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MAJOR REVIEW

Central Disorders of Vision in Humans

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Abstract. Over the past 20 years, researchers have discovered over 30 separate visual areas in the cortex of the macaque monkey that exhibit specific responses to visual and environmental stimuli. Many of these areas are homologous to regions of the human visual cortex, and numerous syndromes involving these areas are described in the neurologic and ophthalmic literature. The focus of this review is the anatomy and physiology of these higher cortical visual areas, with special emphasis on their relevance to syndromes in humans. The early visual system processes information primarily by way of two separate systems: parvocellular and magnocellular. Thus, even at this early stage, visual information is functionally segregated. We will trace this segregation to downstream areas involved in increasingly complex visual processing and discuss the results of lesions in these areas in humans. An understanding of these areas is important, as many of these patients will first seek the attention of the ophthalmologist, often with vague, poorly defined complaints that may be difficult to specifically define. (**Surv Ophthalmol 45**:379–405, 2001.

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Ophthalmologists tend to view the striate cortex as an afferent structure receiving visual information mostly from the lateral geniculate nucleus (LGN). Indeed, most of our efforts as ophthalmologists center on the preservation or restoration of these inputs into the visual cortex. However, a wide variety of visual disorders may occur from damage to the visual cortex and its occipitofugal connections with associative visual areas. These syndromes are often called "disorders of higher cortical function," and they remind us that the striate cortex is not the end of the line, but the beginning of a complex system of visual analysis that ultimately leads to global awareness of the visual environment.

I. Functional Segregation of Visual Inputs

A. RETINOGENICULATE PATHWAYS

Functional segregation in the visual system has its earliest subdivision in the retina. Over 22 types of ganglion cells exist in the primate retina,[212] but only three types appear to be involved in visual perception and project to specific locations within the LGN.[55,153,192] The *midget* ganglion cells have small receptive fields and project to layers 3–6 of the parvocellular LGN. *Parasol* cells have much more extensive receptive fields and project to layers 1 and 2 of the magnocellular LGN.[261] A third type of retinogeniculate ganglion cell, the *bistratified* ganglion

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cell, projects to the koniocellular layers of the LGN.[56,111,164]

The parvocellular system (P-pathway) is a static firing system that conveys information from the retina to the LGN concerning wavelength selectivity and low-contrast retinal imagery with high spatial resolution.[157,222,223] High band-pass resolution perimetry (ring perimetry) is an attempt to selectively evaluate the P-pathway.[85] In contrast, the magnocellular system (M-pathway) conveys high-contrast, low-resolution information that is color blind.[157,223] The magnocellular system is a phasic system, thus is well suited for the analysis of moving stimuli. Perimetric techniques, such as frequency-doubled perimetry[113] and motion-detection automated perimetry,[237] are used in an attempt to isolate the M-pathway. The koniocellular system (K-pathway) conveys information concerning blue-yellow color opponency.[54] Short-wavelength automated perimetry (SWAP) uses a blue stimulus presented against a yellow background and may evaluate the responses processed through this pathway (Fig. 1).

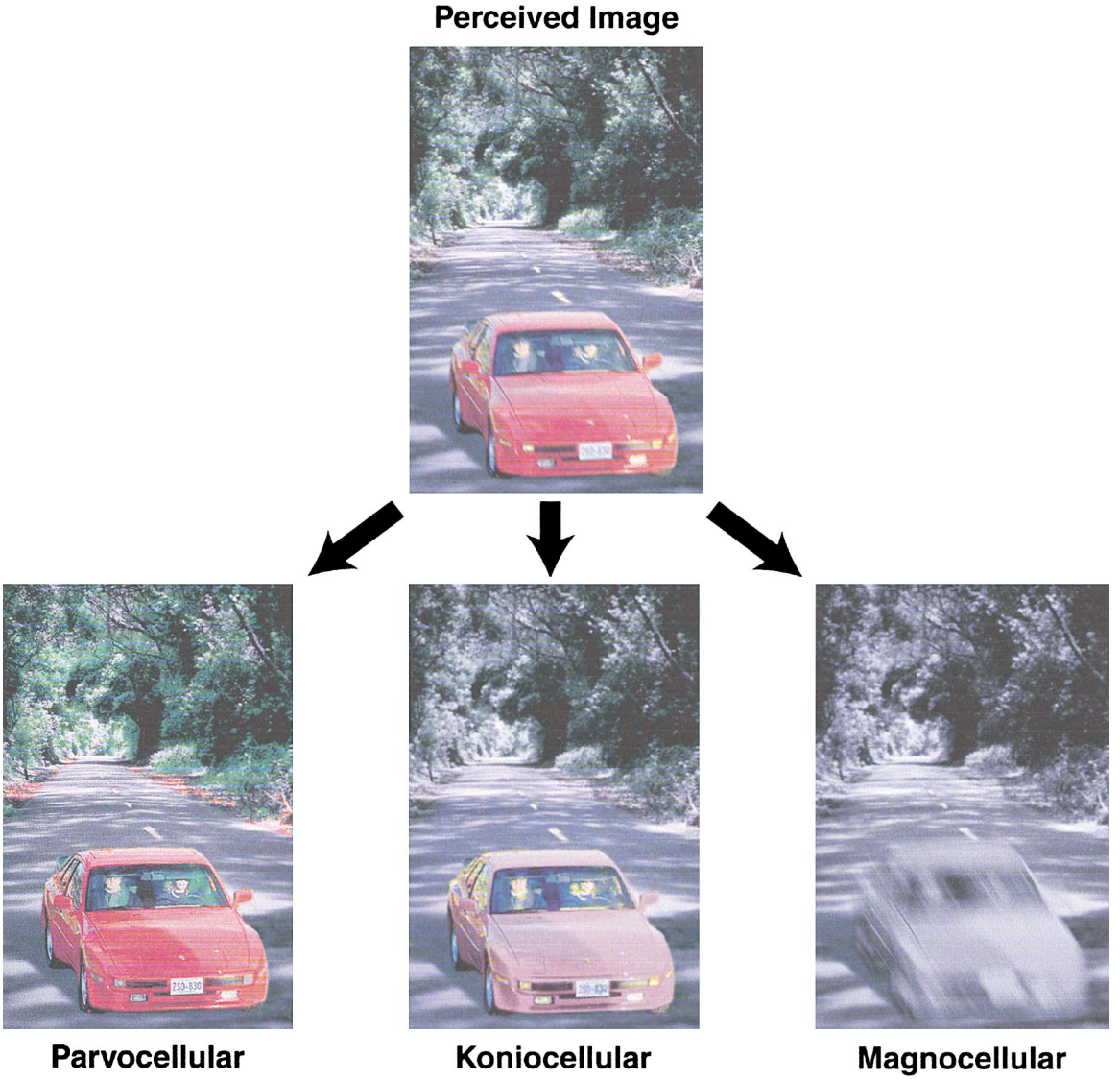

Fig. 1. Visual information that is used to create the perceived image of a visual scene (*top* photograph) is conveyed to the lateral geniculate through three pathways. The lower photographs were manipulated to simulate the characteristics of the perceived image that are conveyed along each of these pathways. The parvocellular pathway (*lower left* photograph) conveys fine spatial detail and is thought to be wavelength selective primarily for red and green opponency. The koniocellular pathway conveys information concerning blue-yellow opponency and low spatial detail (*lower middle* photograph). The magnocellular pathway (*lower right* photograph) conveys color-blind information of low spatial detail, sensitive to motion. (Artist: David Fisher.)

The M-, P-, and K-pathway inputs, although differing in response characteristics, have some overlap in the type of visual stimuli to which they are activated. Thus, perimetric techniques may emphasize one pathway over another, but do not completely isolate the responses processed through a given pathway. In addition, inputs from the parallel systems are processed in a complex and interrelated manner by the visual cortex and higher cortical centers.

B. CORTICAL VISUAL AREAS

Over the past 20 years, more than 30 visual cortical areas have been isolated in macaque monkeys. These areas comprise almost 50% of the entire cortical volume. Although the function of most of these areas is unclear, studies of the visual cortex in lower primates[67,258,266,283] and clinical correlation with cerebral lesions in patients,[118,207,208,260] along with electrophysiologic studies,[18,80] postmortem histologic examinations,[32,38] and functional imaging studies,[48,72,227,251,282] have identified several cortical areas that may have clinical importance in humans.

The visual cortex in the macaque was initially divided into six sub-regions named visual areas 1–6 (Areas V1–V6). Area V1 is the primary visual cortex, and it corresponds to the striate cortex in both humans and lower primates. Areas V2–V6 are extensively interconnected visual areas that lie anterior to V1 and contain specialized maps of the visual field.[74,284] These areas are best visualized in the macaque in a horizontal section through the occipital lobe (Fig. 2).

Area V2 is immediately adjacent to area V1 in most primates, including humans. It corresponds to Brodmann's area 18 and was previously called the *parastriate cortex.*

Hubel and Wiesel initially believed that Brodmann's area 19, also called the *peristriate cortex* in humans, was composed entirely of the human homolog of V3,[74] but further studies indicated that the peristriate cortex is composed of two functionally distinct areas, V3 and V3A.[251]

Area V4 in the macaque lies in the lateral occipital lobe. Zeki claimed that "human V4" was located in the caudal lingual and fusiform gyri within Brodmann's area 18.[281] This area is involved in color processing in humans (see below); however, whether or not it is homologous to area V4 in the macaque is controversial.[167]

Area V5, also called area MT because of its location in the middle temporal gyrus of the owl monkey, is located in humans in the gyrus subangularis of the ventrolateral occipital lobe.[267]

Area V6 in the macaque has no clear homolog in humans; however, an area associated with visuospatial processing in the posterior parietal cortex is the most likely candidate. Fig. 3 illustrates the location of several of the corresponding visual areas in humans. Only those cortical areas associated with distinct clinical syndromes will be discussed.

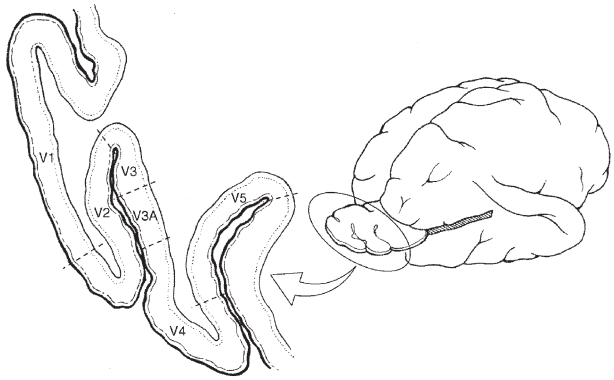

Fig. 2. Posterior view of the macaque monkey brain. A horizontal slice through the occipital lobe has been displaced to reveal the six initially described sub-regions of the visual cortex that surround the striate cortex (V1). (Artist: David Fisher.)

C. OCCIPITOFUGAL PATHWAYS

Based on numerous studies of lesions in humans,[59,61] functional imaging of normal subjects,[48] and experiments in monkeys,[258] it is clear that the information processed by the striate cortex and visual associative areas is projected through two occipitofugal pathways: a ventral occipitotemporal pathway and a dorsal occipitoparietal pathway (Fig. 4).[109] The ventral pathway, often called the "what" pathway, is involved in processing the physical attributes of a visual image that are important to the perception of color, shape, and pattern. These, in turn, are crucial for object identification and object-based attention.[259] The ventral pathway originates in V1 and projects through V2 and V4 to specific inferior temporal cortical areas, the angular gyrus, and limbic structures. It provides visual information to areas involved in visual identification, language processing, memory, and emotion.[234] Thus, a lesion in this pathway may cause a variety of associative defects, including visual alexia and anomia, visual agnosia, visual amnesia, and visual hypoemotionality.

