Chapter 6
Cerebellar Disorders: At the Frontiers of Neurology, Psychiatry, and the Modern Approach to Psychology

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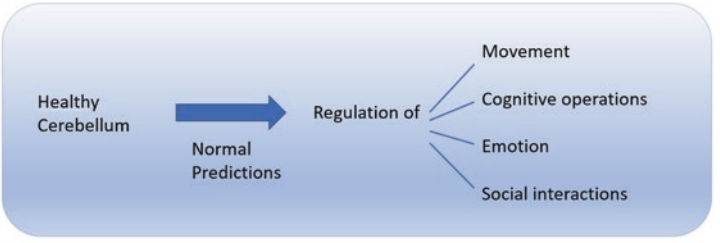

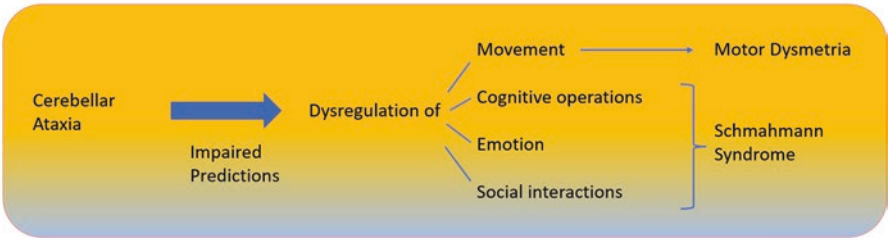

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Abstract Cerebellum contributes to numerous motor and non-motor functions, optimizing motor skills and contributing to a wide array of behaviors. This is not surprising if one considers that the cerebellum contains about 60% of the brain neuronal population and on the basis of the topographically organized communication in multiple segregated cerebello-cerebral loops running in parallel between the cerebral cortex, brainstem, cerebellum, and thalamic nuclei. It is also now established that cerebellum communicates directly with the basal ganglia through disynaptic connections. Cerebellum plays a critical role in forward models allowing anticipation. Indeed, cerebellar machinery is a critical CNS structure to perform motor predictions related to body dynamics and to environmental changes. These predictions not only apply to motor acts but are also involved in cognitive/affective/social operations and are likely a substrate in the rise of *Homo sapiens* as underlined by Vandervert. Cerebellar cortex shapes cerebellar nuclei discharges by a mechanism of inhibition/disinhibition and interacts closely with the inferior olive through multiple olivo-cortico-nuclear modules. After two centuries of clinical observations showing a considerable variability in the semiological expression of cerebellar disorders, the field of clinical ataxiology is now based upon three groups of cerebellar symptoms gathered in a cerebellar motor syndrome (CMS), a vestibulocerebellar syndrome (VCS), and the Schmahmann's syndrome (SS/CCAS: cerebellar cognitive affective syndrome). All these clinical deficits can be grasped as the consequences of impaired predictions leading to a common denominator: dysmetria. Thanks to the numerous forms of plasticity and its anatomical property of redundancy, the cerebellum is highly reconfigurable. This feature should be exploited to reduce the neuropsychological, neurological, and psychiatric burden of cerebellar disorders, both for prevention and therapeutic approaches.

Scheme of the Consequences of a Cerebellar Lesion Upon Motor, Cognition, Emotion, and Social Interactions

Must-Read Quick Overview for All Students

Cerebellar circuitry has attracted researchers for many centuries. The geometrical arrangement of cerebellum is unique, made of a repetitive configuration. It was originally supposed that the cerebellum is a pure motor coordinator, but it is now established that its roles extend to cognitive operations, linguistic skills, affective regulation, and social interactions. This has huge impacts for the daily management of all the disorders affecting the cerebellum. Brain can be compared to your bank account in terms of number of neurons. The cerebellum would represent the majority of the money in this account. You understand why the research interest in the understanding of cerebellar circuitry has grown exponentially. In this chapter, you will follow the history of cerebellar research and the milestones achieved during 250 years of research. You will learn how the cerebellar circuitry is connected with cerebral cortex, how the semiology is currently applied in the clinic, and the

importance of a multidisciplinary approach. Once you have put a foot in the understanding of the secrets of cerebellar circuitry, you will understand why cerebellar researchers are fascinated by this part of the brain.

History of the Cerebellum and Cerebellar Disorders

The cerebellum has been a subject of interest for centuries. It was initially suggested that it conveyed strength to motor nerves (Galen) and was a center of memory (Albertus Magnus) or a center controlling cardiovascular activities (Thomas Willis) (Schmahmann, 2016a, b). In the early 1800s, Gall, the creator of phrenology, argued that cerebellum was the area of self-preservation of the species (Gall & Spurzheim, 1809).

