Handbook of Behavioral Neuroscience

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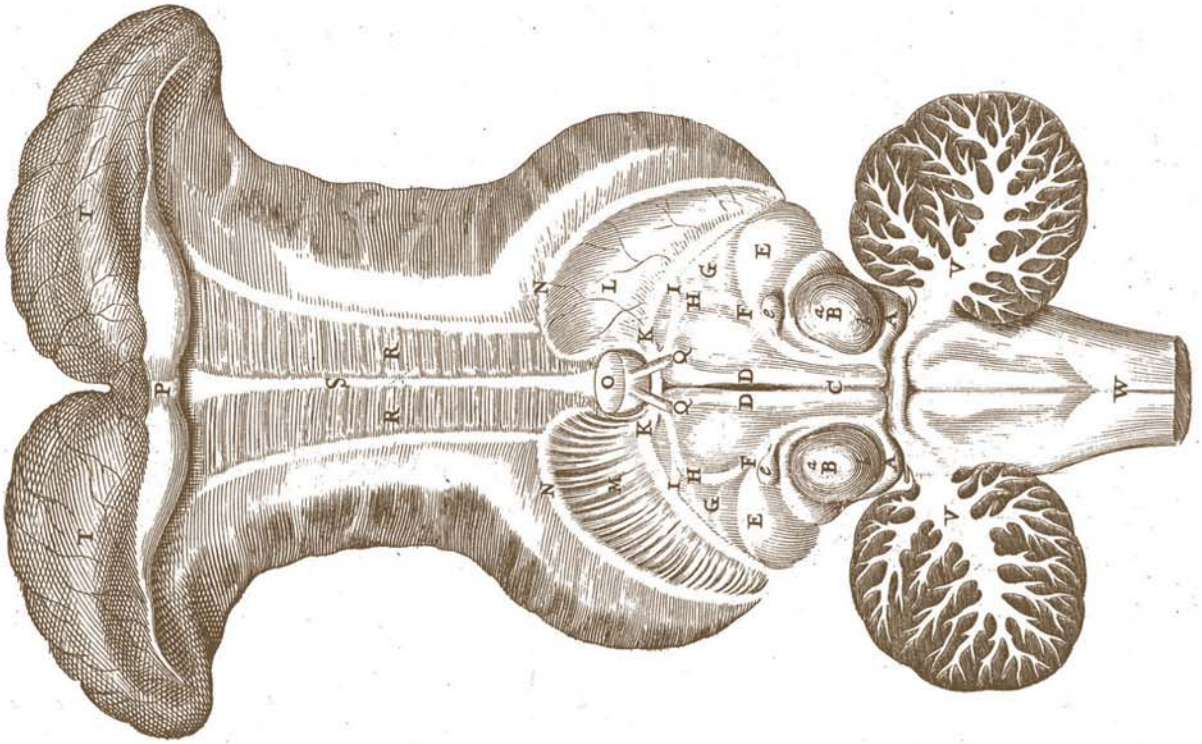
Handbook of Basal Ganglia Structure and Function

Second Edition



Edited by Heinz Steiner and Kuei Y. Tseng

Volume 24

HANDBOOK OF BASAL GANGLIA STRUCTURE AND FUNCTION

SECOND EDITION

Edited by

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CHAPTER

2

The History of the Basal Ganglia: The Nuclei

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I. INTRODUCTION

"The basal ganglia—the *corpora striata* and *optic thalami*—are ganglionic masses, intercalated in the course of the projection system of fibers which connect the cortex with the *crura cerebri*, and through these with the periphery. The corpora striata are the 'ganglia of interruption' of the projection system of the foot or basis of the crus, an anatomical indication of their motor signification."

This is how Sir David Ferrier (1843–1928), the distinguished Scottish neurophysiologist, named and described the set of subcortical structures to which the present book is devoted (see chapter: The Neuroanatomical Organization of the Basal Ganglia for an overview). The description appeared in a highly comprehensive review of the 19th-century efforts to unravel the complexities of the brain that Ferrier published under the title *The Functions of the Brain* (Ferrier, 1876). If the epithet "basal" adequately reflects the location of the nuclei at the basis of the forebrain, the term "ganglia" is a misnomer. In modern literature, this appellation is largely limited to neuronal clusters located in the peripheral nervous system, whereas those present in the central nervous system are commonly referred to as "nuclei." Such a distinction was obviously not in the mind of early anatomists, and the term *basal ganglia* progressively became a catchword for all those interested in the anatomical organization and functional significance of these large basal forebrain structures.

The anatomical nomenclature regarding the basal ganglia has nevertheless always been problematic. The situation is due in part to the fact that, much like the limbic system concept, terms such as *basal ganglia* and *extrapyramidal system* have no precise anatomical limits. The use and abuse of the epithet "striatum" has also contributed to the confusion, particularly in the comparative neurology literature, which is cluttered with terms such as *archistriatum*, *paleostriatum*, *hyperstriatum*, and *epistriatum*, whose intended meanings vary markedly. A further complication results from the existence of significant interspecific differences in the organization of the basal ganglia. For example, the striatum in rodents stands out as a single entity, whereas it is largely separated into two major components—the

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caudate nucleus and the putamen—by fibers of the internal capsule in primates. There also exist major variations between primate and nonprimate mammals in regard to the arrangement of the pallidum. In primates, the structure consists of an internal and an external segment juxtaposed to one another and lying parallel to the putamen, with which they form the so-called *lentiform nucleus*. In contrast, the two pallidal components are widely separated from one another in nonprimate mammals: the lateral subdivision—simply termed *globus pallidus*—is directly apposed to the internal surface of the putamen, whereas the medial subdivision—called the *entopeduncular nucleus*—is deeply embedded within the fibers of the internal capsule. Despite the fact that some early anatomists, such as Thomas Willis (1621–1675), had a profound knowledge of comparative anatomy, these topographical interspecific variations did not attract their attention, which was largely orientated toward the largest and major integrative component of the basal ganglia, namely the *corpus striatum*.

If Ferrier's term "*basal ganglia*" was retained, his description of the structures has been largely forgotten because it is essentially based on 17th-century knowledge (see below). A more accurate picture of the anatomical organization of the basal ganglia emerged during the course of the 20th century, thanks to the massive amount of new findings that stemmed from a multitude of experimental and clinical studies.

The basal ganglia, as we know them today (see chapter: The Neuroanatomical Organization of the Basal Ganglia), are a large set of interconnected subcortical hemispheric structures that plays a crucial role in the control of movement, as exemplified by the motor disturbances that occur when these nuclei are pathologically affected, such as in Parkinson's disease or Huntington's chorea. Historically, the presence of large structures at the basis in the brain was already noted in the Antiquity, but the basal ganglia per se were not fully recognized before the 19th century. The present chapter relates the long and arduous endeavors, which led to the discovery and detailed characterization of the complex group of interconnected nuclear masses of diverse forms and functions that are today united under the term basal ganglia. The first half of the chapter concerns the core structures of the basal ganglia, that is, the striatum and the pallidum or globus pallidus. These are the most voluminous and distinct parts of the basal ganglia and, because they occupy a vast portion of the cerebral hemisphere, their presence was noted very early in the history of neuroscience. The second half of the chapter is devoted to the subthalamic nucleus and the substantia nigra, two nuclei that lie at the margin of the core structures but are intimately interconnected with the latters, a position that allows them to modulate the flow of neural information that courses through the basal ganglia. Being smaller than the core structures and located at different levels of the neuraxis, their discovery is more recent and their intimate relationship with the former has been firmly established only during the second part of the 20th century.

