of clinical neurologists trained in connectional neuroanatomy, was starting to show with his colleagues that rats subjected to hemispherectomy develop impaired spatial navigation skill, unrelated to motor control (Petrosini et al. 1996).

The Road Forward

In my grant applications in the early years I suggested that because of the apparent role of the cerebellum in the sleep-wake cycle, the exacerbation or control of seizures and the structural basis for schizophrenia and autism, understanding the cerebellum more completely may facilitate a new approach to these and other cerebellar disorders and contribute to their resolution. It was clear to me from my immersion in the early literature that there was already sufficient evidence to suggest that cerebellum influences nonmotor function, and from the vantage point of then-contemporary behavioral neurology and systems neuroscience, it was possible to view the cerebellum as a critical component of the distributed neural circuits subserving intellect and emotion.

But prospective and rigorous investigation would be necessary to specifically test these ideas. The early clinical

reports were often in patients with cerebellar malformations or degeneration, and involvement of cerebral cortex could not be excluded with certainty. The physiology was largely from an earlier era, and the experimental behavioral studies, clinical neuropsychology and neuroanatomical approaches that had already come to characterize systems neuroscience had not been directed to these questions. So how to proceed?

The mid-1980's was a time of great excitement in molecular biology, and one could not attend a lecture or scientific meeting without tripping over electrophoresis gels. Anatomy was regarded as an old art form, practiced by a few aficionados, studying pathways that were thought to have already been discovered. What more was there to learn? In later years Dee Pandya and I would look at each other over the microscope and joke about how we were having fun looking at pathways and connections, while the "real" scientists were studying genes and gels. But the neurobehavioral manifestations of my cases with subcortical lesions convinced me that the systems approach would be optimal to address the unanswered questions of whether cerebellum is engaged in the processing of higher order information and thus contributes to cognition and emotion; and so the anatomical route was the one I chose.

The Corticopontine Projection

Through the guidance of my teachers Tom Sabin and Tom Kemper, I sought out Dr. Deepak (Dee) Pandya as a teacher and mentor in neuroanatomy to work with me in examining the projections from cerebral association areas to the basis pontis in rhesus monkey. Dr. Pandya is professor of neuroanatomy and neurobiology at Boston University (BU) School of Medicine. His work in connectional neuroanatomy, and his approach to the evolutionary and functional aspects of cortical connections and the importance of association areas as the substrates for higher function were then, and continue to be, essential knowledge in the understanding of the primate nervous system. I first came across Dr. Pandya's work in reading about the cortical connections of the basal ganglia in a paper by Edward Yeterian and Gary Van Hoesen (Yeterian and Van Hoesen 1978), both mentees of Pandya's. It was the unanimous opinion of my mentors that Dee was the person to approach, as much for his encyclopedic knowledge of the anatomy and connections of the primate nervous system as for what I was to learn firsthand of his humility, gentle style, and generosity of spirit. With the support of Dr. Alan Peters, then chair of the BU department of anatomy and neurobiology, I was brought on to the NIH training grant in 1985 to work on the corticopontine connections in the rhesus monkey with Dee at his lab at the Bedford Veterans Hospital while at the same time starting to hone my skills as a clinician on the faculty of the Neurological Unit at the BCH.

The corticopontine connections are a critical element in the cerebral cortical interactions with the cerebellum. The pathways that link the cerebral cortex to cerebellum emanate from layer V neurons in the cerebral cortex, course in the cerebral peduncle and terminate around the dendrites of neurons in the basis pontis. From here, the pons sends projections through the contralateral middle cerebellar peduncle to terminate in the cerebellum. The intrinsic circuitry of the cerebellum links the cerebellar cortex to the deep cerebellar nuclei, which in turn project back to thalamus, from where the projections return to the cerebral cortex. Thus the cerebral cortex is linked via a two-stage feedforward limb through the pons; and two-stage feedback limb via the thalamus.

The question that Dr. Pandya and I first addressed was whether there are anatomically identifiable contributions to the feedforward limb of the corticopontocerebellar circuit from association and paralimbic areas of the cerebral hemispheres. In other words, does the cerebellum have access to higher order information concerning social, emotional and cognitive behavior?

There is a rich history of prior corticopontine studies in the experimental animal (e.g., Brodal 1978; Fries 1990; Glickstein et al. 1985; Hartmann-von Monakow et al. 1981; May and Andersen 1986; Nyby and Jansen 1951; Wiesendanger et al. 1979). These studies focused mostly on the inputs from sensorimotor related cortices with less attention paid to the projections from supramodal areas in the posterior parietal, multimodal temporal, prefrontal and cingulate cortices, although physiological studies had already indicated that posterior parietal lobe areas are interconnected with parts of the lateral cerebellar hemispheres (Allen and Tsukahara 1974; Sasaki et al. 1975). Those earlier authors who did report minor pontine projections from temporal, parietal and occipital areas did not consider these inputs from the perspective of a role for cerebellum in nonmotor functions. Abbie (1934), for example, concluded that the temporopontine projection "undertakes the task of weaving all sensory impulses—tactile, proprioceptive, equilibratory, vibratory, auditory, and visual—into a homogeneous fabric and translating the resultant in muscular response which is accurately co-ordinated and acutely adapted to the requirements of the situation as a whole". The corticopontine projections from association areas thus were viewed, at most, as facilitating optimal motor responses to the prevailing environment. Associative corticopontine projections had not been studied with the specific intent of determining the degree to which, if at all, these association areas were linked to the cerebellum for the purposes of providing cerebellum with access to higher order information that may be acted upon by the intrinsic cerebellar neuronal circuitry in order to affect not only motor output, but complex behaviors as well. We therefore set about studying this feedforward link from association cortices to the pons.

In a series of studies commencing in 1984, we showed that there are indeed projections to pons from association areas in the posterior parietal cortex concerned with spatial awareness, the supramodal areas of the superior temporal gyrus concerned with language, the posterior parahippocampal areas important for spatial memory, the visual association areas in the parastriate cortices relevant for high order visual processing, and multiple areas in the prefrontal cortex critical for such functions as complex reasoning, judgement, attention and working memory (Schmahmann and Pandya 1989, 1991, 1993, 1995, 1997a). These projections to the pons are arranged with topographic precision in multiple interdigitating patches, each cerebral cortical area projecting to its own field of terminations in the pons (Schmahmann 1996; Schmahmann and Pandya 1997b). With these studies we showed that the cerebellum receives not only motor related information, but higher order information as well, providing an understanding of the pathways by which cerebellum is affected by, and thus in position to influence, the behaviors subserved by these cortical regions. Projections to the pons from the cingulate gyrus had been demonstrated recently by Vilensky and Van Hoesen (1981), a finding we later confirmed (Schmahmann and Pandya 2006).

We recognized from the outset that the cerebrocerebellar link includes the feedback to the cerebral cortex from the cerebellum via the thalamus (Schmahmann 1991). There was compelling evidence from previous monosynaptic tract tracing studies that projections from the pons into the cerebellum are topographically arranged. In addition, cerebellar nuclei that provide the only efferent from cerebellum back to cerebral cortex, project not only to thalamic motor nuclei, but also to nonmotor thalamic nuclei linked with association and paralimbic areas of the cerebral cortex; and aspects of the cerebellar-recipient motor thalamic nuclei project back to cerebral association areas as well (Schmahmann 1994, 1996; Schmahmann and Pandya 1997b). With the advent of the trans-synaptic viral tract tracers (Kuypers and Ugolini 1990) first developed by Dr. Pandya's mentor, Hans Kuypers (1925–1989) whom I had the great pleasure of meeting in Budapest at the IBRO meeting in 1987, and used in the monkey with great skill by Peter Strick and his colleagues, it became demonstrably clear that the cerebellar link with the association areas was indeed reciprocal—cerebral areas that project via pons to the cerebellum in turn receive projections back from the cerebellum (Middleton and Strick 1994). These trans-synaptic tracers also were able to resolve questions of the topography within cerebellar nuclei (Dum and Strick 2003) and cortex of the connections with the cerebral association areas (Clower et al. 2001), a valuable addition to the knowledge concerning the cerebrocerebellar linkage.

Dysmetria of Thought—Origins of the Theory

In 1985, my first full year in the Pandya lab, I attended the Society for Neuroscience meeting in Dallas, TX, a remarkable experience where I heard lectures by, and encountered some of the major figures in contemporary neuroscience. I timidly approached Sir John Eccles (1903–1997) whose authoritative contributions to cerebellar physiology have long been highly regarded, and asked him if he thought cerebellum could play a role in cognition—he thought not; cognition was the purview of the cerebral cortex. I posed the same question to Richard Thompson, whose influential work on conditional associative learning using the rabbit nictitating membrane response was helping to move the cerebellar field from its focus only on motor control to recognition of its role in learning and memory. He thought this quite possible. At that time he was editor of the journal *Behavioral Neuroscience*, and he told me of the manuscript he had received from Alan and Henrietta Leiner and Robert Dow discussing the possible role of the cerebellum in mental skill and emphasizing the evolutionary aspect of the cerebellar dentate nucleus and lateral hemispheres. It was refreshing to read the preprint of their manuscript (Leiner et al. 1986) because it meshed so nicely with my own ideas.

