Handbook of Clinical Neurology, Vol. 154 (3rd series)
The Cerebellum: From Embryology to Diagnostic Investigations
M. Manto and T.A.G.M. Huisman, Editors
https://doi.org/10.1016/B978-0-444-63956-1.00004-7
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Chapter 4

Functional topography of the human cerebellum

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Abstract

Accumulating evidence points to a critical role for the human cerebellum in both motor and nonmotor behaviors. A core tenet of this new understanding of cerebellar function is the existence of functional subregions within the cerebellum that differentially support motor, cognitive, and affective behaviors. This cerebellar functional topography – based on converging evidence from neuroanatomic, neuroimaging, and clinical studies – is evident in both adult and pediatric populations. The sensorimotor homunculi in the anterior lobe and lobule VIII established in early tract tracing and electrophysiologic studies are evident in both task-based and resting-state human functional imaging studies. In patients, damage to the anterior cerebellum, extending into medial lobule VI, is associated with the cerebellar motor syndrome. The cerebellar posterior lobe, including vermal and hemispheric regions of lobules VI and VII, is reciprocally interconnected with cerebral association and paralimbic cortices. Resting-state and task-based neuroimaging studies show functional activation patterns in these regions during higher-level cognitive tasks, and lesions of the posterior cerebellum lead to the cerebellar cognitive affective/Schmahmann syndrome with its characteristic intellectual and emotional impairments. The existence of cerebellar connectional and functional topography provides the critical anatomic substrate for a cerebellar role in both motor and nonmotor functions. It also establishes a framework for interpreting cerebellar activation patterns, cognitive and behavioral outcomes following cerebellar damage, and the cerebellar structural and functional differences reported in a range of neurodevelopmental and neuropsychiatric disorders.

INTRODUCTION

The past three decades have witnessed mounting evidence that the role of the human cerebellum extends considerably beyond motor control. This conclusion is supported by the observation that there are anatomic connections between the cerebellum and association areas of the cerebral cortex, neuroimaging studies showing cerebellar activation during a range of cognitive tasks, and clinical populations in whom cerebellar damage produces nonmotor deficits in cognition and behavior. Further, the anatomic connections/projections between the cerebellum and the cerebral cortex and spinal cord are highly topographically arranged, resulting in functional subregions of the cerebellum which can be broadly divided into sensorimotor, association/cognitive, and limbic regions. This functional topography is evident from neuroanatomic, neuroimaging, and clinical data, and is important when interpreting activation patterns in neuroimaging studies and when considering the potential outcomes of cerebellar damage or dysfunction in clinical and developmental populations. While primarily established in adult populations, there is evidence that this topography is present in pediatric populations. Here we review the anatomic, neuroimaging, and clinical evidence supporting the presence of different functional

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subregions of the cerebellum and discuss the relevance of these findings to the expanding role of the human cerebellum beyond the motor domain.

NEUROANATOMIC CONNECTIONS

The cerebellum is comprised of two cortex-covered hemispheres on either side of the midline vermis, and connects to the brainstem via three paired cerebellar peduncles. Fiber tracts carrying information from the cerebellum to the cerebral cortex route through the superior cerebellar peduncle and cerebral cortical projections to the cerebellum travel via the pontine nuclei and the middle cerebellar peduncle. The inferior cerebellar peduncle carries inputs to the cerebellum from the inferior olive, spinal cord, and vestibular system, as well as efferent fiber tracts from the cerebellum to the spinal cord. There are 10 lobules in the cerebellar cortex (lobules I–X; see Schmahmann et al. (2000) for other naming systems): lobules I–V constitute the anterior lobe of the cerebellum; lobules VI–IX the posterior lobe; and lobule X is the flocculonodular lobe.

Embedded in the white matter of the cerebellum are the deep cerebellar nuclei, including the fastigial, interpositus (globose and emboliform), and dentate nuclei. The cerebellar cortex projects to the deep nuclei in a systematic medial-to-lateral pattern, with projections from the midline vermis to the medial fastigial nuclei, the paravermal regions projecting to the interpositus nuclei, and the lateral hemispheres projecting to the dentate nuclei. From the deep nuclei, projections course in the superior cerebellar peduncle through the contralateral red nucleus to the thalamus, where they synapse before being transmitted to the cerebral cortex, and through the inferior cerebellar peduncle to the brainstem nuclei and on to the spinal cord. Lobule X (the flocculonodular lobe) projects directly to the vestibular nuclei. The cerebellum projects to topographically precise cerebral, brainstem, and spinal cord destinations, and receives input back from these same regions, thus forming multiple, reciprocal, functionally relevant circuits, or closed loops. The patterning of these anatomic connections forms the basis of cerebellar functional topography, and the function of specific regions of the cerebellum is directly related to the type of information (e.g., vestibular vs. cognitive) that a given region of cerebellar cortex has access to via these anatomic connections (see reviews by Schmahmann, 1996; Strick et al., 2009; Stoodley and Schmahmann, 2010).

