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CEREBELLAR CLASSICS XII

Commentary on "The Cerebellar System and What it Signifies from a Biological Perspective: A Communication by Christofredo Jakob (1866–1956) Before the Society of Neurology and Psychiatry of Buenos Aires, December 1938"

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Abstract This commentary highlights a "cerebellar classic" by a pioneer of neurobiology, Christfried Jakob. Jakob discussed the connectivity between the cerebellum and mesencephalic, diencephalic, and telencephalic structures in an evolutionary, developmental, and histophysiological perspective. He proposed three evolutionary morphofunctional stages, the archicerebellar, paleocerebellar, and neocerebellar; he attributed the reduced cerebellospinal connections in humans, compared to other primates, to the perfection of the rubrolenticular and thalamocortical systems and the intense ascending pathways to the red nucleus in exchange for the more elementary descending efferent pathways. Jakob hypothesized the convergence of cerebellar pathways in associative cortical regions, insisting on the intimate collaboration of the cerebellum with the frontal lobe. The extensive lines of communication between regions throughout the association cortex substantiate Jakob's intuition and begin to outline the mechanisms for substantial cerebellar involvement in functions beyond the purely motor domain. Atop a foundation of anatomical and phylogenetic mastery, Jakob conceived ideas that were noteworthy, timely, and have much relevance to our current thinking on cerebellar structure and function.

Keywords Cerebellar histophysiology · Ontogeny · Phylogeny · History of neuroscience

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The academic life and the neurobiological work of Christfried Jakob (1866–1956) has resurfaced in the English scientific literature over the past decade [1, 2]. Born in Bavaria, Jakob moved to Argentina in 1899, where he spent the rest of his life, save a return to Europe in 1910–1912. In Argentina, his chosen country of residence and vocation, his forename initially became "gallicized" to Christian, and subsequently "castillianized" to Christofredo. Jakob left 50 books and 260 papers spanning from macroscopic and cellular neuroanatomy to developmental and evolutionary neuroscience and human neuropathology. Some of his landmark contributions pertain to the onto-phylogeny of the cerebral cortex [3], the emotional brain [4, 5], cortical dynamics and cognition [6–8], the neuroanatomy of language [9, 10], neurophilosophy [11], and neuroeducation [12].

Like numerous other classical neuroscientitsts, Jakob also became interested in the cerebellum. During his early years in Erlangen and Bamberg, Jakob [13, 14] had already written critiques of Frédéric Courmont's book "The cerebellum and its functions," published in Paris in 1891, and of the German edition of Ramón y Cajal's "Contribution to the study of the medulla oblongata, the cerebellum and the origin of cranial nerves," published in Leipzig in 1896.

Decades later, at the initiative of the neurologist Vicente Dimitri (1885–1955), founder and editor-in-chief of the "Neurological Review of Buenos Aires," the young Society of Neurology and Psychiatry of Buenos Aires held a special series of sessions, in December 1938, to mark the successful term of Gonzalo Bosch (1885–1967) as its president for 1937–1938. The themes of the sessions were cerebellar pathology and presenile dementia. Jakob, at 72, was invited to open the series. He delivered his lecture, focusing on the cerebellar system.

In the timeline of cerebellar research, in the period between 1912 and 1962, only a couple of landmark discoveries are generally highlighted: the identification in 1937 by Olof Larsell (1886–1964) of the cerebellar lobules and fissures [15], that later became his widely recognized and unique nomenclature in birds and mammals [16, 17], and the documentation between 1938 and 1940 by Giuseppe Moruzzi (1910–1986) of the role of the cerebellum in modulating cardiovascular activity [18].

It is during that time that Jakob, in his lecture, presented the culmination of a lifetime of neurobiological research. He began with a brief overview of the known facts on the cerebellar tracts and the connections with the frontal, temporal, and occipital lobes. Prompted by his methodological emphasis on ontogeny, phylogeny, histophysiology, and neuropathology, Jakob presented both his own observations and a timely update on the much debated question of cerebellar function. The lecture transcript was expanded and published in two different journals [19, 20], after having added the illustrations (Fig. 1).

