9 THE CEREBRAL CORTEX

CHAPTER OVERVIEW

As noted in the preface, the intended audience for this text primarily was neuropsychologists, behavioral neurologists, and other behavioral scientists with comparable interests. Consequently, our treatment of the cerebral cortex has been greatly expanded relative to most other textbooks on functional neuroanatomy. For convenience, this chapter has been divided into three sections. The first (Part I) provides a brief review of how the cerebral cortex came to be recognized as integral to the expression of complex behavior. Part II will focus on the gross neuroanatomical features of the cortex and related supportive structures, except for the vascular system. The latter will be covered separately in Chapter 10. In addition, Part II will review common syndromes that traditionally have been associated with focal lesions within each cerebral hemisphere. Part III is more theoretical in nature. It attempts to provide a model of brain organization and how the integration of sensory, motor, and emotional or motivational factors result in goal-directed behaviors.

PART I. A BRIEF HISTORY OF LOCALIZATION OF FUNCTION IN THE BRAIN

While the mechanisms by which the brain accomplishes its marvelous feats are still largely a mystery (and probably will remain so for many generations to come), at least it is readily apparent, even to the average person, that the brain itself is central to the thoughts, feelings, and actions that characterize daily experiences. However, this was not always the case. Despite often highly sophisticated advances in other fields in the last 2,000 to 3,000 years (e.g., mathematics), knowledge not only of the operation but even the relative importance of the brain to behavior lagged far behind. As will be pointed out in this section, it was not until the 18th century that the relevance of the brain to purposeful, goal-directed behavior commonly began to be appreciated as a subject of legitimate scientific investigation. Perhaps surprisingly, despite eons of traumatic head injuries, apparently it was not until the following century that specific cognitive functions became clearly identified with focal lesions in the brain. Because it is always interesting to understand the roots of any scientific field of study, Part I presents a brief review of how the brain likely was perceived over the millennia. This begins with the early Egyptians and the Greeks and brings us to the modern era (early 20th century) when questions of *how* the brain operates first began to be asked.

Broadly speaking, the brain came to be widely recognized as important in the mediation of conscious, goal-directed behavior in humans at least since the time of the ancient Greeks. However, it might be noted that the brain's **parenchyma** took second place to the cerebrospinal fluid in order of importance, the former not gaining ascendancy until about the 18th century. Although Galen laid the groundwork for experimental studies on the central nervous system (primarily at the level of the medulla and below) with animals in the second century, the next true systematic, scientific experimental studies involving the cortex did not take place until the early 19th century with Flourens. Most historians seem to trace the real beginning of the application of modern scientific methods to the study of such correlations in humans to the publication of Paul Broca in 1861. Shortly afterward, there was a number of documented associations between various "higher cognitive functions" in humans and specific neuroanatomical sites on the cortex. In reaction to these "localizationists," there was another group of scientists (for whom Lashley became one of the primary spokesperson) who felt it was important to view the functional organization of the brain as being more wholistic. This latter group believed that the brain functioned as a whole, especially when carrying out complex behaviors. As we shall see, elements of both of these approaches are incorporated into most current theories.

ANCIENT CONCEPTS OF THE BRAIN

One of the first recorded mentions of the brain was contained in a papyrus discussing medical observations in ancient Egypt. Although the papyrus itself dates back to at least the 17th century BC, some of the accounts it presents may date as far back as 3500 BC. It described what was apparently an open head trauma that may have produced aphasia (failure to speak, although conscious) and may have led to seizures (extreme "shuddering" when the surface of the brain was touched). Despite this account, the early Egyptians, as well as the Hebrews, most likely attributed the control of most cognitive functions to the heart. As might be suspected, the written records from this period were quite scarce and the first recorded systematic observations of the brain and of the debate as to whether the brain or the heart was central to man's awareness and knowledge came with the Greeks.

Although little is preserved from his writings, Alcmaeon (ca. 500 BC) clearly saw the brain as central to the capacity to appreciate perceptions from the outside world (recognizing the connections between the sense organs and the brain), as well as to thought.

Hippocrates (460 to 370 BC), following the medical traditions of his day, believed that various combinations of the four basic humors were responsible for behavior. He also believed that of the four (air, water, earth and fire), air seemed to be the most critical as our source of knowledge of the world around us. However, it was in the brain that air, in its purest form, was first introduced, and hence, it was the brain that was our ultimate source of knowledge and understanding. It was perhaps during this period that for the first time the brain gained acceptance as the organ of perception and intelligence. Of equal importance was an attempt to lay to rest the misconception that epilepsy (as well as other psychological maladies) was a punishment from the gods. Hippocrates concluded that epilepsy instead was a disease of the brain, even noting the contralateral relationship in focal seizures. This focus on the physical, rather than the spiritual, as a cause of illness in humans obviously was a major impetus for the study of modern medicine. The following is an excerpt from this period:.

> One ought to know that on the one hand pleasure, joy, laughter, and games, and on the other grief, sorrow, discontent, and dissatisfaction arise only from the brain. It is especially by it that we think, comprehend, see, and hear, that we distinguish the ugly from the beautiful.... Furthermore, it is by the brain that we are mad, that we rave, that fears and terrors assail us—be it by night or by day—dreams, untimely errors, groundless anxiety, blunders, awkwardness, want of experience. We are affected by these things when the brain is not healthy, that is when it is too hot or too cold, too moist or too dry, or when it has experienced some other unnatural injury to which it is not accustomed. (Hippocrates or the Hippocratic writers)

However, not all the Greek intelligentsia of the time adhered to this cephalocentric theory of humans. Aristotle (384–322 BC), certainly one of the greatest thinkers of his time, provided rather detailed anatomical descriptions of the brain. One major difference between his observations and current knowledge was that he thought the substance of the brain itself was devoid of a supply of blood. But this fit well with his theory regarding the function of the brain. He stated, "for where there is no blood, there in consequence is but little heat. The brain then tempers the heat and seething of the heart." Thus for Aristotle, the heart, not the brain, was the center for perceptions, knowledge, and awareness. The senses were thought to be in more direct connection with the heart than with the brain. The main purpose of the brain was to cool the blood from the heart. He explained the fact that the brain in men is larger than in women because the "region of the heart *and* lung is hotter and richer in blood" in the former.

Erasistratus had observed in the 3rd century BC that the cortex of man was more convoluted than it was in animals and he surmised that this probably was related to man's superior intelligence. He reasoned that it was within the brain, specifically within the ventricles, that the *vital spirits* (humors) of the blood were changed into the *animal spirits*, which traveled through the (hollow) nerves and then could effect muscular contractions through distention of the body of the muscle.

Galen (131–201 AD) disputed Erasistratus's claim of the functional significance of the cerebral convolutions, in part because he saw the pituitary gland and the ventricles as perhaps the most critical parts of the brain. However, following Erasistratus, he also thought it was within these areas that the "vital spirits" of the blood, after being influenced by the humors entering the body through the sense organs, were transformed into the "animal spirits," which in turn were responsible for all nervous system activity. As an anatomist, Galen was quite familiar with brain structure. Among other things, he identified and named the meninges, the corpus callosum, the fornix, the superior and inferior colliculi, the pituitary gland, and 11 of the 12 cranial nerves. He also performed experimental lesions of the spinal cord in animals. However, it was probably in his capacity as physician to the gladiators that Galen became quite familiar with the effects of head trauma and was aware that injuries to the brain (and spinal cord) were related to both physical and behavioral changes. Because of his eminence as a physician and the force of his writings, his views on the roles of humors or spirits as the major force behind the function of the nerves persisted until well into the 18th century.

THE MIDDLE AGES

Following Galen, apparently there was little advancement in the knowledge of brain mechanisms until the Middle Ages. What little was written on the subject suggested the ventricles, rather than the brain substance, continued to be considered the most important determinant of behavior. Apparently, at least in part, advancement in the knowledge of the nervous system was hampered by widespread religious and cultural proscriptions against dissection of the human body. This began to change around the time of Andreas Vesalius, who provided the first detailed book on the anatomy of the nervous system in 1543. Vesalius thought the purpose of the convolutions and sulci was to allow the blood supply of the pia mater to extend into the cortical surface more efficiently. Other than that, he felt they "cannot be compared to anything more happily than to clouds as they are usually delineated by either untrained art students or by schoolboys."

Archangelo Piccolomini first discussed the distinction between the gray and white matter of the cortex in detail in 1586, referring to the former as the cerebrum and to the latter as the medulla. He also was the first to use the term "medulla oblongata." The term "cortex" apparently is traced to C. Bauhin in 1616. Sylvius de le Boe first described the lateral fissure in his writings in 1663, although its discovery was attributed to him some years earlier.

Rene Descartes (1596–1650) primarily is thought of as a philosopher and mathematician, but he also was a student of physiology and was the first to attempt to define a reflex pathway. His book, *De Homine*, published posthumously in 1662, was one of the first European textbooks in physiology. While he adhered to many of the Galenic principles of the functioning of the nervous system (e.g., the presence of the animal spirits flowing through the nerves and muscles that mediated perceptions and motion), Descartres differed with the prevailing notions regarding the site of the *sensorium commune* ["judgment" or "common sense"], which generally had been placed within the ventricles. In his dualistic philosophy on the nature of man, he envisioned the body of humans and animals as operating as a complex machine that was fueled by the "fire of the heart." This machine or body of man and the animal spirits, which served as the basis for its perceptions and guided its muscles, was similar in its general makeup and functioning to that of the animals. The difference between humans and animals was the presence of a spiritual soul that provided man with will, knowledge, and the power of introspection. He recognized that the soul was dependent on the body to gain knowledge (via the senses) and as a means of expressing its will (e.g., through movement and speech). He perceived of the soul as being a unitary entity (unlike the tripartite notions of the Greeks) that resided in the body as a whole, but not in any one part. However, there needed to be a single place where the soul and the body interacted because there is a unity to our perceptions, and therefore, the soul must be a unity. Following Galenic thought, Descartes decided that the brain must be the site of this interaction (since it was here that all the senses convened) and that the pineal body was the center of the soul. Descartes contended that, in addition to being the only unitary structure in the brain (a unity demanded by the nature of the soul), the pineal body also was critically located (at the juncture of the anterior and posterior ventricular system). From here, the pineal body could be influenced by the spirits coming in from the senses, through which knowledge was obtained, and in turn could influence the spirits that went out from the brain via the nerves to the muscles, whereby the will could express itself. Descartes did not believe the soul resided in the pineal body, but rather this was the "seat" or the place where the soul interacted with the body. Thus, Descartes was perhaps the first to attempt to precisely localize function within the brain itself.

Thomas Willis (1621–1675), after whom the **circle of Willis** is named (although several others before him had described it), helped to focus increased attention on the cortex as an important anatomical entity. He apparently was the first to use the terms "hemispheres" and "lobes" as they are currently applied to the cortex. As did Erasistratus almost 2,000 years before, he pointed to the increased complexity of the convolutions of the brain in humans as a sign of increased intelligence. He reinforced this thesis through the study of comparative anatomy, contrasting, for example, the relatively smooth cortex of the bird, with the somewhat more convoluted cortex of quadrupeds (which seemed to be capable of more complex behaviors than birds), and finally with the highly convoluted cortex of man. However, the role he attributed to the cortex was the production of the animal spirits.

Despite this focus on the relevance of the cortex with regard to intelligence, little further attention seemed to be afforded the study of the sulci and gyri until around the beginning of the 19th century when Gall and Spurzheim began their studies in phrenology. Perhaps one notable exception was Emanuel Swedenborg who in the early to mid 1700s noted the correct location of the motor cortex. However, his findings were still based on a glandular theory of neurophysiology and there was no further confirmation of his theory of motor localization in the cortex until the works of Fritsch and Hitzig, more than a century later. Although not involving the cortex, one early contribution to the localization of function that occurred during this period involved Julian Jean Le Gallois (1770–1814), one of the first French experimental physiologists of the 19thcentury. In 1811, he reported that the anatomical substrate for respiratory control resided in the brainstem (in rabbits).

The cerebral convolutions and many of the subcortical structures were depicted fairly accurately in an anatomy atlas by Felix Vicq d'Azyr (whose name is associated with the mammillothalamic tract) in 1786. But it was not until 1829 that Luigi Rolando, for whom the central sulcus is named, suggested that the gyri and sulci in humans were not randomly arranged, but rather followed regular, predictable patterns. It might be noted that he was not including the gyri of the frontal lobes, which he thought were characterized by a great degree of individual variation. While Rolando recognized that certain general functions, such as consciousness and voluntary action, were dependent on the integrity of the cortex, he did not attempt to localize any other behaviors to specific cortical areas. In fact, he espoused the traditional belief that the "sensorium commune," which might be considered the highest cognitive ability in humans, was probably "localized" in the brainstem.

In 1839, Francois Leuret, a French anatomist, began publishing his studies on the comparative anatomy of the cortex of mammals. In his comparative study from mouse to elephant (including sea mammals such as the whale), he noted the relationship between the complexity of gyral patterns and the native "intelligence" of the organism. In addition to noting the relationship between gyral complexities and their relative phylogenetic development, Leuret concluded that the "number, form, arrangement and connections of the cerebral convolutions are not formed by accident; each family of animals has the brain shaped in a determined fashion." Dying before he could complete his task, his work was continued by Louis Pierre Gratiolet (1854) who provided us with most of the terminology used today in delineating the cortical surface anatomy. He provided the current names for and clarified the boundaries of the four cortical lobes[1] and supplied the current names of most of the gyri. It might be noted that the names of the lobes were derived from the names of the individual bones of the calvarium (skull) under which they lay. While adhering to the doctrine of his predecessor regarding the general relationship between complexity and intelligence, no specific functions or roles were ascribed to the lobes or the gyri that he named.

Thus into the early 19th century, the issue of the interaction or relationship between the "mind" and the "body" still was being strongly contested. Certainly, there was no consensus regarding localization of cortical functions. The brain or more specifically the cerebrospinal fluid was thought to be the source of cognitive functions or of the "sensorium commune." These functions generally were thought to result from the humors or animal spirits that pervaded or resided in this structure (the brain and/or ventricles). Furthermore, it was not until the end of the 18th century (1786–1792) that Galvani's work establishing the electrical properties of nervous tissue was published.

Despite, the admonitions of Hippocrates 2,000 years earlier, many "disorders of the mind" were still considered to be the result of *supernatural anomalies* (e.g., demonic possession). However, the notion that "intelligence" and other "cognitive abilities" reside in the brain was beginning to emerge, creating a scientific community that was receptive to the modern approaches to the study of the brain. Benjamin Rush in America, William Tuke in England, and Philippe Pinel in France had begun a movement for reform in the perception and treatment of the insane in their respective countries. They argued that the psychic afflictions suffered by these "insane" individuals were akin to a "disease" of the mind, rather than a result of spiritual corruption or supernatural disfavor. Although not relating psychiatric disturbances to a specific disease or dysfunction of the brain, they laid the groundwork for the discovery that abnormalities of the brain (which in one way or another was generally associated with cognition) might be related to anomalies of behavior.

BRAIN LOCALIZATION: THE EARLY YEARS

It was about this time that Franz Joseph Gall (1758–1828) and his student, Johann Spurzheim (1776–1832), entered into the picture. Gall was a highly respected anatomist who emphasized the relative importance of the gray matter of the cortex and discussed its relationship to the underlying white matter. As the story goes, supposedly as a schoolboy, Gall was struck by what he perceived to be a correlation between certain physiognomical characteristics of the face and head and specific mental abilities among his schoolmates. He reportedly noticed, for example, that individuals with protruding eyes seemed to have excellent memories. Later he tested these hypotheses by studying criminals and psychiatric patients to determine whether particular aspects of the shapes of their heads or faces were related to obvious or "atypical" personality traits. Partially with Spurzheim's urging (who saw a potential market for these ideas), Gall began to study normal individuals as well. He began with the theories of Thomas Reid and Dugald Stewart of the Scottish school of psychology. Reid and Stewart detailed a variety of "faculties," "traits," or "powers" that alone or in combination were thought to explain most of human behavior or personality. Gall reasoned that it was impossible for a "homogeneous" brain to be responsible for such diverse behavioral traits or faculties. Instead, Gall suggested that it was much more reasonable to assume that the brain was composed of multiple, though interconnected organs, each of which was responsible for a separate observed behavioral characteristic. These "organs," in effect, were delineated groups of cells that made up all or portions of the cortical gyri. His theory was based on the following two assumptions. First, if a faculty, power, or trait was prominent or well developed in an individual, the area of the brain responsible for that trait also must be "well developed" or "prominent" (the converse would hold true if the trait was relatively lacking in the individual). Second, if an area of the brain responsible for such a trait was prominent (or lacking in development), that portion of the skull that covered that region likewise would reflect this difference by being more "prominent" (bulging), or in the case of underdevelopment, show a relative depression. That is, the configuration of the skull would reflect the configuration of the underlying brain. Thus, the study of the "bumps" of the brain, or **phrenology**, was born.

Although the theories of Gall and Spurzheim were quickly discredited among most scientific circles, largely a result of the efforts and persuasiveness of Spurzheim, they did produce a large popular following and managed to garner some respect in the scientific community. Numerous phrenological societies and journals flourished in the United States and abroad. The *Journal of Phrenology* lasted until 1912, approximately a century following Gall's original publications. Despite their extremist positions, Gall and Spurzheim's contributions are noteworthy. Gall was the first to ascribe importance to the gray matter of the cortex. He also was the first to suggest that different parts of the cortex made differential contributions to human behavior, particularly higher cognitive functions. This was quite a dramatic and perhaps somewhat courageous departure from the notion of a "sensorium commune" that had persisted since ancient Greece. Because of their insights regarding these new possibilities of brain organization, Gall and Spurzheim are credited with having marked the beginning of the study of brain localization.

In 1824, Flourens did manage to quiet the "phrenology" movement for a while through his experimental work on animals. First, he noted that he was unable to elicit movement in the dog by manual stimulation of the anterior cortex; it was only by stimulating the quadrigeminal plate that a motor response was obtained. What he felt were his most telling experiments, however, were his studies involving the extirpation studies of the cortex of the pigeon. Basically, after removing the cerebral hemispheres of these birds, he noted that the birds remained in what he called a *state of perpetual sleep*. They would open their eyes if disturbed, but then quickly return to their quiescent state. While no spontaneous movements were observed, if food were placed in their beaks they would swallow it and if they were thrown into the air they would fly (although they would bump into walls). Flourens concluded that when deprived of the entire cerebral cortex, these animals lost all higher cognitive abilities, including sensation, judgment, memory, and volition, while retaining basic motor skills. Additional experimentation revealed that if the cerebellum was removed, the animal was no longer capable of coordinated movement. Thus, Flourens concluded that the cerebellum was primarily responsible for all motor activity.

Using careful scientific methods and precise surgical extirpations of the cortex, Flourens sought to determine whether specific functions were localized to discrete areas in the cerebral hemispheres or whether the cortex as a whole subserved specific functions. He concluded the following:

1. If certain sized lesions were made, regardless of its localization on the cortex, no behavioral effects were noted, suggesting that the remaining, intact cortex could adequately carry out all functions.
2. As larger amounts of cortical tissue were removed, behavioral deficits (sensation, perception, judgment, memory, and volition) began to become evident, and with sufficient loss of brain mass might be lost completely. However, he noted that all of the various functions seemed to decline (or be lost) at the same rate, at the same time, again regardless of the particular site of the lesion. He deduced that although all of these functions reside in the cerebral hemispheres, they must be represented equally throughout the cortex. He did seem to recognize that *each of the various sense organs* might have had a distinct localization within the brain.
3. He also noted that when a function was lost as a result of a circumscribed cortical lesion, it frequently would be restored over time, suggesting a sort of *equipotentiality* principle.

In conclusion, Flourens noted that "the cerebral lobes are the exclusive site of sensations, perceptions and volitions [but these functions] concurrently occupy the same areas in these organs. Therefore the ability to feel, to perceive, and to desire constitute only one essentially single faculty."

Next came Jean-Baptiste Bouillaud, a French physician who was a student of phrenology. In opposition to Flourens' conclusions, he noted that disturbances of motor functions were common and well-known sequelae of cerebral lesions in clinical populations. Furthermore, consistent with the claims of Gall and Spurzheim, he noted, in a paper presented before the Royal Academy of Medicine in 1825, that there was a relationship between disturbances of motor speech and the anterior frontal lobes. He did not relate these impressions, however, specifically to the dominant left hemisphere. His assertions moreover were not well received at the time due to the distrust and disdain associated with any theory supporting phrenology. However, 36 years later, Ernest Auburtin, the son-in-law of Bouillaud and himself a physician, argued for his father-in-law's position about the anterior frontal lobes being responsible for speech. He reported a patient with a traumatic cranial defect over the frontal lobes. When gentle pressure was applied to the frontal cortex of this patient, speech was halted, but returned when the pressure was removed. He felt this case supported Bouillaud's original conclusions.

He also cited other previous cases of disturbed language that eventually revealed frontal pathology. He had a second, critically ill patient with progressive loss of speech, despite preserved comprehension and general intelligence. He predicted, with both his theory and reputation on the line, that on autopsy a focal lesion would be found in the frontal cortex. Among those who heard Auburtin's presentation was an anthropologist and physician, Pierre Paul Broca. As it happened, Broca was familiar with a patient who in addition to suffering from epilepsy also had lost his ability to speak many years earlier, repetitively uttering only the word "tan." He was being seen by Broca following progressive right-sided weakness and cellulitis in his right leg. Reportedly, knowing his interest in this area, Broca had consulted Auburtin on the case. Shortly after Auburtin's formal presentation and predictions, Broca's patient died. Broca performed an autopsy and found a lesion in the left frontal region as has been predicted. Broca's findings were presented at the next meeting of the Anthropological Society. Several months later, another of Broca's patients died who also had a history of expressive language deficits and in whom the lesion was more restricted to the third and portions of the second frontal convolution. In his presentation to the Anatomical Society of Paris later that same year, Broca stated more definitively that the "faculty of expressive speech" is a result of lesions in the "anterior lobes" of the brain. While he thought the second or third frontal convolutions were perhaps the more critical sites, he noted that more confirmatory data were necessary. He did manage to point out that his findings nevertheless were inconsistent with (and thus distancing himself from) phrenological theory that placed this faculty much more anteriorly. From this point on, theories of cortical localization were reestablished. Interestingly, during these early presentations, Broca apparently said nothing about hemispheric localization, but by 1863, after collecting eight additional cases, Broca began to suspect the leading role of the left hemisphere in language. However, it was not until 1865 that he reported, after also noting the frequent absence of speech problems with right frontal lesions, the dominance of the left hemisphere for language. At the time he gave credit to Dax who had suggested the same thing in 1836.

Soon, other clinically based findings supporting localization of function were being reported. Hughlings Jackson (1835–1911), who might well be considered the father of modern neurology, added further credence to the localization of speech from his own clinical observations, despite disagreeing with Broca on the nature of aphasia. From his studies of focal epilepsy, he concluded that these focal seizures likely resulted from focal disturbances in the gray matter of the cortex and varied according to the extremity initially involved. While he recognized that certain regions of the brain seemed to be responsible for certain behavioral effects (e.g., speech, movement), he also cautioned against a strict localization approach, that is, the identification of "centers" for various cognitive functions. He suggested that the nervous system was organized on different levels of vertical organization. Therefore, functions could be represented in different ways at different levels, each contributing to the whole in its own unique manner. Needless to say he was a bit ahead of his time and these theories of brain organization or localization were not widely accepted.

Karl Wernicke (1848–1904) published his doctoral dissertation in 1874 in which he suggested two speech "centers": an anterior or **motor center** that was responsible for the expression of speech (Broca's center) and a posterior or **sensory center** that was responsible for the storage or recognition of auditory images. He placed the latter in the superior temporal gyrus. He later also discussed a third type of aphasia (conduction aphasia) that resulted from a lesion that interfered with the connection between these two primary centers. In describing the latter, he appeared to be the first to recognize the behavioral relevance of different regions of the brain being able to work together in a cooperative fashion, rather than there simply being an independent center for each activity. In doing so, he began laying the groundwork for Geschwind's (1965) discussions of disconnection syndromes in the second half of the next century.

Taking another tack, Eduard Hitzig (1838–1907), Gustav Fritsch (1838–1927), and David Ferrier (1843–1928) used experimental methodology (electrical stimulation and ablation) to map out the motor cortex in animals. Hitzig and Fritsch, working together in a bedroom of Hitzig's home, mapped out the motor cortex of dogs using the electric current from a galvanic pile. They discovered experimentally what Hughlings Jackson had arrived at clinically, namely that the more anterior portions of the cortex were associated with motor functions, while the posterior cortices evoked no motor response when stimulated. They also reaffirmed the principle of contralateral representation. To further substantiate their findings, ablation studies later were performed on those cortical areas that elicited motor responses when stimulated. They found that, following such lesions, contralateral motor limb weakness could be demonstrated.

Ferrier basically replicated the work of Hitzig and Fritsch, but carried it a step further by being much more precise and detailed in his technique and observations. Whereas the former generally produced gross movements of the limbs, Ferrier was able to demonstrate the sensitivity and selectivity of very small muscle groups to cortical stimulation, typically stimulating cortical sites only millimeters apart. Working largely with monkeys, he was able to map out in great detail not only what we now refer to as the frontal motor cortex, but was able to demonstrate regions in the parietal and superior temporal regions that also produced discrete motor responses.

Despite continuing opposition, the trend to establish "maps" for the cortical localization for both simple sensorimotor as well as "higher cognitive abilities" continued well into the 20th century. However, caution was being urged against overly simplifying localization, not only as a reaction to phrenology, but by those who thought that brain organization and function might be much more complex. Among those making the latter argument was the prominent neurologist, Hughlings Jackson, and some of the newer antilocalizationists. These included Friedrich Goltz who had arrived at a mass action interpretation after studying the effects of cortical lesions in dogs; Constantin von Monakow who argued for the effects of diaschisis; and Karl Lashley who studied the effects of progressively larger lesions in rats. Illustrative of the push to identify "centers" of cognitive and behavioral traits or capacities was the functional maps of Kleist (1934) (Figure 9–1). Later, others such as Kurt Goldstein recognized what appeared to be the inescapable conclusion that certain functions, particularly sensory and motor functions, were clearly localizable and tried to reconcile the two approaches. For example, he argued that certain capacities (e.g., basic sensory and motor functions) likely were localized in the peripheral portions of the cortex, whereas the more central cortical areas were responsible for the more abstract and categorical aspects of behavior and operated more on an equipotentiality principle.

Thus, by the beginning of the 20th century, the principle of localization was well established, even if not universally accepted. The next step was to determine in greater detail the pattern of this localization, or perhaps more precisely the functional organization of the brain. Were there indeed "centers" for certain behaviors such as writing or reading? If so, what was the nature of the interaction among these various "centers"? Were certain behaviors more dependent on the functioning of the brain as a whole? Was there some unitary principle(s) that reflected the roles or functions of the various lobes? What was the difference between the hemispheres with regard to the control or expression of behavior? Was this difference simply a matter of differences in the type of behaviors being mediated

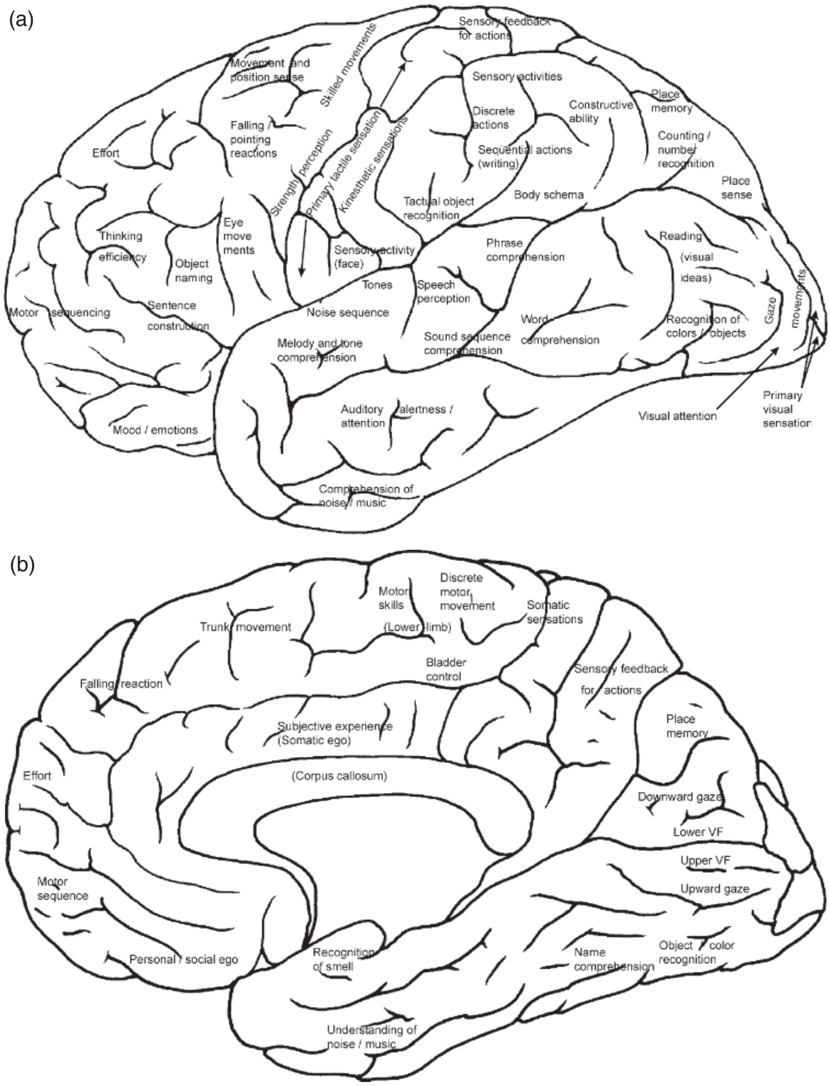


Figure 9–1. Kleist's functional brain maps. Drawings adapted from K. Kleist (1934).

or were the hemispheres organized and did they function in fundamentally different ways? These are the types of questions that characterized much of 20th century neuropsychology and behavioral neurology and which much of Part II will attempt to address.

Endnote

1. Here there seems to be some disagreement in the literature. Some authors attribute the naming of the lobes to Gratiolet. Others suggest that the names of the four major lobes initially were attributable to *Chaussier* (1807) who substituted the names "frontal," "temporal," and "occipital" for the terms "anterior," "inferior," or "medial" and "posterior" divisions first employed by Varolio in 1573, with the delineation of a "superior" (parietal) division being a later development.

CHAPTER 9 ♦ PART II

PART II. NEUROANATOMY AND FUNCTIONAL CORRELATES OF THE CEREBRAL CORTEX

CHAPTER 9, PART II OVERVIEW

As we have progressed from the peripheral and spinal nerves to the diencephalon and limbic structures, the extraordinary complexity of the human nervous system repeatedly has been emphasized. But, as the saying goes, "you ain't seen nothing yet." The cerebral cortex alone probably contains in excess of 10 billion neurons. If we consider that each of these neurons may have as many as 1,000 or more connections, the total number of possible interactions is staggering. When considering the task of trying to understand anything of such cosmic proportions, one British neurologist reportedly observed that if our brain were simple enough for us to understand, then we would be too simple to understand it. In Part I of this chapter, a brief history of the evolution of the appreciation of the brain as the organ responsible for behavior and cognition was presented. With the recognition that we have barely scratched the surface in our understanding of this marvelous organ, the remainder of this chapter hopefully will provide the student with a frame of reference with which they might approach the study of brain pathology and its effect on behavior. Toward this purpose, Part II will focus on some of the major internal and external structural features of the cerebral cortex, as well as a general overview of its functional organization and known behavioral correlates (Part III will continue this investigation by exploring how discrete functional areas might interact to produce integrated behavioral responses).

Knowledge of neuroanatomical nomenclature and structural relationships of the brain are essential when discussing pathology or functional correlates. Part II begins by reviewing the support structures of the cerebral cortex, specifically the skull, meninges, and ventricular system. All three are involved in various pathological processes and knowledge of the latter is crucial in the interpretation or understanding of neuroimaging. The other key supporting elements of cortical functions are the vascular and neurochemical systems. Because of the detail required to do justice to these two systems, separate chapters (Chapter 10 and Chapter 11) will be devoted exclusively to them.

The neocortex itself has both natural and somewhat arbitrary divisions. The most obvious of these are the two cerebral hemispheres and the gyri and sulci. The more arbitrary divisions are the four lobes of the brain and the insular cortex. Although only observable under microscopic techniques, for approximately the past 100 years it has been recognized that the various gyri and lobes also are characterized by variations in their cellular structures, variations that appear to reflect functional differences. Also not obvious on gross inspection but clearly visible on either dissection or on neuroimaging are the white matter (axonal) pathways that interconnect the hemispheres, lobes, gyri, as well as provide a means for the neocortex to communicate with subcortical structures and eventually with the peripheral nervous system.

In addition to a review of basic neuroanatomy, Part II begins to explore the functional organization of these various cortical structures. One of the first things we will discuss is what happens when communications are disrupted between one part of the brain and another. While probably relatively common in cases of brain injury, in certain instances such phenomena create classic (*disconnection*) syndromes that not only are useful for purposes of clinical localization but also provide important insights into the functional organization of the brain. We also will be reviewing hemispheric differences, both in terms of anatomy and function. For the most part, it is believed that the brain functions as a whole. That is, both hemispheres and all four lobes of the brain are likely engaged in carrying out most behavioral activities. However, it also seems likely that each hemisphere and each subregion of the brain is making its own unique contribution to the behavior as a whole. In this section, we will discuss what appear to be the relative contributions of each hemisphere to commonly identified behaviors or syndromes. What is going to be of particular relevance here is not simply trying to identify the locus of a lesion based on a particular behavioral syndrome (current imaging techniques generally do that fairly well), but rather knowing what type of behavioral disturbances to explore given an identified lesion.

By the end of this section, the reader should be able to identify the meningeal layers and discuss their functional/pathological significance. Similarly, one should be able to discuss the ventricular system and discuss ways in which it may be of clinical relevance. One also should be able to localize and name the major gyri and sulci in the brain, identify the boundaries (where possible) of each of the lobes, and discuss the major types of white matter pathways within the brain. Finally, the reader should be able to identify and discuss the major behavioral symptoms and syndromes commonly associated with functional disturbances of the right and left hemispheres (assuming typical patterns of dominance).

CEREBRAL ORGANIZATION: AN INTRODUCTION

As was noted in Part I of this chapter, Broca's presentations on aphasia in the 1860s provided the long-needed impetus (and scientific credibility) for the systematic study of the cerebral cortex as the repository for complex mental and emotional behaviors. Over the next 100 years, many neurobehavioral scientists attempted to develop increasingly refined functional maps of the cortex. These functional cortical maps were derived primarily through the use of ablation and stimulation techniques in animals, the study of naturally occurring and surgical lesions in man, electrical recordings, and the tracing of neuroanatomical pathways. By the early part of the 20th century, to many of the "localizationists," the situation must have looked fairly promising. The general parameters of the sensorimotor cortices were fairly well outlined. Many aspects of speech and language had been generally localized to the perisylvian areas of the left hemisphere. In 1924, Gerstmann first identified a quartet of symptoms consisting of finger agnosia, agraphia, right–left confusion, and acalculia which were present in a single patient. By 1930, after having collected additional cases, he was convinced that these four symptoms (later authors often included visual–spatial constructional deficits as a fifth) represented a specific neurobehavioral syndrome associated with lesions of the dominant angular gyrus, a syndrome that still bears his name (**Gerstmann's syndrome**).

Despite these early discoveries, other investigators felt that the promise of the localizationists was not to be easily fulfilled. While recognizing the capacity to identify certain basic motor and sensory "centers," these individuals contended that the more complex the behavior, the more difficult it was to "localize." If the cortical representations of elementary sensory and motor activities were relatively easily identified, attempting to localize one's capacity for abstraction, concept formation, judgment, learning and memory, and other "intellectual" and problem-solving behaviors proved more elusive. Even with regard to speech and language, naming ability appeared to be fairly widely distributed in the left hemisphere.[2] It has been only relatively recently that the "nondominant" hemisphere has been identified as critical in mediating certain affective valences of speech and language (Ross, 1981).

Constructional disability, which will be discussed in greater detail below, represents a good example of the problems in attempting to localize a specific neurobehavioral symptom. Broadly defined as a difficulty in the visual–motor reproduction of two- or three-dimensional spatial patterns, constructional ability initially was thought to represent a relatively circumscribed behavioral skill mediated by the "dominant" or left hemisphere. Later it came to be viewed as a major indicator of "nondominant" or right hemisphere pathology, specifically of the parietal lobe. However, by the 1950s it was well established that constructional disability could result from lesions of either hemisphere and the search was on to qualitatively differentiate hemispheric involvement by types of errors made. Now we seem to recognize that constructional disability is a highly complex behavior that is not readily "localized" to any single hemisphere or lobe of the brain. The more complicated the task, such as copying the Rey–Osterrieth figure or reproducing a difficult pattern of Kohs blocks (see below), the more likely that planning, organization, problem solving, and self-monitoring abilities, in addition to visual–spatial skills will be involved.

Perhaps it was a realization of the inherent complexity of the brain and behavior, as well as the limitations of a strict localization theory, that prompted a number of prominent neurobehaviorists to seek alternate solutions to the secrets of the functional organization of the brain. One such solution was to view the brain from a more wholistic standpoint. While acknowledging that certain more elementary or even intermediate types of behavior might be capable of being “localized” within discrete cortical regions, it was believed that many higher-level cognitive abilities reflected the operation of the brain as a whole and could not be separated into individual components. As we have seen, Karl Lashley, with his theories of **mass action** and **equipotentiality**, probably reflected the epitome of this position. However, others, notably Kurt Goldstein, also were convinced that certain functions, such as abstractive abilities, relied on the integrity of the brain as a whole. This philosophy, in part, seemed to underlie attempts by a number of investigators to develop single or one-dimensional tests of brain injury, particularly from the 1940s into the 1960s.

While both the strict localizationist and more wholistic theories have made important contributions to our understanding of the brain, neither adequately explains all the facts. Nevertheless, by nature we tend to be *chunkers* and *labelers*. Perhaps, in part, because of this proclivity, a localization bias has remained fairly pervasive in our thinking and in our research. This trend is reflected, for example, in many current texts of neuropsychology and behavioral neurology. Under the headings of frontal, parietal, temporal, or occipital lobes, they often list functions, symptoms, or psychometric test results thought to be associated with those particular lobes or specific areas within the lobes of the brain. Despite its limitations when applied to functional neuroanatomy, even a relatively simple localizationist approach has its merits. In addition to providing convenient and more or less easily manageable labels for exceptionally complex phenomena, these synopses or generalizations may serve as guideposts in generating working hypotheses or making certain types of clinical predictions in diagnostic investigations. Assume, for example, that a patient presents with a particular functional deficit that is thought to be associated with a particular region of the brain or that the site of a lesion is already known from imaging studies. In such instances, the clinician normally will want to carefully assess for other functional deficits typically associated with that particular brain region.

The advent of static and functional neuroimaging techniques has provided a renewed impetus in the ongoing search for improved functional maps of the cortex. In contrast to the static neuroimaging techniques, such as computerized tomography (CT) and magnetic resonance imaging (MRI) scans, which simply show the structural status of the nervous system, functional neuroimaging techniques, such as regional cerebral blood flow (rCBF), positron emission tomography (PET), single photon emission tomography (SPET), and functional MRI (fMRI), provide a glimpse into the actual functioning of the brain. One limitation is that functional neuroimaging technology still looks at behavior rather macroscopically. For example, subjects are asked to engage in certain types of mental activities while localized cortical areas with the highest level of glucose utilization at that time are noted. It is then inferred that the cortical area with the greatest glucose utilization is “critical” for the experimental task elicited. However, even such seemingly simple mental activities as naming pictured objects or performing calculations are the result of the integration of a number of more elementary processes.

To use what is obviously a very limited analogy, suppose we look at the brain as a collection of stores. We can allow the different lobes to represent different types of stores. Thus, the frontal lobe could represent a hardware store and the parietal a grocery store. Different areas within each of the lobes may represent sections within that store. Hence, for the frontal lobe, the dorsolateral, orbital, medial, premotor, supplementary motor, and primary motor areas could represent the plumbing, electrical, lumber, gardening, paint, and tool sections of the store. While these distinctions among the various areas may be useful for general descriptive purposes, this methodology fails to identify the individual items (i.e., elementary functions) contained therein. In this one respect, this analogy might approximate our current status with regard to the functional neuroanatomy of the brain. Perhaps with increasing advances in functional scanning technology and through subtraction techniques using overlapping zones, we may continue to refine our functional maps.

However, progress in the quest to understand brain–behavior relationships ultimately may depend not so much on technological advances as in how we define and measure function. Take the example of constructional disability used earlier.[3] As noted, constructional deficits may become manifest as a result of lesions in diverse cortical areas, including the anterior or posterior portions of either hemisphere. In this sense, constructional disability could be described more as a behavioral *symptom*, such as a fever, a common sign reflecting various possible etiologies. In this respect, the manifest behavior (constructional disability) may be the result of the confluence of multiple, more elementary behavioral phenomena such as visual perception, spatial judgment, motor integrity, somatosensory (kinesthetic) feedback, planning ability, self-monitoring capacity, and the simultaneous integration of any combination of these. Additionally, each of these behaviors in turn may represent a constellation of even more elementary "functions." If we begin with the premise that there are highly circumscribed (micro) functions that indeed may reside in or are mediated by very circumscribed areas of the cortex, we then can conceptualize most observable behavior (such as constructional ability) as the final result of the successful integration of all these more elementary "functions" distributed in various parts of the brain. Such an approach would then readily account for the fact that constructional deficits may be observed following lesions to various cortical sites. At the same time, knowing that separate regions of the brain make their own unique contributions to the overall behavior allows for the possibility of qualitative differences in the manifestation of that behavior. In turn, this could help identify the source of the disturbance by an analysis of the particular elementary functional disturbances or nature of the behavioral deficit.

This basically is the approach espoused and initially elaborated by Aleksandr Luria (1966) in his work, *Higher Cortical Functions in Man,* and more recently discussed by Heilman and Valenstein (2003) and Mesulam (2000). On the one hand, Luria's approach can be viewed as a strict localizationist approach, merely attempting to break down behaviors into much smaller chucks (a more microscopic perspective). At the same time however, it incorporates some key wholistic tenets, focusing on the integration of the brain as a whole, or at least multiple parts thereof, in the production of behavior. Although it has been more than 40 years since Luria's original manuscript was published, no subsequent investigations have offered a substantially different model for conceptualizing brain–behavior relationships.

This chapter will discuss the functional anatomy of the cerebral cortex from this general perspective, borrowing heavily from Luria, Mesulam, and other writers. Let the reader be warned from the outset that there are limitations to this approach. Perhaps the main one is its inherent complexity. There are no simple lists of functional–anatomical correlates to memorize. Rather, as was done in previous chapters, the hope is to present a way of looking at the brain that emphasizes both its horizontal (anterior–posterior; right–left) and vertical (cortical–subcortical–subtentorial) organization.

As we go through this chapter, it may seem that there is a somewhat greater ease in discussing left as opposed to right hemispheric functions. Although we experience and respond to the world around us in a multidimensional fashion, we tend to conceptualize and explain those experiences in verbal terms. Furthermore, even though the processing of verbal information by the brain is incompletely understood, at least language itself is perceived as being a very logical, sequential, and orderly phenomena or process, readily lending itself to rational analysis (i.e., it is easy to use words to explain words). In contrast, right or "nondominant" hemisphere functions appear predominately (if not exclusively) nonverbal, intuitive, and gestaltist and as such do not readily lend themselves to verbal explanations or encoding, even if the "insights" were available. Another factor may be that the functions subserved by the dominant left hemisphere are more discretely localized, and therefore behavioral dissociations are easier to isolate and identify than those of the nondominant right hemisphere, where inherent functions, such as affective processing and attention seem to be more widely distributed.

Because of our limited understanding of the brain and its cognitive operations, we recognize that the following discussions may raise more questions than answers. However, it is our hope that reviewing a theoretical model of the function and organization of the brain will promote a deeper analysis of behavior and appreciation of the need to constantly test and refine such models in our clinical practice. However, before beginning to explore this particular model, it may be useful to review some of the more salient structural aspects of the cerebral cortex and their possible behavioral implications.

SUPPORT STRUCTURES OF THE CEREBRAL CORTEX

Although not technically part of the neuroanatomy of the cerebral cortex proper, we shall begin our discussion by reviewing the skull and the roles of the meninges and ventricular system, all of which play a vital role in the normal functioning of the brain. The vascular system and the biochemical aspects of brain function will be covered in separate chapters.

The Skull

Structurally, the brain is really a fairly delicate organ. In its natural state, it has a consistency not too dissimilar from a jellyfish. Collectively, the cranial vault, meninges, and ventricles with their cerebrospinal fluid help preserve the structural integrity of the brain. However, as we shall see, under certain conditions, even these protective structures can have an adverse effect on the brain. The skull provides the first line of protection. Once the individual bony plates that make up the skull are completely fused in early childhood, they offer a fair amount of resistance to outside physical forces that might otherwise traumatize the brain. However, being rather tightly enclosed in this solid structure at times can create its own problems. Two of the more common examples include acceleration–deceleration injuries and increased intracranial pressure. If one is traveling in a linear direction and the skull comes to an abrupt stop (as when the forehead hits the windshield in a motor vehicle accident) the brain tends to keep moving forward, slamming into the interior surfaces of the cranium, producing either coup (on the site of the initial impact) and/or contracoup (produced by the brain rebounding off the inside of the skull opposite the side of the impact) injuries or contusions. Often such injuries are most acute in the frontal and temporal poles where the physical forces are more concentrated given the curvature of the brain and the bony cavity in which it sits.

In the adult brain, there is very little extra space inside the skull and the only "opening" is the foramen magnum at the base of the skull through which the brain stem exits. In situations where there might be swelling of the brain, such as in the case of closed head trauma, large infarcts (which are often accompanied by edema), major hemorrhages, infections, or hydrocephalus, the brain has virtually no room to expand. The resulting shifting of intracranial content strains axonal connections and puts increased focal pressure on certain parts of the cortical tissue which produces further disruptions of function. If this swelling is of sufficient magnitude, especially if it occurs rather rapidly, the medial portions of the temporal lobes can be literally squeezed down through the tentorial notch (see next section). This produces what is referred to as "uncal herniation" through the tentorium which can affect the structures in and around the midbrain, resulting in third nerve deficits, long tract findings or paresis (due to compression of the cerebral peduncles), or symptoms related to involvement of the posterior cerebral arteries. Increased pressure can affect subtentorial structures either directly, as a result of mass lesions in the posterior fossa (i.e., cerebellum, and brain stem), or indirectly by too rapid a reduction in spinal fluid pressure, such as conducting a spinal tap in an individual with increased intracranial pressure. If the medullary centers in the brain stem that control vital functions such as respiration and heart rate are compromised by herniation of the cerebellar tonsils through the foramen magnum, death may result.

The Dura Mater

Within the skull, the brain is further protected by the **meninges**, particularly by the outermost, the **dura mater** (or simply the *dura*), and the middle layer, the **arachnoid**. The innermost layer or the **pia mater** (or *pia*) lies immediately in contact with the brain tissue itself. It is a very delicate, thin membrane that attaches some of the extremely fine blood vessels to the surface of the cortex. By contrast, the dura is a relatively dense, tough fibrous tissue that adheres to the inner surface of the skull. While the dura can easily be cut, it would be extremely difficult to pull apart by hand. It lines the entire cranial vault, except for the area around the midbrain where it forms the tentorial notch. In addition to covering the outer surfaces of the brain, the dura also dips into the longitudinal fissure between the hemispheres, extending to the vicinity of the corpus callosum. This portion is known as the **falx cerebri** (Figure 9–2). The dura also takes another deviation, creating a separation between the cerebellum and the occipital lobes. This latter portion of the dura is called the **tentorium** (tent) **cerebelli** (or simply, the tentorium). Thus the term *supratentorial* refers to the brain above the level of the midbrain or above the tentorium cerebelli and the *posterior fossa*

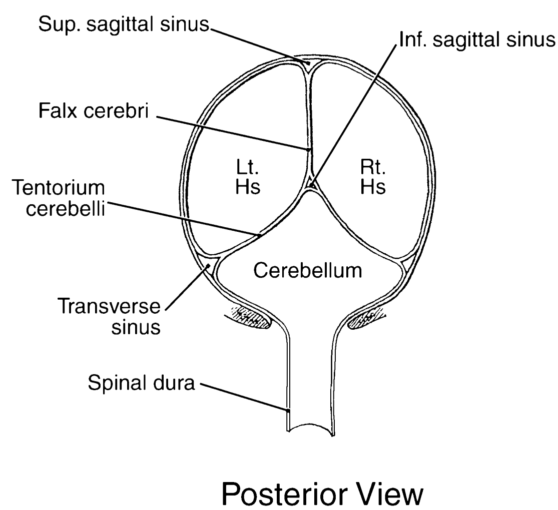


Figure 9–2. Schematic representation of the dura mater providing an external covering for the brain and spinal cord. The figure illustrates the falx cerebri, which forms a partition between the dorsal portions (above the corpus callosum) of the cerebral hemispheres, and tentorium cerebelli, which separates the occipital lobe and the cerebellum in the posterior fossa. Also illustrated is the continuation of the dura into the vertebral foramen of the spinal cord where it surrounds the spinal cord and the spinal nerve roots. Not shown is the tentorial notch, which is an opening around the base of the brain forming a passage for the midbrain. Also shown are several of the venous sinuses that are embedded within the dura.

encompasses those structures that lie below (*subtentorial*) the tentorium cerebelli (i.e., the brain stem and cerebellum). These dural structures help support the brain within the skull.

In addition to this structural support, the dura also serves a critical circulatory function. At several convergence zones that follow the bony contours of the inner table of the skull, the dura separates into two layers creating channels or **sinuses** through which venous blood and cerebrospinal fluid (CSF) flow (Figure 9–3). The major sinuses include the

1. **Superior sagittal sinus:** formed along the superior longitudinal fissure at the top of the brain, it serves to collect blood from surface veins, as well as a point of reabsorption for the cerebrospinal fluid.
2. **Inferior sagittal sinus:** found along the free edge of the falx cerebri, it collects blood from deep cerebral veins.
3. **Straight sinus:** connects the inferior sagittal sinus with the superior sagittal sinus.

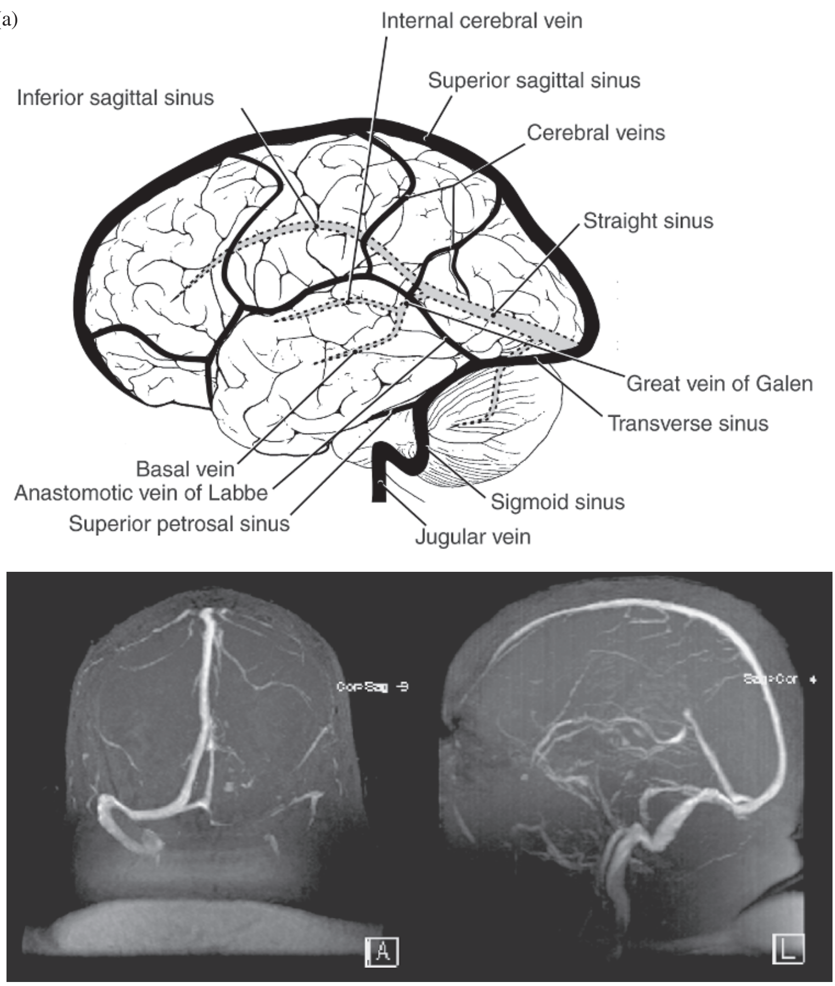


Figure 9–3. (a) Major external (solid, dark) and internal (dotted, lighter) veins draining the cerebral hemispheres. (b) A-P and lateral views of venous drainage on MRA. (a) Adapted from DeArmond, Fusco, and Dewey (1989). (b) Courtesy of Dr. Jose Suros,

4. **Transverse sinuses:** begins at the confluence of the superior sagittal and transverse sinuses and runs laterally along the outer edges of the tentorium cerebelli.
5. **Sigmoid sinuses:** a continuation of the transverse sinuses, they soon empty into the jugular veins, which return the deoxygenated blood to the heart.

While the major types of cerebrovascular events will be reviewed once again in Chapter 10, those that specifically involve the meninges deserve mention here. Two such events related to the dura are **epidural** and **subdural hematomas.** The dura itself is supplied by blood vessels that lie between the dura and the skull. Since the dura attaches to the inside of the skull, there is no space between the two, but there is a *potential epidural space*. If one of the meningeal arteries that supply the dura is ruptured, typically due to skull fractures (less commonly due to laceration of the dural sinus), bleeding can occur between the dura and the skull within this potential space, which results in an **epidural hematoma**. If arterial blood, which is under a fair amount of pressure, is involved, a sizeable hematoma can develop fairly rapidly. Although the blood does not come into direct contact with brain tissue, it can create a rapid and often fatal increase in intracranial pressure (recalling the skull does not allow room for expansion) unless surgically drained. In addition, the hematoma is confined to the epidural space along the skull sutures, as the dura is fixed to the cranial sutures, thus creating a "lens" type appearance on imaging studies. Because the development of this type of hematoma can develop hours (occasionally days) following a head injury, it is important to carefully observe victims of significant head trauma for changes mental status.

A more common, although typically less disastrous, condition can occur when there is a tearing (usually as a result of closed head trauma) of the bridging veins between the arachnoid and the dural sinuses in the subdural space between the dura and the arachnoid. This can result in a **subdural hematoma**, creating a pool of blood between the dura and the arachnoid layers. Since it typically involves venous blood under lower pressure than arterial blood, the bleeding usually is much slower and more self-limited, although the blood can track along the contours of the brain as this space is not restricted by the dural attachments at the sutures. Chronic alcoholics and the elderly are especially prone to subdurals for two reasons. First, with the chronic, heavy use of alcohol or with aging, there tends to be atrophy of the brain that is thought to cause stretching of these bridging veins, making them more vulnerable to the shearing forces of traumatic injury. Second, both alcoholics and the elderly are more prone to head traumas as a result of falls or violence perpetrated against them.

While a subdural hematoma can produce neurological or neuropsychological symptoms depending on its size, it is not uncommon to find evidence of old subdurals on autopsy that never were reported by the patient. This may be due in part to the fact that the cortical atrophy that typically accompanies these conditions also results in more potential space around the brain that can accommodate larger volumes of blood without compression and resultant brain injury.

Other relatively common pathologies involving the dura include meningiomas and infection. **Meningiomas** are very slow growing encapsulated tumors that arise from meningeal tissue, most commonly along the base of the brain or along the falx (see Figure 9–4). As these tumors do not involve the brain parenchyma itself ("extrinsic" tumor), their symptoms often can be rather subtle, especially in the early stages. Their presence commonly is noted because of the pressure they exert on nervous tissue. However, because they are so slow in developing, allowing the brain to compensate for their presence, unless they impinge directly on a cranial nerve, they may grow to considerable size without producing the mass effect (decompensation) created by the more rapidly developing hematomas. **Meningitis**, whether bacterial, viral, or fungal, represents an inflammation or infection of the meninges. These infectious or inflammatory processes can lead to any number of problems, including:

1. Focal swelling of the brain tissue itself (encephalitis).
2. Diffuse, nonobstructive hydrocephalus as a result of inflammation of the subarachnoid layer, which blocks the outflow of CSF (see below).
3. Infarctions secondary to involvement of the blood vessels.
4. Cranial nerve deficits.

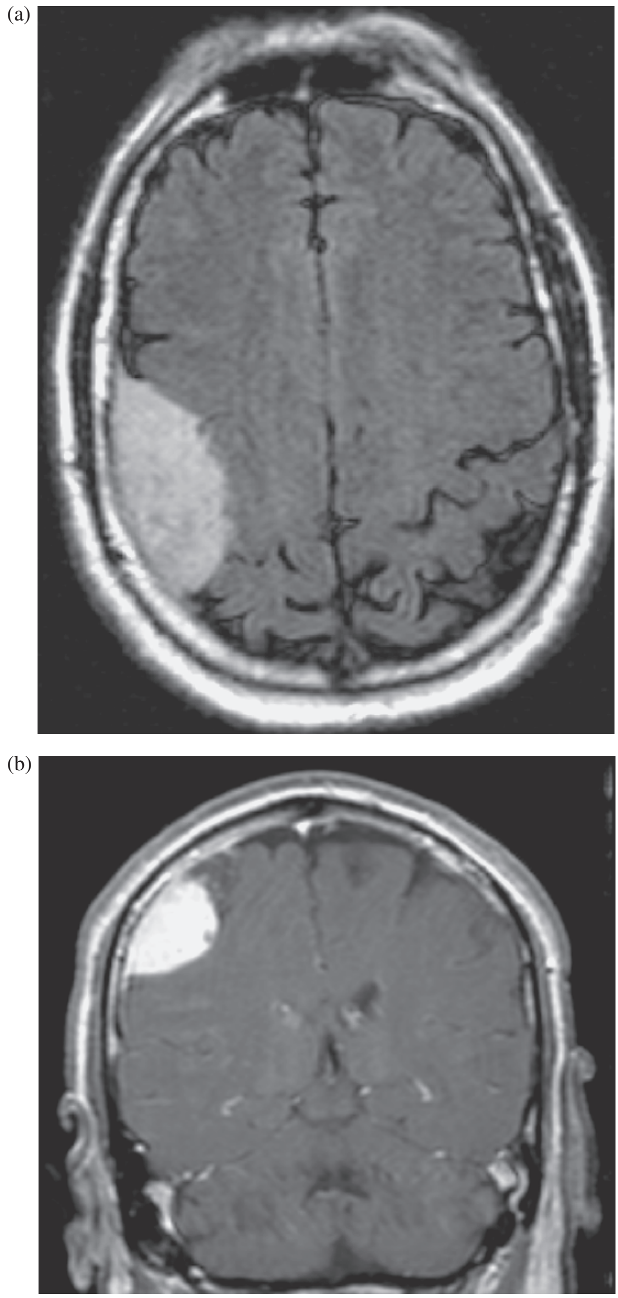


Figure 9–4. (*Continued*)

(c)

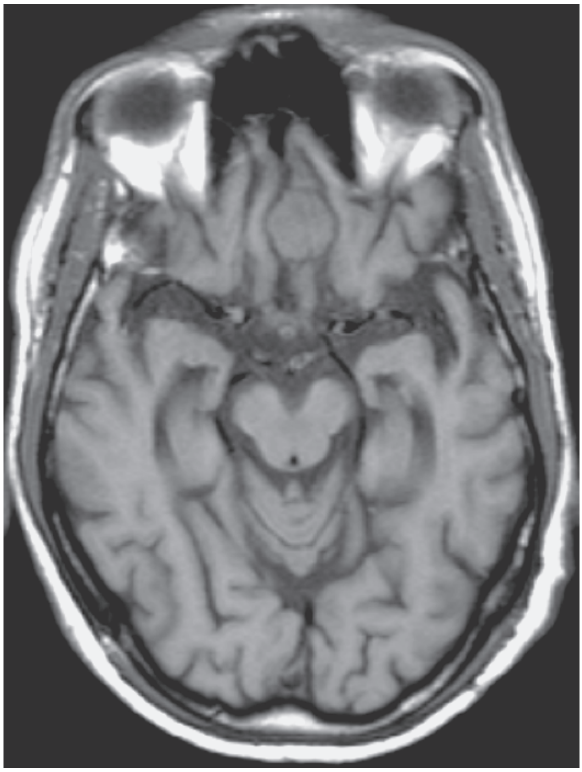


Figure 9–4. (a,b) Meningiomas arising from the convexity and from (c) the olfactory groove.

It should be noted that the dura is pain-sensitive, with the anterior and middle fossa being supplied by the trigeminal nerve and the posterior fossa by the second and third cervical nerves. Brain tissue itself is not pain-sensitive. Thus certain types of headaches that involve intracranial irritants (e.g., bleeds, tumors, infections) generally are thought to result from irritation of the meninges, not the brain itself.

The Arachnoid Layer

The arachnoid represents the middle meningeal layer. It adheres to the inner surface of the dura but creates a space (*subarachnoid space*) between itself and the pia beneath it (Figure 9–5). Since the dura and the arachnoid do not follow the pia into the sulci, the subarachnoid space tends to be greater in these areas. There also is excessive space around certain other concavities of the brain, such as in the area of the peduncles, the corpora quadrigemina, the cerebellar–medullary junction, and the optic chiasm, which are referred to as **cisterns**. The subarachnoid space, in addition to containing most of the surface arteries and veins, contains CSF. The larger cisterns, which therefore contain greater amounts of CSF, show up nicely on both MRI and CT scans. One of the net effects of this fluid-filled subarachnoid layer is that it appears to provide an additional cushion and/or supportive structure for the brain and spinal cord.

A number of pathological conditions are associated with the subarachnoid layer. Subarachnoid or porencephalic **cysts** or collections of CSF that do not communicate with the ventricular system can develop following trauma, hemorrhage, tumors, or surgery. Clinically, they may present with headaches, seizures, or other focal findings secondary

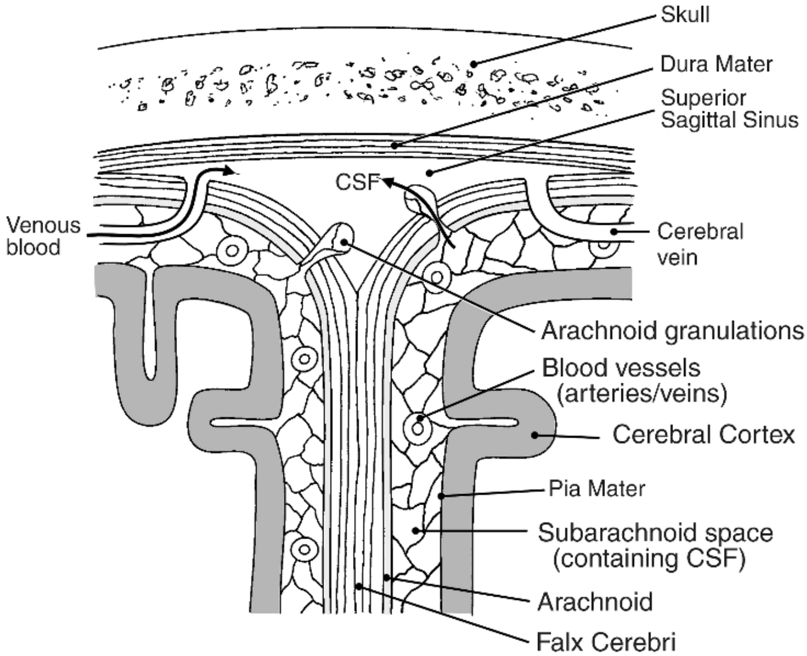


Figure 9–5. Arachnoid space, illustrating relationship to dura and pia and entry for venous blood and CSF into the superior sagittal sinus.

to the pressure they exert on surrounding brain tissue. On occasion such cysts may arise developmentally, usually in the middle fossa (temporal region). Despite possibly growing to great size and associated with agenesis of the temporal lobe, such cysts may be clinically silent and only serendipitously be discovered. Figure 9–6 shows such a lesion in a young man with totally normal physical and mental development and unremarkable findings on neuropsychological examination. Leakage or rupture of surface vessels, such as from

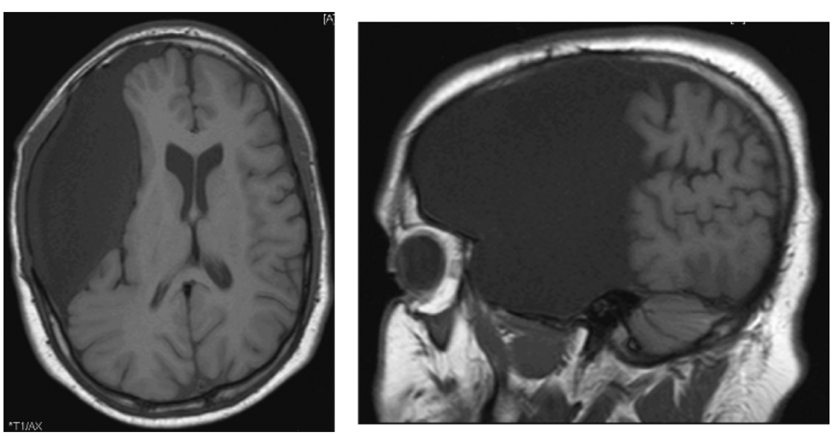


Figure 9–6. Subarachnoid cyst. Despite its huge size, this cyst was virtually asymptomatic clinically, both in terms of cognition and sensorimotor functions. Note the lack of effacement of cortical sulci adjacent to the cyst and the minimal midline shift.

arteriovenous malformations, aneurysms, or other causes, can result in a **subarachnoid hemorrhage**. Since in this case the presence of the blood in the subarachnoid space can produce localized compression of adjacent parenchyma, vasospasms, edema, and absorption delays for the CSF, behavioral effects may be more pronounced and more focal than with subdural hematomas.

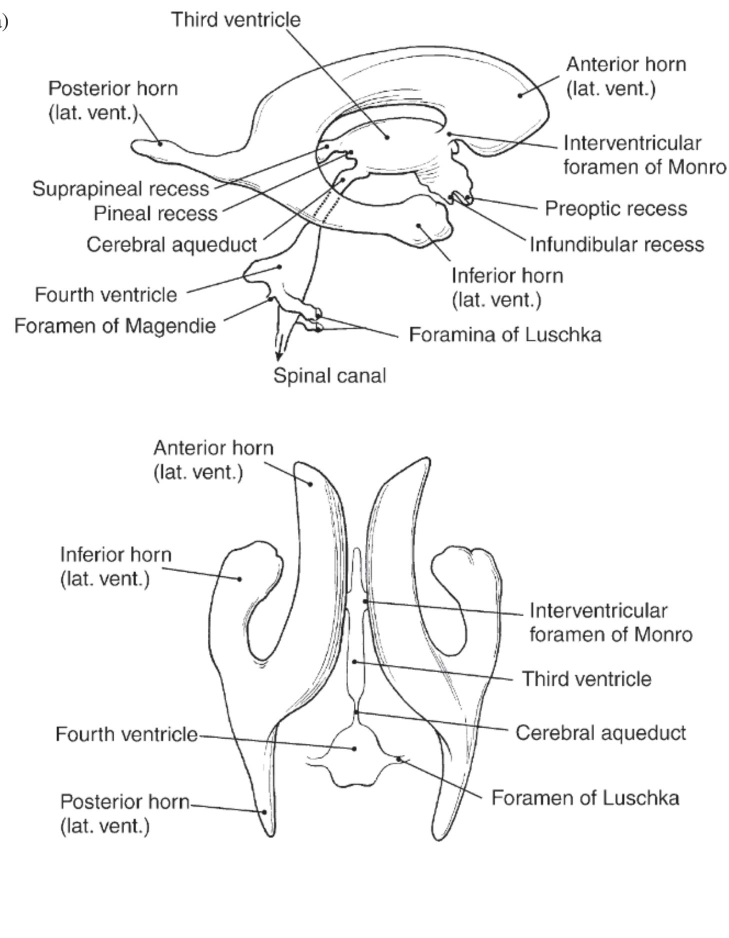
The Pial Layer

The pia is the very thin, delicate membrane encapsulating fine blood vessels that closely adheres to the surface of the brain, following all the gyral and sulcal patterns. At times differentiating the pia from the innermost arachnoid layer is difficult, and in fact the two sometimes simply are referred to collectively as the *leptomeninges*. Finally, it should be noted that these same meningeal layers also continue into the vertebral column surrounding the spinal cord.

The Ventricular System

In the course of embryonic development, the central nervous system starts out as a long, hollow neural tube. The cerebral cortex develops at one end of this tube, with the remainder becoming the brain stem, cerebellum, and the spinal cord. However, vestiges of the central, hollow portion of this neural tube remain in the fully developed CNS as the spinal canal and the ventricular system of the brain. The latter consists of the two lateral ventricles, the third and fourth ventricles, and their associated passageways. As we shall see, the fourth

(a)



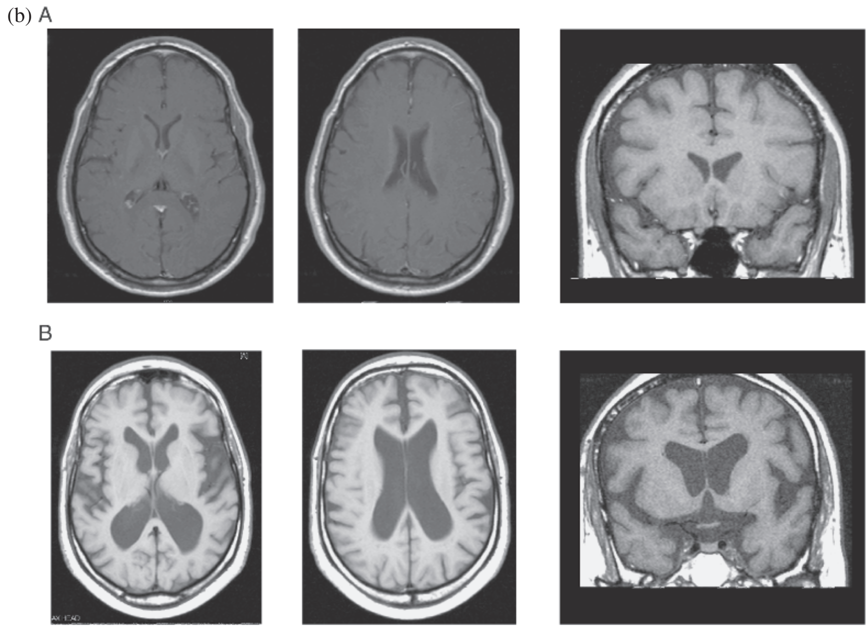


Figure 9–7. (a) Representation of ventricles as seen on lateral (top) and superior views. Flow of CSF is from lateral ventricles to the third via the interventricular foramina, then to the fourth via the cerebral aqueduct. From the fourth ventricle, some CSF may enter the spinal canal, while most is extruded into the subarachnoid space in the posterior fossa where it surrounds the exterior surfaces of the brain and spinal cord prior to being picked up by the arachnoid villi and deposited in the venous sinuses. Adapted from Carpenter and Sutin (1983). (b) Normal (top row) and moderately enlarged ventricles (bottom row) as seen on neuroimaging.

ventricle is continuous with the spinal canal. The ventricles, along with the subarachnoid spaces (cisterns) are filled with CSF. As noted earlier, one functional contribution of this system may be to help support and cushion the CNS; however, there also is evidence that the CSF helps maintain proper electrolytic and/or metabolic balance in the extracellular fluids of the brain. For our current purposes, an understanding of the basic anatomy and mechanics of the ventricular system helps to provide a basis for understanding various types of neuropathology.

The largest of the ventricles are the two lateral ventricles located bilaterally in the cerebral hemispheres. As can be seen from Figure 9–7, these may be conceived of as beginning in the frontal lobes on either side of the midline, just beneath the genu of the corpus callosum and are bounded laterally by the head of the caudate nucleus. This area represents the **anterior** or **frontal horns** of the lateral ventricles. As the ventricles proceed posteriorly, they enlarge somewhat (the **body** of the lateral ventricles) and then curve down, out, and forward again into the medial portions of the temporal lobes (the **temporal horns**). That portion of the body of the ventricle that curves to begin forming the temporal horns is called the **trigone** or **atrium**. From these latter regions, two smaller cavities, known as the **posterior or occipital horns**, extend into the parietal–occipital cortices.

On the ventromedial aspect of each of the lateral ventricles, just anterior to the thalamus are two openings, known as the **interventricular foramen** or the **foramen of Monro**, which allow drainage of CSF from the lateral ventricles of the left and right cerebral hemispheres into the single, midline third ventricle (see Figure 6–1c). The third ventricle is surrounded by the thalamus and basically separates the paired nuclei of the thalamus (or thalami) and the hypothalamus, except for a small region (which is present in most, but not all people) where the two thalami are connected: the **massa intermedia**. At the ventral and posterior extent of the third ventricle, there is a small canal that passes down through the midbrain and opens up into the fourth ventricle. This passage, known as the **cerebral aqueduct**, allows for CSF communication between the third and fourth ventricles. (see Figure 4–4a)

The fourth ventricle lies in the brain stem, extending from the level of the pons, slightly into the medulla. For the most part, the floor of the fourth ventricle is made up of the pons and upper medulla, while its roof is the cerebellum (although there are actually two thin sheets of tissue known as the superior and inferior medullary veli which cover much of the dorsal surface of the ventricle). There are several openings of significance in the fourth ventricle. First, the fourth ventricle, at its caudal extension, is continuous with the spinal canal that reflects the original neural tube. Second, there are three openings that allow the CSF to get outside the ventricular system and into the subarachnoid space, the importance of which will be discussed shortly. At the two points where the fourth ventricle widens out in somewhat of a diamond shape, there are two openings: the **foramina of Luschka**, located laterally, and the **foramen of Magendie,** medially located in the caudal portion of the roof of the ventricle.

The Choroid Plexus and Cerebrospinal Fluid Circulation

Within all the ventricles are glandularlike structures known as the **choroid plexus**. The choroid plexus produces most of the CSF. The cerebrospinal fluid, which is the clear fluid that is found both within and around the outside surface of the brain and spinal cord, can play a crucial role in the diagnosis of many types of neuropathology. Analysis of its composition, typically obtained via a spinal tap or lumbar puncture, can assist in the diagnosis of such CNS problems as infections, hemorrhages, tumors, and multiple sclerosis. However, there also can be problems associated with CSF, the most common being problems of blockage and/or reabsorption. Cerebrospinal fluid is constantly being produced, fully replenishing itself about once every 5 to 6 hours. Obviously, the CSF must be excreted in order to accommodate the demand for additional fluid production. To accomplish this process, the fluid produced in the lateral ventricles flows into the third ventricle through the interventricular foramina, and from the third into the fourth via the cerebral aqueduct. Once in the fourth ventricle, it flows into the subarachnoid spaces of the brain stem through the foramina of Luschka and Magendie. From there it can flow into the subarachnoid spaces of the spinal canal or through the dural opening around the brain stem (tentorial notch) into the subarachnoid space over the convexities of the hemispheres, where most of the absorption takes place via the arachnoid villi (or granulations). These villi, which are specialized groups of cells, protrude into the dural sinuses and are particularly dense along the superior sagittal sinus. It is through these villi that the CSF is passed into the venous system and out of the brain (see Figure 9–5).

Problems occur when some of these passages or apertures fail to properly develop at birth or when they later become compressed or occluded (such as might occur with an intracranial mass). This situation can produce a **noncommunicating** (*obstructive*) **hydrocephalus** when the CSF within the ventricles cannot communicate or flow from one ventricle to another, and thus cannot flow out into the subarachnoid space to be reabsorbed. Noncommunicating hydrocephalus results from an obstruction of the flow of CSF from the lateral ventricles, through the aqueduct, or at the outlets of the fourth ventricle. Another type of problem can occur if the problem occurs at the point of production (choroid plexus) or reabsorption by the arachnoid villi. This latter condition is referred to as a **communicating hydrocephalus** (the CSF retaining its capacity to flow or *communicate* with the subarachnoid space). Meningitis and subarachnoid hemorrhages are two of the more common causes of communicating hydrocephalus. Bleeding into the subarachnoid space also can interfere with the ability of the villi to transport CSF. Meningitis can have a similar effect as a result of residual scarring or adhesions. In certain cases, these processes also can interfere with the ability of the CSF to flow from the brain stem cisterns through the tentorial notch (because of adhesions in this area) into the subarachnoid spaces over the hemispheres.

Additional Diagnostic Considerations

Analysis of the shape, size, displacement, or in some cases, absence of the ventricles on CT or MRI scans can have major diagnostic utility. In the days before the CT scan, the pneumoencephalogram was a frequently used diagnostic tool. It involved displacing the CSF in the ventricles with air. The air, being considerably less dense that the surrounding tissue, provided a nice profile of the ventricular system with standard skull X-rays. One of the major drawbacks to this procedure is that it also frequently left the patient with a severe headache that could last for days. Current neuroimaging techniques (CT or MRI scans) provide noninvasive means of visualizing the ventricular system. Although a normal leftward asymmetry of the lateral ventricles has been well documented, significant compression and distortions of the lateral ventricles or one of its horns can suggest either the presence of a mass or "mass effect" lesion (if compressed) or focal atrophy (e.g., from an old infarct) if the ventricle is dilated. This same principle also may help differentiate between a recent versus an old infarct (new infarcts either may compress the ventricle due to edema or leave them relatively unaffected). Lateral displacement of the ventricles from midline also is suggestive of mass effect from a space-occupying lesion. Distortions of the normal shape of the ventricles also can be of diagnostic significance. For example, the anterior horns typically have a boomerang type appearance due to the lateral encroachment by the head of the caudate nucleus. In **Huntington's** disease, in which there is early atrophy of the caudate, the lateral surfaces of the frontal horns will take on an uncharacteristic convex shape.

Enlargement of the ventricles, along with prominent cortical sulci, suggests generalized cortical atrophy. While generalized atrophy often accompanies specific degenerative dementias, of themselves enlarged ventricles are not necessarily diagnostic of a clinically or behaviorally identifiable neuropathological process. It is not uncommon to find large ventricles in the elderly (and occasionally in the young) with no indications of compromised mental status. On the other hand, the presence of enlarged, symmetric ventricles with effacement (diminution) of the cortical sulci may suggest **normal pressure hydrocephalus** in an adult with appropriate clinical symptoms. Hyperdensities ("bright spots" on imaging studies) within the body or temporal horns of the lateral ventricles and in the third ventricle simply may reflect normal calcification of the choroid plexus that occurs with age.

