The cerebral cortex of the human brain contains ~20 billion neurons spread over an area of 2.5 m². The primary sensory and motor areas constitute 10% of the cerebral cortex. The rest is subsumed by modality-selective, heteromodal, paralimbic, and limbic areas collectively known as the association cortex (Fig. 26-1). The association cortex mediates the integrative processes that subserve cognition, emotion, and comportment. A systematic testing of these mental functions is necessary for the effective clinical assessment of the association cortex and its diseases. According to current thinking, there are no centers for “hearing words,” “perceiving space,” or “storing memories.” Cognitive and behavioral functions (domains) are coordinated by intersecting large-scale neural networks that contain interconnected cortical and subcortical components. Five anatomically defined large-scale networks are most relevant to clinical practice: (1) a perisylvian network for language, (2) a parietofrontal network for spatial orientation, (3) an occipitotemporal network for face and object recognition, (4) a limbic network for explicit episodic memory, and (5) a prefrontal network for the executive control of cognition and comportment. Investigations based on functional imaging have also identified a default mode network, which becomes activated when the person is not engaged in a specific task requiring attention to external events. The clinical consequences of damage to this network are not yet fully defined.

THE LEFT PERISYLVIAN NETWORK FOR LANGUAGE AND APHASIAS

The production and comprehension of words and sentences is dependent on the integrity of a distributed network located along the perisylvian region of the language-dominant (usually left) hemisphere. One hub, situated in the inferior frontal gyrus, is known as Broca’s area. Damage to this region impairs fluency of verbal output and the grammatical structure of sentences. The location of a second hub, critical for language comprehension, is less clearly settled. Accounts of patients with focal cerebrovascular lesions identified Wernicke’s area, located at the parietotemporal junction, as a critical hub for word and sentence comprehension. Occlusive or embolic strokes involving this area interfere with the ability to understand spoken or written language as well as the ability to express thoughts through meaningful words and statements. However, investigations of patients with the neurodegenerative syndrome of primary progressive aphasia (PPA) have shown that sentence comprehension is a widely distributed faculty jointly subserved by Broca’s and Wernicke’s areas, and that the areas critical for word comprehension are located in the anterior temporal lobe rather than Wernicke’s area. All components of the language network are interconnected with each other and with surrounding parts of the frontal, parietal, and temporal lobes. Damage to this network gives rise to language impairments known as aphasia. Aphasias should be diagnosed only when there are deficits in the formal aspects of language, such as word finding, word choice, comprehension, spelling, or grammar. Dysarthria, apraxia of speech, and mutism do not by themselves lead to a diagnosis of aphasia. In ~90% of right-handers and 60% of left-handers, aphasia occurs only after lesions of the left hemisphere.

CLINICAL EXAMINATION

The clinical examination of language should include the assessment of naming, spontaneous speech, comprehension, repetition, reading, and writing. A deficit of naming (anomia) is the single most common finding in aphasic patients. When asked to name a common object, the patient may fail to come up with the appropriate word, may provide a circumlocutious description of the object (“the thing for writing”), or may come up with the wrong word (paraphasia). If the patient offers an incorrect but related word (“pen” for “pencil”), the naming error is known as a semantic paraphasia; if the word approximates the correct answer but is phonetically inaccurate (“plentif” for “pencil”), it is known as a phonemic paraphasia. In most anomas, the patient cannot retrieve the appropriate name when shown an object but can point to the appropriate object when the name is provided by the examiner. This is known as a one-way (or retrieval-based) naming deficit. A two-way (comprehension-based or semantic) naming deficit exists if the patient can neither provide nor recognize the correct name. Spontaneous speech is described as “fluent” if it maintains appropriate output volume, phrase length, and melody or as “nonfluent” if it is sparse and halting and average utterance length is below four words. The examiner also should note the integrity of grammar as manifested by word order (syntax), tenses, suffixes, prefixes, plurals, and possessives. Comprehension can be tested by assessing the patient’s ability to follow conversation, asking yes-no questions (“Can a dog fly?” “Does it snow in summer?”), asking the patient to point to appropriate objects.

FIGURE 26-1 Lateral (top) and medial (bottom) views of the cerebral hemispheres. The numbers refer to the Brodmann cyto-architectonic designations. Area 17 corresponds to the primary visual cortex, 41–42 to the primary auditory cortex, 1–3 to the primary somatosensory cortex, and 4 to the primary motor cortex. The rest of the cerebral cortex contains association areas. AG, angular gyrus; B, Broca’s area; CC, corpus callosum; CG, cingulate gyrus; DL PPC, dorsolateral prefrontal cortex; FEF, frontal eye fields (premotor cortex); FG, fusiform gyrus; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; LG, lingual gyrus; M PFC, medial prefrontal cortex; MTG, middle temporal gyrus; OFC, orbitofrontal cortex; PHG, parahippocampal gyrus; PPC, posterior parietal cortex; PSC, peristriate cortex; SC, striate cortex; SMG, supramarginal gyrus; SPL, superior parietal lobule; STG, superior temporal gyrus; STS, superior temporal sulcus; TP, temporopolar cortex; W, Wernicke’s area.

s for the 20th Edition of Harrison’s Textbook of Medicine

Harrison’s Principles of Internal Medicine, 20th Edition, McGraw Hill, 2018
Impaired

