Chapter 3
Pivotal Insights: The Contributions of Gordon Holmes (1876–1965) and Olof Larsell (1886–1964) to Our Understanding of Cerebellar Function and Structure

Duane E. Haines

Abstract Among the notables who have contributed to our knowledge of cerebellar structure and function, two individuals stand out. The neurologist Gordon M. Holmes, consequent to his clinical observations on patients with cerebellar damage, especially those with injuries in WW I, provided a remarkable understanding of deficits, their laterality in relation to lesion location, and whether or not it involved cortex, nuclei, or both. He also defined, and refined, the clinical terminology describing cerebellar deficits to a level of accuracy, and especially relevance, that it is commonly used today. The anatomist Olof Larsell, in 1920, embarked on a line of investigation that would result, over 25+ years later, in a coherent and organized terminology for the lobes and lobules of the cerebellum that is widely used today and was the structural basis for numerous later experimental investigations. In this effort Larsell used a developmental approach, mapped the sequential approach of the cerebellar fissures and folia, and offered a terminology that clarified the existing, and confusing, approach that existed prior to 1920.

Keywords Gordon Holmes • Olof Larsell • Cerebellum •History of neuroscience

Discoveries in function commonly follow the clarification provided by dogged investigations of brain morphology. Based on chronology, one could argue that the reverse is seen in the contributions of the protagonists in this brief story: the British clinical neurologist, Gordon Morgan Holmes (Feb. 22, 1876-Dec. 29, 1965) and the American neuroanatomist Olof Larsell (Mar. 13, 1886-Ap. 8, 1964).

D.E. Haines (✉)
Department of Neurobiology and Anatomy, Wake Forest School of Medicine,
1 Medical Center Blvd, Winston-Salem, NC 27157-1010, USA
e-mail: dhaines@wakehealth.edu

D.L. Gruol et al. (eds.), *Essentials of Cerebellum and Cerebellar Disorders*,
DOI 10.1007/978-3-319-24551-5_3

3.1 Gordon M. Holmes

Holmes (Fig. 3.1) received his medical training at Trinity College, Dublin (1899). Consequent to a successful stint at the Richmond Asylum, Dublin, he spent over 2 years studying with Karl Weigert and Ludwig Edinger where he gained appreciation for the intricacies of brain morphology. He went on to hold positions at the National, Charing Cross, and Moorfields Ophthalmic Hospitals.

With the beginning of World War (WW) I Holmes attempted to enlist but was rejected (he was myopic). He bypassed this obstacle by joining a Red Cross hospital immediately behind the front where he rose through the ranks. The combination of his work ethic, skill as a neurologist and the unfortunate availability of injured soldiers, provided the means for Holmes to make clinical observations that were remarkably insightful for their time.

This great World War provided literally hundreds of soldiers with injury to the occipital region and the cerebellum, due to poorly designed helmets. This provided Holmes the opportunity to observe, study, and refine clinical concepts of cerebellar function that stand to this day. Quotes are liberally used here to clearly illustrate the contemporary nature of Holmes' (and Larsell's) descriptions.

Fig. 3.1 Holmes (*light suit, hands in pockets*) during a stay at the Senkenberg Institute. Back row, *L to R*: Juliusberg, Rosenberg, Jensen, Philipp, Franz. Front row, *L to R*: Von Jagic, Southard, Edinger, Holmes, Herxheimer, Tiegel, Kunicke, Friedmann. Sitting, Weigert (Courtesy of *The Cerebellum*, 2007; 6: 141–156)

Holmes published a large body of information regarding cerebellar influence on somatomotor activity from his clinical research (Holmes 1917), and presented in his Croonian Lectures of 1922 (Holmes 1922a, b, c, d). He acknowledged that his cases were:

> …determined largely by the opportunities I have had of observing the effects of local lesions of the cerebellum in both warfare and civil life.