Vicq d'Azyr (1786) depicted the gross anatomy of the cerebellum, and Malacarne (1776) was the first to provide a detailed description of the human cerebellum. He described cerebellar foliation and used the terms vermis, lingula, pyramid, and tonsils, which are used nowadays. Malacarne suggested that the number of cerebellar folia was influenced by the environment, providing the first step in our current understanding of neuroplasticity (Zanatta et al., 2018). He quantified the number of cerebellar folia to about 600 laminae. He presumed that cerebellum was related to intelligence.

Historically, the studies of Rolando (1809) were decisive since they demonstrated a link between cerebellum and motor control. Rolando performed ablation of the cerebellum in animals and observed abnormal posture and erratic movements. Rolando was aware of the experiments of Galvani (1780s) on "animal electricity" (Galvani thought of a fluid secreted by the brain) and Volta (1799: a battery based on pairing of silver and zinc plates separated by brine-soaked paper disks). For Rolando, a part of the brain should work as a battery and should be constituted of overlapping disks (Coco & Perciavalle, 2015). The cerebellum seemed the right structure given its characteristic overlapping laminae. Rolando presumed that, if the cerebellum is the battery that produces electricity for muscle activity, its removal would produce paralysis: "Qual maggior prova per dimostrare, che dal suddetto viscere si separa un fluido analogo a quello, che dallo strumento citato si sviluppa? Qual più retta conseguenza, se esportato guasto o distrutto il cervelletto cessa ogni influsso del fluido nerveo nei muscoli destinati alla locomozione?" (What most evidence to prove that the said organ generates a fluid similar to that which develops from the mentioned device? What most direct consequence if removed, destroyed, or spoiled the cerebellum ceases any influence of the nervous fluid on the muscles for locomotion?) (Coco & Perciavalle, 2015). Rolando removed the cerebellum in a young goat and observed that the animal could no longer stand up "non altrimenti che se fosse paralitico" (not otherwise than if it was paralyzed). Rolando made thus for the first time the link cerebellum-electricity-motor activity. Fodera (1823) assessed in particular the effects of cerebellar lesions in pigeons and guinea pigs. He confirmed the role of the cerebellum in the control of postural tone. Flourens (1824)

was probably the first scientist underlining that the cerebellum was critical for coordination of movements: “dans le cervelet réside une propriété dont rien ne donnait encore l’idée en physiologie, et qui consiste a ordonner ou coordonner le mouvements voulus par certaines parties du système nerveux, excités par d’autres” (in the cerebellum lies a property which nothing still gave the idea in physiology, that is to put in order or to coordinate movements wanted by certain parts of the nervous system, excited by others) (Flourens, 1824). At the same period, Magendie pointed out that a key function of the cerebellum is the control of equilibrium. In 1891, Luciani (1891) formulated a set of cerebellar symptoms: atonia, asthenia, astasia (the three symptoms forming Luciani’s triad), and added later dysmetria (Manni & Petrosini, 1997). He stressed the role of the cerebellum in regulation of postural tone and muscle strength. He denied wrongly the contribution of the cerebellum in coordination.

In terms of cellular organization, Purkyné (1837) reported the Purkinje neuron and at the beginning of the twentieth century, and both Golgi and Cajal reported the first detailed report of the cellular organization of the cerebellar cortex. Mossy fibers, glomeruli, climbing fibers, and parallel fibers were reported, establishing the fundamentals of cerebellar microcircuitry.

At the beginning of the twentieth century, Holmes provide detailed reports of the consequences of cerebellar injuries on clinical deficits. In particular, he examined injured soldiers during the first World War. The injuries to the occipital region and the cerebellum were common due to poorly designed helmets (Haines, 2016). He insisted on the motor consequences of a lateral cerebellar lesion, with a disruption of movements ipsilaterally. He noted that lesions restricted to the cerebellar cortex tended to recover more quickly than lesions involving cerebellar nuclei. He also found that hypotonia could be observed in large cerebellar injuries. Holmes pointed out the importance of dysmetria (movements wrongly proportioned) and subdivided this core symptom into hypermetria (excessive movement) and hypometria (premature arrest). He provided a detailed observation of the rebound phenomenon (failure of the antagonist muscles to stop the limb) and diadochokinesia (alternate movements). He also reported on intention tremor. Babinski described asynergia and was probably the first to report on diadochokinesia, before Holmes.

