Higher Cortical Visual Disorders

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REVIEW ARTICLE

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ABSTRACT

PURPOSE OF REVIEW: This article reviews the disorders that result from disruption of extrastriate regions of the cerebral cortex responsible for higher visual processing. For each disorder, a historical perspective is offered and relevant neuroscientific studies are reviewed.

RECENT FINDINGS: Careful analysis of the consequences of lesions that disrupt visual functions such as facial recognition and written language processing has improved understanding of the role of key regions in these networks. In addition, modern imaging techniques have built upon prior lesion studies to further elucidate the functions of these cortical areas. For example, functional MRI (fMRI) has identified and characterized the response properties of ventral regions that contribute to object recognition and dorsal regions that subserve motion perception and visuospatial attention. Newer network-based functional imaging studies have shed light on the mechanisms behind various causes of spontaneous visual hallucinations.

SUMMARY: Understanding the regions and neural networks responsible for higher-order visual function helps the practicing neurologist to diagnose and manage associated disorders of visual processing and to identify and treat responsible underlying disease.

INTRODUCTION

The diagnosis of disorders of higher visual processing often poses a considerable clinical challenge.[1,2] While lesions affecting the eye, optic nerve, chiasm, radiations, or primary visual cortex present with easily recognized patterns of monocular, bitemporal, or homonymous visual field loss, lesions in higher-order visual areas affect vision in nuanced ways specific to the particular functions of those areas. Patients with disorders of higher visual processing may have difficulty describing their symptoms, and routine evaluations of visual function may not readily identify the problem. A refined examination of higher visual functions is often necessary to correctly localize and identify these syndromes.

The original detailed descriptions of each disorder of higher visual processing, often from European literature from the 19th century and early 20th century, demonstrate how careful clinical observation coupled with postmortem anatomic investigation yielded tremendous insights that contributed to the foundations of modern neurology. More recently, scientific investigations using functional neuroimaging and other techniques have offered further insights into the complex

CITE AS:
CONTINUUM (MINNEAP MINN) 2019; 25(5, NEURO-OPHTHALMOLOGY): 1329–1361.

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Dr Prasad serves as an associate editor for the *Journal of Neuro-Ophthalmology*, receives publishing royalties from McGraw-Hill, and has provided expert medicolegal opinion on legal cases involving idiopathic intracranial hypertension, ischemic optic neuropathy, and traumatic brain injury. Dr Dinkin serves as an associate editor for the *Journal of Neuro-Ophthalmology* and as an editor for *Practical Neurology* and has received compensation for travel for speaking engagements from The American Austrian Foundation and research/grant support from the Helen and Robert Apel Foundation. Dr Dinkin has provided depositions and expert testimony on medicolegal cases involving idiopathic intracranial hypertension, ischemic optic neuropathy, and head trauma.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
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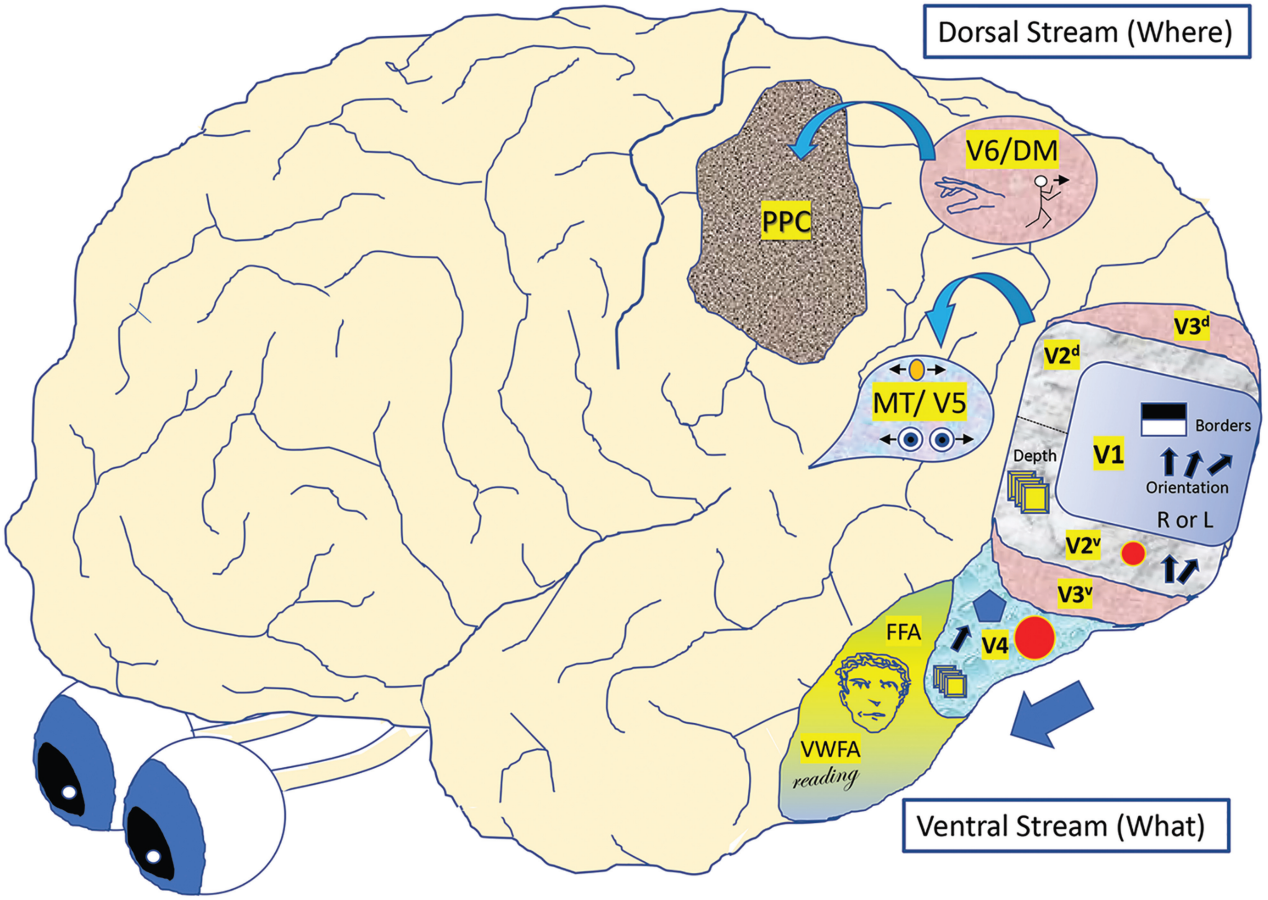

FIGURE 7-1

Simplified representation of striate and extrastriate cortical regions involved in visual processing. Visual data feed anteriorly through successive specialized regions of the extrastriate cortex (V1–V6). These regions of the extrastriate cortex are considered part of either the ventral or dorsal stream. V1, the striate cortex, lies posteriorly and receives raw visual information from the optic radiations. The basic position and orientation of borders of visual stimuli are encoded at this level. The ventral stream, which processes features of visual object identity (the "what" pathway) begins with $V2^v$ (ventral V2), which begins to analyze color and the foreground/background (level of depth) of visual stimuli. Further processing occurs in $V3^v$ and continues in V4, which plays an important role in color discrimination and contains neurons whose response frequency is tuned to different wavelengths of light. Basic geometric shapes are encoded at this level as well. Information is fed anteriorly to the inferotemporal cortex, where the fusiform face area (FFA) resides, encoding facial features to enable efficient facial recognition. The visual word form area (VWFA) also resides within the fusiform gyrus and, when disrupted, may cause pure alexia, without associated hemianopia. Visual spatial processing proceeds along the dorsal stream or "where" pathway in $V2^d$ and $V3^d$ and feeds anteriorly to the mesial temporal visual area (MT/V5), which plays an important role in the perception of motion. The dorsomedial cortex (V6/DM) responds to visual stimuli associated with self-motion and helps guide reaching and other visually guided motor actions. Further visuospatial processing occurs in the posterior parietal cortex (PPC).

L = left; R = right.

structure-function relationships of the human visual system. Disorders of higher visual processing not only have significant clinical importance but also shed light on important neuroscientific questions regarding normal visual processing in the brain. Visual disorders resulting from discrete lesions in the brain's visual processing areas often highlight the ways in which higher visual functions may be separable, leaving certain aspects of visual processing preserved while others are impaired.

KEY POINT

● After initial processing in the primary visual cortex, numerous adjacent cortical areas continue the work of analyzing specific aspects of visual information. These areas, which are situated in the occipital, temporal, and parietal lobes, are given names such as V2, V3, V4, V5, lateral occipital area, or fusiform face area.

PRIMARY VISUAL CORTEX AND HIGHER VISUAL AREAS

Visual inputs to the brain are conveyed from the anterior visual pathway through the lateral geniculate nucleus of the thalamus and then the optic radiations to arrive in the primary visual cortex, also called *area V1*, on the mesial surface of the occipital lobe. No other area of the brain receives such concentrated afferent sensory input. The abundant myelinated axons of the optic radiations synapse in cortical layer 4, where they are visible even on gross inspection of the brain, forming what is termed the *stripe of Gennari*.[3] (This distinctive feature gives the primary visual cortex its other names, which are *striate* [striped] or *calcarine* [chalky] cortex.) An important feature of the primary visual cortex is that the arrangement of its inputs is strictly retinotopic, precisely corresponding to spatial locations in the contralateral homonymous visual field. Neurons in the primary visual cortex are selective for specific orientations of luminance contrast; thus, the response properties of these neurons endow them with the ability to identify the edges of a visual object.[4] In addition, initial processing of color composition, brightness, and direction of motion occurs in the primary visual cortex.[5]

After the initial processing in the primary visual cortex, numerous adjacent cortical areas continue the work of analyzing specific aspects of visual information. These areas, which are situated in the occipital, temporal, and parietal lobes, are given names such as V2, V3, V4, V5, lateral occipital area, and fusiform face area (FIGURE 7-1). A key property of the organization of the cortical visual system is that the size and complexity of a neuron's receptive field progressively increases from lower-order to higher-order processing areas. Unlike the retinotopic organization in the primary visual cortex, where responses greatly depend upon circumstantial variables such as the position, orientation, and lighting of an object within the visual field, in higher-order visual areas, responses show considerable constancy despite changes in viewing conditions.[6,7] Neuronal representations in these higher areas do not possess the strict point-to-point retinotopic arrangement that is seen in lower areas.[8] In higher cortical areas, integrated information processing endows neurons with receptive fields responsive to content and context rather than the simpler aspects of image composition.

THE DORSAL AND VENTRAL STREAMS

The visual processing areas that follow area V1 are spatially arranged by the type of processing that they perform. The overarching concept of a dorsal ("where") pathway and ventral ("what") pathway was put forth by Ungerleider and Mishkin[9] in 1982. They proposed that occipitotemporal areas in the ventral stream selectively process the identity of visual objects, with regions that are specialized for identifying faces, specific objects, or visual scenes. Meanwhile, occipitoparietal areas in the dorsal stream are selective for spatial features of

visual processing, such as the direction and speed of motion; previously, subcortical areas such as the superior colliculus were thought to be the major contributors to the spatial aspects of visual processing.

Ungerleider and Mishkin supported the dorsal/ventral stream model with several converging lines of evidence, relying heavily on experiments previously published by Pohl[10] in which selective lesions were placed in the frontal, parietal, or temporal lobes of macaque monkeys. Monkeys with parietal lesions had significant difficulty judging spatial relationships between objects. Conversely, monkeys with temporal lobe lesions showed impaired performance on an object identification task.

Ungerleider and Mishkin's influential "what/where" concept of visual processing provides a useful framework with which to localize the clinical syndromes that occur in humans when a discrete lesion causes a specific disorder of higher visual processing. One criticism of this classification of the visual systems, however, is that the distinction is not absolute and categorical; to some

CASE 7-1

A 48-year-old man presented with complete loss of vision following bilateral occipital cardioembolic strokes. He denied blindness and said he felt "super" (VIDEO 7-1). He confabulated that he could see objects in front of him but when asked to describe them in detail, said "I don't know how to tell." He had no difficulty identifying objects when he held them in his hand. Even following demonstrations that he was not seeing properly, he insisted "my vision is OK." Despite the severe visual loss, the remainder of his mental status examination was normal, and the fundus examination and pupillary responses were normal. Diffusion-weighted MRI showed acute bilateral occipital infarcts (FIGURE 7-2). Several months later, the patient had mild improvement of vision, and he became fully aware of the extent of visual loss that remained.