While he acknowledged the numerous prior studies that attempted to answer fundamental questions he noted:

> …there is still a remarkable divergence between the symptoms attributed in various text-books and monographs to lesions of the cerebellum in man.

Holmes made detailed studies of patients (acute and long term) with cerebellar lesions to clarify the unique traits of particular somatomotor deficits. Using this patient population, he made definitive observations that not only clarified previous misconceptions, but expanded the understanding of cerebellar function at that time. Many ideas and concepts were clarified, or discovered, by Holmes and described in terms/phrases that could come from any twenty-first century comprehensive textbook.

First, Holmes definitively clarified the fact that

> The effects of cerebellar injuries fall almost exclusively upon the motor system, … of the same side.

This is now a well established concept, along with the newer recognition of the wider role of the cerebellum.

Second, Holmes noted the difficulty of sorting out what difference may exist between lesions of only the cerebellar cortex versus cortex plus nuclei. He described deficits resultant from clearly superficial lesions (cortex) and those with deeper damage (cortex + nuclei) and concluded:

> … we find that when the lesion is so superficial that the nuclei cannot have been directly injured the symptoms are less intense, less regular, and that they disappear much more rapidly. … rapid improvement is never seen when the damage extends to the neighborhood of the central nuclei.

This is observed in the contemporary clinic: a distal PICA lesion (cortex) results in a cascade of vestibular and motor deficits that resolve quickly, within days to very few weeks, while a SCA lesion (cortex + nuclei) results in a similar cascade of motor deficits lasting weeks, months, or years.

Third, Holmes noted that a "…*most striking feature*…" is a decrease in muscle tone. He reported that;

> When a lesion involves a large part of one-half of the cerebellum, … the hypotonia is rigidly limited to … the same side … often most pronounced at the proximal than at the distal joints.

He clarified the variety of tests that could be used to arrive at an accurate diagnosis.

Fourth, Holmes accurately described the variety of movement disorders that characterize cerebellar lesions;

> Dysmetria … striking abnormality in the affected limbs … their movements are not correctly adapted or proportioned … they are ill-measured.

He noted that dysmetria may exist in two forms:

> "… the range of movement is most commonly excessive …" (hypermetria) or that "… the movement is arrested or slowed down before the point the patient wishes to attain is reached …" (hypometria).

Fifth, three common cerebellar deficits are the rebound phenomenon, diadochokinesia, and the intention tremor. Concerning the first Holmes noted (see also Koehler et al. 2000):

> … resistance that effectively prevents a movement of a normal limb in response to a strong voluntary effort be suddenly released, the limb, after moving a short distance … is arrested abruptly by the action of the antagonist muscles… this sudden arrest fails frequently in cerebellar disease … when the grasp is suddenly relaxed the hand on the affected side swings violently toward his face or shoulder, and … may be flung above his head.

Diadochokinesia is the inability of a patient to rapidly;

> … pronate and supinate his forearms … a very striking difference is noticed between the movements on the two sides ….

Holmes noted that if the limb was hypotonic the abnormal movements may be slow, irregular in "… *rate and range* …" and "… *become more pronounced the longer the effort is continued* …". Holmes described the intention tremor as complex movements, its individual components are disrupted, uncoordinated, and largely ineffective. He noted:

> In the early part of the movement the limb sways about in a purposeless manner as soon as it is raised from its support … in trying to touch his nose, his finger, for instance, often comes to his cheek or eye.

A remarkable element of the work by Holmes on the cerebellum is its accuracy, detail, insights, and relevance to modern day neurology. In fact, one can read Holmes and get information that is just as detailed, correct, and useful with respect to the motor phenomena following cerebellar injury as in any contemporary text.