The cerebellum is reciprocally connected with both sensorimotor and association regions of the cerebral cortex via feedforward corticopontocerebellar loops and feedback cerebellothalamocortical loops. The organization of anatomic projections from the cerebral cortex to the cerebellum in monkey is evident at the level of the pontine nuclei, where these projections synapse in the pons before decussating and entering the middle cerebellar peduncles to terminate in the cerebellum (Brodal, 1978; Schmahmann and Pandya, 1989, 1991, 1997a, b; Schmahmann et al., 2004a). The corticopontine projections arise from primary and supplementary sensory and motor cortices, as well as from high-order cerebral association areas in posterior parietal cortices concerned with spatial awareness, supramodal areas of the superior temporal gyrus concerned with language, posterior parahippocampal areas important for spatial memory, 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, judgment, attention, and working memory (Schmahmann and Pandya, 1989, 1991, 1993, 1995, 1997a; Schmahmann et al., 2004b). These projections terminate in multiple interdigitating patches in the nuclei of the basis pontis, with each cerebral cortical area projecting to its own field of terminations (Schmahmann, 1996; Schmahmann and Pandya, 1997b).

Sensorimotor projections to the cerebellum show a predictable topography, with electrophysiology (e.g., Snider and Eldred, 1951) and neuroanatomy (see Manni and Petrosini, 2004, for review) studies revealing body maps in the anterior lobe (extending into medial regions of lobule VI) and lobule VIII. For example, tract-tracing studies confirm that lobules IV, V, and VI of the cerebellum project to sensorimotor cortices (Hoover and Strick, 1999). Functional neuroimaging studies support the mapping of these sensorimotor homunculi to lobules IV–VI and VIII in humans (see below).

Lobule VII comprises ~48% of the cerebellar cortex in humans (Diedrichsen et al., 2009), and is subdivided into crus I, crus II, and VIIB (Schmahmann et al., 2000). This posterior lobe of the cerebellum shows different connectivity patterns than the anterior lobe and lobule VIII: tract-tracing studies reveal that lobule VII is linked with parietal and prefrontal cortices (Kelly and Strick, 2003), providing an anatomic substrate for a role for the cerebellum in nonmotor tasks. Consistent with these anatomic studies, the posterior lobe of the cerebellum is engaged during a range of cognitive tasks in human volunteers even when the motor demands of the tasks are controlled for or eliminated (see below, and Stoodley and Schmahmann, 2009; Stoodley, 2012).

There is evidence that projections from the cerebellar hemispheres to the dentate nuclei are also organized according to their targets in the cerebral cortex, such that the dorsal dentate contains neurons that project to supplementary and primary motor cortices, and fibers from the ventrolateral dentate project to prefrontal cortices (e.g., Brodmann area 46) (Middleton and Strick, 1994; Dum and Strick, 2003; Akkal et al., 2007). Diffusion-weighted imaging studies in humans also support the presence of separate sensorimotor (lobules V–VI with the primary motor and dorsal premotor cortices) and cognitive (crus I/II with lateral prefrontal cortices) cerebrocerebellar tracts (Salmi et al., 2010). Diffusion imaging studies of cerebrocerebellar pathways have also revealed that there is a larger number of connections between the human cerebellum and cognitive regions of the cerebral cortex relative to sensorimotor cortices. For example, in the monkey, the majority of corticopontine fibers arise from sensorimotor cortices, whereas in the human, the majority of corticopontine fibers originate in the prefrontal cortex (Ramnani et al., 2006). Similarly, Re et al. (2017) report that in the vast majority (96%) of their newborn to young adult subjects the cognitive component of the middle cerebellar peduncle was larger than the motor component, as defined by cognitive projections from the rostral pons to the posterior cerebellum and motor tracts running from the caudal pons to the anterior cerebellum (Schmahmann et al., 2004b). In the superior cerebellar peduncle, a similar pattern emerges: the majority (~80%) of diffusion tensor imaging streamlines connected the cerebellum with cerebral cortical association areas, relative to connections between the anterior cerebellum and premotor/motor cortices (~15%; Palesi et al., 2015). Palesi et al. (2015) also showed strong correspondence between the anterior cerebellum (I–V) and lobule VI and premotor and primary motor cortices, whereas lateral regions of crus I/II showed the most robust correspondence with the prefrontal cortex, consistent with the proposed topography described above.

NEUROIMAGING

Structural neuroimaging

Structural imaging studies have revealed regional differences in the timecourse of development within the cerebellum, with cerebellar subregions mirroring patterns seen in interconnected regions of the cerebral cortex. Like the cerebral cortex, cerebellar gray matter shows an overall inverted-U-shaped trajectory (Tiemeier et al., 2010), and regions associated with cognitive function peak later than those associated with sensorimotor processing (Tiemeier et al., 2010; Bernard et al., 2015). These developmental trajectories reinforce the presence of functional subregions based on anatomic connectivity patterns, and suggest that cerebellar regions involved in higher-order functions show a more prolonged course of development, consistent with patterns seen in the cerebral cortex (Gogtay et al., 2004).

