WHEN PAIN LINGERS

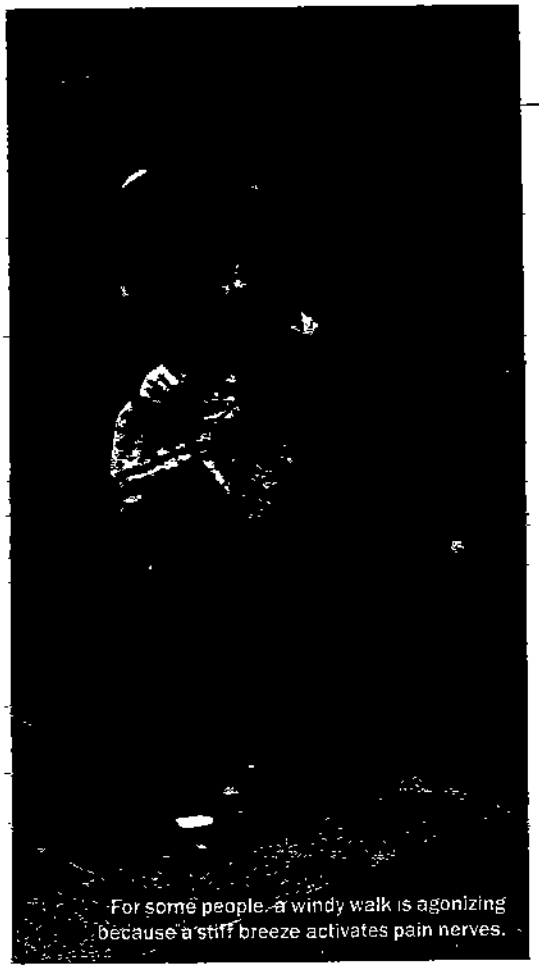
Researchers are revealing the biological basis of persistent, pathological pain—and providing clues to better treatments

■ BY FRANK PORRECA AND THEODORE PRICE

Imagine you are a doctor treating a patient who has been in nearly constant pain for four years, ever since the day he sprained his ankle stepping off a curb. Physical therapy only briefly dulled the agony. Painkillers were not much better, and the most effective drugs made your patient exhausted and constipated. He is now depressed, sleeping poorly and having difficulty concentrating. As you talk with him, you realize that his thinking also seems impaired. Your exam confirms that the original injury has healed. Only pain and its consequences remain—and your options for helping this man are running out.

This scenario plays out every day in doctors' offices around the world. Fifteen to 20 percent of adults worldwide suffer from persistent, or chronic, pain. Half the primary care patients who develop a chronic pain condition fail to recover within a year, according to surveys conducted by the World Health Organization. Common causes of such unrelenting discomfort include physical trauma, arthritis, cancer, and metabolic diseases such as diabetes that can damage nerves. In many cases, however, the pain's origins are mysterious.

Indeed, despite decades of intense research into the biology of pain and how pain is perceived, many mysteries still surround chronic pain and its treatment. No one knows for sure why some injuries, even minor ones, result in persistent pain or why it occurs in some people but not in others. Nevertheless, researchers are pinpointing telltale changes in the neurons that underlie persistent pain. In particular, they have documented abnormal excitability among neurons at every level of the body's pain network. For instance, in the spinal cord, some cells aberrantly amplify pain signals after undergoing a type of molecular "learning" that is similar to what happens in the brain during the formation of long-term memories.



For some people, a windy walk is agonizing because a stiff breeze activates pain nerves.

Chronic pain is more emotionally fraught than acute pain—which comes on quickly but lasts a relatively short time. Changes in brain regions governing feelings and complex thoughts in chronic pain states may help explain some of the unwanted emotional and cognitive problems, from depression to attention deficits, that can sometimes emerge after years of suffering. Researchers have even uncovered signs that chronic pain might be a type of neurodegenerative disease, affecting parts of the brain that deal with attention, memory and decision making. A firmer understanding of these processes could lead to new treatments that would alleviate the relentless chronic pain experienced by millions of people worldwide.

Disease of Discomfort

We sense pain using specialized sensory neurons called nociceptors; these cells extend to most of the body, their fibers running alongside other sensory neurons in large bundles that make up peripheral nerves. Nociceptors normally respond selectively to strong stimuli, such as pressure, heat or cold. They then send their messages to neurons in the spinal cord, which, in turn, relay neuronal indications of potential or real tissue damage to the brain centers where pain perception occurs [*see box on opposite page*]. Activation of this pain pathway is critical for reflexive and coordinated protective responses to escape something that could damage the body, such as a stinging insect or a hot stove. Detecting circumstances in which we might experience harm is a vital protective function of our nervous system.