**TABLE 26-1 Clinical Features of Aphasia and Related Conditions Commonly Seen in Cerebrovascular Accidents**

<table>
<thead>
<tr>
<th></th>
<th>COMPREHENSION</th>
<th>REPEATITION OF SPOKEN LANGUAGE</th>
<th>NAMING</th>
<th>FLUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wernicke’s</td>
<td>Impaired</td>
<td>Impaired</td>
<td>Impaired</td>
<td>Decreased</td>
</tr>
<tr>
<td>Broca’s</td>
<td>Preserved (except grammar)</td>
<td>Impaired</td>
<td>Impaired</td>
<td>Decreased</td>
</tr>
<tr>
<td>Global</td>
<td>Impaired</td>
<td>Impaired</td>
<td>Impaired</td>
<td>Decreased</td>
</tr>
<tr>
<td>Conduction</td>
<td>Preserved</td>
<td>Impaired</td>
<td>Impaired</td>
<td>Preserved</td>
</tr>
<tr>
<td>Nonfluent (anterior transcortical)</td>
<td>Preserved</td>
<td>Impaired</td>
<td>Impaired</td>
<td>Preserved</td>
</tr>
<tr>
<td>Fluent (posterior) transcortical</td>
<td>Preserved</td>
<td>Impaired</td>
<td>Impaired</td>
<td>Preserved</td>
</tr>
<tr>
<td>Isolation</td>
<td>Impaired</td>
<td>Impaired</td>
<td>Echolalia</td>
<td>No purposeful speech</td>
</tr>
<tr>
<td>Anomic</td>
<td>Preserved</td>
<td>Impaired</td>
<td>Impaired</td>
<td>Preserved</td>
</tr>
<tr>
<td>Pure word deafness</td>
<td>Impaired only for spoken language</td>
<td>Impaired</td>
<td>Preserved</td>
<td>Preserved</td>
</tr>
<tr>
<td>Pure alexia</td>
<td>Impaired only for reading</td>
<td>Impaired</td>
<td>Preserved</td>
<td>Preserved</td>
</tr>
</tbody>
</table>

The lesion site most commonly associated with Wernicke’s aphasia is the posterior portion of the language network. An embolus to the inferior division of the middle cerebral artery (MCA), to the posterior temporal or angular branches in particular, is the most common etiology (Chap. 419). Intracerebral hemorrhage, head trauma, and neoplasm are other causes of Wernicke’s aphasia. A coexisting right hemianopia or superior quadrantanopia is common, and mild right nasolabial flattening may be found, but otherwise, the examination is often unrevealing. The paraphasic, neologistic speech in an agitated patient with an otherwise remarkable neurologic 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. Prognosis for recovery of language function is guarded.

**Broca’s Aphasia** Speech is nonfluent, labored, interrupted by many word-finding pauses, and usually dysarthric. It is impoverished in function words but enriched in meaning-appropriate nouns. Abnormal word order and the inappropriate deployment of bound morphemes (word endings used to denote tenses, possessives, or plurals) lead to a characteristicagrammatism. Speech is telegraphic and pithy but quite informative. In the following passage, a patient with Broca’s aphasia describes his medical history: “I see ... the dotor, dotor sent me ... Bosson. Go to hospital. Dotor ... kept me beside. Two, tee days, doctor send me home.”

Output may be 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 impaired. Comprehension of spoken language is intact except for syntactically difficult sentences with a passive voice structure or embedded clauses, indicating that Broca’s aphasia is not just an “expressive” or “motor” disorder and that it also may involve a comprehension deficit in decoding syntax. Patients with Broca’s aphasia can be tearful, easily frustrated, and profoundly depressed. Insight into their condition is preserved, in contrast to Wernicke’s aphasia. Even when spontaneous speech is severely dysarthric, the patient may be able to display a relatively normal articulation of words when singing. This dissociation has been used to develop specific therapeutic approaches (melodic intonation therapy) for Broca’s aphasia. Additional neurologic deficits include right facial weakness, hemiparesis or hemiplegia, and a buccofacial apraxia characterized by an inability to carry out motor commands involving oropharyngeal and facial musculature (e.g., patients are unable to demonstrate how to blow out a match or suck through a straw). The cause is most often infarction of Broca’s area (the inferior frontal convolution; “B” in Fig. 26-1) and surrounding anterior perisylvian and insular cortex due to occlusion of the superior division of the MCA (Chap. 419). Mass lesions, including tumor, intracerebral hemorrhage, and abscess, also may be responsible. When the cause of Broca’s aphasia is stroke, recovery of language function generally peaks within 2–6 months, after which time further progress is limited. Speech therapy is more successful than in Wernicke’s aphasia.
Conduction Aphasia Speech output is fluent but contains many phonemic parapraxies, comprehension of spoken language is intact, and repetition is severely impaired. Naming elicits phonemic parapraxies, and spelling is impaired. Reading aloud is impaired, but reading comprehension is preserved. The responsible lesion, usually a CVA in the temporoparietal or dorsal perisylvian region, interferes with the function of the phonological loop interconnecting Broca’s area with Wernicke’s area. Occasionally, a transient Wernicke’s aphasia may rapidly resolve into a conduction aphasia. The paraphasic output in conduction aphasia interferes with the ability to express meaning, but this deficit is not nearly as severe as the one displayed by patients with Wernicke’s aphasia. Associated neurologic signs in conduction aphasia vary according to the primary lesion site.