In our grant applications to obtain support to perform this anatomical work, and in the introductions to our early published abstracts (Schmahmann and Pandya 1987) and papers on corticopontine projections (referenced above) we laid out the historical background and the relevance of these studies for investigating the role of the cerebellum in cognition. We concluded that the pontine nuclei receive multimodal information invested with motivational and affective significance from association areas in the parietal, frontal, temporal, and limbic cortices. The functional implication was that the cerebellum was part of the circuitry necessary to modulate higher-order, behaviorally relevant information in the domains of attention, executive function, visual-spatial cognition, language and emotion. But the Introduction and Discussion sections in these anatomical publications were necessarily restricted to the pertinent study, the grant applications were not disseminated, and I saw the need to discuss in a more readily accessible forum my ideas about the potential cerebellar role in cognition and emotion and its possible relevance for neuropsychiatric disease. The Emerging Concept paper that was finally published in 1991 took a number of years to be accepted. The early drafts of 1986 evolved into the manuscript that was rejected from the journal *Neurology*, and when it was about to suffer the same fate at the Archives of *Neurology*, the editor, Dr. Robert Joynt kindly agreed with my rebuttal letter and sent it out for a third opinion to the reviewer who declared himself through his comments to be Dr. Dow—expressing strong support for the paper and urging its publication. I remain indebted to

Dr. Dow for this stance. In the paper I reviewed the work I felt to be essential to the rationale for the nonmotor role of cerebellum; laid out the known anatomy of the cerebrocerebellar circuitry relevant to the cerebellar role in cognition—both the feedforward and feedback limbs; considered the topographic arrangement in cerebellum of motor versus nonmotor functions; introduced the concept, anatomy, and terminology of the dysmetria of thought hypothesis for the first time; and discussed the relevance of this notion for the cerebellar role in cognitive and behavioral disorders as well as specifically in mental illness including, notably, schizophrenia and autism. The dysmetria of thought hypothesis and its anatomical underpinnings of the constancy of the cerebellar circuitry, on the one hand, and its complex and highly ordered connections with extra-cerebellar structures on the other, provided a theoretical framework within which to consider the cerebellar contribution to higher function. In this view, the cerebellum modulates behavior, maintaining it around a homeostatic baseline appropriate to context. In the same way that cerebellum regulates the rate, force, rhythm and accuracy of movements, so does it regulate the speed, capacity, consistency and appropriateness of mental or cognitive processes. Dysmetria of movement (the Greek term referring to the traditional ataxic gait or irregular and uncoordinated movements of the extremities resulting from cerebellar lesions) is then matched by dysmetria of thought, an unpredictability and illogic to social and societal interaction. The overshoot and inability in the motor system to check parameters of movement are equated, in the cognitive realm, with a mismatch between reality and perceived reality, and erratic attempts to correct the errors of thought or behavior (Schmahmann 1991). The relevance of this theoretical framework and the results of our published and ongoing anatomical experiments served as the basis of my first chapter on this topic written at the invitation of Bauman and Kemper for their volume on the Neurobiology of Autism (Schmahmann 1994). The potential role of the cerebellum in psychiatric diseases including autism and schizophrenia was intriguing, because these disorders are common and disabling, and available therapeutic strategies often achieve only modest results. Perhaps by approaching these disorders from the perspective that there is a cerebellar contribution to their pathophysiology, new insights and avenues for treatment may be facilitated. The idea of the universal cerebellar transform (UCT)—the computation that is unique to cerebellum, and the universal cerebellar impairment (UCI)—i.e., dysmetria, were terms introduced later to help further define essential elements of the dysmetria of thought theory (Schmahmann 2000, 2001, 2004). Dysmetria of movement is the cerebellar motor syndrome; whereas dysmetria of thought manifests as the various components of the cerebellar cognitive affective syndrome (CCAS). I further explored the anatomical basis and the clinical

relevance of the dysmetria of thought hypothesis in a paper in Human Brain Mapping (Schmahmann 1996) that arose out of a lecture I delivered to the Research Imaging Center at the University of Texas Health Science Center at San Antonio at the invitation of Peter Fox in 1995; and in a Special Issue of Trends in Cognitive Science (Schmahmann 1998) devoted to the Cerebellum.

The Cerebellar Cognitive Affective Syndrome

The syndrome that I described in the journal *Brain* (Schmahmann and Sherman 1998) and in preliminary form the previous year (Schmahmann and Sherman 1997) with my neuropsychology colleague Janet Sherman with the support of my research assistant Amy Hurwitz, came about because there was no clear picture at that time as to what the “behavioral” or nonmotor manifestations of cerebellar lesions in patients actually were. I was questioned by clinicians about this issue from the time of my first lectures on this topic in 1986 to Neurology Grand Rounds at Brown University School of Medicine in Providence, RI at the invitation of my colleague Eileen McNamara, and on home turf at the Boston City Hospital, and then to Neurology Grand Rounds in the Ether Dome at the Massachusetts General Hospital (MGH) when I came on staff in the department of neurology in 1989. Under the daunting gaze of some of the senior neurologists in our field—Drs. Raymond Adams (1911–2008), C. Miller Fisher and neurology chair Joseph Martin, it was not sufficient to rely on the reports of earlier investigators whose patients may not have had pure cerebellar disease and who did not usually come to autopsy. The clinical features, they insisted, needed to be studied prospectively.

Careful scrutiny of a single case can shed new light on neurological diseases and provide novel insights into brain organization. I had my own moment of recognition with the two patients who set me on this journey in the first place, and a similar situation occurred with the proband case in our CCAS series. This young woman who slipped on ice in the Boston winter came in to the hospital emergency room in 1990 for a head computerized tomography scan, which revealed a midline cerebellar tumor. There were no symptoms associated with this. In the days following the uneventful surgery for resection of the histologically benign mass, she was noted by the nurses to have a marked personality change, becoming disinhibited, disrespectful and childlike. Bedside mental state testing using the simple tools of behavioral neurology revealed impairments in working memory, perseveration, distractibility, and lack of mental flexibility, together with agrammatism in her writing and spontaneous conversation. She showed deficits on visual spatial performance in her drawings. Over the next

few months her mother recounted that the patient would report inability to make a sandwich—not knowing what to do first, and in what order. With time she improved many of her abilities, but executive functions remained impaired, and the next two decades have revealed a pattern of personal choices, psychosocial interactions and judgment that have left her requiring regular family intervention to provide support and safety. This combination of mood and personality changes with the cognitive impairments that could be demonstrated at the bedside and on neuropsychological testing were the first indicators of the persistent pattern of executive, visual spatial, linguistic, and affective impairments in the remaining 19 patients that we studied prospectively over the next 6 years, and which we identified and named the CCAS. We viewed these findings from the perspective of the dysmetria of thought hypothesis, noting that the clinical manifestations resemble deficits that arise in the cerebral cortical areas with which the cerebellum is interconnected—loss of the cerebellar contribution to the distributed neural circuits subserving these areas leading to the observed clinical phenomena. We also saw in this cohort a pattern of deficits such that lesions involving the vermis were more readily associated with changes in emotional tone; and further, that the CCAS resulted from lesions that involved the cerebellar posterior lobe but not when the lesions were predominantly confined to the cerebellar anterior lobe. This medial-lateral dichotomy of affect vs. cognition was predicted in the 1991 paper, but the anterior–posterior dichotomy of motor vs. cognitive manifestations (hiding in plain sight, as it turns out from subsequent review) was not previously predicted nor had it been explicitly shown.

The description of the CCAS has proven to be clinically important. We replicated this in children who had undergone resection of cerebellar tumors—work performed by then graduate student at Boston University, Lisi Levisohn, in collaboration with her BU mentor, Alice Cronin Golomb (Levisohn et al. 2000). An Italian group reported similar observations later the same year (Riva and Giorgi 2000). There are now numerous reports of this constellation of deficits in patients with cerebellar lesions of different etiologies, in patients of different ages, and from research groups in different continents (e.g., Molinari et al. 1997, 2004; Neau et al. 2000; Rapoport et al. 2000; Sadeh and Cohen 2001; Steinlin et al. 2003; Exner et al. 2004; Baillieux et al. 2010; Timmann et al. 2010). Some studies fail to document these findings (Gomez Beldarrain et al. 1997; Richter et al. 2007), a result that may be related to lesion location, as outlined later. Affective change may be clinically relevant in this population, and patients can feel substantially better on mood elevating medications. The phenomenon of markedly restricted verbal fluency and paucity of spontaneous output that we noted in some adult patients with CCAS,

and the mutism that occurs in some of the children who underwent cerebellar tumor resection via a midline approach, was consistent with the finding of post-operative mutism (posterior fossa syndrome, PFS) described a few years earlier (Pollack et al. 1995; Wisoff and Epstein 1984). Not all children with the CCAS experience mutism, but those with PFS generally go on to demonstrate the spectrum of features that characterize the CCAS.

