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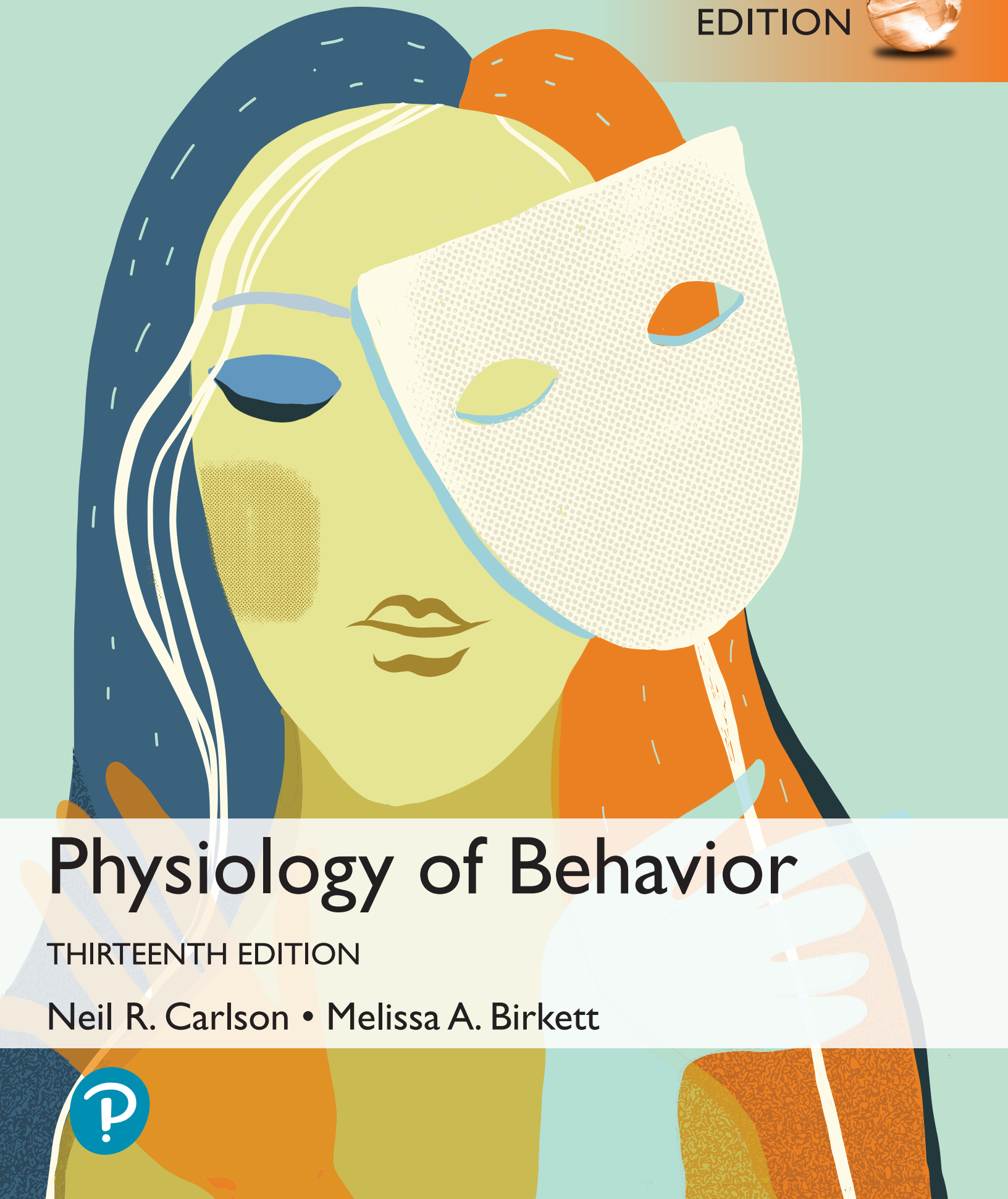