FAST FACTS

Pain but No Gain

1» **Researchers are pinpointing telltale changes in neurons that underlie persistent pain. In particular, they have documented abnormal excitability among neurons at every level of the body's pain network.**

2» **Chronic pain is more emotionally fraught than short-lived pain. Changes in brain regions governing feelings and complex thoughts in chronic pain states may help explain some of the unwanted emotional and cognitive problems, from depression to attention deficits, that can sometimes emerge after years of suffering.**

3» **A firmer understanding of the biology of chronic pain could lead to new treatments that would alleviate the debilitating condition in millions of people worldwide.**

But the protective pain we experience as a result of daily living is quite different from that which leads patients to seek medical attention. Instead of becoming active only in the presence of strong and potentially damaging stimuli, the pain transmission pathway can become pathologically revved up in reaction to movement of joints, light touch or other actions that are normally innocuous—a phenomenon termed allodynia. In some sufferers, donning clothes, taking a shower or going for a walk on a breezy day is excruciating because the fabric, water or wind on their skin abnormally stimulates pain pathways.

In other cases, pain can occur spontaneously, without any obvious cause. Patients who have endured nerve damage as a result of diabetes, for example, may feel intense burning pain while doing nothing more than sitting quietly in a chair.

Unlike ordinary pain messages, spontaneous pain and pain produced by mild stimulation do not signal impending damage to tissues and do not provide a survival advantage. Pain produced under these conditions reflects pathological changes in pain pathways and represents a disease in and of itself.

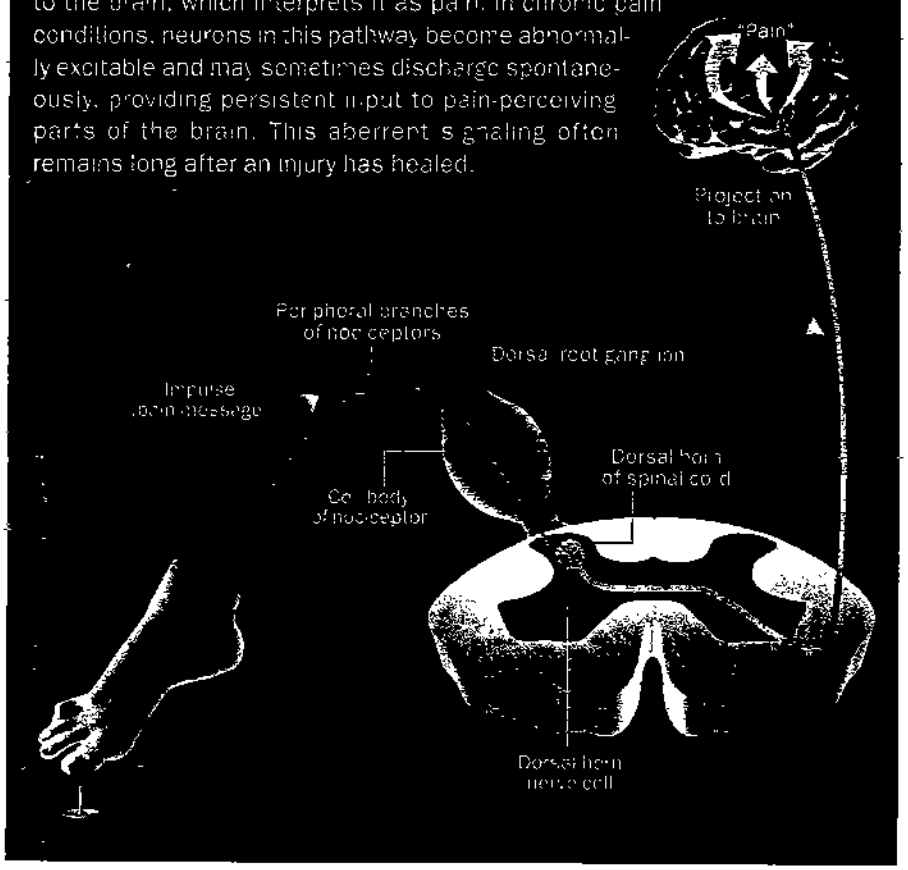
Too Much Excitement

In the early 1980s researchers began to learn the sources of such pathological pain. Studies in rats by neuroscientist Clifford Woolf of University College London and Harvard University and his colleagues revealed, for example, that following an injury to a rat's paw, neuronal signals from nociceptors near the skin to neurons in the spinal cord became amplified, much like turning up the volume on an iPod. These altered neurons unleash exaggerated reactions to tissue-damaging input; in addition, they become more easily excited, responding to stimuli that are ordinarily too mild or weak to produce a reaction.

Hormones or inflammatory molecules that the body produces in response to injury may sensitize nociceptors, making them more impulsive, a change that could instigate the development of chronic pain and abnormal sensitivity to

Perceiving Pain

In a healthy system for perceiving pain, a tissue injury causes pain-sensing nerve cells, or nociceptors (*pink*), to send a message to nerve cells in the dorsal horn of the spinal cord. These spinal cord cells pass the message to the brain, which interprets it as pain. In chronic pain conditions, neurons in this pathway become abnormally excitable and may sometimes discharge spontaneously, providing persistent input to pain-perceiving parts of the brain. This aberrant signaling often remains long after an injury has healed.