Transcortical Aphasias: Fluent and Nonfluent Clinical features of fluent (posterior) transcortical aphasia are similar to those of Wernicke’s aphasia, but repetition is intact. The lesion site disconnects the intact core of the language network from other temporoparietal association areas. Associated neurologic findings may include hemianopia. Cerebrovascular lesions (e.g., infarctions in the posterior watershed zone) and neoplasms that involve the temporoparietal cortex posterior to Wernicke’s area are common causes. The features of nonfluent (anterior) transcortical aphasia are similar to those of Broca’s aphasia, but repetition is intact and agrammatism is less pronounced. The neurologic examination may be otherwise intact, but a right hemiparesis also can exist. The lesion site disconnects the intact language network from prefrontal areas of the brain and usually involves the anterior watershed zone between anterior and MCA territories or the supplementary motor cortex in the territory of the anterior cerebral artery.

Global and Isolation Aphasias Global aphasia represents the combined dysfunction of Broca’s and Wernicke’s areas and usually results from strokes that involve the entire MCA distribution in the left hemisphere. Speech output is nonfluent, and comprehension of language is severely impaired. Related signs include right hemiplegia, hemisensory loss, and homonymous hemianopia. Isolation aphasia represents a combination of the two transcortical aphasias. Comprehension is severely impaired, and there is no purposeful speech output. The patient may parrot fragments of heard conversations (echolalia), indicating that the neural mechanisms for repetition are at least partially intact. This condition represents the pathologic function of the language network when it is isolated from other regions of the brain. Broca’s and Wernicke’s areas tend to be spared, but there is damage to the surrounding frontal, parietal, and temporal cortex. Lesions are patchy and can be associated with anoxia, carbon monoxide poisoning, or complete watershed zone infarctions.

Anomic Aphasia This form of aphasia may be considered the “minimal dysfunction” syndrome of the language network. Articulation, comprehension, and repetition are intact, but confrontation naming, word finding, and spelling are impaired. Word-finding pauses are uncommon, so language output is fluent but paraphasic, circumlocutory, and uninformative. The lesion sites can be anywhere within the left hemisphere language network, including the middle and inferior temporal gyri. Anomic aphasia is the single most common language disturbance seen in head trauma, metabolic encephalopathy, and Alzheimer’s disease.

Pure Word Deafness The most common causes are either bilateral or left-sided MCA strokes affecting the superior temporal gyrus. The net effect of the underlying lesion is to interrupt the flow of information from the auditory association cortex to the language network. Patients have no difficulty understanding written language and can express themselves well in spoken or written language. They have no difficulty interpreting and reacting to environmental sounds if the primary auditory cortex and auditory association areas of the right hemisphere are spared. Because auditory information cannot be conveyed to the language network, however, it cannot be decoded into neural word representations, and the patient reacts to speech as if it were in an alien tongue that cannot be deciphered. Patients cannot repeat spoken language but have no difficulty naming objects. In time, patients with pure word deafness teach themselves lipreading and may appear to have improved. There may be no additional neurologic findings, but agitated paranoid reactions are common in the acute stages. Cerebrovascular lesions are the most common cause.

Pure Alexia Without Agraphia This is the visual equivalent of pure word deafness. The lesions (usually a combination of damage to the left occipital cortex and to a posterior sector of the corpus callosum—the splenium) interrupt the flow of visual input into the language network. There is usually a right hemianopia, but the core language network remains unaffected. The patient can understand and produce spoken language, name objects in the left visual hemifield, repeat, and write. However, the patient acts as if illiterate when asked to read even the simplest sentence because the visual information from the written words (presented to the intact left visual hemifield) cannot reach the language network. Objects in the left hemifield may be named accurately because they activate nonvisual associations in the right hemisphere, which in turn can access the language network through transcortical pathways anterior to the splenium. Patients with this syndrome also may lose the ability to name colors, although they can match colors. This is known as a color anomia. The most common etiology of pure alexia is a vascular lesion in the territory of the posterior cerebral artery or an infiltrating neoplasm in the left occipital cortex that involves the optic radiations as well as the crossing fibers of the splenium. Because the posterior cerebral artery also supplies medial temporal components of the limbic system, a patient with pure alexia also may experience an amnesia, but this is usually transient because the limbic lesion is unilateral.

Apraxia and Aphemia Apraxia designates a complex motor deficit that cannot be attributed to pyramidal, extrapyramidal, cerebellar, or sensory dysfunction and that does not arise from the patient’s failure to understand the nature of the task. Apraxia of speech is used to designate articulatory abnormalities in the duration, fluidity, and stress of syllables that make up words. It can arise with CVAs in the posterior part of Broca’s area or in the course of frontotemporal lobar degeneration (FTLD) with tauopathy. Aphemia is a severe form of acute speech apraxia that presents with severely impaired fluency (often mutism). Recovery is the rule and involves an intermediate stage of hoarse whispering. Writing, reading, and comprehension are intact, and so this is not a true aphasic syndrome. CVAs in parts of Broca’s area or subcortical lesions that undercut its connections with other parts of the brain may be present. Occasionally, the lesion site is on the medial aspects of the frontal lobes and may involve the supplementary motor cortex of the left hemisphere. Ideomotor apraxia is expressed when commands to perform a specific motor act (“cough,” “blow out a match”) or pantomime the use of a common tool (a comb, hammer, straw, or toothbrush) in the absence of the real object cannot be followed. The patient’s ability to comprehend the command is ascertained by demonstrating multiple movements and establishing that the correct one can be recognized. Some patients with this type of apraxia can imitate the appropriate movement when it is demonstrated by the examiner and show no impairment when handed the real object, indicating that the sensorimotor mechanisms necessary for the movement are intact. Some forms of ideomotor apraxia represent a disconnection of the language network from pyramidal motor systems so that commands to execute complex movements are understood but cannot be conveyed to the appropriate motor areas. Buccofacial apraxia involves apraxic deficits in movements of the face and mouth. Ideomotor limb apraxia encompasses apraxic deficits in movements of the arms and legs. Ideomotor apraxia almost always is caused by lesions in the left hemisphere and is commonly associated with aphasic syndromes, especially Broca’s aphasia and conduction aphasia. Because the handling of real objects is not impaired, ideomotor apraxia by itself causes no major limitation of daily living activities. Patients with lesions of the anterior corpus callosum can display ideomotor apraxia confined to the left side of the body, a sign known as sympathetic dyspraxia. A severe form of sympathetic dyspraxia, known as the alien hand syndrome, is characterized...
by additional features of motor disinhibition on the left hand. **Idiopathial apraxia** refers to a deficit in the sequencing of goal-directed movements in patients who have no difficulty executing the individual components of the sequence. For example, when the patient is asked to pick up a pen and write, the sequence of uncapping the pen, placing the cap at the opposite end, turning the point toward the writing surface, and writing may be disrupted, and the patient may be seen trying to write with the wrong end of the pen or even with the removed cap. These motor sequencing problems usually are seen in the context of confusional states and dementias rather than focal lesions associated with aphasic conditions. **Limbic-apralia** involves clumsiness in the use of tools or objects that cannot be attributed to sensory, pyramidal, extrapyramidal, or cerebellar dysfunction. This condition can emerge in the context of focal premotor cortex lesions or corticobasal degeneration.