Studies of Jansen and Brodal led to the subdivision of the cerebellum into a medial zone (vermis/fastigial nucleus: control of posture and gait), an intermediate zone (paravermal cortex/nucleus interpositus: control of skilled movements of the ipsilateral limb), and a lateral zone (hemispheral cortex/dentate nucleus: control of skilled and fast movements of the ipsilateral limb). Larsell’s work has led to a coherent terminology of lobes and lobules (I–X), which is widely used today (Haines, 2016). With the identification of the primary fissure and the posterolateral fissure, he delineated the anterior lobe (lobules I–V) from the posterior lobe (lobules VI–IX) and the posterior lobe from the flocculo-nodular lobe (lobule X). Crus I and Crus II correspond to the superior and inferior semilunar lobules, respectively. Larsell emphasized the mediolateral continuity of the lobules of the vermis and hemispheres (Voogd & Marani, 2016). Voogd (1964, 1969) demonstrated that the cerebellum is organized into parasagittal zones (vermis, zones A and B; paravermis,

zones C1–C3; hemispheres, zones D1 and D2). While the lobules are formed by the structural foliation of the cerebellar cortex, stripes are formed by the longitudinal distribution pattern of Purkinje cell subsets of given molecular expression profiles (Sugihara, 2021). Indeed, Purkinje neurons are heterogeneous in terms of molecular expression, as shown by the striped distribution of aldolase C (zebrin II). Stripes arise from a reorganization of embryonic Purkinje cell clusters, with both afferent (climbing fiber axons, mossy fiber axons) and efferent (Purkinje cells) axonal projection patterns being tightly correlated to the organization in both lobules and stripes in the cerebellar cortex (Sugihara, 2021). In other words, lobules and stripes frame the topography of axonal projections.

In the 1960s, Eccles reported the precise neuronal connectivity in the cerebellar cortex and Ito discovered that the projection from Purkinje neurons to cerebellar nuclei was inhibitory. Climbing fibers were found to provide a very powerful excitatory synaptic input to Purkinje neurons, resulting in action potentials known as complex spikes, whereas simple spikes (which can be considered as regular action potentials) are generated intrinsically and following mossy fiber-parallel fiber inputs.

In the years 1940s and 1950s, autonomic hypothalamic outburst and rage-like behavior following electric stimulation of the cerebellum. Prescott (1970) suggested that the cerebellum is involved in emotion. Heath investigated the influence of the cerebellum on the activity of the septal region, hippocampus, and amygdala of cats and rats (Heath et al., 1978). Stimulation of the vermis, fastigial nucleus, and midline folia of the cerebellum facilitated units in the septal region and inhibited the hippocampus, potentially suggesting specific types of cerebellar simulation in the treatment behavioral disorders and epilepsy.

Around 1970, Marr (1969), Ito (1970), and Albus (1971) have conceptualized the computational principle of the cerebellum, referred as the Marr-Albus-Ito model (Yamazaki, 2021). The hypothesis is based on two major assumptions:

– Mossy fibers project to granule cells which encode the signals and distribute processed messages to Purkinje neurons.
– Climbing fibers adjust the strength of granule cells-Purkinje neurons synapses (see also plasticity below).

According to this model, the inferior olive is the source of error signals conveyed by the climbing fibers in order to drive learning mechanisms.

The current leading theory is the theory of internal models. Because of the inevitable delay in reaching the brain, the sensory feedback information cannot be processed online: the brain always observes the past state of the body (Tanaka et al., 2021). By a simulation of the skeletomuscular physics (internal model), the brain can control movements without relying on the peripheral feedback (Wolpert et al., 1998). Numerous psychophysical findings support the hypothesis that the CNS uses internal models (Ebner, 2013). A typical example is the change in grip forces anticipation during manipulations of object load with slippage. Compensatory actions occur without delay, implying an absence of sensory feedback from the hand for an immediate adaptation. The CNS acquires internal models predicting the trajectory of the hand. Another example showing that the CNS adapt and retains novel motor

patterns is the adaptation of reaching movements to environmental changes in a force field and the subsequent aftereffects in absence of exposure to the field (Shadmehr & Mussa-Ivaldi, 1994).

The concept of internal model can be applied to cognition, affective behavior, and social interactions (Koziol et al., 2014; Ito, 2008). Cerebellum might encode internal models reproducing the essential properties of mental representations in the cerebral cortex (Ito, 2008). This would represent a mechanism by which intuition and implicit thought might function (see this volume). Both forward and inverse internal models of thought would be embedded in the cerebellum (Ebner, 2013). The forward model would represent the control of mental models/representations performed by the prefrontal cortex. The cerebellar machinery would generate the signals needed to manipulate an object. The implementation of a mechanism allowing predictions has likely played a prominent role in the evolution of culture, language, and stone-tools use, which are at the essence of *Homo sapiens* behavior (Vandervert, 2018).

