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PAIN: PHYSIOLOGICAL MECHANISMS

In the late 1960s, John F. Hahn, a sensory generalist in the tradition of Henri Piéron and Frank Geldard, taught that pain is not only a sensation in search of a stimulus, but in search of a receptor as well. In the years since those discussions, understanding of the mapping of stimulus on receptor to sensation has not changed much. There is no question that pain is a dramatic and attention-grabbing event when it occurs—when skin temperature is too high or too low, when we taste or touch chemicals, such as capsaicin (from chilies) or when we stub our toe—and then again a few seconds later, but perceived differently—duller and less sharp. But one could argue that the most interesting aspect of pain is when it doesn’t occur and yet seems like it should. Phenomena such as phantom limb pain, the wounded soldier who continues to fight unaware of an injury, or the “anesthetic” effect of clenched fists in response to stubbing a toe underscore the fact that pain is a separate, complex sensory-perceptual experience. These also illustrate that the experience of pain is strongly subject to nonsensory (“top-down”) central influences, like affective state and peripheral modulating influences. Perhaps more than any other sensory modality, it can’t easily be explained by stimuli activating a pain receptor and being transmitted to the brain, challenging straightforward physiological analyses. But physiological mechanisms must underlie at least the initial triggering of the experience. This entry begins by placing the search for physiological mechanisms in historical context and then describes the results of contemporary research on physiological mechanisms.

Pain Is Different From Other Tactile Sensations

The perception of pain is different from other sensory experiences, and the physiology of “pain receptors” has been similarly difficult to define. At least tactually, pain is not just “very intense touch.” Historically, there had been a debate whether painful stimuli were just examples of very intense energy of some type (heat, pressure, etc.), reported by our touch receptors responding to these extremes on a continuum from normal and innocuous to painful, injurious, and noxious. The alternative view has been that there were specific receptors, called nociceptors, for the stimulus extremes. Observations described in the following text relating certain fiber types to stimuli described as “painful” support the latter notion. The brain, which reports the presence of pain or inhibits our appreciation of this illusive experience, can be explored surgically without resulting in pain, as Wilder Penfield was able to demonstrate in his explorations of cortical function during procedures when the patient was awake, because there are no pain receptors in the brain itself. Possessing only free nerve endings, somehow the cornea of the eye is able to distinctly report touch, temperature, and pain. (Bruce MacIver and Darrell Tanelian do point out that there is a distinction in the way in which the nerves branch out in the cornea, but there is no other apparent specialization in the endings.) So pain involves both affective (central) and sensory (peripheral) components. Other entries discuss some of the cognitive determinants of pain, its measurement, and current theories involving central nervous system pathways and interactions among them. This entry discusses the physiological bases of pain, particularly in the responses of specific peripheral receptor systems, called nociceptors.

Fiber Types Provide Evidence for Separate Pain Pathways

Historically, there have been a number of approaches to understanding the physiological basis of this perceptual experience, some of which have led to fairly aggressive experiments. For example, Stanley Finger relates how Sir Henry Head, in the 1890s, frustrated at the impatience of his students, cut the radial and other sensory nerves conducting signals from the skin toward the brain in his own arm to
observe the course of recovery of the cutaneous senses. Head noted that initially, regardless of the stimulus—cold, warm, or touch—pain would also be evoked. He argued that this phenomenon indicated that pain must be subserved by the finest of sensory nerve endings that regrow most rapidly, rather than the larger fibers. We experience something similar after our arm or leg "falls asleep" (paresthesia): The "pins and needles" during recovery reflect disorganized return of our sensations. This distinction, between the response of fine fibers and that of the larger fibers, would continue through the literature. This division fell into line with observations by Magnus Blix (ten years earlier), who explored the sensitivity of punctuate ("pointlike") spots on the skin with electrical and thermal stimuli and reported that those regions sensitive to pressure, warmth, cold, and pain did not appear to overlap.

It was only a few years later that Herbert Gasser and Joseph Erlanger conducted the earliest nerve block studies in which they induced ischemia in the arm with a tourniquet, starving the nerves by cutting off their blood/oxygen supply. This created an anesthetic state in the limb. Although the senses of touch were perceived to disappear quickly, sensitivity to pain remained—at least for a little while longer, again supporting the notion that these sub-modalities were served by separate underlying systems. They were further able to demonstrate that electrical signals recorded from the whole nerve showed distinctly different speeds of conduction (indicating activity in nerve fibers of distinctly different sizes). These were related to the serial disappearance of specific sensations, further linking the sense of touch to the faster (larger) fibers and pain to the slower (smaller) fibers. In other studies, local anesthetics like lidocaine or Novocain have been found to block the electrical activity in the smallest fibers first and the larger ones later. Perceptually, use of these anesthetics leads to a progressive loss of pain sensitivity before cold and touch disappear—just the opposite order to that found with ischemia. Similar dissociations among skin sensations are seen as symptoms in affected spots with syphilis, where pain and itch are lost, and with leprosy (Hansen's disease), where only touch and temperature are lost.