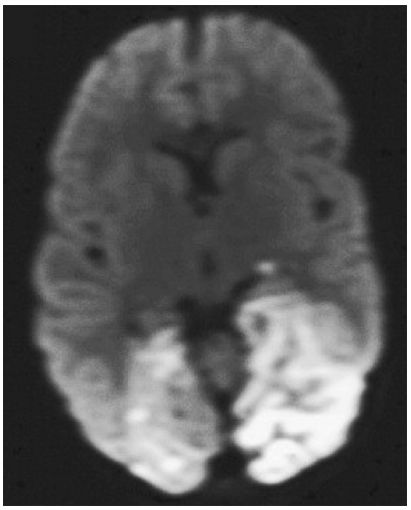

FIGURE 7-2
Imaging of the patient in CASE 7-1 with Anton syndrome. Axial diffusion-weighted MRI shows acute bilateral occipital infarcts with complete loss of vision following bilateral occipital cardioembolic strokes.

COMMENT

The case illustrates that when severe visual loss localizes to the bilateral occipital cortex, as opposed to the anterior visual pathway, the visual loss can be accompanied by the fascinating feature of anosognosia constituting Anton syndrome.

degree, significant overlap exists in the specialization of discrete visual areas and their functions are not fully separable. Nevertheless, the conceptual framework retains important value, an idea nicely encapsulated by the cognitive psychologist Martha Farah: "It would be quite surprising if the visual system happened to conform to the precise meanings of English-language words like 'what,' 'where,' or for that matter, 'how.' The search for the perfect everyday word to label these neural systems, or the worry that not all features of these words' meanings are appropriate to describing these systems' functions, may distract us from the important points: the insight that there is extensive, if not total, division of labor between these two systems."[11]

KEY POINT

● Anton syndrome refers to cortical blindness with lack of awareness (ie, anosognosia) of the deficit.

ANTON SYNDROME

Anton syndrome refers to blindness due to bilateral occipital lesions with lack of awareness (ie, anosognosia) of the deficit.

Clinical Presentation

Patients with Anton syndrome have a dramatic presentation characterized by lack of awareness or denial of complete visual loss owing to bilateral occipital lesions (CASE 7-1). Even after direct demonstration of their severe visual loss, they remain certain that their vision has no significant impairment. They often confabulate responses when asked to describe the visual features of an object presented to them. The anosognosia accompanying cortical blindness generally wanes over weeks to months, as patients begin to demonstrate recognition of the loss of vision that has occurred. As with all cases of postgeniculate vision loss, the pupillary responses and optic nerve appearance on funduscopy remain normal.

Historical Background

In 1899, the Austrian neuropsychiatrist Gabriel Anton[12] described a 56-year-old woman who was unware of her severe acute visual loss. At autopsy, he found infarction of both occipital lobes. Based on these findings, he advanced the powerful concept of network connections in the brain, accounting for the fact that bilateral occipital lesions would produce profound visual loss while functional disturbances in distributed networks would give rise to anosognosia.

Neuroscientific Investigations

The precise neuroanatomic substrate for the loss of awareness of the profound vision loss in patients with Anton syndrome is not known, but a good deal of work has been done to try to elucidate the mechanisms that govern conscious awareness of vision in general. One model proposes that activity in regions of the visual cortex immediately downstream of area V1 form the neural correlate of visual awareness. For example, using functional MRI (fMRI) to assess responses to visual masking illusions (in which the same simple stimulus is either perceived or not perceived depending on the timing of presentation of a specific surrounding context), Tse and colleagues[13] found that activity in area V3 and other downstream regions of the extrastriate cortex correlated with visual awareness. In contrast, activation in areas V1 and V2 did not reflect conscious visual perception.

Along these lines, some investigators emphasize that the intensity of activation in visual areas is a critical component of awareness. Moutoussis and colleagues[14]

CASE 7-2

A 23-year-old woman presented with severe visual impairments after hypoxic arrest from a narcotic overdose. She described her vision as distorted or blurred. She could tell an object was in front of her but could not tell what it was. Faces were "completely distorted" (VIDEO 7-2). She could not identify any visually presented objects, could not read letters, and could not copy simple line drawings correctly. Visual acuity, tested with the preferential looking test (in which the patient directs the eyes toward a set of black-and-white stripes, with the thickness of the stripes in some examples approximating 20/20 vision) was normal, and she had no other cognitive deficits. Despite the profound difficulty with visual processing, she avoided obstacles when walking, reached for targets, and grasped objects accurately. Fluid-attenuated inversion recovery (FLAIR) MRI showed sulcal hyperintensity from hypoxic injury in occipital areas (FIGURE 7-3).

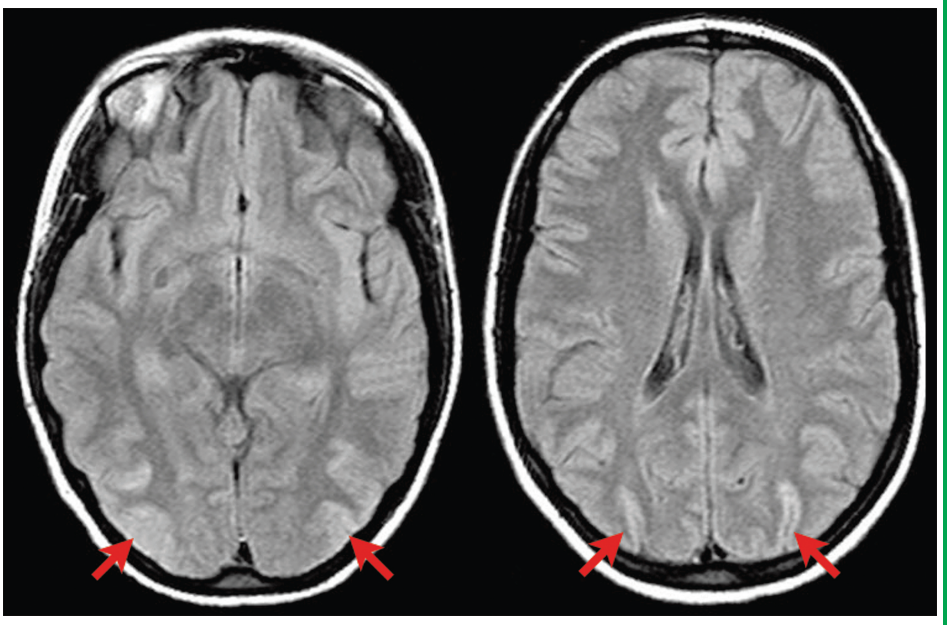

FIGURE 7-3
Imaging of the patient in CASE 7-2 with apperceptive visual agnosia. Axial fluid-attenuated inversion recovery (FLAIR) MRIs show bilateral occipital cortical hyperintensities (*arrows*).

COMMENT

This case exemplifies the profound visual processing defect that occurs with apperceptive visual agnosia, obliterating visual object recognition although elementary visual acuity remains essentially normal, with relative sparing of reaching, grasping, and navigating under visual guidance.

used a dichoptic color fusion experimental paradigm (in which simple two-colored line drawings of houses or faces were shown to each eye with either the same color contrast, so the composite image was visible to the subject, or the opposite color contrast, so the composite image was invisible). fMRI data collected during this experiment revealed that the same face-responsive areas and house-responsive areas were activated in both conditions but activated more strongly in the condition in which the objects were perceived consciously. These data suggest that it is not just the presence but also the strength of activation in key visually responsive areas that may determine visual awareness.

Another model proposes that visual awareness involves more distributed regions of the brain, including frontoparietal areas. Lumer and colleagues[15,16] used a binocular rivalry experiment (presenting a face to one eye and moving stripes to the other eye) while fMRI images were acquired to elucidate which regions reflected the conscious perception of a particular image. The authors found that activation in the extrastriate visual cortex, inferior parietal areas, and prefrontal areas together correlated with conscious visual perception. These findings emphasize that conscious visual perception may be determined by interactions in widely distributed networks rather than modular activation in specific visual areas.

Godwin and colleagues[17] built on this idea by showing that visual awareness relates to decreased modularity of functional networks of the brain. They used graph theory analytical methods to evaluate functional connectivity fMRI data acquired during a visual masking experiment (in which presentation of a visual target stimulus may or may not have been consciously perceived depending on the masking effect of a second brief stimulus that was shown almost immediately before or after the target). Their results showed that conscious perception correlated with distributed cortical areas activating in concert rather than as separate modules.

It remains unclear which explanations will prove to best define the neural correlates of visual awareness, and the proposed models may not be mutually exclusive. It is clear, however, that the clinical phenomenon of Anton syndrome demonstrates how acute injury to the primary visual cortex can disrupt functioning of the neural mechanisms that normally allow recognition of a lack of vision.

KEY POINT

- **Visual agnosia refers to a specific impairment of the ability to recognize or interpret visually presented information although elementary aspects of vision remain intact.**

APPERCEPTIVE AND ASSOCIATIVE VISUAL AGNOSIA

Visual agnosia refers to a specific impairment of the ability to recognize or interpret visually presented information although elementary aspects of vision remain intact.

Clinical Presentation

Patients with visual agnosia cannot identify objects presented visually, but other cognitive functions are normal and patients have no difficulty identifying objects perceived through touch or sound (CASE 7-2). These patients cannot read because they incoherently process visual forms, so a standard eye chart cannot be used to measure the preserved visual spatial acuity. Despite the profound abnormality of visual processing, the spatial acuity remains essentially normal in these patients, which can be demonstrated with tests that do not require conscious visual processing. One example is the preferential looking test, in which a patient does not need to recognize or name any visual stimulus but

simply looks at black-and-white gratings if they are perceived. The different gratings comprise a range of spatial frequencies, including some that approximate 20/20 vision.

In apperceptive visual agnosia, although spatial acuity is preserved, the remaining steps of visual processing are disrupted at a very early stage, rendering patients unable to perceive even the most basic geometric relationships that create the contours of a visual object. For example, they cannot judge the position or orientation of a line; perceive the way in which a group of contours come together to create a coherent, unified perceptual whole; or judge how one visual object might overlap and partially obscure another. Essentially, their visual system does not perform the basic automatic geometric analyses that are the building blocks of visual perception.

Most cases of apperceptive visual agnosia result from anoxic injury, such as respiratory arrest or carbon monoxide poisoning.[18–20] Some patients with apperceptive visual agnosia will try to trace the visual stimulus overtly with a finger, or sometimes covertly with head movements, because the kinesthetic sense may allow them to perceive the composition of a shape based on its local contours.[19]

Historical Background

Heinrich Lissauer[21] described visual agnosia in an extensive case report published in 1889. He described an 80-year-old man with severe difficulty visually recognizing even the most common objects, but testing his vision in a manner akin to the preferential looking test showed that his visual acuity was essentially normal. After autopsy analysis of the case, Lissauer concluded that visual agnosia is caused by moderately extensive damage to the occipital cortex. Lissauer proposed the existence of two types of visual agnosia: *apperceptive*, in which the patient does not coherently perceive the geometric relationship of contours defining visual objects, and *associative*, in which the patient can perceive and even copy the shape of an object but is unable to recognize it.

Neuroscientific Investigations

Defining the edges of a visual object is a necessary step in the efficient handling of large volumes of visual information. Without the ability to segment an image into regions corresponding to objects, we would have no way of understanding complex visual stimuli and would fruitlessly try to recognize nonobjects composed of overlapping or juxtaposed items.

Area V2 makes significant contributions to image segmentation by manipulating the inputs it receives from area V1. The image segmentation that occurs at this stage is critically influenced not just by objective bottom-up inputs but also by internal top-down mechanisms representing the current perceptual interpretation of the visual stimulus. The Kanizsa triangle is a dramatic illustration of this phenomenon; when three "Pac-Man" figures are positioned in a specific orientation relative to one another, the image is perceived as being composed of a triangle lying atop three circles (FIGURE 7-4).[22] The edges of the perceived triangle are illusory and are not, in fact, part of the physical visual stimulus. In a remarkable illustration of the neural mechanisms underlying image segmentation and perceptual grouping, Von der Heydt and colleagues[23] showed that unlike neurons in area V1 that respond to true contours alone, neurons in cortical area V2 respond to illusory contours as well. This finding is supported by similar studies[24] also showing that neuronal processing in area V2 blurs the distinction between truth and perception.