That event offered Jakob an opportunity to revisit the evolution of his own ideas on cerebellar structure and function, from his first atlas of clinical neurology [21–24] (Fig. 2), through his early lectures to medical students on the anatomy and physiology of the nervous system and the cerebellum in particular [25], to the larger atlas of the human brain [26] (Fig. 3) and the anatomic pathology of clinical cases of ataxia [27–30]. As a matter of fact, a distinct form of lower bilateral ("bibasal") cerebellar degeneration combined with dementia was given the name "Jakob type" by Aranovich [31], based on morphological criteria; it was identified in 15 of 31 cases of cerebellar atrophy in women over 50 years old. The lesions involved a loss of Purkinje cells, originating in the depth of the horizontal fissure (aka *le grand sillon circonférentiel* of Vicq d'Azyr), with a striking separation of its lips, and progressing through the destruction of neighboring lamellae and an atrophy of the subjacent white matter and the middle cerebellar peduncles.

For Jakob, structure and function in biology were one. Thus, he consistently approached neuromorphology in a functional context. This is the principle that guided him in his theorizing about the integrative function of the nervous system. Jakob considered form as "…*stabilized function*…" and function as "…*change of form*…". He insisted upon "the vital energy of an organism being a single entity, which will present

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EL SISTEMA CEREBELOSO Y SU SIGNIFICACION BIOLOGICA (*)

POR EL

Prof. CHR. JAKOB

Al publicar en el año 1895 mi primer atlas del sistema nervioso (**), terminaba la exposición acerca de la organización cerebelosa con la siguiente constatación: "no sabemos, actualmente, nada con certeza sobre su organización", y sin embargo, ya en los remotos tiempos de Aristóteles y de Galeno, se conocía la existencia del cerebelo como también lo grueso de su configuración. De Malacarne, y sobre todo de Willis, llegaron a nosotros nociones de su morfología (pedúnculos, árbol de la vida, etc.); de Vieussens, del cuerpo dentado; de Vicq D'Azyr, de su configuración interior; de Tarín, las válvulas que llevan su nombre; De Burdach, el núcleo rojo y de Reil las comisuras y entrecruzamientos. Estos últimos autores describieron con gran prolijidad, a principios del siglo pasado, la topografía macroscópica de sus centros y vías.

Con Purkinje comienza el estudio de su histología, quien en 1837 descubre sus células eferentes. Stilling, más tarde, examina sus ganglios centrales, pero es recién con Kölliker y con Ramón y Cajal que llegamos al período clásico de la histología fina cerebelosa, en tanto que por otro lado, Flechsig, Bechterew, Dejèrine y sus discípulos investigan la sistematización de sus vías.

Basado en estos hechos conocidos, al finalizar el siglo pasado, resumí en la obra citada la organización biológica del cerebelo en la siguiente forma:

"El cerebelo ejerce, indudablemente, una influencia sobre la coordinación estática y la conservación del equilibrio del cuerpo erguido y en la marcha". "Recibe para ese fin, por las vías centrípetas, estímulos musculares (también tactiles y otros de la periferia)". "Por los cuerpos restiformes, pasan vías procedentes de los núcleos cordonales posteriores que van al cerebelo, como así también, llegan a este órgano, el haz cerebeloso lateral (de función desconocida) y fibras de los nervios vestibular y trigémino (sistema directo sensorial cerebeloso)".

(*) Comunicado a las sesiones extraordinarias de la Sociedad de Neurología y Psiquiatría. (Diciembre de 1938).

(**) Chr. Jakob: Atlas del sistema nervioso normal y enfermo, 1895.