Topography of Cerebellar Inflow/Outflow Tracts and Modern Imaging

Cerebellum is highly connected with the spinal cord, vestibular system, brainstem, basal ganglia, and cerebral cortex. Multiple pathways convey information from the body to the cerebellum (Ruigrok, 2016). Spinal pathways can be subdivided into (a) systems that will end as mossy fibers and (b) systems that reach the cerebellum via the inferior olive and will end as climbing fibers (Ruigrok, 2016). Spinocerebellar tracts target the anterior lobe of the cerebellum and lobule VIII (Oscarsson, 1965), which correspond to the sensorimotor cerebellum; Snider and Stowell (1944) had initially observed in animal responses in discrete regions of the cerebellar cortex, which were organized as follows: one map in the anterior lobe and two maps in the posterior lobe of the cerebellum (somatotopic organization with homunculi). The majority of neurons in inferior olive do not receive spinal projections and target the posterior lobe of the cerebellum. Cerebellar output toward the spinal cord is mediated by several routes, including the corticospinal, rubrospinal, tectospinal, vestibulospinal, and reticulospinal tracts (Ruigrok, 2016).

In addition to the pathways linking the cerebellum with the spinal cord, the cerebellum has also massive reciprocal connections with the cerebral cortex and subcortical structures, being part of multiple segregated loops running in parallel (Schmahmann, 2016a, b). The cerebrocerebellar projections are mediated in particular by the corticopontine and pontocerebellar tracts. Corticopontine projections arise from pyramidal neurons of layer V, especially Brodmann areas 4 and 6 according to studies in monkey (Glickstein et al., 1985). Projections from motor cortices and from the sensory cortex terminate preferentially in the caudal half of the pons.

Furthermore, the pons receives numerous projections from cerebral association areas (Schmahmann, 2016a, b):

- Prefrontal areas arising from dorsolateral and dorsomedial prefrontal cortices. Areas 8 (conjugate eye movements), 9/46 (spatial memory, working memory), 10 (planning and judgment), 9/32 (decision-making), and 44/45 (language) contribute also.
- Posterior parietal areas.
- Temporal lobe areas: superior temporal sulcus, superior temporal gyrus.
- Parastriate cortices and posterior parahippocampal gyrus.
- Cingulate areas.
- Anterior insular cortex.

The caudal pons is preferentially linked with the anterior lobe of the cerebellum, whereas the rostral pons is linked with the posterior lobe of the cerebellum. In other words, the anterior lobe (especially lobules IV–V) and lobule VIII (paramedian) receive afferents from pericentral motor and sensory cortices, and the posterior lobe (Crus I/II) receives afferents from cerebral association areas (Schmahmann, 2016a, b).

The cerebello-thalamo-cortical pathway (feedback limb) is arranged in a topographically precise manner. Cerebral association areas projecting to the cerebellum via the pons receive projections back via the thalamus, as showed by viral retrograde transneuronal transport experiments (Middleton & Strick, 1994). Cerebellar cortex projects to cerebellar nuclei with a mediolateral distribution. The anterior lobe and the dorsal dentate nucleus are linked with primary motor/premotor cortex, while the posterior lobe and ventral dentate nucleus are linked with prefrontal and posterior parietal regions (Dum & Strick, 2003). Thus, the dentate nucleus contains anatomically and functionally distinct motor and nonmotor domains. Cerebellar projections from cerebellar nuclei are directed to motor thalamic nuclei (VPLo, VL, nucleus X), ventral anterior nucleus, intralaminar nuclei, and medial dorsal nucleus.

In addition to the corticopontine projections, the inferior olive receives also indirect input from motor and associative regions of the cerebral cortex via the zona incerta and red nucleus (Schmahmann, 2016a, b). These signals will be conveyed to the cerebellar nuclei/cerebellar cortex through climbing fibers. The inferior olive is thus enrolled in loops linking cerebral cortex and brainstem nuclei with the cerebellum.

It is currently considered that cerebellum is composed anatomically of multiple modules. These correspond to a conglomerate of nonadjacent parasagittal bands of Purkinje neurons projecting to specific area of the cerebellar nuclei and gating segregated projections from the inferior olive; modules include assemblies of Purkinje neurons coherently active during some specific operations (D'Angelo & Casali, 2013). This modular organization subserves the multitude of activities of daily life.

Cerebellum is also connected reciprocally with the basal ganglia, the hypothalamus, and the limbic system (Schmahmann, 2016a, b; Maiti & Snider, 1975). The subthalamic nucleus projects to both motor and non-motor regions of the cerebellar cortex via the pons in a disynaptic projection, and dentate nucleus projects back in