Physiology of Behavior

THIRTEENTH EDITION

Neil R. Carlson • Melissa A. Birkett

Physiology of Behavior

Thirteenth edition

Global edition

NEIL R. CARLSON
University of Massachusetts, Amherst

MELISSA A. BIRKETT
Southern Oregon University

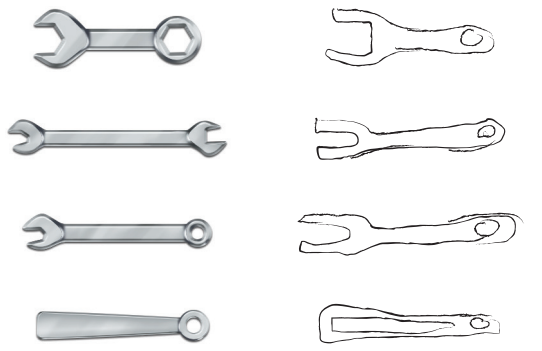
Pearson

Harlow, England • London • New York • Boston • San Francisco • Toronto • Sydney • Dubai • Singapore • Hong Kong
Tokyo • Seoul • Taipei • New Delhi • Cape Town • São Paulo • Mexico City • Madrid • Amsterdam • Munich • Paris • Milan

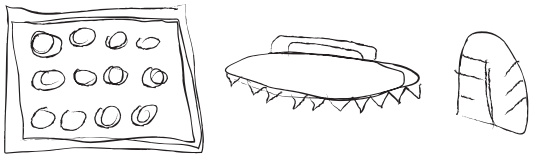
Figure 7.27 Tactile Agnosia

(a) Drawings of wrenches felt but not seen by M. T. Although the patient did not recognize the objects as wrenches, he was able to draw them accurately. (b) Drawings of objects felt but not seen by E. C. The patient could neither recognize the objects by touch nor draw them accurately.

Source: Based on Nakamura, J., Endo, K., Sumida, T., and Hasegawa, T. (1998). Bilateral tactile agnosia: A case report. *Cortex, 34,* 375–388; and Reed, C. L., Caselli, R. J., and Farah, M. J. (1996). Tactile agnosia. Underlying impairment and implications for normal tactile object recognition. *Brain, 119,* 875–888. Reprinted with permission.



(a)



Casette tape | Staple remover | Plug adaptor

(b)

Cox and colleagues (2006) studied three families from northern Pakistan whose members included several people with a complete absence of pain and discovered the location of the gene responsible for this disorder. The gene, an autosomal recessive allele located on chromosome 2, encodes for a voltage-dependent sodium channel. The case that brought the families to the researchers' attention was a 10-year-old boy who performed a "street theater" during which he would thrust knives through his arms and walk on burning coals without feeling any pain. He died just before his fourteenth birthday after jumping off the roof of a house. All six of the affected people in the three families had injuries to their lips or tongues caused by self-inflicted bites. They all suffered from bruises and cuts, and many sustained bone fractures that they did not notice until the injuries impaired their mobility. Despite their total lack of pain from any type of noxious stimulus, they had normal sensations of touch, warmth, coolness, proprioception, tickle, and pressure.

Some environmental events diminish the perception of pain. For example, Beecher (1959) noted that many wounded American soldiers back from the battle at Anzio, Italy, during World War II reported that they felt no pain from their wounds. They did not even want medication. It would appear that their perception of pain was diminished by the relief they felt from surviving such a terrible ordeal. There are other instances in which people report the perception of pain but are not bothered by it. Some tranquilizers have this effect, and damage to parts of the brain does, too.

Perceiving Pain

LO 7.17 Describe why pain is experienced, the components of pain, and how pain perception can be modified.

Pain is a curious phenomenon. It is more than a mere sensation; it can be defined only by some sort of withdrawal reaction or, in humans, by verbal report. Pain can be modified by opiates, by hypnosis, by the administration of placebos, by emotions, and even by other forms of stimulation, such as acupuncture. Recent research efforts have made remarkable progress in discovering the physiological bases of these phenomena.

WHY DO WE EXPERIENCE PAIN? We might reasonably ask *why* we experience pain. The answer is that in most cases pain serves a constructive role. For example, inflammation, which often accompanies injuries to skin or muscle, greatly increases the sensitivity of the inflamed region to painful stimuli. This effect motivates the individual to minimize the movement of the injured part and avoid contact with other objects. The effect is to reduce the likelihood of further injury.

COMPONENTS OF PAIN Pain appears to have three different perceptual and behavioral effects (Price, 2000). First is the sensory component—the pure perception of the intensity of a painful stimulus. The second component is the immediate emotional consequences of pain—the unpleasantness or degree to which the individual is bothered by the painful stimulus. The third component is the long-term emotional implications of chronic pain—the threat that such pain represents to one's future comfort and well-being.

