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Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing

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Abstract

Patients with cerebellar damage often present with the cerebellar motor syndrome of dysmetria, dysarthria and ataxia, yet cerebellar lesions can also result in the cerebellar cognitive affective syndrome, including executive, visual-spatial, and linguistic impairments, and affective dysregulation. We have hypothesized that there is topographic organization in the human cerebellum such that the anterior lobe and lobule VIII contain the representation of the sensorimotor cerebellum; lobules VI and VII of the posterior lobe comprise the cognitive cerebellum; and the posterior vermis is the anatomical substrate of the limbic cerebellum. Here we analyze anatomical, functional neuroimaging, and clinical data to test this hypothesis. We find converging lines of evidence supporting regional organization of motor, cognitive, and limbic behaviors in the cerebellum. The cerebellar motor syndrome results when lesions involve the anterior lobe and parts of lobule VI, interrupting cerebellar communication with cerebral and spinal motor systems. Cognitive impairments occur when posterior lobe lesions affect lobules VI and VII (including Crus I, Crus II, and lobule VIIB), disrupting cerebellar modulation of cognitive loops with cerebral association cortices. Neuropsychiatric disorders manifest when vermis lesions deprive cerebrocerebellar limbic loops of cerebellar input. We consider this functional topography to be a consequence of the differential arrangement of connections of the cerebellum with the spinal cord, brainstem, and cerebral hemispheres, reflecting cerebellar incorporation into the distributed neural circuits subserving movement, cognition, and emotion. These observations provide testable hypotheses for future investigations.

Keywords

cognition; motor; limbic; dysmetria; imaging; connections

1. Background

It has now become apparent that the cerebellum is critical for many functions other than the coordination of movement, and is engaged also in the regulation of cognition and emotion (Baillieux et al., 2008; Leiner et al., 1986; Schmahmann, 1991, 1996, 1997; Schmahmann and

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Sherman, 1998). In contrast to the understanding of the regional cerebellar anatomy for motor control (see Manni and Petrosini, 2004, for review), the putative functional topography of the cerebellar modulation of cognition and emotion remains unclear. The cerebral cortex can be parcellated on the basis of architectonic heterogeneity (Brodmann, 1909), but the main components of the cerebellar cortex are essentially uniform throughout (Ito, 1984), although differences are found in the preferential distribution of unipolar brush cells in the vestibulocerebellum and in the molecular identities of cerebellar cortical neurons (see Schilling et al., 2008 for review). A central question therefore emerges when considering this newly appreciated wider role of the cerebellum in the nervous system: which parts of cerebellum are engaged in these different functions?

We have previously hypothesized that there is a functional dichotomy between the anterior lobe (lobules I-V) and lobule VIII that are predominantly sensorimotor; and lobules VI and VII (including Crus I and II and lobule VIIB) that contribute to higher-level processes (Schmahmann, 1991, 1996, 2004; Schmahmann et al. 2009b). Lobule IX is considered essential for the visual guidance of movement (Glickstein et al., 1994), although functional connectivity magnetic resonance imaging (fcMRI) data indicate that it contributes to the default mode network (Habas et al., 2009). Lobule X has long been thought to be the substrate of the vestibulocerebellum. Here we consider anatomical, functional imaging, and clinical data to test the hypothesis of topographic organization in the cerebellum of sensorimotor control, cognition and emotion.

2. Anatomical evidence for cerebellar motor-nonmotor dichotomy

2.1 General organization of the cerebellum

Figure 1 provides an overview of the general organization of the cerebellum into ten lobules (I-X) (Bolk, 1906; Larsell and Jansen, 1972; Schmahmann et al., 2000c). The cerebellum has traditionally been recognized as having three anterior-posterior divisions: the anterior lobe (lobules I – V) is separated from the posterior lobe by the primary fissure, and the posterior lobe (lobules VI – IX) is separated from the flocculonodular lobe (lobule X) by the posterolateral fissure. The lateral cerebellar hemispheres have expanded massively through evolution (Larsell and Jansen, 1972), in concert with the cerebral association areas and the ventral part of the dentate nucleus (Dow, 1942, 1974; Leiner et al., 1986; Whiting and Barton, 2003). Much of this lateral cerebellar region (the neocerebellum) comprises the hemispheric extensions of lobules VI and VII.

There is rich heterogeneity in the variety, complexity, and functional specialization of the areas of spinal cord, brainstem and cerebral hemispheres with which the cerebellum is interconnected. A brief overview of these connectional patterns provides insights into the functional organization of the cerebellum.

2.2 Spinal and olivary inputs to cerebellum differentiate motor versus nonmotor regions

The cerebellum receives extensive projections carrying cutaneo-kinesthetic information from the limbs directly via the spinocerebellar tracts and from the face and head via the trigeminocerebellar tracts, and indirectly via the nuclei of the inferior olivary complex relaying afferents conveyed in the spino-olivary tracts. In cat the dorsal and ventral spinocerebellar tracts terminate in the anterior lobe and lobule VIII (Brodal, 1981); the trigeminocerebellar projections terminate in the face representation principally in lobule VI, with some extension into lobules V and sparse involvement of lobules VII and VIII (Carpenter and Hanna, 1961; Hesslow, 1994; Ikeda, 1979; Snider, 1950). The medial and dorsal accessory olivary nuclei relay their spinal inputs through climbing fibers to these same cerebellar lobules (lobules I-V;

VI; VIII) as well as to the interpositus nuclei (Brodal, 1981; Oscarsson, 1965; Voogd, 2004).