The Need for a Monograph

In 1994, about half way through our study of patients with cerebellar lesions, the anatomical circuitry of cerebrocerebellar connections had become better defined, functional imaging data were appearing with increasing volume about cerebellar activations in cognitive paradigms, and theoretical notions about the cerebellum and its wider role were receiving renewed interest. It seemed that the time was right to engage in a project that would help coalesce the emerging field of cerebellum and cognition and hopefully promote this new field of neuroscientific inquiry. Graham Lees, neuroscience editor at Academic Press, took a chance on my book proposal that resulted in the *Cerebellum and Cognition* multi-author volume with an international roster of contributors (Schmahmann 1997a). The book provided a widely read forum for ideas and observations from multiple disciplines within the neurosciences, and its inclusion in the *International Review of Neurobiology* series, accessible through Medline, helped disseminate the ideas. I met Dr. Robert Heath in New Orleans at the time of the Society for Neuroscience annual meeting in 1997, and was delighted that he agreed to write the foreword to the book. Similarly, Joe Berman, then retired from neurosurgery, agreed to allow us to reprint his early paper with Prescott on the effects of cerebellar lesions on aggression in monkeys. My meeting with Dr. Berman in 1998 was memorable, and his encouragement—both professional and through grant support, had a lasting impact on my own scientific path. The book project was exciting and challenging as editorial responsibility was new to me, but the authors were all gracious, and the success of the work (approximately 1,400 citations by 2010) attests to the considerable efforts of all the collaborators.

The Need for a Cerebellar Atlas

For the cover image of *The Cerebellum and Cognition* I chose a diagram from the chapter by Julie Fiez and Marc Raichle (Fiez and Raichle 1997), reflecting activation in the right posterolateral and midline cerebellum by the verb-noun generation paradigm in positron emission tomography and functional magnetic resonance imaging scans. Cerebel-

lar activation by movement had been demonstrated in Dr. Raichle's lab at Washington University in St. Louis, MO (Fox et al. 1985), but the finding of cerebellar activation in language tasks by that group (Petersen et al. 1988) was something of a surprise. Around this time, a number of studies of activation by cognitive paradigms neglected to discuss the obvious findings of cerebellar activation that occurred together with the cerebral hemispheric activations. The focus on cerebellum that began in the early 1990's provided a welcome change, with studies designed by experimental psychologists beginning to address questions of cerebellar activation beyond the motor domain. But the findings and their interpretation were not always clear.

What was clear from these imaging studies, however, was that the activations in cerebellum were described using only generalities—e.g., anterior vs. posterior cerebellum, lateral vs. medial. Those attempting to describe activation sites more accurately were hampered by clumsy and often conflicting cerebellar nomenclatures. The atlas of the human brain in wide use by the neuroimaging community was that of Talairach and Tournoux (1988) that carefully delineated structures in the cerebral hemispheres on the one hand, but included only dotted outlines of the cerebellum with no detail of its lobular divisions or internal structure. The most comprehensive atlas of cerebellum available (Angevine et al. 1961) was by Jay Angevine, Elliott Mancall, and Paul Yakovlev (1894–1983), created at the Massachusetts General Hospital. This atlas was published prior to the development of noninvasive brain imaging, and could not take into account the need for identifying brain areas within coordinate space. It used the earlier nomenclature, but included a comprehensive historical account of earlier terminologies that laid a foundation for the revision of the nomenclature that we adopted.

I had examined the gross morphology of a number of post-mortem monkey cerebella in Dr. Pandya's lab in 1984 prior to commencing my fellowship, and I had more recently studied a number of specimens of human cerebella kindly provided by Dr. Tessa Hedley-Whyte, chief of neuropathology at the MGH. My attempt to understand the complex detail of cerebellar lobular organization and nomenclature led me to the important work of Olaf Larsell (1886–1964), including the posthumous volume of his work edited by Jan Jansen (Larsell and Jansen 1972). In 1995 when I was invited to address the neuropsychology group at the Montreal Neurological Institute (MNI) under Dr. Brenda Milner, I met Dr. Julien Doyon who was then a visiting fellow with Dr. Milner. Shortly thereafter, Julien and I began our collaboration with Alan Evans, director of the McConnell Brain Imaging Center at the MNI, and Michael Petrides, neuropsychologist and a neuroanatomy colleague of mine through his work with Dee. Our mission was to study the cerebellum in the “Colin brain”—the same individual scanned 27 times and averaged

to enhance the signal-to-noise ratio, taking advantage of the great clarity of the data and the computer-enhanced ability to view the brain in the three cardinal planes simultaneously. Julien and I toiled over the atlas between 1995 and 1999, gnashing teeth over the ansoparamedian fissure and the like, trying to determine what was truly asymmetric and what may have been a “fake-out”. In the end, the sophistication of the technology and the precision of Larsell's work regarding the organization and the gross and comparative anatomy of the cerebellum allowed us to revive his nomenclature with a few variations that took into account our new observations. The organization such that each vermal lobule has a hemispheric counterpart; the ability with the imaging to resolve old conflicts about continuity of structures across the midline or lack thereof; and the ability to resolve the old conflicting names allowed us to enhance our understanding of the cerebellum (Fig. 2). Just as we were finishing up the project, I asked Dr. Verne Caviness, then chief of pediatric neurology at the MGH and pioneer of the Center for Morphometric Analysis (CMA) at MGH, for his opinion. Wonderful, he thought, but where are the nuclei? Well of course they were not there, because the T1 weighted image used for the Colin brain at the MNI does not reveal the cerebellar nuclei. I had seen the work of Arthur Toga and colleagues based on his cryosection data in the Laboratory for Neuroimaging at the University of California Los Angeles when I met with him and John Mazziotta during an earlier visit to the west coast in 1988. Arthur came on board the Atlas project with the cryosections of a single cerebellum that I analyzed in the three cardinal planes, using the approach we had defined while studying the Colin MRI brain. I was able to identify the cerebellar fissures, the cerebellar lobules that they demarcated, and the locations in the deep white matter of the cerebellar nuclei. Aided by brain slices provided to me by Tom Kemper, we showed the histology of the nuclei together with their locations in MNI space along with the MRI data. We published a subset of the images in *NeuroImage* (Schmahmann et al. 1999), and with the assistance first of Graham Lees and then Jasna Markovac of Academic Press, the full Atlas appeared the following year (Schmahmann et al. 2000). The Atlas remains a primary reference source for the imaging community, and recently available web-based iterations using normalized templates for cerebellar cortical (Diedrichsen 2006) and nuclear identification (Dimitrova et al. 2006) have relied on the work that came out of that collaboration. The foreword to the superb Atlas of Angevine and colleagues had been written by Dr. Raymond D. Adams, emeritus chief of neurology at the MGH. We were greatly honored, therefore, that Dr. Adams accepted my invitation to write the foreword to what we hoped would be the successor to the earlier contribution.

My colleagues Nikos Makris and David Kennedy at the CMA had been very helpful in acquainting me with the