The dorsal, or "where" pathway, begins in V1 and projects through V2 and V3 to V5.[234,259] From V5, this pathway continues to additional areas in the parietal and superior temporal cortex.[232] These projections are involved in visuospatial analysis, in the localization of objects in visual space, and in modulation of visual guidance of movements toward these objects.[96,257] Thus, lesions of this pathway may cause a variety of visuospatial disorders, such as Bálint's syndrome and hemispatial neglect.

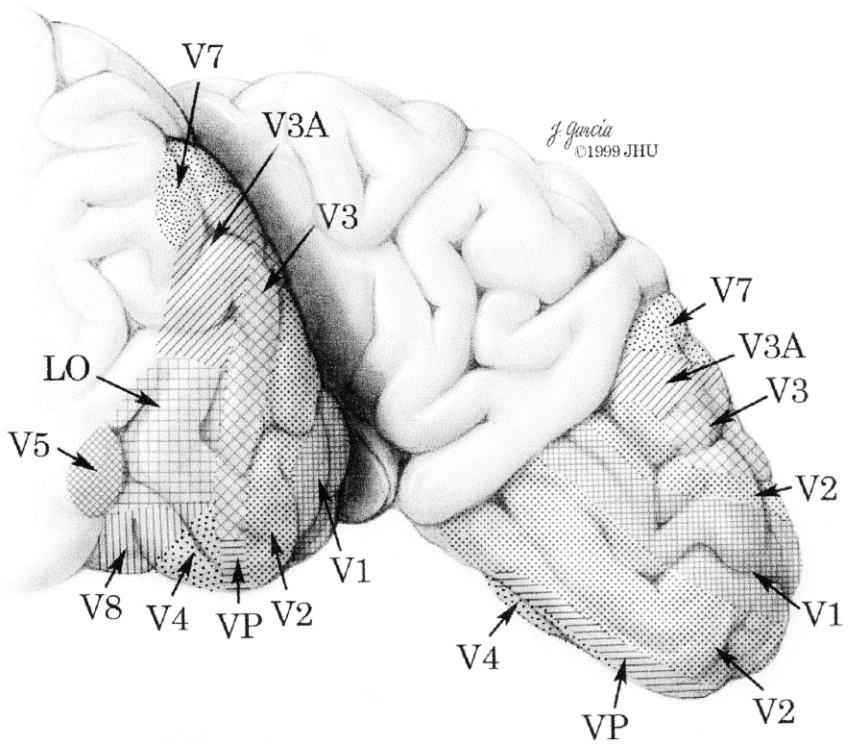

Fig. 3. Posterior lateral view of the human visual cortex showing several of the visual associative areas. The cerebellum has been removed and the hemispheres have been separated and displaced to display medial and lateral occipital regions. V1 corresponds to the primary of striate visual cortex. The other associative visual areas are discussed in the text except V7, V8, and LO (lateral occipital, which plays a role in object processing), because these areas have not been associated with distinct clinical syndromes. (Artist: Juan Garcia.)

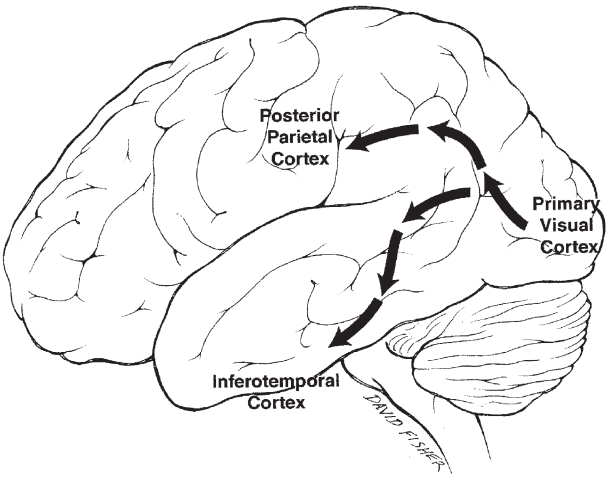

Fig. 4. Parallel visual processing pathways in the human. The ventral or "what" pathway begins in the striate cortex (V1) and projects to the angular gyrus for language processing (visual–verbal pathway), the inferior temporal lobe for object identification (visual–visual pathway) and limbic structures (visual– limbic pathway). The dorsal or "where" pathway begins in the striate cortex and projects to the posterior parietal cortex (PPC) and superior temporal cortex and is concerned with visuospatial analysis. This pathway continues forward to project to the premotor cortex (PMC) and the frontal eye fields (FEF) to convey visuospatial information used in the guidance of limb and eye movements. (Artist: David Fisher.)

Although the ventral and dorsal pathways are clearly involved in the analysis of different aspects of the visual environment,[259] they are extensively interconnected laterally and in feedback and feedforward directions, indicating that the flow of perceptual processing does not necessarily proceed in a stepwise, hierarchic manner.[234] This "what" and "where" dichotomy of visual processing is an oversimplification of how these cortical areas function, but it serves as a useful framework in which to develop a clinical model of cortical visual processing. A number of specific syndromes in humans involving the central processing of visual information can be localized primarily to one of the six visual cortical areas or one of the two occipitofugal pathways and thus are of clinical value. These are summarized in Table 1.

II. Syndromes Associated with Damage to the Striate Cortex (Area V1)

A. ANTON SYNDROME

Denial of blindness, or Anton syndrome,[7] is an uncommon form of anosagnosia that usually follows extensive damage to the striate cortex.[9,177] Although Anton syndrome usually occurs with geniculostriate lesions, it may occur from any etiology, including

TABLE 1

Syndromes Localized to One of the Visual Cortical Areas or Fungal Pathways

1. Area V1
   - A. Anton syndrome
   - B. Blindsight
   - C. Riddoch phenomenon
   - D. Transient achromatopsia
   - E. Visual ataxia
2. Area V2 and V3
   - A. Quadrantic homonymous hemianopia
3. Area V4
   - A. Cerebral achromatopisa
4. Area V5
   - A. Akinetopsia
5. Dorsal occipitofugal pathway
   - A. Bálint syndrome
   - B. Hemispatial neglect
   - C. Visual allesthesia
   - D. Enviromental rotation
6. Ventral occipitofugal pathway
   - A. Visual–verbal disconnection
     - i. Pure alexia
     - ii. Color anomia
     - iii. Object anomia
   - B. Visual–visual disconnection
     - i. Prosopagnosia
     - ii. Object agnosia
   - C. Visual–limbic disconnection
     - i. Visual amnesia
     - ii. Visual hypoemotionality

blindness from prechiasmal disorders, such as optic neuropathies and retinal detachment.

Patients with Anton syndrome will deny they are blind and often confabulate to mask their visual loss. We recently examined a hospitalized patient who was blind following a bilateral occipital stroke but who adamantly believed he could see. He could not see to feed himself and would feel his way around the room, yet he falsely identified objects when presented to him.

There are several theories regarding the etiology of Anton syndrome, but a definitive etiology remains elusive.[152] Geschwind noted that patients with this condition often had altered emotional reactivity, with a "coarse and shallow" affect similar to some patients with frontal lobe lesions. He attributed the denial of blindness to damage to higher cognitive centers.[152] Psychiatric denial may explain other cases.[126] Finally, lesions of the geniculostriate pathway that disrupt input to the visual cortex may also interfere with output from the visual cortex to areas involved in the conscious awareness of visual perception. In such cases, the striate cortex is unable to communicate the nature of the patient's visual loss to areas concerned with conscious awareness.[126]

B. BLINDSIGHT

Studies of visually guided behavior following removal of the striate cortex in monkeys demonstrate definite preservation of visual sensory function.[178] A similar phenomenon is thought to occur in humans who experience severe damage to one or both occipital lobes.[198] Weiskrantz coined the term *blindsight* to refer to this rudimentary level of visual processing that occurs below the level of visual awareness.[272] Over the past 20 years, the phenomenon of blindsight has been extensively studied in humans and lower primates. This entity encompasses a wide variety of visual processing mechanisms, all occurring without conscious awareness.[240]

Some authors expand blindsight to refer to any preserved visual function that occurs below the level of visual awareness in patients with cortical blindness.[240] These authors include neuroendocrine responses[53] and visual reflexes,[269] such as preservation of the photic blink reflex,[104] as types of blindsight. However, most authors refer to blindsight strictly as preserved higher levels of visual processing following an occipital stroke.

Higher levels of cortical processing have been evaluated in humans by both implicit processing, which measures induced responses to stimuli presented to the blind field,[162,197,254,271] and direct responses, including forced-choice experiments, saccadic localization tasks, and manual pointing to objects presented in the blind hemifield.[26] Using these techniques, researchers have shown that rare patients exhibit preservation of the ability to detect direction of motion,[162] wavelength,[241] target displacement,[24] stimulus presence,[272] orientation,[180] and object discrimination.[272] Behavior studies in monkeys and humans have demonstrated that this unconscious discrimination exhibits a learning effect, with increased accuracy with extensive training.[285] However, the potential use of blindsight in visual rehabilitation is controversial.[285]

The methods described above have been criticized in the past, leading to the questioning of the existence of blindsight in humans. Ocular scatter and residual functional islands of striate cortex have both been used as alternate explanations of blindsight.[36,78] However, controlled experiments involving blind spot stimulation,[180] along with improved fixation controls, have made these alternative hypotheses less likely.[270] Additionally, functional imaging studies have failed to show residual activity in the striate cortex in several of these patients.[12,79,243] Nevertheless, although recent experimental evidence may indicate that blindsight in humans is more than just an experimental artifact, even those who accept the idea admit that it can be demonstrated in only a