In contrast, the principal olivary nucleus, which has little or no spinal cord input (Sugihara and Shinoda, 2004), sends climbing fibers to lobule VII and the dentate nucleus, and to a smaller degree to lobule VI, but not to the anterior lobe or lobule VIII. This double dissociation in the olivo-cerebellar connections is evident in now-classical anatomical studies (Brodal, 1981; Oscarsson, 1965) as well as in contemporary anatomical investigations (see Azizi, 2007 for review), and provides part of the anatomical substrate for our proposed cerebellar motor-nonmotor dichotomy.

2.3 Motor, cognitive, and limbic loops in the cerebrocerebellar system

The cerebellum is linked to the cerebral cortex via two-stage feedforward and feedback systems. Input from cerebral cortical regions terminates on nuclei in the basis pontis, which in turn convey mossy fiber efferents to the cerebellum. Feedback projections from the cerebellar cortex travel via the deep cerebellar nuclei and terminate in the thalamus, which then sends projections back to the cerebral cortex. The organization of the cerebro-cerebellar system indicates that information from sensorimotor vs. association cortices is processed in different regions of the cerebellum.

2.3.1 Cortico-ponto-cerebellar projections—Histological tract-tracing studies in monkeys have defined the topographically arranged projections to the basis pontis from sensorimotor, association and paralimbic cortices.

Motor-related cortices project preferentially to pontine neurons situated in the caudal half of the pons, and these motor corticopontine projections are somatotopically arranged (Brodal, 1978; Hartmann-von Monakow et al., 1981; Nyby and Jansen, 1951; Schmahmann et al., 2004a,b; Sunderland, 1940). From here, pontocerebellar fibers travel through the opposite middle cerebellar peduncle to terminate mostly in the contralateral cerebellar anterior lobe. Association cortex projections from prefrontal, posterior parietal, superior temporal, parastriate, parahippocampal and cingulate regions also show topographic organization in the pons (see Schmahmann, 1996; Schmahmann and Pandya, 1992, 1997). Prefrontal fibers terminate more medially and rostrally, whereas projections from the posterior cerebral hemisphere favor the dorsal, lateral and ventral pontine nuclei. These associative corticopontine inputs are conveyed in the middle cerebellar peduncle to the cerebellar posterior lobe.

Physiological studies have shown that, in contrast to arm and leg sensorimotor representations in the anterior lobe and lobule VIII, with face representation additionally in lobule VI (Snider and Eldred, 1951), the anterior cingulate region projects to medial parts of Crus I and II. Association cortices project to the posterior lateral cerebellar hemispheres (Allen and Tsukahara, 1974), and in particular parietal lobe cortex is linked with lobule VII, including Crus I, Crus II and paramedian VIIB (Sasaki et al., 1975). Trans-synaptic viral tract-tracing studies provide confirmation of these physiological observations, demonstrating that whereas the motor cortex is linked with cerebellar lobules IV, V, and VI, prefrontal and posterior parietal cortices are reciprocally interconnected with cerebellar lobules Crus I and Crus II, the hemispheric extensions of lobule VIIA (Hoover and Strick, 1999; Kelly and Strick, 2003). Diffusion tensor imaging of the cerebral peduncles indicate that in the monkey the majority of corticopontine fibers are from the motor system (centrally situated in the peduncle), but in the human brain there are larger numbers of fibers from prefrontal regions (situated more medially in the peduncle; Ramnani et al., 2006).

In addition to corticopontine afferents from motor and nonmotor regions, the cerebellum also receives inputs from the medial mammillary bodies engaged in memory (Aas and Brodal, 1988; Haines and Dietrichs, 1984) and multimodal deep layers of the superior colliculus. It also has reciprocal connections with the hypothalamus (Dietrichs, 1984; Haines and Dietrichs, 1984) and with brainstem areas (ventral tegmental area, periaqueductal gray, and locus ceruleus) that are linked with limbic and paralimbic regions (Snider and Maiti, 1976). Paralimbic cortices in the cingulate gyrus concerned with motivation, emotion and drive (Devinsky et al., 1995; Paus, 2001) communicate with the cerebellum via their projections to the pontine nuclei (Brodal et al., 1991; Vilensky and Van Hoesen, 1981), and the caudal inferior parietal lobule, multi-modal regions of the superior temporal gyrus, and the posterior parahippocampal formation that are interconnected with paralimbic structures also contribute to the cortico-pontine projection (see Schmahmann, 1996; Schmahmann and Pandya, 1997).

Anatomical studies have not conclusively identified the vermis as the principal target of such limbic connections, but physiological and behavioral studies provide support for the postulated relationship between the cerebellar midline structures and the modulation of emotion (Heath, 1977; Schmahmann, 1991, 2000a). For example, stimulation of the cerebellar vermis modulates firing patterns in hippocampus, amygdala, and septum (Babb et al., 1974; Berman et al., 1997; Bobee et al., 2000; Moruzzi, 1947; Zanchetti and Zoccolini, 1954), and vermal stimulation can ameliorate aggression in patients (Heath et al., 1978).