These three components of pain appear to involve different brain mechanisms. The purely sensory component of pain is mediated by a pathway from the spinal cord to the ventral posterolateral thalamus to the primary and secondary somatosensory cortex. The immediate emotional component of pain appears to be mediated by pathways that reach the anterior cingulate cortex (ACC) and insular cortex. The long-term emotional component appears to be mediated by pathways that reach the prefrontal cortex. (See Figure 7.28.)

Let's look at some evidence for brain mechanisms involved in short-term and long-term emotional responses to pain. Several studies have found that painful stimuli activate the insular cortex and the ACC. In addition, Ostrowsky and colleagues (2002) found that electrical stimulation of the insular cortex caused reports of painful burning and stinging sensations. Damage to this region

Figure 7.28 The Three Components of Pain

A simplified schematic diagram shows the brain mechanisms involved in the three components of pain: the sensory component, the immediate emotional component, and the long-term emotional component.

Source: Adapted from Price, D. B. (2000). Psychological and neural mechanisms of the affective dimension of pain. *Science, 288*, 1769–1772.

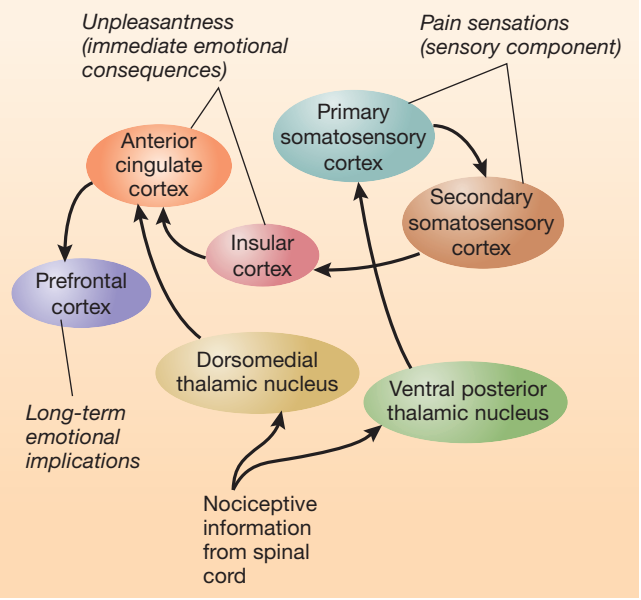
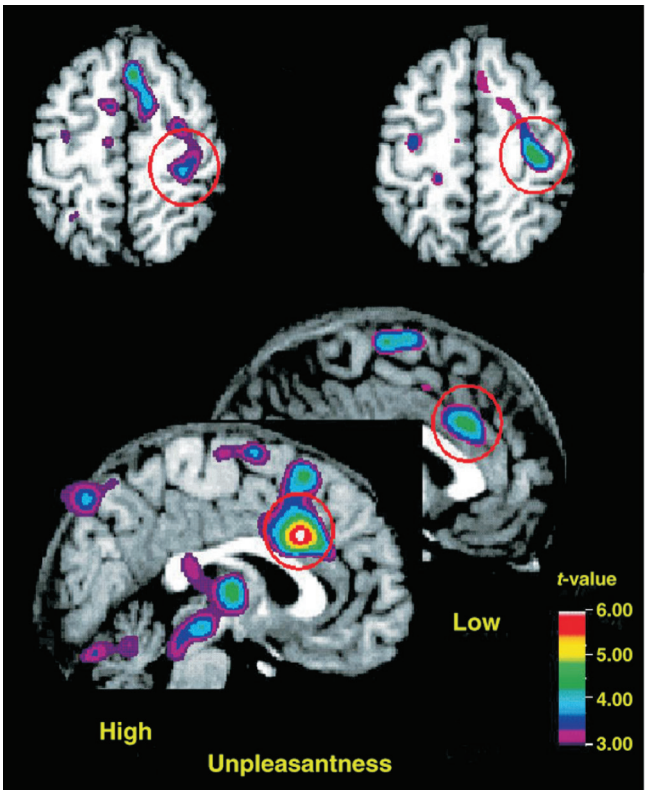


Figure 7.29 Sensory and Emotional Components of Pain

The PET scans show brain regions that respond to pain. *Top:* Dorsal views of the brain. Activation of the primary somatosensory cortex (circled in red) by a painful stimulus was not affected by a hypnotically suggested reduction in the unpleasantness of a painful stimulus, indicating that this region responded to the sensory component of pain. *Bottom:* Midsagittal views of the brain. The anterior cingulate cortex (circled in red) showed much less activation when the unpleasantness of the painful stimulus was reduced by hypnotic suggestion.