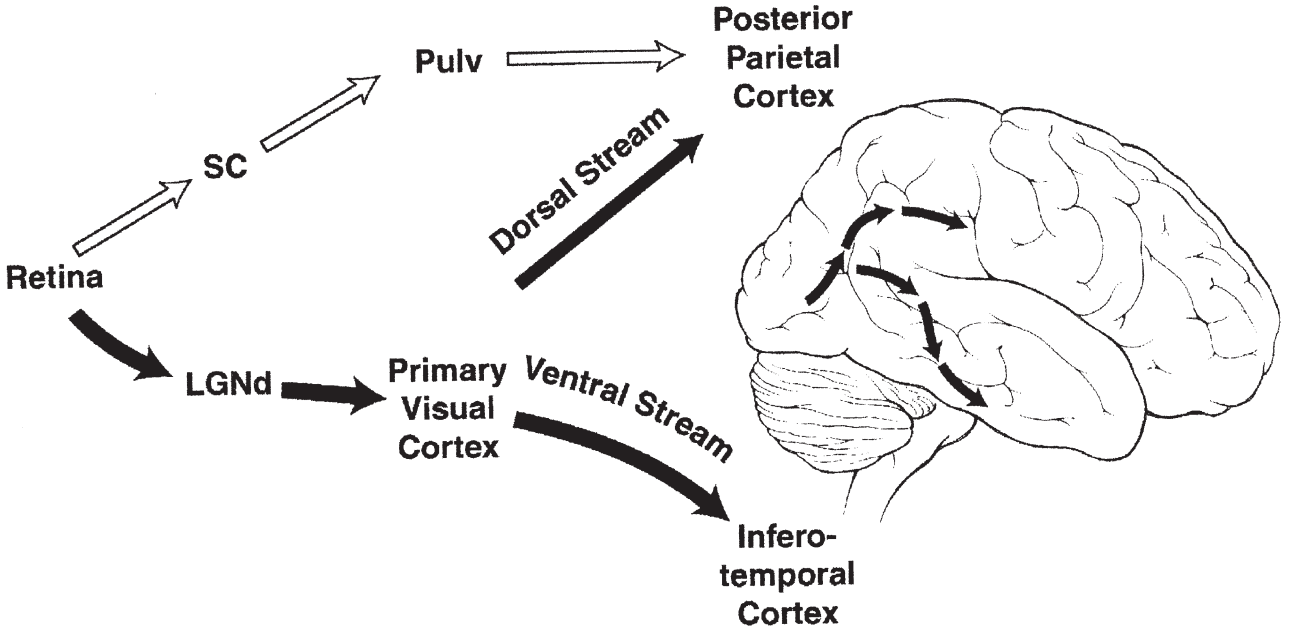

Fig. 5. Two proposed pathways involved in blindsight. *A*: Visual information is transmitted to associative visual areas in the dorsal occipitofugal pathway via a subcortical pathway that includes the superior colliculus (SC) and pulvinar (Pulv) thus bypassing the pathway to the primary visual cortex through the dorsal lateral geniculate nucleus (LGN). *B*: Pathways from the LGN convey visual information to extrastriate cortical areas that may bypass the striate cortex. (Artist: David Fisher.)

limited number of patients and is dependent upon training and time after cortical injury, possibly because of plasticity in the visual cortex seen in patients with long-standing central field defects.[199]

Anatomic studies in lower primates,[178,188,189] as well as functional imaging[14,181] and electrophysiologic studies[79,231] in humans, have provided some insight into the functional anatomy of blindsight. These studies suggest that a subcortical pathway involving the superior colliculus and pulvinar processes some aspects of the unconscious perception demonstrated in these rare cases (Fig. 5).[18,19,270] However, the retino-tecto-pulvinar-cortical pathway lacks information concerning color opponency, thus cannot explain the presence of color discrimination in some subjects with blindsight.[50,241,242] Alternatively, blindsight may be secondary to surviving connections from the LGN to associative visual areas that bypass the striate cortex.[51]

Although much controversy still surrounds the existence of and pathways involved in blindsight in humans, the availability of improved functional imaging methods and techniques of reversible cortical deactivation may help resolve these conflicts in the future. Indeed, an understanding of this condition may eventually provide crucial clues toward an understanding of the neural correlates of visual awareness and may even contribute to the design of techniques for visual rehabilitation in patients with cortical blindness.

C. RIDDOCH PHENOMENON

In 1917, George Riddoch, a captain in the Royal Army Medical Corps, described 10 patients with wounds to the occipital area who were able to perceive movements within their blind hemifield.[202] Several studies of similar patients by other investigators subsequently confirmed what became known as the *Riddoch phenomenon*: preservation of motion perception in an otherwise complete scotoma.[172,280]

The etiology of the Riddoch phenomenon is not clear. It has been suggested that patients who exhibit this phenomenon have preserved islands of function within the striate cortex,[202] or that extrastriate areas, V5 in particular, may be involved through activation of subcortical pathways that bypass V1.[36,280] Alternatively, statokinetic dissociation may be related to lateral summation of moving images. It has been demonstrated in normal subjects that a kinetic target may be seen more readily in some areas of the visual field than nonmoving objects of the same intensity and size.[101] Variable degrees of dissociation of perception between moving and nonmoving stimuli have been demonstrated in normal subjects[88] and in patients with compression of the anterior visual pathways.[217,276]

Clinically, the Riddoch phenomenon can be a useful prognostic indicator. For example, patients with the Riddoch phenomenon following an occipital stroke or in the setting of an occipital lobe tumor are more likely to recover function in the affected field, spontaneously in the first setting or after removal of the tumor in the second.[255]

D. TRANSIENT ACHROMATOPSIA

Although cerebral achromatopsia—i.e., loss of color perception from a lesion in one or both cerebral hemispheres—usually occurs from a lesion involving area V4 (see below), transient achromatopsia has been reported in some patients with vertebrobasilar insufficiency.[147] Achromatopsia in the latter setting may occur from dysfunction of wavelength-selective regions in areas V1 or V2. Both of these areas exhibit increased metabolic activity compared with surrounding areas and thus may be more vulnerable to ischemia.[274]

E. VISUAL ATAXIA

Patients with an homonymous hemianopia from an occipital lobe lesion may experience loss of balance associated with a sensation of falling toward the blind hemifield.[213] Such patients have an intact vestibular system, and this "visual ataxia" is thought to be secondary to unopposed tonic input from the intact contralateral occipital lobe. *Visual ataxia* is a disturbance in balance and should not be confused with *optic ataxia*, which is a disturbance in visually-based limb guidance (see below).

III. Syndromes Caused by Damage to the Parastriate and Peristriate Visual Cortex (Areas V2 and V3)

Both primate and human studies have demonstrated that area V2 may play a role in the detection of illusionary contours.[193,194] This perceptual task is of great importance in the detection of obscured objects, such as a camouflaged predator. Patients with early posterior Alzheimer's disease demonstrate impaired detection of illusionary contours, possibly due to degeneration of area V2.

The effect of lesions of V2 and V3 in humans is unclear. Horton and Hoyt reported two patients with lesions thought to involve the superior parastriate and peristriate cortex.[118] Both patients had homonymous quadrantic visual field defects that respected the horizontal and vertical meridians. This report not withstanding, lesions of V2 induced by ibotenic acid fail to produce a visual field defect in monkeys.[171] The apparent discrepancy between these two observations may be related to the fact that ibotenic acid destroys cell bodies while preserving axons and, therefore, may spare the fibers of the optic radiations passing deep to the parastriate cortex. Of course, a congruous homonymous quadrantanopia is not specific to parastriate lesions; it not infrequently results from striate lesions as well.[165]

IV. Syndromes Caused by Damage to the Human Color Center (Area V4)

A. PERCEPTION OF COLOR AND AREA V4

Unlike a camera, the visual system has the ability to compensate for the changing spectral components of a light source. Therefore, in most viewing situations, a red object will appear red regardless of the wavelength of light that illuminates it, even though the dominant spectral component reflected from the object may vary with lighting conditions. This effect is called *color constancy*. The visual system creates the concept of color by comparing areas of the visual field.[142] Thus, a red object appears red not because it reflects long-wavelength light, but because it reflects *relatively more* long-wavelength light than do other objects within the visual field. A neural structure that performs this comparison of wavelengths across large areas of the visual field requires cells that can combine wavelength-selective information obtained from disparate areas of the visual field.[70] The cells in area V4 in the monkey fulfill these requirements. They respond to both wavelength and perceived color, whereas neurons in areas V1 and V2 respond only to wavelength.[279] These physiologic experiments, along with lesion studies in macaques, have led some investigators to conclude that area V4 is the site of color constancy in lower primates.[278]

Although the localization of a "color center" in humans has been clearly identified,[160] whether or not this area is homologous to area V4 in monkeys and whether or not cerebral achromatopsia in humans is a defect of color constancy alone are currently unresolved issues.[39,114,129] Many authors use the term *human color center* interchangeably with the term *human V4*.[167] However, the complaints of patients with cerebral achromatopsia from damage to this region are not entirely explained by loss of color constancy.[207] In addition, extirpation of area V4 in the monkey does not lead to achromatopsia, for the animals retain the ability to discriminate and order hues despite clearly impaired form recognition.[92,220,221]

B. CEREBRAL ACHROMATOPSIA

Cerebral achromatopsia is an acquired defect in color perception caused by damage to the ventromedial visual cortex.[278] Affected patients describe a world that looks faded, gray, and washed out, or completely devoid of color, like a black-and-white photograph. Patients with the most pure form of ce-

rebral achromatopsia cannot arrange graded isoluminant, but retain normal sorting for graded gray objects.[49] However, many affected patients have some residual hue discrimination, thus view the world as if looking though a colored filter. Such patients are probably more correctly classified as having cerebral dyschromatopsia rather than achromatopsia.[278] Additionally, many patients reported to have achromatopsia have not received an adequate neuropsychologic assessment and could actually be exhibiting color anomia or aphasia, thus further confusing this issue.[278]

Unlike patients with congenital achromatopsia, patients with acquired cerebral achromatopsia show preserved trichromacy and intact cortical responses to chromatic visual evoked potentials (VEPs).[49] The chromatic pathways from the retina to the striate cortex are intact. Because of preserved function of wavelength-selective cells in the striate cortex, achromatopsic patients may still retain the ability to distinguish the border between two adjacent isoluminant colored patches[49] and may perform well on testing with pseudoisochromatic plates.[168]

Verrey, in 1888, provided the first pathologic correlation in cerebral achromatopsia, localizing the lesion to the posterior fusiform and lingual gyri (Fig. 6). Subsequent investigators have described the pathologic findings in patients with this condition.[278] Bilateral infarction in the posterior cerebral artery distribution is the most common etiology and is often caused by vertebrobasilar ischemia.[147] Additional causes include metastatic tumors,[97] posterior cortical dementia,[82] and herpes simplex encephalitis.[113] Transient achromatopsia may occur with migraine,[149] focal seizures,[2] and vertebrobasilar insufficiency.[147]

Cerebral achromatopsia is often associated with a superior homonymous visual field defect from damage to the inferior striate cortex.[57] In such cases, the residual inferior field on that side is achromatopsic. Furthermore, because of the ventral location of the lesions in these patients, central achromatopsia is often accompanied by deficits caused by damage to the ventral occipitofugal pathway, including prosopagnosia, topographagnosia, visual object agnosia, pure alexia, and defects of visual memory (see below). Global amnesia may be present if the lesion damages large areas in the temporal lobe.[57] Defects in pattern processing are also well described, possibly reflecting a role for color in form analysis.[92]

Three-dimensional magnetic resonance imaging (MRI) in patients with cerebral achromatopsia indicates that the critical lesion involves the middle third of the lingual gyrus or the white matter posterior to the tip of the lateral ventricle.[62] Cerebral achromatopsia may be complete or affect only one homonymous hemifield.[190] Bilateral lesions are required for a complete achromatopsia, whereas unilateral lesions produce hemiachromatopsia.