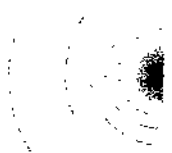
mild stimuli. (Such molecules also account for the aches a person may feel during normal movement a day after lifting weights, an activity that can lead to mild muscle damage.) Chronic pain conditions often begin when a peripheral nerve is injured, making that nerve—a bundle of fibers of which some are nociceptors—and neighboring ones more excitable. Hyperexcitability within the uninjured nerves that intermingle with the wounded nerve is probably paramount for the persistence of pain after the original injury is gone because many of the damaged nerves degenerate.

In addition to becoming more excitable, injured neurons may sometimes start signaling spontaneously. Injuries to peripheral nerves from trauma, diseases such as diabetes and cancer, drug treatments or excessive use of recreational drugs such as alcohol can spark such relentless electrical discharge, or ectopic activity, in the damaged nerves. These nerves then provide persistent input to the rest of the pain transmission pathway, a process that is believed to drive spontaneous pain. Often the recalcitrant signaling that underlies the pain remains long after an injury has healed.

In recent years researchers have revealed a molecular basis for this low-level ectopic activity. Voltage-gated sodium channels—proteins that conduct sodium ions into a cell in response to voltage changes—on the membranes of these neurons are essential for their ability to transmit electrical messages; their abundance and activity—how often they open and shut, for example—play an important role in how sensitive or excitable a neuron is. The latest data indicate that in chronic pain states these channels cluster where they count most, at the endings of the neurons near the skin and all along the nerve, most likely making the neurons more responsive to input.

For example, in a 2003 study one of us (Porreca) and his colleagues used fluorescent molecules to visualize a sodium channel called $Na_v1.8$ in the peripheral nerve cells of rats after a type of nerve injury that leads to chronic pain. We saw that the nerve membrane undergoes a "remodeling" so that the $Na_v1.8$ channels accumulate near the injury. This study suggests that injury prompts the nerve cells to ship lots of these proteins from their neuronal cell bodies near the spinal cord outward to the nerve terminal. This redistribution appears to be critical to the experience of neuropathic pain, because blocking the cells from producing this sodium channel made the rats' pain disappear, as evidenced by a return to their normal behavior. Neuroscientists have also discovered support for a similar transport of sodium channels in human tissues from studies on patients who have nerve injuries that produce persistent pain.

Other researchers have been homing in on the underpinnings of chronic pain in the dorsal horn of the spinal cord, where the peripheral pain fibers end. In 1999 neuroscientist Patrick W. Mantyh, then at the University of Minnesota, and his colleagues found that a subset of these dorsal horn neurons—just 1 to 3 percent of cells in this region—of the spi-



AMADEO BACHAR

After an injury, signals from pain-sensing cells in the body's periphery become amplified, much like turning up the volume on an iPod. The exaggerated input can lead to pathological pain.

A molecular mechanism that brain cells use to form certain types of memories may also underlie the ability of spinal cord neurons to sustain a state of chronic pain.

nal cord are major culprits in chronic pain. Using a Trojan horse strategy, they chemically coupled a toxin to a neurotransmitter, a neural signaling substance, so that when the neurotransmitter bound to its receptor on another cell, the receptor-transmitter complex served as a chemical "scalpel," deleting (killing) the recipient cell. Without these dorsal horn neurons, rats failed to show signs of chronic pain after local inflammation or nerve injury—symptoms that plagued rats that still had these neurons. The elimination of this neuronal subset did not affect ordinary pain perception, however, implicating these cells primarily in pathological discomfort.

