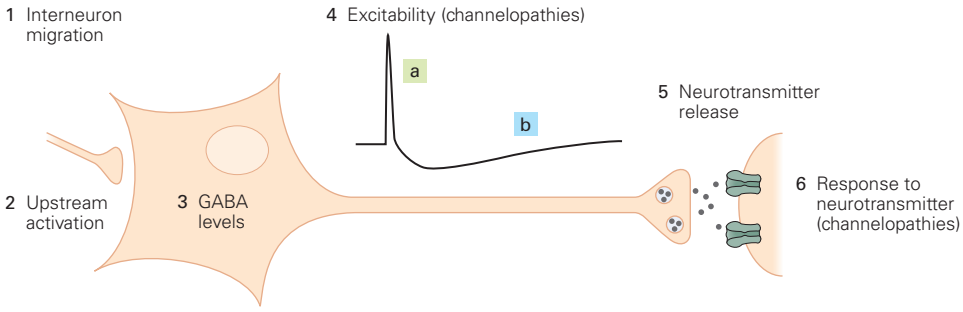

	Channel	Subunits affected	Epilepsy
a	Voltage-gated Na^+	Na_V 1.1, Na_V 1.2, β1	Generalized epilepsy with febrile seizures plus (GEFS+) Severe myoclonic epilepsy of infancy Benign infantile epilepsy
	Voltage-gated K^+	K_V 1.1	Temporal lobe epilepsy
	Ca^{2+}-activated K^+	Ca_V 1.1	Absence epilepsy
b	$GABA_A$ receptor	α1, β3, γ2	GEFS+ Juvenile myoclonic epilepsy Childhood absence epilepsy
	M-type K^+	KCNQ2/3	Benign neonatal epilepsy
	Voltage-gated Ca^{2+}	Ca_V 2.1	Absence epilepsy
	Cl^-	CLCN2	Juvenile myoclonic epilepsy

Figure 58–15 **Channelopathies are a major, but not the only, cause of monogenic human epilepsies.** The human epilepsy genes discovered so far can affect multiple phases of synaptic transmission including the migration of interneurons (**1**), upstream activation of interneurons (**2**), γ-aminobutyric acid (GABA) levels within interneurons (**3**), the excitability of excitatory and inhibitory neurons (**4**), the release of neurotransmitters (**5**), and the postsynaptic response to neurotransmitters (**6**). The inset shows that the impact of mutations in these genes on neuronal excitability can affect the shape of the action potential as well as the afterpotentials and synaptic events that follow. Mutations indicated near the spike (**a**) affect the repolarization of the action potential. Other mutations shown in (**b**) affect the afterhyperpolarization, synaptic conductances, or interspike interval.

secondary action on cell migration, network formation, or patterns of gene expression.

In the early days of research on epilepsy genes, it was widely expected that the genes would mostly underlie generalized epilepsies, based on the idea that a gene mutation (eg, in an ion channel) would be expected to affect most neurons. However, the very first autosomal dominant epilepsy gene discovered by Steinlein and colleagues caused a focal onset (frontal lobe) epilepsy, and another gives rise to seizures originating in the temporal lobe with an auditory aura. In retrospect, this should not be so surprising because channel subunits are rarely expressed uniformly in the brain, and some brain regions are more likely to generate seizures than other regions.

Timing of gene expression is also important. For example, *totterer* mice with mutations in the pore-forming $Ca_V2.1$ subunit of P/Q-type Ca^{2+} channels show spike-wave–type seizures that begin in the third postnatal week, presumably because N-type Ca^{2+} channels are the predominant functional isoform earlier in development, whereas P/Q-type Ca^{2+} channels predominate later. The neurological phenotype begins once the mutant channel is functionally required during development.