THE CEREBRAL HEMISPHERES

We believe that anatomists first began to examine the human brain at least some 2,500 to 3,000 years ago. One of their first observations must have been to note that the surface of the brain (the cerebral cortex) was divided into two, seemingly identical, hemispheres, each being characterized by extensive, apparently random, convolutions (sulci and gyri). As was seen in Part I of this chapter, it was not until the 19th century that either of these concepts was seriously challenged. First came the realization that some gyral patterns are generally consistent among individuals. By the second half of the 19th century, the functional asymmetry of the hemispheres was becoming accepted in the scientific community. Although anatomical asymmetries between the cortical hemispheres were discussed in the late 1800s, it was not until *Geschwind and Levitsky's* study in 1968 (see below) that the notions of functional and anatomical asymmetries were truly integrated.

The Cerebral Gyri and Sulci

Before discussing hemispheric asymmetries, it may be useful to briefly review some of the structural features of the cerebral hemispheres. Probably the most obvious are the gyri (ridges) and sulci (grooves) on the surface of the brain. Although study of the surface of the human cerebral cortex demonstrates that there is considerable individual variability in patterns of gyrification (morphology) within and between the cerebral hemispheres, the major gyri and sulci generally are similar across individuals, making it possible to identify specific gyri and sulci within the brain. Knowledge of these patterns provides the clinician and scientist with a topographical or structural road map of the lobes of the brain, and it is in these terms that the findings of clinical neuropsychology, behavioral neurology, and functional neuroanatomy frequently are framed. Hence, a familiarity with the names and locations of the major gyri and sulci is crucial to the study of brain–behavior relationships (see Figure 9–8a–d). However, again a word of caution: although one may diligently memorize the diagrams presented here, when looking at representations in other texts or even an actual human brain, one may still find himself or herself struggling to identify certain specific gyri or sulci due to some minor individual variability.

It is this morphology or pattern of sulci and gyri that gives the human brain its characteristic convoluted appearance. Normal aging or certain disease processes, most notably primary degenerative disorders, can cause a loss of neuronal tissue resulting in shrinking of gyri (and consequent enlargement of the sulci), making them appear more prominent and easier to study. Such changes can be easily observed on MRI or CT scan.[4] Before exploring some of the specific sulci and gyri, it is interesting to consider how this particular morphology developed in man.[5] Clearly, the convoluted brain is not unique to humans. Most, if not all, mammalian brains also are characterized by some degree of convolution, albeit very rudimentary in some instances, such as in rodents, while those of the porpoise and the great apes rival that of humans in terms of the number or complexity of gyral patterning. Brain size seems to be largely a function of two rather independent factors: body size and behavioral complexity (*animal intelligence*, if you wish). Both seem to play an important role. In the case of the elephant, for example, although generally considered to be a highly "intelligent" animal, it is not thought to be more intelligent than the human. Its body size, then, would seem to largely account for the fact that its brain is at least three times the size of man's. Yet the brain cavities of some of the dinosaurs, despite their immense bulk, are thought to have been quite small. Thus, once body size is taken into account, behavioral complexity also would seem to be related to the size of the brain and its gyral complexity. The underlying principle would appear to be that "more brain" is necessary in order to carry out more sophisticated and adaptive behaviors. As we shall see later in this chapter, it is those areas of the cerebral cortex that mediate the highest levels of integrative functions (the tertiary association areas) that show the greatest amount of relative development in man. The convoluted cortex thus would allow for increasingly larger cortical surface area and more complex brain morphology that still fits into a manageable-sized head. It might be interesting also to note that as the human fetus develops there is a corresponding increase in gyral development, another instance where ontogeny recapitulates phylogeny.

Both gyri and sulci may vary in size (e.g., length, depth, or breadth). However, regardless of size, a gyrus is still referred to as a gyrus, not so with sulci. A very large (deep) sulcus is referred to as a fissure. There are only two such sulci associated with the cerebral cortex. The first is the very deep fissure that runs longitudinally between the two cerebral hemispheres known as the **superior longitudinal fissure**, or the **superior sagittal fissure**. The other is the **lateral** or **Sylvian fissure** (after Sylvius de le Boe who described it in the 17th century). Present bilaterally, the lateral fissure represents the enfolding of the frontal and parietal cortices along its dorsal margin and the temporal cortex ventrally. Its anterior end is readily identified as the division between the temporal and frontal lobes. The posterior extension of the lateral fissure is surrounded by the **supramarginal gyrus**, which is how the latter

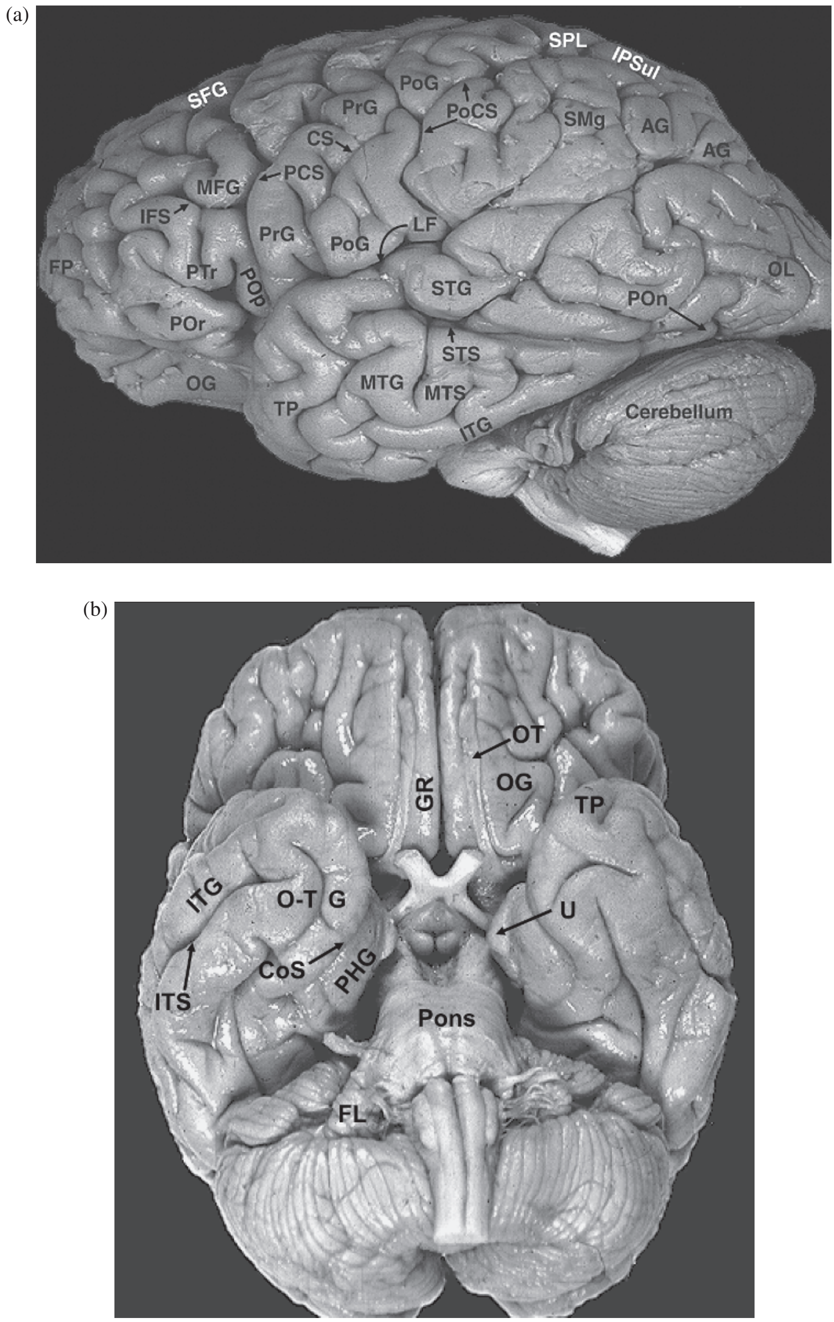


Figure 9–8. (*Continued*)

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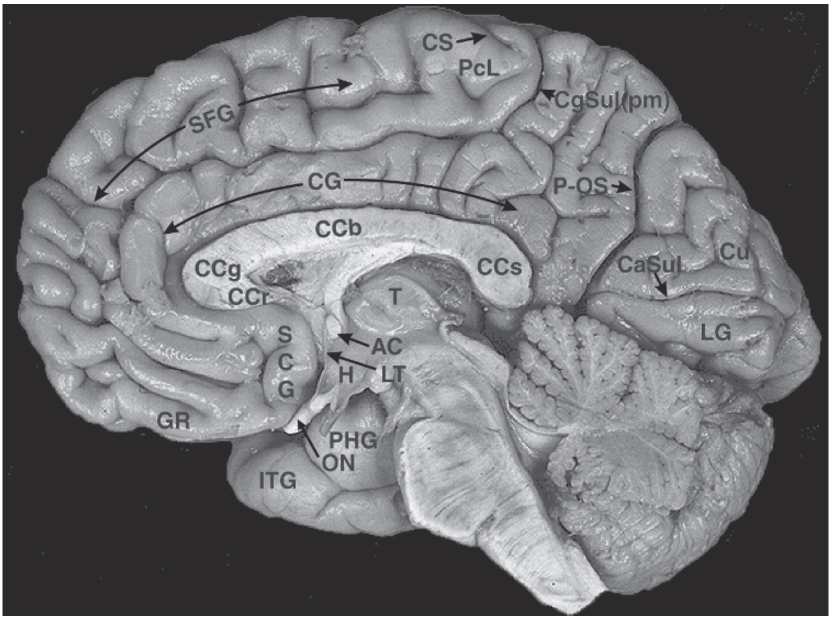

Figure 9–8. Lateral, ventral, and medial surfaces of the brain with major gyri and sulci. Brain images were adapted from the *Interactive Brain Atlas* (1994), courtesy of the University of Washington.

Lateral, Ventral & Medial Surfaces of the Brain

Gyri	Sulci	Other Features
AG, angular gyrus	CS, central sulcus	AC, anterior commissure
C, cuneus	CaSul, calcarine sulcus	CCb, body of corpus callosum
CG, cingulate gyrus	CgSul, cingulate sulcus	CCg, genu of the corpus callosum
Fl, flocculus	$\text{CgSul}_{(pm),}$ cingulate sulcus, pars marginalis	CCr, rostrum of corpus callosum
GR, gyrus rectus	CoS, collateral sulcus	CCs, splenium of corpus callosum
ITG, inferior temporal gyrus	IFS, inferior frontal sulcus	F, fornix
LG, lingual gyrus	Ipsul, intraparietal sulcus	FP, frontal pole
MFG, middle frontal gyrus	ITS, inferior temporal sulcus	H, hypothalamus
MTG, middle temporal gyrus	LF, lateral fissure	LT, lamina terminalis
OG, orbital gyrus	MTS, middle temporal sulcus	OC, optic chiasm
OTG, occipitotemporal (fusiform) gyrus	PoCS, postcentral sulcus	OL, occipital lobe
PC, precuneus	P-OS, parietooccipital sulcus	ON, optic nerve
PcL, paracentral lobule	PrCS, precentral sulcus	OT, olfactory tract
PHG, parahippocampal gyrus	STS, superior temporal sulcus	POn, preoccipital notch
PoG, postcentral gyrus	SulCC, sulcus of the corpus callosum	SPL, superior parietal lobule
POp, inferior frontal gyrus, pars opercularis		T, thalamus
POr, inferior frontal gyrus, pars orbitalis		TP, temporal pole
PrG, precentral gyrus		U, uncus
PTr, inferior frontal gyrus, pars triangularis		
SCG, subcallosal (parolfactory) gyrus		
SFG, superior frontal gyrus		
SMg, supramarginal gyrus		
STG, superior temporal gyrus		

may be identified (see Figure 9–8a). The cortical areas around the rim of the fissure and penetrating into its depths are known as the **opercular cortex** (e.g., *frontal operculum*, *temporal operculum* or *parietal operculum* depending on the particular region). It is within the temporal opercular region that the **Heschl's gyrus** lies, the primary auditory projection cortex and the **planum temporale**, both of which become important in the discussion of language. As seen in Figure 9–9, the lateral (Sylvian) fissure in a typical adult human brain is composed of five segments:

1. Anterior horizontal ramus extending from A to B (AHR)
2. Anterior ascending ramus from B to C (AAR),
3. Posterior horizontal ramus from B to D (PHR)
4. Posterior ascending ramus from D to F (PAR)
5. Posterior descending ramus from D to E (PDR)

The central sulcus (see below) also can be used to divide the PHR of the Sylvian fissure into a pre- and postcentral segment. These divisions of the lateral fissure are important in relation to functional cortical regions and asymmetries, which will be discussed later. If the lateral fissure is pried apart (or if you look at either an axial or coronal section), deep within the fissure is found a section of "hidden" cortex called the **insula** (see Figure 9–11).

Of other major sulci worthy of special comment (see Figure 9–8), one is the **central sulcus** (the older eponym, **sulcus of Rolando**, is seldom used today). The central sulcus (CS) demarcates the **precentral** (primary motor) from the **postcentral** (primary somatosensory) **gyrus** and represents the boundary between the frontal lobes and parietal lobes. On a postmortem brain, the central sulcus can be recognized by identifying the two adjacent gyri in the central region of the lateral cortex, which are primarily oriented in a vertical direction. These are the pre- and postcentral gyri with the central sulcus between them.

Within the parietal lobe, approximately two thirds of the way up is a horizontally oriented sulcus (not always easy to find). This is the **intraparietal sulcus** which separates the superior parietal lobule from the inferior parietal lobule. The inferior parietal lobule includes both the supramarginal gyrus and angular gyrus, both of which are prominently mentioned in neuropsychological literature.

In pursuing the surface anatomy of the cortex from the lateral to the inferior surface of the temporal lobe, several horizontal (although not necessarily continuous) sulci are

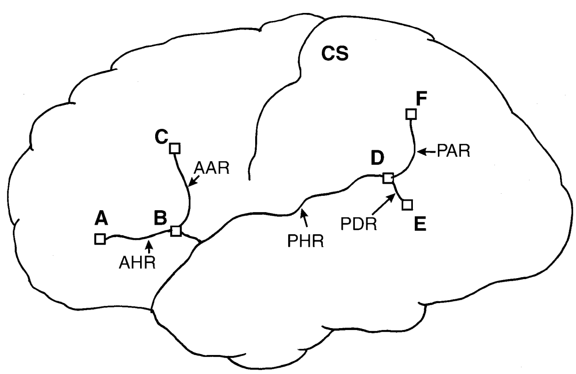

Figure 9–9. Schematic view of various branches of the lateral (Sylvian) fissure. Abbreviations: AAR, anterior ascending ramus; AHR, anterior horizontal ramus; PAR, posterior ascending ramus; PDR, posterior descending ramus; PHR, posterior horizontal ramus. As will be seen later, the angle of the posterior ramus typically differs in the right versus left cerebral hemispheres.

encountered. Respectively, these are the **superior** (STS), **medial** (MTS), and **inferior temporal sulci** (ITS) and the **collateral sulcus**. If one follows the superior temporal sulcus back as it curves up into the inferior parietal lobule, it becomes surrounded by the **angular gyrus.** The **superior**, **middle,** and **inferior temporal gyri** each lie immediately above their respective sulci. Thus, the superior temporal gyrus lies between the superior temporal sulcus and the lateral fissure (sulcus), the middle temporal gyrus between the superior and middle temporal sulci, and the inferior temporal gyrus between the middle and inferior sulci. Between the inferior temporal and collateral sulci the **occipitotemporal** or **fusiform gyrus** lies. Finally, just medial to the collateral sulcus is the **parahippocampal gyrus**, located on the ventromedial surface of the temporal lobe.

On the lateral surface of the frontal lobes are two horizontal sulci, the **superior** and **inferior frontal sulci**, which separate the cortex of the anterior frontal convexity into the superior, middle, and inferior frontal gyri. The inferior frontal gyrus is composed of the **pars orbitalis**, **pars triangularis**, and **pars opercularis** (the latter two comprising **Broca's area**). Generally, these two frontal sulci and their three divisions are much easier to see on coronal sections rather than on the lateral surface.

On the medial surface, the fairly deep **parietal–occipital sulcus** marks the boundary between the parietal and occipital lobes. The **callosal** and **cingulate sulci** also are quite prominent above the corpus callosum and **cingulate gyrus,** respectively. Finally, the **calcarine sulcus** also rather easily can be identified. It divides the primary visual cortex of the occipital lobe into its more dorsal portion, the **cuneus** (the term "gyrus" is not used here) and **lingual gyrus** located on its ventral bank.[6]

Lobes of the Cerebral Cortex

The cerebral cortex (neocortex) of the telencephalon (forebrain) consists of four distinct lobes within each hemisphere: the frontal, parietal, temporal, and occipital lobes. Developmentally, the skull in which the brain is housed is formed from a number of separate bones that eventually fuse to form the solid, bony covering of the brain. Even casual inspection of an adult skull reveals the suture lines formed by the union of these bones. As noted in Part I of this chapter, it is commonly accepted that when Gratiolet provided us with the modern names for these lobes in the mid-19th century, they were so named because of their location under the respective bones of the skull. Perhaps, in part, because of this rather arbitrary designation, initially no attempt was made to attach any specific functional significance to the various lobes. Over time, however, there has been a natural tendency to assign unique behavioral phenomena to each of the lobes, a process that has met with some limited success. The general anatomical boundaries of the four lobes are depicted in Figure 9–10.

The Frontal Lobe

The frontal lobes are the largest of the human brain, comprising approximately one third of its lateral surface. The frontal lobe is the only lobe of the brain for which fairly clear anatomical boundaries exist. Its anterior, superior, and anterior–inferior boundaries are defined by the respective limits of the cranial vault. Its posterior limit is the central sulcus. The inferior portion of the frontal lobe clearly is separated from the temporal lobe by the lateral (Sylvian) fissure. Like the parietal and occipital lobes, its medial surface extends down into the superior longitudinal fissure. Both structurally and functionally, the frontal lobe has been divided into a number of distinct but often overlapping areas. As noted above, the frontal lobe can be divided horizontally by the superior and inferior frontal sulci into the superior, middle, and inferior frontal gyri. Vertically, the frontal lobe can be divided into a posterior portion, often termed simply the *frontal* or *frontal motor* cortex and a larger, anterior portion that is called the *prefrontal* cortex. This division is based on similar cytoarchitectural structure in these respective regions. The "frontal" region consists primarily of *agranular* cortex (enhancement of layers III and V), while relative enlargements of layers II and IV (frontal granular cortex) characterize the "prefrontal" region (see below). It should be noted that even within these two general cytoarchitectural categories there are multiple subdivisions that are thought to have unique functional properties. It is common,

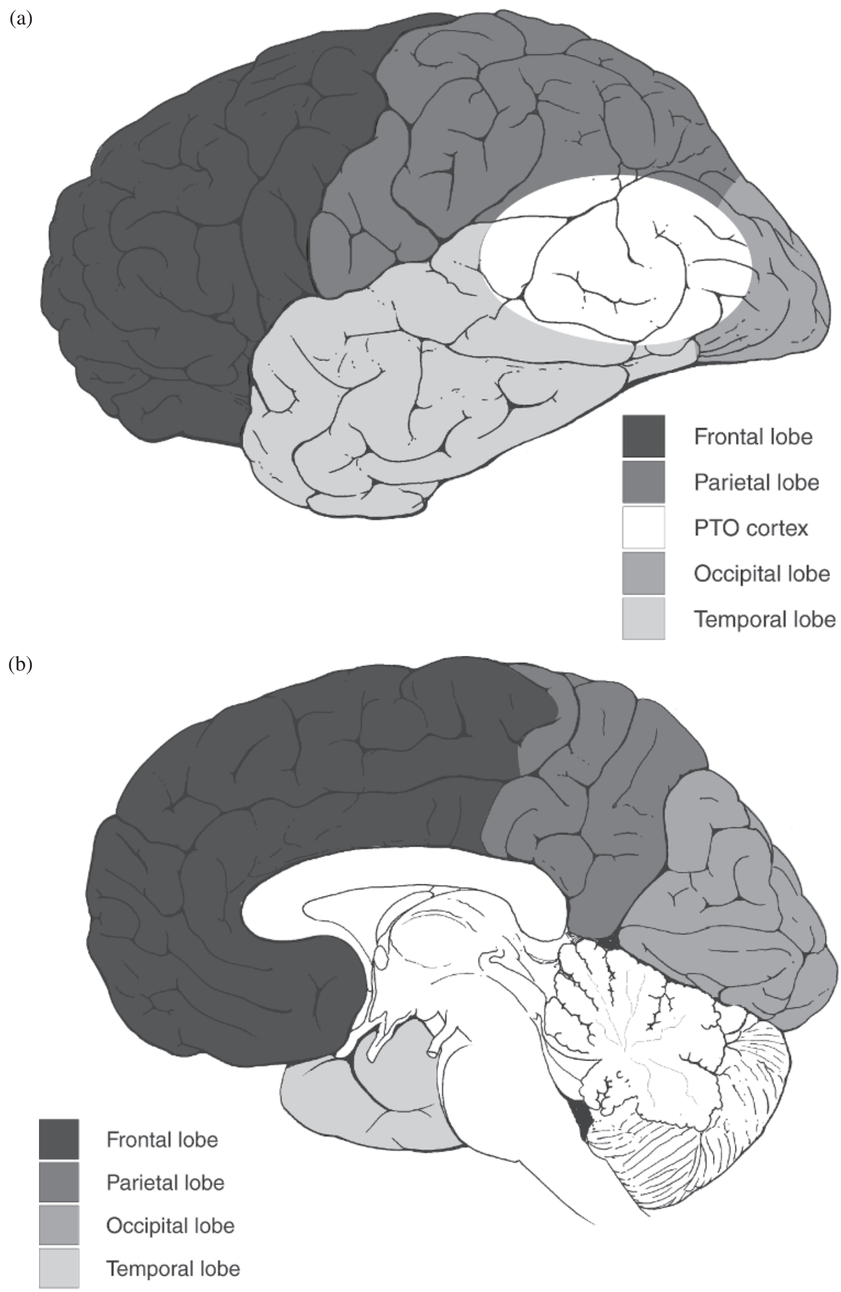

Figure 9–10. (*Continued*)

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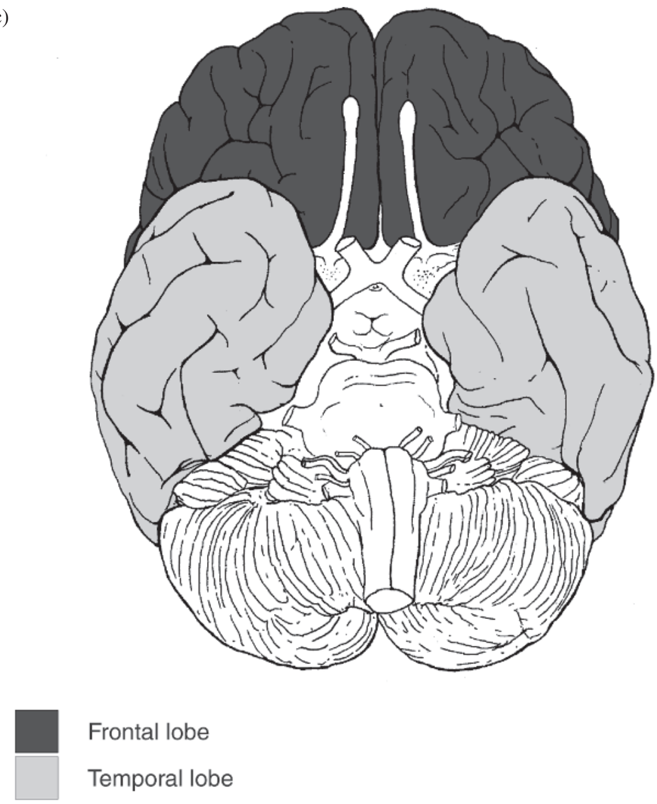


Figure 9–10. Lobes of the cortex. Figures illustrate the relative positions of the four lobes on the (a) lateral, (b) medial, and (c) ventral surfaces of the brain. Note the white area on Figure 9–10a. Because the boundaries of the parietal, temporal, and occipital cortices are indistinct as they converge on the lateral surface, this area is sometimes referred to as "PTO" cortex (see text below).

for example, to distinguish between dorsolateral, orbital and inferiomedial, and dorsomedial areas of the frontal granular cortices.

Albeit overly simplistic, for now the frontal lobes usually are described as playing a critical role in carrying out the *executive* functions of the brain. The more anterior portions of the frontal lobes, particularly the dorsolateral cortices, are thought to be primarily responsible for higher-order behaviors, for example, deciding *when*, *where*, *why*, *how,* and *if* one should respond in certain situations. The orbital and inferiomedial frontal cortices appear to be important in processing and/or modulating internal drive states, whereas the dorsomedial granular cortex appears crucial for maintaining optimal arousal and motivation. The primary motor and motor association cortices are thought to be responsible for the final organization, control or modulation, and implementation of the actual motoric response.

The Parietal Lobes

The anterior extent of the parietal lobe is demarcated by the central sulcus, which also denotes the posterior boundary of the frontal lobe. On its medial surface, the parietal lobe is separated from the occipital lobe by the parietooccipital sulcus. The separation of the parietal from the occipital lobe on the lateral convexity can be approximated by imagining a line extending from the parietooccipital sulcus on the medial surface to the preoccipital notch. The latter is a small sulcal indentation on the ventrolateral surface of the brain that also approximates the posterior extent of the temporal lobe. Except for at its more anterior extent along the posterior horizontal ramus (PHR) of the lateral fissure, it is difficult to differentiate the boundary between the parietal and temporal lobes (see discussion of PTO cortex below). The posterior–inferior extent of the parietal lobe on the lateral surface of the brain can be approximated by extending an imaginary line from the PHR of the lateral (Sylvian) fissure to a perpendicular line drawn upward from the preoccipital notch. The main surface features of the parietal lobe are the postcentral gyrus (primary somatosensory cortex) and the division of its more posterior portions into the **superior** and **inferior parietal lobules** by the intraparietal sulcus. As noted above, the inferior parietal lobule is composed of the **supramarginal gyrus** [Brodmann's area (BA) 40] and the **angular gyrus** (BA 39).

If the frontal lobes are seen as primarily responsible for controlling if, when, why, and how we respond to situational demands, the posterior cortices, including the parietal lobes, may be viewed as being responsible for **collecting, encoding, integrating,** and **storing** sensory information upon which the frontal lobes rely to carry out their activities. In part, the parietal lobes appear to take the lead in processing and interpreting somatosensory input and developing an appreciation of internal (body schema) and extended or external space.

The Temporal Lobes

The dorsal limits of the anterior temporal lobe are easily identified by the PHR of the lateral fissure. The cranial vault essentially defines the anterior and inferior extents of the temporal lobes. The posterior extent of the temporal lobe is not defined by a precise sulcus, but rather by the "imaginary lines" described above that separate the parietal and temporal lobes on the lateral surface of the brain. Important regions of the temporal lobe include **Heschl's gyrus** (primary auditory cortex) and auditory association cortex, which includes the **planum temporale** in the temporal operculum; the **superior**, **middle,** and **inferior temporal gyri**; and the **occipitotemporal** (*fusiform*) **gyrus**. On the inferiomedial surface of the temporal lobe lies the **parahippocampal gyrus,** which contains the **hippocampal formation**. On the medial aspect of the anterior portion of the parahippocampal gyrus is the **uncus**, a small bulge on the surface of the brain that marks the general location of the **amygdala** lying beneath this surface feature (see Figures 5–4b; 6–1b).

The temporal lobes perhaps most commonly are associated with the processing of auditory input and with the encoding of memory. However, among other possibilities, the temporal lobes also are believed to play a substantial role in the processing of affective information, language, and in certain aspects of visual perception.

The Occipital Lobes

The main portion of the occipital lobe lies on the medial surface of the hemisphere. As previously noted, its main surface feature is the calcarine sulcus, which separates the cuneus (above) from the lingual gyrus (below). The area around the calcarine sulcus represents the primary projection area for the optic radiations. The functional–anatomical significance of the calcarine sulcus is that the visual cortex immediately above it (**cuneus**) processes information that comes from the (contralateral) inferior visual field, while the **lingual gyrus** mediates input from the superior visual field (see Chapter 5). One way to keep this straight is to think of the visual cortex as not only reversing the visual fields horizontally (contralateral representation), but also vertically (in the contralateral fields: see Figure 5–6).

Behaviorally, the occipital lobes are linked primarily to visual perception, including color, form, and motion. However, when considering the interactions among the occipital, parietal, and temporal lobes, occipital lobes also are seen as critical for a host of spatial, linguistic, and object recognition functions.

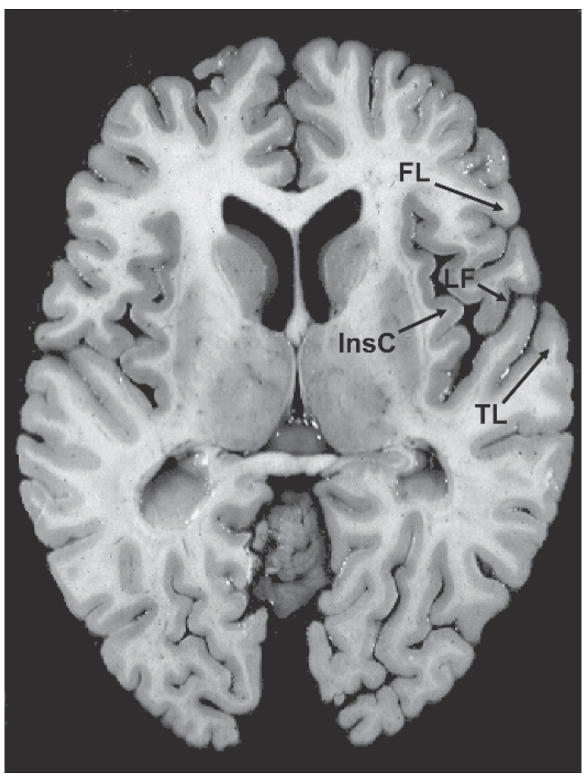
"PTO" Cortex

Because the area where the parietal, temporal, and occipital lobes converge on the lateral surface of the hemispheres is difficult to delineate, this area often is referred to as "PTO" (parieto-temporo-occipital) cortex. This area is primarily composed of higher-order heteromodal association cortex (see below) that serves as a point of convergence for unimodal inputs from adjacent auditory, visual, and somatosensory secondary association cortices. The linking of concurrent sensory inputs is thought to provide a basis for creating highly complex, multimodal percepts. These, in turn, provide a foundation for language, abstraction, problem-solving and other complex cognitive activities. Consider, for example, the following. While the visual cortex enables us to accurately perceive the written word "fleur," it is through the interaction of the temporal and occipital lobes that one learns to associate this visual pattern with a particular sound. However, if one is unfamiliar with French, the word "fleur" still will be devoid of meaning. However, once we learn that "fleur" means "flower" (through subsequent visual, auditory, or other associations), then it immediately takes on a whole new, rich dimension, complete with visual images, olfactory, tactile, and perhaps even symbolic associations as a result of other previously established, multimodal connections.

The Insular Cortex

Although not typically considered to be a part of the frontal, temporal, or parietal lobes, the **insula** or the *Island of Reil* is a small area of cortex buried deeply within the lateral (Sylvian) fissure. On an axial or coronal section (Figure 9–11), the insular cortex can be identified lying lateral to the putamen, separated from this basal ganglia structure by two thin fiber tracts,

(a)



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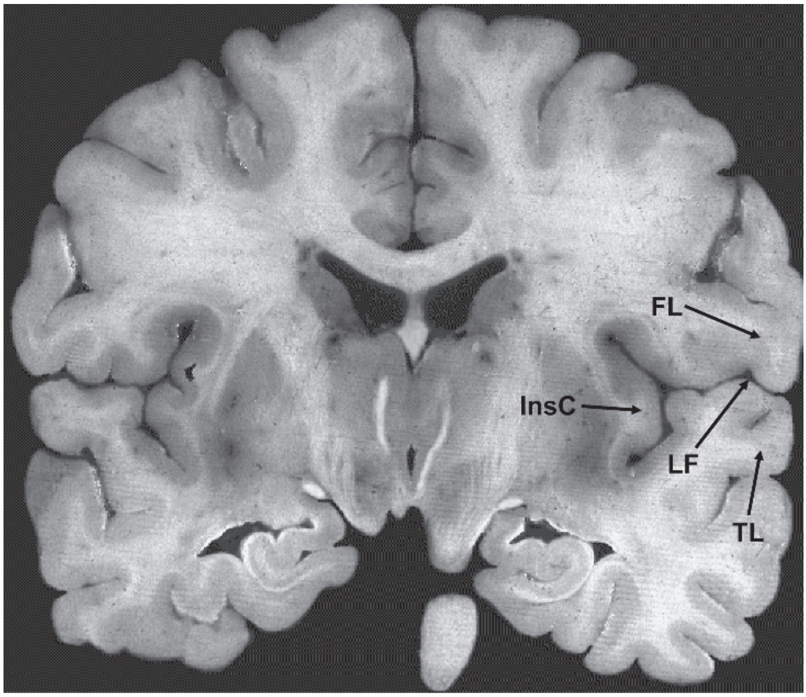


Figure 9–11. Insular cortex. The insular cortex is shown in (a) axial and (b) coronal slices in the depths of the lateral fissure. It is bounded medially by the claustrum and the extreme and external capsules. Brain images were adapted from the *Interactive Brain Atlas* (1994), courtesy of the University of Washington.

the external and extreme capsules and the claustrum (the thin band of gray matter that is sandwiched in between these two capsules). Compared to the other cortical areas, relatively little is known about the specific function of the insula in humans. It certainly does not seem to be a vestigial structure as it shows increased development in apes and humans, and like the other parts of the cortex it is highly convoluted. Several shorter gyri characterize the anterior portions, with one or two longer gyri making up the posterior aspect. The insula has extensive connections to neocortical, limbic, and paralimbic structures. The insula is linked to somatosensory, visual, and auditory association areas, as well as to the prefrontal areas and primary motor cortex. While specific functions are difficult to ascribe to the insula, its anterior portions appear to be more closely related to olfactory and gustatory sensations and to autonomic (especially, gastrointestinal) activities, whereas more posterior portions may be more responsive to visual, tactile, and auditory input. Because of its association with limbic and paralimbic centers, it has been postulated (see Mesulam & Mufson, 1985) that the insula may be an important link in the process of imbuing sensory experiences with emotional valances and/or responding affectively to sensory stimuli. The insula's possible role in certain epileptic and psychiatric conditions also has been suggested (Bauman, 1992). More recently, lesions in the insula were found to reduce nicotine cravings (Naqvi, Rudrauf, et. al., 2007).

Cytoarchitectonic Organization of the Cerebral Cortex

As was noted in the section on the history of cerebral localization, one potentially promising approach to studying the functional organization of the brain was the discovery of the cytoarchitectural organization of the cerebral cortex. Variations in the pattern and organization of the cellular processes in the different cortical areas define the cytoarchitectural organization of the brain. Although the microscope was available to Gall in the early part of the 19th century, he cautioned that there was "little to be learned" from an analysis of the cells of the brain. However, at the beginning of the 20th century, it also was noted that while all the "neocortex" was similar in that six distinct "layers" of cell organization generally could be identified, the pattern, prominence, or distribution of certain types of cells varied from one area of the cortex to another. On the assumption that changes in this pattern of cellular structure (cytoarchitecture) reflect differences in function, Brodmann (1909) analyzed these variations and mapped out the entire cortex, assigning numbers to each of approximately 50 contiguous regions where such a change in structure was detected (Figure 9–12). However, Brodmann himself never actually used his system of cytoarchitectural classification to define areas of functional specialization in the brain; this was to come much later. In publishing his own version of a cytoarchitectural map of the cortex in 1929, von Economo, although identifying approximately twice the number of regions defined by Brodmann, was able to reduce the categories to five basic types of cortex. Vogt and Vogt (1919) found what they believed were over 200 distinctive cytoarchitectural areas in the cortex. However, it is Brodmann's classification system that has been most

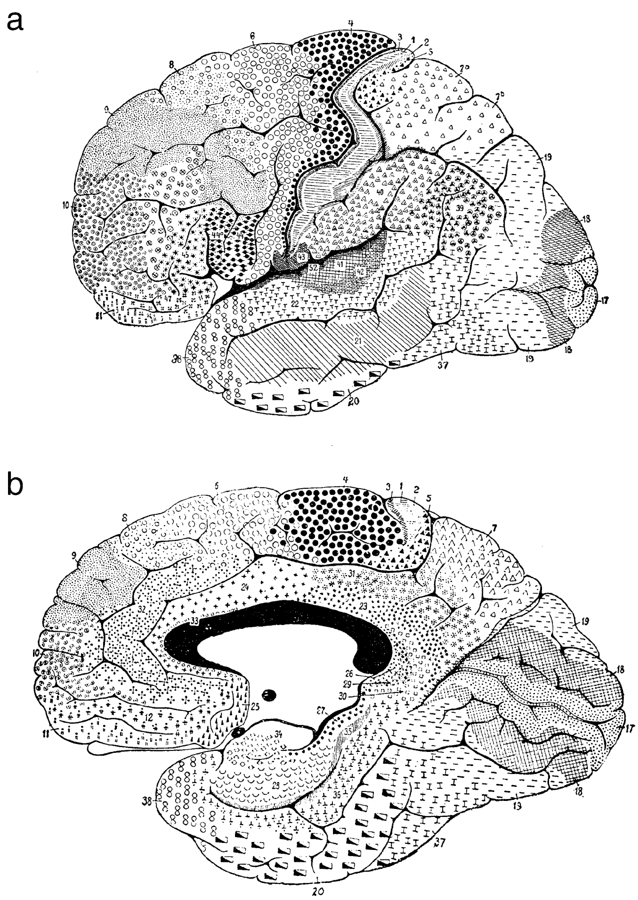


Figure 9–12. Brodmann's classification of cortical areas based on cytoarchitectural variations. From P. Bailey and G. Von Bonin (1951). With permission of the University of Illinois Press.

extensively used as a means of labeling cortical areas. Brodmann's classification system will be discussed more thoroughly in Part III of this chapter.

The Six-Layered Neocortex

The exterior layers of the neocortex (gray matter) contain neurons, neuroglia (supporting cells), and blood vessels. Underlying the gray matter is the white matter, which consists of axonal processes connecting the cortical mantle with other parts of the central nervous system (the various white matter pathways will be discussed in greater detail below). The neurons making up the gray matter of the cortical mantle can be divided into two major types: **pyramidal** and **nonpyramidal neurons**. Pyramidal neurons primarily are located in layers III and V. These layers, especially layer V, are the major source of cortical efferents (output fibers). In contrast, layers II and IV (granule cell layers) are composed primarily of nonpyramidal neurons (stellate, polymorphic, granule, and Golgi type II cells) and are the major sites of cortical afferents (inputs). As noted above and illustrated in Figures 9–13 and 9–14, the relative distribution of these cells form the six distinctive layers upon which cytoarchitectonics are based. However, the relative prominence of these various layers, as well as the relative prominence of certain types of cells within each layer, will vary depending on the area of cortex involved and its general function. Areas of the cortex that are characterized by a relative absence of the larger pyramidal cells and a greater abundance of stellate or granule cells and small pyramidal cells (as in the primary sensory cortices) are known as **granular cortex**. Areas in which larger pyramidal cells predominate are referred to as **agranular cortex** (the latter are typical of motor output areas). Collectively, both of these more extreme types of tissue are referred to as **idiotypic** or **heterotypical** cortex, whereas the more "balanced" cortical areas, in which the six layers are more clearly differentiated, are known as **homotypical** cortex.

From the pial surface inward, the six cortical layers are:

I. The **molecular** or **plexiform layer,** which is the outermost layer (closest to the surface of the cortex). It contains relatively few cells but a rather dense collection of dendritic processes. This layer is the site of termination of cortical-projecting fibers from the thalamic association nuclei.

II. The **external granular layer,** which consists of a large number of closely packed, small granule and pyramidal neurons whose dendrites terminate in the molecular layer and the majority of whose axons terminate in deeper cortical layers, while additional axons enter the white matter where they project to other cortical areas. Along with layer III, this layer is the termination site of most corticocortical projections.

III. The **external pyramidal layer,** consisting of medium pyramidal neurons whose dendrites largely ascend to the first layer, while the majority of the axons enter the white matter as either association or commissural fibers. In addition to being a major source of efferent fibers to other cortical areas, the external pyramidal layer is a major termination site for afferent fibers coming from other areas of the cortex.

IV. The **internal granular layer,** consisting primarily of closely packed stellate and granule cells. Most of these intrinsic neurons have short axonal processes that stay within the same layer. Other longer axons may go to other layers or enter the white matter. This layer is the site of termination of most of the thalamocortical fibers originating in the specific thalamic nuclei.

V. The **internal pyramidal layer,** consists primarily of medium- to large-sized pyramidal neurons, along with some intrinsic granular cells. Again the dendritic processes of the pyramidal neurons tend to ascend to the molecular layer, although

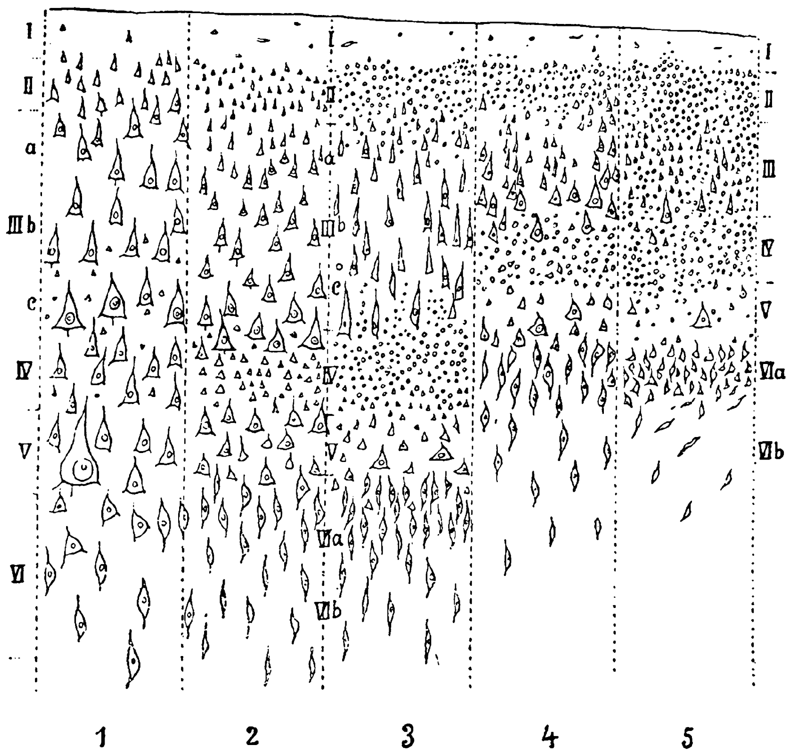


Figure 9–13. Schematic representation of the five fundamental types of isocortex according to von Economo (1929). Roman numerals represent the cortical layers and Arabic numerals indicate the five basic type of neocortex:

1. "Motor cortex": prominence of pyramidal cells ("agranular"), especially prominent in layers III and V. Some very large pyramidal cells (Betz cells) present. Found primarily in Brodmann's areas 4 and 6.
2. "Frontal association cortex": pyramidal cells still quite obvious in layers III and V, but more granular cells appear, especially in layers II and IV. Typical of the prefrontal and some posterior association areas.
3. "Posterior association cortex": even greater development of the granular layers (II and IV). Seen in the cortices of the inferior parietal lobule and superior temporal gyrus.
4. "Polar cortex": has well-differentiated layers representative of homotypical cortices like 2 and 3, but thinner. Found in orbital frontal and surrounding the primary visual cortices.
5. "Primary sensory cortex": represents idiotypic (heterotypical) cortex that, like "motor cortex," has poor differentiation among the layers, but most consists of granule type cells (koniocortex). Present in primary visual (17), auditory (41,42) and somatosensory (3,1,2) cortices.

From P. Bailey and G. Von Bonin (1951). With permission of the University of Illinois Press.

many will terminate in layer IV. The axonal processes of the pyramidal cells enter the white matter as either association or primarily as projection fibers that proceed to areas outside the cortical mantle, for example, the basal ganglia, the thalamus and other subcortical nuclei, the limbic lobe, the cerebellum, and the spinal cord.[7]

VI. The **multiform or fusiform layer,** is made up chiefly of spindle-shaped cells, as well as stellate and granular cells. Some dendrites will ascend to the molecular layer, but most will either terminate in layer IV or remain in layer VI. Thus both the cells of

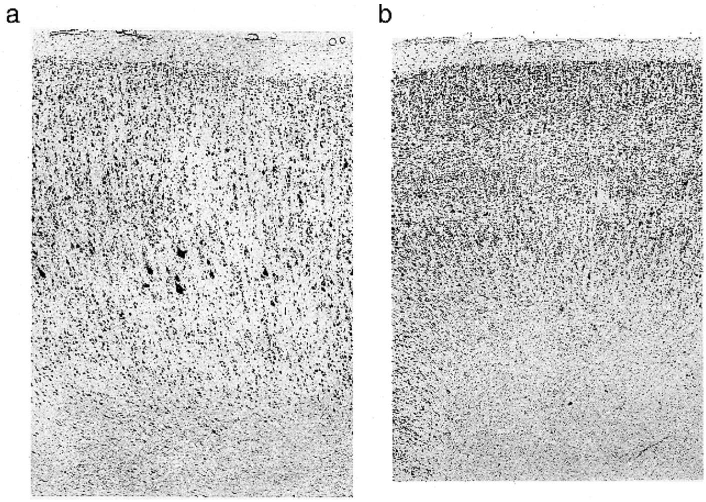


Figure 9–14. Examples of (a) agranular (motor) and (b) granular (sensory) cortex taken, respectively, from the precentral and visual cortices. Note the presence of several large Betz cells in the motor cortex. From P. Bailey and G. Von Bonin (1951). With permission of the University of Illinois Press.

layers V and VI (whose axons project both within and outside the cortex) come into direct, extensive contact with thalamic projections terminating in layer IV. Many of the axons of the spindle cells end up as either projection or association fibers. The stellate cells (intrinsic neurons) are thought to be a main source of the shorter association fibers that connect the cells of one gyrus with those of an adjacent one. Fibers originating in the intralaminar nuclei of the thalamus tend to terminate in this layer. (Table 9–1 provides a summary of the major features of these six cortical layers).

The more highly differentiated **neocortex**, which contains these six layers (not always clearly distinct), comprises about 90% of the cerebral hemispheres. In contrast, more primitive **allocortex** contains three distinct layers of cells and includes the olfactory cortex (**paleocortex**), the hippocampus, and dentate gyrus (**archicortex**). There is a third cortical region, which includes the cingulate cortex and portions of the parahippocampal gyrus and is transitional from allocortex to neocortex, that contains three to six layers depending on

Table 9–1. Summary of Features of Cortical Layers

I	**Molecular:** Consists of dendrites of pyramidal cells and a few intrinsic neurons, receives input from thalamic nuclei
II	**External granular:** Consists of small pyramidal cells and intrinsic neurons, receives from and projects to other cortical areas
III	**External pyramidal:** Consists of medium pyramidal cells, source of association and commissural fibers
IV	**Internal granular:** Consists of intrinsic neurons (stellate and granular cells), receives input from specific thalamic nuclei
V	**Internal pyramidal:** Contains large pyramidal cells, source of association and projection fibers
VI	**Multiform:** Contains intrinsic and pyramidal neurons, primary source of U-fibers to adjacent gyri.

the location. This transitional cortex sometimes is referred to as mesocortex or paralimbic cortex. Using these general cytoarchitectural divisions as a starting point, Mesulam (2000b) categorized cortical tissue into five basic subtypes that also may possess more or less distinct functional properties. As outlined in Figure 9–15, these are:

1. **Idiotypic (heterotypical) cortex**, consisting of "granular" (sensory) and "agranular" (motor) areas
2. **Homotypical (unimodal) isocortex**
3. **Homotypical (heteromodal) isocortex**
4. **Mesocortex or paralimbic cortex**
5. **Corticoid** and **allocortical** or *limbic* **regions**

Each of these five basic cortical subtypes will be discussed below.

Corticoid Regions

Corticoid (cortexlike) structures involve areas in or around the basal forebrain that do not manifest clear cellular layering, but nevertheless appeared to be part of the neocortex. Included in this group were the **septal nuclei**, **substantia innominata** (which includes

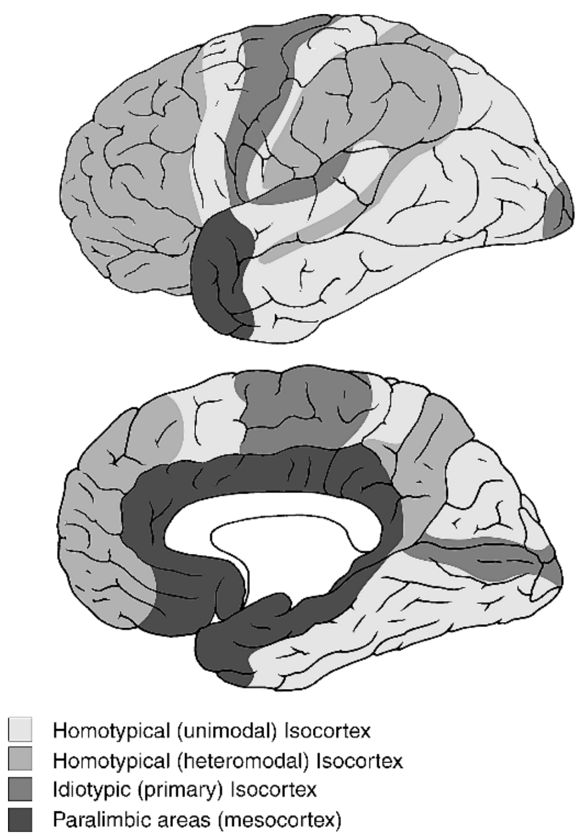


Figure 9–15. General location of Mesulam's (2000b) five basic types of cortex. Not shown are the deeper, more primitive cortical tissues defined by Mesulam as "corticoid" (e.g., septal nuclei, parts of the amygdala, and adjacent basal frontal areas) and "allocortical" (e.g., hippocampal formation). Figure adapted from Mesulam (2000b).

the **nucleus basalis of Meynert**, the source of acetylcholine), and the **amygdala**. *Allocortex* refers to a structurally and phylogenetically primitive type of cortex. While allocortex shows a clear layering effect, it consists of only one or two layers of cells. Two subtypes of allocortex are described (1) those areas in the anterior temporal lobe that serve as the primary cortical projections site for the **lateral olfactory stria** (*pyriform or paleocortex*), and (2) the **hippocampus proper** (*archicortex*). All of these areas tend to have extensive connections with the hypothalamus and are considered to be some of the more primitive parts of the "limbic system" (or the brain as a whole). As was seen in Chapter 8, these areas are involved in very basic drive states and survival mechanisms.

Mesocortical Regions

The "meso" or paralimbic cortex consists of the **cingulate gyrus**, portions of the **parahippocampal gyrus** and temporal pole, the **insula**, and the **caudal orbitofrontal cortex**. As noted above, these tissues are characterized by three to six layers of cells and represent a transition from the more "primitive" allocortex and the more highly developed neocortex. Functionally, these areas appear to be related to "higher-order drive states," or motivation (e.g., maternal instincts, socialization), learning and memory, and autonomic activity (Mesulam, 2000b).

Homotypical Isocortex

Homotypic isocortex and idiotypic cortex constitute the neocortex, which in humans represents by far the largest majority of cortical tissue. As in all neocortical tissue, these regions are characterized by a six-layered cellular structure. The major structural difference between the homotypical and idiotypic cortex is that in the **homotypical cortex** the six layers tend to be more distinct, whereas in the **idiotypic cortex** there is greater blurring or greater degrees of uniformity in the cellular layers (particularly II though V). The homotypic cortex is further divided into the unimodal and heteromodal association cortices. Although there apparently are some subtle differences between the unimodal and heteromodal cortices cytoarchitecturally, the major differences appear to be in their pattern of connections.

Homotypical Unimodal Isocortex

Unimodal or modality-specific cortices are comparable to Luria's "secondary" association areas. They receive input only from a single sensory modality (e.g., auditory, visual, or somatosensory) and only from the idiotypic cortex with which they are associated (or from other areas within the same modality-specific unimodal region). The output of the unimodal cortices in large part (though not exclusively) is to the heteromodal areas. These unimodal cortices seem to be responsible for further processing of specific sensory input, and hence, lesions to these areas generally will result in modality-specific deficits, depending on the specific area involved. Three unimodal sensory association areas are typically identified: auditory (along the superior temporal gyrus), visual (peristriate, midtemporal, and inferior temporal areas), and somatosensory (parts of the postcentral gyrus and superior parietal lobule). The premotor areas anterior to the precentral gyrus also generally are considered to be part of a motor equivalent of the sensory unimodal cortices. These cortices always lie interposed between the "primary" (idiotypic) and the "tertiary" (heteromodal) cortices.

Homotypical Heteromodal Isocortex

Heteromodal (*tertiary association*) cortices, in contrast to the unimodal areas just discussed, receive input from multiple modalities via the unimodal or "secondary" association cortices (apparently they receive no direct input from the "primary" or idiotypic areas). Because of the fact that they are privy to and can integrate this diversity of information, these areas seem to be associated with cross-modal cueing and associations, abstractive capacity, and what are commonly termed "higher-level executive functions." The inferior parietal lobule (angular and supramarginal gyrus) and the prefrontal cortex (that portion of the frontal lobe that lies anterior to the premotor area) constitute the primary heteromodal cortices in humans. As can be seen in Figure 9–15, portions of the superior parietal lobule and the temporal cortex (BA 37) also may have multimodal connections and are considered homotypic heteromodal isocortex by some anatomists.

Idiotypic Isocortex

Idiotypic (also called *primary*) cortex differs from homotypical isocortex both with regard to its cytoarchitectonic structure, connections, and hence, functional role. In homotypic isocortex, there is a clearer differentiation of the cortical layers (especially layers II through V) based on the predominance of cell types in the respective layers. For example, stellate or granule cells tend to be more manifest in layers II and IV, while pyramidal cells are relatively more common in layers III and V. In primary sensory (idiotypic) cortex, stellate cells tend to predominate in layers II through V, whereas in primary motor (idiotypic) areas pyramidal cells tend to be more prominent.

Idiotypic Motor Cortex. Since pyramidal cells tend to be associated with longer fiber tracts (as are found in the motor pathways), it makes sense that the primary motor area (precentral gyrus or BA 4) is characterized by this relative proliferation of pyramidal cells. Because of the relative lack of stellate or granule cells, the primary motor cortex often is referred to as *agranular* cortex. The latter term also occasionally is applied to the premotor (unimodal homotypical isocortex), which also tends to have a greater ratio of pyramidal to stellate cells. As will be discussed in Part III, the primary motor cortex appears to represent the final common upper motor pathway for executing voluntary motor responses.

Idiotypic Sensory Cortex. By contrast, the cortical regions that are the major cortical projection sites for the medial and lateral geniculates and the VPL and VPM nuclei of the thalamus have very few pyramidal cells. They represent those cortical areas concerned with the initial processing of incoming auditory, visual, and somatosensory information, respectively; hence, the term, *primary sensory* cortices. As noted above, due to the preponderance of stellate cells, the cortical layers in these regions have a finer "granular" appearance, and thus, also are referred to as *granular* [8] or *koniocortex* (meaning "*dust-like*" – see Figure 9–14). These areas include:

1. **Primary visual cortex** (BA 17): located in the occipital lobe surrounding the calcarine fissure on both its superior (cuneus) and inferior (lingual gyrus) bank.
2. **Primary auditory cortex** (BA 41 and probably part of 42): located primarily within the temporal operculum (Heschl's gyrus) on the superior surface of the superior temporal gyrus.
3. **Primary somatosensory cortex** (BA 3,1,2): located on the postcentral gyrus, between the central and postcentral sulci.
4. **Primary olfactory cortex**: less well defined, but as was seen in Figure 5–4b, generally is thought to include the basal forebrain in the region of the anterior perforated substance or basal nuclei, portions of the amygdala (cortical amygdaloid nucleus), and adjacent pyriform and entorhinal cortices. This olfactory cortex differs from the other primary sensory cortical regions in a couple of important ways. First, these areas involve limbic and more primitive allocortex. Second, the sensory input is more direct, rather than being relayed through the thalamus.

In addition to the horizontal lamination of the cortex into cellular layers, a vertical or columnar organization of cells has been identified [9] (Szentagothai, 1979; Szentagothai & Arbib, 1974). Initially identified in sensory areas of the cortex, all cells (within these vertical units, only fractions of a millimeter in diameter) were found to respond to a particular type (and locus) of stimulation. These vertical columns or units are thought to represent one of the more elementary functional units in the cortex. Short axons within these vertical columns make connections to neurons in adjacent columns to form distinct closed chains or *modules*. In turn, these modules are interconnected with other modules that may reside in divergent areas of the cortex, providing a neural network for more complex (cortical) "functions." Thus, distinct cortical "functions" each may be represented by particular patterns of interconnected modules, making up these larger (macro) functional units. While the same modules or subsets of modules might be shared by other macrofunctional units, each of these larger behavioral (functional) units would have their own unique set of modules. The preceding forms the basic premise for **distributed systems** as a model or theory of cortical organization (see Mountcastle, 1979, 1997; Cytowic, 1996, pp 80–84; Cummings & Coffey, 1994; Duffy, 1984). This approach, which will be addressed again later in this chapter, would help explain how a single lesion can affect a variety of behavioral functions, and conversely how lesions at various cortical sites may disrupt a given behavior.

FUNCTIONAL ORGANIZATION OF CEREBRAL CORTEX: OVERVIEW

Clearly, there is some correlation between certain cytoarchitectural features and function. Brodmann's divisions have survived in part because of their fairly good correspondence with areas of the cortex with known functional distinctions. This is particularly true with regard to primary and secondary cortical zones. Thus we have come to associate the primary motor cortex with (Brodmann's) area 4; the motor association cortex with area 6; frontal eye fields with area 8; the primary visual cortex with area 17; the visual association cortex with areas 18 and 19; the primary somatosensory cortex with areas 3, 1, and 2; the primary auditory cortices with areas 41 and 42; and the auditory association cortex with areas 21 and 22. Within the "tertiary" or heteromodal association cortices, it becomes more difficult to associate specific "functions" with specific Brodmann areas, although reference often is made to areas 39 and 40 in conjunction with the angular and supramarginal gyri, respectively.

However, despite what would appear to be some degree of anatomical validity for Brodmann's classification systems, this means of classification failed to offer a comprehensive explanation of cortical function. A unifying theory still was needed into which these anatomical findings could be integrated. Some type of framework incorporating structural data with known clinical correlates needed to be developed to begin to understand how the brain integrates elementary sensory input into meaningful, complex, multimodal perceptions and concepts, thus allowing the organism to respond in a complex, goal-directed manner. The discussion of such a working model will be the primary focus of Part III of this chapter. For now, a few additional observations on possible unifying principles of cortical organization may be helpful.

Sensory Input

One approach to studying the organization of the neocortex is to consider the levels of processing required from sensory input to behavioral output. We might begin by considering the sensory input. Externally driven behaviors typically are elicited by sensory input. This input can be visual (an object or a written word), auditory (environmental sounds, words, or music), somesthetic (texture, temperature, or shape), or chemical (the smell of a flower or taste of a strawberry). As noted earlier, each of these sensory inputs is processed at a basic level in the corresponding primary cortical sensory area represented by idiotypic, granular cortex. In turn, these primary cortical projection areas have important common anatomical relationships that are important to subsequent levels of processing. For example, each of these primary sensory cortices is adjacent to and has extensive connections with its corresponding modality-specific (unimodal) association area. These connections allow for increasingly complex levels of information processing. Specifically, primary visual cortex (BA 17) is adjacent to visual association cortices (BA 18 and 19) in the occipital lobe, primary auditory cortex (area 41) is adjacent to auditory association areas (BA 22 and probably part of 42)[10] in the temporal lobe, and primary somatosensory cortex (BA 3, 1, 2) is adjacent to somatosensory association cortex (BA 5 and 7) in the superior parietal lobule. Additional processing of modality-specific input occurs within each of these unimodal (secondary) sensory association areas such that recognizable and reproducible percepts are formed, although specific meanings or significance may not be attached at this stage. Next, each of these modality-specific areas converges onto adjacent heteromodal association cortices (e.g., the supramarginal (BA 40) and angular (BA 39) gyrus). It is within these heteromodal areas, through the richness of cross-modal sensory associations, that these unimodal percepts are imbued with complex meaning and symbolism, forming the basis for higher-order functions such as concept formation and abstractive capacities.

Thus far, this model of neocortical organization has been discussed with reference to externally driven sensory inputs. In addition to these externally driven sensory inputs (auditory, visual, and somatosensory), internally driven inputs are processed and can be experienced at the sensory level. For example, recalling the memory of a negative experience might arouse subjective feelings of fear or shame and involve activation of more primitive limbic structures.

Motor Output

The motor output system of the cerebral cortex appears to be organized in a manner similar to the sensory input system but, in some respects, in reverse. In sensory systems, information can be conceived as being processed from the bottom (from primary or idiotypic sensory cortex) up (to heteromodal cortex). In the motor or executive system, it is perhaps more logical to think about the flow of information from the heteromodal, higher-order frontal granular cortex to the primary or idiotypic motor cortex (i.e., from more complex to less complex levels of processing). If the sensory systems (posterior cortices) provide the organism with the information it needs to survive and prosper, it is the frontal (executive–motor) systems that decide where and how that information needs to be translated into actions. Thus, the information that was processed by the homotypic isocortex of the parietal, temporal, and occipital lobes must be made available via association pathways (discussed below) to the heteromodal frontal association cortices. Here the information is weighed in light of the current needs and circumstances of the organism, immediate or long-term goals, and other available information to decide if and how the organism should respond. Once a particular response is decided on, this information then is conveyed from the heteromodal to the unimodal frontal cortex or premotor areas (e.g., BA 6, 8, 44, 45) where the response is programmed and orchestrated. The final step in this process is for the idiotypic motor (agranular) cortex or primary motor area (BA 4) to actually execute the planned motor response.[11]

Clinical Implications

How does this model of neocortical organization affect the analysis of deficits associated with cortical lesions? Again, this topic will be addressed in greater detail later, but a brief overview in the context of the present discussion may be useful.

Two distinct cortical visual pathways have been described: a ventral (object vision) pathway and a dorsal (spatial vision) pathway (Ungerleider & Mishkin, 1982). Each of these visual pathways consists of multisynaptic circuits that flow from primary visual to visual association to heteromodal association cortex, as described above. The ventral stream flows from occipital to temporal heteromodal cortex following the course of the inferior longitudinal fasciculus and/or the inferior occipitofrontal fasciculus (see immediately below), while the dorsal stream flows from occipital to parietal heteromodal cortex following the superior longitudinal fasciculus. The corticocortical connections of these two visual streams in part determine the functional specificity of each pathway. Within each of these visual pathways, primitively formed visual information flows from primary visual cortex (BA 17) to adjacent visual association areas (BA 18 and 19) for further processing into visually integrated percepts. The visual information then is thought to flow into one of the two visual streams: the ventral object vision pathway or the dorsal spatial visual pathway. Whereas the ventral occipitotemporal pathway is thought to be crucial for object identification, the dorsal occipitoparietal pathway is considered crucial for the visual location of objects. Each pathway has connections to more remote cortical regions that determine associated visual functions. For example, the ventral visual pathway has connections to limbic structures in the temporal lobe that may enable the individual to associate visual objects with emotion and memories. Both pathways likely connect to frontal cortices to mediate motor responses.

This organization and pattern of connections of these pathways determine the nature of the specific deficits produced by discrete cortical lesions. Such lesions will reflect the organization and levels of processing that occur within the lesioned region. In humans, ablative or destructive lesions to the primary visual cortex (BA 17) produce the characteristic visual field defects as described in Chapter 5. Bilateral lesions to primary visual cortex may result in "cortical blindness." Excitatory lesions (e.g., seizures) to primary visual cortex (although relatively rare) may result in poorly formed visual hallucinations consisting of amorphous colors or flashes of light. Destructive lesions at the next level of processing, that is, involving the visual association cortex, produce more complex and heterogeneous deficits that differ behaviorally depending on which pathway (dorsal or ventral) is lesioned and depending on the specific location within visual association cortex. For example, lesions affecting the more ventral pathways may result in deficits in visual object recognition or color agnosia, whereas a more dorsally situated lesion might result in problems with visual spatial perception or reading. All deficits, however, share specificity for processing of visual information.

Lesions that are generally limited to heteromodal association cortex tend to produce more complex behavioral, cognitive, and emotional–affective disturbances, while preserving more basic perceptual and motor capacities. For example, destructive lesions affecting PTO areas or the frontal granular cortex may result in disturbances of such skills as propositional speech, language comprehension, arithmetical and abstractive abilities, visual–spatial construction, problem solving, "executive" abilities, learning and memory, or even breakdowns in emotional/social behaviors. Excitatory lesions (seizures) lesions to heteromodal association cortices (more commonly in temporal regions) can produce well-formed visual images or visual hallucinations.

The cortical visual pathways presented above have been studied quite extensively and offer a model for discussion. However, many of the structural and functional organizational principles can be applied to the other sensory systems.

Limitations

Models of cortical organization and the distribution of neural networks that mediate precise cognitive functions contribute to an understanding of brain–behavior relationships. Although the models of cortical organization and interconnections presented here and in other sections of this chapter provide a schema for understanding general patterns of behavior, the application of these anatomic and neuropsychological principles to lesion localization in humans has its limitations. Ablation or destructive lesion paradigms, which study the correlation of lesion sites with specific behavioral deficits, have been the basis for the study of many higher cortical functions. However, the drawbacks of these paradigms are important to consider. First, damage to the human brain rarely respects cytoarchitectonic boundaries. Consequently, multiple cytoarchitectonic regions usually are involved in a single lesion, which may account for the diversity of behavioral deficits observed on clinical examination. In addition, deficits normally associated with a particular cortical region can be produced by lesions remote to the site as a result of disturbance of other structures or sites (both cortical and subcortical) that are part of the distributed system for that particular function. In addition, lesions to *inter*hemispheric (commissural) or *intra*hemispheric (association) pathways may produce **disconnection syndromes,** which can result in a wide variety of cortical behavioral deficits. Such syndromes, which have been well articulated by Geschwind (1965), will be discussed at the end of the next section. Finally, most neuropsychological tests used to assess neurobehavioral syndromes are themselves multidimensional and may show impairments for different reasons in different subjects. Despite these limitations, the study of clinical cases with discrete lesions represents an important methodology to study brain–behavior relationships and is an important clinical tool.

CORTICAL PATHWAYS AND THEIR CLINICAL SIGNIFICANCE

Most observed behavior results from the integrated functioning of the brain and the rest of the nervous system, with each part making its own unique contribution. In order for such integration to occur, there must be a constant sharing of information (intercommunication) within the system and an infrastructure that supports such communication. With respect to the cerebral cortex, two general communication systems are readily identified. One might be considered a more diffuse, analogue-type system that establishes the background state or cortical tone within which the second system operates. The neuronal mechanisms for this first system are largely represented by various neurochemical pathways that will be reviewed in Chapter 11. The second system may be characterized as a more discrete, digital communication network that conveys highly specific information. It is this latter system that will be the focus of this section. One should be mindful that while this analogy makes a useful dichotomy for the following discussion of cortical pathways and disconnection syndromes, it does so at the risk of vastly oversimplifying the process.

Types of Pathways

The interchange of information involving the cerebral cortex is mediated largely by collections of vertical and horizontal axonal fibers. Vertical connections consist of ascending and descending pathways between cortical and subcortical, brain stem, or spinal nuclei, while horizontal communications are represented by either intrahemispheric or interhemispheric connections. Respectively, these constitute the three major types of information highways within the brain: **projection**, **association**, and **commissural pathways**. Whether looking at coronal, axial, or parasagittal images of the brain, the extent of these white matter pathways beneath the cortical mantle readily can be appreciated. A basic awareness of these pathways is essential in attempting to understand brain–behavior relationships and clinical neuropathology.

A few basic cortical connections already have been presented in the discussion of cytoarchitectonics, including the fact that:

1. Sensory information is conveyed to the idiotypic sensory cortex from peripheral receptors after synapsing in the thalamus (via ascending projection pathways).
2. After being processed in the primary sensory cortex, this information is passed on to the homotypic sensory cortices (via short association fibers).
3. Reciprocal feedback with the frontal granular and agranular cortices (via longer association pathways) then allows for utilizing previous and current sensory input to decide if a response is indicated, and if so how that response might best be planned, monitored, and executed.
4. Finally, the primary motor cortex actually executes the behavioral response (via descending projection fibers).

What was not mentioned earlier was the fact that at both the sensory or perceptual level and at the executive or motor level there is a sharing of information across the midline (via commissural pathways). Both cerebral hemispheres are normally recruited in the above processes, along with other subcortical structures (e.g., basal ganglia), via ascending and descending projection pathways.

In previous sections and chapters, we already have mentioned the critical role each of these various cortical zones or subcortical nuclei play in behavior and the potential impact of lesions to these various areas. In this and later sections (particularly the one on disconnection syndromes) the focus will be on the effect of lesions which disrupt communications between or among these various cortical and subcortical sites as a result of impingement on one or more of these pathways. For now, consider the following analogy. You have a television set that is in perfectly good condition, the nuclear power plant 20 miles away is up and running, and the geosynchronous communications satellite is sending perfectly good signals to your local cable company. However, if the underground cables (conducting electrical power or TV signal) interconnecting any of these three locations are disturbed, your TV viewing will be adversely affected. This is basically what happens with many brain lesions. While some lesions may be more or less limited to the cortical mantle (gray matter) or to subcortical nuclei, most also encroach on fibers of passage as well. Other lesions or disease processes (e.g., lacunar infarcts, leukoencephalopathy, and multiple sclerosis) primarily may involve white matter or fiber tracts. The behavioral effects of lesions that interfere with normal communications within or between the hemispheres (i.e., association or commissural fibers) result in what commonly are referred to as **disconnection syndromes**. Some of the more common disconnection syndromes will be reviewed shortly. For now, let us consider the three major types of fiber tracts within the brain. These are (1) **commissures**, (2) **association pathways**, and (3) **projection pathways**.

Cerebral Commissures

By definition, ***commissural fibers connect a region or area on one side of the brain either with its homologous area, or a closely related area, on the opposite side of the brain.*** This arrangement allows for rapid and effective interchange of information between the two hemispheres and has a number of important functions. First, one side of the brain often is privy to unique sensory input that may be important to share with the other cerebral hemisphere. A simple example is when we put our left hand in our pocket to find something. The sensory feedback via the dorsal columns, medial lemniscus, and ventral posterior nucleus of the thalamus initially is directed to the right hemisphere only. Literally, if the right hand is to know what the left one is doing, this must be accomplished through the commissures.[12] As will be discussed shortly, one hemisphere may be better adapted to perform certain behavioral or cognitive functions (the leading or “dominant” hemisphere for that function). Thus, if the hand ipsilateral to the hemisphere that is “dominant” for a particular function wishes to assist in performing that function, the information or directions about how best to carry out such tasks needs to be conveyed to the contralateral hemisphere (the one controlling the hand ipsilateral to the "dominant" hemisphere). As we shall see, ideomotor apraxia provides a good example of such specialization and interhemispheric communication.

In addition to taking a leading role in directing different aspects of either our internal or external experiences, each hemisphere also seems to process information in very different ways. This duality serves a complementary function and provides for a greater richness of experience. Examples might include "semantic" versus "prosodic" (affective) components of speech and language, or focusing on "gestalt" versus "local" internal details in constructional abilities. In these cases, each hemisphere makes unique contributions to the total behavioral response. Since efficient behavior typically requires an integration of both types of information, communication between the hemispheres is essential. One such purpose may be to maintain some type of internal or experiential balance. It is not uncommon to hear people talk about "right-brain" versus "left-brain" individuals. Theoretically, "right-brained" individuals tend to act on a "gut-level, instinctual, emotional, immediate, overall impression" basis, whereas the "left-brained" individual takes a more logical, measured, or considered approach to problems or situations. Think of it as the difference between Captain Kirk and Spock in the original *Star Trek* series. This is obviously a gross oversimplification of a very complex phenomenon. Whatever element of truth there may be to such a "right-brain/left-brain" dichotomy, in the vast majority of situations it is likely that the two hemispheres constantly interact, each contributing its own unique influence, in an effort to maintain some balance or equilibrium in terms of how we respond to our environment. Again, it would appear that the commissures are important in facilitating such communications or interactions. In some respects, the role of the commissures and the corpus callosum in particular can be dramatically demonstrated by clinical cases where there has been a substantial disruption of these crossing fibers. However, even in cases of apparently complete commissurectomies, there still is a remarkable unity of experience, suggesting other subcortical mechanisms also play an integral role in this process (e.g., Liederman, 1995). A review of some of these specific findings will be presented below under Disconnection Syndromes.

In the human brain there are a number of such commissures. The **posterior** commissure, located at the upper end of the brain stem beneath the anterior portion of the pineal body, is a rather small commissure[13] that appears to be largely involved in carrying information regarding visual reflexes. Even smaller is the **habenular** commissure, interconnecting the habenular nuclear groups on the posterior–dorsal aspect of the thalamus. The **fornical** or **hippocampal** commissure allows for interhemispheric communications among various limbic structures, particularly the hippocampus. The **anterior** commissure, another relatively small commissure that lies in the area above the optic chiasm in the third ventricle, transfers information from one anterior temporal region to comparable areas in the opposite hemisphere (see: Figure 9–16). This pathway also appears to carry olfactory information.

However, all the above commissures combined pale by comparison in terms of sheer magnitude to the **corpus callosum**, the major commissure that interconnects the two cerebral hemispheres. Lying between the lateral ventricles below and the cingulate gyrus above, in an anterior–posterior dimension, the corpus callosum stretches for approximately half the length of the cerebral hemispheres. The corpus callosum is clearly visible on coronal sections throughout its length as the large band of white matter crossing the midline immediately below the cingulate gyri (Figure 9–17). On a midsagittal section, its five divisions are clearly visualized. Beginning anteriorly, these divisions include the **genu** (knee), which represents the anterior curvature or bend of the commissure, and the **rostrum,** which is the ventral or inferior continuation of the corpus callosum. The main posterior portion that continues over the superior surface of the lateral ventricles is called the **body**, with the slight narrowing

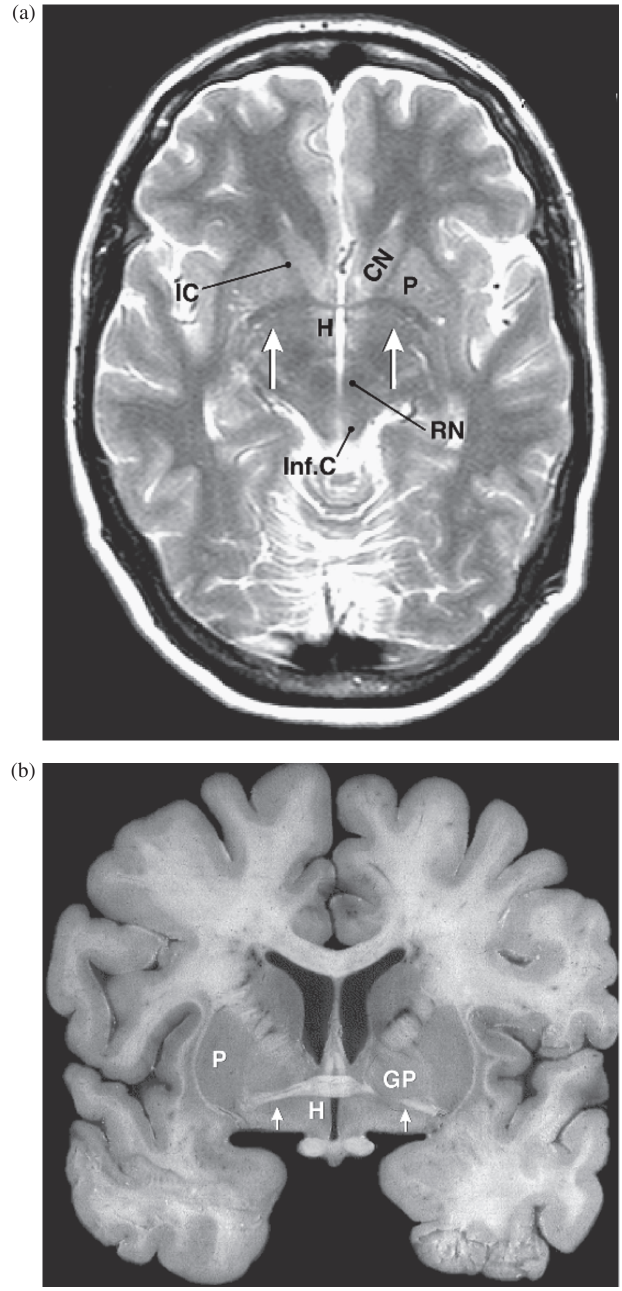
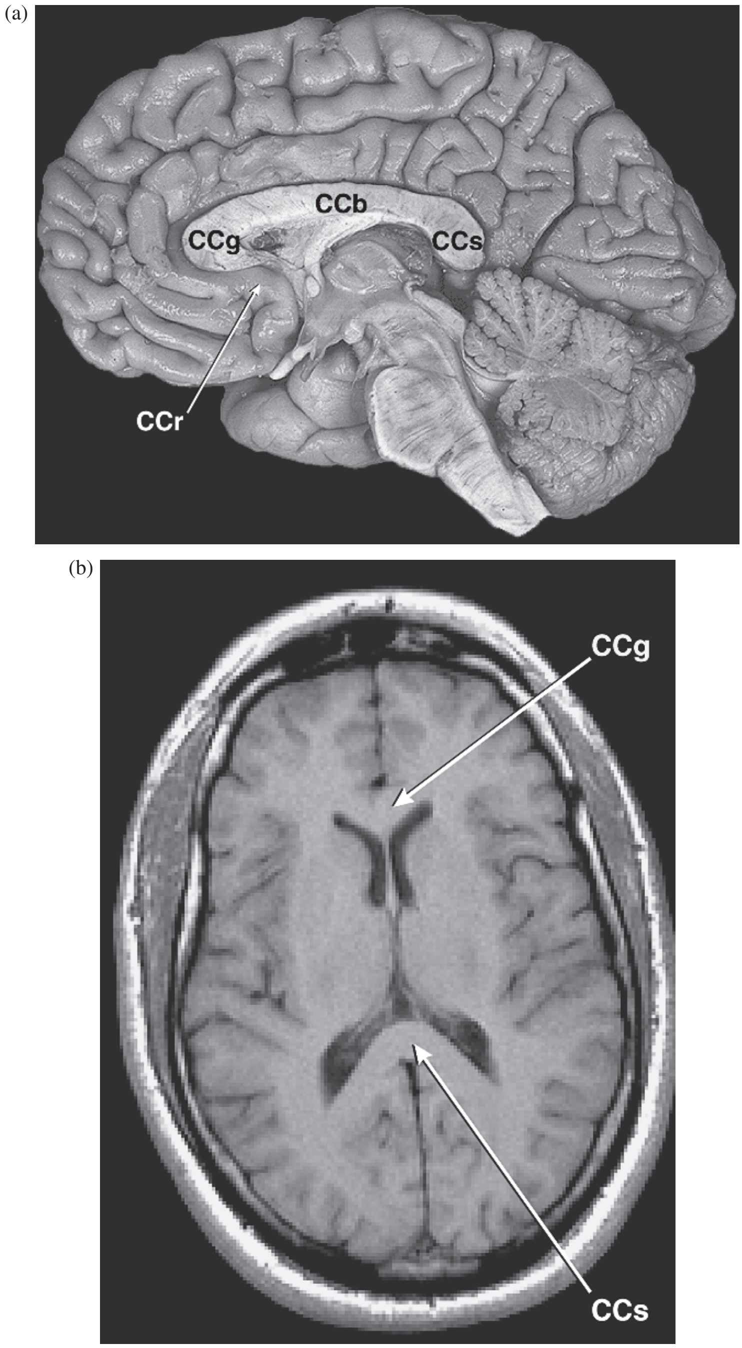


Figure 9–16. Anterior commissure as seen on (a) axial MRI and (b) coronal brain section (arrows). Note: Axial cut is at the level of the midbrain. Abbreviations: CN, caudate nucleus; GP, globus pallidus; H, hypothalamus; IC, internal capsule (anterior limb); Inf C, inferior colliculus; P, putamen; RN, red nucleus. Brain image (b) was adapted from the *Interactive Brain Atlas* (1994), courtesy of the University of Washington.

at its posterior extent being referred to as the **isthmus**. Finally, the more bulbous posterior end of the corpus callosum is referred to as the **splenium**.

