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## Review

# Quest for the basic plan of nervous system circuitry

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### ABSTRACT

The basic plan of nervous system organization has been investigated since classical antiquity. The first model centered on pneumas pumped from sensory nerves through the ventricular system and out motor nerves to muscles. It was popular well into the 17th century and diverted attention from the organization of brain parenchyma itself. Willis focused on gray matter production and white matter conduction of pneumas in 1664, and by the late 19th century a clear cellular model of nervous system organization based on sensory, motor, and association neuron classes transmitting nerve impulses was elaborated by Cajal and his contemporaries. Today, revolutionary advances in experimental pathway tracing methods, molecular genetics, and computer science inspire systems neuroscience. Seven minimal requirements are outlined for knowledge management systems capable of describing, analyzing, and modeling the basic plan of nervous system circuitry in general, and the plan evolved for vertebrates, for mammals, and ultimately for humans in particular. The goal remains a relatively simple, easy to understand model analogous to the one Harvey elaborated in 1628 for blood circulation in the cardiovascular system. As Cajal wrote in 1909, “To extend our understanding of neural function to the most complex human physiological and psychological activities, it is essential that we first generate a clear and accurate view of the structure of the relevant centers, and of the human brain itself, so that the basic plan – the overview – can be grasped in the blink of an eye.”

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## 1. Introduction

The first chapter of Santiago Ramón y Cajal's greatest work is called *Basic plan of the nervous system: the structural framework of neural centers and laws governing them in animals* (Cajal, 1909–1911). It is a brilliant manifesto for modern neuroscience – crystallizing the paradigm shift that allowed a deep cellular explanation of macrostructure – that has been refined and modified extensively during the last century with advances in cell and molecular biology, but not replaced by a qualitatively new and more powerful global systems model. This essay is inspired by reflections on the centenary of the 1906 Nobel Prize to Cajal and his great rival Camillo Golgi. For perspective, the first part is a brief history of early theories about the basic plan of the nervous system, followed by an outline of Cajal's contribution. Then some major insights gained later in the 20th century are reviewed, and the last part entertains some conjectures about the future.

## 2. The classical era: macrostructure and functional systems

The general principles of neural systems analysis have never been stated more clearly than by Nicolaus Steno in 1669, “There are two ways only of coming to know a machine: one is that the master who made it should show us its artifice; the other is to dismantle it and examine its most minute parts separately and as a combined unit... [And] since the brain is a machine [Descartes, 1664], we need not hope to discover its artifice by methods other than those that are used to find such for other machines... I mean the dismantling of all its components, piece by piece, and consideration of what they can do separately and as a whole” (Steno, 1965, p. 139). A three-fold starting point, in other words, is a comprehensive parts list, an understanding of how each part works individually, and an account of how all of them are interconnected and work together.

The early history of information about the nervous system is understandably obscure, although we do know that the ancient Egyptians were familiar with the human brain and spinal cord (Brestead, 1930; Nunn, 2002), that the Hippocratic writers probably recognized the ventricular system (Hippocrates, 1972), and that Aristotle began the process of brain regionalization by distinguishing between cerebrum and cerebellum in animal brains (Clarke and O'Malley, 1996). Shortly thereafter (c. 335–c. 280 BC), in Alexandria, the great physician–scientist Herophilus discovered through dissection of animals and human cadavers the cranial and spinal nerves, distinguishing them for the first time from arteries, veins, tendons, and ligaments, and distinguishing as well between

sensory and motor nerves he suggested are hollow (Solmsen, 1961; von Staden, 1989; Longrigg, 1993; Clarke and O'Malley, 1996). In his *On the Names of the Parts of the Human Body*, Rufus of Ephesus (c. 100 AD) referred for the first surviving time to the brain, spinal cord, and craniospinal nerves as an anatomical unit (Clarke and O'Malley, 1996), although reference to these terms together, along with the ventricles, as “the nervous system” in the modern sense was not introduced for another 1600 years (Monro, 1783).

Galen was, of course, the greatest anatomist of antiquity and the founder of experimental physiology as well—and his best work in these arenas focused on the nervous system (Galen, 1968, 1999; Clarke and O'Malley, 1996; Rocca, 2003). In his general system – which was probably derived from Herophilus's contemporary Erasistratus (see Manzoni, 1998) – the liver generates veins that convey natural pneuma (from the Greek, natural spirit from the Latin), the heart generates arteries that convey vital pneuma (spirit), and the brain generates nerves that convey psychic pneuma (Greek, animal spirits from the Latin). Although Galen's views on nervous system function are complex and scattered through his many works, overall his dissections and experiments led him to propose that the brain is the seat of sensations from the five external senses; the site of all mental or psychic functions, including what were regarded as the internal senses of imagination, thought, and memory; and the source of voluntary movement (Manzoni, 1998).

The alternate view, that the heart is the seat of mental functions, or at least some of them, was held by Aristotle and others (see Longrigg, 1993; Clarke and O'Malley, 1996; Manzoni, 1998), and is deeply embedded in Western culture. Recall Portia's song in Shakespeare's *Merchant of Venice*, “Tell me where is fancie bread/Or in the heart or in the head.”

### 2.1. The first model: pneumatic–ventricular

In the first truly global, synthetic view of nervous system structure and function, Galen also proposed that sensory function is supported by psychic pneuma flowing from sensory organs through hollow sensory nerves to the lateral ventricles, that the three mental or psychological functions of the rational soul (imagination, thought, and memory) are accomplished by psychic pneuma refined in the brain ventricles, and that voluntary movement is effected by psychic pneuma flowing from our fourth (cerebellar) ventricle through motor nerves to the muscles. This essentially hydraulic model drew heavily on Galen's understanding of the cardiovascular system: based partly on experimental evidence, he regarded the brain as a kind of pump, and proposed that it draws psychic pneuma from the sensory nerves into the lateral ventricles and then

forces it into motor nerves from the fourth ventricle (Manzoni, 1998).

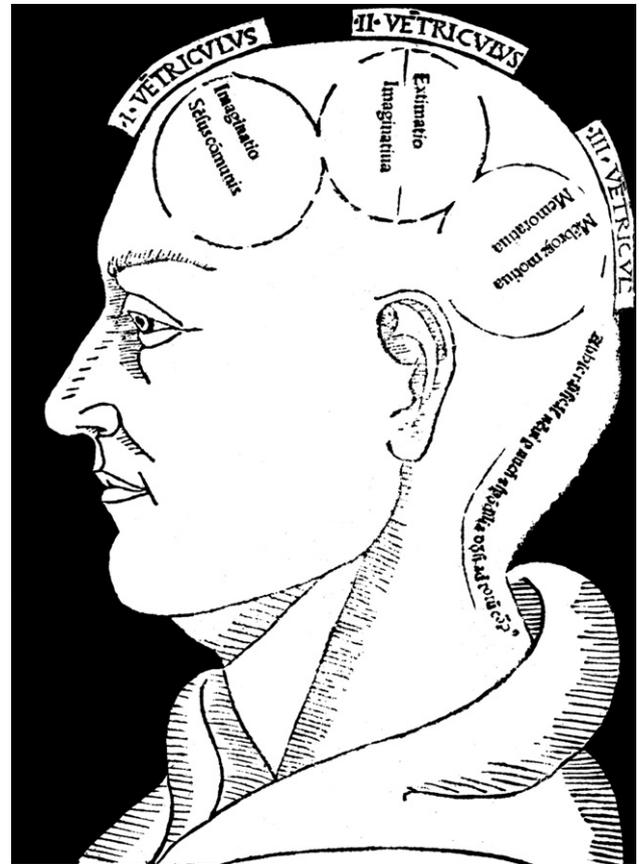
Psychic pneuma – a term one might loosely equate with “neural activity” today – was viewed by Galen and his followers as something akin to highly refined air, and its course through nerves and the ventricular system was considered all important. Based on this assumption or theoretical framework, psychic pneuma is responsible for sensation, thought, and movement—so that, in contrast, the structural organization of brain substance itself is inconsequential, an insignificant line of research as editors of the highest profile modern journals are fond of saying.

