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The Theory and Neuroscience of Cerebellar Cognition

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Keywords

cerebellar cognitive affective syndrome, universal cerebellar transform, dysmetria of thought, ataxia, functional topography, principles of organization

Abstract

Cerebellar neuroscience has undergone a paradigm shift. The theories of the universal cerebellar transform and dysmetria of thought and the principles of organization of cerebral cortical connections, together with neuroanatomical, brain imaging, and clinical observations, have recontextualized the cerebellum as a critical node in the distributed neural circuits subserving behavior. The framework for cerebellar cognition stems from the identification of three cognitive representations in the posterior lobe, which are interconnected with cerebral association areas and distinct from the primary and secondary cerebellar sensorimotor representations linked with the spinal cord and cerebral motor areas. Lesions of the anterior lobe primary sensorimotor representations produce dysmetria of movement, the cerebellar motor syndrome. Lesions of the posterior lobe cognitive-emotional cerebellum produce dysmetria of thought and emotion, the cerebellar cognitive affective/Schmahmann syndrome. The notion that the cerebellum modulates thought and emotion in the same way that it modulates motor control advances the understanding

of the mechanisms of cognition and opens new therapeutic opportunities in behavioral neurology and neuropsychiatry.

Contents

1. INTRODUCTION

The cerebellum had been thought for almost 200 years to be devoted exclusively to motor control. This may now be regarded as a quirk of history, resulting from a focus on obvious motor deficits while neglecting cognitive or neuropsychiatric phenomena that did not conform to established dogma. Vincenzo Malacarne (1776), who wrote the first treatise on the cerebellum and named many of its structures, studied the cerebellum to explore the relationship between the number of its folia and intelligence (Zanatta et al. 2018). We now know that the cerebellum is engaged in almost all neurological functions, i.e., sensorimotor, vestibular, cognitive, emotional-social-psychological, and autonomic, and that lesions of its different parts affect each of these domains.

This review commences with a consideration of a theoretical approach to the role of the cerebellum in the nervous system. It then discusses anatomical circuits defined in tract-tracing experiments, insights derived from functional imaging studies in humans, clinical syndromes, and therapeutic implications of this paradigm shift in understanding the cerebellum and its disorders.

2. THEORETICAL FORMULATIONS

2.1. The Universal Cerebellar Transform and Dysmetria of Thought

The mostly invariant architecture of the cerebellar cortex contrasts with the heterogeneity of cerebellar connections with extracerebellar structures. The repeating corticonuclear microcomplexes (Eccles et al. 1967, Ito 1984) provide the anatomical and physiological substrates for a consistent cerebellar computation (Dow 1974, Schmahmann 1991), which is termed the universal cerebellar transform (UCT) (Schmahmann 2000, 2004). It has been proposed that by integrating multiple internal representations with external stimuli and appropriate responses, the UCT maintains behavior around a homeostatic baseline, automatically and without conscious awareness, serving as an oscillation dampener to optimize performance according to context (Schmahmann & Pandya 1989, 1997a,b; Schmahmann 1991, 1996, 2000, 2004; Schmahmann & Sherman 1998). Embedded in the UCT theory is the corollary that when the cerebellum is dysfunctional, the clinical manifestation, dysmetria (from Greek, meaning lack of order or impaired judgment and execution in space, velocity, or time), should be consistent across domains. Disorders that emerge from nonmotor cerebellar dysfunction are the basis of the dysmetria of thought (DoT) theory. "In the same way as the cerebellum regulates the rate, force, rhythm and accuracy of movements, so may it regulate the speed, capacity, consistency and appropriateness of mental or cognitive processes" (Schmahmann 1991, p. 1183). The DoT theory predicts that dysmetria manifests differently according to lesion location. Lesions of (*a*) cerebellar motor regions manifest as the cerebellar motor syndromes of gait ataxia, limb dysmetria, and dysarthric speech; (*b*) cerebellar vestibular regions produce the cerebellar vestibular syndrome; and (*c*) cognitive-limbic regions of the cerebellum give rise to the constellation that is known as the cerebellar cognitive affective syndrome (CCAS)/Schmahmann syndrome, the third cornerstone of clinical ataxiology.

2.2. Other Theories of the Role of the Cerebellum in Nonmotor Function

The architecture of the cerebellar cortex has inspired many ideas regarding the nature of the computation or transform. These include motor learning that draws on the interaction of mossy fiber and climbing fiber inputs to the Purkinje cell (PC) dendritic tree (Marr 1969, Albus 1971); cerebellar cortex with its individual lines or beams (Eccles et al. 1967) responding to sequences of events, producing sequences of signals as output, and acting as a biological clock in the millisecond range (Braitenberg 1967, Braitenberg et al. 1997); cerebellum as a timing machine (Ivry & Keele 1989), critical for error detection (Fiez et al. 1992, Ito 2008), sequence learning (Molinari et al. 1997), automatization (Doyon et al. 1998), prediction and preparation (Akshoomoff et al. 1997, Sokolov et al. 2017), dynamic state monitoring (Paulin 1993), and sensory preprocessing of information (Bower 1997); neuronal machine-like function with long-term depression supporting memory, encoding internal models for motor control as well as mental representations in the cerebral cortex (Ito 2006, 2008), helping the frontal lobe in the skilled manipulation of muscles, information, and ideas (Leiner et al. 1986); and implementing supervised learning using computational and engineering organizational principles (Raymond & Medina 2018; see also Baumann et al. 2015). These notions are all compatible with the theories of the UCT and DoT.

2.3. General and Specific Principles of Organization of the Cerebral Cortex

The UCT and DoT theories are nested within the proposed overarching concepts of the evolution, anatomy, and function of the nervous system based on the study of white matter tracts and the cortical and subcortical projections emanating from multiple different regions of the cerebral cortex (Schmahmann & Pandya 2006, 2008).

2.3.1. General principle of cerebral cortical organization. The general principle of organization of cerebral cortical connections is that every cerebral cortical area gives rise to efferent fibers to five sets of targets: (*a*) Association fiber tracts terminate in cerebral cortical areas in the same hemisphere. (*b*) Corticostriate fibers in the external capsule or the subcallosal fascicle of Muratoff terminate in the caudate nucleus, putamen, or claustrum. (*c*) Commissural fibers in the corpus callosum or anterior commissure terminate in the opposite cerebral hemisphere. (*d*) A subcortical, or projection, bundle conveys fibers to the thalamus and diencephalon. (*e*) Pontine bundle fibers descend into and terminate in the brainstem, including the basis pontis, or continue into the spinal cord.

The first stage of the feed-forward limb of the cerebrocerebellar system (corticopontine projections) is thus integral to the general principle, incorporating the cerebellum into the distributed neural circuits arising from multiple domains of processing in the cerebral cortex.

2.3.2. Specific principle of cerebral cortical organization. The specific principle is that the connections of each cerebral cortical area are arranged with great topographic precision, and the following three points hold true.

First, architecture determines the transform. The architecture and connections of each cerebral cortical and subcortical node within a distributed neural circuit facilitate a neural computation, or transform, that is unique to that region and consistent throughout the architectonically defined node.

Second, architecture drives connections. Evolutionary architectonics and connectional studies in monkey show the interdependence of a cerebral cortical area and its connections (Pandya et al. 2015). Whether the architecture of a cerebral cortical area determines its connections or the architecture and connections are a result of the same genetic influence has not yet been established.

Third, connections define behavior. Anatomically precise and segregated connections between nodes facilitate the integration of the different transforms and in this way define behavior. Association fiber tracts are necessary for cross-modal integration, and these are unique to the cerebral cortex.

2.3.3. Clinical implications of the general and specific principles. Clinical manifestations of brain lesions are determined by which node is damaged and which subpopulation of neurons within that node or its connecting axons are destroyed. Lesions of subcortical structures can mimic deficits resulting from lesions of the cerebral cortex, but there are qualitative differences between the manifestations of lesions in functionally related areas (Schmahmann & Pandya 2008). In the motor system, cerebellar lesions cause ataxia, basal ganglia lesions produce hypokinetic or hyperkinetic movement disorders, and cerebral cortical or cerebral white matter lesions result in weakness or spasticity. The same is predicted to hold true for cognitive and emotional disorders.