Several studies have shown that regional cerebellar gray matter (GM) is associated with motor and cognitive performance in a manner consistent with cerebellar functional topography. Processing speed measures correlate with GM in cerebellar regions associated with sensorimotor circuits (e.g., IV/V and VI; Genova et al., 2009; Eckert et al., 2010; Bernard et al., 2015), whereas higher IQ scores are associated with increased GM in the posterior cerebellum (Frangou et al., 2004; Hogan et al., 2011). In healthy older adults, motor skill positively correlated with the volumes of the anterior lobe and lobules VI and crus I, while cognitive performance was associated with posterior lobe volumes, including crus II, VIIB, VIII, and IX (Koppelmans et al., 2017). Both unique and overlapping posterior cerebellar regions have been shown to correlate with a range of cognitive tasks, with greater GM associated with better scores on measures of language (lobules VIIB and VIIIA; Grogan et al., 2009; Richardson and Price, 2009), reading (bilateral crus I; Kronbichler et al., 2008; He et al., 2013), working memory (left lobule VI and crus I; Ding et al., 2012; Bernard and Seidler, 2013), and executive function (medial and right posterior cerebellum; Ridler et al., 2006).

In children, the direction of the relationship between cerebellar GM and cognitive measures may depend on the developmental stage of the population (Bernard et al., 2015; Moore et al., 2017), with negative relationships between GM and cognitive scores rather than the more typical positive associations seen in adult cohorts. As in adults, cognitive scores tend to be associated with GM volumes in the posterior cerebellum, with significant relationships reported between posterior cerebellar and vermal regions of interest and working memory, verbal learning, and spatial learning in participants aged 12–65 years (Bernard et al., 2015). In a recent study in children and adolescents (aged 8–17 years), increased cerebellar GM in lobules VII and VIII was associated with better cognitive scores on measures of vocabulary, reading, working memory, and set shifting (Moore et al., 2017); these regions are engaged during similar tasks in functional neuroimaging studies (see below, and Stoodley and Schmahmann, 2009; Keren-Happuch et al., 2014). Further, there was evidence of a changing developmental relationship between GM and cognitive scores, which tracked with the predicted peak in cerebellar GM in posterior cerebellar cortices (Moore et al., 2017): in younger children, a negative relationship was observed between cerebellar GM and cognitive scores, whereas later in adolescence the relationship was positive, as is typical in adult populations. This suggests that a more mature cerebellar GM profile in posterior cerebellar regions is associated with better cognitive scores in children (Moore et al., 2017).

Functional connectivity

Resting-state functional connectivity studies further support the presence of functional circuits that vary depending on cerebellar region. The anterior lobe and lobule VIII show functional connectivity with sensorimotor cortices, whereas the posterior hemispheres are functionally connected with frontal and parietal association cortices (Fig. 4.1; Krienen and Buckner, 2009; O'Reilly et al., 2010; Buckner et al., 2011; Bernard et al., 2012). Functionally defined cortical networks also show similar anterior vs. posterior patterns of connectivity, with sensorimotor networks showing strong functional connectivity with the anterior lobe and lobule VIII, whereas posterior cerebellar regions show functional connectivity with a range of cortical networks, including the frontoparietal/executive control network (particularly crus I/II), dorsal and ventral attention networks, and the default-mode network (Habas et al., 2009; Buckner et al., 2011).

A large study involved 500 healthy young adults with a replication sample of another 500 healthy young adults (Buckner et al., 2011; Fig. 4.1). This study examined the functional connectivity of the cerebellar cortex to either 7 or 17 cerebral cortical networks based on a winner-takes-all approach: each cerebellar voxel was mapped