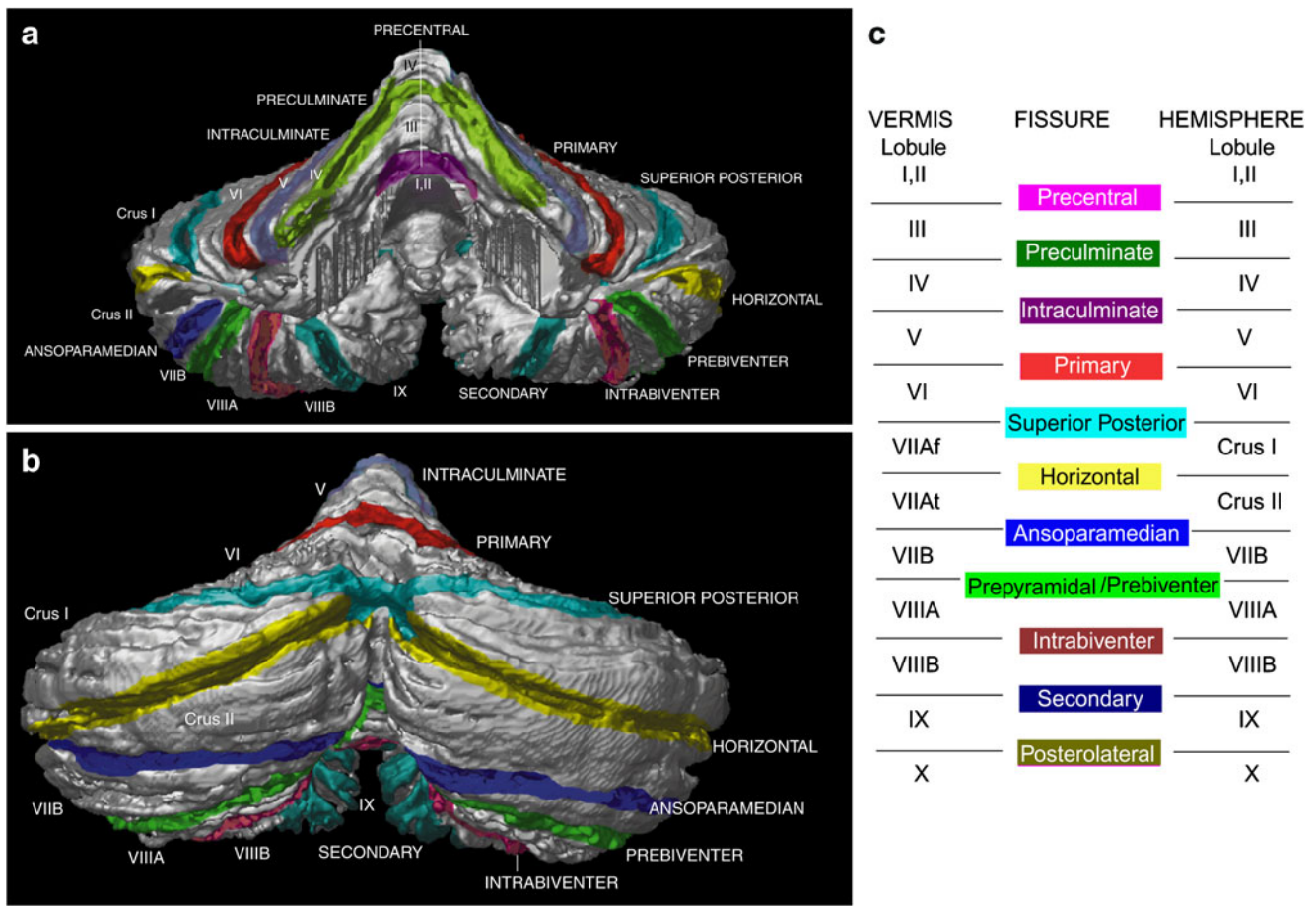


Fig. 2 Figures showing three-dimensional reconstructions from MRI of the external surfaces of the cerebellum with the fissures that demarcate the lobules identified in color in (a), anterior view, and (b), posterior view. (c), Table identifying the relationships between lobules

in the vermis and hemispheres. The cerebellar fissures are color-coded as in the illustrations in (a) and (b). (Reproduced with permission from Schmahmann et al. 2000)

Freesurfer program to develop a better understanding of the lobular organization of the human cerebellum on MRI prior to my collaboration with the MNI. Together with this CMA team we subsequently went on to perform volumetric analyses of the cerebellar lobes and lobules (Makris et al. 2003), and developed a semi-automated computerized approach to flattening the cerebellum (Makris et al. 2005) that represented an advance over our earlier hand-crafted attempt, described below.

Functional Topography

With the availability of the Atlas I thought it would be possible to perform a meta-analysis of functional imaging studies of cerebellum completed to date, to test the topography predictions of the dysmetria of thought hypothesis. With my students Russell Loeber, Amy Hurwitz and Jennifer Marjani, we developed a flattened map of the cerebellum based on the Atlas before its publication, and

then sifted through functional imaging studies to identify areas in cerebellum of activation by sensorimotor versus a variety of cognitive tasks. This project in the end was unsuccessful and unpublished outside of abstracts (Schmahmann et al. 1998a, b). Our choice of domains was too broad, the experimental paradigms in many of the studies we included were not sufficiently discrete, and centers of activation in the studies were not clear enough. We were not alone in desiring a map of functional representation in cerebellum. John Desmond (then at Stanford) and Julie Fiez (at Pittsburgh) also produced a schematic representation of selected cognitive tasks around this time (Desmond and Fiez 1998); but these were admittedly all first-pass attempts that would require refinement. What was evident from our first meta-analysis endeavor, however, was that there appeared to be an anatomically identifiable motor-nonmotor dichotomy in the cerebellum. We resurrected this study 8 years later, when Catherine Stoodley came to my lab as a postdoctoral fellow returning from her time at Oxford University. Using the newly available Activation Likelihood Estimation approach

(Turkeltaub et al. 2002; Laird et al. 2005), our meta-analysis (Stoodley and Schmahmann 2009) demonstrated what the earlier attempt had suggested. By selecting a small subset of well-defined studies in the domains of sensorimotor activation, verbal working memory, verb-for-noun generation paradigm, and (probably weak) limbic activation by images from the International Affective Picture Scale, we showed that there is sensorimotor representation in the cerebellar anterior lobe (and part of lobule VI) with second representation in lobule VIII B, whereas the cognitive and limbic cerebellum is in the posterior lobe, with discrete topographic representation depending on the precise domain. These findings are consistent with the sensorimotor observations of Snider and colleagues in the cat, and with the cognitive topography derived from the locations of lesions in patients with the CCAS. We followed this up first with a study of functional topography in the cerebellum in a single subject (Stoodley et al. 2010), which to my surprise has apparently not been previously attempted even for the cerebral cortex, and demonstrated that this topographic arrangement exists within a single individual (Fig. 3). In a subsequent analysis in a group of 9 subjects we show very similar results (Stoodley et al. 2010b).

The neurology community has generally been slower than the neuroscience community to come to the realization of the nonmotor role of cerebellum. There is a tradition in neurology dating back at least to Galen (A.D. 129/130–200/201) and the ancient Greeks, and resurrected successfully in the mid-1800s by Paul Broca (1824–1880), Carl Wernicke (1848–1905) and by those who described focal brainstem syndromes (Wolf 1971) of using structure–function correlation in patients with discrete brain lesions to discern the functional relevance of the brain’s constituent parts. It occurred to me to draw on this history in the following manner. Conventional wisdom in neurology holds that the cerebellum is purely a motor control device. The null hypothesis of an investigation searching for purely cognitive (not motor) areas of cerebellum is that a lesion anywhere in cerebellum will result in motor deficit, i.e., there are no cerebellar areas devoid of an overt role in motor control. This has not previously been evaluated, although there are reports of cerebellar stroke presenting only with vertigo (Duncan et al. 1975; Lee et al. 2006). To study the question whether there are nonmotor areas of cerebellum we used a conservative neurological approach—I examined 39 patients with stroke confined to the cerebellum (Schmahmann et al. 2009a) and evaluated their motor system using an ataxia rating scale (Trouillas et al. 1997; Schmahmann et al. 2009b) to determine whether the strokes produced motor impairment. Together with my research assistant Jason MacMore and biostatistician Mark Vangel we found that the cerebellar motor syndrome resulted from strokes involving the anterior lobe (including any part of lobules I through V), but not

from stroke confined to any part of lobules VII through X of the posterior lobe. Strokes involving lobule VI produced minimal motor impairment (Figs. 4 and 5). These findings show that cerebellar stroke does not always result in motor impairment, and they provide clinical evidence for topographic organization of motor versus nonmotor functions in the cerebellum.

We thus come to the double-dissociation in the cerebellum with respect to its topographic arrangement. Motor deficits arise from lesions that involve cerebellar areas engaged in motor control as shown by physiology, connections, and functional imaging. In contrast, there are no motor deficits arising from lesions of those parts of cerebellum that have no connections with the motor system. Furthermore, when taken together with previous studies in our lab and elsewhere, cognitive and emotional deficits arise from lesions in those parts of the cerebellum that are linked not to motor regions, but to association and paralimbic cerebral cortices (Stoodley and Schmahmann 2010). These findings compare well with the results of anatomical and physiological investigations showing that the cerebellar anterior lobe and parts of lobule VI as well as the second representation in cerebellar lobule VIII (“the sensorimotor cerebellum”) receive cutaneous kinesthetic information about the extremities and trunk through spinocerebellar tracts (Oscarsson 1965), and are reciprocally interconnected with sensorimotor cortices (Brodal 1978; Thach 1987; Hartmann-von Monakow et al. 1981; Kelly and Strick 2003; Schmahmann et al. 2004). The anterior lobe is also reciprocally linked with parts of the inferior olivary nuclei (the medial and dorsal accessory olive) that provide climbing fiber afferents to the cerebellum and which receive sensorimotor information from the spinal cord (Brodal 1981; Voogd 2004). In contrast, cerebellar lobule VII (“the cognitive cerebellum”) is essentially devoid of connections with the motor cortex or spinal cord (Brodal 1981; Voogd 2004), and is linked instead in a reciprocal manner with association areas in the cerebral cortex (Schmahmann 1991, 1996; Kelly and Strick 2003; Schmahmann and Pandya 1997b), and with parts of the olivary nucleus (the principal olive) that has minimal spinal cord input (Sugihara and Shinoda 2004).