3. ANATOMICAL INVESTIGATIONS

Anatomical studies have elucidated the critical substrates that support the proposed principles of the organization of cerebral cortical connections and the theories of the UCT and DoT.

3.1. The Uniform Architecture of the Cerebellar Cortex

In contrast to the cerebral cortex, there is no cytoarchitectonic heterogeneity in the cerebellar cortex. Malacarne's interest in cerebellar folia was followed by Johan Christian Reil's (1808), who regarded the "laminae and their connections [as] the essential components of the concept of the cerebellum…their structures, which are apparently very heterogeneous, are nothing else but mere modifications of this one concept" (quoted in Clarke & O'Malley 1996, p. 648). Ramón y Cajal (1909) provided the first detailed histological depictions of a trilaminar cerebellar cortex with its molecular, PC, and granule cell layers invariant throughout. Its modular circuity is also constant, with climbing fibers originating from the inferior olivary complex and mossy fibers from essentially all other afferents. Cerebellar histology is not entirely uniform or homogenous, though. Unipolar brush cells, the only excitatory interneurons in the cerebellum, are confined to the vestibulocerebellum (Mugnaini et al. 2011). And parasagittal zonation with zebrin-positive and -negative banding in the cerebellar cortex is ubiquitous throughout mammalian species (Hawkes & Leclerc 1989, Hawkes 2014), with PC simple and complex spike frequencies higher in zebrin-negative modules (Zhou et al. 2014). Nevertheless, the regular lattice-like feature of the cerebellar cortex is the key anatomic basis of the UCT theory.

3.2. Heterogeneity and Topographic Specificity of Extra-Cerebellar Connections

In contrast to the repeating nature of the cerebellar cortical architecture, the afferent and efferent connections of the cerebellum with the spinal cord, brainstem, and cerebral hemispheres are markedly heterogeneous, and they demonstrate precise topographic arrangement. This connectivity provides the anatomical basis for the functional heterogeneity of the cerebellum, modulating a wide range of nervous system domains.

3.2.1. Sensorimotor connections. Physiological and/or anatomical investigations have consistently revealed topographic arrangement in the cerebellum of sensory-motor afferents from the spinal cord and cerebral cortex. Less appreciated was the fact that these studies demonstrated the absence of sensory-motor afferents to large swaths of the cerebellum—territories we now know to be cognitive-limbic. The physiological studies in cat and monkey by Snider and colleagues (Snider & Stowell 1944; Snider & Eldred 1948, 1952; Snider 1950) established cerebellar sensorimotor topography, proposed previously by Bolk (1906), based on comparative anatomical investigations (**Figure 1*b***). The presence of a simiunculus in the anterior lobe extending into lobule VI, and a second representation in the medial part of the posterior lobe, now lobule VIII, was the final departure from the notion of van Haller in the 1700s [Neuburger 1981 (1897)] and Flourens (1824) that the cerebellum was equipotential throughout, from Rolando's (1809) idea that the cerebellum exerted a diffuse influence on all motor activities (Clarke & O'Malley 1996), and from Luciani's (1891) view that the cerebellum was "an organ functionally homogeneous…in which each segment has the same functions as the whole and is capable of compensating for the deficiencies of others" (quoted in Clarke & O'Malley 1996, p. 664). Cerebellar somatotopy was subsequently confirmed in anatomical and physiological investigations of afferents to the cerebellum from the spinal cord (Chambers & Sprague 1955; Grant 1962a,b; Oscarsson 1965; Brodal 1981) and vestibular system (Walberg et al. 1958, Brodal & Hoivik 1964, Brodal 1972, Carpenter et al. 1972, Barmack & Yakhnitsa 2013) (**Figure 1*c***).

3.2.2. The inferior olivary nucleus. The cerebellar cortex projections to the deep cerebellar nuclei, the corticonuclear microcomplex, form the functional unit of the cerebellum, and they

are also linked in tight reciprocal fashion with the inferior olivary nucleus (Jansen & Brodal 1940, Haines 1989). Olivocerebellar projections terminate in the parasagittal zebrin zones with exquisite topographic arrangement (Sugihara et al. 2001, Herrero et al. 2006, Voogd et al. 2013, Zhou et al. 2014). Spino-olivary inputs convey proprioceptive information to the medial and dorsal accessory olivary nuclei, which send climbing fibers to cerebellar sensorimotor zones (anterior lobe, lobule VI, and lobule VIII) as well as to the motor-related interpositus nuclei from which they receive reciprocal projections. The principal olive (PO) receives no spinal cord inputs and projects to the laterally situated C2 and D zones in the cerebellar posterior lobe and to the ventral and lateral

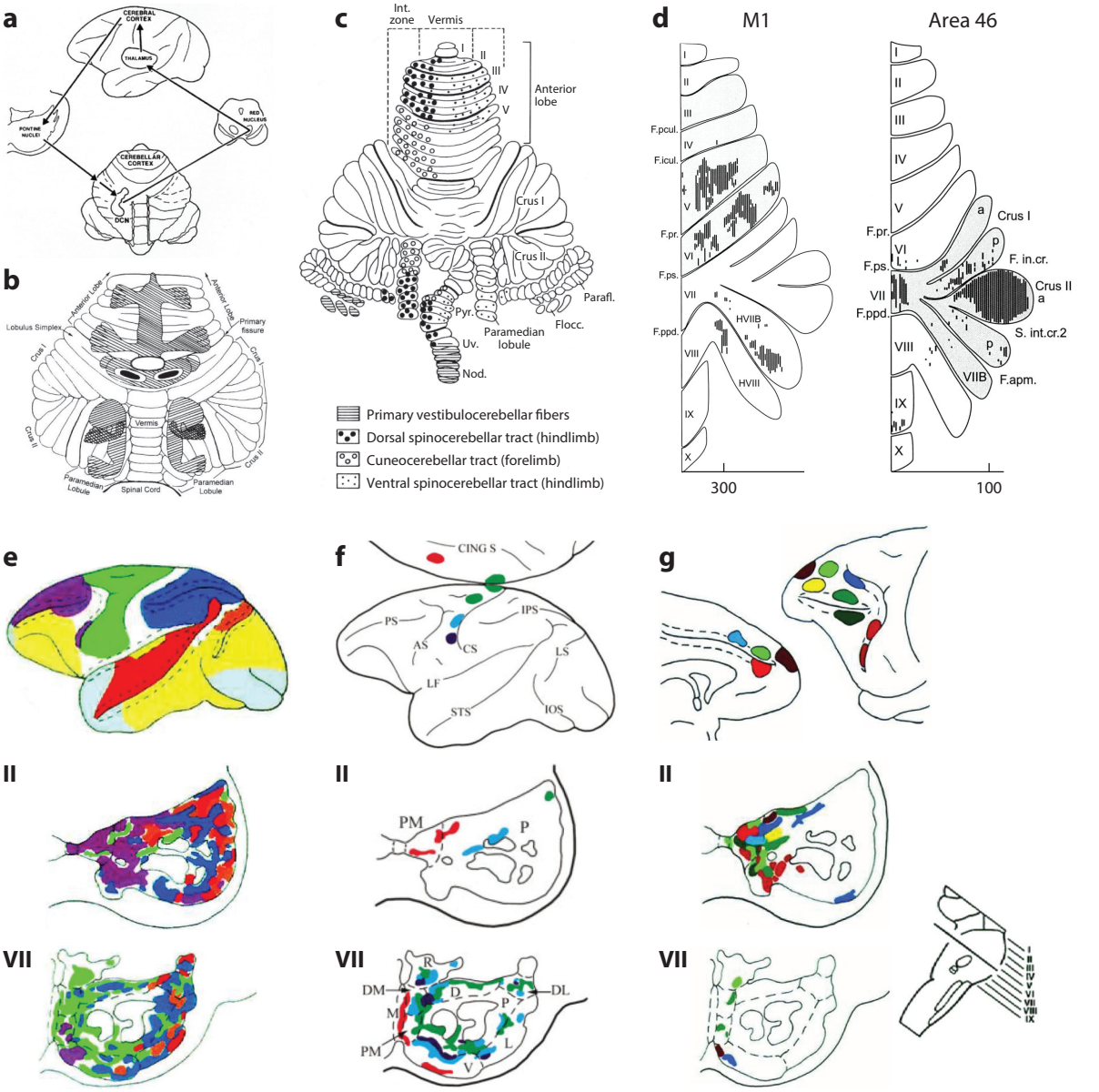

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Figure 1 (*Figure appears on preceding page*)