Beginning in the 4th and 5th centuries AD, this “ventricular–pneumatic doctrine” of nervous system functional localization was extended by theologian–philosophers in a way that attributed special mental functions to differentially refined psychic pneumas in our lateral, third, and fourth ventricles. In this era, which recent scholarship suggests was initiated by Nemesius, Bishop of Emesia (c. 390–c. 400 AD), the ventricles were often referred to as cells, and the “three-cell theory” of brain function held that the first cell (the right and left lateral ventricles together) subserves association of the five basic external sensations (the “common sense” or *sensus communis*) accompanied by imagination, the second cell (our third ventricle) subserves thinking or cogitation, and the third cell (our fourth ventricle) subserves memory. Manzoni (1998) has critically reviewed the history of the “three-cell theory,” which became more and more elaborate and remained popular well into the 17th century. In essence, the three basic internal senses (imagination, cogitation, and memory) were parceled into at least 7 different faculties, which were refined and combined in over 70 different ways.

The first printed illustration of the brain was in a 1490 edition of Albertus Magnus’s *Philosophia pauperum sive philosophia naturalis* (written in the 13th century), and it is a schematic representation of the medieval “three-cell theory” projected on a head drawn in elegant high-Renaissance style by an unidentified artist (Fig. 1). This figure shows the output side of the system: the text leading out of the third cell – his third ventricle and our fourth, where the faculties of memory and the power that moves the limbs are indicated – reads, “The nerves radiate through the neck and all the vertebrae to the whole body” (Clarke and Dewhurst, 1996).

The input side of the system was illustrated elegantly in a figure that appeared in the first modern encyclopedia, Gregor Reisch’s *Margarita philosophica* (*The Pearl of Wisdom*; first edition 1503). Here, nerves associated with olfaction, gustation, vision, and audition are shown converging in the rostral end of the lateral ventricles, associated with the *sensus communis* (Fig. 2). In this version of the three-cell theory, the faculties of fantasy and basic imagination are also localized to the first cell, and their flow into the second cell is regulated by the *vermis* (choroid plexus extending through interventricular foramen). The faculties of logic and estimation are localized in the second cell and they proceed to the third cell through an opening corresponding to the cerebral aqueduct.

In summary, Galen’s pneumatic–ventricular theory was the first global model of nervous system functional localiza-



**Fig. 1** – The first printed rendering of the brain illustrates a then current version of the “three-cell theory” of nervous system function. The first cell or ventricle (I ventriculus) corresponds to our right and left lateral ventricles together.

It is regarded the convergence site for the five external senses (*sensus communis* or the common sense) and also refines a flavor of psychic pneuma subserving basic imagination (*Imaginatio*). The second cell or ventricle corresponds to our third ventricle (the hole between the two ventricles represents our interventricular foramen), and its flavors of psychic pneuma subserves the level of cogitation thought to be shared by all animals (*Ex[st]imatio*) and the creative imagination regarded as unique to humans (*Imaginativa*). The third cell or ventricle corresponds to our fourth ventricle and its psychic pneuma supports memory and limb movement. The hole between ventricles II and III represents our cerebral aqueduct. From Albertus Magnus (1490), photograph courtesy of the National Library of Medicine.

tion and dynamics. Psychic pneuma was pumped through the sensory nerves into the lateral ventricles, then forced through the ventricular system where it generated sensation, thought, and memory, and finally pumped out of the fourth ventricle through the motor nerves to produce behavior. Beginning around 400 AD and continuing well into the 17th century (Fig. 3), various aspects of psychic or mental function were localized in many different ways to various parts of the ventricular system.

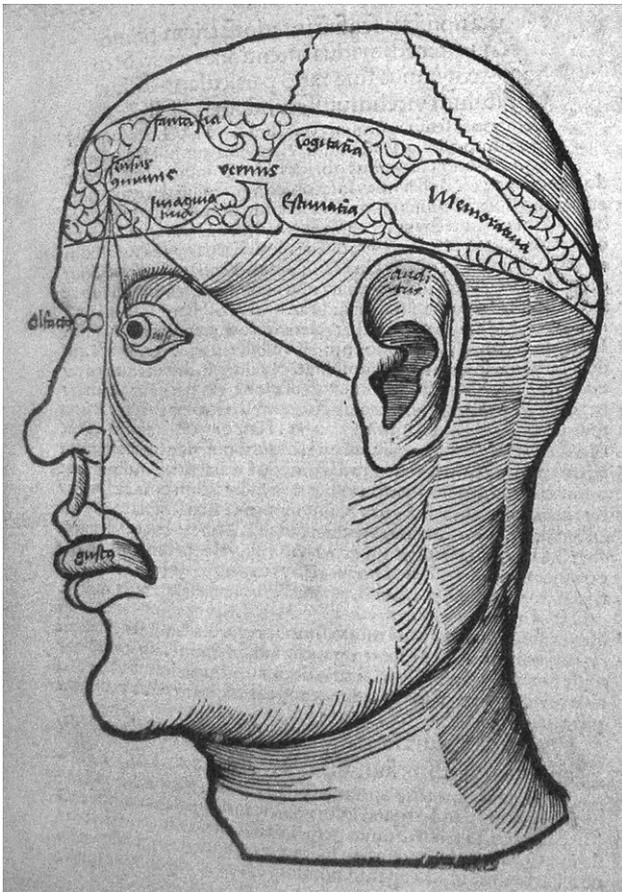


Fig. 2 – Perhaps the most famous illustration of the three-cell theory of brain functional localization, and the sequential elaboration of cognitive processes leading to behavior (illustrated in Fig. 1). An elongated sagittal “window” on the brain, cut into the skull (note the rather inaccurately placed coronal and lambdoid sutures at the top), reveals schematically the ventricular system, surrounded by what may be rough indications of cerebral gyri, with the olfactory, gustatory, optic, and auditory nerves converging in the rostral end of the anterior (lateral) ventricles. From Gregor Reisch (1504 second edition), photograph courtesy of the UCLA Louise M. Darling Biomedical Library, Department of History and Special Collections.

## 2.2. The second model: gray matter production–white matter conduction

It is remarkable, in light of strides naturalistic European art made in the 15th century, that the first realistic drawings of the brain were not published until 1517 by Johannes Schott (Roberts and Tomlinson, 1992), and they were relatively crude, as were the few others published until 1543 (Singer, 1952; Clarke and Dewhurst, 1996), when Andreas Vesalius’s vast *De humani corporis fabrica libri septem* appeared—one of the two most important books (Vesalius, 1543; along with Harvey’s 1628, *De Motu Cordis*) in the life sciences between antiquity and Darwin. Vesalius set out to describe systematically by personal dissection, rather than by authority, the entire

human body, to correct earlier errors, and to illustrate the results with the best available artistic methods.

Nothing highlights Vesalius’s genius more than a comparison of Reisch’s drawing (Fig. 1) with one of the drawings of the head and brain from the *Fabrica* (Fig. 4). Here is Vesalius’s comment on Reisch’s figure, which he used in medical school, “...we were shown a figure from some Philosophic Pearl [the *Margarita philosophica*] which presented to the eyes the ventricles so discussed. This figure we pupils portrayed, each according to his skill as a draughtsman, adding to it our notes. It was suggested to us that this figure comprehended not merely the three ventricles but all relevant parts of the head, and especially the brain! Such are the inventions of those who never look into our Maker’s ingenuity in the building of the human body! How such people err in describing the brain will be demonstrated in our subsequent discussion.” (Singer, 1952, p. 6).

