Neural Substrates of Behavior: The Effects of Focal Brain Lesions upon Mental State

The clinical syndromes associated with focal brain lesions provide important insights into the biological substrates of mental function. The behavioral features and pathophysiological mechanisms of these syndromes have already become the focus of extensive monographs. The purpose of this chapter is to provide a highly selective introduction to this subject and to explore its relevance to differential diagnosis in psychiatry.

Brain Organization and Large-Scale Networks

The central nervous system is engaged in 3 major operations: (1) reception of sensory stimuli from outside and from within (input); (2) execution of motor acts (output); and (3) intermediary processing interposed between input and output. Thought, language, memory, self-awareness, and even many aspects of mood and affect constitute different manifestations of intermediary processing. The neural substrates for these intermediary processes are located principally within the limbic system and cortical association areas. From a behavioral point of view, therefore, the cerebral hemispheres can be divided into 4 major components: primary sensory cortex, primary motor cortex, association cortex, and the limbic system (Figure 6.1; Table 6.1). It is the latter 2 components, those associated with intermediary processing, that are most relevant to the substance of this chapter. Of these, the limbic component is involved predominantly in the modulation of mood, motivation, and memory, whereas the association component is involved predominantly in perceptual elaboration and motor planning.

The hypothalamus is the head ganglion of the internal milieu and the chief repository of neural programs for instincts and drives. Among the structures listed in Table 6.1, only limbic regions have substantial monosynaptic interconnections with the hypothalamus. The limbic system is therefore polarized toward the internal environment and its requirements. In contrast, the primary sensory and motor areas are polarized toward the outside world: the sensory areas provide portals for the entry of information about extrapersonal events, and the motor areas coordinate the movements through which the environment is manipulated. Hypothalamic nuclei have very few direct connections with primary sensory and motor cortical areas. This arrangement ensures that motor proficiency and perceptual accuracy are not unduly influenced by sudden shifts in the emotional state of the individual. Communications between the sensorimotor apparatus and the hypothalamus occur through obligatory relays within limbic and association cortex. The limbic and association regions therefore provide neural bridges that mediate between the inner urges of the individual and the contingencies of the extrapersonal environment (Mesulam, 1985).

Intermediary processing increases the flexibility of behavior so that drives can be satisfied according to the limitations and opportunities that exist within the extrapersonal world. Animals comparatively lower in the phylogenetic scale have relatively underdeveloped association cortex and display remarkable behavioral rigidity. In these animals specific stimuli can automatically trigger predetermined responses that are described as instinctive. For example, a turkey hen with a newly hatched brood will attack every moving object that does not utter the specific “peep” of its chicks. If a turkey hen is made deaf, it will proceed to kill its own progeny (Schleidt and Schleidt, 1960). The behavioral repertoire of higher species, especially humans, is characterized by greater flexibility. The neural substrate for much of this flexibility is provided by the interposition of limbic and association areas between stimuli and responses, between hypothalamic urges and external reality. These intermediary areas of the brain act like and gates and or gates in a programming board. Hence identical stimuli can trigger vastly different responses depending on situational context, past experience, and present needs. It is the phylo-
Figure 6.1 Brodmann’s (1914) map of the human brain. Abbreviations: AG, angular gyrus; B, Broca’s area; CC, corpus callosum; CG, cingulate gyrus; FEF, frontal eye fields; IN, insula; IPL, inferior parietal lobule; OF, orbitofrontal region; PC, prefrontal cortex; PO, parolfactory region; S, splenium; SG, supramarginal gyrus; SMA, supplementary motor area; SPL, superior parietal lobule; TP, temporopolar region; W, Wernicke’s area.
genetic development of this intermediary processing that is responsible for choice among options, flexible shifts away from unsuccessful responses, adaptation to new situations, delay of premature gratification, and even for self-awareness, thought, and play behavior. As in so many other areas of biology, however, advantages rarely come without special vulnerabilities. In this case intermediary processing could be said to bring with it the susceptibility for apprehension, doubt, rumination, and excessive inhibition. Some of these more speculative aspects of brain-behavior interactions are not yet accessible to direct analysis by the neurological approach. But the examination of patients with lesions in limbic and association areas has provided substantial insights into the neural substrates of many other behavioral and cognitive realms.

The relationships between mental function and brain structure are complex. There are no dedicated centers for memory, emotion or language. According to current thinking, cognitive and behavioral functions (domains) are coordinated by intersecting large-scale networks which contain interconnected cortical and subcortical components. The network approach to higher cortical function has at least four implications of clinical relevance: (1) a single domain such as language or memory can be disrupted by damage to any one of several areas, as long as these areas belong to the same network; (2) damage confined to a single area can give rise to multiple deficits, involving the functions of all networks that intersect in that region; (3) damage to a network component may give rise to minimal or transient deficits in the relevant domain if other parts of the network undergo compensatory reorganization; and (4) individual anatomical sites within a network display a relative (but not absolute) specialization for different behavioral aspects of the relevant function. Five anatomically defined large-scale networks are most relevant to clinical practice: a perisylvian network for language; a parieto-frontal network for spatial orientation; an occipito-temporal network for object recognition; a limbic network for memory, emotion, and motivation; and a prefrontal network for attention and comportment.

The Limbic Network

The term limbic system is used to designate a heterogeneous set of structures in the brain stem, diencephalon, striatum, basal forebrain, and cortex (Table 6.1; Figures 6.1 and 6.2). Four major reasons can be identified for lumping these structures into a single network: (1) The components that make up the limbic system are tightly interconnected through monosynaptic pathways (Figure 6.2). In the 1930s Papez pointed out that the relatively few

Table 6.1 Some behavioral subdivisions of the cerebral cortex

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<tr>
<th>Primary sensory cortex</th>
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<tr>
<td>Visual (area 17 in Figure 6.1)</td>
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<td>Auditory (areas 41, 42)</td>
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<td>Somatosensory (areas 3, 1, 2, but mostly area 3b)</td>
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<th>Primary motor cortex</th>
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<td>Area 4 and caudal part of area 6</td>
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<th>Association cortex</th>
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<tr>
<td>Unimodal motor (rostral area 6, caudal area 8, area 44)</td>
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<tr>
<td>Unimodal visual (areas 18, 19, 20, 21, 37)</td>
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<td>Unimodal auditory (area 22)</td>
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<td>Unimodal somatosensory (area 5, rostral area 7)</td>
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<td>Heteromodal prefrontal (areas 9, 10, 11, 45, 46, 47, rostral area 8, rostral area 12, rostral area 32)</td>
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<td>Heteromodal parietotemporal (areas 39, 40, caudal area 7, banks of superior temporal sulcus, area 36)</td>
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<th>Limbic system (cortical and subcortical components)</th>
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<td>Paralimbic cortex (insula; temporopolar cortex—area 38; caudal orbitofrontal cortex—caudal areas 12, 13; cingulate complex—areas 23, 24, 33, 31, 26, 29; parolfactory region—area 25, caudal area 32; parahippocampal cortex—areas 28, 34, 35, 30)</td>
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<td>Core limbic formations (hippocampus, amygdala, substantia innominata, septal nuclei, piriform olfactory cortex)</td>
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<td>Limbic basal ganglia and related structures (nucleus accumbens, medial globus pallidus, ventral tegmental area of Tsai, habenula)</td>
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<td>Limbic thalamus (midline nuclei, anterior tubercle nuclei, laterodorsal nucleus, dorsomedial nucleus, medial pulvinar nucleus)</td>
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<td>Hypothalamic nuclei</td>
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connections then known formed a mammillo-thalamo-cingulo-hippocampo-mammillary loop. This circuit now bears his name. Many additional neural connections have been described since then, and it is important to realize that the Papez circuit is only one of many possible limbic loops. (2) Components of the limbic system may contain common immunological properties. For example, the herpes simplex virus has a preferential affinity for the cortical components of the limbic system. Conceivably this virus recognizes a common antigenic site shared by limbic cortical areas. (3) Limbic regions display common pharmacological properties. For example, cholinergic, dopaminergic, and opioid innervations are particularly intense within limbic structures. Furthermore, procaine, lidocaine, and cocaine have an activating effect that is selectively targeted to the limbic and paralimbic parts of the cerebral cortex (Mesulam, 1987b; Ketter et al., 1996). (4) Components of the limbic system have common behavioral affiliations. Thus even substantial limbic lesions can leave most sensory and motor functions intact while profoundly impairing behaviors related to memory and emotion. The limbic network can be divided into amygdaloid and hippocampal spheres of influence (see Figure 6.2). The hippocampus and its connections are more closely affiliated with memory function, whereas the amygdala and its pathways are more closely affiliated with emotion and motivation.

**Emotion and Limbic Epilepsy**

The limbic system provides a crucial anatomical substrate for the coordination of emotion and motivation. Depth electrodes in patients who are being investigated for the surgical treatment of intractable epilepsy, for example, show that strong emotional experiences are associated much more commonly with discharges from limbic structures (especially the amygdala) than with discharges from the nonlimbic components of the temporal lobe (Gloor et al., 1982). Moreover, sensory stimuli that do not initially activate the amygdala or hypothalamus do so when they are associated with an emotionally relevant stimulus (LeDoux et al., 1983).

Each component of the limbic system participates in neural events related to mood and emotion. The hypothalamus seems to act as a neural repository for triggering skeleto-motor and autonomic patterns associated with specific emotions. The amygdala and the paralimbic regions with which it is interconnected (see Figure 5.2) appear to play a crucial role in the channeling of emotion to the proper object and mental content. Downer (1962) showed that complex visual stimuli triggered appropriate emotional responses in rhesus monkeys only if the visual information had access to an intact amygdala. This finding helps in understanding the neural basis of the Kluver-Bucy syndrome, wherein bilateral damage to the amygdala and surrounding temporopolar cortex in monkeys results in 3 dramatic behavioral changes: incessant and inappropriate mouthing of inedible objects, attempts to copulate with unlikely sexual objects, and an uncharacteristic friendliness to human beings. Although the drives that are being expressed in this syndrome are part of the physiological behavioral repertoire, they are no longer directed to the proper extrapersonal target, reflecting the presence of a sensory-limbic disconnection (Geschwind, 1965). Some components of the Kluver-Bucy syndrome can be seen in patients who develop bilateral degeneration of the temporal pole in the course of Pick's disease or herpes simplex encephalitis.

**Temporolimbic epilepsy.** The limbic components of the temporal lobe (amygdala, hippocampus, parahippocampal gyrus, temporal pole) and the paralimbic cortices of the insula, frontal lobe, and cingulate gyrus have a low seizure threshold and frequently become the source of epileptic activity. Such seizures may be associated with characteristic automatisms such as staring, lip smacking, head turning, forced walking, running (epilepsia cursiva), and epigastric sensations. These symptoms readily raise the suspicion of temporolimbic epilepsy, especially when ac-
compounded by olfactory or gustatory hallucinations. In other patients these characteristic features may be absent, and the manifestations of temporolimbic epilepsy may be confined to behavioral and psychiatric symptoms. Some of these symptoms are brief and related mostly to ictal epileptic discharges; others are more prolonged and tend to occur during the interictal state.

Ictal manifestations include déjà vu, jamais vu, feelings of unreality, depersonalization, fear, panic attacks (with or without associated autonomic discharges), elation, erotic sensations, depression, and forced thoughts that may take obsessive-compulsive proportions. These are designated as the experiential phenomena of temporolimbic epilepsy. The sudden, transient, unprovoked, repetitive, and stereotyped nature of the symptomatology provides a clue to the underlying epileptic etiology.

It is relatively easy to understand how transient epileptic discharges in the brain can be associated with transient (ictal) experiential phenomena. It is more difficult to understand the relationship of temporolimbic epilepsy to long-term behavioral changes. Some of these changes take the form of altered personality traits, whereas others may resemble conventional psychiatric syndromes. Anecdotal observations, as well as quantitative studies, have hypothesized the existence of a relatively characteristic cluster of behavioral traits in these patients. Some patients with temporolimbic epilepsy are said to act as if the entire world were saturated with intense emotional significance. These patients may lack a sense of humor, become overly serious and brooding, develop excessive philosophical interests, an obsessive hyperreligiosity, a curious tendency to write excessively, and a low threshold for moral outrage and aggressive outbursts. Many show difficulty in getting to the point during conversation, become lost in inextricable detail, and display a characteristic circumstantiality of thought patterns. Patients may manifest wide mood swings, unpredictable explosive behaviors in response to minor provocations, and diverse alterations of sexual practice. The circumstantiality, obsessive rumination, humorlessness, and intense emotionality lead to a rather striking style of interpersonal interaction that has been described as “interpersonal viscosity.”

There is a good deal of debate whether these traits are peculiar to temporolimbic epilepsy and whether they constitute a specific interictal behavioral syndrome. Hypergraphia is the one component of this hypothetical interictal syndrome that appears to have the most specific association to temporolimbic epilepsy (Spiers et al., 1985). Not all patients with temporolimbic epilepsy have this cluster of behavioral traits. Conversely, not all patients with these traits turn out to have temporolimbic epilepsy. But when these behaviors are marked (especially the tetrads of viscosity, hyperreligiosity, hyposexuality, and hypergraphia), the clinician should have a higher index of suspicion for the presence of temporolimbic epilepsy. It is important to understand that this description refers to truly extraordinary deviations from normal behavior. Some of these patients will have multiple religious conversions from one faith to another. Others may maintain detailed diaries and compose exceedingly long letters (that they may never mail) for the sheer pleasure of writing. A patient who developed temporolimbic epilepsy in middle age and had no prior literary tendencies explained that the urge to express her thoughts and feelings in writing was so intense that she would sit with a pencil in her hand in front of a pad to make sure that nothing worth writing down would be missed. Another patient decided to copy Webster’s dictionary page by page in longhand.