Neuroanatomy. (*a*) The cerebrocerebellar circuit. Panel *a* adapted from Schmahmann (1996). (*b*) Somatotopy identified by physiological mapping in monkey. Note the silence of lobule VII (the hemispheric extensions of which are crus I and II). Panel *b* adapted from Snider & Eldred (1952). (*c*) Somatotopy in cat with fibers from the dorsal and ventral spinocerebellar tracts and external cuneate nucleus (Grant 1962a,b) and primary vestibular fibers (Brodal & Hoivik 1964), all avoiding crus I and II. Panel *c* adapted from Brodal (1981, p. 315). (*d*) Reciprocal cerebrocerebellar connections between primary motor cerebral cortex (M1) and cerebellar lobules V, VI, and some in lobule VIIB contrasted with connections of dorsolateral prefrontal cortex area 46 with crus I and II and some in lobule IX. Panel *d* adapted from Kelly & Strick (2003). (*e*) Corticopontine projections to pontine levels II and VII from multiple cerebral cortical areas and regional heterogeneity and interdigitation of terminations. Panel *e* adapted from Schmahmann (1996). (*f*) Motor cortex projections to the basis pontis topographically arranged in the caudal pontine nuclei. Note the relative abundance of projections in level VII compared to level II. Panel *f* adapted from Schmahmann et al. (2004). (*g*) Prefrontal cortex projections to the basis pontis topographically arranged and interdigitated in the rostral pontine nuclei. Note the relative abundance of projections in level II compared to level VII. Panel *g* adapted from Schmahmann & Pandya (1997a). Abbreviations: AS, arcuate sulcus; CING S, cingulate sulcus; CS, central sulcus; D, dorsal pontine nucleus; DCN, deep cerebellar nucleus; DL, dorsolateral pontine nucleus; DM, dorsomedial pontine nucleus; F.apm., ansoparamedian fissure; F.icul., intraculminate fissure; F.in.cr., intracrural fissure; Flocc., flocculus; F.pcul., preculminate fissure; F.ppd., prepyramidal fissure; F.pr., primary fissure; F.ps., posterior superior fissure; int., intermediate; IOS, inferior occipital sulcus; IPS, intraparietal sulcus; L, lateral pontine nucleus; LF, lateral fissure; LS, lunate sulcus; M, median pontine nucleus; Nod., nodulus; P, peduncular pontine nucleus; PM, paramedian pontine nucleus; PS, principal sulcus; Pyr., pyramis; R, reticular pontine nucleus; S.int.cr.2, second intracrural sulcus; Uv., uvula; V, ventral pontine nucleus.

parts of the dentate nucleus from which it receives efferent feedback (Azizi & Woodward 1987; Ruigrok & Voogd 1990, 2000; Matsushita et al. 1992). We therefore regard the PO as equivalent to the pulvinar of the thalamus (Schmahmann 2003)—participating in topographically arranged, reverberating circuits with the cerebellum; engaged in thought, planning, and mood; and devoid of sensorimotor connections or properties.

3.3. The Cerebrocerebellar System

The nuclei of the basis pontis are the obligatory synapses in the corticopontocerebellar feed-forward limb of the cerebrocerebellar circuit. The thalamic nuclei are the obligatory synapses in the cerebrocerebellar feedback limb of the cerebrocerebellar circuit (**Figure 1*a***).

3.3.1. Feed-forward limb. Somatotopically arranged projections to the pons arise from sensorimotor representations in the cerebral cortex, more heavily identified in the mid and caudal parts of the pons (Brodal 1978, Schmahmann et al. 2004) (**Figure 1*e*,*f***), and from extrastriate visual areas (Schmahmann & Pandya 1993, Glickstein 1997). The cerebral association areas in the prefrontal cortex, posterior parietal cortex, superior temporal polymodal regions, cingulate gyrus, and posterior parahippocampal gyrus also have highly organized corticopontine projections, which are more peripherally situated than sensorimotor projections and are more prominent in the rostral and mid pons than the caudal pons (Schmahmann & Pandya 1989, 1991, 1993, 1997a,b) (**Figure 1*e*,*g***). Caudal pons projections (more heavily motor oriented) are directed to the cerebellar anterior lobe and rostral pons projections (more heavily associative) to the cerebellar posterior lobe (Brodal 1979), a dichotomy first noted with myelin staining (Bechterew 1885).

3.3.2. Feedback limb. The cerebellar corticonuclear projections are arranged in a precise mediolateral fashion. Cerebello-thalamic and thalamocortical projections are reviewed elsewhere (Schmahmann 1994, 1996, 2007). Traditionally, motor cerebellar-recipient thalamic nuclei (VPLo, VLc, VLps, and X) project to the motor and premotor cortex and also to the supplementary motor area and dorsolateral prefrontal (areas 8 and 46), posterior parietal, and multimodal temporal lobe regions. The intralaminar and medial dorsal thalamic nuclei, interconnected with association and limbic cortices, also receive inputs from the deep cerebellar nuclei.

IN VIVO NEURAL RECORDING OF CEREBELLAR COGNITION

Physiological studies in rodents echo the anatomical reality that the cerebellum communicates with a wide array of extracerebellar areas not limited to motor territories. For example, amygdala inactivation alters learning-related neural activity in the cerebellum (Farley et al. 2016). Granule cell activity represents not only motor and sensory context but also nonmotor aspects of contextual information such as expectation of reward (Wagner et al. 2017) [for a review of technological advances in monitoring large populations of granule cells, see Badura & De Zeeuw (2017), and for a review of specific neurophysiological mechanisms by which granule cells might contribute to cerebellar function across motor and nonmotor domains, see Lackey et al. (2018)]. Furthermore, optogenetic studies demonstrate direct cerebellar nuclear projections to the ventral tegmental area (VTA) in the midbrain (Carta et al. 2019). This work shows that the cerebellar-VTA pathway is necessary for the expression of social behavior and suggests that the cerebellum dynamically encodes social-related signals, relaying them to the VTA for the specific purpose of modulating behavior.

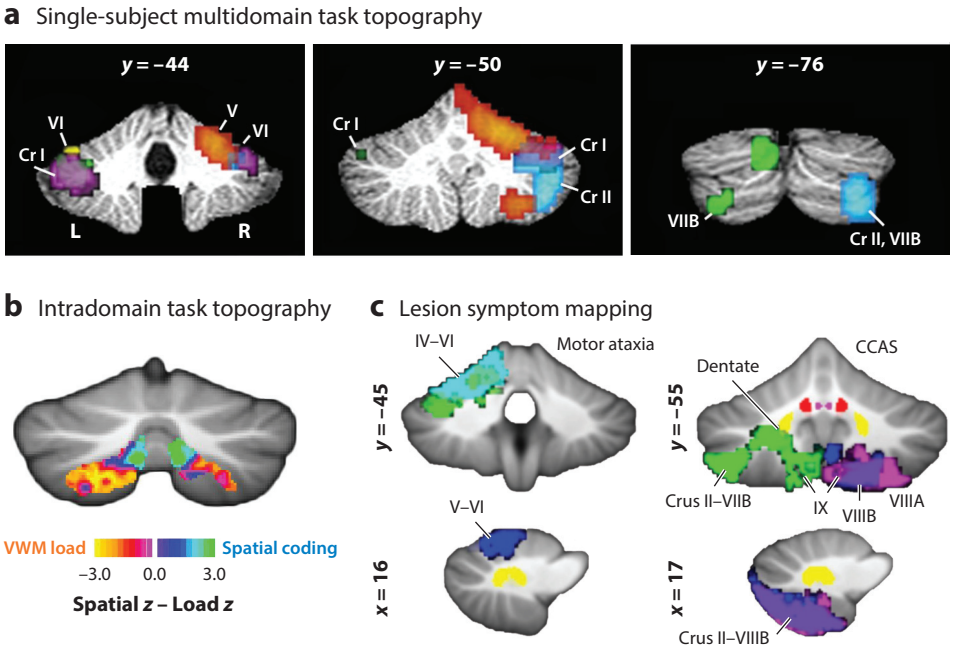
3.3.3. Transsynaptic tracers reveal cerebrocerebellar connections. Transsynaptic viral tracers reveal the primary motor cortex (M1) feed-forward and feedback linkage with cerebellar lobules III–VI and VIII and dorsolateral prefrontal cortex area 46 connections with crus II and lobule X (Kelly & Strick 2003) (**Figure 1*d***). They also demonstrate the intranuclear topography of projections to M1 from the dorsal part of the dentate and interpositus nuclei and to area 46 from the ventral part of the dentate nucleus (Middleton & Strick 1994, Dum & Strick 2003). Furthermore, cerebellar circuits have multisynaptic linkage with the subthalamic nucleus, providing evidence for cerebellar-basal ganglia communication (Hoshi et al. 2005), and the hypothalamus is reciprocally interconnected with the cerebellar cortex and nuclei (Haines et al. 1997). In vivo neural recording in rodents echoes the anatomical reality that the cerebellum communicates with a wide array of extracerebellar areas not limited to motor territories (see the sidebar titled In Vivo Neural Recording of Cerebellar Cognition).

