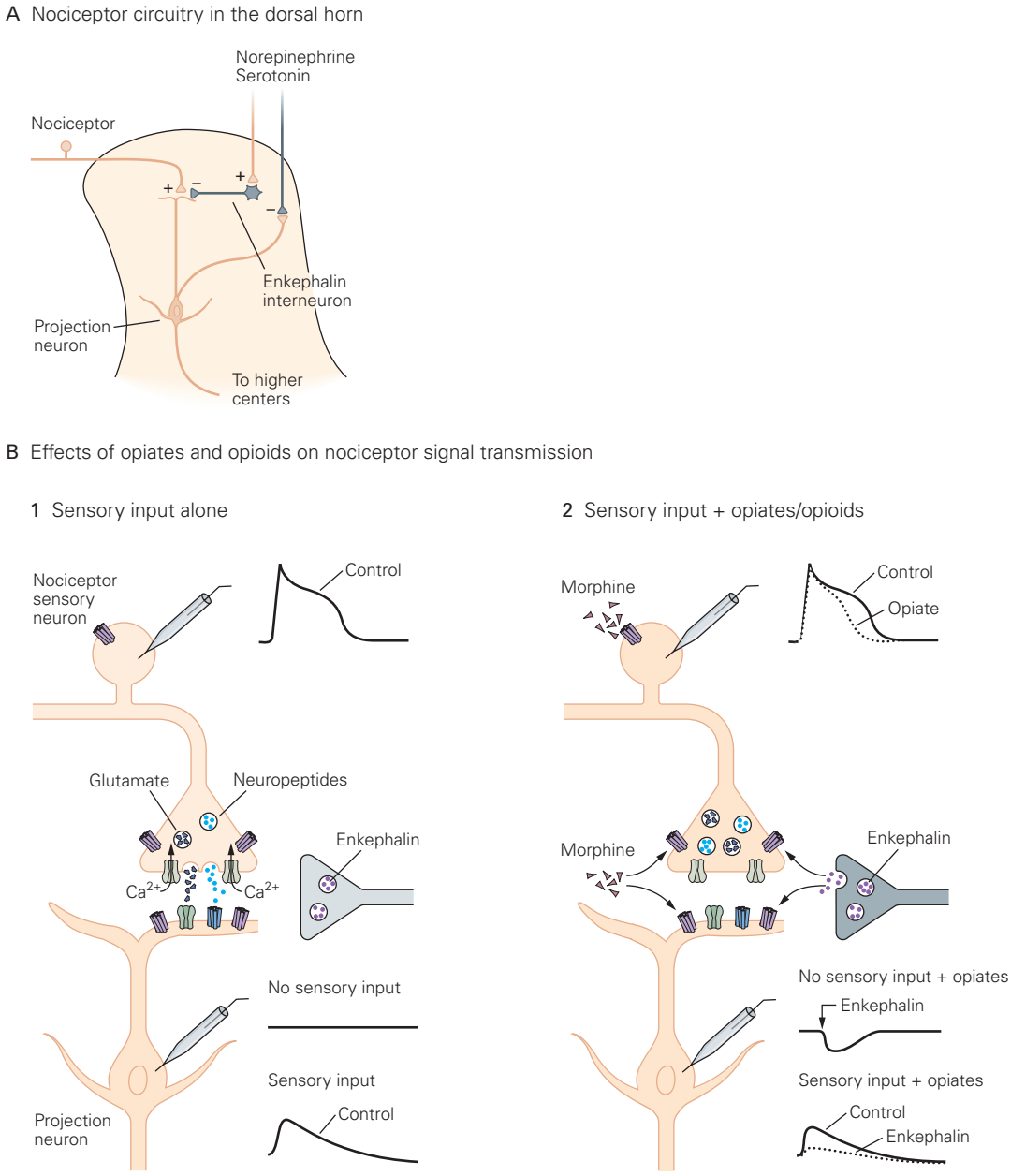

Figure 20–19 Local interneurons in the spinal cord integrate descending and afferent nociceptive pathways.

