Chapter 1

A HISTORICAL PERSPECTIVE ON COGNITIVE NEUROSCIENCE

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ANTIQUITY THROUGH THE EIGHTEENTH CENTURY

The most fundamental fact of cognitive neuroscience was established in ancient times, when the Greeks first determined that the brain was the physical seat of the mind. Alcamaeon of Croton, who may have been a student of Pythagoras, is credited with making this basic advance in the fifth century B.C. on the basis of his observations of human patients with brain damage. The alternative hypothesis held the heart to be the organ responsible for sensation and thought. This was the accepted view among Egyptian writers and continued to attract adherents in ancient Greece centuries after Alcamaeon. Although Hippocrates and Plato held a cerebrocentric view of the mind, no less a thinker than Aristotle remained in the cardiocentric camp.

Among the ancient cerebrocentrists, the nature of the mind-brain relation was poorly understood. The brain itself was considered by many to be a mere package for the real substance of thought, the cerebrospinal fluid, and the most important anatomical features of the brain were therefore the ventricles. Although brain tissue itself was considered important by some writers, including Galen, for many centuries the mind was predominantly identified with cerebrospinal fluid. The present-day use of the word *spirit* to refer both to certain fluids and to the soul is vestige of this idea.

For the entire period of the middle ages in Europe (approximately the fourth to fourteenth centuries), the ventricles continued to be the focus of theories relating mind and brain.[1] For example, according to fourth-century church fathers, the anterior ventricles were associated with perception (later to be known as the *sensorium commune*), the middle with reason, and the posterior with memory.[2] It has been suggested that this focus on the ventricles accorded better with the dualism of Christian theology, as the hollow cavities could be said to contain the soul without hypothesizing an identity between mind and the physical substrate of brain tissue.[1] Figure 1-1 shows an early illustration of the ventricular system.

During the Renaissance, the ventricular doctrine and the role of the *rete mirabile* began to lose their influence on theories of mind-brain relations.[2,3,4] The seventeenth-century writings of René Descartes mark a transitional phase, in which the interaction between fluid in the ventricles and brain tissue itself was hypothesized to explain intelligent action, as shown in Fig. 1-2. For reflexive action, Descartes proposed a simple loop, in which stimulated nerves caused the release of animal spirits in the ventricles, which, in turn, caused efferent nerves and muscles to act. For intelligent human action, this loop was modulated by the soul via its effects on the pineal gland. The pineal gland was chosen in part because it is unpaired and centrally located and also because it is surrounded by cerebrospinal fluid. It was also mistakenly thought to be uniquely human. Of course, the pineal gland was just the vehicle for the mind's influence on the body; Descartes' theory still denied any form of identity between the mind and neural tissue.[3,5-8]

Descartes' theory was formulated at a time when neuroanatomic knowledge was quite primitive. This situation began to change with the work of such figures as Thomas Willis later in the seventeenth century[3,10] and Malpighi Pacchioni and Albrecht von Haller in the eighteenth.[11,12] For example, Von Haller stimulated the nerves of live animals in an effort to discover the pathways for perception and motor action, thus establishing the experimental method in neurophysiology. This work set the stage for the explosion of experimental and clinical research of the nineteenth century, in which the brain organization underlying perception, action, language, and many other cognitive functions was revealed.

THE LOCALISM/HOLISM DEBATE OF THE NINETEENTH CENTURY

One of the more notorious figures in the history of behavioral neurology is Franz Josef Gall, shown in Fig. 1-3. In the late eighteenth and early nineteenth centuries, he and his collaborator Johann Spurzheim made a number of important contributions to functional neuroanatomy, including proving by dissection the crossing of the pyramids and establishing the distinction between gray and white matter.[13–15] Gall is also credited with one of the earliest descriptions of aphasia linked to a lesion of the frontal lobes.[16] He is most famous, however, for his general theory of cerebral localization, known today as phrenology. At the age of 9, Gall had noted that his schoolmates who excelled at rote memory tasks had quite prominent eyes, "*les yeux à fleur de tête*" (cow's eyes). He reasoned that this was the result of the overdevelopment of the subjacent regions of the brain, and speculated that these regions of the brain might be particularly involved in language functions and especially verbal memory.

Gall identified 27 basic human faculties and associated them with particular brain centers that could affect the shape of the skull, as shown in Fig.

Figure 1-1
The ventricular system according to Albertus Magnus from his Philosophia naturalis (1506).[2]

1–4. These included memory of things and facts, sense of spatial relations, vanity, God and religion, and love for one's offspring.[15] His theory was based on hundreds of skulls and casts of humans and beasts. For instance, the disposition to murder and cruelty was based on a bump above the ear possessed by carnivorous animals. He located the same feature in sadistic persons whom he had examined personally,[3] skulls of famous criminals, and the busts and paintings of famous murderers.[12] Gall taught and practiced medicine in Vienna from 1781 to around 1802, until Emperor Francis I banned Gall's public lectures because they were materialistic and thus opposed to morality and religion.[12] Gall then took to the road,