2.3.2 Cerebello-thalamic-cortical projections—The feedback projections from the cerebellum to the cerebral cortex close the cerebro-cerebellar loops to motor and nonmotor (cognitive and affective) regions. Output to the thalamus from the cerebellar deep nuclei is directed to both motor (ventrolateral nucleus; nucleus X) and nonmotor (intralaminar, centralis lateralis and paracentralis; centromedian-parafascicular; and mediodorsal) thalamic nuclei. Different subdivisions of the cerebellar nuclei target motor and prefrontal cortices: motor cortex receives projections from neurons in the interpositus and dorsal parts of the dentate nuclei, whereas prefrontal cortex area 46 is targeted by the evolutionarily-newer ventrolateral dentate nucleus (Middleton and Strick, 1994, 1997). Further, neurons situated dorsally in the dentate nucleus project to the supplementary motor area (SMA), which in turn projects to the primary motor cortex and spinal cord; ventrally-located dentate nucleus neurons project to the pre-SMA, which is densely interconnected with prefrontal regions (Akkal et al., 2007).

2.4 Anatomical summary

In sum, spinal cord, brainstem (inferior olivary nucleus and neurons of the basis pontis), and cerebral cortical areas concerned with sensorimotor processing are linked with the cerebellar anterior lobe (lobules I – V) and lobule VIII, and to a smaller degree with lobule VI, together with the interpositus nuclei (globose and emboliform). In contrast, cerebral association areas and nuclei of the inferior olive and basis pontis that receive nonmotor inputs target lobules VI and VII and the dentate nucleus. Available evidence points to limbic-related structures being interconnected with the cerebellar vermis and fastigial nucleus. These anatomical connections provide the structural basis for the theoretical formulation of the sensorimotor vs. cognitive/affective functional dichotomy in the cerebellum.

3. Neuroimaging in humans

Neuroimaging studies report cerebellar activation during a multitude of tasks, including studies of motor control, and higher-level tasks in which activation due to overt responses is eliminated through subtraction analyses. Our recent activation likelihood estimate (ALE) meta-analysis of functional activation patterns within the cerebellum (Stoodley and Schmahmann, 2009a) found converging evidence for activation in anterior lobe (lobule V) and lobules VI and VIII during sensorimotor tasks, and posterior lobe (lobules VI and VII) activation during language,

spatial, executive, working memory and affective tasks. Here we present an overview of studies that demonstrate cerebellar activation during sensorimotor, cognitive, and affective processing.

3.1 Sensorimotor cerebellar activation

The somatotopic representations of the human body have been demonstrated using functional MRI during sensorimotor tasks (Bushara et al., 2001; Grodd et al., 2001, 2005; Nitschke et al., 1996; see also Takanashi et al., 2003; Thickbroom et al., 2003). These are reflected in a body map in the anterior lobe and lobule VI with a second representation in lobule VIII of the posterior lobe, corresponding well with electrophysiological studies in the cat (Snider and Eldred, 1951). Movement of the hand localizes to ipsilateral lobules V and VIII (Grodd et al., 2001); tactile stimulation of the hand activates lobule V ipsilaterally with a second area of activation in lobules VIII B and IX (Bushara et al., 2001). Leg and foot sensorimotor representations are observed in lobules II and III (Nitschke et al., 1996), whereas orofacial movements activate paravermal anterior lobe regions extending into medial parts of lobule VI (Dresel et al., 2005; Urban et al., 2003). Our meta-analysis corroborated selected aspects of the somatotopy identified in these and other studies; activation patterns for sensorimotor tasks involving the right index finger were localized to the anterior lobe (lobule V), with a secondary focus in lobules VIII A/B (Stoodley and Schmahmann, 2009a).

3.2 Cerebellar activation during cognitive tasks

Activation of the cerebellum in cognitive tasks was first demonstrated in positron emission tomography (PET) studies of language (Petersen et al., 1998; Raichle et al., 1994). Subsequent evaluations showed cerebellar activation in a variety of nonmotor tasks including sensory processing (Gao et al., 1996), appreciation of timed intervals (Jueptner et al., 1995), anticipatory planning and prediction (shifting attention tasks) (Allen et al., 1997; though see Bischoff-Grethe et al., 2002), verbal working memory (Desmond et al., 1997), and mental imagery (Ryding et al., 1993). Since these early studies, cerebellar activation has been found consistently during language, working memory, visual spatial and executive function tasks.