3.2 Olof Larsell

Larsell (Fig. 3.2, Mar, 13, 1886-April 8, 1964) was born in Rättvik, Sweden and came to the United States with his mother at age 5; his father had established a home in Tacoma, Washington. He received the B.S degree (in Biology) from McMinnville (now Linfield) College in 1910. His academic travels were circuitous. He taught at Linfield (1910–1913), attended Northwestern University (1913–1914, M.S. degree in Zoology), taught at Linfield (1914–1915), re-entered Northwestern in 1915 and received his Ph.D. degree in 1918 (Haines 1999).

Fig. 3.2 Olof Larsell in his office at the University of Oregon Medical School, ca. 1945. Author's collection (Courtesy of Mr. Robert Larsell)

During the summers of 1913 and 1914 Larsell took summer courses at the University of Chicago under the renowned American neuroanatomist, Charles Judson Herrick. These fortuitous summer experiences greatly influenced Larsell's thinking, research direction, and life-long fascination with brain anatomy.

3.3 The Problem

During the period spanning the 1880s and up to about the mid 1940s, the terminology utilized to designate the lobes/lobules, folia, and fissures of the cerebellum was highly variable. It consisted of different names being given to the same folia/lobes/lobules; in some cases lower and upper case letters intermixed with numbers/numerals (Arabic and Roman) and what constituted a lobe was inconsistently applied (Angevine et al. 1961). For example, the vermis part of the culminate lobule (IV and V of Larsell) was called the culmen, culmen monticule, pars culminus of the lobus anterior, lobe B, or lobules 3 and 4. This represented a significant confusion of terminology.

Stemming from his time with Herrick, Larsell began a series of studies that would span over 40 years and focus on the morphology of the cerebellum utilizing a developmental approach. Whether or not Larsell realized it, this approach would reveal homologies in lobes, lobules, and fissures across a wide range of biological forms that are not evident in a study of the adult form. This would clearly establish a broad-based biological pattern. Larsell's first paper, published in 1920, and identifies the source of his motivation:

> It was at the suggestion of Professor Herrick that the present study was begun. It is a pleasure for the writer to acknowledge his sense of indebtedness to Professor Herrick….

3.4 Early Studies, 1920–1932

Larsell's first paper, "The cerebellum of Amblystoma" appeared in 1920. This early period focused on non-mammalian forms. Interestingly, Larsell listed his first affiliation as the "Anatomical Laboratories of the University of Chicago" and "the University of Wisconsin" where he was an Assistant Professor (1918–1920). While Herrick had influenced the study, and provided some material, Larsell was not in residence at Chicago.

In this time frame Larsell methodically detailed the cerebelli of the tiger salamander, frog, newt, and a variety of snakes and lizards. He used silver impregnation methods (Golgi, Cajal), myelin and hematoxylin stains, and the Marchi method. He described aspects of development and the external anatomy of adult forms, specified a larger corpus cerebelli and a smaller auricular lobe, the cortical histology of these primitive forms, and the primordial cerebellar nuclei. He did not use a lobule designation, but the dye was cast (Larsell 1920, 1923, 1925, 1926, 1931, 1932a, b).

3.5 The Middle Period, 1932–1947

In this period Larsell expanded on the concept of a large cerebellar mass, the corpus cerebelli. The first superficial feature to appear was a shallow fissure along the caudal and lateral edge of the cerebellar anlage. Larsell identified the lateral part of this groove as the "*parafloccular fissure*" and the medial part as the "*uvulonodular fissure*" (or floccular fissure), terms used by previous investigators. This combined fissure separated a large rostral part of the cerebellum, the "corpus cerebelli", from a smaller caudal part, the "vestibular floccular lobe" (Larsell 1931, 1932a, 1934, 1936a, b, 1937, 1947a, b).

In studies during this period on opossum, bat, and human specimens, Larsell carefully refined the basis for his new nomenclature. He noted that a "*posterolateral fissure*" (his term) replaced the combined terms of parafloccular and uvulonodular fissures, that this fissure was first to appear in the cerebellar anlage dividing it into a "*flocculonodular lobe*" and "*corpus cerebelli*", and that the "*primary fissure*" was the second to appear and divided the corpus cerebelli into anterior and posterior lobes. Larsell (1935, 1936a, b, 1945, 1947a, b) noted:

> The flocculonodular lobe and the corpus cerebelli are the fundamental cerebellar divisions morphologically, and … functionally.