**Gerstmann’s Syndrome** The combination of acalculia (impairment of simple arithmetic), dysgraphia (impaired writing), finger anomia (an inability to name individual fingers such as the index and thumb), and right-left confusion (an inability to tell whether a hand, foot, or arm of the patient or examiner is on the right or left side of the body) is known as Gerstmann’s syndrome. In making this diagnosis, it is important to establish that the finger and left-right naming deficits are not part of a more generalized anoma and that the patient is not otherwise aphasic. When Gerstmann’s syndrome arises acutely and in isolation, it is commonly associated with damage to the inferior parietal lobule (especially the angular gyrus) in the left hemisphere.

**Pragmatics and Prosody** Pragmatics refers to aspects of language that communicate attitude, affect, and the figurative rather than literal aspects of a message (e.g., “green thumb” does not refer to the actual color of the finger). One component of pragmatics, prosody, refers to variations of melodic stress and intonation that influence attitude and the inferential aspect of verbal messages. For example, the two statements “He is clever.” and “He is clever?” contain an identical word choice and syntax but convey vastly different messages because of differences in the intonation with which the statements are uttered. Damage to right hemisphere regions corresponding to Broca’s area impairs the ability to introduce meaning-appropriate prosody into spoken language. The patient produces grammatically correct language with accurate word choice, but the statements are uttered in a monotone that interferes with the ability to convey the intended stress and effect. Patients with this type of aprosodia give the mistaken impression of being depressed or indifferent. Other aspects of pragmatics, especially the ability to infer the figurative aspect of a message, become impaired by damage to the right hemisphere or frontal lobes.

**Subcortical Aphasia** Damage to subcortical components of the language network (e.g., the striatum and thalamus of the left hemisphere) also can lead to aphasia. The resulting syndromes contain combinations of deficits in the various aspects of language but rarely fit the specific patterns described in Table 26-1. In a patient with a CVA, an amnic aphasia accompanied by dysarthria or a fluent aphasia with hemiparesis should raise the suspicion of a subcortical lesion site.

**Clinical Presentation and Diagnosis of PPA** Aphasiies caused by CVAs start suddenly and display maximal deficits at the onset. These degenerative diseases have an insidious onset and relentless progression. The neuropathology is usually a FTLD with tautopathy but can also be atypical form of AD pathology.

**Logopenic PPA** The logopenic variant is characterized by preserved fluency and syntax but poor single-word comprehension and profound two-way naming impairments. This kind of aphasia is not seen with CVAs. It differs from Wernicke’s aphasia or posterior transcortical aphasia because speech is usually informative and repetition is intact. Comprehension of sentences is relatively preserved if the meaning is not too dependent on words that fail to be understood allowing the patient to surmise the gist of the conversation through contextual cues. Such patients may appear unimpaired in the course of casual small talk but become puzzled upon encountering an undecipherable word such as “pumpkin” or “umbrella.” Peak atrophy sites are located in the left anterior temporal lobe, indicating that this part of the brain plays a critical role in the comprehension of words, especially words that denote concrete objects. This is a part of the brain that was not included within the classic language network, probably because it is not a common site for focal CVAs. The neuropathology is frequently an FTLD with abnormal precipitates of the 43-kDa transactive response DNA-binding TDP-43 of type C.

**Semantic PPA** The semantic variant is characterized by preserved syntax and comprehension but frequent and severe word-finding pauses, anoma, circumlocutions, and simplifications during spontaneous speech. Repetition is usually impaired. Peak atrophy sites are located in the temporoparietal junction and posterior temporal lobe, partially overlapping with traditional location of Wernicke’s area. However, the comprehension impairment of Wernicke’s aphasia is absent because the underlying deep white matter, frequently damaged by CVAs, remains relatively intact in PPA. The repetition impairment suggests that parts of Wernicke’s area are critical for phonological loop functionality. In contrast to Broca’s aphasia or agrammatic PPA, the interruption of fluency is variable so that speech may appear entirely normal if the patient is allowed to engage in small talk. Logopenic PPA resembles the anomic aphasia of Table 26-1 but usually has longer and more frequent word-finding pauses. When repetition is impaired the aphasia resembles the conduction aphasia in Table 26-1. Of all PPA subtypes, this is the one most commonly associated with the pathology of AD, but FTLD can also be the cause. In addition to these three major subtypes, there is also a mixed type of PPA where grammar, fluency and word comprehension are jointly impaired. This is most like the global aphasia of Table 26-1. Rarely, PPA can present in the form of pure word deafness or Gerstmann’s syndrome.