Verbal fluency, verb-for-noun generation, semantic judgment, and word stem completion tasks reliably activate the cerebellum in healthy populations (Buckner et al., 1995; Desmond et al., 1998; Frings et al., 2006; Gurd et al., 2002; Herholz et al., 1996; Hubrich-Ungureanu et al., 2002; Lurito et al., 2000; McDermott et al., 2003; Noppeney and Price, 2002; Ojemann et al., 1998; Raichle et al., 1994; Schlosser et al., 1998; Seger et al., 2000; Tieleman et al., 2005; Xiang et al., 2003). These studies controlled for articulation or employed paradigms that did not require subjects to verbalize their responses, and found activation in the posterior lobe, including lobules VI and VII (Crus I/II). In particular, language-related tasks activate the right posterolateral cerebellum in right-handed individuals, in concert with left prefrontal regions (Buckner et al., 1995; Desmond et al., 1998; Fiez and Raichle, 1997; Gurd et al., 2002; Ojemann et al., 1998; Palmer et al., 2001; Petersen et al., 1998; Schlosser et al., 1998). Laterality of cerebellar activation varies according to cerebral hemisphere dominance for language – right cerebellar activation occurs during verbal fluency (word generation) and working memory tasks in right-handed subjects (Hubrich-Ungureanu et al., 2002; Jansen et al., 2005; Ziemus et al., 2007), whereas the left cerebellum activates during these tasks in left-handed subjects (Jansen et al., 2005). Our meta-analysis (Stoodley and Schmahmann, 2009a) provided further evidence that language-related activity is focused in lateral, posterior cerebellar regions, including lobules VI and Crus I/II. Notably, the cerebellar anterior lobe is not active when the motor components of speech (articulation) are excluded, although it has been argued that cerebellar activation during cognitive tasks reflects inner speech or subvocal rehearsal (e.g., see Ackermann et al., 2007).

Also reflecting these contralateral cerebro-cerebellar connections, cerebellar activation patterns during spatial tasks tend to be more left-lateralized, consistently involving posterior lobe regions, particularly lobule VI (Stoodley and Schmahmann, 2009a). This is exemplified by line bisection tasks that involve the right parietal cortex and left cerebellum (Fink et al., 2000). Mental rotation and spatial transformation tasks also tend to activate posterior regions in lobules VI / Crus I (e.g., Bonda et al., 1995; Jordan et al., 2001; Parsons et al., 1995; Vingerhoets et al., 2002; Zacks et al., 2002).

Working memory paradigms, such as the n-back task, activate bilateral regions of the cerebellar posterior lobe (Honey et al., 2000; LaBar et al., 1999; Tomasi et al., 2005; Valera et al., 2005). Chen and Desmond (2005a,b) have proposed that the superior cerebellum (lobules VI/ Crus I) is involved in the articulatory control aspect of this task while the inferior cerebellum (lobules VIIB/VIIIA) is important for phonological storage. Cerebellar posterior lobe activation is also found during executive function tasks, such as the Tower of London, random number generation and complex decision-making tasks (Blackwood et al., 2004; Daniels et al., 2003; Harrington et al., 2004; Jahanshahi et al., 2000; Schall et al., 2003), and tends to specifically involve regions within lobules VI/Crus I and VIIB on the left (Stoodley and Schmahmann, 2009a).

A consistent feature of the cerebellar activation by tasks of cognitive processing such as language, working memory, spatial and executive tasks is that it is located in the posterior lobe and does not involve the anterior lobe.

3.3 Cerebellar regions active during affective processing

Functional imaging of affective / emotional processing in healthy controls also highlights posterior cerebellar regions. Viewing emotional vs. neutral images from the International Affective Picture Scale (IAPS; Lang et al., 2005) activates cerebellar regions in the posterior lobe, including lobules VI and VII (Bermpohl et al., 2006; George et al., 1993; Hofer et al., 2007; Lane et al., 1997; Lee et al., 2004; Paradiso et al., 1997, 1999, 2003; Takahashi et al., 2004). The act of identifying emotional intonation produces cerebellar activation in midline lobule VII and the lateral posterior hemisphere (lobule VI bilaterally and right Crus I) both during fMRI (Wildgruber et al., 2005) and PET imaging (Imaizumi et al., 1997).

Cerebellar vermis activation is seen in neuroimaging studies investigating panic (e.g., Reiman et al., 1989), sadness and grief (Beauregard et al., 1998; Gundel et al., 2003; Lane et al., 1997). Autonomic processing (Parsons et al., 2000), including the autonomic cardiovascular arousal that occurs during both exercise and mental arithmetic stressor tasks (Critchley et al., 2000), and air hunger (Evans et al., 2002) result in activation of posterior cerebellar regions in both the midline and lateral hemispheres. The cerebellum is also active during painful stimulation (Becerra et al., 1999; Borsook et al., 2007; Ploghaus et al., 1999; Singer et al., 2004) – anterior regions are activated by the experience of pain, whereas posterior regions are active during the anticipation of pain (Ploghaus et al., 1999). Further, different cerebellar regions are involved when processing one's own painful experience (posterior vermis) as opposed to experiencing empathy for another's pain (lobule VI; Singer et al., 2004). The activation of hemispherical lobule VI and vermal lobule VII is quite consistent across these studies of emotionally salient stimuli (Stoodley and Schmahmann, 2009a), and like the activation patterns seen within the cerebellum for cognitive tasks, the focus of the cerebellar activation varies according to the demands of the task. It is possible that hemispheric lobule VI and VII activation reflects more cognitive components of task performance (e.g., empathy), due to the connections of these regions with association cortices, and more "limbic" tasks (including autonomic processing) may particularly involve the posterior vermis, our putative limbic cerebellum.

3.4 Functional neuroimaging summary

Data from neuroimaging studies in healthy subjects indicates that the anterior lobe, lobules VI and VIII are engaged in tasks involving overt motor processing (finger tapping, articulation) whereas lobules VI and VII activation is evoked during language, spatial tasks, executive function and affective processing. Recent studies of resting-state functional connectivity between the cerebellum and cerebral cortices support these findings, showing that activity in the anterior lobe and adjacent parts of lobule VI is correlated with sensorimotor regions of the cerebral cortex, as opposed to activity in lobule VII that correlates with association areas in the prefrontal cortex, posterior parietal region, and superior and middle temporal gyri (Habas et al., 2009; Krienen and Buckner, 2009).