4. FUNCTIONAL MRI IN HUMANS

Cerebellar activation patterns from functional neuroimaging studies are consistent with the anatomy of cerebrocerebellar circuits: The anterior lobe and lobule VIII are engaged during overt movements (Rijntjes et al. 1999, Bushara et al. 2001), whereas posterior and lateral cerebellar regions are active during cognitive tasks. Two meta-analyses of the functional imaging literature have established that cerebellar activation patterns are task dependent, with broad sensorimotor (anterior lobe, medial lobule VI, lobule VIII) and nonmotor regions (lateral posterior hemispheres, including lateral lobule VI, crus I, crus II, and lobule VIIB) (Stoodley & Schmahmann 2009, Keren-Happuch et al. 2014). Language tasks show greater right-lateralization, consistent with the contralateral connections with the cerebral cortex; working memory and other executive function tasks are bilateral; and visual-spatial tasks are left-lateralized, a topography that is evident at the single-subject level (Stoodley et al. 2010, 2012) (**Figure 2*a***). Tasks that share common processes and engage similar regions of the cerebral cortex [e.g., working memory and verb generation (Stoodley et al. 2012)] show activation overlap, consistent with the idea that cerebellar activation is dependent on the specific cerebrocerebellar circuits that support task performance. The cerebellum is engaged in tasks of social cognition (Van Overwalle et al. 2014), revealing posterior cerebellar activation during mentalizing tasks and more anterior engagement during mirroring (i.e., observing body movements).

4.1. Resting-State Functional Connectivity MRI

Resting-state connectivity provides new insights into cerebellar organization and functional connections in humans (Habas et al. 2009, Krienen & Buckner 2009, O'Reilly et al. 2010, Buckner et al. 2011, Guell et al. 2018a) (**Figures 2*d*** and **3*a***). Intrinsic connectivity networks (ICNs) in the cerebral hemispheres comprise geographically distant brain areas that are functionally coupled.



d Task and resting-state activation topography and multiple representations of motor and nonmotor domains

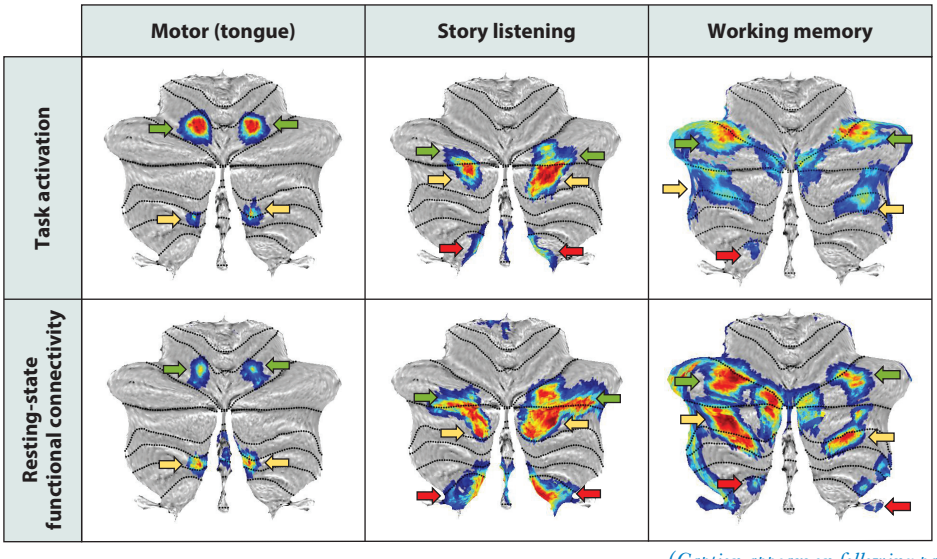


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Figure 2 (*Figure appears on preceding page*)

Human functional topography. (*a*) Intraindividual topography of task-based activations in the cerebellum for finger tapping (*red*), working memory (*purple*), verb generation (*blue*), and mental rotation (*green*) (Stoodley et al. 2010). (*b*) Spatial gradients within the dorsal attention network in lobule VIIB on a working memory task. The locus of spatial attention encoding is medially situated; attentional load content is more lateral. This gradient of activity also exists within the cortical dorsal attention network (not shown). Panel *b* adapted from Brissenden et al. (2018). (*c*) In patients with stroke, lesions of lobules IV–V of the anterior lobe extending into adjacent lobule VI produce the cerebellar motor syndrome of ataxia. Lesions confined to posterior lobe lobules crus II through lobule IX produce the cerebellar cognitive affective/Schmahmann syndrome but no motor ataxia. Panel *c* adapted from Stoodley et al. (2016). (*d*) Task and resting-state activation topography in motor and nonmotor domains. Task activation (*top row*) reveals a pattern of two motor (*first column*) and three nonmotor representations (*second and third columns*). An overlapping pattern was observed when calculating resting-state functional connectivity from cerebral cortical activation peaks for each corresponding task activity contrast (*bottom row*). First motor (lobules I–VI) or first nonmotor representation (VI/crus I) (*green arrows*), second motor (VIII) or second nonmotor representation (crus II/lobule VIIB) (*yellow arrows*), and third nonmotor representation (IX/X) (*red arrows*) are shown. First and second nonmotor representations can be contiguous (as in story listening) or separate (as in working memory). Panel *d* adapted from Guell et al. (2018a). Abbreviations: CCAS, cerebellar cognitive affective syndrome; Cr, crus; L, left; R, right; VWM, verbal working memory.

Note, however, that functional connectivity is not synonymous with anatomic structural connectivity. The ICNs identified to date subserve movement, attention, and limbic valence and include frontoparietal networks and the default network concerned with creativity and imagination. The networks mapping onto the cerebellum include motor networks, which map onto sensorimotor regions in the anterior lobe and lobule VIII, and dorsal attention, ventral attention, frontoparietal, default mode, and salience networks, which map onto focal areas within the posterior lobe.

4.2. Cerebellar Functional Topography and the Universal Cerebellar Transform in the Human Connectome Data Set

Contemporary centralized and optimized methods of neuroimaging data acquisition, storage, and dissemination (Van Essen et al. 2013) have enabled the investigation of in vivo human brain organization with unprecedented power. Large amounts of high-quality resting and task-based fMRI data originating from these initiatives have made it possible to replicate and extend the original descriptions of human cerebellar functional neuroanatomy.