II. THE CORE STRUCTURES OF THE BASAL GANGLIA: STRIATUM AND PALLIDUM

A. From Antiquity to the 18th Century

Galen (Claudius Galenus, c.129–201), the famous Greek physician and anatomist who worked in Rome in the 2nd century of our era was probably one of the first to pay attention to the large masses of nervous tissue lying at the base of the lateral ventricle, which he referred to as the gluteal parts of the brain. In some of his treatises he used the Greek term γλυτια (*glutia* or buttocks) to describe these structures, whereas in others he compared them to human thighs (Galen, 1490). It is difficult to know precisely what Galen had in mind when he used these terms, because the original texts in which he alluded to these brain structures and that survived long enough to be scrutinized and translated by medieval scholars were not accompanied by any illustrations. Nevertheless, Galen's view went unchallenged for more than a millennium, the same type of awkward terminology being still in use in the Medieval and early Renaissance periods.

A typical example of the anatomical nomenclature employed in the Middle Ages to the designated basal ganglia is that of the Bolognese anatomist Mondino de' Liuzzi (Mondinus, c.1270–1326), who courageously sought new knowledge, not in Galenic treatises, but directly from human body dissection, a procedure that had been forbidden since the Alexandrian period in the 3rd century BC. Mondinus referred to the basal ganglia as *anchae* (haunches), an appellation that first appeared in his *Anathomia* (he coined the term), a short manuscript that he wrote in 1316 for his students, but which later went through several printed editions and was to guide European anatomists for more than 200 years (Mondino de' Liuzzi, 1482). Another famous Italian physician and surgeon, Jacopo Berengario da Carpi (c.1460–1530), who was one of the first anatomists to call upon capable artists to illustrate his treatises, used the term *nates* (Latin for buttocks) to describe the same structures (Berengario da Carpi, 1523).

Later in the Renaissance, a still crude but much clearer delineation of the basal ganglia appeared in the literature, thanks to the work of the famous Flemish anatomist Andreas Vesalius (1514−1564), who worked in Padua but published his landmark treatise *De humani corporis fabrica libri septem* (*On the Fabric of the Human Body in Seven Books*) in Basel (Vesalius, 1543). In the seventh book of this treatise, a surprisingly detailed outline of the various basal ganglia components appears in a figure that we probably own to the Flemish artist Jan van Calcar (c.1499−1545), who belonged to the Titian Venetian School (Fig. 2.1). Unfortunately, neither in the figure legend nor elsewhere in the text did Vesalius name these structures nor comment upon their possible function. Vesalius was apparently more interested in differentiating gray matter clumps from the white fiber groupings rather than identifying the various nuclear masses that lie in this portion of the brain. His drawing nevertheless shows rather clearly the contours of what are known today as the putamen, the caudate nucleus, the pallidum, and even the thalamus (Fig. 2.1).

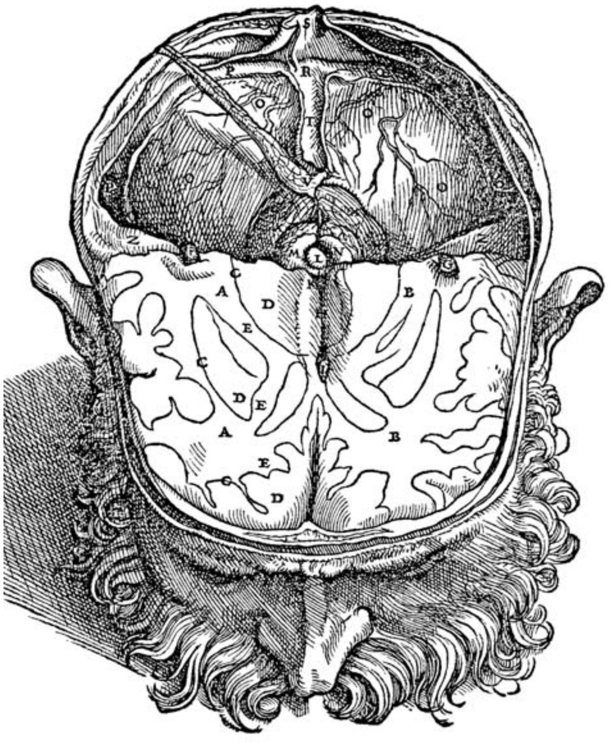

FIGURE 2.1 Andreas Vesalius' depiction of the basal ganglia as found in his *De humani corporis fabrica* (Vesalius, 1543). This horizontal section through the human brain provides a rather accurate view of the basal ganglia, particularly in the right hemisphere. Bundles of white matter (identified by the letter E), corresponding roughly to our internal capsule, are shown separating masses of gray matter (D), the lower medial one corresponding to the thalamus and the upper lateral one to the putamen. The caudate nucleus is also clearly outlined as a structure separated from the putamen by white matter. Also note, on the right side, the unmarked line separating the putamen from the pallidum.

A first breakthrough in the history of the basal ganglia occurred in the 17th century when the Oxford physician and anatomist Thomas Willis arrived on the scene. Willis decided to dissect the brain out of the cranium and to look at it from below, discovering the points of emergence of cranial nerves (9 pairs, not 7 as in Galen) as well as the arrangement of the vascular polygon (Galen's *rete mirabile*) to which his name is still attached. His new, blunt dissection method allowed him to discover embedded deeply in the brain of humans as well as that of several nonhuman species, a structure displaying a typical gray and white matter striation at the apex of the brainstem and which he called *corpus striatum* (streaked or chamfered body). In his celebrated *Cerebri anatome* (*Brain Anatomy*), published in 1664, Willis describes the topographical location and overall morphological appearance of the corpus striatum as follows: "*Corpus striatum seu medullae oblongatae apices, sunt duo prominentiae lentiformes, quae intra piores cerebri ventriculos*" (The corpus striatum or the apex of the brainstem stands as two lens-like prominences, which are beheld within the anterior ventricles) (Willis, 1664). Willis benefited from the great artistic talent of Christopher Wren (1632−1723) to provide striking illustrations of the corpus striatum in *Cerebri anatome* (Fig. 2.2).

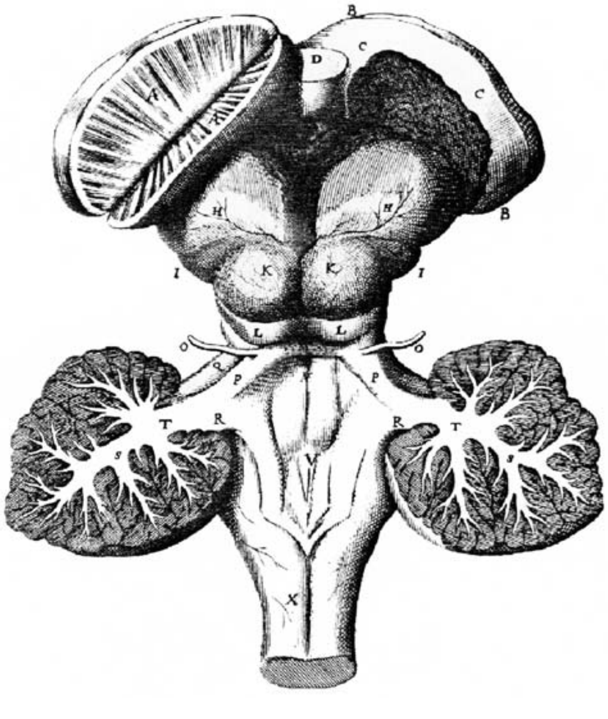

FIGURE 2.2 Thomas Willis' view of the basal ganglia as illustrated in his *Cerebri anatome* (Willis, 1664). This drawing shows a dorsal view of the brainstem and basal ganglia in a sheep. The superficial portions of the hemispheres have been removed to better illustrate the basal ganglia, and the corpus striatum on the left side has been cut open to show its characteristic striations.

Willis was the first to clearly distinguish anatomically the corpus striatum (see Part B) from the thalamus, which he called *Thalami nervorum opticorum*. However, he did not recognize the globus pallidus as a distinct part of his lens-like prominences (our present-day *lentiform nucleus*, which includes the putamen and the internal and external segments of the globus pallidus). On a functional point of view, Willis considered the corpus striatum as a nodal point in the control of both motor and sensory information (Galen's *sensus communis*). Willis thought that the marked striatal atrophy he noted while dissecting the brain of patients who suffered from paralysis supported the corpus striatum's involvement in the control of voluntary movement. Willis' view of the subcortical or striatal origin of motor behavior lasted until the end of the 19th century, at which time the role of the cerebral cortex in the initiation of motor acts began to be appreciated.