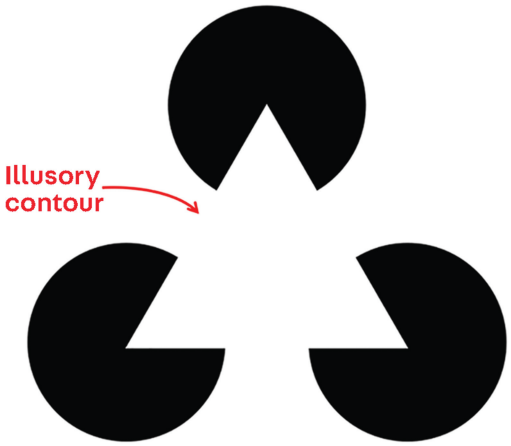

FIGURE 7-4
Efficient image segmentation in the visual system. The Kanizsa triangle is a vivid demonstration of the role of illusory contours in visual processing, allowing efficient image segmentation and perceptual grouping of objects.

Further insights about the nature of apperceptive visual agnosia emerged from landmark studies of a 35-year-old woman who experienced severe carbon monoxide poisoning in 1988.[20] Like other patients with apperceptive visual agnosia, she demonstrated severe deficits in shape recognition and orientation, despite preserved acuity, color vision, and tactile discrimination. When she was shown a mail slot at varying angles, she could not describe or match its orientation in space; however, when she reached her arm forward to put a card into the slot, her accuracy was perfect. Similarly, when she was shown objects of various sizes, she could not describe the dimensions; however, when she reached for the object, her grip aperture scaled perfectly relative to its size. Based upon these detailed psychophysical investigations, Goodale and Milner[25] refined the traditional concept of the Ungerleider-Mishkin what/where framework. They suggested that, in addition to its characterization as a "where" pathway, the dorsal stream should be recognized as a "how" pathway, emphasizing its role in using visual information to guide limb movements that allow a person to interact with and manipulate the environment. fMRI studies in this patient have supported their theory, revealing severe disruption of regions in the ventral stream but preserved activity in regions of the dorsal stream during visually guided motor actions.[26,27]

In patients with associative visual agnosia, as opposed to apperceptive visual agnosia, basic aspects of visual perception are generally preserved, but the visual percept is no longer associated with relevant stored semantic knowledge. In the words of Teuber,[28] the visual percept for a patient with associative visual agnosia becomes "stripped of its meaning." Patients with associative visual agnosia can see an object well enough to describe its appearance, make an accurate drawing of it, and correctly distinguish it as the same or different from other examples, although they cannot state its name or describe its purpose. In one well-documented case, a physician developed associative visual agnosia after hypoxic brain injury and described a stethoscope as a "long cord with a round thing at the end" and could not recognize what it was used for.[29] The failure of object recognition is limited to visual perception alone; patients are able to answer factual questions about objects and can recognize them when queried through other sensory modalities, such as touch or hearing.

CENTRAL HEMIACHROMATOPSIA

Abnormalities of color vision are a common consequence of disorders of the optic nerve or retinal photoreceptors, including congenital color blindness due

KEY POINTS

- In apperceptive visual agnosia, although spatial acuity is preserved, the remaining steps of visual processing are disrupted at a very early stage, rendering patients unable to perceive even the most basic geometric relationships that create the contours of a visual object.
- Associative visual agnosia describes a disorder in which basic visual perception is preserved, including grouping of visual forms, but visual percepts cannot be associated with relevant stored semantic knowledge.

KEY POINT

● Central hemiachromatopsia describes loss of color recognition in the hemifield contralateral to a lesion of V4, a region in which neurons are selectively responsive to specific wavelengths of light. In clinical practice, lesions often encompass this area as well as the adjacent inferior striate cortex (V1), causing an overlapping superior quadrantanopia, so that the achromatopsia is only evident in the seeing inferior visual field.

to inherited differences in the responses of cone photoreceptors. In these cases, the impairment of color vision affects one or both eyes. Lesions of the central nervous system can also lead to altered color perception in which the deficit is limited to one homonymous visual field. Such a deficit, called *central hemiachromatopsia*, arises when a lesion disrupts area V4 in the inferior occipital cortex, which is specialized for color vision processing in the contralateral hemifield.

Clinical Presentation

Although rare, a circumscribed lesion isolated to area V4 in one hemisphere would produce hemiachromatopsia affecting only the contralateral hemifield; other visual functions, including color vision in the ipsilateral visual field, would be spared. In clinical practice, it is more common to encounter a lesion that affects V4 in the inferior occipital cortex but also includes the inferior bank of the primary visual cortex. In this case, a contralateral superior field defect also occurs, and the color vision impairment in the contralateral hemifield will be detected only in the inferior quadrant (FIGURE 7-5, CASE 7-3).

Historical Background

In 1888, the Swiss ophthalmologist Louis Verrey[30] first reported loss of color vision isolated to a homonymous visual field. Carefully examining a 60-year-old woman, he found that color perception was abolished in one binocular hemifield and the colored object had to be brought into the other hemifield for its color to be recognized. At autopsy, he found that the patient had a hemorrhagic stroke

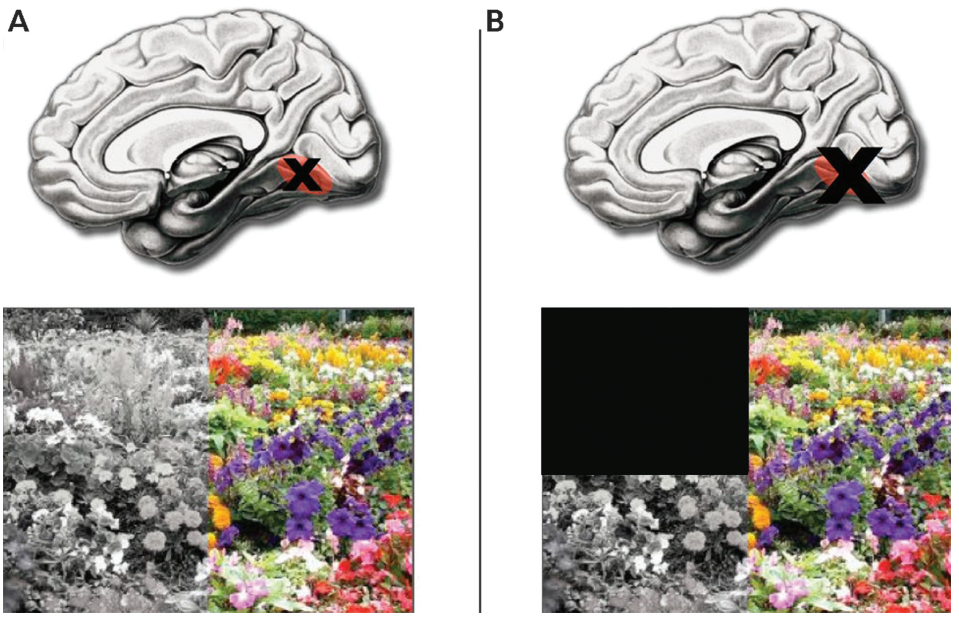

FIGURE 7-5

Consequences of lesions involving area V4. *A*, A lesion circumscribed to area V4 in the inferior occipital cortex (*red oval*) would cause loss of color vision perception in the contralateral homonymous visual field. *B*, In clinical practice, it is more common to see a lesion that involves area V4 but also involves the inferior bank of area V1, producing a loss of color vision perception in the contralateral homonymous visual field coupled with a contralateral superior quadrant field deficit.

in the inferior occipital cortex and concluded that this region was specialized for color vision in the contralateral hemifield. For many years, Verrey's notion of a cortical center for color was rejected, including by prominent neurologists such as Holmes,[31] because it was not yet appreciated that different aspects of visual processing were subserved by discrete cortical areas.

Neuroscientific Investigations

Verrey was finally vindicated in 1973, when Zeki[32] used single-cell recordings to identify a region of neurons in a macaque whose responses were, in fact, purely selective for color, with each neuron responding to a certain band of wavelengths. He named this cortical region area V4. Shortly afterward, the homologous cortical area specialized for color processing was identified in humans using functional neuroimaging.[33,34]

Color-specific cortical responses in human V4 have also been studied in patients undergoing intracranial EEG monitoring; direct electric stimulation of area V4 in

CASE 7-3

A 57-year-old woman presented with a left superior quadrant homonymous field deficit due to a right inferior occipital stroke. Examination showed that she was unable to discriminate colors in the left inferior homonymous field, saying that cards of various colors shown in that area were gray or white (VIDEO 7-3). Diffusion-weighted MRI showed acute right inferior occipital infarction involving the inferior bank of area V1 and area V4 (FIGURE 7-6).

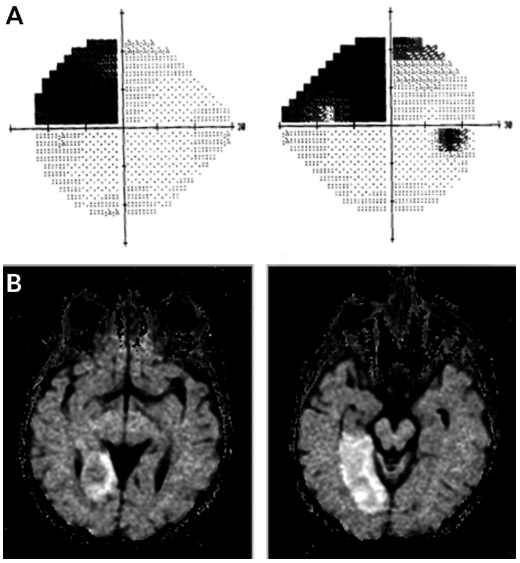

FIGURE 7-6
Findings of the patient in CASE 7-3 with central hemiachromatopsia. *A*, Automated perimetry shows left superior quadrant homonymous field deficit. *B*, Axial diffusion-weighted MRI shows acute right inferior temporooccipital infarction involving the inferior bank of V1 and area V4.

COMMENT

If the left superior quadrant homonymous field deficit were due to a lesion disrupting the inferior optic radiations (the Meyer loop), then color vision in the spared inferior quadrant would be expected to be normal. Instead, this case demonstrates loss of color vision in the spared inferior quadrant of the contralateral homonymous visual field, implicating a lesion in the inferior occipital cortex affecting both the inferior bank of area V1 and area V4.

these patients produces alterations in color perception.[35] In addition to its critical role in color processing, area V4 plays an important role in processing form, such as the aspect ratio and spatial frequencies of a visual stimulus.[36] It is the major source of input to downstream areas in the temporal lobes that process different types of visual objects.

Since Verrey's time, much has been learned about how color vision is analyzed at each level of the visual system before the specialized processing that occurs in area V4 within occipital cortex. Color vision inputs are processed and relayed from retinal cone photoreceptors to P-type retinal ganglion cells, to parvocellular cell layers in the lateral geniculate nucleus, to blob and interblob regions in layers 2 and 3 of primary visual cortex, to the thin stripes of area V2, and finally to area V4. Unlike all the color-responsive areas before it, however, area V4 is unique in that it encodes a key aspect of color perception called *color constancy* (FIGURE 7-7). The normal perception of the color of an object not only accounts for the wavelengths of light that are reflected by the object but also the spectral composition of the lighting conditions. For example, a red bike will reflect very different wavelengths of light in daylight or dusk or under a fluorescent light bulb, but it will generally be perceived as being red in all these conditions. Before area V4, color-responsive neurons convey information about the precise wavelengths of light that are reflected from the object and are significantly influenced by changes in overall illumination. Remarkably, this is not the case in area V4; processing in V4 adjusts for the spectral balance of incident light so that the redness of the bike is perceived as being fairly constant despite considerable differences in lighting environments. As Land[37] showed in 1977, V4 neurons are not influenced by changes in illumination, and their responses match the color that is consciously perceived. V4 neurons accomplish color constancy because their receptive fields have large inhibitory surrounds,[38] allowing correction for wavelengths comprising the background illumination.