4.2.1. Functional topography reaffirmed. Task-based analyses utilizing the human connectome project data set (787 subjects) revealed that distinct regions of the cerebellar cortex are engaged in movement, language, working memory, social, and emotional task processing (Guell et al. 2018a) (**Figure 2*d***). Motor processing engages lobules IV–VI and VIII, and nonmotor processing engages mostly lobule VII (including the hemispheric extensions of lobule VIIA, namely crus I and crus II, and lobule VIIB) as well as lobule IX. Effect size–based thresholds, an optimal approach in the context of a large sample, revealed functional specialization for motor versus nonmotor activation and for distinct aspects of nonmotor processing. No overlap was observed between these cognitive and affective tasks, except for language and social processing activation maps, likely reflecting an overlap in the characteristics of the tasks rather than in cerebellar functional specialization (see Van Overwalle et al. 2015). Cerebrocerebellar functional connectivity using resting-state functional connectivity MRI provided convergent validation of these topographic maps, as resting-state connectivity calculated from cerebral cortical task activation peaks largely overlapped with each corresponding task-activation map in the cerebellum (Guell et al. 2018a).

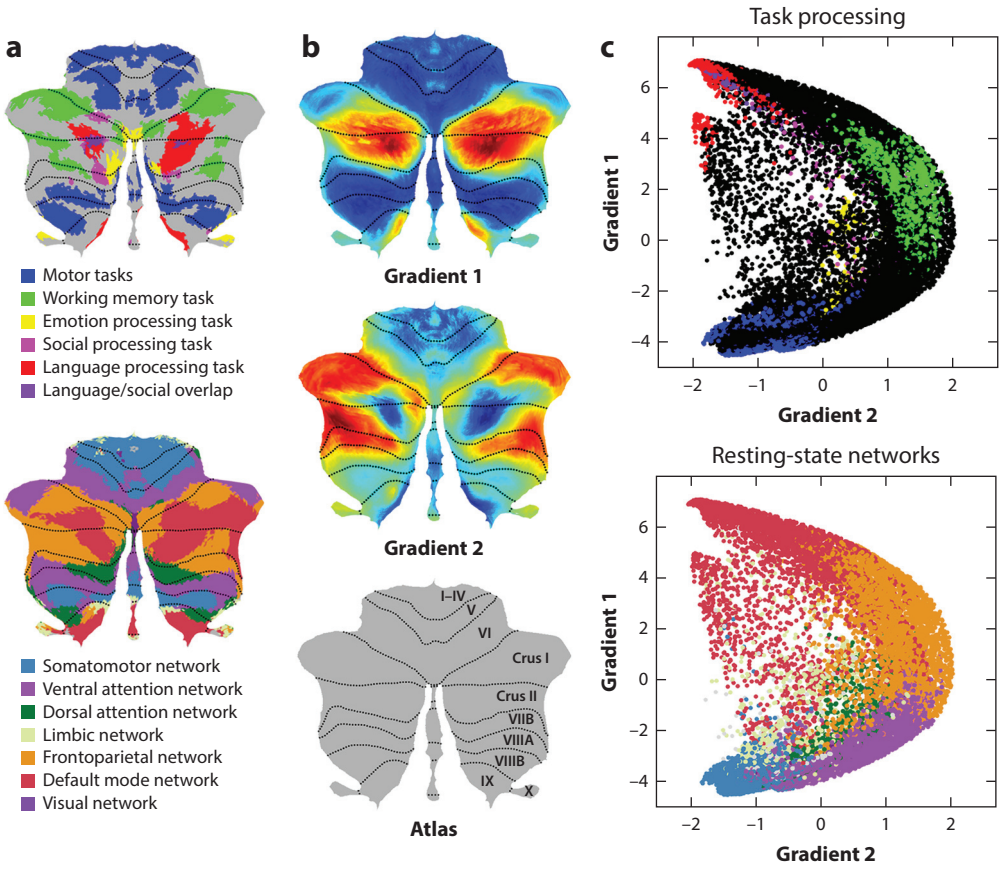

Figure 3

Functional gradients. (*a*) Discrete task activity maps (adapted from Guell et al. 2018a) and resting-state maps (adapted from Buckner et al. 2011). (*b*) Cerebellar gradients 1 and 2 and the cerebellum flatmap atlas. (*c*) Voxel map along gradients 1 and 2. Gradient 1 extends from the language task/default mode network to motor regions, and gradient 2 isolates working memory/frontoparietal network areas. Each dot corresponds to a cerebellar voxel. The position of each dot along the *x*- and *y*-axes corresponds to the position along gradient 1 and gradient 2 for that cerebellar voxel. The color of the dot corresponds to the task activity (*top*) or resting-state network (*bottom*) associated with that voxel. Panels *b* and *c* adapted from Guell et al. (2018c).

4.2.2. Multiple representations in motor and nonmotor domains. These imaging studies replicated the double motor representation: primary representation in lobules IV and V extending into the rostral aspect of lobule VI and second representation (after Woolsey 1952) in lobule VIII. They also revealed multiple representations of cognitive and affective processing simultaneously engaging focal areas within three cerebellar regions: (*a*) lobule VI to crus I, (*b*) crus II to lobule VIIB, and (*c*) lobules IX–X (Buckner et al. 2011, Guell et al. 2018a) (**Figure 2*d***). For example, working memory task processing (Guell et al. 2018a) and frontoparietal network connectivity (Buckner et al. 2011) simultaneously engaged lobule VI/crus I (first representation), crus II/lobule VIIB (second representation), and lobule IX (third representation). First and second nonmotor representations may be separate, as in working memory task activation or frontoparietal network connectivity, or contiguous, as in story listening task activation or default mode network connectivity, which include contiguous aspects of crus I and II. This notion of

DIFFERENCES BETWEEN EACH AREA OF MOTOR AND NONMOTOR REPRESENTATION

Unlike the first cerebellar motor representation, lesions of the second cerebellar motor representation produce little or no motor deficit (Dow 1939, Schmahmann et al. 2009, Stoodley et al. 2016). The functional connectivity of the first cerebellar motor representation targets the primary motor cerebral cortex (M1), and the second cerebellar motor representation targets regions surrounding M1. Similarly, although the functional connectivity from the first and second representations of task-focused cognition in the cerebellum targets task-focused cognitive processing areas in the cerebral cortex, the third representation targets cerebral regions surrounding task-focused cognitive processing areas (see figure 3 and figure 3-supplement 5 in Guell et al. 2018c). A similar relationship is observed in task-unfocused processing. Second motor and third nonmotor representations share hierarchical similarities when mapped in functional gradient space (see also figure 3 and figure 3-supplement 1 in Guell et al. 2018c).

THE ROLE OF EACH REPRESENTATION

The cerebellar first motor representation is engaged in motor control, whereas the second motor representation may be less purely engaged in motor control and more important for movement planning rather than movement execution. Similar logic might extend to the three nonmotor representations: The relationship between the first and second motor representations resembles the relationship between the first/second and third nonmotor representations (Guell et al. 2018c).

a triple nonmotor representation requires further study to address fundamental properties of cerebellar organization (see the sidebars titled Differences Between Each Area of Motor and Nonmotor Representation and The Role of Each Representation).

4.2.3. Gradient analysis of relationships between functionally distinct cerebellar regions. In the cerebral cortex, a hierarchy from primary to transmodal processing governs the relationship between functional areas (Margulies et al. 2016, Mesulam 1998). Novel methods of analysis of resting-state data show that a similar macroscale principle of organization dictates the positions of and relationships between different functional territories in the cerebellum (Guell et al. 2018c). As in the cerebral cortex, cerebellar functional specialization follows a graded organization, from motor to goal-directed (task-focused) cognitive processing and to goal-undirected (task-unfocused) cognitive processing (Guell et al. 2018c) (**Figure 3**). A secondary axis isolates task-focused processing. Previous clinical (Schmahmann et al. 2009, Stoodley et al. 2016) and seed-based functional connectivity analyses (Kipping et al. 2013) point to functional differences between the first and second cerebellar motor representations. The position of each area of motor and nonmotor representations along functional gradients indicates that there may also be functional differences between the three nonmotor representations (Guell et al. 2018c). Specifically, the third nonmotor representation (processing in lobules IX–X) might be functionally distinct from the first (lobule VI/crus I) and second nonmotor representations (crus II/lobule VIIB), and there may be functional similarities between the third nonmotor and second motor representations (Guell et al. 2018c) (see the sidebar titled The Clinical Implications of Multiple Nonmotor Representations and Functional Gradients).