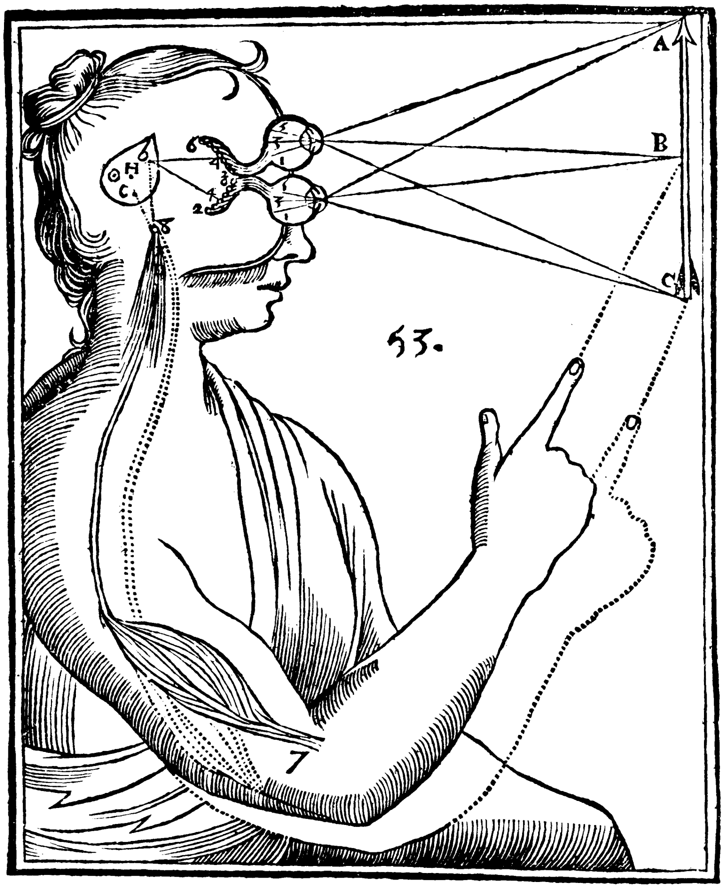


Figure 1-2
Descartes' conception of sensation and action as conceived in his De homine *(1662). Light was transferred from the retina to the ventricles, causing the release of animal spirits. The pineal gland modulated this mechanism for voluntary action.*[9]

lecturing across Europe to enthusiastic popular audiences. By the time he settled in Paris in 1807, he was hugely popular and internationally known. However, phrenology continued to create controversy in scientific circles.

The best-known critic of Gall was Marie-Jean-Pierre Flourens. Flourens mounted a scientific research program to disprove Gall's theory, but it appears to have been motivated at least as much by religious discomfort with the implications of Gall's straightforward mind-brain equivalences as by scientific considerations. Flourens viewed Gall's theory as tantamount to denying the existence of the soul, because it divided the mind and brain into functionally distinct parts and Flourens believed the soul to be unitary.[12,17–19] He carried out extensive lesion experiments on a variety of animal species to demonstrate the equipotentiality of cortex.

Gall's status as a popularizer, and Flourens's empirical attacks, helped to push localism out of the mainstream of contemporary scientific thought in the early nineteenth century. When, in 1825, Jean-Baptiste Bouillaud, shown in Fig. 1-5, presented a large series of clinical cases of loss of speech following frontal lesions,[12,18,19] his work was largely ignored. This landmark work, in which speech per se was distinguished from nonspeech movements of the mouth and tongue, is still relatively unknown.

Bouillaud was not the only one to suggest a frontal location for language functions. During this period and lasting up to the 1860s, numerous clinical reports of patients with frontal lobe

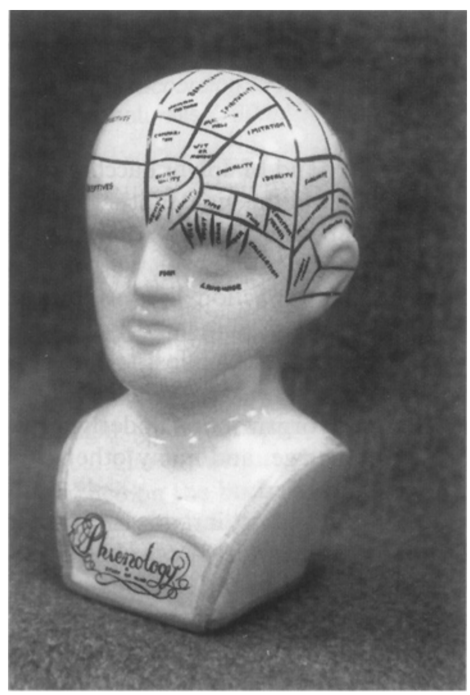
Figure 1-3
Franz Josef Gall (1758–1828).

damage and loss of speech were recorded in Europe and America. Indeed, this idea had considerable historical precedence throughout antiquity.[20–22] However, intense interest in localization of brain functions, particularly language, was now developing. It was during this time that Marc Dax noted the association between left-hemispheric damage, right hemiplegia, and aphasia, based upon his examination of 40 patients over a 20-year period. This paper was handwritten in 1836 and not published at the time,[23] but copies may have been distributed to friends and colleagues.[3]

It was not until 1861 that the field reconsidered localism with a more open mind. That year the Société d'Anthropologie in Paris held a series of debates between Pierre Gratiolet, arguing in favor of holism or equipotentiality, and Ernest Aubertin, the son-in-law of Bouillaud, arguing in favor of localism.[12,24,25] Aubertin, shown in Fig. 1-6, reported his clinical observations of a patient whose frontal bone was removed following a suicide attempt. He reported that when the blade of a spatula was applied to the "anterior lobes," there was complete cessation of speech without loss of consciousness.[3,12,25] Aubertin went on to describe a patient of Bouillaud's who had a speech disturbance and was near death. Aubertin boldly vowed if this patient lacked a frontal lesion he would renounce his views.[12,24–27]

The 1861 debate is best known not for the presentations of Gratiolet and Aubertin but for the eventual participation of the society's founder and secretary, Paul Broca, shown in Fig. 1-7. Although Broca did not initially take a strong position, his observations of a patient then under his care led him to play a pivotal role in the debate. His patient, Leborgne, suffered from epilepsy,

Figure 1-4
An example of a porcelain phrenology bust with demarcations that demonstrate the reflection of the human faculties on the skull. (Photograph courtesy of Joseph A. Hefta.)



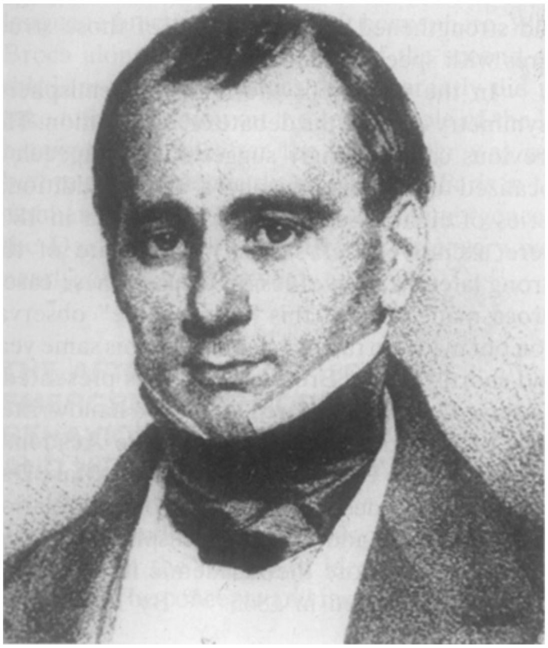


Figure 1-5
Jean-Baptiste Bouillaud (1796–1881).