a disynaptic path to the striatum via the thalamus (Bostan et al., 2010). There is now a consensus for a dynamic interplay between cerebral cortex and the two major subcortical structures: the cerebellum and basal ganglia likely interact directly, and both of them are linked to the cerebral cortex (Caligiore et al., 2017). An integrated network has emerged: the motor, cognitive and affective territories of each node are interconnected and might explain how abnormal activity at one node can have network-wide effects in neurological and psychiatric disorders (Bostan & Strick, 2018). Regarding hypothalamic nuclei, they project to the caudal third of pontine nuclei and also diffusely in the cerebellum (Aas & Brodal, 1988). Dentate nuclei project back to the contralateral hypothalamus. The mamillary bodies project to pontine nuclei and also directly to the anterior and posterior lobe of the cerebellum. A mamillo-pontocerebellar pathway has been demonstrated in cats, likely mediating learning and motivational processes (Aas & Brodal, 1989). Hippocampus, septal nuclei, and amygdala are also interconnected with the cerebellum. Overall, all these anatomical nodes form a complex network which allow the cerebellum to modulate parameters of movement, cognitive and affective processes, emotion, and autonomic control (Schmahmann, 2016a, b).

The advent of the 3D MRI atlas of the cerebellum has greatly facilitated the understanding of the contribution of the cerebellum in numerous sensorimotor tasks, updating Larsell's nomenclature toward a clinical use and allowing scientific applications of functional imaging (Schmahmann et al., 2000). The topography of the areas of the cerebellum involved in motor control, cognitive tasks, social tasks, and emotion is much better understood now (Stoodley et al., 2012). The cerebellum can be divided into areas depending on connectivity with sensorimotor versus multimodal association cortices. Finger-tapping activates ipsilateral cerebellar lobules IV–V and VIII, in agreement with descriptions of the cerebellar homunculi. Verb generation activates right cerebellar lobules VI–Crus I and a second cluster in lobules VIIB–VIIIA. Working memory tasks, which are essential for daily activities by holding finite amount of information in mind until no longer required, activate bilateral regions of lobules VI–VII (Marvel et al., 2019; see also this volume). Overall, overt movement activates sensorimotor cortices along with contralateral cerebellar lobules IV–V and VIII, whereas more cognitively demanding tasks activate prefrontal and parietal cortices along with cerebellar lobules VI and VII (Stoodley et al., 2012). Resting state connectivity studies and diffusion tension imaging (DTI)-based tractography have pushed our understanding of cerebellar networks one step further. However, DTI-based tractography still faces challenges in terms of spatial resolution, which prevents a full mapping of the corticopontocerebellar fibers (van Dun et al., 2016). The independent component analysis-based functional connectivity has demonstrated the following parallel cerebro-cerebello-cortical networks (Habas, 2016):

– The sensorimotor network: motor and premotor cortex, lobules V–VI and VIII.
– The right and left executive networks: dorsolateral prefrontal cortex, parietal cortex, and Crus I/II.

– The limbic salience network: frontal and insular cortices, lobules VI/VII. This network is implicated in interoception, emotions, and autonomic regulation.
– The default-mode network: dorsomedian prefrontal cortex, posterior cingulate cortex, retrosplenial and parahippocampal cortices, precuneus, and lobules VII and IX. This network is involved in consciousness, self-agency, memory, and mental imagery.

Plasticity of the Cerebellum and Cerebellar Reserve

At a cellular level, several forms of plasticity have been demonstrated in the cerebellar circuitry, a key feature underlying the learning properties and the reconfiguration potentialities of the cerebellar machinery. The concomitant low-frequency stimulation of parallel fibers and climbing fiber inputs induces an attenuation of the parallel fiber-Purkinje neuron synapse, called long-term depression or LTD (Ito et al., 1982). This plasticity is mediated in particular by glutamate receptors (mGluR, AMPA-R) and a rise of intracellular calcium. In addition, the parallel fiber-Purkinje neuron synapse is also the site of long-term potentiation (LTP), which is stimulus frequency-dependent. Plasticity occurs also at the level of GABAergic synapses such as the interneuron-Purkinje cell synaptic LTP (Hausser & Clark, 1997). Plasticity is also observed at the level of the mossy fiber-granule cell synapse and cerebellar nuclei (Shen, 2016).

The rich repertoire of plasticity mechanisms makes of the cerebellum a unique machinery contributing to the cerebellar reserve. The various cerebellar ataxias (CAs) encountered in clinical practice result from various lesions both in terms of location and mechanisms and present clinically with motor, oculomotor, and cognitive/affective/social deficits. Surprisingly, cerebellar deficits may recover remarkably, as pointed out by Holmes in 1917 (Mitoma & Manto, 2021). Cerebellar reserve is defined as the capacity for compensation and restoration consecutively to pathological lesions in the cerebellar circuitry. Both the enrichment in numerous forms of plasticity and the redundancy of cerebellar inputs are key features of cerebellar reserve (Mitoma et al., 2021). Mossy fibers conveying peripheral and central information run mediolaterally over a wide area of the cerebellum, resulting in the innervation of multiple adjacent microzones. Thus, a single microzone receives redundant information, a property that can be used in pathological conditions.