Willis was a central figure of the Oxford group (the *virtuosi*), whose efforts led to the creation of the Royal Society of London in 1660. Like other *virtuosi* of his time, he had an irrepressible urge to find a functional significance for his structural discoveries. Hence, besides attributing to the corpus striatum a major role in sensorimotor integration, Willis hypothesized that the corpus callosum was the seat of imagination, whereas he saw memory deeply embedded within the convolutions of the cortical mantle: "*Inter plica cerebri memoria et reminiscencia*" (Willis, 1664).

These speculations were soon to be criticized by Niels Stensen (Nicolaus Stenonis in Latin, or Steno in English; 1638–1686), a young Danish anatomist who acquired recognition following his discovery of the parotid gland excretory duct (still called *ductus stenonianus*). Stensen's objections are to be found in a remarkable *Discours sur l'anatomie du cerveau* (*Lecture on the Anatomy of the Brain*) that he pronounced in Paris in 1665, that is only 1 year after the publication of Willis' *Cerebri anatome*. In this discourse, which is characterized by a healthy skepticism that gives it a truly modern flavor, Stensen makes it clear that he was not ready to sacrifice scientific objectivity on the altar of clinical speculation. The major reproaches that Stensen addresses to Willis concern his unsupported speculations about the localization of brain functions. He stated: "Willis is the author of a very singular hypothesis. He lodges common sense in the corpora striata, the imagination in the corpus callosum, and the memory in the cortical substance. [...] How can he then be sure that these three operations are performed in the three bodies which he pitches upon? Who is able to tell us whether the nervous fibers begin in the corpora striata, or if they pass through the corpus callosum all the way to the cortical substance? We know so little of the true structure of the corpus callosum that a man of tolerable genius may say about it, whatever he pleases" (Stensen, 1669). While admitting that Willis' diagrams were by far the best then available, he did not hesitate in pointing out several inaccuracies in these drawings. For example, he found unfaithful the representation of cross sections of the striatum in some of Willis' illustrations because they do not accurately depict ascending and descending fibers.

Some of these negative remarks are obviously justified, but Stensen's overall critical attitude can be attributed to his youthful enthusiasm that tended to blind him to the merits of contemporary neuroanatomists, including such prominent ones as Thomas Willis, who made a major and long lasting contribution to our knowledge of the anatomical and functional organization of the brain. True to his nature, Willis accepted positively the criticisms formulated by Stensen, whose contribution he greatly praised in his *De anima brutorum* (*On the Souls of Brutes*) published only a few years after Stensen's *Discours* (Willis, 1672). Willis recognized that his "pleasant speculations" about brain functions, such as the role he attributed to imaginary animal spirits, were not based on direct observation, but at the same time he ingenuously admitted that he could not easily overcome such a tendency toward wild speculations. The latter attitude was typical of pre-Newtonian scientists, whose boundless scientific optimisms allowed them to overthrow their scholastic adversaries, but prevented them from realizing the limits of their own endeavors (Isler, 1968).

Slightly later in the 17th century, Raymond Vieussens (1641–1715) of Montpellier referred to the basal ganglia as *le grand ganglion cerebral* (the great cerebral ganglion). In his treatise entitled *Neurographia universalis* (Vieussens, 1684), he subdivided this large structure into six different sectors, the anterior one corresponding to Willis' corpus striatum and the posterior one to the thalamus. More than a century later, the French anatomist Félix Vicq d'Azyr (1748–1794) provided a remarkably accurate depiction of the basal ganglia. His *Traité d'anatomie et de physiologie* (Vicq d'Azyr, 1786) contains several plates in which the various components of the basal ganglia, including the caudate nucleus, the putamen, and the pallidum are clearly delineated from one another (see below). Unfortunately, somewhat like Vesalius before him, Vicq d'Azyr did not name these structures individually, focusing more on the fiber fascicles, which he called *arcades*, separating the various nuclear masses.

B. From the 19th to the 20th Century

At the very beginning of the 19th century, both Johann Christian Reil (1759–1813) first in Halle and later in Berlin, and Franz Joseph Gall (1758–1828), in Vienna and later in Paris, made important contributions to the anatomy of the brain in general and of the basal ganglia in particular. Like Vieussens before him, Gall referred to the basal ganglia as *le grand ganglion cerebral*, but insisted only on its superior and inferior parts, which respectively correspond to Willis' corpus striatum and thalamus (*couche optique*). In the treatise entitled *Anatomie et physiologie du système nerveux*, which he published in collaboration with Johann Kaspar Spurzheim (1766–1832) (Gall and Spurzheim, 1810), Gall provided astonishingly accurate illustrations of the basal ganglia, with an outer and an inner portion of the *corps strié* (corpus striatum), corresponding respectively to our putamen and caudate nucleus. As for Johann Christian Reil, in addition to the epithet *ganglion* (Greek for swelling), he was among the first to use the term *Kern* (German for core or kernel that became *nucleus* in Latin) to designate masses of gray matter located inside the brain. Reil also frequently employed the word *Hügel* (German for hillock or monticule) for the same purpose as, for example, in *Vierhügel* (superior colliculus) and *Sehhügel* (thalamus). In regard to the basal ganglia, Reil noted the presence of *Capseln* (fiber capsules) around the great cerebral ganglion, whose external surface, he remarked, had the shape of a *Linse* (lens or lentil) (Reil, 1809). However, Willis had noted the lenticular aspect of the external portion of the corpus striatum as early as 1664 (see above).

A second major breakthrough in the history of the basal ganglia occurred when the German physician Karl Friedrich Burdach (1776–1847), who occupied the chair of anatomy and physiology at Konigsberg's university, wrote his three-volume treatise entitled *Vom Baue und Leben des Gehirns* (*Of Structure and Life of the Brain*), which was published over a period of 7 years (Burdach, 1819–1826). This masterpiece in neuroanatomy contains a detailed and strikingly modern depiction of the basal ganglia that Burdach referred to as the anterior portion of the *Hirnstammganglien* (brainstem ganglion). After careful examinations of frontal and parasagittal human brain sections, Burdach was able, for the first time, to clearly differentiate the caudate nucleus from the putamen (Fig. 2.3). He used the word *Streifenhügel* (streaked hillock) to designate the caudate nucleus, but gave credit to Vincenzo Malacarne (1744–1816) for having been the first to mention the existence of such an elongated mass of gray substance in the brain. However, Malacarne himself might have picked up this observation from a translation of Galen's work provided by Avicenna (c.980–1037) early in the Middle Ages.

Burdach also gave a very detailed description of our lentiform nucleus, which he named *Linsenkern* (lens-shaped nucleus), a term that he admittedly borrowed from his compatriot Reil, who himself picked it up from Willis. He also recognized that his *Linsenkern* was not topographically and cytologically a monolithic entity. He called his more grayish lateral part *Schale* (shell, peel) or *putamen*. He further identified a paler structure (*blasser Klumpen*) within the inner portion of his Linsenkern that he called *globus pallidus*, and correctly identified its inner and outer segments (*innern und äussern Theil*) (see chapter: Organization of the Globus Pallidus). He noted that the major basal ganglia nuclei were separated from one another by fiber fascicles that he termed *inner Capsel* and *äussre Capsel*, which correspond to our internal and external capsules, respectively. He termed *begränzende Markblat* (bordering white matter) the fiber laminae that separate the various segments of the lentiform nucleus.