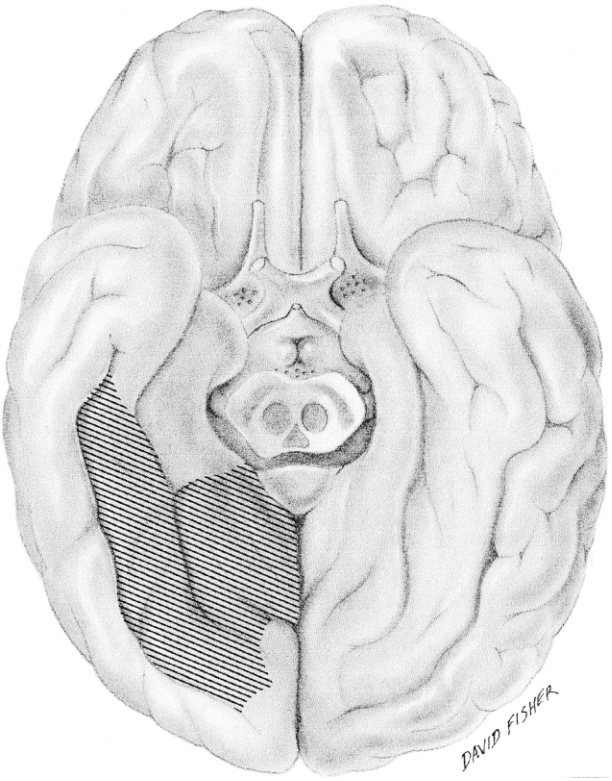

Fig. 6. View of the ventral surface of the brain with the cerebellum removed. The posterior fusiform and lingual gyri, which contain the human color center, are highlighted. (Artist: David Fisher.)

Zeki and coworkers used functional MRI (fMRI) to define the representation of the visual field in the human color center.[167] This study localized the color center to the lateral aspect of the collateral sulcus on the fusiform gyrus. Additionally, these investigators described a retinotopic organization of the fusiform gyrus, with the superior field being represented within the medial fusiform gyrus and the inferior field located more laterally.

If achromatopsia were due solely to defective color constancy, then patients with the condition should not see the world as gray or desaturated, but instead they should experience dramatic fluctuations in color as environmental lighting conditions change. Since this is not the case, the defect in achromatopsia may involve more than just color constancy. Indeed, Rizzo et al have hypothesized that color constancy, like lightness constancy, is generated by earlier visual associative areas.[211] Alternatively, lesions of the fusiform gyrus may disrupt white matter deep to the collateral sulcus and disconnect the striate and extrastriate areas from a more rostral color center, possibly an area homologous to a wave-

length-selective inferior temporal area in monkeys that, when extirpated, produces a deficit similar to cerebral achromatopsia in humans.[49] Recently, a color-selective area has been demonstrated in humans in a similar region and has been labeled V8.[105] There is some controversy as to whether this is a new visual area or merely the anterior portion of V4.[281]

Although there is still much controversy regarding the function of the human color center and its relationship to area V4 in lower primates, it is clear that lesions that produce cerebral achromatopsia in humans are invariably located in the ventromedial occipital lobe (Figs. 3 and 6).

V. Syndromes Caused by Damage to Area V5

A. NEUROPHYSIOLOGY OF MOTION PERCEPTION

Functional imaging;[252,282] experiments using myelin, cytochrome oxidase, and monoclonal-antibody staining;[253] and cortical stimulation experiments suggest that the most likely location of area V5 in humans is the ventrolateral occipital gyrus, a key area involved in the perception of visual motion (Fig. 3). In addition, transcranial magnetic deactivation of this area demonstrates deficits in motion perception.[17] However, the analysis of motion involves a complex system of several interrelated cortical areas that are involved in processing various components of motion perception and that may adapt to the loss of area V5.[77,252] This would explain the preservation of some aspects of visual motion perception in patients with akinetopsia (see below) and the rarity of this syndrome in humans.

B. AKINETOPSIA

Akinetopsia is the loss of perception of visual motion with preservation of the perception of other modalities of vision, such as form, texture, and color. Although isolated deficits in motion vision in humans were reported in the early 20th century, these cases were poorly documented.[277] It was not until the report of Zihl et al in 1983 that an example of akinetopsia was clearly described.[286] The patient, LM, described by these investigators, is one of only two patents who have been extensively studied. She developed bilateral cerebral infarctions involving the lateral occipital, middle temporal, and angular gyri, secondary to sagittal sinus thrombosis (Fig. 7). She described moving objects as jumping from place to place. For example, when pouring tea, she observed that the liquid appeared frozen like a glacier, and she failed to perceive the tea rising in the cup. She did, however, have definite evidence of residual motion processing at modest levels of background noise on psychophysical tests, such as random-dot cinematograms. Indeed, she was able to distinguish moving from nonmoving targets and to distinguish shape and three-dimensional structure from motion.[208] These abilities may reflect preserved function of associated areas of motion processing and emphasize that motion perception is not completely isolated to a single cortical region.[233]

Subtle deficits in motion processing in the contralateral hemifield in patients with unilateral occipitoparietal lesions involving area V5 have also been described.[260] This "hemiakinetopsia" is often obscured by coexistent incomplete homonymous field defects.

In a study using fMRI, Eden et al found almost no activation of area V5 in dyslexic patients.[71] The results of this study support previous psychophysiologic and anatomic data suggesting that patients with dyslexia have anomalous magnocellular responses.[158] The superior temporal area that is activated while normal patients view moving stimuli overlaps areas involved in language processing, leading some investigators to conclude that some disorders of phonologic awareness may result from a global deficit in processing temporal properties of vision.[158]

VI. The Dorsal Occipitofugal Pathway and Visuospatial Processing in Humans

A. NEUROANATOMY AND NEUROPHYSIOLOGY

The dorsal or "where" pathway receives information primarily from area MT and, to a lesser extent, area V4.[259] This information is conveyed along the dorsal longitudinal fascicles to the posterior parietal cortex, frontal motor areas, and frontal eye fields (FEF). This pathway is concerned with spatial localization, visuomotor search and guidance, and visuospatial synthesis.[109] Lesions of the dorsal pathway produce visuomotor and attention deficits, in contrast to the visuoassociative deficits produced by ventral lesions.

The posterior parietal cortex is neither a purely sensory nor a purely motor area; rather, it combines characteristics of both. Thus, it serves as a junction between multimodal sensory input and motor output, linking the afferent and efferent arms of the visual pathways and providing the connection that encompasses the entire field of neuro-ophthalmology, from the eyes to the extraocular muscles.[4]

One model proposed for the modulation of spatial attention is that the posterior parietal cortex contains several maps of the visual environment, which are used in visually guided movement,[5] modulate attention,[47,179] and plays a role in visuospatial perception. These maps code the location of visual targets in a variety of coordinate systems tailored to

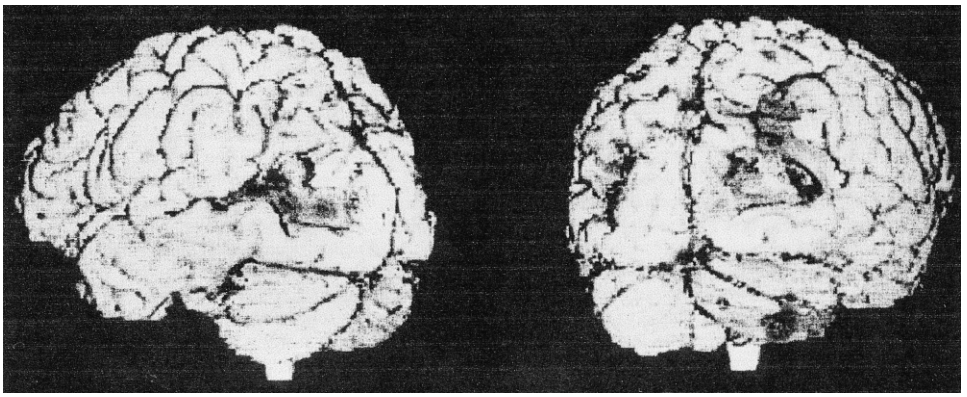

Fig. 7. Three-dimensional magnetic resonance imaging reconstructions of bilateral temporo-occipital lesions of a patient who developed akinetopsia associated with a sagittal sinus thrombosis. *Left*: View of the left posterior brain. *Right*: View of the right posterior brain. (Reprinted from Shipp S, de Jong BM, Zihl J, et al233 with permission of *Brain* and the authors.)

the guidance of eye movements, head movements, and arm movements.[44] Specialized areas encode visual space in oculocentric coordinates, i.e., relative to the center of gaze, for guiding eye movements[244] and in craniocentric coordinates, combining proprioceptive input from the orbit with visual information.[44] These "gaze-locked" cells respond maximally only to stimuli in a specific position of gaze.[87] Other posterior parietal areas contain representations of visual space based on limb-centered coordinates that relate object position to limb position and are used in the visual guidance of arm movements.[218] Additionally, "real-position" cells located in the parietal lobe in the macaque combine visual, proprioceptive, and vestibular inputs to convey the "true" position of the visual objects in space relative to the observer.[87]

B. SYNDROMES OF THE DORSAL OCCIPITOFUGAL PATHWAY IN HUMANS

1. Bálint Syndrome

Bálint syndrome is classically defined as the combination of simultanagnosia, optic ataxia, and acquired oculomotor apraxia, also called *psychic paralysis of gaze*.[11,263] The components of Bálint syndrome are not closely bound together[186] and may occur in isolation or in association with other disorders of visuospatial perception. Thus, this triad has no specific anatomically localizable correlate.[108,186] Most authors believe that the concept of Bálint syndrome as a specific clinical entity offers little to the scientific or clinical understanding of visuospatial processing and, although historically interesting, should be abandoned. We will, therefore, consider the specific components of this "syndrome" separately.

a. Dorsal Simultanagnosia

Patients with dorsal simultanagnosia can perceive whole shapes, but their perception of these shapes is limited to a single visual area because they are unable to shift visual attention.[76] Patients with this condition thus behave as if they are blind even though they have intact visual fields. Dorsal simultanagnosia, although clearly a visuospatial disorder of attention, is discussed in more detail below in the section with apperceptive agnosias and ventral simultanagnosia because of the clinical similarities among these conditions.

b. Optic Ataxia

Optic ataxia is a disorder of visual guidance of movements in which visual inputs are disconnected from the motor systems.[191] Thus, patients reach for targets within an intact field as if they were blind.[210] A complex sensory-motor network involves the posterior parietal lobe, motor areas, ventromedial cortical areas, and subcortical structures, such as the cerebellum, that modulate the control of visually guided limb movement.[204] Thus, a variety of lesions that affect this network can produce optic ataxia.[205] Lesions of superior parietal cortex are more likely to damage areas involved with limb guidance, whereas inferior parietal lesions are more likely to affect visual attention and thus produce neglect syndromes.[84,128]

c. Spasm of Fixation (Acquired Oculomotor Apraxia)

Spasm of fixation or psychic paralysis of gaze is sometimes erroneously called *ocular motor apraxia*, thus adding to the confusion already surrounding this phenomenon. Spasm of fixation is characterized

by loss of voluntary eye movements with persistence of fixation on a target. However, in contrast to true ocular motor apraxia, saccades easily are made to peripheral targets in the absence of a fixation target. Thus, a patient asked to fixate an object centrally and then move the eyes to a peripheral target cannot do so, whereas a patient who is not fixing on any object in particular easily can move the eyes to fixate a peripheral target when asked to do so.