A great deal has been written about violence and limbic epilepsy (Pincus, 1981; Hood, Siegfied, and Wieser, 1983). In animals, amygdaloid damage seems to have an overall taming effect, whereas amygdaloid stimulation may trigger unprovoked aggressive attacks. These observations have led to the suggestion that some abnormally violent individuals (e.g., those with the episodic dyscontrol syndrome) may have amygdaloid overactivity, perhaps in the form of covert seizures, and that they may benefit from the surgical ablation of the amygdala when other therapeutic modalities prove ineffective (Mark and Ervin, 1970). This association between violence and temporolimbic epilepsy has to be interpreted in light of clinical experience which shows that excessive aggression occurs only in a very small minority of patients with temporolimbic epilepsy. In some of the epileptic patients who do become violent, dramatic and murderous acts of violence can be committed during fugues and related dissociative episodes. Others display sudden and unprovoked episodes of violence, occasionally associated with surprising feats of strength. The associated acts of violence usually occur without premeditation, but this is not a general rule. Amnesia for the episode may not be a consistent feature. In contrast to psychopathic conditions where the patient may experience little guilt, patients who are aggressive in conjunction with temporolimbic epilepsy tend to be very remorseful. In addition to ictal aggressive outbursts, which are probably quite rare, temporolimbic epilepsy is also associated with personality traits that increase the likelihood of explosive behaviors. In between the infrequent explosive outbursts, the patient with temporolimbic epilepsy has no difficulty controlling aggressive outbursts. The only limbic lesions which trig-
ger uncontrolled and consistent attack and biting behaviors in humans are those associated with a direct involvement of the hypothalamus (Reeves and Plum, 1969).

Temporalolimbic epilepsy has also been described in conjunction with more conventional psychiatric syndromes such as schizophrenia, psychosis, affective disorders, multiple personality, conversion reactions, and obsessive-compulsive disorders. The strongest association is with schizophreniform conditions and depression. The frequency of such disturbances is much higher among temporalolimbic epileptics than in the general population (Slater and Beard, 1963; Mendez, Cummings, and Benson, 1986). In contrast to idiopathic schizophrenia, patients with the schizophreniform reaction of temporalolimbic epilepsy generally lack a family history of psychosis, rarely show temporal deterioration, tend to maintain adequate interpersonal contact, and do not show flattening of affect. But these patients do have hallucinations, delusions, and distinctly idiosyncratic paranoid ideation. There is some evidence indicating that left-handed women who develop temporalolimbic epilepsy on the basis of cystic or hamartomatous lesions in the left hemisphere are the most prone to develop schizophreniform reactions (Taylor, 1975). In clinical practice, it is prudent to consider the possibility of temporalolimbic epilepsy in patients with schizophreniform states, affective disorders, multiple personality, and especially panic attacks.

Women with the psychiatric manifestations of temporalolimbic epilepsy usually show a characteristic exacerbation of epileptic discharges and behavioral symptoms in synchrony with the menstrual cycle. Sometimes this catamensial effect is very much exaggerated and can assist in raising the suspicion of underlying temporalolimbic epilepsy. The amygdala, which is very frequently the site of abnormal epileptic discharges, is monosynthetically interconnected with the hypothalamus. Patients with temporalolimbic epilepsy may therefore develop abnormalities in the hypothalamomotor regulation of endocrine function, leading to infertility, testicular atrophy, decreased sperm motility, endometriosis, cystic mastitis, and other manifestations of polycystic ovarian disease (Herzog et al., 1986). Sometimes these endocrinological abnormalities improve on antiepileptic medication. The characteristic hyposexuality and some of the other behavioral manifestations in patients with temporalolimbic epilepsy may be influenced by these endocrinological consequences of temporalolimbic epilepsy.

The cerebral abnormality caused by temporalolimbic epilepsy is not confined either to the site of the primary focus or to the period of ictal discharges. Ictal activity originating at one limbic structure very frequently spreads to other components of the limbic system. Evidence obtained with positron emission tomography shows that the epileptic focus is in an abnormal hypometabolic state even during interictal states (Kuhl et al., 1980). Patients with temporalolimbic epilepsy therefore have a baseline limbic dysfunction accentuated by ictal discharges that invade the entire limbic system. In view of the pivotal role that the limbic system plays in channeling emotion, these disturbances could lead to a distorted and inappropriate mapping of feelings onto thought and experience (Mesulam, 1981). The resultant chaos and the patient's attempts at reintroducing internal coherence into the fabric of mental life may collectively lead to the associated psychiatric symptomatology. In some of the patients, temporalolimbic epilepsy leads to an intensification of affective coloring (e.g., "limbic hyperconnectivity") that can promote behavioral traits such as hyperreligiosity and hypergraphia (Bear, 1979). In others, the incongruity of affective mapping may lead to schizophreniform and dissociative states.

Epileptic discharges can result from many different causes that alter the electrical stability of the neuron. In most cases the triggers for specific seizure events remain unknown. In a small number of patients, however, epileptic discharges are triggered by identifiable experiences. This condition is known as reflex epilepsy. In some patients the trigger may be a certain color or a certain visual pattern. In others it is extremely specific, such as a certain piece of music or the chiming of a particular church bell. When such complex triggers exist, the focus of the epilepsy is commonly located within the temporal lobe. Sometimes the reflex epilepsy leads to intense experiential phenomena. For example, in a now famous case, the sight of a safety pin induced epileptic discharges that were associated with intensely pleasurable erotic feelings (Mitchell, Falconer, and Hill, 1954). In time, looking at or thinking about the safety pin became a major source of sexual gratification for the patient, suggesting that reflex epilepsy could conceivably become an etiological factor in fetishism. Another example is provided by a patient who complained of abrupt and unprovoked mood fluctuations. She reported feeling intensely depressed and tearful when listening to a certain piece of dance music. The music did not sound particularly moody to other observers, and was not associated with any particularly sad event in her life. When the music was played in the electrophysiological laboratory, it triggered spike discharges in the electroencephalogram (EEG), depression, and crying. There were no other sensory, motor, or autonomic manifestations of epilepsy. In a minority of patients, the reflex epilepsy leads to a feeling of elation. Such patients may seek the triggering event and work to induce seizures...
(Ames and Safer, 1983; Faucht et al., 1986). In other patients the reflex epilepsy can be triggered by cognitive activities, such as reading, doodling, or mental arithmetic (Anderson and Wallis, 1986).

**Diagnosis and management of temporolimbic epilepsy.** The seizure focus in temporolimbic epilepsy is located in the basal and medial parts of the brain and may therefore elude detection by routine surface EEGs. A thorough workup should include activation procedures such as the induction of sleep. Obtaining the tracing during periods of particularly intense symptomatology is also useful. Negative EEGs do not rule out temporolimbic epilepsy; it is possible that the patient was studied at a time when spiking activity was absent or that the placement of the electrodes was not optimal. It is also important to keep in mind that behavioral manifestations that appear to be interictal by surface recording may turn out to be ictal if invasive procedures for depth recording are used.

When psychiatric disorders occur in a patient with temporolimbic epilepsy, the clinician should consider two possible types of relationships. One possibility is that the two conditions are causally related, in which case the treatment of the epilepsy should have a beneficial effect on the psychiatric state. Alternatively, the epilepsy and the psychiatric symptoms may each constitute independent manifestations of an underlying limbic disease, in which case the treatment of the epilepsy should have little impact on the psychiatric state. In some patients who manifest some of the symptomatology described above, neurodiagnostic tests occasionally reveal the presence of non-epileptic temporolimbic abnormalities such as a cyst in the medial temporal lobe or a focal temporal slowing of the EEG. The term *temporolimbic dysfunction* (TLD) can be used to designate this condition and to set it apart from temporolimbic epilepsy (TLE).

I have seen patients with temporolimbic epilepsy in whom antiepileptic medication has helped to alleviate depression, panic attacks, hallucinations, memory disturbances, and circumstantiality. Such medication is usually less helpful for the schizophreniform and dissociative conditions. In general, patients with the conjunction of temporolimbic epilepsy and psychiatric symptomatology need an integrated program of treatment that includes antiepileptic management, psychotherapy, and psychoactive medication. Group therapy for patients with temporolimbic epilepsy may be particularly effective for sharing highly unusual experiences and dispelling the sense of uniqueness. The physician who manages such patients usually finds himself in the midst of a most challenging mind-body dilemma. When dealing with disturbing symptomatology the patient may frequently ask, “Is this me or is this a seizure?” The answer to this very difficult question needs to be individualized for each patient.

**Limbic Control of Autonomic and Endocrine Function**

Emotional states are associated with specific patterns of autonomic responses. It is therefore not surprising that limbic regions should also participate in the regulation of autonomic tone. The amygdala and hypothalamus have a powerful influence on autonomic function, reflecting the direct connections they have with autonomic nuclei in the brain stem. Electrical stimulation in the cortical components of the limbic system (for example, anterior insula, caudal orbitofrontal cortex, temporal pole, cingulate gyrus) also results in marked and consistent autonomic responses. Insular stimulation tends to produce gastrointestinal responses, whereas stimulation of the other cortical components leads to cardiovascular and respiratory changes. Some of these responses are quite dramatic and may include inhibition of gastric peristalsis, respiratory arrest, and blood pressure changes of as much as 100 mm of mercury. Even multifocal cardiac necrosis can be obtained when monkeys with no intrinsic cardiovascular disease receive electrical stimulation into the caudal orbitofrontal cortex (Hall and Cornish, 1977).

The importance of interactions between mental state and autonomic activation patterns is well known in medical practice. Mental stress can increase blood pressure, promote the formation of ulcers, lead to abnormal esophageal motility, and even induce cardiac arrhythmias in the absence of cardiovascular predisposing factors. Individual emotions, and even different cognitive states, may be associated with relatively specific patterns of autonomic activation. Conceivably the influence of mental state upon autonomic activation in both normal and abnormal conditions is coordinated principally by cortical components of the limbic network. Future research may well determine that these parts of the brain provide a potential anatomical substrate for psychosomatic disease, essential hypertension, and certain types of heart disease. These are some of the considerations that have led to the alternative designation of the limbic system as “the visceral brain” (MacLean, 1949).

**Memory and Amnesia**

Memory permeates all aspects of mental life. Common sense may therefore lead to the expectation that this faculty should have a large safety margin and that it should be impaired only by the largest of brain lesions. The facts, however, lead to a different conclusion: neurological dis-
eases frequently lead to severe memory deficits, and the responsible lesions can be quite small, as long as they are located within the confines of the limbic system.

The amnestic syndrome. This is the most severe form of memory disturbance and displays the following characteristics: (1) There is a retrograde amnesia for information acquired before the onset of the illness. The retrograde amnesia obeys a temporal gradient, also known as Ribot's law, so that memories acquired just before the onset of the amnesia are less accessible than more remote ones. This probably reflects the fact that more remote information is highly overlearned and more extensively incorporated into the contents of consciousness. Thus patients with the amnestic form of senile dementia have relatively little difficulty remembering intimate details of distant events at a time when they cannot recall more recent events. The fact that amnesic patients almost never forget their own names or birthplaces is also consistent with Ribot's law. (2) The patient has severe anterograde amnesia, which interferes with the conscious (e.g., declarative or explicit) recall of new experience. Patients may not recall what they had to eat a few minutes ago or who visited them the day before. Disorientation to time and also to persons and places new to the patient arises as a consequence of this anterograde amnesia. Patients with the amnestic syndrome are extremely vulnerable to interference. They can retain information for many minutes if undisturbed, but even the briefest distraction leads to the loss of the pertinent memory traces. (3) One of the most colorful consequences of the amnesia is confabulation. If the examiner asks, "Do you know who I am?" the patient may provide a confabulatory response such as: "Of course I know you. Weren’t you the salesmen who sold me a car?" This confabulation (a false-positive retrieval response) may occur because the patient is not fully aware of his memory problem and also because he lacks the mechanisms for critically evaluating whether a retrieved item fits the present context and his past experience. Confabulation is not a necessary feature and is present mostly during the acute states of the amnestic syndrome. (4) The patient is alert, attentive, and motivated. In contrast to devastated explicit memory function, other cognitive faculties such as language and visuospatial skills are quite intact. In fact, severely amnestic patients may obtain superior scores in IQ tests.

The patient with an amnestic syndrome is usually unaware of current news, cannot learn the route to a new destination, loses personal items within the house, may leave the stove on, and may pay the same bill several times or not at all. The acute amnestic syndrome is not compatible with independent existence and frequently leads to institutionalization. Although the ability to give an explicit verbal account of newly acquired experience is always severely impaired in the amnestic syndrome, implicit memory, as assessed by the acquisition of new motor skills, autonomic conditioning, and perceptual priming, can be preserved. In this context, implicit learning refers to diverse settings where prior exposure to a task or stimulus influences future responses even when the subject is unable to recall explicitly the prior exposure. On a motor coordination task such as mirror drawing, for example, an amnestic patient may show a learning curve indistinguishable from that of normal subjects. At the beginning of each daily training session, however, the same patient may deny knowledge of any prior exposure to the task (Milner, Corkin, and Teuber, 1968).

Components of emotionally relevant experiences may also be retained, though not necessarily at the level of explicit knowledge. For example, patients who have a condition known as prosopagnosia (inability to recognize faces by sight) emit an autonomic response indicative of physiological arousal when shown the face of a familiar person, even though they give no verbal indication of having recognized that individual (Bauer, 1984; Tranel and Damasio, 1985). A similar conclusion emerges from a clinical anecdote reported by Claparède (Claparède, 1911). He was taking care of an amnesic patient who showed no signs of recognizing him despite his daily visits. Apparently annoyed at this ingratitude, Claparède concealed a thumbtack in his hand and gave the patient a powerful pinprick during his customary daily handshake. The next morning the patient still denied recognizing the doctor, but was most reluctant to shake his hand. Clearly the painful consequence of the handshake had been stored in some implicit form and influenced subsequent behavior, although no verbalizable conscious knowledge was associated with the event. The phenomenon of implicit memory may provide useful models for exploring the biological foundations of unconscious mental processes.

When the amnestic syndrome occurs in isolation, it is always associated with a focal destructive lesion in the limbic system. Many neurological diseases can give rise to an amnestic state. These include tumors (of the sphenoid wing, posterior corpus callosum, thalamus, or medial temporal lobe), infarctions (in the territories of the anterior or posterior cerebral arteries), head trauma, herpes simplex encephalitis, Wernicke-Korsakoff encephalopathy, paraneoplastic limbic encephalitis, and degenerative dementias such as Alzheimer's or Pick's disease. The one common denominator of all these diseases is that
they lead to bilateral lesions in one or more components in the limbic network. Occasionally left-sided unilateral damage to the limbic network may give rise to an amnestic state, but this is usually transient. Not all the limbic structures shown in Figure 5.2 have to be involved to produce an amnesia. For example, bilateral infarctions confined to the limbic thalamus, bilateral anterior temporal lobectomy, bilateral damage to the septum or basal forebrain, and bilateral medialiencephalic lesions (as in the Wernicke-Korsakoff syndrome) have each been associated with amnestic states (Signoret, 1985). Although the site of damage does influence the clinical details of the amnesia, the major aspects of the amnestic state listed above are present in most of these patients. In general, bilateral damage to structures in the Papez circuit tend to yield the most severe amnestic states. Damage confined to the amygdala may selectively interfere with the facilitatory effect of emotional arousal upon recall without giving rise to a full-fledged amnestic state (Cahill et al., 1995).