Cerebellar reserve contains two components: a structural aspect and a functional aspect. The *structural cerebellar reserve* refers to a compensation of a structural lesion in a given area of the cerebellum (for instance, in case of a cerebellar stroke, traumatic injury, local tumor, or abscess) by an unaffected area of the cerebellum: cerebellar structures located around the lesion or contralateral cerebellar hemisphere. The degree of reversibility of symptoms is assumed to depend on the extension of the lesion. Moreover, reversibility might be determined by the proximity of the area lesioned with the substitution area (Mitoma et al., 2020). If the backup structure is near the lesion, the capacity to restore the function might be decreased

(high-risk cerebellar reserve). The *functional cerebellar reserv*e designates a compensatory mechanism or a restoration process, which takes place within the lesion site as a result of a functional reorganization. This occurs for instance in case of degenerative ataxia, immune ataxias, or metabolic ataxias. It is well-known that intensive rehabilitation may promote functional restoration in degenerative disorders such as spinocerebellar ataxias. It is remarkable to note that motor recovery may be considerable in case of extensive cerebellar lesions, as shown for instance by the experimental model of hemicerebellectomy (Federico et al., 2006). However, a second lesion may trigger a decompensation. This has been reported experimentally for a subsequent lesion at the level of the sensory cortex (Mackel, 1987). Indeed, if the sensory cortex is removed secondarily to an initial cerebellar lesion and after a phase of recovery, the motor performance is much worse again. In addition, removal of the sensory cortex ahead of the cerebellar damage increases the cerebellar deficits and severely impacts on the recovery process, which follows a cerebellar damage. Extra-cerebellar structures participate in the relearning of lost cerebellar functions. Evidence of an interplay between the cerebellum and the sensory cortex exists also in human. Patients with a cerebellar stroke may fully recover and subsequently show a cerebellar decompensation caused by a stroke at the level of the posterior parietal association area (Manto et al., 1999).

The concept of cerebellar reserve is particularly relevant for neuropsychological, neurological, and psychiatric evaluation of cerebellar patients. It is now possible to assess the cerebellar reserve, thanks to psychometric tools, neuropsychological assessments, and advance imaging techniques. This is particularly pertinent for the follow-up of patients and from a therapeutic perspective (Mitoma & Manto, 2021). The development of novel tools based on the quantification of predictive mechanisms is promising (Mitoma et al., 2020).

The Three Cerebellar Syndromes

The current clinical view of cerebellar deficits considers that cerebellar symptoms can be gathered into three groups of symptoms:

- A cerebellar motor syndrome (CMS).
- A vestibulocerebellar syndrome (VCS).
- Schmahmann syndrome/cerebellar cognitive affective syndrome (SS/CCAS) (Cabaraux et al., 2021).

The common denominator of cerebellar deficits is dysmetria, encompassing both motor dysmetria and dysmetria of thought. Dysmetria is also observed in CAs in the domains of affective regulation and social behavior.

Cerebellar Motor Syndrome (CMS)

The cerebellar motor syndrome is typically observed in patients presenting lesions of the anterior lobe (lobules I–V). Patients with lesions of the lobules VI–X show relatively minor motor symptoms. There is a somatotopic correlation, which can be summarized as follows:

- Lesions of the vermal/paravermal lobules III–VI are correlated with ataxia of lower limbs.
- Lesions of vermal/paravermal/hemispheral lobules IV–VI are correlated with upper limb ataxia.
- Lesions of paravermal/hemispheric lobules V–VI are correlated with dysarthria.
- Lesions of the superior vermis (lobules II, III, IV) are correlated with ataxia of posture/gait (Schoch et al., 2006).

Regarding cerebellar nuclei, lesions of fastigial nuclei cause ataxia of stance/gait, lesions of the interposed nuclei/adjacent dentate nuclei are associated with limb ataxia, and lesions of the dentate nuclei trigger dysarthria/limbs ataxia. The typical presentation of stroke in the superior cerebellar artery (SCA) territory includes ipsilateral motor dysmetria, dysarthria, and gait ataxia/lateropulsion, usually in the absence of cognitive/affective deficits or in association with subtle cognitive dysmetria.

Vestibulocerebellar Syndrome (VCS)

Oculomotor deficits are often manifest in CAs. Patients exhibit various combinations of dysmetria of saccades, saccadic pursuit, impaired vestibulo-ocular reflex (VOR), deficits in fixation, and errors in vergence. Causal lesions are found at the level of the vermis and/or the flocculo-nodular lobe.