In addition to hemiachromatopsia that results from a lesion in area V4, other cortical disorders relating to color processing also exist. *Color anomia* is a categorical language disorder in which patients have a specific impairment in producing the names of colors but can name other types of objects.[39] Color

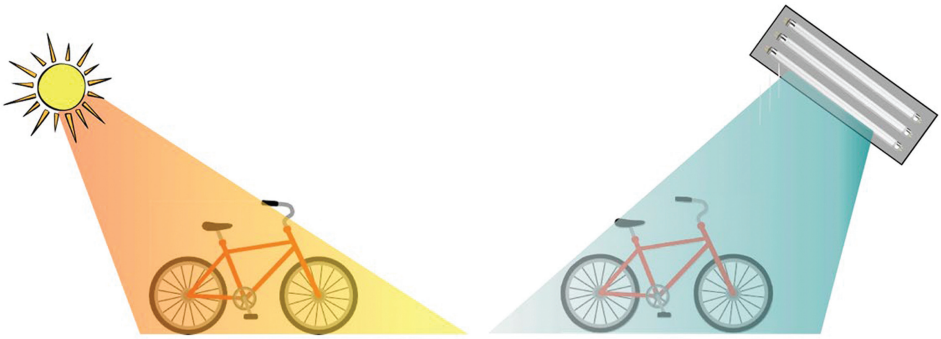

FIGURE 7-7

Color constancy. A red bike is perceived as red despite considerable changes in lighting conditions. Lower-level areas processing color signals, beginning with cone photoreceptors in the retina, are sensitive to the exact wavelengths of light being reflected in these settings. In contrast, area V4 accounts for the ambient spectra of light to achieve the psychophysical property of color constancy.

perception is intact in this disorder; although colors cannot be named correctly, performance remains normal on a color-matching task. Another entity referred to as *color agnosia* lacks a clear definition and has been interpreted in various ways.[40–42] The most common interpretation is that it refers to impaired semantic knowledge about colors despite intact color perception (eg, not knowing that a strawberry is red or a school bus is yellow).

ALEXIA WITHOUT AGRAPHIA

Alexia without agraphia, also referred to as *pure alexia* or *pure word blindness*, describes the loss of the ability to read, although the ability to write remains intact (CASE 7-4).

Clinical Presentation

The deficiency in alexia without agraphia is limited to the perception of written language; production and comprehension of spoken language is fully preserved, indicating that the patient does not have a broader aphasia and that language areas remain intact. Patients with alexia without agraphia read extremely slowly and make numerous errors. They may try to compensate by using letter-by-letter reading but frequently confuse similar looking letters. They have extreme difficulty with irregular phonemic words (such as *yacht* or *colonel*.) Degraded writing, such as handwriting rather than typed script, often poses even greater challenges. Remarkably, patients will not be able to read a sentence that they have written themselves.

In most cases, alexia without agraphia results from a lesion in the left occipital cortex that also involves the splenium of the corpus callosum. Alexia occurs because vision cannot be transmitted to intact language areas; there is no vision processing in the left occipital cortex, and the splenium lesion disconnects visual areas in the right occipital cortex from the left hemisphere (FIGURE 7-9). As such, alexia without agraphia is a type of disconnection syndrome in which primary regions responsible for neurologic function are intact (in this case, vision within the left field and language centers), but pathways allowing cross talk between them are not.

In rare cases, a version of alexia without agraphia can occur without a right homonymous hemianopia. These cases result from a discrete lesion situated in the visual word form area in the fusiform gyrus (FIGURE 7-10).[43]

Historical Background

The syndrome of alexia without agraphia was first described by Joseph Jules Dejerine[44] in 1892 in a 68-year-old man who was walking in Paris when he suddenly noticed that he could no longer read. Dejerine found that the patient had normal spoken language, with no trace of aphasia. The patient's writing was normal, with no mistakes or spelling errors. However, it was impossible for the patient to read. The patient was frustrated, writing words and then saying, "I still know how to write letters; here they are; why am I unable to read them?"[44] Dejerine called the deficit *pure word blindness*. The patient had a right homonymous visual field deficit, as occurs in most (but not all) patients with alexia without agraphia. At autopsy, the patient was found to have an ischemic stroke affecting the left occipital lobe, extending anteriorly to involve the splenium of the corpus callosum.

Dejerine knew that normal reading requires that vision be linked to language areas in the dominant hemisphere, and he reasoned that the syndrome

KEY POINTS

- Processing in V4 adjusts for the spectral balance of incident light so that the apparent color of an object is perceived as being fairly constant despite considerable differences in lighting environments. This phenomenon is known as *color constancy*.
- Alexia without agraphia, also referred to as *pure alexia* or *pure word blindness*, describes the loss of the ability to read, although the ability to write remains spared. It is often the result of a lesion affecting both the left occipital cortex and the splenium of the corpus callosum. A right homonymous hemianopia ensues, while visual information in the right occipital cortex cannot reach the left-sided language areas to allow linguistic analysis of the visualized symbols.
- Alexia without agraphia may also result from a single lesion in the visual word form area within the fusiform gyrus.

CASE 7-4

A 41-year-old man with an infiltrating glioma involving the left occipital lobe and splenium of the corpus callosum (FIGURES 7-8A and 7-8B) had a profound inability to read words with both regular or irregular phonemic spelling, although writing and spoken language remained normal. He was unable to read a sentence he had written himself, saying "I don't know, it's almost like I didn't write it" (VIDEO 7-4). Examination demonstrated a right superior greater than inferior homonymous hemianopia (FIGURE 7-8C).

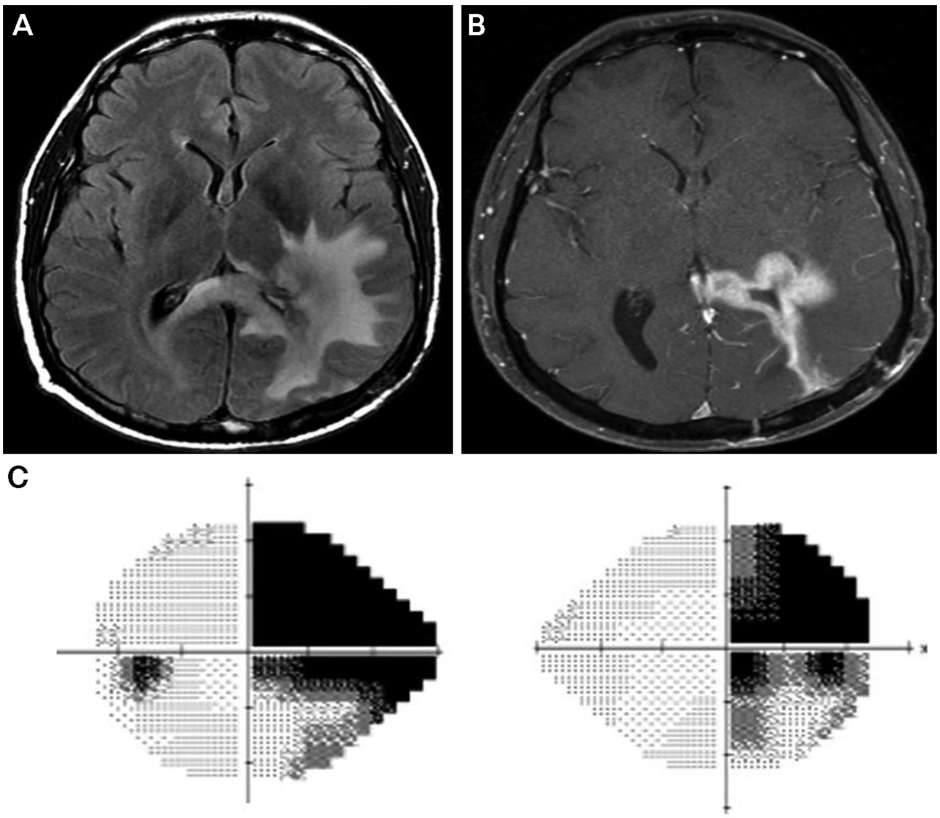

FIGURE 7-8
Findings of the patient in CASE 7-4. *A,* Axial fluid-attenuated inversion recovery (FLAIR) MRI demonstrates edema within the left occipital and temporal cortices and across the splenium of the corpus callosum. *B,* Axial contrast-enhanced T1-weighted MRI demonstrates enhancing tumor extending into the left occipital cortex. *C,* Humphrey automated perimetry demonstrates a right superior greater than inferior hemianopia.

COMMENT

This case demonstrates pure alexia. The ability to write remains normal, and the patient has no disturbance of spoken language. Language areas in the left hemisphere remain intact, but the connections from visual areas are disrupted, rendering the patient unable to read the language in which he was once fluent. As in most cases of alexia without agraphia, the responsible lesion involves the left occipital cortex and crossing fibers in the splenium of the corpus callosum. As such, a right homonymous field defect is also present.

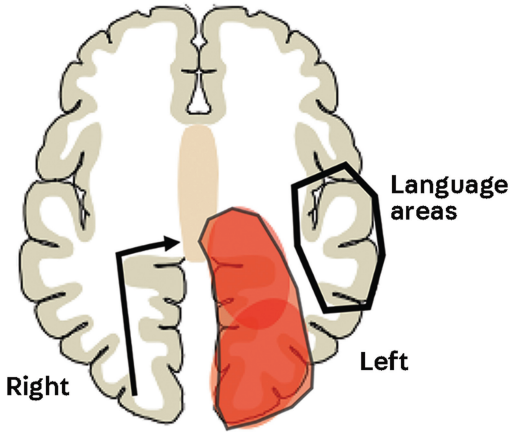

FIGURE 7-9
Anatomy of alexia without agraphia showing disconnection of intact vision in the right hemisphere from language areas in the left hemisphere.

of alexia without agraphia occurred when visual information could no longer be relayed to intact language areas. The large left occipital lesion in this patient disrupted any visual information being processed in the left occipital lobe, and the posterior corpus callosum involvement meant that visual information in the right occipital lobe was disconnected from intact language areas on the left (FIGURE 7-8C).

Neuroscientific Investigations

Geschwind[45] popularized the idea that alexia without agraphia was one of the classic neurologic disconnection syndromes. The Damasios[46] subsequently analyzed a series of cases and confirmed the localization of lesions to the left occipital lobe, compromising both interhemispheric and intrahemispheric visuo-language pathways. Since that time, functional imaging studies have shown that a

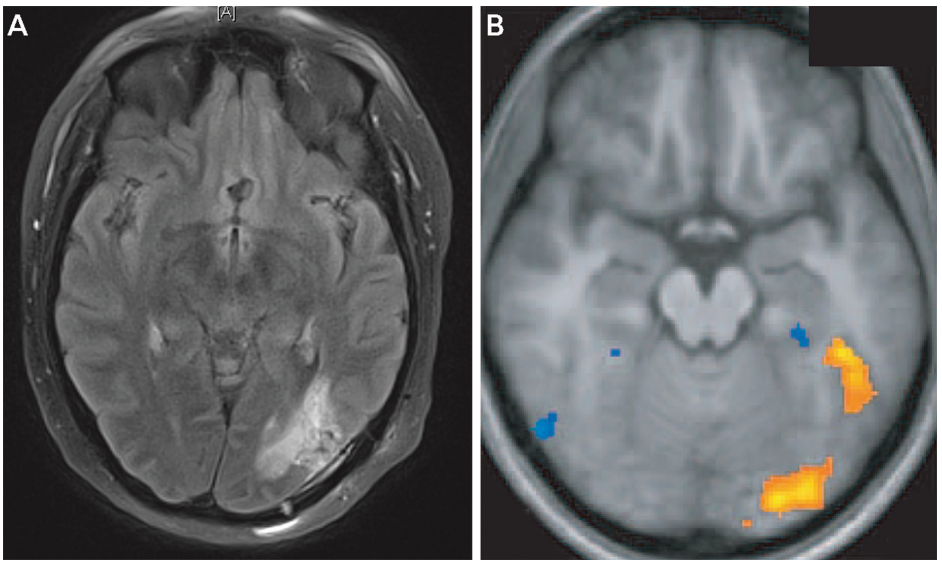

FIGURE 7-10
Pure alexia and the visual word form area. A 59-year-old woman developed difficulty reading due to a glioblastoma involving the visual word form area in the left occipitotemporal lobe. Writing and spoken language were normal. Visual field testing was also normal, without a homonymous field deficit. *A*, Axial fluid-attenuated inversion recovery (FLAIR) MRI of this patient showing postsurgical changes following biopsy of a left lateral occipitotemporal glioblastoma. *B*, Functional MRI (fMRI) showing the location of the visual word form area (*yellow areas*) in healthy individuals demonstrated by experiments identifying responses selective for written words more than nonword stimuli otherwise matched for the amount of visual information.
Panel B reprinted with permission from Dehaene S, Cohen L, Trends Cogn Sci.[43] © 2011 Elsevier Ltd.

particular region in the left inferior occipital lobe known as the visual word form area is specialized for words compared to other arbitrary symbols.[47,48] A 2005 investigation using MRI diffusion tensor tractography in a patient with alexia without agraphia demonstrated a reduction of interoccipital fibers and left occipitotemporal fibers.[49] Some have suggested that alexia without agraphia is a circumscribed type of simultanagnosia, impairing the ability to process multiple letters at a time and thus forcing the patient to read letter by letter.[50]

Conversely, agraphia without alexia, in which reading is intact but motor output of written graphemes is impaired, may occur in the setting of a left

CASE 7-5

A 37-year-old woman presented with difficulty distinguishing faces due to a metastatic lesion involving the right occipitotemporal cortex in the fusiform face area. She said that faces look "smoother and less defined." She called it the "Instagram filter in my brain" (VIDEO 7-5). The remainder of her examination was normal, including visual acuity and visual field testing. Brain MRI showed a large postoperative surgical resection cavity in the right inferior temporal cortex (FIGURE 7-11).