A. Nociceptive afferent fibers, local interneurons, and descending fibers interconnect in the dorsal horn of the spinal cord (see also Figure 20–3B). Nociceptive fibers terminate on second-order projection neurons. Local GABAergic and enkephalin-containing inhibitory interneurons exert both pre- and postsynaptic inhibitory actions at these synapses. Serotonergic and noradrenergic neurons in the brain stem activate the local interneurons and also suppress the activity of the projection neurons. Loss of these inhibitory controls contributes to ongoing pain and pain hypersensitivity.

B. Regulation of nociceptive signals at dorsal horn synapses. **1.** Activation of a nociceptor leads to the release of glutamate and neuropeptides from the primary sensory neuron, producing an excitatory postsynaptic potential in the projection neuron. **2.** Opiates decrease the duration of the postsynaptic potential, probably by reducing Ca^{2+} influx, and thus decrease the release of transmitter from the primary sensory terminals. In addition, opiates hyperpolarize the dorsal horn neurons by activating a K^+ conductance and thus decrease the amplitude of the postsynaptic potential in the dorsal horn neuron.

Opiates also act on receptors in the cerebral cortex. There is evidence, for example, that opiates can influence the affective component of the pain experience by an action in the anterior cingulate gyrus. Most interestingly, there is considerable evidence that placebo analgesia involves endorphin release and can be reversed by naloxone. This finding emphasizes that responses to a placebo do not indicate that the pain was somehow imaginary. Moreover, placebo analgesia is a component of the overall analgesic action of any pain-relieving drug, including morphine, provided that the patient believes that the treatment will be effective. On the other hand, some other psychological interventions to relieve pain, namely hypnosis, do not appear to involve release of endorphins.

Tolerance to and Dependence on Opioids Are Distinct Phenomena

The chronic use of morphine invites major problems, most notably tolerance and psychological dependence (addiction) (Chapter 43). The repeated use of morphine for pain relief can cause patients to develop resistance to the analgesic effects of the drug, such that progressively higher drug doses are required to achieve the same therapeutic effect. One theory holds that tolerance results from uncoupling of the opioid receptor from its G protein transducer. However, as the binding of naloxone to μ-opioid receptors can precipitate withdrawal symptoms in tolerant subjects, it appears that the opioid receptor is still active in the tolerance state. Tolerance may therefore also reflect a cellular response to the activation of opioid receptors, a response that counteracts the effects of the opiate and resets the system. It follows that when the opiate is abruptly removed or naloxone is administered, this compensatory response is unmasked and withdrawal results.

Such physiological tolerance differs from dependence/addiction, which is a psychological craving for the drug, one that is associated with its misuse and that contributes to opiate use disorders. Given the alarming increases in opiate-related deaths, either because of misuse and overdose of prescription opioids or a host of socioeconomic factors, further studies of the mechanisms that contribute to the development of and distinguish between tolerance and addiction are essential. Unquestionably, morphine and other opiate drugs are very useful in the management of postoperative pain. Whether they are equally effective for the management of chronic pain in noncancer patients remains controversial and needs further study.

Highlights

1. Peripheral nociceptive axons, with cell bodies in dorsal root ganglia, include small-diameter unmyelinated (C) and myelinated (Aδ) afferents. Larger diameter Aβ afferents respond only to innocuous stimulation but, following injury, can activate central nervous system pain circuitry.
2. All nociceptors use glutamate as their excitatory neurotransmitter; many also express an excitatory neuropeptide cotransmitter, such as substance P or CGRP.
3. Nociceptors are also molecularly distinguished by their expression of different receptors sensitive to temperature, plant products, mechanical stimuli, or ATP. As many of these molecules, including the Nav1.7 subtype of voltage-gated Na^+ channels, are exclusively expressed in sensory neurons, their selective pharmacological targeting suggests a novel approach to analgesic drug development.
4. Nociceptors terminate in the dorsal horn of the spinal cord where they excite interneurons and projection neurons. Neuropeptides are also released from the peripheral terminals of nociceptors and contribute to neurogenic inflammation, including vasodilatation of and extravasation from peripheral vessels. The development of antibodies to CGRP, to block vasodilation, is a new approach to managing migraine.
5. A major brain target of dorsal horn projection neurons is the ventroposterolateral thalamus, which processes location and intensity features of the painful stimulus. Other neurons target the parabrachial nucleus (PB) of the dorsolateral pons. PB neurons, in turn, project to limbic regions of the brain, which process affective/emotional features of the pain experience.
6. Allodynia, pain produced by an innocuous stimulus, results in part from peripheral sensitization of nociceptors. Peripheral sensitization occurs when there is tissue injury and inflammation and involves NSAID-sensitive production of prostaglandins, which lower the threshold for activating nociceptors. A great advantage of NSAIDs is that they act in the periphery, illustrating the importance of efforts to develop pharmacotherapies, such as antibodies to NGF, which cannot cross the blood–brain barrier, thus reducing their likelihood of having adverse side effects in the central nervous system.
7. Hyperalgesia (exacerbated pain in response to a painful stimuli) and allodynia also arise from