The location of the lesion that causes spasm of fixation is obscure. The FEF is required for the release of fixation for voluntary saccades, and lesions of this region may prolong saccadic latency. Posterior parietal, middle temporal, and superior temporal areas mediate cortical maintenance of fixation by inhibition of attention shifts. Thus, damage to the FEF that spares these regions may prevent the release of fixation by disinhibiting the inhibitory effect of the substantia nigra pars reticulata on the superior colliculus, suppressing the generation of saccades.[125]

2. Hemispatial (Hemifield) Neglect

Complex visual scenes constantly bombard the visual system. Because cognitive and motor activities are generally concerned with one object at a time, these elements of the visual scene must compete for the limited resources of focal attention.[13,37] Modulation of attention occurs at many levels in the visual system, even at the level of area V1.[136,262]

Numerous lines of evidence suggest that a complex network of cortical and subcortical areas primarily in the dorsal occipitofugal pathway is involved in the modulation of spatial attention. These include the superior colliculus, the posterior parietal cortex, the striatum, the pulvinar, and areas in the prefrontal cortex.[43] In particular, the posterior parietal cortex, the FEF, and cingulate gyrus play key roles in spatial-based attention mechanisms. The posterior parietal cortex builds the sensory representation of extrapersonal space, the FEF plans and initiates exploratory movements, and the cingulate gyrus provides the motivational potential.[43]

A positron emission tomography (PET) study in normal humans demonstrated activation of the cingulate gyri (greater on the right), the posterior parietal cortex, and the medial and lateral premotor cortical areas during covert shifts of attention.[184] The results of this study are consistent with the concept that these cortical areas form the core of a neural network for spatial attention.

Damage to the components of the dorsal occipitofugal pathway or their interconnections may cause hemispatial neglect to the contralateral side.[173] One attractive hypothesis is that the right hemisphere coordinates attention throughout extrapersonal space, whereas the left hemisphere coordinates attention only in the contralateral right hemispace; thus, only left hemispatial neglect is seen as a persistent phenomenon.[268] Hemispatial neglect involves multiple sensory modalities,[133] but visual extinction often is the most prominent feature. Affected patients see stimuli presented separately in either their right or their left hemifield, but ignore stimuli in the left hemifield when both hemifields are stimulated simultaneously. Thus, any patient who appears to have a homonymous hemianopia when bilateral simultaneous stimulation confrontation testing is performed should undergo testing of each homonymous hemifield separately to determine if the apparent field defect is real or the consequence of hemifield extinction. In fact, some patients with hemifield extinction also have an homonymous visual field defect, most commonly a lower left quadrantanopia. Such patients will demonstrate a homonymous quadrantic field defect when each hemifield is tested separately but complete neglect of the left homonymous hemifield when tested with bilateral simultaneous stimulation. In patients with full visual fields, double simultaneous stimulation or testing line bisection are excellent bedside examination techniques to detect hemifield neglect.

3. Visual Allesthesia

Classic visual allesthesia is a disorder of visuospatial perception in which the retinotopic visual field is rotated, flipped, or even inverted (Fig. 8, center left and right sketches). This syndrome localizes to two seemingly diverse areas of the brain: the lateral medulla and the occipitoparietal area, usually on the right side. Although visual allesthesia is a common component of the lateral medullary syndrome of Wallenberg[214] and is usually due to infarction, a variety of disorders that affect the cerebral cortex can produce visual allesthesia, including infarction,[112] neoplasm, trauma, infection,[8] and multiple sclerosis.[226] Transient visual allesthesia can occur during seizures[183] and migraine attacks.[103]

Several theories have been proposed to explain visual allesthesia; however, an all-encompassing explanation remains elusive. Jacobs suggested that allesthesia may involve transcallosal transmission of the contralateral hemifield to the damaged parietal cortex, with retention of the image as a palinoptic phenomenon.[121] Although this theory might explain the patient he described who had transposition of the visual field from left to right, it fails to explain the varieties of rotational or inverted allesthesia described by other patients.

Alternatively, visual allesthesia may be the result of a disorder of integration of visuospatial input. The causative lesion may disturb the integration of visual and otolithic inputs at the level of the medulla, as in

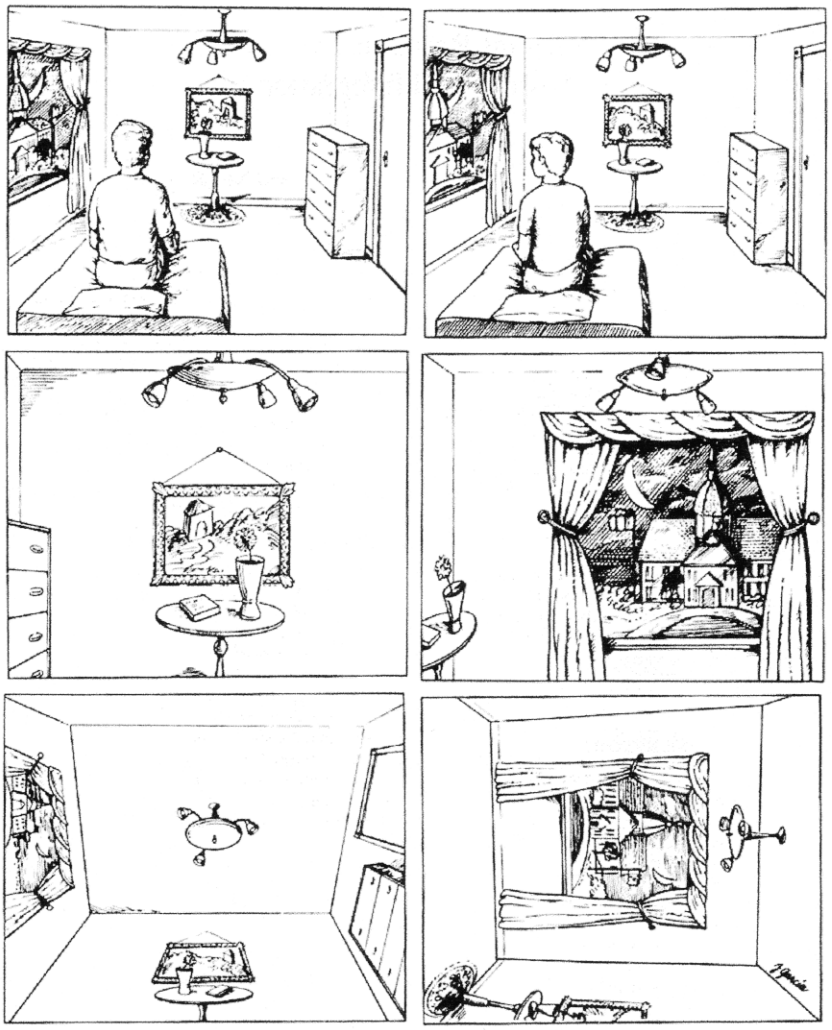

Fig. 8. Illustrations on the left show the view and orientation looking forward. Illustrations on the right show the view and orientation looking to the left. Upper left and upper right figures show a third person view of the patient's room indicating the head position and the orientation of the environment that would be seen by a normal person looking forward (left) a to the left (right). Center left and center right figures illustrate the appearance of the environment that would be seen by a patient with classic visual allesthesia looking forward (center left) and to the left (center right). Note that there is transposition of the visual field. Lower left and lower right figures illustrate the environmental rotation experienced by our patient in contrast to the visual field rotation in classic allesthesia. Note that the rotation in our patient is independent of head position. (Reprinted from Girkin CA, Perry JD, Miller NR95 with permission of *J Neuro-Ophthalmology*.)

Wallenberg syndrome, in which otolith inputs are interrupted directly, or at the site of integration in the posterior parietal cortex.[249]

4. Environmental Rotation

Classic visual allesthesia is characterized by tilting or rotation of the visual field. However, some patients have a form of visual allesthesia in which the environment rather than the field is rotated. For example, we reported a patient who experienced transient episodes of static rotation of the visual environment following a ventriculoperitoneal shunt placed through the right occipitoparietal cortex for normal pressure hydrocephalus.[95] During each episode, the patient noted that the environment was rotated 90 degrees, independent of head position (Fig. 8, lower left and right sketches). This visuospatial derangement abated 6 days after surgery. As discussed above, the parietal lobe integrates visual information with vestibular and proprioceptive input to form internal models of visual space that represent the "real-position" of objects independent of head-centered coordinates.[29] We believe that the phenomenon experienced by our patient resulted from a disorder of the "real-position" system[86] in the posterior parietal lobe and was caused by irritation from the shunt.

VII. The Ventral Occipitofugal Pathway in Humans

A. NEUROANATOMY AND NEUROPHYSIOLOGY

The ventral occipitofugal or "what" pathway is conducted mainly through the inferior longitudinal fascicles. Lesions of this pathway were initially divided into three types of disconnection syndromes: 1) *visual–visual disconnection*, which isolates visual inputs from the inferior temporal areas, producing an agnosia; 2) *visual–verbal disconnection*, which isolates the language centers in the dominant angular gyrus from visual input, producing alexia and anomia; and 3) *visual–limbic disconnection*, which isolates visual inputs from the amygdala and hippocampus, produc-

ing deficits in visual memory and emotion.[68] Although this disconnection theory was helpful in developing a general categorization scheme for these defects, it is inadequate in that it assumes that visual perception, semantic understanding, and memory are all processed in a staged, modular fashion. This separation is not distinct, and patients seldom display completely isolated manifestations of these syndromes. For example, visual–verbal defects may occur in combination with visual-visual defects, and disorders previously categorized as visual–verbal disconnections, such as pure alexia, are now considered by some authors as subtypes of visual agnosia (see below).

B. LESIONS OF THE VENTRAL OCCIPITOFUGAL PATHWAY IN HUMANS

1. Visual–Visual Disconnection

Visual information processed in area V4 projects anteriorly to the temporal cortex, where it is integrated with stored memory templates.[16] Lesions of this pathway may cause true visual agnosia; i.e., unimodal deficits in object knowledge.[75] In contrast to object anomia, patients with pure visual agnosia cannot provide the name or the associative features of an object, thus indicating a defect in *recognition*, not just in naming. For example, a patient with object anomia cannot name a shovel but may be able to describe it as a tool for digging. A patient with visual agnosia not only is unable to name it, but also is unable to describe its function. However, a clear distinction between anomic defects and agnosia is difficult in that many patients will exhibit a constellation of defects that include perceptual difficulties, agnosia, and anomias.[272] This again illustrates that there may not be distinct separation between those cerebral processes involved in visual perception, object identification, and naming.

Neuropsychologists generally divide the agnosias into two groups: *apperceptive* and *associative*.[76] This division was based upon theoretical models developed by Lissauer in 1890,[156] which, in turn, were based upon models of staged visual processing that assumed that perception of the visual environment is distinctly separated from the aquisition of a state of knowledge concerning that perception. Thus, apperceptive agnosia is an inability to accurately develop a visual perception of an object, whereas associative agnosia is an inability to associate the perceived visual object with areas involved in processing and storing memories to eventually achieve global semantic knowledge of the object within the visual environment. Although these theoretical models are not entirely valid, in the clinical setting patients tend to fall into two relatively homogenous groups with characteristics that roughly correspond to these early theories.[76]

a. Apperceptive Agnosias

The term *apperceptive agnosia* has been applied to patients with impaired object recognition due to perceptual difficulties in which elementary visual function remains intact.[247] Perception involves the integration of visual information to form an internal image of an object. Thus, such patients may have good visual acuity, color vision, and brightness discrimination, but still may be unable to perceive an object because of an inability to integrate incoming visual information. These patients often have visual field defects, but their perceptual deficit cannot be explained by their field loss. They perceive their visual environment in a piecemeal fashion, being unable to integrate multiple characteristics of a visual scene into a global perception.