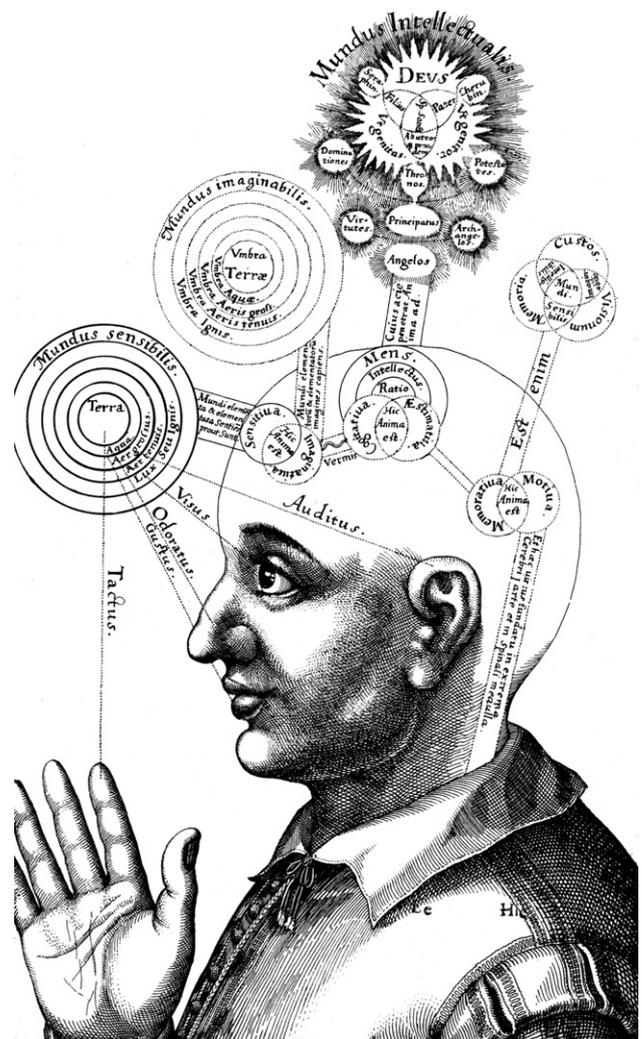
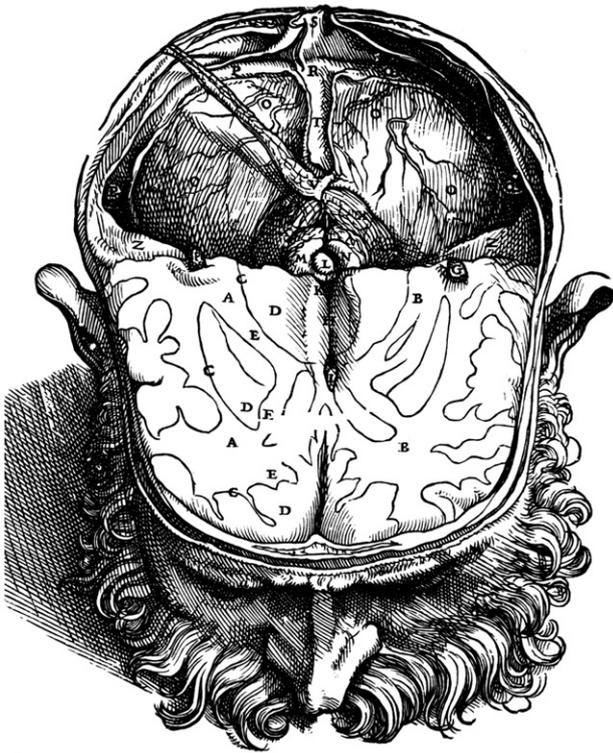


Fig. 3 – The ultimate illustration of the three-cell theory of brain functional localization, from Fludd (1617–1621). Its debt to earlier work is obvious (see Figs. 1 and 2), and modern guides to its interpretation can be found in Clarke and Dewhurst (1996) and Manzoni (1998). Photograph courtesy of the National Library of Medicine.



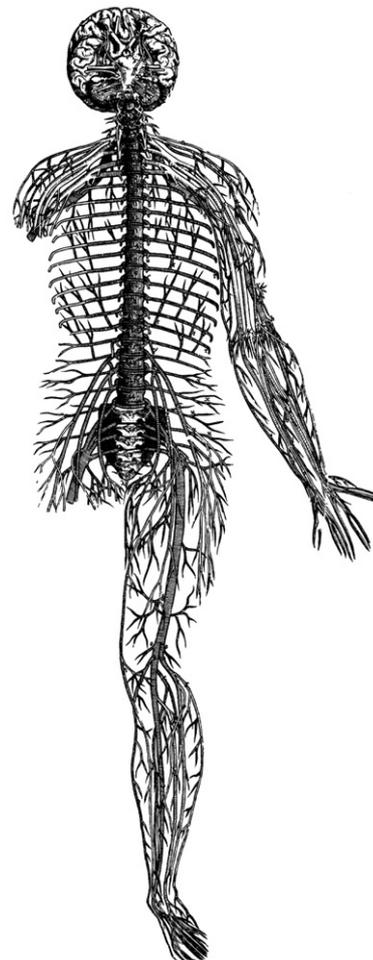
**Fig. 4** – An illustration of brain macrostructure from Vesalius’s *Fabrica*. At this dissection stage (15 were illustrated), the skullcap is removed, the cerebrum cut horizontally, and the occipital lobes removed (top of the figure) to expose the pineal gland (L), tectum (M, N), and dura over the cerebellum (O). In the remaining cerebrum on the figure’s left side the third ventricle; thalamus; posterior and anterior limbs of the internal capsule; globus pallidus, putamen, and caudate nucleus; external capsule and corona radiata; and cerebral cortex are illustrated sequentially, starting near the pineal gland and moving toward the lower left. The only previous indication of a distinction between gray and white matter was in a crude diagram by Dryander (1536, his Fig. 6; see Lind, 1975). Reproduced from the second illustrated edition of the *Fabrica* (Vesalius, 1555).

Vesalius paid great attention to the structure of the brain substance as well as the ventricular system, but was careful not to speculate wildly on how the brain works, “I can in some degree follow the brain’s functions in dissections of living animals [physiological experimentation], with sufficient probability and truth, but I am unable to understand how the brain can perform its office of imagining, meditating, thinking, and remembering, or following various doctrines, however you may wish to divide or enumerate the powers of the Reigning Soul” (Singer, 1952, p. 4). Vesalius did, however, distinguish very clearly between outer gray matter and inner white matter in drawings of the cerebrum (Fig. 4) and cerebellum; and he illustrated brilliantly the entire nervous system, including brain, spinal cord, and craniospinal nerves (Fig. 5)—an exceptionally challenging technical feat even today.

Harvey’s book on the circulation of the blood had a profound influence on neuroscience in the sense that it

inspired Thomas Willis a few years later (and even Bell and Magendie two centuries after that) to propose a similar theory for nervous system function—not unlike Galen’s much earlier analogies between cardiovascular and nervous systems. Willis’s most lasting book on the brain, the *Cerebri anatome* (Willis, 1664), was highly original, had a profound influence on neurological terminology, and was very speculative, as pointed out immediately by distinguished contemporaries like Steno and Giovanni Borelli.

In the *Cerebri anatome* Willis proposed the first original model of nervous system structure–function since the pneumatic–ventricular theory of Galen. It is a complex scheme, but in essence states that animal spirit (psychic pneuma) is generated in the gray matter of the cerebral and cerebellar cortices and that it ebbs and flows or circulates through the fibrous white matter of the brainstem and spinal cord, from the sensory and to the motor nerves—and that there is a topographic separation of functionally distinct fiber types



**Fig. 5** – Vesalius’s illustration of the adult human nervous system, as seen from the front, with the brain tilted upward to expose the cranial nerve roots emerging from the base. For practical reasons associated with the dissection, he left the spinal cord within the vertebral column. Most of the features illustrated here were described clearly by Galen thirteen centuries earlier. Reproduced from the 1555 edition of the *Fabrica*.

within the white matter and its continuation, the nerves. Furthermore, he proposed that the cerebral gray matter controls voluntary (“spontaneous”) behavior whereas the cerebellar cortex controls involuntary movements, and that certain white matter tracts known at the time, like what we call the superior cerebellar peduncle, interconnect the cerebral and cerebellar cortices. He also speculated that the corpus callosum mediates imagination, the basal ganglia (“corpus striatum”) are the site of Aristotle’s “common sense,” the thalamus is the “common passage” of all the senses on their way to the corpus striatum, and the tectum handles all communication between cerebrum and cerebellum.