For the most part, like the other commissures, the corpus callosum connects either homologous or closely related cortical areas in each cerebral hemisphere (Zaidel et al., 1990;

Zaidel, 1995). There are two notable exceptions. The primary visual cortex (BA 17) is connected with areas 18 and 19 of the opposite hemisphere. There apparently are few if any direct callosal connections between the primary visual cortices. Also, there appears to be minimal if any connection between the primary motor cortex that mediates hand movements with the comparable area in the opposite hemisphere. Actually, in retrospect, this seems quite logical. By necessity, the hands often need to function quite independently,



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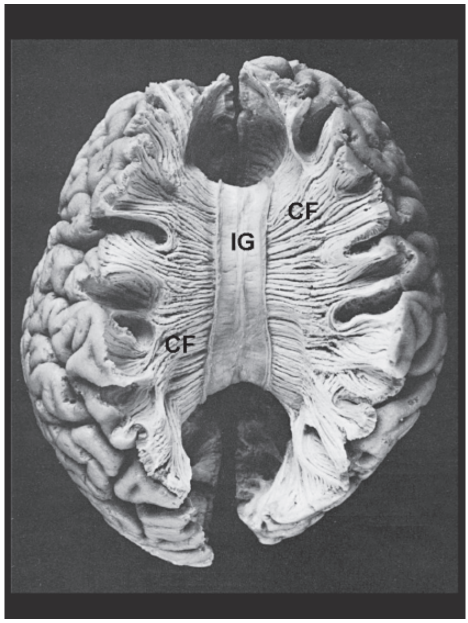

Figure 9–17. Corpus callosum as seen on (a) midsagittal brain section, (b) axial views MRI image, and (c) blunt dissection. Abbreviations: CCb, CCg, CCr, and CCs represent the body, genu, rostrum and splenium of the corpus callosum, respectively; CF, commissural fibers; IG, indusium griseum. Brain image was adapted from the *Interactive Brain Atlas* (1994), courtesy of the University of Washington. Blunt dissections (c) of the brain from Gluhbegovic, N. and Williams, T.H. (1980). Used with permission.

as witnessed in playing any number of musical instruments or other work or engaging in bimanual activities (typing on a keyboard). Too much direct feedback from one hand to the other might interfere with this independent operation. In the case of the eyes, since the two hemispheres are processing information from two visual fields, it would seem important to keep such information free from contamination.

Association Pathways

Association pathways, by contrast, interconnect different parts of the same hemisphere. Such association pathways may be very long, in which case they are typically termed *fasciculi*. In other instances, they may be relatively short, perhaps simply consisting of U-shaped (*arcuate*) fibers connecting one gyrus with an adjacent gyrus, or lateral or horizontal connections within the gyrus itself (e.g., *bands of Baillarger*). Just as it is important for one hemisphere to share information with the other, it also is important that different areas within the same hemisphere be in communication with one another. For example, it may be simply a matter of the cortical motor neurons that control the movements of the fingers in using a screwdriver needing sensory feedback (e.g., stereognosis, pressure or resistance, proprioception, kinesthesia, and visual alignment with the screw). On perhaps a more complex level, the prefrontal cortex requires access to ongoing, current (perception) and previous (memory) information in the planning and execution of a response. In either case, there has to be some mechanism for getting this information from one part of the hemisphere to another. This is probably accomplished, for the most part, by association fibers.

Any attempt to provide a detailed description of all such association pathways, given their complexity and the fact that some are still poorly defined, would be impractical if not impossible. For our present purposes, it is sufficient to outline a few of the major identified fasciculi. What is critical is for the reader to develop some appreciation of the presence of these intrahemispheric connections (both short and long), the general functional purposes they serve, and the potential effects that lesions of these pathways can exert on behavior. And their general locations can be seen in Figure 9–18a. These pathways generally are conceived as interconnecting the more anterior portions of the brain with more posterior parts. While this is indeed correct, it also should be noted that many fibers likely enter

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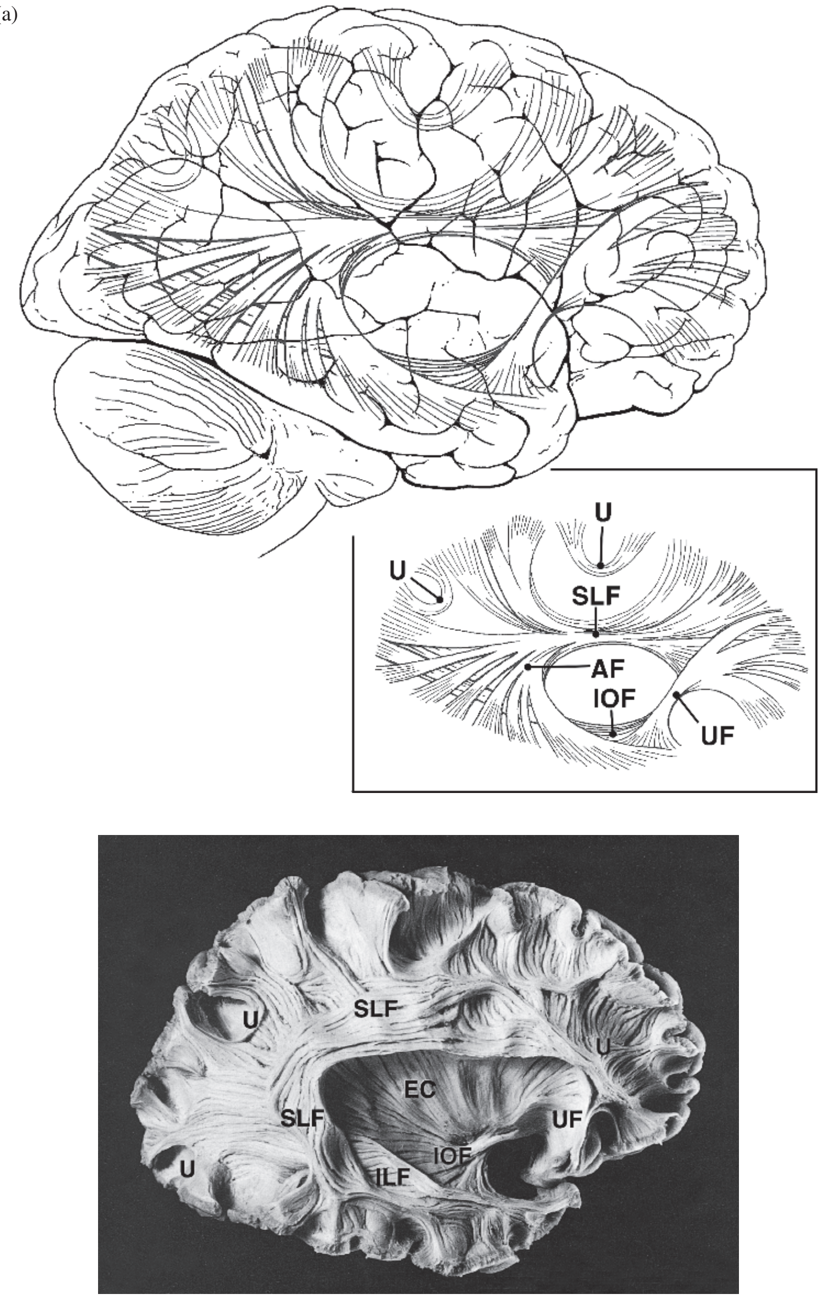

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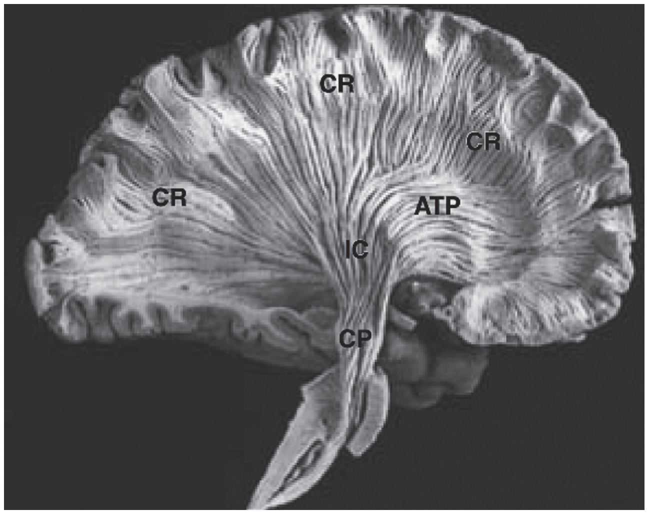

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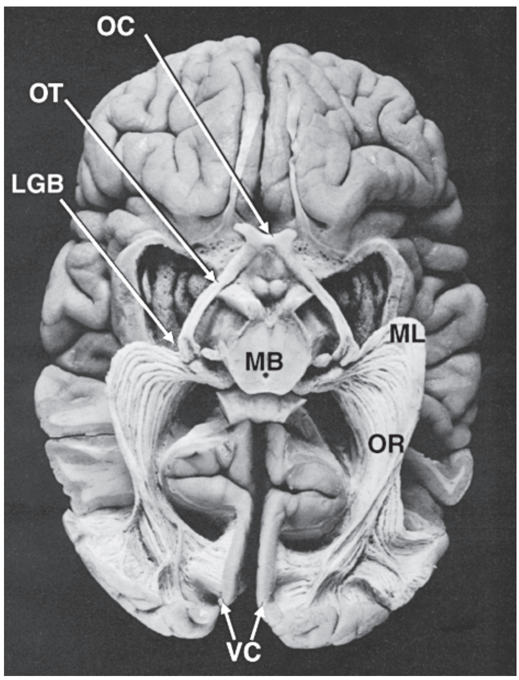


Figure 9–18. Association and projection pathways. Schematic drawing and photographs showing (a) association pathways within the brain, (b) coronal radiata forming the internal capsule, and (c) optic radiations (a major projection pathway). Abbreviations: AF, arcuate fasciculus; ATP, anterior thalamic peduncle; CP, cerebral peduncle; CR, coronal radiata; IC, internal capsule; ILF, inferior longitudinal fasciculus; IOF, inferior occipitofrontal fasciculus; LGB, lateral geniculate body; MB, midbrain; ML, Meyer's loop; OC, optic chiasm; ON, optic nerve; OR, optic radiations; OT, optic tract; SLF, superior longitudinal fasciculus; U, U-fibers; UF, uncinate fasciculus; VC, visual cortex. Photographs are adaptations of blunt dissections of the brain from Gluhbegovic, N. and Williams, T.H. (1980). Used with permission.

and exit throughout the course of these fasciculi. These fibers connect the frontal lobe with the parietal, posterior temporal, and occipital lobes, or the frontal with the temporal and occipital lobes. One such fasciculus is the rather prominent **superior longitudinal fasciculus**, portions of which are referred to as the **arcuate fasciculus**, and as we shall see, may be involved in the disconnection syndrome of conduction aphasia, as well as in some aspects of ideomotor apraxia. The **uncinate fasciculus**, which travels with the more anterior portions of the **inferior occipitofrontal fasciculus**, interconnects the more ventral and orbital frontal cortices with the anterior temporal regions. There is also a **superior occipitofrontal fasciculus,** which on a coronal section can be seen dorsolateral to the head of the caudate nucleus. Another large association pathway that previously was discussed is the **cingulum**. This pathway connects the frontal lobes and septal regions with the cingulate gyrus and more distally with the parahippocampal areas. Finally, an **inferior longitudinal fasciculus** also frequently is described in neuroanatomical texts. However, the existence of an inferior longitudinal fasciculus, which previously was described as a direct connection between the occipital and temporal lobes, has been challenged (Tusa & Ungerleider, 1985). Instead of a long, continuous fasciculus, it is suggested that these areas are indirectly linked by a series of short, "U" fibers that interconnect various portions of the occipital and inferior temporal cortex.

Projection Pathways

The third general types of white matter pathways within the cerebral cortex are the projection fibers. Recall that commissures and association fibers basically connect one cortical area with another. Projection fibers by contrast represent connections (projections) either from the cortex to noncortical structures or to the cortex from noncortical structures. The former are descending projection pathways, while the latter represent ascending pathways. Directly or indirectly, most of the major projection pathways have been reviewed in previous discussions of the motor and sensory systems, basal ganglia, cerebellum, and thalamus. Nonetheless, a brief review may be useful. Among the projection pathways, the most prominent are the **internal**, **external**, and **extreme capsules**, **cerebral peduncles**, and **optic radiations**. The **internal capsule** (see Chapter 7 for more detail on its internal structure) consists of both ascending and descending fibers. The descending fibers include projections to the neostriatum (caudate nucleus and putamen). The **cerebral peduncles** represent a caudal continuation of the internal capsule (see Figures 9–18b and 1–6b). They consist of corticobulbar, corticopontine, and corticospinal fibers that mostly end up on various brain stem nuclei, in the cerebellum (after synapsing with the pontine nuclei), or on the anterior horn cells of the spinal cord. Ascending fibers within the internal capsule represent the various thalamocortical projections. Recall that, with the possible exception of olfaction, all information we obtain from the outside world is funneled to the cortex via the thalamus. Even the cerebellum, basal ganglia, and other subcortical structures involved in the control of movement project back to the cortex via the thalamic nuclei.[14] A major thalamocortical projection pathway are the **optic radiations**. As was seen in Chapter 05, the optic radiations represent the visual pathways from the lateral geniculates to the primary visual cortices on the banks of the calcarine sulci (see Figures 9–18c and 5–5).

These various projection pathways, similar to the commissures and the long association fibers, tend to consist of both tight, compact bundles as well as flared arrays of fibers. The descending fibers start out from diffuse cortical areas and narrow as they enter the internal capsule, whereas the opposite is true for the ascending fibers. They start out, mostly from the thalamus, in a more compact arrangement and then branch out as they head to their cortical destinations. This flaring out is what constitutes the **coronal radiations**. By contrast, the commissures and the projection fibers tend to form more compact bundles in the middle of their course and diffuse out at each end. The reason for emphasizing this general feature is that if damage occurs where these fibers of passage are more densely packed, the resulting behavioral deficit can be quite substantial, even from a small lesion. One common example is hemiplegia following a lacunar infarct in the posterior limb of the internal capsule. Figure 9–19 illustrates all three types of pathways in an axial brain section.

While we tend to think of lesions of projection fibers as producing motor or sensory deficits, they in fact can produce a whole host of behavioral deficits. For example, white matter lesions that undercut thalamofrontal connections may result in a *frontal lobe syndrome*, whereas disconnections between the temporal, parietal, or occipital lobes and the thalamus may lead to symptoms of aphasia, neglect, or other sensory–perceptual disturbances. As was discussed in Chapter 5, homonymous quadrantic visual field cuts commonly are associated with lesions that encroach on the optic radiations. Although the term *disconnection syndrome* most commonly is applied to disruptions of the commissures or association pathways, in effect lesions of the projection pathways also may be viewed as a type of disconnection as well. In this case, they disrupt the normal communications between the cortex and

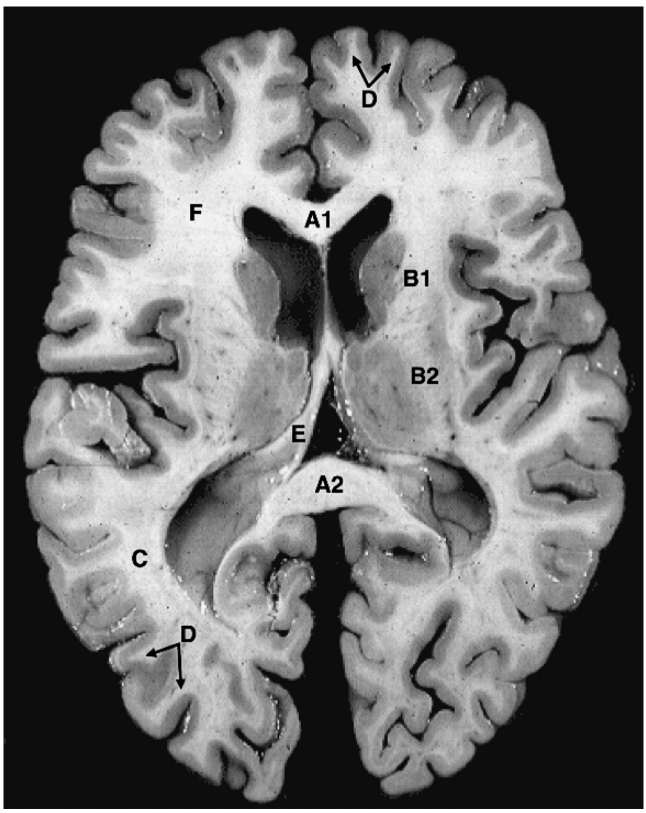


Figure 9–19. Commissural, association, and projection pathways evident in this axial view through the thalamus. (A1) genu and (A2) splenium of the corpus callosum. (B1) anterior and (B2) posterior limbs of the internal capsule, (C) optic radiations, and (E) fornix all represent projection pathways. (D) Marks short arcuate (association) fibers connecting adjacent gyri. The (F) ventral extension of the centrum semiovale is essentially a mixture of commissural, association and projection fibers. Brain image adapted from the *Interactive Brain Atlas* (1994), courtesy of the University of Washington.

the subcortical, brain stem, or spinal nuclei, and thus produce functional deficits without necessarily directly impinging on gray matter.

DISCONNECTION SYNDROMES

If one of the basic assumptions in neuroanatomy is that different areas (parts) of the brain subserve different functions, for complex behavior to occur it is essential that these areas communicate with one other. The exact nature of this communication still is unclear. One possibility is that some aspect of the information that is processed in one area(s) is conveyed or transferred to another area(s) of the brain, which in turn further processes this integrated information in the context of other information it has received from yet other parts of the brain or nervous system. As this process is repeated, multiple brain areas are recruited (either simultaneously or successively), leading to an integrated response (Goldman-Rakic, 1988).[15]

Another and seemingly more likely hypothesis is that rather than an actual "transfer" of information from one part of the brain to another, there is a unique linkage (temporal–spatial integration) of various areas of the brain, which is specific to the current condition of the organism, stimulus, or stimulus–response pairing. Such temporal–spatial patterns then may be evoked and/or combined with other patterns in subsequent situations as stimulus conditions warrant (see, for example, Liederman, 1995). Regardless of the actual mechanisms involved in the recruiting of diverse brain areas to produce an integrated response, central to both these hypotheses are that different areas of the brain must be in communication with one another. The integrity of the long axonal pathways is critical to this process. Earlier in this chapter three general types of long axonal pathways within the brain were discussed: commissures, association, and projection pathways. Disconnection syndromes result from the disruption of these pathways, effectively shutting off communication between or among areas that they normally interconnect. However, traditionally it is only when corticocortical connections are involved (i.e., commissures or association pathways) that the term *disconnection syndrome* has normally been applied.

Lesions producing such syndromes may result from any of a number of neurological conditions, although disconnection syndromes most frequently are associated with strokes and tumors. Some of the more dramatic cases have been the result of surgical lesions, especially the so-called *split brain* studies in which the corpus callosum is cut, typically in cases of severe and intractable seizure disorders to prevent the spread of excitation from one hemisphere to the other. Occasionally, there are individuals in whom there is an agenesis of the corpus callosum. Interestingly enough, such individuals rarely show evidence of a disconnection syndrome, perhaps because of the enhancement of other pathways (e.g., anterior commissure) or greater bilateral representation of function (Bogen, 1993).

Although the basics of disconnection syndromes were established very early in the history of neurology, the modern appreciation of this phenomenon largely was advanced by Geschwind's paper entitled, "Disconnexion Syndromes in Animals and Man" (Geschwind, 1965). While theoretically at least there may be a large number of disconnection syndromes, for illustrative purposes only those that are most commonly recognized will be discussed here. These include ideomotor apraxia, alexia without agraphia, conduction aphasia, and callosal transections (split-brain preparations).

Ideomotor Apraxia

First described around the turn of the 20th century, ideomotor apraxia may result from lesions of either association or callosal fibers, although its expression will be somewhat different depending on the actual site of the lesion. Ideomotor apraxia is defined as an ***inability to carry out a discrete, previously learned, skilled movement, most commonly to verbal command, in the absence of any primary language or sensorimotor deficits.*** Such commands typically involve asking the patient to carry out either a transitive (e.g., demonstrating the use of a tool) or intransitive (e.g., a symbolic gesture) action using either the upper extremities or buccofacial musculature. Examples might include demonstrating the use of a hammer or screwdriver, sucking through a straw (transitive gestures), or saluting or sneezing (intransitive). The disturbance at times may be somewhat subtle, as evidenced by a distortion of fine, distal movements or improper orientation of the hand when demonstrating the use of a screwdriver. Typically tested in the absence of the actual object, performance may improve if the object is provided.

To provide a brief and very schematic review of the neuroanatomy of ideomotor apraxia, consider the following command: "Show me how you would use a hammer with your left hand." Assuming normal patterns of dominance, according to Heilman and Rothi (1993) the following systems not only must be in place and working, but must be in communication with one another:

1. Auditory input and comprehension (Heschl's gyrus and left superior temporal gyrus).
2. Memory engrams for the particular motor skill (left inferior parietal lobule).
3. Left motor association area (premotor cortex).
4. Right motor association area.
5. Right motor cortex.
6. Corticospinal projection fibers.[16]

Thus, lesions affecting the arcuate fasciculus, an association pathway connecting parietotemporal and frontal cortices, potentially could result in a bilateral apraxia, as the cortical areas thought to be responsible for the sensorimotor engrams governing these skills are "disconnected" from the frontal motor cortices. The latter are hypothesized to be essential in their final organization, initiation, and/or execution.

In contrast, a lesion affecting callosal fibers connecting the left motor association area to the homologous area in the right hemisphere may result in an isolated left-sided apraxia. In this latter case, since the information regarding both the command and the sensorimotor template for these actions can be communicated to the left motor association cortex, the right hand would be able to carry out the requested action. Because the right motor association cortex is dependent on the specific information (or cooperation) from the left hemisphere via the callosal fibers from the left motor association cortex, the left hand will be unable to properly execute the task to verbal command alone. However, it may improve with imitation or if the actual object is provided. The left hand may carry out other spontaneous actions with little or no apparent difficulty.

Finally, in the case of lesions encroaching on the left motor association areas, as is frequently seen in Broca's aphasia, it is not uncommon to find right-sided weakness and left-sided ideomotor apraxia. This is consistent with the scenario described above where the right motor association areas are dependent on the integrity of their counterparts on the left. The presumption is that if it were testable, the right hand would show similar deficits. Although they arrive at slightly different conclusions regarding the cortical areas primarily responsible for the storage and/or initiation of the motor engrams responsible for the learned actions tested in ideomotor apraxia, both Geschwind (1975), as well as Heilman and Rothi (1993) and Heilman, Watson, and Rothi (1997) provide excellent, detailed descriptions of this particular disconnection syndrome. Figure 9–20 summarizes this schema as outlined by Heilman and his associates.

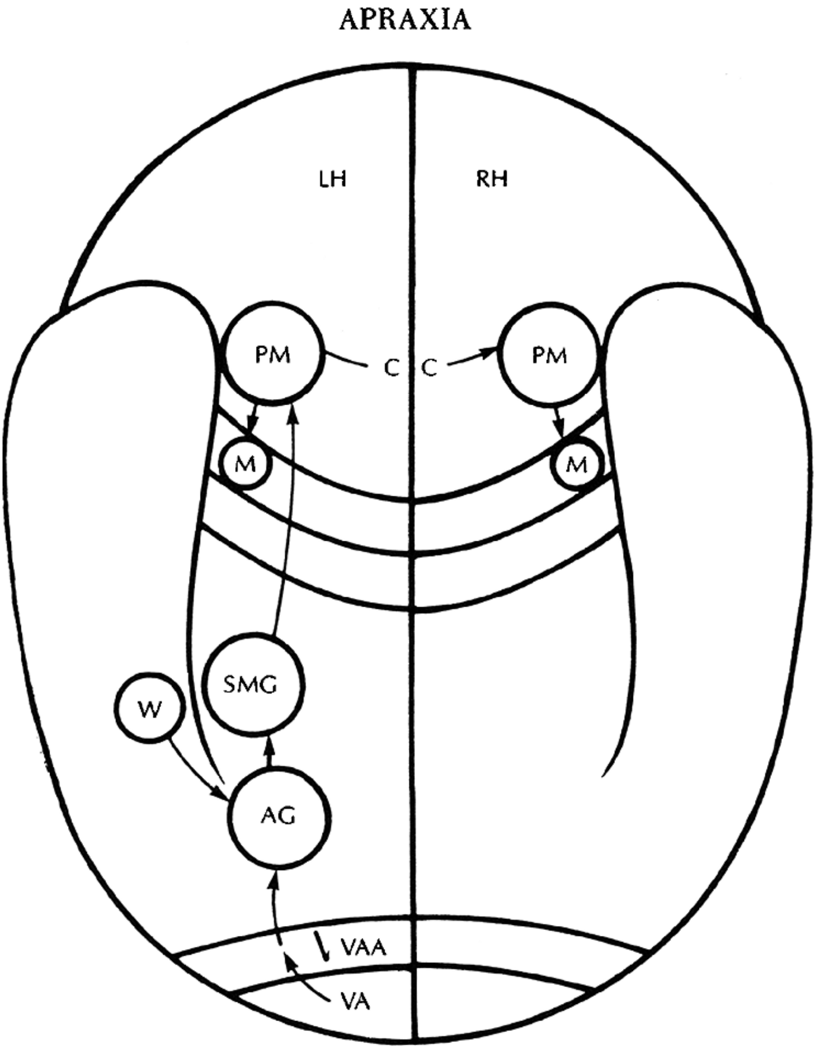


Figure 9–20. Drawing of the major pathways thought to be involved in ideomotor apraxia. From Heilman and Valenstein (2003), with permission of the author. Abbreviations: AG, angular gyrus; CC, corpus callosal fibers; LH, left hemisphere; M, primary motor area; PM, premotor area; RH, right hemisphere; SMG, supramarginal gyrus; VAA, visual association area; VA, primary visual cortex; W, Wernicke's area.

Alexia without Agraphia

Dejerine recognized this disconnection syndrome as early as the late 1800s. Generally the result of an infarction of the left posterior cerebral artery (see Chapter 10), this syndrome typically results from a lesion of the **splenium** of the corpus callosum and the left (or language-dominant) occipital cortex, the latter resulting in a right homonymous hemianopia (Geschwind, 1965; Damasio & Damasio, 1983). The patient retains the ability to write because the left temporal, parietal, and frontal cortices essential to this process remain intact. However, the input of lexical information is limited to the right hemisphere (because of the right visual field deficit) and this information cannot be shared with or communicated to the left temporal speech areas for decoding because of the disconnection of the relevant callosal

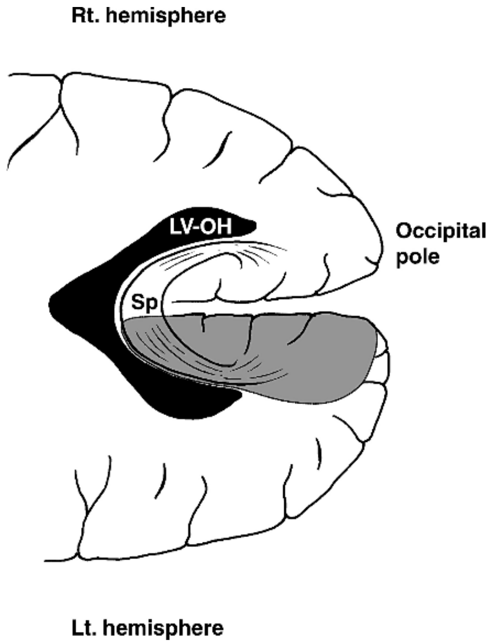


Figure 9–21. General location of lesion typically associated with the syndrome of alexia without agraphia (dominant visual cortex and splenium of corpus callosum). Abbreviations: LV-OH, occipital horns of the lateral ventricles; Sp, splenium of the corpus callosum.

pathways (see Figure 9–21). Hence, the patient is able to write, but if later presented is unable to read what he or she has written. Interestingly enough, the patient may have little or no difficulty naming objects seen by the right occipital cortex. One possible explanation is that other association pathways may be utilized in object recognition that proceed more anteriorly before making trans-hemispheric, callosal connections.

Conduction Aphasia

One classic aphasic disorder that frequently has been associated with a disconnection syndrome is conduction aphasia. This disorder is characterized primarily by marked disturbances of repetition in the presence of reasonably intact (or at least relatively better) language comprehension, adequately articulated speech with abundant literal paraphasic errors, and disturbances of confrontation naming. The decoding of auditory verbal input into phonetically meaningful units (e.g., phonemes, words) appears to take place largely in the temporal areas surrounding Heschl's gyrus or the primary auditory cortex. In order to repeat what was heard, perceived speech must be converted into phonological codes and conveyed to the area of the frontal operculum. The arcuate fasciculus was thought to be one of the critical pathways over which this information is communicated, and if interrupted, repetition deficits might occur (Geschwind, 1965) (see Figure 9–22). However, identifying the anatomical basis for this disorder has proved not to be that simple. While lesions affecting the arcuate fasciculus were believed to be associated with conduction aphasia, this was not always found to be the case (Albert et al., 1981, Benson, 1979, 1993; Benson & Geschwind, 1985); more recently, Damasio et al. (2000) have suggested that at least one of two cortical areas (the supramarginal gyrus or the dominant primary auditory cortices) are typically compromised.

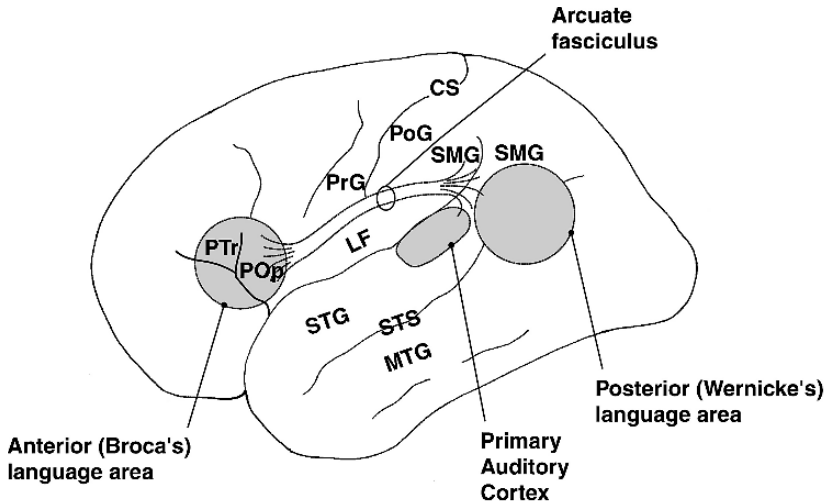


Figure 9–22. General language areas associated with conduction aphasia. Lesion most commonly thought to involve arcuate fasciculus, supramarginal gyrus, and/or primary auditory projection areas. Abbreviations: CS, central sulcus; LF, lateral fissure; MTG, middle temporal gyrus; PoG, postcentral gyrus; Pop, inferior frontal lobe, pars opercularis; PrG, precentral gyrus; PTr, inferior frontal lobe, pars triangularis; SMG, supramarginal gyrus; STG, superior temporal gyrus; STS, superior temporal sulcus.

Conduction aphasia might be contrasted with two other classic aphasic syndromes: Wernicke's and transcortical sensory aphasias. While repetition similarly is compromised in Wernicke's, comprehension is usually no better, if not worse. In the latter, the connections between the secondary auditory association areas and the frontal cortex are presumed to be intact. However, either the connection between the secondary auditory association area and the semantic association areas of the posterior temporal regions (and/or the semantic association areas themselves) are thought to be disrupted. Thus, in transcortical sensory aphasia, repetition is relatively intact, while by contrast auditory comprehension notably is impaired.

Callosal Syndromes

When discussing disconnection syndromes, the most fascinating examples probably are those provided by the split-brain studies of Gazzaniga, Bogen, and Sperry (1962, 1965, 1967). This procedure typically involves the severing of all or part of the corpus callosum and occasionally other commissural fibers as well. For some time this procedure was thought to have no significant behavioral consequence as many patients failed to evidence noticeable change in their normal activities following the early recovery period (Akelaitis, 1944). However, in the early 1960s Bogen, Sperry, and Gazzaniga proved that major behavioral consequences indeed could be demonstrated if only the right questions were asked of the patient.

Initially, Bogen and his colleagues found that if information were restricted to one hemisphere (e.g., through tactual input to one hand only or to one visual field through tachistoscopic presentation), the other hemisphere did not appear to know what had taken place. For example, if an object were placed in the patient's right hand, the left hand could not retrieve its match from assorted objects. If an object or picture of an object were placed in a subject's left hand or projected to the left visual field, the patient (i.e., the left hemisphere) could not name the object, despite the fact that the left hand (right hemisphere) accurately could demonstrate its use. If the anterior commissure is also severed, the patient may be able to pick out with his left hand objects associated with a particular smell presented to his left nostril but fail to be able to name the smell.[17]

As a result of their studies, these investigators provided additional support for some of the theories of hemispheric specialization. They were able to demonstrate, for example, that the left hemisphere normally was dominant for language. Although the right hemisphere evidenced some capacity to comprehend simple words, it could not initiate speech or produce intelligible spontaneous writing.

Following such surgical disconnections, while the left hand is likely to evidence ideomotor apraxia, it also is likely to perform better than the right in tests of visual–spatial constructional ability. Again, this would suggest right hemisphere superiority for these tasks. Most of these findings, along with specific suggestions for examining patients suspected of having callosal syndromes, are described in greater detail by Bogen (1993).

If all this appears fairly straightforward and predictable, consider the studies by Cronin-Golomb (1986) and Sergent (1987). Here "split-brain" patients were presented with independent visual stimuli to each hemifield. If asked whether the two stimuli were identical or not, the patients were unable to respond above chance. However, if asked to arrive at some judgment regarding the two stimuli, such as whether they were categorically related (e.g., a shoe and a sock) or whether the total number of dots in both hemifields combined were greater or less than 10, the patients performed reasonably well. This was despite the fact that they still could not verbalize what stimuli had been presented to their left visual field! Although Liederman (1995) interprets these findings as evidence of subcortically mediated, implicit awareness, others have discounted the reliability or validity of such findings (Corballis, 1994; Kingstone & Gazzaniga, 1995).

Reconsider the studies of Downer (1961) with macaque monkeys discussed in Chapter 8. Using split-brain preparations in which the optic chiasm also was cut (sagittally), thus restricting vision in each eye to the ipsilateral hemisphere, these monkeys were subjected to unilateral temporal lobectomies. Macaques normally do not particularly care for humans and frequently become agitated when they come into view. However, Kluver and Bucy (1939) had demonstrated that following bilateral temporal lesionsthese monkeys tended to be docile in the presence of humans (as well as showing indifference to a variety of other previously frightening stimuli). If the monkeys in Downer's study were fitted with a patch over the eye ipsilateral to the temporal lesion and then exposed to humans, they responded like a normal macaque (e.g., showed signs of agitation). However, if the eye ipsilateral to the lesion were the only one left uncovered, they remained placid at the sight of humans. Do such animals have one or two brains? In his chapter cited above, Bogen (1993) reports how in some instances the two hemispheres (when disconnected) appear to be working at cross-purposes or with "two minds at the same time." For example, one patient reportedly was observed buttoning his shirt with one hand and unbuttoning it with the other. Yet for the most part what is intriguing is that in most situations the behavior of such individuals appears perfectly normal, with the deficits generally becoming evident only under specific test conditions.[18]

Finally, one must attempt to resolve the discrepancies between naturally occurring and surgically induced lesions. While surgical lesions of the corpus callosum routinely produce the symptoms described above, naturally occurring agenesis of the corpus callosum does not. In contrast, naturally acquired lesions of the anterior portion of the corpus callosum (e.g., stroke, tumor) often lead to left-sided apraxia, but surgical lesions restricted to this region fail to produce this effect (Risse et al., 1989).

These latter phenomena once again demonstrate the mysteries of the nervous system. Again, the possible organization and integrated operation of the brain will be discussed from a broader perspective in Part III. The reader is forewarned, the goal will not be to provide definitive answers, but rather to offer a heuristic model that may lead to a better appreciation of the complexities of brain-behavior relationships and hopefully generate a conceptual framework with which clinical problems can be approached. For now, attention will be turned to structural and functional asymmetries.

HEMISPHERIC SPECIALIZATION

Anatomic Asymmetries

The existence of functional asymmetries in the human brain has been accepted as an axiomatic principle in neurology for well over a century. It commonly is accepted that the left hemisphere is specialized for language and other symbol-based functions and is probably the leading hemisphere in carrying out certain skilled motor activities and in mediating certain aspects of body awareness (body schema). In contrast, the right cerebral hemisphere seems to be specialized for *nonverbal*[19] functions, including directed attention, emotional–affective processing, certain aspects of musical abilities and in particular visuospatial or visuoperceptual abilities. However, as will be seen, while this dichotomy works reasonably well for most right-handers, the situation becomes more complicated with left-handers and there also appear to be gender differences (for review, see Hellige, 1993; Molfese & Segalowitz, 1988; Geschwind & Galaburda, 1984). With the advent of more reliable neuroradiographic and neurobehavioral techniques for in vivo investigations of the brain, it has become increasingly apparent that there often is considerable individual variation in the structural and functional organization of the cerebral hemispheres. Before exploring functional hemispheric differences, it may be helpful to explore what currently is known regarding structural hemispheric differences.

Postmortem Studies

Although cerebral dominance has been studied for over 140 years, the neuroanatomical substrates for lateralized behaviors have received only recent and relatively scant attention. At the turn of the 20th century, anatomists observed some measurable gross anatomical asymmetries of the lateral sylvian fissure and language-related cortical areas (von Economo & Horn, 1930; Eberstaller, 1890; Cunningham, 1892; Pfeifer, 1936). In fact, some of these anatomists were reporting these asymmetries at the same time that neurobehaviorists like Paul Broca and Carl Wernicke were advocating that functional brain asymmetries existed. The anatomists, however, generally felt that the gross asymmetries observed were not significant enough to account for the suspected behavioral asymmetries. It was not until 1968 that anatomical asymmetries of language-related cortex were proposed to be related to known functional asymmetries. Geschwind and Levitsky (1968) measured the **planum temporale** (Figure 9–23), which constitutes part of Wernicke's area, in 100 postmortem brains and found that the left planum temporale was larger in 65% of the brains studied compared to only 11% in which the right was larger. Although individual language dominance and hand preference was unknown in their sample, given that language is functionally lateralized to the left hemisphere in most right-handed individuals, Geschwind and Levitsky proposed that the asymmetry of the planum temporale was compatible with the known functional asymmetries, and therefore might represent the neuroanatomical substrate for language. This notion is supported by the fact that the planum temporale encompasses both auditory association areas, which are important in higher-order processing of language input and part of Wernicke's area, which when lesioned produces fluent aphasia with impaired comprehension, repetition, and naming. In addition, subsequent studies (Tezner et al., 1972; Witelson & Pallie, 1973; Wada, Clarke, & Hamm, 1975; Galaburda et al., 1987)

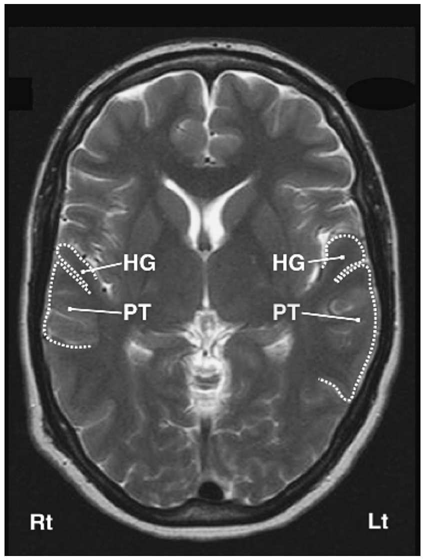


Figure 9–23. Approximation of the planum temporale (PT) in an axial MRI showing the asymmetry between right and left hemispheres. Also shown is Heschl's gyrus (HG).

have replicated Geschwind and Levitsky's findings and demonstrated that the predominant leftward asymmetries of the planum temporale exist as early as the 29th gestational week. The finding that asymmetries of speech-related cortex are present before language acquisition suggests that the human brain has biologically determined, anatomical substrates that are preprogrammed for the asymmetric representation of speech–language functions in most right handers.

The asymmetries of the planum temporale reflect in part asymmetries of the lateral sylvian fissure. As described earlier in the section on cerebral sulci and gyri, the sylvian fissure has five segments (see Figure 9–9). The longest segment is the posterior horizontal ramus (PHR) of the sylvian fissure. The length and distribution of this segment has been measured in studies of asymmetries of the sylvian fissure as far back as the 19th century. Specifically, in a majority of cases studied, the **left posterior horizontal ramus** (PHR) was found to be longer on the left (Eberstaller, 1890) and less angled than the PHR on the right (Cunningham, 1892). More recently, in examining 36 postmortem brains, Rubens, Mahowald, and Hutton (1976) confirmed the asymmetries of the PHR reported by these earlier investigators and demonstrated that these sylvian fissure asymmetries were related to asymmetries found in the planum temporale and in the inferior parietal lobule. It is reasonable to assume that these asymmetries of the sylvian fissure and adjacent cortical areas provide the anatomical substrate not only for language, but perhaps for other hemispheric functional differences as well. For example, there is a relative expansion of the anterior portions of the parietal operculum and a reduction in the posterior portions of the parietal operculum in the left cerebral hemisphere when the sylvian fissure is longer in the left hemisphere. In contrast, the parietal operculum is enlarged posterior to the sylvian fissure in the right hemisphere due to the shorter sylvian fissure length and more angled terminal upswing to the sylvian fissure (Figure 9–24). These hemispheric differences in asymmetries of anterior and posterior portions of the parietal operculum appear to support the notion that the enlarged anterior left parietal regions may be more crucial for left hemisphere dominant functions, such as language and praxis. In contrast, the enlarged posterior portions of the

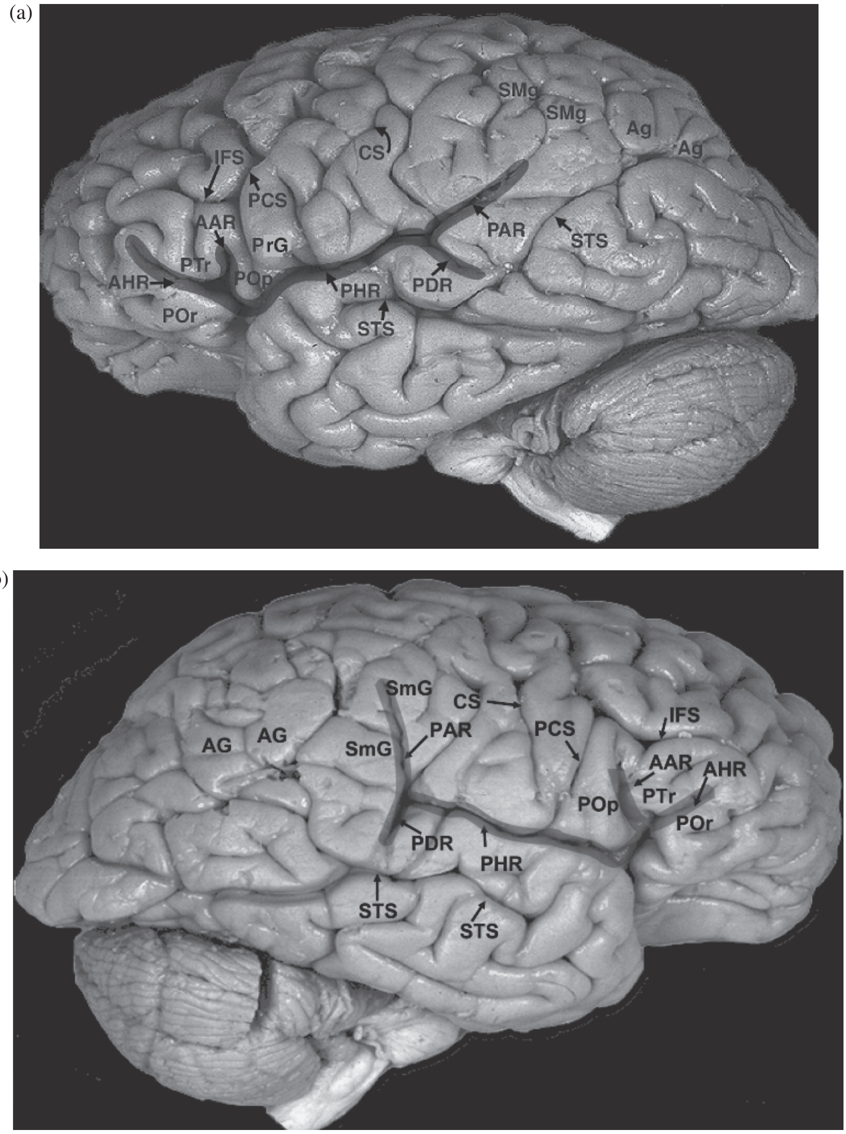


Figure 9–24. As illustrated in the figure, the most noticeable difference in the lateral fissure between the two hemispheres is the sharper rise in the posterior ascending ramus in the (b) right hemisphere. Abbreviations: AAR, anterior ascending ramus; AHR, anterior horizontal ramus; PAR, posterior ascending ramus; PDR, posterior descending ramus; PHR, posterior horizontal ramus (see Figure 9–8 for additional keys). Brain images adapted from the *Interactive Brain Atlas* (1994), courtesy of the University of Washington.

right parietal operculum may be more important in visuospatial and attentional systems, which are more commonly lateralized to the right hemisphere.[20]

Anatomical asymmetries of the frontal operculum have been more difficult to study. Eberstaller (1890) first described in detail the anatomy and complex morphology of the rami that comprise the inferior frontal gyrus. He noted that the frontal operculum is highly convoluted and that the lateral surface anatomy may not reflect the true relationships of the rami that form the frontal, language-related cortex. Before asymmetries of this region are discussed, the anatomical boundaries of Broca's area need to be described. As also can be seen in Figure 9–24, the inferior frontal gyrus is divided into three constituent parts by the anterior rami of the sylvian fissure: **pars opercularis**, **pars triangularis**, and **pars orbitalis.** Broca's area is composed of two adjacent regions: **pars triangularis** and **pars opercularis**. Pars triangularis (Brodmann's area 45) is bounded superiorly by the inferior frontal sulcus, inferiorly by the anterior horizontal ramus (AHR), and posteriorly (caudally) by the anterior ascending ramus (AAR). Thus, the base of the "triangle" is formed by the inferior frontal gyrus and the sides are formed by the AHR and AAR. The size of pars triangularis depends on the angle that these rami form with each other. Within the angle formed by the AHR and AAR, there may be two or more sulci that reach the surface and give this region the appearance of multiple convolutions within the larger triangular gyrus. Pars opercularis (Brodmann's area 44) is located adjacent to the pars triangularis but in a more caudal or posterior location. Pars opercularis is bounded superiorly by the inferior frontal sulcus, anteriorly by the AAR, and posteriorly by the precentral sulcus. In many cases, pars opercularis is divided into halves by the diagonal sulcus, which is a branch of the sylvian fissure. In some cases the diagonal sulcus is absent or branches directly from the AAR. The foregoing discussion illustrates the complex morphology of Broca's area. Given that the planum temporale, which constitutes part of the posterior speech region (Wernicke's area) is anatomically a flat triangular plane on the surface of the superior temporal gyrus, asymmetries in the latter have been easier to measure. In contrast, attempts to measure asymmetries in Broca's area have met with more limited success, although the pattern of gyrification of the third frontal convolution was noted to be more elaborate and perhaps deeper in the left hemisphere on postmortem brains (Wada, Clarke, & Hamm, 1975; Falzi et al., 1982; Nikkuni et al., 1981; Albanese et al., 1989). These findings were suggestive that an anatomical asymmetry existed in the region of Broca's area such that the total surface area of this region was larger in the left hemisphere. This again would support the notion that this area on the left is critical for some aspects of speech–language functions.[21] For additional reviews of this subject, see Witelson and Kigar (1988).

In Vivo Studies

Anatomical asymmetries derived from post-mortem brains have contributed significantly to our understanding of anatomical brain asymmetries of language related cortex that probably reflect some aspects of hemispheric specialization for language functions. However, two major limitations to these studies are the uncertain correlation between structural asymmetry and lateralization of language function in any given case and the need to wait for the individual to die before the brain could be studied. In order to overcome these limitations, a noninvasive way to study structural differences in individuals while they were alive and a way to more definitively document language lateralization (and handedness) were needed. While handedness easily can be established for most individuals, language was another matter. The advent of the Wada procedure in 1949 (see Wada & Rasmussen, 1960) was one solution to part of the problem. By selectively injecting a barbiturate into one of the internal carotid arteries, and hence selectively sedating one cerebral hemisphere, it was possible to derive a reasonably reliable estimate of the leading hemisphere for language functions. The other factor in the equation was to find a way to visualize the brain in the patient while he or she was still alive. The development of pneumoencephalography, cerebral angiography, and particularly advanced radiographic techniques, such as computerized axial tomography in the 1970s and magnetic resonance imaging scans in the 1980s, provided investigators with the necessary tools. By combining these methodologies (brain imaging and Wada testing), it became possible to explore these structure–function relationships more directly.

Pneumoencephalography, a radiographic method that involves injecting air into the ventricular system and then radiographically visualizing the contours of the lateral ventricles on lateral or coronal views was one of the earlier techniques available for visualizing the brain. Although the clinical information provided by the pneumoencephalograms was rather limited, early studies demonstrated asymmetries of the occipital horns of the lateral ventricles. The most common pattern was a longer left occipital horn in right-handed individuals (McRae, 1948). However, McRae, Branch and Milner (1968) failed to demonstrate any relationship between language dominance determined by selective hemispheric anesthesia (Wada testing) and occipital horn length. Two possible explanations were suggested. First, it was noted that the exact length of the occipital horns derived from pneumoencephalography might be unreliable in some cases due to difficulty in visualizing the anterior extent of the lateral ventricles. Second, the patient population was composed of individuals with intractable epilepsy who may have had early brain injury that resulted in anomalous brain organization or reorganization of biologically preprogrammed of language functions.

Cerebral angiography was another investigative tool. A lateral view of the arterial phase of the middle cerebral artery (MCA) provides an estimate of the length, angle, and morphology of the sylvian fissure. Hochberg and LeMay (1975) found that this angle differed in right- and left-handers. Whereas the most common pattern in right- handers was the expected greater angulation of the right sylvian fissure, this pattern was observed in only 21% of the left-handers. These findings were thought to support the notion that "typical" patterns of asymmetry are more common in right-handers but less common in left-handers. From these data, however, it still was unclear whether these anatomical asymmetries correlated with hemispheric specialization of language.

The advent of **computerized tomography** (CT scans) and later **magnetic resonance imagery** (MRI) allowed the brain to be viewed in situ with much greater clarity and accuracy (Pieniadz & Naeser, 1984). In a series of CT scan studies, LeMay (1976, 1977) noted typical patterns of skull-based asymmetries that differed in right- and left-handers. In right-handers the most common pattern was to have a greater frontal protuberance or *petalia* on the right, with a greater occipital protuberance on the left. In contrast, left-handers less commonly exhibited this "typical" pattern and were more likely to have an "atypical" left frontal and/or a right occipital protuberance. Other investigators confirmed these handedness differences (Chui & Damasio, 1980; Koff et al., 1986). As we shall soon see (under Anomalous Dominance), atypical patterns of hemispheric dominance may offer some advantages, for example, greater recovery of acquired language disturbance following strokes.

With the development of the volume acquisition MRI, which involves the rapid acquisition of thin, contiguous images, the brain readily could be visualized in vivo in ways that previously were inaccessible using conventional CT or MRI scans or even postmortem specimens. In particular, regions of the brain, such as the planum temporale, could be accurately measured using these methodologies with techniques pioneered by Steinmetz and colleagues (1989). They were able to demonstrate that asymmetries of the planum temporale differ by hand preference, such that right-handers have an increased incidence and magnitude of leftward asymmetry (greater surface area) in contrast to left-handers who have a reduced leftward asymmetry (Steinmetz et al., 1989, 1991). Foundas and colleagues (1994) subsequently measured the planum temporale on volumetric MRI scans of patients who had selective hemispheric anesthesia (Wada testing) performed for language lateralization. A leftward asymmetry of the planum temporale was found in all 11 subjects who had language lateralized to the left hemisphere. The one subject, who had a marked rightward asymmetry of the planum temporale, had language lateralized to the right hemisphere. Although these data must be interpreted cautiously given the clinical population of patients and small sample size, these data support the notion that the planum temporale plays an important role in language dominance and that anatomic asymmetries measured on volumetric MRI may predict some aspects of language dominance.

The planum temporale was not the only anatomic asymmetry that could be shown to predict language dominance using volumetric MRI measures. The depths of the convolutions that constitute Broca's area (e.g., pars triangularis) also were more accessible to measurement using the MRI than on routine postmortem investigation. Using these techniques with a group of normal right- and left-handers, Foundas, Leonard, and Heilman (1995) found that seven of eight right-handers examined had a leftward asymmetry of the pars triangularis and one had equal measures. In contrast, the pars triangularis was larger on the left in three of eight left-handers, was equal in one, and larger on the right in four of eight left-handers. Furthermore, when the pars triangularis was measured on volumetric MRI scans of patients who had undergone Wada testing for language localization, nine of the ten patients with language lateralized to the left had a leftward asymmetry of the pars triangularis. The one patient with language lateralized to the right hemisphere had a significant rightward asymmetry of the pars triangularis (Foundas et al., 1996). These data offer further evidence that cortical asymmetries (in this case, the pars triangularis) underlie some aspects of language lateralization.

Functional Specialization

Handedness

In discussing the functional aspects of hemispheric specialization, both historically and at present, probably the two concepts that most frequently come to mind are language and handedness. Hand preference is an easily observed behavior and will be discussed in some detail. Before reviewing some of the data on the relationships among handedness, language, and hemispheric specialization, it might be useful to briefly define handedness. When speaking of handedness, one is referring to the fact that one side of the body is "better" (i.e., more facile) in performing certain skilled tasks, such as writing (perhaps the most commonly used index of handedness), throwing (or kicking) a ball, and using a spoon or a fork. The implication is that this preference is a result of genetics or innate hard wiring in the nervous system rather than a practice effect or a concession to a contralateral insult or impairment early in life. However, unilateral preference is not an all-or-none phenomenon. An individual may show preferences for the use of a particular eye (e.g., when sighting a rifle), a particular ear (for listening on the phone), a particular foot (for kicking a ball), or a particular hand (when writing). Although these preferences are often on the same side in right-handers, they are dissociable. Even the preferred hand may not be consistently favored for all skilled manual tasks. This seems to be especially true of left-handers who as a group often are not consistently left-handed. In fact, it is not uncommon for left-handers to preferentially use the right hand for many unimanual tasks. Furthermore, many left-handers may be more skillful or dexterous with their "nondominant" right hand for certain activities (Satz, Achenbach, & Fennel, 1967). Although it remains to be empirically tested, it may be that the left-handers who are more *anomalous* (less consistently left-handed) also are more anomalous with regard to hemispheric specialization of language and visuospatial abilities (also see below under Concepts of Cerebral Dominance, and anomalous Dominance).

As noted above, several structural asymmetries between the cerebral hemispheres have been established. However, it is not always clear to what extent these differences may reflect dominance for language, rather than handedness per se. With regard to the anatomical bases for language, as we have seen it appears that the perisylvian "language" areas, such as portions of the inferior frontal gyrus and the planum temporale, may be enlarged and more complex on the left. Comparable findings have not been as firmly established for other primary motor areas other than those related to oral motor speech. Several investigators have studied anatomical asymmetries of cortical and subcortical structures and motor pathways that are associated with lateralized motor functions, including handedness. For example, White et al. (1994) found a trend for increased neuronal density in the area surrounding the central sulcus; Kooistra and Heilman (1988) reported that the globus pallidus was larger in the left hemisphere[22]; and Kertesz and Geschwind (1971) found an asymmetry in the crossing of the corticospinal fibers at the decussation of the pyramids (fibers from the left hemisphere tended to cross above the level of those from the right), although the reliability of the later phenomenon has been called into question by other authors (Witelson & Kigar, 1988). Asymmetries in the central sulcus (in right-handers) and the size of the pars opercularis (in both right- and left-handers) were found to be correlated with handedness using MRI data (Foundas et al., 1998a,b).While these findings may be suggestive of an anatomical correlate of handedness, the precise relationship of these reported asymmetries to lateralized motor behaviors is speculative and what constitutes the neurological basis for handedness remains a mystery. Is it a matter of increased neuronal or dendritic density, complexity of associations, an interaction of practice effects, or other factors that account for the increased skill demonstrated by the dominant hand? These are questions that remain to be investigated.

The next question to be addressed is the relationship between handedness and language localization. In 1865, Dax postulated the doctrine of cerebral dominance which contends that language is mediated by the cerebral hemisphere opposite to the preferred hand for writing. This hemisphere was considered to be the "dominant" hemisphere, while the hemisphere ipsilateral to the preferred hand was considered to be the "nondominant" hemisphere. According to Dax's doctrine, right-handers would have language lateralized to the left hemisphere, while left-handers would have language lateralized to the right hemisphere. Numerous clinical and neurobehavioral studies have demonstrated that this doctrine is not completely correct. What has been found is that indeed language is lateralized to the left hemisphere in anywhere from about 95 to 98% of right-handers (Milner, 1974; Rossi & Rosadini, 1967). However, left-handers are not the mirror image of right-handers. About 70% of left-handers have language lateralized to the left hemisphere, suggesting dissociation between hemispheric dominance for manual hand preference and language in these individuals. The hemispheric localization of language for the remaining 30% of left-handers is divided between those in whom language appears to be organized primarily in the right hemisphere versus those in whom language seems to be bilaterally represented (Herron, 1980).[23]

Nonetheless, there are more left- than right-handers with language functions lateralized to the right hemisphere or bilaterally represented, a condition referred to as anomalous dominance (Hellige, 1993; Molfese & Segalowitz, 1988; Geschwind & Galaburda, 1984). Thus, while Dax essentially was correct with regard to right-handers, there still is a fair degree of uncertainty with respect to patterns of dominance and handedness, especially in left-handed individuals.

Concepts of Cerebral Dominance

Speculation about the existence and nature of hemispheric or cerebral dominance is at least as old as speculation about functional differences between the cerebral hemispheres (Broca, 1861; Dax, 1865; Wernicke, 1874) and has remained a major focus of scientific study into the present (e.g., see Davidson & Hugdahl, 1995). The term "dominance" can be used in a more restricted or in a very broad sense. In its more classically and narrowly defined form, we refer to the dominant hemisphere, meaning the hemisphere that is primarily responsible for understanding and expressing language and, in right-handers at least, the hemisphere controlling the "dominant" hand. This is the context in which the term thus far has been used in this chapter. Because of the preeminence of language with regard to studies of hemispheric specialization, this generally will be its connotation in the following discussions on anomalous dominance. However, the term "dominance" also can be used in a more general manner. In this context, when speaking of "cerebral dominance," it is fair to ask, *dominance for what?* One might just as readily speak of "dominance" for visuospatial abilities, directed attention, musical abilities, emotional responsiveness, social perceptiveness, or other equally relevant skills or abilities. The implication here is that skills, functions, or abilities, other than language, also may be differentially organized or distributed in the two cerebral hemispheres. This differential organization will be discussed in greater detail later, but first, it may be useful to once again apply the general principle of **distributed systems** (Mountcastle, 1979) in the current context of cerebral dominance.

At the most basic level, the concept of cerebral dominance appears relatively simple: a particular given function, such as language, primarily is organized in, or mediated by, a particular hemisphere. Behaviorally, this would imply that if critical areas of the "dominant" hemisphere were damaged, that particular function should be expected to suffer. Conversely, if the opposite, "nondominant" hemisphere is lesioned, regardless of the site of the injury, no disruption of that function should result. Thus, an infarction of the proximal branches of the left middle cerebral artery in a right-handed individual should produce significant aphasic deficits, whereas a comparable lesion of the right middle cerebral artery should not. While, for the most part, this may be true, even with regard to language (which, at first blush, would appear to be a highly lateralized function in most individuals), things are not quite that simple.

One cerebral hemisphere may be associated with a particular behavioral function (such as language) or preferentially processing certain types of information, and hence, said to be "dominant" for that cognitive process. However, components of most behavioral functions or types of information processing are likely to be distributed between both cerebral hemispheres. There is now ample reason to believe that most cognitive processes require some input from each cerebral hemisphere, although one hemisphere may be the "leading" or dominant hemisphere. Hughlings Jackson originally proposed this idea in the latter part of the 19th century. This conceptualization of hemispheric specialization with distribution of cognitive processes across the hemispheres utilizes principles that were supported by both the *localizationists* (such as Joseph-Jules Dejerine) and the *wholists* (such as Pierre Marie) in the early part of the 20th century.[24]

Currently, the idea that the left cerebral hemisphere is specialized for all speech and language functions has been replaced by the view that specific components are mediated by the left and right hemispheres. Whereas the propositional and linguistic aspects of speech production, phonetic decoding, syntax, and semantic language functions are thought to be mediated by the left hemisphere, certain nonverbal aspects of speech appear to be primarily controlled by the right hemisphere (Meyers, 1994). These nonverbal speech/language functions include (1) the use of inflections or intonations in spoken language to convey specific emotional tones; (2) comprehension of similar inflections or emotional aspects in the speech of others, (3) certain metalinguistic aspects of language such as the appreciation of humor and metaphors and understanding the underlying message or context of complex communication, and (4) the overall organization of written or spoken prose (see Right Hemisphere Specialization).

In addition to language skills, different components of visuospatial processing also are thought to be relegated to both the left and right cerebral hemispheres. Whereas the right hemisphere likely processes global (wholistic) aspects of visuospatial input, it is believed that the left hemisphere processes "local features" (Delis et al., 1988). Edith Kaplan (1988) and colleagues (Milberg, Hebben & Kaplan, 1986; Kaplan et al., 1991) have demonstrated these hemispheric differences in processing visual–spatial information by analyzing the different approaches used by left versus right hemisphere-damaged patients to solve the Block Design and Object Assembly subtests of the Wechsler Adult Intelligence Scale. She found that whereas the left hemisphere-damaged patients attended to the outer contour or "gestalt" on the Kohs blocks and tended to preserve the outer configuration (matrix), the right hemisphere-damaged patients attended to the inner details or "features" of the design and often would break the outer configuration. Thus, the left hemispheric patients were utilizing the preserved right hemispheric "global" or gestalt abilities to solve the block design, while the right hemispheric patients seemed to be relying more on specific details or "local features" (functions better served by the intact left hemisphere). Similarly on Object Assembly, right hemisphere patients had more difficulty in recognizing the overall configuration of the puzzle, while the left hemisphere patients reportedly had difficulty with the details. Earlier, a number of investigators found those types of errors (e.g., left-sided neglect, fragmentation, loss versus preservation of gestalt, amount of elaboration) tended to differentiate graphomotor copies of geometric figures completed by individuals with either right or left hemispheric lesions (Arena & Gainotti, 1978; Gainotti & Tiacci, 1970; Hecaen & Assal, 1970; Warrington et al., 1966; Arrigoni & DeRenzi, 1964; Piercy et al., 1960)

Finally, it also has been suggested that not only do the hemispheres differ in the types of information they process, but in fact may organize and process that information in fundamentally different ways. The left hemisphere is thought to organize information in a more focal or discrete manner, thus enabling it to use a more linear or sequential and logical approach, which may explain its greater facility in handling detail. In contrast, the right hemisphere appears to rely on a more diffusely organized, simultaneous, gestaltist model, which would better prepare it for perceiving more global patterns, configurations, or relationships (DeRenzi & Faglioni, 1967: Semmes, 1968; Delis et al., 1988). Such a functional organization and operational strategy is believed to be compatible with abstractive capacities and rational thought characteristic of the left hemisphere and the emotional, nonlinear, intuitive approach that often is attributed to the right hemisphere. If different hemispheric functional approaches are indeed the case, this model may help explain why the organization of language in both hemispheres, while enhancing the verbal skills of certain groups or individuals, may do so at the expense of developing extraordinary visuospatial abilities and vice versa. Data that would support these ideas, which will be reviewed next, are still controversial and circumstantial.

Anomalous Dominance

Handedness and dominance for language typically are mediated by the left hemisphere in the vast majority of right-handed individuals. Thus, a lesion to the left cerebral hemisphere, particularly one that involves the middle cerebral artery distribution, might be expected to produce an **aphasia** (a disorder of language), **hemiparesis** (a disorder of motor strength, dexterity, and skill) affecting the dominant hand, and somewhat less consistently a bilateral limb **apraxia** (a disorder of learned skilled limb movements). Since this pattern of brain organization is typical of most right-handers, it generally is considered to be the "dominant" or typical pattern of brain organization. In contrast, any pattern of organization that differs from this "typical" pattern commonly is considered to be "anomalous" and in some cases "dysfunctional." Such anomalous patterns are more likely to occur in left-handers. As noted earlier, it is estimated that approximately 30% of left-handers exhibit some form of anomalous dominance for language (i.e., language being organized either primarily in the right hemisphere or represented bilaterally). Although anomalous dominance can occur in right-handers, it probably is quite rare. Other associations that have been reported to be related to anomalous patterns of hemispheric organization of language are female gender, mixed hand preference (ambidexterity), and family history of sinistrality. Less well documented is writing position, with the inverted hand position reportedly being more frequently associated with left-hemispheric dominance for language (see Geschwind & Galaburda, 1985; Herron, 1980).

One intriguing finding with regard to hemispheric specialization has centered on possible gender differences both in the structure and functional organization of the cortex. While there probably is considerable overlap or individual variation, it has been suggested that differences in cognitive functions may exist between the sexes when these two groups are considered as a whole, and that these differences reflect not merely social or cultural factors but basic differences in the way cognitive functions are organized in the cerebral hemispheres (Geschwind & Galaburda, 1984; McGlone, 1977, 1986). Specifically, it has been proposed that language may tend to develop earlier, become more highly developed, and may be more bilaterally represented in women. In contrast, it has been suggested that in men language tends to be more unilaterally organized, resulting in a relatively greater development of visuospatial skills as compared to language (Halpren, 1991). Although there still is considerable controversy surrounding this issue, it always is interesting to speculate how, from a Darwinian standpoint, this might occur. For example, one possible scenario is that if the males of the species were indeed the primary hunters and defenders of their family units or tribes, it is easy to imagine how enhanced visuospatial abilities may have had important survival value (and hence, a valuable trait in natural selection). Whatever factors determine handedness and rate of cerebral maturation of the hemispheres, it is likely that gender differences and hormonal influences are not without some effect. (Annett, 1985, 1995).

Lending support to these speculations of functional and developmental difference between the sexes, certain gender-based, structural differences also have been identified. Gender differences in human brain anatomy were first reported by Crichton-Browne (1880), who suggested that the weights of female cerebral hemispheres were more symmetric than male brains. Wada, Clarke, and Hamm (1975) in a study of 100 adult and infant postmortem brains reported that variations in the typical leftward asymmetry of the **planum temporale** was more likely to occur in males than in females. Using current in vivo technology, males were found to have a more significant leftward asymmetry of the planum temporale, in contrast to females where the expected leftward asymmetry was reduced (Witelson & Kigar, 1992; Kulynych et al., 1994). Similarly, a functional greater asymmetry in the frontal speech areas was demonstrated in male as opposed to female subjects using functional neuroradiology techniques (Shaywitz et al., 1995).

While what has been described as the more “typical” pattern of brain organization (strong left hemispheric lateralization for language and strong right hemispheric lateralization for visuospatial skills) would appear to offer some advantages, there may be a few unique, even if not universally expressed, advantages to anomalous patterns of dominance. For example, it has been suggested that left-handers may suffer less severe aphasic syndromes, on average, and recover more quickly (Subirana, 1964, 1969; Luria, 1970; Benson & Geschwind, 1985; Pieniadz et al., 1983). As has been mentioned, the tendency for greater bilateral representation of speech may give certain individuals a greater verbal advantage. There would appear to be a disproportionate number of highly successful professional females who are left-handed as well as individuals who perform exceptionally well on the Scholastic Aptitude Test (Benbow, 1988). It also has been suggested that while additional delays in the maturation of the left hemisphere in males may lead to an increased incidence of language-related problems (e.g., stuttering, learning disabilities), it also may lead to the development of extraordinary nonverbal talents or skills in such individuals (Geschwind & Galaburda, 1987; Smith et al., 1989). Although such ideas are provocative, additional research is needed before their validity and/or the specific factors that are responsible for these effects can be more definitively established.

Left Hemisphere Specialization

Language

The special association between the left hemisphere and language functions has been repeatedly emphasized throughout this chapter. However, so far, the precise nature of those functions has not been elaborated. While an analysis of the possible functional organization of language and its interaction with other aspects of behavior will be offered in Part III, at this point, it might be useful at least to list in greater detail the linguistic and other contributions of the left hemisphere. A good starting point for this discussion might be to recall the beginnings of language localization. As noted earlier, in 1861, Paul Broca described eight right-handed patients who lost the facility of speech and were found to have left hemispheric lesions. Broca thought that the left third frontal convolution, including the **pars triangularis** (*Brodmann's area 45*) and **pars opercularis** (*Brodmann's area 44*), was critical for speech, since this portion of the frontal operculum was lesioned in his patients. In 1874, Carl Wernicke demonstrated that a lesion in the posterior portion of the left **superior temporal gyrus** (*Brodmann's area 22*) produced a syndrome different from that described earlier by Broca. Whereas Broca's patients lost the ability to speak fluently but retained auditory comprehension, Wernicke's patients retained the ability to speak but were impaired at the level of auditory speech comprehension. These two observations basically set the two anchors for the role of the left hemisphere with regard to localized language functions. Although far from reflecting pure dichotomies of function, Broca's findings have come to represent the external production of speech or language, whereas Wernicke's findings generally symbolize the ability to internally utilize or process language or linguistic symbols. Lesions that directly affect these areas or lesions of association pathways to or from these areas produce deficits of language function thought to be mediated by the left hemisphere. These include:

1. Spontaneous production of oral (speech) or written language.
2. Reproducing patterns of speech or language generated externally (e.g., repetition or transcription).
3. Generating linguistic associations (e.g., word finding and confrontation naming).
4. Making meaningful associations from linguistic stimuli symbols (e.g., auditory or written comprehension.
5. Using internal language to solve problems or reach new insights (e.g., abstract thinking).

While each of these functions will be reviewed briefly below, for a more in-depth coverage of language disorders the reader is referred to the works of Albert et al. (1981), Benson (1979), Goodglass (1993), and Goodglass and Wingfield (1997).

Production of Oral or Written Language. Normal spontaneous speech begins with the intent to communicate followed by the internal organization of the thought, access to the words to be used in expressing the thought or idea and their phonetic representations (word sounds), the initiation of the intention, and finally the actual production (articulation) of speech. Spontaneous writing makes similar demands, except rather than requiring the external articulation of phonemes, the phonemes are converted into written symbols (graphemes).

In typical dominance patterns, most of these language functions are mediated primarily by the left hemisphere. Whether the left, right, or both hemispheres are "responsible" for the *intent* to communicate is unclear. However, the failure to initiate spontaneous communication typically has been associated with left anterior (frontal) lesions (usually termed *dynamic* or *transcortical motor* aphasia). As demonstrated by split-brain studies (see, for example, Zaidel, 1985), access to words for expression and phonetic or graphic representation appears fairly restricted to the left hemisphere. Depending on location, lesions of the left hemisphere may result in either a paucity of words (most commonly associated with *nonfluent* or *Broca's* type aphasia), an inability to access the desired word (*verbal or semantic paraphasia*), or an inability to access its proper phonetic representation (*literal* or *neologistic paraphasia*). The latter are more characteristic of *fluent* or *Wernicke's* aphasia. While the left hemisphere also appears to play the primary role in converting the phonemic forms of language into intelligible speech sounds or written symbols [including the graphomotor and orthographic (spelling) components], damage to the right hemisphere has a more limited impact on speech and writing. Since the musculature controlling speech output (tongue, larynx, pharynx) is bilaterally innervated, interference with these centers or pathways in the right hemisphere can result in disturbances of articulation (*dysarthria*) without an underlying disturbance of language per se. The effects of right hemisphere lesions on writing typically are limited to problems with spatial organization and occasionally perseveration or repetition of individual letters. More subtle problems with the organization of either written or oral discourse also may be affected by damage to the right hemisphere and will be discussed in greater detail under "Right Hemisphere Functions."

Language Reproduction. In contrast to language production, language *reproduction*, in its broadest sense, refers to the ability to reproduce language in either the same or alternate form from which it was perceived. Typically, when we think of this aspect of language, we think of the repetition of spoken language or the transcription of spoken or written language. However, reading aloud (as opposed to silent reading for comprehension) also may be considered language reproduction. Disturbances in repetition can result from faulty sensory integration or comprehension, production disturbances, disruptions between sensory input and sensory integration areas (e.g., *pure word deafness*, *pure alexia,* or *alexia without agraphia*), or disconnections between the anterior and posterior language areas. The latter is commonly referred to as *conduction* aphasia and was discussed under the section Disconnection Syndromes. Written transcription or reproduction may involve either writing to dictation or transcribing print into script. As described, these functions appear to be mediated solely by the left hemisphere. Except for possible problems with articulation (dysarthria) or the spatial or perseverative errors described above, or reading disturbances secondary to hemispatial neglect, right hemisphere lesions typically have little or no impact on these language reproduction abilities.

Word-finding Ability. The ability to associate a "word" with either an internal (thought or recollection) or external (perception) representation of an object or idea is a fundamental function of language. Creating these associations (i.e., words) and then retrieving them, either spontaneously or on cue (e.g., when a patient is asked to provide the name for a particular object, action, color, attribute), appear to be skills relegated to the left hemisphere in cases where normal patterns of dominance are present. Studies on split-brain preparations in humans reveal virtually no capacity of the right hemisphere to carry out these activities (Bogen, 1993).

Word Recognition. In addition to being able to generate or retrieve a word when needed (verbal expression), linguistic communication also demands that when a word is perceived, either aurally (auditory comprehension) or visually (reading comprehension), its meaning and/or associations are understood (verbal comprehension). Language comprehension may be broken down further into its semantic and syntactic components. **Semantics** refers to the ability to make concrete associations between an individual word and its referent (e.g., the word "rose" conjures up the image of a particular type of flower; "running," a particular type of activity; or "red," a particular color). **Syntax** refers to the ability to understand the relationship between words, which in turn conveys additional meaning to the communication. For example, the sentence, "Jane hit Bob on the head," has less syntactic complexity than, "Mary's mother's brother [Uncle Bob] was hit by his father's mother" [Grandma Jane]. While the left hemisphere clearly is dominant for comprehending both semantics and syntax, again in split-brain studies the right hemisphere has been shown to have some limited semantic capacity and even more limited ability to process syntax independent of the left hemisphere (Bogen, 1993; Zaidel, 1985). However, somewhat paradoxically, in the presence of an intact left hemisphere, right hemispheric damage may lead to significant difficulties in appreciating subtle or thematic aspects of communication, especially when metaphors or sarcasm are employed (see Right Hemisphere Functions). Table 9–2 provides a summary of commonly identified aphasic syndromes.

Internal Use of Language. Language not only is used for communicating with others, it also is used internally. It serves as an important base for abstract reasoning and problem solving. While both hemispheres contribute to the development of new and creative insights into the world around us, many of the problems presented to us on a day-to-day basis are represented in verbal terms. Even if not, we often try to assign words to our ideas, motivations, imaginings, and conflicts in order to analyze, manipulate, and weigh their various permutations and potential outcomes. Strictly speaking, what we define as rational thought and abstractive capacities appear to be the application of formal linguistic principles to a particular problem. Again, while the split-brain work has suggested that the right hemisphere certainly is capable of problem solving and decision making (in certain circumstances, apparently even more efficiently than the left hemisphere), it appears that it is the left hemisphere that mediates such thought processes in most individuals.[25]

Ideomotor Praxis

As discussed earlier under "Disconnection Syndromes" (p. 328), one functional disturbance often associated with the left hemisphere is **ideomotor apraxia**. The term, *praxis*, refers to the accurate execution of an action. Therefore, *apraxia* refers to the inability to carry out an action. However, this failure should not be the direct result of a loss of primary sensory or motor disturbances, an inability to understand what is being requested, or a general cognitive defect. Because the term apraxia has been applied to a wide variety of other perceptual–motor, visuospatial, and other difficulties (thus creating the potential for confusion), Table 9–3 lists and briefly reviews various ways in which the term apraxia has been used.

According to Geschwind (1975), ideomotor apraxia is the classic and perhaps only legitimate form of apraxia. Typically considered a disconnection-type syndrome, ideomotor apraxia results in the inability to properly carry out a previously learned skilled movement. The movements disrupted in ideomotor apraxia may involve transitive ("Show me how you would use a hammer") and/or intransitive ("Make a salute") gestures, and depending on the site of the lesion may be expressed in one or both hands. Inability to carry out an action requiring the use of the facial muscles ("Pretend to blow out a candle"), is called **buccofacial apraxia**, but this is thought to be simply another form of ideomotor apraxia by some investigators (Kimura, 1982), although these behaviors often are dissociable, and therefore may be mediated by partially independent neural networks (Raade, Rothi, &

Heilman, 1991). Typically, the most sensitive procedure is to have the patient pantomime an action, having provided only the verbal command. Patients with less severe pathology may improve markedly if allowed to use the real object. As noted above, in order to qualify as an apraxic deficit, the inability to properly execute the command should not result from basic disturbances in motor or sensory skills or from the inability to comprehend instructions.