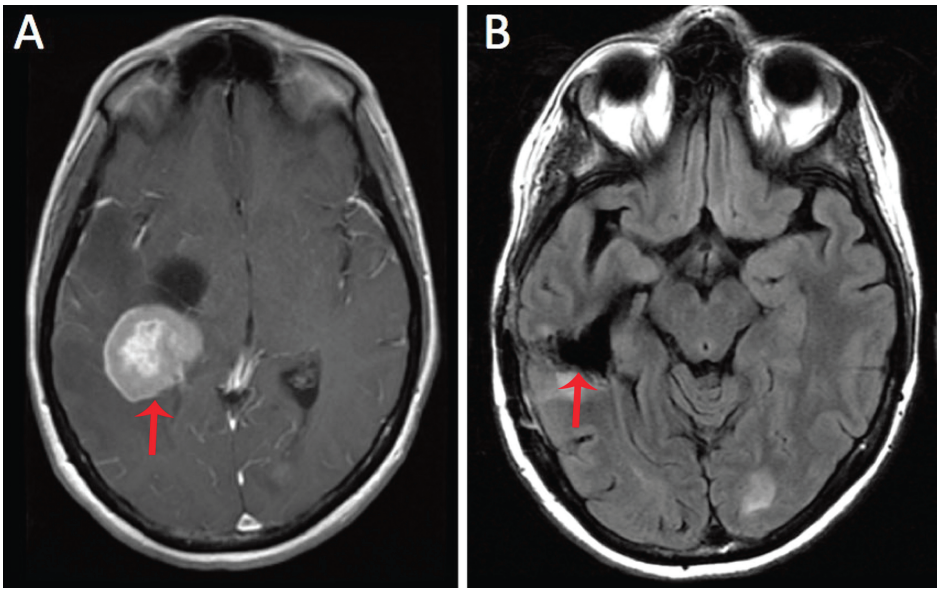

FIGURE 7-11
Imaging of the patient in CASE 7-5 with prosopagnosia. *A*, Axial postcontrast T1-weighted MRI shows a large metastatic lesion in the right temporal lobe (*arrow*). *B*, Postoperative fluid attenuated inversion recovery (FLAIR) MRI shows the surgical resection cavity in the right temporal lobe (*arrow*). The lesion disrupts the fusiform face area, which contributes to the normal visual processing of faces as a special category of objects.

COMMENT

This case illustrates the specific isolated deficit in visual processing of faces that can result from a lesion that affects face-selective processing areas in the inferotemporal cortex.

angular gyrus lesion.[51] When agraphia is accompanied by acalculia, left-right confusion, and finger agnosia (the inability to name the different fingers), it is known as *Gerstmann syndrome*.[52]

KEY POINT

● Prosopagnosia is a specific form of visual agnosia in which face perception is impaired while elementary aspects of vision, such as acuity and visual field, remain intact.

PROSOPAGNOSIA

Prosopagnosia is a specific form of visual agnosia in which face perception is impaired while elementary aspects of vision, such as acuity and visual field, remain intact (CASE 7-5).

Clinical Presentation

Patients with prosopagnosia lack the ability to perceive the unique features that distinguish an individual face from others. They have significant difficulty recognizing the identity of a face or distinguishing whether it is familiar to them. When looking in a mirror, even their own face is not recognized as being their own. Typically, patients with this debilitating disorder rely on identifying individuals by using other clues, such as gait, physical mannerisms, clothing, or voice.

Historical Background

The term *prosopagnosia* was first used by Bodamer[53] in 1947. He described three patients who lost the ability to identify faces after sustaining injury to the occipitotemporal lobes. One of these cases was a 24-year-old man who had suffered a bullet wound to the left occipitotemporal lobe and then described faces as looking "blurred, pressed flat, without particular expressions." He described an inability to see what was special or unique about an individual face. Bodamer performed an experiment in which the man was unable to distinguish his wife when she stood beside several nurses who were of a similar height and weight and dressed the same. He concluded that normal visual perception includes specialization for face processing and defined prosopagnosia as the selective disruption of this capacity.

Neuroscientific Investigations

Human beings are expert at extracting information from a face to accurately and effortlessly identify it. In many ways, most people are face experts, possessing a critical ability to discern subtle identifying features between one face and the next. Unlike the generality with which we identify many other objects, in most cases, the specific identity of a face must be determined. Adding to this complexity is the fact that the exact visual information contained in the contours of a face can be highly variable depending on the viewing angle and illumination.

Human expertise for face perception stems from a specialized group of neurons in the ventral processing stream known as the *fusiform face area*. Kanwisher and colleagues[54] first identified this area of inferior occipitotemporal cortex in their 1997 fMRI experiments detecting areas that were selectively more responsive to faces than other types of objects or scrambled images (FIGURE 7-12). The concept that face identification has a privileged status in the visual system was not unique, however. For example, the 17th century Italian artist Giuseppe Arcimboldo created a popular series of paintings depicting a bowl of fruit or vegetables, but when the paintings were inverted, it became very easy to see a face "hiding" in the picture (FIGURE 7-13[55,56]). Over 400 years before Kanwisher's fMRI experiments identified the fusiform face area, Arcimboldo was well aware of the human visual system's innate tendency to see faces

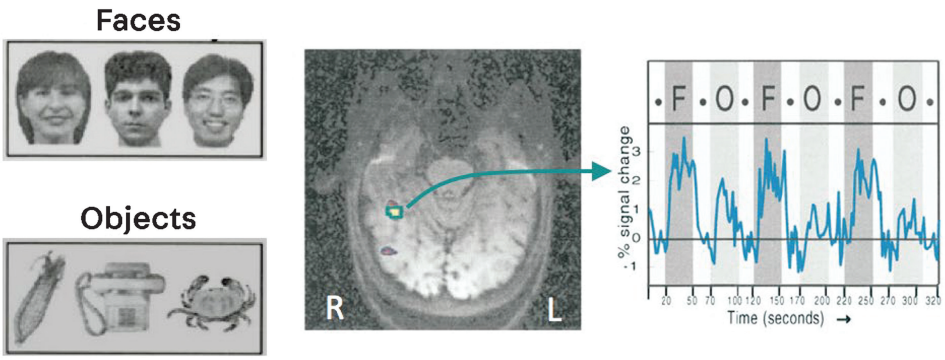

FIGURE 7-12

The fusiform face area. Functional MRI (fMRI) studies in healthy individuals identified cortical areas showing specialization for face processing. This image is from Kanwisher's landmark study showing the selective neural responses to faces (*F*) compared to objects (*O*). The fusiform face area exists in the bilateral occipitotemporal cortex in most individuals, with preferential lateralization to the right more than left hemisphere.

Modified with permission from Kanwisher N, et al, J Neurosci.[54] © 1997 Society for Neuroscience.

wherever it could. In fact, his paintings presaged the finding that facial recognition in the visual system is particularly sensitive to the orientation of an image, much more so than other types of object processing.[57] This phenomenon is the basis of the "Thatcher illusion" created by the psychologist Peter Thompson, which dramatically shows how changes in facial features (in this case, inverting the eyes and mouth in an image of Margaret Thatcher) are easily detected in a right-side up representation when the fusiform face area processes the image but not in an upside-down representation when object recognition areas process the image instead (FIGURE 7-13).

A key question arises when considering how the visual system processes faces: Is face perception simply a component of a general object recognition system or does it represent a distinct specialized neural mechanism? Although some patients with prosopagnosia also have difficulty recognizing other types of objects, in most cases, face perception is affected almost in isolation.[58] In contrast, other patients with a general visual agnosia will frequently have the opposite pattern—a severe deficit for object recognition but relative sparing of face perception.[59,60] For example, one report describes an episode in which a patient with visual object agnosia, who had normal face perception, struggled to drink his coffee because he could not identify which object in front of him was the coffee mug.[60] When this patient viewed paintings by Arcimboldo, he would see the face but not the fruits or vegetables comprising the picture. Thus, the dual dissociation between disorders of face perception and object perception suggests that the neural processes mediating face perception are, to some degree, independent of the processes involved generally in object perception.

Although evidence suggests the existence of right-hemispheric specialization for face processing, in most individuals a significant contribution is made by the fusiform face area in both hemispheres. For this reason, cases of acquired prosopagnosia that are severe typically require bilateral lesions involving inferotemporal cortex. Damasio and colleagues[61] described three original cases of prosopagnosia and 10 previously reported cases with autopsy confirmation of the lesion localization, finding bilateral lesions in every case. On the other

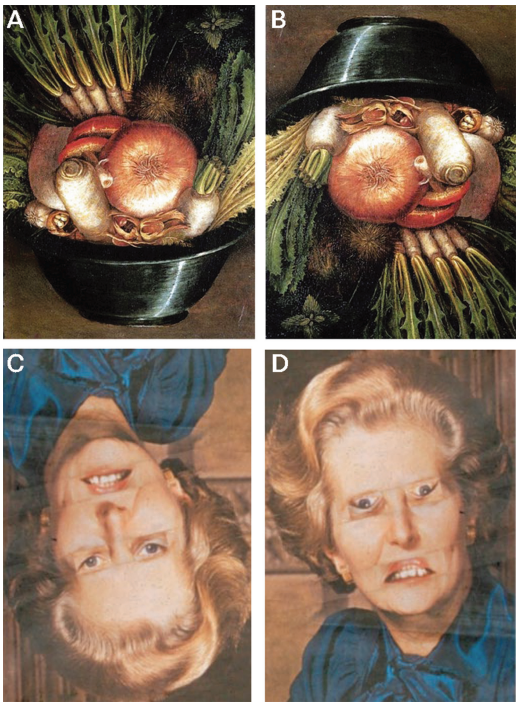

FIGURE 7-13

Specialization for face perception in the human visual system. The 17th century Italian artist Giuseppe Arcimboldo created a series of pictures that took advantage of the proclivity of the human visual system to extract the features of a face. This example shows a bowl of vegetables (*A*), but when the picture is inverted (*B*), face-selective regions activate and a face is inevitably perceived. Similarly, in the striking example of face-specific processing known as the Thatcher illusion, one can barely notice something wrong with this manipulated image of Margaret Thatcher's face when it is upside down (*C*), but when the face is viewed right side up (*D*), the features that do not conform to a normal face are easily recognized.

Panels A and B reprinted from *giuseppe-arcimboldo.org*.[55] Panels C and D reprinted from Thompson P, Perception.[56] © 1980 SAGE Publications.

hand, although quite infrequent, occasional cases may occur in which a single right- or left-sided lesion in this location is sufficient to cause clinically significant prosopagnosia.[62]

In contrast to cases of acquired prosopagnosia (from lesions in the inferior occipitotemporal cortex), some individuals demonstrate developmental prosopagnosia from childhood not due to any apparent cortical injury. fMRI studies in some of these individuals have shown diminished face-specific activation in the region normally identified as the fusiform face area.[63] Similarly, measurement of evoked potentials in these individuals also demonstrates loss of expected face-selective waveforms in the region containing the fusiform face area.[64]

RIDDOCH SYNDROME

Riddoch syndrome describes the preserved ability to detect motion in an otherwise blind visual field.[65] This phenomenon is referred to as *statokinetic dissociation*, in which the presence of an object is perceived only if it is moving (FIGURE 7-14, VIDEO 7-6).

Clinical Presentation

Patients with Riddoch syndrome have a visual field deficit in which the form and color of an object cannot be appreciated. The patient is unaware of an object if it is stationary. However, if the object moves, it can be reliably but coarsely perceived, albeit without accurate sense of form or color. The preserved motion discrimination can include the ability to distinguish features such as direction and speed of motion. A similar, related phenomenon is termed *blindsight*, in which patients lack conscious awareness of vision, yet their actions indicate awareness of some aspects of visual information, such as motion alone.