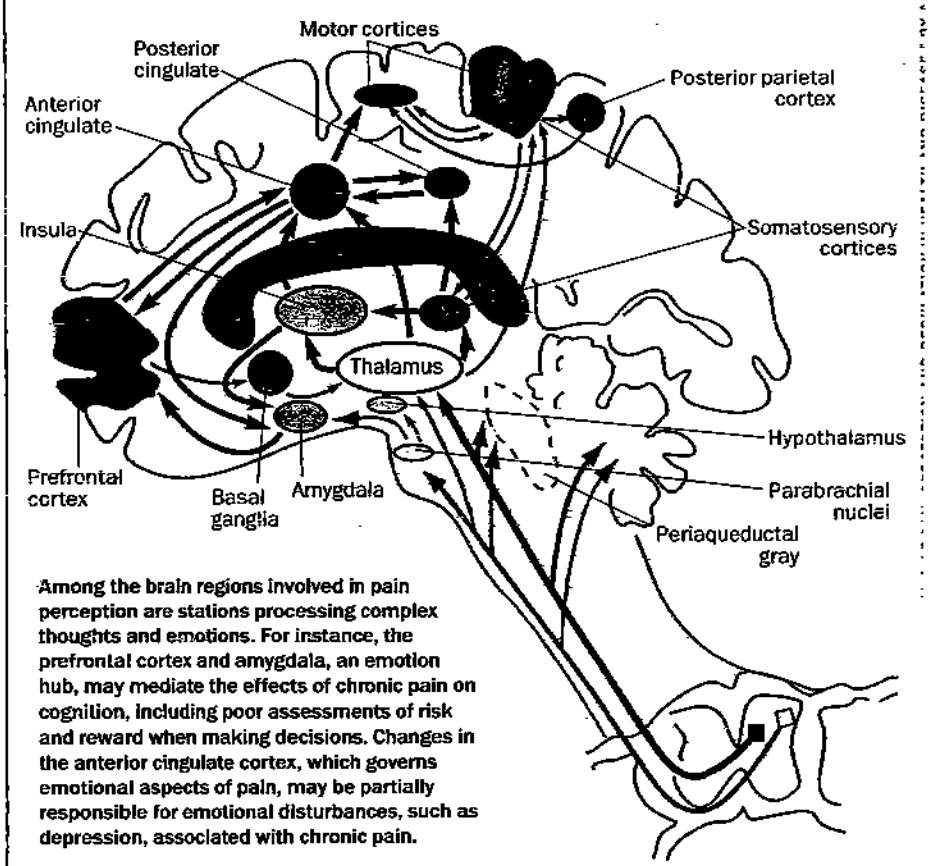
But what happens in these spinal cord neurons when pain becomes chronic? Recent data hint that they undergo a process called long-term potentiation (LTP), a long-lasting improvement in communication between two neurons that also underlies the formation of certain types of memories in the brain. Although LTP in the brain generally requires high-frequency input, 100 hertz or above, in a 2006 study neurophysiologist Jürgen Sandkühler of the Medical University of Vienna and his colleagues demonstrated that low-frequency stimulation from injured peripheral nerves in rats can lead to LTP in some dorsal horn neurons. In LTP, input from one neuron leads to a heightened response in the recipient cell, an effect that should enable spinal cord cells to amplify incoming pain signals. And just as LTP represents a molecular mechanism of memory storage in brain cells, it may underlie the ability of spinal cord neurons to sustain a state of chronic pain.

Nerve circuits that arise in the brain and lead down to the spinal cord can also profoundly influence the incoming pain signals and the resulting experience of pain. In this circuit, cells in the periaqueductal gray area of the midbrain receive input from the various regions of the brain's outer layer (the cortex) as well as from interior sections, such as the amygdala and the hypothalamus. This midbrain region then relays information to the rostral ventromedial medulla (RVM) in the brain stem, the lower part of the brain adjoining the spinal cord. Activation of this circuit mediates the powerful suppression of pain that occurs during trauma, intense stress or excitement [see illustration on page 44 of "The Psychology of Pain," by Howard L. Fields].

This same circuit, and in particular the RVM, also plays a major role when pain from an acute injury persists. Work from our laboratories has shown that when nerves are injured in rodents, a specific set of cells in the RVM sends out a signal that amplifies, rather than diminishing, incoming pain signals and sets the stage for chronic pain. In 2001, for example, a team led by Porreca used the toxin-based Trojan horse strategy to selectively snip out these RVM neurons in rats. Without these cells, the rats still developed pathological pain in their hind paw after a nerve injury, but that pain was short-lived, suggesting the RVM harbors a critical "switch" for the maintenance of chronic pain.

In an important 2008 study neuroscientist Irene Tracey of the University of Oxford and her colleagues found that neural activity in this brain stem region

Pain in the Brain



Among the brain regions involved in pain perception are stations processing complex thoughts and emotions. For instance, the prefrontal cortex and amygdala, an emotion hub, may mediate the effects of chronic pain on cognition, including poor assessments of risk and reward when making decisions. Changes in the anterior cingulate cortex, which governs emotional aspects of pain, may be partially responsible for emotional disturbances, such as depression, associated with chronic pain.

People who experience chronic pain may have problems assessing risk and reward when making decisions, such as during a poker game.

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in human volunteers paralleled the duration of painful symptoms (induced by exposure to the hot pepper compound capsaicin) that were similar to those of chronic pain patients. Current evidence suggests that ectopic input from injured nerves may alter these RVM cells so that their messages to the spinal cord facilitate, instead of inhibiting, incoming pain signals.

Painful Feelings

In addition to operating the pain-control circuit, pain-processing regions of the brain interpret input from the spinal cord and from other brain regions to create an overall impression of the discomfort. This interpretation depends on the setting and on a person's past experience, attentiveness and mood, among other psychological factors [see "The Psychology of Pain," on page 42]. To that end, pain not only stimulates sensory areas of the brain but also powerfully activates brain areas involved in emotion, such as the anterior cingulate cortex (ACC), a region governing emotional aspects of pain, and the amygdala, which mediates fear and other feelings. These areas—which are part of a so-called pain axis in the brain—can become hyperactive in chronic pain conditions and may, in turn, play a significant role in enhanced responses to stimulation in these patients.