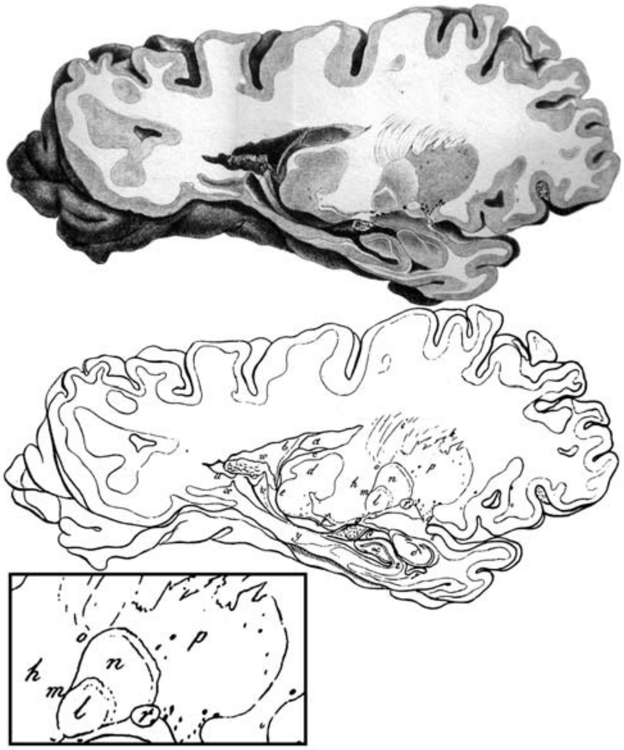

FIGURE 2.3 Friedrich Burdach's representation of the basal ganglia as found in his *Vom Baue und Leben des Gehirns* (Burdach, 1819–1826). This reproduction shows a parasagittal slice of the left hemisphere of a human brain in which the various basal ganglia components are visible and their location indicated by letters in the line drawing of the lower panel, a part of which has been enlarged (inset at the bottom) to better appreciate the details. The letter a points to the tail of the caudate nucleus; d to thalamus; h to internal capsule; l–p to lenticular nucleus, with the putamen (p) clearly differentiated from the internal (l) and external (n) segments of the globus pallidus.

Burdach had an obvious gift for naming brain structures; his neuroanatomy treatise contains a multitude of new names for various nuclei and fiber systems of the central nervous system, including the claustrum, pulvinar, amygdaloid complex, red nucleus, lamina terminalis, pallium, cingulum, subiculum, alveus, cuneus, precuneus, and the fasciculus cuneatus to which his name is still attached. Of course, Burdach did not discover all these structures, but he nevertheless provided the first accurate description and illustration of many of them, thanks to the help of the talented draftsman and engraver Johann Friedrich Schröter (1770−1836).

As a genuine *Naturphilosophen* (nature philosopher), Burdach attributed much importance to the historical aspect of the advancement of knowledge to which he devoted a 300 page long section of the second volume of *Vom Baue und Leben des Gehirns*, which he titled *Anmerkungen* (comments) (Burdach, 1819−1826). This historical review of brain anatomy surpasses by far the earlier works of the French physician and anatomist Antoine Portal (1742−1832) (Portal, 1770−1773) and the Swiss physiologist Albrecht von Haller (1708−1777) (Haller, 1757−1766). Burdach's physiological considerations on the basal ganglia are those of a typical *Naturphilosophen* who indulged in speculation on the discrete localization of functions in specific brain areas. He believed that the basal ganglia were the site of sensory perception and consciousness. Volition, he thought, emerges from the corpus striatum, whereas sensation, particularly visual, and consciousness originate from the thalamus. However, he had no firm experimental observations to support any of these affirmations, and he did not even feel the need to search for such evidence. At the end of his career, Burdach's speculations were out of the realm of the vigorous neuroscience research that was going on at that time. For example, he did not take seriously into account the results that were emerging from the use of the microscope, including the cell theory.

Despite some weaknesses in his physiological concepts, Burdach's description of the core structures of the basal ganglia is still largely valid today, except for some minor adjustments and additions that were made throughout the 20th century. For example, Oskar Vogt (1870−1959) and his wife Cécile Vogt-Mugnier (1875−1962), who worked first at the Kaiser Wilhelm Institute in Berlin and later at their own *Institut für Hirnforschung und allgemeine Biologie* (*Institute of Brain Research and General Biology*) in Neustadt, made a significant contribution to our understanding of the functional organization of the basal ganglia of primates, including man. For many years, the caudate nucleus had been considered a distinct structure among primate basal ganglia, whereas the putamen was closely associated with the globus pallidus, both entities forming the so-called *nucleus lenticularis* or *nucleus lentiformis* (lenticular or lentiform nucleus). The Vogts departed from this long-held view when they realized that the caudate nucleus and the putamen belonged to the same basal ganglia component (Vogt and Vogt, 1920). They also recognized that the caudate nucleus and the putamen were linked together at anterior and ventral levels through the *nucleus accumbens*, the three structures forming a single cytoarchitectonic entity, which they simply termed *striatum*.

The large fiber system that emerges from the striatum has attracted the attention of several neuroanatomists early in the 20th century. Among scientists who looked seriously at the connections of the striatum with other brain structures was the American neurologist Samuel Alexander Kinnier Wilson (1878−1937). In regard to basal ganglia terminology and functional organization, Wilson is remembered for having formulated the concept of *extrapyramidal system* (Wilson, 1912). The renowned clinician suggested to merge the core structures of the basal ganglia with virtually all brain nuclei connected with them into a single functional system, whose major output consisted of descending motor projections coursing outside the bulbar pyramids. Wilson proposed this novel terminology mainly to underline the distinct manner whereby the subcortical basal ganglia and the cortical pyramidal motor system exert their control over motor behavior. It should be noted, however, that the epithet *extrapyramidal* was used well before Wilson. Indeed, terms such as *Extrapyramidenbahnen* (extrapyramidal tracts) were commonly employed at the end of the 19th century by the members of the prestigious Vienna school of neurology then dominated by the figure of Theodor Meynert (1833−1892) (Prus, 1898). Although still popular in clinical neurology, the concept of extrapyramidal system progressively lost its heuristic and didactic value, at least in the opinion of most basic researchers, who never really abandoned the original basal ganglia notion. Wilson's name remains also attached to the hepatolenticular degeneration (Wilson's disease) as well as to the proximal portion of the striatofugal fiber system, which we used to call *Wilson's pencils* (Wilson, 1914). As they pierce the internal capsule, the same set of striatofugal axons were often termed *Edinger's comb bundle* in reconnaissance of the Frankfurt neurologist Ludwig Edinger (1855−1918), who made a major contribution to our knowledge of the comparative anatomy of basal ganglia (Edinger, 1908).

The most recent breakthroughs in the study of basal ganglia occurred with the development of various tract-tracing methods initiated in the last quarter of the 20th century. These powerful neuronographic tools have revealed how closely the various core structures of the basal ganglia are interrelated with one another, but this issue does not yet belong to the historians. Being at the heart of contemporary researches on basal ganglia, it will be dealt with in detail elsewhere in this volume.

III. TWO CONTROL STRUCTURES OF THE BASAL GANGLIA

A. Substantia Nigra

The discovery of the substantia nigra (see chapters: The Substantia Nigra Pars Reticulata and Subtypes of Midbrain Dopamine Neurons) has long been attributed to the great German scientist and philosopher Samuel Thomas von Sœmmerring (1755–1830), to whom we owe the description of various brain structures as well as the first accurate classification of cranial nerves (12 pairs, not 9 as in Willis) reported in his treatise *De basi encephali* (*The Basis of the Brain*) (Sœmmerring, 1778). Most neuroanatomy textbooks published during the 19th and the first half of the 20th century refer to the substantia nigra as *Sœmmerring's substance*, *substantia nigra of Sœmmerring*, or *locus niger Sœmmerringii*. However, Sœmmerring does not mention the existence of the substantia nigra in his 1778 treatise. It is only in a revised version of his book published 14 years later (Sœmmerring, 1792) that he alluded to this structure recognizing that it was originally identified and perfectly well characterized by the French anatomist Félix Vicq d'Azyr (1748–1794). Like Sœmmerring, Vicq d'Azyr was a typical medical figure of the Age of the Enlightenment; he had a vast and deep knowledge of medicine and biology that encompasses several fields of investigation, including epidemiology, comparative anatomy, social medicine, and neurology. He was one of the founders of the Royal Academy of Medicine and he remained the Perpetual Secretary of this prestigious institution until it was abolished by the French revolutionaries in 1793.