Finally, medical reports regarding spinal cord injury have shown that this functional separation is followed into the spinal cord—with one set of tracts carrying non-noxious tactile information, and a separate one carrying pain information (the lateral spinothalamic tract). Within the spinal cord, possibilities of interactions exist—not only within the fiber group containing pain information, but with descending controls from cortical structures as well. Therapists have been able to take advantage of these functional spinal separations between touch and pain and the existence of modulating interactions within the spinal cord in attempts to treat intractable pain. For example, surgeons can actually sever the pain pathway (in a procedure called anterolateral cordotomy, first performed in 1911 by Edward Martin and Artur Schüller), leaving touch intact. In other cases, stimulating modulating areas in the spinal cord electrically (transcutaneous electrical nerve stimulation) can reduce pain. Neither is completely successful, for reasons including anatomical variability as well as perceptual and cognitive factors.

Gate-Control Theory

Additional evidence supports a further separation of function by fiber type within the group of small fiber pain systems. The first is made up of the smallest of the A fibers (called A delta or Aδ). Larger A fibers appear to be responsible for "normal" touch. The whole population of A fibers is characterized as being myelinated, which means that the nerve fibers are "wrapped" by a particular type of cell, called Schwann cells, that have the effect of speeding nerve conduction. The second type consists of unmyelinated C fibers, and because of their small size and lack of myelination they conduct nerve impulses at a fraction of a meter per second—several times slower than the Aδ fibers. The differences between these two fiber types, especially their conduction speeds, underlies the experience of "double pain" felt, for example, when we stub a toe. Edward Perl and Lawrence Krueger give a brief history of the percept of a fast sharp pain followed later by a deep dull pain. Perl and another colleague, Bruce Lynn, further review studies of these two groups of small fibers tested with microneurographic techniques. In these studies, humans were asked to report sensations produced when the fibers were electrically stimulated, providing the important link between the neural
events that occur deep in the skin and perceptual experience. When a fiber in the forearm was electrically stimulated through the microelectrode, the subject would feel "something" at the distal termination of that nerve, for example, in the fingertip. This percept is described as a "referred" sensation. Two different kinds of pain sensation were described at the referred sites: "sharp, pricking pain" was felt when Aδ fibers were stimulated, whereas the sensations resulting from C fiber stimulation depended on the type of skin. If the referred site was in glabrous (smooth) skin, like the palm of the hand, stimulation was felt as dull, whereas for referred sites in hairy skin, it was felt as burning.

The differentiation between these two types of "pain" fiber types was used as the basis of one of the more useful physiological models to explain the way in which the perception of pain produced by the incoming ("afferent") neural activity was modulated by descending ("efferent") information from other sites, including the central nervous system. This efferent control of the incoming signals is proposed to occur in the spinal cord, and is described in the Melzack-Wall gate-control theory. While responses to noxious stimuli enter the "gate" through the small fibers, efferent influences can close it, modulating or reducing the pain. This model has more recently been elaborated into the neuromatrix theory. As James Craig and Gary Rollman relate, this theory attempts to bring together the information from the peripheral nervous system with the modulating influences from higher cortical levels to determine whether our response to aversive or noxious stimuli is perceived as pain, but this linkage is far from straightforward or well understood. For example, Mark Hollins and his colleagues studied how vibration on the forearm modulates the noxiousness of a brief burst of laser-produced radiant heat. In order to separate the changes in sensitivity from the possibility of changes in bias, he had to use an extended application of signal-detection methodology to show that over a wide range of frequencies and intensities, vibration could reduce pain mediated by Aδ fibers. This laboratory demonstration quantifies the everyday experience that occurs when one is able to "mediate" the pain from a minor injury at one body site (e.g., being kicked in the shin) by squeezing one's hands or rubbing the overlying skin. So it should not be surprising that if some types of pain can be controlled in this simple case, there can be more profound descending central influences—including the individual's attentional and affective states—on other types of pain.