Moreover, one mutation can give rise to different epilepsy phenotypes, or different mutant genes can cause the same epilepsy phenotype. As an example of the latter, the ADNFLE syndrome, first discovered as a mutation in the α4-subunit of the nicotinic

ACh receptor, can also be caused by a mutation in the α2-subunit. But not all family members who carry this autosomal dominant mutation have epilepsy, indicating that even in this form of monogenic epilepsy other genes as well as nongenetic factors can influence the phenotype. The GEFS+ syndrome (generalized epilepsy with febrile seizures plus) is a good example of this heterogeneity. It is a childhood syndrome and can involve different seizure types in different family members. GEFS+ is seen in families with mutations in the genes for one of three different Na^+ channel subunits or one of two $GABA_A$ receptors. Family studies of generalized onset epilepsy suggest that seizure types may be heritable within families. These findings indicate that even monogenic epilepsies are likely modified by other genes, environmental influences, and even experience-dependent changes in synapses.

Altered cortical development may be a common cause of epilepsy. The increased resolution of MRI scans has revealed an unexpectedly large number of cortical malformations and localized areas of abnormal cortical folding in patients with epilepsy. Thus, mutations that disturb the normal formation of the cortex or network wiring are candidate genes for epilepsy. This idea is supported by the mapping of two X-linked cortical malformations with epileptic phenotypes: familial periventricular heterotopia and familial subcortical band heterotopia. The genes responsible for these two disorders that encode filamin A and doublecortin, respectively, are presumably important in neuronal migration. Small focal cortical dysplasias can function as seizure foci that give rise to partial and secondarily generalized seizures, whereas more extensive cortical malformations can cause a variety of seizure types and usually are associated with other neurological problems.

Another X-linked gene, *aristaless related homeobox* (*ARX*), is an example of a cell type–specific transcription factor altering migration, because it is expressed only in interneuron precursors. A particularly instructive example is the association of epilepsy with tuberous sclerosis complex (TSC), an autosomal dominant genetic disorder that results from the lack of the functional Tsc1-Tsc2 complex, leading to hyperactivity of the mammalian target of rapamycin (mTOR) complex 1 (mTORC1) signaling pathway. Early clinical trials of mTOR inhibitors as treatment for refractory epilepsy in these patients have been promising. Such examples provide hope for linking the underlying biology of epilepsy syndromes to clinically relevant treatments.

The epilepsy genome is rapidly expanding, driven by clinical exome sequencing and an appreciation of the biological pathways leading to neural network instability. Unfortunately, the vast majority of cases of epilepsy cannot yet be explained by even the recent surge in the identification of epilepsy genes. The identification of large numbers of patients through online registries may provide the population samples needed to evaluate susceptibility genes that underlie complex inheritance patterns.

The Genesis of Acquired Epilepsies Is a Maladaptive Response to Injury

Epilepsy often develops following a discrete cortical injury such as a penetrating head wound. This injury serves as the nidus for a seizure focus, leading at some later point to seizures. This has led to the idea that the early insult triggers a set of progressive physiological or anatomical changes that lead to chronic seizures. That is, the characteristic "silent" interval (usually months or years) between the insult and the onset of recurrent seizures may reflect progressive maladaptive molecular and cellular changes that might be amenable to therapeutic manipulation. Although an attractive hypothesis, a unified picture of this process has yet to emerge. The most promising evidence has come from studies of tissue removed from patients undergoing temporal lobectomy and rodent models of limbic seizures.

In one experimental model, hyperexcitability is induced by repeated stimulation of limbic structures, such as the amygdala or hippocampus. The initial stimulus is followed by an electrical response (the afterdischarge) that becomes more extensive and prolonged with repeated stimuli until a generalized seizure occurs. This process, called *kindling*, can be induced by electrical or chemical stimuli. Many investigators believe that kindling may contribute to the development of epilepsy in humans.

Kindling is thought to involve synaptic changes in the hippocampal formation that resemble those important in learning and memory (Chapters 53 and 54). These include short-term changes in excitability and persistent morphological changes, including generation of adult-born neurons, axonal sprouting, and synaptic reorganization. Rearrangements of synaptic connections have been observed in the dentate gyrus of patients with long-standing temporal lobe seizures as well as following kindling in experimental animals. In addition to axonal sprouting (Figure 58–16), changes include alterations in dendritic structure, control of transmitter release, and novel expression and alterations in subunit stoichiometry of ion channels and pumps.