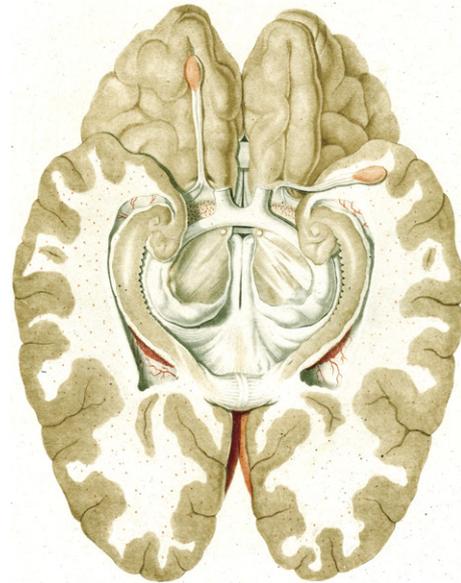
Willis did not illustrate his gray matter–white matter systems model of nervous system function, and it never really had a profound influence like the pneumatic–ventricular theory—except in the very general and important sense of shifting attention away from the ventricular system to brain and spinal cord parenchyma, focusing attention especially on differences between gray and white matter. This in turn led to the method of scraping away gray matter to follow the course of white matter tracts, devised by Willis (1672) after criticism of the *Cerebri anatome* by Steno (1669), and perfected by Vieussens (1684) and Reil (see Mayo, 1823)—and the basic macroscopic anatomy of the central nervous system (Fig. 6) was elucidated almost to the extent known today by the early 19th century (see Vic d’Azyr, 1786; Burdach, 1819–1826).

### 3. The modern era: cell theory, neuron doctrine, and functional polarity law

A life sciences revolution as profound as that sparked by Vesalius and Harvey accompanied formulation of the cell theory by Schleiden (1838) and Schwann (1839). The story of the discovery of vertebrate nerve cells by Ehrenberg in 1833, and then the origin of nerve fibers from nerve cell bodies by Remak in 1838, followed by Wagner’s tentative distinction between dendrites and axon in 1846 – along with all the related ambiguities, hints, and confirmations – has been recounted thoroughly (see Cajal 1909–1911; van der Loos, 1967; Mayer, 1971; Shepherd, 1991; Jacobson, 1993; Clarke and O’Malley, 1996). Johannes Purkinje (1838) provided the seminal work especially relevant here: the first general survey of neuronal cell body size, shape, and distribution throughout the central nervous system (Fig. 7). This was the birth of nervous system cytoarchitectonics, which provided the first criteria other than gross location for regionalizing gray matter, and remains an essential (if largely ignored) field of study today.

#### 3.1. A third model: hierarchical projection system

Based on the understanding of nerve cells gained in the preceding decades, Meynert (1872) arranged what he and others had learned about the disposition of “gray nodal masses” and “conducting nerve tracts” into a global model of nervous system organization more synthetic than anything attempted since Willis, whose influence is nevertheless obvious. Meynert described but did not illustrate schematically a hierarchical system with three projection systems, starting in the cerebral cortex. The first was to the cerebral



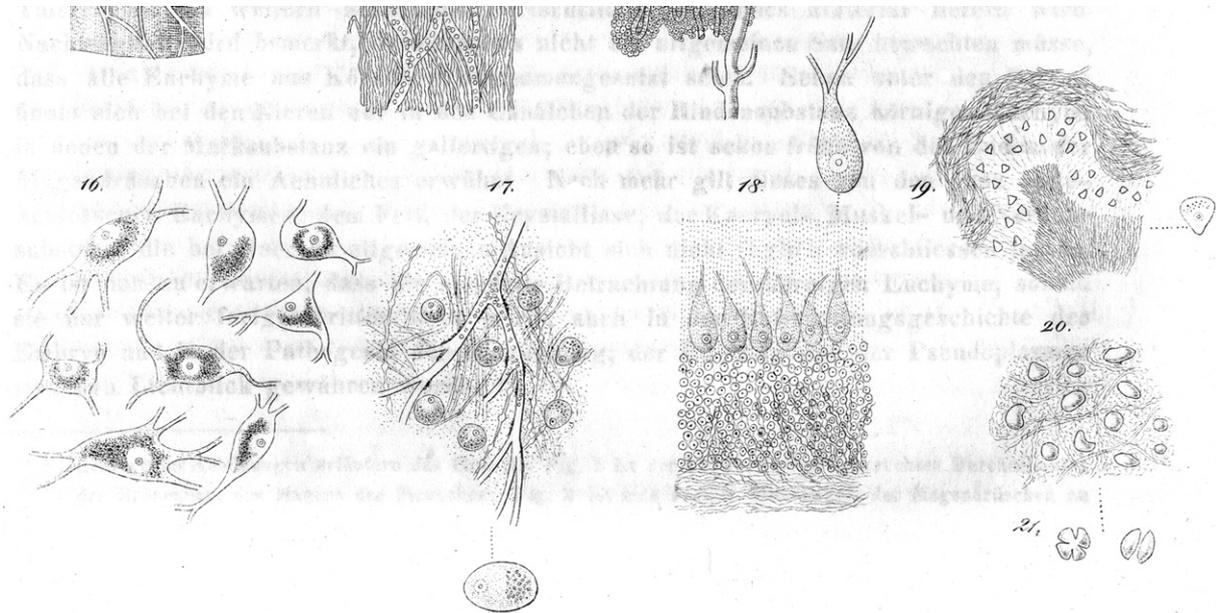
**Fig. 6 – The macroscopic or gross structure of the human brain was known in considerable detail by the beginning of the nineteenth century. This plate from the work of Felix Vicq d’Azyr (1786) is a view of the human brain from the base, with a horizontal slice removing lower regions of the occipital and temporal lobes to reveal the hippocampus on either side, lying along the medial edge of the lateral ventricle’s inferior horn. Red dots in the white matter indicate blood vessels cut transversely. For orientation also note the optic chiasm between the “heads” of the hippocampi, and the splenium of the corpus callosum (with the longitudinal striae of Lancisi) just caudal to their “tails”. Reproduced from the original.**

(basal) ganglia from cerebral cortex, the second was to central tubular gray matter (the brainstem and spinal cord) from cerebral ganglia via the cerebral peduncles, and the third was through the nerves from central tubular gray. The cerebral peduncles had two parts: basis, which contributed a massive input to the cerebellum, and tegmentum, a part of the central tubular gray.

There are two fundamental problems with Meynert’s scheme; it was based on the reticular theory of anastomosis or direct continuity between axons and dendrites (Fig. 8), and the arrangement of nerve tracts between gray masses was not determined experimentally (see Section 4). The great discovery that helped resolve the first problem was Golgi’s (1873) black reaction. The method based on it revealed much more than anything else available about the morphology of cell bodies, axons, and dendrites, and with it Golgi rejected the theory that dendrites anastomose. It remains a source of wonder how little Golgi’s method was used by others until it was refined and applied systematically by Cajal, starting in early 1887.