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Al publicar en el año 1895 mi primer atlas del sistema nervioso (**) terminaba la exposición acerca de la organización cerebelosa con la siguiente constatación: "no sabemos, actualmente, nada con certeza sobre su organización", y sin embargo, ya en los remotos tiempos de Aristóteles y de Galeno, se conocía la existencia del cerebelo como también lo grueso de su configuración. De Malacarne, y sobre todo de Willis, llegaron a nosotros nociones de su morfología (pedúnculos, árbol de la vida, etc.); de Vieussens, del cuerpo dentado; de Tarín, las válvulas que llevan su nombre; de Burdach, el núcleo rojo y de Reil las comisuras y entrecruzamientos. Estos últimos autores describieron con gran proligidad, a principios del siglo pasado, la topografía macroscópica de sus centros y vías.

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(*) En las postrimerías de la laudable y eficaz presidencia del Profesor Gonzalo Bosch (período 1937 - 38), la Sociedad de Neurología y Psiquiatría de Buenos Aires ha celebrado una serie de reuniones extraordinarias (Diciembre de 1938) tratando como tema especial —además de las demencias preseniles— la patología del cerebelo. Como cada uno de los trabajos presentados por los relatores han sido extensos y algunos de ellos acompañados de abundantes e interesantes demostraciones iconográficas, lo que no permitió detenerse mayormente sobre ellas, dada la brevedad del tiempo, en el acto de la sesión, creímos necesario y de utilidad reproducir la serie de estos trabajos en el presente número y en el próximo de nuestra revista, siguiendo el orden en que fueron expuestos. No dudamos aportar con esta colaboración una interesante información sobre el tema, pues la originalidad de algunos de estos relatos, se alterna con el interés de los otros, que tratan el asunto exponiendo casuística en general, observaciones personales o poniendo al día la tan debatida cuestión de la función cerebelosa. — *La Dirección.*

(**) *Chr. Jakob:* Atlas del sistema nervioso normal y enfermo (1895).

Fig. 1 The transcript of Jakob's lecture was published in the "Journal of the Argentinian Medical Association" and in the "Buenos Aires Neurological Journal" [19, 20]