Table 9–2. Aphasic Syndromes

Broca's Aphasia (Non-fluent, Motor, Expressive aphasia)
- **Speech:** Effortful, dysarthric, agrammatic, telegraphic, non-fluent (sparse output) speech; anomic errors, literal paraphasias, if present (distinguish from dysarthria)
- **Repetition:** Impaired, but typically better than spontaneous speech
- **Auditory Comprehension:** Some impairment, but typically much better than expressive abilities, particular difficulties with complex syntax
- **Reading:** Difficulty reading aloud, paraphasic errors. Reading comprehension similar to auditory
- **Writing:** Similar to speech in terms of output and errors; misspellings; poorly formed block letters
- **Lesion:** Frontal opercular area, with subcortical extension in more severe cases

Wernicke's Aphasia (Fluent, Sensory, Receptive aphasia)
- **Speech:** Effortless, circumlocutory (loss of substantive, content words); frequent anomic errors; paraphasic errors common (literal, verbal, neologistic)
- **Repetition:** Impaired
- **Auditory Comprehension:** Significant impairment, may respond better to simple, whole body commands
- **Reading:** Significant deficit, both aloud and for comprehension
- **Writing:** Similar to speech in terms of content; graphically fluent, cursive style, but often meaningless
- **Lesion:** Posterior superior temporal gyrus

Conduction Aphasia (Central, Afferent-motor aphasia)
- **Speech:** Fluent, though blocking is possible due to recognition of anomic errors. Literal paraphasias most common, Stock phrases easily produced
- **Repetition:** Marked impairment relative to other aspects of language
- **Auditory Comprehension:** Some impairment, especially for formal, syntactically complex commands, fair with conversational speech
- **Reading:** Aloud: marked paraphasic errors common; Comprehension: similar to auditory comprehension
- **Writing:** Fluent, cursive script, with excessive paraphasic and spelling errors
- **Lesion:** Arcuate fasciculus underlying supramarginal gyrus

Transcortical Motor Aphasia (Dynamic aphasia, Anterior isolation syndrome)
- **Speech:** Markedly reduced output without marked dysarthria; output frequently limited to single words or common, repetitive phrases
- **Repetition:** Relatively intact. Corrects grammatical errors and completes sentences
- **Auditory Comprehension:** Fair for social, conversational speech, may have difficulties with complex syntax of formal commands
- **Reading:** Aloud: deficient - doesn't produce; Comprehension: fair, except for complex syntax
- **Writing:** Non-fluent, agrammatical
- **Lesion:** Rostral and dorsal to "Broca's area," possibly deep

Transcortical sensory aphasia (Isolated speech area syndrome)
- **Speech:** Normal articulation and rate, but speech empty and circumlocutory; may be echolalic
- **Repetition:** Relatively good, echoes instructions or questions; fails to correct grammatical errors or complete sentences
- **Auditory Comprehension:** Severe impairment, similar to Wernicke's

Reading: Aloud: variable; Comprehension: severe impairment
Writing: Severe impairment
Lesion: Posterior parietotemporal; auditory association area intact

Anomic aphasia (Amnestic aphasia - controversial whether exists as separate aphasic syndrome)
Speech: Normal articulation with frequent word-finding pauses; loss of content words make speech "empty" and circumlocutory; verbal paraphasias common
Repetition: Normal or near normal
Auditory Comprehension: May be mildly deficient, especially for isolated nouns
Reading: Variable
Writing: Variable
Lesion: Variable; angular gyrus common, if initially presents as pure anomia with other Gerstmann's signs.

The above "Syndromes" may vary considerably, both in terms of type and severity of symptoms depending on extent of lesion, individual differences, and recovery.

The underlying premise behind this phenomenon is that the learned sensorimotor codes (*engrams*) for carrying out these actions either have been directly impaired as a result of a lesion or have been disconnected from the primary motor areas (see also Disconnection Syndromes).

Table 9–3. Other Disorders to Which the Term "Apraxia" Is Commonly Applied

Constructional apraxia Refers to the inability to reproduce geometric designs, patterns, or an assembly of three-dimensional objects either by drawing or through the manipulation of actual objects, such as the Block Design subtest from the Wechsler intelligence scales (see Critchley 1969). Although constructional deficits may result from lesions of either the right or left hemisphere, it more commonly is seen and often is more severe following right hemispheric damage. While qualitative differences occasionally can be found between groups of right and left hemisphere-damaged patients, except for unilateral neglect, these differences are not very reliable predictors of hemispheric involvement in individual cases (for review, see Hecaen & Albert, 1978).

Dressing apraxia Describes an inability or difficulty in dressing oneself. Somewhat more common in right hemispheric lesions, dressing apraxia often is seen in association with unilateral neglect and/or severe visuospatial or visuoperceptual deficits (Brown, 1972).

Gait or frontal apraxia Describes the characteristic gait problems in which there is particular difficulty in the initiation of movements of the foot or legs (Meyer & Barron, 1960). Also referred to as a "magnetic gait," this disorder typically results from conditions that involve the frontal lobes bilaterally and/or disrupt descending pathways (e.g., normal pressure hydrocephalus).

Apraxic agraphia Describes difficulties forming letters in writing and may occur independently of other types of apraxia. Assuming normal patterns of cerebral dominance, this type of agraphia typically is associated with left hemisphere lesions (Roeltgen, 1985; Hecaen, 1978).

Ideational apraxia Refers to a inability to carry out a sequence of actions utilizing real objects (e.g., folding a letter, putting it in an envelope, sealing and affixing a stamp to it). Most commonly associated with either extensive bilateral posterior lesions or a generalized dementia, ideational deficits usually are accompanied by significant perceptual disturbances (e.g., apperceptive visual agnosia), visuospatial deficits, aphasia, and/or general mental incapacitation.

Limb-kinetic apraxia Refers to the inability to make fine, rapid, or precise distal movements with or without the use of an object. This difficulty usually is confined to a single limb and affects only the side of the body contralateral to the lesion and is not related to dominance. Although the exact site(s) of the lesion causing this difficulty is still debated, the contralateral premotor and/or somatosensory cortices are the most likely sites (Heilman & Rothi, 1993).

While bilaterally expressed ideomotor apraxia is not uncommon with left hemisphere lesions in right-handed patients, bilateral ideomotor apraxia virtually never occurs following isolated right hemisphere lesions (in right-handers). However, isolated left-sided deficits occasionally may be found with right hemisphere lesions,[26] usually following lesions to transcallosal pathways. Taken together, these findings suggest that in right-handers these motor "engrams" may reside solely in the left hemisphere or be distributed bilaterally, but never (as far as is known) solely in the right hemisphere. With left-handers, the situation is less clear. Based on far fewer case studies, the assumption is that ideomotor praxis tends to be mediated primarily by the left hemisphere (or bilaterally) in left-handers as well; however, unlike right-handers, this function may reside solely within the right hemisphere. Thus, for right-handers, ideomotor praxis is never totally dissociated from language, but occasionally this may be true with left-handers (for review, see Heilman & Rothi, 1993).

Most of the other forms of apraxia, other than ideomotor and possibly apraxic agraphia, typically are associated with and likely in large part result from other elementary disturbances in motor, perceptual, or cognitive abilities. Hence, some authors, following Geschwind's suggestion that the term *apraxia* be restricted to ideomotor type deficits, have begun to use different designations in referring to these other phenomena (e.g., *constructional disability*, *dressing difficulties*).

Calculations

Numbers, like letters, are abstract symbols to which specific meaning has been attached and can be manipulated or rearranged into a variety of sequential patterns according to specific logical rules. Just as words that have become disconnected from their referents or have lost their associative value cannot be understood or used effectively to express a thought or idea, so too numbers may be deprived of their meanings (Benson & Denckla, 1969). As with words, the loss or deficit often is likely to be partial and transient rather than absolute. However, unlike language in which correct interpretations often can be made without complete comprehension, this is not true of mathematics. Disturbances in the interpretation and/or manipulation of mathematical symbols are known as **dyscalculias.** Just as grammar in language follows certain rules, arithmetic or the ability to calculate requires both access to and the ability to apply the rules governing computational operations. A disturbance of the latter, called **anarithmetria**, may occur independently of the ability to appreciate the symbolic aspect of numbers, although elements of both usually are present in the same patient. Disturbances in the reading, writing, or appreciation of the symbolic significance of numbers, inability to compare the relative value of numbers, or a primary disturbance in the ability to carry out basic calculations commonly reflect left hemisphere dysfunction (Levin et al., 1993; McCloskey et al., 1991).

However, in addition to their symbolic aspects, calculations and arithmetical problem solving also require other cognitive abilities, not necessarily restricted to the left hemisphere, that may affect such tasks (Kahn & Whitaker, 1991; Boller, 1985; Hecaen, 1962). For example, carrying out arithmetical operations involving multiple digit numbers require that they be done in a prescribed spatial order. As will be discussed shortly, disturbances of visual–perceptual abilities may result in what has been termed **spatial dyscalculia** (see Visual–Perceptual Abilities under Right Hemisphere Specializations). In a similar vein, unilateral spatial neglect may produce errors in calculation if numbers on the affected side are ignored. Some arithmetical word problems require a higher-level conceptual analysis and reasoning ability that may tap the integrity of bilateral frontal or more diffuse brain systems (see Luria, 1966, pp, 463–467).[27] Depending on their nature, level of difficulty, and how they are presented, problems involving calculations may be affected by disturbances of attention, concentration, or working memory. Finally, not only are education and motivation critical factors, especially when more complex mathematical operations are required, but a developmental deficit involving arithmetical abilities, independent of any recent acquired brain disease, also may contribute to impaired calculations.

Gerstmann's Syndrome and Disturbances of Body Schema

Josef Gerstmann (1940) described a symptom complex of **finger agnosia**, **right–left disorientation**, **acalculia,** and **agraphia** that he associated with lesions of the left angular gyrus. This quartet of symptoms has come to be known as ***Gerstmann's syndrome*** (see Critchley, 1966; Benson & Geschwind, 1985). It also has been noted that when these four symptoms are present, **constructional deficits** also likely are to be seen (Stengel, 1944; McFie & Zangwill, 1960). Although it is controversial as to whether or not this original group of four symptoms constitutes a true syndrome (Benton, 1961; 1977b; Critchley, 1969; Geschwind & Strub, 1975; Poeck & Orgass, 1966; Roeltgen et al., 1983), it generally has been agreed that if all four (or five, if constructional deficits are included) symptoms are present, there is a strong probability that the lesion involves the left angular gyrus (Geschwind & Strub, 1975). Writing and calculations already have been established as primarily left hemispheric phenomena. On the other hand, finger agnosia and right–left disorientation constitute part of what has been termed a *disturbance of body schema* (Frederiks, 1969; Benton & Sivan, 1993).

In childhood, we develop a sense of personal right–left orientation. Not only do we become aware that the right and left sides of our bodies are different (e.g., that one hand is stronger or better at doing certain things than the other), but we also learn to readily distinguish between them (i.e., personal right–left orientation) and to identify them by name (i.e., "right" versus "left"). Only later do we become facile in identifying right versus left in others (extrapersonal right–left orientation). Benton's (1959) review of both the developmental and neuropathological correlates of right–left orientation and finger agnosia is still one of the more comprehensive treatments of this subject.

Finger agnosia is the ability to distinguish and identify individual fingers. If truly present as part of Gerstmann's syndrome, it should present bilaterally (i.e., the patient should have equal difficulty identifying fingers on either hand). Finger agnosia actually is considered to be one facet of **autotopagnosia**, or the inability to identify one's own body parts. However, the inability to name or identify parts of the body (other than the fingers) in the absence of aphasia or other generalized deficits (such as severe unilateral neglect) is exceedingly rare. Complete finger agnosia is not particularly common and generally some fingers (e.g., thumb, little, and index) are easier to identify than others (middle and ring). Testing for finger agnosia involves asking the patient to name or point to a named finger or to otherwise identify (e.g., by matching) fingers by touch or sight.

In terms of anatomical correlates, while there does appear to be some relationship between disturbances of body schema (such as finger agnosia and right–left disorientation) and the left hemisphere, one should be cautious in drawing conclusions from these observations. Both right–left disorientation and finger agnosia, if demonstrated in the presence of aphasic disturbances, simply may be a function of the language disturbance (Poeck & Orgass, 1966). Both right–left disorientation and finger agnosia also may be present in right (or bilateral) hemispheric lesions, especially if general confusion is present. If finger agnosia is tested using tactual stimulus procedures and unilateral deficits are observed, disturbances in the contralateral somatosensory fields are a more likely explanation. Finally, while personal right–left disorientation in the absence of language or other cognitive deficits indeed may reflect a disturbance of body schema (and hence, possible left hemisphere involvement), isolated extrapersonal right–left confusion probably is more indicative of right hemisphere dysfunction (Ratcliff & Newcombe, 1973). For further review of disorders of body schema, see Benton & Sivan (1993); Denes (1989); Ogden (1985); Frederiks (1969); Benton (1959); Critchley 1969.

Verbal Learning and Memory

While both hemispheres contribute to most learning and memory tasks, there is substantial evidence that the left hemisphere assumes greater importance when learning verbal information (Christianson, Saisa, & Silfvenius, 1990; Cohen, 1992; Frisk & Milner, 1990; Gainotti, Cappa, Perri, & Silveri, 1994; Loring et al., 1991; Saling et al., 1993). This left hemisphere superiority for verbal learning undoubtedly is related to the fact that language tends to be organized predominately in the left hemisphere. However, performance on memory tests is not strictly dichotomized. Often left hemispheric lesions will be accompanied by difficulties on visuospatial, as well as verbal memory tasks (the converse is true with right hemispheric lesions, although perhaps to a lesser degree). At least two potential explanations come to mind. The first is that as highly verbal creatures we tend to verbally encode information, including nonmeaningful, geometric designs, such as the Rey-Osterrieth figure or those from the Wechsler Memory Scales. If one is unable to fully utilize such verbal cues as a result of aphasic deficits, their performance might be expected to suffer when compared to controls. Conversely, precisely because of the availability of verbal cues, some right hemispheric patients may be able to perform better than they might otherwise if such cues were less accessible (e.g., using visuospatial stimuli less amenable to verbal labeling). A second explanation for impaired memory for certain visuospatial memory tasks in some left hemispheric-lesioned patients may be a function of the presence of visuospatial constructional deficits that may occur in association with lesions of the left posterior cortices, particularly the left angular gyrus (Loring et al., 1988). Certainly, other more general factors associated with either frontal lobe impairments or loss of abstract attitude also may negatively impact on learning, regardless of the content.

Color Naming and Association

As might be expected, the left hemisphere, particularly the inferior occipitotemporal region, is thought to mediate color naming in the absence of more elementary color imperception which could interfere with this ability. However, in a more abstract sense, the ability to associate colors with particular objects also appears to be mediated primarily by the left hemisphere. For example, the color red is associated with the inside of a watermelon, while green is associated with the outside. Although disturbances in the ability to make these latter associations (even when a nonverbal testing format is used) often are associated with color-naming problems, the two abilities typically are considered to be separate functions (DeRenzi & Spinnler, 1967; Faglioni et al., 1970).

Right Hemisphere Specialization

Recall that the left hemisphere is thought to process information in a logical, analytical, sequential manner and to attend to details necessary for the mediation of propositional speech and related phenomena. By contrast, it has been suggested that the right hemisphere not only is responsible for very different kinds of mental activities (e.g., nonverbal, spatial–perceptual, affective, creative, divergent), but that the right hemisphere may operate in a fundamentally different manner than the left (DeRenzi & Faglioni, 1967; Semmes, 1968; Harris, 1978; Mesulam, 2000b; Delis et al., 1988; Joseph, 1988, 1990). The right cerebral hemisphere is thought to function in a more wholistic or gestalt type mode, processing multiple types of information in a more simultaneous or global manner. Such processing would allow for an immediate, "gut-level," or "instinctual" overall impression or analysis of a situation without having to "stop and think about it." Thus, it may be that the right hemisphere facilitates "seeing the big picture" or grasping the meaning of a situation without being bogged down or possibly even distracted by details. It also has been suggested that the right hemisphere may be more adept in handling novel situations that call for greater flexibility and innovative responding (Goldberg, Podell, & Lowell, 1994; Kittler, Turkewitz, & Goldberg, 1989). Finally, as the right hemisphere more often has been associated with emotional processing, one might speculate that it also is the right hemisphere that tells us that there is something about a situation that "doesn't feel right," although we cannot exactly identify the problem (i.e., "we can't put it into words").

At the beginning of this section on Hemispheric Specialization, it was noted that the right cerebral hemisphere is specialized for nonverbal functions such as emotional–affective processing, visuospatial abilities, spatial memory, musical abilities, directed attention, and unilateral neglect. Each one of these cognitive processes briefly will be discussed in turn, with specific attention to possible anatomic bases of behavioral disturbances in each of these domains.

Emotional–Affective Processes

Mood and affect are multiply determined or influenced. Social or psychological events, including physical illness or disability; changes in hormonal or neurochemical transmitter concentrations; or direct damage to those neurological structures that mediate emotions may all impact on an individual's mood (internal feeling) or affect (external expression), or the relative lack thereof. For purposes of the present discussion, we will restrict our focus to the neuroanatomical substrates of mood and affect. However, even with this limitation, the complexity of deciphering the neurological correlates of affect or emotion readily becomes manifest. For example, as was noted in the previous chapter, subcortical (limbic and hypothalamic), as well as cortical structures play a major role in emotions (e.g., Liotti & Tucker, 1995). This discussion will be limited to those aspects of emotional–affective processing that are thought to be mediated by cortical systems directly or by components of the limbic system that are modulated by cortical inputs.

Emotional Expression in Communication. Emotional "messages" as displayed by postures and facial expressions are powerful communication tools throughout much of the animal kingdom. While the development of language adds a whole new dimension to human communication, we have not divorced ourselves from our phylogenetic roots. Not only do we continue to employ some of the same bodily and facial expressions to communicate our feelings as our four-legged ancestors, but even our language itself has become imbued with and enhanced by affective coloring. There is a large volume of clinical research that suggests that the right cerebral hemisphere plays a predominant role in emotional expression in general and in its association with verbal communication in particular.

In comparison to listening to an actor on the stage or a politician, much of our day-to-day conversations at first glance may appear rather flat and uninspired. What little emotional affect we perceive in our own speech might seem to impart little additional significance to the message conveyed by the words we use. However, this is generally far from the case. The tone (*emotional coloring*) that normally accompanies speech adds a richness (even though at times subtle) to our verbal communications and enhances social interactions. Recall your own reaction to someone who speaks in a total monotone, without facial expression (which itself could have been a deliberate attempt to convey a particular message).

In addition to simply enhancing the aesthetics of communication, the presence of emotional tone provides added clarity and emphasis to our words. The manner (tone) in which something is said often conveys as much if not more information about the attitude, urgency, or meaning behind the communication as the words themselves. In fact, in some cases, the words and the affect or tone are discordant and the true meaning is derived not from the words but in the manner in which they are spoken. It is this discrepancy that typically forms the basis for sarcasm, ridicule, or at times humor. In these situations, the ability to interpret the tone is more critical than the literal translation of the words themselves.

As implied above, this "affective coloration" of speech has two fundamental components: expressive and receptive. We add emotional accents to our own speech appropriate to the mood or meaning we wish to convey (expressive), and at the same time it is imperative that we accurately interpret the mood and meaning behind the communications of others (receptive). Take, for example, the question, "You bought us two season tickets?" It is semantically neutral. However, depending on whether the speaker is (1) a football fan, (2) lives in a city with a losing franchise, or (3) deeply concerned about the family's financial situation, the affective tone with which this sentence is uttered may be quite different, and hence, may convey vastly different messages to the listener. Disturbances in the ability to either add the intended emotional tone to one's speech or to interpret the tone added by others has been termed **aprosodia**. It has been proposed that these affective–emotional components of language in the right hemisphere mirror similar expressive and receptive verbal language deficits in the left hemisphere (Ross, 1981, 1985; Gorelick & Ross, 1987). Thus, depending on the site of the lesion in the right hemisphere, one might expect to find a predominately **motor** (in the area of the frontal operculum), **sensory** (posterior temporal operculum), **conduction** (arcuate fasciculus), **transcortical** (anterior or posterior watershed), or **global** type deficits. Thus, a patient with motor aprosodia might manifest difficulty imparting proper affective or emotional inflections to his spontaneous speech. In a sensory type aprosodia, the individual might have difficulty recognizing the affective intonation used by the speaker (e.g., anger, sadness, or delight), and hence, may misinterpret the underlying meaning of the communication. These have been termed **disturbances of affective prosody.**

In addition to affective intonations, the meaning of a spoken statement may be changed by variations in the stress or pitch applied to a given word or the use of critical pauses between certain words. In the example used above ("You bought us two season tickets?"), note how the meaning is altered as stress is applied to different words in the sentence. This latter phenomenon is referred to as **linguistic prosody**. While the right hemisphere generally is thought to be dominant for both affective and linguistic prosody, it generally is agreed that syndromes of aprosodia are more widely distributed and clinically variable than aphasic disturbances (Heilman et al., 1975, 1984; Tucker et al., 1977; Schlanger et al., 1976; Weintraub et al., 1981; Ross, 1997).

Facial expression and "body language" (i.e., nonsymbolic gesturing)[28] also facilitate and contribute to communication of emotional states. It has been suggested that the right hemisphere also is dominant both for the recognition of facial expressions (Adolphs et al., 1996; Bowers et al., 1985) and for emitting facial expressions appropriate to the situation (Borod et al., 1988). These deficits appear to be independent of disturbances of visuoperceptual abilities or facial recognition in general, both of which are often associated with right hemisphere injuries.

Experience of Emotion Outside of Language. While there is a general consensus that prosody and the recognition of facial expression is most likely mediated primarily by the right hemisphere, the potential leading role of the right hemisphere in controlling emotions in general is more controversial. It has been noted, for example, that patients with left hemispheric lesions (particularly anterior strokes) are more likely to be depressed, while those with right hemispheric damage are more likely to be seen as euphoric or indifferent (Gainotti, 1972; Starkstein et al., 1987). It is a common clinical observation that despite the presence of dense aphasia, it often is easy to ascertain the mood of the left hemispheric patient. Also, once any initial depression has lifted, patients with left hemispheric lesions are perceived as being more likely to maintain their premorbid affective bonds with their families. In contrast, right hemispheric patients often become emotionally aloof, cold, or indifferent to previously close family members. Although neither of these types of reactions by any means is universal, this perceived tendency has led to the assumption that the right hemisphere may be the more dominant of the two in controlling or engaging negative emotions (withdrawal responses), while the left hemisphere may be responsible for more positive emotions (approach responses) (Sacheim et al., 1982; Davidson, 1995).

However, alternate explanations have been offered to help account for these apparent discrepancies in emotional tone or mood following unilateral brain injuries. It has been suggested, for example, that the loss of the ability to communicate (most notably with left anterior lesions) readily could account for a patient's depressed mood (Ross & Rush, 1981), while diminished awareness of deficits and/or reduced capacity to express emotions (motor or expressive aprosodia) might help explain a right hemisphere-lesioned patient's apparent indifference or limited emotional responsiveness. Nonetheless, while recognizing the probable contribution of both hemispheres, there appears to be a consensus that the right hemisphere plays a special if not leading role in the processing, expression, and/or experiencing of emotions (Gainotti, 1997; Heilman & Satz, 1983: Heilman, Bowers, & Valenstein, 1993; Kolb & Whishaw, 1990, pp. 607–642; Liotti and Tucker, 1995; Morrow et al., 1981).

Additional Contributions to Language Processes. It has been noted that, while propositional language is thought to be mediated by the left hemisphere, both affective and linguistic prosody appear to be primarily under the direction of the right hemisphere. However, there are other elements of speech or language that may be related to or affected by changes in the functional integrity of the right cerebral hemisphere. One of these is the appreciation of context. Most sentences, whether declarative, imperative, or interrogatory (prosodic variations aside), are probably fairly straightforward and easily comprehended. However, this is not always the case. Longer, more complicated narratives are difficult to process word-by-word, sentence-by-sentence, or perhaps even paragraph-by-paragraph. If narratives are to be followed and fully understood or appreciated, they have to be broken down in terms of their major and possibly secondary themes. Discovering such themes provides a framework or structure into which the individual elements of the discourse can then be woven (i.e., placed into context). However, the need to discover and adhere to this structure applies not just to comprehension on the part of the listener, but also to the organization of the speaker. In listening to a story or discourse (especially if complex), individuals suffering damage to the right hemisphere have been described as having difficulty:

1. Identifying its point or moral.
2. Discerning major or central themes from minor details.
3. Deciphering incongruities.
4. Appreciating humor (both verbal and visual).
5. Drawing inferences or conclusions.
6. Interpreting metaphors, idioms, or sarcasm.[29]

Conversely, when engaging in conversation, individuals with right hemispheric lesions may use a lot of words but convey relatively little information, stray off on tangents rather than getting to the point, and have difficulty taking turns or allowing others equal time (Garner et al., 1975, 1983; Wapner et al., 1981; Diggs & Basili, 1987; Hough, 1990; Meyers, 1993, 1994).

The "indirect command" or "indirect request" provides a good model for appreciating the occasional failure of right hemispheric patients to take into account social context and how this may impact on verbal communications. An indirect command is a communication in which the initiator, in opting for a question or simple declarative rather than an imperative statement, nonetheless expects the listener to respond in a particular fashion given the particular situational or environmental cues. Thus, in visiting a friend on a warm summer day and seeing a beer commercial on television, one might say, “Boy, that sure looks good!” Given the circumstances, obviously the statement is meant to be interpreted as, “I sure would like a beer right now, do you happen to have a cold one handy?” This would be the “pragmatic” interpretation. However, the same statement also might be interpreted quite literally, in which case the response might be, “Yes, I guess it does, but personally I prefer Cokes” (without an offer of either forthcoming). Such a response, which is more typical of right then left hemispheric-lesioned patients (Foldi, 1987), appears indicative of their failure to integrate nonverbal, contextual cues in social communication.

Given the notion of “distributed functions” as the most likely explanation of brain organization, one must be cautious in attributing perceived deficits in the highly complex behaviors outlined above as being exclusively attributable to a right hemisphere dysfunction.[30] However, right hemisphere involvement in or possibly control over these aspects of language are understandable. Rather than strictly adhering to the formal rules of propositional speech in formulating or comprehending language, these behaviors require an awareness or simultaneous processing of a multiplicity of social (environmental) cues, divergent thinking, and in general an appreciation of the gestalt, features that are more commonly associated with the right hemisphere. Table 9–4 summarizes some the right hemisphere’s impact on communication.

Table 9–4. Right Hemisphere Contributions to Communication

Expressive affective prosody: verbal
Imparting the desired emotional valence to one’s speech through appropriate affective intonations (e.g., “sounding angry” when you are indeed upset).

Expressive linguistic prosody: verbal
Ability to vary the meaning of spoken expression through the use of appropriate tonal inflection to key words or phrases (e.g., “YOU (the perennial cheapskate) bought us two tickets to the football game?” versus “You BOUGHT (when I could have gotten them free at the office) us two tickets to the football game?” versus “You bought us two tickets to the FOOTBALL game (when you know I don’t like football)?”

Expressive prosody: non-verbal
Expression of mood or emotional state through non-verbal means (e.g., facial expression, body posture).

Receptive affective prosody: verbal
Deciphering the meaning of oral verbal communication or mood of the speaker by accurately interpreting tonal inflections.

Receptive linguistic prosody: verbal
Appreciation of humor, sarcasm, or emphasis in the speech of others

Receptive prosody: non-verbal
Ability to accurately decipher the mood of others, or the “message” they are sending by accurately interpreting facial expressions or body postures.

Meta-aspects of oral or written communication
- Organization of oral or written discourse - “staying on course, or keeping to the point.”
- Responsive to social cues (e.g., turn-taking, awareness of the impact one’s discourse is having on others-via verbal and non-verbal receptive prosody).
- Discerning the “point” or “theme” in the discourse of others.
- Interpreting the “message” in light of the overall context or circumstances in which it was delivered.

Finally, other more general cognitive–perceptual deficits also generally associated with right hemispheric damage may affect other language-related abilities. In reading, for example, individuals with right hemispheric-based severe visual–spatial deficits may have difficulty making smooth transitions from one line to the next, although this difficulty also might result from disturbances in visual tracking abilities. If unilateral neglect is present (see below), the individual may ignore words on the left side of the page or the initial letters or prefixes to words (e.g., seeing the word "key chain" as "chain"). Writing may begin toward the center of the page, well away from the left margin, and may tend to slant upward at about a 15° angle (especially on unlined paper). There may be a tendency to perseverate certain letters, especially double le*tt*ers (e.g., le*ttt*ers) when writing (Ardila & Rosselli, 1993; Roeltgen, 1993). Obviously, either failure to grasp the central theme of what is being read, or rambling, nonfocused written compositions may result in problems similar to those discussed earlier in relation to spoken discourse.

Spatial-Perceptual Processing

Beyond left-sided deficits in sensorimotor abilities, the behavior most commonly associated with the right hemisphere is the integration and processing of spatial–perceptual information. In turn, spatial–perceptual abilities most frequently are associated with tasks that tap visual information, such as measures of "visual spatial," "visual–constructive," or "visual–perceptual" abilities. However, as with communication skills, the situation is far more complex. First, while it appears that the right hemisphere plays a dominant role in certain aspects of spatial judgment or analysis, this superiority probably transcends any single modality. Congenitally blind individuals, for example, develop good topographical maps of their environment without the benefit of visual input. Spatial disturbances may also affect tactile performances (DeRenzi & Scotti, 1969; Corkin, 1978). More importantly, even those tasks that appear to be predominately visual–spatial in nature, such as the Kohs blocks from the Wechsler intelligence scales, frequently are disrupted by left hemispheric lesions (Kaplan, 1988; Kaplan et al., 1991). A brief review of various types of spatial–perceptual tasks that traditionally have been associated with right hemisphere processes may help to illustrate the right hemisphere's role in spatial–perceptual processing, while at the same time demonstrating the hazards in making broad generalizations with regard to hemispheric specialization.

Visual–Spatial Ability. While there are numerous formal and informal tests that make visual–spatial demands on an individual (Paterson & Zangwill, 1944; Walsh, 1994, pp. 251–279; Benton & Tranel, 1993; Lezak, 1995, pp. 385–417), most are either functionally very complex or readily lend themselves to verbally mediated solutions. Use of such tests in clinical settings without sufficient controls or systematic manipulation of the constituent variables (factors) often can confound attempts to arrive at some understanding of hemispheric specialization. For example, **topographical orientation** or **topographical memory** in its most basic form represents a spatial map or mental blueprint that allows an individual to appreciate from memory where a particular location or object exists relative to those around it. However, tests of these abilities (e.g., localization of cities on a schematic map, route description, or drawing floor plans or maps of familiar places) may be confounded by verbal associations, constructional disabilities, or hemispatial neglect that make it difficult to tease out the pure spatial element. While a right hemisphere superiority often is suggested for the spatial aspect of many of these topographical memory tasks, deficits often are observed following unilateral lesions of either hemisphere, probably because of the multiplicity of factors involved (Benton & Tranel, 1993; DeRenzi, 1997a).

One task that appears to be a somewhat purer (i.e., less contaminated) measure of visual–spatial ability is judgment of angularity or **line orientation**. This approach was originally developed by DeRenzi et al., (1971) and later formalized by Benton et al., (1975) and was found to be strongly associated with the right hemisphere, that is, deficits on this task occurred with a much greater frequency following unilateral right-sided lesions (Benton et al., 1983). Although typically used as a measure of visual–spatial ability, judgment of line orientation also can be adapted for tactile presentation (Meerwaldt, 1982), where it retains its right hemispheric superiority.

Visual–Constructive Ability. Although visuoconstructive tasks can be classified as a measure of visual–spatial ability, they merit independent consideration because of their common constructive component and because they constitute some of the more well known and frequently used measures in neuropsychology and behavioral neurology. Unfortunately, these tasks also are among the most misunderstood. Visuoconstructive measures represent a highly diversified group of tasks. These might include:

1. Drawing familiar patterns, such as a clock or a daisy.
2. Copying (drawing) two- or "three-dimensional" designs, (e.g., a house, or a cube).
3. Drawing the floor plan of one's house or hospital unit.
4. Recreating geometric patterns using the Kohs blocks (e.g., Block Design from the Wechsler intelligence batteries).
5. Reconstructing two- or three-dimensional arrays using matchsticks or assorted wooden blocks (Critchley, 1969; Benton et al., 1983).
6. Reassembling fragmented pictures (e.g., Object Assembly from the Wechsler intelligence batteries).

As we will see later, increasing the demands on the spatial analysis, planning, and organization can increase the level of difficulty on some of these tasks. One way of increasing the visual–spatial complexity is by attempting to incorporate a three-dimensional perspective in two-dimensional space, as is the case in trying to draw a solid cube,[31] a house from an oblique angle, or other quasi-three-dimensional design (see Figure 9–25). The Rey-Osterreith figure illustrates another way of increasing complexity by simply increasing the number of individual elements in the design.

All of the above tasks likely tap slightly different aspects of visuospatial ability. Depending on level of complexity, some are less demanding than others, while others might be more

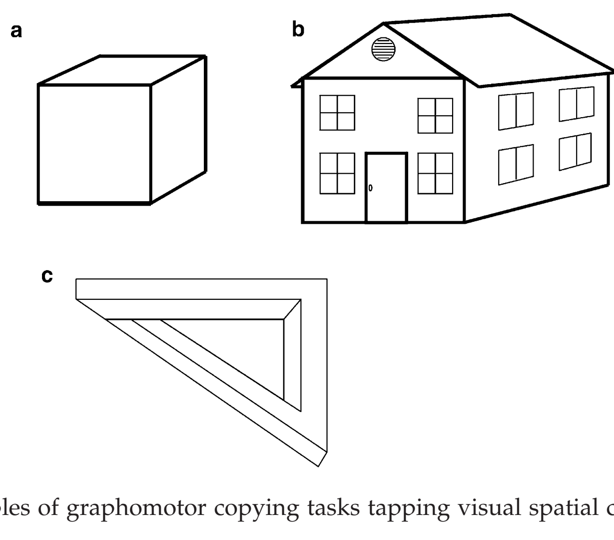


Figure 9–25. Examples of graphomotor copying tasks tapping visual spatial construction ability.

conducive to verbal mediation (e.g., Object Assembly).[32] The multidimensional nature of most of these tasks readily is apparent, and hence, potentially subject to factors other than pure visual–spatial ability. In general, drawing tasks probably are more sensitive to disturbances of motor praxis than those requiring object manipulations. Basic visual disturbances, especially syndromes involving unilateral neglect (see below), may adversely affect performance on all these measures. While the successful completion of most of these tasks will benefit from good organizational and planning ability, some will be less affected by a piecemeal, trial-and-error approach. Virtually all of these tasks require some degree of self-monitoring ability. Some visuoconstructive tasks obviously require a fair degree of problem-solving skills, and as a result have been incorporated into formal intelligence tests (e.g., Block Design, Object Assembly). However, even relatively simple drawing tasks may be affected by sociocultural and intellectual factors (Strub et al., 1979). Because of the multiplicity of factors involved, it is not surprising that (1) the intercorrelations among these various tests are far from perfect (Benton, 1967; Dee, 1970), (2) they are extremely sensitive to most types of brain injury, and (3) are often impaired following either right or left hemispheric lesions.

With regard to hemispheric localization, originally constructional deficits were thought to reflect damage to the left parietal lobe. Later they came to be recognized as more of a right hemisphere syndrome when it was believed that right-sided damage (again, in the parietal area) led to more frequent and more severe constructional deficits. Eventually, there was a realization that constructional deficits could occur with lesions to either hemisphere (Warrington, 1969). Although parietal lobe involvement still was thought to be critical, attempts were begun to differentiate laterality by qualitative analyses of drawings. Deficits in construction resulting from right hemispheric lesions were thought to be characterized by greater fragmentation in the designs, a loss of gestalt and three-dimensional perspective (if present), and a tendency to ignore features on the left side of the design (left unilateral spatial neglect). The basic problem in right hemisphere deficits was thought to result from a breakdown in spatial integration or perception. Constructions by patients with left hemisphere lesions frequently were described as manifesting a breakdown in planning and executive abilities (apraxia), resulting in overly simplified but spatially more intact (greater perseveration of the gestalt) designs that were more likely to show difficulties in replicating internal details (see DeAjuriaguerra & Tissot, 1969; Hecaen & Assal, 1970; Kaplan, 1979). While these observations may have considerable merit, with the exception of noting the presence of consistent unilateral neglect, these signs have not proven sufficiently robust to provide definitive markers in individual cases (Black & Strub, 1976; Arena & Gainotti, 1978; Benton & Tranel, 1993). Finally, while parietal lesions, particularly bilateral parietal pathology (as is frequently present in Alzheimer's disease), may result in more classic, severe instances of constructional deficits, frontal lesions also may produce deficits on these tasks [presumably, in part, due to deficits in organization, planning, and self-monitoring (Benson & Barton, 1970; Luria & Tsvetkova, 1964)].

Visual–Perceptual Abilities. Most visual–perceptual activities involve various degrees of spatial analysis and integration. Printed words and (multidigit) numbers depend on an accurate perception of the spatial order of their constituent units (letters or arithmetical symbols) for their proper interpretation. Pure color discrimination may be one notable exception to this rule. Historically, there has been a frequent tendency to associate impairments on a wide variety of "nonverbal, visuoperceptual" tasks with right hemisphere dysfunction. In addition to discrimination of line orientation noted above, other examples of such tasks have included:

1. **Discrimination among unfamiliar faces** (as opposed to recognition of familiar faces or prosopagnosia) (Benton, 1990; Benton & Van Allen, 1968; DeRenzi, 1997b).
2. **Incomplete, fragmented, overlapping figures**, or **familiar objects viewed from an unusual perspective** (Boyd, 1981; DeRenzi & Spinnler, 1966; Warrington & Taylor, 1973).
3. **Mental rotations of patterns or figures in space** (Butters & Barton, 1970; Ratcliff, 1979; Fischer & Pellegrino, 1988; Benton & Tranel, 1993**).**
4. **Localization of objects in space** (Warrington & Rabin, 1970; Hannay, Varney, & Benton, 1976).
5. **Discrimination of complex visual patterns** (Benton et al., 1983; Corkin, 1979).
6. **Visual mazes**, **map making**, and **route finding ability** (Benton et al., 1974; see also Lezak, 2004).
7. **Depth perception** (Carmon & Bechtoldt, 1969).

While such tasks often have been identified as being particularly sensitive to right hemispheric pathology (i.e., deficits on these various tasks appear to occur with somewhat greater frequency following right focal lesions), as noted by Lezak (2004) in her review of these tasks, deficits often can be found following lesions to either hemisphere. In fact, deficits in most if not all of these tasks tend to be most severe in cases of bilateral, posterior disease. This implies that both hemispheres contribute to the perceptual–cognitive operations demanded by these various tasks.

However, in keeping with the commonly accepted theories of hemispheric asymmetry, the presumption is that the contributions made by each hemisphere are different or unique. A good example may be the **Hooper Visual Organization Test** (HVOT). This test consists of fragmented schematic drawings of common objects that are to be identified (Figure 9–26). Some items, such as the candle (item No. 18) and the cat (No. 20) readily can be identified by simply analyzing a single fragment, a task easily accomplished by the left hemisphere. On the other hand, the correct identification of items such as the flower (No. 21) and the broom (No. 30) are greatly facilitated by the individual's ability to mentally integrate the fragments, arguably a process better suited to the right hemisphere. In fact, while potentially disrupted by various brain injuries, the HVOT has not proven to be selectively sensitive to right hemisphere pathology, probably at least in part because so many of the items can be recognized using left hemispheric strategies. However, as noted by Sergent (1995), another difficulty in using any such measure to unlock the secrets of hemispheric function is that we often are attempting to reduce exceeding complex, multidimensional phenomena to a single, bipolar principle. While such endeavors may provide useful insights, we are still a long way from piecing together the puzzle.

Sergent's admonitions notwithstanding, one rather clever strategy that has been used in an attempt to tease out these different hemispheric mechanisms is the global versus local perceptual paradigm devised by Navon (1977) that consists of large letters (or other figures) composed of strings of contrasting smaller letters (or figures). Recognition of the larger letter (**global processing**) was thought to better reflect right hemispheric, gestaltist mechanisms, while recognition of the smaller, constituent letters (**local processing**) seemed to evince the analytic capacities of the left hemisphere (Figure 9–27). While some studies using such stimuli in focal brain-injured populations have provided support for this hypothesis (Delis, Robertson, & Efron, 1986), again the results have not always been consistent, suggesting that other intervening factors also need to be considered (Brown & Kosslyn, 1995; Hellige, 1995). One of the recurring lessons to be derived from these various studies of visual perception (also true of most other mental abilities) is that both cerebral hemispheres normally work in concert when processing (and responding to) everyday stimulus input, regardless of its

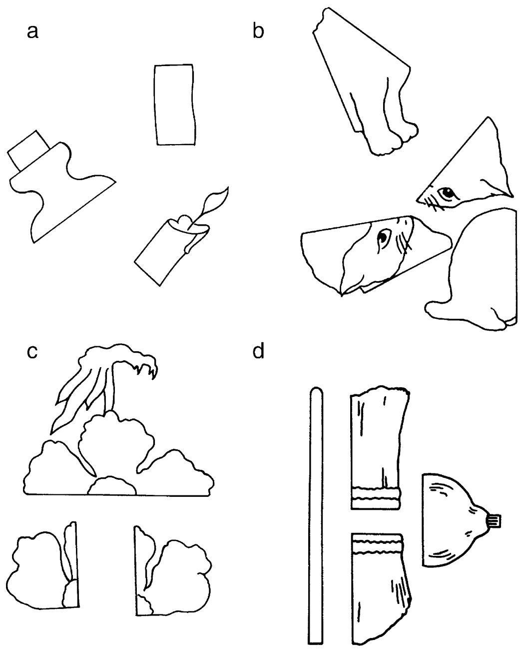


Figure 9–26. Examples from the Hooper Visual Organization Test that might be identified from a single fragment (a,b) versus those in which integration of all elements is commonly necessary (c,d). Material from the VOT copyright © 1957 by H. Elston Hooper. Reprinted by permission of the publisher, Western Psychological Services, 12031 Wilshire Boulevard, Los Angeles, California 90025, *www.wpspublish.com.* Not to be reprinted in whole or in part for any additional purpose without the expressed, written permission of the publisher. All rights reserved.

nature. The dichotomies that we establish in describing certain tasks as being mediated by or representative of the right or left hemispheres are largely our own inventions, not nature's. Still, this does not prevent us from asking the question, "what does each hemisphere (lobe or gyrus) contribute to this behavior and how is the behavior altered when that particular contribution is missing?"

There are certain visual–perceptual syndromes that typically only become manifest following bilateral insults to the brain. **Balint's syndrome** is one example (ideational apraxia, which was discussed earlier, being another). Balint's syndrome is primarily characterized by (dorsal) **simultanagnosia** (the inability to perceive more than one object at a time) and

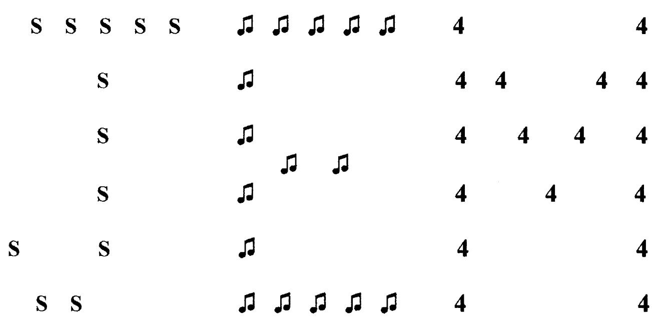


Figure 9–27. "Global" versus "local" processing. Figures constructed for illustration purposes.

marked disturbances of spatial disorientation (e.g., difficulty in localizing objects in space, impaired depth perception, and loss of topographical memory). It is a relatively rare disorder that generally results from bilateral parietooccipital lesions. Despite what may be normal visual acuity, such individuals virtually are unable to negotiate their visual environment (Holmes & Horax, 1919; Rafal, 1997a).[33]

As noted earlier, even certain aspects of symbolic, linguistic abilities such as reading, writing, and calculations may be affected by "spatial" deficits. For example, certain aspects of syntax may require a spatial type analysis (e.g., "over," "above," "after," and "before"). As noted earlier, disturbances in reading, writing, and arithmetic also may be associated with right hemispheric lesions. Mathematical operations are carried out in two-dimensional space and follow certain spatial rules. Whether performed mentally or in writing, complex calculations require precise spatial operations, such as (1) keeping the columns and rows of numbers in correct alignment, and (2) proceeding in an orderly spatial fashion, both horizontally and vertically. While simple calculations that rely on previously memorized associations may not be readily affected, the likelihood of error increases with the use of multidigit numbers. An even greater demand may be placed on spatial integrity when such calculations are presented and must be performed mentally, rather than in writing. While these types of deficits (**spatial dyscalculia**) have been more commonly associated with right hemisphere lesions (Cohn, 1961; Hecaen & Angelergues, 1961, also cited in Hecaen & Albert, 1978; Rosselli & Ardila, 1989), "spatial" errors have been identified following lesions of either hemisphere (Dahmen et al., 1982; Collignon, Leclerq & Mahy, 1977, also cited in Levin et al., 1993; Grafman et al., 1982). Finally, errors in estimation of magnitude also have been associated with right hemisphere lesions (Dehaene & Cohen, 1991).

Spatial (Nonverbal) Memory

As the right hemisphere long has been perceived as being the "dominant" hemisphere for nonverbal, spatial, particularly visual–spatial abilities, the superiority of the right hemisphere in mediating nonverbal, visual–spatial memory has been well established in clinical lore. Certainly, some of the earlier studies by Corkin (1965), Kimura (1963), and Milner (1965, 1968, 1972) helped to support this notion. More recently, the notion of separate verbal and visual–spatial working memories, with the latter being identified primarily with the right hemisphere in PET studies, has provided further credence to this hypothesis (Baddeley, 1994; Jonides et al., 1993). However, while some more recent studies have been able to demonstrate a hemispheric effect on tests of visual/spatial memory in clinical populations (Christianson, Saisa, & Silfvenius, 1990; Cohen, 1992; Gainotti, Cappa, Perri, & Silveri, 1994), the effect appears to be neither consistent nor robust. The problem is that when the performance of patients with lesions lateralized to one hemisphere are compared on most commonly used tests of visual–spatial memory, the difference in scores often is either insignificant or there is such overlap between the two groups that the predictive validity of these measures in localizing lesions is not very good. This includes the visual–spatial memory tests from the Wechsler Memory Scale, one of the more widely used psychometric measures of memory (Chelune & Bornstein, 1988; Naugle et al., 1993). For a relatively recent review of the capacity of other specific tests or measures of visual–spatial memory relative to differentiate focal hemispheric lesions, the reader is referred to Lezak (2004). However, the bottom line is that most studies utilizing these measures fail to clearly discriminate right versus left hemispheric-lesioned patients on the basis of overall level of performance.

This is not to suggest that certain patterns of performance or qualitative features are without clinical merit. For example, marked and consistent discrepancies between verbal and visual–spatial abilities, including "non–verbal" tests of learning or memory indeed may be indicative of right hemisphere pathology. This is particularly likely where performance on predominately "verbal" tasks are markedly and consistently superior to "visual–spatial" measures, especially if there are clear signs of left spatial neglect. Problems are encountered when isolated or borderline findings are used to make such predictions without considering other factors or possibilities.[34]

Thus, the failure of memory tests to reliably differentiate right from left hemispheric-lesioned patients may not lie so much with the theory as with the practice. It may well be that the right hemisphere, particularly the hippocampus and surrounding regions (e.g., dentate gyrus, subicular region, and entorhinal and perirhinal cortices) are critical for encoding and retrieving certain types of visual–spatial or related information. However, as noted, most of the commonly used visual–spatial, "nonverbal" memory tests actually are multidimensional and capable of substantial verbal encoding. Impairment of this process in left hemispheric patients may reduce their performance, while utilization of these verbal cues may help right hemispheric patients compensate for their "nonverbal" deficits. Similarly, problems with visual perception or perceptual–motor (constructional) difficulties associated with left hemisphere damage (see above) may result in impaired performance on these tests. Finally, it is possible that some of the studies that have failed to find significant differences between right and left hemispheric-damaged patients on these measures themselves may be flawed. It has been demonstrated that the exact locus and extent of damage to the hippocampal region is critical in the amount of memory impairment that might be expected (Zola, 1997). In clinical studies, such precision in establishing right versus left hemispheric groups is virtually nonexistent.

Musical Abilities

Musical abilities provide another example of hemispheric specialization and hemispheric cooperation. The appreciation as well as the expression of musical melodies frequently has been associated with the right hemisphere (Basso, 1993; Benton, 1977a; Gates & Bradshaw, 1977a; Henson, 1985). The preservation of one's ability to reproduce familiar melodies, despite extensive disturbances of expressive language following dominant hemispheric lesions, repeatedly has been documented (Smith, 1966; Yamadori et al., 1977). On the other hand, music, like language, is composed of individual, temporally sequenced notes, each capable of being analyzed with regard to specific individual characteristics such as pitch and timbre, functions that would appear to be more in keeping with the suspected operations of the left hemisphere. Yet, it would seem that well-trained musicians and composers would be considerably more adept in processing music in this fashion than the majority of us who lack such training or abilities. In fact, there is evidence that trained musicians indeed may rely more heavily on the left hemisphere for processing certain aspects of music when compared to nonmusicians (Bever & Chiarello, 1974; Shannon, 1984). However, reliably ascribing specific aspects of musical abilities to either the left or right hemisphere in this group has proven difficult (Sergent et al., 1992). It also has been noted that familiar pieces of music may be more readily recognized by the left hemisphere (Gates & Bradshaw, 1977b). Thus, not only may different aspects of music more readily lend themselves to processing by one hemisphere versus the other, but also the strategies by which these various musical elements are approached also may be important in determining which may be the leading hemisphere in a given situation. In summary, while both the right and left hemisphere apparently are involved in the expression and perception or appreciation of music regardless of level of training, the specific contributions of each are still somewhat of a mystery.

Directed Attention and Unilateral Neglect

Patients with certain unilateral lesions, particularly if the lesion was of acute onset (e.g., strokes) may display problems that commonly are interpreted as difficulties with attention to or awareness of the contralateral side of the body or the contralateral hemispace. Also referred to as problems of directed attention or unilateral neglect, these symptoms are considerably more likely to occur following damage to the right side of the brain than the left.[35] The problem may be manifested in terms of external hemispace, hemibody awareness or hemibody stimulation, and/or hemibody movement.

Hemispatial Neglect. In its most classic presentation, **hemispatial neglect** is characterized by the patient's failure to report or attend to visual stimuli that are present in the hemispace contralateral to the lesion (in the absence of primary sensory defects). For example, following a right hemispheric lesion the patient may fail to report objects or movement presented in the affected left visual field or left hemispace by the examiner. He or she also may fail to complete the left side of drawings or puzzles and ignore food on the left side of the tray and words or letters on the left side of a page. At times, it may be difficult to distinguish between a left homonymous hemianopia and a severe left visual neglect as in either condition the patient may fail to spontaneously respond or attend to visual stimuli confined to the affected hemifield. However, severe neglect, in the absence of a visual field defect, occasionally may be identified by directing the patient's attention to the affected field, for example, informing the patient that the stimulus will be presented on that side and that the patient needs merely to report *when* (as opposed to *if*) the stimulus occurs. Also, patients with field cuts without neglect normally search the affected field if given an opportunity, so they may perform normally on cancellation tasks and typically will fail to show the other signs of neglect listed above.

More common than the failure to report single stimuli presented to the affected field, hemispatial neglect often is manifested by the presence of extinction (suppression) on **double simultaneous stimulation** (DSS). In double (bilateral) simultaneous stimulation, the patient may respond normally (or near normally) when stimuli are presented singly and independently to one or the other hemifield or hemispace but fail to respond to stimuli on the side contralateral to the lesion when comparable stimuli are presented simultaneously to both fields. Depending on the severity of the neglect, such a failure to respond may be absolute

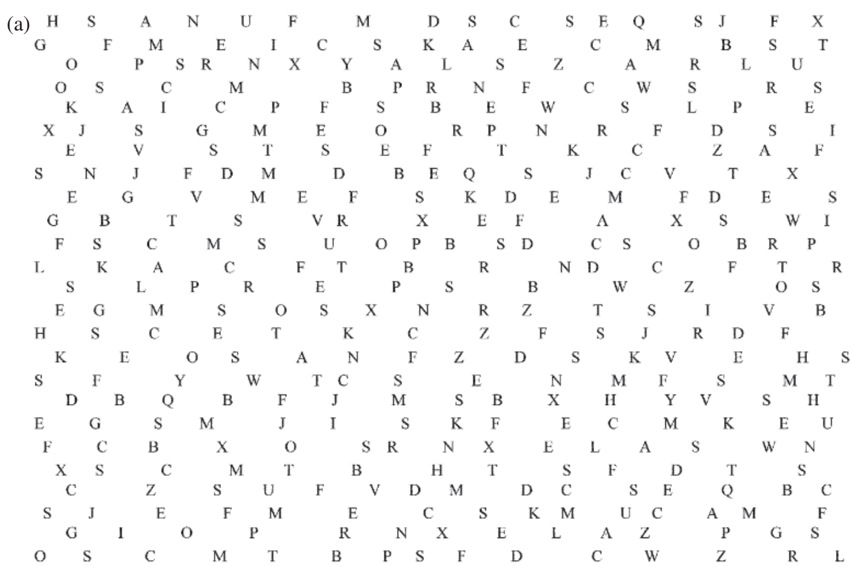


Figure 9–28. (*Continued*)

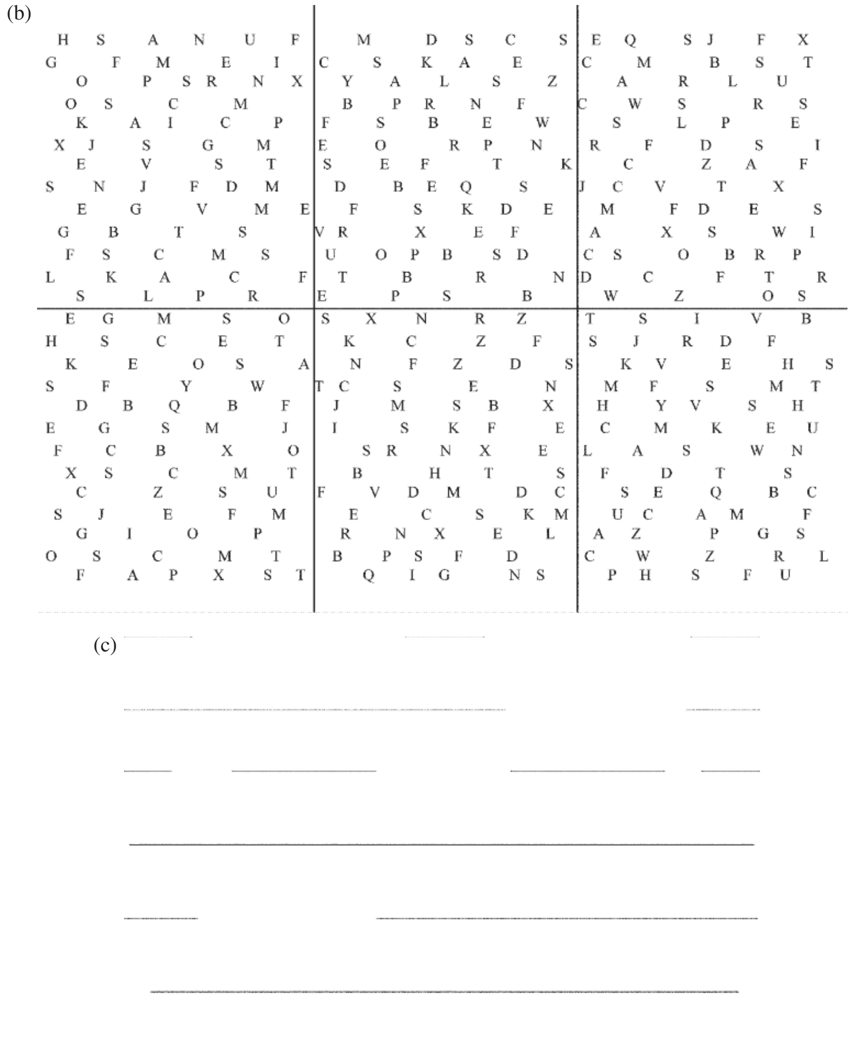


Figure 9–28. Cancellation and line bisection tasks. The cancellation task contains a total of 60 "S"s and 30 "F"s, 20 and 10, respectively, in each lateral third of the figure and 10 and 5, respectively, in each sixth. The reader is free to reproduce and enlarge figures for their personal use.

(i.e., occurring on 100% of the trials) or relative (occurring on a significant percentage of the trials).

Two common bedside methods of directly testing for hemispatial neglect involve (1) visual and auditory confrontation exams (e.g., the presentation of unilateral or bilateral (DSS) stimuli, in a random order, to each side of the body or hemispace), and (2) the use of visual cancellation and/or line bisection tasks (Figure 9–28). However, as noted above, signs of hemispatial neglect may be observed in other situations. For example, the patient may fail to attend to someone standing on his/her affected side, even though both ears are monitoring the sound of their voice, which is inputted into both hemispheres. In drawing symmetrical figures or objects, there may be an omission or degradation of details in the affected hemispace. Again, in the case of a right hemispheric lesion, the patient routinely may begin working on the right side in a task like Block Designs and may make significantly more errors on the left side of the design. The patient may have trouble negotiating external space (getting lost on the ward) because of their inability to use landmarks in their affected field. At times, such patients even may evidence difficulty recalling from memory details of familiar scenes when the information to be recalled from their visual imagery falls in the affected field.

As the patient begins to recover from the acute brain insult that resulted in the unilateral neglect syndrome, there normally is a noticeable improvement in the symptoms. This is commonly first noted in “predictable” situations, that is, situations in which the patient knows to “expect” stimuli in both spatial hemispheres. For example, the patient “learns” to search the left side of his tray for his cup of coffee, or learns to scan to the left until he reaches the end of the page before reading a line (thus, he no longer omits words on the left side of the page). There also may be improvements on cancellation and line bisection tasks or with confrontation exams where DSS is employed. However, more subtle deficits may persist, especially in situations where the patient is confronted by a multiplicity of stimuli, where he/she is expected to respond quickly, or where there is less predictability regarding the presence or absence of a particular stimulus. This is why, despite the presence of more or less normalized responses on clinical examination, one might be cautious about advising a patient with a recent history of unilateral visual neglect that it is safe to resume driving once the more obvious symptoms of neglect dissipate on formal examination.

Hemibody Awareness. In addition to impaired awareness of external space, lateralized lesions also may result in impaired perception of stimuli impacting on or diminished awareness of one half of the body itself. This impairment can take one of several forms: (1) lack of awareness or suppression of tactile stimuli, (2) lack of or diminished awareness of impaired capacity (denial of illness), or (3) failure to recognize one’s own limb(s). As in the case of hemispatial neglect, these phenomena are more likely to be seen following acute lesions to the right hemisphere.

Neglect of contralateral tactile stimulation in the absence of primary sensory disturbances, as with vision, may occur with either single stimulation (less sensitive) or DSS (more sensitive). Occasionally, single tactile stimulation applied contralateral to the lesion may result in reports of the stimulus being perceived (subjectively displaced) to the homologous region on the ipsilateral side (of the lesion). This phenomenon is known as **allesthesia**. In using DSS, the patient may be touched in homologous areas or in nonhomologous areas (e.g., right face–left hand). While this latter procedure is very sensitive to subtle signs of neglect, it is not uncommon for nonlesioned controls to make errors on this task; hence, repeated measures with adequate comparison of the right and left sides of the body are particularly important when using nonhomologous stimulation.

Tactile neglect, as described above, probably occurs with approximately the same frequency as visual neglect and may or may not occur simultaneously with neglect in other modalities (vision or hearing). On rare occasions one may encounter a more unusual phenomenon where the patient may deny ownership of the affected limb(s). While not actively denying that the affected limb belongs to them, other patients may effectively fail to attend or ignore one side of their body (or parts thereof) when engaging in such activities as dressing or shaving. One patient with a right hemisphere stroke, for example, managed to put on his robe; however, when asked to tie the belt together, he immediately secured the end on his right side but never searched past midline for the other end hanging from the left side. An alternate explanation is that this failure could represent an example of directional hypokinesia or a hesitancy to move into the hemispace contralateral to the lesion (Coslett et al., 1990).

In the initial period following a lesion, a patient, while not disowning a paretic limb, may deny that there is anything wrong with it. This is known as **anosognosia**. These more dramatic symptoms of denial generally occur immediately after an acute event, such as a cerebral vascular accident. However, even as these symptoms begin to subside over time, the patient still may underestimate the significance or potential impact of their disability. For example, although acknowledging a persisting weakness on one side, if asked the patient may indicate he anticipates being able to return to work (which requires strenuous manual labor) after "a few days of rest." This latter phenomenon is referred to as **anosodiaphoria**.

Diminished or Distorted Motor Responses. In addition to loss of sensory awareness (either internal or external), the patient with a lateralized lesion may show a diminished tendency to (1) spontaneously utilize the hand contralateral to the lesion, (2) move either limb in the affected hemispace (**directional hypokinesia**), or (3) deviate the eyes toward the affected hemispace. For example, another right hemispheric stroke patient was searching for his soft drink can that was on the left side of his tray. The author picked up the can and held it in his right hand while facing the patient (thus, in the patient's left hemispace). When the patient was informed that the examiner was holding the soft drink in his hand, the patient immediately focused on the examiner's left hand (patient's right hemispace). After he expressed some bewilderment, the patient was informed that the can was in the examiner's *other* hand and was asked to find it. Despite multiple verbal cues as to the likely location of the "other" hand, the patient's eyes never deviated to the left of midline in his search, despite evidence of his ability to move his eyes in that direction when following a moving target.

At times it may be difficult to determine whether the patient's failure to respond may result from a lack of awareness of one hemispace (e.g., not searching to the left for the soft drink can since that "space" no longer existed for the patient) or whether there is simply an inertia to move into that hemispace. Either or both behaviors may be present in different patients. Heilman, Watson, and Valenstein (1995) review several techniques by which these features might be dissociated. Understanding these phenomena are critical in neuropsychological or neurobehavioral examinations since many of the tests and measures used require either a visual (e.g., Picture Arrangement) or tactual–motor (e.g., Sequin-Goddard formboard) exploration of (and response to) right and left hemispace.

As noted, while all of the above behaviors can occur with lesions in either hemisphere, these various manifestations of unilateral neglect are most likely to be found following right hemispheric lesions. In a way, this is consistent with what has been said previously about the role of the right hemisphere in behavior. If the right hemisphere is charged with the responsibility of arriving at an immediate global, gestaltist impression of a situation, not by initially attending to or analyzing its specific details (the hypothesized role of the left hemisphere), but by attending to the whole situation at once, then it also has to be able to immediately attend to or pick out those features of the situation that are immediately most salient. To effectively accomplish this task, it must attend in a general way to stimuli in both fields or on both sides of space, that is, it must be capable of directing attention both in the contralateral as well as in the ipsilateral half of space. Conversely, the left hemisphere, not so compelled, may tend to "limit its attention" to only the contralateral space. Hence, the right hemisphere may be better capable of compensating for the contralateral attentional loss following left hemisphere lesions than is the left hemisphere following right hemisphere lesions (Mesulam, 2000c; Heilman, 1995; Heilman, Watson, and Valenstein, 1995). For readers interested in a more detailed explanation of these neglect syndromes, in addition to these sources, one may wish to review Critchley (1969) and Rafal (1997b), *Visual Imagery*

Mental imagery is a complex construct that requires explicit definition prior to a discussion of the theories regarding hemispheric specialization. Mental imagery involves the perception of an image without sensory input. The mental image of an object, such as a coffee cup, is conjured up in the "mind's eye" from memories of the visual representation of either a prototypic or a specific coffee cup (depending on the "sharpness" of the image). Mental images also can be experienced in other sensory modes, like auditory or gustatory.

It once was thought that the right hemisphere primarily was responsible for generating visual imagery. Presently, the more predominant opinion seems to be that specific components of imagery are preferentially processed in the right and the left cerebral hemisphere. Kosslyn (1988) has suggested that two broad types of processes are required to generate a visual image. These processes include (1) the activation of stored memories of parts of the visual image, and (2) the arrangement of these parts into the proper configuration using a coordinate system. It is argued that the process of accessing the parts of the object to be imaged are predominantly in the domain of the left cerebral hemisphere, while the process of spatially arranging these parts into the whole object would be in the domain of the right cerebral hemisphere. Although still controversial, it seems that the integrity of visual association cortex is crucial for the preservation of visual imagery. Patients with cortical blindness and lesions limited to primary visual cortex have been demonstrated to have intact visual imagery (Chatterjee & Southwood, 1995), suggesting that primary visual systems are not critical for the generation of visual images. For a review of this topic, the reader is referred to Sergent (1990).

FUNCTIONAL HEMISPHERIC SPECIALIZTION: FINAL THOUGHTS

Just as different parts of the brain in its anterior–posterior axis (e.g., the frontal versus the parietal lobes) have different structural features and subserve different functions, so too do the two hemispheres. Actually, it is likely that such functional divisions (beyond contralateral sensorimotor representation) also characterize subcortical structures such as the thalamus, basal ganglia, and limbic structures (e.g., Liotti & Tucker, 1995). However, our knowledge of these functional divisions or distinctions is still very rudimentary. For example, given a typical right-handed individual, it is known that the left hemisphere is primarily responsible for processing prepositional speech and language. However, is there a fundamental difference in the function, structure, organization, or interconnectivity of the cells of the left hemisphere (distinct from those on the right) that serve as the basis for this linguistic advantage? That is, do the left and right hemispheres process information in fundamentally different ways? Besides propositional language, what are the other major functions of the left hemisphere and is there a more general way of describing or encompassing these functions? If the left hemisphere primarily is the "language" (at least in its semantic or propositional aspects), how is the function(s) of the right hemisphere best characterized? To what extent are right and left subcortical structures specialized? While it is known, for example, that lesions affecting the left thalamus or basal ganglia are more likely to produce aphasic-like syndromes than comparable lesions on the right, is this the result of primary functional differences in these structures themselves or are these effects simply a result of their cortical connections? While some tentative hypotheses have been offered for some of these questions, others have been barely explored.

Sergent notes that it is difficult to define the different roles played by each hemisphere in a relatively circumscribed task like facial recognition. It certainly is unlikely that we could ever identify "a single, bipolar principle that would encompass the functional properties of the two hemispheres..." (Sergent, 1995, p. 178). Recognizing these limitations, the most prudent approach may be to emphasize the complexities involved in describing hemispheric specialization rather than to attempt definitive statements about the functions of a specific hemisphere. It needs to be emphasized that the descriptions provided in the preceding sections are the result of attempts to define and categorize extremely complex and often incompletely understood phenomena. The problem may be especially compounded when trying to discuss right hemisphere functions. For example, if we are substantially correct in asserting that the right hemisphere primarily is responsible for certain "nonverbal" and "gestaltist" aspects of behavior, we find ourselves trying to analyze, describe, categorize, and verbally label behaviors that by their very nature are not amenable to these types of verbal analysis or description. Second, and perhaps most importantly, it is important to keep in mind that behavior itself is not dichotomized, but rather the result of an integrated brain, functioning in an integrated manner, to produce an integrated response. Whether one is referring to a predominately "left hemispheric behavior" such as language or to what might appear to be a predominately "right hemisphere behavior" such as visual–spatial memory, it is clear that both the left and right hemispheres, acting in a complementary manner, contribute to the final output.

As noted earlier, Mountcastle's (1979) concept of a "distributed system" or distributed functions provides an excellent model for describing this behavioral interaction on a hemispheric level. To briefly review, the basic premise of this concept is that there probably are small groups of cells that perform very specific and circumscribed (micro) functions. Even the simplest, elementary behavioral response (or "macro" function) is a result of the interconnection and coordinated response of a specific subset of these groups of cells (or microfunctions) representing varied and diffuse cortical and subcortical areas. Another behavioral response may share some of these same microfunctions, while encompassing others not used by the first. At the hemispheric level, a comparable phenomenon likely occurs. Different neural networks both at a micro- and macrolevel are likely incorporated from both hemispheres for each and every behavioral response. The best we can hope for is to attempt to tease out the unique contributions of each hemisphere (or portion of each hemisphere) by careful analysis of and attention to the behavior in question, the circumstances under which it occurs, and the stimulus and response demands placed on the organism at a given place and time. Through the study of the differential effects of unilateral lesions, we attempt to discern not only the different behavioral effects of hemispheric lesions, but also the often subtle differential effects on a given behavior (e.g., differences in constructional tasks between right and left hemispheric damaged patients). Conversely, in observing or analyzing behavior, there needs to be an awareness of the complexity of the behavior and the multiplicity of factors that contribute to it, including factors that represent potential contributions of both hemispheres. Attention to the "spatial" aspects of mathematical calculations or to the benefits of internal "verbal" cueing in copying a complex geometric design are two, very simple examples.

In the next and final section of this chapter we will review the functions of the primary, secondary, and tertiary cortical zones and explore possible ways in which the cortex processes information and effects behavioral responses.

Endnotes

2. A recent study suggests that the anatomical basis for different classes of words may be much more specifically localized than previously thought (Damasio et al., 1996).

3. The concept of "function" is a construct that humans impose on behavior. What we define as "functions" are not necessarily unitary, invariant, or homogeneous operations of the brain.
4. As noted earlier, there is a fairly weak association between the appearance of this type of cortical atrophy in the elderly and mental status changes. An elderly individual may show signs of significant atrophy on a CT without any significant loss of cognitive ability. In the earlier stages of Alzheimer's disease, there may be significant mental impairment with little or no evidence or cortical atrophy.
5. For a more detailed treatise on this subject, see Evolution and Development of the Cerebral Cortex in *Trends in Neuroscience* (Special Issue) Vol. 18 (9), 1995).
6. The calcarine sulcus passes right through the primary visual projection area. The visual cortex above it (cuneus) processes information that comes from the inferior visual field (contralaterally), while the lingual gyrus is responsible for the superior field.
7. In addition to fibers that enter and exit the cortex vertically, horizontal bands of fibers interconnect neurons in adjacent cortical fields. While present in all cortical layers, they tend to be most prominent in layers IV and V, especially in the primary sensory areas. Generally known as the **bands of Baillarger**, in primary occipital cortex (where they are readily seen by the naked eye), they are called the **line of Gennari**.
8. Occasionally, one might see the term "frontal granular cortex" used with reference to the "prefrontal" or "heteromodal" frontal cortices. Although these frontal cortical areas are not characterized by the same degree of granularity as is found in the primary sensory areas, relatively speaking they are more granular than premotor and primary motor areas (in the posterior portion of the frontal lobes).
9. A distinction needs to be made between these vertical columns (which are fully within the cortex itself), and the broader concept of vertical organization within the brain and CNS as a whole. Again, the latter refers to the fact that integrated feedback loops involving cortical, subcortical, brain stem, cerebellar, or spinal cord structures are essential in effecting specific behaviors.
10. There seems to be some uncertainty whether area 42 should be considered a primary or secondary association area. While parts of 42 receive direct projections from the medial geniculate nuclei, it also receives input from area 41. In addition, area 42 does not show the typical granular pattern characteristic of the other primary sensory cortices (Nolte, 1993, p. 376; Carpenter & Sutin, 1983, p. 678). Regardless, the secondary (unimodal) auditory association cortex in the left hemisphere incorporates Wernicke's area.
11. The reader should recognize this as not only a speculative and highly schematized account of what might transpire at the cortical level, but also, at least for the moment, ignores the contribution of subcortical structures.
12. In theory, there may be other ways for one hemisphere to cue the other than through commissural connections, but this certainly is the most common way this occurs.
13. The posterior commissure is one example where, despite being called a commissure, many of the fibers connect nonhomologous areas of the brain (e.g., oculomotor nuclei with pretectal nuclei). Strictly speaking such fiber systems, which cross the midline to nonhomologous areas on the opposite side, are termed "decussations."
14. Some projection fibers from the olfactory and limbic structures have direct connections with the cortex, rather than going through the thalamus.
15. These concepts will be discussed in greater detail in Part III. For now, they briefly are introduced as to illustrate several classic syndromes to be discussed bellow.

16. According to both Geschwind (1975) and Heilman and Rothi (1993) it appears that the motor engrams for overlearned, skilled movements normally reside in the dominant hemisphere. Thus, for the nondominant left hand to demonstrate such movement, the information must cross from the left to the right hemisphere. The assumption is that this sharing or transfer likely takes place via the corpus callosum between the left and right motor association cortices.
17. In a related example cited by one of the early investigators, slightly embarrassing pictures were flashed to the right hemisphere of a split-brain patient. Although being aware of an emotional reaction to the stimulus (blushing), the patient's left hemisphere was at a loss to explain their reaction, even denying that anything had been seen.
18. While "normalized" behavior in such patients is often explained by cross-cueing between the hemispheres, findings such as this help to raise the question of whether at least in split-brain patients there is one mind or two, a question raised early in the course of these investigations (Sperry, 1968), but as of yet still not satisfactorily resolved.
19. Although commonly used in this context, the designation of function by means of a negative antonym ("nonverbal") likely reflects our limited understanding and/or capacity to succinctly describe the role played by the right hemisphere. This topic will be revisited later.
20. In addition to these gross structural differences, asymmetries of cytoarchitectonic areas within auditory association cortex (Galaburda & Sanides, 1980) and inferior parietal lobule (Eidelberg & Galaburda, 1984) have been reported.
21. As was the case with the temporoparietal areas, certain cytoarchitectonic differences were noted in the frontal regions that might be suggestive of increased complexity in the left frontal speech areas (Shiebel, 1984; Hayes & Lewis, 1993).
22. It should be recalled that the basal ganglia in general (including the globus pallidus) are involved in a broad range of cognitive as well as sensorimotor activities.
23. It is generally presumed that included among left-handers is a small percentage of "pathological left-handers." This would represent those individuals who despite being genetically destined to have language and handedness organized in the left-hemisphere became left-handed (right or mixed hemispheric dominant for language) as the result of early pathology affecting the normal development of the left hemisphere. While there also may be "pathological right-handers," statistically these should be even rarer.
24. This functional dichotomy of the cerebral hemispheres also has been eagerly embraced by the popular press with notions of "right brain" or "left brain" potential (e.g., Edwards, 1979).
25. Before proceeding, we should be reminded that these dichotomies exist more in our mind than in reality and that the brain functions as a whole. Simple introspection provides convincing evidence that even one's performance on tasks that at first glance might appear largely visuoperceptual in nature (e.g., Raven's Progressive Matrices or memory for geometric designs) are heavily influenced by verbal mediation. Although perhaps not as obvious, the converse likely holds equally true for tasks that appear primarily verbal. Thus, when looking at the effects of unilateral or focal brain injury, rather than witnessing how a damaged area of the brain distorts performance on a given task what we may actually be observing is how the rest of the brain carries out a that task without the normal input of the lesioned area. This point will be a major focus of discussion in Part III of this chapter.
26. Alf Brodal, MD, a well-known neuroanatomist, in reporting his own personal experience with a right hemispheric stroke that resulted in a left hemiparesis, describes his subsequent attempts to tie his own tie, a previously well-practiced skill. He writes,

> The appropriate finger movements were difficult to perform with sufficient strength, speed and co-ordination, but it was quite obvious . . . that the main reason for the failure was something else. Under normal conditions the necessary numerous small delicate movements had followed each other in the proper sequence almost automatically, and the act of tying when first started had proceeded without much conscious attention. Subjectively the patient [Brodal] felt as if he had to stop because "his fingers did not know the next move" . . . It was felt as if the delay in the succession of movements (due to paresis and spasticity) interrupted a chain of more or less automatic movements. Consciously directing attention to the finger movements did not improve the performance; on the contrary it made it quite impossible" (Brodal, 1973, p. 679).

27. For illustrative purposes, the following are examples of arithmetical word problems generated by one of the current authors (JEM) in mental status examinations: (1) "If a man has $4 more than his son and, together, they have $13, how much does each have?" (2) If you have four quarters and half that many dimes, how much money would you have?" While the first was intentionally designed to be mathematically simple but conceptually difficult, the latter was intended to be both arithmetically and conceptually fairly simple. The former turned out to be exceedingly difficult for most normal controls, even many college graduates, while the latter proved conceptually difficult for a high percentage of an adult population from limited socioeconomic backgrounds upon which it was tested.
28. "Symbolic gesturing" such as raising a clenched fist (anger or defiance) or a "thumbs up" (praise or approval) is an ideomotor-type response and as such is more likely to be mediated by the left hemisphere (Goodglass & Kaplan, 1963).
29. McDonald and Pearce (1996) provide a good discussion of various elements involved in the detection of sarcasm and the role of the frontal lobes in this process.
30. Assuming the presence of a normal as opposed to an anomalous pattern of dominance, which of course one can never be fully certain.
31. A solid cube generally provides a more stringent test of constructional praxis than asking the patient to reproduce a "transparent" cube. This is because most people have learned how to accomplish the latter by simply drawing two overlapping squares and connecting the respective corners. At times, a patient will use this same strategy to produce a solid cube, but if it happens to face in the wrong direction from the model (or if the model is changed), they often are unable to proceed. A cautionary note: the ability to perform this task, like many others used in neuropsychological investigations, shows considerable variation in a "normal" population and care should be taken to avoid interpreting all performance deficits as "pathological."
32. Individual Object Assembly subtest items from the Wechsler IQ tests may offer varying degrees of cues that are more accessible to the left hemisphere. For example, the "local" cues or internal details present on the "elephant" may be readily recognized by the left hemisphere, thus facilitating its solution. Whereas, the "butterfly" (WAIS-III) provides no such cues.
33. **Dorsal simultanagnosia**, which is associated with Balint's syndrome and results from bilateral occipitoparietal lesions, is differentiated from **ventral simultanagnosia**. The latter, which typically is associated with unilateral, left occipitotemporal lesions, is characterized by greater flexibility in shifting from one visual percept to another, although the ability to integrate the individual visual elements into a meaningful perceptual whole is still impaired (see Endtnote 50).
34. Here we are focusing on cognitive/perceptual processes. However, one should recall that generally the most reliable signs of hemispheric lesions are lateralized changes

in sensorimotor functions, followed by aphasic deficits. Even here, one needs to be aware of two obvious caveats. The first is to rule out more caudal lesions along the neuroaxis or peripheral pathology (in the case of sensorimotor deficits), and second, left-handedness (in the case of aphasic deficits). In the latter situation, recall that while the odds still favor left-hemisphere involvement, the probability is reduced compared to natural right-handers.

35. While neglect seems to be most frequently associated with lesions involving the posterior, heteromodal association cortices, it also can be seen following lesions to the frontal cortex, subcortical structures, and even upper brain stem.