#### 3.2. A fourth model: sensory, motor, and association neurons

Like the history of the neuron’s discovery, the history of how the neuron doctrine and functional (dynamic) polarity law



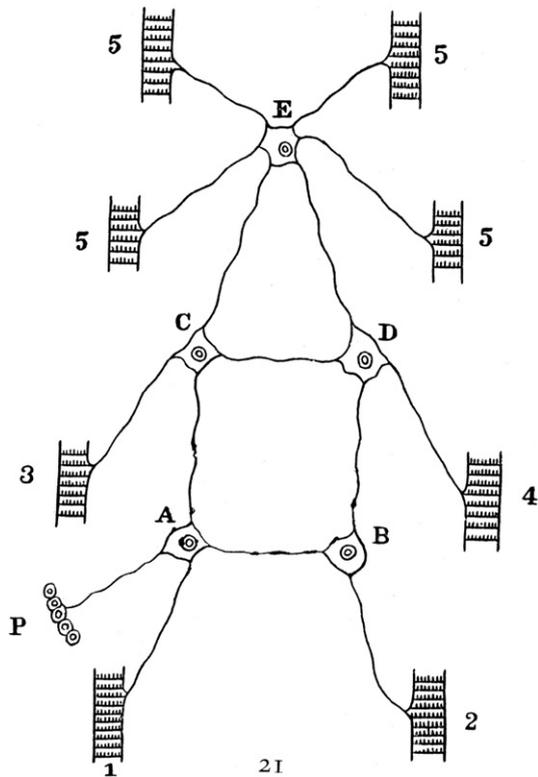
**Fig. 7** – The first general survey of how nerve cell bodies appear in different regions of the brain and spinal cord – their topographic spatial distribution – based on Purkinje’s work and published in 1838. Part 16 shows cell bodies in the substantia nigra, red nucleus, and/or “anterior angle of the fourth ventricle”, Part 17 in the thalamus, Part 18 in the cerebellum, and Part 19 in the inferior olive. Part 20 illustrates “starch-like granules” in the region of the olfactory tubercle, diagonal band nucleus, and/or stria terminalis. The origins of cytoarchitectonics can be traced back directly to this work, especially Fig. 18, where a row of what became known as Purkinje cells are clearly depicted between a relatively cell-free layer above and a layer of tiny (granule) cells below, with a fiber layer at the very bottom. Reproduced from the original at the original size.

were elaborated by Cajal and his contemporaries has been examined thoroughly (Cajal, 1909–1911; Shepherd, 1991; Jacobson, 1993; Clarke and O’Malley, 1996). Briefly, the neuron doctrine stated that nerve cells interact by way of contact rather than continuity (axons and dendrites generally do not anastomose), whereas the functional polarity law stated that in the context of normal neural circuits impulses are generally transmitted from dendrites and soma to axon—and then from the axon to its terminals on other neurons or effector cells. These two principles were the cornerstones of Cajal’s nervous system analysis in vertebrates and invertebrates alike—and remain the starting points of contemporary neural systems analysis, whether acknowledged specifically or not. On the other hand, Cajal freely admitted that exceptions to the general rules are possible, especially under certain pathological and experimental conditions, though he doubted that the exceptions would invalidate the overall model.

This brings us back to the first chapter of Cajal’s *Histology of the Nervous System*, mentioned at the start of the essay: *Basic plan of the nervous system: the structural framework of neural centers and laws governing them in animals*. He began by pointing out that evolution has provided the most highly organized structure in the animal kingdom, the nervous system, and that its dominant role in ever increasing coordination of mechanisms for nutrition and defense (reproduction was mentioned later)—and at the highest echelons for feelings, thought, and will—is obvious. Then he outlined four broad eras in nervous system evolution, followed by an elaboration of principles underlying these stages, and the consequences of these principles.

The first era was that of irritability, which actually characterizes certain cells in plants and the simplest animals without a nervous system, including sponges. The second era was that of sensory and motor nerve cells derived from the outer covering of the first animals with a nervous system, coelenterates. These sensory neurons have a simple bipolar shape, functionally polarized with a receptive dendrite oriented toward the environment and a conductive axon oriented inward (prototypical illustrations of the functional polarity law), whereas in these early forms motor neurons were thought typically to extend an axon to muscle cells and other processes that are impossible to distinguish as axon or dendrite (like those associated with the amacrine cells Cajal named in the retina). The third era was characterized by worms, where neurons between sensory and motor—called interneurons or association neurons—assume an equally important role (Fig. 9).

The fourth era is characterized by a dominant role for a second broad class of association neuron, derived from cerebral ganglion in advanced invertebrates, and cerebral cortex in vertebrates—a class named psychomotor or second-order motor neurons by Cajal (Fig. 10). He emphasized that as evolution proceeds, the products of earlier eras are preserved and incorporated in more advanced forms; for example, the sensory-motor neuron stage characteristic of coelenterates is found in the mammalian enteric nervous system. He also maintained that the hierarchy of conditions required for psychological experiences (associated with cerebral cortical psychomotor neurons) is ultimately linked to the nature of



**Fig. 8** – An illustration of the reticular theory of nerve cell communication in networks, from Landois and Sterling’s *Textbook of Human Physiology* (Landois, 1891). Note that processes of nerve cells (A–E) are in direct continuity, even with muscle (5) and sensory regions (P). Thus there are no synapses in the network, and the direction of impulse transmission is indeterminate (compare with Fig. 9). Photograph courtesy of the UCLA Louise M. Darling Biomedical Library, Department of History and Special Collections.

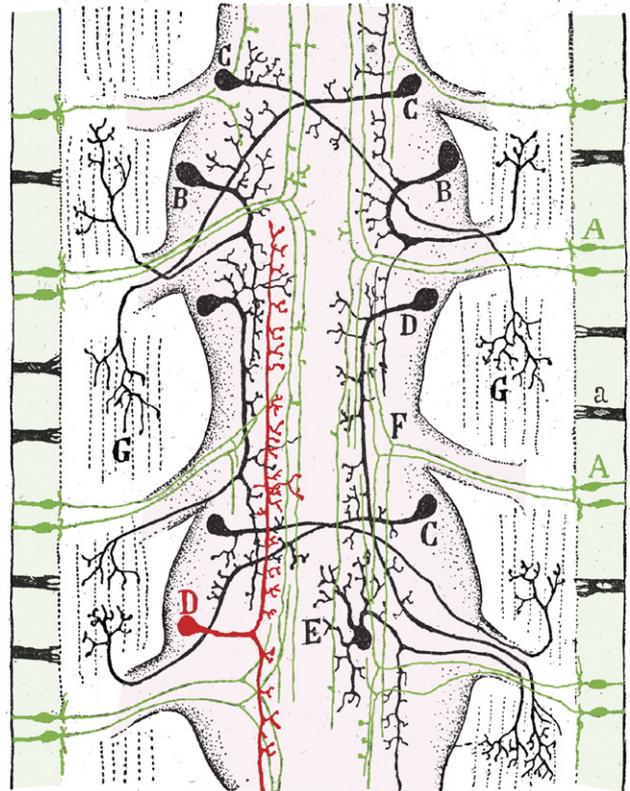
highly differentiated sensory inputs, especially visual and auditory.

Cajal perceived three principles underlying these broad, overlapping stages of nervous system evolution. First, the proliferation of neurons and their processes increases the complexity of relationships that can be maintained between various tissues and organs, the latter increasing as animals became larger and more differentiated. Second, adaptive differentiation of neuronal morphology and fine structure increases the capacity for impulse conduction. And third, a progressive concentration of neural elements into gray matter masses (ganglia, nuclei, and areas) results in a shortening of many processes and thus an increased rate of impulse conduction (along with a conservation of neuronal cytoplasm).