Vicq d'Azyr's major contribution to human brain anatomy is to be found in a remarkable work entitled *Traité d'anatomie et de physiologie* (Treatise of anatomy and physiology) published only 3 years before the beginning of the French Revolution and dedicated to King Louis the sixteenth (Vicq d'Azyr, 1786). This large folio volume contains 35 nature-sized, colored, human brain figures of a quality and exactitude never attained before. The color illustrations are accompanied by line drawings with minutely detailed explanations of the various brain structures identified and a critical history of the descriptions of the same structures given by preceding anatomists. All the plates in this treatise were drawn and engraved by Alexandre Briceau, draftsman to the anatomy cabinet of Alfort Royal Veterinary School. They were made with a combination of aquatint, line-engraving, and stipple-engraving and printed in colors (Fig. 2.4). The core of the work is preceded by a very elegant discourse on anatomy, which philosophically elevates this science to a degree not reached before and which strongly argues for the development of a general nomenclature that could be applied to all species. The book was to be the first of a long series of volumes on vertebrate anatomy, but the work came to an abrupt end with the advent of the French Revolution, Vicq d'Azyr having had the bad idea of becoming Queen Marie-Antoinette's private physician.

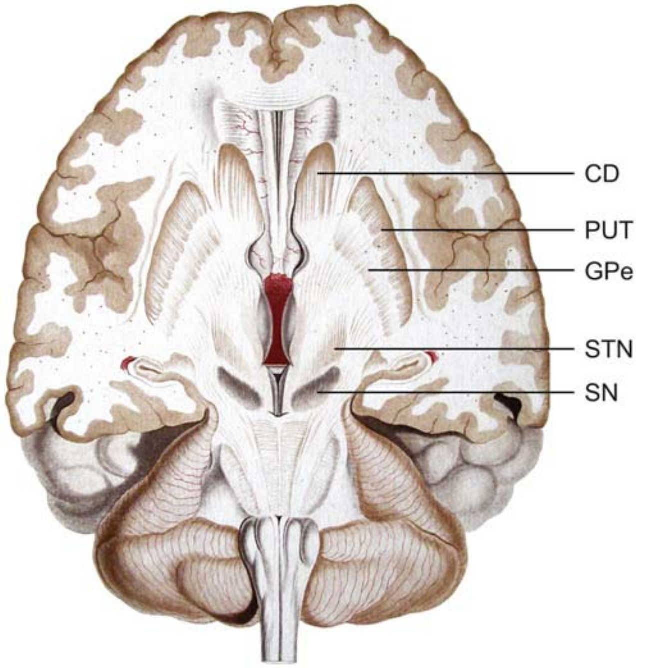

FIGURE 2.4 Felix Vicq d'Azyr's representation of the basal ganglia from his Traité d'anatomie et de physiologie (Vicq d'Azyr, 1786) (labels added to facilitate identification). This horizontal section of the human brain, which passes through the basal ganglia anteriorly and the brainstem and cerebellum posteriorly, depicts the caudate nucleus (CD), putamen (PUT), and globus pallidus external segment (GPe) separated from one another by groups of nerve fibers, as well as the subthalamic nucleus (STN) and substantia nigra (SN).

Vicq d'Azyr's dissection of the human brain was facilitated by a fixation technique that he borrowed from the Dutch anatomist Frederik Ruysch (1638–1731) and which consists of a combination of alcohol, saltpeter, and hydrochloric acid. His original dissection technique included scraping along the white matter fibers, a method that was to be extensively used later by Gall and Spurzheim. With the help of this procedure, Vicq d'Azyr was able to complement the pioneering description of the basal ganglia provided by Willis in 1664 (see Section II.A). Vicq d'Azyr clearly depicted these basal ganglia components but did not name them, a task that was accomplished 50 years later by Burdach. The substantia nigra is also clearly outlined in at least two of the magnificent illustrations of Vicq d'Azyr's treatise (Fig. 2.4). Vicq d'Azyr noted the dark pigmented nature of this structure, a feature that prompted him to call it *tache noirâtre* (dark spot) or *locus niger crurum cerebri* (dark region of the cerebral peduncles). Burdach, who referred to the same structure as *schwarzgraue Schicht* (black-gray layer) or its Latin equivalent *stratum nigrum* in his neuroanatomical treatise, gave full credit to Vicq d'Azyr for its discovery (Burdach, 1819−1826). Neither Vicq d'Azyr nor Burdach commented on the cellular aspects of the substantia nigra, a task that was left to late 19th-and early 20th-century microscopists.

The French alienist (psychiatrist) Jules Bernard Luys (1828−1897), who worked at la Salpêtrière and later at la Charité hospital in Paris, was probably the one who provided the first images of nigral neurons. These findings appeared in Luys' copious neuroanatomy treatise entitled *Recherches sur le système cérébro-spinal, sa structure, ses fonctions et ses maladies* (*Studies on the Structure, Functions and Diseases of the Nervous System*), which contains significant advances to human brain anatomy, including the prime description of the subthalamic nucleus (Luys, 1865) (see Section III.B). In his description of the human substantia nigra, Luys emphasized the fact that it harbors numerous densely packed neurons with ovoid or polygonal perikarya from which emerge numerous elongated processes. He also noted that nigral neurons stained intensely because they contained dark pigments. Unfortunately, Luys refers to the substantia nigra as the *locus niger de Sœmmering* [sic] in his 1865 treatise and this has greatly contributed to the perennial nomenclature confusion alluded to above. Furthermore, Luys depicted nigral neurons as having long processes that literally merge with one another, a detail that betrays his acceptance of the then commonly held reticularist view of the tissular organization of the central nervous system.

More than 20 years after the publication of Luys' pioneering work, the Italian neuroanatomists Giovanni Mingazzini (1859−1929) and Domenico Mirto (date unknown) and the Japanese morphologist Torata Sano (date unknown) provided more detailed descriptions of nigral neurons. Mingazzini depicted the human substantia nigra as a highly stratified structure composed principally of a dorsal layer containing several types of pyramidal cells and a ventral layer harboring "atypical" cells (Mingazzini, 1888). He mentioned that the pyramidal cells had a cylinder axis (axon) that coursed forward within the midbrain tegmentum. Mirto noted for the first time the close morphological resemblance between neurons of the substantia nigra and those of the globus pallidus, and further recognized that the vast majority of nigral neurons were Golgi type I (projection) cells (Mirto, 1896). Sano reported the results of an extensive comparative study of the substantia nigra in a wide range of species, including man, and provided a detailed description of nigral neurons that is still valid today (Sano, 1910). Sano subdivided the substantia nigra into a *pars compacta*, which harbors a densely packed population of pigmented neurons (dopamine neurons; see chapters: Subtypes of Midbrain Dopamine Neurons and Neurophysiology of Substantia Nigra Dopamine Neurons: Modulation by GABA and Glutamate), and a *pars reticulata*, which contains a smaller number of nonpigmented neurons that are rather loosely scattered within a dense fibrillary meshwork (see chapter: The Substantia Nigra Pars Reticulata).

This nigral subdivision, which is still in use today, was largely based on an earlier suggestion made by Santiago Ramón y Cajal (1852−1934) in his description of the substantia nigra that was first published at the very end of the 19th century (Ramón y Cajal, 1899). Using the Golgi staining procedure, Ramón y Cajal provided a clear depiction of the different types of neurons that populate each of the two major portions of the substantia nigra that he called superior and inferior zones. He also emphasized the existence of long and dorsoventrally oriented dendritic bundles that emerge from the large pyramidal-shaped neurons located within the superior zone (pars compacta) of the substantia nigra. However, despite the quality of the material he had in hand, he was unable to trace the axonal projection of nigral neurons, except for small distances within the midbrain tegmentum. Ramón y Cajal underlined the confusion that existed over this issue and indicated that the Russian neurologist Vladimir Bechterev (1857−1927) was the only one at that time who believed that nigral neurons were projecting their axons as far rostrally as the striatum (Ramón y Cajal, 1899).