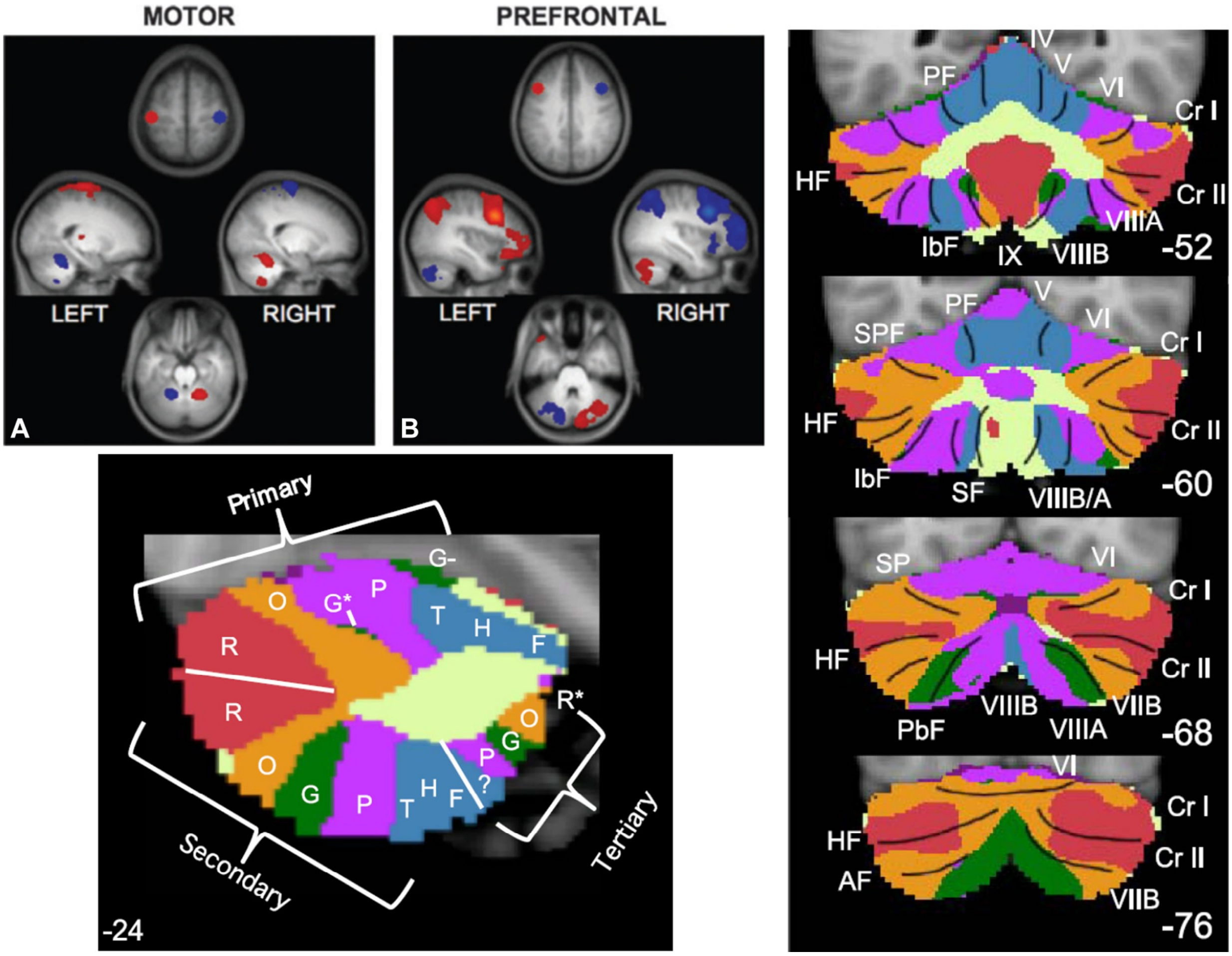

Fig. 4.1. Functional connectivity mapping reveals cerebellar functional topography. Top left, Krienen and Buckner (2009) showed that seeds in the primary motor cortex (**A**) are contralaterally functionally correlated with the anterior cerebellum and lobule VIII, whereas prefrontal seeds (**B**) show functional correlations with the posterior cerebellum. Right and bottom left, functional connectivity patterns in the cerebellum based on cerebral cortical functional networks show sensorimotor network representation (blue) in the anterior lobe and lobule VIII (F = foot; H, hand; T, tongue), whereas ventral attention (purple, P), dorsal attention (green, G), frontoparietal (orange, O), and default-mode (red, R) networks map to posterior cerebellar hemispheres. The data suggest that there are at least two, and potentially three, complete maps of the cerebral cortical networks in the cerebellum (bottom left). *AF*, ansoparamedian fissure; *Cr I*, crus I; *Cr II*, crus II; *HF*, horizontal fissure; *IbF*, intrabiventer fissure; *PbF*, prepyramidal/prebiventer fissure; *PF*, primary fissure; *SF*, secondary fissure. (Adapted with permission from Buckner RL, Krienen FM, Castellanos A, et al. (2011) The organization of the human cerebellum estimated by intrinsic functional connectivity. J Neurophysiol 106: 2322–2345.)

based on the particular cortical network that its resting-state blood oxygen level-dependent signal maximally correlated with. This revealed extensive functional connectivity between the cerebellum and the cerebral cortex – all cerebral cortical networks were represented in the cerebellum, with the exception of the primary visual cortices. Further, this study suggested the presence of at least two, and possibly three, near-complete representations of cerebral cortical networks in the cerebellum (Fig. 4.1; Buckner et al., 2011). This work has since been replicated (Guell et al., 2018) in an even larger cohort using data from the Human Connectome Project (n = 787).

Similar to structural connectivity patterns, dorsal and ventral subregions of the dentate nucleus also show functional connectivity differences, with the dorsal dentate showing functional connectivity with the anterior cerebellum and primary motor cortex, and the ventral dentate showing functional connectivity with cerebellar crus I and the prefrontal cortex (Bernard et al., 2014). The robust findings from functional connectivity studies, and the strong correlation between these findings and those from neuroanatomic approaches, provide further evidence that different cerebellar subregions form functional circuits with other neural systems in a consistent manner.