Our observations from the ataxia-stroke study are in line also with other contemporary studies using voxel based morphometry in patients with stroke (Timmann et al. 2008), although we have been challenged with the assertion that it is not the cerebellar cortex, but the deep nuclei, that are responsible for the motor phenomenology. The cortico-nuclear microcomplex is the functional unit of cerebellum (Ito 1984); the motor cerebellum is linked with the interpositus nucleus (globose and emboliform in human), the cognitive cerebellum is linked predominantly with the dentate nucleus, and the limbic cerebellum with the midline

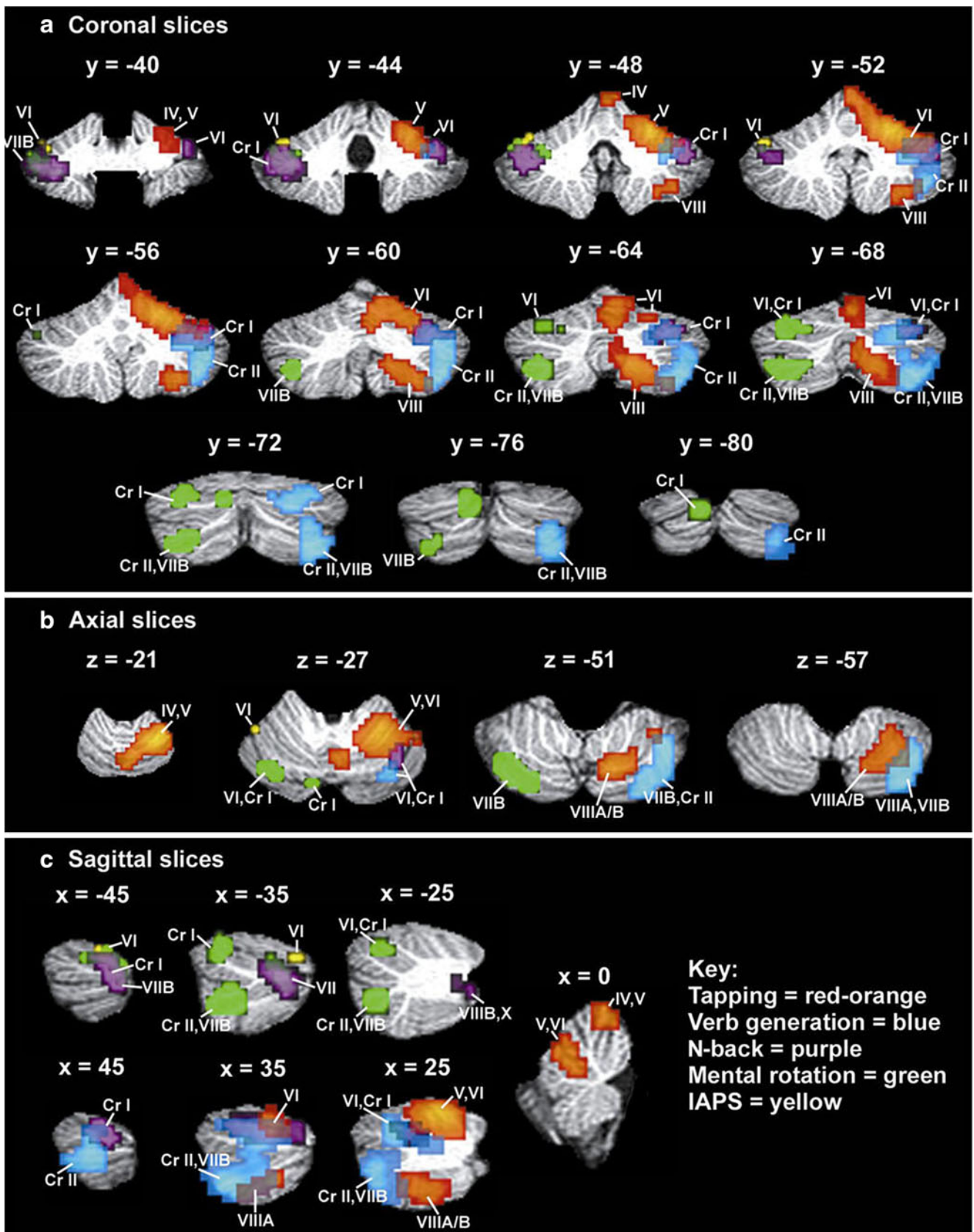


Fig. 3 **a** Coronal, **b** axial, and **c** sagittal slices through cerebellum showing activation patterns for all tasks in a single-subject multiple domain functional imaging study. Color-coding of activations produced by different tasks is in the key at bottom right. Left cerebellum is shown on the left in the coronal and axial slices; a negative x-value indicates left in the sagittal slices. Lobules are labeled according to Schmahmann et al. (2000). Abbreviations: Cr I, Crus I; Cr II, Crus II. (Reproduced with permission from Stoodley et al. 2010a)

fastigial nucleus (Jansen and Brodal 1940; Chambers and Sprague 1955a, 1955b; Evarts and Thach 1969; Haines and Rubertone 1977; Voogd and Glickstein 1998). Thus there is every reason to believe that deficits resulting from lesions of the cerebellar deep nuclei necessarily reflect their interconnections with the overlying cerebellar cortical lobules and their associated functional attributes.

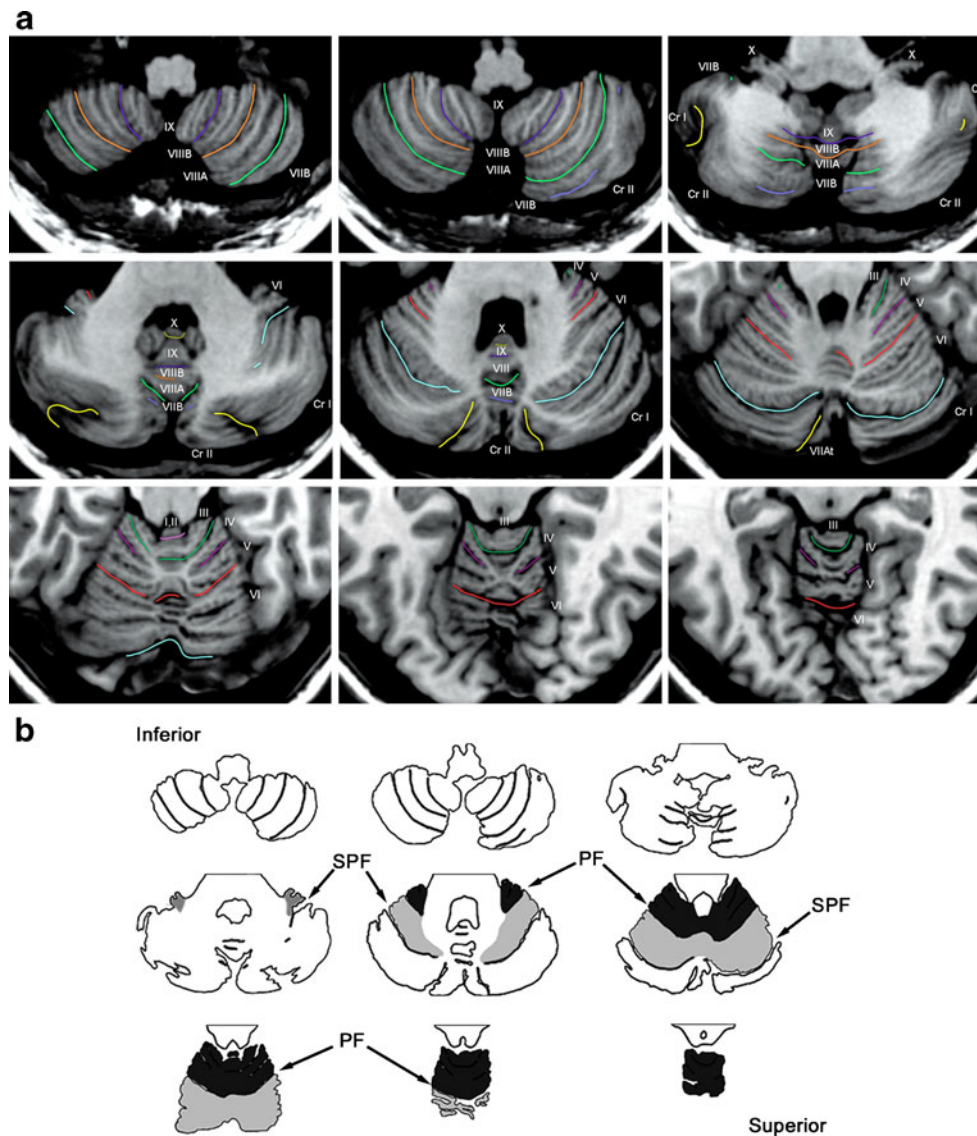


Fig. 4 **a** Selected horizontal MRI images through the cerebellum with fissures and lobules identified. Inferior (posterior lobe) at top left, to superior (anterior lobe) at bottom right. Fissures are color coded: pink, precentral fissure (f), between lobules I/II and lobule III; light green, preculminate f, between lobules III and IV; purple, intraculminate f, between lobules IV and V; red, primary f, between lobules V and VI; light blue, superior posterior f, between lobule VI and crus I; yellow, horizontal f, between crus I and crus II; dark blue, ansoparamedian f, between lobules VIIIB and VIIIA; dark green, previventer f, between lobules VIIIB and VIIIA; brown, intraviventer f, between lobules VIIIA and VIIIB; mauve, secondary f, between lobules VIIIB and IX.