altered activity in the dorsal horn—a central sensitization process that contributes to spontaneous activity of pain-transmission neurons and amplification of nociceptive signals. Glutamate activation of spinal cord NMDA receptors and activation of microglia and astrocytes contribute, in particular, to the neuropathic pains that can occur after peripheral nerve injury. Understanding the consequences of central sensitization is critical to preventing the transition from acute to chronic pain.

8. Under normal conditions, input carried by large-diameter, nonnociceptive afferents can reduce the transmission of nociceptive information to the brain by engaging GABAergic inhibitory circuits in the dorsal horn. This inhibitory control is the basis of the pain relief produced by vibration and transcutaneous electrical stimulation. However, when injury induces central sensitization, Aβ input mediates mechanical allodynia.
9. Opiates are the most effective pharmacological tool for the management of severe pain. The inhibitory action of opiates and the related endogenous opioid peptides result from reduced neurotransmitter release or by hyperpolarization of postsynaptic neurons. All opioid actions can be blocked by the opiate receptor antagonist naloxone.
10. Endogenous opioids, including enkephalin and dynorphin, and their opioid receptor targets are not expressed only in pain-relevant areas of the brain. As a result, systemic administration of opiates is associated with many adverse side effects, including constipation, respiratory depression, and activation of the reward system. The latter can lead to psychological dependence and eventual misuse. Many of these adverse side effects limit opiate use for long-term pain control.
11. The brain not only receives nociceptive information leading to a perception of pain, but also regulates the output of the spinal cord to reduce pain by an endorphin-mediated pain control system. Electrical stimulation of the midbrain periaqueductal gray can engage a descending inhibitory control system, likely involving endorphins, which reduces the transmission of pain messages from the spinal cord to the brain.
12. The pain relief produced by some psychological manipulations (e.g., placebo analgesia) involves endorphin release; other manipulations, such as hypnosis, do not.
13. Tolerance and psychological dependence can arise after prolonged opiate use. Tolerance is manifested as a requirement for higher doses of the opiate to achieve the same physiological endpoint. Psychological dependence, in contrast, involves activation of the brain's reward system and the development of craving that can lead to misuse of opiates. Development of nonrewarding opioid analgesics, which can regulate the sensory-discriminative but not the emotional features of the pain experience, may significantly impact the ongoing opioid epidemic.

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21

The Constructive Nature of Visual Processing

We are so familiar with seeing, that it takes a leap of imagination to realize that there are problems to be solved. But consider it. We are given tiny distorted upside-down images in the eyes and we see separate solid objects in surrounding space. From the patterns of stimulation on the retina we perceive the world of objects and this is nothing short of a miracle.

—Richard L. Gregory, *Eye and Brain*, 1966

Most of our impressions of the world and our memories of it are based on sight. Yet the mechanisms that underlie vision are not at all obvious. How do we perceive form and movement? How do we distinguish colors? Identifying objects in complex visual environments is an extraordinary computational achievement that artificial vision systems have yet to duplicate. Vision is used not only for object recognition but also for guiding our movements, and these separate functions are mediated by at least two parallel and interacting pathways.

The existence of parallel pathways in the visual system raises one of the central questions of cognition, the binding problem: How are different types of information carried by discrete pathways brought together into a coherent visual image?