4. Clinical findings

4.1 Motor symptoms and anterior lobe damage

The cerebellar motor syndrome is most commonly characterized by impairment of balance and gait ataxia, limb dysmetria, dysarthria, and oculomotor disorders (Babinski, 1899; Holmes, 1939). The progressive motor disability that accompanies the neurodegenerative cerebellar ataxias in particular can be so prominent as to overwhelm other aspects of the clinical presentation, and may account for the long-held view that the cerebellum is purely a motor control device. The motor syndrome has an anatomical signature, however, as determined by studies of patients with focal cerebellar lesions.

Balance and gait impairment result from lesions of the anterior superior cerebellar vermis in alcoholic cerebellar degeneration (Baloh et al., 1986; Diener et al., 1984; Mauritz et al., 1979; Victor and Adams, 1953), and in children and adults with tumors involving the fastigial nucleus, anterior lobe vermal lobules I – III, and lobules VIII and IX of the posterior lobe (Ilg et al., 2008; Konczak et al., 2005; Schoch et al., 2006).

Lesion-deficit correlations in cerebellar stroke patients reveal that limb and gait ataxia are more strongly associated with stroke in superior cerebellar artery (SCA) territory than in the posterior inferior cerebellar artery (PICA) territory (Kase et al., 1993; Richter et al., 2007b; Tohgi et al., 1993). However, it is important to note that the SCA and PICA territories do not obey lobular boundaries. The SCA irrigates more anterior regions, but also lobules VI and Crus I, and the dorsal portion of the dentate nucleus (Schmahmann, Hurwitz, Luft and Hedley-Whyte in Schmahmann, 2000b; Tatu et al., 1996). The PICA irrigates more posterior regions, including lobule VIII and the ventral aspect of the dentate nucleus (Schmahmann, 2000b; Tatu et al., 1996). Voxel-based morphometric evaluation in 90 patients with cerebellar lesions (Schoch et al., 2006) showed significant correlations between scores on the International Cooperative Ataxia Rating Scale (ICARS; Trouillas et al., 1997) and damage to the anterior lobe, including lobules II-V, with some involvement of lobule VI of the posterior lobe, supporting the idea that the anterior lobe and lobule VI are involved in sensorimotor processing.

We have shown that there is a motor – nonmotor dichotomy in the clinical manifestations of patients in the acute and subacute stages following cerebellar stroke (Schmahmann et al., 2009b). We studied thirty-nine patients with infarction confined to the cerebellum and grouped them according to lesion location, which was determined by analysis of MRI or CT scans using the MRI Atlas of the Human Cerebellum (Schmahmann et al., 2000c). A modified and validated version of the ICARS (Modified ICARS, or MICARS; Storey et al., 2004; Schmahmann et al., 2009a) was used to show that subjects with anterior lobe involvement ($n=20$) had significantly higher MICARS scores (mean \pm standard deviation, 19.1 ± 11.2) than subjects with damage confined to lobules VII-X (2.5 ± 2.0 ; $p < 0.0001$), who scored within the normal range. Patients with strokes involving lobule VI experienced minimal motor impairment. In this study there

was no significant effect of nuclear involvement on MICARS scores. These findings showed that focal but sizeable cerebellar lesions do not necessarily result in motor deficits – a clinical test of the notion that there are regions within the human cerebellum that are neither necessary nor sufficient to support normal motor performance.

Dysarthria occurs when lesions involve anterior cerebellar areas irrigated by the SCA, including lobule VI (Ackermann et al., 1992; Amarenco and Hauw, 1990; Amarenco et al., 1991). Patients with infarction in the territory of the PICA and anterior inferior cerebellar arteries may also be dysarthric, but analysis of lesion location on MR reveals that the anterior lobe is consistently involved in these cases, particularly at the rostral paravermal region (Urban et al., 2003). This same area is activated in healthy controls by movements of the tongue and orofacial muscles (Urban et al., 2003).

These findings provide clinical support for the assertion that the cerebellar motor signs of ataxia, dysmetria and dysarthria do not always result from insult to the cerebellum, but rather the motor deficits are a consequence of injury to sensorimotor cerebellar regions located within the cerebellar anterior lobe and regions of lobule VI. The precise contribution to motor function of lobule VIII, the putative cerebellar second somatosensory area (Snider, 1950; Snider and Eldred, 1951; Snider and Stowell, 1944; Woolsey, 1950), remains to be shown.

4.2 Cognitive and affective symptoms from posterior lobe damage

If damage to lobules VI and VII largely spare motor function, what are their functional roles? Clinical findings provide support for regional functional specialization in cerebellum of cognitive and affective processes, and they point to the posterior lobe, not the anterior lobe, as being critical in this regard (e.g., Exner et al., 2004; Schmahmann et al., 2009b; Schmahmann and Sherman, 1998; Tavano et al., 2007).