Schmahmann Syndrome/Cerebellar Cognitive Affective Syndrome (SS/CCAS)

Lesions of the posterior lobe are associated with a constellation of deficits in the executive functions, in visuospatial performances, in linguistic processing, and in regulation of affect (Schmahmann & Sherman, 1998). This is detectable during the assessment of working memory, ideational set shifting, perseverations, drawings, verbal fluency, and prosodia. Visuospatial sequences are particularly distorted, including for the conceptualization of figures. Patients with lesions in the territory of the posterior inferior cerebellar artery (PICA) or with vermian lesions often exhibit a flattening of affect, disinhibition, and impulsivity and often make

inappropriate comments. The general consequence is a lowering of intellectual functions, especially in case of bilateral and acute lesions. The spectrum of clinical deficits corresponds to a genuine link between neuropsychology, neurology, and psychiatry (Schmahmann et al., 2007). Following the report/identification of Schmahmann syndrome, the syndrome has been reported in a majority of cerebellar disorders, encountered in the clinic from sporadic ataxias to hereditary disorders, and is still likely overlooked in many patients (Argyropoulos et al., 2020).

The posterior fossa syndrome is an example of a severe Schmahmann syndrome occurring mainly in children after posterior fossa tumor surgery, even if cases may occur following trauma, infection, or stroke. Patients show a transient mutism associated with a combination of neuropsychological, neurolinguistic, and neurological motor symptoms. Daly and Love provided the first description in 1958 in a 14-year-old posterior fossa tumor patient who exhibited a clinical syndrome encompassing "akinetic mutism", cognitive, affective, and neurological deficits (Daly & Love, 1958). Rekate and colleagues were the first to point out a "muteness of cerebellar origin," now recognized as cerebellar mutism (Rekate et al., 1985). The authors reported a temporary loss of speech in six children with an acute bilateral damage to large areas of both cerebellar hemispheres, including the dentate nuclei. Muteness lasted 1–3 months. All patients were severely dysarthric during recovery. The sequence of events is the following: transient mutism occurs with a delayed onset of 0–15 days (mean of 2 days) and has a limited duration extending from 1 day to 2.5 years (mean of 43 days). Mutism is followed by dysarthria, hence the terminology of mutism and subsequent dysarthria. Preoperative symptoms often include various degrees of inattention, depression, irritability, impaired verbal fluency, slowed speech, motor ataxia, headache, and vomiting. The range of postoperative symptoms is wide (Marien & Manto, 2016). In particular, patients show irritability, apathy, stereotypies, bizarre behavior, and autistic traits. Obviously, there are strong similarities between Schmahmann syndrome reported in adults and the posterior fossa syndrome observed in children. The executive, visuospatial, affective, and linguistic domains are affected in both cases. Risk factors to develop the posterior fossa syndrome include the midline location of the tumor, brainstem extension, and tumor type. Cerebellar mutism is presumed to result from damage to dentate nuclei and/or the dentato-thalamo-cortical pathways. Midline tumors infiltrate local tissues and cause edema. The delayed onset of symptoms after surgery might be related to ischemia consecutively to surgical manipulation, vasospasm (vasospasm is a well-known complication of subarachnoid hemorrhage and typically starts from 3 days to 14 days after the bleeding), and diaschisis. Traction may cause axonal injuries or axonal distortions in white matter bundles as supported by MRI/DTI studies, and pons compression has been observed in several cases (Morris et al., 2009; McMillan et al., 2009). The resolution of symptoms might be related to a normalization of cerebellar blood flow (Marien & Manto, 2016). Recovery is rarely complete. Sequelae include motor ataxia, nystagmus, dysarthria, attentional problems, impaired verbal comprehension, affective symptoms, behavioral deficits, and cognitive dysfunction. Overall, patients are more likely to present obsessive-compulsive behavior, social difficulties, anxiety, and depression. The mean IQ tends

to be lower and academic achievement is often poor. Special education may be needed.