Visual Perception Is a Constructive Process

Vision is often incorrectly compared to the operation of a camera. A camera simply reproduces point-by-point the light intensities in one plane of the visual field. The visual system, in contrast, does something fundamentally different. It interprets the scene and parses it into distinct components, separating foreground from background. The visual system is less accurate than a camera at certain tasks, such as quantifying the absolute level of brightness or identifying spectral color. However, it excels at tasks such as recognizing a charging animal (or a speeding car) whether in bright sunlight or at dusk, in an open field or partly occluded by trees (or other cars). And it does so rapidly to let the viewer respond and, if necessary, escape.

A potentially unifying insight reconciling the visual system's remarkable ability to grasp the bigger picture with its inaccuracy regarding details of the input is that vision is a biological process that has evolved in step with our ecological needs. This insight helps

explain why the visual system is so efficient at extracting useful information such as the identities of objects independent of lighting conditions, while giving less importance to aspects like the exact nature of the ambient light. Moreover, vision does so using previously learned rules about the structure of the world. Some of these rules appeared to have become wired into our neural circuits over the course of evolution. Others are more plastic and help the brain guess at the scene presented to the eyes based on the individual's past experience. This complex, purposeful processing happens at all levels of the visual system. It starts even at the retina, which is specialized to pick out object boundaries rather than creating a point-by-point representation of uniform surfaces.

This *constructive* nature of visual perception has only recently been fully appreciated. Earlier thinking about sensory perception was greatly influenced by the British empiricist philosophers, notably John Locke, David Hume, and George Berkeley, who thought of perception as an atomistic process in which simple sensory elements, such as color, shape, and brightness, were assembled in an additive way, component by component. The modern view that perception is an active and creative process that involves more than just the information provided to the retina has its roots in the philosophy of Immanuel Kant and was developed in detail in the early 20th century by the German psychologists Max Wertheimer, Kurt Koffka, and Wolfgang Köhler, who founded the school of Gestalt psychology.

The German term *Gestalt* means configuration or form. The central idea of the Gestalt psychologists is that what we see about a stimulus—the perceptual interpretation we make of any visual object—depends not just on the properties of the stimulus but also on its context, on other features in the visual field. The Gestalt psychologists argued that the visual system processes sensory information about the shape, color, distance, and movement of objects according to computational rules inherent in the system. The brain has a way of looking at the world, a set of expectations that derives in part from experience and in part from built-in neural wiring.

Max Wertheimer wrote: "There are entities where the behavior of the whole cannot be derived from its individual elements nor from the way these elements fit together; rather the opposite is true: the properties of any of the parts are determined by the intrinsic structural laws of the whole." In the early part of the 20th century, the Gestalt psychologists worked out the laws of perception that determine how we group elements in the visual scene, including similarity, proximity, and good continuation.

We see a uniform six-by-six array of dots as either rows or columns because of the visual system's tendency to impose a pattern. If the dots in each row are similar, we are more likely to see a pattern of alternating rows (Figure 21–1A). If the dots in each column are closer together than those in the rows, we are more disposed to see a pattern of columns (Figure 21–1B). The principle of good continuation is an important basis for linking line elements into unified shapes (Figure 21–1C). It is also seen in the phenomenon of contour saliency, whereby smooth contours tend to pop out from complex backgrounds (Figure 21–1D). The Gestalt features that we are disposed to pick out are also ones that characterize objects in natural scenes. Statistical studies of natural scenes show that object boundaries are likely to contain visual elements that lie in close proximity, are continuous across intersections, or form smooth contours. It is tempting to speculate that the formal features of objects in natural scenes created evolutionary pressure on our visual systems to develop neural circuits that have made us sensitive to those features.

Separating the figure and background in a visual scene is an important step in object recognition. At different moments, the same elements in the visual field can be organized into a recognizable figure or serve as part of the background for other figures (Figure 21–2). This process of segmentation relies not only on certain geometric principles, but also on cognitive influences such as attention and expectation. Thus, a priming stimulus or an internal representation of object shape can facilitate the association of visual elements into a unified percept (Figure 21–3). This internal representation can take many different forms reflecting the wide range of time scales and mechanisms of neural encoding. It could consist of transient reverberating spiking activity selective to a shape or a decision, lasting a fraction of a second, or the selective modulation of synaptic weights during a particular context of a task or an expected shape, or circuit changes that could comprise a long-term memory.