Historical Background

Riddoch[66] described the phenomenon of statokinetic dissociation in 1917. He described 10 patients, all soldiers in World War I who had been injured with

KEY POINTS

- **Facial recognition in the visual system is particularly sensitive to the orientation of an image, much more so than other types of object processing.**
- **Riddoch syndrome describes the preserved ability to detect motion in an otherwise blind visual field.**

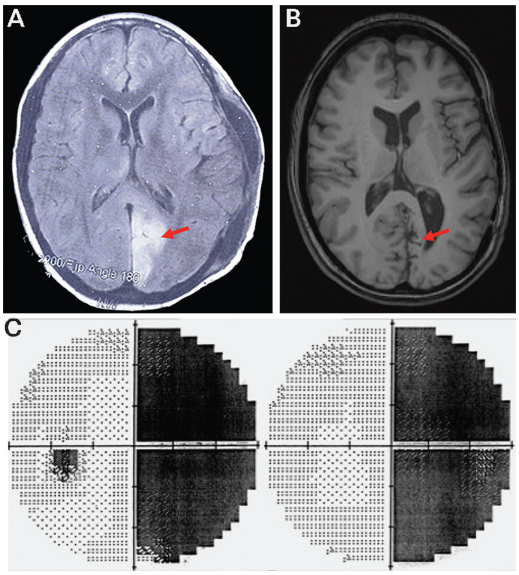

FIGURE 7-14
Riddoch syndrome. A 15-year-old developed a dense right homonymous visual field deficit after a left PCA stroke following a traumatic head injury with expansion of an epidural hematoma. As she recovered, she found that she could detect motion in the otherwise blind field. *A*, Axial fluid-attenuated inversion recovery (FLAIR) MRI shows a left posterior cerebral artery stroke (*arrow*) in the acute phase. *B*, Axial T1-weighted MRI 2 years later shows atrophy of the left occipital cortex (*arrow*) with dilatation *ex vacuo* of the left lateral ventricle. *C*, Static Humphrey automated perimetry demonstrates a right homonymous field defect.

shrapnel from bullets. British soldiers at that time wore what was known as a Brodie helmet, which had the shape of a soup bowl; it offered protection from projectiles bursting above but did not protect the base of the head, leaving soldiers vulnerable to penetrating trauma affecting the occipital lobe. Performing confrontation visual field testing on these patients, Riddoch found that fingers were not perceived in the blind hemifield when they were kept stationary but were accurately identified when they were moving. By examining the location of the entry wound and x-ray films, he reasoned that a circumscribed portion of the primary visual cortex was affected and that nearby motion processing areas were spared.

Neuroscientific Investigations

The cortical area specialized for processing motion is called V5 and is situated dorsal to the primary visual cortex in the occipital lobe. Some controversy persists regarding how visual inputs arrive at this area to give rise to the statokinetic dissociation seen in Riddoch syndrome. Some researchers have assessed fMRI responses in a patient with this disorder and, failing to find responses in V1, have suggested the existence of additional direct subcortical projections to area V5.[67,68] Furthermore, MRI diffusion-weighted tractography has suggested the presence of an intact structural connection between the lateral geniculate nucleus and V5 in patients with blindsight, which is not preserved in patients without blindsight.[69] Kinoshita and colleagues[70] studied the phenomenon of hemifield blindsight induced in monkeys following inactivation of neurons in the ventrolateral pulvinar that receive superior colliculus input. They argue that this ventrolateral pulvinar–superior colliculus pathway plays an important role in preservation of motion detection in blindsight through direct communication with extrastriate areas, including V5.

On the other hand, the clinical phenomenology of Riddoch syndrome does not necessarily need to rely on spared direct inputs to area V5. Other investigators have found small islands of activation within the lesioned portion of the primary visual cortex; these spared areas may be too sparse to support aspects of vision processing such as shape, color, or form, yet they may adequately relay

information to V5 that is sufficient for motion processing.[71] Along these lines, it is known that severely impoverished inputs at any level of the visual system will compromise most aspects of visual processing while leaving coarse motion perception preserved (FIGURE 7-15).

BALINT SYNDROME

Balint syndrome describes a profound disruption of visuospatial attentional mechanisms resulting from bilateral parietal lesions. Despite preservation of elementary aspects of vision (such as acuity) and ventral stream functions (such as object recognition), patients are profoundly affected by an inability to disengage and shift their attention to various parts of a visual scene (CASE 7-6).

Clinical Presentation

One deficit in patients with Balint syndrome is simultanagnosia, which refers to an ability to perceive the local elements of a scene but not the global elements in their totality. In colloquial terms, this perceptual problem might be described as "missing the forest for the trees." This may be tested using a Navon figure, which is a large letter (eg, *S*) composed of many smaller letters (eg, *E*) (FIGURE 7-17); the patient with simultanagnosia will see the small letters but be unable to see the larger one.[72] In clinical practice, simultanagnosia may also be detected by asking the patient to describe a visual scene, such as the National Institutes of Health Stroke Scale cookie theft picture. The patient may recognize individual items, such as water, a child, cookies, and dishes, but fail to recognize the overall story being depicted in the scene. Another component of Balint syndrome is *optic ataxia*, referring to impaired reaching under visual guidance. Unlike cerebellar ataxia, the movement back to touch one's nose remains accurate with optic ataxia, since proprioception, not visuospatial attention, is required for this action. A third component is termed *ocular apraxia*, which describes the inaccurate saccades that are made when a patient tries to shift gaze from one object to another target in the environment.

Virtually all cases of Balint syndrome result from bilateral parietooccipital damage. When the presentation is subacute, a common cause is posterior cortical atrophy,[73] a neurodegenerative disease predominately affecting the posterior cortex, which is often, but not always, caused by underlying Alzheimer pathology. Other causes of Balint syndrome include metastatic

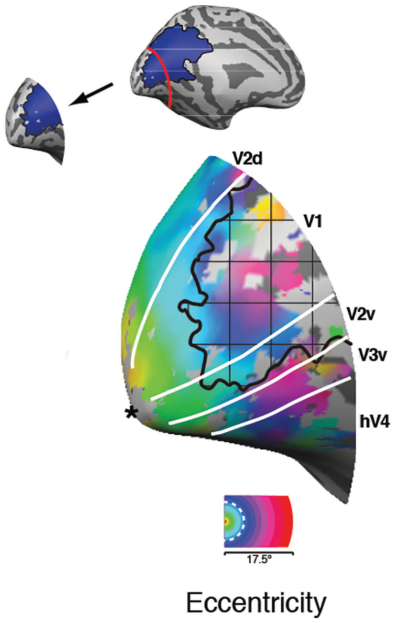

FIGURE 7-15
Theoretical explanations for Riddoch syndrome. While some data suggest the existence of direct projections to area V5, many cases result from incomplete lesions that disrupt visual inputs in early areas such as V1, allowing only motion perception to persist without other visual abilities. The image shows functional MRI (fMRI) data from a 16-year-old with Riddoch syndrome, revealing islands of spared activation in the lesioned cortex (depicted in *dark blue*) spanning area V1.
Reprinted with permission from Radoeva, et al, J Cogn Neurosci.[71] © 2008 Massachusetts Institute of Technology.

KEY POINTS

- **Balint syndrome describes a profound disruption of visuospatial attention mechanisms resulting from bilateral parietal lesions. Its key features are simultanagnosia, optic ataxia, and ocular apraxia.**
- **Simultanagnosia refers to an ability to perceive the local elements of a scene but not the global elements in their totality.**
- **Optic ataxia refers to impaired reaching under visual guidance, in which reaching under proprioceptive guidance (ie, back to one's own nose) is preserved. Ocular apraxia refers to inaccurate saccades stemming from a disorder of visuospatial attention.**

CASE 7-6

A 70-year-old woman reported difficulty reaching for things such as forks and cups. She could read single words but had difficulty moving from one word to the next and often lost her place in the text. She felt confused when she entered a place with complex visual stimuli, such as a supermarket. Neurologic examination revealed intact visual acuity and fields. Reaching for targets was inaccurate, although she could accurately bring her finger to her own nose (optic ataxia) (VIDEO 7-7). Saccadic searching eye movements were also inaccurate (ocular apraxia). When asked what letter she saw in a picture of an H made of little As, she answered "A," even when directed to look at the whole picture (simultanagnosia). Balint syndrome was diagnosed, and an MRI showed severe cortical atrophy, especially in the posterior parietal and occipital regions, leading to a diagnosis of posterior cortical atrophy (FIGURE 7-16).

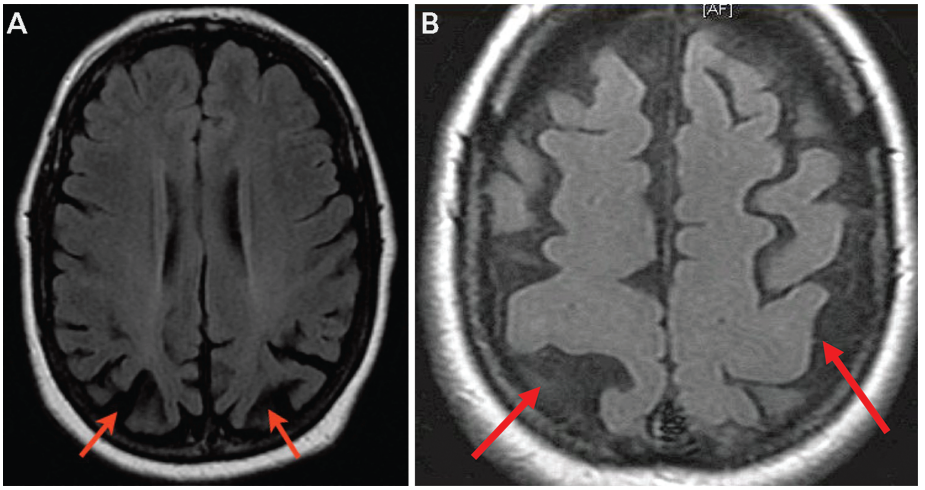

FIGURE 7-16
Imaging of the patient in CASE 7-6 with Balint syndrome. Axial MRIs show severe cortical atrophy, especially in the posterior parietal and occipital regions. (*A*, *B*, *arrows*).

COMMENT

This case illustrates the severity of visual symptoms that can occur with significant disruption of the mechanisms that control normal visuospatial attention. Although visual acuity and object recognition were normal in this patient, she had a severe deficit of disengaging and shifting attention in a coordinated fashion to relevant elements of the visual environment.

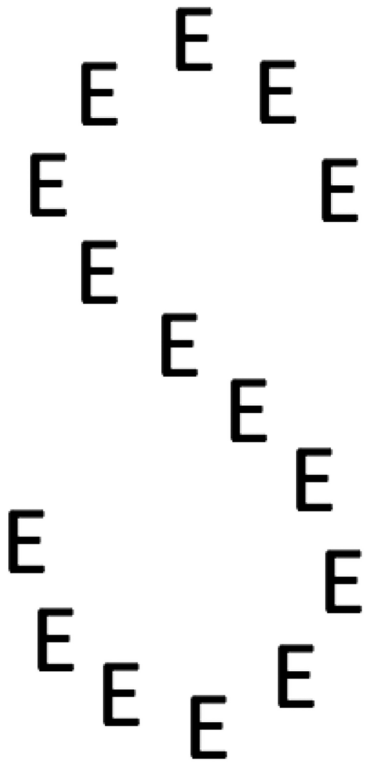

FIGURE 7-17
Navon figure to assess for simultanagnosia. While a person with normal perception will identify a large S composed of many small Es, a person with Balint syndrome will report only seeing small Es.

lesions, hypotensive insult affecting the bilateral watershed zones between the middle and posterior cerebral arteries,[74] the Heidenhain variant of Creutzfeldt-Jakob disease, posterior reversible encephalopathy syndrome (PRES),[75] and progressive multifocal leukoencephalopathy.[76]

Historical Background

In 1909, the Hungarian physician Rudolph Balint[77] described an engineer who could no longer assemble models because of a profound inability to shift spatial attention, although visual acuity, strength, and dexterity were normal. He tried to light a cigar in the middle rather than the end and directed his knife outside the plate when trying to cut a steak. At autopsy, he was found to have bilateral parietal infarcts. In 1918, Holmes[78] expanded on Balint's concept of "psychic paralysis of gaze," using the term *ocular apraxia* to describe five patients who could direct their eyes accurately to the location of a sound or to a region verbally described by the practitioner but not to a target that was presented visually.[78]

Of note, simultanagnosia was not actually described as a component of Balint syndrome until Wolpert's[79] case description in 1924. When observing his patient try to describe the events in a scene (which showed a boy being scolded after breaking a window during a snowball fight), he found that the patient saw "only details that he could not sum up" and was unable to recognize the action represented in the figure.