The long-term changes that lead to epilepsy also are likely to involve specific patterns of gene

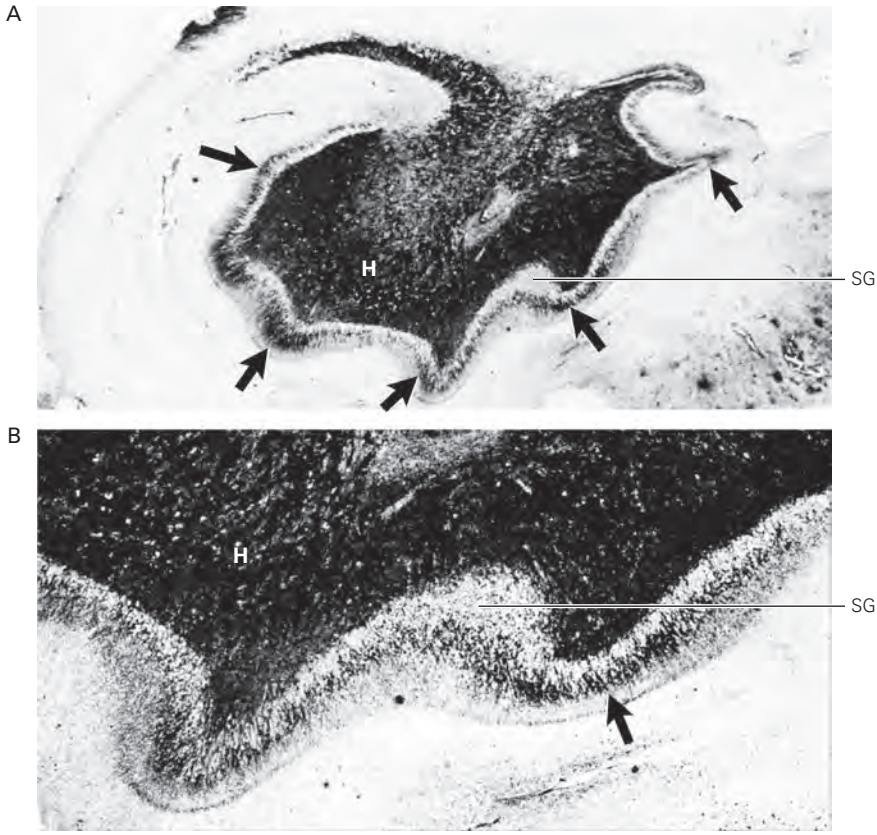

Figure 58–16 Mossy fiber synaptic reorganization (sprouting) in the human temporal lobe may cause hyperexcitability. (Reproduced, with permission, from Sutula et al. 1989. Copyright © 1989 American Neurological Association.)

A. Timm stain of a transverse section of hippocampus removed from a patient with epilepsy at the time of temporal lobectomy for control of epilepsy. The stain appears black in the axons of the dentate granule cells (mossy fibers) due to the presence of zinc in these axons. The mossy fibers normally pass through the dentate hilus (**H**) on their way to synapse on CA3 pyramidal cells. In the epileptic tissue shown here, stained fibers appear in the supragranular layer of the dentate gyrus (**SG, arrowheads**), which now contains not only the granule cell dendrites but also newly sprouted mossy fibers. These aberrant sprouts of mossy fibers form new recurrent excitatory synapses on dentate granule cells.

B. This high magnification of a segment of the supragranular layer shows the Timm-stained mossy fibers in greater detail.

expression. For example, the proto-oncogene c-*fos* and other immediate early genes as well as growth factors can be activated by seizures. Because many immediate early genes encode transcription factors that control other genes, the gene products that result from epileptiform activity could initiate changes that contribute to or suppress the development of epilepsy by altering such mechanisms as cell fate, axon targeting, dendritic outgrowth, and synapse formation.