Chapter 9 ♦ Part III

PART III. THEORIES OF FUNCTIONAL ORGANIZATION OF THE BRAIN

CHAPTER 9, PART III OVERVIEW

Hopefully, some of the things that separate the scientist–practitioner from the average technician are an appreciation of the principles underlying the observed phenomena and the ability to integrate new phenomena into useful and meaningful constructs based on an understanding of unifying theoretical models. While theories have abounded in physics and mathematics for centuries, complete understanding of true unifying principles often remains elusive. In physics, for example, it has been the search for a model that would explain and integrate the strong nuclear force that binds the subatomic particles in the nucleus of the atom with those of the weak nuclear force accounting for radioactivity and the electromagnetic force that explains the orbits of electrons. As suggested earlier, the neurobehavioral sciences are still in their relative infancy and we are likely much further from discovering such unifying principles. This, however, should not dissuade us from the search, for it is from the search itself that knowledge and understanding progresses. In this final section on the cerebral cortex, there is an attempt to provide some very tentative ideas into what may prove to be one of nature's greatest mysteries: the functional organization of the brain. No great insights or revelations are promised. To the contrary, most of the ideas presented here are not new. Rather they are derived, for the most part, from models introduced by earlier theorists, notably Luria, Mesulam, Geschwind, Heilman, Mountcastle, among others. What is hoped is simply to provide the reader with a framework by which he or she may think of brain function (or dysfunction) in a dynamic fashion, to hone and further define their own conceptualization of how the brain responds to internal and external cues and demands, and of how thoughts become translated into actions. Even as the final solutions continue to evade us, we trust that the joy will be in the search as much as in the discovery.

In this section, following Luria's model, we divide the brain into three primary functional units: those basically responsible for attention and arousal (motivation), processing and storage of information, and expressive behavior. With regard to the first functional unit, the role of subcortical structures and the limbic system in initiating or maintaining cortical arousal briefly will be explored. Next, we will discuss how sensory information (primarily vision, audition, and somesthesia) might be transformed from elementary sensations to meaningful, unimodal percepts, and ultimately to complex, multimodal concepts. We shall discuss how the latter may allow for abstractive abilities and other higher-level cognition. Along the way, we also shall review how lesions affecting the various stages in this process may result in specific behavioral syndromes. Finally, considerable attention will be devoted to the frontal lobes or what has been described as the "executive system." Here we will explore the suspected neuroanatomical substrates of decision-making, including the individual's response to such questions as "if, when, where, why, and how should I respond?" In the course of trying to answer such questions, we will address the suspected role of the prefrontal cortex in arousal, intention, attention, inhibition, planning and organization, comparison of performance to goals, and modulation or control of basic drives, and again how disturbances of these functions might be expressed behaviorally. Finally, we will examine how plans and intentions likely are translated into overt motor behavior via the primary and secondary motor cortices.

Thus, at the conclusion of this chapter, one should have a better understanding of the neuroanatomy of the cerebral cortex and its general functional correlates. In addition, hopefully one will begin to consider the brain's potential organization and how even the simplest of actions are likely the result of complex interactions involving wide expanses of brain tissue. Conversely, one might derive a fuller appreciation of how diverse lesions may differentially affect similar behaviors. Again, we are merely scratching the threshold in our attempt to understand this magnificent organ, but the deeper the puzzle, the more intriguing the search.

INTRODUCTION

In Part II of this chapter a number of the better known associations between specific symptoms or behaviors and specific regions of the cortex were reviewed . As we have seen, these correlations initially were established through the study of the effects of focal brain injuries (and more recently supported by technological advances in brain mapping, such as the PET scan and functional MRI). While these approaches provide valuable clinical and scientific information, a fundamental question still remains: "Is there any type of unifying theory to help account for these observations?" Beginning with Broca and continuing into the early part of the 20th century, most of the aphasic, apraxic, and agnosic syndromes that we know today were identified. In some respects, however, these findings might be viewed as the new and improved (albeit more clinically relevant and scientifically sound) "phrenology." The names of the functions were changed and the cranial bumps were gone, but in many respects the principle remained pretty much the same, namely to identify "centers" for various behavioral functions that could be associated with specific areas of the cortex. In this endeavor, behaviors were matched or associated with specific gyri or cytoarchitectural areas simply as a matter of clinical correlation. In these earlier stages of discovery, there seemed to be relatively little effort to understand or explain *why* that particular gyrus or area was necessarily involved with a particular function.

Using only this correlation approach, it was difficult to explain why lesions in different cortical areas, sometimes even in different hemispheres, appeared to produce comparable deficits on similar tasks. Also, while specific cortical areas might be fairly reliably associated with certain specific signs, symptoms, or behaviors, as the behaviors or tasks became more complex, such predictions often became less reliable. Beyond the strict "localizationists" and those espousing the theory of "mass action and equipotentiality," there were few other attempts to develop a unifying theory to account for the observed relationships between structure and function.[36] It might be noted that even during the late 1800s when enthusiasm for localization of function was perhaps at its peak, Hughlings Jackson began to question what localization actually meant. From the very outset, Jackson argued for a vertical organization of behavior. He suggested that behavioral functions were likely organized in different ways, at different levels of the nervous system, and as a result the localization of a *symptom* did not necessarily mean the localization of a *function*. Despite Jackson's contributions, overall there was little progress in the early part of this century to integrate the emerging clinical data into a more unified theory of brain organization. Perhaps the first truly comprehensive attempt to do this is reflected in the efforts of Aleksandr Romanovich Luria (1966) in his book, *Higher Cortical Functions in Man.* First published in Russia in 1962, this work still serves as the most comprehensive, macroscopic model of brain organization available to date.

The third part of this chapter will attempt to present a heuristic model, based in part on the theories outlined by Luria, for conceptualizing behavioral functions and their organization in the brain, particularly with regard to the cortex. This model hopefully will provide the reader with a tool to systematically analyze a broad range of behaviors, including performance on neuropsychological measures.

Defining "Function"

Luria gave credit to Hughlings Jackson and to Pavlov for redefining the concept *function*, thus setting the stage for the concept of **dynamic localization.** Luria suggested that the first step in developing a theory of brain organization and function was to understand how behavior itself ("function") was defined or conceptualized. The early localizationists tended to look at "functions" as circumscribed, self-contained behavioral units that were controlled by equally circumscribed, self-contained groups of cells in a particular area of the brain. Luria pointed out that while such a description might be adequate when speaking of the "function" of the pancreas (i.e., to produce insulin), as behavior became more complex, this approach to defining function became less meaningful. He suggested that the behaviors that we normally attribute to the brain, behaviors such as speech, perception, arithmetical calculations, and learning, are infinitely more complex and should be referred to as **functional systems**. Luria's notion was that such behaviors are composed of many elements, involving multiple cortical (and subcortical) units, acting in a coordinated fashion to effect the desired goal. Depending on time and circumstance, some of the individual elements (brain units) called upon might vary, although the behavioral goal should remain constant.

To illustrate, if someone is asked to point to a picture of a flower, what "function" is being tapped? One possibility is that there is a group of "flower recognition" neurons located 237 millimicrons due east of the end of the superior temporal sulcus that carries out this task all by itself, which we "strongly suspect" is not the case. Although oversimplified, the following scenario may be closer to what actually happens. First, there must be a general level of awareness or cortical activation so that the nervous system is capable of responding. That awareness or "attention" must be focused on the examiner and the test materials. Assuming that the peripheral auditory (and visual) mechanisms are intact, the examiner's instructions must be processed cortically. This is not a single-step process. In the case of the command "point to the flower," the incoming auditory stimuli need to be decoded into individual phonemes and then encoded into phonemic groupings that can be recognized as a specific word, "flower." The "word" must be associated with a variety of past experiences (e.g., shape, color, smell, and texture) to give the word meaning. In this latter process, a certain amount of abstraction or synthesis of all individual experiences is required so that such diverse shapes and colors as represented by the rose and a dandelion will be considered as potential choices. Simultaneously, visual input must be decoded in the striate cortex and then encoded into an integrated pattern that separates figure from ground. This "percept" also is compared to previous experiences that may elicit multiple associations, including tactile, olfactory, as well as the auditory association with the word "flower." Probably somewhere between the idiotypic cortices of the occipital pole and the middle of the superior temporal gyrus (the primary visual and auditory reception areas), these two processes come together so that the auditory percept and the visual percept are recognized as relating to the same entity. This is still not the end of the process. This "information" is then conveyed to the prefrontal cortices where, after "consulting" with parts of the limbic system to check on the prevailing mood state and current "feelings" with regard to the immediate situation and/or this particular examiner, a "decision" is made as to whether a response is to be made and what the nature of that response might be. Only if and when a response is chosen are signals then conveyed through the premotor to the motor cortex to effect the desired movement. The smooth, accurate execution of this movement also requires the integration of subcortical (e.g., basal ganglia, cerebellar) and cortical (occipitoparietal) feedback.

A central idea in much of Luria's writing is that behavior can be disrupted at any point ("point" meaning either behavioral or structural) in the stimulus–response process. Hence, while different areas of the brain may have uniquely contributed to each stage in this process, for the behavior to be smoothly and efficiently executed multiple areas of the brain acting in concert are required. This basically is the same principle behind the notion of **distributed systems** that was discussed earlier in this chapter. The corollary is that depending at which stage or locus in the brain problems might have been encountered, the nature of the behavioral disturbance varies. When such variations are taken into account, clues are provided as to which areas of the brain or what pathways might be involved. Similar analyses also are useful in identifying what elementary behavioral process(es) are likely disturbed. Such information not only allows for a better understanding of immediately observed deficits, but also allows for better prediction of potential difficulties across multiple tasks or situations.

To summarize, Luria (1973) suggested that the study of brain–behavior relationships should begin with two critical steps. The first requires an examination of the particular "mental activity" (symptom, behavior) in question to determine what specific factors (i.e., more elementary functions) are essential for its successful execution. The second is to analyze the expression of that behavior in the brain-injured individual, paying particular attention to the types of errors made, in order to develop hypotheses as to the specific nature of the underlying deficit(s) in a given case. These insights then are combined with information regarding the specific focus of the lesion across cases, comparing the common elements or factors that appear to result from lesions in a given cortical area, as well as analyzing how similar behaviors are differentially affected by lesions in different cortical areas. Over time a picture should begin to emerge both as to how "functions" are mapped within the brain and how these individual functions are integrated to produce specific, observed behaviors.

Before proceeding, however, two additional points are worthy of mention. The first is that while at first glance this seems to be simply a resurrection of 19th century localization theories, there are some significant differences. The earlier theories focused on *molar* (more complex) behaviors that were thought to be more or less self-contained within a limited cortical area. The latter approach focuses on discrete, *molecular* (more elementary) behaviors distributed throughout the brain that are combined and recombined in a multitude of varying organizational patterns and that we observe as complex behavior. Second, even these patterns or interconnected networks of microbehavioral elements are not necessarily fixed and immutable within or between individuals. Different individuals may have learned different strategies or approaches to accomplish a given task. For the same individual, dynamic changes may occur over time with learning or experience (e.g., when first learning to read, one often attends to the learned acoustical patterns associated with particular letters; however, once well learned this process is discarded or reduced in importance).[37]

FUNCTIONAL ORGANIZATION OF THE BRAIN: LURIA'S MODEL REVISITED

In searching for a theoretical model to conceptualize, and hence, approach a fuller understanding of the higher level mental activities of the brain, Luria began by dividing the brain into three functional (quasivertical) units and the cortex into three horizontal zones. Volitional mental activity was thought to require the integrity of these three functional units with the various cortical zones working in concert with one another. The cortical zones, to be covered in a later section, provide a framework for understanding the progressive analysis and integration of behavior. More immediately, the focus will be on the three major functional units of the brain, which are (1) attention and arousal, (2) information processing, and (3) executive functions. The first unit, which Luria described as the unit responsible for **regulating cortical tone**, will be divided into three separate components: (1) the reticular activating system, which is responsible for general, nonspecific arousal; (2) the thalamus, which is largely responsible for selective attention and cortical modulation; and (3) the "limbic" structures, which is involved in emotion, motivation, or "goal-directed" arousal, as well as learning and memory. The second or **gnostic** functional unit encompasses the temporal, parietal, and occipital lobes and is thought to be responsible for obtaining, processing, and storage of information from the outside world. Finally, the third or **executive** unit, which primarily involves the frontal systems, can be characterized as being concerned with programming, regulating, and verifying mental activity.

The following discussion largely represents a synopsis of the theories as originally set forth in Luria's *Higher Cortical Functions in Man* (1966), and in *The Working Brain* (1973). Since that time, his approach to understanding the functional operation of the brain has continued to evolve through the work of such individuals as Norman Geschwind, Marsel Mesulam, Kenneth Heilman, and Edith Kaplan, among others. The remainder of this chapter will attempt to revisit and elaborate on those ideas.

THE FIRST FUNCTIONAL UNIT: ATTENTION AND AROUSAL

Directed and Non-directed Attention: The Reticular Activating System and the Thalamus

Goal-directed behavior generally is predicated on the capacity for focused and sustained attention. In order to achieve and maintain this state, two more basic elements are required: (1) a certain level of optimal arousal of the cerebral cortex, and (2) adequate drive or motivation. Diminished arousal (e.g., in states of lethargy, stupor, or obtundation) or hyperexcitability (e.g., excessive anxiety or panic) both can interfere with efficient mental operations. Lack of sufficient drive states also can result in the failure to initiate behavior (despite adequate alertness or arousal) or result in the inability to sustain and direct behavior long enough to accomplish its intended goal. Because of the importance of optimal levels of arousal underlying all successful mental activities, the reticular activating system (RAS) and the thalamus were thought to be the cornerstones of this first functional unit. Since the structure and function of the RAS and the thalamus were discussed in some detail in Chapters 4 and 7, only a few general comments will be made here.

The RAS and the thalamus are thought to be responsible for the tonic or "state-dependent" arousal of the two other functional units of the brain. In turn, these regions are responsive to external stimuli, as well as internal influences (e.g., hypothalamic or cortical feedback). We have all experienced the *arousal* value of an "unexpected" tap on our shoulder or a sudden loud noise. By contrast, an "expected," "nonthreatening" stimulus might evoke relatively little response, unless of course it takes on added signal value as a function of past experiences, expectations, or enhanced vigilance. The latter might be present, for example, in anxiety or paranoid states. This type of signal enhancement generally is the result of input from higher-level functional units, or is produced at a higher level within the first functional unit (e.g., limbic system). Such descending influences, which can be either excitatory or inhibitory, are often state-dependent. For example, the smell of food will have a different arousal value on the RAS in a sated versus a hungry organism. Similarly, the recollection or thought of a test the next day might have different "arousal" value in the well-prepared versus the not-so-well-prepared student.

As noted in Chapter 7, the role of the thalamic nuclei in the activation of the cortex is not completely understood. Whereas different nuclei may subserve somewhat different functions, collectively these nuclei appear to be responsible for altering cortical tone or arousal by serving as gating or filtering mechanisms for incoming stimuli. Recall that the thalamus apparently selectively screens out (or selectively attends to) those sensory inputs or cortical processes most critical at the moment. In addition, some thalamic nuclei may serve to selectively modulate or "shift attention" to different cortical zones depending on circumstances. If this type of selective attention and activation did not occur, the organism might either (1) attempt to attend to everything at once, or (2) selectively attend to stimuli primarily based on intrinsic properties of the stimulus (e.g., stimulus intensity or novelty) rather than on its teleological relevance. While the latter does occur to some extent, maximal efficiency of cognitive/behavioral functioning demands that under normal circumstances attention is focused on stimuli related to a narrow range of problems or goals at any given time. Because the function of this first unit is so essential to the optimal operation of the second and third functional units, the patient's level of arousal must be taken into account when considering any apparent breakdown in "higher cortical behaviors" such as learning and memory, perception, or problem solving. The inability to selectively attend to relevant or to screen out irrelevant stimuli and the subsequent compromise of cognitive efficiency appears to be part of the problem in diverse pathological conditions. These may include conditions where there is diminished levels of arousal (e.g., severe depression), excessive levels of arousal (e.g., manic or anxiety states, amphetamine abuse), and/or disruptions of the filtering system such as would appear to be the case in such diverse conditions as agitated delirium, head trauma, or attention deficit disorders.

Drive: The Role of the Limbic System in Arousal (Motivation)

The third subdivision of this first functional unit[38] primarily consists of structures generally associated with the "limbic system." While these structures and their functions were discussed in detail in Chapter 8, it may be useful to briefly revisit the limbic contributions of this first functional unit and preview a few key relationships between the first functional unit and the second and third units.

Although Luria primarily focused on the second (gnostic) and third (executive) functional units, he recognized that the "activating" and/or "motivating" influences of the first unit were an essential component of behavior. He postulated that changes in homeostasis as well as external stimuli were important in cortical "arousal" and in initiating (i.e., prompting) behavioral responses. These responses were thought to be mediated primarily via their influence on the ascending RAS. In addition, he recognized the potential for the brain itself, specifically the third functional unit (the "executive system"), to evoke behavioral responses, as in the establishment of goals and the formulation of the plans by which they might be achieved. However, he also appreciated the fact that the "energy" (drive, motivation) to implement these activities probably was derived not from the third functional units itself but rather from phylogenetically older structures or more intermediate cortex comprising the medial zones of the cerebral hemispheres. These areas, which now frequently are referred to as the “limbic system,” were thought to serve an important link between the cortex and the RAS. He stated:

> the principle function of these brain zones [limbic structures] is not communication with the outside world (the reception and analysis of information, the programming of actions), but the regulation of the general state, modification of tone, and control over the inclinations and emotions (Luria, 1973, p. 60).

Today, these limbic structures still are associated with such constructs as “drive,” “energy,” “will,” or “motivation.” As Luria suggested, the influence of these limbic structures, including the hypothalamus, in prompting and sustaining goal-directed behavior is extensive. As noted, the stimuli to which the structures of this first functional unit respond may be either internal or external and may involve (1) the regulation of basic biological homeostatic mechanisms, (2) instinctually guided behaviors, (3) acquired or learned response patterns, or at the highest level (4) abstract or long-range goals or ideas. Their impact is both ascending (affecting the telencephalon)[39] as well as descending (having an influence on the brainstem and the RAS). This influence may elicit positive (approach) or negative (avoidance) or even relatively neutral response patterns, depending on the overall state of the organism or the environmental context in which the stimulus occurs.

By way of brief review, hunger or thirst provides a good example of basic biological needs or homeostatic drives that may be “initiated” by the first functional unit at the level of the hypothalamus. The “drive” state initiated at this level subsequently recruits the second and third systems to satisfy this need by implementing a search for and/or coordinated response to potential sources of food or water. “Nest building” and the feeding and protection of one’s offspring are examples of “instinctual behaviors” that are thought to be mediated by more recently developed limbic structures, such as the cingulate gyrus in vertebrates, and whose analogues can be seen in human parental behaviors. Highly species-specific avoidance-type responses also seem to be built into most individuals in the animal kingdom. Whether it is a sudden “dimming” stimulus (for the frog), the silhouette of a flying hawk (for the chicken), or perhaps the sight of a decapitated body (for primates, including humans), there normally is a strong drive to take some type of evasive action. The capacity of certain stimuli to elicit approach or avoidance responses based on the previous experiences also is well known. The sight of a loved one following a prolonged absence versus that of a neighborhood bully by a child may elicit equally strong, but highly divergent emotional and behavioral responses.

In the examples presented above, the stimuli, which lead to a state of arousal or a response drive, relate primarily to the first functional unit itself (homeostasis) or to stimuli associated with the second functional unit (i.e., external stimuli that have acquired a specific emotional coloring, either as a result of the preprogramming or past experiences of the individual). However, there is one other important source of drive or emotional valance listed above, namely that which is derived from more abstract or long-range goals or plans. It is the latter that usually is specifically linked to the third (executive) functional unit (the frontal lobe) and perhaps is most readily appreciated in humans. Immediate stimuli, initially perceived as affectively neutral or even imagined or anticipated stimuli (including abstract ideas), can take on motivational significance (i.e., have arousal value) because of their relationship to long-range goals or plans. For example, one may have the plan to attend college. The goal eventually may be to land a well-paying job in order to have financial security and all the other things this provides. To secure this goal, you need not only the initial motivation to get started (e.g., going to college), but sustained drive and energy throughout the process to meet the more intermediate goals (e.g., passing the next exam). The drive or emotion necessary to sustain these efforts on a day-to-day basis likely requires the mediation of limbic structures.

While experimental evidence for this type of frontal–limbic interaction is difficult to obtain in humans, there is strong clinical evidence of its existence. It is not uncommon to find patients, particularly those with bifrontal lesions, who repeatedly make elaborate plans to return to work or to engage in other meaningful, productive endeavors yet never demonstrate the motivation or initiative to carry out these plans. If they manage to actually get started, they often falter, especially if difficulties are encountered. Thus, it is not the ability the make plans that is affected by such lesions, but the motivation, energy, or emotional drive to execute and sustain them. It is easy to speculate that the critical lesion in such cases is the severing of the connections between the dorsolateral frontal lobes and the limbic or paralimbic structures. As we have seen, further evidence is derived from the observation that lesions that are more or less restricted to the anterior cingulate gyrus or dorsomedial frontal cortices also have been shown to produce marked apathy or inertia in patients.

In addition to providing the drive for future goals or plans, these frontal–limbic connections play a role in many other aspects of day-to-day behavior. One of these roles is the motivational or emotional influence of learned socialization on behavior. Social approval (or disapproval) normally is a very powerfully motivating force, whether it is encoded as the social mores or religious beliefs of the larger community or in the idiosyncratic customs or expectations of one's peer group. In these cases, often the reinforcement does not have to be immediately present. Simply the memory (which also may be mediated by certain limbic structures) of past, more direct social reinforcements (e.g., a hug or a smile, or perhaps a scolding) or the capacity to predict the possibility of such future reinforcements, whether positive or negative, usually is sufficient to guide the behavior. As we will see, frontal lesions can lead to a breakdown in these patterns of "emotional control" (reinforcement) over behavior. Patients with certain types of frontal pathology, especially if the orbitofrontal areas are implicated bilaterally, may behave as if they are "indifferent" to the social consequences of their behavior. They may become crude, impulsive and, at times, grossly socially inappropriate. An example of the latter would be the frontally impaired gentleman, previously considered to be very refined, who stopped to urinate in public while accompanying his wife out to dinner. While the "indifference" to personal hygiene and grooming sometimes seen in "frontal" patients also might be interpreted as a failure in socially derived motivation, it may reflect a disturbance of even more primitive, instinctual phenomena, as similar behavior can be seen in lower-order primates with frontal lesions.

These observations emphasize a critical aspect of frontal–limbic connections, namely the importance of reciprocal control or modulation between these cerebral systems. Phylogenetically, it is likely that most basic drive states are preprogrammed for more or less immediate gratification. If the organism is hungry, it seeks food; if it is frightened, it flees; if its young are threatened, it attacks; if it is sexually stimulated, it seeks fulfillment. However, as we have seen, it may not always be in the best interest of the individual to immediately respond to each and every stimulus or drive state the moment it is experienced. One may decide it is better to delay immediate gratification in deference to a future, acquired (abstract or social) goal or objective. Conversely, one might choose to confront rather than avoid a frightening or unpleasant situation now in order to achieve a long-term goal or to avoid the possibility of an even greater unpleasant future consequence (e.g., "Do I want to satisfy my need for sleep or try to stay up and study so I can pass the exam?").

Not infrequently, the immediate gratification of two or more current drive states may be incompatible. In these cases, the individual must determine which goal has the greater priority or perhaps derive a strategy whereby one drive might be satisfied without sacrificing the other. This prioritization or assigning of values to different drive states is thought to be a primary function of "higher cortical centers," specifically the third functional unit. The role of the third functional unit will be discussed in greater detail later in this chapter. For now the reader should simply be aware that lesions can disrupt either the source of this capacity for decision making or judgments (i.e., the frontal lobes) or its reciprocal connections with the limbic structures. Either might produce a variety of clinical pictures that may result in behavioral disinhibition, poor judgment, inability to delay gratification, or impulsivity. In addition to the brief examples presented above, the following section offers a glimpse into a few other situations where a disturbance of these frontal–limbic connections might impact behavior.

Other Behaviors Likely Associated with Frontal–Limbic Disconnections

Pseudobulbar Affect

Patients with bilateral frontal damage (either cortical or subcortical) may evidence increased emotional lability under certain stimulus conditions. For example, they may be moved to crying in situations that elicit feelings of tenderness or sympathy for others or by discussions that may remind them of their own losses. While such a reaction is not necessarily inappropriate, many individuals have learned that certain emotional displays, such as crying, are not "expected" in certain situations. As a result, the expression of certain types of emotions (e.g., crying) are commonly suppressed, particularly in public, and often even in situations where it may be considered appropriate, such as funerals. Patients with bilateral frontal or subfrontal lesions commonly are not so inhibited. Such patientsoften are said to "show emotions," despite the absence of any apparent underlying affect (the so-called *pseudobulbar affect*).[40] While the cause of the displayed affect (usually crying) may not be immediately obvious, on careful questioning a specific stimulus or underlying mood consistent with the affect being expressed usually can be uncovered. A disconnection between the frontal and limbic systems, resulting in diminished frontal control or modulation of these emotional drive states would appear to be a likely contributor to this condition. The fact that the mood may be very transient and the provocation minimal not only might help explain the significance of such disconnections in eliciting this effect but also might explain the patient's reticence to admit to breaking down given such a minimal provocation. As a corollary to this hypothesis, it might be noted that children also are less likely to suppress their emotions. On the one hand, it might be argued that this is because they have not yet learned the social stigma attached to such emotional expression. However, their relative lack of constraint with regard to emotional expression also might be related to developmental delays in the myelination of the frontal lobes.

Sociopathy

The capacity to link previously experienced feelings to the anticipated outcome or consequences of our own behavior in part allows one to develop a sense of empathy for others. Empathy is not simply a cognitive awareness of the connection between behavior and affect (an awareness that the sociopath or "con man" clearly manipulates to his [or her] advantage), but the capacity to vicariously "experience" the emotion. For true sociopaths, one might suspect a "hard wiring" defect (e.g., a type of learning disability) that interferes with either the capacity to fully experience certain emotions (limbic deficit) and/or an inability to establish these connections as a result of frontal or frontal–limbic aberrations. This hypothesis, however, is not meant to discount the role of environment and learning in shaping these behaviors.

Real Life versus "Abstract" Judgment

The role of the third functional unit in modulating limbic emotional or drive states becomes an important consideration in the mental status examination of brain-injured patients. It is common practice to estimate a patient's judgment by asking how he or she would respond in given situations, for example, "What should you do if you noticed a fire in a movie theater?" In this instance, we might witness a breakdown in "judgment" simply due to cognitive impulsivity. However, the essential element that typically is missing in this situation is the presence of intense emotional stimulation. It is one thing to ask a patient with frontal–limbic lesions how they *should* respond in a hypothetical situation that at the moment is relatively free of any strong affective pull versus observing how they would respond in the actual situation with its normally attendant emotional arousal (e.g., fear). In the context of the mental status examination, the patient merely has to fall back on previously learned cognitive associations or at best reasoning capacity. However, in real-life situations, there has to be an active subordination of the initial behavioral impulse elicited by the emotional or affective pull of the situation (e.g., to flee in the case of a fire) in service of another overriding goal or consideration, namely the superordinate goal of avoiding panic and ensuring the safety of others.

THE SECOND FUNCTIONAL UNIT: INFORMATION PROCESSING

The Three Horizontal Zones of the Second Functional Unit

The second functional unit encompasses the parietal, occipital, and temporal lobes, excluding the medial limbic and paralimbic structures. Luria refers to this functional unit as the "gnostic" portion of the brain. While the first unit was responsible for arousal and drive, the second functional unit is believed to be primarily responsible for the reception, analysis, and storage of information, largely but not exclusively obtained from the outside world. This input, which primarily comes from the sensory modalities (e.g., visual, auditory-vestibular, somatosensory, gustatory, and olfactory), first needs to be "decoded" from the bioelectrical impulses carried from the peripheral receptors to the brain. Next, this information then must be encoded into meaningful units, analyzed, and integrated with other previous or concurrent information to enable the organism to arrive at some understanding of its immediate environment. These data then are cataloged and stored to provide a "library of information" through which we gradually increase our capacity to appreciate, anticipate, and manipulate our environment. Finally, it is this data bank that facilitates the development of superordinate concepts based on common and overlapping elements. In humans, at least, these processes likely also provide the substrate for abstract thought and the communication of ideas.

A key to understanding the second functional unit involves an appreciation of its division into primary, secondary, and tertiary (horizontal) zones.[41] Mesulam (2000b) describes these functional regions as "modality-specific" or "unimodal" association cortex when referring to Luria's secondary zone and "higher-order" or "heteromodal" association cortex when referring to the tertiary zone. Both the secondary (modality-specific) and the tertiary (heteromodal) cortices also are referred to as "homotypical" cortex, while the first or primary zones have been designated as "idiotypic" cortex (Mesulam, 2000b).

Before proceeding to a more in-depth look at these various zones within the second functional unit, a brief review of several concepts touched on earlier might be useful. Each of the three major senses represented in the second functional unit (vision, hearing, and somesthesia) has its own primary and secondary zones (the third zone, by definition, being multimodal).[42] Each primary zone of the second functional unit consists primarily of granular or koniocortex cortex. These zones represent the primary cortical projection areas for each of the respective senses via the specific sensory relay nuclei of the thalamus. The cells in these areas respond only to the sensory input from that modality and are responsible for the initial decoding of that information. The comparable zone in each hemisphere selectively may respond to the spatial source of the incoming stimuli (i.e., right versus left fields, particularly vision and touch). However, at this level there would appear to be much less (if any) functional differentiation as to the exact nature of the stimuli, that is, it is not certain that there is clear hemispheric specialization in the decoding of information at the level of the primary zones. Hemispheric differentiation in the processing of sensory input becomes increasingly evident as information gets channeled through the secondary and tertiary zones. Thus, lesions involving the primary zones theoretically will result in primary sensory disturbances (e.g., blindness, deafness, and loss of tactile sensation). However, because of the redundancy that is built into the system, with the exception of lesions involving the primary visual cortices and the resulting visual field cuts, unilateral lesions generally have limited effects. The cortical projections of these primary zones are to their respective secondary zones that surround or are adjacent to each of the primary zones. It is likely that these projections to the secondary zones are contralateral as well as ipsilateral.

The secondary zones, in turn, would appear to be responsible for the further organization of the output of their respective primary cortical projection areas into more highly integrated, meaningful percepts such as recognizable phonemes, words, or visual or tactile images or percepts. Information processing in each of the secondary zones still is thought to be largely, if not totally, restricted to each of the respective sensory modalities. That is, the secondary zones are modality-specific (unimodal association cortex) and damage restricted to these areas lead to modality-specific, perceptual deficits, while elementary sensations may remain essentially intact. As opposed to the primary zones, hemispheric specialization likely is to be observed at this level. Again, there likely is to be interhemispheric transfer of information between these homologous zones, as well as to the third functional units in each hemisphere.

Finally, each of these secondary, or unimodal, association areas provides convergent input to the tertiary zone(s) of the second functional unit. In these regions, evoked potential responses can be elicited from multimodal stimuli, perhaps even in individual cells. Very little of the knowledge we have about the outside world is strictly unimodal. As we step into a hot shower, we appreciate the temperature of the water on our skin (*somesthesia*), as well as observing the steam or the fog forming on the windows (*vision*). Similarly, we associate the volume or amount of water being used by the force with which it strikes our skin (*mechanical, pressure receptors*), as well as by the intensity of the sound made by the water as it falls to the floor of the tub (*audition*). Even if our experience is not immediately multisensory, we can call on past experiences to build on such associations. For example, as a result of past experiences, by simply seeing a chair, one can make an estimate of what it will feel like to sit on it or how heavy it will be if one tries to lift it. It is in the tertiary zones of the second functional unit within each hemisphere that the processed, integrated percepts from each of the senses can be combined, compared, and associated with one another. In turn, it is this higher-order, multimodal integration of information that, as noted above, allows for the full richness of associative knowledge of the outside world and that in humans forms the basis for deriving abstract concepts. As a result, damage to these areas are not restricted to any single modality, and it is in these tertiary regions of the second functional unit in which hemispheric specialization is most evident. Additional examples of how multimodal sensory integration may take place in this tertiary zone will be presented below as the various modalities are individually discussed.

Auditory Processing in the Second Functional Unit

The Primary and Secondary Auditory Zones

The primary cortical projection area for the auditory system and the medial geniculate nuclei is Heschl's area, located along the Sylvian fissure on the transverse gyrus of Heschl

(Brodmann's area 41), with the adjacent area 42 apparently also receiving some direct projections from the medial geniculates. Area 22, which constitutes a portion of the superior temporal gyrus, immediately surrounds areas 41 and 42. Area 22 (the posterior portion of which is commonly referred to as Wernicke's area) likely comprises the major part of the secondary auditory cortex or auditory unimodal association cortex. Parts of area 21 also at times are included as part of this secondary zone.

Unlike the primary visual and somatosensory cortices, there is an admixture of contralateral and unilateral pathways throughout much of the auditory system beginning with fibers leaving the cochlear nuclei. Hence, by the time the auditory projections (which originate in the organ of Corti) reach the cortex, approximately 60% of the fibers represent contralateral pathways, with the remaining 40% consisting of unilateral fibers. The primary auditory cortex is characterized by an organized pattern of "topographical" representation (not unlike the visual and somatosensory systems). In the case of audition, however, this representation becomes a matter of *tonotopic* organization, with lower frequencies being located at different cortical sites than higher frequencies. The function of the primary auditory cortex likely involves the preliminary decoding and transformation of incoming auditory information and storage of this information (probably short term) prior to higher-level analysis. The secondary or unimodal association auditory cortices then are thought to be responsible for decoding (analyzing) and encoding (synthesizing) the auditory input into meaningful or recognizable "chunks" or percepts. This latter process appears to be hemispherically differentiated, for example, phonemes and words in the left hemisphere and nonverbal patterns in the right hemisphere.

Effects of Lesions to the Primary Auditory Cortex. As a result of the bilateral projections to the auditory cortex, unilateral hearing deficiencies following unilateral cortical damage to Heschl's area tend to be very subtle. The only difficulties that may be observed in such lesions are increased difficulty with sound localization and a mildly elevated threshold for sound perception in the contralateral ear. Even the results of dichotic listening tasks, which have been used to study such lesions, often are seen as inconclusive. Although rare, central (cortical) deafness may result from bilateral lesions of Heschl's gyrus or ascending subcortical white matter pathways. Left-sided (dominant hemisphere) lesions, if limited to the primary auditory cortex, typically do not result in any observable language-related deficits. In addition to reflecting the general lack of functional lateralization in the primary cortical zones, this also suggests that auditory input to Heschl's area in the right hemisphere is not funneled exclusively to the primary auditory cortex of the left hemisphere via commissural pathways. Rather, there probably are interhemispheric connections between the primary zones and the contralateral secondary auditory zones. There would appear to be evidence of a comparable arrangement in the visual system. In the visual system, lesions isolated to the left primary visual cortex producing a right visual field defect do not impair reading ability for stimuli in the left visual field unless the interhemispheric connections are disrupted by extension of the lesion into the splenium of the corpus callosum (see: *alexia without agraphia, p. 329*).

Effects of Lesions to the Secondary Auditory Cortex. A major cortical lesion, which is restricted to the secondary auditory association area of the left hemisphere, would account for the somewhat rare phenomenon of pure word deafness or verbal auditory agnosia. In this syndrome, the patient has intact hearing; can identify nonverbal, environmental sounds; can speak, read, and write normally; but cannot understand or repeat spoken language (a comparable deficit with nonverbal sounds may occur with nondominant hemispheric lesions). Less complete lesions of this area would be expected to produce increased difficulty in processing phonemic material without a complete loss of capacity. Thus, while simple, highly familiar, single words might be understood, anything that puts additional stress on the system might lead to impairment. Examples might include someone speaking in a thick, foreign accent, listening in the presence of background noises or in a group where multiple people may be speaking at once, or having to process a string of words or multistep commands, especially if they are not well articulated or complex. These types of deficits reflect problems that still are at a relatively basic perceptual level. If such a lesion were to take place prior to or during the early stages of language or speech development, especially if bilateral, one would expect that a sound-based language (as opposed to a visual-based language) either would, never develop or would be extremely compromised. We might expect such results because the basic building blocks for aural language, that is, the appreciation of phonemes and the capacity to integrate or group phonemes into word units, have been disrupted.

Audition and the Posterior Heteromodal (Tertiary) Cortices

As noted above, the secondary or unimodal auditory association cortex serves an intermediary role, transforming the relatively elementary sensory input to primary auditory cortical zone (Heschl's gyrus) into more refined, organized, wholistic (yet still unimodal) percepts (i.e., words or word-sounds).[43] At this point, however, these word-sounds, while perhaps recognizable (i.e., familiar sounding), probably are devoid of meaning or reference. The next step in the auditory process is for this information in the unimodal, homotypic cortex (secondary zone) to be transmitted to or linked with the posterior, heteromodal association cortex of the tertiary zone. Here the information can be integrated with information coming from the unimodal, secondary zones of other sensory systems. It is probably only then as a result of this convergence of concurrent and/or previous multisensory experiences at this tertiary level that the word-sound takes on its full semantic, associative value (meaning).

Consider, for example, how a child learns a language. It is not simply from hearing the words, but rather from associating the word-sound with another sensory experience, frequently but not invariably involving a second or a third sensory modality. When we first heard the word "hat," it likely was associated with being shown either an actual hat or a picture of one (visual input) or having one being placed on one's head (as in, "Here, let's put on your hat": visual and tactile input). Similarly, we came to associate the word "sun" with an exceedingly bright, round body that is well beyond our reach and that gives off light and warmth (visual, tactile, and visual–tactile or "spatial" percepts). Later, on learning that the sun is composed of burning gases, we added the visual and tactile images of the words "fire" and "gas" to our sensory images of the word "sun," thereby enlarging our original semantic/sensory associations. Without such multimodal associations, certain concepts or word-meanings would be difficult if not impossible to grasp.[44]

With experience, the depth, variety, and complexity of these associations increased geometrically. Thus, the sentence, "The man tipped his hat," might elicit a very specific scene from our past experience or more likely a whole host of more general associations. These might include "man": human, male, adult; "hat": Stetson, fedora, tophat; "tipped": person likely wearing it on his head at the time; hand rising with thumb and forefinger touching its brim, deflecting it slightly downward, perhaps accompanied by a slight nod of the head. Again, based on previous sensory experiences (perhaps watching old movies on television), one may make additional inferences beyond the immediate verbal–visual associations to the words themselves. For example, one might infer the presence of a woman and a certain type of breeding or character in the man himself.

It is such diversity of learned associations, which are mediated by the tertiary, heteromodal cortices, that not only enrich our language but also establish the basis for convergent and divergent thinking and the development of higher-order abstractive capacities. For example, the word "hat," having been associated with such a wide variety of specific stimuli, allows us to conceptualize certain common features that all such associations share. Thus, we come to a general "abstract concept" of what constitutes a hat, such that we recognize both a paper bag and cooking pot turned upside down on the head of a child as a "hat."

So far we have tried to trace the verbal stimulus from the primary auditory reception area to the secondary cortex where it develops its phonemic morphology to the tertiary association cortex where it derives its full semantic and logical–grammatical meaning. This process also works in reverse. One may generate the idea of "something that cuts" that triggers the association with the phonemic pattern "knife". Similarly, if shown a picture of a knife (assuming the relative intactness of the visual association cortices to ensure an accurate visual percept), because of its previous pattern of associations in the heteromodal cortex we may immediately know "what" it is. Simultaneously, perhaps, the visual image also elicits the verbal word form "knife." Similar associations are built up between the lexical or written form of the word "knife" and its phonemic or spoken form.

These various intermodal associations, via the heteromodal association area(s), would seem to form the basis for the various disconnection syndromes that provide important cues in our attempt to develop a theory or understanding of the structural/functional organization of the brain. Thus, we witness the dissociation between the phonemic words for and the perception of color that may be distinct from the phonemic words for and the perceptions of visual forms (objects) or body parts. We also witness individual differences between one's inability to spontaneously recall the phonemic form of the word for an object versus one's ability to recognize (or inability to recognize) a word when either phonetic cueing or the entire word itself is provided. These differences would appear to relate to which associative feedback loops are disrupted by the lesion. Developmental factors also may be important to our understanding of these relationships. For example, children for whom the lexical–phonetic associations are particularly vulnerable during the learning stage will show marked decrements in their comprehension if they are required to hold their tongue between their teeth (thus hindering their ability to "sound out" the word) while reading. Even as adults, we often resort to sounding out a difficult or less familiar word prior to attempting to spell it.

Effects of Lesions to the Tertiary Cortex. Lesions that encroach upon the tertiary cortex of the dominant hemisphere would be expected to interfere not only with the semantic aspects of language (word-meaning), but abstractive capacities as well. While some variation in symptoms can be seen depending on the exact locus of the lesions, this in fact is what tends to be seen in aphasic syndromes that involve more extensive portions of PTO cortex, such as **Wernicke's** and **transcortical sensory aphasia**. Luria (1973) also describes the tertiary or heteromodal cortex, especially portions of the left parietal lobe, as critical for the understanding of what he terms "quasispatial," logical–grammatical relationships. He describes these relationships at times as being dissociable from the more purely semantic associations described above. As a result, lesions that involve more parietal or occipitoparietal portions of this tertiary cortex might be expected to produce a syndrome in which the meanings (semantic associations) of individual words may be relatively well preserved, while the meaning of the phrase or sentence, which is derived from logical and/or grammatical relationships expressed by the verbal construction as a whole, may be impaired. An example of the latter might be the sentence: "Bill's brother's father saw his father's brother," or the command: "Touch your ear before your nose, but after your chin."[45]

Audition and Other Functional Units. While much of the output of the unimodal, auditory association cortex, like the other unimodal cortical association areas, is to the heteromodal (tertiary) parietal–temporal cortex, some fairly direct connections between these unimodal, auditory association areas and frontal association cortices likely exist as well. This is suggested, in part, by the syndrome, **transcortical sensory aphasia**, in which despite severe auditory comprehension deficits repetition of auditory verbal input is relatively preserved. **Conduction aphasia** also may be considered to provide evidence of the same or similar pathways, although from a different perspective. In its classic form, while the patient with conduction aphasia evidences relatively well-preserved auditory (and reading) comprehension, both repetition of heard speech as well as spontaneous articulations (e.g., confrontation naming) are disturbed. This impairment in repetition (or spontaneous speech), which is characterized by literal paraphasias, would appear to reflect a breakdown between those cortical areas responsible for phonological analysis of speech and the frontal motor speech areas. Lesions responsible for this syndrome traditionally have been thought to involve association pathways underlying the supramarginal gyrus (the **arcuate fasciculus**), suggesting that the auditory, unimodal association areas must be connected to the frontal speech areas. These connections may be fairly direct, or what appears more likely also may involve the inferior parietal lobule (postcentral and/or supramarginal gyrus), with the latter providing the kinesthetic link between acoustical patterns and motor programming for the actual articulation of phonemes.[46]

In addition to being necessary for repetition (and articulation), feedback loops between the second and third functional units also likely play a role in language comprehension, especially the frontal heteromodal association cortex. This would appear evident, for example, in situations that call for critical analysis of complex commands or instructions, especially those involving the type of convoluted, logical–grammatical relationships cited above. We have all had the experience of reading a paragraph (or listening to an instruction) only to realize that we probably failed to appreciate its full significance or realize that it "didn't seem to make sense" in light of other information available to us. In such cases, we make a conscious attempt to review all or part of what we have heard or read in an attempt to decipher its true meaning (e.g., "Given what I know, that [communication] didn't make sense. I better clarify it before I start"). As will be seen later, this type of active, goal-directed analysis, self-monitoring, comparator operation is the type of activity traditionally associated with the prefrontal cortex.

In speaking of the processing of auditory information (and language), thus far the emphasis has been simply on the decoding or semantic interpretation of speech as a means of communicating ideas or information. However, language often is intended not simply to communicate information but to stir passions or emotion. Language has the power to make us cry, laugh, arouse sympathy, or ignite anger or resentment. Obviously, this is a complex process that likely takes place at a variety of levels, involving multiple areas of the brain. But, it would appear that at least some of these responses are mediated by connections between the heteromodal cortex and limbic/paralimbic structures. For example, upon hearing the word "knife," we may conjure up a variety of visual and tactile images, such as how it looks and how it feels when held. But if we had the misfortune to be mugged at knifepoint recently, this word also may elicit emotional reactions such as fear, anger, and helplessness. The capacity of music and the cry of a baby to stir certain emotional responses also are familiar phenomena that link components of the first functional unit to auditory processes.

Processing "Nonverbal" Auditory Input

This section on audition thus far has focused on the auditory perception of verbal stimuli or language. In large part, this was due to the fact that we probably have a lot more information about verbal auditory perception (language) than we do about nonverbal auditory perception. However, many of the same type of secondary and tertiary associative processes that take place in the language-dominated, left hemisphere probably also take place in the right hemisphere, involving either "non-language," environmental sounds, certain aspects of music, or "non-semantic" aspects of speech. For example, just as the combination of certain phonetic sounds (words) eventually become matched to or associated with certain visual stimuli (e.g., the word "dog" with the visual image of a dog), non-linguistic sounds independently become associated with other transmodal stimuli. Thus, the sound of barking also becomes associated with visual images of dogs. As in language, both generalizations and specificities of associations are possible through the building up of experiences. We learn to associate a variety of different types of barks as possibly emanating from a dog(s). With practice, we also can learn to differentiate the bark of a dog from the bark of a seal, to distinguish the bark of one dog as opposed to another, and even the particular "meaning" behind a certain bark. While we frequently are aware of "verbalizing" (at least internally) such interpretations, the initial processing and understanding of such information (associations) may be mediated by the right or "nondominant" hemisphere. In addition to such "environmental sounds," many aspects of music also are thought to be mediated by the right hemisphere, especially for one not well trained in music for whom certain notes or musical phrases are not readily encoded in symbolic fashion.

Finally, even within the realm of language, the auditory processing capacity of the right hemisphere would appear extremely crucial for understanding language in its proper social context. This of course has to do with the accurate perception (secondary or unimodal association cortex) and interpretation (heteromodal or tertiary cortex) of the affective or emotional tone of the discourse. Again, just as we learn to associate phonemic patterns with objects, qualities of objects, or action states through simultaneous intermodal stimulation, we also become adept at discerning certain "nonverbal" messages depending on tone of voice, inflections, and timing of the discourse. If the affective tone is consistent with the verbal message, we still can obtain valuable information about the level of intensity or seriousness of the speaker. If the two are incompatible, depending on the emotional tone, we may choose to ignore the message (as in a joke) or to interpret it very seriously, but in a manner opposite to that dictated by the semantic connotations (sarcasm).[47] These nonverbal, auditory cues then may be reinforced in light of other multimodal information available at the time, including visual cues (posture, gestures, facial expression) and the overall situational context. As in the case of semantic information, communication between the anterior and posterior heteromodal cortices, as well as with limbic/paralimbic structures, are integrated as part of the total behavioral experience.

Visual Processing in the Second Functional Unit

The Primary and Secondary Visual Zones

The primary cortical projection area for the lateral geniculates by way of the optic radiations is Brodmann's area 17. Located on the medial surface of the occipital poles along the banks of the calcarine fissure, this area commonly is referred to as the striate cortex because of the horizontal stripe of myelinated fibers transversing this region (**line of Gennari**). The secondary association cortex surrounding area 17 variously is referred to as the **parastriate** cortex (area 18) and the **peristriate** cortex (area 18 and 19). As will be recalled from Chapter 5, each occipital pole receives input from the lateral half of the ipsilateral eye and the nasal half of the contralateral eye. Effectively this means that the primary visual zone in the left hemisphere processes visual information coming from the contralateral right visual field and vice versa for the right hemisphere. Additionally, the projections to the superior banks of the calcarine fissure (**cuneus**) are from the superior portions of the retina (inferior visual fields), whereas the inferior bank (**lingual gyrus**) receives input from cells in the inferior portion of the retina (superior visual fields).

As is the case with the other sensory systems, the role of the primary visual cortical projection zone is not clear. Again, it is suspected that area 17 generally is responsible for preliminary transformation and/or integration of incoming data that facilitates the eventual processing and combining of the data into more highly integrated and organized percepts by the secondary zones. Lesions of this primary zone in humans typically lead to homonymous field cuts or hemianopia in the contralateral visual fields. On the other hand, stimulation of these areas typically produces the subjective experience of fairly primitive or elementary visual phenomena such as poorly or unformed flashes of lights or colors. These usually are restricted to the contralateral visual field.

In discussing the visual unimodal association cortices, Mesulam (2000b) departs somewhat from Luria in extending this region from areas 18 and 19 to also include areas 21, 22, and 37 in the middle and inferior temporal gyri. Within this larger region, smaller areas can be defined that seem to respond to different aspects of visual processing, for example, object form, color, spatial localization, and movement. Another general distinction is made between the more posterior peristriate cortices and the more anterior ventral temporal regions. Both project to their respective contralateral areas in the opposite hemisphere and to the heteromodal association cortices. While both also project anteriorly to the frontal cortex, the main projection of the peristriate cortex would appear to be to the frontal eye fields (area 8), while the temporal region has more extensive projections to the frontal heteromodal cortex. Another major difference in terms of projections is that, while the majority of the input to the peristriate cortex is from the primary visual projection area (17), the more anterior temporal region receives most of its projections from the peristriate area. From a functional standpoint, it would appear that, while remaining unimodal in character, these more anterior association areas seem to be adapted to handling more complex visual perceptions and the posterior areas more elementary visual percepts.[48] Finally, the more anterior (temporal) visual association areas appear to have more extensive projections to the limbic and paralimbic structures than do the more posterior peristriate areas.

A key to understanding the role of the unimodal visual association areas and the effects of cortical lesions in these regions is to appreciate the diversity that is present within this system. While primates in general, including humans, have a well-developed visual system, they do not have the sharpest vision in the animal kingdom. That distinction likely is reserved for the birds of prey. However, whatever primates may be lacking in acuity seems to be more than made up for in the complexity and richness of the visual experience. While the full extent of this functional diversity probably is beyond our grasp, for the sake of discussion it may be useful to attempt to identify a few of its more basic dimensions, at least in very broad terms. First of all, like other predators, primates have binocular vision, which allows for more accurate judgments of distance and spatial relationships. As is true even of certain lower-order vertebrates, such as frogs, there also would appear to be specific motion detectors within the visual cortex. Another feature that we share with many other animals is our capacity to distinguish forms, shapes, and patterns. Within this latter domain, there still is considerable diversity: from distinguishing a circle from a cross, to appreciating the subtle nuances necessary for facial recognition, to instantly recognizing the complex patterns that characterize the individual words on this page, even when they are "mesplled." Apart from this, and unlike some other mammals, we have the capacity to recognize and appreciate subtle nuances of color.

The fact that certain sites within the visual cortex differentially respond to different types of visual stimuli and that lesions may variously affect these different aspects of vision suggest that even within the secondary association areas different pathways as well as levels of visual organization are likely involved (Van Essen & Maunsell, 1983). As noted earlier, Ungerleider and Mishkin (1982) identified at least two of these apparently independent systems. A more dorsal, occipitoparietal system that appears to play a more predominant role in the spatial localization of an object and a more ventral, occipitotemporal pathway that is more concerned with object identification. In keeping with the general principle outlined earlier, there may be different types and levels (degree of complexity) of perceptual organization (i.e., percepts) that take place or different aspects of the stimulus field to which select groups of visual cells may respond. However, as long as these processes take place within the secondary association areas themselves, they remain unimodal in nature. This notion is important in trying to comprehend lesion effects.

Effects of Lesions to the Secondary Cortex. As suggested above, depending on its particular location, lesions restricted to the unimodal visual association areas may result in a variety of deficits. However, there are common features that generally tend to characterize such lesions. First, the person is not blind. While there may be a visual field cut (as a result of a lesion encroaching on the optic radiations or portions of the primary visual cortex), the deficit should be able to be demonstrated in the intact field. Second, the deficit should be one of perception or the synthesis of primary visual input, not simply an inability to name, identify, or interpret what is being seen.[49] Thus, the patient may have difficulty on matching to sample or simple discrimination type tasks. This may entail matching or discriminating objects or pictures of objects, symbols (e.g., letters), spatial arrays, faces, or colors. Because it is difficult to clinically assess quadrantic or even hemifield deficits of this type, they would most likely be identified only following bilateral lesions. Even though the lesions would not necessarily have to be symmetrical (one lesion might involve the primary visual cortex producing a hemianopia; the other lesion limited to the unimodal association cortex), in practice such isolated deficits tend to be identified only on rare occasions. Again, depending on the specific locus of the lesion within the secondary visual cortices, different types of perceptual problems may become manifest. For example, difficulties with pure color perception are more likely to involve ventral (occipitotemporal regions), whereas pure symbol (number, letter) discriminations are more likely to be affected by occipitoparietal lesions. If the lesion is in the more posterior portions of the secondary visual cortex, the patient may evidence greater selective impairment of more elementary visual attributes such as the perception of movement or shape. By contrast, more anterior lesions may impair the synthesis of more complex visual features such as the perception of a face or an object.

These visual–perceptual disturbances may be quite severe or relatively mild. Extensive, bilateral lesions, as might be expected, tend to produce greater deficits than more restricted or circumscribed, unilateral lesions. In severe cases, the patient may show virtually no capacity to integrate or process visual input and demonstrate virtually no recognition or capacity to copy or match visual stimuli of either a particular class (e.g., color, objects, or faces) or multiple classes. In less severe or more restricted disturbances, the patient may be able to process individual parts of the picture but not perceive or integrate as a whole, a phenomena referred to as **simultanagnosia**.[50] Patients with mild apperceptive disturbances may be able to accurately perceive actual objects better than pictures or sketches (simple line drawings) of objects. In turn, pictures or line drawings that are presented in a perceptually unencumbered fashion likely will be perceived more readily and more accurately than pictures of objects presented in such as way as to produce visual "interference." Examples of the latter might include "degraded" images, pictures overdrawn with crosshatched or parallel lines, drawings that have overlapping outlines or "cluttered" backgrounds, or familiar objects presented from an unfamiliar perspective. Even for "unencumbered" stimuli, the speed and efficiency of visual processing may be compromised, especially as the stimuli become more complex. Thus, it is possible that modality-specific memory problems (e.g., memory for visual stimuli) could result not from a disconnection with limbic structures (see below), but rather from the inefficient processing of the information at the perceptual level.

However, "pure" lesions that are strictly confined to the secondary visual cortex tend to be either (1) somewhat rare or (2) if present, not clinically obvious, especially if unilateral. The effects of lesions involving these unimodal association areas nonetheless may manifest themselves in other ways. Since higher-level, integrative activities (e.g., those involving the tertiary zones) are predicated on the integrity of elementary perceptual processes, disturbances of the latter may affect the former. Thus, cognitive and perceptual–motor activities involving learning and memory, problem solving, linguistic, or constructional abilities that depend on efficient and/or accurate visual perception may be slowed, limited, or impaired. The degree and nature of the impairment will depend in part upon the severity, extent, and nature of the perceptual difficulties. Some of these effects are reviewed under Hemispheric Specialization in Part II and in the following section.

Vision and the Posterior Heteromodal (Tertiary) Cortices

Primates have evolved into highly "visual" creatures. One can easily witness the difference in the reactions of a cat or a dog versus a monkey that is placed in front of a television set. Despite quite adequate visual abilities, only on rare occasions will most dogs attend to a television screen, and if they do it will be only momentarily and typically only if the picture is accompanied by the barking of another dog. Many primates, on the other hand, will attend for long periods to almost anything that is showing.[51] One result of this proclivity is that visual input plays a major role in our multimodal associations. For example, from a very early age, there is a selective affective response in infants to face-like stimuli. Early exploration and manipulation of the environment largely is through visual–motor associations. These associations will be reviewed below. For now, the immediate focus is on the multisensory associations that take place in the tertiary zone of the second functional unit. At least in humans, some of the more obvious examples center on language development. While it is possible for language to develop in the absence of such multisensory input, as witnessed by the story of Helen Keller, such limitations make it a much more arduous undertaking. As noted above, in the normal course of language development, the first associations are largely sounds paired to visual images. Later, at a more symbolic level, we learn to associate sounds to visual letters and patterns of letters (written words).

Visual–tactile associations also are routinely made. Having touched, held, and used a knife, we can make some preliminary judgments regarding the weight, feel, texture of a particular knife simply by seeing a picture of it. We also have seen how, through multiple associations, the brain is able to "abstract" common features from a class of visual objects to form higher-order concepts. Similarly, through visual-tactile associations we come to "know" an object. Thus, although perhaps never having actually seen it before, one is able to "see" a long piece of obsidian, which is being held in a certain manner, as a "knife."

In addition to assisting in the multimodal "identification and classification" of objects, somatosensory or sensorimotor–visual associations also important in a way that we might not typically consider: the development of *spatial concepts.* As we move our body through space, either as a whole (as in walking), or in part (as in moving our arms), we generate a concept of both personal and extrapersonal space. By pairing these concepts with visual input, especially with binocular vision and concepts of size and the apparent converging of parallel lines, this concept of "space" is enhanced to include not only to objects that are within versus just outside our reach but to "traveling" distances and relational (i.e., three-dimensional) space. Audition also plays its part as we also learn to judge distance by the relative volume (or echoes) of certain sounds.

Obviously, some visual–visual, auditory–auditory, or tactile–tactile associations also are possible. Assume that a child's first exposure to knives was watching his mother use one in preparing to cook. Without being told anything or actually using it herself, by seeing the knife and witnessing the use to which it is being put the child would learn something about knives and what they can do. However, a more complete appreciation of its qualities only comes from having used a knife one's self, just as the mother's admonition that "knives are dangerous" (or "the stove is hot") unfortunately never may be fully appreciated until one actually cuts or burns one's self.

Colors are another common example of visual–visual associations. Except in exceedingly rare circumstances (e.g., certain hallucinogenic drugs) or congenital conditions, the experience of color does not directly trigger other, non-visual sensory associations. However, we do make direct associations between color and other visual images. For example, it is difficult to think about a slice of watermelon without picturing a multitude of colors (the green rind, the black seeds, and the red pulp). At the same time, given a color, certain visual images readily come to mind (e.g., the color red may elicit pictures of cherries, strawberries, apples, and maybe even convertibles).[52] Regardless, of whether such associations are intramodal or intermodal, the assumption is that they all likely take place in the tertiary association cortices.

In summary, it is through these pairings of visual, sensorimotor, and other primary sensory feedback that we are able to predict, even from a distance, that the grass in the shade of a big oak tree is likely to be cool and soft, or upon hearing the song of a mockingbird or the roar of a motorcycle to visualize the source of these sounds even though they may not be immediately before us. These associations also lay down a basis for the verbal identification (naming), classification, and categorization of objects. Finally, the multilevel associations that take place in the posterior tertiary zones allow for the development of higher-order concepts (such as, time and space) and provide the foundations for abstract ideas.

Effects of Lesions to the Tertiary Cortex on Visual Processes. The effects of lesions to the primary visual cortex (visual field cuts) and to those involving the unimodal association cortex (perceptual deficits) already have been discussed. What then are the effects of lesions to the tertiary, heteromodal areas to visually mediated functions? Before attempting to answer this question, we need to recall that there would appear to be at least three fundamental ways that behaviors associated with these areas could be affected: (1) by disruption of the input to these areas (e.g., lesions to the secondary cortical zones or their connections), (2) lesions that affect output or feedback loops (e.g., connections with frontal systems), or (3) lesions affecting the tertiary zones themselves. The visual agnosias, which will be discussed next, in part may reflect this first type of deficit. The effects of loss of feedback from the third functional unit (frontal systems) also will be addressed below. For now, consider the effect of lesions to the posterior tertiary zone on visual functions.

Although the posterior heteromodal association area extends beyond the angular gyrus (i.e., likely includes at least the supramarginal gyrus and portions of the temporal lobe), lesions centering in and on the angular gyrus are most likely to result in symptoms that either have a direct or indirect visual component. This is true in lesions of either the right or left hemisphere. Perhaps one of the clearest indications of this phenomenon is the presence of difficulties on various tasks requiring visual–spatial and visual–perceptual analysis and synthesis. Constructional disabilities, along with difficulties on visual puzzle type tasks [e.g., Object Assembly from the Wechsler IQ tests, reversible operations in space (Butters & Barton, 1970), or judgment of line orientation (Benton, Hannay, & Varney, 1975)] all have been associated with parietal lobe lesions.[53] **Gerstmann's syndrome** (Gerstmann, 1940), which includes dysgraphia (both lexical and apraxic dysgraphia), dyscalculia, right–left disorientation, and finger agnosia, classically is associated with lesions of the "dominant" angular gyrus, as are disturbances in reading. By contrast, dressing difficulties, "spatial dysgraphia," "spatial dyscalculia," and unilateral spatial neglect or visual inattention more frequently are associated with lesions affecting the "nondominant" parietal lobe (Benton & Tranel, 1993; Critchley, 1969, 1966; Walsh, 1994, Chapter 6). As already has been discussed, Balint's syndrome and problems of visual–spatial orientation commonly are associated with bilateral parietal lesions. Even subtle visual–spatial or visual–perceptual problems likely will produce interference on learning and memory tasks that employ such stimuli. Subjective analysis of each of the above symptoms clearly suggests the visual–perceptual or visual–spatial contributions of each.

Associative Visual Agnosias. At this point, it may be important to discuss associative visual agnosias. As previously noted, lesions that disrupt the unimodal visual cortex tend to produce **apperceptive visual agnosias**, which are characterized by the patient's retained ability to see but difficulty perceiving (e.g., matching to sample) visual objects, drawings, or colors. This type of deficit is to be differentiated from **associative visual agnosias** that appear to represent either a more subtle form of unimodal deficit or a type of disconnection between unimodal and heteromodal and/or limbic (memory) areas of the cortex. Several types of visual associative agnosias are commonly identified: (1) visual object agnosia, (2) color agnosia, (3) prosopagnosia (agnosia for familiar faces), and (4) agnosic alexia (inability to recognize letters or symbols).

Visual Object Agnosia. In visual object agnosia, if an object is presented visually to a patient, he or she is unable to name the object, demonstrate its use, or sort it into its proper category. Similarly, the patient is unable to retrieve a named object from among a group of objects. This is despite apparently adequate visual acuity and elementary perception, as might be demonstrated, for example, by the patient's ability to visually match an object to a sample or to draw it. However, if the object is presented in another modality (e.g., tactually or by verbal description) naming and identification are possible. Visual object agnosia is relatively rare in its pure form (i.e., without associated perceptual difficulties or more widespread cognitive deficits) and little is known about its underlying pathology other than it is likely to involve bilateral lesions of the posterior cerebral artery distribution (medial and ventral occipitotemporal areas).[54] Somewhat more common are disturbances in the recognition of faces (prosopagnosia), letters (agnosic alexia), and colors.

Color Agnosia. Deficits involving the perception, naming, and/or recognition of color are fairly convoluted and judging from the literature still are poorly understood. Three separate syndromes relating to disturbances of color perception generally are described: (1) achromatopsia, (2) color anomia, and (3) color agnosia. In order to appreciate color agnosia, it must be differentiated from these other two conditions. **Achromatopsia** basically entails a loss of color vision. In milder conditions (*dyschromatopsia*), colors are described as "dull," "washed out," or "faded." This syndrome typically results from inferior, posterior occipitotemporal lesions involving the lingual and/or fusiform gyri and reflects disturbances of the secondary visual association areas. Depending on whether bilateral or unilateral lesions are involved, the deficit in color perception may be manifested as a full or partial field deficit, with visual depth and form or shape perception being intact. If the lesion is restricted to the left hemisphere, a right, superior quadrantanopia and associated alexia is not uncommon. With bilateral lesions, prosopagnosia is also likely to be present.

As its description implies, **color anomia** reflects an inability to name colors (or to point to colors named by the examiner) in the absence of a more general naming or aphasic disorder.

It may occur independently of problems with color perception or recognition (i.e., the patient still may be able to match or sort colors or even be able to respond to questions about the colors of objects, such as: "What is the color of lettuce?"). This deficit usually is associated with a lesion involving the left mesial, occipitotemporal area, a right-field defect, and the syndrome of alexia without agraphia. Thus, color anomia reflects a *disconnection syndrome* in which color information from the intact left visual field cannot get to the language area in the left hemisphere, and vice versa.

By definition, **color agnosia** is a loss of color knowledge. Again, although relatively rare, a patient manifesting this syndrome would be expected to have difficulty naming or pointing to a named color (in the absence of a more generalized aphasic disturbance). He also would have difficulty matching colors to familiar colored objects (e.g., cherries, lettuce, watermelon), either verbally or visually, despite relatively preserved color perception (i.e., ability to match or to identify the numbers on the Ishihara plates) (Damasio, Yamada, et al., 1980; Damasio, 1985; Meadows, 1974; Tranel, 1997). The problem is that this particular syndrome, at least in its pure form, infrequently is encountered clinically and its anatomical correlates, like that of object agnosia, are ill-defined.

Agnosia for Familiar Faces (Prosopagnosia). As was true of disturbances of color perception, a distinction must be made regarding one's ability to perceive faces, namely the difficulty in recognizing familiar faces versus difficulty in distinguishing unfamiliar faces. These two syndromes are both clinically dissociable and typically have different anatomical substrates. The inability to distinguish between or match unfamiliar faces, for example, as measured by Benton's *Test of Facial Recognition* (Benton, Hamsher, Varney, & Spreen, 1983), is not a true agnosic deficit, but rather seems to reflect a problem of perceptual discrimination. Patients who are unable to recognize familiar faces may perform normally on facial discrimination tasks, and those who perform poorly on tests of facial discrimination may still be able to recognize familiar faces (Benton, 1980, 1990; Benton & Tranel, 1993).

In **prosopagnosia** (agnosia for faces), there is an inability to recognize familiar faces simply by an analysis of general facial features. As in other true agnosias, there is no clear evidence of a major problem with visual perception.[55] The patient suffering from this disorder still may be able to recognize gender and accurately interpret emotional facial expressions. As noted above, such patients are often may able to perform normally on tests of facial discrimination or matching-to-sample. Prosopagnosia is not the result of a general amnestic deficit, as the patient may readily recognize the person before them by the sound of their voice or sometimes by idiosyncratic visual cues (e.g., clothes, hairstyle, eyeglasses, or perhaps by a scar or mole on the individual's face) (Bauer, 1993; Damasio, Tranel, et al., 2000; DeRenzi, 1997b). In addition to having difficulty recalling information that previously had been associated with a particular face (retrograde deficit), these patients also have difficulty attaching new information to faces (anterograde deficits). Finally, while recognition of familiar human faces typically represent the most obvious functional disruption, many such patients will show comparable deficits in making specific individual identifications of other objects, both animate and inanimate, that is, while correctly identifying a picture of a cat, they may have difficulty identifying their own cat.

The lesion(s) responsible for prosopagnosia and disorders of facial discrimination are still a matter of some debate. Benton and Tranel (1993) suggest that the only lesions responsible for problems with facial discrimination are likely to be posterior and are more likely to be in the right than in the left hemisphere (if in the left, the individual is likely to show signs of receptive aphasia). As previously noted, prosopagnosia is likely to occur in association with achromatopsia when bilateral lesions are present. Most authors agree that bilateral lesions involving the mesial and inferior aspects of the occipitotemporal association cortex (with extension to the underlying white matter association pathways) can produce difficulties in identifying familiar faces. The question is whether bilateral lesions are necessary or can this syndrome result from unilateral lesions? Most seem to agree that the right hemisphere is crucial. DeRenzi et al. (1994) and Hecaen and Angelergues (1962) present evidence for right-sided lesions being sufficient to account for this syndrome, whereas Damasio (1985) presents arguments to the contrary. However, again there would appear to be a general consensus that both a disruption of unimodal association areas and/or some type of disconnection (e.g., white matter involvement) between these association cortices (whether unilateral or bilateral) and other "multimodal" brain areas (most likely limbic structures) are crucial elements in this syndrome.

Agnosia for Written Words (Alexia without Agraphia). In the syndrome of alexia without agraphia (also known as *pure alexia*, or *pure word blindness*), the patient retains the capacity to recognize individual letters [i.e., he or she can copy letters or even "read" by sounding out (spelling aloud) the letters]. However, the visual representation of the word itself has lost its associative value (meaning). As writing, spelling, and other language skills remain essentially intact, aphasic disturbances cannot account for the observed deficits, although achromatopsia and other color disturbances may be present. While a variety of lesions may produce this syndrome (Damasio & Damasio, 1983; Henderson, 1986), all basically involve a disconnection between the visual cortex and the left angular and superior temporal gyri that mediate the orthographic and semantic aspects of language (see also under Disconnection Syndromes – p. 329).

Summary. If identification of a given stimulus is restricted to input through the visual modality without evidence of more primary (apperceptive) visual disturbances, then the likelihood of a visual agnosia, which disconnects the unimodal visual areas from cortical or limbic multimodal areas, should be considered. However, in practice, these distinctions may not always be easy. Subtle apperceptive deficits may be present (although not sufficiently contributory), or present and contributory but not clearly identified. If, on the other hand, the lesion is in a heteromodal area, deficits are likely to be observed with multimodal inputs. Another sign of tertiary involvement, especially in the left hemisphere, is loss of abstract attitude. As an example, a number of years ago a patient with a dense aphasia resulting from a large infarct in the perisylvian area was in speech therapy. Using Amerind, a type of concrete, representational sign language, the patient was being taught to associate hand gestures with pictures of common objects (e.g., a cup, comb, spoon, etc). Although he was highly cooperative and easily replicated the appropriate signs in practice sessions with the speech therapist, when presented with the actual objects there was no evidence of transfer of training (he also failed to spontaneously use these gestures to communicate his needs). Such patients also often fail to appropriately sort objects (e.g., accordingly to use, such as a hammer and a nail), despite showing recognition of individual objects.

Vision and Other Functional Units

Visual–Frontal Connections. Visual perception is not a passive process. It is not like a camera that simply captures and records whatever image is placed before it. In most instances, perception is a dynamic process, becoming increasingly active as the stimulus complexity increases and/or the response demands become more critical or more refined. The eye actively scans the stimulus or environment, and depending on the situation focuses on (1) inherently salient features in stimulus itself (e.g., the eyes, nose, and mouth of a face), (2) those features that are aberrant, unpredicted, or unusual, or (3) those features that are essential to critiquing the situation or effects of one's action prior to initiating or altering one's response. This selective attention/visual guidance system in large part thought to be mediated by the frontal association cortex and executed through area 8 (frontal eye fields).[56] Luria describes how frontal lesions can impair interpretations of thematic pictures as a result of loss of executive control to guide the visual search (Luria, Karpov & Yarbuss, 1966). While not specific to lesions of the frontal systems, visual search tasks certainly are sensitive to disruptions of this frontal–visual connection (Teuber, 1964).

Visual–Limbic Connections. By way of introduction, the multimodal images resulting from the confluence of sensory inputs into the posterior tertiary or heteromodal cortex form the ultimate building blocks for our knowledge of the world around us. From these more elementary "blocks," higher- order concepts, generalizations, and abstract thought are developed. In fact, one of the hallmarks of the evolutionary process is the increasing capacity of organisms to better adapt to and manipulate their environment as a function of experience (i.e., an increased capacity to learn). However, from an evolutionary standpoint, perhaps there is even a more basic prerequisite for survival, that is, the capacity to immediately recognize those stimuli that should be approached (e.g., potential food or shelter) and those that need to be avoided. If the fox loses a toe the first time he encounters the hunter's trap, it serves him well to recall and avoid the area less he potentially lose much more than a toe the second time. Thus, at a very basic level, it is not only important that the organism recall or remember a particular stimulus (whether visual, tactual, auditory, or olfactory), but that he be able to attach a particular affective response to that stimulus or experience. For example, did it involve pleasure or satisfaction of a need, or fear and pain? Working in concert, the limbic and paralimbic structures would appear to play a crucial role both in laying down the memory traces for the stimulus (event) and in attaching an affective or emotional significance to it. We already have noted the probable connections between the olfactory and auditory systems and these limbic structures; clearly the same holds true for the visual system.

Evidence of these connections comes from multiple sources. From phylogenetic studies of perception and behavior and simple observation, we know that organisms respond in a highly specific manner to a host of visual stimuli. In many instances these stimulus–response connections appear innate, while others appear to be the result of either classical or operant conditioning. Depending on circumstances, the stimulus may be rather general or highly specific. Frogs, for example, will respond to a sudden dimming of light (shadow) by jumping off the lily pad into the water (a highly adaptive response), while chickens, which will also run for cover if a dark silhouette is passed overhead, will do so if the shape is consistent with that of a soaring hawk but not if it is made to resemble a goose. Certain colors or other visual stimuli will sexually excite members of various species, while other visual stimuli seem to innately elicit fear or revulsion in numerous members of the primate family, including humans (e.g., snakes, decapitated bodies, precipices). People who own dogs frequently witness the classic conditioning that occurs with respect to a leash (a positive response if it generally means going for a walk, a negative response if the leash is only used for visits to the vet or to get a bath). Under certain conditions, humans seem to respond affectively simply to the absolute level of illumination. If one is walking alone down a dark street in a questionable neighborhood, any sudden or unexpected movement likely will trigger an affectively charged, orienting response. Such emotional responses probably are not mediated through the heteromodal cortices; they likely represent a straight shot from the visual association cortex to the limbic system.

Disconnections between the unimodal visual association areas and the limbic/paralimbic structures, or damage to the limbic structures themselves, depending on the nature of the lesion, might be expected to produce at least two rather specific types of problems. The first might be a failure to benefit normally from purely visual experiences. The second could be a failure to recognize or show previous normal affective response to the stimulus, while demonstrating intact perception or discrimination capacity. An example of the former might include diminished capacity to learn certain geometric designs, despite normal copying ability.[57] Prosopagnosia would appear to provide a good example of how previously acquired information may be dissociated from visual input as a result of lesions apparently involving this system. It might be recalled that despite an inability to recognize familiar faces, patients suffering from prosopagnosia generally are able to identify and respond to emotional facial expressions. However, the discrimination of emotional facial expression is not merely a dispassionate, objective exercise. One of the teleological purposes served by facial expressions is to elicit an appropriate emotional response in the observer; hence, the limbic system must be involved for something other than episodic or declarative memory. In fact, lesions to the limbic system, specifically the amygdala, interfere with the appreciation of facial expression (Adolphs et al. 1994). Similar examples have been discussed in reference to the Kluver–Bucy syndrome and Downer's (1961) experiments with monkeys in Chapter 8. As you will recall, in both of these cases, previously aversive visual stimuli no longer elicit an emotional response following lesions to the amygdala or lesions that disrupt visual input to this structure.

Somatosensory Processing in the Second Functional Unit

The Primary and Secondary Somatosensory Zones

The primary somatosensory projection area (SI) is located along the postcentral gyrus, represented by Brodmann's areas 3a, 3b, 1, and 2. Each of these areas reflect their own, well-defined somatotopic organization with the face area being the most ventral (closest to the lateral sulcus), followed dorsally by the hand, arm, trunk, and upper leg. The lower leg and foot are represented along the medial surface of the hemispheres.[58] The major input to this region is from the VPL and VPM nuclei of the thalamus. Recall that, respectively, these nuclei receive input from the medial lemniscus and the spinothalamic tracts (carrying sensations of pain, touch, temperature, stereognosis, and position sense from the trunk and extremities) and the trigeminothalamic tracts (which transmit comparable information from the face, tongue, and throat).[59] Sensations of taste also appear to project to the VPM nuclei, and hence, are likely mediated by the same general cortical area as these other somesthetic sensations.

The primary efferent projections from SI are to:

1. Homologous areas for the "submodalities" of somatosensory perception within the postcentral gyrus of the same hemisphere (e.g., area 1 for the right hand to area 2 for the right hand).
2. Homologous areas for somatosensory perception in the contralateral hemisphere (except for the hands and feet, whose input remains unilateral, at least for SI).
3. Precentral gyrus (primary motor cortex).
4. Unimodal somatosensory association cortices (areas 5 and the more anterior or dorsal portions of 7 in the superior parietal lobule).
5. SII (see below) in the same hemisphere.
6. SII in the contralateral hemisphere.

A second somatosensory area (SII) is also topographically organized; but unlike SI, which appears to primarily receive contralateral somatosensory input, SII has a substantial amount of ipsilateral as well as contralateral innervation. Much of the input to SII, especially to its more caudal regions, seems to represent spinothalamic fibers mediating pain and temperature fibers via the posterior thalamic nuclei (Jones & Powell, 1969a,b). The SII has reciprocal connections with SI and the motor cortices, but unlike SI, it does not appear to have direct connections with the superior parietal lobule.

Brodmann's areas 5 and 7, which constitute the major portion of the superior parietal lobule (see Figure 9–13) appear to represent the main portion of the secondary (unimodal) somatosensory association cortices. However, Kaas (1983) argues that areas 1 and 2 may represent unimodal association areas, while Mesulam (2000b) suggests that the posterior portion of area 7 may be heteromodal in nature. It is generally accepted, however, that the area(s) closest to the central sulcus (areas 3, 1, and 2) likely represent more elementary somatosensory functions, while the more posterior regions, which include areas 5 and 7 (and some believe, even areas 1 and 2), represent higher levels of somatosensory integration. A third, independent, somatosensory association area had been postulated to exist on the medial aspect of the hemisphere involving the mesial portion of area 5 (Penfield & Jasper, 1954).

In many respects, the somatosensory system appears more complex and less well understood than the auditory and visual systems. This should not be surprising given the wide range of stimuli and types of receptors from which somatosensory information is derived.[60] These sensations often are broken down into several broad categories that include mechanical cutaneous (pressure, touch), nonmechanical cutaneous (pain, temperature), and sensations from muscles and joints. For the purposes of this chapter, it may be useful to try to categorize somatosensory processes as a function of the level of integration that would appear to be required. Using this approach, we can divide somatosensory information as (1) elementary, (2) the product of an intermediate level of integration, or (3) the product of a high level of sensory integration.

Those sensations that at least at first glance would appear to be rather primary or elementary include simple touch, gross localization, pressure, vibration (rapid, alternating pressure?), pain, temperature, and kinesthesia (awareness that movement has occurred in a joint or limb). Even though in contrast to the auditory and visual systems, some if not most of these sensations may be mediated either at the subcortical (thalamic) level or by multiple cortical sites (including motor cortices), they are generally considered representative of the sensations processed by the primary somatosensory cortex (i.e., area 3, and probably areas 1 and 2).

At an intermediate level, an integration of these elementary sensations occurs to produce a higher-order perception, although still purely tactile in nature. Examples might include determinations of size, shape, texture, weight, and position sense. Analysis of these perceptions would suggest that they are not immediate, elementary sensations. Whether we are holding a grain of sand between our thumb and forefinger or holding an apple, the determination of size requires a simultaneous comparison of which cutaneous receptors are being stimulated and which are not (i.e., the extent of the stimulation field). In the case of the apple, the degrees to which our fingers are extended (position sense) also provide a clue as to size. Given even larger objects, determination of size by tactile stimulation requires a summation of cutaneous feedback as the hand explores the object (cutaneous and kinesthetic feedback). The determination of shape and texture also is generally determined, not only by pressure and simple touch, but also by a manipulation of the object or movement across the surface of the skin. Perception of weight often is the result of both pressure on the surface of the hand and kinesthetic feedback (the subjective judgment of the weight of an object often is accomplished by slight vertical movements of the hand, testing how much effort is required to overcome gravity). Even position sense is not an instantaneous perception, but often requires some reflection, as is generally greatly assisted by cutaneous and/or kinesthetic feedback.