Various known triggers of chronic pain seem to alter the ACC in particular. Peripheral nerve injury and chronic inflammation precipitate neural restructuring in the ACC. In addition, psychological factors such as mood, expectation and hypnotic suggestion can modulate pain responses in the ACC, according to human imaging studies [see "The Truth and the Hype of Hypnosis," by Michael R. Nash and Grant Benham; SCIENTIFIC AMERICAN MIND, June 2005]. Thus, the ACC may integrate sensory input with emotional state and may partially underpin some of the "affective" disturbances associated with chronic pain, such as depression, sleep disorders and pain catastrophizing, a condition in which patients expect and fear that pain will be intense and unmanageable. (Neuroscientists have shown that pain catastrophizing specifically engages the ACC.) The involvement of the ACC and the pain axis in general might also help explain the common occurrence of pain in patients with conditions such as depression and post-traumatic stress disorder.

A hyperactive pain axis not only increases pain intensity but also augments the aversive qualities of the experience. Chronic pain may thus reflect a switch from a bottom-up condition in which painful sensory information dominates to a top-down state in which emotional and cognitive assessments control pain behavior.

Certain cognitive deficits may also result from the toll chronic pain takes on patients. In 2004 neuroscientist A. Vania Apkarian of Northwestern University's

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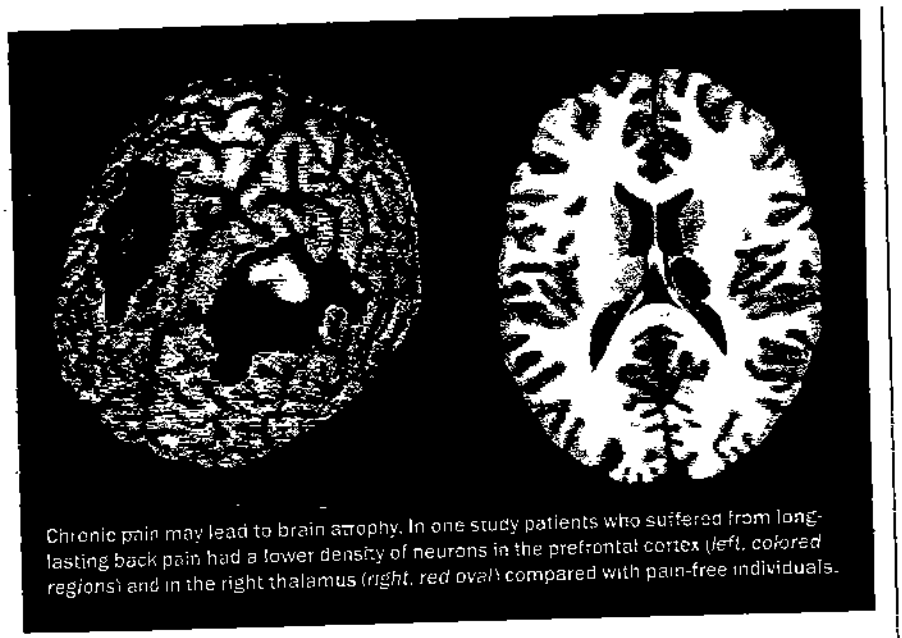
Feinberg School of Medicine and his colleagues demonstrated that individuals with chronic back pain or complex regional pain syndrome, a debilitating condition that can develop after trauma, showed a decreased ability to accurately assess risk and reward when making decisions. All the patients took part in the Iowa Gambling Task, a card game in which players choose between "bad" decks of cards that yield high immediate gain but substantial future losses and "good" decks that produce lower immediate gain but minimal losses later. Pain-free participants chose cards from the good decks—the most profitable strategy—more frequently than the pain patients did. The patients also tended to be fickle, frequently switching between decks, suggesting that the unpleasant emotions that accompany a state of persistent agony may interfere with judgments in other situations, such as weighing options in a gambling game.

In recent work presented at international pain meetings, neuroscientists Volker Neugebauer of the University of Texas Medical Branch and Vasco Galhardo of the University of Porto in Portugal showed that arthritic rats display a similar impairment. Given a choice between a "high-risk" food-dispensing lever that yields three food pellets in three out of 10 visits and a "low-risk" lever promising one pellet eight times out of 10, arthritic rats over time developed a preference for the high-risk lever (risking going hungry in seven of 10 visits), whereas normal rats more consistently picked the low-risk lever (missing only two snacks in 10). In this study the researchers associated a change in the brain with the inappropriate risk assessment: alterations in chemical signaling within neural circuits connecting the amygdala to the prefrontal cortex—a region governing higher cognitive functions, including attention, decision making and working memory—of the arthritic rats.

Previous work by Neugebauer and his colleagues suggests that chronic experimental pain in rats can lead to amplification of neural signals coming into the so-called nociceptive amygdala, a part of the amygdala governing pain. This augmented input then magnifies the messages—which are inhibitory in nature—that the nociceptive amygdala sends to the prefrontal cortex. The increased inhibition of the prefrontal cortex may impair an animal's (or human's) ability to accurately assess the risks of options when making important decisions.