Although the limbic network is the site of damage for amnestic states, it is almost certainly not the storage site for memories or motor skills. The sensory data related to experienced events constitute the essential building blocks of memory and are stored in widely distributed form throughout association cortex. The role attributed to the limbic network is to bind these distributed fragments into events and experiences that have the level of coherence necessary for conscious recall. Damage to the limbic network does not necessarily destroy memories but interferes with their conscious (declarative) recall in coherent form. The individual fragments of information remain preserved in sensory association cortex and sustain implicit memory (Mesulam, 1994).

Partial amnesias. The full-fledged amnestic syndrome is global and influences the declarative recall of all aspects of experience, in all sensory modalities. Occasionally, when the limbic damage is unilateral, material- or modality-specific amnesias arise. Right-sided lesions may selectively impair memory for complex perceptual patterns, whereas lesions confined to left-sided structures may preferentially impair memory for words. Left hemisphere lesions result in amnesias for verbal material that are usually more severe than the amnesias for nonverbal material that result from lesions in the right hemisphere (Signoret, 1985). This may indicate a left hemisphere dominance for memory or the fact that even nonverbal items may be memorized through some verbal mediation. The binding function attributed to the limbic system necessitates the integrity of sensory-limbic interconnections. Lesions in the temporal lobe can disrupt visuo-limbic, auditory-limbic or somatosensory-limbic interactions and can lead to partial amnesias confined to the relevant sensory modality (Ross, 1980). A visuo-limbic disconnection, for example, may disrupt the ability to learn new visual associations without interfering with the learning of information acquired through other modalities of input.

Transient global amnesia. This dramatic syndrome is usually seen in middle-aged individuals, especially after a period of physical stress (sexual activity, a dip in cold water, exercise, and so on). The onset of the memory loss is quite sudden. A component of retrograde amnesia occurs and can encompass a period ranging from a few hours to several years preceding the onset of the illness. During the ictus the patient manifests severe anterograde amnesia similar to the one described for the amnestic state. Total disorientation is the rule, and the patient may even forget biographical information. In contrast to the amnestic syndrome, there is usually considerable anxiety and even agitation. The patient continually asks what is happening to him, what he is doing here, and who the other person is. The episode may last from 12 to 72 hours and sometimes even longer. Following recovery, the patient usually cannot recall events that occurred during the ictus. Vascular insufficiency in the territory of the posterior cerebral artery, migraine, temporolimbic epilepsy, and even brain tumor have been associated as etiological factors for this syndrome, but it is also fairly common to find no obvious cause in some patients. In most instances there is a single episode without recurrence. However, transient global amnesia could also be the harbinger of a stroke in the posterior cerebral circulation. Transient global amnesia can be misinterpreted as having psychogenic causes.

Epileptic and narcoleptic memory disturbances. Temporolimbic epilepsy may result in powerful feelings of déjà vu (illusion of familiarity) or jamais vu (illusion of unfamiliarity). Prolonged episodes of jamais vu could give rise to states during which the patient denies being acquainted with familiar persons, places, and facts. This condition may give the impression of an amnestic state. When these patients are questioned, however, they will readily distinguish the feeling of unfamiliarity from a true loss of the relevant factual memory.

Temporolimbic epilepsy can also lead to dissociative fugue states. The patient may lose memory for past information, including biographical data and identity. During the fugue state—which can last from minutes to hours and in unusual circumstances even days—the patient may engage in complex acts ranging from routine to criminal.
External appearance may be quite unremarkable. Occasionally behavior seems automatic, driven, and inflexible. Despite the marked retrograde amnesia, the patient may show little if any anterograde amnesia, so that new information can be acquired during the ictus. Following the episode, the patient may not retain any knowledge of events that occurred during the fugue state. Some patients with frequent fugues complain that they "lose time." Similar, but usually briefer, fugue states can also be seen in narcolepsy.

Many patients with temporolimbic epilepsy complain of memory difficulties. Neuropsychological testing frequently reveals abnormal memory function, but the deficits are usually material-specific and rarely severe. In a few patients, temporolimbic epilepsy can lead to severe amnestic conditions, occasionally with unusual clinical features. Some of these patients may show an abnormal acceleration of forgetting. Anterograde memory may appear unremarkable when retention is tested within relatively short intervals of minutes to hours, but the patient may not be able to retain information related to experiences that happened a few days ago (Ahern et al., 1994). Some other patients show multiple "islands" of amnesia for isolated significant events in the past. These unusual amnesias may reflect an impairment of memory consolidation.

Depression, aging, and memory function. Depressed patients frequently complain of memory failure. In some individuals this is part of the self-deprecation characteristic of depression, and objective testing fails to reveal memory difficulties. In others, the syndrome of endogenous depression may contain a bona fide component of memory loss. The deficit is neither as severe nor as generalized as the one in the amnestic syndrome. In contrast to the patient with the fully developed amnestic syndrome, those who suffer memory loss in conjunction with depression are very much concerned about this deficit. Testing may reveal that the memory loss is due mainly to ineffective registration and retrieval (Weingartner et al., 1981). If additional drilling is allowed at the stage of registration or if cues are provided during recall, the deficit is usually overcome. In sharp contrast to the amnestic state, where confabulation may be a central feature, patients who have the memory loss of depression tend to give false negative responses in the form of "I don't know." When the patient is coaxed to provide an answer, the memory loss turns out to be less severe than reported. The memory loss of endogenous depression appears to be particularly marked in the aged individual. Young patients with depression usually do not have significant cognitive deficits.

Many modalities of treatment for depression (electroconvulsive therapy, lithium salts, antidepressants with anticholinergic effects) can also lead to memory impairment. In managing a depressed patient who complains of faulty memory, one must decide whether the symptom is associated with the underlying disease or with its treatment. Treatment of the depression or withdrawal of the offending medication is often associated with an improvement of memory function in some of these patients.

Aging itself may lead to a decrease in memory capacity, but this deficit is usually mild and rarely interferes with age-appropriate daily living activities. This type of memory disturbance has been called benign senescent forgetfulness to set it apart from the more rapidly progressive and malignant amnesia of dementia (Kral, 1962). The benign forgetfulness of aging impedes mostly the ability to remember names and dates rather than events. As most of the difficulty appears to be at the stage of retrieval, peripheral cues in the forms of written reminders and date books can be very helpful. Although no fixed structural brain lesion has been associated with the memory disturbances of depression and aging, impairments of cholinergic transmission (in aging) and norepinephrine innervation (in depression) could play a role in these conditions.

Psychogenic amnesias. Many disparate states have been included under the rubric of psychogenic amnesia. Some individuals tend to retain little if any conscious recollection of unpleasant or traumatic events. The process of repression is invoked to explain this phenomenon. The resultant memory discontinuity can sometimes be eliminated by hypnosis, sodium amytal injections, or during psychotherapy. These patients have isolated lacunae in memory but no other manifestations of amnesia. In contrast to patients with fugue states, the memory gaps are for specific events rather than for time periods. In patients with the condition of multiple personality, some of the personalities may be amnesic for the experience of the others.

The malingerer has a vested interest in failing to recall a certain event. Some malingering may take the form of "theatrical (or Hollywood) amnesia," whereby a person is suddenly found to have lost all prior memory, including who he is (Sigmore, 1985). The person gives no evidence of ongoing anterograde amnesia, however, and can acquire new information quite normally. This condition needs to be distinguished from fugue states, which usually last for short periods and rarely if ever for days on end. The loss of information about personal identity is an important differentiating feature because patients with organic amnesias (with the possible exception of fugue
states and the late stages of dementia), ordinarily do not forget their own names, birthplaces, or birthdates.

**Distorted memory.** Reduplicative paramnesia and the Capgras syndrome are closely allied conditions of distorted memory (Alexander, Stuss, and Benson, 1979). *Reduplicative paramnesia* (a term coined by Arnold Pick) refers to the delusional belief that a place (usually new to the patient) is actually situated in a different and usually more familiar geographic site. For example, a resident of Providence hospitalized at the Beth Israel Hospital in Boston may insist that he is at the Providence Beth Israel Hospital. When confronted with the information that the sign at the entrance indicates that this is the Boston Beth Israel Hospital and that Providence does not have a Beth Israel Hospital, or when shown evidence that his present surroundings exactly match those of Boston, the patient may express wonderment but remain unshaken in his conviction. He may suggest that there could be an exact duplicate or branch of the Boston Beth Israel Hospital situated in Providence, perhaps built just recently. Sometimes the patient may wonder why anybody would go to such lengths as to reproduce the Boston skyline in Providence. Although the patient is capable of comprehending the implausibility of such circumstances, logical arguments usually have little if any effect in altering this belief. Sometimes the patient confesses that he “knows” this to be impossible but that it nonetheless “feels” true. Patients with reduplicative paramnesia usually have no additional thought disturbances, delusions, or hallucinations. Temporal disorientation may be present, but patients with this syndrome do not usually have other features of an anterograde amnesia. They can retain new information, which makes their persistence in this delusional mislocation of their environment even more puzzling.

The *Capgras syndrome* refers to the strongly held delusional belief that others (usually family members) and sometimes even the self have been replaced by doubles or impostors. Often the patient believes that an underlying plot is motivating the impostors. At other times no paranoid features are present. In one clinical case that was reported, a patient insisted that his wife and 5 children had been replaced by doubles. He assumed that his original wife had deserted him, and he was very thankful that she had been thoughtful enough to find a replacement (Alexander, Stuss, and Benson, 1979). It has been pointed out that the Capgras syndrome is not based on a perceptual problem, since the patient will clearly state that the putative impostor looks “exactly like” the original person. Therefore, as in reduplicative paramnesia, the problem is mostly one of distorted belief associated with the process of recognition (Benson, 1983).

In neurological practice the most common setting for reduplicative paramnesia and the Capgras syndrome occurs in patients with relatively severe head trauma who initially develop an amnestic syndrome (indicative of limbic involvement) but who subsequently recover most memory functions. These patients will usually also have bifrontal damage that is almost always more severe in the right side. In normal waking life, the sensory impressions related to familiar persons and places do change from time to time. The intact brain tends to assume continuity and to use this new information to update and expand the relevant associations. In patients who recover from an amnestic state and who also have bifrontal lesions, the mechanisms for updating knowledge and for critically assessing contextual plausibility seem to be disrupted, leading to the dramatic occurrences of the Capgras syndrome and reduplicative paramnesia. In clinical practice these conditions must be distinguished from experiences of *jâmais vu*, which can lead to transient feelings of unfamiliarity associated with places and persons.

**The biological vulnerability to memory distortion.** The dramatic manifestations of reduplicative paramnesia, the Capgras syndrome, epileptic fugue, *jâmais vu*, and *jâmais vu* help to show that memory is not an all-or-none phenomenon and that it is vulnerable to various forms of distortion. This vulnerability has recently attracted a great deal of attention in relation to hypnotic suggestibility, the effect of emotional trauma on the accuracy of recall, and the reliability of eyewitness accounts (Schacter et al., 1995). A review of pertinent physiological studies suggests that each neuron is likely to participate in the storage of hundreds of thousands of memories. In turn, the storage of a new experience is likely to represent a distributed process involving hundreds of thousand of neurons, each of which already contains information related to components of past experience. Consequently, past memories are likely to influence the way in which new experience is stored at the same time that they are being modified by the new experience.

The distributed mode of memory storage enables the same experience to be recalled in many different combinatorial forms and through many different associative approaches. Although this organization enriches the process of recall, it also makes it vulnerable to distortion. Memory is both fragile and resilient. Traces of consciously experienced events may never completely disappear from memory, but they are rarely, if ever, reproduced with complete fidelity. All acts of recall are also acts of imagination and reinterpretation. The tendency for distortion is a byproduct of this complex organization. The ultimate goal of memory is not to maximize the accuracy of recall but to
optimize its value for adaptive survival. It can even be argued that a superior talent for accurate factual recall could constitute a sign of brain disease. In some types of autism, for example, otherwise mentally retarded individuals, also known as idiots savants, are capable of remarkable feats of accurate recall. These individuals cannot reorganize facts creatively, and their phenomenal memory ability is of little benefit (and often an impediment) in the pursuit of life achievements.

Although memories are naturally prone to distortion and reinterpretation, adaptive conduct requires that the resultant re-creations remain within the boundaries of the reality principle. The limbic system helps to bind fragments of information into coherent experiences, whereas the frontal lobes play an important role in determining boundaries of contextual plausibility. Under severe emotional stress or after damage to fronto-limbic structures, this boundary is crossed and the re-creation of reality takes the form of implausible confabulations. The frontal lobes tend to mature relatively late, and this may explain why children are particularly prone to confabulation.

The foregoing discussion suggests that the neural substrate of memory can be conceptualized as containing three interacting components. The limbic system provides the basic machinery for encoding, retrieval, and binding; sensory association cortex contains the factual building blocks of experience; high order association cortex, including prefrontal cortex, introduces contextual boundaries for constraining the creativity with which the past is reconstructed. Considering all this complexity, what is surprising is not that we occasionally forget a fact or a face, but that we can remember at all (Mesulam, 1995b).

Language and Aphasial

The ultimate product of mental activity is thought. Language is one of the most important vehicles through which thought is encoded, modeled, and transmitted. I once read an evocative description comparing thought to an April cloud that sheds a shower of words. Although the biological study of thought is in its mere infancy, great strides have been made in the study of words and language, especially through the examination of brain lesions that give rise to aphasias (Benson, 1985; Mesulam, 1990; Damasio, 1992). The neural substrate of language takes the form of a distributed network centered in the perisylvian region of the left hemisphere. The posterior pole of this network is known as Wernicke’s area and includes the posterior third of the superior temporal gyrus and a surrounding rim of the inferior parietal lobule. An essential function of Wernicke’s area is to transform sensory inputs into their neural word representations so that these can enter the distributed associations that lead to meaning. The anterior pole of the language network, known as Broca’s area, includes the posterior part of the inferior frontal gyrus and a surrounding rim of prefrontal heteromodal cortex. An essential function of this area is to transform neural word representations into their articulatory sequences so that the words can be uttered in the form of spoken language. The sequencing function of Broca’s area also appears to involve the ordering of words into sentences so that the resulting statement has a meaning-appropriate syntax (grammar). Wernicke’s and Broca’s areas are interconnected with each other and with additional perisylvian, temporal, prefrontal, and posterior parietal regions, making up a large-scale distributed network subserving the various aspects of language function. Damage to any one of these components or to their interconnections can give rise to language disturbances (aphasia). Aphasia should be diagnosed only when there are deficits in the formal aspects of language such as naming, word choice, comprehension, spelling, or syntax. Dysarthria and mutism do not, by themselves, lead to a diagnosis of aphasia.