Proprioception, or the awareness of our body moving in space, appears to represent an even more sophisticated integration of position sense and kinesthesia. Cortical areas 5 and 7 (anterior portion) may be particularly involved in monitoring and integrating proprioceptive information that is directly associated with goal-directed, exploratory behaviors (Mountcastle et al. 1975). Certainly, any type of somatosensory perception that includes an element of discrimination or comparison of any two stimuli would appear to fall within this intermediate category. Examples might be determining which of two stimuli is heavier, smoother, warmer, or larger or whether in fact there are two stimuli instead of one (e.g., two-point discrimination). All these various functions are likely under the control of the unimodal, somatosensory areas (i.e., area 5, the anterior portions of area 7, and perhaps with significant contributions from areas 3, 1, and 2; see below).

At the highest level of integration are the recognition of objects through tactual means (*tactile asymbolia*) and the development of an integrated **body schema**. The latter would include concepts of front and back, up and down, right and left, awareness of the body's orientation in space, its ability to function as a coordinated unit, personal physical integrity (i.e., possession of one's limbs), and an awareness of defect or impairment. These latter functions would seem to represent the contributions of multimodal input, especially vestibular and visual input, and depend heavily on the integrity of the posterior portions of area 7, as well as the supramarginal and angular gyri.

Somesthesia and Motor Functions. In addition to its importance for tactile identification and discrimination, somatosensory feedback serves another important role. As witnessed in the spinal, cerebellar, and basal ganglia systems, there is a close interaction and interdependence between motor and somatosensory functions. In fact, in addition to receiving extensive input from the parietal cortex, the motor cortex itself contains cells that are directly responsive to somatosensory stimuli. While most motor activity, especially that involving the striate muscles, relies on sensory feedback, this is most evident in discrete, voluntary movements. Such feedback is important not only for maintaining muscle tone (largely accomplished at an unconscious level), but also for consciously gauging and controlling the speed, intensity, direction, and duration of movement. It is not unusual for one of the initial symptoms of cerebral disease to be that patients notice that they have a tendency to drop things they are holding in their hand, especially when their attention is distracted. The problem is not motor, but sensory.

As noted in Chapter 3, with practice many of our skilled motor activities seem to become almost automatic and,as a result there is diminished awareness of the role of proprioceptive and cutaneous feedback in the execution of these actions. However, certain circumstances readily can call these processes to one's attention. For example, try writing a sentence with your eyes closed, using your nondominant hand. You become much more aware of the importance of proprioceptive feedback than when writing with your dominant hand. A more dramatic demonstration would involve the elimination of afferent feedback,while preserving motor function. There are at least two circumstances, which most of us have experienced, in which this happens. The first is associated with a trip to the dentist, where the mandibular portion of the trigeminal nerve is anesthetized. The second involves laying or sitting in such a position that the hand or foot "falls asleep." In the former condition, one is aware of the increased difficulty with articulation. While the latter condition also may directly involve muscle groups, it often seems that the impaired sensory feedback is the main limiting factor in carrying out fine motor tasks during the acute phase of this temporary paresthesia. Finally, in trying to explore an unknown or unidentified object through tactile perception alone, not only can one readily appreciate how the manipulation of the objects is guided and directed by cutaneous feedback, but how proprioceptive feedback assists in determining the size and shape of the object to be identified.

Effects of Lesions to the Primary and Secondary Cortices on Somatosensory Processes. In contrast to the auditory and visual systems, lesions affecting the primary somatosensory cortex, whether defined as area 3 or areas 3, 1, and 2 do not typically result in a permanent loss of elementary somatosensory information. Thus, even with substantial lesions of the postcentral gyrus, the sensation of touch, pressure (including vibration), pain, and temperature are not abolished. Although there may be some substantial change in thresholds (i.e., tactual sensitivity), especially for the perception of light touch and temperature, these too may diminish over time. The reason for this relative preservation of sensation again is unclear, but probably reflects either the perception of certain stimuli at a thalamic level, at multiple cortical sites, or perhaps bilaterally (as in SII).[61]

In addition to changes in threshold sensitivity, lesions of SI or the postcentral gyrus result in contralateral sensory impairments of tactile or somatosensory discrimination, again most notable in the more acute stages. Thus, the individual may have increased and perhaps permanent difficulty making judgments regarding the relative size, shape, sharpness, weight, thickness, temperature, texture, or other surface features between two stimuli. Similarly, two-point discriminations, localization (of the stimulus), and position sense may be adversely affected. **Astereognosis**, which probably reflects a higher-level apperceptive deficit (which will be discussed in the next section), also may be present. Extinction or relative neglect also may be present with such lesions, although the latter are more likely to result from inferior or posterior parietal or even frontal–subcortical lesions. However, to reiterate, not all aspects of somatosensory function typically will be suppressed at the same time and the pattern of deficits may vary greatly from one individual to another. Due to the topographical organization of this area, more dorsal lesions selectively may affect the lower extremities, while more centrally placed lesions will affect the upper extremities. As will be noted below, lesions at the base of the postcentral gyrus (near the lateral fissure) will affect the face and articulatory mechanisms.[62]

Lesions along the postcentral gyrus also can impact directly on certain motor activities, including fine motor manual skills and speech. As noted, voluntary motor activity, especially discrete, skilled-motor activities, are constantly being modulated by somatosensory feedback. In the absence or disruption of such feedback, motor skills will be adversely affected. Luria (1973) used the previously coined term, *afferent paresis*, to describe this phenomenon. If such somatosensory feedback to the motor cortex is compromised by lesions affecting the postcentral gyrus, the movements become coarse, clumsy, imprecise, or unrefined. Symptoms may be more pronounced when attempting to handle or manipulate objects without the aid of vision. If the patient is allowed to visually observe the intended action, some improvement may be observed but some difficulty would be expected to persist. The more complex the action, the more likely deficits will become manifest. Thus, writing (penmanship) may be observed to be slower, more laborious, and less precise than before the injury. Another sign, which may reflect a disturbance of afferent feedback, sometimes can be observed when a coin or other small object is placed in the palm of a patient's hand and he or she is asked to identify it by touch alone. The normal response is for the individual to transfer the coin to the fingertips where it more easily and thoroughly can be manipulated in order to discover its identity. Patients with parietal lesions may simply close the hand, allowing the fingertips, moving "en masse," to simply palpate the object as it lies in the palm. While identification may be possible using this technique, it is clearly much less effective.[63]

If the lesion to the postcentral gyrus is more caudal, encroaching upon the face area, speech articulation deficits may be observed. Luria (1966) describes this loss of afferent feedback as *afferent motor aphasia*. He suggested that it primarily results in the confusion or substitution of letters or sounds with similar articulation characteristics (e.g., "pat" for "bat" or "dog" for "log"). The problem is thought to result from impaired feedback regarding the position and/or movements of the organs of articulation (i.e., the tongue and lips).

Lesions affecting the secondary association areas may not always be easily differentiated from those involving the primary somatosensory cortices. Both are likely to present with difficulties in making subtle tactile discriminations and other judgments based on proprioceptive feedback.[64] There may be two explanations for this. From a theoretical perspective, the capacity for making subtle tactual discriminations is predicated on the integrity of elementary perceptions. Despite the lack of total loss of tactile sensation with lesions of the postcentral gyrus, if such lesions disturb or disrupt sensory analysis, then the higher-order functions on which they depend (in this case discriminatory judgment) also will be disrupted. The practical explanation is that the literature does not appear to provide unambiguous data where lesions restricted to specific cytoarchitectural divisions of the somatosensory cortex are compared and contrasted in a systematic fashion in humans. As stated earlier, there still is controversy as to which somatosensory areas represent primary versus secondary cortex. Rather than being a source of discouragement to the practitioner, the fact that the functional organization of this region of the brain is still largely an enigma should stimulate and encourage its clinical exploration. For the interested reader, although originally published in 1953, Critchley's (1969) book on the parietal lobes still offers one of the more comprehensive and clinically useful treatments of somatosensory disorders and their assessment.

Somesthesia and the Posterior Heteromodal (Tertiary) Cortices

The integration of visual, auditory, and tactual information in the posterior heteromodal association cortex as the probable foundation for the development of language, abstract concepts, and the ability to perceive, imagine, or identify objects from a multidimensional perspective already has been discussed. Similarly, the development of our concept of space and spatial relationships in general in large part was attributed to the integration of somatosensory and visual processes. While these observations can help account for many of the higher-level associative deficits seen in parietal lesions, it would be useful to briefly revisit and expand on several of these notions, particularly as they relate to what has been referred to as **disorders of body schema**.

The perception we have of our bodies is central, not only to the perception of the self, but ultimately to the rest of the world around us. From a very early age we not only establish the physical parameters and integrity of our body, but also set up a basic dichotomy: that which is "me" versus that which is "not me" (i.e., the rest of the world around us). We also learn from an early age that through the physical command that we have of our bodies, we can impact and control (at least to some extent) our environment to either satisfy our needs or to avoid being impacted in a adverse manner.[65] Thus, more than the later-developing telereceptors (e.g., vision, hearing), cutaneous feedback and proprioceptors provide the most primitive means of knowing in what manner our bodies are being directly affected by our environment and, along with the capacity for muscular contraction, how we respond to it.

It is from this process of differentiation and manipulation that the concept of body schema would appear to develop. Assisted in part by visual feedback, we learn to identify various parts of our body and their relationship one to another. We also develop awareness that vertically the two halves of our bodies for the most part are symmetrical but nonetheless distinct. Not only do we learn to verbally label these two similar but distinct halves but also to recognize that this spatial directionality (i.e., right versus left) may be applied to external bodies (often by means of a visual reversal). Also, as noted earlier, in addition to the notion of "right and left," concepts of "up and down," "top and bottom," "near and far," "front and back," "above and below" are readily conceived, first in terms of our own bodies and then in relationship to the environment. Thus, the whole notion of body image or body sense would appear to be rooted in our awareness of our bodies, a supramodal (integrated) concept on which even higher-order concepts (such as "space") are developed.

So far, however, we have largely explored only relatively static concepts of body image based on somatosensory feedback. There is yet another whole dynamic dimension that needs to be addressed. In the process of attempting to manipulate our environment, whether this involves moving an object at rest (picking up a fork, or a bowling ball), moving ourselves within our environment (walking or running), or interacting with a moving object (returning a tennis ball or catching a pass), we gain a sense of mastery over our bodies. When combined with vestibular input, we begin to appreciate notions of balance, equilibrium, and stability. When combined with visual input, in particular, these sensorimotor "experiments" also provide for or augment our understanding of concepts such as speed or velocity; mass, density, or inertia; gravity; vectors; effort, energy, or force; and related physical laws. Again these higher-level concepts would appear to be rooted in our awareness of our own bodies and how it responds (motorically) in a three-dimensional environment. It is not difficult to imagine how the parietal lobe, in its juxtaposition between the primary somatosensory–motor cortices and the visual cortex, would be an ideal site for this multimodal integration.

Finally, as was mentioned earlier, in addition to body schema, the parietal lobes also may be important for tactual object recognition and identification. Phylogenetically, this is probably a relatively late development. For most species, object identification likely occurs through other sensory modalities, such as vision, olfaction, or even taste or hearing. While differentiation of the physical characteristics of the terrain may take place through the pads of the feet in some species, it is in primates, with the evolution of the opposable thumb, that this capacity truly developed. Although the tactual modality ordinarily is not the primary means for identifying objects or other stimuli, even in humans, the level of skill that can be developed using this method can be exceptional. This is most evident in cases of the visually impaired who are able to learn to read using Braille.

Effects of Lesions to the Tertiary Cortex on Tactual Processes. Lesions that impact on the posterior portions of the superior parietal lobule, as well as the inferior parietal lobule (supramarginal and angular gyri), all have been associated with symptoms or syndromes in which there seems to be a somesthetic component. In general these include (1) disturbances in tactual object recognition, (2) disorders of body schema, including neglect, and (3) ideomotor apraxia. While each of these will be reviewed briefly, our purpose is not to provide a comprehensive review of these syndromes and how they might be assessed, but rather to illustrate the multimodal nature of these cortical areas. While we will address some of the confusion that may surround these topics, for a more detailed discussion of these syndromes, the reader again is referred to Critchley (1969) and Hecaen & Albert (1978).

Tactile Agnosia. Tactile agnosia implies the failure to recognize an object by touch in the absence of more basic disturbances of sensation or perception (or, if perceptual disturbances were found, they would not appear sufficient to account for the failure to identify the object). Thus, for example, a patient, when given a hammer to identify by touch alone should be able to describe its general shape, size, and contours, as well as its weight and texture, perhaps even venturing that it seems to be made of metal, but unable to identify it as a hammer or even as a tool. If given a pencil and paper, he should be able to make a reasonable drawing of it (at which point, he may be able to identify it, given the visual image of the drawing). Obviously, the failure to identify the tactually presented object should not be the result of a more general language problem (he also should be unable to demonstrate its use).[66] In practice, however, such syndromes have proved to be exceedingly rare (Bauer, 1993; Reed & Caselli, 1994).

However, there is potential for confusion here. In the past, the term, **astereognosis**, has been used interchangeably for the terms (and the concept) **tactile agnosia** or **tactile asymbolia**. At times, "astereognosis" still is used to refer to an inability to name or identify an object by touch (i.e., as an associative-type agnosia), which, as was just pointed out, is rare. More recently, there has been a tendency to restrict the use of this latter term to refer to an apperceptive-type deficit, which in fact is much more common and is associated with lesions affecting the primary or secondary somatosensory areas. Yet, even when used in this manner, the term, astereognosis, is subject to some confusion. Strictly speaking, astereognosis refers to the inability to appreciate the physical qualities of an object as a whole by touch alone. The term reflects the broader integration of more elementary percepts, a process typically associated with unimodal association cortex. In this case, it represents an inability to appreciate both the *form* of the object (e.g., its size, shape, or contours), as well as the nature of the material from which it is made [e.g., its density (weight) and texture], in the absence of more gross tactual sensory losses.[67] Because the pathways mediating this ability originate in the dorsal columns, lesions in the spinal cord, brainstem (medial lemniscus), thalamus, or cortex may all result in astereognosis, which most likely is to be expressed unilaterally, often in combination with graphesthesia.

Disorders of Body Schema. Disorders of body schema, or *asomatognosias*, are a fairly common finding following parietal lesions. Although such disturbances of body schema may be expressed in a variety of ways, they usually involve either a lack of, awareness of, or difficulty identifying specific parts of the body. Probably the most common and certainly the most dramatic of these phenomena involve various types of **unilateral neglect**, either of the body itself or of the affliction from which it may suffer (see also under **Hemispheric Specialization: Right Hemisphere Functions**, p. 362). In both instances, there can be gradations in the severity of the disorder. If present, these disturbances tend to be most severe in the early stages following an acute event (e.g., a stroke), often becoming less noticeable with the passage of time. In the case of neglect, the individual may behave as if one side of the body did not exist. The person may fail to wash, shave, or dress the affected side. If asked to point to a part of the body on the affected side, they may fail to cross midline. If there is no associated hemiparesis, the individual may show no difficulty walking or using both hands in a cooperative fashion to carry out a bimanual task, such as putting on a pair of socks. However, there may be a noticeable inhibition to use the affected extremity (usually the hand and arm) in situations where it might be appropriate.[68] Such patients may fail to respond to tactile stimuli on the left side, especially with bilateral simultaneous stimulation. Occasionally, tactile stimulation of the affected side will be reported to have occurred in the homologous area of the unaffected side (**allesthesia**). Typically, such personal neglect also is associated with neglect of extrapersonal space (i.e., visual neglect on the affected side), although this may not always be the case (Guariglia & Antonucci, 1992).

A related, but less frequently observed symptom of unilateral neglect is denial of unilateral deficits (**anosognosia**) or failure to demonstrate sufficient concern or appreciation for such afflictions (**anosodiaphoria**). Again, most common in the early stages of acute illness, anosognosia typically is manifested by the patient's failure to acknowledge illness, usually a hemiplegia, on the affected side. If asked to move the affected limb, the patient may respond by moving the unaffected limb (**allokinesia**). If the lack of ability to move the hemiparetic limb is pointed out by the examiner, the patient may make up an explanation ("It fell asleep") or even may deny ownership of the affected limb. As the time from the onset of the illness passes, the patient will usually come to acknowledge that the limb is impaired but fail to show appropriate concern or appreciate the consequences of the weakness or paralysis (anosodiaphoria). For example, while acknowledging the existence of the impaired limb, the patient may report that he or she plans to return to work after leaving the hospital, despite the fact that their injury would preclude a return to their former occupation. While both types of unilateral neglect can occur with lesions of either hemisphere, they are more frequently noted following lesions of the nondominant hemisphere (Bisiach & Geminiani, 1991; Hecaen & Albert, 1978, pp. 303–304; Heilman, Watson, & Valenstein, 2003; Weinstein, 1991).

The other disturbance of body schema that appears to reflect a higher-order, integrative deficit, suggestive of tertiary cortical involvement, is **autotopagnosia**. This syndrome refers to a failure or difficulty in identifying body parts and appreciating their relative relationships to one another (Frederiks, 1969). Although not common, when present autotopagnosia involves both sides of the body, thereby not only distinguishing it from unilateral neglect or other more elementary somatosensory deficits, but also adding credence to its designation as a integrative deficit. It typically is manifested by a marked difficulty in naming or identifying specific body parts on command. The difficulty is not simply in reference to one's own body, but to the bodies of others, whether real or pictured. The fascinating thing about this syndrome is its apparent specificity with regard to the body itself, particularly the human body. In their reviews of this disorder, Hecaen and Albert (1978) and Benton and Sivan (1993) point out that such patients may be able to name parts of clothes (e.g., a "sleeve"), but be unable to identify the arm that it covers. While apparently somewhat more variable, these patients may show a greater facility in identifying body parts of animals than those belonging exclusively to humans (e.g., a paw or tail is more likely to be identified than a hand or arm) (Ogden, 1985).

Finger agnosia, the inability to identify or differentiate individual fingers, would appear to be a special case of autotopagnosia, but generally only when expressed bilaterally.[69] As noted clinically by Critchley (1966) and experimentally by Benton (1959), the three "center" fingers (especially, the "middle" and "ring" fingers) are the most likely to be confused. Occurring more frequently than autotopagnosia for the body as a whole, the hand likely represents a particular sensitivity to disruption. This may, in part, reflect the hand's special role in tactile exploration, as well as the fact that the fingers, particularly the central ones, are neither visually nor tactually as distinct as the thumb and little finger. However, as with other clinical measures, identifying body parts, especially finger recognition, is not a unidimensional task. As a result, disruptions may result from factors that must be considered in assessing the potential clinical implications of these findings. As indicated above (see footnote), the presence of unilateral findings or primary somatosensory deficits may suggest very different mechanisms at work.

Right–left disorientation is yet another symptom that commonly is associated with disturbances of body schema. Recall, if you can, when you first learned to discriminate your right side from your left. For most people this is not automatic; you must develop some strategy. It likely took even longer to be able to reliably differentiate right versus left on others, as this involved another, distinct cognitive process. On average, about 10% of the normal population continues to have some difficulty making this distinction (Wolf, 1973). For most others, the earlier strategies (e.g., which arm felt stronger when you "made a muscle") have long been abandoned, replaced by some sort of "intuitive insight" as to which is the right side and which is the left. However, while the concept of right versus left appears rooted first and foremost in one's own body, introspection suggests that this is not simply a somatosensory process, but a “visual–spatial” one as well, at least for most individuals. Finally, from a clinical perspective, a much greater than chance association between finger recognition and right–left orientation frequently has been observed (Benson, 1979; Hecaen & Albert, 1978; Strub & Geschwind, 1974), even by Benton (1959) who casts doubt on the existence of “Gerstmann’s” syndrome (Benton, 1961).

Since autotopagnosia, finger agnosia, and right–left orientation often are demonstrated by asking the patient to either name or point to the body part or finger named by the examiner, aphasic syndromes in some instances could help account for the observed deficits (Sauguet, Benton, & Hecaen, 1971). If the patient’s difficulty on tests of finger agnosia or right–left orientation primarily is tested through identification or matching using extrapersonal stimuli, the difficulty may stem from problems involving reversible operations in space. If tested only in the tactual modality, finger recognition in particular requires sustained concentration and attention. Hence, any general cognitive deterioration may adversely affect performance (Gainotti, Cianchetti, & Tiacci, 1972). However, as body and finger recognition deficits frequently can be demonstrated using nonverbal means (e.g., drawing, matching to sample) and can be found in patients who appear to suffer neither from aphasia nor general cognitive deterioration (Sauguet, Benton, & Hecaen, 1971; Ogden, 1985), these conditions cannot account for all autotopagnosic-type deficits.[70] In those cases where neither aphasic nor general cognitive deterioration would appear sufficient to account for these deficits, the most common lesion site is in the region of the inferior parietal lobule, particularly in the left hemisphere (Kinsbourne & Warrington, 1962b; Sauguet, Benton, & Hecaen, 1971; Varney, 1984). Although the data are still equivocal, they suggest that indeed there may be an area in the tertiary cortex that is critical for integrating visual and somatosensory information. Such integration allows for the development of a supraordinate concept of the body and its parts, commonly referred to as a *body schema* (Hecaen & Albert, 1978, Pp. 319–330 offer additional theoretical explanations for these phenomena).

While *ideomotor apraxia* appears to represent a very different phenomenon from those just discussed, it sometimes is included under the rubric of disorders of body schema (Goldenberg, 1997). For a more complete discussion of this syndrome, the reader is referred to the section on Disconnection Syndromes (p. 328). For now, what is important to note is that in order to carry out tasks that measure ideomotor praxis (e.g., brushing one’s teeth, hammering a nail), a mental template delineating how that action is supposed to be carried out has to have been established as a result of repeated practice or associations derived from use of the objects in question. Clearly there are somesthetic associations (cutaneous and proprioceptive). At the same time, most of us learned these actions by observing others as well as utilizing visual feedback to monitor the effectiveness and efficiency of these actions. Thus, these tactile–visual associations constitute a template (“engram”) by which parts of the body are programmed to respond in a four-dimensional environment (the fourth dimension being “time”). According to Heilman and Rothi (1993) it is the parietal (tertiary) association cortex of the dominant hemisphere that serves as the integration point for these engrams, or what they term *praxicons*, to become established. Table 9–5 summarizes some of the various classes of disturbances associated with lesions of the somatosensory areas.

Somesthesia and Other Functional Units

As had been noted, there are strong associations between the motor and somatosensory zones. The third functional unit, particularly the primary and premotor zones (see below), are intricately linked to somesthetic feedback systems as a prerequisite for efficient, coordinated muscular activity, especially goal-directed activity. Cells in the parietal, somatosensory cortex are observed to fire, even if one is just thinking about performing an action. This relationship will be discussed in greater detail later in this chapter in reviewing the motor zones.

Table 9–5. Summary of Somatosensory Disturbances

Perception Difficulty appreciating elementary sensations, such as heat, pain, or simple touch. Generally not permanently disrupted by lesions of the somatosensory cortices.
Sensitivity Changes in intensity of the stimulus required for perception to take place.
Discrimination Difficulty differentiating two stimuli along a single dimension (e.g., which stimulus is more painful, heavier, or hotter, or "two-point" discrimination).
Recognition Difficulty "knowing" what an object is. May reflect an apperceptive deficit (e.g., astereognosis), or, more rarely, an associative deficit (tactual asymbolia).
Body Schema Lack of awareness of one's body or the forces acting upon it. May include unilateral neglect, anosognosia, bilateral finger agnosia, and right–left disorientation.
Sensorimotor "Afferent paresis" or "ideomotor apraxia" resulting from the loss of somatosensory feedback or disruption of visual–tactile engrams for skilled movements, respectively.

As is true of other sensory areas, the somatosensory cortices would appear to have fairly direct connections with the first functional system. While the somatosensory areas are important in providing general information regarding one's external or internal environment in order to plan and execute goal-directed behaviors, cutaneous stimulations also are associated with more immediate alerting or arousal reactions, as well as directly mediating many approach–avoidance responses. Unexpected tactual stimulation can have a dramatic arousal or withdrawal response. The almost violent (as in "excessive") nature of the response in some situations may have something to do with the possibility of imminent danger to the organism.[71] One might envision slipping one's feet under the bed covers at night and feeling something small, furry, and *moving*! Unless you happen to own a lot of hamsters and this is a frequent occurrence, chances are you are not going to continue to palpate the object with your toes, trying to discern what it is before you decide how to respond. Certainly noxious or painful stimuli would be expected to trigger negative affective responses.[72] On the other hand, tactile stimulation also often is associated with positive affective responses. Grooming in animals, in addition to controlling parasites (and perhaps adding a bit of protein to the diet), also has a calming influence and helps establish social bonds. In humans, the fact that many individuals derive pleasure from having their hair stroked or backs rubbed in part may represent residuals of these grooming behaviors and their impact on limbic structures. Although it may be counterconditioned as a result of negative experiences, the strong positive reinforcement normally associated with tactual stimulation during sexual arousal is but another example.

THE THIRD FUNCTIONAL UNIT: EXECUTIVE CONTROL

Overview

The cortical substrates of the third functional unit basically encompasses the frontal lobes.[73] However, the frontal lobes are neither functionally nor anatomically homogeneous. As was seen from Figures 6–5 and 9–13, different parts of the frontal lobes are characterized both by cytoarchitectural variations and differences in their subcortical connections. From a cytoarchitectural perspective, the frontal lobe has been divided into two general types: (1) **agranular**, and (2) **granular cortex**. The agranular cortex, characterized by a well-defined layer III and prominent pyramidal cells in layer V, consists of the **primary motor** (area 4) and **premotor zones** (areas 6, 44, and, to a lesser extent, the more caudal portions of 8).[74] As we shall later see, these two zones roughly correspond to the primary and secondary areas in the posterior sensory cortices in that while they are both unimodal in nature, only the premotor areas have direct connections with the tertiary cortices. It is the area rostral to these two agranular zones that constitutes the **frontal granular cortex**. Also known as the **prefrontal cortex**, these areas lack the pyramidal cell concentrations of the motor and premotor zones, hence taking on the more uniform, granular appearance that is characteristic of heteromodal zones of the posterior lobes. These prefrontal, heteromodal cortices of the frontal lobes receive substantial input from polysensory areas of the posterior cortical areas, and along with the heteromodal zones of the (PTO) cortex appear to represent the areas of the greatest cortical development in the human brain.

The structural aspects of the frontal lobes, along with their interconnections to other brain areas, will be addressed in greater detail below. For now, it may be helpful to briefly preview several functional considerations as they apply to this behavioral unit. If the role of the second functional (gnostic) unit is to gather, process, and store information (primarily about the outside world), the role of the third functional unit may be viewed as putting that information to use to formulate and then carry out the needs, desires, or intentions of the organism with respect to that world. As will be seen, the functions of the frontal lobes are multiple and complex. However, for these preliminary purposes, they can be broken down into two broad categories: (1) deciding *if, where, why, how,* and *when* to respond, and (2) actually going through the motions of carrying out that response. This latter function is mediated by the frontal agranular cortices (motor and premotor areas), while the former is thought to be the providence of the frontal granular (prefrontal or heteromodal) cortices.[75]

In one respect, the third function unit (or frontal lobes) is similar to the second functional unit in that both consist of primary, secondary, and tertiary cortical units arranged to function in a hierarchical fashion with decreasing specificity and increasing higher-order and multimodal capacity. However, as the frontal lobes (or third functional unit) are considered to be the executive unit of the brain, with the motor outcome representing its logical and final common mode of expression, we might think of its organization as being just the opposite of the second functional unit. In gnostic or sensory systems, information initially arrives at the primary sensory zones and is processed there before proceeding to higher levels of perceptual integration in the unimodal association cortices. These unimodal or secondary association areas, in turn, funnel their information to the PTO (heteromodal) cortex, where well-integrated, multimodal images, generalizations, or abstract concepts are established. Conversely, in the frontal executive system, the process would appear to progress from the tertiary to the primary areas. Thus, based on the information provided by the first and second functional units, the tertiary cortex of the frontal lobes selectively attends to and evaluates the relative significance of the available data (including internal and external input, as well as past memories) and balances affective vectors associated with those inputs. This tertiary frontal zone also is thought to be important in devising plans of action that (hopefully) best meet both the immediate and the long-range goals or interests of the organism. Once these plans of action are formulated, the information is forwarded to the premotor zones to coordinate an integrated motor response. The primary motor area, representing the final common cortical pathway for expressing the will of the organism, then executes this motor response.[76]

The remainder of this chapter will focus primarily on three general topics:

1. Reviewing the suspected role of the prefrontal cortex in man in general, including the behavioral effects produced by disturbances in this system.
2. Attempting to differentiate the specific roles of different portions of the frontal heteromodal cortex.
3. Delineating the probable functions of the premotor and motor zones.

However, before proceeding with this task, several general caveats or comments may be in order:

1. As difficult a task as it was to attempt a description of the organization and operation of the first and second functional units, trying to describe the operation of the frontal or executive unit is even more precarious. The best we can hope for is to come away with broad working hypotheses of its role in behavior. The following hypotheses are derived, in large part, from an analysis of the functional deficits seen following "frontal lobe" lesions and to some extent from knowledge of its structural connections with other parts of the brain.
2. While it is common to speak of the "prefrontal cortex" as a homogeneous structure, this is not the case. The frontal lobes are composed of areas with diverse cytoarchitectural structure and with different patterns of afferent and efferent connections. While, the prefrontal cortex often is subdivided into dorsolateral, mesial, and orbital components, attempts to define the functional specificity of these smaller areas have met with only limited success.
3. Although behavioral differences occasionally are identified as resulting from right versus left frontal (hemispheric) lesions, such dichotomies generally have not been as pronounced with regard to the frontal lobes as is the case with the posterior cortices. The effects of bilateral frontal lesions often seem qualitatively different than lesions of the right or left hemisphere alone.
4. The nature of frontal lobe deficits themselves often is difficult to define. Unlike the posterior cortices in which deficits typically are defined in terms of specific patterns of sensory-based, behavioral decrements, most of the deficits observed following anterior insults are truly supramodal in character. Rather than simply responding to a set of stimulus parameters, the prefrontal cortex responds to the entire "context" in which those parameters are set, including current drive states, the affective valence of the stimulus, current goals or behavioral intentions, immediately preceding response sets, as well as anticipated consequences of current response possibilities.[77]
5. As is the case with studies of the posterior heteromodal association areas, the use of animal models to gain insight into the effects of prefrontal lesions probably has limited benefits. In some ways, trying to fully comprehend frontal lobe functions in humans from animal studies may be comparable to trying to understand the mechanics of aphasia from the study of temporal lesions in cats.

In contrast to the approach taken with the second functional unit, where the primary and secondary zones were discussed prior to discussing the tertiary zones, here we will start with the tertiary zone or the prefrontal cortex. This approach was adopted since, as noted above, it seems logical that the flow of information in the third functional unit primarily proceeds from the tertiary to the secondary and primary motor cortices. While the main focus of this section, like the rest of the third portion of this chapter, is devoted to an exploration of the possible role(s) of the prefrontal cortex in behavior, it may be helpful to first briefly review its anatomical parameters.

Anatomy of the Prefrontal Zone

The frontal or granular cortex generally is considered to encompass everything that lies rostral to the premotor cortex and the frontal eye fields. In humans, this represents the majority of the frontal cortices. However, as noted earlier, the prefrontal cortex is not a homogeneous area, neither anatomically nor functionally. While additional subdivisions likely will be identified in the future, for most clinical purposes three to four subdivisions are now commonly identified. As seen in Figure 9–29, these include the **dorsolateral, orbitofrontal, mesial,** and **paralimbic** cortices. In addition to the paralimbic area, the orbitofrontal and ventral mesial cortices all appear to have strong limbic connections.[78]

The major connections to the prefrontal areas would appear to derive from the (1) heteromodal zones of the posterior cortices, (2) temporal lobes, (3) limbic/paralimbic structures,

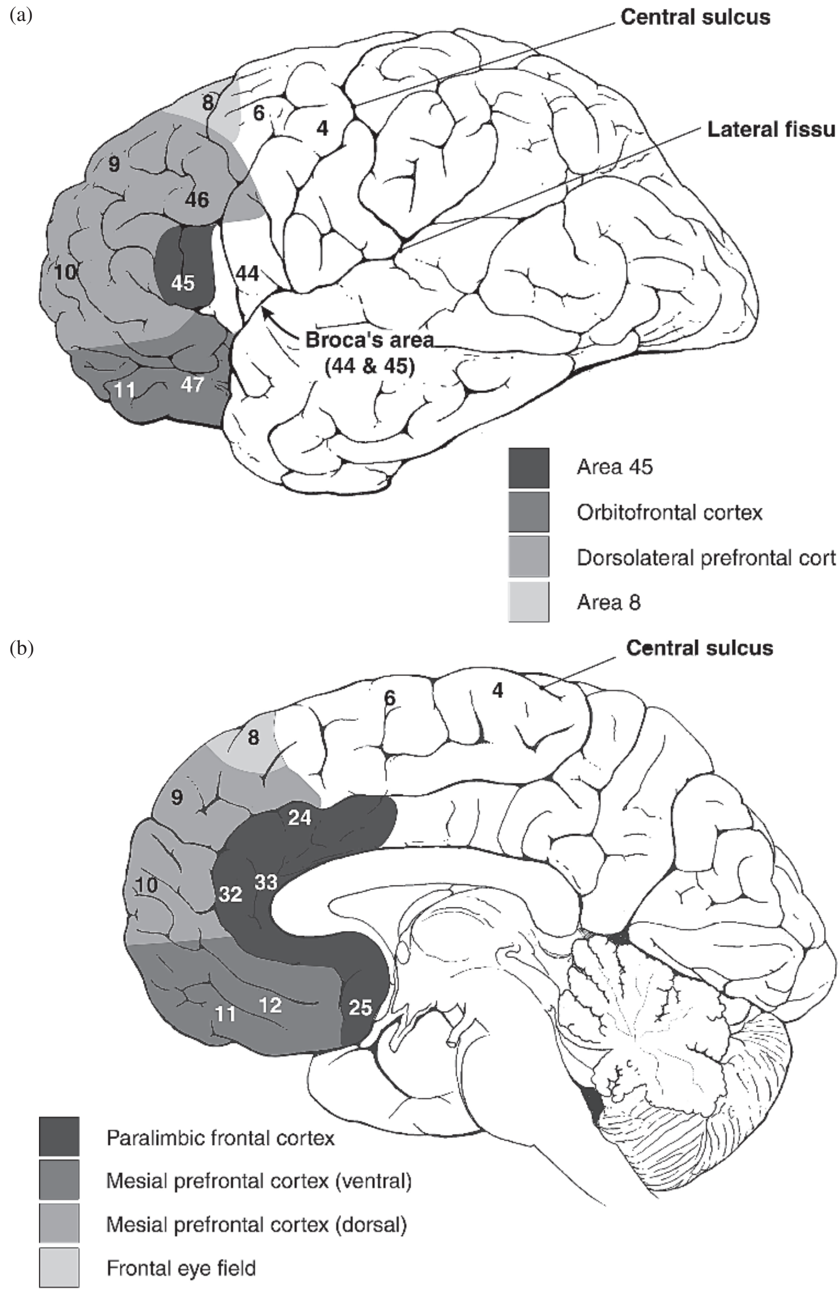


Figure 9–29. (*Continued*)

(c)

Figure 9–29. "Prefrontal" cortex, (a) lateral, (b) mesial, and (c) ventral views. Demarcations are approximate. Area 45 and the more rostral portions of area 8 (frontal eye fields) are most commonly classified as being part of the prefrontal, heteromodal cortex. Transitional areas include "paralimbic" cortices.

(4) hypothalamus and brainstem, (5) olfactory system, (6) thalamus, and (7) the contralateral prefrontal cortex via the corpus callosum (Stuss & Benson, 1986; Barbas & Pandya, 1991). The posterior tertiary cortex, which carries multimodal and highly integrated information, reaches the prefrontal areas primarily via the **superior longitudinal fasciculus**, whereas information from the more medial or anterior portions of the temporal lobe is carried by the **uncinate fasciculus**. The parahippocampal gyrus in turn also is connected with the prefrontal cortex via both the **inferior orbitofrontal fasciculus** and the **cingulum** (Goldman-Rakic et al., 1984). The orbitofrontal and basomedial portions of the frontal lobes appear to have substantial connections with the amygdala and septal nuclei, as well as with hypothalamic/midbrain nuclei (including the reticular nuclei). The cingulate cortex in turn appears to project to both the dorsolateral and the more orbitomesial portions of the prefrontal cortex (primarily via the cingulum). The olfactory system appears to have both direct and indirect (via the amygdaloid nuclear complex) connections with the basomedial frontal areas. As appears to be true of most cortical areas, the prefrontal region in one hemisphere is in communication with the prefrontal cortex in the opposite hemisphere via commissural fibers. Finally, the prefrontal association cortex in part also is defined by the fact that it is the primary, if not exclusive, cortical recipient of afferent fibers from the dorsomedial nuclei of the thalamus.

While most of the above afferent projections to the prefrontal cortex likely have reciprocal connections with these various structures or sites, there also are prefrontal efferent pathways that likely have no direct afferent counterparts. The best known of these is the connections between the prefrontal cortices and the corpus striatum. While the dorsolateral prefrontal cortex likely sends some fibers to the putamen, the majority of its output is to the head of the caudate. In contrast, the orbitomesial portions of the prefrontal cortex appear to project to the region of the nucleus accumbens or the ventral striatum, along with projections from the amygdala. The dorsolateral prefrontal cortices also have substantial connections with the premotor zones of the frontal cortex, through which motor action can be initiated. Finally, the prefrontal cortex makes an extensive contribution to the corticopontine pathways that after synapsing in the pons proceed to the cerebellum.

Functional Correlates of the Prefrontal Zone

As is true of much of neuroanatomy, hypotheses concerning the role of the prefrontal cortices in behavior are generated through observations of behavioral change following damage or injury to these areas. Perhaps the earliest and most well-known report of frontal lobe damage in the modern era is Harlow's (1868) account of the case of Phineas Gage. Following an injury that certainly compromised his frontal lobes, marked personality and behavioral changes were noted (particularly disinhibition and loss of work ethic), despite the relative preservation of his "intellectual faculties."[79] Other case studies of personality change associated with focal lesions of the frontal lobes in the late 19th and early 20th century reported problems of disinhibition or impaired judgment, puerility, *Witzelsucht* ("cruel or tasteless joking"), lack of concern, and general apathy in such patients (for review, see Benton, 1991). However, despite these early reports, two additional findings were seen as being somewhat "positive." First, patients with lesions confined to the anterior portions of the frontal lobes appeared to suffer neither physical impairments nor loss of basic intellectual capacities, at least as measured by formal IQ tests at the time. Second, studies with primates suggested that surgical lesions of the frontal lobes might have a "calming" effect on behavior. Subsequently, frontal lobotomies or leucotomies became a relatively common treatment option in certain centers for a wide range of behavioral and emotional problems by the 1940s. The justification and continued use of this procedure was facilitated in part by the observation that certain patients who suffered loss or damage of frontal lobe tissue continued to function with apparently minimal behavioral disruptions (e.g., Hebb, 1945). These practices continued into the 1950s and beyond despite reports, often from the surgeons themselves, of the potential deleterious effects of such procedures (Freeman & Watts, 1942; Rylander, 1948; Strum-Olsen, 1946; Partridge, 1950; Tow, 1955). About this same period, evidence continued to mount from independent studies of war-related frontal lobe injuries, documenting and expanding on earlier findings that suggested that the frontal lobes indeed were critical not only for normal behavior but also for certain higher-level cognitive functions (Goldstein, 1939, 1944). It only was after the advent of more effective psychotropic drugs and increased awareness of patients' rights issues that the role of psychosurgery began to come under closer scrutiny (Valenstein, 1980).

In retrospect, these early studies of the frontal lobes from the first half of the 20th century managed to identify what we still perceive to be important behavioral correlates of the frontal lobe, such as:

1. Initiating and persevering in goal-directed behavior, especially with regard to long-range goals.
2. Modulating emotions, basic drives, and instincts to conform to social standards, and developing a sense of self-awareness.

3. Achieving optimal levels of arousal (drive) and sustaining and directing attention.
4. Considering the circumstances and potential consequences of behavior when planning an action.
5. Maintaining cognitive flexibility in problem solving.

In attempting to summarize these ideas, we might say that the role of the prefrontal cortex in humans is to balance, coordinate, and integrate physiological, social, and "existential" needs with external (environmental) demands or conditions to effect desired goals. Although behaviorally there probably is considerable overlap, for purposes of discussion this more general notion of prefrontal cortical functioning in turn can be broken down into two broad categories: (1) planning and execution of cognitive–behavioral programs, and (2) modulating or controlling internal drives and emotions. As will be seen, the former tends to be more associated with the dorsolateral prefrontal cortices, while the latter is usually linked to the orbitofrontal or mesial frontal zones.

In what remains of this section on the prefrontal zones we will attempt to review each of these two broad functional areas in greater detail and to suggest how, in executing these behaviors, the prefrontal areas rely on or influence other portions of the CNS. Although separated for the purposes of discussion, one should keep in mind that cognitive programming and behavioral control do not necessarily function independently of one another in day-to-day activities, but in fact likely complement one another. Finally, examples of specific behavioral deficits that might result from breakdowns or disruptions of these frontal systems will be reviewed.

The Planning and Execution of Cognitive–Behavioral Programs

A good place to start is to ask, "In what situations is the prefrontal cortex most critical?" Although there is no clear, simple answer to this question, we know that many patients with massive frontal lesions, despite some changes and limitations, continue to function, often in an apparently fairly sophisticated, complex, and goal-directed manner. They may be able to take care of their basic biological needs. They carry out many activities of daily living, including dressing, shopping, conversing, engaging in recreational activities, and finding their way around. They are capable of learning, may recall prior events, and may be capable of solving certain types of cognitive tasks. In fact, as previously noted, it was not uncommon for patients with damage to the frontal lobes, including frontal leukotomies, to perform adequately on formal tests of intelligence or other neuropsychological measures (Ackerly, 1937; Freeman & Watts, 1944; Benton et al., 1981; Stuss & Benson, 1986; Damasio & Anderson, 1993). In contrast to the preceding observations, Duncan et al. (2000) report a study in which subjects were administered cognitive tasks while undergoing PET scans. They conclude that the frontal lobes, particularly the dorsolateral areas, possibly reflect the primary neural substrate for Spearman's "g" factor (i.e., general intelligence).

The entire brain, including the prefrontal cortex, likely participates in most if not all cognitive behavior. However, it also is believed that certain areas of the brain probably are more critical for successfully executing certain behaviors or responding effectively under certain circumstances than others. This realization largely has come about by studying the effects of focal brain lesions on various classes of behavior. At the risk of oversimplification, one might consider the following as general examples of types of situations where the integrity of the prefrontal cortices may be most critical.

1. Where it becomes necessary to control or inhibit conflicting or situationally inappropriate drive states.
2. Where it becomes necessary to harness drive states (via inhibition or facilitation) to achieve future or abstract goals.

3. To make appropriate judgments in problem-solving situations where there are conflicting, ambiguous, unfamiliar, vacillating, distracting stimuli or task demands, and/or equally compelling response alternatives.
4. Where persistence is required in maintaining goal-directed behaviors in the face of distracters and/or changes in response contingencies or demands.

While the first two situations would appear to involve critical components of the orbitofrontal and mesial cortices (to be discussed below), the latter two more clearly relate to the planning and execution of cognitive–behavioral programs. In trying to devise an "entertaining," yet meaningful analogy of the type of situation where the dorsolateral cortices might be critical, again the crew of the "Starship Enterprise" comes to mind. Consider the following possible scenario:[80]

While returning from a routine mission to its starbase, the planet Zercot in the Beta Centauri system, and despite traveling at warp speed, any of the first officers could easily command the ship. Even minor problems or malfunctions such as the loss of communications with Starfleet Command when passing through a gamma-charged radiation belt or the overloading of the main engines due to premature hydrogen ionization could be handled by Lt. Uhuru and Scotty, the chief engineer. Captain Kirk remains available, if necessary, but he and the chief science officer, Spock, are spending some leisure time with the ship's computer library classifying and cataloging the new life forms encountered during their last voyage through Sector 12 of the Andromeda galaxy. The presence of Kirk and Spock is not needed for these fairly routine activities. However, as the Enterprise approaches Zercot, a strange phenomenon is encountered. A series of three, extremely bright objects, approximately 50 miles in diameter, come into view from their stationary orbit on the far side of the planet. Preliminary data from the sensors suggest that these "objects" are pure light energy, with no mass and apparently emitting no significant heat. Before further analysis can be made, the light energy suddenly increases by a factor of 10, all but blinding the crew. Simultaneously, Scotty reports that the matter–antimatter reactor is dangerously overheating, causing not only a loss of power, but unless corrected will result in an explosion that will vaporize the vessel. The first impulse of the crew is immediately to activate the shields, but they are not responding, and with the loss of power evasive action is impossible. A message is being received from the planet. It is from the Klingons, who contrary to Federation treaties have invaded the sector and seem to be transmitting from deep within the interior of the planet. They warn the Enterprise that unless they immediately and unconditionally surrender, the starship will be annihilated. A quick check of the ship's phasers reveals they also have been rendered inoperative.

Now would be the time for Captain Kirk and Spock to be summoned to the bridge (i.e., for the frontal lobes to really kick into action). Routine, previously programmed response patterns are no longer adequate. Panic must be avoided and all energies must be focused and channeled into creative strategies to deal with the emergency. A review of all current and historical data, a thorough systems check, and analysis of all conceivable response options, both conventional and unconventional, is essential. However, since this "situation" is unprecedented, despite efforts to anticipate the consequences of contemplated actions, accurate predictions are impossible. Even with such planning, a trial-and-error approach is likely, with each initiative being carefully monitored, as the crew of the Enterprise prepares to quickly adopt new strategies as dictated by Klingon response.

The above example was intentionally extreme. Obviously, the frontal lobes routinely respond under far less dramatic and complex circumstances. However, the potential value of this example is twofold. First, it illustrates that even in the absence of the frontal lobes (in this case represented by Captain Kirk and Science Officer Spock) many complex activities still may be accomplished. Second, it suggests that certain complex cognitive activities depend heavily on the integrity of the prefrontal cortex. Having provided this more general example, it now may be helpful to review in greater detail several aspects of prefrontal (particularly, dorsolateral) behavior that are deemed critical for successfully carrying out complex cognitive-behavioral programs. Although the list certainly is not exhaustive, we shall consider the following:

- **Arousal**
- **Intention** and **initiation**
- **Selective attention**
- **Inhibition**
- **Planning** (strategy) and **execution**
- **Self-monitoring**

Arousal

As is true of the entire cortex, a certain optimal level of arousal is necessary for efficient functioning to occur. Cortical arousal is likely mediated by at least two systems: one specific and one nonspecific (Heilman, Watson, & Valenstein, 1993). Nonspecific arousal would appear to be a function of the diffuse norepinephrine pathways that emanate from the mesencephalic reticular formation (see Chapter 11). More specific arousal in large part probably results from thalamocortical projections. In the case of the prefrontal cortices, these projections originate primarily in the dorsomedial nuclei of the thalamus. The hypothalamus and "limbic system" likewise play an integral part in cortical, particularly prefrontal, arousal. It also appears likely that the prefrontal cortex itself plays a key role in initiating and maintaining arousal under certain circumstances. The respective roles of these various systems and how they can specifically impact one's general behavior will be discussed in greater detail under the heading: **The Modulation of Internal Drives and Emotions** (p. 443). What is important to note here is that any action that requires sustained planning, prolonged execution, and constant monitoring also require sustained arousal or drive to ensure proper levels of cortical activation throughout the process. Any disturbances that result in fluctuating or inadequate levels of arousal significantly may impede these operations.

Intention and Initiation

Closely related to the notion of arousal discussed in the previous section is the concept of creating a stable intention to perform some action or carry out some activity. Both arousal and intention would appear to involve the interplay of limbic mechanisms. With arousal, the emphasis is more on gearing up or energizing the organism to respond to some perceived need or demand, more or less independent of whatever specific course of action that is subsequently to be taken. **Intention** would appear to take this process one step further by combining the notions of will and motivation to create a stable "intention" that the goal be reached. To do so means to be motivated (i.e., have the intention) to develop, initiate, and/or adhere to whatever plan of action is necessary to reach the goal. It means the willingness and effort to bring in whatever resources are essential to this process, including attention, active perception, memory retrieval, planning and organization, and where necessary prolonged mental and/or physical exertion. Obviously, that intention also must be stable over time, at least over the time period necessary to carry out the plan or program until the goal is reached.

An example might be to consider the following situations. You are walking down the street in a brand new suit and your obnoxious neighbor's big, friendly St. Bernard runs up and puts his muddy paws on your shoulders, knocking you down into a large puddle of water. You probably would not need your prefrontal lobes to later recall what happened as you relate the incident to your lawyer. However, if while walking down the street you were to witness a burglar running out your front door with a jewelry box in hand, the proper operation of the frontal lobes would be much more important. In order to remember all the essential details to provide to the police (e.g., his approximate height, weight, and age, hair color, clothes, shoes, whether or not he wore glasses, the make, model, color of his car) you might have to create a stable intention to remember, including rehearsing the facts while waiting for the police to arrive. Providing a patient with a long list of words to recall over several trials is more like the second than the first scenario. In order to be successful, it requires the stable intention to pay particular attention to and/or covertly rehearse those items not recalled on the previous learning trial.

Similar and probably related to disorders of arousal and intention in prefrontal patients are problems of **initiation**. As noted, with problems of arousal and intention, the patient may demonstrate either insufficient motivation to respond or failure to act in such a manner that is consistent with a stable intention to prepare and plan for the successful completion of a complex or sustained activity. Failure of initiation is most often reflected in the failure of the patient to engage spontaneously in goal-directed behaviors. Although the patient may engage in elaborate discussions and make detailed plans regarding future goals (e.g., getting a job, fixing the washing machine, or preparing a Thanksgiving dinner), he or she may never take the necessary steps to carry them out. Even if they do begin, they may abandon these efforts within a short period of time.[81] Other patients with severe, bilateral damage to the prefrontal areas may revert from a very active, productive existence to that of a couch potato. **Transcortical motor aphasia** (a "frontal" type aphasia) appears to reflect a similar dynamic. These patients engage in little if any spontaneous speech, although they are perfectly capable of speech as witnessed by their generally intact repetition, even to the point of becoming echolalic at times.

In summary, the three functions just discussed—,arousal, intention, and initiation of behavior—seem to share a common feature, that is, they all are concerned with ensuring that the thought or idea is converted into appropriate action.[82] The frontal lobes would appear to play a critical role not only in harnessing limbic drives (see below), but also in facilitating the cognitive (conscious) generation of certain drive states and the channeling of drive states into overt, goal-directed activity. Obviously, failure to act or failure to act in a highly efficient, dedicated manner at times maybe attributable to factors other than frontal lobe pathology.[83] Depression, anxiety, passive aggressiveness, and malingering are but a few of the "psychological" factors that could inhibit or interfere with completing long-range goals.

Depending on the severity and/or locus of the pathology, deficits in arousal, intention, or initiation may be relatively subtle or quite profound. In certain cases, catatonia, or what Luria (1973) referred to as **apathetico-akinetico-abulic** syndromes can result from frontal lobe damage. Again, these conditions will be discussed in greater detail below under **The Modulation of Internal Drives and Emotions**, however, a few preliminary anatomical observations can be offered here. While the more severe abulic-like conditions are most likely to be seen following extensive, bilateral frontal lobe damage, variants of these conditions may be associated with lesions involving the dorsolateral convexities, the orbitomesial regions, as well as more dorsomedial lesions. Two general mechanisms can be postulated as possibly contributing to these deficits. One is that frontal lobe lesions (particularly orbital and mesial lesions) disconnect the prefrontal cortices from the energizing or activating influences of the mesencephalic reticular, norepinephrine pathways, the dorsomedial nuclei of the thalamus, and/or the dorsal (cingulate) or ventral (amygdala, hypothalamus) limbic structures. The second possibility is that damage to the dorsolateral convexity itself may disrupt either its capability to harness and channel these limbic influences to carry out behavioral programs or to generate and execute these programs themselves.

Less dramatic, more subtle alterations in drive states easily may go unnoticed or be attributed to premorbid personality or psychological reactions in more restricted or less obvious frontal system damage. Thus, the patient simply may be characterized as "unreliable," "lazy," or "lacking in ambition." In contrast to but occasionally accompanying deficits in sustained intention and initiation are problems of what might be described as "hyperactivity" or extreme restlessness in patients suffering frontal lobe damage. First noted in early research with animals (Benton, 1991), this latter syndrome is most commonly found following orbital or ventromesial lesions (Benson & Stuss, 1982). On rare occasions, more overt manic disorders may occur from lesions that include prefrontal cortices (Clark & Davidson, 1987; Starkstein et al. 1987). The more benign manifestations of restlessness and milder hypomanic states in part may be related to disturbances of attention or inhibition, topics that will be addressed next.

Selective Attention

Unless one is engaged in a sensory deprivation experiment, in most normal waking states, at any point in time we are constantly exposed to a myriad of external stimuli that vie for our attention. Simultaneously, multiple thoughts, feelings, or memories may well up from within that also potentially command our attention. If not impossible, it is certainly inefficient to attempt to attend to all such stimuli as they might arise. We need to be selective in terms of those stimuli that merit our attention at any given moment. The prefrontal cortex would appear to be critical to this selection process.

Before discussing the possible role of the frontal lobes, it is important to recognize that all stimuli by their very nature are not equally compelling. There are various features that may affect the relative salience of a stimulus. **Intensity** of the stimulus is clearly a major factor. Thus, for example, the sudden burst of bright light and booming sound associated with a nearby flash of lightning readily will command our attention simply because of the intensity of the stimulus. In contrast, to use a well-worn example, you were probably not aware of the watch on your wrist or the shoe on your foot until your attention was called to them. **Contrast** also may heighten stimulus value. This may be a discordant note on the piano, the red wine stain on the white carpet, or even the teacher beginning to speak in a soft voice amid the din of the classroom. Uniqueness, novelty, or the "unexpected" (which may be simply other variants of contrast) also frequently commands attention. This may be represented by an atypical use of form or color in the paintings of Picasso or Pollock, an experimental "concept" car at an auto show, or the presence of a cat in church. Any stimulus that has some type of ***emotional tag***, whether positive or negative, also is likely to capture our attention. This could range from the smell of a freshly baked apple pie, to a scantily clad model,[84] to the sight of a snake or unconfined blood.

Directed/Voluntary Attention. The above examples, to a large extent, represent stimuli that elicit what might be termed *involuntary attention.* While we may later chose to divert our attention from them, when initially presented they literally "command" our attention. Conversely, we can think of another type of attention, namely *voluntary* or *directed* attention. Voluntary attention often but not invariably involves stimuli that are not necessarily particularly compelling in and of themselves, but rather derive their importance from their relationship or relevance to something else, such as a behavioral goal or plan. The role of the prefrontal cortex may be somewhat different depending on which general class of stimuli is involved, that is, those commanding involuntary attention versus those that are more likely to be the object of voluntary attention.

Luria (1973, p. 216) described how a normal person, when shown a thematic picture, will alter his or her patterns of eye movements (active searching or scanning) in looking at the picture depending on what questions are asked. The idea behind this exercise was that depending on the question the subject would have to scan different parts of the picture that might be expected to provide the answer. For example, if asked about the age of the subjects in the picture, one might scan their facial features, whereas if asked about their social status, attention might be better directed to their clothes or furnishings. Conversely, a patient described as having a "massive" frontal lesion was observed to exhibit a constant pattern of more or less random scanning regardless of the questions posed.

The principle illustrated in the above example easily can be extrapolated to any number of situations. When faced with any task demand or problem, the number of stimulus options (again, both internal and external) to which one possibly might attend usually are considerable. In many cases this does not present a difficulty. As a result of previous experiences with the same or similar demands, the individual simply relies on well-entrenched stimulus–response patterns. However, the situation is different when the solutions are not so clear-cut or when, as noted earlier, one is confronted by ambiguous, conflicting, unfamiliar, vacillating, or equally compelling stimuli or response alternatives for which one has no prior "blueprint" to fall back on. In such situations, one must explore (i.e., selectively attend to) those stimuli that may hold the key to successively completing the task, just as the subjects had to visually explore the picture to look for information to answer the examiner's questions. But to be maximally efficient two things must happen: (1) the search must not be random but rather guided by certain logical strategies or principles, and (2) it must be flexible (i.e., it must be possible to rapidly shift attention from one set of stimuli, thoughts, or memory engrams to another, either as the problem evolves or potential solutions are explored and discarded).

It would appear that the prefrontal cortex is ideally positioned to handle directed attention. Through feedback loops, predominately between the dorsolateral cortices and the second functional unit (i.e., the parietal, temporal, occipital lobes), the frontal lobes could facilitate focusing attention on those perceptual processes, concepts, or memory stores that would appear immediately salient based on current strategies, plans, or feedback.[85] In trying to come up with an example, one is faced with the difficulty of separating out problems of distractibility (which will be addressed shortly), faulty strategy, or inadequate self-monitoring capacity versus problems of selective attention per se. Perhaps, for most practical purposes, these various processes are largely inseparable. However, a clue might be found in analyzing the process that optimally takes place when attempting to learn a list of unrelated words that exceed one's immediate retention span. When a patient is presented with such a list for the first time, a certain percentage of the words are recalled (usually based on primacy or recency effects). When the list is read again, what strategy(i.e.s) might be employed in order to enhance recall? As the word list is being repeated by the examiner, one strategy might be to identify and selectively attend to (i.e., concentrate on or covertly rehearse) those words not recalled on the previous trial. Frontal patients may have difficulty utilizing this strategy. Luria (1966) reported that when presented with such lists, frontal patients tend not to significantly improve over trials.[86]

Distractibility. In addition to its apparent role in guiding voluntary or selective attention, the prefrontal cortex also is important for controlling involuntary attention. As noted in the introduction of this topic, one constantly is being bombarded with multiple stimuli from a variety of sources, again both internal and external. The overwhelming majority of these stimuli simply represent "noise" in relation to whatever task is at hand. The student who is trying to complete a difficult exam is best served if he or she can refrain from attending to "extraneous" stimuli, such as the sounds of conversations in the hallway, the bird perched on the window ledge, or thoughts of either last night's or tomorrow night's date. This process represents the flip side of selective or directed attention. Attentional capacity is limited; most people effectively can attend to only one or two things at a time. If one must direct their attention to a particular set or class of stimuli, especially if prolonged or intensive concentration is required, this is most effectively accomplished if other potentially distracting stimuli can be ignored (i.e., prevented from intruding on one's consciousness). This capacity to ignore irrelevant stimuli then would appear to be an integral part of the role of the frontal lobes in planning and executing behavioral programs. In fact, problems of distractibility as a consequence of frontal lobe lesions have been repeatedly reported in both humans and animals (Brutkowski, 1965; Chao & Knight, 1995; Fuster, 1997; Hecaen & Albert, 1978; Stuss & Benson, 1986; Woods & Knight, 1986). If present, distractibility can lead to significant impairments on a wide variety of clinical tests, especially those requiring more intense levels of concentration and attention, such as learning and memory tasks. One of the more common signs suggestive of problems with distractibility on the clinical exam is loss of mental set. This might be seen, for example, on the Wisconsin Card Sorting test, on serial reversal tasks (such as serial 7s), or reciting the months in reverse order. On the former, the subject might forget the current sorting principle if pulled by the saliency of another stimulus. On the above serial reversal tasks, the individual may lose track of the task as demonstrated either by subtracting by another number or reverting to the more accustomed task of reciting the months in the forward order. Figure 9–30 appears to illustrate this same phenomenon on clock drawing. Here the patient became immediately distracted by the insertion of the number "12" and continued the number series until running out of room.

Motor impersistence (Heilman & Watson, 1991), which is the inability to sustain an action (such as keeping one's eyes closed or tongue protruded) over a specified period of time, and **utilization behavior,** which is the tendency to pick up any nearby object and begin to use it either without being asked or when circumstances would not dictate such behavior (Lhermitte, 1983: Shallice & Burgess, 1991), both may be seen as expressions of distractibility.

Perseveration. We routinely selectively attend to those internal or external events that are relevant to current problems or task demands and filter out irrelevant stimuli. In addition, we also must be able to abandon or shift our fixation on a stimulus once it is no longer relevant or when circumstances normally would dictate that attention should be focused elsewhere. This finding is less frequently identified as an outstanding finding in the clinical literature (Ackerly, 1937, as reported by Benton, 1991, being one notable exception). However, **perseveration**, which is not an uncommon finding following frontal injuries, may reflect

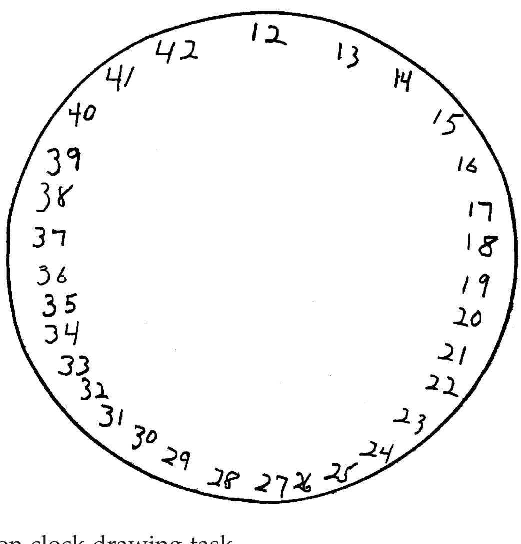


Figure 9–30. Loss of set on clock drawing task.

difficulties in shifting attention (Sandson & Albert, 1987). As will be discussed below, perseveration also may be associated with difficulty inhibiting prepotent response sets and can be demonstrated on a wide range of tasks. While it may be associated with various types of pathology, it is perhaps most frequently associated with lesions of the prefrontal zone or underlying structures (Iverson & Mishkin, 1970; Luria, 1966; Sandson & Albert, 1987).

Neglect. Finally, it should be noted that symptoms of unilateral neglect (see earlier discussions), while more frequently associated with the posterior cortices (Heilman, Valenstein, and Watson, 1983) also may accompany lateralized frontal (or anterior cingulate) lesions (Crowne, 1983; Damasio, Damasio, & Chui, 1980; Heilman & Valenstein, 1972).[87] Frontal neglect, which likely reflects a special form of an attentional disorder, can be demonstrated in all sensory spheres. However, it most readily may be evidenced in visual neglect of contralateral space (see Figure 9–31) and certainly may be exacerbated by involvement of the frontal eye fields. The neglect need not be complete or consistent. In fact, neglect secondary to frontal lobe lesions often is subtler or less dramatic than neglect syndromes seen following parietal–temporal lesions. As is true of neglect in general, left-sided neglect following right hemisphere lesions appears to be more common than with lesions of the left hemisphere.

Summary. The frontal lobes would appear to instrumental in (1) facilitating our ability to focus or concentrate only on those stimuli that are currently relevant to the task at hand, (2) maintaining that focus as long as the situation dictates (i.e., not allowing ourselves to become distracted by "irrelevant" stimuli), and (3) being able to appropriately shift attention as task demands or contingencies change. However, one also must keep in mind that in any given situation it may be difficult not only to differentiate attentional problems of "organic" versus "functional" origin, but also difficult to differentiate or separate out other functional disturbances, such as planning errors, disinhibition, impaired self-monitoring capacity, or more general arousal difficulties. All may be associated with frontal pathology, and all may present behaviorally as disturbances of attention.

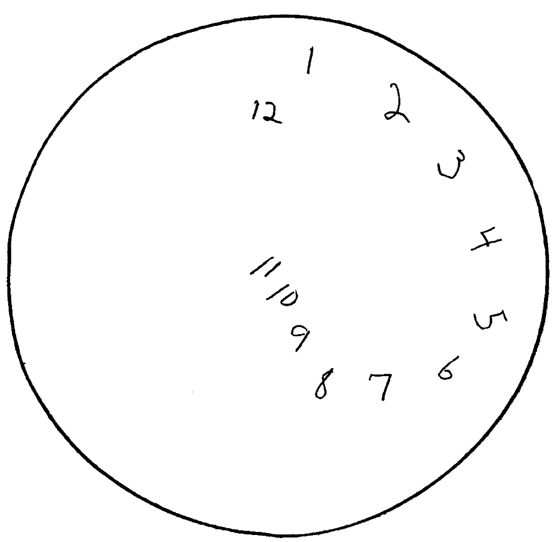


Figure 9–31. (*Continued*)

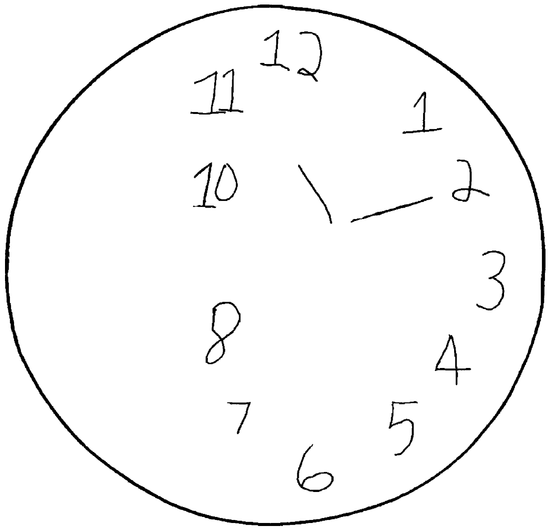


Figure 9–31. Examples of left visual neglect on clock drawing.

Inhibition

Damage to the prefrontal areas often is associated with problems of disinhibition or failure to inhibit inappropriate responses. Both behaviorally and anatomically, there would appear to be justification for dividing problems of inhibition into three broad categories. The first generally involves problems in inhibiting biological or affectively driven responses, particularly in situations where such expressions might be considered socially inappropriate. Clinically, such behavior is usually termed ***behavioral disinhibition***. The second might be characterized as difficulty inhibiting cognitive response sets that may have been appropriate at one point but which are no longer appropriate or effective. A related phenomenon might be the inability to distance oneself from a particular stimulus or stimulus cue in order to produce an appropriate response. The third type of disinhibition might be conceived of as difficulties inhibiting kinetic programs once they are initiated, again despite the fact that they are no longer useful. Problems of "behavioral disinhibition" will be addressed below under the heading **Modulation of Internal Drives and Emotions**. Here the focus will be on problems of inhibiting cognitive and motoric response sets.

Cognitive Disinhibition. The problem in inhibiting inappropriate cognitive response sets is in itself a multidimensional phenomenon. While there may be some benefit in subsuming this class of behaviors under a single rubric, many factors likely contribute to the observed deficits. Hopefully, this will become clear as we proceed through the next few paragraphs. On a very basic level, many if not most of our behavioral responses are stimulus-bound. Our response in a given situation is dictated in large part by the stimulus parameters that constitute the particular situation at any given point in time. In some instances our response choice will be predicated on similar stimulus–response patterns that proved effective in the past. This has a certain practical value. Instead of having to sort through or individually analyze the myriad of potential responses available, we can respond quickly and efficiently in a more or less preprogrammed manner based on previous successful experiences. However, there also are times when such approaches may not be the best choice.

Normally, if the selected response proves ineffective or if the stimulus parameters (the situation) are sufficiently unique, a new trial-and error-approach will be adopted. If this new approach is successful (i.e., produces the desired result or otherwise positively reinforced), it will continue; otherwise it likely will be discarded in favor of yet another approach. Choosing what response to make in a given situation and deciding when and under what circumstances certain responses need to be abandoned in favor of new, more effective responses are what might be termed **executive functions,** and are thought to be largely mediated by the prefrontal, dorsolateral cortices.

With damage to the prefrontal (especially, dorsolateral) cortices this "executive" process can be disrupted. As suggested above, this can happen for a number of different reasons. First, a particular stimulus or aspect of a situation may trigger an association with a previously learned response. Two examples of the types of errors that might be made in this situation are failure to take the entire situation into account or simply difficulty in inhibiting a "prepotent" (overlearned) response. The patient who described the two pictures in Figure 9–32 as a "pipe" and a "plumber's helper" failed to inhibit his "first impression" based on partial information, ignoring the remaining salient features of the stimuli.

In the Stroop Test, where the names of colors (e.g., "red" or "blue") are printed in different colored inks, the patient may persist in giving the color designated by the words rather than the color of the ink in which the word is printed as instructed. In this latter situation, the patient accurately may retain the verbal instructions, but have difficulty inhibiting the prepotent response in face of the pull of the stimulus. This latter phenomenon also might be termed becoming *stimulus-bound*.

Additional examples might include the patient who either places the hands of a clock pointing at the "10" and the "11," or places an extra "10" between the 11 and the 12 when asked to set the time to "ten after eleven" (see Figure 9–33). It should be noted that the kinds of errors shown in these clocks also might result from failures of self-monitoring capacities (see below). Finally, patients with frontal lobe pathology will occasionally experience difficulty with the following task. If asked to "Close your eyes and raise the hand opposite

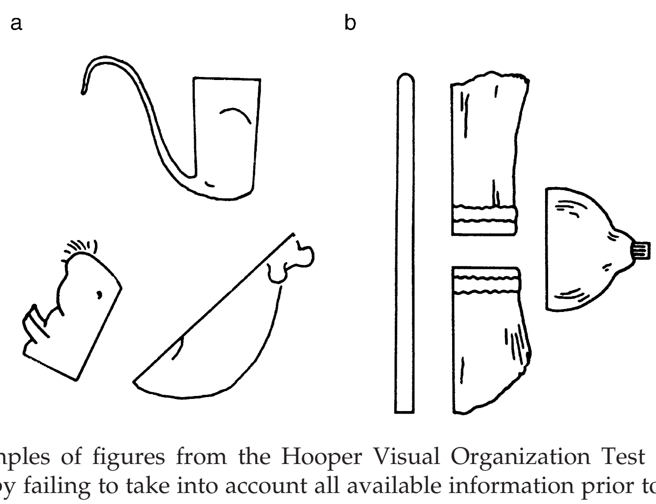


Figure 9–32. Examples of figures from the Hooper Visual Organization Test that might result in incorrect response by failing to take into account all available information prior to responding, identifying (a) as a "pipe" and (b) as a "plunger." Material from the VOT copyright © 1957 by H. Elston Hooper. Reprinted by permission of the publisher, Western Psychological Services, 12031 Wilshire Boulevard, Los Angeles, California, 90025, www.wpspublish.com. Not to be reprinted in whole or in part for any additional purpose without the expressed, written permission of the publisher. All rights reserved.

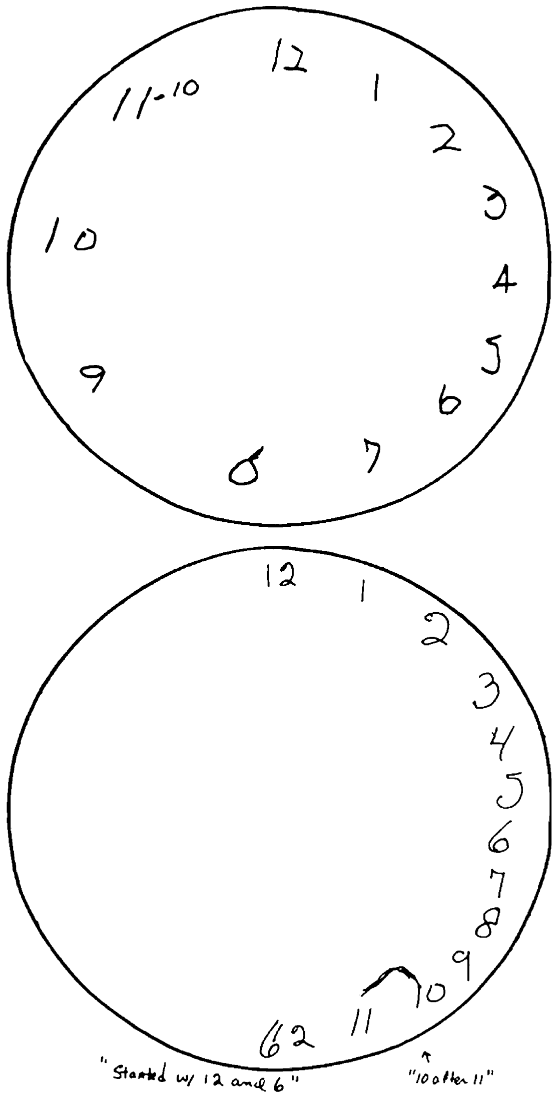


Figure 9–33. Examples of what might be interpreted as stimulus-bound responses on a clock drawing task.

the one I touch," they may persist in raising the hand touched by the examiner (i.e., have difficulty in overcoming the tactile stimulus). This response can occur despite the capacity to accurately repeat the instructions.

Closely associated with the type of deficit described above, a second type of "executive" error may be linked to ***perseveration***. As noted earlier, perseveration on occasion may eflect difficulty shifting attention, but in some situations, it also simply might be the case of getting stuck in a particular response set. In this latter situation, the prepotency does not necessarily represent a well-ingrained stimulus–response pattern (as was saying *blue* regardless of the color of the ink when the letters b-l-u-e were presented). Rather, the patient might adopt the first readily accessible response that comes to mind based on its recent use in another context. Thus, if in response to the question, "How are an apple and a banana alike?" the patient responds, "They are both good to eat," he may provide a similar answer (e.g., "both are edible") to the next question, "How are a fish and a bird alike?"

Perseveration, as a sign of failure of inhibition, also frequently occurs in prefrontal patients when "previously reinforced" response patterns no longer are appropriate because of changes in the task demands or changes in the tasks or goals themselves. As suggested above, very few tasks or situations are truly static; most are fluid and dynamic. Stimuli and/or response contingencies constantly change, either as a result of our (the organism's) actions or as a result of forces independent of our actions. Alternately, as one goal or stage within the process of achieving a goal is accomplished, there is a need to shift to the next stage or goal. Response strategies that are initially adopted in the attempt to accomplish a particular goal ultimately may prove ineffective. In all these instances, behavioral (mental) flexibility is required. While self-monitoring, which will be discussed shortly, certainly is critical in ascertaining response effectiveness on an ongoing basis, behavioral responses must remain fluid and flexible. Perseveration would appear to reflect a loss of this behavioral or mental flexibility.

The Wisconsin Card Sorting Test (WCST) (Grant & Berg, 1948; Milner, 1963) and the Category Test (Boll, 1981) are examples of formal psychometric measures that specifically tap this type of mental or behavioral flexibility. Although differing in their stimuli and presentation format, both tasks essentially selectively reinforce a particular response pattern. However, once that response pattern is well entrenched, the patient is required to adopt a different response to what are essentially comparable if not (in the case of the WCST) identical stimuli. On such tasks the patient with significant frontal lobe pathology may continue to rely on previously reinforced response patterns, even though they are obviously no longer effective (Robinson et al., 1980: Osmon & Suchy, 1996).[88] Because of their sensitivity to "loss of mental flexibility" and/or perseverative response tendencies, these two measures frequently are designated as "frontal lobe tests." While they indeed are frequently sensitive to lesions of the prefrontal cortex, it is important to bear in mind that like most tests that are sensitive to brain injury, these are multifaceted tests and as such are subject to disruption by lesions in various parts of the brain (Anderson et al. 1991; Grafman et al., 1990; Wang, 1987). Conversely, absence of deficits on such tests does not preclude the possibility of lesions in a given area of the brain, including the frontal lobes.

Sorting tests, such as those found in the Delis-Kaplan Executive Functions System (published by Harcourt Assessment) and the stimuli in Figures 9–34a and 9–34b offer additional examples of tasks that also would appear to tap what frequently has been characterized as mental flexibility. This capacity might be defined as the ability to look at the same set of data from different perspectives or to explore alternate solutions to an old problem. This requires one to abandon, at least temporarily, previous notions and to be creative in searching for new ones. In the two figures below, each item has something in common with each other item in the array. One's task simply would be to identify ten ways in which the five items within each array share a common feature.

A final example of cognitive response–inhibition difficulty might be the situation where there is no immediate or clear-cut solution to a given problem. Suppose, for example, the problem in question would appear to offer several potentially equally viable responses, at least initially. In order to ensure the maximal probability of success, the most appropriate response might be to delay (inhibit) responding until such time as either the problem can be analyzed in greater detail or the various response possibilities can be given more careful consideration with regard to their potential appropriateness and/or anticipated consequences. Patients with marked frontal pathology often demonstrate a persistent disinclination to delay their response under such circumstances, resulting in perceived poor judgment and impulsive behaviors. While such behaviors can occur under a variety of

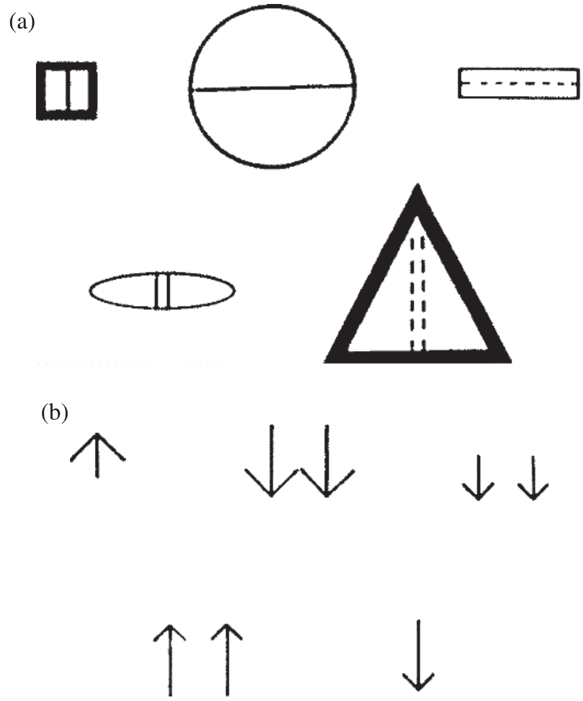


Figure 9–34. "Mental flexibility" type task for bedside exam.

circumstances, even among "normals," the problem likely is to be exacerbated in the presence of certain frontal lobe lesions, especially in basal or orbital lesions and when strong emotions or biological urges are present, topics that will be addressed independently later.

In the situations just described, the ability to keep in perspective both one's immediate and overall goals are critical. Anticipation of possible consequences or predicted outcomes prior to actually carrying out a response should constitute an essential preliminary filtering process. Often the "favored" (prepotent) response might have to be abandoned in lieu of one that, although perhaps less routine, may have a higher probability of success given the circumstances. Thus, response inhibition is not an isolated process. To be maximally effective, it also must involve other aspects of frontal lobe functioning including selective attention, maintaining a stable intention, planning, and self-monitoring ability.