How might cerebellar correlations with the cerebral cortex change with age? Bernard et al. (2016) examined changes in cerebrocerebellar networks in adolescents and young adults (ages 12–21 years), each scanned on two occasions separated by 1 year (Bernard et al., 2016). Changes in functional connectivity were evident for crus I and II, but not lobule V, consistent with the longer course of development of posterior vs. anterior cerebellar regions (Tiemeier et al., 2010). Further, the reduced functional connectivity seen between crus I and II and prefrontal regions between timepoints was associated with increased integrity in cerebrocerebellar white-matter tracts, suggesting ongoing development of these networks throughout adolescence (Bernard et al., 2016).

Task-based imaging

Functional magnetic resonance imaging and positron emission tomography studies also reveal cerebellar functional topography:sensorimotor tasks tend to engage the cerebellar anterior lobe and lobule VIII, and cognitive tasks activate the posterior cerebellar hemispheres (Stoodley and Schmahmann, 2009; Stoodley, 2012; Stoodley et al., 2012; Keren-Happuch et al., 2014). Different cerebellar activation patterns are evident during a wide range of tasks, depending on task demands (e.g., overt movement, eye movement, articulation, motor learning, tool use, language, working memory, visual-spatial, social cognition, and affective processing).

Neuroimaging during sensorimotor tasks localizes, as expected, to cerebellar regions associated with the particular body part being used, in a manner that is consistent with the cerebellar homunculi in the anterior lobe and lobule VIII (e.g., Nitschke et al., 1996; Bushara et al., 2001; Grodd et al., 2001, 2005). Activation patterns associated with leg and foot movements localize to lobules II and III (Nitschke et al., 1996), hand movements to lobule V (Bushara et al., 2001; Grodd et al., 2001), and orofacial movements engage medial regions of lobule VI (Urban et al., 2003; Dresel et al., 2005), overlapping with regions engaged during articulation (lobules IV–VI; Riecker et al., 2005). Tactile simulation of the hand and foot activates lobule V and VIIIB/IX (Bushara et al., 2001). Medial regions of the vermis (particularly lobules VI and VII) tend to be engaged during eye movements (Nitschke et al., 2004; Konen et al., 2005; Schraa-Tam et al., 2009; Alvarez et al., 2010), although activation related to the optokinetic reflex, smooth pursuit, and saccades are reported to extend into adjacent medial regions of crus I and crus II (Glickstein et al., 2011). When motor tasks are more complex (e.g., involve motor planning or tool use), activation patterns can shift more laterally into lobules VI and VII (Imamizu and Kawato, 2009; Schlerf et al., 2010), particularly when mental imagery is involved (Higuchi et al., 2007) or during the early stages of motor learning (Bernard and Seidler, 2013). In tasks with motor planning demands (e.g., motor sequencing), activation is seen in both motor execution regions (e.g., IV–V and VIII) and lobules VI and VII (Debas et al., 2010). A similar pattern is seen during eye blink conditioning paradigms (Dimitrova et al., 2002), with specific learning-related activation in lobules VI and crus I (Ramnani et al., 2000). Just as anatomic studies suggest that dorsal parts of the dentate nucleus project to sensorimotor areas of the cerebral cortex and ventral dentate protections are directed to cerebral association areas, activation patterns during articulation are seen in the rostral and dorsal dentate, rather than the ventral dentate (Thurling et al., 2011). These findings support the idea that motor execution involves sensorimotor cerebellar regions, with posterior regions involved depending on task demands.

Activation patterns during nonmotor cognitive task paradigms likewise mirror the functional topography established based on neuroanatomic connections. Cerebellar activation during a range of cognitive task paradigms reveals predominantly posterolateral activation (see Stoodley, 2012, for review), with language-associated activation patterns being more strongly right-lateralized, consistent with the contralateral connections between the right cerebellum and left cerebral cortex (for review of activation patterns during language tasks, see Stoodley and Schmahmann, 2015). Two meta-analyses of functional imaging data confirm this pattern across studies (Stoodley and Schmahmann, 2009; Keren-Happuch et al., 2014), with converging evidence that language tasks engage bilateral VI and right VII, reading similarly involves lobules VI and VII, working memory measures show activation in bilateral VII and right VIIIA, visuospatial tasks engage bilateral VI, and executive function tasks involve bilateral VII (specifically crus I). A meta-analysis of social cognition revealed multiple regions of cerebellar activation (Van Overwalle et al., 2014), with the strongest evidence for right crus I and lobule IX engagement during abstract mentalizing tasks. Finally, meta-analytic connectivity modeling, which analyzes regions that are concurrently active during task performance, revealed co-activation of crus I and II with prefrontal and parietal cortices and lobules V–VI and VIII with sensorimotor regions, including primary motor and somatosensory cortices, supplementary motor area, and basal ganglia (Balsters et al., 2014). Activation in crus I and II was most commonly associated with cognitive tasks, whereas activation in V–VI and VIII was most often associated with action/execution tasks (Balsters et al., 2014).

This functional topography is evident even within individual participants (Stoodley et al., 2010), when multiple tasks are performed. For example, finger tapping with the right hand activated the right anterior lobe and right VIII, whereas verb generation and verbal working-memory tasks engaged VI, crus I and crus II (Stoodley et al., 2010). Similar patterns are evident at the group level, when multiple participants complete both motor and cognitive tasks (Stoodley et al., 2012) (Fig. 4.2).