The brain analyzes a visual scene at three levels: low, intermediate, and high (Figure 21–4). At the lowest level, which we consider in the next chapter (Chapter 22), visual attributes such as local contrast, orientation, color, and movement are discriminated. The intermediate level involves analysis of the layout of scenes and of surface properties, parsing the visual image into surfaces and global contours, and distinguishing foreground from background (Chapter 23). The highest level involves object recognition (Chapter 24). Once a scene has been parsed by the brain and objects recognized, the objects can be matched with memories of

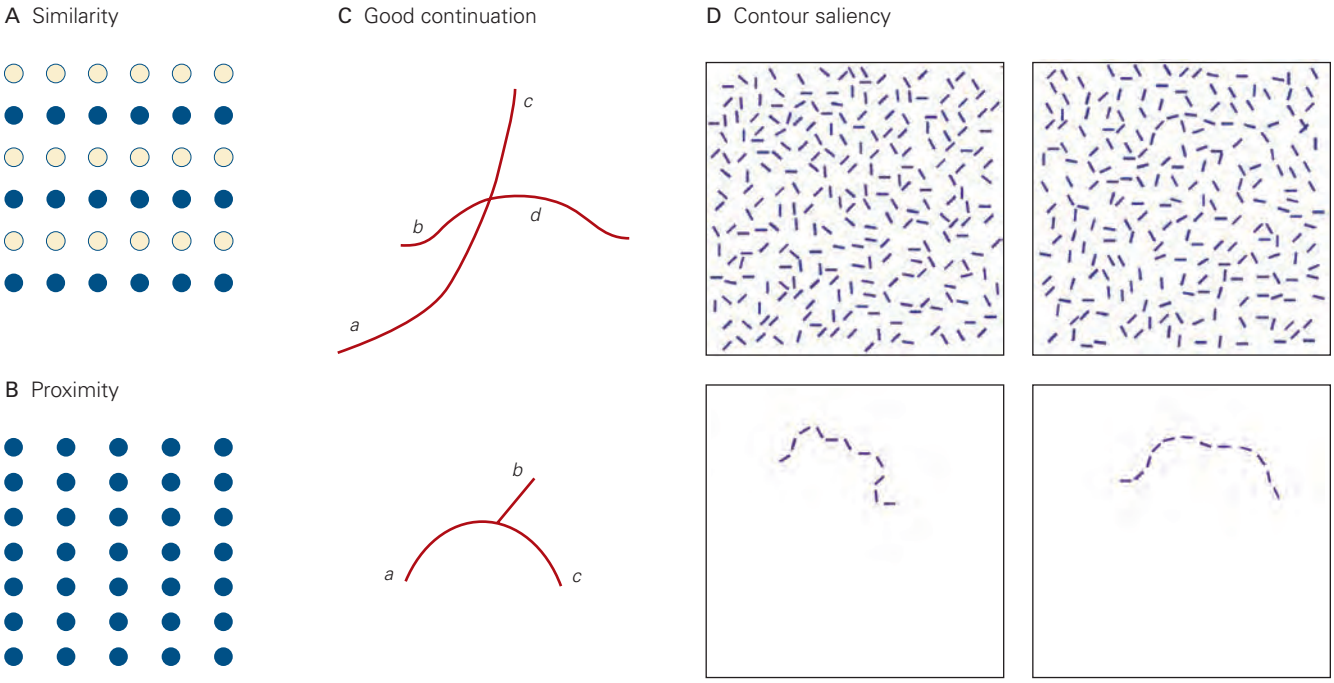

Figure 21–1 **Organizational rules of visual perception.** To link the elements of a visual scene into unified percepts, the visual system relies on organizational rules such as similarity, proximity, and good continuation.

A. Because the dots in alternating rows have the same color, an overall pattern of blue and white rows is perceived.

B. The dots in the columns are closer together than those in the rows, leading to the perception of columns.

C. Line segments are perceptually linked when they are collinear. In the top set of lines, one is more likely to see line segment **a** as belonging with **c** rather than **d**. In the bottom set, **a** and **c** are perceptually linked because they maintain the same curvature, whereas **a** and **b** appear to be discontinuous.