Although patients with apperceptive agnosia may exhibit behavior that is superficially similar to the behavior of patients with associative agnosia, the underlying deficit in apperceptive agnosia, when interpreted in the narrowest sense, applies only to patients who exhibit a disorder in which only local contour is perceived. These patients have difficulty matching, copying, and recognizing even simple shapes, and although they can trace these shapes, they often exhibit "derailment" when trying to follow the lines that make up an image or symbol.[33]

Apperceptive agnosia usually develops in association with diffuse lesions to the posterior brain. It has most frequently been described following carbon monoxide[34] or mercury[145] poisoning, both of which can cause diffuse cerebral injury. Carbon monoxide poisoning causes multifocal interlaminar disruption, whereas mercury poisoning causes white matter damage. In both settings, the damage is primarily to the connections among neurons rather than to the neurons themselves.

Three other conditions are also categorized by some authors as types of apperceptive agnosia because of the similarity in the "piecemeal" nature of perception; however, on closer inspection, the nature of the deficit in these disorders is quite distinct from true apperceptive agnosia.[76] These three conditions are dorsal simultanagnosia, ventral simultanagnosia, and perceptual categorization deficit.

i. Dorsal simultanagnosia. Dorsal simultanagnosia results from lesions of the "where" pathway and was initially considered part of Bálint syndrome (see above). Unlike patients with true apperceptive agnosias, patients with dorsal simultanagnosia can perceive whole shapes, but their perception of these shapes is restricted to a single visual area because of

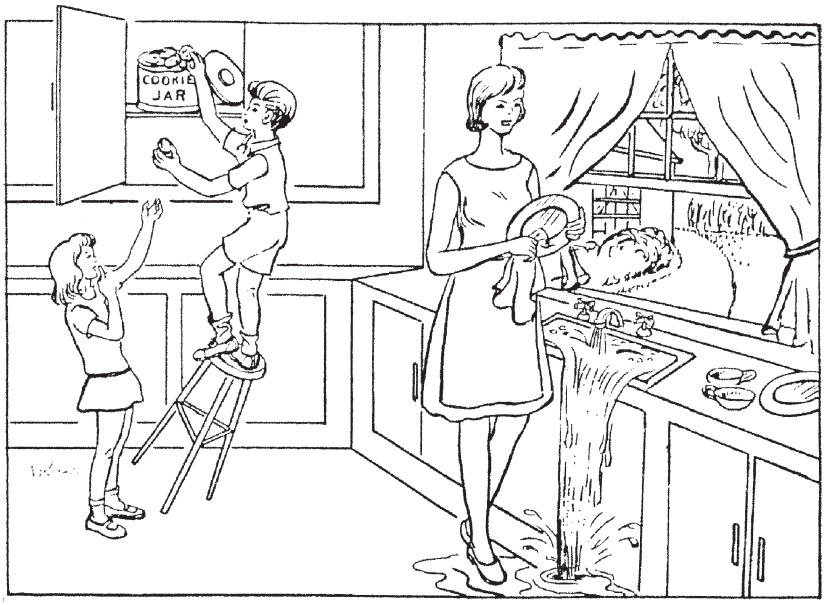

Fig. 9. The "Cookie Theft Picture" from the Boston Diagnostic Aphasia Examination. This picture contains a balance of information among the four visual field quadrants. A patient is asked to describe the events in the picture, a task that requires assimilation of the entire visual scene. A person with simultagnosia would only be able to describe disconnected fragments of the scene such as the cookie jar or the faucet and would not be able to describe the events related to the scene.

their inability to shift visual attention. These patients thus behave as if they are blind even though they have intact visual fields.[76]

Synthesis of the visual environment requires constant scanning of visual space and integration of information from multiple foveations to continuously update the internal representation of external space. Patients with dorsal simultanagnosia fail to integrate this information into a global image of visual space and thus are unable to sustain awareness of multiple areas in the visual environment at any given time despite intact visual inputs.[76] They describe only fragments of a scene that fall within central fixation and sometimes note the disappearance of peripheral objects. Peripheral visual field defects may simulate simultanagnosia and must be excluded. Simultanagnosia is not a true agnosia, defined as a unimodal disorder of recognition, but instead is a disorder of sustained visual attention to multiple areas in visual space. This is in contrast to hemifield neglect, in which attention is relatively diminished in one hemifield more than the other.[132] The cookie-theft picture (Fig. 9) may be used in the examination of patients with simultanagnosia. This scene requires higher-order synthesis of multiple objects scattered throughout four quadrants of the picture to achieve a global understanding of the image.

Dorsal simultanagnosia can result from a variety of lesions, most of which cause bilateral damage to the dorsal occipitofugal visual information stream, including strokes (especially watershed infarcts),[209] tumors, encephalitis from human immunodeficiency virus infection,[224] degenerative diseases (e.g., Alzheimer's disease),[116] and following rupture of a basilar aneurysm.[176]

ii. Ventral simultanagnosia. Patients who sustain damage to the left inferior temporal region of the brain may exhibit a syndrome that has been called *ventral simultanagnosia.*[135] These patients can identify single objects; however, they have difficulty with multiple visual objects and complex visual scenes. Unlike dorsal simultanagnosia, which is a disorder in shifting of attention, patients with ventral simultanagnosia can "see" and shift attention to multiple objects. They cannot, however, integrate single components into a whole object. Also in contrast to patients with dorsal simultanagnosia, patients with ventral simultanagnosia can navigate a room and manipulate single objects normally. However, they are unable to recognize a complex object like a car, even though they can identify the components of the car, such as the tires or the fender. Thus, ventral simultanagnosia is often called *integrative simultanagnosia.*[146]

iii. Perceptual categorization deficit. Apperceptive agnosia has also been applied to a group of patients in whom perception of an object is difficult only when the object is viewed from an unconventional perspective or in uneven lighting conditions.[65]

Patients with this condition have little trouble with identification of objects when they are presented in their usual fashion. For example, a patient may correctly identify and be able to match faces when they are presented upright, but when the faces are tilted or photographed from different angles, the patient fails to identify them.[265] This deficit is often elicited only in experimental conditions and is usually seen in patients with damage to the right posterior inferior parietal lobule.[265]

b. Associative Agnosia

Patients with true associative agnosia have intact perception and can draw and match objects, but are unable visually to identify objects or categories of objects.[76] Tactile and auditory recognition is intact in these patients.[216] This condition occurs most often from lesions that damage the ventral posterior cortex bilaterally and disturb occipitotemporal interactions responsible for correlation of visual perception to memory centers involved in object recognition.[60] Although patients with associative agnosia do not display the gross perceptual deficits seen in patients with apperceptive agnosia, mild perceptual disturbances can be found in many of these patients with careful neuropsychiatric testing, indicating that the separation between perception and semantic understanding is indistinct.[76]

c. Subtypes of Agnosia

Agnosias may be generalized or restricted to specific classes of objects. Prosopagnosia and pure alexia (see below under visual–verbal disconnection) are specific subtypes of agnosia restricted to individual categories of visual objects.

i. Prosopagnosia. Patients with prosopagnosia have impaired ability to recognize familiar faces or to learn new faces, often relying on nonfacial clues, such as posture or voice, to distinguish friends, colleagues, and family from strangers.[60] They are usually but not universally aware of this deficit. The retained ability to identify people by nonfacial cues differentiates this disorder from person-specific amnesia, which has been reported in patients with lesions of the temporal poles and presumably renders the personal identity nodes inaccessible.[107] Patients with prosopagnosia usually can match faces and distinguish among unfamiliar faces, and some can accurately judge age, sex, and emotional expression from facial information, thus indicating that perception of some facial information is intact.[64] However, performance of these tasks is often abnormal, indicating some degree of perceptual disturbance.[64]

As with all lesions in the ventral stream, prosopagnosia is often associated with superior homonymous unilateral or bilateral visual field defects from extension of damage to the inferior striate cortex. Often, a left homonymous hemianopia is present,[55] and achromatopsia (with bilateral lesions) or hemiachromatopsia (with unilateral lesions) also is frequently, but not universally present.[206] Topographagnosia (a rare navigational disorder), agnosia extending to other classes of objects,[143] or generalized object agnosia may also be demonstrated in these patients.[63] In addition, other ventral stream defects may occur in the visual–verbal and visual–limbic pathways. If the lesion extends superiorly, dorsal stream syndromes, such as dorsal simultanagnosia[31] and left hemifield neglect, may occur.[122]

The majority of cases of prosopagnosia result from bilateral damage to the inferior portions of the occipitotemporal cortex, notably the lingual and fusiform gyri,[60] areas that show increased activity by PET and fMRI studies in response to objects in general, but particularly to faces.[127,228] Rare cases of prosopagnosia have been reported with unilateral lesions[130,250] and as a developmental defect.[63] The most frequent lesions causing prosopagnosia are infarctions in the territory of the posterior cerebral artery, trauma, and viral encephalitis.[60] An autosomal-dominant case of developmental prosopagnosia was described in a patient with the Asperger syndrome of autism.[141]

ii. Generalized Object Agnosia. Generalized object agnosia refers to agnosias that extend to include a wide variety of classes of objects. The causative lesions and associated findings in generalized object agnosia are similar to those of prosopagnosia.[130] That agnosias may be specific to a variety of classes of objects has led many researchers to assume that object recognition is achieved in a modular fashion, with specific areas in the brain that are responsible for recognition of various classes of objects.[60] However, it is more likely that these class-specific agnosia result from differences in the way in which different types of stimuli are processed in the brain.[216] It has been proposed that there are two basic types of associative agnosias, one that involves the recognition of multiple shapes within an image, requiring decompensation of an image into separate elements, and one that involves the processing of these individual elements themselves.[216] The latter type of processing is required to identify objects (visual–visual integration) and usually occurs in association with bilateral lesions that involve the inferior temporal-occipital cortex, whereas the former is required for word *recognition (visual–verbal integration) and is caused by lesions of the left temporal occipital cortex (see below).*

2. Visual–Verbal Disconnection

A visual–verbal disconnection produces difficulties in naming objects despite intact object recognition. These deficits must be distinguished from agnosia, in which identification of objects is defective (see above).[148] Three main syndromes of visual–verbal disconnection have been described in humans: pure alexia (alexia without agraphia), color anomia, and object anomia (optic aphasia).

a. Pure Alexia (Alexia Without Agraphia)

Patients with pure alexia can write and converse normally; however, they have profound difficulties

reading, even words they have just written. Because identification of lexical stimuli is intact by other sensory modalities, patients with pure alexia may be able to identify words by tracing. The degree of deficit is variable. Most patients exhibit slow, letter-by-letter reading, whereas others are completely unable to identify words, letters, or symbols.[23] Many cases of pure alexia are overlooked or wrongly attributed to the hemianopic defects frequently seen in these patients.[146]

Déjerine published the first postmortem findings in pure alexia.[66] His patient had damage to the left occipital lobe and the posterior aspect of the corpus callosum. Based on this study, as well as on subsequent anatomic and neuroimaging studies, pure alexia was thought to result from disconnection of visual inputs from the dominant angular gyrus.[195]

Some authors consider pure alexia to be a subtype of visual agnosia specific to lexical symbols,[174,264] whereas others consider it a form of ventral simultanagnosia, an apperceptive disorder in which multiple objects cannot be interpreted simultaneously (see above). This explains the letter-by-letter reading strategy exhibited by many of these patients.[155]

The dominant parietal cortex is involved in the evaluation of lexical symbols. The most common lesions associated with this deficit damage the left striate cortex and the splenium of the corpus collosum (Fig. 10), although lesions that damage the left LGN and splenium can also cause this syndrome.[59] Affected patients usually have a right homonymous hemianopia. Thus, no visual information is transmitted from the left striate cortex to the ipsilateral (dominant) angular gyrus. In addition, although their right (nondominant) striate cortex is intact, information from this region cannot be transmitted to the dominant angular gyrus because of the associated damage to the splenium of the corpus callosum, through which this information is normally conducted.[100] Lesions in the left subangular white matter may also cause pure alexia by isolating incoming information at a more distal level.[99] Patients with such lesions may or may not have a hemianopic defect, depending on whether or not the optic radiations are also involved. In cases with hemianopia, the alexia is not caused by the visual field defect, but rather by disruption of visual inputs to higher order linguistic centers.