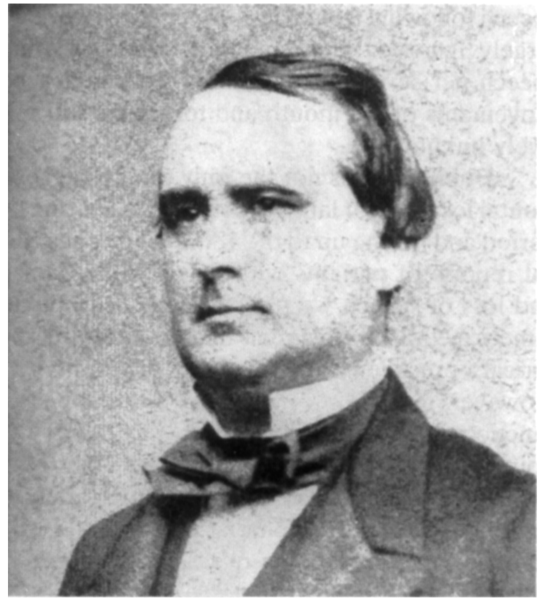


Figure 1-6
Ernest Aubertin (1825–1865).

right hemiplegia, and loss of speech, the last for a period of over 20 years. Leborgne had been institutionalized for some 31 years and throughout the hospital was known by the name "Tan," as this was his only utterance along with a few obscenities.[3,9] In light of Aubertin's declaration, Broca invited him to examine Tan, which Aubertin did and afterward concluded that indeed the patient met the critieria of his prior challenge. Six days later Leborgne died; the following day, April 18, 1961, Broca presented the brain to the society along with a brief statement but without firm conclusions.[25] Figure 1-8 shows the brain of Leborgne.

Four months later, at a meeting of the Société Anatomique de Paris in August, Broca made a more extensive report. The brain of Leborgne had demonstrated an egg-sized fluid-filled cavity located in the posterior second and third frontal convolutions, with involvement of adjacent structures as well, including the corpus striatum.[36] In this report, Broca claimed that his findings would "support the ideas of M. Bouillaud on the seat of

Figure 1-7
Paul Broca (1824–1880).

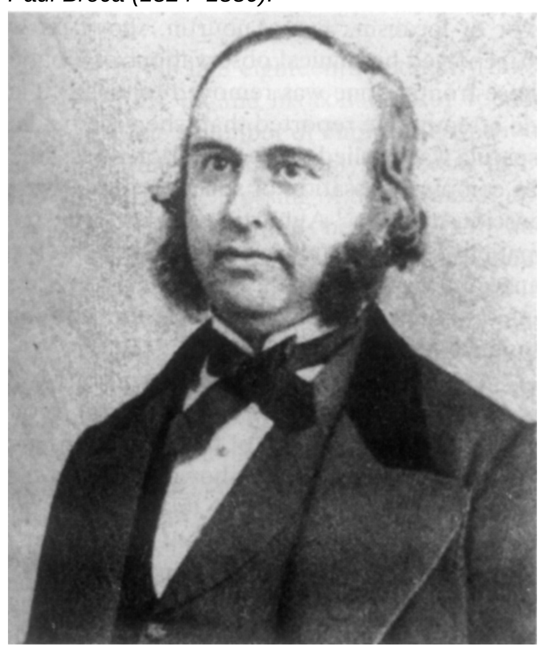


Figure 1-8
Photograph of the brain of Broca's first patient, Leborgne ("Tan"). It is now housed in the Musée Dupuytren.

the faculty for language";[25,28] he later suggested a possible localization of speech functions to the second or more probably third frontal convolution. Later the same year, Broca presented another patient with speech disturbance, an 84-year-old laborer whose lesion also involved the left second and third frontal convolutions. The lesion was more circumscribed than that found in Leborgne and strengthened the association of those structures with speech localization.

In the mid-1860s the issue of hemispheric asymmetry entered the debate on localization. The previous cases strongly suggested that speech is localized to the left hemisphere, and an additional series of eight cases published by Broca in 1863 were exclusively left-sided.[3,23,29] In spite of the strong lateralization of lesion locus in these cases, Broca made note of this "remarkable" observation but made no further claims.[23] In this same year and shortly before Broca's paper was presented,[3] Gustave Dax, son of Marc Dax, sent a handwritten copy of his father's manuscript to the Académie de Médecine in Paris. In this document, Marc Dax had previously described his view on the relation between speech and the left hemisphere. The paper was read before the Académie in December 1864 and published in 1865.[30,31] By 1865, Broca clearly expressed the opinion that the left hemisphere played a dominant role in speech production.[32,33] As far as the issue of priority of discovery is concerned (a matter of controversy among historians), most writers agree that the Dax paper in its original form in 1836 had no influence on Broca or the scientific community when first written. This paper did, however, make clear the association of language functions and the left hemisphere. While Broca alone clarified the role of the second and third frontal convolutions, he apparently did not take a firm position on the specific role of the left hemisphere until after the Dax paper was read before the Académie de Médecine in Paris in December 1964.[3] It appears that the reemergence of the Dax manuscript and Broca's discovery were nearly simultaneous events.

THE AFTERMATH OF 1861: THE EMERGENCE OF MODERN NEUROPSYCHOLOGY

The events in Paris in the 1860s constituted a turning point in the history of ideas regarding brain function. The concepts and methods developed in the course of debating the localization of speech were extended to a variety of different higher functions, experimental work on animals also developed apace. From this period onward, it is impossible to trace a single line of scientific development. Here we simply present a summary of some of the major advances seen in the behavioral neurology and neuropsychology of the late nineteenth and early twentieth centuries.