At this point two old concepts were disproven; first, the primary fissure was not the first to appear in development, and second, the concept of a 'median lobe' was no longer viable,

3.6 Later Studies and the Solution, 1948–1954

After 10 years of study on the avian cerebellum, Larsell used, for the first time (1948), the unique terminology that he had been working toward since 1920. He noted that the posterolateral fissure was first to appear in the cerebellar plate dividing it into a *flocculonodular lobe* and the *corpus cerebelli*. Larsell (1948) indicated that an orderly appearance of subsequent fissures in the corpus cerebelli resulted in an adult structure of 10 main folia (Roman numerals I–X).

> For convenience of description they will be numbered I to X beginning anteriorly.

In this introduction of his method Larsell used the term "…*folia*…" recognizing the simple structure of the avian cerebellum, which lacked a hemisphere, and the vermis consisted of leaf-like structures.

Between 1952 and 1954 Larsell reported his extensive observations on the cerebellum of the white rat, cat, monkey, pig, and human using developmental stages and adult specimens (Larsell 1952, 1953a, b, 1954; Larsell and Dow 1939; Larsell and Whitlock 1952). Using these mammals he clearly showed that the mature mammalian cerebellum was composed of subdivisions called "…*lobules*…".

> I have pointed out…the striking similarities between folia I–X of birds and the vermian segments of the rat which the present investigation has brought to light … I shall call these segments lobules I–X, corresponding to the similarly named avian folia.

Each lobule of the vermis, beginning with the lingual and ending with the nodulus, was identified by Roman numerals (I, II, III … X). The lateral extension of each vermis lobule, the hemisphere portion, was identified by the same Roman numeral but with the prefix H (HII, HIII … HX) specifying "*hemisphere portion of*…". Larsell recognized that the basic pattern of a cerebellar plate being transected by two fissures (joining to make one – the posterolateral) formed a larger corpus cerebelli and a smaller flocculonodular lobe. In concert he noted that the development of the primary fissure, the second to appear and first in the corpus cerebelli, resulted in an anterior lobe (lobules I–V) and a posterior lobe (lobules VI–IX); the further development of additional fissures in these lobes clearly established to a fundamental plan. He postulated that this ten lobule arrangement would prove to be applicable to a wide range of forms, a point well-taken.

In studying Larsell's correspondence with Herrick, it is clear that he was a quiet, reserved man who was concerned about the wider impact of his life-long work. In a letter to Herrick (dated July 20, 1948) Larsell says;

> I treaded on Brouwer's and Ingvar's toes somewhat – gently enough I hope…, but I do not think my work will need repeating.

Indeed, it did not merit repeating, and by the late 1950s and 1960s was adopted by giants of the day and, to the present, is the standard.

References

Angevine JB, Mancall EL, Yakolev PI (1961) The human cerebellum: an atlas of gross topography in serial sections. Little, Brown and Company, Boston, pp 1–138

Haines DE (1999) In: Garraty JA, Carnes MC (eds) American national biography, vol 13. Oxford University Press, New York, pp 204–206

Holmes G (1917) The symptoms of acute cerebellar injuries due to gunshot. Brain 40:461–535

Holmes G (1922a) Clinical symptoms of cerebellar disease and their interpretation, lecture I. Lancet 202:1178–1182

Holmes G (1922b) Clinical symptoms of cerebellar disease and their interpretation, lecture II. Lancet 202:1232–1237

Holmes G (1922c) Clinical symptoms of cerebellar disease and their interpretation, lecture III. Lancet 203:59–65

Holmes G (1922d) Clinical symptoms of cerebellar disease and their interpretation, lecture IV. Lancet 203:111–115