Neuroscientific Investigations

While optic ataxia and ocular apraxia frequently co-occur, they localize to unique regions of the posterior parietal cortex. Functional imaging studies suggest that optic ataxia stems from damage to the pathways connecting the parietal reach region and medial interparietal area to the dorsal premotor cortex, while ocular apraxia results from disrupted connections from the lateral interparietal area to the superior colliculus and frontal eye fields.[80] Dorsal area 5 appears to be involved in online control of reaching, meaning that it helps correct for mistakes in reaching movements during an action based on proprioceptive and visual feedback.[81] Difficulty with grasping for objects, which also may occur in patients with Balint syndrome, appears to localize to damage to the anterior interparietal area and its connections to the ventral premotor cortex (FIGURE 7-18).

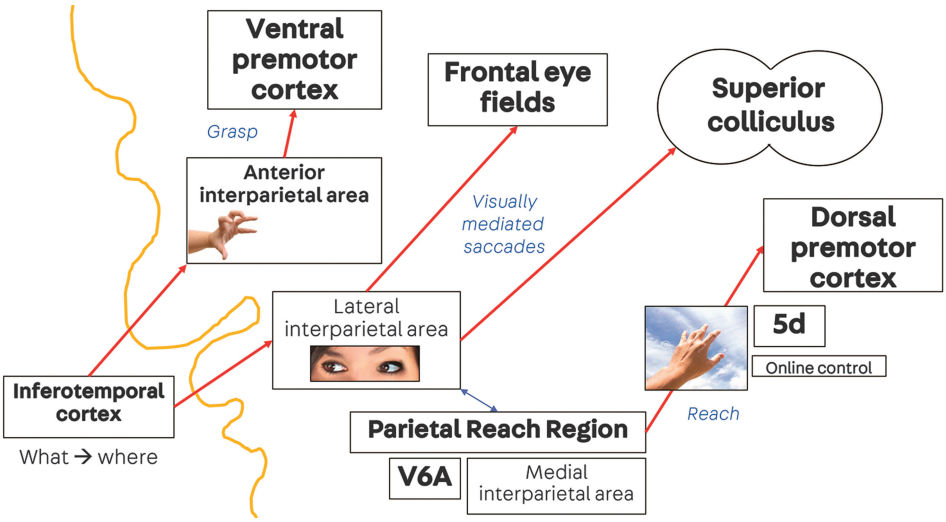

FIGURE 7-18

Anatomy of optic ataxia and ocular apraxia. The parietal reach region (PRR), which includes area V6A and the medial interparietal area (MIP), connects with the dorsal premotor cortex and governs visually guided reach. The MIP may play a role in the finer aspects of reach. Dorsal area 5 (5d) is important for online control, correcting mistakes in reach, based on visual feedback. Disruption of the PRR/MIP/5d network leads to optic ataxia. The lateral interparietal area makes connections with the frontal eye fields and superior colliculus, subserving visually mediated saccades; lesions in this area produce ocular apraxia. The anterior interparietal area (AIP) projects to the ventral premotor cortex, and disruption of these pathways causes deficits in grasping for objects. Note there is input to the system from inferotemporal cortical regions; ie, the "what" pathway feeds information into the "where" pathway.

HEMISPATIAL NEGLECT

Unilateral parietal lobe lesions, especially of the right parietal cortex, often cause the syndrome of hemispatial neglect to the contralateral side.

Clinical Presentation

Hemispatial neglect not only affects visual perception of extrapersonal space but also often involves perception of personal space (one's body) as well. Patients may be able to consciously perceive the contralateral field when sparse stimuli are presented, but when multiple stimuli are presented simultaneously and compete for visual attention, the patient demonstrates a rightward attentional bias and the stimulus on the left becomes "extinguished." When asked to show the midpoint of a horizontal line, patients with left hemispatial neglect will mark a line to the right of center. On a target cancellation test in which multiple lines on a page must be crossed out, patients will start toward the right side and miss several targets on the left side.[82,83] When asked to circle all the As on a page with both As and Bs, the patient with neglect will miss the letters on the neglected side, while a patient with a simple hemianopia will still search into the blind area and is therefore less likely to miss letters on that side.

The coordinates by which left hemispatial neglect is defined can differ between patients. It might occur in egocentric coordinates that are centered primarily to the patient's body, head, or eyes. In other patients, the left neglect may be defined by coordinates of a given object, regardless whether it is to the patient's right or left side.

Historical Background

Hemispatial neglect was described as a "hemianopic weakness of attention" by Poppelreuter[84] in 1917. In 1945, Paterson and Zangwill[85] described a right parietal syndrome in a 34-year-old man who had an irregular mortar fragment shot through his right parietal lobe. The patient demonstrated a marked neglect of the left side of his environment and his left upper extremity as well as significant difficulty copying figures, drawing, or arranging puzzles. The doctors drove the patient through Edinburgh and found that while he could name streets, he could not successfully figure out how to navigate to other parts of the city. Attempts to draw his neighborhood demonstrated major errors, and a freehand drawing of Scotland omitted the entire left side.

KEY POINT

- **Unilateral parietal lobe lesions, especially of the right parietal cortex, often cause hemispatial neglect to the contralateral side.**

Neuroscientific Investigations

A major question to consider when studying hemispatial neglect is why left hemispatial neglect following a right hemispheric lesion is so much more common than right hemispatial neglect following a left hemispheric lesion. One explanation is that the left hemisphere is capable of shifting visuospatial attention only toward the right, but the right hemisphere is capable of shifting attention to either side. Patients do not commonly have significant hemispatial neglect following a lesion in the left hemisphere because the right hemisphere remains capable of directing attention to either side. Following a right hemispheric lesion, however, the left hemisphere directs attention to the right, and the mechanisms that should direct attention to the left are no longer intact. In essence, the syndrome of left hemispatial neglect represents an unchecked rightward bias of attention, without the ability to effectively shift attentional mechanisms leftward.

Evidence supporting this theory comes from the classic experiment of Posner and colleagues,[86] who measured response time and accuracy of individuals to detect a target presented either in the right or left visual field after attention was briefly cued with an indication of where the target would appear. On a "valid" trial, the target appeared in the location where attention was cued. On an "invalid" trial, attention would be cued to one side, but the target would appear on the opposite side. Individuals without neurologic lesions and those with left hemispheric lesions did reasonably well on both types of trials. In contrast, patients with right hemispheric lesions had significant difficulty on invalid trials if their attention was cued to the right but the target appeared to the left. However, their performance was essentially normal on valid trials and on invalid trials in the opposite direction, where attention was cued to the left but the target then appeared to the right. This experiment illustrates the rightward bias in attention that commonly occurs following a right hemispheric lesion.

Left hemispatial neglect not only affects the way an individual perceives and interacts with the external surrounding environment but also affects internal representations and mental imagery. In one famous experiment conducted by Bisiach and Luzzatti,[87] two Italian patients with left hemispatial neglect were asked to imagine themselves standing in the Piazza del Duomo in Milan, facing the cathedral in the center of the square, and name the buildings they could recall. The patients named buildings on the right side of the square but failed to name buildings on the left. Later, the investigators asked the same patients to imagine themselves standing in the square but on the steps of the

cathedral facing the opposite direction as before. This time, with the right and left side of the square flipped in their mental representation, the patients only named the buildings on the side opposite of the buildings they had named previously.

CHARLES BONNET SYNDROME

Charles Bonnet syndrome refers to "release" hallucinations that occur in the context of visual loss (VIDEO 7-8).

Clinical Presentation

Release hallucinations are typically nonthreatening; patients often describe seeing small people, animals, or flowers. Auditory hallucinations are not typical. It is important to recognize this syndrome based on these characteristics and correctly differentiate it from other causes of hallucinations, including psychotic disorders.

CASE 7-7

A 66-year-old man presented with the sudden onset of vivid visual hallucinations during wakefulness following bariatric surgery. Apart from describing the hallucinations, he was alert, attentive, and fully oriented without any confusion. Examination showed normal visual acuity and visual fields. Nevertheless, he described seeing synchronized swimmers dressed in red, white, and blue in his hospital room (VIDEO 7-9). He also saw snakes crawling up to the bed, numbers melting off the clock, and plumes of smoke at the nursing station. Diffusion-weighted imaging (DWI) and apparent diffusion coefficient MRI demonstrated a mesencephalic stroke consistent with a diagnosis of peduncular hallucinosis (FIGURE 7-19).

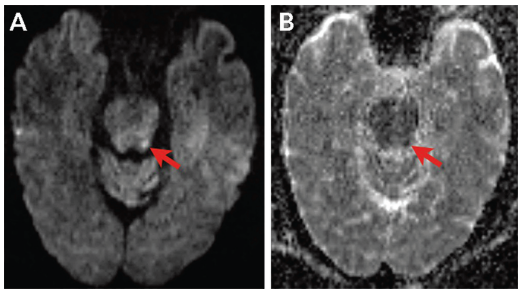

FIGURE 7-19
Imaging of the patient in CASE 7-7 with Lhermitte peduncular hallucinosis. Diffusion-weighted imaging (DWI) (*A*) and apparent diffusion coefficient MRI (*B*) demonstrated a mesencephalic stroke (*arrows*), consistent with a diagnosis of peduncular hallucinosis.

COMMENT

This case illustrates the acute, vivid, formed visual hallucinations that can occur with a rostral brainstem or thalamic stroke. The patient had no visual deficits to suggest a diagnosis of release hallucinations. His cognition was normal, not suggestive of a delirious state, and he was not intoxicated. Although he had no objective neurologic deficits to localize the lesion clinically, MRI demonstrated the responsible lesion.

Historical Background

The syndrome is given its eponym because it was described by Charles Bonnet,[88] a Swiss naturalist and lawyer, in 1760. He described a man with normal cognitive function who experienced formed hallucinations of men, women, birds, cars, and buildings. The man that Bonnet described was his own 87-year-old grandfather, who was nearly blind from cataracts.

Neuroscientific Investigations

Functional imaging studies have shown spontaneous increases in activity in visual association areas in the ventral extrastriate cortex that temporally correlate with the reported hallucinations.[89] These findings lend credence to the idea that in the absence of receiving external sensory information, the visual system can generate internally formed hallucinations instead.

LHERMITTE PEDUNCULAR HALLUCINOSIS

Lhermitte peduncular hallucinosis describes vivid, dreamlike hallucinations that occur during normal wakefulness (CASE 7-7) and that typically result from lesions of the brainstem or thalamus.

Clinical Presentation

The hallucinations in this fascinating disorder generally begin abruptly and are attributed to a lesion in the upper brainstem or thalamus. Some patients have objective deficits referable to the location of the lesion in the brainstem, but other patients have isolated hallucinations without coexisting abnormalities on examination.[90] After the acute onset of the hallucinations, patients tend to show some gradual improvement over time. Other cognitive faculties remain normal in these patients.

Historical Background

This condition was described in 1922 by Lhermitte[91] in a 72-year-old woman who reported bizarre, formed hallucinations including "radiant" animals, people dressed in tinsel, and strange-appearing children. Lhermitte inferred that the acute hallucinations were caused by a lesion in the upper brainstem (called the *peduncle* in French), localizing the lesion on the basis of the patient's coexisting eye movement abnormalities although a confirmatory autopsy was not available. Lhermitte offered the provocative explanation that the vivid hallucinations were essentially a dream state intruding upon wakefulness. Five years later, Van Bogaert[92] described a similar patient with the sudden onset of vivid hallucinations and showed at autopsy that the patient indeed had infarction of regions of the midbrain.