Most cases of pure alexia are caused by infarctions in the territory of the left posterior cerebral artery; [23] however, pure alexia has been reported in patients with herpes simplex encephalitis,[73] intracranial hemorrhage,[110] arteriovenous malformations,[1] metastatic and primary tumors,[256] and focal posterior cortical dementia,[82] as well as following neurosurgical procedures in the left subangular region.[98] Because

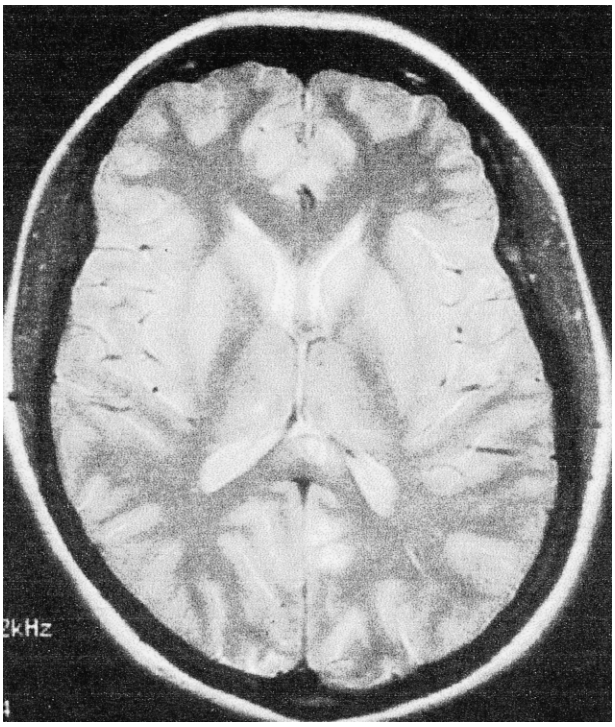

Fig. 10. T2-weighted magnetic resonance image through the splenium of the corpus callosum of a patient who developed alexia without agraphia following hypovolemic shock. A well-defined infarction involving the splenium is evident.

the damage is to ventral structures, the homonymous visual field defect may be limited to the superior quadrant, but it is more often complete. Hemiachromatopsia may occur if the lesion includes area V4. Naming of objects and colors may also be impaired by more extensive lesions.[58] Additionally, other properties conveyed in the ventral stream may be affected, and some patients demonstrate agnosic and memory deficits that may be easily confused with anomia.[59]

Lesions of the splenium alone may cause a left hemialexia associated with other signs of callosal disconnection, such as tactile anomia and agraphia with the left hand.[23] Additionally, right hemialexia was reported in a patient with a left ventromedial occipital lobe lesion presumably affecting the left prestriate cortex while preserving other visual functions in the right hemifield.[35] Lesions that involve the left angular gyrus itself will also impair writing ability, causing alexia with agraphia. This syndrome is usually associated with elements of Gerstmann's syndrome, including acalculia, right-left confusion, and finger agnosia.[21]

b. Color Anomia

Although cases exist in which color is disproportionally affected, most cases of color anomia are part of a more general visual–verbal defect with coexistent pure alexia.[91,218] Patients with color anomia can match colors: they do not have achromatopsia or an agnostic deficit. Their semantic recall of color is intact, and they are, thus, able to recall accurately the color of known objects (i.e., the color of a banana or an apple).

c. Object Anomia (Optic Aphasia)

Object anomia is characterized by a generalized defect in visual naming. Affected patients are unable to recall the names of objects presented visually, although their recall based on tactile and auditory input is preserved. Object matching and recognition are also intact. Such patients may be able to describe the characteristics of an object and its purpose, but they cannot provide the name of the object based solely on visual information. Often deficits in object identification are also present, making the separation between agnosia and aphasia difficult. The anatomic bases for color anomia, pure alexia, and object anomia are not entirely clear, but probably represent variations in the disruption of visual information reaching the angular gyrus. Object anomia may results from more extensive isolation of visual information from the angular gyrus than that which produces color anomia or pure alexia alone.[90] However, color anomia, optic aphasia, and pure alexia can occur together or in isolation. This double dissociation implies different anatomic substrates for these processes.

3. Visual-Limbic Disconnection

The sensory-limbic system plays a critical role in processing the emotional impact of sensory stimuli and in reinforcing certain aspects of multimodal sensory memory traces that are emotionally relevant through reciprocal circuits involving the temporal lobe.[90] Thus, lesions of the limbic system may cause multimodal amnestic disorders that impair recall of the recent past and an inability to establish new memories.[69] Lesions that disconnect visual input to this system may cause a modality-specific deficit. Two such disorders associated with lesions that disrupt visual axons projecting to the ventromedial temporal lobe are visual amnesia and visual hypoemotionality. These syndromes are rarely reported because object agnosia or prosopagnosia often mask their presence.

a. Visual Amnesia

Visual amnesia is a modality-specific disorder in which patients are unable to learn new visual objects, patterns, and faces, or to remember visual surroundings. In contrast to visual agnosias, consolidated visual knowledge is intact, whereas visual learning and recent recall are defective.[215] Isolated visual amnesia is rare. More commonly, it occurs in association with visual agnosia.

b. Visual Hypoemotionality

Isolated visual hypoemotionality is a rare syndrome in which emotional responses to visual stimuli are blunted or absent. Emotional reaction to other sensory modalities, such as listening to music, remains intact. Visual hypoemotionality is most frequently associated with prosopagnosia.[102] The damage in patients with this disorder is to the medial occipitotemporal area, sparing the associative areas involved in object recognition. One patient with this condition was said to be so visually unarousable that he cancelled his subscription to *Playboy* magazine.[15]

VIII. Visual Hallucinations and Illusions

Visual hallucinations are internally generated perceptions. That hallucinations are consciously perceived implies that these internal perceptions utilize mechanisms similar to those that generate conscious visual awareness, presumably through reciprocal activation of visual processing areas. Thus, we may gain insight into the neurobiology of visual awareness through the study of these internally generated stimuli.

Hallucinations may be caused by a variety of conditions. They are a common manifestation of a variety of psychiatric disorders, including schizophrenia, narcolepsy,[161] psychotic depression, and mania.[238] They also occur in patients with neurologic disorders, such as Alzheimer's disease[151] and epilepsy,[89] metabolic derangements, such as during alcohol withdrawal,[176] and in febrile states. Strokes may also cause hallucinations through release mechanisms and through seizures.[6,131]

Strokes involving the mesencephalon may cause peduncular hallucinations.[229] These are usually multimodal complex hallucinations to which patients may lack insight. Generally, peduncular hallucinosis is associated with other signs of midbrain disease, such as ocular motor nerve palsies, hemiparesis, gait ataxia, or hemiparkinsonism.[137] Interestingly, these patients almost invariably have inversion of the sleep-wake cycle, probably caused by damage to the pedunculopontine nucleus.[166] Thalamic infarcts may cause peduncular hallucinations of past events.[185]

Drugs, both prescribed and illicit, can induce hallucinations.[238] Some of the more common drugs associated with visual hallucinations are indomethacin,[28] digoxin,[41] bupropion,[3] vincristine,[93] cyclosporine,[239] lithium,[219] lidocaine,[219] and dopamine.[150] Visual hallucinations can also occur in patients given

topical homatropine,[201] scopolamine,[106] atropine,[140] or other topical agents.[140,287] Withdrawal of certain medications, such as baclofen,[203] may cause hallucinations. The most frequent types of visual hallucinations are release hallucinations, visual migraines, and visual seizures.

A. RELEASE HALLUCINATIONS (CHARLES BONNET SYNDROME)

Visual hallucinations frequently occur in patients who lose vision in both eyes, regardless of the location of the causative lesion or lesions. This association was first reported by Charles Bonnet, a Swiss naturalist, who described complex formed hallucinations experienced by his 89-year-old grandfather, who, although cognitively intact, was blind from cataracts.[27] The gentleman reported "amusing visions" of silent "figures of men, women, birds . . . etc." Cogan postulated that hallucinations occurring in blind or near-blind individuals were "released" by removal of normal visual afferent input to association cortex.[42] He therefore called them "release phenomena," and other authors refer to patients experiencing them as having the *Charles Bonnet syndrome.*

Release hallucinations may be simple or complex, with simple hallucinations occurring more frequently than complex ones. Simple hallucinations usually consist of brief flashes of light, phosphenes, or various shapes and textures. Complex hallucinations are specific objects, such as people, animals, plants, or imaginary creatures. They may appear as black-and-white figures, or they may be seen in color. Some of these complex visions reflect past visual memories. We recently examined a patient with count fingers vision from retinitis pigmentosa who began seeing a visually detailed hallucination of her sister as she appeared 30 years earlier, when the patient still retained relatively good vision. Another patient had recurrent hallucinations of a previous business partner. Some patients experience progression from simple to complex hallucinations.[235]

Release hallucinations often begin shortly after the loss of vision, but they may not develop until years later and may even precede visual loss.[139] They can occur during sensory deprivation,[187] for instance, in patients who have undergone bilateral ocular patching because of corneal damage from welding injuries or in patients who are bilaterally patched in preparation for ocular surgery ("black patch psychosis"). Patient surveys demonstrate that release hallucinations are quite common, occurring in 11–13% of blind patients.[117] Frequently, these patients do not mention them to their physicians, friends, or family, because they know they are experiencing hallucinations and are afraid that they will be considered "crazy." This is in contradistinction to patients with schizophrenia, who believe that their visual hallucinations are real.