Highlights

1. Seizures are one of the most dramatic examples of the collective electrical behavior of the mammalian brain. The distinctive clinical pattern of partial seizures and generalized seizures can be attributed to the distinctly different patterns of activity of cortical neurons.
2. Studies of focal onset seizures in animals reveal a series of events—from the activity of neurons in the seizure focus to synchronization and subsequent spread of epileptiform activity throughout the cortex. The gradual loss of GABAergic surround inhibition is critical to the early steps in this progression. In contrast, generalized onset seizures are thought to arise from activity in thalamocortical circuits, perhaps combined with a general abnormality in the membrane excitability of all cortical neurons.
3. The electroencephalogram (EEG) has long provided a window on the electrical activity of the cortex, both in normal phases of arousal and during abnormal activities such as seizures. The EEG

can be used to identify certain electrical activity patterns associated with seizures, but it provides limited insight into the pathophysiology of seizures. Several much more powerful and noninvasive approaches are now available to locate the focus of a partial seizure. This has led to the widespread and successful use of epilepsy surgery for selected patients, particularly those with complex partial seizures of hippocampal onset. The promise of invasive approaches to seizure detection and seizure prevention provides additional hope for improved control of seizures.

4. The increasing power of genetic, molecular, and modern cell-physiological approaches applied to the study of seizures and epilepsy also gives new hope that an understanding of these disruptions of normal brain activity will provide new therapeutic options for patients afflicted with epilepsy, as well as new insights into the function of the mammalian brain.
5. Further neurobiological studies of the progression from an acute seizure to the development of epilepsy should provide alternative strategies for treatment beyond the standard options of anticonvulsants or epilepsy surgery.

Gary Westbrook

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59

Disorders of Conscious and Unconscious Mental Processes

Although cognitive neuroscience emerged at the end of the 20th century as a major new discipline, a precise meaning of the term *cognition* remains elusive. The term is used in different ways in different contexts. At one extreme, the term *cognitive* in cognitive neuroscience connotes what was meant by the older term *information processing*. In this sense, cognition is simply what the brain does. When cognitive neuroscientists say that visual features or motor acts are *represented* by neural activity, they are using concepts from information processing. From this point of view, the language of cognition provides a bridge between descriptions of neural activity and behavior because the same terms can be applied in both domains.

At the other extreme, the term *cognition* refers to those higher-level processes fundamental to the formation of conscious experience. This is what is meant by the term *cognitive therapy*, an approach to treatment pioneered by Aaron Beck and Albert Ellis and developed from behavior therapy. Rather than trying to change a patient's behavior directly, cognitive therapy has the aim of changing the patient's attitudes and beliefs (Box 59–1).

In common parlance, the term *cognition* means thinking and reasoning, a usage closer to its Latin root *cognoscere* (getting to know or perceiving). Thus, the *Oxford English Dictionary* defines it as "the action or faculty of knowing." Indeed, we know the world by applying thinking and reasoning to the raw data of our senses.

This idea is implicit in our characterization of many kinds of disorders of cognition. After brain damage, some patients can no longer process the input supplied by the senses. This type of disorder was first delineated by Sigmund Freud, who called it agnosia, or loss of knowledge (Chapter 17). Agnosias can take many forms. A patient with visual agnosia can see perfectly well but is no longer able to recognize or make sense of what he sees. A patient with prosopagnosia has a specific problem recognizing faces. A patient with auditory agnosia might hear perfectly well but is unable to recognize spoken words.

Cognition is sometimes impaired from birth so that a person has difficulty in acquiring knowledge. This might lead to general mental retardation or, if the problem is more localized, to specific learning difficulties such as dyslexia (difficulty learning about written

Box 59–1 Cognitive Therapy

Dissatisfaction with psychological treatments based on Freud's theories of unconscious motivation intensified in the middle of the 20th century. Not only did these theories have no relevance to experimental psychology, but there was no empirical evidence that psychodynamic treatments actually worked.