More obvious brain changes may underlie other types of cognitive decline, among them muddled thinking and difficulty concentrating, in chronic pain patients. In 2004 Apkarian and his colleagues reported a shrinking of the prefrontal cortex in patients with very long-lasting back pain. The decreased brain volume was proportional to the duration of the pain in these patients but roughly equivalent to that seen in 10 to 20 years of aging. Since then, other research teams have revealed preliminary evidence of possible atrophy in the brains of some patients afflicted with other persistent pain conditions. These results hint that pain might actually be a neurodegenerative disease leading to remodeling of the prefrontal cortex and possibly other cognitive regions of the brain.

Recent findings hint that pain might actually be a neurodegenerative disease leading to remodeling of the prefrontal cortex and possibly other cognitive regions of the brain.



Chronic pain may lead to brain atrophy. In one study patients who suffered from long-lasting back pain had a lower density of neurons in the prefrontal cortex (*left, colored regions*) and in the right thalamus (*right, red oval*) compared with pain-free individuals.

No one knows for sure how chronic pain could lead to neurodegeneration, but the increased neuronal excitability that we now know characterizes chronic pain may provide a clue. Such excitability often leads to excessive release of the neurotransmitter glutamate, and glutamate is known to be toxic to neurons in large quantities. At this point, however, the glutamate explanation is purely speculative, and researchers are actively investigating various possible molecular causes of this neurodegeneration.

Calming Nerves

The recent insights into the mystery of why pain becomes chronic may point to new therapies. Medical researchers are attempting to block amplification of neuronal signals at every stage of the body's pain network. A few current and emerg-

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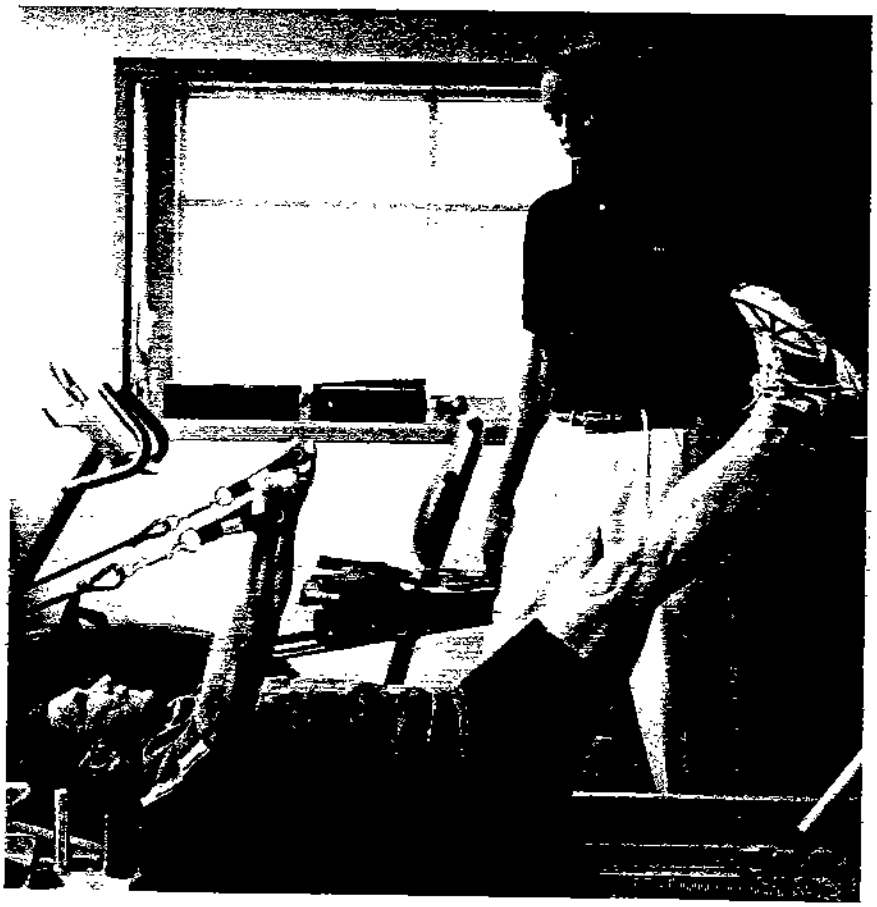


Exercise and intellectual challenges such as puzzle solving might help chronic pain patients combat the cognitive decline that can occasionally accompany their condition.

GETTY IMAGES (exercising); AGE FOTOSTOCK (puzzle solving)

ing medicines are geared toward countering abnormal activation of nociceptors. Some of these therapeutics act as "sponges" to absorb inflammatory proteins or nerve growth factors that are thought to boost the excitability of these pain-transmitting neurons. Other compounds that target neuronal hyperexcitability include sodium channel blockers and inhibitors of enzymes such as nitric oxide synthase that yield active neurotransmitters.