4.2.1 Cognitive deficits after cerebellar damage—The recognition of the cerebellar cognitive affective syndrome (CCAS; Schmahmann and Sherman, 1998) established the clinically relevant parameters of the nonmotor aspects of cerebellar function. This syndrome is characterized by a range of executive, visual-spatial, linguistic and affective deficits in patients with cerebellar damage. It was apparent from the outset that the CCAS occurs following lesions of the cerebellar posterior lobe but not the anterior lobe. This constellation of cognitive and neuropsychiatric impairments has been replicated in subsequent studies in adults and children, and the observation that the syndrome results from lesions of the cerebellar posterior lobe has also withstood scrutiny (Exner et al., 2004; Levisohn et al., 2000; Molinari et al., 2004; Neau et al., 2000; Rapoport et al., 2000; Riva and Giorgi, 2000; Schmahmann et al., 2007b; Steinlin et al., 2003). One study (Neau et al., 2000) found no difference in cognitive scores between patients with SCA and PICA strokes, but this likely reflects the fact that SCA strokes rarely spare lobule VI (Schmahmann et al., 2009b; Tatu et al., 1996), which is activated by many cognitive paradigms in functional imaging studies (see Section 3, above).

A critical test of the concept of a sensorimotor-cognitive dichotomy in cerebellar organization is whether the CCAS occurs in the absence of motor impairment. In a study reporting impaired phonemic fluency in 19 patients with pathology restricted to the cerebellum, only three patients had substantial motor deficits (Leggio et al., 2000) – two had infarcts in the AICA territory, and one had a medulloblastoma. Further, language and cognitive difficulties can persist after cerebellar stroke, even after the cerebellar motor syndrome has resolved (Fabbro et al., 2004; Marien et al., 1996), and cognitive and affective symptoms can occur in the absence of motor difficulties (Paulus et al., 2004). In a study of children following surgery for cerebellar astrocytomas, neuropsychological deficits were present in all children, but only 60% had motor symptoms or signs (Aarsen et al., 2004). Further, in a study of adults with cerebellar damage, there was no correlation between neuropsychological measures and patients' motor skills

(Gottwald et al., 2003). Similarly, the small cerebellar volumes in very preterm babies correlate significantly with performance on cognitive measures, but not motor tasks (Allin et al., 2001). These observations add weight to the original evidence (Levisohn et al., 2000; Schmahmann and Sherman, 1998) that focal cerebellar lesions may result in cognitive and emotional deficits in the absence of the cerebellar motor syndrome.

Projections between the cerebral and cerebellar cortices are largely (though not exclusively) contralateral (Brodal, 1979), leading to the prediction that the right cerebellum is more concerned with linguistic processing, whereas the left cerebellar hemisphere is more relevant for spatial information. This prediction is supported by functional neuroimaging findings that language and spatial functions are lateralized within the cerebellum (see above), and clinical reports that language impairments such as impaired verbal fluency (Akshoomoff et al., 1992; Appollonio et al., 1993; Gasparini et al., 1999; Gebhart et al., 2002; Hassid, 1995; Leggio et al., 1995, 2000; Levisohn et al., 2000; Molinari et al., 1997; Richter et al., 2007b; Riva and Giorgi, 2000; Schmahmann and Sherman, 1998) and agrammatism (Ackermann et al., 2004; Kalashnikova et al., 2005; Marien et al., 2001; Schmahmann and Sherman, 1998; Silveri et al., 1994; Zettin et al., 1997) generally arise following right cerebellar hemisphere lesions. In contrast, visual-spatial difficulties are more likely to occur after left cerebellar damage (see Botez-Marquard et al., 1994; Fiez et al., 1992; Gebhart et al., 2002; Gottwald et al., 2004; Gross-Tsur et al., 2006; Hokkanen et al., 2006; Levisohn et al., 2000; Riva and Giorgi, 2000; Scott et al., 2001; Wallesch and Horn, 1990), although these findings are less consistent than the link between the right posterolateral cerebellum and language.

The suggestion that language problems are primarily due to motor (articulatory) impairment is not supported by patient studies. We have found that patients with cerebellar degeneration show poorer performance on verbal fluency and word stem completion tasks even when the effect of their slower articulation speed is accounted for (Stoodley and Schmahmann, 2009b). Our results are in agreement with several reports that cerebellar patients are impaired on verbal but not semantic fluency (see Brandt et al., 2004; Leggio et al., 2000), tasks which have equivalent motor demands but are thought to tap different processing streams (see Borowsky et al., 2006).

Some studies have failed to demonstrate that cerebellar patients have language or spatial deficits. One group found no difficulties on a verb generation task in adults with cerebellar degeneration (Richter et al., 2004) and stroke (Richter et al., 2007a), or in children following removal of cerebellar tumors (Frank et al., 2007; Richter et al., 2005b). Other studies have shown preserved learning on a verb generation task in cerebellar patients (Helmuth et al., 1997), and absence of language difficulties in children (Frank et al., 2007; Richter et al., 2005b) or adults with cerebellar damage (Gomez-Beldarrain et al., 1997; Richter et al., 2007b). In addition, spatial deficits have not consistently been observed in patients with cerebellar lesions (e.g., Appollonio et al., 1993; Dimitrov et al., 1996; Frank et al., 2007; Gomez-Beldarrain et al., 1997; Richter et al., 2005b). It is possible that these negative findings may be accounted for by location of the cerebellar injury, as most studies make group comparisons between patients and controls without sub-grouping patients according to lesion location.