The posterolateral f. between lobules IX and X is seen at the vermis (Reproduced with permission from Schmahmann et al. 2000). **b** Diagram of horizontal sections through cerebellum taken from the MRI images above, demarcating the anterior lobe (shaded black) rostral to the primary fissure (PF); lobule VI (shaded gray) between the primary and superior posterior fissures (SPF); and posterior lobe plus lobule X (not shaded) caudal to the superior posterior fissure. Strokes that spare the anterior lobe and lobule VI do not produce the cerebellar motor syndrome. Even gait is unaffected, once the vertigo from infarction of the vestibular-cerebellar regions has subsided. (Reproduced with permission from Schmahmann et al. 2009a)

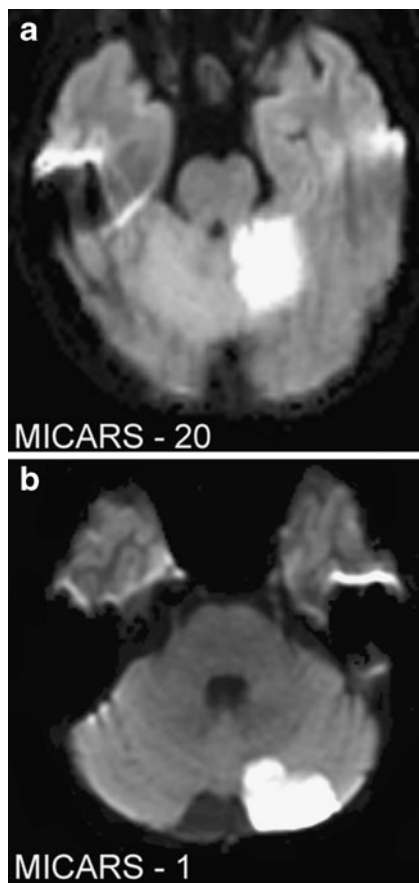


Fig. 5 Representative axial sections of diffusion weighted MRI in patients with acute cerebellar stroke. **a** infarction in the anterior lobe (lobules III through V), with an ipsilateral cerebellar motor syndrome of moderate degree (MICARS, 20). **b** infarction confined to the posterior lobe, involving lobule VI, crus I and crus II. This patient had no ataxia or dysmetria (MICARS 1). MICARS, Modified International Cooperative Ataxia Rating Scale (Trouillas et al. 1997; Schmahmann et al. 2009b)

Developments in magnetic resonance imaging technology add weight to this motor-nonmotor topographic dichotomy in cerebellum. The recent advent of resting state functional connectivity magnetic resonance imaging mapping (fcMRI) now provides a counterpart in the human brain to the anatomical tract tracing studies in monkeys and provides empirical support for the hypothesis that there are separate areas in cerebellum engaged in motor versus higher order behavior. The data from the fcMRI investigations are in accord with the results of fMRI studies and the clinical observations, showing that cerebral sensorimotor areas are linked with the anterior lobe and lobule VIII (with involvement of parts of lobule VI); whereas the cerebral association areas are heavily linked with cerebellar lobule VII (crus I and crus II), with spread into lobule VI (Krienen and Buckner 2009; O'Reilly et al. 2010). The role of lobule IX is hinted at in fcMRI studies—preliminary indicators are for a role in the default mode network (Habas et al. 2009).

The Fiber Pathways Project: Principles of Brain Organization and the Concept of Subcortical Disconnection

Throughout the time period of 1994 through 2006 while the cerebellar work in our lab was continuing, Deepak Pandya and I were engrossing ourselves in the work that would result in the monograph published by Oxford University Press, *Fiber Pathways of the Brain* (Schmahmann and Pandya 2006). In our earlier corticopontine studies using the isotope tract tracing technique (Cowan et al. 1972) we were struck by the order, elegance and beauty of the organization of the fiber tracts as they emanated from the cortical injection site and coursed through the cerebral hemisphere to the brainstem before terminating in the pons (Schmahmann and Pandya 1992). Dr. Pandya had previously written on selected association fiber pathways in the cerebral hemispheres with Michael Petrides (Petrides and Pandya 1988) and Ben Seltzer (Seltzer and Pandya 1984), but there had been no attempt since Joseph Jules Dejerine's (1849–1917) monumental work (Dejerine 1895) to use experimental material to perform a comprehensive analysis and synthesis of the fiber tracts that comprise the bulk of the white matter of the brain. Using the brains of 36 rhesus monkeys injected with the isotope tract tracer, we mapped the origins, trajectories and terminations in cortical and subcortical regions of the fiber pathways emanating from cortical areas throughout the cerebral hemisphere. This became a labor of love, the process itself being a source of great joy, intended to last three or four years, but continued for twelve. By following a passion in this endeavor that at first seemed unrelated to the question of cerebellum and cognition, we recognized certain principles of brain organization that have implications for the evolving understanding of the cerebellum as well as for the cerebral cortex.

We noted that there was a pattern of projections arising from the cerebral cortex that was consistent throughout all the brain areas we studied: every cortical area gives rise to efferent systems coursing to 5 sets of destinations organized as follows.

(1) Association fiber tracts course to cortical areas in the same hemisphere (local or U-fibers, neighborhood fibers to nearby regions, and the named long association fibers to distant cortical areas e.g., superior longitudinal fasciculus, cingulum bundle). (2) Corticostriate fibers travel in the external capsule or the subcallosal fascicle of Muratoff, and course towards their terminations in the caudate nucleus, putamen or claustrum, depending on the origin in the cortex. An intense aggregate of fibers we designated the “cord” (which is how it appears on the coronal sections following injections in single cases) carries axons destined for (3) the opposite hemisphere, (4) the thalamus, and (5) the pons / brainstem / spinal cord. The cord segregates first

into two components; commissural fibers that course to the opposite hemisphere in the corpus callosum or anterior commissure, and a subcortical, or projection, bundle. The subcortical bundle segregates further into fibers that peel off to terminate in the thalamus via various thalamic peduncles, depending on the site of origin in the cortex. The remaining fibers in the subcortical bundle (which we designated the pontine bundle) course into the brainstem with terminations that include the basis pontis, or descending further into the spinal cord, depending on the site of origin in the cerebral cortex. We regarded this arrangement of fibers (the pattern of 5—association, striatal, commissural, thalamic, pontine/brainstem/spinal) as the *general principle of organization* of cerebral cortical connections. We also recognized that different cortical areas are interconnected with great specificity with unique ensembles of neurons in subregions of cortical and subcortical areas. When Dr. Pandya and I first noted this arrangement in our study of thalamocortical projections to parietal lobe (Schmahmann and Pandya 1990), we concluded that a cortical area could be defined by its patterns of subcortical and cortical connections. We consider this predictable topographic precision to be the *specific principle of organization* of cerebral cortical connections (Schmahmann and Pandya 2006, 2008).

Our earlier consideration of the role of cerebellum in cognition now became useful in thinking about the functional significance of these principles of organization, and in turn was informed by the findings of the Fiber Pathways project. Dr. Pandya and I had discussed this issue of cortical and subcortical connectional specificity from the early days of our work together, and we finally committed our ideas to paper in a contribution to a special issue in *Cortex* on disconnection syndromes (Schmahmann and Pandya 2008) at the invitation of our colleague Marco Catani at the Institute of Psychiatry of King's College London. In that essay, we reviewed motor, cognitive and neuropsychiatric disorders in patients with focal lesions in the cerebellum, basal ganglia or thalamus, noting that lesions in these subcortical areas mimic deficits resulting from cortical lesions, but with qualitative differences between the manifestations of lesions in functionally related areas of cortical and subcortical nodes. To account for these findings we drew on the anatomical observations from tract tracing studies, and viewed the clinical phenomena as disconnection syndromes (after Geschwind 1965a, b) reflecting loss of the contribution of subcortical nodes to the distributed neural circuits subserving cognition. We adopted a reductionist approach in which we proposed that neural architecture defines function. In this view, the architecture and microconnectivity unique to each cortical and subcortical structure facilitates a neural computation, or transform, that is unique to that region. I had introduced the

universal transform concept with reference to the cerebellum (Schmahmann 1991, 1996, 2000) in which the histology is essentially uniform throughout; the term “universal” here denotes a functional transform at the physiological level that is consistent throughout an architectonically defined node. We now suggested that the concept is more generalizable, however, and applies to every brain region that can be defined by its architectonic features.

The relevance of the *specific principle* of brain organization, we proposed, is that whereas architecture may define the transform of each node, connectional patterns are likely to determine behavior. Each node in the distributed neural system is required to contribute its unique transform in order to support the ultimate behavior pattern. Further, each node may be engaged in a number of different domains of behavior, which are subserved by anatomically distinct subpopulations of neurons within the node. Clinical manifestations of lesions in the different nodes of the distributed neural system are therefore determined by two central factors—which node is lesioned, and which subpopulations of neurons within that node or its connecting axons are destroyed. Lesions of subcortical structures may mimic deficits resulting from lesions of the cerebral cortex, but there are qualitative differences between them. This can be illustrated using selected clinical examples.