As in motor tasks, the specific pattern of cerebellar regional activation during cognitive performance depends on task demands. For example, activation associated with verbal working memory and verb generation overlap in right lobule VII (Stoodley et al., 2012), presumably due to shared components of the tasks, such as the processing of verbal information. Within language paradigms, overt articulation engages medial lobule VI (Thurling et al., 2011), while covert verb generation is associated with activation in lobules VI and VII on the right (Frings et al., 2006), consistent with the predominant demands of the task on sensorimotor vs. cognitive processes, respectively. This pattern was evident even in an early positron emission tomography study (Petersen et al., 1989), with anterior cerebellar activation during speech, and right posterolateral cerebellar engagement during verb-for-noun generation. In verbal fluency tasks, bilateral VI is engaged during overt naming, together with right VI, crus I, and VIIB, which remain active when articulation-related activation is removed (Kircher et al., 2011; Nagels et al., 2012). A similar pattern is evident when considering activation associated with reading aloud (bilateral lobules V–VI) vs. making a lexical decision (right lateral lobule VI; Carreiras et al., 2007).

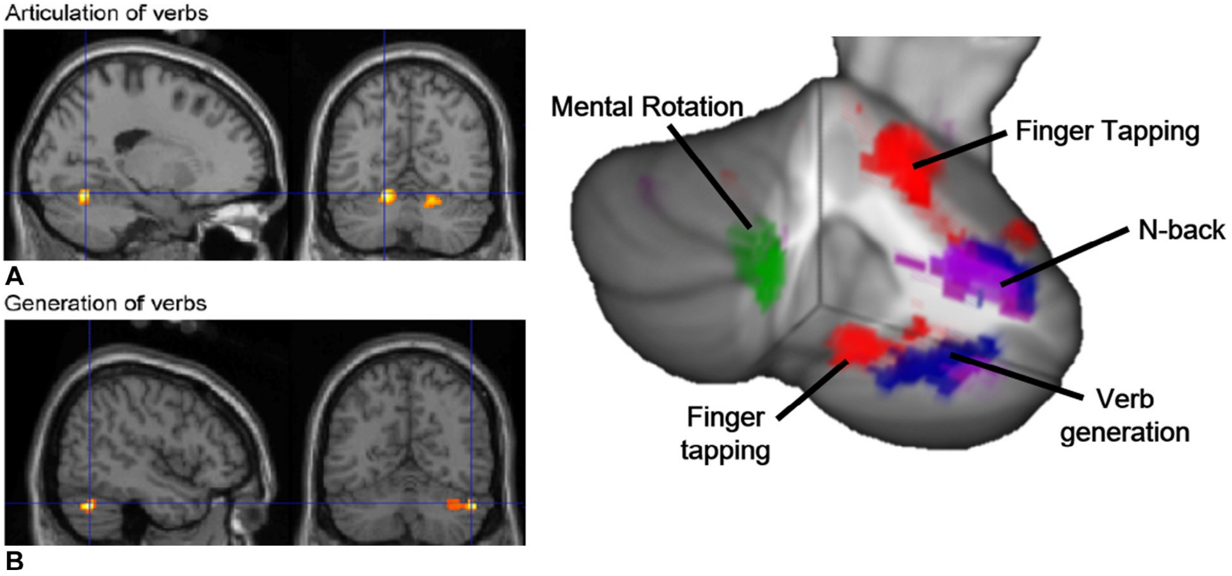

Fig. 4.2. Functional topography is evident in task-based functional magnetic resonance imaging studies. Left, Frings and colleagues (2006) showed that articulation-associated activation maps to medial lobule VI (**A**), whereas activation for covert verb generation was right-lateralized in crus I (**B**). Right, functional topography was evident when participants each performed a range of motor (finger tapping, red) and cognitive tasks (mental rotation, green; *n*-back working memory, violet; verb generation, blue). (Reproduced from Stoodley CJ, Valera EM, Schmahmann JD (2012) Functional topography of the cerebellum for motor and cognitive tasks: an fMRI study. Neuroimage 59: 1560–1570.)

Working-memory paradigms also show task-specific cerebellar activation patterns. There is evidence that verbal and spatial working-memory tasks show differences in the degree of lateralization in the cerebellum, with verbal working memory right-lateralized and spatial working-memory tasks showing more left lateralization (Bernard and Seidler, 2013). In addition, it has been suggested that different components of working-memory tasks engage different regions of the cerebellum: the articulatory loop involves lobules VI and crus I, and activation in lobule VIII reflects the phonologic store (Chen and Desmond, 2005a, b; Keren-Happuch et al., 2014).

Summary

Together, structural and functional neuroimaging studies in humans confirm the broad functional topography that has been established based on connectivity patterns between the cerebellum and the cerebral cortex. For individual task paradigms, cerebellar activation patterns reflect the demands of the task and the type of information being processed. These data confirm that the anterior lobe of the cerebellum forms functional circuits with sensorimotor regions of the cerebral cortex to support motor execution, and the cerebellar posterior lobe forms functional circuits with association cortices to support a range of functions, from motor planning to working memory.