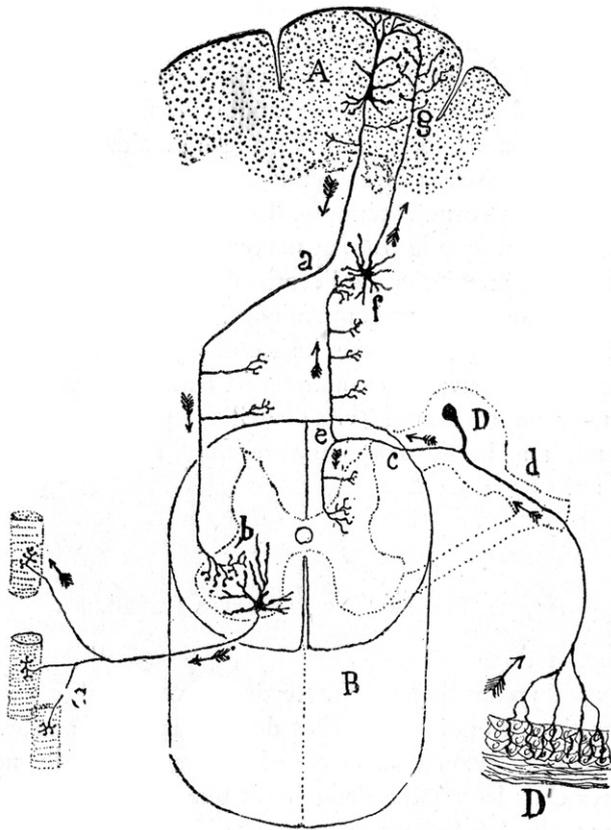
Cajal then went one critical step further, “What utilitarian goal has nature (which never seems to act in vain) pursued in forcing nervous system differentiation to these lengths? The objective – or at least one that seems to follow most logically from all the factors considered above – is the refinement and enhancement of reflex activity, which protects the life of both the individual and the species... [However] in [vertebrates] (and possibly in higher invertebrates), neural and nonneur-

onal structures are not simply under the influence of external stimuli; they are also subject to internal stimuli arising from control centers within the organism itself.” (Cajal, 1909–1911, English translation p. 16).

The basic concepts outlined in this first chapter, and then substantiated in the rest of the book’s 2000 pages, continue to inspire research, theory, and teaching in neuroscience for at least four reasons. First, Cajal and his contemporaries provided a deep cellular interpretation of nervous system macrostructure or gross anatomy. Second, Cajal elaborated a global structure–function classification scheme for neuron types based on phylogeny. Third, he outlined reasonable tendencies, principles, or laws displayed during nervous system evolution. And fourth, he generated an explanation of behavior and psychological experience based on the cellular organization of neural centers and their interconnections within the nervous system as a whole.



**Fig. 9** – The first illustration in Cajal’s *Textura del sistema nervioso* (Cajal, 1899–1904). It shows in schematic horizontal view the location, shape, and connections of the three basic neuron types found in a generalized worm (compare with Fig. 8). Bipolar sensory neurons (dark green) have their cell body and dendrite in the integument (light green), whereas their axon enters and bifurcates (F) in the ganglionic chain (light red). Crossed (C) and uncrossed (B, D, E) motor neurons (black) have their cell body in the ganglionic chain and generate a process that sends one branch (clearly an axon) to muscle (G) and other branches to various parts of the ganglionic chain. Interganglionic interneurons or association neurons (red D) also have their cell body in the ganglionic chain and generate an axon that remains entirely within the chain. Reproduced from the original; color added.



**Fig. 10** – Cajal's explanation of the simple mammalian reflex arc in terms of the neuron doctrine and functional polarity law (arrows), as well as an illustration of the four basic neuron types he defined (see Section 3.2 and compare with Fig. 9). The peripheral process (d, which he regarded as a dendrite) of a dorsal root sensory ganglion cell (D) begins in the integument (D'), and a central process (c, which he regarded as the axon, for reasons summarized in Chapter 5 of Cajal, 1909–1911) extends into the spinal cord (B) where it bifurcates (e). One bifurcation branch ends on a motoneuron (b) or on a spinal interneuron (unillustrated) – mediating a simple reflex to muscle fibers (C) – whereas the other bifurcation branch ends on an interneuron or association neuron (f) whose axon terminates (g) in the cerebral cortex, influencing a second association neuron that he called a psychomotor or second-order motor neuron (A), whose axon (a) descends to influence also the output of primary motoneurons (b). Reproduced from Cajal (1894).

### 3.3. A fifth model: tiger salamander circuitry on a flatmap

Although Cajal provided a general framework for analyzing nervous system organization with his neuron type classification scheme, he did not attempt a global model of nervous system structure–function organization along the lines proposed by Galen, Willis, and Meynert. C. Judson Herrick (1948) provided the next classic example, using the brain of the tiger salamander as a prototype for vertebrates, roughly between fish and mammals. A severe limitation of Golgi's method is the inability to follow axons reliably from individual neurons any great distance away from the cell

body. The adult tiger salamander brain has the advantage of being only about 7 mm long—but even more importantly its gray matter is confined to a relatively thin periventricular zone, and individual nuclei or areas typically are arranged like irregular tiles, rather than stacked in multiple, irregular layers as in the mammalian brainstem (the dorsal thalamus is a classic example).

Herrick analyzed about 500 specimens from early embryonic to adult stages with a variety of normal (in contrast to experimental) neurohistological methods, including those of Golgi, Nissl, Cajal (reduced silver), and Weigert—and plotted the overall results on a schematic flatmap of the brain (Fig. 11), relatively easy to prepare and interpret because of the simple distribution and regionalization of gray matter outlined above. In a technical and analytical tour de force of original observation and synthesis, Herrick presented a complete network analysis of the tiger salamander brain with the methods available. Whereas Cajal attempted a systematic account of neuron types and local connections throughout the vertebrate nervous system, Herrick tried to do the same for the amphibian brain, while adding a much more complete account of projection pathways interconnecting the gray matter differentiations (nuclei and areas).

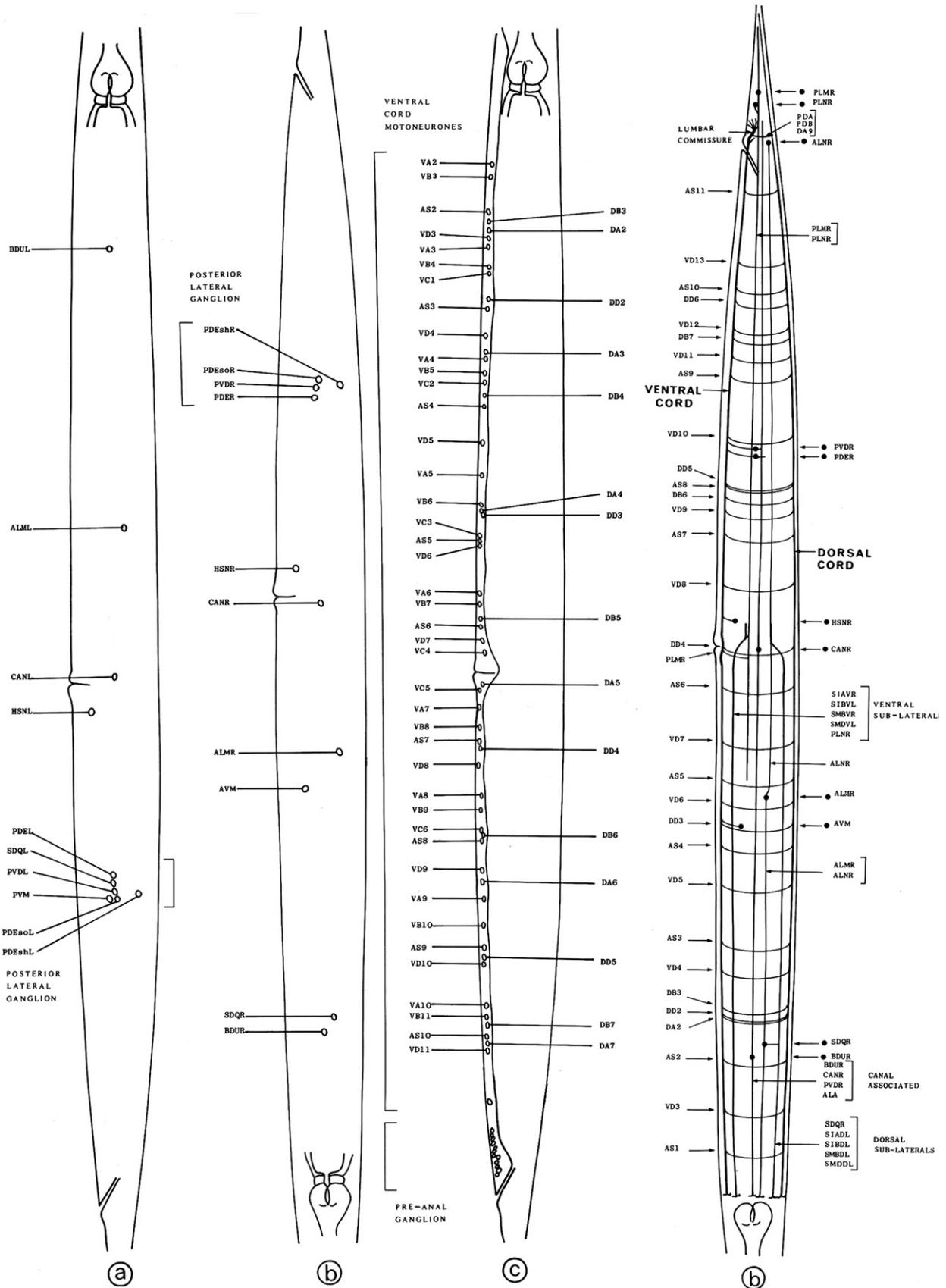
### 3.4. A sixth model: the entire worm in 3D