Release hallucinations are most common in patients with vision of 20/60 or worse in their better eye. Age may play a role, as 80% of patients who experience these types of hallucinations are over age 60. Social isolation may also predispose to the phenomenon.[117] Studies associating cognitive impairment and the development of dementia in patients with release hallucinations have yielded conflicting results.[46,279] Also confusing are the development of such hallucinations in patients with poor vision in one eye but normal or near-normal vision in the other. An association with periventricular white matter lesions on MRI has been asserted but not confirmed.[230]

Several theories have been proposed to explain release hallucinations.[225] Visual seizures have been suspected in patients with intracranial pathology, but these patients tend to have repetitive stereotyped visual phenomena associated with other signs of a seizure disorder (see below). Theories of sensory deprivation are supported by sensory deprivation experiments and may be analogous to the musical hallucinations of deafness and the phantom limb phenomenon following amputation.[30] Expansion of the receptive fields of adjacent cortical neurons has been found after retinal ablation in animals. The denervated cortical neurons may regain activity within several months.[94] Thus, spontaneous discharges from denervated cells along with alterations in cortical receptive fields may explain some cases. However, modification and activation of denervated striate cortex neurons cannot explain adequately the complex hallucinations experienced by some of these patients. Direct stimulation of the temporal lobe produces complex visual hallucinations. In addition, a recent fMRI study demonstrated activation of cerebral activity in ventral extrastriate visual cortex during hallucinations of color, faces, textures, and objects.[81] Thus, activation of the associative visual areas, disinhibited by the loss of visual input, may be responsible for at least some complex hallucinations.[225]

Most patients are not disturbed by release hallucinations, and some patients may even enjoy them; however, identification of this syndrome is important to avoid unnecessary neuroimaging and psychiatric evaluations.[248] In rare patients, the hallucinations are troublesome, but no consistently effective treatment exists to treat them. Anticonvulsants,[22] haloperidol,[235] and tiapride[10] have all been used with mixed success. Removing patients from socially isolated environments may abolish these hallucinations.[45]

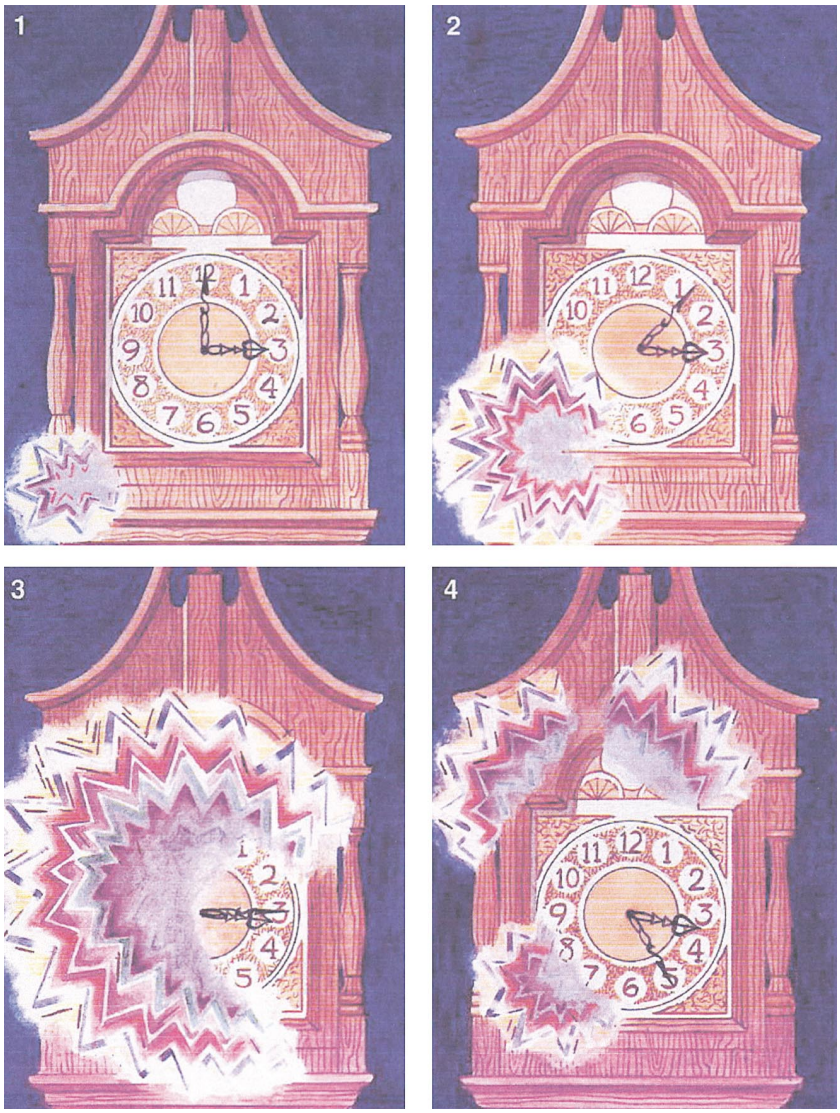

Fig. 11. Artist's rendition of fortification spectra seen during a migraine. (Reprinted from Hupp SL, Kline LB, Corbett JJ[120] with permission of the authors. Artist: William Dean Mosher.)

B. VISUAL MIGRAINES AND VISUAL SEIZURES

The typical fortification spectra of visual migraines (migraine with visual aura or visual aura without headache) usually consist of a moving arc of either colored or black-and-white zigzag lines that expand toward the periphery with concurrent increase in the size of lines (Fig. 11). These scintillations reflect the cytoarchitectural arrangement of the orientation columns as a wave of excitatory activity spreads across the striate cortex. The scotoma that trails behind fortification spectra represents an area of transient inactivation of cortical neurons. These phenomena usually last about 20 minutes and may or may not be followed by headache. A variety of atypical hallucinations also may occur during migraine attacks, including formed hallucinations, micropsia, macropsia, palinopsia, and visual allesthesia.[120]

Visual seizures involving the occipital or, occasionally, the temporal lobe may cause unformed hallucinations similar to those experienced during a classic migraine attack.[273] Patients with visual seizures usually lack the typical history of migraines, have an atypical frequency and duration of hallucinations, and often exhibit other seizure phenomena, such as eye deviation or rapid blinking. Temporal and even occipital lobe seizures may cause formed visual hallucinations, thus mimicking the Charles Bonnet syndrome.[138] Although a careful history usually will differentiate visual seizures from other visual hallucinations, the diagnosis in some cases can be made only by seizure monitoring.[246]

C. VISUAL PERSEVERATION

Visual perseveration, or palinopsia (from Greek *palin*, meaning "again"), refers to the pathologic

Fig. 12. Artist's rendition of one type of palinopsia, or visual perseveration. As the patient looks to the right of the clock, the visual image of the clock is preserved and persists as multiple fading afterimages. (Artist: David Fisher.)

persistence or recurrence of a previously seen visual image. Palinopsia is usually associated with a homonymous field defect and occurs in the affected portion of the field.[169] It may also be associated with other visuospatial abnormalities, such as micropsia, macropsia, metamorphopsia,[275] and allesthesia.[275] Rarely, patients with palinopsia also have ventral-stream deficits.[144] For example, one patient with palinopsia also exhibited somatosensory perseveration.[52]

Although several theories for palinopsia exist, an all-encompassing explanation remains elusive. Some cases may represent visual seizures, and such patients may improve when treated with anticonvulsants.[182]

Mescaline, lysergic acid diethylamide (LSD), and 3,4-methylenedioxymethamphetamine (Ecstasy) may cause palinopsia that is occasionally permanent.[134,154] Additionally, patients taking clomiphene,[200] trazodone,[119] or interleukin-2[83] have reported palinopsia. Metabolic disorders such as nonketotic hyperglycemia have been reported to cause palinopsia.[124] Psychiatric patients in active psychotic states occasionally complain of palinopsia.[163] One patient with palinopsia eventually developed Creutzfeldt-Jakob disease.[163] Most commonly, palinopsia results from a cerebral lesion. In such cases, the lesion most often involves the right parieto-occipital area, an area involved in visuospatial analysis (see above).[40] The localizing value of palinopsia is questionable, however, because patients with bilateral as well as left-sided lesions have been reported, as have patients with temporal lobe and medial occipital lobe lesions.[175]

Palinopsia may resolve spontaneously, especially when associated with a resolving visual field deficit due to stroke, or it may persist indefinitely. No clear treatment is consistently effective, but anticonvulsant medication helps some patients.[25,236] Palinopsia may be separated into temporal and spatial varieties.[46]

1. Temporal Palinopsia

Temporal palinopsia is defined as the perseveration of a previously viewed image in time.[20] Thus, an affected patient may report seeing previously viewed stimuli from the recent or, occasionally, the distant past. Multiple afterimages sometimes are reported trailing palinoptic images. Thus, temporal palinopsia may overlap and coexist with spatial palinopsia (see below, Fig. 12). Temporal palinopsia may be immediate or delayed. Kinsbourne and Warrington suggested that immediate temporal palinopsia represents a prolongation of the physiologic afterimage response.[134] Delayed palinoptic images may be reported minutes to weeks after viewing an object.

Some patients describe a combination of both types.[169]

2. Spatial Palinopsia

Spatial palinopsia is defined as persistence of a visual image in space. This form of palinopsia can be subdivided into illusory visual spread and cerebral polyopia. In illusory visual spread, patients report extension (bleeding) of a pattern beyond the boundaries of the object being viewed.[20] In these cases, a pattern from one object, such as striped shirt, spreads to appear to cover adjacent objects. In cerebral polyopsia, copies of an object are reproduced within the visual field, often in geometric rows or columns.

In contrast to ocular polyopia caused by optical aberrations, the images in cerebral polyopia are seen with equal clarity, do not improve with pinhole testing, and lack the ghost-image quality seen with optical disorders.[115] Patients may report seeing only two images, in which case strabismus must be a consideration. Other patients, however, report seeing dozens or even hundreds of images (entomopia).[159]

A homonymous field defect is often present in patients with cerebral polyopia, as may achromatopsia or ventral-stream deficits.[20] Most often, cerebral polyopia develops in patients with dominant or nondominant parietal or parieto-occipital lesions. Occipital lobe injures, encephalitis, seizures, multiple sclerosis, migraines,[170] and tumors[245] have all been reported to cause this disorder. The origin of cerebral polyopia remains unclear.

IX. Concluding Remarks

As investigators uncover the complexities of the higher visual system, a greater understanding of these clinical syndromes will become clear. Familiarity with these syndromes will enable the ophthalmologist to identify patients with such disorders and perform appropriate testing. Additionally, the study of higher cortical disorders may provide insight into the mechanisms of visual awareness and the global sense of the perception of our environment. Understanding this crucial function of the mind will be an integral step in forming a global theory of consciousness.

Methods of Literature Search

The literature search was conducted through Medline, including all years covered in the database. Secondary sources primarily for historic articles were obtained from our own files. Several references and the overall organizational scheme were obtained from Rizzo and Barton's extensive review of this subject, "Central Disorders of Visual Function" in the 1998 edition of Walsh and Hoyt. Keywords used in the Medline search were: *alexia, agraphia, anomia, Anton syndrome, allesthesia, blindsight, brain damage, brain mapping, color perception, color vision defects, cerebral cortex, dyslexia, epilepsy, form perception, limbic system, motion perception, neglect, parietal lobe, palinopsia, psychophysics, retinal ganglion cells, space perception, sleep deprivations, spatial neglect, space perception, occipital lobe, optic aphasia, visual cortex, visual hallucinations, visual fields, visual pathways, visual hypoemotionality, visual attention, visual perception, vision disorders, V1, V2, V3, V3A, V4*, and *V5*. Additionally, specific author names that were used in the search were: *Anderson, Barbur, Dacey, Damasio, Hubel, Livingstone, Rizzo, Ungerleider, Weiskrantz, Zeki*, and *Zihl*.

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Outline

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  B. Cortical visual areas
  C. Occipitofugal pathways
II. Syndromes associated with damage to the striate cortex (Area V1)
  A. Anton syndrome
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      b. Optic ataxia
      c. Spasm of fixation (acquired oculomotor apraxia)
    2. Hemispatial (hemifield) neglect
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        ii. Ventral simultagnosia
        iii. Perceptal categorzation deficit
      b. Associative agnosia
      c. Subtypes of agnosia
        i. Prosopagnosia
        ii. Generalized object agnosia
    2. Visual–verbal disconnection
      a. Pure alexia
      b. Color anomia
      c. Object anomia (optic aphasia)
    3. Visual–limbic disconnection
      a. Visual amnesia
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VIII. Visual hallucinations and illusions
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IX. Concluding remarks

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