**The ParietoFrontal Network for Spatial Orientation** Adaptive spatial orientation is subserved by a large-scale network containing three major cortical components. The **cingulate cortex** provides access to a motivational mapping of the extrapersonal space, the **posterior parietal cortex** to a sensorimotor representation of salient extrapersonal events, and the **frontal eye fields** to motor strategies for attentional behaviors (Fig. 26-2). Subcortical components of this network include the

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**PART 2**

Cardinal Manifestations and Presentation of Diseases
HEMISPATIAL NEGLECT and is much more -

BÁLINT’S SYNDROME, SIMULTANAGNOSIA, optic ataxia oculomotor apraxia simultanagnosia -

Clinical Examination

Patients with severe neglect may fail to dress, shave, or groom the left side of the body; fail to eat food placed on the left side of the tray; and fail to read the left half of sentences. When asked to copy a simple line drawing, the patient fails to copy detail on the left, and when the patient is asked to write, there is a tendency to leave an unusually wide margin on the left. Two bedside tests that are useful in assessing neglect are simultaneous bilateral stimulation and visual target cancellation. In the former, the examiner provides either unilateral or simultaneous bilateral stimulation in the visual, auditory, and tactile modalities. After right hemisphere injury, patients who have no difficulty detecting unilateral stimuli on either side experience the bilaterally presented stimuli as coming only from the right. This phenomenon is known as extinction and is a manifestation of the sensory-representational aspect of hemispatial neglect. In the target detection task, targets (e.g., A’s) are interspersed with foils (e.g., other letters of the alphabet) on a 21.5–28.0-cm (8.5–11 in.) sheet of paper, and the patient is asked to circle all the targets. A failure to detect targets on the left is a manifestation of the exploratory (motor) deficit in hemispatial neglect (Fig. 26-3A). Hemianopia is not by itself sufficient to cause the target detection failure because the patient is free to turn the head and eyes to the left. Target detection failures therefore reflect a distortion of spatial attention, not just of sensory input. Some patients with neglect also may deny the existence of hemiparesis and may even deny ownership of the paralyzed limb, a condition known as anosognosia.

BÁLINT’S SYNDROME, SIMULTANAGNOSIA, DRESSING APRAXIA, CONSTRUCTION APRAXIA, AND ROUTE FINDING

Bilateral involvement of the network for spatial attention, especially its parietal components, leads to a state of severe spatial disorientation known as Bálint’s syndrome. Bálint’s syndrome involves deficits in the orderly visuomotor scanning of the environment (oculomotor apraxia), accurate manual reaching toward visual targets (optic ataxia), and the ability to integrate visual information in the center of gaze with more peripheral information (simultanagnosia). A patient with simultanagnosia “misses the forest for the trees.” For example, a patient who is shown a table lamp and asked to name the object may look at its circular base and call it an ashtray. Some patients with simultanagnosia report that objects they look at may vanish suddenly, probably indicating an inability to compute the oculomotor return to the original point of gaze after brief saccadic displacements. Movement and distracting stimuli greatly exacerbate the difficulties of visual perception. Simultanagnosia can occur without the other two components of Bálint’s syndrome.

A modification of the letter cancellation task described above can be used for the bedside diagnosis of simultanagnosia. In this modification, some of the targets (e.g., A’s) are made to be much larger than the others (7.5–10 cm vs 2.5 cm [3–4 in. vs 1 in.] in height), and all targets are embedded among foils. Patients with simultanagnosia display a counterintuitive but characteristic tendency to miss the larger targets (Fig. 26-3B). This occurs because the information needed for the identification of the larger targets cannot be confined to the immediate line of gaze and requires the integration of visual information across multiple fixation points. The greater difficulty in the detection of the larger targets also indicates that poor acuity is not responsible for the impairment of visual function and that the problem is central rather than peripheral. The test shown in Fig. 26-3B is not by itself sufficient to diagnose simultanagnosia because some patients with a frontal network syndrome may omit the strange looking large letters, perhaps because they lack the mental flexibility needed to realize that the two types of targets are symbolically identical despite being superficially different.

Bilateral parietal lesions can impair the integration of egocentric with allocentric spatial coordinates. One manifestation is dressing apraxia. A patient with this condition is unable to align the body axis with the axis of the garment and can be seen struggling as he or she holds a coat from its bottom or extends his or her arm into a fold of the garment rather than into its sleeve. Lesions that involve the posterior parietal cortex also lead to severe difficulties in copying simple line drawings. This is known as a construction apraxia and is much more severe if the lesion is in the right hemisphere. In some patients with right hemisphere lesions, the drawing difficulties are confined to the
A progressive form of spatial disorientation, known as the posterior cortical atrophy (PCA) syndrome, most commonly represents a variant of AD with unusual concentrations of neurofibrillary degeneration in the parieto-occipital cortex and the superior colliculus (Fig. 26-4). Lewy body disease (LBD), CJD, and FTLD (corticobasal degeneration type) are other possible causes. The patient displays progressive hemispatial neglect, Bálint’s syndrome, and route finding impairments, usually accompanied by dressing and construction apraxia.