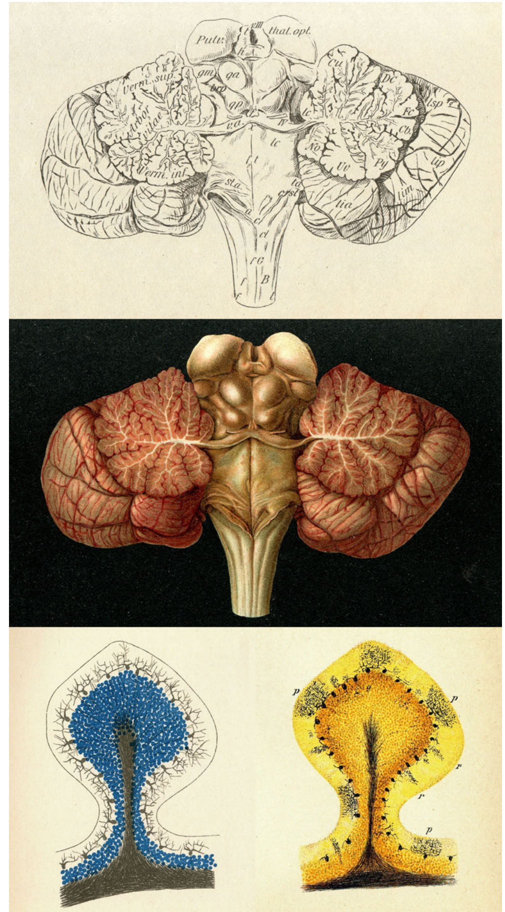

Fig. 2 *Upper and middle row*, the human brainstem and rhomboid fossa seen from above. The vermiform process of the cerebellum is divided by a sagittal section, exposing the fourth ventricle. The floor of the ventricle is formed by the rhomboid fossa, which contains the ala cinerea *(a)*, calamus scriptorius *(c)*, and funiculi teretes *(f.t)*. Locus coeruleus *(lc)*; posteriorly on either side are the restiform bodies *(c.rst)* and the tuberculum acusticum *(ta)*. At the entrance of the aqueduct of Sylvius, covered by the anterior medullary velum *(v.a)*, and frenulum *(f)*, is the trochlear nerve *(IV)*. In front of the rhomboid fossa lie the corpora quadrigemina: corpus quadrigeminum anterius *(qa)* and posterius *(qp)*, and the medial geniculate body *(gm)* receiving the posterior brachium *(brp)*. In front of the corpora quadrigemina are the optic thalami *(thal.opt)*, the posterior segment of which has received the name pulvinar *(Pulv.)*, and between them the ganglion habenulae *(h)* and the taenia thalami *(t)*. The epiphysis has been removed from its pedicle. Third ventricle *(vIII)*. Behind the rhomboid fossa: columns of Goll *(f.G)* and Burdach *(f.B)*; lateral column of the spinal cord *(f.l)*; the nuclei of the columns of Goll unite above to form the clavae *(cl)*. In the vermiform process of the cerebellum: *lc*, lobulus centralis; *Cu*, culmen; *Dc*, declive; *Fc*, folia cacuminis; *Cb*, commissura brevis; *Py*, pyramis; *U*, uvula; *No*, nodulus; *lsp*, lobulus superior posterior; *lip*, *lim*, *lia*, lobulus inferior posterior, medius, anterior. From the second edition of Jakob's atlas of clinical neurology, plate 10 [23]. *Lower row*, the structure of the cerebellar cortex in two variants drawn by Jakob, based on silver impregnation preparations, for the first *(left)* and the second *(right)* edition of his atlas of clinical neurology (plate 16, Fig. 4 [21], and plate 20, Fig. 2 [23], respectively). *Lower left:* The white matter (*black*) is narrow. Close to it is the granule cell layer *(zona granulosa)* of the cerebellar cortex, on the borders of which are the large Purkinje cells. Their ramifications form, as well as those of other myelinated fibers, the molecular layer *(zona molecularis)* of the surface. Then comes the closely apposed pia covering (not shown). A portion of cells in the granule cell layer (not shown) have short branches of the Golgi type. *Lower right:* A cerebellar convolution. A few isolated fibers from the narrow white matter (*black*) can be seen passing, through the granule cell layer, to the cortical layer proper, which is also very narrow. At the foot of the cortical layer, we see a row of Purkinje cells *(P)* with their elaborate arborizations; a few mossy-like fibers *(r)* and some individual granule cells *(g)* are shown

itself as form in the latent state and as function in the kinetic state" [32]. He kept repeating that "…*form, structure and function are inseparable, if not identical. It is only scholastic science that has managed to separate them. Only a basis that is fundamentally biological, morphostructural and histophysiological at the same time, unified in an ample ontogenetic and phylogenetic context, can let us address in legitimate ways the serious questions of modern neuro- and psychobiopathology…*" [33].

The "triple-synthesis" (evolutionary, developmental, and histophysiological) has been viewed as one of Jakob's prime