CLINICAL POPULATIONS

Cerebellar functional topography is also evident when the effects of cerebellar damage or disease are examined in clinical populations (for review in pediatric populations, see Stoodley and Limperopoulos, 2016; in adults, see Schoch et al., 2006; Schmahmann et al., 2009; Stoodley et al., 2016). The cerebellar motor syndrome (including ataxia, dysmetria, and dysarthria; Holmes, 1939) has been associated with damage to anterior cerebellar regions in both adult (see Schoch et al., 2006; Schmahmann et al., 2009; Maderwald et al., 2012; Stoodley et al., 2016) and pediatric populations (for review, see Stoodley and Limperopoulos, 2016). Likewise, strokes impacting the superior cerebellar artery are more likely to cause limb and gait ataxia than posterior inferior cerebellar artery strokes (Kase et al., 1993; Tohgi et al., 1993; Timmann et al., 2008; Schmahmann et al., 2009; Stoodley et al., 2016).

A large lesion symptom-mapping study of ataxia revealed that anterior-lobe damage (lobules II–V, extending into VI) was associated with higher ataxia scores (Schoch et al., 2006), consistent with the sensorimotor homunculus in the anterior lobe; dysarthric speech has been associated with medial lobule VI damage, where orofacial movements engage the cerebellum (Urban et al., 2003). A recent study investigating the relationship between lobular volumes and motor and cognitive measures in patients with cerebellar disease also showed that anterior-lobe and lobule VI volumes were associated with motor function (Kansal et al., 2017). In patients with multiple sclerosis, anterior (but not posterior) lobe volume was an independent predictor of peg-moving performance (D’Ambrosio et al., 2016). In preterm infants with early cerebellar damage, gross motor scores were associated with the volume of sensorimotor cortices (Limperopoulos et al., 2014), again suggesting that the specific disruption of cerebrocerebellar sensorimotor circuits underpins motor deficits following cerebellar damage.

Damage to the deep cerebellar nuclei can also produce predictable motor outcomes based on their connectivity patterns. Upper-limb ataxia was associated with damage to the interpositus nucleus (which receives projections from medial cerebellar regions) and the dorsal (motor-related) part of the dentate nucleus in children following cerebellar tumor removal (Konczak et al., 2005), and damage to the dorsal dentate has also been associated with limb ataxia in adult populations (Maderwald et al., 2012). Poor postural control has been associated with damage to the fastigial nucleus in children and adolescents following cerebellar tumor removal (Konczak et al., 2005).

In contrast, cognitive deficits are more commonly associated with damage to the posterior cerebellum or the ventral dentate nucleus. Indeed, since its initial description in both adults (Schmahmann and Sherman, 1998) and children (Levisohn et al., 2000), the cerebellar cognitive affective syndrome (CCAS) has been associated with damage to the posterior cerebellum (Tedesco et al., 2011). Consistent with the anatomic connectivity and functional activation patterns in the posterior cerebellum, the CCAS is characterized by deficits in language, visual spatial, and executive functions, and affective dysregulation following cerebellar damage. Cognitive task performance has been associated with volumes in lobules VI, VII, and IX in patients with cerebellar disease (Kansal et al., 2017) and with posterior lobe volume in patients with multiple sclerosis (D’Ambrosio et al., 2016). Within the set of symptoms associated with the CCAS, language deficits tend to be associated with right-lateralized cerebellar damage to lobule VII (Riva and Giorgi, 2000; Scott et al., 2001), while there is some (albeit weaker) evidence that visual-spatial difficulties are more likely following left cerebellar damage (Riva and Giorgi, 2000; Scott et al., 2001). Consistent with a right cerebellar involvement in language, decreased volume in the right lateral cerebellum in children with cerebellar malformations has been associated with poorer expressive language (Bolduc et al., 2012).

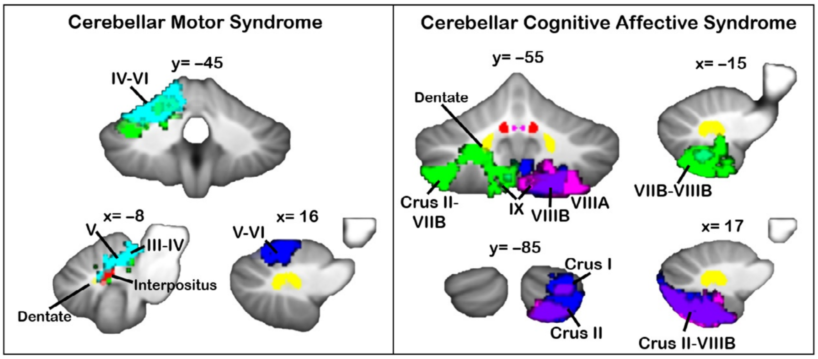

Fig. 4.3. Lesions associated with cerebellar motor syndrome (left) and cerebellar cognitive affective syndrome (right). Different colors represent individual patient's lesions. The patients with cerebellar motor syndrome did not have cognitive deficits, and the patients with cerebellar cognitive affective syndrome did not have motor deficits. The cerebellar deep nuclei are shown in yellow (dentate), red (interpositus), and violet (fastigial) based on the Spatial Unbiased Infratentorial Template (SUIT) atlas (Diedrichsen et al., 2009). (Adapted from Stoodley CJ, Macmore JP, Makris N, et al. (2016) Location of lesion determines motor vs. cognitive consequences in patients with cerebellar stroke. Neuroimage Clin 12: 765–775.)