The first form of alternative psychological therapy to emerge from laboratory studies is known as *behavior therapy*. The fundamental assumption of this approach is that maladaptive behavior is learned and can therefore be eliminated by applying the Pavlovian and Skinnerian principles of stimulus-response learning. So, for example, a child who has been attacked by a dog can become fearful of all dogs, but this fearful response can be extinguished if the child learns that the conditioned stimulus (the sight of a dog) is not followed by the unconditioned stimulus (being bitten).

Behavior therapy was shown to be quick and effective for phobias, but many mental disorders are better characterized in terms of maladaptive thinking rather than maladaptive behavior. In the 1960s, Aaron Beck and Albert Ellis initiated a new kind of therapy in which the principles of learning are used to change thoughts rather than behavior. This is known as *cognitive therapy* or *cognitive behavior therapy*.

This form of therapy has been particularly successful in the treatment of depression. Depression is typically associated with negative thoughts (eg, a person remembering only the bad things that have happened to him/her) and negative attitudes (eg, a person believing that he/she will never achieve his/her goals). Cognitive therapists teach their clients methods for reducing the frequency of negative thoughts and changing their negative attitudes into positive ones.

language) or autism (difficulty in learning about other minds). Finally, cognition can become dysfunctional so that the knowledge acquired about the world is false. These disorders of thinking lead to the sort of false perceptions (hallucinations) and false beliefs (delusions) associated with major mental illnesses such as schizophrenia.

Conscious and Unconscious Cognitive Processes Have Distinct Neural Correlates

Cognition—deriving knowledge through thinking and reasoning—is one of three components of consciousness (see Chapter 42 for discussion of the conscious aspects of emotions, often called feelings). The other two are emotion and will. It used to be taken for granted that thinking and reasoning were under conscious voluntary control and that cognition was not possible without consciousness. By the end of the 19th century, however, Freud developed a theory of unconscious mental processes and suggested that much human behavior is guided by internal processes of which we are not aware.

Of more direct importance for neuroscience was the idea of *unconscious inference*, originally proposed by Helmholtz. Helmholtz was the first to carry out quantitative psychophysical experiments and to measure the speed with which afferent signals in peripheral nerves are conducted. Prior to these experiments, sensory signals were assumed to arrive in the brain immediately (with the speed of light), but Helmholtz showed that nerve conduction was actually quite slow. He also noted that reaction times were even slower. These observations implied that a great deal of brain work intervened between sensory stimuli and conscious perception of an object. Helmholtz concluded that much of what goes on in the brain is not conscious and that what does enter consciousness (ie, what is perceived) depends on unconscious inferences. In other words, the brain uses evidence from the senses to decide on the most likely identity of the object that is causing activity in the sensory organs but does this without our awareness.

This view was extremely unpopular with Helmholtz's contemporaries and, indeed, still is today. Most people believe that consciousness is necessary for making inferences and that moral responsibility can be assigned only to decisions that are based on conscious inference. If inferences could be made without consciousness, there could be no ethical basis for praise or blame. Helmholtz's ideas about unconscious inferences were largely ignored.

Nevertheless, by the middle of the 20th century, evidence began to accumulate in favor of the idea that most cognitive processing never enters consciousness. After the development of electronic computers and the emergence of the study of artificial intelligence, researchers began to study how, and to what extent, machines could perceive the world beyond themselves.

It rapidly became clear that many perceptual processes that at first seem simple are actually very complex when defined as a set of computations.

Visual perception is the prime example. In the 1960s, almost no one realized how difficult it would be to build machines that could recognize the shape and appearance of objects, because it seems so easy for us. I look out of the window and I see buildings, trees, flowers, and people. I am not aware of any mental processes behind this perception; my awareness of all these objects seems instantaneous and direct. It turns out that teaching a machine how to work out which edges go with which object in a typical cluttered visual scene containing many overlapping objects is exceptionally difficult. The computational approach to vision revealed the underlying neural processes on which our seemingly effortless perception of the world depends. Similar processes underlie all sensory perception and especially the perception of sounds as speech. Most neuroscientists now believe that we are not conscious of cognitive processes, only our perceptions.