Motor impairment may result from focal lesions in the precentral gyrus, basal ganglia, thalamus and cerebellum. The nature of the clinical impairment differs, however, depending on the node affected. The clumsy or paralyzed arm results from stroke involving the upper extremity representation in the precentral gyrus; slowness of movement results from lesions of the motor regions of the putamen; the motor cerebellum in the anterior lobe produces incoordination of movement; and the ventral lateral thalamic nucleus lesion may produce ataxic hemiparesis.

Cognitive impairments in the executive domain result from lesions of the dorsolateral prefrontal cortex, and its interconnected areas in the dorsolateral part of the caudate nucleus, medial dorsal thalamic nucleus, and crus I and II of cerebellum. Visual spatial impairments follow lesions of the posterior parietal cortex, the head of the caudate nucleus, the lateral posterior thalamic nucleus and pulvinar, and the posterior lobe of the cerebellum. Disorders of affect, drive and motivation occur following lesions of the cingulate gyrus, the ventral striatum, the anterior thalamus, and the cerebellar vermis. Cognitive impairments following these subcortical lesions have been conceptualized as follows. The slowness of movement (bradykinesia), thought (bradyphrenia), and mnemonic retrieval that characterize lesions of the basal ganglia suggest that the striatal deficits impair the initiation of behavior, and the ability to chunk information into manageable quanta (Graybiel 1998). The thalamus is thought to contribute a specific alerting or

engagement response to the different domains of function to which it contributes (Nadeau and Crosson 1997). And the cerebellar role in automatization and optimizing behavior around a homeostatic baseline has been encapsulated in the dysmetria of thought theory—applying the same transform to cognition and emotion as it does to motor control (Schmahmann 1991; Schmahmann 1996, 2000).

In this view cerebellum is integrally incorporated into the distributed neural circuits subserving cognition and emotion, anatomically, clinically and conceptually. Further, the lessons we have learned from the detailed exploration of the cerebellar role in cognition, including the notion of the universal cerebellar transform, the dysmetria of thought theory, and the importance of topography in the relationship of cerebellum to the rest of the nervous system, fed back to enable us to elucidate the postulated concepts and rules that govern the cortical and other subcortical components of the distributed neural circuits.

The Clinical Imperative

I learned early on from my patients of their level of frustration with the medical system when confronted with family members whose disorders of intellect and emotion occurred in the setting of cerebellar disorders. The lack of understanding of this relationship by caregivers, the dismissal of the symptoms as being “in the mind” or a reaction to the reality of a neurological disorder, did not sit well with patients and their families, and was not helpful therapeutically. The “need to know imperative” is a concept I came to in this setting. To the patient and family invested in the disease process and engaged in attempts to maximize function and limit disability, the knowledge of the evolving work in the field of cerebellum and cognition has been a source of comfort and validation. The description of the CCAS and its scientific underpinnings has also opened new avenues of evaluation and approaches to treatment that will hopefully become increasingly sophisticated and targeted with further effort in this direction. What started for me as a challenging and interesting intellectual journey has developed into a gratifying and humbling awareness that this new understanding of cerebellar cognition actually touches people’s lives and makes a difference. Patients appreciate knowing that difficulties they experience in the setting of their cerebellar disorders may not, indeed, be “in their head”, but in their brain. This extends even to patients with pathologic laughing and crying in the setting of cerebellar type multiple system atrophy (Parvizi et al. 2007), a clinical feature that is thought to result from damage to pontocerebellar systems in this disorder, and that responds to pharmacologic treatment.

Relevance in Children

An important development in the human side of this intellectual journey is the relevance of the cerebellar role in higher function for the developing nervous system, that is, what this means for children and their families. The earliest reports of cerebellar malformations included descriptions of children with deficits in intellectual function and social-emotional processing, couched in quasi-medical terminology that we now regard as derogatory if not frankly offensive. Our report of the neurobehavioral consequences of cerebellar tumor resection in children (Levisohn et al. 2000) provided a glimpse of the range of disorders of executive, linguistic, visual-spatial and affective performance that may be observed in children, as well as behaviors that are considered within the psychiatric domain including impulsivity, apathy, withdrawal, agitation, and psychosis. Our own experience with children born with most of the cerebellum missing (near complete cerebellar agenesis) (Chheda et al. 2002) indicated to me that the CCAS manifested not only in adults and children with acquired lesions, but in children with lesions that were either developmental or acquired in utero or in the early post-natal period. This has been borne out in a recent study of children with agenesis (Tavano et al. 2007), and is in line also with the observations in a range of neurodevelopmental disorders (Eugen Boltshauser, pediatric neurologist, University Children’s Hospital Zurich, personal communication).

Earlier this decade I was approached by Adre dePlessis, a classmate from the University of Cape Town now a neonatal neurologist at Boston Children’s Hospital, whose post-doctoral fellow in occupational therapy, Catherine Limperopoulos, had an interest in studying cerebellum. Cerebellar hemorrhage occurs at a high rate in the very premature infant, and conventional wisdom has been that this would lead to motor incapacity alone. I strongly encouraged the prospective study of this clinical population because it provided an excellent opportunity to determine the long term consequences of cerebellar injury at a very early age, and to assess specifically whether these lesions would result in neurobehavioral and psychiatric sequelae. From this group we now have compelling evidence that cerebellar injury in the neonate leads not only to motor incapacity, but to cognitive and psychiatric manifestations including autistic behaviors (Limperopoulos et al. 2005; Limperopoulos et al. 2007), a finding that may be understood in the context of the pathologic observations in autistic brains (Kemper and Bauman 1998; Whitney et al. 2009), and the observations in children following cerebellar tumor resection (Levisohn et al. 2000; Riva and Giorgi 2000). Defining the range of deficits that affects children following neonatal cerebellar hemorrhage adds urgency to finding ways to prevent the hemorrhage in this

period, to informing parents of the potential significance of the complications, and to work with available services to maximize function in these children as they progress through the school system.

The Neuropsychiatry of the Cerebellum

The nature of the cognitive impairments in the CCAS is now relatively well established, although certainly there is more to be learned. A central aspect of the CCAS is the dysregulation of affect that occurs when lesions involve the limbic cerebellum (including, at least, the vermis and fastigial nucleus). The range of affective impairments appears to be quite broad. My reading of the early work, and my interpretation (discussed in the Emerging Concept paper) of the importance of the limbic cerebellum in psychiatric disorders including autism, schizophrenia and psychosis, together with our observations in the adults and children with focal cerebellar injury made it clear to me that this needed to be better defined. In an attempt to achieve this goal, I compiled a list of the findings on examination and the reports of families based on their own observations, of the neurobehavioral impairments in a series of patients with cerebellar injury whom I follow clinically (Schmahmann et al. 2007).

These included adults and children with congenital lesions—cerebellar agenesis, dysplasia, and hypoplasia, and acquired conditions—cerebellar stroke, tumor, cerebellitis, trauma, and neurodegenerative disorders. The behaviors that my colleagues and I witnessed and that were described by patients and families included distractibility and hyperactivity, impulsiveness, disinhibition, anxiety, ritualistic and stereotypical behaviors, illogical thought and lack of empathy, as well as aggression and irritability. Ruminative and obsessive behaviors, dysphoria and depression, tactile defensiveness and sensory overload, apathy, childlike behavior, and inability to comprehend social boundaries and assign ulterior motives were also evident. I then grouped these disparate neurobehavioral profiles into five major domains, characterized broadly as disorders of attentional control, emotional control, social skill set, autism spectrum disorders, and psychosis spectrum disorders. Jeffrey Weilburg and Janet Sherman, my colleagues at the MGH in psychiatry and neuropsychology who had seen and evaluated some of the patients in the cohort, worked with me to help sculpt this approach. Drawing on the dysmetria of thought hypothesis, we conceptualized the symptom complexes within each putative domain as reflecting either exaggeration (overshoot, hypermetria) or diminution (hypotonia, or hypometria) of responses to the internal or external environment. Some patients fluctuated between these two states, and even demonstrated them simultaneously—an observation that

harkens back to the original CCAS paper in which I noted that patients could be disinhibited and inappropriate while at the same time displaying a flattened affect. This catalogue of psychiatric and social-emotional manifestations needs to be re-evaluated prospectively using the statistical power of correlation analysis and factor analysis, and it will be interesting to see if our approach using *a priori* hypothesis melds with the results of such a blinded study. It will also be interesting to determine whether lesion location, nature of disease, and age of patient, among other factors, determine which neuropsychiatric manifestations dominate—schizophrenia / schizophreniform behavior, depression, autism, obsessive compulsive behavior, panic, anxiety, or the other manifestations that we now know can occur in the setting of cerebellar lesions.