In the future, new analgesics might target the small subset of cells in the dorsal horn of the spinal cord that Mantyh, now at the University of Arizona, and his team tied to chronic pain or analogous cells in the RVM. A better understanding of the role of the ACC in chronic pain conditions might lead to novel therapeutic strategies that ameliorate pain, along with its psychological consequences. Ideally, these antiamplification therapies will not only ease patients' suffering but also prevent structural brain changes and possibly neurodegeneration that accompany extreme forms of chronic pain. That is, the best treatments would not just reduce symptoms but also reverse the disease process.

Drug treatments might make up just a part of the eventual strategy for ending intractable pain. Advanced diagnostic techniques might help determine the underlying cause of persistent pain. Some researchers are trying to identify "biomarkers," or molecular signs, of chronic pain that they could find in a blood or tissue sample, enabling early detection—and treatment—of abnormal changes in the nervous system that signal chronic pain. This technique could also point to the therapies most likely to work in an individual.

For patients who have a long-standing problem, doctors may want to prescribe behavioral techniques to address any emotional and cognitive fallout from the pain. Patients might be advised, for example, to supplement their medication with mind-preserving strategies, including intellectual challenges such as puzzle solving and physical exercise. Such a multipronged attack on relentless pain and its consequences should ultimately offer greater hope for the afflicted. M

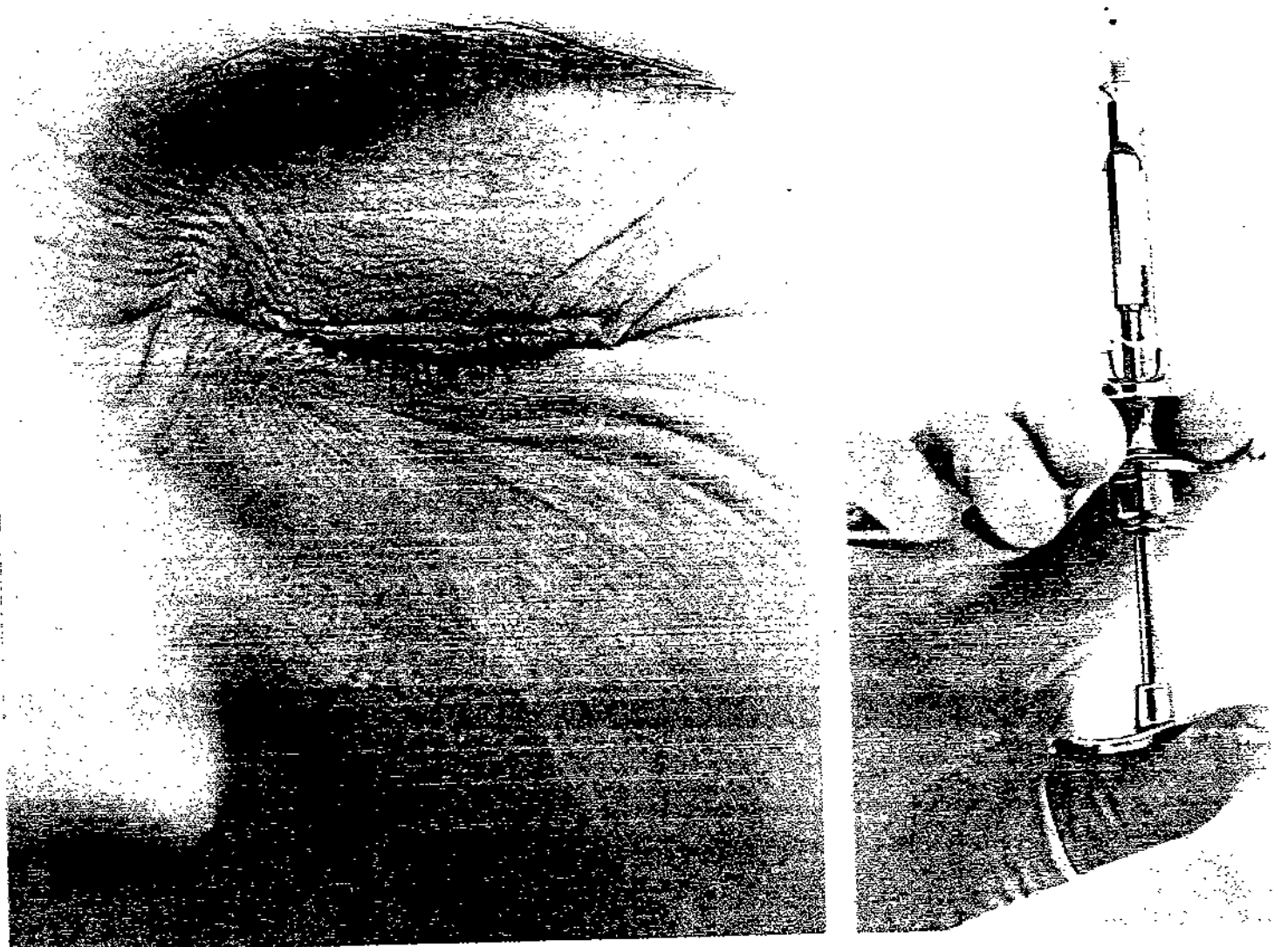
(Further Reading)