The evidence for unconscious cognitive processes comes not only from artificial intelligence studies but also studies of cognition in people with brain damage. The effects of unconscious processes on behavior can be demonstrated most strikingly in certain patients with "blind sight," a disorder first delineated in the 1970s by Lawrence Weiskrantz. These patients have lesions in the primary visual cortex and claim to see nothing in the part of the visual field served by the damaged area. Nevertheless, when asked to guess, they are able to detect simple visual properties such as movement or color far better than is expected by chance. Despite having no sensory-based perception of objects in the blind parts of the visual field, these patients do possess unconscious information about the objects, and this information is available to guide their behavior.

Another example is unilateral neglect caused by lesions in the right parietal lobe (Chapter 17). Patients with this disorder have normal vision, but they seem unware of objects on the left side of the space in front of them. Some patients even ignore the left side of individual objects. In one experiment by John Marshall and Peter Halligan, patients were shown two drawings of a house. The left side of one house was on fire (Figure 59–1). When asked if there were any differences between the houses, patients replied "no." But when asked which house they would prefer to live in, they chose the house that was not burning. This choice was thus made based on information that was not represented in consciousness. Blind sight and unilateral neglect are just two examples of the abundant empirical evidence for the existence of unconscious cognitive processes, evidence not available to us through introspection.

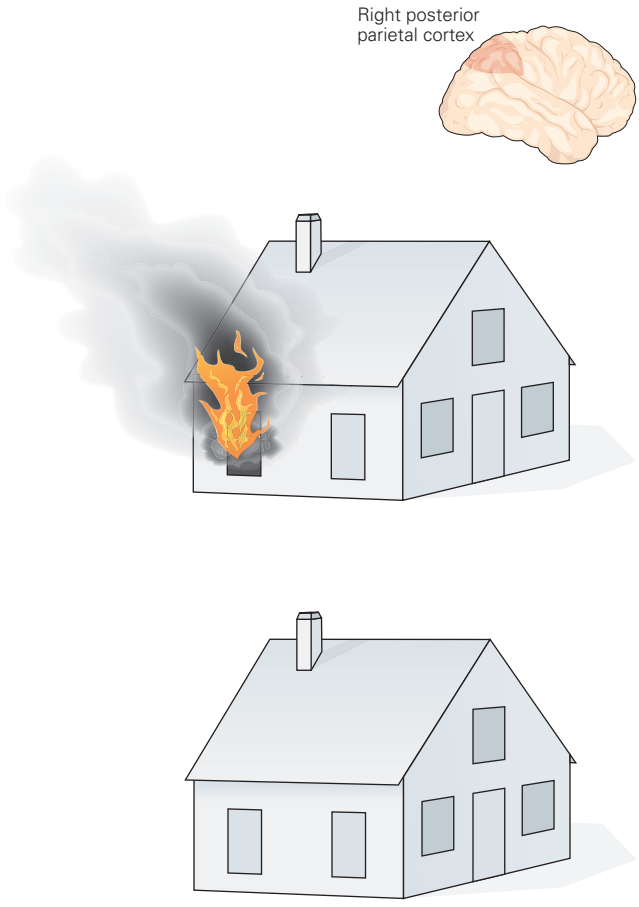


Figure 59–1 Unconscious processing in cases of spatial neglect. After damage to the right parietal lobe, many patients seem to be unaware of the left side of space (unilateral neglect syndrome). When such patients are shown the two drawings reproduced here, they say that the two houses look the same. However, they also say that they would prefer to live in the lower house, indicating that they have unconsciously processed the image of the fire in the other house. (Adapted from Marshall and Halligan 1988.)

Currently, one of the most exciting areas of investigation in neuroscience concerns the search for the *neural correlates of consciousness* initiated by Francis Crick and Christopher Koch. The aim is to demonstrate qualitative differences between the neural activity associated with conscious and unconscious cognitive processes. This research is important not only because it may give us answers to the difficult question of the function of consciousness but also because it is relevant to our understanding of many neurological and psychiatric disorders. The weird experiences

and delusional beliefs of patients with certain cognitive disorders were once dismissed as beyond understanding. Cognitive neuroscience provides us with a framework for understanding how these experiences and beliefs can arise from specific alterations in normal cognitive mechanisms.