The Search for Pain Receptors

The question remains, though, whether these nerve fibers, associated with painful sensations, are linked to specific structures in the periphery that exclusively encode painful (as opposed to nonnoxious) stimuli. As elusive as the search for receptors for the other submodalities of the skin's senses (e.g., vibration or temperature) has been, the search for "pain" receptors has been even more difficult. What has been established is that there are, in fact, neural systems that are truly nociceptive. But what underlies those peripheral sensory spots, some of which were described by Blix as only generating a painful sensation when pricked or pinched or burned? Joe Stevens and Barry Green suggested that these sites probably represented the subcutaneous presence of individual low-threshold receptors tuned to those particular types of energy, or dense aggregates of similarly sensitive receptors, or even regions where more complex neural coding might be taking place. There does appear to be an underlying physiological difference in the receptor sites for different intensities of tactile stimuli: When mechanoreceptors or thermoreceptors are stimulated with levels of energy that humans describe as painful, their neural response either stops altogether or the response is just a bit higher than their response to lower energy levels. For example, although "warm" thermoreceptors will respond to skin temperatures approaching the painful range of about 41 to 43° Celsius, their firing rate is simply higher than that evoked by the normal-to-warm temperatures of 35 to 40°. However, heat-sensitive nociceptors will only respond to the hot-to-painful potentially injurious range of temperatures from about 43 to 50° (or higher). In their comprehensive description, Bruce Lynn and Edward Perl detail the receptor systems that seem to subserve the basic submodalities of information that one would classify as painful. But in their description, only one type of noxious stimulus has been tied to a particular gross neural structure—the morpholoev (form and
structure) of the A mechano-nociceptor nerve ending appears to have a unique appearance in the skin. None of the other nociceptor types, A or C fiber, mechanical, thermal, or chemical, appear to have particular terminal structures or organization that would best suit them to process potentially injurious stimuli. However, at the level of the nerve membrane, recent research has explored specialization of specific receptors that open or close ion channels in response to specific noxious stimuli. The monograph edited by Uhtaek Oh describes a number of these membrane-level mechanisms in nociceptive nerve fibers and even discusses the cloning of receptors specific to particular noxious stimuli, such as capsaicin.

**Characteristics of Pain Receptors**

Researchers now know that there are unique nociceptors in a wide range of structures and organs in the body—the teeth, the cornea of the eye, the heart, the testes, the uterus, and others. However, this section deals primarily with those described in the skin, our largest organ. Lynn and Perl can be referred to for details on some of these other sites. Those in the skin have been best studied, and their functions and sensitivity to noxious stimuli seem to be divided between the small A and C fibers. A nociceptors are of two types: those sensitive to mechanical stimulation (like pinching or hard probing) and those sensitive to heat or chemicals. The mechano-sensitive nociceptors tend to have multiple receptive fields, much like cutaneous type II SA receptors in hairy skin. Those responsive to heating (in the 40-50° range) seem to be more common, with some firing vigorously in the very high (>50°) range, particularly with long-duration stimuli. It is likely that some human responses to very high heat may be mediated by these because response times are too rapid to be mediated by the other population of heat-sensitive nociceptors, the C fiber temperature-sensitive ones.

C fiber nociceptors conduct more slowly and appear to be the source of that duller, slower pain in “double pain” experience. They typically have single well-demarcated receptive fields, in contrast to the A pattern. Furthermore, they are often polymodal. That is, they respond in a regular fashion (increasing their neural firing rate as the stimulus intensity increases) to very strong mechanical and high-temperature noxious stimuli as well as to chemical irritants like capsaicin, acids, histamine, or mustard oil. Some have also been reported to respond to extreme cold (about 15°), in contrast to cool receptors that respond to nonaversive cold stimuli produced by as little as a 1° reduction from normal skin temperature (about 35°). C fiber nociceptor populations have also been found that are only sensitive to noxious mechanical (but not thermal) stimuli, only to high temperatures but not mechanical pressure, to chemical stimulation only, and, rarely, only to cold stimuli.