Koehler PJ, Bruyn GW, Pearce JMS (2000) Neurological eponyms. Oxford University Press, Oxford, pp 172–178

Larsell O (1920) The cerebellum of amblystoma. J Comp Neurol 31:259–282

Larsell O (1923) The cerebellum of the frog. J Comp Neurol 36:89–112

Larsell O (1925) The development of the cerebellum in the frog (*Hyla regilla*) in relation to the vestibular and lateral-line systems. J Comp Neurol 39:249–289

Larsell O (1926) The cerebellum of reptiles: lizards and snake. J Comp Neurol 41:59–94

Larsell O (1931) The cerebellum of *Triturus torosus*. J Comp Neurol 53:1–54

Larsell O (1932a) The cerebellum of reptiles: chelonians and alligator. J Comp Neurol 56:299–345

Larsell O (1932b) The development of the cerebellum in *Amblystoma*. J Comp Neurol 54:357–435

Larsell O (1934) Morphogenesis and evolution of the cerebellum. Arch Neurol Psychiat (Chicago) 31:373–395

Larsell O (1935) The development and morphology of the cerebellum in the opossum. Part I. Early development. J Comp Neurol 63:65–94

Larsell O (1936a) The development and morphology of the cerebellum in the opossum. Part II. Later development and adult. J Comp Neurol 63:251–291

Larsell O (1936b) Cerebellum and corpus pontobulbare of the bat (*Myotis*). J Comp Neurol 64:275–302

Larsell O (1937) The cerebellum: a review and interpretation. Arch Neurol Psychiat (Chicago) 38:580–607

Larsell O (1945) Comparative neurology and present knowledge of the cerebellum. Bull Minn Med Found 5:73–85

Larsell O (1947a) The cerebellum of myxinoids and petromyzonts, including developmental stages in the lampreys. J Comp Neurol 86:395–445

Larsell O (1947b) The development of the cerebellum in man in relation to its comparative anatomy. J Comp Neurol 87:85–129

Larsell O (1948) The development and subdivisions of the cerebellum of birds. J Comp Neurol 89:123–189

Larsell O (1952) The morphogenesis and adult pattern of the lobules and fissures of the cerebellum of the white rat. J Comp Neurol 97:281–356

Larsell O (1953a) The cerebellum of the cat and the monkey. J Comp Neurol 99:135–199

Larsell O (1953b) The anterior lobe of the mammalian and the human cerebellum. Anat Rec 115:341

Larsell O (1954) The development of the cerebellum of the pig. Anat Rec 118:73–107

Larsell O, Dow RS (1939) The cerebellum: a new interpretation. West J Surg Obstet Gynaecol 47:256–263

*Larsell O, Jansen J (1967) The comparative anatomy and histology of the cerebellum from myxinoid through birds. The University of Minnesota Press, Minneapolis, pp 1–291
*Larsell O, Jansen J (1970) The comparative anatomy and histology of the cerebellum from monotremes through apes. The University of Minnesota Press, Minneapolis, pp 1–269
*Larsell O, Jansen J (1973) The comparative anatomy and histology of the cerebellum: the human cerebellum, cerebellar connections, and cerebellar cortex. The University of Minnesota Press, Minneapolis, pp 1–268, 67 plates
Larsell O, Whitlock DG (1952) Further observations on the cerebellum of birds. J Comp Neurol 97:545–566

Letter: Larsell to CJ Herrick, July 20, 1948, The Herrick Collection, Neurology Collection, C. J. Herrick papers, Kenneth Spencer Research Library, University of Kansas Libraries, Lawrence, Kansas.

[*]Although Larsell began writing his monographs in the early 1940s, at his death in 1964 it fell to Jan Jansen, a friend of many years, to assume the significant task of seeing the partially finished manuscripts to completion (Larsell and Jansen, 1967, 1970, 1973).