Motor Disinhibition. Before discussing planning and self-monitoring ability, we need to briefly review what might be considered a third type of behavioral disinhibition, that is, **difficulty inhibiting motor action programs once they have begun**. Luria (1965, 1966, 1973) described at least two general types of motor perseveration or failures of inhibition in writing or drawing tasks. The first, as illustrated in Figure 9–30, seems to represent more of a cognitive-type deficit. In this type of deficit the "action program" is contaminated by intrusion of "stereotypic" components from either preceding programs or preceding aspects of the current program. For example, when asked to copy an array of three designs as part of a memory-for-designs task (Figure 9–35), patients with lesions affecting the prefrontal lobes might carry over elements of the first design (e.g., the circles) into the second or third figures. While occasionally seen during the copying part of the task, it is even more likely to

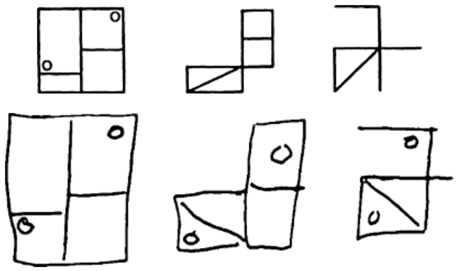


Figure 9–35. Example of perseveration on a memory-for-designs task.

occur during the immediate and delayed memory phases. Similar phenomena might occur if the patient is asked to carry out some type of alternating, sequential motor task. As seen in the second example in Figure 9–36, the more complex pattern dissolves into a tendency to repeat one element of the task.

In contrast, for other patients the problem may be even more basic. There may be no disintegration of the action program itself; rather the problem is that once the motor action is begun, there is a breakdown in the mechanisms that normally would terminate the motor action once it is completed. As a result, the action continues in a perseverative, meaningless fashion well beyond that which is requested. Figure 9–37 provides an example of the latter. In another instance, a patient was asked to write three sentences about how parents should raise or treat their children. The patient filled up the half page allotted for this task and then, turning the page over, proceeded to fill up most of the next page with (on target) sentences until finally stopped by the examiner. When subsequently asked, the patient had retained the original instructions ("Write three sentences…") but apparently had become "stuck in set." Whereas the disintegration of the motor program itself is suggestive of dorsolateral involvement, the inert repetition of the elementary motor responses, although relatively rare, when seen are more likely to result from deep frontal lesions that affect frontal–striatal feedback loops.[89]

Planning (Strategy) and Execution

Because of their relatively recent phylogenetic expansion, the prefrontal cortices had come to be thought of as more or less the seat of man's higher cognitive or intellectual ability. Hence, as noted earlier, the discovery that many frontal lobectomy patients did not appear substantially impaired on IQ tests (see Stuss & Benson, pp. 197–198) must have come as a bit of a surprise to many investigators. In trying to break down the individual factors that are relevant to the role played by the prefrontal zones in higher cognitive functioning and problem-solving behavior (which would appear to underlie "intelligence"), Luria suggested that they become particularly critical in situations where the problem itself fails to outline the response patterns necessary to arrive at its solution or where one simply cannot fall back on previous experience. Thus, the prefrontal zones were thought to be critical in situations where one must (1) carefully analyze the problem, searching for critical clues (while avoiding

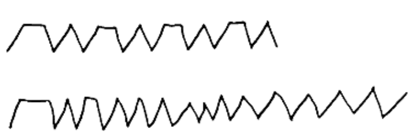


Figure 9–36. Perseveration and "simplification" in a Lurian type alternating pattern task.

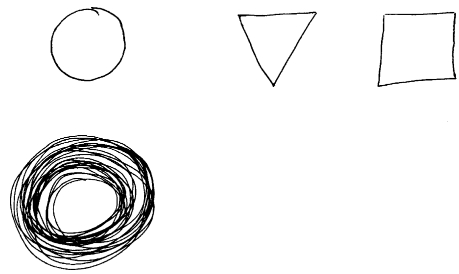


Figure 9–37. Inability to terminate motor action once initiated on a simple copying task.

being distracted by noncritical ones), (2) anticipate the potential consequences of various response options, and (3) develop a general plan of action or strategy that then must be systematically executed in a orderly, sequential manner. After all of the above have been accomplished, one still has to assess the outcome of the action to ensure that it has had its desired effect, or that either the previous goal is still viable, or "rules of the game" have not changed.

This type of analysis and planning ability obviously transcends a large range and variety of situations, both in terms of what one might experience in his or her normal environment and those that might be presented psychometrically (i.e., in neuropsychological test batteries). Yet, at the same time, we often are struck by how well individuals with demonstrable frontal lobe lesions adapt and respond, not only to environmental demands, but also on formal neuropsychological test batteries. This can be seen with both smaller focal lesions and following more extensive lesions involved in psychosurgical procedures. In fact, unless marked by significant personality changes such as increased disinhibition or apathy (which are more likely to result from orbital and mesial lesions) or the individual is engaged in occupations that require extensive and elaborate planning and mental flexibility on a daily basis (i.e., where one simply cannot fall back on more established routines or past experiences), many lesions that are restricted to the dorsolateral prefrontal cortices often may go relatively unnoticed.

In part because of the difficulty in demonstrating planning and other related cognitive deficits on clinical examination, there has been a long history of attempting to identify or develop specific psychometric measures that would enhance such predictions. These efforts have met with limited success. Among the tests that appear to be most commonly listed as probably measuring planning ability are the Porteus Mazes (or similar mazes) and "tower" tests (Damasio & Anderson, 1993; Fuster, 1997; Lezak, 2004; Mapou, 1995; Stuss & Benson, 1986).[90] While traditional visual maze-type tests have proved sensitive to frontal lobe impairment (Milner, 1965; Smith, 1960), the "planning strategy" required for successful performance is relatively straightforward and remains more or less constant, not only throughout the task but also from one problem to the next. Basically this strategy involves delaying the response at each choice point in order to mentally trace the alternate available pathways, thus ensuring that the one selected does not lead to a blind alley. However, impulsivity, failure to anticipate the consequences of a particular response, or "forgetting" to employ this strategy is not the only source of potential error on mazes. Impaired performance also also may result from an inability to profit from past experience (errors) or failure to adhere to the "rules," such as cutting through walls. These latter difficulties at least in part are likely to reflect difficulties with self-monitoring (see below).

"Tower" tests such as the Tower of London (Shallice, 1982) and the Tower of Toronto (Saint Cyr & Taylor, 1992) tasks would appear to benefit heavily from planning ability, especially for the more difficult problems. As can be seen in the accompanying illustration, the subject is required to anticipate the potential effect of each of several possible moves on his or her ability to accomplish the final goal.[91] Despite some correlation between maze or tower tests and prefrontal pathology, the ability of these tests to identify frontal lobe lesions are not exceptionally robust (Shallice & Burgess, 1991; Levin, Goldstein, et al., 1991). This also is true of many if not most measures that commonly are referred to as "frontal lobe tests". Figure 9–38 shows a variation on these tower-type tasks. While it certainly is possible to reach the desired goal by trial and error alone, developing some type of plan or strategy clearly facilitates finding its solution. Before exploring some possible reasons for the frequently marginal association between these and similar-type tasks and frontal pathology, it might be useful to review planning ability as it can influence other types of tasks.

Visual–Spatial Constructions and Planning Ability. Although visual–spatial construction difficulties generally are associated with disturbances of the second functional unit, specifically the parietal (parietal–occipital) cortices, lesions of the dorsolateral prefrontal cortex also may result in impaired performance on such tasks (Benson & Barton, 1970; Black & Strub, 1976; Luria & Tsvetkova, 1964). The reasons are not difficult to appreciate if one considers the processes involved, especially in the more complex constructional tasks. Think about building a house or planning a garden. One does not start by nailing 2 x 6s together for the rafters before the walls are framed, nor does one simply start to put seeds in the ground in a random fashion. Before either project is begun, there usually is a plan and strategy in place, not only in terms of laying out the basic parameters, but also at least a general idea of the best sequence in which to proceed.

The execution of many visual–spatial construction tasks can be greatly facilitated by following a similar approach. For example, in attempting to copy the Rey-Osterreith figure, one is greatly benefited by starting out with a systematic approach, such as first drawing the

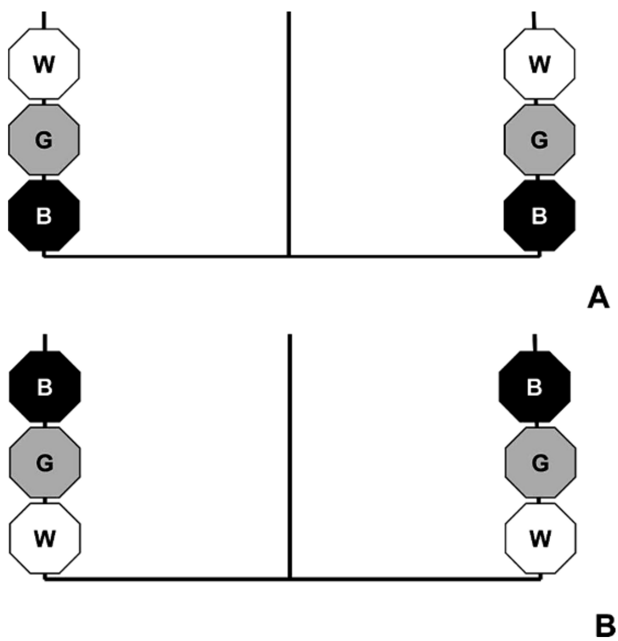


Figure 9–38. Starting with arrangement A, the goal is to end up with B by shifting the pieces one at a time to either a center or end stack. No stack can ever exceed three objects. (*This test can be tried safely at home using any three identifiable pairs of stackable, crash-resistant objects*).

central rectangle, the diagonals, and the vertical and horizontal divisions before attempting the internal details. Patients with significant frontal pathology, as well as those with right hemisphere lesions in general, are more likely to be observed adopting a more "piecemeal" approach to this task (Figure 9–39). Similarly, asking patients to produce drawings showing the floor plans of their homes generally will be greatly facilitated if they begin with an outline of the perimeter of the building and subsequently putting in the various rooms and hallways rather than beginning with a single room and adding the others as they go.

"Planning errors" also may be seen in other constructional tasks. Figure 9–40 illustrates examples of such errors in clock drawing. As might be expected, it was found that planning errors on this task are more likely to be elicited if the patient is provided with a large clock face with which to work and, with the exception of the "12," is forced to write in the numbers in sequence (Mendoza et al., 1989, 1993). Although not always as obvious as in the case of the Rey figure or clock drawing, planning errors also may be present in block reconstruction-type tasks. While patterns, such as shown in Figure 9–41a & b, are less likely to be affected by planning deficits, clinical experience has suggested that those in which the boundaries of the constituent blocks are not immediately discernable (e.g., Figure 9–41c & d) are more vulnerable to such errors. When presented with the latter patterns, one is more likely to benefit from a preliminary analysis of the design to establish those boundaries. It is this type of preliminary analysis and planning ability that often is compromised in patients with prefrontal lesions. Illustrative of this deficiency is the fact that frontal lesion patients are much more likely than posterior lesion patients to profit from the external cues provided by placing a grid placed over the design as compared with posterior patients (Luria & Tsvetkova, 1964).

Learning and Memory and Planning Ability. Lesions that are restricted to the dorsolateral prefrontal cortices do not appear to impact on the ability to establish new memory associations per se or the ability to retrieve old memories. This does not mean that frontal lobe lesions have no impact on learning and memory. Deficits in delayed recall following lesions to the dorsolateral cortex in primates (Jacobson, 1936; Oscar-Berman, McNamara, & Freedman, 1991) was one of the earliest and most persistent experimental findings of frontal pathology, and more recently certain experimental procedures using "conditional memory" paradigms were found to be sensitive to such lesions (Petrides, 1985, 1990).[92] Luria (1973, pp. 211–212) also notes that prefrontal lesions can interfere with the learning process in part as a result of an inability to "create stable motives . . . and to maintain the active effort" to learn.

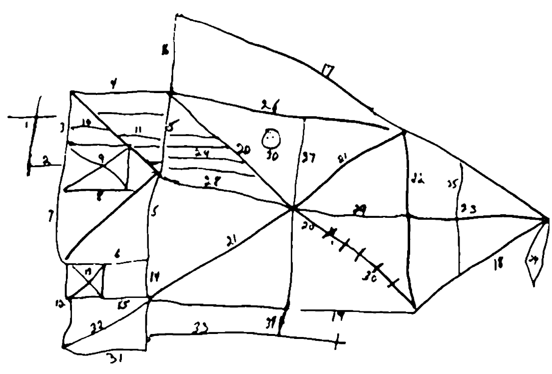


Figure 9–39. Adopting a piecemeal approach in copying complex designs such as the Rey-Osterreith figure increases the probability of significant distortions of the original design.

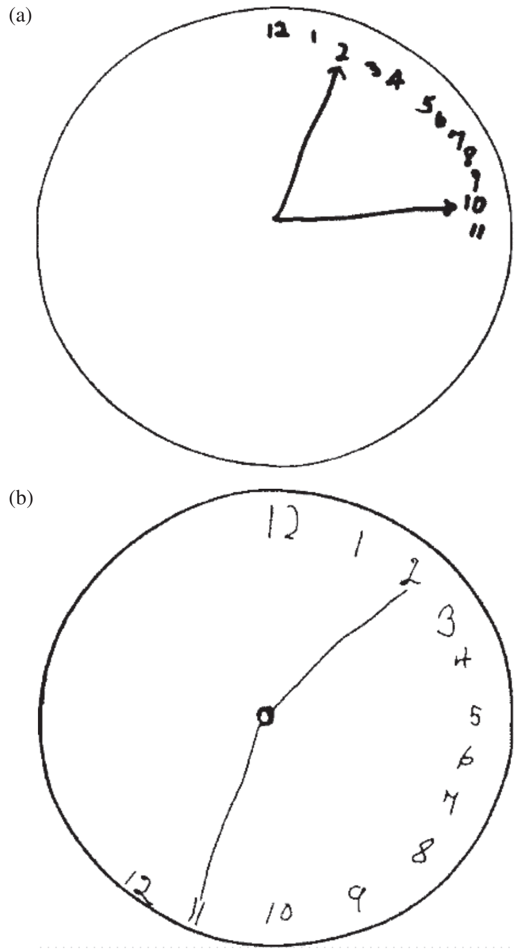


Figure 9–40. Clock drawing and planning ability. The type of error seen in (b) might easily be mistaken for left visual field neglect rather than a planning error. If the patient has adequate self-monitoring capacity, such "planning" errors may be recognized and eventually corrected. Requiring the patient to write the numbers "in order" on a large clock face places a greater demand on spatial planning.

Again clinical observation would suggest that patients with dorsolateral frontal lesions generally perform better when presented with tests that measure logical verbal memory (e.g., paragraphs or stories) than free verbal learning (e.g., word lists), especially those that exceed one's immediate memory span. It is easy to speculate why this might be the case. Paragraphs have a built in structure of their own and do not need to be imposed from without. By contrast, when presented with a long (10 to 15) list of words to remember, such is not the case. If given a list of totally unrelated words to learn, such as the Rey Auditory Verbal Learning Test (RAVLT) (Lezak, 2004), it is impossible to recall all the words after a single trial. However, since these tests typically are administered over several trials, it is possible to improve, but some planning or strategy is essential. As noted previously, one such strategy is to concentrate more intensely on those words not recalled on the previous trial as the words are repeated over subsequent trials. Another strategy would be to actively create meaningful associations among various words. But this takes planning. A variation

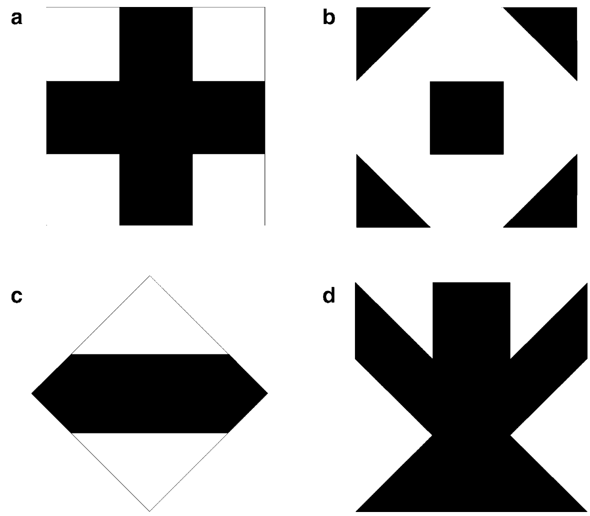


Figure 9–41. Planning ability and solving Kohs' blocks type tests (Kohs, 1919). In figures (a) and (b), one more easily can discern the placement and orientation of the nine individual blocks used in creating the patterns shown, especially (a). In (c) and (d) this is much less clear, requiring more preliminary analysis and planning to be maximally efficient.

of this type of test is the California Verbal Learning Test (CVLT) (Delis et al., 1987). Like the RAVLT, the subject is presented with a long (16) list of words. However, the words in the CVLT can be grouped into four general categories (e.g., tools, spices). Although the patient is not advised of this fact beforehand, if the patient "discovers" this fact and attempts to group the items into these categories prior to recall, performance should be enhanced. Again, this involves the patient having to discover and utilize this strategy (plan) in order to benefit.

The same principle (e.g., focusing more intensely on elements not previously recalled) applies to more complex tests of nonverbal memory in which successive learning trials might be given. An additional consideration would apply when using a highly complex figure like the Rey-Osterreith as a test of memory. As noted above, right hemisphere as well as certain frontal patients are somewhat more likely to take a piecemeal approach in simply copying the design prior to being asked to copy it from memory. Even so, despite using a disorganized approach in copying this design, the patient still may produce a reasonably accurate facsimile, especially if the posterior cortices are intact. However, even if they manage a decent reproduction of the figure, a less-than-systematic approach will make it more difficult to reproduce the design from memory, since "chunking" becomes more difficult. Thus despite producing a "reasonably" representative figure as seen in Figure 9–42a, the number of "elements" to be remembered is greater than the 18 to 20 elements (depending on how one designates individual elements) should a more "organized" approach have been adopted (e.g., starting with the central rectangle and the central vertical, horizontal, and diagonal lines). "Memory" for the design is even more likely to show impairment if the piecemeal approach results in a significant distortion of the original, as seen in 9–42b.

Borrowing and expanding on a term used by Dobbs and Rule (1987), Shimamura, Janowsky, and Squire (1991) define the use of planning, organizational strategies, self-monitoring, and initiation (remembering to remember) in order to facilitate the learning of new information or the recall of previously learned information as *prospective memory*. The use of this term emphasizes the notion that efficient memory is an active and not merely a

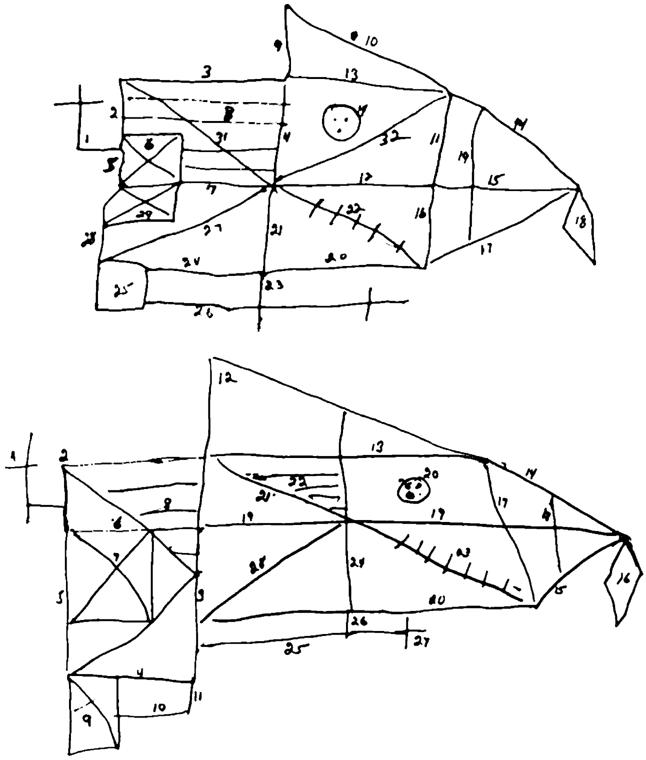


Figure 9–42. Poor planning in copying of the Rey-Osterreith figure can result in weaker "memory scores" either as function of (a) having more individual elements to remember or due to (b) the distortion of the original design.

passive process. While the frontal lobes may not be involved in the encoding of the memory engrams themselves (most likely this is a function of the hippocampal system), the frontal lobes play an important role in setting the stage for this process (Baddeley, 1986).[93]

Arithmetical Word Problems and Planning Ability. Patients with lesions to the prefrontal cortices generally will have little difficulty with arithmetical word problems when the nature of the mathematical operations to be performed is clearly delineated in the way the problem is presented. Consider, for example, the following problem: "How much would 12 tickets cost if each ticket sold for $3.25?" It does not require any sophisticated reasoning to recognize that one simply must multiply $3.25 times 12. While it is possible that a patient with limited arithmetical skills or attention–concentration difficulties might encounter significant difficulties with the above problem, it is unlikely that the difficulty would stem primarily from an analysis and planning error.

However, consider the following problem: "If a man has $4.00 more than his son and together they have $13.00, how much does each have?" Here the problem necessitates preliminary analysis in order to determine ("plan") what operations need to be carried out. Although the calculations themselves in this latter problem are relatively simple, this represents the type of problem for which patients with lesions of the dorsolateral cortex might be expected to show particular difficulty.[94] Most patients, including those with nonfrontal pathology, will simply try to find two numbers that add up to 13 that are separated by "4." They typically will try "5" and "8," or "9" and "4," obviously, neither of which will be correct. In order to efficiently solve this problem, one must first truly analyze it and then devise a plan or strategy for its solution.

Despite its modest difficulty, the above problem still may not be suitable for many patients. However, it illustrates the type of planning that often goes into arithmetical word problems and how frontal lesions might compromise performance on such tasks. Luria (1973, p. 339) offers the following example: "A candle is 15 cm long; the shadow from the candle is 45 cm longer. How many times is the shadow longer than the candle?" Not only does this problem require some forethought ("analysis and planning"), but also one must inhibit the tendency to impulsively respond, "Oh, that's easy, the shadow is three times longer than the candle."

Additional Measures Involving Planning Ability. In addition to the tests mentioned above, many complex cognitive measures utilize varying degrees of analysis and strategic planning. Disruptions of these processes, while not necessarily precluding the possibility of successfully completing these tasks, may impair the efficiency with which they are executed. Picture Arrangement, one of the subtests from the Wechsler IQ tests, might be a good example of one such task. Success on this particular test requires not only systematically scanning each of the individual pictures to search for relevant cues, but the ability to systematically envision alternate scenarios while simultaneously considering the antecedents and consequences of human behavior. The "tinker toy" test devised by Lezak (1982) also can entail a fair amount of planning and organization. Those who stop and think (plan) what they want to make are expected to do better than those who simply begin to more or less randomly put pieces together. Another nonverbal test that also benefits from developing an organized plan of attack is the Sequin-Goddard formboard (also called the Tactual Performance Test from the Halstead–Reitan battery). One eventually may succeed by more or less randomly trying to fit each block on the board. However, identifying a particular block or shape on the board and then systematically searching for its match (cutout with the same shape) is a much more effective strategy.[95]

Another simple test designed to tap planning ability is shown in Figure 9–43. The task is to generate an itinerary that would involve traveling to all the cities listed visiting one, but only one, city twice. The goal would be to create a trip that would log as *many* miles as possible. Thus the would be to inhibit the natural tendency to draw routes that connect more or less adjacent cities, while traveling back and forth across the country as often as possible.

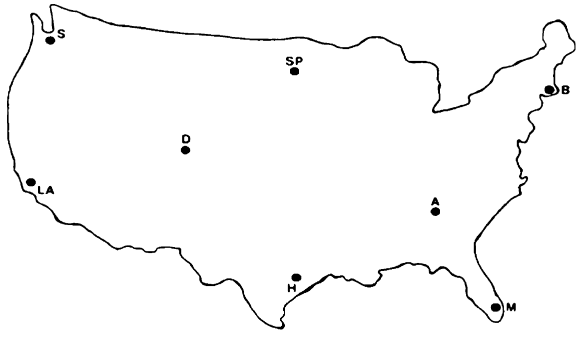


Figure 9–43. Map test. A task requiring simple planning ability (see text for explanation.

Verbal Planning Tasks. Although often more subtle, a variety of verbal tasks also relies on developing and adhering to an organized strategy. Perhaps some of the clearer examples of this are the semantic word generation (fluency) tasks (e.g., animals, items in a grocery store). In animal naming (Randolph et al., 1993), an effective strategy might be to sequentially picture animals in various setting or subcategories (e.g., farm, zoo, African, animal, pets, or birds). For a grocery store, one could take an imaginary trip down the produce, meat and dairy, frozen, canned goods, or condiments isles. Such approaches likely would be more effective than thinking of items at random.

Success with verbal abstractions tends to be correlated with education and intelligence and many might be answered relying on well-learned prior associations. However, a previously unfamiliar pairing (e.g., windmill and river) might require a systematic review of multiple independent associations (a form of planning behavior) prior to discovering a common potential for generating energy. Finally, even certain complex verbal commands, such as "Touch your nose before your chin but after your ear") require forethought, before responding.

Problems of Measurement and Diagnosis. If "planning ability" indeed is a primary function of the prefrontal lobes, why then is it so difficult to devise a test of planning ability that is selectively sensitive to frontal lobe lesions? The answers are probably multiple, but briefly exploring two of them at this point may be useful in thinking in broader terms about the relationship between "mental functions" and brain localization and their assessment. Perhaps the most challenging test of "planning" and "strategy" that is commonly available is the game of chess. As it is played by those who are truly proficient (the authors not included), it is primarily a game of strategy. Perhaps except for some classic opening gambits, moves must be planned well in advance,based not only on your current position, but also predicated on the moves you believe your opponent will make in response to your own (if these predictions fail to hold, new strategies must then be developed). Unfortunately chess is not practical to use as a clinical measure as it is too complex and difficult. As a result, while it might be a very sensitive test of the dorsolateral prefrontal cortex, it likely would not be very specific to such damage. For example, an individual may have difficulty succeeding because (1) by nature he is reckless and impulsive rather than thoughtful and deliberate, (2) external distractions may cause him to lose sight of the original plan, or (3) he simply may be not too bright and easily can be outmaneuvered by a more astute opponent.

The reason for going into such detail is that many of the tests that are construed as measures of frontal lobe functioning (including planning ability), like chess, tend to be fairly complex or multidimensional in nature. As noted previously, such tasks tend to be sensitive to lesions in multiple areas of the brain (Grafman et al., 1990; King & Snow, 1981) or other psychological processes (Watts et al., 1988).[96] Not all tests of frontal lobe function necessarily are highly complex. Luria, in fact, was noted for devising relatively simple techniques to assess brain functions (Christensen, 1975). However, in the latter case we have the opposite problem: tests that might be more specific, but less sensitive.

In trying to identify tests that are sensitive to deficits in planning (or other symptoms of prefrontal dysfunction), not infrequently one encounters patients with "frontal lesions" who perform normally on "frontal lobe tests" (Shallice & Burgess, 1991; Damasio, Tranel, & Damasio, 1991; Eslinger & Damasio, 1985). This point leads us to other potential explanations as to why certain tests may not appear especially sensitive to frontal pathology. Certainly one hypothesis is that either the test itself is not as demanding as one might hope or the patient is able to figure out an alternative way of solving the problem (perhaps using previous experiences). However, there probably is an even simpler reason. Just as we traditionally may have thought of the parietal or temporal lobes or the basal ganglia in monolithic terms, often so too is the case with the frontal lobes. Although the current tendency is to divide the prefrontal areas into a few anatomical regions (as were done in this chapter), in fact, almost certainly there are many more areas that make specific functional contributions. As is the case with other systems, if lesions spare certain critical areas of the prefrontal cortex, much more so an entire hemisphere, it is possible that many tests may remain relatively unaffected.[97]

While at present we may lack formal precise, practical, and reliable tests that tap planning ability, this does not mean that such problems necessarily are difficult to isolate and identify. What one should keep in mind is that planning ability is not a test construct but rather a process. As we have just seen, evidence of planning and organizational deficits may appear in a variety of tasks, many of which on the surface would seem to be designed to measure quite disparate functions. Understanding how such tasks may be impacted by prefrontal pathology may help illustrate this process at work.

Before proceeding to the next section, once again two caveats are in order. First, it is important to remember that all the tasks described above are multidimensional and as such may present difficulties for individual patients for many different reasons. This may include "psychological" factors, limited intelligence or education, as well as any number of either elementary or complex cognitive and perceptual difficulties resulting from lesions affecting other functional units of the brain. Thus, not every person who has difficulties on these or comparable tasks suffers from lesions of the prefrontal cortex. Such a diagnosis, if made, should come only after a careful review and integration of all available psychometric, historical, and medical data. The above examples are provided only as models for thinking about planning ability and the role of the frontal lobes in this process. Second, it is equally important to keep in mind that not all patients with lesions encroaching on the prefrontal lobes will always show impairment on any or all of these tasks. If critical areas of the frontal lobes are not involved or if the patient can rely on previous experiences or other compensatory mechanisms, he or she may achieve relative success on some of these tasks. Obviously, the more extensive the lesion(s), particularly if the dorsolateral cortices are involved bilaterally, the more likely deficits on these tests will become manifest. However, in such instances, the behavioral history itself should provide strong indicators of frontal pathology, independent of formal assessments.

Self-Monitoring Behavior

One final aspect of the frontal "executive" functions to be discussed is the capacity to spontaneously monitor one's own behavior. Self-monitoring, in this context, refers to one's capacity and propensity to monitor his or her response(s) to a problem or task based largely on the original goal, intervening circumstances, and approximate success in meeting that goal. The purpose of such monitoring is to ensure that:

1. Any preliminary steps or responses are in keeping with or serve to forward one's original plan or goal.
2. The original plan or strategy, as well as the goal itself, remains credible, given either the inadequacy of the response, changes in the nature of the problem, or the current circumstances with which one is faced.
3. The final response is internally consistent with other sources of previous or current information.
4. The action or response, in fact, accomplishes the intended purpose.

This process has been described as a *comparator* function. Thus, one of the roles of the frontal lobes might be to "compare" the results of one's analyses (of the problem), actions, plans, or strategies with behavioral outcomes as they relate to our ultimate goals.[98]

The benefits of such an activity should be obvious. Problem solving or coping with one's environment is necessarily a very dynamic process. Just as we cannot expect that our analysis of a given problem or situation always will be perfect, neither can we expect that our initial plans or strategies will be the best nor that the responses will always be on target or perfectly executed. Independent of whatever action taken, circumstances or environmental demands change, often necessitate a change in plans, strategies, response patterns, or even in the goals (or subgoals) themselves. Constant feedback is required to ensure that our responses and goals stay on course and remain appropriate. Additionally, there always is some degree of uncertainty in most situations. Response B in large part will depend on the result of having executed response A. Whether consciously or subconsciously, we often employ some form of "hypothesis testing" approach to our environment. If our response proves to be inappropriate or lacking in its anticipated consequences, reevaluations are required. On a simpler level, consider what movement would be like in three-dimensional space if we did not have access to visual and proprioceptive feedback from our muscles and joints. In the motor system, this feedback is mediated largely by the dorsal columns (although the anterolateral or spinothalamic and visual pathways also contribute). In the dorsolateral prefrontal system, feedback is obtained via reciprocal connections with the second (and probably parts of the first) functional systems. Of course, all self-monitoring activity also ultimately is predicated on the proper concern or motivation to produce an adequate response.[99]

Observing the concrete results of our actions or responses once they have been executed is certainly one means of self-monitoring. However, it is not the only or even necessarily the best way of carrying out self-monitoring activities. In many situations, once an overt response has been made, the possibilities for correction or compensation are greatly reduced; it is like writing with ink on a piece of fine parchment. A much better procedure might be to compare an anticipated response (plans or strategies) either with the possible long-range consequences of that action, not only vis-a-vis the immediate intended goal, but also its potential effect on other ancillary, unstated, or less immediate goals. In either case, this ability to mentally consider the potential consequences of an action prior to its execution requires another aspect of frontal lobe functioning that was previously introduced, namely, inhibition. Thus, in summary, one might ask

1. "Has my response been properly executed" (or, if intended, what are the odds that it can be?).
2. "Has my response accomplished its intended purpose (i.e., was it correct?) or can I reasonably anticipate that it will be?"
3. "Did my response have any unintended and/or undesirable effects that need to be corrected or might I reasonably expect such unintended effects?"
4. "Does my response (goal, plan, or strategy) need to be changed, either due to its ineffectiveness, inappropriateness, or changes in circumstances?"

Failures in self-monitoring represent frequent, although not necessarily invariable, sequelae of prefrontal lobe damage. When present, they usually cut across a wide variety of tasks or situations (see below for examples). Regardless of their level of severity, their behavioral significance should not be underestimated. The frontal patient who evidences little or no insight into his performance errors (poor self-monitoring of completed responses) might make no spontaneous attempt to correct or compensate for his or her errors or to solicit assistance from others. Inadequate responses not only will be allowed to stand unchallenged or uncorrected, but subsequent behaviors, which might be predicated on fallacious assumptions resulting from the original erroneous response, might only compound the error. Failure to monitor or consider the consequences of responses before they are executed frequently will result in impulsive, inappropriate behaviors.

Although, when present, obvious deficits in self-monitoring behaviors are frequently considered pathognomonic of frontal lobe disease, as with the other signs suggestive of frontal pathology some caution in making this interpretation is advised. Other factors could be contributing to the observed behavior. Going back to the analogy of the relationship between muscular contractions and proprioception, movement disturbances might result either from lesions that affect the motor system directly or the sensory feedback loops. Similarly, in order to effectively carry out self-monitoring activities, the frontal lobe is very much dependent on the posterior cortices to provide accurate sensory feedback, and the limbic system and the first functional unit to provide access to an ongoing memory of events and experiences, optimal arousal, and sustained drive or motivation. Patients who suffer some compromise of these latter systems, their connections with the frontal lobes, or a generalized deterioration of the brain (as in Alzheimer's disease) might be expected to show either limited or more generalized compromise of these essential feedback loops. For this reason, sometimes it is useful to speak of disturbances of **frontal systems** rather than lesions of the frontal lobes without clear, indisputable evidence of such pathology.

The following illustrate some instances in which deficits in self-monitoring ability might represent contributing factors in common neuropsychological measures of mental status:

Self-Monitoring Errors and Memory. Some of the "memory difficulties" exhibited by frontally impaired patients might reflect self-monitoring errors. For example, if when asked to provide the name of the current president or the current year, the patient responds with an answer that clearly is out of date, or when asked what he did the previous night (which was spent in the hospital) the patient responds with a story about attending a retirement party for a friend, deficits in self-monitoring should be suspected. Similarly, problems with self-monitoring ability might be reflected in situations where, when asked to recall a long list of words or a paragraph, the patient might repeat items from previous tasks (perseverations) or simply include numerous non-list words or ideas or images that never were present in the original story. These latter failures, which may be classified as *contaminations* or *confabulations*, might result from a failure to inhibit prepotent (or otherwise inappropriate) responses, combined with a subsequent failure to adequately self-monitor (Mercer et al., 1977; Shapiro et al., 1981). Similar perseverations or intrusion errors also might be seen in nonverbal memory tasks (Vilkki, 1989).

As noted above, when attempting to learn a large amount of material over repeated trials, a good strategy is to selectively attend or covertly rehearse those items or elements not recalled on the previous trial. Such a strategy, however, is predicated on awareness of and attention to the adequacy of the previous response (self-monitoring).

When testing memory for complex geometric designs, one occasionally may want to "test the limits" of a patient who shows significant immediate retention deficiencies by affording multiple learning trials. Such a patient might be given three or four additional trials with timed exposures (e.g., 10 to 15 seconds) to the stimulus, resulting in very limited if any increased retention. Under such circumstances, the author then might inform the patient that he or she will be allowed to "look at the design for as long as you want." Recognizing their difficulty in learning the task, most patients will continue to look at the design as long as permitted (it is usually withdrawn after 60 to 75 seconds). However, others will indicate they have "got it" after only 10 seconds or less (clearly they did not). Where lack of cooperation does not seem to have been an issue, the latter reasonably might be said to have had some type of self-monitoring deficiency.

In addition to the potential for failing to detect or correct performance errors on tests of memory, patients with frontal lobe pathology may fail to appreciate the presence of significant memory deficits per se. Frontal damage itself is not usually associated with severe memory disorders (i.e., general amnestic syndromes). However, in the presence of additional frontal findings, such as might be seen following anterior communicating artery aneurysms or Korsakoff's syndrome patients are more likely to either fail to appreciate or substantially minimize the severity of their memory disturbances (for review, see Schacter, 1991).

Self-Monitoring Errors and Visual–Spatial Constructions. Although major difficulties on visual–spatial constructional tasks generally are associated with lesions of the posterior cortices, some constructional or other visual–perceptual tasks may be compromised following damage to the prefrontal regions. As noted earlier, such errors may result, for example, from impaired planning ability, becoming stimulus-bound, or perseveration. However, regardless of whether the basic deficit is parietal or frontal, it is easy to see how deficits in self-monitoring ability might contribute to either the initial production of such errors or the failure to recognize and/or spontaneously self-correct errors once they have been made. For example, as seen in Figures 9–44 and 9–45, errors may result from the failure to compare one's performance with either external (Kohs' block construction) or internal (clock drawing) models. In attempting block construction, part of the planning and executive process involves comparing the end product of one's response to the original goal (in this case, the external model) to determine whether the two are identical and if not making an attempt to correct the response. In the case of clock drawing there typically is no external model; here the patient must rely on an internal model (perceptual memory of a clock face), but the self-monitoring process otherwise is the same.

Clearly, not all failures to recognize or correct errors necessarily reflect a deficiency in self-monitoring ability. Patients with severe perceptual difficulties (especially, unilateral visual neglect) may be hampered in their ability to identify performance errors. This often will be true also of patients with generalized dementia, severe attention deficits, or as noted earlier even patients with certain emotional or psychiatric disorders. Differential diagnosis largely is based on clinical judgment and observation after having taken into account the patient's performance across multiple tasks and situations.

Self-Monitoring Errors and Other Higher Cognitive Tasks. Obviously, breakdowns in self-monitoring capacities can influence performance and become manifest in any of a variety of cognitive tasks or situations. Take, for example, the arithmetical word problem presented

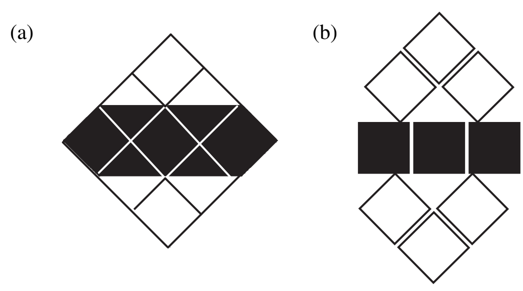
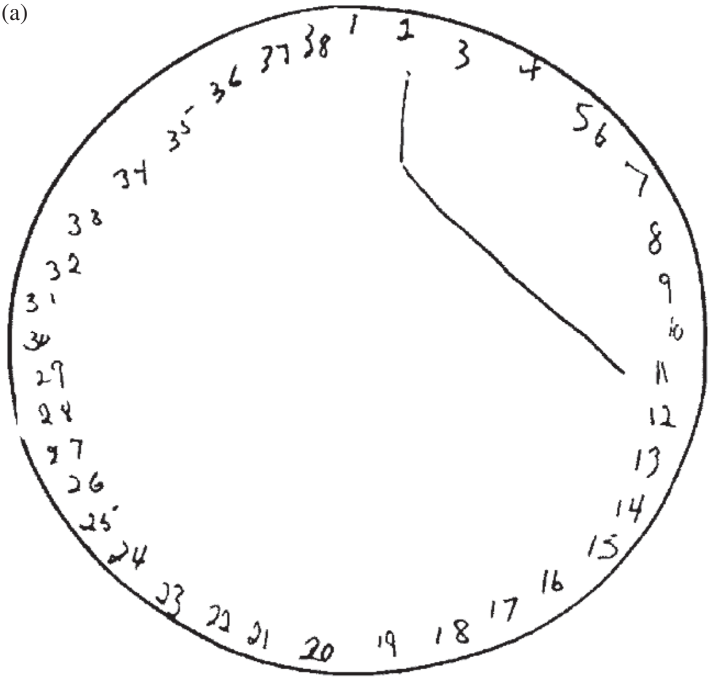
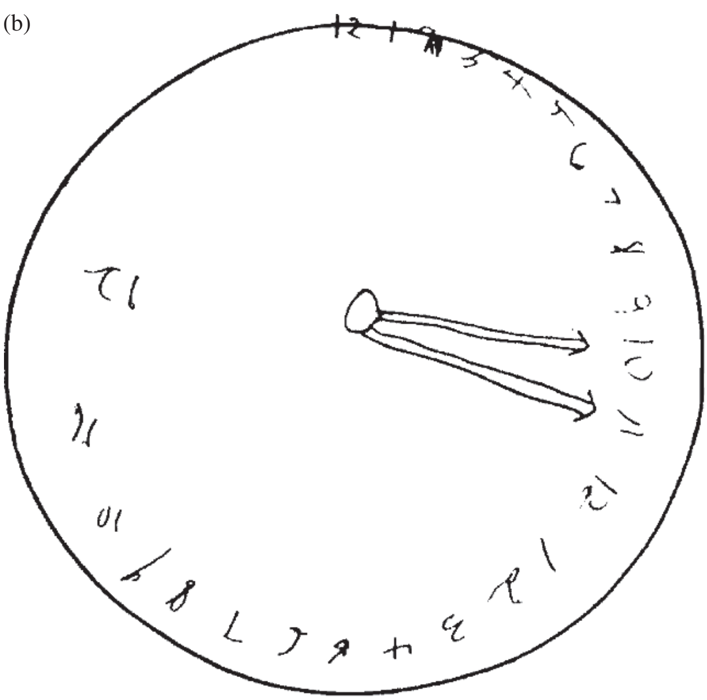


Figure 9–44. Illustration of the type of self-monitoring error that can occur in a Kohs' block design type task. While more or less reproducing the general internal detail of the design, there can be a failure to appreciate the external (3 × 3) configuration of the design and to recognize the discrepancy between the model (a) and the reproduction (b).

(a)



(b)



(c)

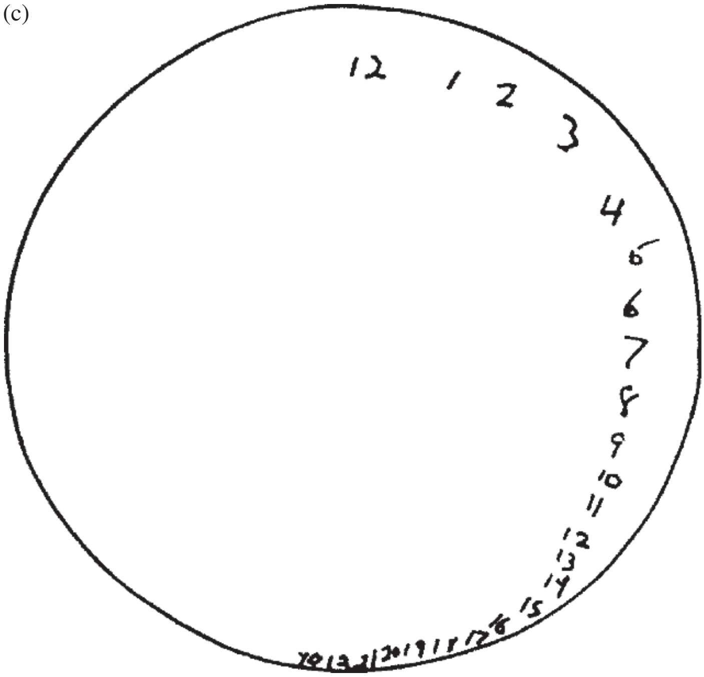


Figure 9–45. Errors in self-monitoring in clock drawing. Superfluous numbers are seen in all three clocks, although none were trying to produce a 24-hour military clock (as is occasionally seen). In (a) hand lengths are reversed and lack a central pivot point. In (b), the hands are not set at "10 after 11" as requested. In (c) there was no attempt to set the time. None of the patients appreciated their errors.

earlier: "If a man has $4.00 more than his son, and together they have $13.00, how much does each have?" While it is not unusual for patients to make a preliminary guess, perhaps coming up with either "eight dollars and five dollars," or "nine dollars and four dollars" (each of which add up to $13.00), most patients usually discover their error when they check their response against the original problem. They then discover that neither response fulfills the original condition, namely that there needs to be a $4 difference between the two amounts. While they still may be unable to arrive at the correct solution, at least they recognize that their initial responses are incorrect. Frontal patients with deficits in self-monitoring ability may never take this second step to discover their error.

The following represent what would appear to be additional examples of this phenomenon. In administering the Information subtest from the WAIS-R to a patient in Chicago who was suspected of experiencing frontal degeneration, he was asked to make a guess as to the current population of the United States. His response was "two million." He then was asked to guess the current population of the Chicago metropolitan area at the time. He correctly estimated that it was "approximately five million." After being told that his latter response was correct, he was then asked to make another estimate of the population of the United States. He again said "two million." Going through the above exercise a second time produced the same results. While his second response (regarding the US population) might be interpreted as simply perseveration, in effect he failed to compare the correct information he gave for Chicago to his response for the country as a whole.

Another Chicago patient with a frontal tumor was being seen in the examiner's office. It was winter and a steam heater that was directly under the window was making a slight "ticking" noise. The patient remarked that "it must be raining," mistaking the sound being made by the steam heater for raindrops. However, this window, which was only a few feet away and directly in front of the patient, had its curtains fully extended, clearly exposing a perfectly beautiful, blue, cloudless sky. Here the patient was drawing a conclusion based on a single source of sensory input (auditory), totally ignoring a second source of information (visual) that was readily available to him.

A third example was a patient who had suffered significant frontal lobe injuries as a result of a head trauma. This was a patient whom I had known for some time and with whom I often conversed. One day, on noticing a picture of my child on the wall, he asked how long I had been married. Jokingly, I replied "59 years." Without missing a beat, he inquired as to what we had done to celebrate our 50th wedding anniversary. At this point I was still in my early forties and despite my graying hair I dare say I would not normally have been taken to be 30 years older than my actual age. (Even when this obvious discrepancy was brought to his attention, he still was unable to reconcile the facts with which he was presented with his own observations. It never occurred to him that I might have been joking about being married for 59 years).[100]

In all three cases, all of which involved patients with evidence of frontal lobe damage, the patients failed to "compare" their responses or perceptions with other, obviously contradictory information immediately available to them. This was true whether such information could be gleaned from their senses (second and third cases) or from their own knowledge base (first case).

Deficits in Self-Monitoring and Executive Abilities: Concluding Thoughts. While this section has focused on the limited ability of certain frontally impaired patients to monitor the appropriateness or adequacy of specific responses, particularly in regard to whether they satisfy immediate goals or needs, self-monitoring also can be viewed in the broader context of self-awareness or insight. In this context, we might consider both awareness of deficit and awareness of the impact of one's behavior on others. Frontal lobe patients, especially those with more significant lesions, frequently are deficient in both these areas.[101] With regard to awareness of deficit, the problem typically is not so much one of failing to recognize or appreciate physical handicaps or limitations (anosognosia) as much a failure to appreciate cognitive changes or limitations. In addition, although frontal lobe patients frequently manifest marked personality and behavioral changes (Blumer & Benson, 1975; Lishman, 1973), they commonly fail to acknowledge the pathological nature of these changes or to recognize the negative impact these changes may have on others. As a result of this lack of insight, combined with their frequent lack of drive or motivation (points that will be addressed in greater detail in the following section), patients with significant frontal lobe impairment often have marked difficulty in social and occupational rehabilitation (Prigatano, 1991).[102]

Stuss & Benson (1986, pp. 244–249) emphasize the preeminence of self-awareness and executive ability in the hierarchy of human behavior in general and of the function of the frontal lobes in particular. Although for didactic purposes we may separate out individual aspects of these more global behavioral concepts, such as attention, intention, planning and goal-selection, inhibition, and self-monitoring ability, we should be aware that in practice they often are difficult to dissociate. It is as if these behavioral elements are like the individual threads woven into a complex tapestry. Even though at times it may be possible to isolate the separate components, their full richness and meaning can be appreciated only when observing the behavior as a whole.

Thus far we have focused mainly on self-awareness in relation to the executive aspects of human behavior. We have just seen how a failure to compare the appropriateness of a response to determine whether it served its intended purpose and/or was compatible with previously selected internal or external goals or criteria indeed is central to disorders of planning and execution. It was further noted that such disturbances typically were associated with lesions of the dorsolateral convexities of the frontal lobes. Next, we will explore a very different type of problem with self-awareness, one that also may lead to deficits in self-monitoring capacity, although for very different reasons. As alluded to previously, the deficits to be discussed in the following section are generally derived from a lack of genuine concern about specific future or long-range consequences and/or generalized apathy. Typically associated with orbitofrontal or mesial frontal pathology, as will be seen these latter deficits often appear to result from a disconnection between limbic structures and the dorsolateral frontal zones.

The Modulation of Internal Drives and Emotions

Differentiation from "Executive" Functions

In reviewing the role of the prefrontal cortex, the focus thus far has been on the more "executive" aspects of behavior. The preceding discussions have included such concepts as directed attention; freedom from distractibility; mental flexibility; planning ability; and the propensity to monitor and self-correct responses, particularly as they apply to cognitive-type tasks. However, well before these executive behavioral functions were correlated with frontal pathology, clinical case studies revealed that lesions of the frontal lobes were associated with more general disturbances of "personality," emotion, and drive states. Whereas "executive" functions came to be linked to lesions of the dorsolateral cortices, destruction of the orbital and mesial aspects of the frontal lobe more often were related to disruptions of "social" behavior. Such behavioral disturbances might range from apathy or depression to mania, restlessness, and/or (social) disinhibition; from increased agitation or irritability to a childlike euphoria; or from social withdrawal to sociopathy (Blumer & Benson, 1975; Hecaen, 1964; Holmes, 1931; Freeman & Watts, 1942; Greenblatt, Arnot, & Solomon, 1950; Levin, Benton & Grossman, 1982; Lishman, 1968; Malloy & Duffy, 1994; Petrie, 1952; Rylander, 1948; Tow, 1955). As we will see, most of these disturbances seem to be related to failures in properly accessing or modulating basic drive states or emotional impulses. As such, the lesions that result in these disturbances generally are thought to result from either (1) a disconnection syndrome between limbic/hypothalamic structures and the dorsolateral frontal zones, (2) disturbances of limbic structures directly or those deep mesial or ventral cortical zones with which they interface, or (3) a disruption of those neurochemical pathways that regulate the activities of the frontal zones.

There is an extensive literature on the subject of personality and behavioral change associated with damage to frontal systems. For the purposes of this chapter, however, the majority of these findings can be subsumed under two general rubrics: the effective utilization of drive states (arousal) and the inhibition of competing drive states or emotions (social inhibition). In the remainder of this section we will explore the probable role of the prefrontal cortex in the modulation of these functions, some of their probable anatomical substrates, and the behavioral effects produced by lesions to these areas.

Utilization of Drive States (Arousal)

The Role of the Reticular Activating System. Typically we think of the first functional unit, specifically the ascending reticular activating system (ARAS) through its thalamic connections, as being initially responsible for diffuse cortical activation (arousal) (Moruzzi & Magoun, 1949). However, for our present purposes, it is important to differentiate among (1) general cortical activation or arousal, (2) specific or selective cortical arousal, and (3) drive states. The brainstem ARAS would appear to be concerned with alerting the cortex in a general manner, either informing the cortex that "there is something happening out there that may be important, pay attention," or "there are some needs that have to be met, let's get on the stick and do something about it." While the level or intensity of this alerting response may vary depending on the situation, qualitatively (in terms of telling the cortex what to attend to) its influence is likely quite limited. This alerting or arousal of the cortex by the ARAS probably is mediated both via its influence on the intralaminar nuclei of the thalamus, as well as through diffuse neurochemical pathways (e.g., norepinephrine).

How does the ARAS know when and to what degree the cortex needs to be alerted or aroused? As previously mentioned, there probably are three basic mechanisms at work. The first, is external stimulation. Most, if not all, sensory receptors have fairly direct connections with or provide input to the brainstem. Thus, pain, simple touch, sound, light, or movement (vision), or even the smell of coffee and bacon in the morning depending on the circumstances may have strong arousal value.[103] Internal biological needs also may trigger a response. Thus, the cortex can be aroused during states of hunger, thirst, oxygen depletion, or other homeostatic deviations that are essential to the basic biological integrity of the organism. While the initiation of such responses may come directly from somatic receptors of the autonomic nervous system, they are likely supported and reinforced by hypothalamic connections (e.g., the medial forebrain bundle, the dorsal longitudinal fasciculus, or the mammillotegmental tract).

However, it also is likely that the cortex itself, particularly the prefrontal lobes, through feedback loops itself can have an activating influence on the ARAS, helping to maintain optimal levels of arousal under given conditions. Consider, for example, the following situations. One is walking or traveling through a questionable part of a large city late at night. He might be thinking, "While I don't see anything to be afraid of, I know that the circumstances are potentially dangerous and I need to be on guard." Or, take the case of a college student after a night on the town with perhaps a few too many beers, who suddenly realizes that she is ill-prepared for a test the next day. Despite the sedating influence of the alcohol, she manages to arouse herself sufficiently to hit the books for an hour (the influence of more abstract or long-range goals in generating arousal). One would strongly suspect that in these two latter instances the frontal lobes probably play a significant role in generating cortically initiated activation of the ARAS, which in turn may activate the cortex in general. Among the pathways potentially involved in such a situation again are the medial forebrain bundle, connecting the basal forebrain with the brain stem, as well as the stria medullaris of the thalamus and the habenulointerpeduncular tract. Combined, these provide alternate routes to the midbrain from the basal and mesial frontal areas.

The Role of Frontal–Thalamic Connections in Selective Attention or Arousal. At any one point in time, our external senses constantly are being bombarded by a multiplicity of stimuli. Numerous internal thoughts or recollections also may be vying for our attention. There has to be some central gating mechanism that serves to control or direct attention, basically telling us what is important to attend to under the circumstances. As noted earlier, the prefrontal lobes likely play a key role in this process, especially with regard to more purely "cognitive" type tasks, and disruption of this system is likely to result in increased distractibility, neglect, or difficulty shifting response set (mental flexibility), or selective or sustained attention (concentration). However, rational considerations are not the only factors that determine the focus of our attention. Certainly affective drive states (motivation), which are more closely linked with the orbital and mesial portions of the prefrontal lobes, also help shape the direction of attentional processes. Hence, either directly or indirectly, the orbital and mesial frontal areas likely participate in selective attention.

While the anatomical mechanisms that might mediate selective attention are not clear, at least three possibilities readily come to mind. As suggested earlier, one is the possibility that the frontal ("executive") cortex might influence directly the posterior ("gnostic") cortices via corticocortical association pathways. The second and third possibilities both involve frontal–cortical influences on thalamocortical projections. Theoretically, this might occur in one of two ways. First, recall that the frontal association cortex projects heavily to the head of the caudate, which in turn projects to the thalamus. While there is a tendency to see these corticostriatal–thalamocortical loops as being "closed" (i.e., projecting back to the same general areas from which they originated), there also are thought to be "open" circuits that allow for much broader influences. Mega and Cummings (1994) postulate that these circuits are crucial in all aspects of behavior, including selective attention. Finally, the prefrontal lobes have direct connections with the thalamus. Although these connections primarily are to the dorsomedial nucleus, which in turn projects back to the frontal cortices, all corticothalamic fibers pass through the reticular nuclei of the thalamus, which basically surrounds the lateral surface of the dorsal thalamus. Since these reticular nuclei subsequently project back to the other thalamic nuclei (the only thalamic nucleus whose efferent connections remain within the thalamus), the input from the frontal cortex has the potential for influencing vast cortical regions via the various thalamic relay and association nuclei (see Mesulam, 2000b, Chapter 3).

The Role of Frontal—Limbic Connections in Drive and Motivation. In Chapter 8 the role of various limbic structures (including the anterior cingulate gyrus, the amygdala, the hypothalamus, and possibly the septal area) in biological drives and emotions were extensively discussed. Also, as previously suggested, such drives or emotions provide the impetus, fuel, or energy to initiate and sustain all types of goal-directed activities. From a philosophical perspective, we can view all behavior as a combination of sensation, intellect, and will. For present purposes, *will* can be defined simply as the intention, desire, or motivation to initiate and/or sustain an action to obtain a desired goal (i.e., the result of operant, as opposed to classical, conditioning). The goals in question may be abstract (to be a "good person") or concrete (to satisfy one's thirst), immediate (to flee from imminent danger) or remote (to study hard in order to graduate and secure a good paying job several years from now). Again, as noted in Chapter 8, there is good reason to believe that "will" or "drive" derives from limbic structures. So, what is the role of the frontal cortex in this process?

In simpler organisms there is little need for sophisticated frontal systems. Many, if not most, behaviors are the product of either innate preprogramming ("fixed action patterns") or simple operant conditioning. As organisms became more complex, however, so too did the behavioral responses and/or the goals from which they were able to choose. It seems reasonable then to assume that frontal systems may have developed for two basic purposes: (1) to better meet the challenge of choosing, planning, and executing increasingly complex or varied response options in order to secure particular behavioral goals, and (2) to make more efficient choices when confronted with competing drives or goals (see below). Thus, while the prefrontal systems probably are not themselves the source of the basic physiological or "psychological" drives or "will," they harness and utilize these drive states to determine if, when, and how to best respond to a given situation and to persist in those efforts despite potential hardships or difficulties.

Although the exact nature of this interface between the prefrontal cortices and the energizing influence of the limbic structures is still a matter of some speculation, there is evidence primarily from lesion data to suggest that mesial–frontal–limbic connections are crucial to this process. Again, from the discussions in Chapter 8, you may recall that basic homeostatic drives (such as hunger), innate or learned fear responses, as well as generalized emotional responsiveness can be altered by lesions that directly affect the hypothalamus, amygdala, and anterior cingulate regions, respectively. This finding should not be surprising if, as suggested, limbic structures primarily are involved in generating these affective drive states.

Depressive-type States. It also has long been observed in both animal and human subjects that lesions of the prefrontal regions, some of which also likely involve the anterior cingulate gyrus, can result in apathy and hypokinesis, depending on the severity of the lesions (Blumer & Benson, 1975; Freeman & Watts, 1942; Fuster, 1997; Greenblatt et al., 1950; Hecaen, 1964; Luria, 1966; Rylander, 1948; Tow, 1955). While such responses have been reported in lesions (usually bilateral) involving the dorsolateral frontal cortices, mesial lesions appear more likely to result in diminished emotional responsiveness. Thus, it may well be that we are dealing with a diffusely projecting, interactive motivational system that encompasses limbic, mesial, and dorsolateral frontal areas and is essential for sustained, goal-directed executive activity.

Because of the nature and pattern of the affective changes that often are found following major insults to the frontal lobes, particularly the mesial and dorsolateral regions, the term *pseudodepression* has been applied to these behavioral states (Blumer & Benson, 1975). In certain frontal lobe patients, the appellation certainly seems apropos. Spontaneous emotional expression and individual initiative may be markedly diminished. While such patients may render lip service to carrying out work-related tasks or accomplishing long-term goals, in fact, they may do very little on a day-to-day basis, even to the point of appearing hypokinetic on occasion. They may show little interest or pleasure in former pursuits (*anhedonia*) and demonstrate reduced inclination to attend to their own personal hygiene. Hence, such patients often look and act "depressed," although as a rule they do not display dysphoric mood or affect or express feelings of worthlessness, negative preoccupations, or suicidal ideations that more frequently characterize typical "clinical" (psychiatric) depressions.

However, in considering this general behavioral syndrome, several qualifications are in order. First, depending on the extent and nature of the deficits, the clinical picture may show considerable variation. Often the individual may not evidence the level of inertia described above, but rather demonstrate subtler dysfunction. Thus, the patient may attend school or return to work, but with less intensity, drive, or enthusiasm than before. Projects may be initiated but either not carried through to completion or completed in a less conscientious manner. At times, evidence of mild to moderate apathy may be intermixed with emotional lability and irritability. Finally, while certain drive states (especially those associated with more abstract or long-term goals) may appear reduced, other more basic biological drives (e.g., sexual) may appear to be enhanced.[104]

Certainly, one also must consider the possibility that a depressive-type syndrome may result from the "psychological" reaction of having sustained a brain injury, perhaps with some related loss of function and/or change in psychosocial status. However, this explanation cannot account for many of the behavioral changes found after frontal lesions. In addition to the fact that behaviorally many of these individuals do not resemble "psychiatrically depressed" patients, hemispheric differences in the expression of depressive-type syndromes have been noted, specifically a greater incidence in "depressive" symptomatology following left frontal lesions (Gainotti, 1972; Eastwood, Rifat, Nobbs, & Ruderman, 1989; Robinson & Price, 1982). While one possible explanation for depression following left frontal lesions is the co-occurrence of Broca's aphasia (Robinson & Benson, 1981), depressive conditions have not only must been found in the absence of Broca's aphasia, but have been positively associated with lesions of the more anterior portions of the left frontal lobe that are less likely to produce major expressive disturbances (Robinson et al., 1984; Robinson & Szetela, 1981; Sinyour et al., 1986). Finally, left subcortical lesions that affect structures directly associated with frontal systems (e.g., anterior limb of the internal capsule and the head of the caudate nucleus) also have been associated with increased incidence of depression in stroke patients (Starkstein, Robinson, Price, 1987; Starkstein et al., 1988). In the final analysis, there would appear to be at least two possible neuroanatomical explanations for these findings of increased apathy and/or depression following lesions to the frontal lobes. One is, as suggested above, a disconnection between the frontal executive system and critical limbic structures that are critical in initiating drive and emotion. The other possibility (and the two are not necessarily mutually exclusive) is that certain frontal lesions may disrupt ascending noradrenergic and serotonergic brainstem pathways (Starkstein & Robinson, 1989).[105]

Inhibition of Competing Drive States or Emotions (Social Inhibition)

In the preceding discussions, mention was made of the difficulties patients with frontal lobe lesions might encounter when faced with distracting but irrelevant stimuli or prepotent response sets. Because of failures of inhibition in these situations, patients may experience difficulty in staying on task or fall into perseverative response patterns. Much more problematic for certain frontal lobe patients, or at least for those around them, are difficulties in inhibiting affective or emotional responses or emotional drive states. It is not clear whether these two problems represent an overall problem with inhibition in general following frontal lobe lesions or whether they reflect fairly independent processes. The fact that phenomenologically they are frequently also dissociated might argue for at least partially independent mechanisms. While we do not intend to belabor this point, what is important to note is that behaviorally and possibly anatomically affective or emotional disinhibition presents as a very different type of problem from the inhibition of cognitive response sets previously discussed.

The failure to inhibit affectively or emotionally charged behavioral responses in situations where it normally would be appropriate to do so represents one of the classic syndromes associated with frontal lobe pathology. In reviewing this behavior, it first might be noted that there is obvious teleological value to affective drive states and the behaviors with which they tend to be associated. Such drive states often are essential either for the propagation of the species or important for the well-being or survival of the individual. Examples of affectively driven behavior might include sex, hunger and thirst, fear, anger, or aggression. Perhaps even humor and criticism have evolved as means of social communication and jockeying for social position. However, more often than not, the organism is faced not with a single goal or drive but with multiple and often competing or mutually exclusive drives. In humans at least many of these drives reflect more abstract or long-range needs rather than more immediate, biological urges. Thus, as humans and society have evolved, many behavioral expressions, especially those based on what might be described as more "primitive" emotional drive states are not given indiscriminate free rein, but rather are often subjugated to commonly accepted systems of internal checks and balances (the process we know as *acculturation*). As previously noted, this latter process would appear to be mediated primarily if not exclusively by the frontal lobe as part of its planning and self-monitoring capacities. Among the operations carried out by the frontal lobes prior to acting on various drives or impulses are the following considerations:

1. Is this the *time* and *place* to respond (to this impulse/emotion)?
2. What might be the *long-range consequences* of such a response?
3. If negative consequences occur, should I consider an alternate response or delay responding for a better time, place, or circumstance?
4. Is responding to this drive or impulse consistent with my other immediate or long-range goals?
5. What impact might this action have on others (empathy, compassion)?

Pseudopsychopathy. Patients with frontal lobe damage, particularly when the damage affects the orbitofrontal regions, often act as if they fail to weigh these considerations prior to acting. As a result, they are seen as disinhibited, indiscreet, impulsive, or lacking social judgment. Blumer and Benson (1975) characterized this behavioral syndrome as *pseudopsychopathic*, indicating the apparent disregard for social convention or future consequences. Also, as noted earlier, such patients often exhibit a tendency to behave in a childish, petulant manner and may be given to blunt, inconsiderate remarks or inappropriate humor (*Witzelsucht*). A classic example of such behavior was the case of Phineas Gage, a case that is still cited in many modern psychiatric and neurobehavioral texts and still elicits scientific curiosity (Damasio et al., 1994). Briefly, Phineas Gage reportedly was a somewhat reserved, pleasant, hard-working man prior to having a tamping iron driven through his face and skull, destroying a substantial portion of his frontal lobes. The following is a brief quote from the description of his case at the time (Harlow, 1868):

> The equilibrium or balance, so to speak, between his intellectual faculty and animal propensities, seemed to have been destroyed. He is fitful, irreverent, indulging at times in the greatest profanity (which was not previously his custom), manifesting but little deference for his fellows, impatient of restraint or advice when it conflicts with his desires, at times pertinaciously obstinate, yet capricious and vacillating, devising many plans of operation, which are no sooner arranged than they are abandoned in turn for others appearing more feasible. A child in his intellectual capacity and manifestations, he has the animal passions of a strong man (cited from Blumer & Benson, 1975, p. 153).[106]

The problem in such individuals may not necessarily lie in their cognitive ability to make accurate judgments about the potential consequences of their behavior. Rather, the difficulty may be in the patient's tendency either (1) not to be concerned about making such judgments in the first place, or even if it were possible to make these rational deliberations on a cognitive level, (2) to act as if these deliberations or the consequences of the actions were immaterial. In practice, the cognition of patients who exhibit serious problems with impulse control frequently can be demonstrated to be relatively intact (see Eslinger & Damasio, 1985), as are their emotional drives or affective responsiveness. The problem in the case of certain orbitofrontal-lesioned patients is that these two processes seem be disconnected, most likely as a result of a disruption of frontolimbic pathways. Davidson, Putnam, and Larson (2000) review evidence suggesting that disturbances in the orbitofrontal cortex and other prefrontal–limbic connections may be linked to aggressive behaviors, especially more impulsive (as opposed to premeditated, planned) aggressive outbursts.

From a psychological perspective, these fronto–limbic connections might be viewed as bridging those processes that, in psychoanalytic jargon, are connoted by the *id* and the *superego*. Under this model, the role of the frontal lobes ("superego") is to temper the limbic impulses ("id"). When lesions interfere with this process, either by severing or disrupting these connections or by damaging areas of the frontal cortex directly, there is a loss or disruption of these mediating influences. Consequently, what might be seen in such patients is poor judgment, inability to delay gratification or impulsivity, social inappropriateness, affective lability or disinhibition, restlessness, and/or "unbridled euphoria." For a review of various psychiatric conditions associated with frontal lobe pathology, see Malloy and Duffy (1994).

From a neurobehavioral standpoint, we can couch these phenomena in slightly different terms. For example, we might say poor judgment typically results from a failure (absolute or relative) to anticipate or consider possible negative or long-term consequences or learned social prohibitions or to compare probable outcomes with personal goals or interests. For this process to be effective, there must be some way for the various behavioral alternatives faced by the patient to be directly linked to the anticipated emotional consequences of each potential behavioral response. Thus, in considering potentially available responses, it would appear to be quite advantageous (as a part of planning and self-monitoring functions) to vicariously experience the possible emotional ramifications of those choices. For this to happen, the various "mental images" and/or past memories associated with these responses need to be "linked to" relevant "emotional tags." Damasio and his colleagues (Damasio, Tranel, & Damasio, 1990, 1991; Bechara, Tranel, Damasio, & Damasio, 1996) refer to this process as the activation of "somatic markers." Anatomically, it is thought that this process likely minimally involves connections among the orbitofrontal cortices, the ventroanterior portions of the basal ganglia (e.g., nucleus accumbens, ventral pallidum), the anterior and medial temporal regions (including the amygdala), possibly the hypothalamic areas, and the dorsomedial nuclei of the thalamus. For a review, see Chapter 6, section Lateral Orbitofrontal Circuits and Limbic Circuits (this volume) (Mega & Cummings, 1994; Davidson, Putnam, & Larson, 2000).

Additional Clinical Considerations. As noted, impairment of judgment or impulsivity in patients with frontal lobe lesions most often involves the inability to inhibit inappropriate impulses or perhaps more properly impulses that given the time, place, or circumstance in which they occur would be inappropriate to express. Again, we should keep in mind that this is not merely a cognitive exercise or simply an impairment of "cognitive judgment." For example, the patient with frontal injuries may respond perfectly appropriately to the question "What one should do if, while in a theater, they are the first to see smoke or fire?" When posed during the course of a mental status examination, there is no strong affective pull to respond otherwise. On the other hand, if that person were actually in that situation (e.g., where there was a real fire), his or her response might be quite different.

This raises another important question. If a person placed in the situation described above were to yell, "Fire," or simply run out of the theater without taking the time to warn or notify anyone, does that mean they are likely suffering from frontal lobe damage? It is important to remember that the world is full of people who routinely tell inappropriate jokes, make "thoughtless" but hurtful or embarrassing comments and observations about others in their presence; who constantly act in ways that would suggest they fail to consider the long-range consequences of their behavior; who frequently act in an impulsive, often self-destructive manner; or who otherwise disregard social convention or fail to use "good judgment" when it comes to modulating or curbing their emotional propensities. For example, are the individuals who habitually blow most of their paychecks on drugs, liquor, gambling, sex, jewelry, shoes (or whatever) suffering from frontal lobe damage? Certainly the possibility of a frontal type of learning disability readily comes to mind in trying to explain the behavior of many of these individuals.[107] Obviously, however, many other learning and environmental factors also may help explain such behavior. What is important from a clinical or diagnostic standpoint is to note whether these behaviors reflect a change from the patient's normal personality or response pattern.

It should be noted that poor judgment or behavioral improprieties do not necessarily reflect an all-or-none situation. The extent or likelihood that someone with frontal lobe damage will act out in an inappropriate manner will depend on a variety of factors. First, and perhaps most importantly, what areas of the frontal lobes or pathways are affected? As a rule, such behavioral problems are more likely to occur following basal–medial or orbitofrontal lesions, particularly if they are bilateral. However, lesions in this area do not always produce such deficits and lesions in other areas also may be associated with problems of judgment and impulsivity. The age of the patient also may be important. A frontal lesion in an adolescent or young adult is more likely to result in behavioral disturbances than a comparable lesion in an older adult. It is suspected that the normal impetuosity and higher energy levels of youth may have an additive effect in potentiating such acting out. Circumstances may also dictate to some extent the expression of impulsive behavior. For example, the patient who needs to relieve his bladder or bowels generally will do so in an appropriate place and manner, especially when it is convenient to do so. However, if such a place is not convenient, then the patient may not go to any great pains to delay gratification he will not be deterred by the anticipation of social consequences, choosing instead to relieve himself in whatever place is handy (*disinhibition*).

Another consequence of the reduction of cortical control mechanisms is that the patient is more at the whim of his or her immediate drives or affective states, rendering the individual more emotionally labile, restless, and perhaps appearing no longer "in control." Finally, because the frontal–limbic connections discussed above represent a two-way street, disruptions of these connections also may help explain why certain cognitive considerations are less able to take on appropriate affective coloration. We already have discussed one possible consequence of this, namely apathy or reduced drive or initiative. Another possible consequence is that without the normal inhibitory influences of the frontal lobes (which can, in turn, give rise to more somber considerations), there may be an imbalance of affective or drive states. Such a formulation might help explain the childlike euphoria that often is seen in frontal lobe-damaged patients.

Other Specific Prefrontal Pathology and Frontal Dementias. The prefrontal cortex and related structures, like all parts of the brain, potentially are subject to a wide variety of pathological processes. These can range anywhere from small, focal lesions to relatively large, diffuse, or multifocal processes. While the potential etiology of such lesions essentially are similar to that which might be found in other parts of the brain (e.g., vascular accidents, tumors, penetrating and closed head injuries, infections, metabolic, demyelinating and degenerative disorders), certain pathologies have an increased predilection for the frontal lobes. Deceleration head trauma and certain type of degenerative diseases are common examples. As is true elsewhere in the brain, the exact nature and extent of the resulting behavioral disturbances following such lesions typically depends on a host of factors. This would include, for example, the size, extent, and exact location of the lesion, its specific etiology or pathological process, and the nature of onset and/or progression. At times, even the age and sex of the individual could be a major factor in the clinical manifestation of the disorder. While it is beyond the scope of this chapter to review all the potential types of lesions or disease processes, it might be useful to mention a few specific dementia syndromes that commonly affect the frontal lobes.

When we think of dementia, typically the first disease process that comes to mind is Alzheimer's. This is understandable since it appears to be the most common form of the degenerative processes and of dementias as a whole. While it can and does affect the frontal lobes, in the earlier stages it tends to have its most profound effects on the parietal and temporal lobes and in particular the hippocampus (Cummings & Benson, 1992). However, there are other degenerative disorders that tend to primarily affect the prefrontal cortices from the very beginning. While generally referred to as **frontal lobe degeneration of the non-Alzheimer type (FLD)** (Brun, 1987; Gustafson, 1987), actually a number of somewhat related degenerative disorders have been identified as having an early impact on the frontal lobes. These include **frontotemporal dementia (FTD)**, **Pick's disease**, and **progressive aphasia (PA)** (Brun & Gustafson, 1999; Cummings & Benson, 1992; Filley & Cullum, 1993; Gustafson, Brun & Risberg, 1990; Kertesz, Davidson, & Munoz, 1999; Miller et al., 1991; Neary, Snowden, Northen & Goulding, 1988; Neary et al., 1998). What most of these frontal dementias tend to have in common are early

Table 9–6. Early Clinical Characteristics of "FLD"

General Behavior	Social disinhibition, poor judgment, impulsivity, diminished insight, decline in personal hygiene, hyperorality,[a] hypermetamorphosis[a] (utilization behavior).
Affective Behavior	Emotional blunting (apathy, "depression," loss of empathy, interpersonal warmth), combined with emotional lability and inappropriateness (e.g., aggressiveness, irritability, puerility); diminished concern and/or drive with regard to long-range goals.
Speech and Language	Variable, from reduction in spontaneous output to excessive talkativeness (inappropriately so); output may be stereotypic, perseverative, echolalic, confabulatory; verbal paraphasia and/or anomia are common. Receptive typically better than expressive language.
Cognition/Perception	Distractibility, mental rigidity, diminished "executive functions" and problem-solving abilities; complex learning and selective retrieval may be compromised, but routine memory grossly intact, along with basic visual–spatial abilities.
Motor	Restlessness, "hypomania," stereotypic, meaningless repetitions, frontal release signs, incontinence may be present.

[a] Components of the Kluver–Bucy syndrome.
Adapted from Neary et al., (1998), Brun & Gustafson, 1999.

changes in social judgment, personality, insight, and/or affect. While disturbances of speech or language also tend to become manifest early on, unlike Alzheimer's, memory and visual–spatial skills typically are *relatively* well preserved in the early stages of these disorders.[108] Table 9–6 presents the main clinical features of FLD. In addition, several other degenerative diseases are identified as significantly affecting frontal–subcortical systems. These include **Huntington's disease (HD)**, **progressive supranuclear palsy (PSP)**, and **dementia with Lewy bodies (DLB)** (Brun & Gustafson, 1999; Cummings, 1990; Duke & Kaszniak, 2000; McKeith, 1999; McKeith et al., 1996; Wechsler et al., 1982). Table 9–7 compares and contrasts some of the main clinical features among the more common degenerative dementias.

LOCALIZATION OF PREFRONTAL LOBE FUNCTIONS

As noted in the introduction of this section, the prefrontal regions of the frontal lobes are composed of cytoarchitecturally diverse cortex. Each of these areas is characterized by varying patterns of cortical and subcortical connections (Fuster, 1997; Grafmann, Holyoak & Boller, 1995; Passingham, 1993). The prefrontal cortex also is divided into the right and left cerebral hemispheres. As a result of these cytoarchitectural, connective and hemispheric differences it is likely that functional differences follow. Some of this functional differentiation was alluded to in the foregoing discussion in reference to the rather broad divisions within the prefrontal cortex, namely the dorsolateral, orbital, and mesial zones (see Table 9–8).

Caution is advised, however, when attempting to draw diagnostic conclusions regarding either the specific locus of a lesion or even the presence or absence of a prefrontal lesion based on behavioral findings alone. First, whether looking at "personality" (i.e., gross behavioral traits) or performance on specific cognitive tasks, rarely are we witnessing behavior that is the result of a circumscribed cortical area. As previously discussed, most

Table 9–7. Comparing Early Dementia Syndromes

	SDAT	PD	DLB	FTD	Pick's
Memory	Impaired	Slow; improved recognition	Intact early	Poor, if effortful	Relatively intact
Language	Dysnomic, empty speech, weak comprehen	Hypophonia, micrographia	Intact early	Variable output,[a] dysnomia	Early anomia
Visual–Spatial	Typically impaired	? Mildly impaired	Impaired	Relatively intact	Relatively intact
Executive Functions	No selective impairment	Slow in shifting	Impaired	Diminished judgment, initiation	Impaired
Behavior/ Affect	Relatively preserved[b]	Frequent depression	Freq. visual hallucinations	Disinhibited, apathetic, labile	Disinhibited, labile, Kluver-Bucy
Motor	Intact	Bradykinesia rigidity, tremors	Like PD, but w/o tremors	Intact	Intact

[a] Frequently diminished output, stereotypic utterances
[b] Anxiety, depression may be seen early while insight is relatively preserved
Legend: SDAT, Senile dementia, Alzheimer's type; PD, Parkinson's disease; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; Pick's (dementia)

behaviors are the result of distributed processes that not only involve multiple regions of the prefrontal cortices, but also nonfrontal cortices and subcortical areas of the brain. For example, we have just discussed the importance of frontolimbic connections in guiding or modulating certain behaviors. Other cortical–subcortical circuits or connections involving the basal ganglia, thalamus, and other subcortical structures were reviewed extensively in Chapter 6. Included among these were specific and apparently independent circuits incorporating the dorsolateral, orbitofrontal, and mesial portions of the prefrontal cortices. Lesions or disease processes affecting any portions of these neural circuits could result in behavioral disturbances similar to those found with lesions directly affecting those cortical areas (Cummings, 1990, 1995; Litvan, 1999). While advancements in neuroimaging continue to offer new insights into structural/behavioral correlates, the variable and erratic nature of naturally occurring lesions and the still less-than-precise ability of such techniques to identify the exact anatomical boundaries of dysfunctional tissue limit our insights into those correlates, and hence, clinical predictability.