THE CLINICAL IMPLICATIONS OF MULTIPLE NONMOTOR REPRESENTATIONS AND FUNCTIONAL GRADIENTS

Functional connectivity abnormalities in autism spectrum disorder are consistent with the three nonmotor representations (Arnold Anteraper et al. 2018). By mapping cerebellar neuroimaging results along functional gradients, it may be possible to capture critical aspects of cerebellar functional neuroanatomy undetectable with discrete mapping techniques (Guell et al. 2019). Recent neuroimaging analyses have described novel methods of brain mapping (Varoquaux et al. 2018) and brain-behavior prediction (Marquand et al. 2017). Within this context, single-subject functional cerebellar organization (Marek et al. 2018) and rich multidomain task experiments (King et al. 2018) are likely to further increase the nuanced understanding of the cerebellum, including the characterization of structural and functional cerebellar abnormalities in spinocerebellar ataxias (e.g., Olivito et al. 2017a,c; Hernandez-Castillo et al. 2017, 2018) and in cerebellar-linked disorders such as autism (e.g., Arnold Anteraper et al. 2018).

This hypothesis is supported by the finding of fine-scale gradients within cognitive networks, namely, in the dorsal attention system. Spatial encoding of a visual working memory task is found in medial portions of lobule VIIB, whereas visual working memory load is encoded in more lateral portions of VIIB, even though both regions are involved in working memory. This pattern is repeated within the intraparietal sulcus, with more posterior regions representing space and anterior regions representing load (Brissenden et al. 2018).

Gradients of connectivity between cortical areas in the cerebral hemispheres are determined by cerebral cortical association fibers (Mesulam 1998, Schmahmann & Pandya 2006), and reciprocal thalamocortical interactions are postulated to play a role as well (Guillery 1995). There are no association fibers in the cerebellum, i.e., direct connections from one cerebellar cortical region to another (Schmahmann 1996, Schmahmann & Pandya 2008), recurrent collaterals of PCs notwithstanding (Palay & Chan-Palay 1974). The fact that intracerebellar functional gradients are similar to cerebrocerebellar functional gradients (Guell et al. 2018c) indicates that functional relations between cerebellar territories are driven by their topographically arranged interactions with extracerebellar structures.

4.3. MRI Test of the Anatomical Basis of the Universal Cerebellar Transform Theory

The UCT theory predicts that functional specialization in the cerebellum is determined not by variations in microstructure but by variations in anatomical connectivity. We tested the theory using T1w/T2w MRI intensity as a proxy measure of microstructure and functional gradients derived from resting-state connectivity as a proxy measure of functional specialization. Strong microstructure-function correlations were observed in the cerebral cortex, whereas microstructural variations did not correlate with functional variations in the cerebellum (Guell et al. 2018b). This mismatch is concordant with the duality of invariant cerebellar cortical architecture but heterogeneous and topographically precise cerebellar corticonuclear and extracerebellar connections, and it provides empirical support for the UCT theory.

4.4. Cerebellar Circuit Modulation Alters Cerebral Cortical Connectivity and Physiology

The UCT theory predicts that stimulation of different subregions of the cerebellum should modulate different cerebral cognitive networks and that the underlying nature of the physiological

effects on cerebral cortical networks produced by the cerebellar stimulation should be similar. One approach to testing this theory is to use transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) to produce transient changes in local activity and measure the subsequent network impact. The following neuromodulation studies support the concepts of both cerebellar functional topography and the UCT, indicating that the cerebellar modulation of cerebral cortical circuits is anatomically and functionally specific.

4.4.1. Neural circuit topography. Neuronavigated cerebellar intermittent theta-burst TMS applied to vermal lobule VII and crus I/II was able to show a differential network impact. Vermal stimulation led to increased connectivity within the dorsal attention network, whereas lateral crus I/II stimulation led to increased default network connectivity (Halko et al. 2014) (**Figure 4**). These network-wide changes were found in both cerebrocerebellar and cerebral cortico-cortical functional connectivity measures. Concordant results have been found using continuous theta-burst TMS, in which lateral cerebellar hemisphere stimulation decreased functional connectivity with frontal and parietal cognitive regions, while connectivity with motor regions remained unaltered (Rastogi et al. 2017).

4.4.2. Physiological uniformity. With a similar design, but examining resting-state electroencephalogram (EEG) signals, it was possible to show a shared physiological effect of the TMS, namely, that cerebellar intermittent theta-burst TMS increases the temporal complexity of the cerebral network EEG signals as measured by multiscale entropy (**Figure 4**). Furthermore, it does so in a network-specific manner: Vermal stimulation impacts high-beta/low-gamma-range oscillations, whereas lateral stimulation impacts low-theta- and high-gamma-range oscillations (Farzan et al. 2016), consistent with the changes observed in functional connectivity MRI networks (Halko et al. 2014). These findings provided new evidence and a novel mechanism for the nature of the UCT, namely, how specific cerebellar subregions control the temporal dynamics of the networks they are engaged in (Farzan et al. 2016).

4.4.3. Transcranial magnetic stimulation and direct current stimulation to assess the role of the cerebellum in language prediction. Cerebellar neuromodulation disrupts performance on language tasks requiring prediction. This was shown in a visual world task, in which right cerebellar TMS disrupted performance only when prediction was required (Lesage et al. 2012), and in functional MRI (fMRI) studies showing enhanced cerebellar activation in right lobule VII during sentence-completion tasks in which sentence context leads to a strong prediction as to the best word to complete the sentence (Moberget et al. 2014, D'Mello et al. 2017). Modulation of right crus I/II with anodal tDCS led to signal changes in the cerebellum during predictive language processing and increased functional connectivity within reading/language networks [left inferior frontal and supramarginal gyri (D'Mello et al. 2017)], suggesting a cerebellar role in feed-forward models and predictive processing (Sokolov et al. 2017).

5. THE CLINICAL NEUROSCIENCE OF CEREBELLAR COGNITION

5.1. Historical Background

Plausible reasons to account for the now-defunct exclusive motor view of the cerebellum include the obvious cerebellar motor syndrome in animal models and neurodegenerative ataxias, the fact that neuropsychology and cognitive neuroscience had not become established fields, and that there was no theoretical basis within which to conceptualize these wider observations. It is also useful