Differences Between Conscious and Unconscious Processes in Perception Can Be Seen in Exaggerated Form After Brain Damage

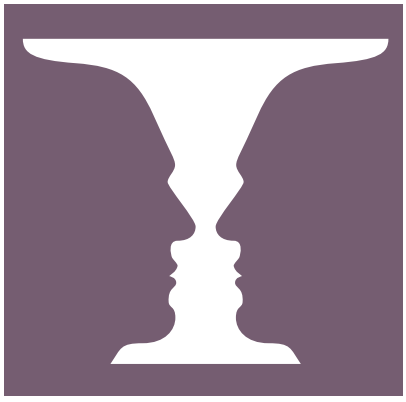
The relationship between sensory stimulation and perception is far from direct. Perception can change without any change in sensory stimulation, as illustrated by ambiguous figures such as the Rubin figure and the Necker cube (Figure 59–2). Conversely, a big change in sensory stimulation can occur without the observer being aware of this change—the perception remains constant. A compelling example of this is change blindness.

To demonstrate change blindness, two versions of a complex scene are constructed. In one well-known example developed by Ron Rensink, the picture consists of a military transport plane standing on an airport runway. In one of the two versions, an engine is missing. If these two pictures are shown in alternation on a computer screen, but critically interspersed with a blank screen, it can take minutes to notice the difference even though it is immediately obvious when pointed out. (See Figure 25-8 for another example.)

In light of these phenomena, we can explore the neural activity associated with changes in perception when there is no change in sensory stimulation. Likewise, we can discover whether changes in sensory input are registered in the brain even if not represented in consciousness. We can ask whether there is some qualitative difference between the neural activity associated with conscious as opposed to unconscious processes.

Two important results have emerged from studies of the neural activity associated with specific types of conscious percepts. First, certain kinds of percepts are related to neural activity in specific areas of the brain. Those brain areas that are specialized for recognition of certain kinds of objects (eg, faces, words, landscapes) or for certain visual features (eg, color, motion) are more active when the object or the feature is consciously perceived (Figure 59–3). For example, when we perceive the faces in the Rubin figure, there is more activity in the area of the fusiform gyrus, which is specialized for the processing of faces.

This observation also applies to deviant perception (hallucinations). After degeneration of the peripheral visual system leading to blindness, some patients experience intermittent visual hallucinations (Charles Bonnet syndrome). These hallucinations vary from one patient to another: Some patients see colored patches, others see grid-like patterns, and some even see faces. Dominic ffytche found that these hallucinations are associated with increased activity in the secondary visual cortex, and the content of the hallucination is related to the specific locus of activity (Figure 59–4). Schizophrenic patients frequently experience complex auditory hallucinations, which usually have the form of voices talking to or about the patient. These



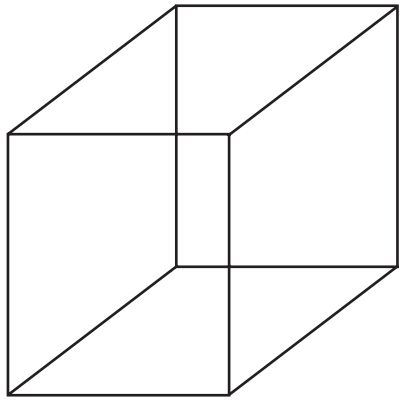


Figure 59–2 Ambiguous figures. If you stare at the figure on the left (the Rubin figure), you sometimes see a vase and sometimes two faces looking at each other. If you stare at the figure on the right (the Necker cube), you see a three-dimensional cube, but the front face of the cube is sometimes seen at the bottom left and sometimes at the top right. In each figure, the brain finds two equally good, but mutually exclusive, interpretations of what is there. Our conscious perception spontaneously alternates between these two interpretations.