Social interactions are highly complex and are also under cerebellar control. CAs may exhibit an autistic-like aspect. Autism is a neurodevelopmental disorder characterized by impaired social interactions, difficulties of communication, and repetitive/stereotyped behaviors. The cerebellum is one of the sites of neurobiological changes in autism. Genetic studies and neuroimaging investigations point toward a key role of the cerebellum. Postmortem studies have demonstrated a reduction in the population of Purkinje neurons, especially in the posterior inferior portions (Bauman & Kemper, 2005). The posterior vermis contributes to behavioral regulation including mental flexibility (Schmahmann et al., 2007). Most animal models of autism show cerebellar abnormalities (Ellegood & Crawley, 2015). Strikingly, preterm infants with isolated cerebellar damage are 40 times more likely to be diagnosed with autism (Limperopoulos et al., 2007). The cerebellum modulates also the reward circuitry, which contributes to social behavior (Carta et al., 2019). The cerebellum sends direct excitatory projections to the ventral tegmental area (VTA), suggesting that cerebellar circuitry is an—so far unsuspected—actor of reward mechanisms. A larger striatum, a smaller cerebellum, and a smaller amygdala are all consistently found in autistic patients. In the limbic system, the hippocampus, amygdala, and entorhinal cortex show small cell size and increased cell packing density at all ages, indicating a pattern consistent with development curtailment. It is now established that lesions of the limbic cerebellum (vermis/fastigial nucleus) are associated with dysregulation of affect (Schmahmann et al., 2007). Premature infants with isolated cerebellar hemorrhagic injury show significantly lower mean scores in motor disabilities, expressive language, delayed receptive language, and cognitive deficits (Limperopoulos et al., 2007). Isolated cerebellar hemorrhagic injury is significantly associated with severe functional limitations in daily activities. Typically, children with congenital lesions including cerebellar agenesis, dysplasia, and hypoplasia exhibit a set of symptoms, which can be interpreted as dysmetric behavior: distractibility, hyperactivity, impulsiveness, disinhibition, anxiety, ritualistic and stereotypical behaviors, illogical thought, lack of empathy, ruminative and obsessive behaviors, dysphoria and depression, tactile defensiveness and sensory overload, apathy, childlike behavior, and inability to appreciate social boundaries (Schmahmann et al., 2007). Both structural and functional connectivity between the cerebellum and cerebral cortical nodes are disrupted (Olivito et al., 2018). Functional connectivity is impaired between (a) right posterior cerebellum and cerebral cortical nodes of language, (b) left dentate nucleus and cerebral cortical nodes of the default mode network, and (c) bilateral Crus I and medial regions of the mentalizing network (Olivito et al., 2017; Van Overwalle et al., 2014). According to the theory of internal models, cerebellar circuitry would allow the anticipation of other person's behavior, detect violations in social interactions, and activate corrections/adaptations in the internal models. Overall, dysmetria of thought and behavior assembles several major psychological domains symptoms: disorders of attention, impaired emotional regulation, social skill set/autism spectrum disorders, and psychosis spectrum disorders (Schmahmann et al., 2007).

Conclusion and Future Directions

As discussed in the chapters of this volume, cerebellar research is at the frontiers of neurology, psychiatry, and the modern approach to psychology. Our view of cerebellar functions is considerably broader than expected. The traditional consideration of the cerebellum as a pure coordinating tool has changed drastically, thanks to detailed neuroanatomical investigations, functional neuroimaging studies, and in-depth neuropsychological assessment of cerebellar patients (Marien & Manto, 2016). This is not surprising given the huge number of neurons in the cerebellar circuitry and its vast network of communications with cerebral cortex, limbic system, basal ganglia, brainstem nuclei, and spinal cord. No other structure in the CNS is better suited than the cerebellum to modulate motor, cognitive, linguistic, affective, and social activities. This is in perfect line with the clinical observations of deficits observed in cerebellar patients. The cerebellum is endowed with the capacity of restoring functional synapses, a unique feature which should be used in the assessment and management of cerebellar disorders. The visionary hypothesis of Malacarne on the impact of environment on cerebellum fits with the cerebellar research performed during more than two centuries. Abnormal functioning in segregated loops between cerebellum and extra-cerebellar hubs contributes to the pathogenesis of major brain pathologies at the frontiers of neuropsychology, neurology, and psychiatry including autism, schizophrenia, and depression. Preventive strategies and therapies tailored to the needs of each patient are needed. Physical, occupational, and cognitive rehabilitation of cerebellar patients should be further improved in individualized approaches, taking into account the various aspects of cerebellar reserve: motor, oculomotor, cognitive, affective, and social. At the level of neuropsychological interventions, neurocognitive rehabilitation should focus on interrelated aspects: attention, executive functions, memory, visuospatial capacities, and verbal communication. The detrimental consequences of the three clinical cerebellar syndromes require a multidisciplinary team, where expertise in neuropsychology, neurology, and psychiatry is mandatory to achieve progress. Therapies will go along with longitudinal studies dedicated to motor, cognitive, affective, and social issues encountered by cerebellar patients. The scientific community can now take advantage of the integration of clinical data, neuropsychological assessments, biological evaluations (blood, CSF, other fluids), and advanced neuroimaging tools, both structural and functional.

Exercises

1. Imagine you are discussing with a friend. How would you explain with your own words Schmahmann syndrome/cerebellar cognitive affective syndrome?
2. Paul has been working in a post office for 20 years. He interacts with many people. He develops a cerebellar stroke and is diagnosed with severe cognitive dysmetria. What could be the impact during his daily work?
3. Return to the Jeremy Schmahmann quote that appears at the beginning of the Table of Contents of this book. In reading through this present chapter, what do you feel is Schmahmann's most interesting contribution to cerebellum research?

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