In almost all dextrals and in about 60% of sinistrals, the left hemisphere is dominant for language. In these individuals damage to the left hemisphere yields severe and occasionally permanent aphasias, whereas even large right hemisphere lesions have no such effect. Some individuals display a pattern of mixed dominance, so that damage to either hemisphere may give rise to aphasias. Very few individuals have a clear-cut right hemispheric dominance for language functions. Because 80–90% of all individuals are right-handed, the cerebral hemisphere that is dominant for complex movements is often (but not always) also dominant for language. This hemispheric asymmetry for handedness and language functions is one of the most fundamental biological facts about the human brain. There is at least one anatomical basis for this behavioral asymmetry: the posterior language area in the left hemisphere is anatomically larger than the equivalent region in the right hemisphere in about 60% of right-handers (Geschwind and Levitsky, 1968).

Wernicke’s aphasia. Wernicke’s aphasia is characterized by two cardinal deficits: the patient cannot understand language in any modality of input and cannot express thoughts in meaning-appropriate words. Language output is fluent and maintains appropriate melody but is highly paraphasic and circumlocutious. Occasionally, the tendency for paraphasic errors is so pronounced that it
leads to strings of neologisms which form the basis of what is known as jargon aphasia. Speech contains large numbers of function words (e.g., prepositions, conjunctions) but few substantive nouns or verbs denoting specific actions. The output is therefore voluminous but uninformative. For example, a 76-year-old man was brought to the emergency room because he started to talk "funny" while playing cards. In the following passage he is trying to describe how his wife accidentally threw away something important, perhaps his dentures:

We don't need it anymore, she says. And with it when that was downstairs was my teeth tick... a... den... dent... my dentist. And they happened to be in that bag... see? How could this have happened? How could a thing like this happen... So she says we won't need it anymore... I didn't think we'd use it. And now if I have any problems anybody coming a month from now, four months from now, or six months from now, I have a new dentist. Where my two... two little pieces of dentistry that I use... that I... all gone. If she throws the whole thing away... visit some friends of hers and she can't throw them away.

Gestures and pantomime do not improve communication. The patient does not seem to realize that his language is incomprehensible and may appear angry and impatient when the examiner fails to decipher the meaning of a severely paraphasic statement. In some patients this type of aphasia can be associated with severe agitation and paranoid behaviors. Testing comprehension in these patients can be challenging. If asked to raise a hand, touch an ear, or perform other actions with the limbs, the patient gives no indication of comprehension. If asked simple questions that require a yes or no answer, such as "Can a dog fly?" the patient answers at random if at all. Yet the same patient will usually follow commands for whole body movements or movements that use axial musculature (such as "Close your eyes; stand up; turn around") with extreme care and rapidity. If the examiner confined the testing to opening and closing the eyes, the existence of severe comprehension deficits could be overlooked. It is said that this dramatic dissociation occurs because the ability to follow whole body and axial commands is subserved by pathways that remain outside the basic language network (Geschwind, 1965). An alternative possibility is that these movements are coordinated by the right hemisphere. In either case this dissociation emphasizes that "comprehension" is not a unitary mental phenomenon, that it can be fractionated with brain damage, and that the examiner has to look into several independent modes of comprehension. The dramatic dissociation between the failure to understand simple questions (e.g., "What is your name?") in a patient who rapidly closes his/her eyes, sits up, or rolls over when asked to do so is characteristic of Wernicke's aphasia and helps to differentiate it from deafness, psychiatric disease, or malingering. In addition to the paraphasic speech and poor comprehension of spoken language, patients with Wernicke's aphasia also have impaired repetition, naming, reading, and writing.

The lesion site most commonly associated with Wernicke's aphasia is located in the posterior parts of the language network, and tends to involve at least parts of Wernicke's area. A cerebrovascular lesion (commonly embolic and in the distribution of the angular branch of the middle cerebral artery) or neoplasm is the most common etiology. With the occasional exception of a right hemi- or quadrantanopia and mild nasalolabial flattening, the conventional neurological examination may be quite normal. The paraphasic, neologistic speech in an agitated patient with an otherwise uneventful neurological examination may lead to the suspicion of a primary psychiatric disorder such as schizophrenia or mania but the other components characteristic of acquired aphasia and the absence of prior psychiatric disease usually settle the issue.

Broca's aphasia. Speech is non-fluent, labored, dysarthric, and interrupted by many word-finding pauses. It is impoverished in function words but enriched in meaning- appropriate nouns and verbs. Abnormal word order and the inappropriate deployment of bound morphemes (e.g., word endings used to denote tenses, possessives, or plurals) lead to a characteristic agrammatism. The resultant output is telegraphic and pithy but quite informative. In the following passage, a 43-year-old man with Broca's aphasia is describing his medical history: "I see... the doctor, doctor sent me... Bosson. Go to hospital. Dotor... kept me behind. Two, tee days, doctor send me home."

Occasionally output is reduced to a grunt or single word ("yes" or "no") which is emitted with different intonations in an attempt to express approval or disapproval. In addition to fluency, naming and repetition are also impaired. Comprehension of spoken language is intact, except for syntactically difficult sentences with passive voice structure or embedded clauses. Reading comprehension is also preserved, with the occasional exception of a specific inability to read small grammatical words such as conjunctions and pronouns. The last two features indicate that Broca's aphasia is not just an "expressive" or "motor" disorder and that it may also involve a comprehension deficit for function words and syntax. Patients with Broca's aphasia can be tearful, easily frustrated, and profoundly depressed. Even when spontaneous speech is
severely dysarthric, the patient may be able to display a relatively preserved articulation of words when singing. This dissociation has been used to develop specific therapeutic approaches (e.g., melodic intonation therapy) for treating patients with Broca’s aphasia. Additional neurological deficits that are usually encountered in these patients include right hemiparesis (or hemiplegia) and right facial weakness. The most characteristic lesion site tends to include parts of Broca’s area. Cerebrovascular lesions (usually based on occlusive disease in the internal carotid or middle cerebral arteries) are the most frequent etiological processes.

**Global aphasia.** Some patients suffer damage to both Broca’s and Wernicke’s areas. They develop a very severe aphasia characterized by an almost total failure of speech output and comprehension. Even some of these patients, however, can attentively follow commands aimed at axial musculature. This syndrome is designated as global aphasia.

**Disconnection aphasias.** Some aphasias occur not because of direct damage to Wernicke’s or Broca’s area but because of a disconnection of these areas with each other and with other parts of the language network. In **conduction aphasia** the lesion is located either in fiber bundles (such as the arcuate fasciculus) that interconnect Wernicke’s area to Broca’s area or in intervening cortical areas that are likely to act as relays between the two (such as the insula, parietal operculum, and inferior parietal lobule). Since the 2 major cortical “centers” of the language network are intact, these patients have relatively few difficulties with language comprehension or with speech fluency. But they do have paraphasic speech that is relatively empty of content and that does not express the intended meaning. During the examination, patients with conduction aphasia have the most difficulty when asked to repeat speech, especially small function words (for example, “No ifs, ands, or buts”).

Damage to the dorsolateral parietotemporal aspect of the left hemisphere may leave Wernicke’s area intact while disconnecting it from other posterior association regions of the brain. These patients, who are said to have a **transcortical sensory (fluent) aphasia,** experience severe difficulties in comprehending language and expressing their thoughts. Because the 2 cortical centers and their interconnections are intact, however, they have no problem repeating speech. An analogous lesion in the dorsolateral frontal lobe interferes with the interactions between Broca’s area and the rest of the frontal lobe, including the medially situated supplementary motor area. This condition gives rise to a **transcortical motor (non-fluent) aphasia.** Patients show a dramatic paucity of spontaneous speech output. When they are forced to speak, the output is generally telegraphic and pithy. Several features of this type of aphasia are reminiscent of Broca’s aphasia. But because Broca’s area and its interactions with Wernicke’s area are intact, the ability to repeat is preserved (see Table 6.2).

**Anomic aphasia.** A disturbance of naming is not a very specific finding because it is a feature of virtually all the aphasias described above and can even occur in conjunction with metabolic encephalopathies. When naming is the only language disorder that exists, the patient is said to have an **anomic aphasia.** Such patients have no problem with comprehension or repetition and they are able to express themselves reasonably well except for occasional paraphasias. They fail in tests of naming, especially when asked to name small parts of common objects, such as the crystal of a watch, the hem of a coat, or the tip of a pencil. Writing may be impaired. Left hemisphere lesions that do not give rise to one of the aphasic syndromes described above are usually associated with an anomic aphasia. Anomic aphasia is also the most common type of aphasia seen after head injury and in the dementias of the Alzheimer and Pick types. The presence of anomia is a very sensitive indicator of left hemisphere dysfunction.

**The angular gyrus and the Gerstmann syndrome.** The inferior parietal lobule is one of the most important high-order association areas of the brain. Some lesions (not as extensive as those giving rise to a transcortical sensory aphasia) destroy parts of the inferior parietal lobule while leaving Wernicke’s area mostly intact. The consequence of such damage may include difficulties with naming, reading, writing, and calculations, a cluster that is referred to as the **angular gyrus syndrome.** Comprehension of spoken language is generally intact, whereas reading comprehension is often impaired. Other patients develop a combination of 4 symptoms: difficulty with calculations (dyscalculia), impaired writing (dysgraphia), an inability to name fingers (finger agnosia), and an inability to distinguish left from right (left-right confusion). This tetrad is known as the **Gerstmann syndrome.** When it occurs in isolation, it is frequently associated with a left inferior parietal lobule (usually angular gyrus) lesion. The correlation of finger-naming difficulties with calculation difficulties is said to reflect the importance of fingers in the acquisition of arithmetic skills.

**Pure word deafness.** In some patients, brain lesions disconnect the language network from a single sensory modality. These relatively rare lesions give rise to the dramatic man-
ifestations of pure word deafness and pure alexia without agraphia. In pure word deafness, either bilateral lesions or a strategically placed unilateral lesion in the left superior temporal gyrus prevents auditory information from reaching the language network. These patients are neither deaf nor aphasic. They have no difficulty registering and comprehending environmental sounds—they will open the door upon hearing a knock and will pick up the phone when it rings. Although these patients have no problem understanding written language, they react to spoken language as if this were in an alien tongue they cannot decipher. Thus a patient who picks up the telephone as it rings will assume a puzzled and occasionally frustrated expression when realizing his inability to comprehend what is being said on the other end of the line. The language output is almost entirely normal. Occasionally, belligerent and paranoid reactions are associated with this syndrome. Because these patients may have no deficits in the routine neurological examination, they can easily be mistaken as having primarily a psychiatric disturbance. The dramatic dissociation between the comprehension of written versus spoken language is diagnostic and distinguishes these patients from those with psychiatric disease.

**Pure alexia without agraphia.** The alexia associated with the angular gyrus syndrome is called a central alexia because it results from the destruction of a brain region necessary for the relevant multimodal interactions. This type of alexia is almost always associated with dysgraphia. Pure alexia, in contrast, is a disconnection syndrome. It is the visual analogue of pure word deafness. Most characteristically, this syndrome is seen when 2 regions, each supplied by the posterior cerebral artery, are simultaneously damaged. One component of the lesion is usually located in the left occipital cortex. By itself this only creates a right homonymous hemianopia. Patients with a right homonymous hemianopia are not necessarily alexic because visual information from the left visual field can

<table>
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<th>Syndrome</th>
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<tr>
<td>Wernicke's aphasia</td>
<td>Fluent, paraphasic, circumlocutional, empty of content</td>
<td>Impaired except for axial commands</td>
<td>Impaired</td>
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<tr>
<td>Broca's aphasia</td>
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<td>Impaired</td>
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<tr>
<td>Global aphasia</td>
<td>Nonfluent, sometimes mute</td>
<td>Impaired</td>
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<tr>
<td>Conduction aphasia</td>
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<td>Intact</td>
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<td>Impaired</td>
<td>Usually impaired</td>
<td>Intact comprehension</td>
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<tr>
<td>Transcortical sensory aphasia</td>
<td>Fluent, paraphasic, circumlocutional</td>
<td>Impaired except for axial commands</td>
<td>Intact</td>
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<tr>
<td>Transcortical motor aphasia</td>
<td>Nonfluent, pithy</td>
<td>Intact</td>
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<td>Anomic aphasia</td>
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<td>Impaired</td>
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<td>Pure word deafness</td>
<td>Intact</td>
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<td>Pure alexia</td>
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reach the right hemisphere and then cross the splenium of the corpus callosum to access the language network in the left hemisphere. If a patient with left occipital damage also sustains an infarction of the splenium (this is not uncommon because this part of the corpus callosum is supplied by the same artery that supplies the occipital cortex), the left hemisphere language network becomes completely disconnected from visual input. These patients have no aphasia, because the language network is intact. They understand and produce spoken language quite normally. They can also write very well, but they cannot read, even what they have written seconds ago, because the pertinent visual information cannot reach the left hemisphere language network. These patients may also have a generalized color-naming deficit or a true color blindness in the spared parts of the right visual field. The latter condition is known as a central achromatopsis.

Transcallosal anomia. Information from the right hemisphere needs to be transferred across the corpus callosum into the left hemisphere in order to elicit appropriate language behavior. If a patient with a corpus callosum lesion is blindfolded and given an object to palpate with the right hand, he will have no problem naming the object or describing its use because somatosensory pathways are crossed and the information from the right hand is conveyed to the left hemisphere. But when a similar object is placed in the left hand, it cannot be named, because the somatosensory information that reaches the right hemisphere cannot be conveyed to the left side of the brain. Such a patient could demonstrate with his left hand how to use the object, thus indicating that he "knows" what the object is. His inability to name the object, however, could also lead to the inference that he "does not know" its identity. This syndrome shows that brain lesions can fragment mental processes and that knowledge is not necessarily a unitary phenomenon (Geschwind, 1965). The most dramatic instances of this syndrome are seen with vascular lesions in the territory of the anterior cerebral arteries.