In the decade following Broca's contributions, two important developments took place in Germany. First, Edward Hitzig and Gustav Fritsch performed a series of experiments in which the cortex of a dog was stimulated while the dog lay on a dressing table in Hitzig's Berlin home.[4,9,34,42] These experiments established that motor functions are localized to anterior cortex and demonstrated experimentally the somatotopic organization of motor cortex inferred indirectly from previous clinical-anatomic correlations in humans. In their report, the investigators specifically noted that their results refuted the holism of Flourens. Following their work, Sir David Ferrier in England confirmed the findings of Hitzig and Fritsch and improved upon their method of stimulation to discover more detailed structure-function relationships.[11]

About the same time, the German neurologist Carl Wernicke began to investigate language functions other than speech. Wernicke, shown in Fig. 1-9, documented a form of aphasia different from the nonfluent variety that followed frontal damage. In what he called sensory aphasia, a posterior lesion in the region of the first temporal gyrus caused a disturbance in auditory comprehension, inappropriate word selection in spontaneous speech, and impaired naming and writing. In his landmark monograph *Der aphasische Symptomen-complex,* Wernicke reasoned that Broca's area was the center for the motor representation of speech, and the posterior first temporal gyrus was the center for "sound images." Wernicke also described global aphasia and explained it as a result of destruction of both anterior and posterior language areas. He also made a prediction that a disturbance of the pathways between these two areas would produce another variety of aphasia he called "conduction aphasia," in which comprehension would be preserved but output would be as impaired as in sensory aphasia.[35–38] Wernicke had, in effect, proposed a model that could explain a number of different aphasic syndromes by lesions to different combination of centers and connections between centers. This type of theorizing came to be known as "associationism," because language use was viewed in terms of associating representations in different brain centers, or as "connectionism," because of the emphasis that view put on the connections between centers, as shown in Fig. 1-10.

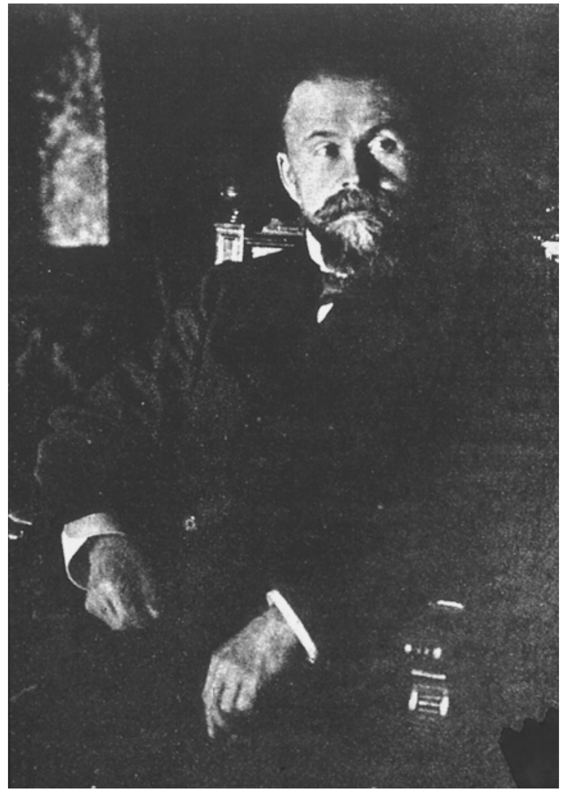


Figure 1-9
Carl Wernicke (1848–1904).

The connectionist paradigm was quickly extended to explain other disorders. Ludwig Lichtheim placed pure word deafness in this framework, predicting the critical lesion site as well as noting that, given the connectionist explanation

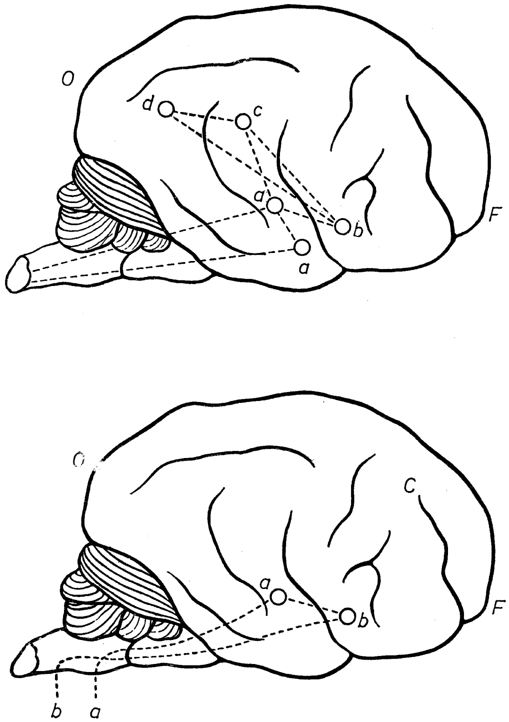


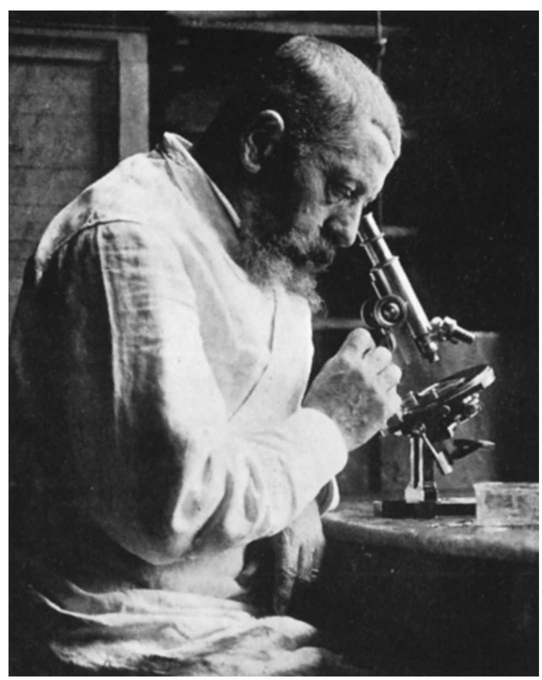
Figure 1-10
Wernicke's model of the speech mechanism.[36] The auditory areas (a) project to centers subserving vocal output (b) and areas which contain tactile (c) and visual (d) images.