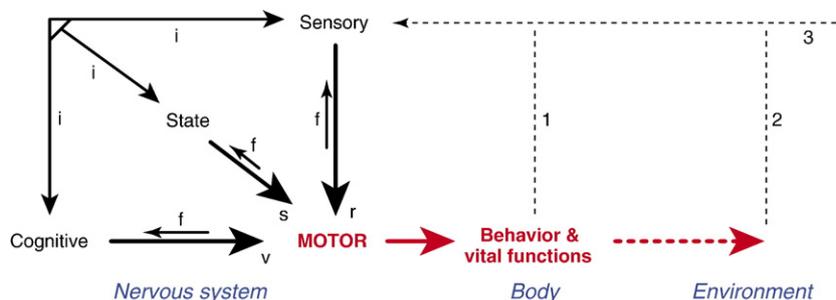
Usually synapses can only be established morphologically with the electron microscope because the synaptic cleft's typical width (20–30 nm) is well below the light microscope's resolution ( $\sim 1 \mu\text{m}$ ). However, the volume of vertebrate brains is so enormous that sampling problems at the ultrastructural level have been severe, and in any event Herrick's analysis was carried out before adequate development of the electron microscope. It was therefore inspired to choose a tiny unsegmented nematode worm, *Caenorhabditis elegans*, with an adult body length of about 1.3 mm and a diameter of about  $80 \mu\text{m}$  – and a Herculean task – to reconstruct the entire animal from serial electronmicrographs (White et al., 1986). From this the wiring diagram established by each of the 302 neurons was extracted and illustrated schematically (Fig. 12). The potential of this model (with its approximately 5000 chemical synapses, 2000 neuromuscular junctions, and 600 gap junctions) for global neural systems analysis – to determine its basic plan and interaction with the rest of the body – is just starting to be exploited, especially with molecular genetic, computer graphics, and mathematical modeling techniques.

## 4. The contemporary scene

Three powerful, recently developed approaches to neural systems analysis fuel today's research. In the 1970s a new generation of pathway tracing methods based on the axonal transport of injected markers was developed and combined with immunohistochemical techniques for the cellular localization of virtually any molecule of interest, for example, those associated with synaptic transmission or gene expression regulation (Kitai and Bishop, 1981; Björklund and Hökfelt, 1983–2005). Then in the 1980s, hybridization histochemistry







**Fig. 13** – A four-component global model of vertebrate nervous system organization. This version of the basic plan of nervous system circuitry postulates that behavior is a direct product of motor subsystem activity, which in turn is a function of activity in three other subsystems: sensory, behavioral state, and cognitive. Sensory (afferent) information from the environment (2, 3) leads directly to the motor (efferent) system for reflex (r) responses, as well as to the state and cognitive systems. Cognitive information elaborated by the cerebral hemispheres mediates voluntary (v) control of behavior, and there is feedback (f) from the motor subsystem to the sensory, state, and cognitive subsystems. In addition, behavior and vital functions within the body produce feedback (1) through the sensory subsystem, as do the effects of behavior and vital functions on the environment (2). Finally, the sensory, state, and cognitive subsystems are bidirectionally interconnected (i). The result is a chain-like circuit with three sequential parts: environment interactions with body, body interactions with nervous system, and intra-nervous system. All nerves, fiber tracts, and gray matter regions can be localized to one of the four nervous system subsystems (Swanson, 2003, 2004, 2005). Adapted from Swanson (2003).

spatial (geographical) and functional descriptions are equally important. Topographic descriptions reflect physical structure, whereas topological depictions preserve boundary conditions but shape and distance are distorted for clarity and/or simplicity. Schematic depictions abandon even topology for simplicity and clarity, and they are most often used for functional explanations, whereas topographic and topological representations are most often used for structural and structure–function explanations. Ideally, transformations between topographic and topological representations should be done mathematically.

At the next level of analysis, all nervous system gray matter regions (nuclei, areas, and ganglia) need to be characterized in terms of neuron type composition (for example, retina: photoreceptor, bipolar cell, ganglion cell, amacrine cell, horizontal cell), and each neuron type in turn must be characterized in terms of inputs and axonal projections, gene expression pattern, neurophysiology, and so on. And finally, each neuron type must be fitted into a global model of nervous system circuit organization, for example, the one shown in Fig. 13.

One requirement of a global systems model instantiated in a knowledge management system and its database is an internally consistent nomenclature. Without a controlled vocabulary, valid inferences cannot be drawn from information in a database (Gruber, 1993; Gomez-Perez et al., 2003). Furthermore, the creation of a reference nomenclature to which all other terms can be indexed, or defined in terms of, is highly advantageous. The reason is simple: if the definition of every term is indexed or related to the definition of every other term, the number of relationships is proportional to  $N^2$ .

In contrast, when all terms are related to a reference nomenclature, the number of specified relationships is proportional simply to  $N$ , and relationships between non-reference terms can be inferred (Dashti et al., 1997). This is a major consideration for neuroanatomy where tens of thousands of terms are used in the literature, and there can be synonyms, partially corresponding terms, and terms with no correspondence.