Neuroscientific Investigations

Analysis of the lesions reported to cause the syndrome of peduncular hallucinosis shows that no single site is uniformly involved, but the responsible lesions most often tend to be in the midbrain or thalamus.[93] In these regions, the reticular activating system and thalamic intralaminar nuclei regulate the state of wakefulness of the brain, permitting vivid dreams to arise during rapid eye movement (REM) sleep. In keeping with Lhermitte's hypothesis about the pathogenesis of hallucinations in this disorder, analysis of network connectivity

KEY POINTS

- **Charles Bonnet syndrome refers to "release" hallucinations that occur in the context of visual loss, often due to anterior lesions such as cataracts or macular degeneration.**
- **Lhermitte peduncular hallucinosis describes vivid, dreamlike hallucinations that occur during normal wakefulness and may result from lesions to areas of the midbrain and thalamus that regulate the sleep-wake state and normally prevent dreams from encroaching on wakefulness.**

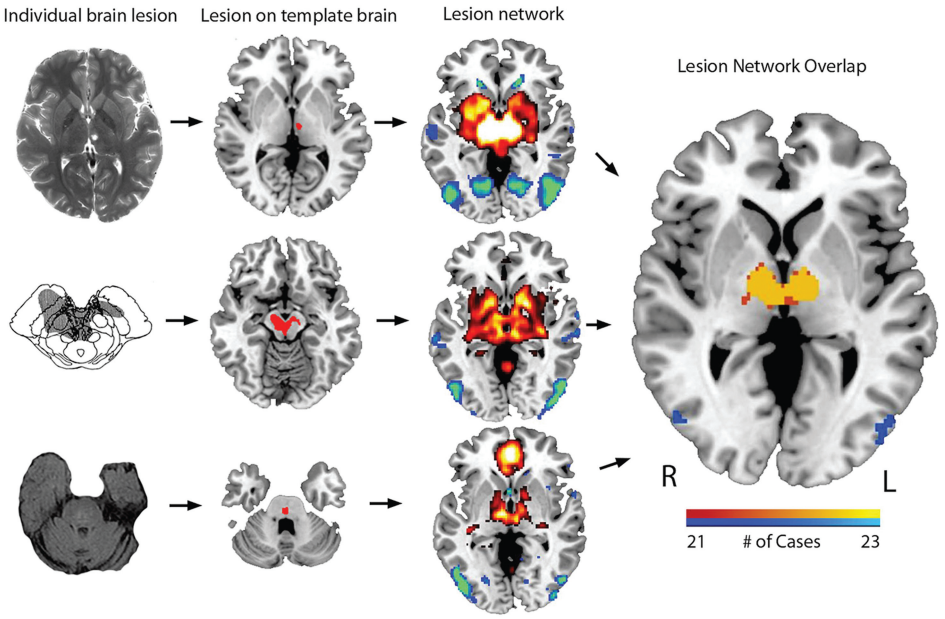

FIGURE 7-20

The lesion-based network mapping method demonstrates the disinhibited networks involved in peduncular hallucinosis. Individual discrete lesions in reported cases of peduncular hallucinosis do not uniformly overlap but tend to occur in the thalamus or midbrain (*columns 1* and *2*, showing 3 of the 23 cases analyzed in this study). A database of resting state functional MRI (fMRI) from healthy individuals can be used to define the distributed network of correlated and anticorrelated neural activity associated with the lesion location in each case (*column 3*). Overlap of these individual network maps reveals the areas of commonality, including visual association areas that are functionally anticorrelated with the location of the lesion in all cases (areas in blue on the overlap image on the right). These findings suggest that the lesions implicated in peduncular hallucinosis engender disinhibited activity in visual association areas that correlates with perceived visual hallucinations.

L = left; R = right.

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shows that lesions producing peduncular hallucinosis are functionally anticorrelated with visual association areas (FIGURE 7-20).[93] This evidence supports the notion that a discrete thalamic or mesencephalic lesion may give rise to internally generated imagery by causing disinhibition of higher visual areas, akin to the dream state intruding upon normal wakefulness suggested by Lhermitte.

CONCLUSION

Timely diagnosis and optimal management of patients with disorders of visual processing are important challenges faced by the practicing neurologist. In these cases, elementary aspects of vision may appear normal on examination and will not account for the patient's particular visual symptoms. Detailed testing of higher visual functions will define specific cortical visual syndromes and have localizing value (FIGURE 7-21). The study of these disorders provides an important framework to consider important neuroscientific concepts regarding the functional organization of the brain.

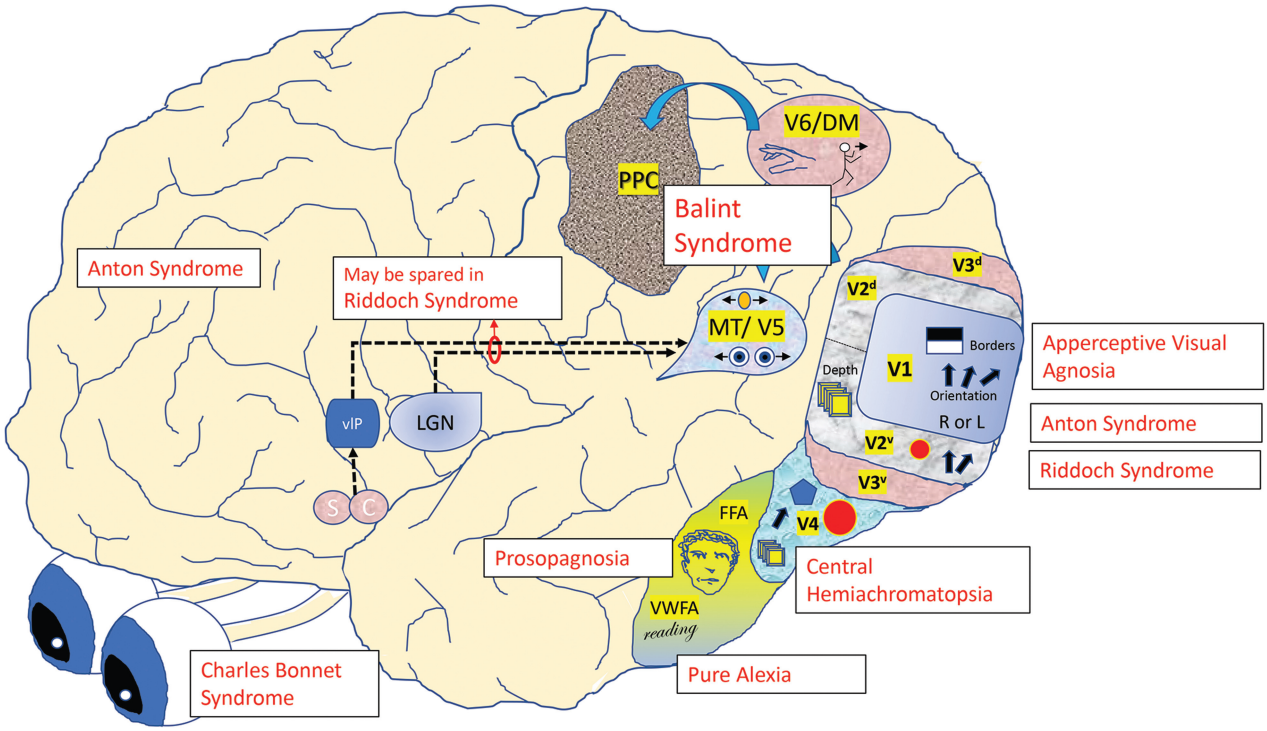

FIGURE 7-21

Higher-order cortical disorders of vision organized by localization. Succeeding regions of extrastriate cortex are labeled as being part of either the ventral or dorsal stream. Anton syndrome, apperceptive visual agnosia, and Riddoch syndrome result from damage to the primary visual cortex (V1). The anosognosia of Anton syndrome presumably relates to dysfunction in broader networks that serve to judge the presence or absence of vision. Connections between the lateral geniculate nucleus (LGN) and mesial-temporal region/V5 (MT/V5), as well as between superior colliculus (SC)–responsive neurons in the ventrolateral pulvinar (vlP) and MT/V5, may play a role in preserved visual function found in blindsight and Riddoch phenomenon. Central hemiachromatopsia localizes to V4 and prosopagnosia localizes to the fusiform face area (FFA) within the fusiform gyrus, which is located more medially than represented here. While alexia without agraphia commonly results from lesions affecting both the left occipital cortex and splenium, it may also result from a more discrete lesion affecting the left-sided visual word form area (VWFA) in the fusiform gyrus. Balint syndrome results from bilateral damage to the occipitoparietal areas that control visuospatial attention. Charles Bonnet syndrome refers to release hallucinations that result from vision loss anywhere along the early visual pathways, but it most commonly results from ocular disease such as cataracts or macular degeneration.

L = left; PPC = posterior parietal cortex; R = right; V6/DM = dorsomedial cortex.

VIDEO LEGENDS

VIDEO 7-1

Anton syndrome. Video shows a 48-year-old man with complete loss of vision following bilateral occipital cardioembolic strokes. He denied blindness and said he felt "super." He confabulated that he could see objects in front of him but when asked to describe them in detail, said "I don't know how to tell." He had no difficulty identifying objects when he held them in his hand. Even following demonstrations that he was not seeing properly, he insisted "my vision is OK."

VIDEO 7-2

Apperceptive visual agnosia. Video shows a 23-year-old woman who developed severe visual impairments after hypoxic arrest from a narcotic overdose. She described her vision as distorted or blurred. She could tell an object was in front of her but could not tell what it was. Faces were "completely distorted." She could not identify any visually presented objects, could not read letters, and could not copy simple line drawings correctly. Visual acuity, tested with the preferential looking test (in which the patient directs the eyes toward a set of black-and-white stripes, with the thickness of the stripes in some examples approximating 20/20 vision) was normal, and she had no other cognitive deficits.

VIDEO 7-3

Central hemiachromatopsia. Video shows a 57-year-old woman who presented with a left superior quadrant homonymous field deficit due to a right inferior occipital stroke. Examination showed that she was unable to discriminate colors in the left inferior homonymous field, saying that cards of various colors shown in that area were gray or white. Diffusion-weighted MRI showed acute right inferior occipital infarction, involving the inferior bank of area V1 and area V4.

VIDEO 7-4

Alexia without agraphia. Video shows a 41-year-old man with an infiltrating glioma involving the left occipital lobe and splenium of the corpus callosum with a profound inability to read words with both regular or irregular phonemic spelling, although writing and spoken language remained normal. He was unable to read a sentence he had written himself, saying "I don't know; it's almost like I didn't write it." The examination also demonstrated a right superior greater than inferior homonymous hemianopia.

VIDEO 7-5

Prosopagnosia. Video shows a 37-year-old woman with difficulty distinguishing faces due to breast cancer metastasis involving the right occipitotemporal cortex in the fusiform face area. She said that faces look "smoother and less defined." She called it the "Instagram filter" in her brain.

VIDEO 7-6

Riddoch syndrome. Video shows a 15-year-old girl who developed a dense right homonymous visual field deficit after left posterior cerebral artery stroke following a traumatic head injury with expansion of an epidural hematoma. As she recovered, she found that she could detect motion in the otherwise blind field. Static Humphrey automated perimetry testing demonstrated the right homonymous field defect.

VIDEO 7-7

Balint syndrome. Video shows a 70-year-old woman who reported difficulty reaching for things such as forks and cups. She could read but had difficulty moving from one word to the next. She stated she could see everywhere but felt visually confused when she entered a place with complex visual stimuli, such as a supermarket. Neurologic examination revealed intact visual acuity and fields. Reaching for targets was inaccurate, although she could accurately bring her finger to her own nose (optic ataxia). Saccadic searching eye movements were also inaccurate (ocular apraxia). When asked what letter she saw in a picture of an H made of little As, she answered "A," even when directed to look at the whole picture (simultanagnosia). Balint syndrome was diagnosed, and an MRI showed severe cortical atrophy, especially in the posterior parietal and occipital regions, leading to a diagnosis of posterior cortical atrophy.

VIDEO 7-8

Charles Bonnet syndrome. Video shows a 93-year-old woman with severe visual loss from macular degeneration and glaucoma who had frequent complex visual hallucinations. She described seeing "a little blond dressed very nice…in a wool plaid suit, skirt, and jacket, and curly, curly hair and big, round eyes." The hallucinations were nonthreatening, and she had no auditory hallucinations.

VIDEO 7-9

Lhermitte peduncular hallucinosis. Video shows a 66-year-old man with the sudden onset of vivid visual hallucinations during wakefulness following bariatric surgery. Apart from describing the hallucinations, he was alert, attentive, and fully oriented without any confusion. He described seeing in his hospital room synchronized swimmers, snakes crawling up to the bed, numbers melting off the clock, and plumes of smoke at the nursing station. Diffusion-weighted imaging (DWI) and apparent diffusion coefficient MRI demonstrated a mesencephalic stroke, consistent with a diagnosis of peduncular hallucinosis.

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