for this syndrome, a disturbance in repetition should accompany conduction aphasia.[38,39] Hugo Liepmann described the apraxias, including ideomotor apraxia,[40] and, with Maas, callosal apraxia,[41] explaining them in terms of connectionist principles. Joseph Jules Déjerine, shown in Fig. 1-11, also used the framework of centers and connections in his explanation of alexia without agraphia.[42]

The nineteenth-century connectionist framework proved to have both parsimony and explanatory power. Rather than hypothesizing a new center for every ability or every observed deficit, after the fashion of Gall, a relatively small number of basic centers (vision, sound images, motor outputs) could be combined through connections to explain a wide variety of higher functions and their deficits. Connectionist explanations of aphasia, apraxia, alexia, and other disorders survived well into the twentieth century; indeed, Norman Geschwind, one of the most influential behavioral neurologists of our time, championed them throughout his career.[43] Despite the current proliferation of theories and approaches in our field, the theories of Déjerine, Liepmann, Lichtheim, and Wernicke are still held to be correct by many.

Nevertheless, as successful as the connectionist framework was in late nineteenth century in explaining a variety of disorders, skeptics continued to reject the localism implicit in it. One of the most influential of these was the English neurologist John Hughlings Jackson, shown in Fig. 1-12. He viewed the nervous system not as a series of centers connected by pathways but rather as a hierarchically organized and highly interactive whole that could not be understood piecemeal.[24] Figure 1-13 shows Pierre Marie, a Parisian student of Broca and Charcot, who also took issue with the connectionist theorizing of the late nineteenth

Figure 1-11
Joseph Jules Déjerine (1849–1917).



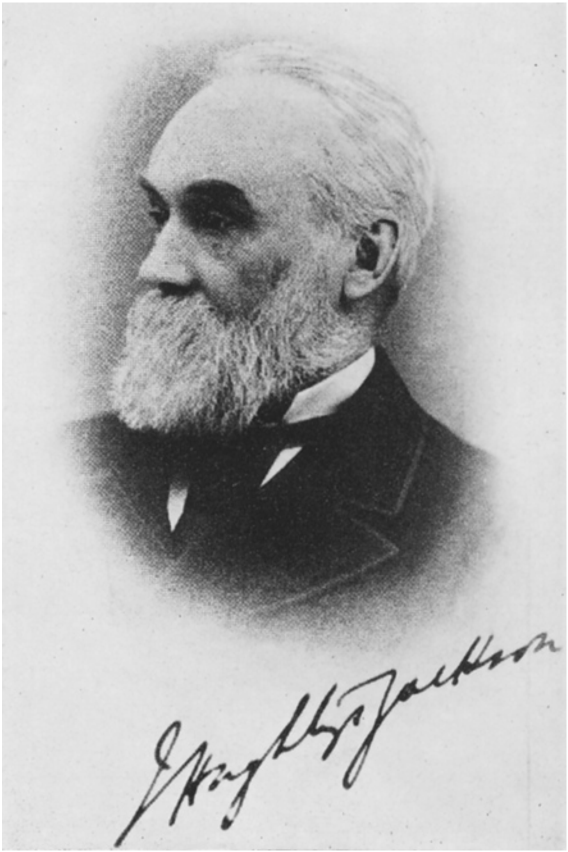


Figure 1-12
John Hughlings Jackson (1835–1911).

century. His style was direct, to say the least. One of his articles was so offensive to Déjerine that it provoked the latter to challenge Marie to a duel. His article questioning the empirical basis of the early claims concerning speech localization was entitled *"La troisiéme circonvolution frontale gauche ne joue aucun rôle spécial dans la fonction du langage*" ("The third frontal convolution plays no special role at all in the function of language").[44] Marie believed that there was just one basic form of aphasia, a posterior aphasia, which was a type of general intellectual loss not specific to language per se. He held that the speech problems of anterior aphasics were motoric in nature. When aphasia is viewed this way, a network of specialized centers is superfluous. A movement toward holism continued into the early twentieth century, with Jackson and Marie followed by a number of influential neurologists and psychologists, including Henry Head in England,[24] shown in Fig. 1-14, Kurt Goldstein in Germany,[45–47] shown in Fig. 1-15, and Karl Lashley in the United States.[48–51] This swing of the pendulum back toward holism has been explained by the waning of German influence following World War I[60] and the growing influence of Gestalt psychology.[61]

While these workers emphasized the brain's unity, other researchers had pointed out the difference between brain regions in cellular morphology, cell densities, and lamination and produced the first cytoarchitectonic maps. Oskar and Cécile Vogt[62,63] and Alfred W. Campbell[64,65] produced some of the earliest examples of these

Figure 1-13
Pierre Marie (1853–1940).

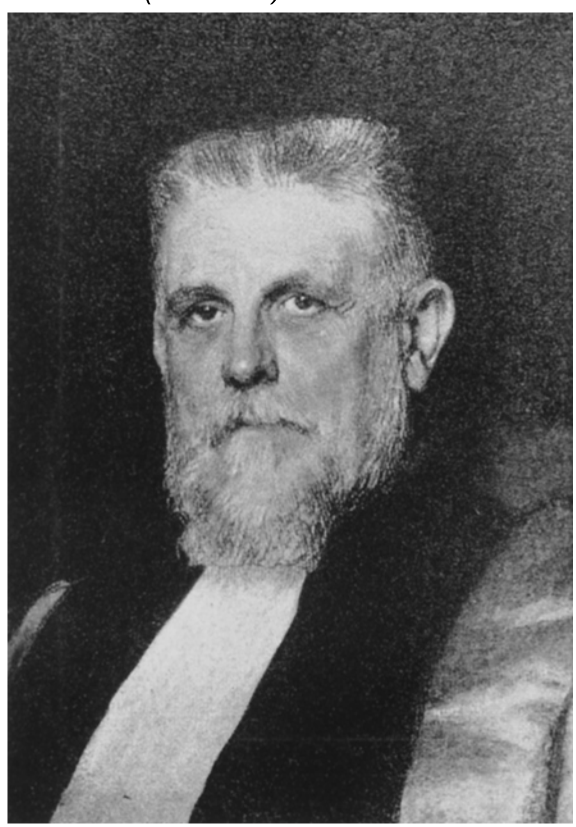


Figure 1-14
Henry Head (1861–1940).

architectonic maps, followed by many others, including those of Korbinian Brodmann,[58] whose cortical maps of the human brain have had the most widespread application. While these workers did not agree on the number and location of cortical areas (the Vogts counted over 200, Brodmann only 52[3]) it could not be contested that there were clear regional neuroanatomic differences.