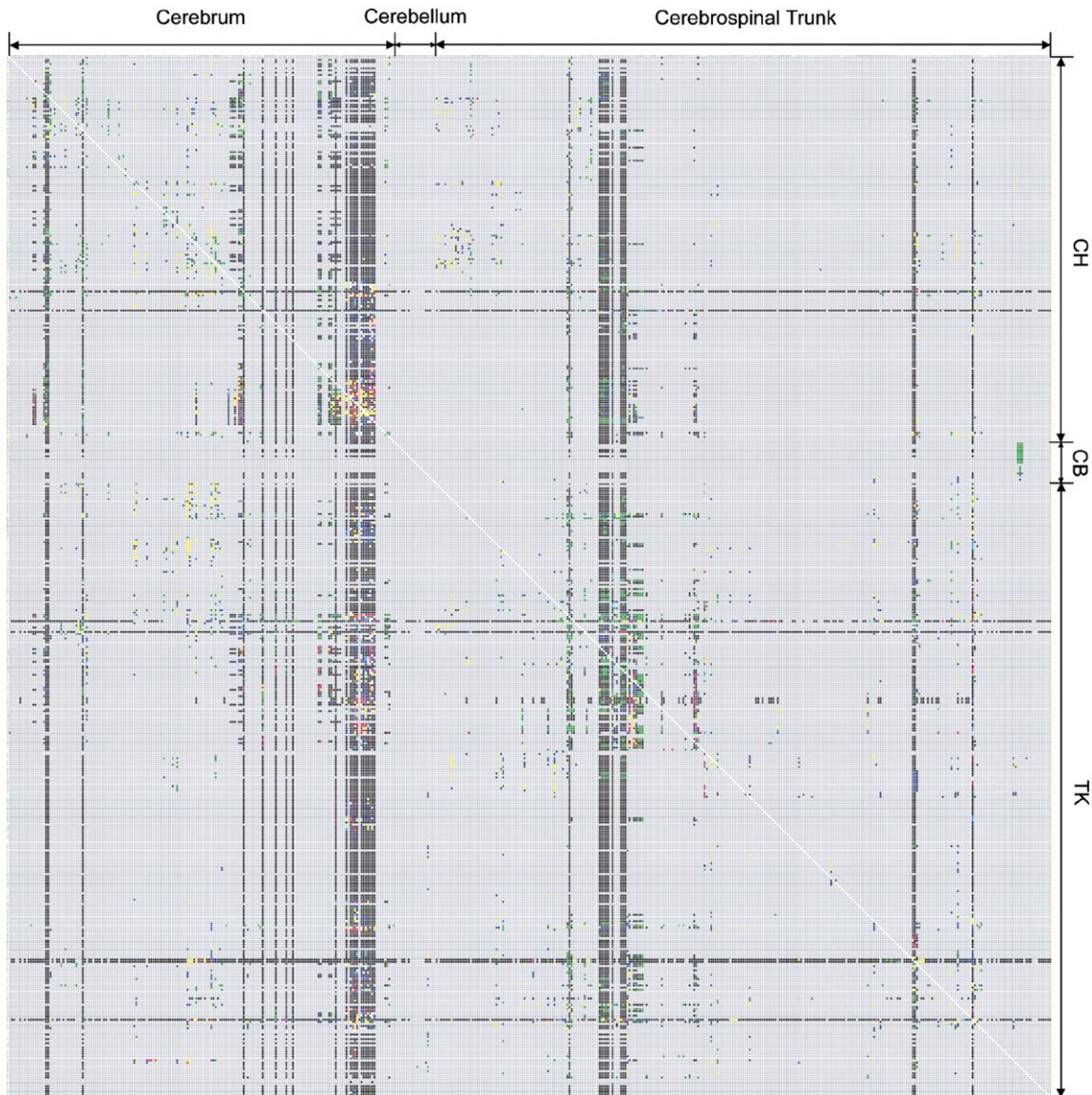
## 5.2. Online knowledge management systems

It may be useful to close with a minimal requirements list, based on considerations outlined above, for the ideal knowledge management system that stores data about, analyzes, and models the basic plan of nervous system circuit organization. Although the list is surely not complete, seven levels of functionality are emerging as essential.

First, a hierarchically organized account of all nervous system parts – gray matter regions, fiber tracts, and neuron types – is necessary. To my knowledge, the only such account available for the vertebrate, now in its third edition, deals with all gray matter regions and fiber tracts of the rat central nervous system (Swanson, 2004). This integrated atlas, flat-map, and set of tables is based on structural, developmental, connectional, gene expression, and functional criteria—and also contains a controlled vocabulary for gray matter regions and fiber tracts, documented from the primary research literature. However, a complete indexing, referenced to the primary literature and historically complete, of all neuroanatomical terms used for even a single species is not on the

**Fig. 12** – Schematic maps indicating the spatial distribution of all 302 neurons found in adult *C. elegans*, with the location of all longitudinal and transverse nerve cords. (a, b left, and c) are left-hand, right-hand, and midline views of neuronal cell body locations, respectively, from original Fig. 4; (b right) is a right-hand view of major nerve cords from original Fig. 7. A separate illustration of each neuron with the distribution of its axon was also published, and is available on the web. Reproduced with permission from White et al. (1986).





**Fig. 15** – A connection matrix for all known gray matter regions (486) of the rat central nervous system, based on the gray matter hierarchical taxonomy of Swanson (1998–1999). The experimentally determined axonal connections displayed were constructed from data in the online Brain Architecture Knowledge Management System, BAMS (Bota et al., 2005; Bota and Swanson, 2006). Projecting regions (from) are on the horizontal axis, receiving regions (to) on the vertical axis. The matrix contains 22,178 cells labeled with a color other than gray (no data), indicating the number of projection reports in the database, representing a coverage factor of 9.4%. No data indicate that either extant literature has not yet been collated or no data exist in the literature. Color code for qualitative projection strength: red, strong; yellow, moderate; blue light; black, none/not detectible. Reproduced with permission from Bota and Swanson (2007).

horizon, and there has been no systematic account of neuron types making up each gray matter region in vertebrates since Cajal (1909–1911).

Second, mathematically defined three-dimensional computer graphics models of the nervous system need to be developed and made available on the web. These models

**Fig. 14** – A flatmap of the adult rat nervous system. The complete file has all known gray matter differentiations (areas and nuclei) of the central nervous system arranged in a standard way, along with all major fiber tracts and peripheral nerves. Complementary flatmaps of gray matter regionalization have been published for major developmental stages of the rat central nervous system (Alvarez-Bolado and Swanson, 1996) and for the adult human central nervous system (Swanson, 1995). In terms of primary gray matter differentiation, red indicates cerebrum, blue cerebellum, and yellow cerebrospinal trunk. Reproduced with permission from Swanson (2004).

should provide a framework for organizing and accessing a wide range of neuroscientific data about individual parts, for determining structural and topological parameters of nervous system parts, and for developing functional models of neuronal systems. A new generation of software to support this functionality is probably necessary because of the complex organic shapes involved. There are two fundamentally different classes of three-dimensional nervous system model, each with different advantages and limitations: voxel-based derived from computed tomographic scans (Raichle, 2000), and vector-based derived from the reconstruction of histological tissue sections (see Swanson, 2001).

Third, computer graphics atlases based on representative series of histological sections are required to display extracted neuroanatomical information. Examples of these digital two-dimensional map sets have proliferated since the first systematic attempt in rat (Swanson, 1993), but none are satisfactory yet in terms of a completely space-filling model where every coordinate has a unique name, and enough sections are provided to reconstruct a highly accurate three-dimensional model.

Fourth, there is a need for nervous system flatmaps, like wall maps of the globe. A history of attempts to produce them is provided elsewhere (Alvarez-Bolado and Swanson, 1996; Swanson, 2000b), although the first bilateral flatmap of the central nervous system, with all known gray matter differentiations (adult rat), is only 15 years old (Swanson, 1992). The current version (3.0) of this computer graphics flatmap, which in principle is a fate map of the embryonic neural plate, includes all known gray matter differentiations as well as all major fiber tracts and peripheral nerves (Fig. 14). Corresponding flatmaps for each major stage of rat central nervous system development, starting with the neural plate (topologically a flatmap), have also been published (Alvarez-Bolado and Swanson, 1996).

Fifth, the need for schematic diagrams of neural circuitry has already been mentioned. There are as yet no established rules or conventions governing their construction as there are in electrical engineering, for example, but a variety of software algorithms are available to optimize the display of connection diagrams or graphs.

Sixth, there is a need for simple connection matrices, that is, connection tables with “from” on one axis and “to” on the other. They are becoming more common in the literature for limited sets of gray matter nuclei or areas, and online sites dealing with connective data have been reviewed recently (Bota and Swanson, 2007). A more ambitious connection matrix involving all recognized rat central nervous system gray matter regions has been published (Figs. 14 and 15), although nothing even remotely similar is available for neuron types composing each gray matter region, the ultimate goal for mammals, including someday humans.

Seventh and most abstractly, the basic plan of nervous system circuitry must ultimately be described and analyzed in rigorous mathematical terms. As emphasized throughout the essay, vast amounts of relatively accurate and reliable data about nervous system organization are accumulating, and yet this is only a tiny fraction of what remains to be gathered. The inspiration for the essay put it well, “... living nature, far from being drained and exhausted, keeps back from all of us, great

and small, immeasurable stretches of unknown territory... even in the regions apparently most worked over, there remain still many unknown things to be cleared up” (Cajal, 1989, p. 279). The need for knowledge management systems to deal with this information is obvious.

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