The definitive demonstration of the nigrostriatal projection and the discovery of its dopamine content and role in Parkinson's disease are the results of intense researches conducted during the second half of the 20th century. This issue will be dealt with in detail elsewhere in the present volume.

B. Subthalamic Nucleus

The subthalamic nucleus (see chapter: The Subthalamic Nucleus) is perhaps the only basal ganglia component that escaped Burdach's scrutiny. The nucleus was discovered by Jules Bernard Luys, who also provided the first depiction of the thalamic *centre* *médian nucleus*, which is now known to be intimately associated with the core structures of the basal ganglia (Fig. 2.5). Luys was a highly dedicated neuroanatomist who contributed significantly to our knowledge of the organization of the central nervous system. His highly original insights and descriptions are to be found in his 1865 treatise in which Luys portrayed his original concepts through his own elegant three-dimensional diagrams assembled in the atlas that accompanied his 660-pages book (Luys, 1865). Luys was also a pioneer in applying the art of photography, then still in its infancy, to the illustration of brain anatomy. The results of his efforts along this line are to be found in a two-volume treatise entitled *Iconographie photographique des centres nerveux* (*Photographic Iconography of Nervous Centers*) that appeared 8 years after his neuroanatomy treatise (Luys, 1873). This very first photographic atlas of the human brain comprised photomicrographs of entire, serial human brain sections displayed in frontal, sagittal, and horizontal planes and accompanied by beautiful drawings identifying the various structures seen on each photomicrograph (Fig. 2.6).

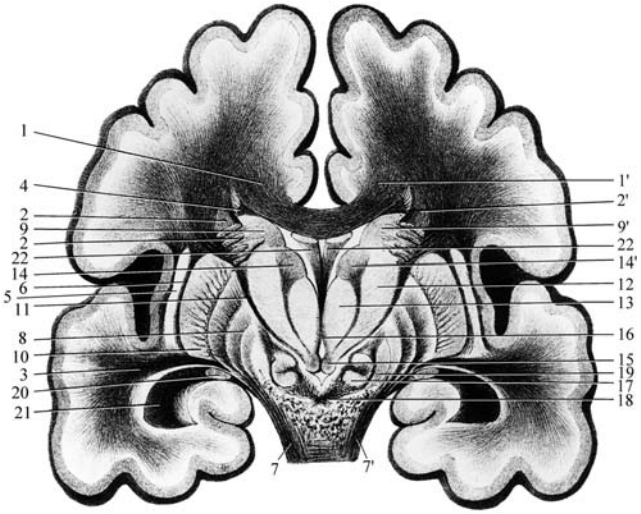

FIGURE 2.5 Jules Bernard Luys' first representation of the subthalamic nucleus that appeared in his *Recherches sur le système nerveux cérébro-spinal* (Luys, 1865). In this frontal and somewhat schematic section of the human disencephalon, the subthalamic nucleus (*bandelette accessoire de l'olive supérieure*) is identified by the number 19 on the right side of the drawing, whereas the *centre médian* is indicated by the number 13. Number 17 on the same side of the illustration points to Luys' *olive supérieure*, which corresponds to Burdach's red nucleus. The subthalamic nucleus appears here as a sort of third segment of the globus pallidus.

In his 1865 opus magnum, Luys employed the term *noyaux gris centraux* (central gray nuclei) to designate the thalamus (*la couche optique*) and the striatum (*le corps strié*), an appellation that has been retained in the French literature (Foix and Nicolesco, 1925). In contrast, the name *bandelette accessoire de l'olive supérieure* (accessory band of the superior olive) that he used to describe the subthalamic nucleus created much confusion and did not last long. This awkward designation, in which the term *olive supérieure* referred to the red nucleus of Burdach, was chosen by Luys to convey his view of the role of the subthalamic nucleus.

According to Luys, the major function of the subthalamic nucleus was to disperse the influence of the

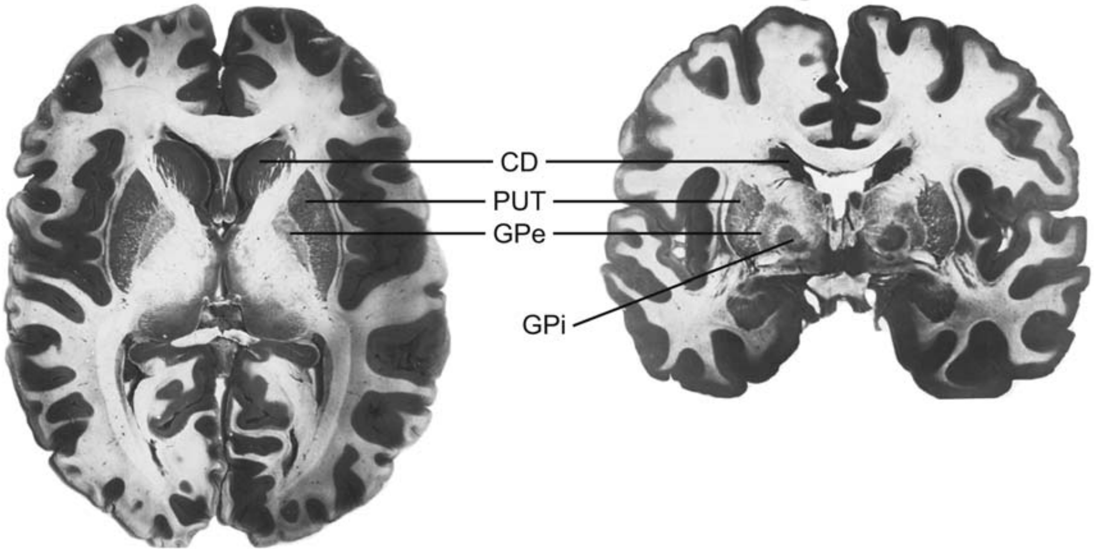

FIGURE 2.6 Jules Bernard Luys' photographic depiction of the human basal ganglia as found in his *Iconographie photographique* (Luys, 1873) (labels added to facilitate identification). The photomicrographs show the basal ganglia in a horizontal (left) and a coronal plane (right). The topographical organization of the core structures of the basal ganglia (*CD*, caudate nucleus; *PUT*, putamen; *GPe*, globus pallidus external segment; *GPi*, globus pallidus internal segment) is well illustrated in these two photomicrographs.

cerebellum upon the striatum, a disposition that allows the structure to play a "crucial role in the synthesis of automatic motor actions" (Luys, 1865). Hence, although he erred in believing that the cerebellum projects to the subthalamic nucleus, the red nucleus (Luys' *olive supérieure*) being the main target of the cerebellum in that brain region, Luys should be praised for having thought of the nucleus as being intimately linked to the basal ganglia. He also described nervous fibrils that linked the subthalamic nucleus with the globus pallidus (the subthalamopallidal connection of the current literature) and depicted a fiber projection from the cerebral cortex to the subthalamic nucleus (Luys, 1865). He also clearly envisaged the fact that the various areas of the cerebral cortex are directly represented at the level of the striatum via the corticostriatal projections (*les projections corticostriées*). Many of these structures and fiber pathways are now central to our current thinking about the anatomical and functional organization of the basal ganglia, as well as to the physiopathology of Parkinson's disease.