The late nineteenth century also saw the beginnings of the modern study of memory and vision. Theodule Ribot introduced the distinction between anterograde and retrograde memory impairments and observed what is now known as "Ribot's law," that the most recently laid down memories were the most vulnerable to brain damage.[59–61] Ribot can also be credited with describing preserved learning in amnesia, thus anticipating the distinction between declarative and nondeclarative forms of memory that has been so intensively investigated in our own recent times. An additional contribution to memory research in the latter nineteenth century was the description by Wernicke and Korsakoff (shown in Fig. 1-16) of the syndrome that bears their names, including Korsakoff's observations of what he called "pseudo-reminiscence," now known as confabulation.[70,71]

In 1881, Hermann Munk reported that when he ablated the occipital lobes of dogs, they seemed unable to recognize objects despite seeing well enough to navigate the visual environment.[72] Shortly thereafter, Lissauer presented one of the earliest clinical descriptions of visual recognition impairment in a human and suggested the distinction between apperceptive and associative impairment—a clinical dichotomy still in use today.[73] Freud would later introduce the term *agnosia* to describe these conditions.[74] In the decades that followed, the visuospatial functions of the right hemisphere finally attracted the attention of neu-

Figure 1-15
Kurt Goldstein (1878–1965).

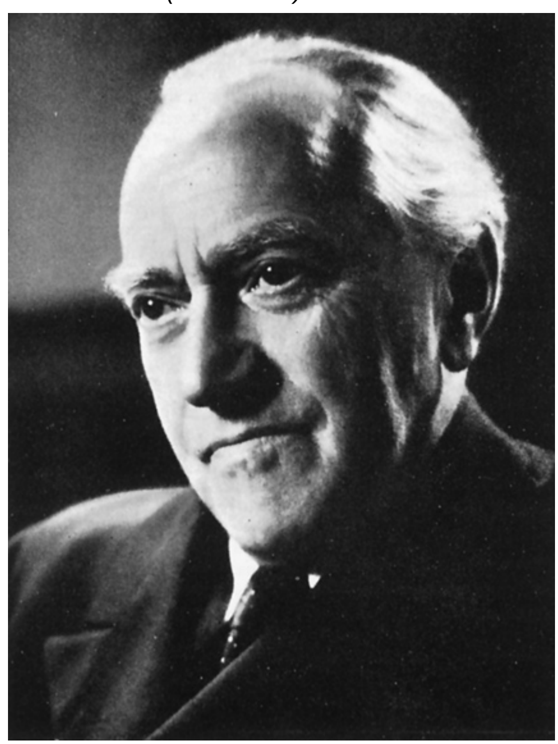


Figure 1-16
Sergei S. Korsakoff (1853–1900).

rologists and neuropsychologists.[67–69] The relatively delayed entry of this realm of functioning into the research arena is probably a result of the field's original focus on language and the left hemisphere, reflected in the nineteenth-century terminology of *major* and *minor hemisphere.*

THE RISE OF EXPERIMENTAL NEUROPSYCHOLOGY

Most of the advances described so far in this chapter were made by studying individual patients, or at most a small series of patients with similar disorders. In many instances, particularly before the middle of this century, patients' behavior was studied relatively naturalistically, without planned protocols or quantitative measurements. In the nineteen sixties and seventies, a different approach to the study of brain-behavior relations took hold. Neurologists and neuropsychologists began to design experiments patterned on research methods in experimental psychology.

Typical research designs in experimental psychology involved groups of normal subjects given different experimental treatments (for example, different training or different stimulus materials), and the effects of the treatments were measured in standardized protocols and compared using statistical methods such as analysis of variance. In neuropsychology, the "treatments" were, as a rule, naturally occurring brain lesions. Groups of patients with different lesion sites or behavioral syndromes were tested with standard protocols, yielding quantitative measures of performance, and these performances were compared across patient groups and with non-brain-damaged control groups. Unlike the impairments studied previously in single-case designs, which were so striking that control subjects would generally have been superfluous, experimental neuropsychology often focused on group differences of a rather subtle nature, which required statistical analysis to substantiate.

The most common question addressed by these studies concerned localization of function. Often the localization sought was no more precise than left versus right hemisphere or one quadrant of the brain (which, in the days before computed tomography, often amounted to left versus right hemisphere with presence or absence of visual field defects and/or hemiplegia). Given the huge amount of research done during this period on language, memory, perception, attention, emotion, praxis, and so-called executive functions, it would be hopeless even to attempt a summary. For those interested in some examples of this approach, we cite here some classic papers from a variety of the active laboratories of the period, addressing the question "Is the right hemisphere specialized for spatial perception of properties such as location,[70–72] orientation,[73,74] and large-scale topography?[75,76]

The influential research program of the Montreal Neurological Institute also began during this period. In the wake of William Scoville's discovery that the bilateral medial temporal resection he performed on epileptic patient H. M. resulted in permanent and dense amnesia, Brenda Milner and her colleagues investigated this patient and groups of other operated epileptic patients. This enabled them to address questions of functional localization with the anatomic precision of known surgical lesions (e.g., see Refs. 77 and 78 for reviews of research from that period on frontal lobe function and temporal lobe function, respectively). At the same time, another surgical intervention for epilepsy, callosotomy, also spawned a productive and influential research program. Roger Sperry and his students and collaborators were able to address a wide variety of questions about hemispheric specialization by studying the isolated functioning of the human cerebral hemispheres.[79]