D. The principle of good continuation is also seen in contour saliency. On the right, a smooth contour of line elements pops out from the background, whereas the jagged contour on the left is lost in the background. (Adapted, with permission, from Field, Hayes, and Hess 1993. Copyright © 1993 Elsevier Ltd.)

Figure 21–2 **Object recognition depends on segmentation of a scene into foreground and background.** Recognition of the white salamanders in this image depends on the brain "locating" the white salamanders in the foreground and the brown and black salamanders in the background. The image also illustrates the role of higher influences in segmentation: One can consciously select any of the three colors as the foreground. (Reproduced, with permission, from M.C. Escher's "Symmetry Drawing E56" © 2010 The M.C. Escher Company-Holland. All rights reserved. www.mcescher.com.)

Figure 21–3 Expectation and perceptual task play a critical role in what is seen. It is difficult to separate the dark and white patches in this figure into foreground and background without additional information. This figure immediately becomes recognizable after viewing the priming image on page 501. In this example, higher-order representations of shape guide lower-order processes of surface segmentation. (Reproduced, with permission, from Porter 1954. Copyright 1954 by the Board of Trustees of the University of Illinois. Used with permission of the University of Illinois Press.)

shapes and their associated meanings. Vision also has an important role in guiding body movement, particularly hand movement (Chapter 25).

In vision, as in other cognitive operations, various features—motion, depth, form, and color—occur together in a unified percept. This unity is achieved not by one hierarchical neural system but by multiple areas in the brain that are fed by parallel but interacting neural pathways. Because distributed processing is one of the main organizational principles in the neurobiology of vision, one must have a grasp of the anatomical pathways of the visual system to understand fully the physiological description of visual processing in later chapters.

In this chapter, we lay the foundation for understanding the neural circuitry and organizational principles of the visual pathways. These principles apply quite broadly and are relevant not only for the multiple areas of the brain concerned with vision but also for other types of sensory information processing by the brain.

Visual Processing Is Mediated by the Geniculostriate Pathway

The brain's analysis of visual scenes begins in the two retinas, which transform visual input using a strategy of parallel processing (Chapter 22). This important neural computation strategy is utilized at all stages of the visual pathway as well as in other sensory areas. The pixel-like bits of visual input falling on individual photoreceptors—rods and cones—are analyzed by retinal circuits to extract some 20 local features, such as the local contrasts of dark versus light, red versus green, and blue versus yellow. These features are computed by different populations of specialized neural circuits forming independent processing modules that separately cover the visual field. Thus, each point in the visual field is processed in multiple channels that extract distinct aspects of the visual input simultaneously and in parallel. These parallel streams are then sent out along the axons of the retinal ganglion cells, the projection neurons of the retina, which form the optic nerves.

From the eye, the optic nerve extends to a midline crossing point, the optic chiasm. Beyond the chiasm, the fibers from each temporal hemiretina proceed to the ipsilateral hemisphere along the ipsilateral optic tract; fibers from the nasal hemiretinas cross to the contralateral hemisphere along the contralateral optic tract (Figure 21–5). Because the temporal hemiretina of one eye sees the same half of the visual field (hemifield) as the nasal hemiretina of the other, the partial decussation of fibers at the chiasm ensures that all the information about each hemifield is processed in the visual cortex of the contralateral hemisphere. The layout of the pathway also forms the basis for useful diagnostic information. As a consequence of the particular anatomy of this visual pathway, lesions at different points along the pathway lead to visual deficits with different geometric shapes (Figure 21–5) that can be distinguished reliably through clinical examination. The deficit could be entirely monocular; if present in both eyes, it could affect noncorresponding or corresponding parts of the visual field in the two eyes; it could be restricted to either the upper or the lower visual field or may extend into both, etc. Thus, the shape of the deficit could give valuable clues about type and location of the