Even within a domain such as language, deficits are consistent with anatomic connectivity and functional activation patterns: dysarthria is associated with anterior-lobe damage, but poorer scores on verbal fluency and verbal working-memory tasks are linked to damage to the posterolateral cerebellum (Richter et al., 2007; Ilg et al., 2013; Bultmann et al., 2014). Similarly, in an auditory working-memory task, children with damage to left lobule VIII following resection of pilocytic astrocytomas showed reduced digit span, whereas damage to the vermis and IV/V was associated with a reduced articulatory suppression effect (Kirschen et al., 2008), supporting differences between articulatory vs. cognitive cerebellar regions. Clinical data also support the conceptualization of the ventral dentate as nonmotor, given that poorer performance on an *n*-back working-memory task was associated with damage to the ventral dentate (Ilg et al., 2013).

It is important to note that the cerebellar motor syndrome can exist in the absence of the CCAS, and the CCAS can be present without motor symptoms (Schmahmann and Sherman, 1998; Paulus et al., 2004; Schmahmann et al., 2009; Stoodley et al., 2016). In a recent lesion symptom-mapping study, patients with cerebellar motor syndrome but no cognitive deficits had damage to the anterior lobe with spared posterolateral hemispheres; the opposite pattern was seen in patients with CCAS but normal ataxia scores (Fig. 4.3; Stoodley et al., 2016). This double dissociation between motor and cognitive sequelae suggests that cognitive outcomes in cerebellar damage are not necessarily due to motor impairment.

Further, cerebellar damage has been associated with behavioral outcomes in a location- and task-specific manner: for example, poorer language scores were associated with right cerebellar damage involving lobule VII, consistent with activation patterns during language tasks in healthy controls; damage associated with poorer performance on a task involving both motor and cognitive performance encompassed both anterior and posterior regions of the cerebellum (Stoodley et al., 2016). In children with postoperative cerebellar mutism and the CCAS (Gudrunardottir et al., 2016; previously posterior fossa syndrome, Pollack, 1997), once the mutism has been resolved, some children have residual agrammatism (Levisohn et al., 2000; Riva and Giorgi, 2000; Gudrunardottir et al., 2016), suggesting that children with this pattern have right cerebellar hemispheric lesions in addition to damage to the posterior vermis (Riva and Giorgi, 2000).

In ex-preterm infants, poorer working memory was associated with decreased volumes of crus I, crus II, and VIIB (Ranger et al., 2015). This anterior–posterior dichotomy is consistent with different outcomes being associated with disruption of different cerebrocerebellar circuits, depending on the location of damage within the cerebellum. The new understanding of the wide range of cerebellar functions and their regional specificity accounts for the observations that, as a group, cerebellar patients (i.e., patients with lesions anywhere in cerebellum) may show only mild impairments either on traditional tests of cerebellar motor function, or on cognitive tests, since the individual variation in lesion pattern seems to be critical in determining outcomes.

IMPLICATIONS OF TOPOGRAPHY FOR THE THEORY OF CEREBELLAR FUNCTION

The Dysmetria of Thought theory holds that the motor deficits, as well as the cognitive and affective symptoms in cerebellar patients (the CCAS (Schmahmann and

Sherman, 1998; Levisohn et al., 2000) or Schmahmann syndrome (Manto and Mariën, 2015)), arise as a consequence of the loss or degradation of the universal cerebellar transform, the singular neurologic process that subserves cerebellar modulation of movement, intellect, and emotion (Schmahmann, 1991, 1996, 2000; Schmahmann and Sherman, 1998; Guell et al., 2015). The Dysmetria of Thought theory is predicated on the existence of two contrasting but complementary anatomic realities. The first is cytoarchitectonic uniformity in the cerebellar cortex (Ito, 1993; Voogd and Glickstein, 1998), the basis of the universal cerebellar transform theory. The other is the existence of topographically arranged cerebellar connections with sensorimotor, association, and paralimbic areas of the cerebral hemispheres as well as with the brainstem and spinal cord (Schmahmann and Pandya, 1997a, b, 2008; Dum and Strick, 2003). The anatomic and functional heterogeneity of cerebrocerebellar connections by way of the pons (feedforward limb) and thalamus (feedback limb) is therefore critical to the development of, and understanding the clinical consequences of, this overarching theoretical formulation of the role of the cerebellum in the nervous system in health and disease.

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