Mutism. Absence of speech is described as mutism. Mute patients need not be aphasic. In addition to bilateral lesions that directly damage oropharyngeal motor pathways, mutism is also seen with medial frontal damage in either hemisphere (in the region of the supplementary motor area) or with basal ganglia, white matter, and frontal cortex lesions of the left hemisphere. The absence of aphasia can be demonstrated by the fact that some of these patients have no difficulty with language comprehension or with writing. The stages of recovery from mutism may include whispered, breathy, and eventually dysarthric speech. On occasion, the term aphemia is used to describe this syndrome and its variants.

Apraxia. Apraxia can be defined as an impairment of learned movement that cannot be explained by deficits of motor function, sensation, or language comprehension. Ideomotor apraxia is said to occur if a patient is unable to convert spoken commands that are clearly understood into the corresponding movements. The patient can be asked to show how he would use a hammer, stamp out a cigarette, and suck through a straw. In the absence of the appropriate objects (hammer, cigarette, and straw), his response to these commands enables the examiner to assess ideomotor praxis in the upper limb, lower limb, and buccofacial musculature, respectively.

When a patient cannot follow a command used to test ideomotor apraxia, the examiner can test comprehension by performing several movements including the correct one. If the patient identifies the correct movement, one may assume he has understood the command. The examiner can test the fact that the patient has no relevant motor impediment either by spontaneous observation, by handing the patient the actual tool or object, or by performing the correct movement and asking the patient to imitate it. Ideomotor apraxia does not interfere with the ability to use real objects or tools and therefore has little impact on daily living activities. Ideomotor apraxia is generally associated with lesions that disconnect components of the language network from the motor areas of the frontal lobe. Patients with Wernicke's aphasia cannot be tested because they do not comprehend the command. Patients with conduction aphasia and Broca's aphasia will frequently show limb and buccofacial apraxia.

Visual Recognition and Agnosias

Perceptual information about faces and objects is initially encoded in primary (striate) visual cortex and adjacent upstream peristriate visual association areas. This information is subsequently relayed first to the downstream visual association areas of occipito-temporal cortex and then to other heteromodal and paralimbic areas of the cerebral cortex. Bilateral lesions in the fusiform and lingual gyri of occipito-temporal cortex disrupt this process and interfere with the ability of otherwise intact perceptual information to activate the distributed multimodal associations that lead to the recognition of faces and objects. The resultant face and object recognition deficits are known as prosopagnosia and visual object agnosia.

The patient with prosopagnosia cannot recognize familiar faces, including, sometimes, the reflection of his/
her own face in the mirror. This is not a perceptual deficit since prosopagnosic patients can easily tell if two faces are identical or not. Furthermore, a prosopagnosic patient who cannot recognize a familiar face by visual inspection alone can use auditory cues to reach appropriate recognition if allowed to listen to the person’s voice. The deficit in prosopagnosia is therefore modality specific and reflects the existence of a lesion that prevents the activation of otherwise intact multimodal templates by relevant visual input. The deficit in prosopagnosia is not limited to the recognition of faces but can also extend to the recognition of individual members of larger generic object groups (Damasio, Damasio, and Van Hoesen, 1982; Damasio, 1985; Mesulam, 1994). For example, prosopagnosic patients characteristically have no difficulty with the generic identification of a face as a face, or of a car as a car, but cannot recognize the identity of an individual face or the make of an individual car. This reflects a visual recognition deficit for proprietary features that characterize individual members of an object class. When recognition problems become more generalized and extend to the generic identification of common objects, the condition is known as a visual object agnosia. In contrast to prosopagnosic patients, those with object agnosia cannot recognize a face as a face or a car as a car. The characteristic lesions in prosopagnosia and visual object agnosia consist of bilateral infarctions in the territory of the posterior cerebral arteries and involve the lingual and fusiform gyri. Associated deficits can include visual field defects (especially superior quadrantanopias) or achromatopsia. Rarely, the responsible lesion is unilateral. In such cases, prosopagnosia is associated with lesions in the right hemisphere and object agnosia with lesions in the left.

Right Hemisphere Syndromes

Patients with right hemisphere injury do not ordinarily display obvious language difficulties. Upon rapid bedside examination these patients may therefore seem to have behavioral impairments that are substantially milder than the frankly aphasic and superficially incoherent patients with left hemisphere injury. This distinction has led to the designation of the right hemisphere as the minor or non-dominant side of the brain. Subsequent research, however, has shown that the right hemisphere does have important, possibly dominant, roles in several realms of behavior. These areas include spatial orientation, visuospatial skills, affect, and paralinguistic communication. In contrast to left hemisphere damage, which leads to aphasia, acalculia, and apraxia, damage to the right hemi-

sphere is characterized by hemispatial neglect, dressing apraxia, constructional apraxia, anosognosia (denial of illness), and impaired paralinguistic skills.

The differences in the behavioral specializations of the 2 hemispheres has generated a number of dichotomies. In contrast to the logical and verbal left hemisphere, the right hemisphere has been characterized as mediating processes that are creative, intuitive, and holistic. Furthermore, some investigators have suggested that the right hemisphere may be the site of unconscious processing. There is little support for these sweeping generalizations, which have permeated much of the popular literature on hemispheric specialization. The association of the right hemisphere with unconscious processes arises from the mistaken impression that nonverbal mental operations can be equated with those that are unconscious. The one clearly established fact is that the 2 hemispheres have widely divergent behavioral specializations but the biological mechanisms responsible for these differences are not yet fully understood.

Hemispatial neglect. The dorsal parieto-frontal cortices of the human brain play an important role in coordinating spatial orientation. Damage to these parts of the brain yield syndromes of spatial disorientation such as hemispatial neglect, Balint’s syndrome, anosognosia, dressing apraxia and construction apraxia. Contralesional hemispatial neglect is a relatively common and devastating consequence of brain injury. It is said to be present when the impact of sensory events upon explicit (conscious) behaviors displays a spatial bias that cannot be attributed to elementary sensory-motor deficits such as weakness, clumsiness, or poor acuity. Patients with severe neglect may fail to shave, groom, or dress the side of the body contralateral to the brain lesion; they may fail to eat the food placed on that side of the tray; and they may fail to read the contralesional half of each sentence. If the patient is asked to draw the face of a clock or to copy a simple figure, he may omit detail on the left side; if given pencil and paper and asked to write, he may squeeze all the words onto the right side of the page. Neglect for the extrapersonal space is not a disorder of seeing, hearing, or moving, but one of looking, listening, and exploring (Mesulam, 1994).

Contralesional neglect is far more common, lasting, and severe after right than after left hemisphere lesions. This asymmetry leads to a model of right hemispheric specialization for spatial orientation whereby the left hemisphere contains the neural mechanisms for attending only to the contralateral right hemisphere, whereas the right hemisphere contains the mechanisms for at-
tending to the entire extrapersonal space. According to this model, left hemisphere damage leads to relatively minor contralateral neglect because the ipsilateral attention mechanisms of the right hemisphere take over attentional processes within the right hemisphere. Right hemisphere damage, however, leads to severe unilateral neglect because the left hemisphere does not have ipsilateral attention mechanisms.

At least 3 behavioral components can be identified in neglect. The first is a sensory-representational component: events occurring within the left hemisphere have a diminished impact on awareness, especially if competing events are simultaneously taking place in the right side. This is best demonstrated with the phenomenon of extinction. In this maneuver the patient successfully detects sensory stimulation from either side of space as long as it is presented unilaterally. When the same stimulation is presented simultaneously from both sides of space, the patient fails to report the stimulus on the left side. Lesser degrees of extinction can also occur in the context of other clinical syndromes (for example, callosal disconnection or sensory dysfunction). But when extinction is multimodal or severe or when it emerges in conjunction with other manifestations of spatial inattention, it reflects the sensory-representational component of the neglect syndrome. The second component of neglect is a motor-exploratory deficit: the patient shows a reluctance to direct orienting and exploratory movements toward the left hemispace. This can be demonstrated by visual target cancellation tasks or by blindfolding the patient and asking him to retrieve a small target from the top of a table with the unaffected right hand. Visual search and manual exploration under these conditions are much more efficient on the right side of space (Figure 6.3). There is also a limbic-motivational component to neglect: the patient behaves as if nothing of importance could be expected to occur in the left side of space. It seems as if the left side of space becomes subjected to an emotional devaluation. As part of this devaluation, some patients develop the curious phenomenon of anosognosia: they deny the existence of left hemiplegia and sometimes even express the delusional belief that the arm belongs to another person. The phenomenon of anosognosia may provide a model for studying the biological bases of denial states.

In keeping with the behavioral complexity of neglect behavior, investigators have shown that the brain regions involved in neglect make up a complex cerebral network (Mesulam, 1981a; Mesulam, 1990). The 3 major cortical

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Figure 6.3 This patient with a right hemisphere lesion was asked to circle all the A's. Although the patient had no visual-field defect, he had a marked left neglect.
components of this network are in the frontal cortex (including premotor cortex, area 6, and the frontal eye fields, area 8; see Figure 6.1), the posterior parietal cortex (areas 39, 40, 7), and the cingulate gyrus. Subcortical components of this network are found in the basal ganglia, the thalamus, and the brain stem reticular formation. A different but complementary mapping of the environment may exist within each of the major cortical components of this network: a sensory representational map of the extrapersonal world in posterior parietal cortex, a map for the distribution of motor exploration in frontal cortex, and a motivational map for the distribution of relevance in the cingulate gyrus. These 3 cortical regions are interconnected by monosynaptic pathways. The interactions among the cortical and subcortical components of this network are necessary for the effective distribution of spatial orientation. Damage to any one of these components or to their interconnections may give rise to neglect. This large-scale network organization explains why neglect behavior can occur after lesions not only in the parietal cortex but also in the cingulate region, the frontal lobe, the basal ganglia, and the thalamus. This large-scale neural network organization of spatial orientation and its dominant control by the right hemisphere have now been confirmed with the help of functional imaging experiments in neurologically intact subjects (Corbetta et al., 1993; Gitelman et al., 1996).

Balint's syndrome and simultanagnosia. Bilateral damage to dorsal parieto-frontal cortices gives rise to a dramatic and global impairment of spatial orientation. The associated clinical picture, known as Balint's syndrome, has three components. First, the patient cannot scan the visual environment in a systematic way, a condition designated as oculomotor apraxia. A second component, an inability to extend the hand appropriately to a visual target, is known as optic ataxia. When viewing a complex visual scene or a large object, the patient tends to base identification exclusively on the feature that falls within the central part of the visual field without being able to integrate this information with additional information contained in the more peripheral aspects of the stimulus field. Thus, when facing a door the patient may initially detect the doorknob alone and verbally try to reason out what a doorknob would be doing by itself, only then reaching the conclusion that he must be looking at a door. This third component of Balint's syndrome is also known as simultanagnosia. Patients with Balint's syndrome experience severe visual recognition difficulties based on their inability to integrate visual percepts. The resulting face and object recognition deficits are known as apperceptive visual agnosias, whereas the prosopagnosia and visual object agnosias described above are known as associational agnosias because they result from the failure of an intact percept to evoke the relevant multimodal associations.

The clinical manifestations of neglect and Balint's syndrome help to highlight the anatomical and behavioral subdivision of visual association pathways into dorsal and ventral components (Ungerleider and Mishkin, 1982; Mesulam, 1994). The dorsal visuospatial pathway is directed toward the dorsal parietal and frontal lobes and is important for visuospatial and visuomotor function. Its unilateral interruption in the right hemisphere leads to the neglect syndrome; its bilateral interruption leads to Balint's syndrome. The ventral visuospatial pathway relays visual information into the limbic system, temporoparietal language areas, and downstream visual association areas of occipitotemporal cortex. Destruction of this ventral component is associated with visual amnesias, the Klüver-Bucy syndrome, pure alexia, prosopagnosia, and visual object agnosia.

Complex perceptual tasks. Patients with right brain lesions, especially in the posterior aspects of the hemisphere, experience a much greater impairment in complex perceptual tasks than those with equivalent lesions in the left hemisphere. In keeping with this relationship, it can be shown that the right hemisphere of the intact brain is more effective in the processing of complex nonlinguistic perceptual information. Experiments based on dichotic listening show a consistent right ear (and therefore left hemisphere) advantage for word and number recognition but a left ear advantage for melody identification (Kimura, 1973). Tachistoscopic experiments have shown a left visual field (and therefore right hemisphere) superiority for depth perception, spatial localization, and the identification of complex geometric shapes (Springer and Deutsch, 1981).

A left visual field (and therefore right hemisphere) superiority has been demonstrated for the processing of perceptual information related to unfamiliar faces. This asymmetry acquires potential behavioral relevance because most faces are distinctly asymmetrical. Thus, when an experimental subject is briefly exposed to a new face, the information in the left visual field (coming from the right side of the other person's face) can be shown to play the most important role in the storage of pertinent information. If the subject in such an experiment is subsequently presented with 2 photographic composites, one consisting of the 2 left sides and the other of the 2 right sides of the same face, he will tend to conclude that the composite made of the right side (which had been viewed
through the left visual field) more closely resembles the original face. Despite this crucial role of the right hemisphere in the perceptual analysis of information related to faces, severe prosopagnosia is usually seen in the context of bilateral lesions, suggesting that both hemispheres take part in the recognition of faces.

Left hemispatial neglect and complex perceptual deficits contribute to the emergence of 3 additional clinical features associated with the right hemisphere syndrome: (1) constructional apraxia, that is, major difficulties in copying simple figures, especially if they also include three-dimensional perspective; (2) dressing apraxia, reflecting a major difficulty in aligning the body axis with the axis of the garment (dressing apraxia can be demonstrated by presenting the patient with a coat that has been inverted or with a sleeve turned inside out; unable to rearrange the garment into the proper orientation, the patient may keep looking at it with a puzzled expression while unsuccessfully fumbling with it); and (3) difficulties in spatial orientation and route finding, even in familiar surroundings. Some difficulties with constructional tasks may also emerge after left hemisphere damage, but in much milder form.