4.2.2 Affective processes after cerebellar damage—The dysregulation of affect noted in the CCAS included hypometric symptoms such as passivity, blunting of affect, and withdrawal on the one hand, and hypermetric emotional lability, disinhibition and inappropriate behavior on the other; these could cycle rapidly in the same person, or indeed coexist simultaneously (Schmahmann and Sherman, 1998). Children surviving surgical excision of cerebellar tumors show a range of abnormal affective symptoms and personality changes when the lesions include damage to the vermis, whereas children without extensive vermal damage

do not demonstrate emotional dysregulation (Levisohn et al., 2000). Vermis damage following cerebellar tumor removal is associated with postoperative mutism that evolves into speech and language disorders and behavioral disturbances (Catsman-Berrevoets et al., 1999; Ozgur et al., 2006; Pollack et al., 1995; Riva and Giorgi, 2000), including apparent increased thoughtfulness, anxiety and aggression (Richter et al., 2005a), with children demonstrating evidence of both hyperspontaneous, disinhibited behavior, and hypospontaneous, flattened affect (Arsen et al., 2004). Malformations and agenesis of the posterior vermis are associated with a range of cognitive impairments and emotional symptoms (Chheda et al., 2002; Tavano et al., 2007), and preterm infants with vermal damage have behavioral profiles indicative of pervasive developmental disorder and significant scores on autism screening questionnaires (Limperopoulos et al., 2007). These posterior vermal regions are also among the brain areas showing structural differences in autism spectrum disorders (Bauman and Kemper, 2005; Courchesne et al., 1988; Penn, 2006).

The posterior vermis is implicated in the genesis of affective symptoms in adults with cerebellar stroke (Paulus et al., 2004), and pathological laughing and crying is noted in patients with cerebellar pathology from stroke (Parvizi et al., 2001), tumors (Famularo et al., 2007), and multiple system atrophy – cerebellar type (Parvizi et al., 2007; Parvizi and Schiffer, 2007). Clinical evaluation of a series of patients with cerebellar disorders designed to further elucidate the nature of the affective dysregulation in the CCAS allowed the identification of five domains of impairments (Schmahmann et al., 2007b). These were categorized as disorders of attentional control, emotional control, autism spectrum, psychosis spectrum and social skill set. Within each of these domains, we recognized evidence of both positive (overshoot/hypermetria) and negative (undershoot/hypometria) symptoms of the affective dysmetria.

This wealth of evidence from contemporary studies in patients indicating that the cerebellar vermis is engaged in the modulation of emotional processing provides support for the clinical relevance of cerebellar-limbic connections, and is in agreement with earlier clinical (Heath et al., 1979) and electrophysiological studies (Nashold and Slaughter, 1969) in patients that led to the first indication of the cerebellum as an “emotional pacemaker” (Heath, 1977). The role of the posterior vermis as the substrate for the putative limbic cerebellum is further substantiated by the finding that patients with cerebellar stroke involving vermis or paravermian regions (Figure 1 in Turner et al., 2007) have increased PET activation in prefrontal regions and decreased activation in limbic structures in response to unpleasant stimuli, and by the observation that the posterior vermis shows activation in substance abusers during reward-related tasks (Anderson et al., 2006).

4.3 Clinical summary

Data from clinical populations provide evidence that the cerebellar motor syndrome results from lesions principally affecting the anterior lobe, whereas cognitive deficits occur following posterior lobe damage. Additionally, converging lines of data suggest that the posterior vermis is a critical substrate for neuropsychiatric impairments.

5. Summary and Future directions

The results of investigations across different disciplines in neuroscience indicate that there is a level of organization in the cerebellum such that sensorimotor control is topographically separate from cognitive and emotional regulation. This new understanding of the cerebellum represents a major departure from conventional wisdom. Given the available evidence, we conclude that the anterior lobe and parts of medial lobule VI, together with lobule VIII of the posterior lobe and the interpositus nuclei constitute the *sensorimotor cerebellum*. Lobule VII and parts of lobule VI, which together with the ventral part of the dentate nucleus has expanded massively in the human, constitute the anatomical substrate of the *cognitive cerebellum*. The

limbic cerebellum appears to have an anatomical signature in the fastigial nucleus and the cerebellar vermis, particularly the posterior vermis. Little is known of the possible cognitive role of lobule IX, although early fcMRI data provide some insights into its potential incorporation into the default mode network (Habas et al., 2009). Lobule X remains an essential node in the vestibular system. This functional heterogeneity, determined by functional imaging, physiological/behavioral studies, and clinical observations, is matched by the intricate connectional heterogeneity between different cerebellar regions and the spinal cord, brainstem and cerebral cortex. Further identification of the precise arrangement within the cerebellum of the multiple different aspects of cognitive and emotional processing is the focus of ongoing investigations.

This wider role of the cerebellum in cognition, emotion, social intelligence and mental health may be viewed within the context of the anatomical substrates that constitute the distributed neural circuits subserving all domains of neurological function. The demonstration across modalities that the cerebellum is incorporated into the neural circuits governing many behaviors, and not only motor control, begs the question as to what it is the cerebellum contributes to these behaviors. This important question is discussed elsewhere (see Schmahmann, 1997; Schmahmann and Pandya, 2008), but the question itself is predicated on the focus of the present report, namely, the recognition that there are indeed distinct cerebrotocerebellar loops linked with motor, cognitive, and emotion circuits, and that this anatomical arrangement leads to organization within the cerebellum that is functionally and clinically relevant.