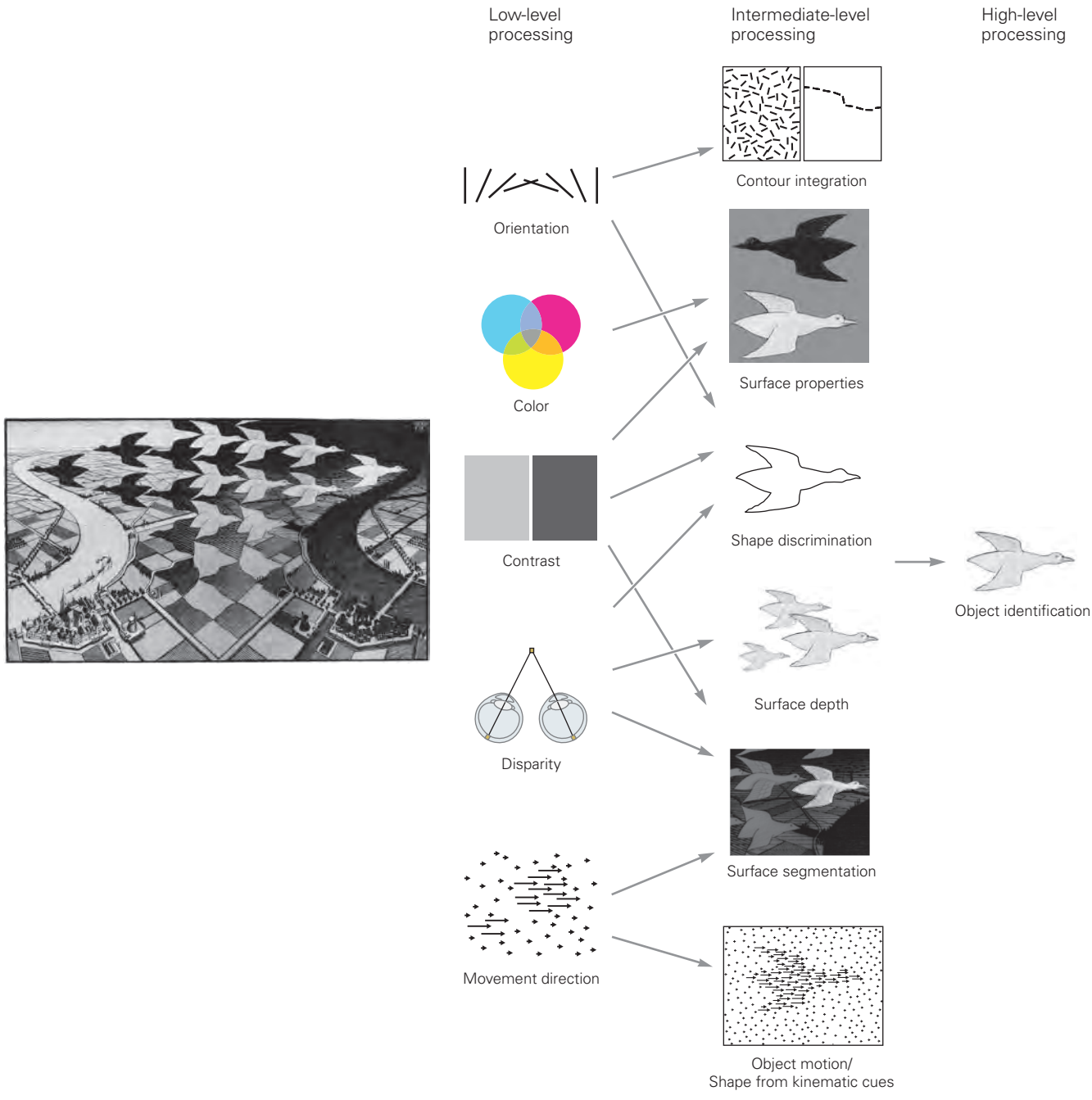

Figure 21–4 **A visual scene is analyzed at three levels.** Simple attributes of the visual environment are analyzed (low-level processing), and these low-level features are then used to parse the visual scene (intermediate-level processing): Local visual features are assembled into surfaces, objects are segregated from background (surface segmentation), local orientation is integrated into global contours (contour integration), and surface shape is identified from shading and kinematic cues. Finally, surfaces and contours are used to identify the object (high-level processing). (M.C. Escher's "Day and Night". © 2020 The M.C. Escher Company—The Netherlands. All rights reserved. www.mcescher.com)