A number of behaviors of nociceptors have been observed at the physiological level (nerve recordings) that are mirrored in behavioral experience. One of the more interesting is C fiber sensitization. Some C fiber nociceptors don't respond until a prior "sensitizing" event occurs. In particular, joint nociceptors have been found that are only active if there is local inflammation. Similarly, stimulation with chemical irritants can induce sensitivity in other C fiber nociceptors to a previously nonadequate stimulus: They become sensitive to classes of noxious stimuli to which they would not previously respond. So these findings suggest that prior injury can activate the system and increase its responsiveness. Conversely, C fiber suppression occurs in other cases where C fiber nociceptors show dramatically reduced responses a short time after aversive (e.g., heat) stimuli. Not only does this suppression last as long as five minutes after the inducing stimulus, but it is directly related to the intensity of the inducer. From an everyday perceptual standpoint, it is interesting to note that the pain resulting from the chemosensory irritation that occurs when eating chili pepper recipes can be attenuated by pausing for five minutes until the pain subsides. Barry Green has found that continuing to eat afterward will be less aversive, but depends on the intermission; the suppression effect will not occur if capsaicin is constantly present in the mouth. These effects, both suppression as well as sensitization, appear to be peripheral in origin, occurring at the end of the fibers that are responsible for the initial encoding of nociceptive stimuli that may be perceived as pain by the central nervous system, and have remarkable perceptual parallels.
PAIN: PLACEBO EFFECTS

The placebo effect is the reduction or the disappearance of a symptom when an inert treatment (the placebo) is administered to a subject who is told, and indeed believes and expects, that it is an effective therapy. Most of the knowledge about its mechanisms comes from the field of pain, thus placebo analgesia is currently the most investigated model. However, other systems and apparatuses, such as the motor, immune, and endocrine systems, are emerging as interesting models. Although the placebo effect has so far been considered a nuisance in clinical research when a new treatment has to be tested, it has now become a target of scientific investigation to better understand the physiological and neurobiological mechanisms that link a complex mental activity to different functions of the body. Usually, in clinical research the term placebo effect refers to any improvement in the condition of a group of subjects that has received a placebo treatment. Conversely, the term placebo response refers to the change in an individual caused by a placebo manipulation. However, today these two terms are used interchangeably.

The placebo effect is basically a context effect, whereby the psychosocial context around the patient plays a key role. For example, the therapist's words, the sight of complex machines, and other sensory inputs that tell the patient that a treatment is being performed, all represent important factors in the occurrence of a placebo response. In the case of pain, this psychosocial context is capable of modulating pain perception. This is the reason why the placebo effect is currently a useful model for understanding the complex psychological modulation of pain. This entry describes the identification and mechanisms of the placebo effect, as well as the nocebo effect (a placebo effect in the opposite direction).

Identification of the Placebo Effect

The investigation of the placebo effect is full of pitfalls and drawbacks because, in order to identify a real psychobiological placebo response, several other phenomena have to be ruled out. For example, most painful conditions show a spontaneous temporal variation that is known as natural history. If subjects take a placebo just before their discomfort starts decreasing, they may believe that the placebo is effective, although that decrease would have occurred anyway. Clearly, this is merely a misinterpretation of the cause-effect relationship. Another example is regression to the
The field of perception is devoted to explaining the operation of the senses and the experiences and behaviors resulting from stimulation of the senses. Perceptual processes such as recognizing faces, seeing color, hearing music, and feeling pain represent the actions of complex mechanisms, yet we usually do them easily. The Encyclopedia of Perception presents a comprehensive overview of the field of perception through authoritative essays written by leading researchers and theoreticians in psychology, the cognitive sciences, neuroscience, and medical disciplines. It presents two parallel and interacting approaches: the psychophysical, or determining the relationship between stimuli in the environment and perception, and the physiological, or locating the biological systems responsible for perception. Are there any processes not associated with perception? Surely there are, but the pervasiveness of perception is truly impressive, and the phenomena of perception and its mechanisms are what this encyclopedia is about.

**key features**
- Contains 16 pages of color illustrations and photographs to accompany the entries
- Offers a varied and broad list of topics, including basic research as well as methodologies, theoretical approaches, and real-world applications of perceptual research
- Emphasizes human perception but includes ample animal research because of its importance in its own right and because of what this research tells us about human perception
- Written by recognized experts from many disciplines but for an audience with no previous background in perception—students and members of the general public alike

**key themes**
- Action
- Attention
- Audition
- Chemical Senses
- Cognition and Perception
- Computers and Perception
- Consciousness
- Disorders of Perception
- Illusory Perceptions
- Individual Differences (Human) and Comparative (Across Species; Not Including Ageing, Disorders, and Perceptual Development)
- Methods
- Perceptual Development/Experience
- Philosophical Approaches
- Physiological Processes
- Sense Interactions
- Skin and Body Senses
- Theoretical Approaches
- Visual Perception