THE OCCIPITOTEMPORAL NETWORK FOR FACE AND OBJECT RECOGNITION

A patient with prosopagnosia cannot recognize familiar faces, including, sometimes, the reflection of his or her own face in the mirror. This is not a perceptual deficit because prosopagnosic patients easily can tell whether two faces are identical. 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...
**FIGURE 26-4** Four focal dementia syndromes and their most likely neuropathologic correlates. AD, Alzheimer’s disease; bvFTD, behavioral variant frontotemporal dementia; DAT, amnestic dementia of the Alzheimer-type; FTLD, frontotemporal lobar degeneration (tau or TDP-43 type); LBD, Lewy body disease; PCA, posterior cortical atrophy syndrome; PPA, primary progressive aphasia.

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 associative templates by relevant visual input. Prosopagnosic patients characteristically have no difficulty with the generic identification of a face as a face or a car as a car, but may not 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 visual object agnosia. A patient with anoma cannot name the object but can describe its use. In contrast, a patient with visual agnosia is unable either to name a visually presented object or to describe its use. Face and object recognition disorders also can result from the simultanagnosia of Bálint’s syndrome, in which case they are known as apperceptive agnosias as opposed to the associative agnosias that result from inferior temporal lobe lesions.

**CAUSES AND RELATION TO SEMANTIC DEMENTIA**

The characteristic lesions in prosopagnosia and visual object agnosia of acute onset consist of bilateral infarctions in the territory of the posterior cerebral arteries that involve the fusiform gyrus. Associated deficits can include visual field defects (especially superior quadrantoparais) and a centrally based color blindness known as 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. Degenerative diseases of anterior and inferior temporal cortex can cause progressive associative prosopagnosia and object agnosia. The combination of progressive associative agnosia and a fluent aphasia with word comprehension impairment is known as semantic dementia. Patients with semantic dementia fail to recognize faces and objects and cannot understand the meaning of words denoting objects. This needs to be differentiated from the semantic type of PPA where there is severe impairment in understanding words that denote objects and in naming faces and objects but a relative preservation of face and object recognition. The anterior temporal lobe atrophy is usually bilateral in semantic dementia whereas it tends to affect mostly the left hemisphere in semantic PPA. Acute onset of the semantic dementia syndrome can be associated with herpes simplex encephalitis.

**LIMBIC NETWORK FOR EXPLICIT MEMORY AND AMNESIA**

Limbic and paralimbic areas (such as the hippocampus, amygdala, and entorhinal cortex), the anterior and medial nuclei of the thalamus, the medial and basal parts of the striatum, and the hypothalamus collectively constitute a distributed network known as the limbic system. The behavioral affiliations of this network include the coordination of emotion, motivation, autonomic tone, and endocrine function. An additional area of specialization for the limbic network and the one that is of most relevance to clinical practice is that of declarative (explicit) memory for recent episodes and experiences. A disturbance in this function is known as an amnestic state. In the absence of deficits in motivation, attention, language, or visuospatial function, the clinical diagnosis of a persistent global amnestic state is always associated with bilateral damage to the limbic network, usually within the hippocampo-entorhinal complex or the thalamus. Damage to the limbic network does not necessarily destroy memories but interferes with their conscious recall in coherent form. The individual fragments of information remain preserved despite the limbic lesions and can sustain what is known as implicit memory. For example, patients with amnestic states can acquire new motor or perceptual skills even though they may have no conscious knowledge of the experiences that led to the acquisition of these skills.

The memory disturbance in the amnestic state is multimodal and includes retrograde and anterograde components. The retrograde amnesia involves an inability to recall experiences that occurred before the onset of the amnestic state. Relatively recent events are more vulnerable to retrograde amnesia than are more remote and more extensively consolidated events. A patient who comes to the emergency room complaining that he cannot remember his or her identity but can remember the events of the previous day almost certainly does not have a neurologic cause of memory disturbance. The second and most important component of the amnestic state is the anterograde amnesia, which indicates an inability to store, retain, and recall new knowledge. Patients with amnestic states cannot remember what they ate a few hours ago or the details of an important event they may have experienced in the recent past. In the acute stages, there also may be a tendency to fill in memory gaps with inaccurate, fabricated, and often implausible information. This is known as confabulation. Patients with the amnestic syndrome forget that they forget and tend to deny the existence of a memory problem when questioned. Confabulation is more common in cases where the underlying lesion also interferes with parts of the frontal network, as in the case of the Wernicke-Korsakoff syndrome or traumatic head injury.

**CLINICAL EXAMINATION**

A patient with an amnestic state is almost always disoriented, especially to time, and has little knowledge of current news. The anterograde component of an amnestic state can be tested with a list of four to five words read aloud by the examiner up to five times or until the
CAUSES, INCLUDING ALzheimer’s DISEASE

Neurologic diseases that give rise to an amnestic state 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, autoimmune limbic encephalitis, and degenerative dementias such as AD and Pick’s disease. The one common denominator of all these diseases is the presence of bilateral lesions within one or more components in the limbic network. Occasionally, unilateral left-sided hippocampal lesions can give rise to an amnestic state, but the memory disorder tends to be transient. Depending on the nature and distribution of the underlying neurologic disease, the patient also may have visual field deficits, eye movement limitations, or cerebellar findings.