In addition to answering questions about localization, the experimental neuropsychology of the sixties and seventies also uncovered aspects of the functional organization of behavior. By examining patterns of association and dissociation among abilities over groups of subjects, researchers tried to determine which abilities depend on the same underlying functional systems and which are functionally independent. For example, the frequent association of aphasia and apraxia had been taken by some to support the notion that aphasia was not language-specific but was just one manifestation of a more pervasive loss of the ability to symbolize or represent ("asymbolia"). A classic group study by Goodglass and Kaplan[80] undermined this position by showing that severity of apraxia and aphasia were uncorrelated in a large sample of left-hemisphere-damaged subjects. A second example of the use of dissociations between groups of patients from this period is the demonstration of the functional distinction, by Newcombe and Russell, within vision between pattern recognition and spatial orientation.[81]

By the end of the seventies, experimental neuropsychology had matured to the point where many perceptual, cognitive, and motor abilities had been associated with particular brain regions, and certain features of the functional organization of these abilities had been delineated. Accordingly, it was at this time that first editions of some of the best-known neuropsychology texts appeared, such as those by Hécaen and Albert,[82] Heilman and Valenstein,[83] Kolb and Whishaw,[84] Springer and Deutsch,[85] and Walsh.[86]

Despite the tremendous progress of this period, experimental neuropsychology remained distinct from and relatively unknown within academic psychology. Particularly in the United States, but also to a large extent in Canada and Europe (the three largest contributors to the world's psychology literature), experimental neuropsychologists tended to work in medical centers rather than university psychology departments and to publish their work in journals separate from mainstream experimental psychology. An important turning point in the histories of both neuropsychology and the psychology of normal human function came when researchers in each area became aware of the other.

THE BIRTH OF COGNITIVE NEUROSCIENCE

Patient-based cognitive neuroscience was born when the theories and methods of cognitive psychology and neuropsychology were finally combined. Both fields had strong incentives to overcome their isolation. Let us begin by reviewing the state of cognitive psychology prior to the birth of cognitive neuroscience.

The central tenet of cognitive psychology is that cognition is information processing. Although the effects of damage to an information-processing mechanism might seem to be a good source of clues as to its normal operation, cognitive psychologists of the seventies were generally quite ignorant of contemporary neuropsychology.

The reason that most cognitive psychologists of the 1970s ignored neuropsychology stemmed from an overly narrow conception of information processing, based on the digital computer. A basic tenet of cognitive psychology was the computer analogy for the mind: the mind is to the brain as software is to hardware in a computer. Given that the same computer can run different programs and the same program can be run on different computers, this analogy suggests that hardware and software are independent and that the brain is therefore irrelevant to cognitive psychology. If you want to understand the nature of the program that is the human mind, studying neuropsychology is as pointless as trying to understand how a computer is programmed by looking at the circuit boards.

The problem with the computer analogy is that hardware and software are independent only for very special types of computational systems: those systems that have been engineered, through great effort and ingenuity, to make the hardware and software independent, enabling one computer to run many programs and enabling those programs to be portable to other computers. The brain was "designed" by very different pressures, and there is no reason to believe that, in general, information-processing functions and the physical substrate of those functions will be independent. In fact, as cognitive psychologists finally began to learn about neuropsychology, it became apparent that cognitive functions break down in characteristic and highly informative ways after brain damage. By the early 1980s, cognitive psychology and neuropsychology were finally in communication with one another. Since then, we have seen an explosion of meetings, books, and new journals devoted to so-called cognitive neuropsychology. Perhaps more important, existing cognitive psychology journals have begun to publish neuropsychological studies, and articles in existing neuropsychology and neurology journals frequently include discussions of the cognitive psychology literature.

Let us take a closer look at the scientific forces that drove this change in disciplinary boundaries. By 1980, both cognitive psychology and neuropsychology had reached states of development that were, if not exactly impasses, points of diminishing returns for the concepts and methods of their own isolated disciplines. In cognitive psychology, the problem concerned methodologic limitations. By varying stimuli and instructions and measuring responses and response latencies, cognitive psychologists made inferences about the information processing that intervened between stimulus and responses. But such inferences were indirect, and in some cases they were incapable of distinguishing between rival theories. In 1978 the cognitive psychologist John Anderson published an influential paper[87] in which he called this the "identifiability" problem and took as his example the debate over whether mental images were more like perceptual representations or linguistic representations. He argued that the field's inability to resolve this issue, despite many years of research, was due to the impossibility of uniquely identifying internal cognitive processes from stimulus-response relations. He suggested that the direct study of brain function could, in principle, make a unique identification possible, but he indicated that such a solution probably lay in the distant future.

That distant future came to pass within the next 10 years, as cognitive psychologists working on a variety of different topics found that the study of neurologic patients provided a powerful new source of evidence for testing their theories. In the case of mental imagery, taken by Anderson to be emblematic of the identifiability problem, the finding that perceptual impairments after brain damage were frequently accompanied by parallel imagery impairments strongly favored the perceptual hypothesis.[88] The study of learning and memory within cognitive psychology was revolutionized by the influx of ideas and findings on preserved learning in amnesia, leading to the hypothesis of multiple memory systems.[89–91] In the study of attention, cognitive psychologists had for years focused on the issue of early versus late attentional selection without achieving a resolution, and here too neurologic disorders were crucial in moving the field forward. The phenomena of neglect provided dramatic evidence of selection from spatially formatted perceptual representations, and the variability in neglect's manifestations from case to case helped to establish the possibility of multiple loci for attentional selection as opposed to a single early or late locus. The idea of separate visual feature maps, supported by cases of acquired color, motion, and depth blindness, provided the inspiration for the most novel development in recent cognitive theories of attention—namely, feature integration theory.[92]

What did neuroscience gain from the rapprochement with cognitive psychology? The main benefits were theoretical rather than methodologic. Traditionally, neuropsychologists studied the localization and functional organization of *abilities,* such as speech, reading, memory, object recognition, and so forth. But few would doubt that each of these abilities depends upon an orchestrated set of *component cognitive processes,* and it seems far more likely that the underlying cognitive components, rather than the task-defined abilities, are what is implemented in localized neural tissue. The theories of cognitive psychology therefore allowed neuropsychologists to pose questions about the localization and functional organization of the components of the cognitive architecture, a level of theoretical analysis that was more likely to yield clear and generalizable findings.