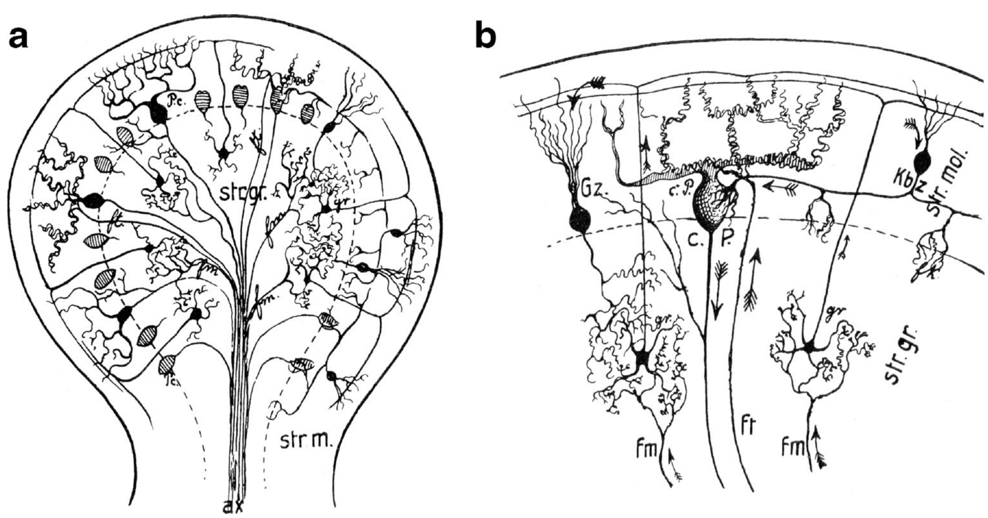

Fig. 3 Schematic drawing of the histological structure of the cerebellar cortical layers: nerve cells and their afferent and efferent connections. From Jakob's large atlas of human neuroanatomy [26]

contributions to neurobiology [34–36]. Already in his early Atlas, Jakob [21, 23] had laid out his plan to study the brain; the approaches he considered meaningful to understand the nervous system were: (1) histological staining and serial section reconstruction of the adult human brain, (2) neuropathological changes and their sequelae, (3) comparative neuroanatomy and neuroembryology, (4) human brain development and myelination, and (5) experimentally induced lesions in animals. Thus, in his cerebellar lecture, Jakob remains faithful to his early methodological paradigm.

After crediting, in his introductory statement, historical personalities for their cerebellar discoveries, he details in greater depth the advances made in cerebellar neurobiology during the preceding 50 years, from Ramón y Cajal's discovery of the detailed cerebellar circuitry in 1888 [37] through Jakob's personal observations on cerebellar ataxias during the late 1930s. He divides cerebellar histophysiology into three evolutionary morphofunctional stages, according to the same scheme that he had proposed for cerebral cortical dynamics, that is, archi-, paleo-, and neo-neuronal organization. He highlights the connectivity between the cerebellum and mesencephalic, diencephalic, and telencephalic structures, and he places the cerebellum, along with the cerebral cortex and the striatum, among the nervous centers that conclude their maturation postnatally (the phenomenon we today refer to as "neoteny"). With regard to cerebellar dynamics, he underlines the "…*multiplying*…" role of the granule cells in the dynamics of the cerebellar cortex, a good two decades before the excitatory action of L-glutamate as a neurotransmitter was even discovered [38]. He similarly mentions the accumulated impulses arriving from "…*central*…" structures via the climbing fibers. He also talks about the concept of *neurodynamic economy*, a principle that Ramón y Cajal [39, 40] had introduced in his classical monographs on the nervous system by formulating the *laws of the economy of conduction time*, *of saving cellular material*, and *of the economy of space* in attempting to explain axonal and dendritic relationships.

In the phylogenetic context, Jakob analyzes neocerebellar structure and function as it appears in humans and other primates, as well as in dolphins, whales, and elephants. These latter mammals had been in the epicenter of cerebellar research by some classical neurologists [41–43]. Moreover, Jakob's comprehensive model of the gnoses and the praxes, which he had already discussed decades earlier [7], involves cortical, striatal, thalamic, and mesencephalic influences, including the red nucleus. To our day, the function of the cerebrorubral, the cerebellothalamocortical, and the corticorubral-olivary loop systems, and their convergence at the meso-diencephalic junction constitute one of the main questions of cerebellar neurobiology [44].