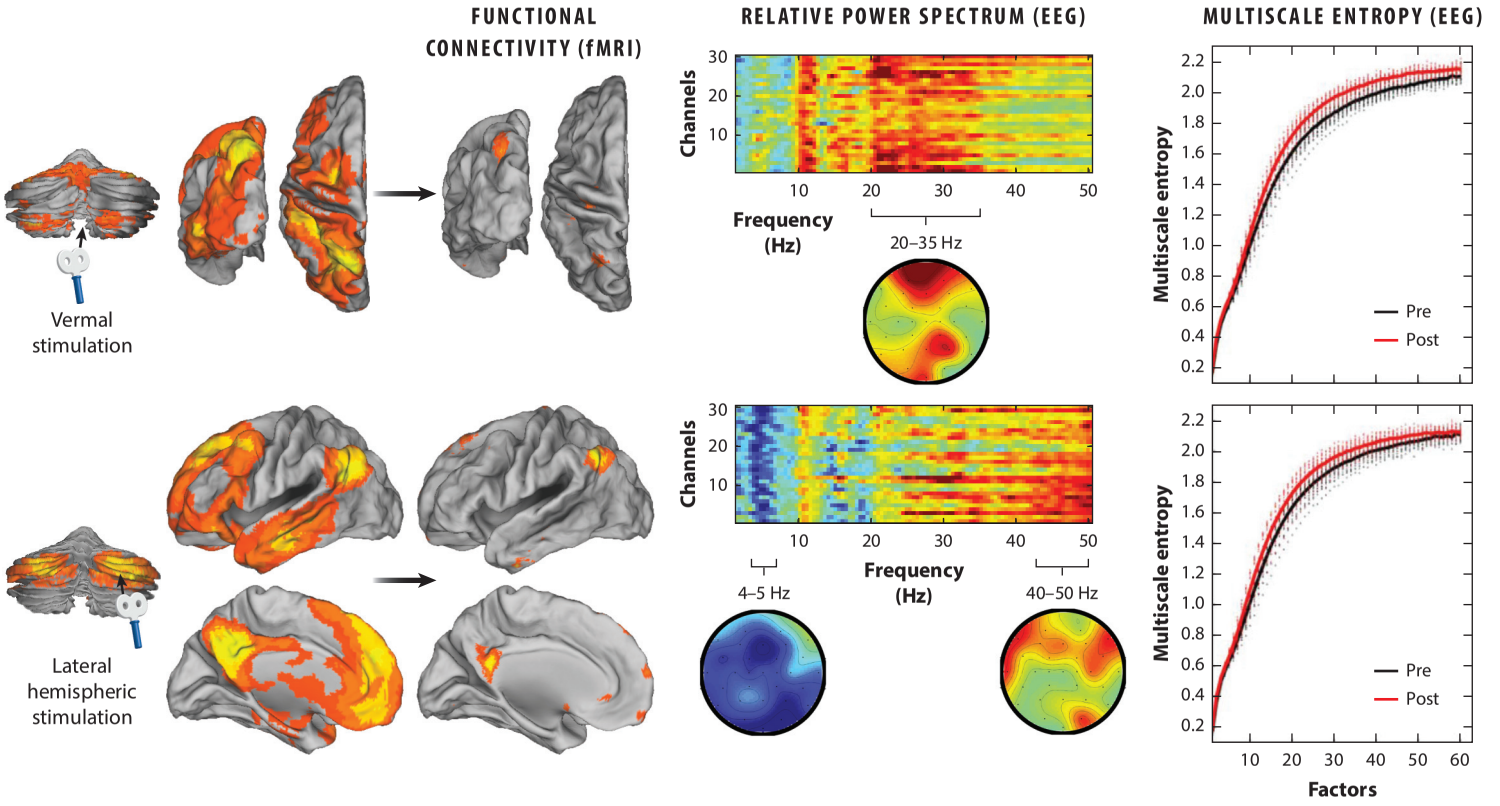

Figure 4

Network-specific transcranial magnetic stimulation modulation of cerebellar-cortical networks. (*Top*) Upregulation of the dorsal attention network via cerebellar midline–targeted stimulation. The parietal dorsal attention network increased functional connectivity following stimulation and frequency-specific modulation of beta to low-gamma oscillations. (*Bottom*) Right lateral cerebellar stimulation targeting cerebellar default network nodes increased functional connectivity within the default network and in high-gamma oscillations. In both cases, multiscale entropy increases, demonstrating increased temporal complexity (*right*). Entropy across increasing timescale factors is shown for pre- and post-stimulation (*black* and *red*, respectively). Larger timescale factors correspond to shorter time windows of complexity. Abbreviations: EEG, electroencephalogram; fMRI, functional magnetic resonance imaging. Figure adapted from Halko et al. (2014) (first column) and Farzan et al. (2016) (second and third columns).

to recall that until Scoville & Milner (1957), the memory engram was thought to be untraceable to any one cortical area (Lashley 1950).

5.2. Description of the Cerebellar Cognitive Affective Syndrome

The field of cerebellar cognition coalesced once it became apparent that there was immediate clinical relevance to the new theories, anatomical observations, and functional imaging observations, notably the cerebellar activation by verb-for-noun generation paradigms (Petersen et al. 1988). In a series of 20 patients with lesions confined to the cerebellum, clinically relevant deficits were noted in executive function, visual spatial performance, and linguistic processing, accompanied by dysregulation of affect particularly when the lesions involved the vermis (Schmahmann & Sherman 1998). This constellation of impairments was named CCAS and was subsequently defined also in children who had undergone resection of cerebellar tumors (Levisohn et al. 2000).

5.3. Recognition and Replication of Cerebellar Cognitive Affective Syndrome

CCAS has been identified by investigators worldwide in many acquired and inherited, focal or diffuse, diseases of the cerebellum in children and adults, giving rise also to the concept of developmental CCAS (Limperopoulos et al. 2007, Koziol et al. 2014, Brossard-Racine et al. 2015, Schmahmann 2018). Regarded as the third cornerstone of clinical ataxiology, CCAS has also been eponymously named Schmahmann's syndrome (Manto & Mariën 2015), and it is now possible to detect CCAS with a validated brief battery of cognitive tests (Hoche et al. 2018). Additional insights include the cerebellar role in metalinguistics (Guell et al. 2015) (see the sidebar titled Metalinguistics) and social cognition (Hoche et al. 2016).

5.4. Functional Topography of Cerebellar Motor and Cognitive Neurology

CCAS arises from lesions of the cerebellar posterior lobe but not the anterior lobe (Schmahmann & Sherman 1998, Stoodley et al. 2016), with prominent affective impairments in patients with midline cerebellar lesions. This is also true for children with pediatric postoperative mutism following cerebellar surgery (Gudrunardottir et al. 2016) whose CCAS includes affective dysregulation from damage to the posterior vermis and superior cerebellar peduncles (Morris et al. 2009).

5.4.1. Structure-function correlation in cerebellar stroke. Vertigo in isolation occurs following stroke in the vestibulocerebellum; infarction in the anterior lobe from occlusion of the superior cerebellar artery produces the cerebellar motor syndrome; and stroke in the posterior lobe from occlusion of the posterior inferior cerebellar artery produces CCAS

METALINGUISTICS

Cerebellar patients revealed metalinguistic deficits that underlie aspects of social communication (e.g., metaphor, ambiguity, inference, sentence generation appropriate to context), contrasting with relatively preserved grammar and semantic abilities (Guell et al. 2015). This pattern of linguistic deficits supports the dysmetria of thought theory that cerebellar cognitive deficits follow a logic like that of the motor deficits: Cerebellar injury disrupts modulation but not generation of movement (resulting in dysmetria but not weakness) and modulation but not generation of language (resulting in metalinguistic deficits but not aphasia).

(Schmahmann et al. 2009, Schmahmann 2012). Voxel-based lesion-symptom mapping provides further details regarding these structure-function correlations (Schoch et al. 2006, Stoodley et al. 2016). Stroke involving the second cerebellar motor area in lobule VIII may produce mild and transient motor deficits, which differentiates this region from the first cerebellar motor representation and from the cognitive cerebellum.

5.4.2. Neural circuit degeneration as an experimental model. Voxel-based morphometry reveals focal atrophy bilaterally in crus I and crus II in Alzheimer's disease and in left lobule VI in behavioral variant frontotemporal dementia (Guo et al. 2016). Volume loss occurs in cerebellar regions that are maximally interconnected with the areas of peak volume loss in the cerebral cortex, and circuit dysfunction/degeneration thus reflects cerebrocerebellar topography (Guo et al. 2016, Schmahmann 2016). Similarly, in multiple sclerosis, which has sensorimotor and cognitive manifestations, cognitive deficits are related to lesions in the middle cerebellar peduncle carrying afferents from the cerebral cortex and not more generally to the burden of cerebellar white matter disease (Tobyne et al. 2018).

5.5. Dysmetria of Thought and Neuropsychiatry

The DoT theory postulates that

> dysmetria of movement is matched by an unpredictability and illogic to social and societal interaction. The overshoot and inability in the motor system to check parameters of movement may thus be 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, p. 1183)

These terms are core psychiatric and neuropsychiatric concepts.

5.5.1. Cerebellum implicated in psychiatric disorders. Much attention has been directed to cerebellar structural, functional, and clinical aberrations in neuropsychiatry, and cerebellar underpinnings of social cognition and emotional processing are under active investigation (reviewed in Schmahmann 1997, 2000, 2018). Cerebellar contributions to autism spectrum disorder, posttraumatic stress disorder, and personality disorders reveal alterations in the cerebellum as part of the disruption/aberration in cerebrocerebellar circuits, and recent investigations demonstrate changes in morphology or connectivity in manifest or premanifest schizophrenia (Moberget et al. 2018) and in bipolar disorder (Shinn et al. 2017). Differences in cerebellar structure and function are among the most common neuroanatomical findings in autism (Bauman & Kemper 1985; Schmahmann 1994; Fatemi et al. 2012; Olivito et al. 2017b, 2018; Arnold Anteraper et al. 2018; for a review, see D'Mello & Stoodley 2015), and evidence from animal models suggests that cerebellar disruption is sufficient to produce restricted/repetitive behaviors and autism-like impairments in social behavior (see, e.g., Tsai et al. 2012, Stoodley et al. 2017).