Luys' description of the subthalamic nucleus is to be found not in the section of his book dealing with the forebrain, as one might expect, but in that pertaining to the cerebellum and its dependencies. There, Luys alludes to the presence of a "novel clump of gray matter that takes the form of a semilunar band, which in turn becomes a center for the dispersion of a new generation of nervous elements" (Luys, 1865). Luys continues on to say that "the accessory band of the superior olive thus formed by the grouping of one portion of its afferent fibers appears as a clump of a grayish substance, displaying a linear form, bulged on its median portion and slandered on each of its extremities." He further specified that the accessory band of the superior olive together with what he calls the *arcades* (arches), which correspond to the various medullary laminae that separate the different components of the lenticular nucleus, form an imbricated structure that encompasses the corpus striatum (Fig. 2.5). Luys affirms that this complex architecture helps to single out "these nuclei of a yellowish substance, whose clear color contrasts so markedly with the dark red tint of the surrounding corpus striatum." Luys' yellow nuclei correspond to the two segments of the globus pallidus, which were clearly singled out 40 years earlier by Burdach (Burdach, 1819–1826).

The Swiss alienist Auguste Forel (1848–1931), who was trained in neuroanatomy and microscopy by Meynert in Vienna and Bernhard Aloys von Gudden (1824–1886) in Munich, reassessed the original description of the subthalamic nucleus provided by Luys in 1865. In a remarkable paper devoted to the organization of the brainstem tegmental region of man and various mammals, Forel provided a clear description of the complex nuclear and fibrillar organization of the tegmental region, many components of which still bear his name (Forel, 1877). This is the case of the *tegmental fields of Forel* (campus Foreli), which included fields H, H1, and H2, the "H" standing for the German word *Hauben* (introduced earlier by Reil), which refers to the nightcap aspect of this region. The fields H, H1, and H2 correspond respectively to the prerubral field, the thalamic fasciculus and the lenticular fasciculus. Forel's field H system consists of the field H2 fiber system that courses in-between the subthalamic nucleus and the zona incerta—a structure that Forel was the first to define—merges with fibers of the ansa lenticularis within field H to finally form the field H1 fiber system that ascends toward the ventral tier nuclei of the thalamus.

In 1895, the Russian-Swiss neuroanatomist Constantin von Monakow (1853–1930), who worked in Zurich, gave a detailed account of the ansa lenticularis (*Linsenkernschlinge*), which he referred to as "the sum of the fiber masses which come from the region of the lentiform nucleus, penetrate the cerebral peduncle, and gain the subthalamic region and the medial division of the thalamus" (Monakow, 1895). Monakow subdivided this massive fiber system into three different components: (1) a dorsal division, commonly termed lenticular fasciculus (Forel's field H2); (2) a middle division, often described separately as fasciculus subthalamicus; and (3) a ventral division, called the ansa lenticularis (Forel's field H1) *sensus strictiori* by later authors. Originally, Monakow believed that the ansa lenticularis had a mixed striatal and pallidal origin (Monakow, 1895). However, the experimental studies undertaken in monkeys by Stephen Walter Ranson (1880–1942) and his colleagues at Northwestern University in Illinois invalidated this view by demonstrating that these three fiber fascicles arise from distinct portions of the globus pallidus (Ranson et al., 1941). Today, these fiber systems are known to convey motor information of pallidal and cerebellar origin to the thalamus and they occupy a central position in our current thinking of the pathophysiology of the basal ganglia. However, the complex arrangement of these markedly intricated fiber systems still remains to be deciphered.

Forel's paper on the tegmental region was widely acclaimed by the scientific community. Among those who wrote personally to Forel to congratulate him on this major contribution was Luys, the discoverer of the subthalamic nucleus, who was particularly proud to see that Forel had attached his name to the structure. Indeed, this component of the subthalamic region is termed *Luysscher Körper*, *corpus luysii*, or *Bandelette accessoire de l'olive supérieure von Luys* in Forel's writings. However, Forel was very critical of the latter name (accessory band of the superior olive) given by Luys to the subthalamic nucleus. In his 1877 paper, one can read: "This term is improper for at least three reasons. First, the word bandelette commonly refers to a band of white matter, whereas the nucleus in question is clearly a mass of gray matter. Second, what Luys called *olive supérieure* corresponds to the red nucleus of Burdach and not to the superior olivary nucleus of Schröder van der Kolk (1797–1862). Third, Luys' nucleus has nothing to do with either the red nucleus or the superior olivary nucleus" (Forel, 1877). Forel's paper includes a much more accurate description and illustration of the subthalamic nucleus than the one provided originally by Luys, and also contains a microscopic drawing of a neuron of the subthalamic nucleus.

In contrast to Forel, who wrote in German but was born in the French part of Switzerland, German-speaking neurologists were reluctant to attach Luys' name to the subthalamic nucleus and this lead to an obvious terminological confusion. For example, the subthalamic nucleus was termed *nucleus amygdaliformis* by Jacob Stilling (1842–1915), who worked at the University of Strasburg (Stilling, 1878), whereas Friedrich Gustav Jacob Henle (1809–1885) in Gottingen called it *corpus subthalamicum* (Henle, 1879). Theodor Meynert in Vienna used the term *discus lentiformis* (Meynert, 1884), whereas Ludwig Edinger in Frankfurt named it *Forel's body* (Edinger, 1908). Finally, in his elegant vascularization study of the subthalamic region, Rolf Denkhaus (1917–1944) of Leipzig referred to the subthalamic nucleus as *nucleus hypothalamicus* (Denkhaus, 1942). In France, however, the name of Luys remained attached to the subthalamic nucleus for quite a long period. In fact, most French neurologists designated the nucleus as *le corps de Luys* until the last portion of the 20th century, when the structure was progressively integrated into the realm of the basal ganglia under the name *subthalamic nucleus*.

Luys' last contribution to the description of the subthalamic nucleus is to be found in a paper entirely devoted to this structure published more than 20 years after his original description (Luys, 1886). In this largely ignored article, Luys no longer alludes to the superior olivary complex in connection with the subthalamic nucleus, but now uses the term *accessory band of the red nucleus of Stilling (corpus Luysii)* to designate this structure. The exact location and biconvex lens shape of the nucleus can be clearly appreciated in a photomicrograph of a horizontal human brain section that illustrates the findings. In this paper, Luys insists on the cytological homogeneity, high cellular density, compactness, small-celled nature, and neuroglial framework of the subthalamic nucleus, which he clearly described as a mass of gray matter. He notes that neurons of the subthalamic nucleus emit numerous short processes that intermingle with those of adjoining cells, thus forming an inextricable fibrillary network. He also mentions the existence of nervous fibers emerging from the cerebral cortex and terminating in the red nucleus and subthalamic nucleus, two fiber systems that are known today as the corticorubral and the corticosubthalamic projections. Luys underlines the physiological and pathological importance of such direct connections between the cortical mantle and the various gray masses that lie within this "still mysterious region of the basis of the brain" (Luys, 1886).

From a pathological point of view, Luys thought that the importance of the conjunctive tissue fabric of these ventral brain regions could explain the frequent sclerotic indurations encountered at the basis of the brain in certain pathological cases he examined. He also believed that, because of the abundance of glial cells, even a small irritation in these brain structures may lead to a rapid glial cell proliferation and ultimately to localized sclerosis, with progressive evolution. These premonitory insights were confirmed slightly later in the 19th century and early 20th century when clinicians realized that lesions of the subthalamic nucleus cause violent, involuntary, wild, flinging movements usually limited to the side of the body contralateral to the lesion. This syndrome, described as *hémichorée post-hémiplégique* (posthemiplegic hemichorea) by Jean-Martin Charcot (1825–1893) (Charcot, 1877), was later termed *Hemichorea* or *Hemiballismus* in the German literature (Greiff, 1883; Sántha, 1928), or more simply *hemiballism* in the English literature (Whittier, 1947).

From a functional point of view, Luys clearly recognized that little, if anything, is known of the physiology of the subthalamic nucleus. He considered the situation a delicate one "destined to keep spellbound for many years to come, the sagacity of the vivisectors of the future" (Luys, 1886). Luys could not have been more right. It is only recently, with the advent of powerful experimental tools applied to various animal models of motor diseases, that the subthalamic nucleus was recognized as a driving force of the basal ganglia, a topic that will be covered in detail elsewhere in this volume. Clinically, the subthalamic nucleus has become the preferential target for neurosurgeons who use the deep brain stimulation approach to alleviate the major motor symptoms related to Parkinson's disease. However, the mechanisms and the specific neuronal elements whereby this approach produces its beneficial effects are still largely unknown.