By defining psychiatric manifestations in patients with identifiable cerebellar pathology, it becomes more readily apparent that abnormal cerebellar anatomy and physiology may play a key role in the pathophysiology of mental illness including schizophrenia and autism, in line with the persistent trail of observations pointing in that direction. The potential cerebellar role in schizophrenia, and the importance of our dysmetria of thought theory for that disorder has since been recognized and adopted both in concept and terminology by other researchers in the this field who have gone on to demonstrate abnormal cerebellar activation in the schizophrenia patient population using functional MRI (Andreassen et al. 1996; Nopoulos et al. 1999; Kim et al. 2000).

Treatment

Almost three decades into this journey, and with the new knowledge that has evolved in this field, we are now in a position to investigate novel treatments for patients with neurobehavioral consequences of cerebellar injury.

There can be no controversy surrounding the need to engage patients and families in therapeutic environments with mental health professionals trained to recognize and cope with the challenges these disorders produce. Validation of the reports of patients and family members through neurocognitive testing can be a powerful tool in itself, and the clinician caring for these patients should be aware of the relationship of cerebellum to higher function in order to address questions as they arise, and preemptively intervene when necessary.

Pharmacologic approaches to alterations in mood and behavior are currently based on a syndromic approach, such as the treatment of depression, anxiety, or psychosis. There is no empirical evidence that these are effective in this population, however, nor are there data regarding the optimal choice of medication. These are readily testable, but to my knowledge these studies have not yet been performed.

Therapeutic interventions by rehabilitation specialists can help manage the cerebellar motor syndrome, and most ataxia physicians rely on these services to enhance patients' quality of life. There is a school of thought suggesting that cerebellar exercises (i.e., physical maneuvers that tap cerebellar motor control) may be effective in relieving other potential manifestations of cerebellar dysfunction. This came to prominence through the work of Levinson (1988) based on a vestibular approach to the treatment of dyslexia. It was revived through the apparent cerebellar exercise program designed to improve attention deficit disorder and dyslexia (Reynolds et al. 2003; Reynolds and Nicolson 2007) based in large part on work showing a cerebellar link to dyslexia (Nicolson et al. 2001; Nicolson and Fawcett 2005) and apparently also on our own work (Wynford Dore, personal communication, 2001). This approach was met with skepticism (e.g., Snowling and Hulme 2003; Bishop 2007), and it is yet to be rigorously proven. The use of physical interventions in the attempt to achieve cross-modal rehabilitation through cerebellar mechanisms is appealing, however, and I included this as one possible approach in my chapter on therapeutic implications in the *Cerebellum and Cognition* monograph (Schmahmann 1997b).

Cognitive rehabilitation for patients with the CCAS is desirable (Maeshima and Osawa 2007), and recent approaches based on cognitive behavioral therapy have been tested in a preliminary manner with promising results (Goal Management Training; Schweizer et al. 2008). In my own experience, an important feature that differentiates cerebellar cognition from disorders of cerebral cortex is that the cerebellar lesion can be compensated for, at least in part, by bringing the issue at hand to conscious awareness, focusing on the problem in order to address it. This is true for selected aspects of the motor impairment (making sure to turn more slowly to avoid the overshoot that produces falling, for example), and it is true also for the failure of automatic multitasking that characterizes many cerebellar patients who benefit from concentrating on one task at a time, be it motor or cognitive, to bring that task to completion successfully before moving on to the next.

I believe there is one new area of potential therapeutic engagement that holds great promise, based on the dysmetria of thought theory, and on preliminary data from an earlier era as well as from our own studies. A central tenet of the dysmetria theory is that the cerebellum modulates behavior, maintaining it around a homeostatic baseline that is appropriate to context. Upregulating the cerebellar modulation of the processes disturbed in neuropsychiatric disorders should theoretically, therefore, improve the cerebellar control of these behaviors and produce clinical improvement. I was struck from the outset by the logic of Heath's view that the cerebellum is an emotional pacemaker; and I was similarly intrigued by the findings of Heath and Cooper who reported improvement in psycho-

social behaviors as well as in epilepsy in patients treated by cerebellar cortical stimulation using implanted subdural electrodes. Deep brain stimulation is now a recognized approach to the treatment of psychiatric disorders including depression (Mayberg et al. 2005) and obsessive compulsive disorder (Rauch et al. 2006), and I wondered about its resurrection for cerebellar stimulation in my 1997 therapeutics chapter. Since then, however, transcranial magnetic stimulation (TMS) has been developed for clinical purposes and has been shown to be effective for depression (Fregni et al. 2006), and preliminary evidence indicates that stimulation over the auditory cortex decreases auditory hallucinations in schizophrenia (Aleman et al. 2007), but it does little or nothing for the disabling behavioral manifestations of schizophrenia.

I have been convinced for some time that a cerebellar approach to the treatment of schizophrenia and other neuropsychiatric disorders may be effective in relieving symptoms. In conversations with my neurological colleague Alvaro Pascual-Leone at the Beth Israel Deaconess Medical Center in Boston and a pioneer in the development and scientific rationale of TMS, we have imagined trying cerebellar TMS for mental disorders to see if we could replicate the Heath–Cooper results in a contemporary setting and with noninvasive methods. With the arrival in Boston of a Turkish post-doctoral fellow in behavioral neurology, Asli Demirtas-Tatlidede, who performed much of the work on the study, along with another post-doc Caterina Freitas and a team of psychiatrists and neuropsychologists including Dost Ongur and Larry Seidman, we were able to make this study a reality. In a pilot study of 8 patients with treatment-refractory schizophrenia (Demirtas-Tatlidede et al. 2010) we localized the vermis (the limbic cerebellum) using state of the art neuronavigation software linked to the MRI images of the brain, and applied repetitive theta burst stimulation. We showed that there were no complications or psychiatric exacerbations, indicating that TMS appears to be safe in schizophrenia. Further, the intervention produced improvement in measures of happiness, sadness, alertness and energy—all aspects of the negative symptoms of schizophrenia that can be refractory to even the most effective of contemporary antipsychotics. And neuropsychological testing revealed improvements in working memory, attention, and visual spatial skill. This work continues. Should it be successful, it would be gratifying to make a difference in this challenging disorder and perhaps in others as well, and it would provide a therapeutic proof of principle of the dysmetria of thought theory of the cerebellar regulation of emotion and cognition in addition to motor control. It would also be gratifying to know that we will have come full circle—learning from patients about the role of the cerebellum in higher order function, and giving back to patients effective treatments derived from these new insights.

Where to Now?

It may be difficult now to fathom how unconventional and unacceptable it was almost three decades ago to propose that the cerebellum has cognitive and limbic roles. The suggestion may initially have been viewed as another unsustainable effort in the tradition of Snider, Prescott, Heath and Cooper, but it transpires that this effort follows in the tradition not only of those investigators but of a number of other eminent and influential early scientists as well, as laid out in this essay and elsewhere. The fact that we can now consider the history of the evolution of ideas and observations in the field of the cerebellum and cognition—an established field of inquiry in neuroscience, marks a turning point in this journey.

It will be exciting to witness the directions this field will take and the innovative approaches that investigators both here and abroad will adopt to further explore the role of cerebellum in motor and nonmotor domains, and to improve function in patients with cerebellar neurocognitive disorders. There is still much to learn. One hotly contested question concerns precisely what the cerebellum is doing, i.e., what is the nature of the universal cerebellar transform. My own views are embodied in the dysmetria of thought theory, but hypotheses abound (Ivry and Keele 1989; Ito 1993; Bower 1995; Courchesne and Allen 1997; Barlow 2002; Doyon et al. 2003; Leggio et al. 2009; see also Schmahmann 1997a and Strick et al. 2009). This question is interesting and important, but it is no more or less vexing for cerebellum than it is for any brain region, including the most well understood areas of the cerebral cortex. The computation that characterizes a neuronal ensemble is important to know, but the lack of a definitive answer neither negates nor diminishes the cerebellar role in these functional domains.

In the Ataxia Unit of the Massachusetts General Hospital we are confronted daily with patients whose inherited or acquired disorders of the cerebellum affect not only their mental function, but deprive them also of their mobility and independence, and in some instances these diseases take lives. These are challenging illnesses, and diagnosing, defining, treating and hopefully preventing them remains a core part of our clinical and research mission. These diseases have excited a great deal of attention. There are novel noninvasive imaging approaches to the evaluation of cerebellar pathways (Granziera et al. 2009) and neuronal integrity in neurological and psychiatric illness (Catani et al. 2008), animal models of the inherited ataxias and mental illness have facilitated new insights into the pathophysiology of these diseases, disorders that were previously lumped together in confusion are now known by their genetic signature, and new therapeutic interventions are being evaluated to interrupt the pathophysiology of the ataxias. Together with the recognition of the cerebellar role in some of the most challenging disorders in neurology

and psychiatry, there is a concerted effort to reveal the secrets of the cerebellum. In this there is hope for greater knowledge leading to prevention and effective treatment of neurodegenerative disorders of the cerebellum, of the cognitive and affective manifestations of cerebellar lesions in children and adults, and the introduction and refinement of cerebellar-based approaches to the treatment of neuropsychiatric disorders.

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