Source: From Rainville, P., Duncan, G. H., Price, D. D., Carrier, B., and Bushnell, M. C. (1997). Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science, 277*, 968–971. Copyright © American Association for the Advancement of Science. Reprinted with permission.



decreases people's emotional response to pain: They continue to feel the pain but do not seem to recognize that it is harmful (Berthier et al., 1988). They do not withdraw from pain or the threat of pain.

Rainville and colleagues (1997) produced pain sensations in participants by having them put their arms in ice water. Under one condition, the researchers used hypnosis to diminish the unpleasantness of the pain. The hypnosis worked; the participants said that the pain was less unpleasant, even though it was still as intense. Meanwhile, the investigators used a PET scanner to measure the regional activation of the brain. They found that the painful stimulus increased the activity of both the primary somatosensory cortex and the ACC. When the participants were hypnotized and found the pain less unpleasant, the activity of the ACC decreased, but the activity of the primary somatosensory cortex remained high. Presumably, the primary somatosensory cortex is involved in the perception of pain, and the ACC is involved in its immediate emotional effects—its unpleasantness. (See Figure 7.29.)

In another study from the same laboratory, Hofbauer and colleagues (2001) produced the opposite effect. They presented participants with a painful stimulus and used hypnotic suggestion to reduce the perceived intensity of the pain. They found that the suggestion reduced participants' ratings of pain and also decreased the activation of the somatosensory cortex. Changes in perceived *intensity* of pain are reflected in changes in activation of the somatosensory cortex, whereas changes in perceived *unpleasantness* of pain are reflected in changes in activation of the ACC.

Several functional-imaging studies have shown that under certain conditions, stimuli associated with pain can activate the ACC even when no actual painful stimulus is applied. Osaka and colleagues (2004) found that the ACC was activated when participants heard Japanese words that vividly denote various types of pain (for example, a throbbing pain, a splitting headache, or the pain caused by being stuck with thorns). In a test of romantically involved couples, Singer and colleagues (2004) found that when women received a painful electrical shock to the back of their hand, their ACC, anterior insular cortex, thalamus, and somatosensory cortex became active. When they saw their partners receive a painful shock but did not receive

Table 7.5 Brain Regions Involved in Perceptual and Behavioral Effects of Pain

Effects of Pain	Brain Regions Involved
Sensory component	Pathway from spinal cord to thalamus to primary/secondary somatosensory cortex
Immediate emotional consequences	Insular cortex, ACC, primary somatosensory cortex
Long-term emotional consequences	Prefrontal cortex

one themselves, the same regions (except for the somatosensory cortex) became active. The emotional component of pain—in this case, a vicarious experience of pain, provoked by empathy with the feelings of someone a person loved—caused responses in the brain similar to the ones caused by actual pain. Just as we saw in the study by Rainville and colleagues (1997), the somatosensory cortex is activated only by an actual noxious stimulus. The final component of pain—the emotional consequences of chronic pain—appears to involve the prefrontal cortex. As we will see in Chapter 11, damage to the prefrontal cortex impairs people's ability to make plans for the future and to recognize the personal significance of situations in which they are involved. Along with the general lack of insight, people with prefrontal damage tend not to be concerned with the implications of chronic conditions—including chronic pain—for their future. (See Table 7.5.)

A unique form of pain sensation occurs after a limb has been amputated. After the limb is gone, up to 70 percent of amputees report that they feel as though the missing limb still exists and that it often hurts. This phenomenon is referred to as the **phantom limb** (Melzak, 1992; Ramachandran & Hirstein, 1998). People with phantom limbs report that the limb feels very real, and they often say that if they try to reach out with it, it feels as though it were responding. Sometimes, they perceive it as sticking out, and they may feel compelled to avoid knocking it against the side of a doorframe or sleeping in a position that would make it come between them and the mattress. People have reported all sorts of sensations in phantom limbs, including pain, pressure, warmth, cold, wetness, itching, sweatiness, and prickliness.