Affect

The limbic system plays a crucial role in the generation and channeling of emotions. But other cortical areas, especially those of the right hemisphere, also play important roles in the modulation of feeling and its expression. In the neurologically intact individual one generally assumes that affect conveyed through tone of voice, gestures, and facial expression is consistent with the underlying feeling state. In patients with brain damage, however, experience and expression can be dissociated from each other. In pseudobulbar palsy, for example, the patient may display crying or laughing behavior that bears little if any relationship to underlying sadness or happiness. The potential for such dissociation indicates that the expression and the experience of emotion may need to be considered independently in patients with brain injury.

Emotional experience and its expression are differentially influenced by each cerebral hemisphere. The literature on this subject can be divided into 2 camps. Some authors suggest that each hemisphere introduces a different emotional valence to experience and behavior. Others, however, suggest that the right hemisphere is dominant for the experience and expression of all emotions. A closer examination of these 2 positions shows that the divergence of opinion is more apparent than real.

Lack of concern and even inappropriate jocularity (anosognosia) in response to hemiplegia is a striking feature of some patients with right hemisphere lesions but is almost never seen after damage to the left hemisphere. In contrast, right hemiplegia and left hemisphere damage are often associated with severe frustration and depression. These observations have led to the hypothesis that normal emotional state represents the outcome of a reciprocal balance between a negatively biased right hemisphere and a positively biased left hemisphere. Experiments in neurologically intact volunteers have provided partial support for this hypothesis (Dimond, Farrington, and Johnson, 1976). Two potential problems are associated with this line of reasoning. First, the expression of jocularity in left hemiplegics may have little relationship to the underlying state of feeling as major discrepancies may arise between emotional state and its expression in patients with brain damage. Despite apparent jocularity, for example, some left hemiplegics may be severely depressed (Ross, 1985). Second, the assumption is usually made that the despondency of the right hemiplegic is analogous to the jocularity of the left hemiplegic, except that it is of the opposite valence. One could argue, however, that despondency is an entirely appropriate reaction to a devastating event such as hemiplegia, whereas jocularity is always inappropriate. This reasoning leads to the somewhat different inference that right hemisphere lesions are more likely to result in abnormal emotional responses to life experiences, an interpretation that is more consistent with the existence of a relative right hemisphere specialization for the modulation of affect and emotion.

Several additional observations support this conclusion. For example, patients with right hemisphere damage may show profound deficits in their ability to express emotional state (positive or negative) through variations in the tone of voice (emotional prosody), facial expression, body posture, and hand gestures. On occasion, the most salient feature in the entire clinical picture of a patient with right hemisphere injury will be a loss of emotional prosody and an inability to impart the proper affective tone onto behavior (Ross and Mesulam, 1979; Ross, 1985). A teacher with this kind of lesion complained that she could no longer maintain discipline in her classroom, which she had previously regulated largely through changes in her tone of voice. Another patient was thought to be inconsiderate and depressed because his demeanor and tone of voice lacked the proper variations (Ross and Mesulam, 1979).

Patients with right hemisphere lesions may also have difficulty understanding (decoding) the emotional expressions of others (Heilman, Scholes, and Watson, 1975;
Ahern et al., 1991). Equivalent difficulties are not seen after analogous damage to the left side of the brain. Deficits in the display (encoding) of emotional expression are associated with lesions in the more anterior frontal parts of the right hemisphere, whereas deficits in the decoding of emotional expressions tend to arise after lesions in the more posterior temporoparietal parts (Ross, 1985). These encoding and decoding deficits are confined to the expression of relatively subtle affective modulations. Outbursts of extreme fear or anger, however, may remain preserved because their primary neural substrates are probably located bilaterally within limbic structures (Ross, 1985).

Evidence obtained in neurologically intact volunteers support the contention that the intact right hemisphere is more effective in both the encoding and decoding of emotional expression. Thus emotional expressions are more accentuated on the left side of the face, and a left visual field advantage exists for the identification of emotional expressions (Sackeim, Gur, and Savay, 1978; Heller and Levy, 1981). This asymmetry leads to a potential paradox. In face-to-face encounters, information from the more expressive left half of the face is likely to fall within the right visual field of the observer, an arrangement that would engender an intrinsic inefficiency in the communication of affective states. Possibly, this arrangement might reflect the adaptive value of making one’s emotions less than perfectly obvious.

In addition to these observations related to the expression of emotion, indirect evidence suggests the possible existence of a right hemisphere specialization also for the experience of emotions. For example, autonomic responses to emotional stimuli are attenuated in patients with right hemisphere lesions but not in those with left hemisphere injury (Zoccolotti, Scabini, and Violani, 1982). In a different and rather remarkable experiment, neurologically intact subjects were asked to stimulate themselves into sexual climax while their EEGs were being monitored. The results showed that EEG amplitude during orgasm was greater over the right hemisphere (Cohen, Rosen, and Goldstein, 1976).

Even the relationship between altered affective states and the motor system is tighter in the right hemisphere. For example, the left side of the body appears more suggestible to hypnosis (Sackeim, 1982), and unilateral hysterical paralysis is more frequently encountered in the left side of the body, even in left-handers (Stern, 1977). In further support of a putative right hemisphere specialization for emotion, the observation has been made that affective disorders may be more closely associated with dysfunction of the right than of the left hemisphere. For example, neurological signs indicative of right hemisphere dysfunction may be seen in depressed patients and may disappear upon treatment (Weintraub and Mesulam, 1983; Brumback, Stanton, and Wilson, 1984). In patients with temporal lobe epilepsy, left-sided foci are more likely to be associated with thought disorders, whereas right-sided foci are more likely to be associated with affective disease (Bear and Fedio, 1977). Affective disorders are also more common in conjunction with right-sided brain damage (Lishman, 1968). In patients with otherwise typical manic-depressive disturbances, the EEG power spectra tend to show greater disturbances over the right hemisphere in the manic as well as the depressed state (Flor-Henry, 1979); and the performance of such patients in dichotic listening tasks is similar to that of individuals with right temporal lobectomy (Yozowitz et al., 1979). A potentially discrepant but controversial observation comes from Robinson and colleagues, who report that depression is more common after left than after right hemisphere lesions (Robinson et al., 1984; House et al., 1990).

The limbic system plays a critical role in the generation and channeling of emotion. The observations reviewed in this section show that other parts of the cerebral cortex also participate in this process by modulating the expression and perhaps also the experience of emotion. Each cerebral hemisphere may impart a differential valence to this process, and it appears that there is an overall right hemisphere specialization in this realm of behavior.

**Paralinguistic Aspects of Communication**

The formal aspects of language (e.g., phonetics, morphology, semantics, and syntax) are under the dominant control of the left hemisphere. Effective communication involves additional paralinguistic components. The encoding and decoding of emotional expression through variations of prosody and facial expression constitute paralinguistic aspects of communication. As already mentioned, these paralinguistic functions are under right hemisphere control. In addition to imparting emotional tone, speech prosody is also used to denote emphasis and attitude (“She is pretty” versus “She is pretty?”). These aspects of prosody also appear to be influenced by right hemisphere activity (Weintraub, Mesulam, and Kramer, 1981). Another aspect of paralinguistic communication is the ability to comprehend situational context through nonverbal channels of information processing. Patients with right hemisphere injury are more severely impaired than those with left hemisphere injury in this type of paralinguistic task (Benowitz et al., 1983).
The modulation of verbal output according to contextual demands, the choice of appropriate forms of address (tu versus vous), and the choice of proper diction or pitch (using a higher frequency when addressing a child) each constitutes additional paralinguistic functions about which we have relatively little neurological information. Some patients have developed major and salient deficits in these areas of behavior following right hemisphere damage. For example, one patient, known to be shy and considerate before suffering a right temporal lobe infarction, became uncharacteristically brazen and abrasive following the stroke. From his hospital room he would keep calling the physician's office and use forms of address and conversational styles that reflected inappropriate familiarity. The same patient also talked excessively and would not take cues to yield the floor during conversation (Mesulam, 1985).

The commonly observed socially inappropriate behaviors of patients with right hemisphere injury may reflect, at least in part, difficulties at the level of paralinguistic behaviors. The patient may not be able to decode nonverbal messages and may not be able to modulate his behavior to fit contextual cues. These difficulties, the denial of disability (anosognosia), and the potential discrepancy between affect and underlying emotional state pose considerable challenges in the rehabilitation and management of patients with damage to the right hemisphere.

The Frontal Lobes, Comportment, and Executive Functions

The frontal lobes account for almost one-third of the total cortical volume in the human cerebral hemispheres. The frontal lobes can be divided into motor-premotor, heteromodal, and paralimbic components. The terms prefrontal cortex and frontal lobe syndrome generally refer only to the paralimbic (i.e., caudal orbitofrontal, anterior cingulate, and parolfactory areas) and heteromodal (i.e., areas 9, 10, 11, 12, 45, 46, and 47) components of the frontal lobes (see Figure 6.1). These cortical areas and the subcortical regions (e.g., the head of the caudate nucleus and the mediodorsal nucleus of the thalamus) with which they are interconnected make up a large-scale prefrontal network. The clinical case of Phineas Gage (also known as the Boston crowbar case), described more than a century ago by Harlow (Harlow, 1868), has been used as a model for the frontal lobe syndrome. Phineas Gage was a reliable and conscientious foreman who became profane, irascible, and irresponsible following an accident during which a tamping rod was blown through his frontal lobes. The many reports published since Harlow's paper have provided additional support for the conclusions that frontal lobe damage can lead to dramatic alterations of personality and conduct while leaving basic cognitive and sensorimotor functions relatively intact.

The orbitofrontal and anterior cingulate areas provide a convergence site for neural inputs from association, paralimbic, and limbic cortices and constitute a zone of intersection for the prefrontal and limbic networks. In keeping with this organization, the prefrontal network plays an important role in behaviors that require an integration of cognition with emotion and motivation. There is no simple formula for summarizing the diverse functional affiliations of the prefrontal network. Its integrity appears important for the simultaneous (on-line) awareness of context, options, consequences, relevance, and perspectives so as to allow the formulation of adaptive inferences, decisions, and actions. Damage to this part of the brain impairs mental flexibility, foresight, judgment, and the ability to inhibit inappropriate responses. Behaviors impaired by prefrontal cortex lesions are often referred to as executive functions.

A wide range of behavioral changes can be observed in patients with prefrontal lesions (Mesulam, 1986). Some become puerile, profane, slovenly, facetious, irresponsible, grandiose, and irascible; others lose spontaneity, curiosity, and initiative and develop an apathetic blunting of feeling, drive, mentation, and behavior (abulia); others show an erosion of foresight, judgment, and insight and lose the ability to delay gratification and often the capacity for remorse. Still others show an impairment of abstract reasoning, creativity, problem solving, and mental flexibility; jump to premature conclusions; and become excessively concrete or stimulus bound. The orderly planning and sequencing of complex behaviors, the ability to attend to several components simultaneously and then flexibly alter the focus of concentration, the capacity for grasping the context and gist of a complex situation, the resistance to distraction and interference, the ability to follow multistep instructions, the inhibition of immediate but inappropriate response tendencies, and the ability to sustain behavioral output without perseveration may each become markedly disrupted.

On neuropsychological investigation (see Weintraub and Mesulam, 1985, for a description of the procedures), patients with prefrontal damage may show deficits in tasks of concentration (e.g., digit span), inhibition (e.g., the go–no go task, the Stroop test), motor sequencing (e.g., the Luria alternating hand postures), mental flexibility (e.g., the visual/verbal test), and hypothesis formation (e.g., the Wisconsin card sort task). The disruption of attentional functions contributes to the emergence of
“working memory” impairments. Working memory refers to the amount of information that can be kept on-line at any given time. Working memory impairments interfere with the ability to maintain a coherent trend of thought and lead to confusion, especially in complex situations that require the simultaneous consideration of several variables. The attentional deficits also disrupt the registration and retrieval of new information and lead to secondary memory deficits. These memory difficulties can be differentiated from those of the amnestic state by showing that they improve when the attentional load of the task is decreased. Working memory (also known as immediate memory) is an attentional function based on the temporary on-line holding of information. It is closely associated with the integrity of the prefrontal network and the ascending reticular activating system. Retentive memory, by contrast, depends on the stable (off-line) storage of information and is associated with the integrity of the limbic network. The distinction of the underlying neural mechanisms is illustrated by the observation that severely amnestic patients who cannot remember events that occurred a few minutes ago may have intact if not superior working memory capacity, as shown in tests of digit span.

Some patients with sizable frontal lobe lesions and severe behavioral disturbances may have routine neurological and even neuropsychological examinations that are quite unremarkable. This paucity of “objective” findings is sometimes responsible for the clinician’s overlooking the possibility of large and treatable frontal lesions. Even patients with a history of major behavioral difficulties associated with frontal lobe damage may behave impeccably in the office. This is in keeping with the clinical observation that such patients are most impaired under circumstances with minimal external control of behavior: the office setting may introduce just enough external structure to suppress some of these behavioral tendencies. Furthermore, a patient who gives perfect answers to questions about hypothetical social or moral dilemmas may act with a total lack of judgment when faced with the real situation. The clinical adage that judgment and complex comportment cannot be tested in the office is particularly pertinent to the evaluation of patients with frontal lobe damage. Numerous case reports describe patients with massive frontal lobe pathology (for example, meningioma, lipoma, or carnipharyngioma) who have carried psychiatric diagnoses for many years. In general, the abulia and apathy can be misinterpreted as depression, whereas the labile, inappropriate, and impulsive behaviors may raise the possibilities of mania, hysteria, psychosis, or character disorder. Such misdiagnoses can have grave consequences, because some of the underlying frontal lobe lesions are treatable if detected early.

Although the term frontal syndrome is used to designate the entire spectrum of these behavioral changes, each patient may have a different cluster of salient deficits. The specific pattern of behavioral deficits is probably determined by the site, size, laterality, nature, and temporal course of the lesion and perhaps also by the past personality of the patient and the age of onset. The most common clinical manifestations of damage to the prefrontal network take the form of two relatively distinct syndromes. In the frontal abulis syndrome, the patient shows a loss of initiative, creativity, and curiosity and displays a pervasive emotional blandness and apathy. In the frontal disinhibition syndrome, the patient becomes socially disinhibited and shows severe impairments of judgment, insight, and foresight. In this second group of patients, the dissociation between intact intellectual function and a total lack of even rudimentary common sense is striking. Despite the preservation of all essential memory functions, the patient cannot learn from experience and continues to display inappropriate behaviors without appearing to experience emotional pain, guilt, or regret when such behaviors repeatedly lead to disastrous consequences.