With a brief reference to cerebellar ontogeny and myelination, Jakob subsequently discusses in detail the afferent, efferent, and associative pathways in the archicerebellar, paleocerebellar, and neocerebellar systems, concluding with the following principle: "…*The cerebellum is responsible for the individual mentality of the conscious human elaborating gnoseopoiesis and praxiopoiesis. These two circuits create the gnoseopraxical associative cortical systems, a framework of the dynamic workings of the human cerebral cortex*…" [2].

Based on the phylogenetic division by Ludwig Edinger (1855–1918) of the cerebellum into paleocerebellum and neocerebellum, Jakob carried on with his own studies on cerebellar morphofunctional phylogeny; he distinguished three evolutionary stages in the perfection of the cerebellar influence on motor acts and emphasized the fact that the structure of the cerebellar cortex stays the same throughout the entire phylogenetic scale. He noted the reduced cerebellospinal connections in humans, compared to other primates, as a consequence of the perfection of the rubrolenticular and thalamocortical systems and the intense ascending pathways to the red nucleus in exchange for the more elementary descending efferent pathways.

A clarification is in place. The book reviewer of the *American Journal of Insanity* (*American Journal of Psychiatry* today) criticized Jakob for attributing mental functions to the cerebellum, not purely motor coordination functions:

> …A few paragraphs are also obscure in their meaning, as, for instance, the fifth one on page 66, in which the declaration is made that …*a study of the development of foetal and childish psychic activity affords an approximate idea of the character of conscious processes in the cerebellar cortex*… Unfortunately we do not know what the function of the cerebellum is, and hence it is idle to write, even as an hypothesis, of psychic activity therein… [45].

Such confusion was brought about by an error in the translation. In the German original, Jakob mentions *Grosshirnrinde* (cerebral cortex), which was inadvertently rendered as *cerebellar cortex* in the English translation. Even the neurologist Henry H. Donaldson (1857–1938) had raised criticism about several aspects of the English translation of the atlas [46].

Since the cerebellum was first mentioned by Aristotle in the fourth century B.C. in *De Partibus Animalium* [47], its function has been on of the major concerns in neurology. Over the past 200 years, physiologists shed light on cerebellar functions. Pierre Flourens (1794–1867) made the fundamental observation that "…*all movements persist following ablation of the cerebellum*……", suggesting that the cerebellum is responsible for coordinating movement. In 1837, Jan Evangelista Purkyně (1787–1869) discovered the "Purkinje" cells. These large cerebellar projection neurons with their profusely branched dendritic trees were apparent in the entire extent of the folial gyrations [48]. Purkinje cells constitute the efferent system from the cerebellar cortex to the cerebellar nuclei—a discovery made in 1897 by Klimoff in Kazan, Imperial Russia [49–51].

Toward the end of the nineteenth century, Luigi Luciani (1840–1919), through improved operative techniques, mentioned three cardinal signs: asthenia, atonia, and astasia as the permanent effects of cerebellar lesions. The unitary concept that the cerebellum acted as a whole was supported by the histological studies of Ramón y Cajal [52, 53] and the view of Sir Charles Sherrington that "…*the cerebellum is the chief coordinative system of the proprioceptors, the head ganglion of the proprioceptive system*…" [54, 55]. Ramón y Cajal, besides his immense contribution to neuroscience with the neuron theory, also discovered, using the Golgi method, the mossy and climbing fibers [56]. After three years of intense work, Ramón y Cajal succeeded in deciphering the organization of the cerebellar circuitry [57, 58].

Neurobiologists have since continued to systematically delve into cerebellar circuits, contributing several new perspectives regarding its function [59–61]. While in the past the cerebellum was considered solely a regulator of movement coordination, today there is general agreement that it works in concert with regions throughout the cerebral cortex involved not only in movement, but also in emotional, language, and higher cognitive functions [62]. This broad conceptual shift emerged from converging evidence across multiple research domains, but only came to fruition with the introduction of non-invasive neuroimaging methods. Studies conducted using positron emission tomography and magnetic resonance imaging have demonstrated localized cerebellar activation, albeit unexpectedly at first, during a variety of cognitive tasks [63–67], providing a basis for expanding our understanding of its functional repertoire (for recent historical overviews, see Buckner [68] and Koziol [69]). A meta-analysis summarizing results across dozens of cognitive neuroimaging studies provides an overview of this breadth, implicating cerebellar lobules in spatial, language, working memory, emotional, and executive functions [70].