The classic explanation for phantom limbs has been activity of the sensory axons belonging to the amputated limb. Presumably, the nervous system interprets this activity as coming from the missing limb. When nerves are cut and connections cannot be reestablished between the proximal and distal portions, the cut ends of the proximal portions form nodules known as *neuromas.* The treatment for phantom pain has been to cut the nerves above these neuromas, to cut the dorsal roots that bring the afferent information from these nerves into the spinal cord, or to make lesions in somatosensory pathways in the spinal cord, thalamus, or cerebral cortex. Sometimes these procedures work for a while, but often the pain returns.

Melzak (1992) suggested that the phantom limb sensation is inherent in the organization of the parietal cortex. The parietal cortex is involved in our awareness of our own bodies. Indeed, people with lesions of the parietal lobe (especially in the right hemisphere) have been known to push their own leg out of bed, believing that it belongs to someone else. Melzak reports that some people who were born with missing limbs nevertheless experience phantom limb sensations, which would suggest that our brains are genetically programmed to provide sensations for all four limbs.

A unique therapy can be helpful for some types of pain or discomfort experienced from phantom limbs. It is further thought that phantom limb pain can arise from a conflict between visual feedback and proprioceptive feedback from the phantom limb. Mirror box therapy requires the patient to substitute visual feedback for the missing limb by reflecting a mirror image of the intact limb. Clinical trials of mirror box therapy support the utility of this intervention for reducing phantom limb pain when the mirror image is used to represent an image of moving and stretching the phantom limb (Chan et al., 2007). (See Figure 7.30.)

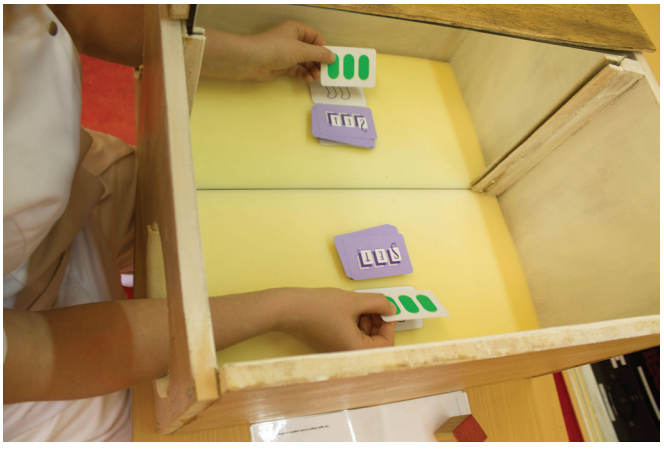
ENDOGENOUS MODIFICATION OF PAIN SENSITIVITY

For many years, investigators have known that perception of pain can be modified by environmental stimuli. Work beginning in the 1970s has revealed the existence of neural circuits whose activity can produce analgesia. A variety of environmental stimuli can activate these analgesia-producing circuits. Most of these stimuli cause the release of the endogenous opioids, which were described in Chapter 4.

Electrical stimulation of particular locations within the brain can cause analgesia, which can even be profound enough to serve as an anesthetic for surgery in

Figure 7.30 Mirror Box Therapy

Mirror box therapy for phantom limb pain requires the patient to substitute visual feedback for the missing limb by reflecting a mirror image of the intact limb.



rats (Reynolds, 1969). The most effective locations appear to be within the periaqueductal gray matter and in the rostroventral medulla. For example, electrical stimulation of the periaqueductal gray matter produced analgesia in rats equivalent to that produced by at least 10 milligrams (mg) of morphine per kilogram (kg) of body weight, which is a large dose (Mayer & Liebeskind, 1974). The technique has even found an application in reducing severe chronic pain in humans: Fine wires are surgically implanted in parts of the central nervous system and attached to a radio-controlled device that permits the patient to administer electrical stimulation when necessary (Kumar et al., 1990).