The most common cause of progressive memory impairments in the elderly is AD. This is why a predominantly amnestic dementia is also known as a dementia of the Alzheimer-type (DAT). A prodromal stage of DAT, when daily living activities are generally preserved, is known as amnestic mild cognitive impairment (MCI). The predilection of the entorhinal cortex and hippocampus for early neurofibrillary degeneration by typical AD pathology is responsible for the initially selective impairment of episodic memory. In time, additional impairments in language, attention, and visuospatial skills emerge as the neurofibrillary degeneration spreads to additional neocortical areas. Less frequently, amnestic dementias can also be caused by FTLD. Transient global amnesia is a distinctive syndrome usually seen in late middle age. Patients become acutely disoriented and repeatedly ask who they are, where they are, and what they are doing. The spell is characterized by anterograde amnesia (inability to retain new information) and a retrograde amnesia for relatively recent events that occurred before the onset. The syndrome usually resolves within 24–48 h and is followed by the filling in of the period affected by the retrograde amnesia, although there is persistent loss of memory for the events that occurred during the ictus. Recurrences are noted in ~20% of patients. Migraine, temporal lobe seizures, and perfusion abnormalities in the posterior cerebral territory have been postulated as causes of transient global amnesia. The absence of associated neurologic findings occasionally may lead to the incorrect diagnosis of a psychiatric disorder.

THE PREFRONTAL NETWORK FOR EXECUTIVE FUNCTION AND BEHAVIOR

The frontal lobes can be subdivided into motor-premotor, dorsolateral prefrontal, medial prefrontal, and orbitofrontal components. The terms frontal lobe syndrome and prefrontal cortex refer only to the last three of these four components. These are the parts of the cerebral cortex that show the greatest phylogenetic expansion in primates, especially in humans. The dorsolateral prefrontal, medial prefrontal, and orbitalfrontal areas, along with the subcortical structures with which they are interconnected (i.e., the head of the caudate and the dorsomedial nucleus of the thalamus), collectively make up a large-scale network that coordinates exceedingly complex aspects of human cognition and behavior. The term salience network has been introduced to designate the parts of the frontal network and their interactions with adjacent paralimbic cortices of the insula and cingulate gyrus. Impairments of social conduct and empathy seen in neurodegenerative frontal dementias are attributed to pathology of the salience network.

The prefrontal network plays an important role in behaviors that require multitasking and the integration of thought with emotion. Cognitive operations impaired by prefrontal cortex lesions often are referred to as “executive functions.” The most common clinical manifestations of damage to the prefrontal network take the form of two relatively distinct syndromes. In the frontal abulic syndrome, the patient shows a loss of initiative, creativity, and curiosity and displays a pervasive emotional blandness, apathy, and lack of empathy. In the frontal disinhibition syndrome, the patient becomes socially disinhibited and shows severe impairments of judgment, insight, foresight, and the ability to mind rules of conduct. 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 feel emotional pain, guilt, or regret when those behaviors repeatedly lead to disastrous consequences. The impairments may emerge only in real-life situations when behavior is under minimal external control and may not be apparent within the structured environment of the medical office. Testing judgment by asking patients what they would do if they detected a fire in a theater or found a stamped and addressed envelope on the road is not very informative because patients who answer these questions wisely in the office may still act very foolishly in real-life settings. The physician must therefore be prepared to make a diagnosis of frontal lobe disease based on historic information alone even when the mental state is quite intact in the office examination.

CLINICAL EXAMINATION

The emergence of developmentally primitive reflexes, also known as frontal release signs, such as grasping (elicited by stroking the palm) and sucking (elicited by stroking the lips) are seen primarily in patients with large structural lesions that extend into the premotor components of the frontal lobes or in the context of metabolic encephalopathies. The vast majority of patients with prefrontal lesions and frontal lobe behavioral syndromes do not display these reflexes. Damage to the frontal lobe disrupts a variety of attention-related functions, including working memory (the transient online holding and manipulation of information), concentration span, the effortful scanning and retrieval of stored information, the inhibition of immediate but inappropriate responses, and mental flexibility. Digit span (which should be seven forward and five reverse) is decreased, reflecting poor working memory; and the fluency in producing words starting with the letter a, f, or s that can be generated in 1 min (normally ≥12 per letter) is diminished even in nonaphasic patients, indicating an impairment in the ability to search and retrieve information from long-term stores. In “go–no go” tasks (where the instruction is to raise the finger upon hearing one tap but keep it still upon hearing two taps), the patient shows a characteristic inability to inhibit the response to the “no go” stimulus. Mental flexibility (tested by the ability to shift from one criterion to another in sorting or matching tasks) is impoverished; distractibility by irrelevant stimuli is increased; and there is a pronounced tendency for impersistence and perseveration. The ability for abstracting similarities and interpreting proverbs is also undermined.

The attentional deficits disrupt the orderly registration and retrieval of new information and lead to secondary deficits of explicit memory. 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. The use of
the term “memory” to designate two completely different mental faculties is confusing. Working memory depends on the on-line holding of information for brief periods of time whereas explicit memory depends on the off-line storage and subsequent retrieval of the information.