IV. CONCLUSION

The present chapter has briefly reviewed the long and convoluted history of a set of subcortical structures that plays a crucial role in the control of motor behavior and sensorimotor integration. The basal ganglia concept, as we know it today, took many centuries to emerge. Its historical evolution did not follow a straight ascending course, but resulted from both significant advances and major drawbacks in our knowledge of brain anatomy. It is the result of immense efforts made by several pioneers of brain anatomy, such as Thomas Willis of Oxford and Karl Friedrich Burdach of Konigsberg, who deserve our respect. In this chapter, we have focused on the core structures of the basal ganglia, namely the striatum and pallidum, and on the subthalamic nucleus and substantia nigra, which are closely linked with the former through closed ancillary loops that are characteristics of basal ganglia circuitry. Recent experimental and clinical studies have radically advanced our concept of the basal ganglia, which are now viewed as a widely distributed neuronal system that acts in concert with the corticofugal system to control the multifarious aspects of motor behavior. The different sets of studies that led to this modern view will be reviewed in detail in other chapters of the present volume.

References

Berengario da Carpi, 1523. Isagogae breves per lucidae ac uberrimae in anatomiam humani corporis a comunis medicorum academia usitam. Nenedictum Hectori, Bologna.

Burdach, K.F., 1819–1826. Vom baue und leben des gehirns, 3 vols. Dyk, Leipzig.

Charcot, J.M., 1877. Leçons sur les maladies du système nerveux, vol. 2. Delahaye, Paris, pp. 329–341.

Denkhaus, R., 1942. Über die Angioarchitektonik des Nucleus hypothalamicus. Arch. Psychiat. 115, 61–81.

Edinger, L., 1908. Vorlesungen über den Bau der nervösen Zentralorgane des Menschen und der Tiere. Vogel, Leipzig.

Ferrier, D., 1876. The functions of the brain. Smith, Elder, & Co, London.

Foix, C., Nicolesco, J., 1925. Anatomie cérébrale. Les noyaux gris centraux et la région mésencéphalo-sous-optique; suivi d'un appendice sur l'anatomie pathologique de la maladie de Parkinson. Masson, Paris.

Forel, A., 1877. Untersuchungen über die Haubenregion und ihre oberen Verknüpfungen im Gehirne des Menschen und einiger Säugethiere, mit Beiträgen zu den Methoden der Gehirnuntersuchung. Arch. Psychiat. Nervenkr. 7, 393–495.

Galen [Claudius Galenus], 1490. Opera (Trans. Diomedes Bonardus), 2 vols. Venice, Pinzi.

Gall, F.J., Spurzheim, J.K., 1810. Anatomie et physiologie du système nerveux en général et du cerveau en particulier. Schoell, Paris.

Greiff, F., 1883. Zur Localisation der Hemichorea. Arch. Psychiat. 14, 598–624.

Haller, A. von, 1757–1766. Elementa physiologiae corporis humani, 8 vols. Bousquet, Lausanne.

Henle, F.G.J., 1879. Handbuch der systematischen Anatomie des Menschen, vol. 3, Nervenlehre. Vierweg, Braunschweig.

Isler, H., 1968. Thomas Willis (1621–1675): Doctor and Scientist. Hafner, New York.

Luys, J.B., 1865. Recherches sur le système nerveux cérébro-spinal, sa structure, ses fonctions et ses maladies. Baillière, Paris.

Luys, J.B., 1873. Iconographie photographique des centres nerveux. Baillière, Paris.

Luys, J.B., 1886. Description d'une nouvelle région de substance grise située à la base de l'encéphale. L'Encéphale. 6, 5–10.

Meynert, T., 1884. Psychiatrie. Klinik der Erkrankungen des Vorderhirns begründet auf dessen Bau, Leistungen und Ernährung. Braumüller, Wien.

Mingazzini, G., 1888. Sulla fine struttura della Substantia nigra Sömmeringii. Reale Acad. Lincei (Roma). 5, 36–40.

Mirto, D., 1896. Sulla fina anatomia delle regioni peduncolare e subthalamica nell'uomo. Riv. Patol. nervosa mentale (Firenze). 1, 57–60.

Monakow, C. von, 1895. Experimentelle und pathologische-anatomische Untersuchungen über die Haubenregion, den Sehhügel und die Regio subthalamica, nebst Beiträgen zur Kenntnis früh erworbener Gross- und Kleinhirn-defekte. Arch. Psychiatr. Nervenkr. 27, 1–128.

Mondino de' Liuzzi, 1482. Anathomia. Bernardinum Venetum, Bologna.

Portal, A., 1770–1773. Histoire de l'anatomie et de la chirurgie. Didot, Paris (6 Vols).

Prus, J., 1898. Uber die Leitungsbahnen und Pathogenese der Rindenepilepsie. Wien Klin Wochenschr. 11, 857–863.

Ramón y Cajal, S., 1899. Textura del sistema nervioso del hombre y de los vertebrados, 3 vols. Gobierno de Aragón, Zaragoza.

Ranson, S.W., Ranson Jr, S.W., Ranson, M., 1941. Fiber connections of the corpus striatum as seen by Marchi preparations. Arch. Neurol. Pychiat. 46, 230–249.

Reil, J.C., 1809. Das verlängerte Rückenmark, die hinteren, seitlichen und vorderen Schenkel des kleinen Gehirns und die theils strangförmig, theils als Ganglienkette in der Axe des Rückenmarks und des Gehirns fortlaufende graue Substanz. Archiv. Physiol. (Halle). 9, 485–524.

Sano, T., 1910. Beitrag zur vergleichenden Anatomie der Substantia nigra, des Corpus Luysii und der Zona incerta. Mschr. Psychiat. Neurol. 27, 110–127.

Sántha, K. von, 1928. Zur Klinik und Anatomie des Hemiballismus. Arch. Psychiat. 84, 664–678.

Stensen, N., 1669. Discours de Monsieur Sténon sur l'anatomie du cerveau à Messieurs de l'Assemblée, qui se fait chez Monsieur Thévenot. R. de Ninville, Paris.

Stilling, J., 1878. Über eine neue Ursprungesstelle des Sehnerven. Cbl. Med. Wiss. 22, 385–386.

Sœmmerring, S.T., 1778. De basi encephali et originibus nervorum cranio egredientium libre quinque. Vandenhoeck, Göttingen.

Sœmmerring, S.T., 1792. De basi encephali et originibus nervorum cranio egredientium libre quinque. In: Ludwig, C.F. (Ed.), Scriptores neurologici minores selecti sive opera minora ad anatomiam physiologiam et pathologiam nervorum spectantia, vol. 2. Junius, Leipzig, pp. 1–112.

Vesalius, A., 1543. De humani corporis fabrica libri septem. Oporinus, Basel.

Vicq d'Azyr, F., 1786. Traité d'anatomie et de physiologie. Didot, Paris.

Vieussens, R., 1684. Neurographia universalis. Certe, Lugduni.

Vogt, C., Vogt, O., 1920. Zur Lehre der Erkrankungen des striären Systems. J. Psychol. Neurol. (Leipzig). 25, 631–659.

Whittier, J.R., 1947. Ballism and the subthalamic nucleus (nucleus hypothalamicus; corpus Luysi). Arch. Neurol. Psychiat. 58, 672–692.

Willis, T., 1664. Cerebri anatome cui accessit nervorum descriptio et usus. Flesher, Martyn & Allestry, London.

Willis, T., 1672. De anima brutorum. Davis, Oxford.

Wilson, S.A.K., 1912. Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver. Brain. 34, 295–507.

Wilson, S.A.K., 1914. An experimental research on the anatomy and physiology of the corpus striatum. Brain. 36, 427–492.