Among patients with reading disorders, for example, some are impaired at reading nonwords (e.g., *plif*) while others are impaired at reading irregular words (e.g., *yacht*). Rather than attempt to localize nonword reading or irregular word reading per se and delineate them as independent abilities, neuropsychologists have been able to use a theory of reading developed in cognitive psychology to interpret these disorders in terms of damage to a whole-word recognition system and a grapheme-to-phoneme translation system, respectively.[93] This interpretation has the advantage of correctly predicting additional features of patient behavior, such as the tendency to misread nonwords as words of overall similar appearance when operating with only the whole-word system.

In recent years the neuroscience of every major cognitive system has adopted the theoretical framework of cognitive psychology in a general way, and in some cases specific theories have been incorporated. This is reflected in the content and organization of the present book. For the most intensively studied areas of behavioral neurology and neuropsychology—namely, visual attention, memory, language, frontal lobe function, and Alzheimer's disease—integrated pairs of chapters review the clinical and anatomic aspects of the relevant disorders and their cognitive theoretical interpretations. Chapters on other topics will cover both the clinical and theoretical aspects together.

COMPLEMENTARY METHODS IN COGNITIVE NEUROSCIENCE: PATIENT STUDIES AND FUNCTIONAL IMAGING

Following its introduction in the 1970s, positron emission tomography (PET) was quickly embraced by researchers interested in brain-behavior relations. This technique provides images of regional glucose utilization, blood flow, oxygen consumption, or receptor density in the brains of live humans. Resting studies, in which subjects are scanned while resting passively, have provided a window on differences between normal and pathologic brain function in a number of neurologic and psychiatric conditions. With the use of radioactive ligands, abnormalities can be localized to specific neurotransmitter systems as well as specific anatomic regions. Activation studies, in which separate images are collected while normal subjects perform different tasks (typically one or more active tasks and one resting baseline) yielded new insights on the localization of cognitive processes. These localizations were not studied region by region, as necessitated by the lesion technique, but could be apprehended simultaneously in a whole intact brain.

Positron emission tomography was soon joined by other techniques for measuring regional brain activity, each of which has its own strengths and weaknesses. Single photon emission computed tomography (SPECT) was quickly adapted for some of the same applications as PET, providing a less expensive but also less quantifiable and spatially less accurate method for obtaining images of regional cerebral blood flow. With new developments in the measurement and analysis of electromagnetic signals, the relatively old techniques of electroencephalography (EEG) and event-related potentials (ERPs), as well as magnetoencephalography (MEG), joined the ranks of functional imaging techniques allowing some degree of anatomic localization of brain activity, with temporal resolution that is superior to the blood flow and metabolic techniques. Most recently, functional magnetic resonance imaging (fMRI) has provided a particularly attractive package of reasonably good anatomic and temporal resolution, using techniques that are noninvasive and can be implemented with equipment available for clinical purposes in many hospitals.

Much of the early work with functional neuroimaging could be considered a form of "calibration," in that researchers sought to confirm well-established principles of functional neuroanatomy using the new techniques—for example, demonstrating that visual stimulation activates visual cortex. As functional neuroimaging matured, researchers began to address new questions, to which the answers were not already known in advance. An important development in this second wave of research was the introduction of theories and methods from cognitive psychology, which specified the component cognitive processes involved in performing complex tasks and provided a means of isolating them experimentally. In neuroimaging studies of normal subjects, as with the purely behavioral studies of patients, the entities most likely to yield clear and consistent localizations are these component cognitive processes and not the tasks themselves. Starting in the mid-1980s, a collaboration between cognitive psychologist Michael Posner and neurologist Marcus Raichle at Washington University led to a series of pioneering studies in which the neural circuits underlying language, reading, and attention were studied by PET (see Ref. 94 for a review). Since then, researchers at Washington University and a growing number of other centers around the world have adapted neuroimaging techniques to all manner of topics in cognitive neuroscience.

To many psychologists and neuroscientists, cognitive neuroscience is equivalent to cognitive neuroimaging. At the very least, we hope this book shows this idea to be mistaken. Although neuroimaging has had a huge and salutary effect on cognitive neuroscience, significantly expanding the range of questions that can be addressed, it has not replaced research with neurological patients. A full discussion of the complementary strengths and weaknesses of the two approaches could easily fill a chapter by itself, but a few of the most consequential differences can be summarized briefly here.

Lumping the different functional neuroimaging modalities together, they generally offer better spatial resolution than can be obtained in inferences from a few patients with focal brain lesions. Imaging also allows us to study normal brains, which lesion studies by definition do not. Furthermore, for some neurological conditions more than others there may be reason to suspect a degree of reorganization of remaining brain systems in response to damage. These are probably the greatest benefits of functional neuroimaging, although by no means the only ones.

The greatest weakness of neuroimaging is its inability to settle any issue concerning what might be called *mechanism.* An important goal of cognitive neuroscience is to identify the causal chain of neural events, or the mechanisms, underlying cognition. The data of functional neuroimaging are correlational: a certain area is activated when a certain cognitive process is occurring. Neuroimaging can never disentangle correlation from causation; in other words, it can never tell us which brain areas are causally involved in enabling a cognitive process. Activated regions could play a causal role or could be activated in an optional or even an epiphenomenal way. For this we must turn to studying the effects of brain damage, the "experiments of nature" that provide a direct test of the causal role of different brain areas by showing us how the system works in their absence. Given the complementary strengths of neuroimaging and patient studies, we predict that the most successful cognitive neuroscience research programs of the twenty-first century will be those that combine the two approaches.

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