The abulisic syndrome tends to be associated with damage to dorsolateral prefrontal cortex, whereas the disinhibition syndrome is more likely to be associated with damage to medial prefrontal or orbitofrontal cortex. These behavioral syndromes tend to arise almost exclusively after bilateral lesions, most frequently in the setting of head trauma, ruptured aneurysms, glioblastomas, and falx or olfactory groove meningiomas. Unilateral lesions confined to prefrontal cortex are very difficult to diagnose clinically and may remain silent until the pathology spreads to the other side. The emergence of developmentally primitive reflexes such as grasping, rooting, and sucking is often considered a sign of frontal lobe disease. However, these reflexes are seen only in patients with very large lesions that extend into the premotor components of the frontal lobes. Occasionally, these reflexes also emerge in the context of metabolic encephalopathies where there are no structural lesions in the frontal lobes. The vast majority of patients with prefrontal lesions and frontal lobe behavioral syndromes do not display these reflexes. The suck, root, and grasp reflexes are therefore not helpful for either detecting or excluding a frontal lobe lesion.

Physiological observations in laboratory primates provide some clues about frontal lobe function. Visual cortex (area 17) neurons sensitive to a certain stimulus orienta-
tion will almost always fire when an object in that orientation enters their receptive field. In contrast, many of the visually responsive neurons in the prefrontal cortex have little specificity for color, size, orientation, or movement. Instead, these neurons are very sensitive to the behavioral relevance of the environmental event. Thus a neuron that responds briskly to a stimulus associated with reward may drastically alter its response to the same visual stimulus when it becomes associated with an aversive or neutral outcome (Kojima, 1980; Thorpe, Rolls, and Maddison, 1983). It could be suggested that this sensitivity to the behavioral relevance rather than to the physical dimensions of stimuli provides the neural substrate for realizing that “all is not gold that glitters.” Without this type of neuron, a given stimulus would automatically call up a predetermined response regardless of context, so that neither autonomy from the environment nor abstract thinking would be possible.

Despite all we have learned in the past few decades, a certain sense of uniqueness is still associated with frontal lobe function. It is quite remarkable, for example, that sizable frontal lobe lesions can remain clinically silent for many years. Even after massive bifrontal lesions, change can often be detected only in comparison with the previous personality of the individual rather than in reference to any set of absolute behavioral standards. Many of the alterations associated with prefrontal lesions appear to overlap with the range of normal human behavior. A vast number of improvident, irresponsible, inappropriate, and facetious individuals, for example, give no evidence of demonstrable brain damage. In contrast, the lack of visible damage to the pertinent cerebral area is a rare occurrence in individuals with aphasia, amnesia, apraxia, or unilateral neglect. A major computational function of prefrontal cortex may be to integrate the activity of multiple cortical areas so as to reach an optimal match between context and response. Damage to this part of the brain would thus result in behavioral deficits that are context dependent rather than static.

The network approach postulates that the same cognitive domain can be impaired after damage to different parts of the brain as long as these parts belong to the same large-scale neural network. Accordingly, lesions in the caudate nucleus or in the mediodorsal nucleus of the thalamus (structures which can be considered subcortical components of the prefrontal network) can also give rise to the clinical picture of a frontal lobe syndrome. This is one reason why the mental state changes associated with degenerative basal ganglia diseases such as Parkinson's or Huntington's disease so often take the form of a frontal lobe syndrome. Bilateral multifocal lesions, none of which are individually large enough to cause specific cognitive deficits such as aphasia or neglect, can collectively interfere with the connectivity and therefore with the integrating function of prefrontal cortex. This is one reason why a frontal lobe syndrome is the single most common behavioral profile associated with a variety of bilateral multifocal brain diseases including metabolic encephalopathy, multiple sclerosis, B-12 deficiency, and others. In fact, the vast majority of patients with the clinical diagnosis of a frontal lobe syndrome tend to have lesions that do not involve prefrontal cortex but that involve either the subcortical components of the prefrontal network or its connections with other parts of the brain. In order to avoid the paradox of making a diagnosis of frontal lobe syndrome in a patient with no evidence of frontal cortex disease, it is advisable to use the diagnostic term “prefrontal network syndrome,” with the understanding that the responsible lesions can lie anywhere within this distributed network.

Modulatory Pathways and the Ascending Reticular Activating System

The neural connections of the cerebral cortex can be divided into two main functional groups. One group contains discrete point-to-point interconnections (e.g., corticocortical, corticostriatal, and thalamocortical) that subserve specific channel functions. The connections between Wernicke’s area and Broca’s area or those between the frontal eye fields and posterior parietal cortex belong to this group of connections. These connections tend to employ excitatory amino acids as transmitter substances and convey content-specific information. The destruction of this type of pathway leads to impairments in the relevant functional domains, and the resultant interruption of information processing cannot be reversed by pharmacological agents.

The second group of cortical connections can be designated as modulatory. They arise from relatively small nuclei in the basal forebrain and brain stem, reach all parts of the cerebral cortex, and regulate overall behavioral states related to all cognitive and comportmental domains. These modulatory connections employ acetylcholine, dopamine, serotonin, and norepinephrine as the transmitter substances. They convey state-specific information. Their dysfunction is implicated in abnormalities of behavioral states related to arousal, attention, mood, and motivation. The activity of these modulatory pathways, and the behavioral states they modulate, can be altered by existing pharmacological agents. There are four major corticopetal modulatory pathways in the human
brain: cholinergic projections originating in the basal forebrain Ch1-Ch4 cell groups, dopaminergic projections originating in the substantia nigra–ventral tegmental area, serotonergic projections originating in the raphe nuclei, and noradrenergic projections originating in the nucleus locus coeruleus (Mesulam, 1990, 1995).

The ascending cholinergic pathway from the basal forebrain to the cerebral cortex acts as an excitatory neuromodulator for cortical neurons. Its activity enhances the response of cortical neurons to novel and behaviorally relevant stimuli. This pathway contributes to the modulation of arousal and attention and may also play an important role in gating sensory-limbic interactions related to memory processes. In keeping with these relationships, cholinergic antagonists suppress the arousal-related low-voltage fast activity of the cortical EEG and the novelty-related P300 response. The degeneration of these ascending cholinergic projections in Alzheimer’s disease may contribute to the emergence of memory and attentional disturbance in these patients.

The behavioral affilations of ascending monoaminergic pathways have been investigated extensively. The dopaminergic cells of the substantia nigra–ventral tegmental area are sensitive to motivational relevant stimuli and to cues that signal their existence (Schultz, 1994). The dopaminergic pathways from the ventral tegmental area and substantia nigra to the cerebral cortex and striatum have therefore been implicated in the modulation of motivational arousal and may contribute to the establishment and maintenance of behaviors related to substance addiction (Fontana, Post, and Pert, 1993; Wilson et al., 1995). Noradrenergic projections from the nucleus locus coeruleus to the cerebral cortex are thought to increase the signal-to-noise ratio and the sharpness of tuning in the response of cortical neurons to sensory stimuli (Foote, Bloom, and Aston-Jones, 1983; Levin, Craik, and Hand, 1988). The activity of neurons in the nucleus locus coeruleus appears to be correlated with the level of arousal and overall efficiency in tasks requiring attentive behavior (Ray, Mirsky, and Pragay, 1982; Aston-Jones et al., 1994). In addition to this role in attention and arousal, the ascending noradrenergic pathway is thought to play an important role in regulating mood and in the influence of emotional arousal on memory and learning (Cahill et al., 1995). The efficacy of noradrenergic reuptake inhibitors in the treatment of depression and the finding of a decreased number of neurons in the nucleus locus coeruleus in suicide victims provide indirect support for this behavioral affiliation (Arango, Underwood, and Mann, 1996). The ascending serotonergic projections from the raphe nuclei to the cerebral cortex are thought to exert additional regulatory influences on emotion and motivation. Serotonergic denervation may promote aggressive behaviors, whereas drugs that increase the availability of serotonin decrease appetite and can relieve depression and obsessive-compulsive symptomatology (Olivier et al., 1995).

Moruzzi and Magoun (1949) had introduced the concept of a brain stem reticular activating system (ARAS) that acted to desynchronize the cortical electroencephalogram via a relay in the thalamus. The foregoing discussion indicates that the original concept of the ARAS needs to be expanded to include the additional ascending corticopetal cholinergic and monoaminergic projections listed above. According to this expanded concept, the ARAS is a network of direct and transthalamic corticopetal connections that modulate overall behavioral states related to arousal, attention, mood, and motivation.

The cerebral cortex is not only the target of ascending modulatory projections from the brain stem, basal forebrain, and thalamus, but also the source of descending feedback projections to several components of the ARAS. Almost all parts of the cerebral cortex project to the reticular nucleus of the thalamus and therefore influence its inhibitory effect upon other thalamic relay nuclei (Jones, 1975). The projection from the cerebral cortex to the reticular nucleus of the thalamus is mostly excitatory, whereas the projections to this thalamic nucleus from the brain stem cholinergic nuclei are inhibitory. The reticular nucleus of the thalamus is thus in a position to act as a site for integrating the reciprocal influence of the cerebral cortex and of the brain stem reticular formation upon the transthalamic processing of information. Although the basal forebrain projects to the entire cerebral cortex, it receives feedback projections from a very limited set of cortical areas, namely, those that belong to the limbic and paralimbic zones of the cerebral cortex (Mesulam and Mufson, 1984). This asymmetry is a feature of all the other ascending modulatory pathways of the ARAS: they project widely to the cerebral cortex but receive very few reciprocal connections from the cerebral cortex (Mesulam, 1987a).

The modulatory pathways reviewed in this section highlight the multiple factors involved in the coordination of cognition and comportment. Language, spatial orientation, attention, memory, emotion, and motivation are each coordinated by the individual large-scale networks reviewed in previous sections. The ARAS introduces a complementary level of control which modulates the overall behavioral states within which the specific behaviors related to these domains can unfold. In the process of remembering, for example, the content of what
is recalled is likely to be determined primarily by the information that flows along the point-to-point sensory-limbic interconnections. However, the speed of recall, and even the emotional coloring of the recollection, may be regulated by the activity of the modulatory pathways that innervate the relevant regions of limbic and association cortex. Among all the complex factors involved in the neural control of comportment and cognition, those that represent the contributions of the ARAS and its modulatory pathways are the most accessible to therapeutic manipulation by existing pharmacological agents.

**Attention and Confusional States (Delirium)**

The waking individual is bombarded by vast quantities of sensory inputs emanating from the environment and a nearly unlimited supply of thoughts generated by the brain itself. Only a fraction of this information can be processed at any given time. Furthermore, the part of the stimulus field that is most relevant for achieving goals of immediate importance (and these could range from food scavenging to resolving deep ethical dilemmas) keeps shifting from one moment to another in a manner that reflects the inner needs of the individual, the dictates of the environment, and the experience gained in the past. Hence there is a need for postulating a neural mechanism that helps to focus awareness on the behaviorally relevant aspects of the stimulus space. The word *attention* is used as a generic term to designate a family of neural mechanisms for selecting the part of the stimulus array that is to capture the center of awareness and for holding the other, potentially distracting, stimuli at bay.

Attentional processes can be divided into 2 major classes. First, there is a *matrix or state* function that regulates the power of concentration, the span of vigilance, the efficiency of detection, and the signal-to-noise ratio. This type of attentional process has been associated with the ARAS, including its cortical components in the frontal lobes. The second class of attentional processes could be conceptualized in terms of *vector or channel* functions that regulate the target of attention in one of the many behaviorally relevant spaces (extrapersonal, mnemonic, semantic, visceral, and so forth). This component is more akin to selective attention and is generally associated with a complex network of cortical structures and their subcortical connections. Spatial orientation represents one aspect of selective attention. The organization of this function and its disruption in the form of hemispatial neglect has been described above.

Disturbances in the matrix aspects of attention are frequently encountered in clinical practice. The term *confusional state* is used to designate a condition where an impairment of the attentional matrix is the most salient aspect of the clinical picture. Additional impairments in other areas of cognition and comportment may also exist, but they are either secondary to the attentional deficit or of lesser severity. The clinical picture of a patient in an acute confusional state is familiar to most physicians. Attention either wanders aimlessly or is suddenly focused on an irrelevant stimulus that becomes the source of distraction. Thought and skilled movement also become vulnerable to interference. The patient may volunteer that “concentration” and “thinking straight” require great effort. The stream of thought loses its coherence because of frequent intrusions by competing thoughts and sensations. Skilled-movement sequences, even those as automatic as dialing the telephone or using eating utensils, lose their coherence and show signs of disintegration, perseveration, and impersistence. When asked to recite the months of the year in reverse order, the patient may say, “December, November, October, September...October, November, December, January,” showing the inability to inhibit intrusion from familiar but inappropriate response tendencies. This clinical description highlights the 3 major features of confusional states: (1) disturbance of vigilance, heightened distractibility, impersistence, and perseveration; (2) inability to maintain a coherent stream of thought; and (3) inability to carry out a sequence of goal-directed movements.

Additional mental state deficits are also common in confusional states. Perceptual distortions may lead to illusions and even hallucinations. The patient is often, but not always, disoriented and shows evidence of faulty memory. Mild amnesia, dysgraphia, dyscalculia, and constructional deficits are common. Judgment may be faulty, insight appears blunted, and affect is quite labile, with a curious tendency for facetious witicism. Some of these deficits are probably secondary to attentional difficulties. For example, if the patient is allowed sufficient drilling during the acquisition stage of a learning task, memory improves. Calculations that appear devastated when tested mentally may prove quite accurate when the patient is allowed to use pencil and paper. Other deficits of mental state (for example, poor judgment and hallucinations) may be affected independently by the underlying pathogen that gives rise to the confusional state.

The most common cause of a confusional state is a toxic or metabolic encephalopathy caused by polypharmacy, renal failure, and the like. Some toxic metabolic encephalopathies, especially those associated with withdrawal states, may lead to agitated and psychotic deliria. When aspects such as hallucinations, delusions, and agitation become more prominent than the attentional deficit in a metabolic encephalopathy, then the des-
ignation of "delirium" or "toxic psychosis" may be more appropriate than that of a "confusional state." Confusional states may also arise as the sole manifestation of subdural hematoma, seizures, multifocal brain disease (such as systemic lupus erythematosus, fat emboli, vasculitis, or degenerative dementia), and even focal cerebral lesions.