Analgesic brain stimulation apparently triggers the neural mechanisms that reduce pain, primarily by causing endogenous opioids to be released. Basbaum and Fields (1978, 1984) proposed a neural circuit that mediates opiate-induced analgesia. Basically, they proposed the following: Endogenous opioids (released by environmental stimuli or administered as a drug) stimulate opiate receptors on neurons in the periaqueductal gray matter. Because the effect of opiates appears to be inhibitory (Nicoll et al., 1980), Basbaum and Fields proposed that the neurons that contain opiate receptors are themselves inhibitory interneurons. Administering opiates activates the neurons on which these interneurons synapse. Figure 7.31 depicts this circuit.

Neurons in the periaqueductal gray matter send axons to the **nucleus raphe magnus**, located in the medulla. The neurons in this nucleus send axons to the dorsal horn of the spinal cord gray matter; destroying these axons eliminates analgesia induced by an injection of morphine. The inhibitory effects of these neurons apparently involve one or two interneurons in the spinal cord.

Pain sensitivity can be regulated by direct neural connections, as well as by secretion of the endogenous opioids. The periaqueductal gray matter receives inputs from the frontal cortex, amygdala, and hypothalamus (Beitz, 1982; Mantyh, 1983). These inputs permit learning and emotional reactions to affect an animal's responsiveness to pain even without the secretion of opioids.

PLACEBO ANALGESIA Pain can be reduced, at least in some people, by administering a pharmacologically inert placebo. When some people take a medication that they believe will reduce pain, it triggers the release of endogenous opioids and actually does so. This effect is eliminated if the people are given an injection of naloxone, a drug that blocks opiate receptors (Eippert et al., 2009). For some people a placebo is not pharmacologically inert—it has a physiological effect. The placebo effect may be mediated through connections of the frontal cortex with the periaqueductal gray matter. A functional-imaging study by Zubieta and colleagues (2005) found that placebo-induced analgesia did indeed cause the release of endogenous opiates. They used a PET scanner to detect the presence of μ-opioid neurotransmission in the brains of people who responded to the effects of a placebo. As Figure 7.32 shows, several regions of the brain, including the anterior cingulate cortex and insular cortex, showed evidence of increased endogenous opioid activity.

An interesting study by Waber and colleagues (2008) found that the efficacy of a placebo was directly related to its perceived value. Volunteers were given a placebo pill that was alleged to reduce pain. Some people were told that the pills normally cost $2.50 each, and others were told that the price had been discounted to 10 cents each. Before and after taking the pill, the participants received

Figure 7.31 Opiate-Induced Analgesia

The schematic shows the neural circuit that mediates opiate-induced analgesia, as hypothesized by Basbaum and Fields (1978).

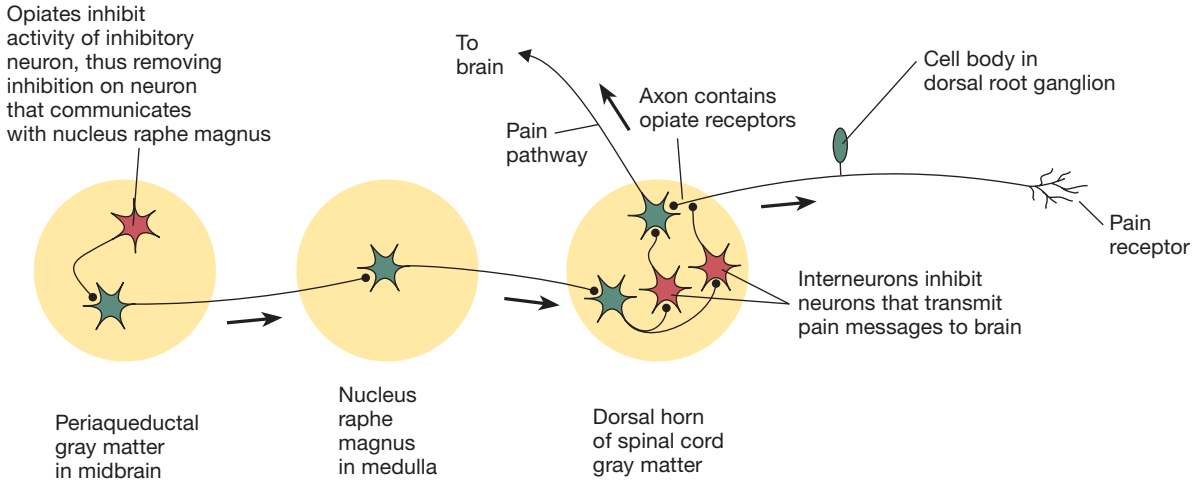
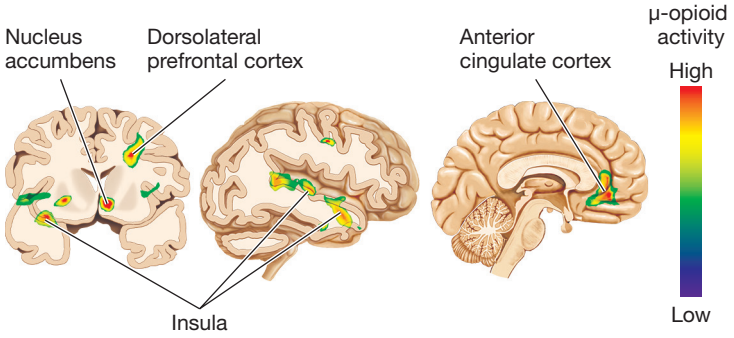