5.5.2. The neuropsychiatry of the cerebellum: insights from the clinic. Patients with cerebellar damage to the vermis and fastigial nucleus can manifest neuropsychiatric symptoms, the affective component of CCAS. This includes personality changes with blunting of affect, lack of initiation, apathy, depression, and loss of empathy or disinhibited, irritable, and inappropriate behavior. Adults with acute vermis and fastigial nucleus infarcts can develop abrupt-onset panic disorder, and pathological laughing and crying are encountered in patients with cerebellar degeneration (Schmahmann 2000, 2004). Children experience emotional lability, dysphoria, irritability, impulsivity, aggression, and poor attentional and behavioral modulation

(Schmahmann & Sherman 1998, Levisohn et al. 2000, Turkel et al. 2004, Gudrunardottir et al. 2016), fulfilling diagnostic criteria for attention deficit hyperactivity disorder, obsessive compulsive disorder, depression, bipolar disorder, and atypical psychosis (Schmahmann et al. 2007). Stereotypies and aberrant interpersonal relations that are clinical features of autism have been described in children who have undergone surgical resection of cerebellar tumors (Riva and Giorgi 2000), a finding also seen in children with cerebellar disruptions in utero or in early neonatal life (Limperopoulos et al. 2007) and in the rare individuals with cerebellar agenesis (Chheda et al. 2002). These observations underscore the trophic or sustaining influence of the cerebellum on developing neural circuits relevant to cognition and emotion (Limperopoulos et al. 2014, Wang et al. 2014).

Based on analysis of patient symptoms and caregiver reports, this affective dyscontrol was conceptualized as the neuropsychiatry of the cerebellum, and the symptoms were grouped into five domains of behavior: attentional control, emotional control, autism spectrum disorders, psychosis spectrum disorders, and social skill set (Schmahmann et al. 2007). Behaviors within these domains were regarded as either excessive or reduced responses to the external or internal environment. The exaggerated, positive, released, or hypermetric responses are analogous to motor (Holmes 1917, 1939) or cognitive overshoot (Schmahmann 1998). The diminished, negative, restricted, or hypometric responses are likened to hypotonia (Holmes 1917) or hypometric movements (undershoot) in the motor system. Some manifestations, like negative symptoms in the social skill set, resemble observations regarding the cerebellar role in theory of mind studies (Brunet et al. 2000, Calarge et al. 2003). These constellations have been used in the Cerebellar Neuropsychiatric Rating Scale, currently in development, to reveal and score neuropsychiatric disorders in patients with cerebellar diseases.

6. FROM THEORY TO THERAPY

6.1. Recognizing and Treating Cognition and Affect in Cerebellar Disorders

Cognitive changes have long been noted in patients with hereditary ataxias with some deficits likely a result of cerebral and basal ganglia involvement. It has become clearer, though, that even immune-mediated PC-antibody syndromes and patients with isolated cerebellar ataxia experience CCAS with executive dysfunction, including impaired executive control of memory and neuropsychiatry of the cerebellum, including depression. Recognizing these problems opens avenues to interventions, including medications for enhancing cognition and mood, cognitive behavioral interventions, and support for patients with cognitive or neuropsychiatric decline. Addressing the patient and family's need-to-know imperative is a respectful way to interact with people faced with the challenges of neurological compromise.

6.2. Cerebellar Modulation as Therapy in Behavioral Neurology and Neuropsychiatry

Earlier efforts at direct cerebellar cortical stimulation did not enter mainstream clinical practice (Cooper et al. 1974, Heath 1977), but advances in deep brain stimulation and noninvasive methods using TMS, tDCS, and now focused ultrasound have the potential to impact patient care. These approaches can leverage modulation of the UCT to improve patient outcomes, particularly in patients with autism or schizophrenia, where few treatment options exist. In the first proof-of-principle open-label study, stimulation of the cerebellar vermis ameliorated negative symptoms in schizophrenia (Demirtas-Tatlidede et al. 2010), an observation that has since been replicated

(Garg et al. 2016). Using targeted neuroimaging, stimulation recovered aberrant cerebellar-prefrontal cortex connectivity patterns associated with negative symptoms of schizophrenia (Brady et al. 2019), providing hope that systematic investigation with biomarkers can improve quality of life in neurological and psychiatric populations. Optogenetic stimulation of thalamic synaptic terminals of lateral cerebellar projection neurons in a rodent model of schizophrenia-related frontal dysfunction rescued timing performance as well as medial frontal activity (Parker et al. 2017). And in the *Tsc1* mouse model of autism, cerebellar neuromodulation of right lobule VII rescued social deficits (Stoodley et al. 2017), consistent with the suggestion that the dysfunction of cerebrocerebellar circuits underlies selected aspects of disrupted behavior in autism (D'Mello & Stoodley 2015).

7. CONCLUDING COMMENTS

This survey of new and historical data about the cerebellum is driven by theoretical formulations that informed many of these studies. The UCT and DoT theories view the cerebellum as an integral node in the distributed neural circuits subserving all brain-based behaviors. A direct implication of this recontextualization of cerebellar structure and function is that it opens new possibilities for improving the lives of people with neurological and neuropsychiatric disorders.

SUMMARY POINTS

1. The cerebellum modulates cognition and emotion in the same way that it modulates motor control.
2. The theories of the UCT and DoT, nested within the principles of organization of cerebral cortical connections, predict and provide a framework within which to understand this paradigm shift in cerebellar function.
3. The repeating lattice-like architecture of the cerebellar cortex and its cortico-nuclear-olivary microcomplex contrasts with the diverse and topographically precise connections with the spinal cord, brainstem, and multiple cerebral hemispheric sensorimotor and cognitive-limbic ICNs, facilitating the cerebellar contribution to multiple domains of neurological function.
4. Task-based and resting-state fMRI in humans demonstrate the previously identified double motor representation in the cerebellar anterior lobe (and adjacent region of lobule VI) and lobule VIII and a new triple nonmotor representation in the cerebellar posterior lobe in lobules VI/Crus I, Crus II/VIIB, and IX/X.
5. Gradients of connectivity within the cerebellum reflect cerebrocerebellar connections and provide novel imaging approaches to explore cerebellar function in health and disease.
6. The clinical neurology and neuropsychiatry of the cerebellum, including the description of CCAS/Schmahmann syndrome and the neuropsychiatry of the cerebellum, emerge from this more complete and nuanced understanding of cerebellar function.
7. Cerebellar modulation is network specific, evoking a physiological response that is consistent across the networks.

8. New opportunities may now be possible for therapeutic intervention in cerebellar disorders and in neuropsychiatry by using a cerebellar-based approach to intervention, targeting focal areas in the cerebellar node of the distributed cerebrocerebellar networks subserving human behaviors.

FUTURE ISSUES

1. What is the role of the second motor representation?
2. What is the role of each cognitive representation in the cerebellum, what are the consequences of damage to each, and what are their distinct contributions to brain dysfunction in neurology and psychiatry?
3. Can functional gradients calculated in the cerebellum capture differences between healthy subjects and patients with neurological or psychiatric diseases?
4. How does the reciprocal cerebellar communication between the cognitive-limbic cerebellum and the principal olivary nucleus influence behavior, and what is the consequence of damage to this limb of the olivocerebellar circuit?
5. How are cerebellar cognitive deficits different from cognitive impairments arising from lesions of cerebral or other subcortical nodes within the same ICN, and can contemporary neuropsychology and cognitive neuroscience methods distinguish between them?
6. How do the timing of onset (acute, subacute, or chronic) and the age of onset (developmental, pediatric, adult, late life) of a cerebellar disease affect the nature and extent of motor and cognitive disability?
7. What determines whether ataxia or dystonia/chorea/bradykinesia in either motor control or cognitive-emotional realms is the principal manifestation of lesions in the circuits that link the cerebellum with basal ganglia?
8. Can modulation of the cerebellar node of distributed neural circuits subserving cognition and emotion provide a realistic opportunity for intervention in neurology and neuropsychiatry using brain stimulation or cerebellum-targeted cognitive rehabilitation exercises?

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