The heterogeneity of functions attributed to cerebellar areas stands in contrast with its consistent cytoarchitectonic organization, indicating that other structural factors such as connections with the cerebral cortex account for its functional diversity. Jakob hypothesized the convergence of cerebellar pathways in associative cortical regions, insisting on the "…*intimate collaboration* [of the cerebellum] *with the frontal lobe*…" [19, 20]. Mapping cortico-cerebellar connectivity, however, poses a distinct challenge due to the indirect projections between these structures. Extensive tract-tracing studies in the macaque monkey have mapped the topographic distribution of connections from cerebral association cortex to the pons, as it provides an anatomical junction for afferent connections to the cerebellum [71–75]. The circuit was further described using transsynaptic viral tract-tracing for mapping projections, which revealed projections from the dentate nucleus to prefrontal areas [76, 77] as well as a closed-loop circuit between Brodmann's middle frontal area 46 (or granular frontal area F*D* of Economo and Koskinas) and Crus II [78, 79]. These extensive lines of communication between regions throughout association cortex substantiate Jakob's intuition, and begin to outline the mechanisms for substantial cerebellar involvement in functions beyond the motor domain [80, 81]. Precise understanding of the extent of cerebellar connections with association cortex remains beyond the scope of these gold-standard, but challenging, techniques.

A recent methodological development from non-invasive neuroimaging—resting-state functional connectivity—has provided further insight into the distribution of connectivity between the cerebellum and association cortex. This approach is founded on the observation that regions which are co-activated during task performance also synchronize in the absence of externally driven task demands [82, 83]. Of critical importance for investigating cerebellar connectivity, this technique is largely consistent with underlying structural projections [84–86], but additionally appears capable of capturing patterns of polysynaptic connectivity with high spatial precision. As early as 2005, the potential for this methodology to be applied to mapping cerebellar-frontocortical connectivity was demonstrated [87]. Numerous studies have since confirmed the widespread functional connectivity between the cerebellum and association cortex [88–93]. One landmark discovery of this line of research is the observation of multiple topographic maps of association cortex within the cerebellum, appearing as a continuation of the somatomotor representations present in the anterior and posterior lobes [94]. The surface area of the cerebellar cortex devoted to each cerebral network also generally corresponded, providing support for the co-expansion of neocerebellar and association regions. Understanding the topographic principles of cortico-cerebellar interaction provides a foundation for future research into the complex dynamics that give rise to higher-order processing.

The cerebellum plays an actual role in driving higher-order brain function. In the rat, it modulates the prefrontal cortical activity [95]. In the clinical setting, the cerebellar circuitry seems to be involved in cognitive conditions, including autism spectrum disorders [96]. Moreover, abnormalities within the cerebellar vermis are detected in diseases such as schizophrenia and epilepsy.

Owing to these diverse lines of research, the question of whether the cerebellum contributes to cognitive function has been superseded by the investigation of how it contributes [69]. How can the role of the cerebellar circuitry in motor processing be extrapolated to cognitive domains? What is the mapping of connections between the association regions of the cerebral cortex and the cerebellum? How does this extensive cortico-cerebellar topography converge with dynamic mechanisms in a neurocognitive theory of cerebellar function? We thus find ourselves at a comparable vantage point, where, atop a foundation of anatomical and phylogenetic mastery, Jakob himself posed similar questions eight decades ago.

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Conflict of Interest The authors declare that they have no conflict of interest.

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