Figure 7.32 Brain Regions Involved in Response to Pain-Relieving Placebo

PET imaging demonstrates the endogenous opioids binding to μ-opioid receptors following administration of a placebo in several brain regions.

Source: Based on: Zubieta, J.-K., Bueller, J. A., Jackson, L. R., Scott, D. J., et al. (2005) Placebo effects mediated by endogenous opioid activity on μ-opioid receptors. *Journal of Neuroscience*, 25, 7754–7762.



electric shocks to their wrists and rated the intensity of the pain that the shocks produced. As Figure 7.33 shows, participants who believed that they had received an expensive pill showed a stronger reduction in pain perception than those who believed they had received an inexpensive one.

A functional-imaging study by Wager and colleagues (2004) supports the suggestion that the prefrontal cortex plays a role in placebo analgesia. They administered painful stimuli (heat or electrical shocks) to the skin with or without the application of an "analgesic" skin cream that was actually an unmedicated placebo. They observed a placebo effect—reports of less intense pain and decreased activity in the primary pain-reactive regions of the brain, including the thalamus, ACC, and insular cortex. They also observed *increased* activity in the prefrontal cortex and the periaqueductal gray matter of the midbrain. Presumably, the expectation of decreased sensitivity to pain caused the increased activity of the prefrontal cortex, and connections of this region with the periaqueductal gray matter activated endogenous mechanisms of analgesia. (See Figure 7.34.)

It appears that a considerable amount of neural circuitry is devoted to reducing the intensity of pain. What functions do these circuits perform? When an animal encounters a noxious stimulus, the animal usually stops

Figure 7.33 Effect of Perceived Price of a Drug on Placebo Analgesia

The graph shows that participants reported less pain reduction from a placebo when they thought it was priced at a discount.

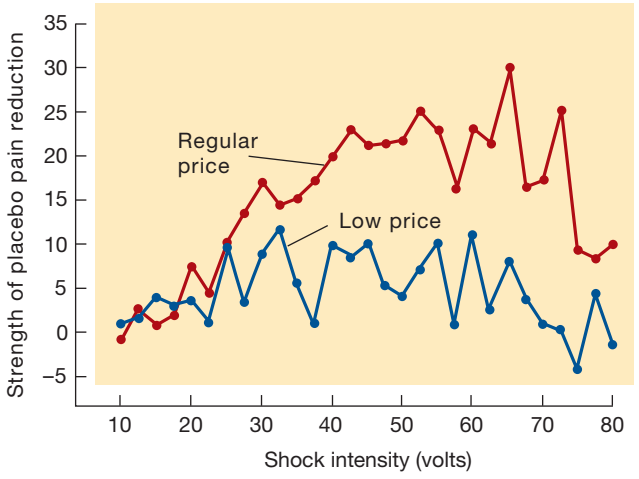
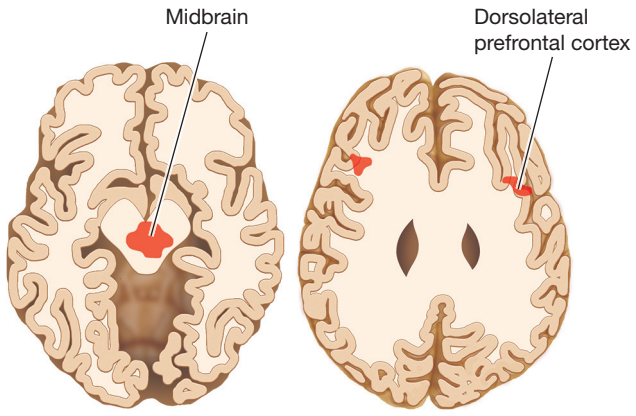


Figure 7.34 The Placebo Effect

Functional MRI scans show increased activity in the dorsolateral prefrontal cortex and the periaqueductal gray matter of the midbrain of participants who showed decreased sensitivity to pain in response to administration of a placebo.