A number of avenues of investigation are available to test the hypothesis that there are separate, topographically-organized cerebellar subsystems involved in processing sensorimotor, cognitive and affective information. Advances in imaging technologies hold promise for defining the structural and functional anatomy of the cerebrotocerebellar loops in humans. For example, diffusion tensor imaging (Ramnani et al., 2006) and diffusion spectrum imaging (Granziera et al., 2009) have the potential to elucidate details of these cerebrotocerebellar pathways. Functional connectivity analyses (Allen et al., 2005; Booth et al., 2007; Habas et al., 2009; Honey et al., 2005; Krienen and Buckner, 2009) and magnetoencephalography (Kujala et al., 2007) make it possible to examine functional relationships between cerebellar and cerebral cortical activity; already these techniques suggest that the cerebellum contributes to the functional networks underlying cognitive tasks such as reading (Kujala et al., 2007). Functional MRI can be used to examine topography within the cerebellum by studying cerebellar activation during a range of different tasks within individuals to determine whether the motor-nonmotor dichotomy, and the patterns of activity suggested by previous studies, can be seen at an individual level.

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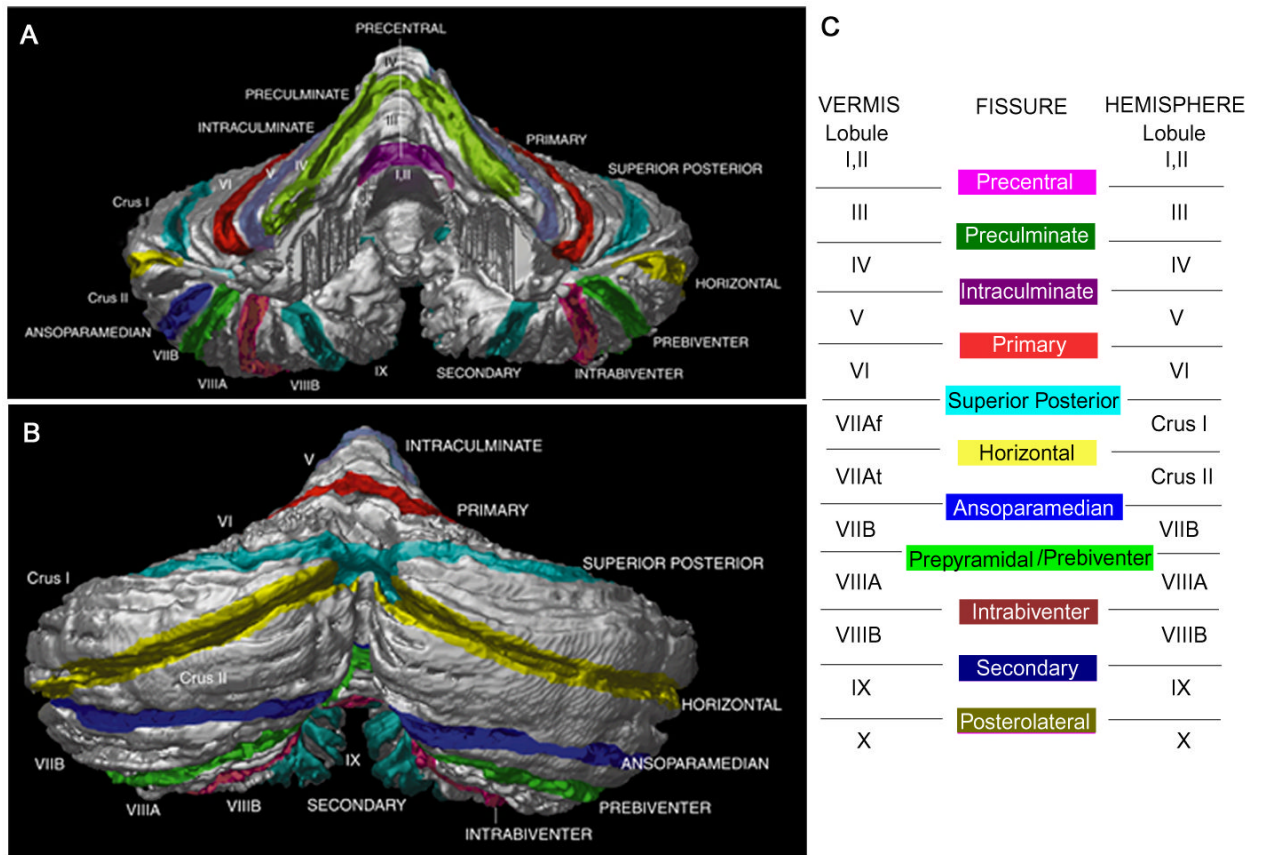


Figure 1. Figures showing three-dimensional reconstructions from MRI of the external surfaces of the cerebellum with the fissures that demarcate the lobules identified in color in A, anterior view, and B, posterior view. C, Table identifying the relationships between lobules in the vermis and hemispheres. The cerebellar fissures are color-coded as in the illustrations in A and B. (From Schmahmann et al., 2000c).