Strokes in the medial temporo-occipital cortex of either hemisphere can trigger agitated confusional states. These patients usually also have visual field deficits. In another group of patients, acute confusional states may arise as the major manifestation of stroke in the inferior parietal lobule and the inferior frontal gyrus of the right hemisphere. These patients may have very few, if any, additional neurological signs, and the presence of a cerebrovascular accident can be overlooked. The occurrence of confusional states with unilateral strokes in the right side of the brain has led to the suggestion that the right hemisphere may have a specialized function in regulating not only spatial orientation but also the matrix aspect of attention. In further support of this hypothesis, some investigators have reported that patients with right hemisphere damage tend to show greater deficits in vigilance (arousal) functions than those with equivalent left hemisphere damage (Boller et al., 1986). As noted above, the prefrontal network plays an important role in regulating the "executive" aspects of the attentional matrix and can give rise to confusional states when damaged bilaterally. The one common denominator of all cortical areas associated with confusional states is that they belong to the group of heteromodal cortex.

Other Neurobehavioral Syndromes

Primary Degenerative Dementia

Dementia is said to exist when a disease of the brain causes a gradual decline of mental function that interferes with daily living activities appropriate for age and background. Dementia can arise at any age but is particularly prevalent in old age. Dementias can be associated with several distinct clinical profiles. The single most common clinical pattern involves an initial deterioration of memory and attention that is soon accompanied by additional impairments of language, visuospatial perception, and comportment. Social graces and concern for external appearance may initially appear relatively preserved, and the patient may look healthy and alert until the terminal stages. The vast majority of patients with this clinical pattern suffer from Alzheimer's disease. Alzheimer's disease is characterized by histological lesions known as senile plaques and neurofibrillary tangles. The disease causes a gradual loss of neurons, synapses, and several transmitter systems, especially the cholinergic innervation of the cerebral cortex. The pathology starts in the limbic system and eventually spreads to other components of association cortex in the temporal, parietal, and frontal lobes. This anatomical predilection pattern of the neuropathology is in keeping with the early and severe impairment of memory function and the subsequent involvement of other cognitive and comportmental domains. Psychiatric manifestations such as depression, hallucinations, delusions, and a variety of obstreperous behaviors are part of the syndrome, especially in its more advanced stages.

Less common clinical patterns in dementia are characterized by a relative preservation of memory in patients who display the gradual dissolution of language functions or the progressive emergence of a frontal network syndrome. These syndromes have been designated as Primary Progressive Aphasia and Frontal Dementia, respectively. In patients with the latter syndrome, uninhibited and bizarre behaviors or apathy may dominate the clinical picture. This is the one group of patients with dementia where erroneous diagnoses of primary psychiatric diseases are common. In contrast to patients with Alzheimer's disease, who usually display anorexia and decreased libido, those with frontal dementias may manifest overeating and hypersexuality. The neuropathological examination in patients with Primary Progressive Aphasia and Frontal Dementia characteristically shows the lesions of Pick's disease or a focal cortical neuronal loss without specific histopathological features. Some patients with these unusual clinical patterns show the neuropathological lesions of Alzheimer's disease, but with an atypical anatomical distribution.

Basal Ganglia Disorders

Traditional neurology tends to associate the basal ganglia almost exclusively with motor function. However, extensive clinical evidence indicates that almost every disease of the basal ganglia is also associated with major changes in mental state. One possibility is that the basal ganglia are directly involved in the coordination of complex behavior. In keeping with this suggestion, it is well known that the basal ganglia have extensive connections with association and limbic cortex. The striatum (i.e., the caudate, putamen, nucleus accumbens) is a component of almost all large-scale neurocognitive networks. In monkeys, lesions confined to the head of the caudate nucleus may give rise to deficits in cognitive tasks without necessarily interfering with motor function. The behavioral affiliations of individual striatal sectors tend to be identical to those of the cortical areas with which they are most
closely interconnected. Degenerative basal ganglia diseases associated with major mental state alterations include Huntington’s chorea, Parkinson’s disease, Wilson’s disease, supranuclear ophthalmooplegia (Steele-Olszewski-Richardson syndrome), olivopontocerebellar degeneration, corticobasalganglionic degeneration, and Hallervorden-Spatz disease. Many degenerative basal ganglia diseases are associated with a certain degree of cortical pathology that could also contribute to the mental state alterations.

The mental state alterations of Huntington’s and Parkinson’s diseases have been studied extensively. Huntington’s disease is genetically transmitted in an autosomal dominant fashion. The genetic defect is based on the mutation of a gene on chromosome 4 that encodes a protein of unknown function known as huntingtin. The disease leads to severe atrophy of the caudate nuclei and sometimes to an additional loss of cortical neurons. Its 2 major clinical components are chorea and mental state alterations. The changes in mental state may precede the chorea by many years. The mental changes are usually very similar to components of the frontal lobe syndrome but can also include psychotic features. Patients show deficits in insight and judgment and may develop a pervasive state of apathy and abulia. Depression is also common and may represent another biological manifestation of the underlying neurological disease. As the degenerative changes of Huntington’s disease become established, the depression tends to blend into a state of apathetic dementia.

Parkinson’s disease is associated with a severe loss of the pigmented cells in the substantia nigra–ventral tegmental area and in the nucleus locus coeruleus. At least one-fourth of elderly patients with Parkinson’s disease develop severe progressive mental state changes compatible with a diagnosis of dementia. The most customary change is an overall slowing of mentation known as bradyphrenia. The resultant attentional deficits tend to cause secondary problems in almost all other cognitive functions. Drugs that alleviate the motor components of Parkinson’s disease are rarely useful for reversing the mental changes. Occasionally an amnestic condition similar to Alzheimer’s dementia may develop, but this is probably associated with the concomitant occurrence of pathological changes characteristic of Alzheimer’s disease. In the late stages of the disease, visual hallucinations of a frightening nature can occur. Patients may not volunteer this information unless they are specifically questioned. Depression is very common. Some have argued that this is a reactive depression to a disabling disease. Others have pointed out that this may reflect the loss of cortical norepinephrine resulting from the loss of neurons in the nucleus locus coeruleus. Antidepressants are useful in the management of these patients.

**The Gilles de la Tourette Syndrome**

The Tourette syndrome includes three features: (1) motor tics in the neck, face, and sometimes lower limbs; (2) vocal tics, which can range from throat clearing to snorting, barking, swearing, and profanity (coprolalia); and (3) obsessive-compulsive symptomatology, which includes recurring thoughts (for example, that family members will get into an accident), repetitive touching, collecting, obsessive orderliness, and sometimes compulsive self-mutilation. The entire triad is present in less than a third of the population with this syndrome. Generally the diagnosis requires one of the first 2 components to be present. It is conceivable, however, that a subset of patients with Tourette’s syndrome will have salient obsessive-compulsive component while the tics may be subtle or perhaps even absent. This possibility introduces additional considerations to the differential diagnosis of obsessive-compulsive disorders. There is a familial pattern of occurrence, even though the exact mode of inheritance has not been determined. This disorder is more common in males and has a typical age of onset between 6 and 20 years.

The colorful symptomatology in these patients may have grave consequences. The tendency for coprolalia or for emitting bizarre noises can make it extremely difficult to continue with schooling or to keep a job. Occasionally the coprolalia will lead to altercations with passers-by or with the police. Sometimes the tics can be so violent that they lead to cervical disc disease and major dental problems. The obsessive-compulsive tendencies are sometimes marked. One patient almost faced divorce because of his compulsive tendency to keep pinching his wife’s cheeks. With the exception of these specific behavioral problems, patients with Tourette’s syndrome tend to be bright, intelligent, and insightful. Treatment of the Tourette syndrome is usually very successful, providing relief to approximately 80 percent of patients (Mesulam and Petersen, 1987). The mainstay of therapy is dopamine-blocking neuroleptics. Success in isolated cases has also been reported with a variety of other agents, especially clonidine.

**Corpus Callosum Syndromes**

The corpus callosum provides a large white-matter tract for interconnecting the 2 hemispheres of the brain. When
this commissure is intact, the brain functions as an integrated whole. Damage to the corpus callosum leads to disconnection syndromes (such as anomia for objects placed in the left hand or ideomotor apraxia in the left limbs). Another and most dramatic syndrome of callosal disconnection has been designated as the "alien hand." This syndrome occurs when a callosal lesion is combined with damage to the frontal lobes. In this condition the patient may report that one hand (usually the left) is out of his control and behaves independently, sometimes in ways that cause physical harm to the patient himself. This clinical condition illustrates how the fabric of volition can be fragmented in patients with brain damage.

Hallucinations

Hallucinations may occur in a large variety of neurological syndromes. They are particularly frequent in toxic metabolic encephalopathies, especially those associated with fever, infection, drug overdose, and withdrawal syndromes. Hallucinations are common in conditions such as Parkinson's disease and narcolepsy. Hallucinations are also seen in several other conditions and can be divided into 2 classes: ictal hallucinations and release hallucinations. Ictal hallucinations are associated with partial epilepsy, especially in the occipital and temporal lobes. These may occur in any modality, but the visual and olfactory hallucinations are probably the most common. If the site of the epileptic discharge is in the occipital lobe, then the visual hallucinations may take the form of flashes, simple geometric shapes, and colors. If the site is in the temporal lobe, especially in the right hemisphere, complex images and scenes are hallucinated. Ictal hallucinations are brief, stereotyped, and sometimes localized to a certain part of the visual field. Similar hallucinations may also occur in patients with migraine, especially as part of the aura.

Release hallucinations occur either when there is a major problem with the peripheral sensory apparatus or when there is central pathology in the brain (McNamara, Heros, and Boller, 1982). Loss of peripheral acuity, as in progressive deafness, macular degeneration, and cataracts, may lead to vivid visual and auditory hallucinations in elderly individuals, even when no other evidence of psychiatric disturbance exists. The visual hallucinations may include small animals and complex colorful scenes, and the auditory hallucinations may take the form of continuously repeating jingles, fragments of tunes, or entire songs. In contrast to the ictal hallucinations, these are continuous and repetitive. Initially these release hallucinations are associated with fear, but eventually they result in annoyance and then resignation. The combination of pathological alterations in the peripheral sensory apparatus and also in visually responsive cortical areas appears to be associated with the most florid hallucinations. On rare occasions brain lesions alone, especially in the distribution of the basilar artery, may result in release hallucinations (for example, peduncular hallucinosis). In those instances investigators have suggested that such lesions permanently release hypothetical mechanisms that inhibit the daytime occurrence of dreaming. A physiological disturbance of the same mechanisms may underlie the hypnagogic hallucinations seen in narcolepsy.

Relevance of Neurological Disease to Psychiatric Practice

The relevance of neurological disease to psychiatric practice can be reviewed from the vantage point of at least 4 patient groups. The great majority of patients who seek psychotherapy have no demonstrable structural or physiological abnormality in the brain. Patients in this group seek help either because they face intolerable circumstances or because they have acquired maladaptive response patterns to life experiences. Except for the symptomatic prescription of medication, the biological approach to brain function is of relatively little assistance in the management of these patients.

Recent observations suggest the existence of another group of individuals in whom genetic (constitutional) or developmental peculiarities in brain organization could impede normal emotional and behavioral maturation without necessarily leaving other traces of a static brain lesion (Weintraub and Mesulam, 1983; Price et al., 1990). From the clinical vantage point, individuals in this hypothetical second group might not be easily differentiated from those in the first. They are, however, likely to develop relatively atypical syndromes that are generally less responsive to traditional treatment.

A third group contains patients with the major psychoses, severe characterological problems, intractable phobias, and pervasive obsessive-compulsive disorders. Increasing evidence suggests that these patients may have underlying abnormalities of brain physiology such as abnormal response to lactate in panic attacks, dopaminergic dysfunction or fronto-limbic pathology in schizophrenia, fronto-striatal dysfunction in obsessive-compulsive disorders, and monoaminergic dysfunction in depression. Despite the putative cerebral pathology within the latter 2 categories, none of the patients in these first 3 groups can be said to have a neurological disease in the traditional sense of the term.

This chapter has focused on yet a fourth group of pa-
patients who suffer disorders of mental state and behavior in conjunction with acquired neurological disease. Sometimes the presence of the underlying brain disease is obvious, whereas in other instances the findings on the traditional neurological examination may be quite subtle or even elusive. The term organic is most commonly associated with syndromes in this fourth group of patients. This chapter has endeavored to show that the spectrum of these syndromes is exceedingly wide, that the nature of the lesion determines the clinical features of the behavioral deficit, and that an understanding of the relevant brain-behavior interactions is essential for accurate differential diagnosis and effective management.

Detecting the neurological disease responsible for behavioral problems is an important exercise. But the task of the psychiatrist does not end there. Even patients with an organic brain syndrome are often in need of psychiatric help. In addition to providing emotional support, the aims of such treatment include teaching new strategies for coping with the disability and for circumventing it. Educating the patient and the family about those behavioral problems that are the immediate consequences of brain damage also helps to lessen frustration and to alleviate misplaced feelings of guilt and anger. The psychiatrist needs to realize, however, that traditional psychodynamic models of mental function and psychotherapy may be only partially applicable to the population of individuals with neurological disease. In the course of treating these patients, for example, the therapist's nonverbal messages (in the form of the approving, disapproving, or questioning "hmm-hmm's") may be misconstrued, the patient's tone of voice may have little relation to his state of feeling, the mechanisms for insight may be shattered, strong affect may reflect seizure activity rather than psychological antecedents, the ability for abstraction may be deficient, memory may be faulty, and bizarre language may not reflect an underlying thought disturbance. In addition to these clinical considerations, new sets of indications may need to be entertained in prescribing psychoactive medication. The use of neuroleptics and antidepressants in temporal lobe epilepsy, for example, must take into account the putative effect of these agents on seizure thresholds (Clifford et al., 1985).

Despite these potential obstacles, the psychiatric treatment of individuals with neurological disease can become a rewarding experience for the patient as well as for the therapist. The expertise needed for managing these patients may eventually lead to the establishment of a multidisciplinary specialty based on closer interactions between neurology and psychiatry. The insights likely to emerge from this interaction could then pave the way for important advances in exploring the neurobiological foundations of mental function.

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**Recommended Reading**