Source: Based on Wager, T. D., Rilling, J. K., Smith, E. E., Sokolik, A., Casey, K. L., Davidson, R. J., Kosslyn, S. M., Rose, R. M., and Cohen, J. D. (2004). Placebo-induced changes in fMRI in the anticipation and experience of pain, *Science, 303,* 1162–1166.



what it is doing and engages in withdrawal or escape behaviors. Obviously, these responses are quite appropriate. However, they are sometimes counterproductive. For example, males fighting for access to females during mating season will fail to pass on their genes if pain elicits withdrawal responses that interfere with fighting. In fact, fighting and sexual activity both stimulate brain mechanisms of analgesia.

Komisaruk and Larsson (1971) found that tactile stimulation of a rat's vagina produced analgesia. Such stimulation also increases the activity of neurons in the periaqueductal gray matter and decreases the responsiveness of neurons in the ventrobasal thalamus to painful stimulation (Komisaruk & Steinman, 1987). The phenomenon also occurs in humans; Whipple and Komisaruk (1988) found that self-administered vaginal stimulation reduces sensitivity to painful stimuli but not to neutral tactile stimuli. Presumably, copulation triggers analgesic mechanisms. The adaptive significance of this phenomenon is clear: Painful stimuli encountered during the course of copulation are less likely to cause the behavior to be interrupted, and the chances of pregnancy are increased.

Module Review: Somatosenses

The Stimuli

LO 7.13 Provide examples of stimuli that activate receptors for the somatosenses.

Mechanical deformation of the skin activates pressure receptors. Changes in temperature activate temperature receptors. Sensations of pain can be caused by many different types of stimuli, but most cause tissue damage and activate nociceptors. Skeletal muscle stretch and limb movement activate kinesthetic receptors.

Anatomy of the Skin and Its Receptive Organs

LO 7.14 Describe the anatomy and somatosensory receptors of the skin.

Skin consists of subcutaneous tissue, dermis, and epidermis. Skin contains free nerve endings and encapsulated receptors. The encapsulated receptors are found in hairy and glabrous skin and are responsible for a variety of functions.

Perceiving Cutaneous Stimulation

LO 7.15 Describe the perception of touch, temperature, pain, and itch.

Mechanoreceptors are activated by vibration. Vibratory movement causes ion channels to open and change membrane potential to transduce the signal. Thermal receptors are free nerve endings that are activated by a relative change in temperature. Pain receptors are free nerve endings that are stimulated by intense pressure, heat, and chemical irritants. Little is known about the receptors that are responsible for the sensation of itch.

The Somatosensory Pathways

LO 7.16 Describe the components of the somatosensory pathways.

Somatosensory axons enter the central nervous system via spinal and cranial nerves. Information from the nerves passes through the medulla, the medial lemniscus of the midbrain, the ventral posterior nucleus of the thalamus, the primary somatosensory cortex, and finally the secondary (association) somatosensory cortex. The sensory cortex includes column organization by stimulus type and multiple maps of the body surface, each corresponding to different types of somatosensory information.

Perceiving Pain

LO 7.17 Describe why pain is experienced, the components of pain, and how pain perception can be modified.

Pain serves a constructive role: to reduce the likelihood of further injury. It consists of three perceptual and behavioral effects: perceptions of the intensity of a painful stimulus, immediate emotional consequences, and long-term emotional implications of chronic pain. Pain perception can be modified by activating analgesia circuits, through the release of endogenous opioids, or by administering exogenous opioids.

Thought Question

Do all placebos have the same effects on pain reduction? Design an experiment to test the effects of various characteristics of a placebo on pain relief. Consider what aspects of a placebo may make it more effective (for example, price was described in the previous module) and how it may be administered or for what kinds of pain it may be most effective.