Another problem in trying to pinpoint frontal lobe functions relates to the nature of frontal lobe functioning itself. Unlike the first and second systems that have relatively specific areas of function that can be identified and more or less directly assessed (such as perception, language, memory, visual–spatial skills, or even basic arousal), the frontal lobes seem to impact or interact with all these functional systems. Furthermore, many of the neuropsychological tests or measures that are commonly used to assess the integrity of the prefrontal cortex are themselves multidimensional tasks and can be adversely affected by lesions outside the frontal areas (Anderson, Damasio, Jones, & Tranel, 1991; Benson, 1979; Grafman, Jones, & Salazar, 1990).[109] As was emphasized by Kaplan (1990), the key to identifying

Table 9–8. Frontal Lobe Syndromes

Syndrome Associated with Lesions of the Dorsolateral Convexities

General Behavioral
Apathetic, "depressed"
Self-neglect (e.g., personal hygiene)
Distractibility/Impersistence
Failures of initiation
Instability in pursuing abstract, long-range goals

Cognitive–Behavioral
Poor planning
Limited use of innovative strategies
Reduced "mental flexibility"
Decreased ability to "shift mental sets"
Difficulty inhibiting prepotent response sets
Perseveration
Frequent loss of mental set
Diminished "abstractive ability"
Reduced "self-monitoring" capacity
Diminished performance on fluency, "motor programming" tasks
Poor judgment (inadequate cognitive-perceptual analysis)

Syndrome Associated with Lesions of the Orbitofrontal Areas

General Behavioral
"Personality" changes
Disinhibition or diminished impulse control
Poor "social" or moral judgment
Irritability/explosiveness
Emotional lability
Limited insight into behavioral deficits
Restless/hypomanic/euphoric
Facetiousness, puerility, "Witzelsucht"
Anosmia[a]

Cognitive–Behavioral
Occasional learning/memory difficulties with confabulations

Syndrome Associated with Lesions of the Medial Frontal Areas

General Behavioral
Apathy, diminished drive[b]
Hypokinesis, diminished spontaneity
"Akinetic mutism" (in more severe states)
Abulia
Incontinence
Gait disturbances

[a] The olfactory bulbs and tract lie on ventral surface of orbitofrontal cortex, hence bilateral damage to this area may result in anosmia.
[b] May be more profound than with lesions of the dorsolateral zones.
Adapted in part from Duffy & Campbell (1994); Cummings (1985); Chapter 6.

frontal pathology is not so much a matter of determining which tests or tasks are impaired but how the tasks are approached and in analyzing the nature of the deficits or errors.

Finally, not all behavioral sequelae normally associated with frontal lobe pathology necessarily are the result of structural lesions such as tumors, strokes, infections, or traumas that might be identified using neuroimaging procedures. The prefrontal cortices are extensively supplied by a variety of neurochemical transmitters, including norepinephrine, serotonin, dopamine, and acetylcholine. Selective depletion of these neurochemical transmitters (as are found in some of the disease states mentioned above) can result in specific neuropsychological or neurobehavioral deficits as different regions of the prefrontal cortex may be selectively supplied by the different neurotransmitters, hence subject to differential compromise (Campbell, Duffy, & Salloway, 1994; Glick et al., 1982; Fuster, 1997; Javoy-Agid et al., 1989; Litvan, 1999; Mega & Cummings, 1994; Mesulam, 1988; Oscar-Berman, McNamara, & Freedman, 1991; Weinberger, Berman, & Zec, 1986; also see Chapter 11, this volume).

Hemispheric Differences

Unlike smaller, unilateral lesions in the posterior heteromodal (tertiary) association cortices that often can result in obvious and occasionally almost pathognomonic deficits, unilateral lesions of the prefrontal cortices often are far more subtle in their clinical presentation. As a general rule, many of the more dramatic "frontal lobe syndromes" are likely the result of larger, bilateral lesions.[110] One notable exception to this rule, of course, is when the posterior, agranular areas (i.e., Brodmann's areas 4, 6, and 44) become involved and appendicular motor or speech difficulties become evident. These latter symptoms will be reviewed separately below. The presence of "dynamic" or transcortical motor aphasia, which may be associated with lesions involving the "prefrontal," usually is indicative of left frontal damage (Freedman, Alexander, & Naeser, 1984; Luria & Tsvetkova, 1968).

As was mentioned above, while left frontal (especially polar) lesions have been associated with depressive syndromes more frequently than the right, the presence of depression per se is not a reliable index of either brain injury or frontal or hemispheric impairment. Similarly, while disturbances of certain types of verbal, semantic memories have been associated with left frontal lesions and nonverbal, episodic memories with the right frontal lobe (Buckner et al., 1995; Kapur et al., 1995; Milner, 1982; Petrides, 1985), such findings are not particularly robust indices of either frontal or hemispheric damage. Among cognitive measures, tests of verbal versus nonverbal fluency (Benton, 1968; Jones-Gotman & Milner, 1977; Ruff et al., 1994) have proven to be one of the more reliable means of differentiating left from right frontal patients when the two groups are compared in controlled studies. However, these tasks, while sensitive, are not specific to frontal pathology (Stuss & Benson, 1986).[111] Finally, as noted in Part II of this chapter, Goldberg, Podell, and Lowell (1994) suggest that the specialization of the prefrontal lobes may be a function of whether the information being processed is "novel" or dependent on "external" contingencies (the right hemisphere) versus based on "internal" programs or previously learned schemas (left hemisphere). Thus, while a variety of neuropsychological tests have been associated with frontal pathology (see Kimberg, D'Esposito, & Farah, 1997; Lezak, 2004; Malloy & Richardson, 1994; Stuss & Benson, 1986; Walsh, 1994), again, except for those that focus on various motor skills (e.g., Christensen, 1975; Luria, 1966), none would appear to reliably differentiate right versus left frontal lesions. While the general distinctions between right and left hemispheric function discussed under Hemispheric Specialization in Part II continue to have relevance for the frontal lobes (i.e., there may be some material-specific distinctions between operations carried out by the right versus left prefrontal cortex), judgments based solely on such criteria are unlikely to be highly reliable. A recent battery of tests designed to measure mental flexibility shows promise as a means of assessing executive functions mediated in large part by the dorsolateral frontal zones lobe deficits (Delis, Kaplan, & Kramer, 2001).

Summary of Prefrontal Lobe Functions

As we have seen, both in regard to structure and function, the frontal granular cortex is far from being homogeneous. In comparison to the posterior association cortices, the functions of the prefrontal zones generally are more difficult to define in concrete terms and generally more difficult to assess. Most formal tests that currently are employed because of their purported sensitivity to frontal lobe lesions are not highly specific, being sensitive to lesions elsewhere in the brain. For the most part, it is only through informed and considered analysis of both mental status examination data and the spontaneous social behavior that specific features of frontal lobe syndromes begin to emerge. While by no means all-inclusive, the following is an attempt to summarize some of the key features regarding the probable role of the prefrontal cortices in human behavior. The prefrontal zones, which include the dorsolateral, orbitofrontal, and mesial frontal areas, would appear to share primary responsibility for:

1. Harnessing limbic drive to create and maintain stable intentions to achieve long-range, abstract, social goals.
2. Developing and executing higher-order, adaptive behavioral plans, programs, or strategies based on appropriate analyses, especially when faced with unique, challenging situations.
3. Considering response alternatives and weighing their probable effectiveness in view of previous experiences, current contingencies, and ultimate goals.
4. Monitoring one's progress, not only in view of the original goal, but also in terms of the results of the preliminary responses, changing conditions, or environmental demands.
5. Adapting or modifying either one's goal or plan of action as a result of feedback or circumstances.
6. Appreciating and balancing immediate, concrete needs or demands with more abstract or long-range needs and interests.
7. Inhibiting tendencies to respond in a perseverative, capricious, impulsive, or reflexive fashion.

Far from unraveling the mystery of the frontal granular cortex (or, for that matter, any other part of the brain), the preceding discussions at best provide a narrow window that hopefully provides a limited glimpse into the types of operations for which the prefrontal lobes are responsible. For more extensive coverage of this intriguing topic, the reader is referred to the following works: Luria's *Higher Cortical Functions in Man* (1966); Stuss and Benson's *The Frontal Lobes* (1986); Fuster's *The Prefrontal Cortex* (1997); Miller and Cummings' *The Human Frontal Lobes* (1999), Grafman, Holyoak, and Boller's *Structure and Function of the Human Prefrontal Cortex* (1995); Levin's *Frontal Lobe Function and Dysfunction* (1991), and Frackowiak et al., *Human Brain Function* (1997). In addition, the following represent a few of the many book chapters and articles that one might find informative: Damasio and Anderson (1993); Duke and Kaszniak (2000); Kimberg D'Esposito, and Farah (1997); Joseph (1990); Walsh (1994); and Stuss and Benson (1984).

EXECUTION OF MOTOR PROGRAMS

We commonly envision the ultimate goal of the executive unit (i.e., the frontal lobes) of the brain to be the carrying out ("execution") of a voluntary behavioral response. Most commonly, this involves some overt motor response. Such responses might range from relatively "simple" motor acts such as visually scanning an array of stimuli or pressing a button to more complex, highly integrated skilled responses such as speaking or playing a game of tennis. Discussions in the preceding section focused on the role of the frontal lobes in the overall planning, selection, initiation, or in some cases, the *inhibition* of behavioral responses.[112] Here the focus will be on the process of translating those goals, intentions, or directives into concrete motor responses. While as we have seen the former is mediated primarily by the prefrontal, granular cortex, the actual execution of the behavioral (motor) response is more properly the function of the **agranular** divisions of the frontal lobes. Located posterior to the prefrontal areas, the agranular cortex of the frontal lobe generally is considered to be composed of the **premotor** (**PM**), **supplementary motor** (**SMA**), and **primary motor** (**MI**) areas and the frontal eye fields.[113]

Before reviewing the general anatomy and suspected roles of the various divisions of the agranular motor cortex in greater detail, it might be useful to have at least in very broad terms an overall picture of the relationships that seem to characterize the various components of the frontal or executive system. The best analogy that comes to mind is that of the military (or, for that matter, any large corporate organization). Within the military, we normally think of the formulation of a battle plan as ultimately being the responsibility of the commanding general. In formulating these plans, he (she) needs access to and should review information regarding not only the available resources, equipment, and supplies, but also the mood and/or morale of the troops as well as any "gut feelings" about the situation (i.e., a review of internal milieu). In addition, information is needed regarding the status and position of the enemy forces, as well as a good understanding of the strategic situation in which both armies are engaged (external milieu). Finally, there needs to be an awareness of how the enemy might be expected to proceed based on historical precedents (memory). In this analogy, the "general" represents the prefrontal or granular cortex, which gathers essential information from the posterior cortices (concerning the "external milieu"), the limbic structures ("internal milieu"), as well as from personal memory.

When all the necessary information has been gathered and evaluated, the "general" (prefrontal cortex) formulates a plan of action. This includes not only determining the plan of attack, but also deciding when, where, and under what conditions the plan will be executed. Once executed, an ongoing assessment is necessary to determine how the battle plan is unfolding and what if any changes in strategy or objectives are indicated. Lastly, it also is typically the responsibility of the general to determine when or under what conditions the battle plan is to be terminated or aborted. Again, the above functions could be compared to the planning, monitoring, and related actions of the prefrontal zones of the executive unit discussed above.[114]

However, once the plan of action is formulated and the order for its initiation[115] has been given, it still must be executed or carried out. This is more properly the function of the agranular frontal cortex. We might think of this formal execution of action as a two-stage process. One stage is the responsibility of the medial and lateral premotor areas, with the other being the responsibility of the primary motor cortex.

Continuing with our military analogy, while the general (the prefrontal cortex) generates the overall plans, strategies, and timetables, for the campaign to be successfully carried out, most of the details need to be worked out at the battalion and company levels. This first stage might include making preliminary preparations to ensure that all units are ready to respond; coordinating support operations among the various units; and perhaps even making minor adjustments in the overall plan, depending on unexpected fluctuations in internal or external conditions or the results of immediately preceding operations. Such decisions typically are the responsibility of intermediate level officers. Parallels can be seen in the biological organism. While the overall plan may be to initiate a search for food, this usually involves extensive timing and coordination of individual muscles and appendages, constant sensory feedback, and continuous postural and limb adjustments in response to changes in gravity and in the target of the response (e.g., eye–limb coordination). As we shall see, these are functions that are largely, although probably not exclusively, controlled by the "premotor" zones.

In the military, while the planning and strategizing takes place at the division, battalion, or company levels, all of this eventually funnels down to the individual platoons or squads. Here it falls to the enlisted personnel to carry out the battle plan in a concrete fashion. This would be analogous to the second stage of the behavioral response where the enlisted personnel who actually execute the planned actions represent the primary motor cortices. For the most part, primary motor cortex is responsible for triggering the upper motor neurons that compose the corticobulbar and corticospinal tracts. It is this firing that results in the discrete, skilled action that represents the culmination of the directive that originated in the prefrontal cortex. Just as in the military, no platoon or squad is charged with carrying out the entire battle plan, but rather each is assigned a very specific objective, so too the primary motor cortex is divided into discrete units, each of which is devoted to specific muscle groups. Finally, just as the foot soldier must have access to direct, although usually very limited and circumscribed feedback about the effect of his or her initiatives, motor responses also require such feedback. In the case of the premotor area, such feedback comes not from all the senses, but is more or less limited to somatosensory information from the postcentral gyrus.

It is important to make one final point with regard to our military analogy before proceeding. While the chain of command generally may be viewed as that described above, in actuality to ensure maximal efficiency the lines of communication are necessarily quite diverse and the nature of the cooperative interactions should be quite flexible. Information needs to be able to flow not only down the chain of command but both laterally and back up the chain. Similarly, individual components of the frontal executive system (e.g., prefrontal, premotor, supplementary motor, and primary motor) are not only extensively interconnected, thus allowing for constant feedback and coordination of activities within the executive system, but most also are interconnected with both the posterior (gnostic) cortices and subcortical structures (e.g., thalamus, basal ganglia, cerebellum, limbic structures). These latter connections ensure that these frontal systems have access to sensory information, internal (e.g., motivational) states, and critical inhibitory influences not only at the planning stage, but also as required during the preparatory and execution phases.

With this broad framework in mind, we can examine several of the areas commonly identified as making up the frontal agranular cortex. Again, the focus will be on defining basic anatomical and functional correlates and where possible their interrelationship to the executive system as a whole. However, the reader should be advised that despite the renewed and often intense attention that some of these areas have enjoyed in recent years, particularly the supplementary motor areas, there still is considerable controversy, not only with regard to their basic functions, but even concerning their anatomical features (Marsden et al. 1996; Wise et al. 1996).

THE AGRANULAR FRONTAL CORTEX

The agranular regions of the frontal cortex generally are thought to encompass Brodmann's areas 4, 6, and at least the posterior portions of area 8 on the lateral and medial surfaces of the frontal lobes. Area 44 (*pars opercularis*) also typically is associated with the agranular cortex (Damasio, 1991; Kaufer & Lewis, 1999; Mesulam, 2000b; Nieuwenhuys, Voogd, & van Huijzen, 1988); see Figure 9–46. These cortical areas are referred to as "agranular" because of the relative absence of the granular layers (II and IV) and the prominence of the pyramidal cell layers (III and V).[116]

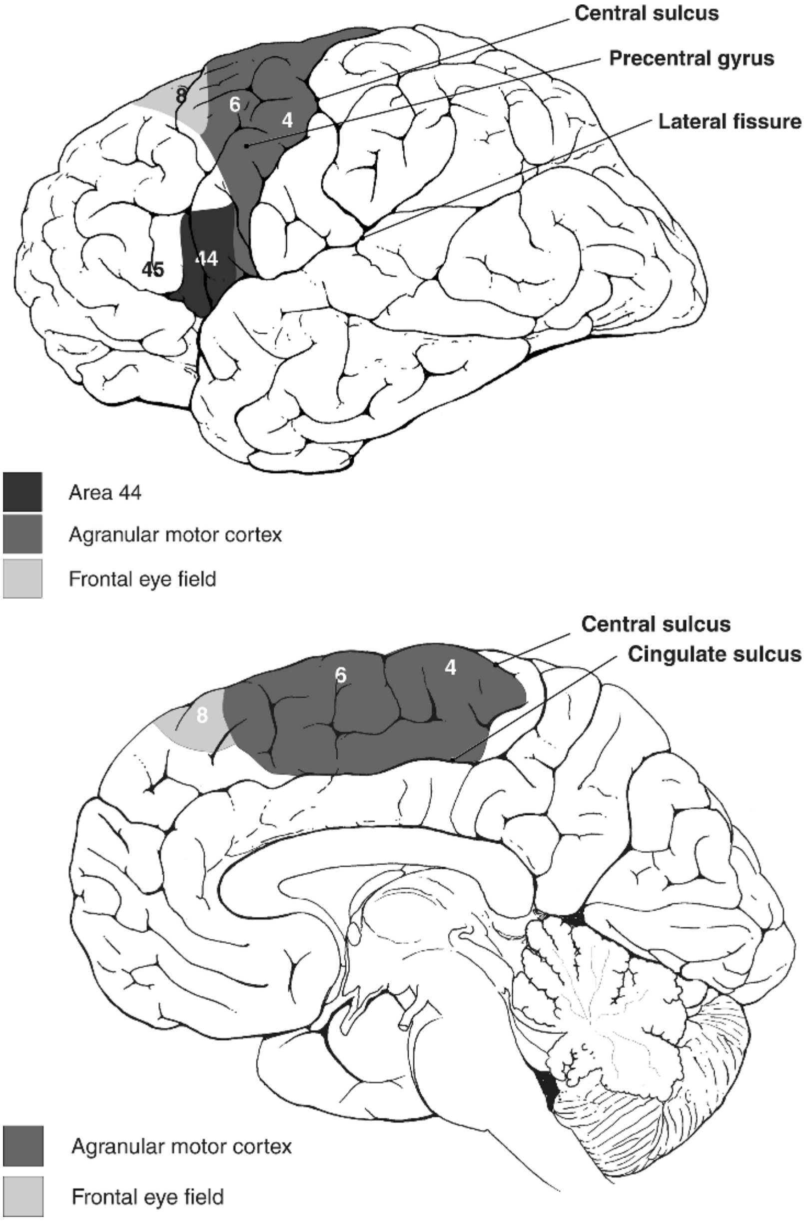


Figure 9–46. Approximate location of the frontal "agranular" cortices on the (a) lateral and (b) medial surfaces of the hemispheres. Area 44, which includes pars opercularis of the inferior frontal gyrus, and the more posterior or caudal portions of area 8 commonly are characterized as being more representative of the unimodal (agranular) motor cortex.

Despite this common feature, as with the prefrontal granular cortex, the frontal agranular cortex is neither structurally (e.g., with regard to its cytoarchitectonics and connections) nor functionally homogeneous. In the monkey, no fewer than ten distinct "motor areas" have been identified (Freund, 1996b). In humans, for most practical purposes the agranular cortex can be divided into three to five separate areas. The most common divisions include the (1) **primary motor cortex** (MI), (2) **premotor area** (PM), (3) **supplementary motor area**

(SMA), and (4) **frontal eye fields** (area 8). Area 8 has been noted to be heterogeneous in its cell structure, with its more rostral portions being more characteristic of the prefrontal, heteromodal cortices, while more caudally it is more similar to premotor cortex (Akert, 1964; Mesulam, 2000b). These caudal areas seem to have more extensive connections with the supplementary motor area (see below). The SMA itself has been subdivided into an *anterior zone* and a *posterior zone*. The latter is referred to as the **supplementary motor area proper** (SMA proper), while the more anterior division is known as the **presupplementary motor area** (pre-SMA).[117]

By way of a brief overview, although several agranular areas (SMA proper, PM, MI) all send projections to the brainstem and spinal cord, only MI is generally associated with discrete, highly differentiated voluntary actions. On the other hand, the SMA and PM areas generally are thought to play a critical role in the planning, sequencing, and integration of motor output leading to the overall coordination of gross motor behavior. Area 8 is thought to be primarily responsible for voluntary gaze, such as in active, selective, or directed scanning of one's external environment. Finally, none of these motor systems work in isolation. These regions are characterized by extensive interconnections and receive extensive input from and provide output to multiple cortical and subcortical structures. For example, in addition to receiving input from the prefrontal zones [which, as previously indicated, probably are responsible for the initiation (or inhibition) of all voluntary action], these motor areas also receive extensive input from the posterior cortices. The latter provide ongoing feedback regarding both tactile and proprioceptive information necessary for coordinated movement and object manipulation. These premotor areas also receive visual–spatial information that is essential in manipulating the external environment or the targeting of external stimuli. Finally, via the thalamus, these cortical motor systems are intimately linked to the basal ganglia and the cerebellum to form elaborate feedback mechanisms that are essential in motor learning and coordination. We will now examine the potential roles of each of these cortical motor areas in greater detail.

Supplementary Motor Area

Anatomy

The supplementary motor area (SMA) is represented by that portion of the premotor cortex (Brodmann's area 6) that lies on the medial surface of the hemispheres. During early electrical mapping of the motor cortex by Penfield and Welch (1951), this area was noted to have a somatotopic organization that was independent of those found on the lateral surface of the frontal lobes and that with sufficient stimulation would elicit complex motor responses. As noted above, recent investigators have further subdivided this region into the more posterior SMA proper and the more anterior pre-SMA zones (Picard & Strick, 1996; Rizzolatti, Luppino, & Matelli, 1996; Tanji, 1994).

Connections

The SMA cortex as a whole receives considerable input from the posterior somatosensory cortices, as well as from the prefrontal, premotor (PM), and primary motor (MI) areas.[118] The supplementary motor area also is an integral part of the basal ganglia and cerebellar feedback loops as witnessed by inputs from VL and VA nuclei of the thalamus. The output of SMA primarily is directed toward the lateral premotor (PM) and primary motor (MI) areas (including some bilateral connections). A relatively small contingent of fibers proceeds directly to the brainstem and spinal cord (mostly from SMA proper). Like most cortical areas, there also are projections to the neostriatum (caudate and putamen) (Bates & Goldman-Rakic, 1993; Luppino, Matelli, Camarda, & Rizzolatti, 1993; Chauvel, Rey, Buser, & Bancaud, 1996; Wiesendanger et al., 1987; Wise, 1996).

According to Rizzolatti, Luppino, and Matelli (1996) research interest in SMA sharply increased following the observation that electrical activity (a phenomena known as the *Bereitschaftspotential*) in the medial frontal zones routinely could be detected prior to the onset of voluntary motor activity (Deecke, 1987). This electrical activity in SMA can be detected even if one is only "thinking about" or "planning" a movement (regardless of whether the movement is ever carried out) (Freund, 1991; Roland, 1987). Despite the recent increased attention given to the SMA (e.g., Bates & Goldman-Rakic, 1993; Halsband et al., 1994; Luders, 1996; Mushiake et al., 1991; Picard & Strick, 1996; Tanji, 1994), there still is considerable controversy regarding the SMAs role in behavior and how its functions are distinguished from the lateral premotor (PM) cortex (Marsden et al., 1996; Tanji & Shima, 1996), and the primary motor (MI) area (Freund, 1996a).

Effects of Lesions/Stimulation

The SMA have been implicated in preparatory responses, both for simple and complex response patterns (Freund, 1996a). Animals with SMA lesions generally have greater difficulty in learning tasks that involve more complex, sequential motor patterns or where there is a paucity of external cues to guide behavior. Thus, it has been suggested that SMA may be critical in carrying out complex, sequential tasks that rely heavily on previously learned patterns of motor responses (sensorimotor engrams) (Mushiake, Inase, & Tanji, 1991; Passingham, 1993; Sergent, Zuck, Terriah, & McDonald, 1992; Tanji & Mushiake, 1996; Tanji & Shima, 1996). Lesion and stimulation studies in humans have offered some additional clues as to the functional significance of SMA. Naturally occurring lesions in humans (which unfortunately lack anatomical precision) have been reported to result in varying degrees of decreased voluntary or spontaneous motor activity in the contralateral limb (hemiakinesia), decreased speech output or facial expression, and occasionally unilateral neglect (Bleasel et al., 1996; Brust, 1996; Damasio & Van Hoesen, 1980; Freund, 1991, 1996b). Extensive cortical lesions that involve the medial frontal granular cortex may be associated with the "**alien hand syndrome**" (Freund, 1996a; Stuss & Benson, 1986, p. 87). Bilateral SMA lesions may result in akinetic mutism (Freund, 1991, 1996a). SMA lesions in humans also may be associated with difficulties performing sequential or rhythmic tasks in the contralateral hand or with difficulty coordinating bilateral reciprocal or simultaneous action patterns (Dick et al., 1986; Freund, 1987; Halsband et al., 1993). By contrast, stimulation of SMA generally results in more proximal, tonic movements, especially of the eyes and contralateral upper extremity. The most common description involves an elevation of the contralateral arm, followed by a turning of the head and eyes "as if following the movement of the hand" (i.e., a fencing posture) (Brust, 1996; Chauvel et al., 1996; Freund, 1996a). If stimulation occurs during speech or other motor activity, these activities will usually cease.

Summary. In broad terms, the medial frontal agranular cortex appears to play a critical role in the preparation and initiation [119] of a motor response. The SMA also appears to be important in the preparation and execution of complex, well-learned motor response patterns. Additional clarification and differentiation may be afforded by reviewing the apparent distinctions between pre-SMA and SMA proper, to which we now shall turn our attention.

SMA Proper versus Pre-SMA

On the basis of differences in cytoarchitecture, responses to electrical stimulation, and their afferent and efferent connections, SMA can be divided into "SMA proper," which lies rostral to area 4 on the medial surface of the frontal lobe, and "pre-SMA," which lies anterior to SMA proper (Matsuzaka, Aizawa, & Tanji, 1992; Rizzolatti, Luppino, & Matelli, 1996; Zilles et al., 1996). Although both are characterized by independent somatotopic organizations and overlapping patterns of anatomical connections, there are notable differences between the two. For example, while both receive input from the VA, VL, and DM nuclei of the thalamus, the pre-SMA area receives a greater proportion of its input from VA and DM, whereas VL is the major contributor to SMA proper. In terms of cortical connections, pre-SMA has greater input from the prefrontal granular cortex and anterior cingulate gyrus, while SMA proper has a greater somatosensory component. Only SMA proper appears to have direct connections with both MI and the spinal cord (Luders, 1996; Luppino et al. 1993; Picard & Strick, 1996; Rizzolatti, Luppino, & Matelli, 1996; Wise, 1996). The boundary between pre-SMA and SMA proper in humans is roughly demarcated by a vertical line drawn from the anterior commissure, perpendicular to a line connecting the anterior and posterior commissures (Luders, 1996; Zilles et al., 1996) (see Figure 9–47).

The functional distinction between pre-SMA and SMA proper is still a matter of some conjecture. However, as a result of recent studies, both in humans and in other primates, some tentative hypotheses have been offered. The pre-SMA areas may serve as an important link or transition between the prefrontal and cingulate cortices and the executive motor areas (Rizzolatti, Luppino, & Matelli, 1996). More specifically, the pre-SMA may be critical in the final planning, preparation, or final decision phase immediately prior to actual movements (when increased activity in this area is most prominent), whereas the SMA proper may be more highly correlated with the actual execution phase (i.e., increased activity during the movement itself) (Halsband, Matsuzaka, & Tanji, 1994; Matsuzaka, Aizawa, & Tanji, 1992; Passingham, 1996). It has been hypothesized that pre-SMA may be more critical for motor response patterns that are less automatic, characterized by greater cognitive demands or that require greater flexibility in terms of response alternatives (Picard & Strick, 1996; Sergent et al., 1992; Shima et al., 1996). SMA proper, by contrast, is thought to play a special role in

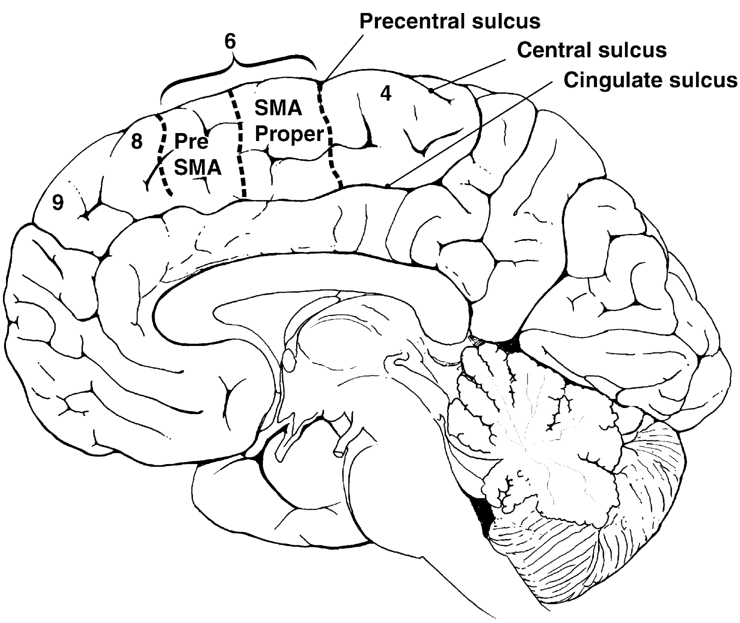


Figure 9–47. Approximate boundaries of pre-SMA and SMA proper on the medial surface of the cerebral hemisphere.

the execution of sequential movements, especially those that are more heavily practiced or overlearned (Marsden et al., 1996; Picard & Strick, 1996; Sergent et al., 1992). It also has been proposed that SMA proper may be important in coordinating axial and/or proximal musculature during overt motor activity (Rizzolatti, Luppino, & Matelli, 1996). As noted above, lesions of SMA often result in decreased spontaneous motor activity, decreased bimanual coordination, limb-kinetic-type apraxias, or "alien hand" syndromes (Bleasel, Comair, & Luders, 1996; Brust, 1996). However, in humans, discrete lesions that are isolated to pre-SMA or SMA proper are sufficiently rare so as not to provide a good model for the systematic study of the functional differences between these two anatomical areas.

Premotor Area

Anatomy

The premotor area most commonly is described as encompassing that portion of Brodmann's area 6, which lies on the dorsolateral surface of the cerebral cortex just anterior to the primary motor cortex (area 4). Other adjacent cortical areas that have similar cytoarchitectural features, particularly area 43, 44, and, less commonly, area 45,[120] are included in this premotor area (Jouandet & Gazzaniga, 1979; Stuss and Benson, 1986; Nieuwenhuys, Voogd, & van Huijzen, 1988; Freund, 1996b). As noted previously, area 8 (frontal eye fields) sometimes is included as part of the premotor cortex. Perhaps more commonly it is seen as an independent motor area, in part due to its distinct functional role. The premotor area, like the other "motor" areas, shows enhancement of layers 3 and 5 but lacks the large Betz cells that are characteristic of the primary motor cortex.

Connections

The premotor area has three general sources of input outside of the other cortical motor areas that are important in appreciating its probable behavioral functions. They are the prefrontal cortex, the posterior association areas (particularly areas 5 and 7), and subcortical input from the basal ganglia and cerebellum via the ventral anterior and the ventral lateral nuclei of the thalamus (Dum & Strick, 1991; Passingham, 1993; Fuster, 1997). These connections appear important for (1) the initiation of behavioral motor programs,[121] (2) sensory feedback in guiding and modulating movements, and (3) the timing and coordination of movements. Significant reciprocal connections also are established with SMA, but probably not the frontal eye fields, The major efferent output of the premotor cortices are to the primary motor cortex (ipsilateral), while transcallosal fibers connect the premotor cortex with its comparable area in the opposite hemisphere. These callosal connections are instrumental in explaining sympathetic dyspraxia following lesions of the premotor area of the dominant hemisphere (see **Ideomotor Apraxia** under **Disconnection Syndromes** p. 328) Geschwind, 1965; Heilman & Rothi, 1993. The premotor cortex also sends fibers caudally to the spinal cord. The latter fibers involve extensive connections in the brainstem that in turn give rise to the various ventral motor tracts in the cord (e.g., reticulospinal tract). These connections likely serve to help maintain postural stability while engaging in other motor activity (e.g., throwing a ball).

Effects of Lesions

The exact role of the premotor area and how it differs from that of the supplementary motor area remains somewhat unclear. Lesions involving the premotor cortex can result in (1) transient weakness, (2) diminished or slowing of spontaneous movement, and (3) limb-kinetic apraxia, or what Luria describes as *loss of kinetic melody* (Luria, 1966, 1973; Freund & Hummelsheim, 1985; Freund, 1991, 1966b; Halsband et al., 1993). These latter phenomena can be defined as the disruption of learned or habitual complex motor tasks as a result of difficulties in making smooth, fluent transitions from one phase of the action or motion to the next. While the goal and general form of the action remains intact, it may be carried out in an awkward or clumsy fashion. Such deficits of manual dexterity are contralateral to the lesion.[122] If the ventral premotor area, particularly area 44 of the dominant hemisphere, is affected, motor speech is likely to show impairment.[123]

A rare, but intriguing finding associated with lesions of the premotor area is the perseveration of elementary motor responses. For example, if asked to draw a circle, the patient may get stuck in set, repetitively drawing overlapping circles (Fig 9–37). When present, this symptom likely represents deep or more extensive lesions, probably including the basal ganglia (Luria, 1973; Stuss & Benson, 1986). While motor deficits following lesions of the premotor area are likely to affect any overlearned motor task requiring dexterity (e.g., playing a musical instrument, typing, drawing or writing), deficits can often be demonstrated by simply requesting the patient to tap out alternating rhythms or perform other complex, sequential movements, whether unilaterally or requiring reciprocal bilateral coordination (Christensen, 1975). In these instances one should be attending to differences in the fluidity of movement beyond that which might be explained by handedness. However, similar deficits also may be found following lesions to SMA (Halsband, Ito, Tanji, & Freund, 1993).

Feedback Mechanisms and the Premotor Cortex

For skilled movements to achieve maximal effectiveness there needs to be the capacity to make rapid, smooth transitions from one discrete movement to another so that each flows easily into the next. This is particularly evident as certain basic or automatic (overlearned) sequences of movements become well established. Yet motor programs must be flexible enough to respond to either changes in goals or plans (e.g., frontal programming) and to conform to the environment in which these actions occur. Both the SMA and the premotor areas rely extensively on both internal and external feedback. While the exact nature and role of such feedback are uncertain, some speculation is possible. As noted earlier, there are at least three primary sources of feedback to which we might attend. These include prefrontal, posterior cortical, and subcortical systems.

Feedback with Prefrontal Systems. Motor actions are designed to carry out a specific plan, goal, or purpose. Once the action has been initiated, it should follow that plan until either it is accomplished or circumstances dictate that the goal be changed. Thus, the actions must stay "on target" via constant monitoring to ensure that the actions are accomplishing their intended purpose. The connections between the prefrontal cortex and the premotor area are likely critical in transmitting these initiatives and directives to the primary motor cortex for execution. While there probably are multiple cortical regions within the motor system engaged in this process (e.g., SMA, basal ganglia), since the premotor cortex, along with the primary motor area, has the most detailed somatotopic organization, it is likely that the premotor area is critical for the more precise or detailed aspects of the preparatory response.

Feedback with Subcortical Systems. The execution of skilled movements requires a smooth transition from one component of the movement to each succeeding one, while maintaining an optimal overall muscular tone. Gross motor activities often require bilateral postural adjustments to maintain balance and ensure maximal efficiency (power) of movement. Even more discrete, fine motor activities often require the coordination of both sides of the body (e.g., typing, playing a musical instrument). The premotor area, with its extensive connections with the basal ganglia, the cerebellum, and the contralateral premotor area via the corpus callosum, appears ideally suited to integrate these various influences to effect this fluid coordination of individual movements.

Thus, for example, if the hand area of the premotor zone and/or its connections is affected, writing may lose its automatic character. Letters may be slavishly and clumsily reproduced. Script may give way to printing, since less fluid transitions between letters are required. Problems may be seen if the patient is required to produce rapid, alternating movements or rhythms using either the affected hand or both hands. If the lesion is more ventrally located, especially on the left side, a dysarthric-type speech may result. The patient may have difficulty making transitions from one articulation to another, especially when asked to repeat multisyllabic words or strings of phonemes requiring major, rapid transitions in the use of the lips, tongue and soft palate such as "bah-kuh-lah."

Feedback with Posterior Systems. The effective execution of movement is very much dependent on sensory feedback.[124] First and foremost, as each movement builds upon the last, one needs to maintain awareness of the position and movement of one's body in space, as well as the force and velocity of movement (e.g., proprioceptive and kinesthetic feedback). With the loss of such feedback, movements become coarse and awkward, especially if unaided by vision. Efficient manipulation of objects requires somatosensory feedback concerning the physical and dynamic qualities of the object itself. Witness the difficulties experienced in attempting to button a shirt or retrieve an object when one's hand "falls asleep." As previously noted, the dorsolateral premotor cortex has extensive connections with the superior parietal lobule. Thus, it would appear that the dorsolateral premotor cortex is critical in evaluating highly integrated somatosensory information either prior to or during movements initiated by the primary motor cortex.

Many movements take place in three-dimensional space, whether it is throwing a dart, catching a ball, writing or drawing, or simply reaching for an object lying on the table. The accuracy of such movements depends on feedback from the posterior association cortices. While there appears to be no consistent evidence of major direct connections between the dorsolateral premotor areas and the inferior parietal lobule, area 7 likely relays some visually processed information.[125] What is apparent is that the dorsolateral premotor area likely has access to visual as well as tactile feedback in that one of the more consistent conclusions regarding possible functional differences between the dorsolateral premotor area (PM) and SMA is that PM has been shown to be particularly active when motor responses are guided or directed by external cues, including visual stimuli (Rizzolatti, 1987; Roland, 1987; Tanji, 1987, 1996).

Summary. While both the SMA and dorsolateral premotor (PM) cortex probably are critical in the preparation and organization of the motor response, given the more precise somatotopic organization present in PM, the latter may assume a more direct role in the final coordination of discrete motor responses. The type of deficits seen following lesions of PM would lend support to this hypothesis. Finally, there has been some evidence to suggest that PM plays a critical role when the motor response is heavily dependent on external cues.

Frontal Eye Fields

Anatomy

The frontal eye fields (FEF) lie on the dorsolateral surface of the frontal lobe in the middle portion of the middle frontal gyrus, just anterior to area 6. Commonly referred to as area 8, the frontal eye fields and area 8 are not coterminal, but the FEF makes up a substantial part of area 8. The FEF sometimes is included as part of the "premotor cortex," but unlike area 6, it has no direct connections with the primary motor area (4). A "supplementary" motor area serving the FEF has been identified lying in or near the midline (Passingham, 1993).

Connections

Like the other frontal motor areas, the FEF has feedback loops through the basal ganglia and thalamus.[126] Of major interest here are its cortical and brainstem connections. The FEF has both ipsilateral and contralateral connections with the prefrontal granular cortex. As is true of the other premotor areas, these connections are important in the initiation (execution) of motor behaviors (in this case, eye movements). In the case of vision, such activity also is critical in establishing and maintaining selective attention to the external environment. The other major cortical inputs to the FEF are from the posterior cortices, especially those parietal and occipitotemporal areas that are important for processing visual information (however, there is no direct connection with the primary visual area) (Barbas, 1988; Fuster, 1997). There is substantial input from the posterior eye fields in area 7 (Cavada & Goldman-Rakic, 1989).

While there probably are reciprocal corticocortical connections, the efferent connections of primary concern are those to the brainstem, particularly those to the superior colliculi, the pretectal area, and either directly or indirectly to the **vertical** and **horizontal** gaze centers. The former is represented by the rostral interstitial nucleus of the medial longitudinal fasciculus and the latter by the paramedian pontine reticular formation. Apparently there are minor if any direct connections with the motor nuclei of the third, fourth, or sixth cranial nerves that innervate the extrinsic muscles of the eye.

Function

The frontal eye field is responsible for *voluntary* eye movements such as might be initiated in active visual searching or in voluntarily directing one's attention to a specific visual stimulus or portion of the visual field. Following the general principle of contralateral representation, the right FEF is responsible for voluntary conjugate gaze directed toward the left visual hemifield and vice versa for the left FEF. In general, this area behaviorally is consistent with area 6, which is responsible for mediating somatomotor responses to carry out the goals established by the prefrontal cortex. The tracking of moving objects (e.g., the opticokinetic reflex) or shifting one's gaze in response to sudden, unexpected noises are mediated by the posterior gaze centers and by reflex mechanisms at the level of the superior colliculi.

Pathology

Just as lesions that affect area 6 result in detectable motor deficits, so too do lesions that affect the FEF. Excessive stimulation of area 8 (as might occur with focal seizures) usually result in the eyes being conjugately driven to the side opposite the seizure focus (i.e., "looking away from the lesion"). Following the termination of the seizure, the eyes may be found deviated toward the lesion. In nonexcitatory, structural lesions (e.g., (stroke) involving the FEF unilaterally, the eyes may show a deviation toward the side of the lesion at rest. Although the eyes frequently may be brought to midline when attention is called to them, even with voluntary effort the patient may have difficulty achieving and/or maintaining conjugate gaze toward the opposite hemifield. Marked contralateral inattention or neglect has been reported in monkeys following unilateral lesions of the FEF. Such neglect or inattention may not necessarily be limited to visual stimuli and may be produced by frontal lesions other than those affecting area 8 (Mesulam, 2000c; Stuss & Benson, 1986).

Finally, despite difficulties in voluntary gaze that may be seen following frontal lesions (e.g., in response to verbal commands to "look" toward the contralateral field), unlike lesions of the PPRF in the brainstem there is no paralysis of conjugate gaze. This readily 'can be demonstrated by having the patient follow a moving object into the affected field or clapping loudly to that side. Under these circumstances the eyes will show the ability to shift, relying on the posterior gaze centers and brainstem reflexes.

Primary Motor Cortex (Area 4)

With the primary motor cortex, we reach what might be considered the final common pathway of the executive system. The axons of area 4 neurons synapse on motor nuclei in the brainstem and on the anterior horn cells in the spinal cord. In terms of our earlier military analogy, this region of the brain can be said to represent the enlisted men and women who ultimately are responsible for carrying out the plans and directives that were conceived, initiated, organized, and coordinated at higher levels in the chain of command.[127]

Anatomy

The primary motor cortex is represented, for the most part, by the precentral gyrus, although in its more ventral aspects much of area 4 lies within the folds of the central sulcus. Area 4 can be distinguished histologically from the other cortical motor areas by the presence of large Betz cells, predominately in layer V. Initially thought to represent the origin of corticospinal fibers, it is now known that these Betz cells reflect only between 1 and 3% of the corticospinal fibers found in the medulla.

Area 4, like area 8 and the postcentral gyrus, is characterized by a well-defined somatotopic organization. The face and oral musculature are located in the most ventral aspects of the precentral gyrus, followed dorsally by the representation of the hands, arms, shoulder, and trunk. The cells that eventually supply input to the lower legs and feet are located along the medial aspects of the hemispheres.[128] The amount of cortex devoted to a given area of the body is proportional to the degree of fine motor control that can be exerted by that body part. Hence, the cortical area reserved for the muscles of the hands and face are quite extensive in humans relative to the other parts of the body. These expanded areas are a function of the increased number of columnar cell units that are allocated to the increased number of discrete motor units, thus permitting increased fine motor control. Such control is further facilitated by equally fine point-to-point feedback from the somatosensory cortex.

Connections

The primary motor cortex has three major sources of input: (1) motor association cortex, (2) somatosensory cortex, and (3) subcortical projections. The major inputs from the motor association cortices are from SMA proper and from the dorsolateral portion of area 6 (i.e., premotor cortex). Somatosensory projections primarily come from those areas that represent proprioception (as opposed to cutaneous) feedback as well as input from area 5, which conveys more highly integrated somatosensory information. Such feedback is instrumental in modulating the force, direction, and accuracy of movements. Finally, as opposed to the motor association cortices that have extensive feedback from the basal ganglia, the subcortical input to area 4 seems to be shifted more to cerebellar input (via the posterior portions of the ventral lateral thalamic nuclei), although some basal ganglia input through the VA nucleus is likely present (Jones, 1987; Passingham, 1993).

As we learned earlier, the motor cortex sends fibers to the striatum (primarily the putamen) and likely has reciprocal connections with the cortical areas from which it receives projections (e.g., the somatosensory cortex, the premotor area and SMA proper, as well as the cerebellum). These various connections provide the anatomical substrate for ongoing feedback to the motor cortex. Those efferent fibers of the primary motor cortex that synapse on the motor neurons of the brainstem and spinal cord probably account for only a little over 30% of the corticospinal fibers (the rest coming from the premotor and somatosensory cortices). The neurons of the primary motor cortex are distinguished by the fact that they exert control over discrete, voluntary motor responses, especially those requiring fine motor skills (Kuypers, 1987).

Effects of Lesions

As noted above, the primary motor cortex represents the final common cortical pathway by which the brain is able to initiate voluntary, goal-directed motor activity, including discrete, fine motor skills. It is through the primary motor cortex that the brain is able to communicate with, exercise its "will," and exert physical control over the external world. Discrete lesions that affect only the primary motor cortex (to the exclusion of either premotor or somatosensory areas or deep fiber pathways) are relatively rare. However, several general observations can be gleaned from the clinical and experimental literature. These are:

1. In the case of small, focal lesions, the resulting deficits will be contralateral, and will differentially affect those areas of the body represented by the site of the lesion.
2. Following the onset of the (acute) lesion, there will be a period of flaccid paralysis, followed by an increase in tone and spasticity, although the degree of spasticity may be less than that seen with lesions of the internal capsule.
3. Pathological reflexes consistent with upper motor neuron lesions (e.g., Babinski, Hoffmann's) may be present.
4. Although some initial recovery often is seen following reductions in edema or restorations of blood flow, residual deficits are common and usually are more prominent distally than proximally.
5. The major functional deficits found after lesions to the primary motor cortex are reduced strength and decreased control of movement.

A FINAL WORD

This concludes the chapter on the cortex. What it tried to convey is that the brain probably acts as a whole, with widely distributed neural networks synchronously activated to produce any volitional behavior. While some tasks likely place a greater demand on some parts of the brain than others, most tasks are indeed highly complex, at least from the perspective of the various brain systems involved. Even the most simple tasks likely require the simultaneous cooperation of major portions of the three functional systems discussed. Disturbances in any of these systems or subcomponents thereof may result in behavioral deficits. Our task as cognitive neuroscientists is to analyze patient behaviors (including the results of neurobehavioral tests) and to search for patterns that enable us to better understand the specific or more elementary breakdowns (deficits) in brain function. To do so not only serves to enhance our understanding of the brain itself, but likely puts us in a better position to understand our patients and more accurately predict the type of difficulties they may expect to encounter in their day-to-day lives.

Endnotes

36. This is not to suggest that, despite whatever advances may have been made in the last 50 years, we are much beyond having barely scratched the surface of this uniquely complex organ!

37. This readily can be demonstrated by observing the difficulties a young child may encounter if he or she attempts to read or write while holding their tongue fixed between their teeth, thus hampering their ability to "sound out" the word.
38. While adhering to the three units as outlined by Luria, this subdivision of the first unit can be construed as having some capacity for arousal via the organism's need to maintain a homeostatic balance, instinctual drives to ensure both personal and species survival, as well as acquired emotional valances. However, the arousal mechanisms mediated by the limbic system would appear quite different from those of the RAS. Consequently, it seems very reasonable to speculate that the limbic structures might be construed as constituting a separate functional unit, one that, among other things, could be characterized as regulating drives and emotions.
39. In addition to influencing "higher cortical centers," it is likely that these structures in turn also may be subject to descending influences from the cerebral cortices, a point that will be addressed later.
40. As originally defined by Wilson (1924), certain areas of the brainstem, if deprived of cortical influence (as in bilateral lesions of the corticobulbar tracts), spontaneously may manifest facial expressions typically associated with certain emotional states, despite the lack of internal emotion, a condition he described as pseudobulbar palsy. While it is possible that certain bilateral, subcortical lesions indeed may produce this effect, emotionality lability ("emotional incontinence") probably is a more common explanation when subcortical (or cortical) frontal lesions are present.
41. The term "horizontal" zone refers to the supposition that once the sensory information is transmitted to the various primary zones, the transformations of the data mentioned above, which proceed from the primary to the tertiary zones, would appear to be largely a cortical phenomena without necessarily involving additional subcortical structures or input.
42. Smell and taste may have similar primary and secondary zones but their sites of cortical representation probably are much smaller and along with their functional analysis are less well understood.
43. For simplicity's sake, we will confine ourselves to auditory language at this point. Non-language, auditory inputs will be considered below.
44. While the words are readily available, the meaning of specific word-names for colors or the concept of color itself cannot be grasped fully by the individual who is congenitally blind.
45. However, these are fairly complex linguistic constructions, and as a result could be affected by other cognitive difficulties as well. Also these are by no means the only symptoms associated with lesions of the posterior tertiary cortex of the dominant hemisphere (see, for example, Gerstmann's syndrome). Many of these symptoms and syndromes will be discussed elsewhere in this chapter.
46. It is beyond the scope of this work to attempt to present a detailed description of the neuroanatomical and behavioral substrates of language and its syndromes. Table 9–4 (p. 347) provides a brief summary of classically defined aphasic syndromes. However, the interested reader is referred to more detailed treatments of this topic that can be found in books by Benson, (1979) and Albert et al., (1981); chapters in Feinberg and Farah, (1997) and Heilman & Valenstein, (1993); as well as an article by Heilman, Tucker, and Valenstein, (1976) that offers an interesting heuristic model for thinking about the organization of various components of language within the brain.
47. These "nonsemantic" aspects of language and the putative role of the nondominant hemisphere were reviewed in greater detail under Emotional-Affective Processes, Chapter 9, Part II, p. 352).

48. For example, it is noted that certain cells in this region are more likely to respond to integrated visual gestalts or percepts such as faces. If stimulated, these more anterior areas are more likely to elicit complex, well-formed visual hallucinations such as images of objects, animals, people, at times including sequences of actions involving such images. On the other hand, stimulation of the more posterior, peristriate areas tends to produce more elementary patterns of light, color, or movement.
49. The perceptual deficits associated with lesions to these secondary association areas often are referred to as **apperceptive agnosias**, in contrast to **associative agnosias** that result from lesions of the heteromodal areas. However, a perceptual (apperceptive) deficit, if sufficiently severe may preclude or interfere with the visual identification of an object or stimulus. Apperceptive agnosias frequently are distinguished from the associative variety by the fact that in apperceptive agnosias the patient not only is unable to name the stimulus (although naming should be preserved if the object or stimulus is presented in another modality, such as tactually or by verbal description), but also unable to draw or copy the figure or object. In contrast, in purely associative agnosias, while naming (or other signs of recognition) is impaired, the patient may retain the ability to draw the object in question. However, some caution is advised in relying solely on these procedures as the act of drawing itself is a higher-level integrative activity and could be present in associative disorders.
50. Simultanagnosia, as noted earlier, is normally associated with Balint's syndrome (although it may occur as a more isolated symptom) and bilateral occipitoparietal lesions. Typically, simultanagnosia (or dorsal simultanagnosia) presents as an inability to attend to or focus on more than one object or aspect of a visual picture or array at a time. Consequently, objects, pictures, or visual scenes may be misidentified or misinterpreted as a result of this failure to attend to all the visual information present (Luria, 1959; Rafal, 1997a). This problem may be exacerbated if there are simultaneous lesions affecting the frontal eye fields that further impair visual searching. Kinsbourne & Warrington (1962a) identified a somewhat more benign version of this disorder (ventral simultanagnosia). Resulting from left occipitotemporal lesions, the individual has difficulty determining how one part of a complex picture or visual percept relates to another, and thus, is unable to accurately interpret it (Cytowic, 1996, pp. 433–436; Bauer, 1993, pp. 224–226). This latter form of simultanagnosia may be associated with particular types of reading disturbances (i.e., letter-by-letter reading, as opposed to normal "whole word" recognition).
51. With the possible exception of most daytime talk shows and prime time sitcoms! Also, this is not meant to imply that members of other mammalian, avian, or even reptilian groups do not possess keen visual skills. Members of the canine family, for example, rely on vision not only for spotting and pursuing prey, but also for "communication" (the attitude of the lips, ears, tail, head, and back all provide extremely important cues regarding intention and social status). The difference in primates may be their greater tendency to visually explore their environment for its own sake.
52. Multisensory images commonly are secondarily (indirectly) associated with color in that, if asked to picture something red, we may visualize an apple. In turn, the image of a juicy red apple may secondarily elicit tactile, gustatory, olfactory, and even auditory associations. Interestingly enough, colors may be associated in a more direct, although less concrete or tangible manner with mood states (limbic structures), a fact not lost on designers and decorators.
53. With the exception of judgment of line orientation that is significantly more highly correlated with lesions of the "nondominant" hemisphere, disruptions of most such visual–spatial tasks can occur following lesions to either hemisphere. However, it also

should be noted that even constructional tasks (such as drawing geometric designs, or reproducing two- or three-dimensional block-type constructions) are complex tasks and, as such, may be disrupted following diverse cortical lesions.

54. One possible explanation for the robustness of visual object recognition is the more diverse associations the brain makes to visual objects (hence, a greater degree of redundancy that is built into the system). Consider that while many objects have direct somatosensory or sensorimotor associations (we sit in a chair, we manipulate a hammer), the same cannot be said for colors, faces, or letters. Such associations may provide additional alternative pathways by which information may be transferred from one part of the brain or one hemisphere to another. This also might help explain why object naming is generally preserved in alexia without agraphia (see Disconnection Syndromes).
55. While there may be some evidence of apperceptive deficits, these generally would not appear sufficient to account for the severity of the deficit manifested. Also, interestingly enough, despite a lack of any conscious awareness of the person to whom a previously familiar face belongs, the patient may show signs of "unconscious recognition," that is, may perform well above chance in a forced-choice paradigm (Sergent & Poncet, 1990; Diamond et al., 1994).
56. As will be noted later, two of the major functions of the frontal tertiary cortices are (1) planning and organization, and (2) self-monitoring, which involves comparing actual with expected outcomes. Both of these activities require constant, directed sensory feedback. Certainly, even simple tasks requiring hand–eye coordination also must rely on visual connections with the sensorimotor cortices.
57. The Visual Reproduction subtest of the Wechsler Memory Scale-Revised, a test that involves the reproduction of geometric designs, was dropped from the primary memory indices in the new WMS-III (Psychological Corporation, 1997) in large part because it failed to adequately differentiate right hemispheric patients (Chelune & Bornstein, 1988; Naugle et al., 1993). One possible explanation for these findings is that the stimuli used in this test (as in many tests of "visual memory") are easily verbally encodable. Hence, despite lesions to the supposedly more "visual" right occipital–temporal–limbic pathways, the left hemisphere (which also has the capacity to lay down visual memories) may have been further "assisted" by verbal encoding. This example is presented to show the inherent difficulty in trying to isolate stimulus–response patterns in the real world.
58. Although each of these cytoarchitecturally diverse cortical projection areas in the postcentral gyrus likely represent different aspects of tactile sensation (submodalities), the exact functional correlates of each are still a matter of speculation. However, area 3a, which lies in the depth of the central sulcus, appears to represent a transitional zone between area 4 and the rest of the somatosensory cortex and likely receives input from muscle (spindles), joints, and Golgi tendon organs. There is some debate as to whether information supplied to 3a reaches a level of conscious awareness. Area 2 seems to respond, at a conscious level, to muscle and joint receptors and would appear to be important in judgments about size, shape, kinesthesia, and position sense. Area 1 appears to respond preferentially to more rapid conducting and surface receptors and may be selectively attuned to texture discrimination. The role of area 3b, which lies along the posterior bank of the central sulcus, appears less clear but it may be responsive to slower conducting, cutaneous receptors (e.g., temperature), as well as capable of mediating mechanical cutaneous input (Kaas, 1983; Warren, Yezierski, & Capra, 1997).

59. While information from both the medial lemniscus and the spinothalamic tracts apparently projects to SI, the lemniscal system, which is better equipped to process discrete somatosensory stimuli, especially information that is the result of active tactile exploration or manipulation, may be preeminent in SI.
60. Among the receptors that provide feedback to the somatosensory cortex are Meissner's corpuscles, Pacinian corpuscles, Ruffini endings, Merkel's disks, Krause bulbs, free nerve endings of various types, including those attached to hair follicles, Golgi tendon organs, muscle spindles, and joint receptors.
61. Lesions of SII tend to produce more subtle, bilateral sensory deficits.
62. Cortical lesions are not necessary to produce these deficits. Thalamic lesions or lesions affecting the thalamocortical pathways may produce similar symptoms. Lesions that affect the spinal–cortical pathways (e.g., the medial lemniscus and the spinothalamic tracts) generally will have a much more profound effect on these elementary somatosensory perceptions than will thalamic lesions.
63. In this, as in many of the signs and symptoms described here, one must be cautious in drawing anatomical conclusions. Not only may similar deficits arise from various vertically placed CNS lesions but they also may arise as a result of lesions to other functional units. In this case, lesions affecting motor programming must also be considered.
64. There is reason to suspect that area 5 and perhaps parts of 7 may be critical for the more elaborate and complex integrative tactile perceptions that rely heavily on proprioceptive, as well as mechanical cutaneous information, particularly as these might relate to guiding motor responses. Also, the more posterior the lesion, the greater the likelihood that vestibular and visual interactions begin to play a critical role (Hecaen & Albert, 1978, Chapter 6).
65. One definition of a narcissist is the person who, while acknowledging that it is theoretically possible for the universe to continue in existence after his demise, does not believe it actually will happen; after all, what would be the point! Even if one does not subscribe to that philosophy, it still is in the interest of most, if not all, sentient organisms to manipulate the environment to meet their needs.
66. Occasionally, patients may be found who are unable to name an object held in the nondominant hand but accurately can demonstrate its use. This does not represent an agnosia, but more likely a disconnection from the dominant hemisphere.
67. **Amorphognosis** refers to the inability to appreciate the form of the object, while **ahylognosia** refers to the inability to determine its substance (material). Theoretically, in astereognosis, the patient should be able to make individual, independent judgments of size, shape, weight, or texture but have difficulty integrating all of them at once. According to Critchley (1969), in practice, however, it is rare to find astereognosic deficits without some evidence of more elementary defects.
68. For example, when asked to right or draw something on a sheet of paper, the right-handed individual usually will rest the left hand on the top of the paper to steady it. Patients with left-sided neglect may fail to do this.
69. Unilateral finger agnosia more likely suggests an underlying disorder other than that related to autotopagnosia (Gainotti & Tiacci, 1973). The manner in which the deficit is elicited may provide some clue. For example, if the deficit is present unilaterally, but only under conditions where visual feedback is unavailable, an elementary somatosensory defect should be ruled out. If present under both visual and tactile conditions, unilateral neglect may account for the findings.
70. Goldenberg (1997), in his review of disorders of body schema, concludes that aphasic disturbances probably account for most of these type deficits in left hemisphere lesions,

while general mental impairments likely account for such findings associated with right hemisphere disease.

71. Unlike vision, hearing, and olfaction, which are all telereceptors, tactile stimulation implies that your body space already has been invaded. One of the authors (JEM) vividly recalls an incident from his childhood that demonstrated this phenomenon. It was a warm spring afternoon and the author's dog, a Doberman pinscher, was quietly sleeping under the shade of a tree. He decided it might be "fun" to see if he could "sneak up" on the sleeping dog. Having successfully accomplished this "mission," he gently but firmly poked the dog on his back. "Instantly" the Doberman was on his feet with his fangs bared and his ears back. Fortunately, just as quickly visual, olfactory, or possibly auditory cues kicked in and the dog resumed his normally friendly posture.
72. Recall from Chapter 8 that anterior cingulate lesions have been known to abolish these negative responses to painful stimuli, at least temporarily. While the patient may continue to report that he or she experiences "pain," it no longer appears to be disturbing. This phenomenon, traditionally referred to as **pain asymbolia**, actually has been reported with various thalamocortical and cortical lesions, most frequently in the area of SII in the dominant hemisphere (Hecaen & Albert, 1978); however, Geschwind (1965) hypothesized that the critical element in all these cases was a disconnection between the cortex and the limbic system
73. While the parietal and temporal lobes of the brain have substantial connections with the basal ganglia and limbic structures, the frontal lobes and the prefrontal cortex in particular have rather special connections with these subcortical structures. Recall that the prefrontal cortex has extensive connections to the basal ganglia, particularly the head of the caudate (see Chapter 6) and are directly associated with the basal and mesial limbic structures (see Chapter 8). As will be seen, these latter connections would appear to exert a major modulating influence on the first functional unit. Since lesions that encroach upon these subcortical connections (including thalamic projections) may adversely affect the functioning of the third unit, at times, reference is made to lesion processes that disrupt *frontal systems*. This terminology is a reminder that the frontal lobes (as well as other parts of the brain) do not operate in isolation, but may be significantly affected by lesions that technically may be outside the cortical boundaries of the frontal lobes themselves.
74. The posterior portions of area 6 sometimes are included as part of the primary motor area, while the more anterior part of area 8 is occasionally classified as heteromodal cortex (see Mesulam, 2000b, pp. 14, 23).
75. The role of this prefrontal, granular cortex was summarized by Luria (1973, pp. 79–80) in the following passage:

> Man not only reacts passively to incoming information, but creates intentions, forms plans and programmes of his actions, inspects their performance, and regulates his behavior so that it conforms to these plans and programmes; finally he verifies his conscious activity, comparing the effects of his actions with the original intentions and correcting any mistakes he has made.

76. This does not imply, however, that motoric responses are always the direct goal or consequence of activity in the prefrontal cortices. The immediate outcome of this activity at times may remain strictly within the mental realm. It also should be noted that the frontal cortices do not act in a vacuum. While the frontal heteromodal cortex likely provides the means for devising plans or strategies, it is the posterior lobes of the brain that supply the data on which the frontal lobes operate. Each would be virtually useless without the other.

77. Because deficits associated with prefrontal regions of the brain often are so context dependent, it sometimes is difficult to devise appropriate laboratory tests that measure content-dependent behaviors. For example, judgment (inhibition) routinely is tested in mental status exams by asking the patient, "What would you do if you saw smoke and fire in a theater"? "Frontally impaired" patients may give perfectly adequate responses in the emotionally neutral setting of the bedside exam but behave quite differently if actually placed in that affective-laden situation.
78. There is no uniform consensus as to these designations or the exact cytoarchitectural areas that constitute them. For example, sometimes it is suggested that areas 24 and 32 could be included as part of the mesial prefrontal cortices (see Benson & Stuss, 1986, p. 16; Benton, 1991, p. 17), while others would classify these two areas along with area 25 as constituting paralimbic cortices (Mesulam, 2000b). On the lateral surface, there also has been debate as to the classification of areas 44 and 45 (otherwise referred to a "Broca's area"). Again, there has been some debate as to how these two areas should be classified (e.g., see: Jouandet & Gazzaniga, 1979). However, the consensus seems to be that, cytoarchitecturally, area 45 is more consistent with the heteromodal, prefrontal cortex, while area 44 is more representative of the unimodal, premotor cortex (Damasio, 1991; Kaufer & Lewis, 1999; Mesulam, 2000b; Nieuwenhuys, Voogd, & van Huijzen, 1988). Finally, as Brodmann's maps do not include the orbital regions of the frontal lobe, the designations for this region were derived from other sources (see H. Damasio, 1991, p. 96; Robin & Macdonald, 1975).
79. For additional detail, see Harlow's 19th-century description of his patient, Phineas Gage (page 448) and Macmillan (1986).
80. Since the original Star Trek characters are most familiar to the author, they were chosen for this example, trusting the younger reader can bridge this obvious "generation gap."
81. Again, see Harlow's description of Phineas Gage (p. 448).
82. Thoughts (plans, schemas, ideas) can be considered a type of "action" and certainly often involve considerable "psychic energy." Consequently, it is not only the translation of ideas into physically executable programs that may suffer, but also the generation of the psychic programs or thoughts themselves.
83. Often the problem is not simply inaction, but the choice of the behavioral goal that is selected to be acted on. For example, it is not uncommon for more long-range, esoteric, or abstract goals to be eschewed in favor of more immediate, primitive, or biological needs. These issues, which relate to another aspect of prefrontal lobe function, will be addressed later.
84. A fact that is well known to most advertising executives.
85. Because of the direct connections between the dorsolateral prefrontal cortex and the frontal eye fields (area 8) and the premotor zones (area 6), visual and tactile exploration of specific aspects of external stimuli easily can be manipulated. Although hearing is not readily capable of such manipulation, certain animals prick up their ears (lacking that capacity, humans may cup their hands behind their ears). Both of us may turn our heads toward a sound to provide a clearer shot for the sound waves to strike the tympanic membrane. Also, see under The Modulation of Internal Drives and Emotions, "The Role of Frontal–Thalamic Connections in Selective Attention or Arousal" for other potential neuroanatomical substrates of selective attention.
86. Again, one could argue that the problem might lie not in deficits of selective attention but in a defective strategy that includes the need for directed or selective attention. Although this easily could develop into a circular argument, the important point is that this attention–perceptual process, which appears to be mediated by frontal systems, is not random but rather is guided and directed by the goals or behavioral programs

operating at the time in order to provide information critical to or consistent with the completion of that goal.

87. Unilateral neglect also may be produced by various subcortical lesions, including lesions of the thalamus, basal ganglia, and midbrain (Heilman, Watson, & Valenstein, 1993).
88. At times a patient may initiate and persevere with a particular response pattern, despite the fact that it is incorrect (i.e., fails to be reinforced).
89. Both of these failures of inhibition also may be seen in speech and writing or other motor programs other than drawing tasks. Also see Sandson and Albert (1987).
90. While the Wisconsin Card Sorting Test and the Category Test also are listed under tests of planning ability by Stuss and Benson (1986), these latter tasks, as noted earlier, are probably better measures of loss of mental flexibility or even decreased ability to profit from feedback (Goldstein & Green, 1995).
91. In some ways these tests are similar to the old word problem we encountered in school that goes something like this: A man had a duck, a sack of corn, and a fox that he needed to transport across a river. His boat was small and could carry only one extra item (in addition to himself) across at a time. However, if he left the duck and the corn together, the duck would eat the corn, and if he left the duck and the fox alone together, the fox would eat the duck. So how could he arrange to get all three safely across?
92. In contrast, several pathological syndromes that either primarily or secondarily may affect the orbital zones of the frontal cortex have been associated with significant amnestic syndromes, often with an accompanying tendency to confabulate. The most notable of these conditions is aneurysms of the anterior communicating artery (ACoA) (Alexander & Freedman, 1984; Damasio et al., 1985; Deluca & Diamond, 1995; Fasanaro et al., 1989; Gade, 1982; Green et al., 1995; Talland et al., 1967; see Chapter 10). Likewise, Korsakoff's syndrome (Butters & Cermak, 1980: Butters et al., 1987), which clinically has much in common with the amnestic syndrome associated with ACoA aneurysms, commonly affects the dorsomedial nucleus of the thalamus whose main cortical projection site is the frontal lobes. Victor, Adams, and Collins (1971) suggest that it is these thalamic lesions that may be primarily responsible for the observed memory deficits in Korsakoff's (see also Cummings, 1990, pp. 63–64).
93. Other more specific constructs or difficulties that have been associated with frontal lobe pathology include increased sensitivity to interference, or disturbances of attention and concentration (Chao & Knight, 1995; Stuss, 1991), defective working memory (Goldman-Rakic, 1987a; Kimberg et al., 1997), difficulty with recency judgments or temporal order (Milner & Teuber, 1968; Milner, 1971), difficulty with source memory (Janowsky et al., 1989), and a failure to inhibit irrelevant responses (Luria, 1966; see section on Self-monitoring).
94. If the solution to this problem does not immediately come to you, do not panic. Chances are your prefrontal cortex is just fine. This problem has temporarily stumped more than a few college graduates.
95. For those readers who may not be familiar with these measures, Picture Arrangement consists of a series of cartoon-style pictures that are presented in a jumbled order. When properly sequenced, they depict a logical, typically humorous, story. In the "tinker toy" test, the patient is presented with predetermined set of pieces from a Tinkertoy set, with the instructions to "make something." Scoring is based on complexity, meaningfulness, and its ability to perform some "function" (e.g., the ability to roll). The Sequin-Goddard_formboard consists of ten cutouts of various geometric shapes (e.g., star, diamond, square, cross, etc.) in a board approximately 12 x 18 inches. While blindfolded and never having seen the board the subject is required to locate and place ten wooden blocks into their corresponding shapes (cutouts) on the board.

96. While such tests are indeed highly sensitive to brain injury, poor performance is not necessarily indicative of brain injury. A number of years ago, one of the authors (JEM) administered the Wisconsin Card Sorting Test to an intern, both as a means of teaching the test and to provide a sense of empathy for test-taking by patients. The intern in question was a very bright student yet he achieved zero categories on the test! As it is now many years later and this particular intern is still a very successful and articulate clinician, the possibility of some occult lesion is highly remote. In this case, the problem if anything seemed to be that the student was searching for more esoteric solutions rather than settling on the obvious.
97. With a few notable exceptions, such as the liver, heart, pituitary gland, and the digestive tract, much of our body is fairly symmetrically represented. Whether or not it reflects the evolutionary plan, this bilateral symmetry does allow for some biological redundancy. This is seen to a large extent in the brain and perhaps to a greater extent in the prefrontal cortices than elsewhere. For most individuals the secondary and tertiary zones of the posterior hemispheres show significant behavioral specificity. While bilateral lesions of the occipitoparietal cortices typically will result in visual–perceptual difficulties much worse than that seen with unilateral lesions, unilateral lesions of the angular gyrus, for example, may themselves produce very dramatic syndromes. While we will later review symptoms associated with unilateral lesions of the prefrontal cortex, as a general rule the prefrontal cortex appears more robust in this regard. Unilateral damage is less likely to result in the marked behavioral deficits. When obvious behavioral disturbances resulting from frontal lobe pathology are present, the damage is likely to be bilateral.
98. A related construct that sometimes is applied to patients with frontal impairment is “lack of insight,” a concept that we will return to later in this section. However, as with many such metasymptoms, one must be cautious in attributing poor insight solely to frontal lesions. The term “insight” can take on a host of meanings but in a neuropsychological context it most commonly refers to a diminished capacity to appreciate one’s deficits or shortcomings. In turn, among other things this can refer to one’s failure to acknowledge physical symptoms, such as a hemiparesis (**anosognosia**) or more general behavioral or cognitive changes. However, at times, specific performance deficits may be due to sensory or perceptual limitations. The latter might include, for example, the failure to appreciate major errors in the attempt to draw a clock as a result of unilateral neglect. As previously noted, while anosognosia for hemiplegia most commonly has been associated with posterior lesions of the right hemisphere, a variety of cortical and subcortical lesions including lesions of the frontal lobes have been associated with this syndrome (Bisiach & Geminiani, 1991; Feinberg, 1997; Heilman, 1991). Poor insight into or lack of apparent concern about behavioral or cognitive changes or deficits frequently is associated with generalized dementias (Cummings & Benson, 1992; McGlynn & Kaszniak, 1991).
99. There may be reasons other than frontal lobe pathology for being relatively unconcerned about the adequacy of one’s response. Depression, agitation, and acute pain are a few of the more common circumstances in which a patient may respond in an uncritical manner. In cases of malingering, the patient intentionally may provide erroneous responses.
100. In this case one can observe several potential signs of frontal pathology: poor comparator function, disinhibition (inappropriate familiarity), decreased ability to appreciate humor and/or concrete thinking, symptoms that also had been reported by others.

101. For a more thorough review of this topic, the reader is referred to Chapters 5 and 7 to 9 in Prigatano and Schacter's (1991) excellent volume that brings together a varied collection of works on deficits in awareness following brain injury.
102. Successful rehabilitation generally is based on several broad principles, including (1) the recognition that a problem exists, (2) the ability to develop a plan or stable intention to work on the problem, (3) the ability to utilize feedback, and (4) the drive or motivation to persevere in the effort to overcome it. With frontal lobe damage one or all of these basic abilities may be impaired. Thus rehabilitation for many of these individuals is like trying to build a house with limited or defective tools. Consider, for example, the potential difficulties posed by impaired self-monitoring capacity in a work setting.
103. Even at this level, however, descending cortical influences likely play a role, since alerting responses will be influenced by such factors as novelty and habituation (Sharpless & Jasper, 1956).
104. The problem may be not so much one of *increased* sexual drive as much as *reduced* inhibition of sexual impulses, a topic that will be addressed in the following section.
105. There also has been considerable interest in recent years over the possible connection between obsessive–compulsive disorders and disturbances in frontal–subcortical (particularly orbitofrontal–caudate) circuits that might normally regulate limbic arousal (Baxter et al., 1987; Malloy & Duffy, 1994; Mega & Cummings, 1994; Otto, 1992; Tallis, 1997; Zald & Kim, 1996a,b).
106. It should be noted that while "behavioral disinhibition" was part of his clinical picture, he (Phineas Gage) also manifested other aspects of frontal pathology, including what appeared to be a loss of cortically induced drive.
107. As noted above, certain types of impulsive, aggressive behaviors are suspected of being linked to frontal system impairment (Davidson, Putnam, and Larson, 2000). Although the evidence has been equivocal, it also has been suggested that sociopathy in general may reflect some type of learning disability or hard-wiring deficit involving the frontal lobes (Damasio, Tranel, & Damasio, 1991; Gorenstein, 1982; Kandel & Freed, 1989; Lapierre, Braun, & Hodgins, 1995; Lueger & Gill, 1990; Meyers et al., 1992; Price, Daffner, Stowe, & Mesulam, 1990).
108. One exception to the above rule is the syndrome of progressive aphasia, in which disturbances of speech and language (nonfluent, agrammatic speech, with marked paraphasic and anomic errors) typically precedes more gross behavioral changes.
109. Take, for example, the command, "Touch your left ear with your right hand." One should be able to generate at least a half-dozen or more "factors" that potentially might cause a failure to properly execute this apparently simple request. Contrast this with a test like the Category or Wisconsin Card Sorting tests.
110. Because of the nature of frontal lobe pathology, even when behavioral changes are detected early, they often are attributed to psychological or psychiatric factors rather than neurological disease. This is particularly true if the pathology has a slow, insidious onset and primarily affects the orbital–mesial areas of the prefrontal cortex.
111. It has been suggested (Malloy & Richardson, 1994) that tests of verbal fluency that require the subject to generate words beginning with particular letters of the alphabet (Benton, 1968) rather than provide words within a semantic category (e.g., fruits or animals) are reportedly more sensitive to frontal lesions.
112. It is important to keep in mind that initiating a particular response frequently involves the inhibition of potentially competing actions or response alternatives. In addition, the selected "response" may be *not to respond* (i.e., not to "go with" your initial or prepotent impulse to act or respond in a particular manner). Whether such response inhibition involves single muscle groups or more elaborate behavioral patterns, it ultimately

is based on an interaction between the prefrontal and agranular cortices (Goldman-Rakic, 1987b, p. 193).

113. Like the rest of the brain, these areas are extremely complex, both structurally and functionally. Only the highlights will be presented here. For those readers who may be interested in more detail, the following works might be recommended: *Motor Areas of the Cerebral Cortex* (Ciba Foundation, 1987); *Advances in Neurology,* Vol. 70: Supplementary Sensorimotor Area (Luders, 1996); *The Frontal Lobes and Voluntary Action* (Passingham, 1993).
114. Just as some routine "housekeeping" functions may be carried out in the military with little if any direct input from the General, so too certain "executive functions" may require little if any direct input from the prefrontal zones. One example might be reflex visual tracking behavior resulting from direct connections among the frontal eye fields, the occipitoparietal or peristriate areas, and the brainstem (e.g., Wise, Boussaoud, Johnson, & Caminiti, 1997).
115. The meaning of the term "initiation" (of action) may vary depending on context. In reference to the prefrontal areas, it refers to the *intention* or *will* to act. The prefrontal zones can be said to "initiate" behavioral (including, motor) programs in that they initiate the process that culminates in a certain action. However, the prefrontal zones do not directly produce (initiate) the depolarization of the corticobulbar or corticospinal fibers. The latter is the responsibility of the primary motor zones.
116. In addition to cytoarchitectonic differences, the frontal granular and agranular cortices also tend to have different thalamocortical connections. The prefrontal or granular areas are generally is associated with the nucleus medialis dorsalis (or "dorsomedial nucleus), whereas the motor and premotor areas are linked to the ventral lateral nucleus of the thalamus (Akert, 1964).
117. Picard and Strick (1996) also identify two additional motor areas on the medial surface along the banks of the cingulate sulcus ("cingulate motor areas"), but relatively little is known about their behavioral significance.
118. The pre-SMA area receives most of its input from the prefrontal area, while the SMA proper has extensive inputs from the primary motor
119. Again, "initiation" in this context does not refer so much to the organism's decision as to whether, when, or how it will respond to a class of stimuli or a set of circumstances as a whole (that most likely is the province of the frontal granular cortex). Rather, it refers to the SMA's role in the mechanics of initiating, planning (preparing to respond), and executing the more specific or elementary motor response patterns once the "go" signal is given to act at a particular time and/or in a particular manner (Freund, 1991).
120. Areas 44 and 45 generally are considered to constitute Broca's area.
121. Goldman-Rakic (1987b) suggests that since the parietal connections with the premotor area are much more substantial than those from the prefrontal area (at least in the monkey), a substantial portion of the prefrontal lobe's influence on the premotor area may be via the parietal lobe. However, in the ensuing discussion following Goldman-Rakic's proposal, other panel members suggest that the situation may be different in humans.
122. **Sympathetic apraxia** (apraxia of the left hand following left hemispheric lesion) is not uncommon following lesions that produce a Broca's-type aphasia and right-sided hemiparesis. However, in such cases the critical site of the lesion is uncertain. According to Heilman and Rothi (1993) lesions that are restricted to the premotor cortex have not been shown to result in ideomotor apraxia of the limbs, although Heilman and his colleagues reported several cases of bilateral ideomotor apraxia following left-sided SMA lesions (Watson, Fleet, Rothi, & Heilman, 1986).

123. While Broca's aphasia may be present in lesions affecting the premotor area, again a more extensive lesion is usually present often extending more anteriorly and/or deeper involving the basal ganglia (Alexander, Benson, & Stuss, 1989).
124. It has been suggested that SMA is associated with movement that is internally initiated. By contrast, the premotor area is more responsive to behaviors elicited by external stimuli. Tanji (1996) rejects this notion but does acknowledge that the premotor area appears critical when external cues help guide the behavior.
125. Although deficits following lesions confined to the premotor area would appear to result more from disruptions of subcortical and/or somatosensory as opposed to visual, feedback loops, the reverse is not true. Lesions that affect the posterior cortices often can result in motor responses that are poorly guided in space, although the action itself may be intact. One example may be difficulty maintaining well-organized, horizontal lines in writing that can be seen following certain parietal lesions. One possibility is that such lesions disrupt frontal–motor connections.
126. In contrast to area 6, which receives substantial input from the VA and VL nuclei of the thalamus, area 8 receives most of its input from the dorsomedial nucleus of the thalamus, similar to much of the prefrontal granular cortex. There also appears to be some connections with the pulvinar that is associated with processed, multisensory information.
127. The frontal eye fields also come close to meeting this description, the primary differences being that (1) the actions they control are intransitive, and (2) their influence on the extrinsic muscles of the eye are indirect.
128. As will be seen in the next chapter, this makes the legs and feet more susceptible to diseases affecting the anterior cerebral arteries and less susceptible to lesions of the middle cerebral artery.

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