**CAUSES: TRAUMA, NEOPLASM, AND FRONTALTEMPORAL DEMENTIA**

The abulic syndrome tends to be associated with damage in dorsolateral or dorsomedial prefrontal cortex, and the disinhibition syndrome with damage in orbitofrontal or ventromedial cortex. These syndromes tend to arise almost exclusively after bilateral lesions. Unilateral lesions confined to the prefrontal cortex may remain silent until the pathology spreads to the other side; this explains why thromboembolic CVA is an unusual cause of the frontal lobe syndrome. When behavioral syndromes of the frontal network arise in conjunction with asymmetric disease, the lesion tends to be predominantly on the right side of the brain. Common settings for frontal lobe syndromes include head trauma, ruptured aneurysms, hydrocephalus, tumors (including metastases, glioblastoma, and fx or olfactory groove meningiomas), and focal degenerative diseases, especially FTLD. The most prominent neurodegenerative frontal syndrome is known as the behavioral variant of frontotemporal dementia (bvFTD). The behavioral changes in these patients can range from apathy to shoplifting, compulsive gambling, sexual indiscretions, remarkable lack of common sense, new ritualistic behaviors, and alterations in dietary preferences, usually leading to increased taste for sweets or rigid attachment to specific food items. In many patients with AD, neurofibrillary degeneration eventually spreads to prefrontal cortex and gives rise to components of the frontal lobe syndrome, but almost always on a background of severe memory impairment. Rarely, the bvFTD syndrome can arise in isolation in the context of an atypical form of AD pathology.

Lesions in the caudate nucleus or in the dorsomedial nucleus of the thalamus (subcortical components of the prefrontal network) also can produce a frontal lobe syndrome affecting mostly executive functions. This is one reason why the changes in mental state associated with degenerative basal ganglia diseases such as Parkinson’s disease and Huntington’s disease display components of the frontal lobe syndrome. Bilateral multifocal lesions of the cerebral hemispheres, none of which are individually large enough to cause specific cognitive deficits such as aphasia and neglect, can collectively interfere with the connectivity and therefore integrating (executive) function of the prefrontal cortex. A frontal lobe syndrome, usually of the abulic form, is therefore the single most common behavioral profile associated with a variety of bilateral multifocal brain diseases, including metabolic encephalopathy, multiple sclerosis, and vitamin B₁₂ deficiency, among others. Many patients with the clinical diagnosis of a frontal lobe syndrome tend to have lesions that do not involve prefrontal cortex but involve either the subcortical components of the prefrontal network or its connections with other parts of the brain. To avoid 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 frontal network syndrome, with the understanding that the responsible lesions can lie anywhere within this distributed network. A patient with frontal lobe disease raises potential dilemmas in differential diagnosis: the abulia and blandness may be misinterpreted as depression, and the disinhibition as idio-pathic mania or acting out. Appropriate intervention may be delayed while a treatable tumor keeps expanding.

**CARING FOR PATIENTS WITH DEFICITS OF HIGHER CEREBRAL FUNCTION**

Spontaneous improvement of cognitive deficits following stroke or trauma is common. It is most rapid in the first few weeks but may continue for up to 2 years, especially in young individuals with single brain lesions. Some of the initial deficits in such cases appear to arise from remote dysfunction (diaschisis) in brain regions that are interconnected with the site of initial injury. Improvement in these patients may reflect, at least in part, a normalization of the remote dysfunction. Other mechanisms may involve functional reorganization in surviving neurons adjacent to the injury or the compensatory use of homologous structures, e.g., the right superior temporal gyrus with recovery from Wernicke’s aphasia. In contrast, neurodegenerative diseases show a progression of impairment but at rates that vary greatly from patient to patient.

**Pharmacologic and non-pharmacologic interventions**

Some of the deficits described in this chapter are so complex that they may bewilder not only the patient and family but also the physician. The care of patients with such deficits requires a careful evaluation of the history, cognitive test results and diagnostic procedures. Each piece of information needs to be interpreted cautiously and placed in context. A complaint of “poor memory,” for example, may reflect an anomaly; poor scores on a learning task may reflect a weakness of attention rather than explicit memory; a report of depression or indifference may reflect impaired prosody rather than a change in mood or empathy; jocularity may arise from poor insight rather than good mood. Although there are few well-controlled studies, several non-pharmacologic interventions have been used to treat higher cortical deficits. These include speech therapy for aphasia, behavioral modification for comportamental disorders, and cognitive training for visuospatial disorientation and amnestic syndromes. More practical interventions, usually delivered through occupational therapy, aim to improve daily living activities through assistive devices and modifications of the home environment.

Determining driving competence is challenging, especially in the early stages of dementing diseases. An on-the-road driving test and reports from family members may help time decisions related to this very important activity. In neurodegenerative conditions such as PPA, transcranial magnetic (or direct current) stimulation has had mixed success in eliciting symptomatic improvement. The goal is to activate remaining neurons at sites of atrophy or in unaffected regions of the contralateral hemisphere. Depression and sleep disorders can intensify the cognitive disorders and should be treated with appropriate modalities. If neuroleptics become absolutely necessary for the control of agitation, atypical neuroleptics are preferable because of their lower extrapyramidal side effects. Treatment with neuroleptics in elderly patients with dementia requires weighing the potential benefits against the potentially serious side effects. This is especially relevant to the case of patients with Lewy body dementia, who can be unusually sensitive to side effects.

As in all other branches of medicine, a crucial step in patient care is to identify the underlying cause of the impairment. This is easily done in cases of CVA, head trauma or encephalitis but becomes particularly challenging in the dementias because the same progressive clinical syndrome can be caused by one of several neuropathologic entities. The advent of imaging, blood, and CSF biomarkers now makes it possible to address this question with reasonable success and to make specific diagnoses of AD, LBD, CJD, FTLD. A specific etiological diagnosis allows the physician to recommend medications or clinical trials that are the most appropriate for the underlying disease process. A clinical assessment that identifies the principal domain of behavioral and cognitive impairment followed by the judicious use of biomarker information to surmise the nature of the underlying disease allows a personalized approach to patients with higher cognitive impairment.

**FURTHER READING**