- **Redistribution of Na(V)1.8 in Uninjured Axons Enables Neuropathic Pain.** Michael S. Gold et al. in *Journal of Neuroscience*, Vol. 23, No. 1, pages 158–166; January 1, 2003.
- **Chronic Pain Patients Are Impaired on an Emotional Decision-Making Task.** A. Vania Apkarian et al. in *Pain*, Vol. 108, Nos. 1–2, pages 129–136; March 2004.
- **Wall and Melzack's Textbook of Pain.** Fifth edition. Stephen McMahon and Martin Koltzenburg. Churchill Livingstone, 2005. www.textbookofpain.com
- **Identifying Brain Activity Specifically Related to the Maintenance and Perceptual Consequence of Central Sensitization in Humans.** Michael C. Lee, Laura Zambreanu, David K. Menon and Irene Tracey in *Journal of Neuroscience*, Vol. 28, No. 45, pages 11642–11649; November 5, 2008.
- **Morphological and Functional Reorganization of Rat Medial Prefrontal Cortex in Neuropathic Pain.** Alexia E. Metz et al. in *Proceedings of the National Academy of Sciences USA*, Vol. 106, No. 7, pages 2423–2428; February 17, 2009.

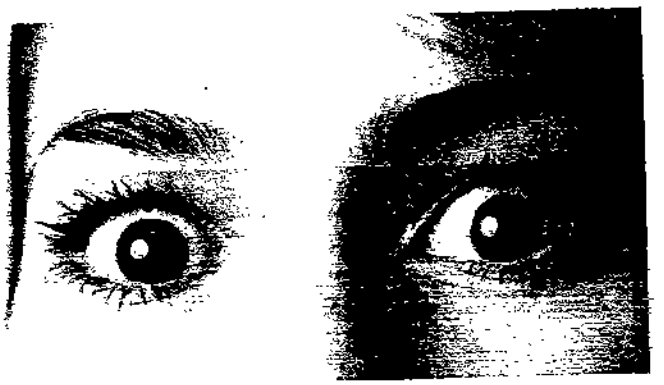
THE PSYCHOLOGY

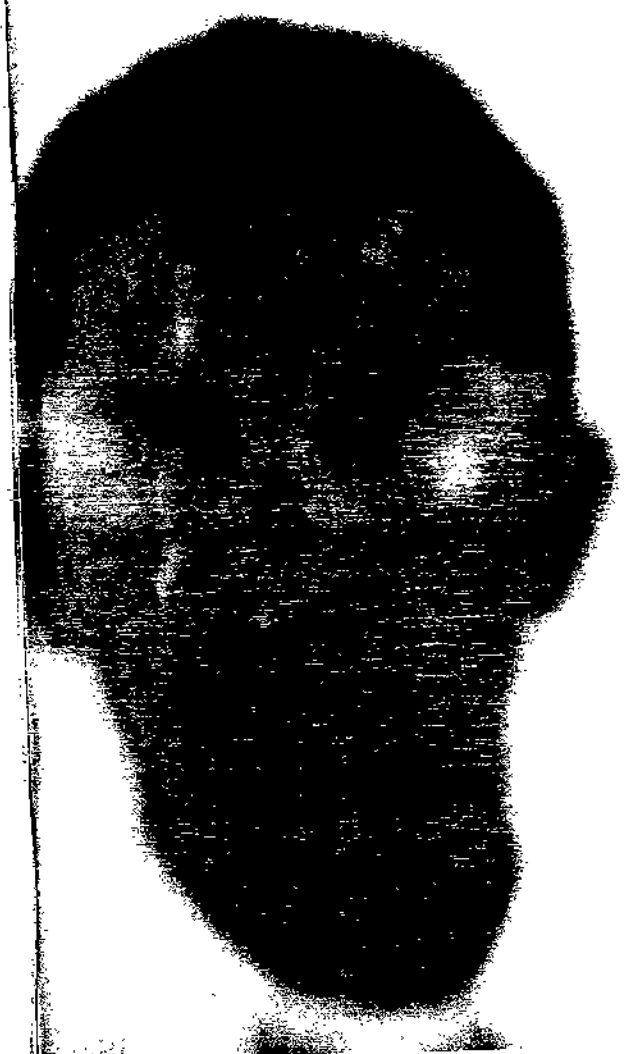
Our expectations, mood and perspective on pain powerfully influence how much something actually hurts—and the decisions we make every day

■ BY HOWARD L. FIELDS



OF PAIN





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Several years ago an elderly man came into the emergency room at Cook County Hospital in Chicago with a large, painful abscess (boil) on the back of his neck. When I told him he needed a minor procedure to lance the boil and drain it, he became ashen, asking, "Doc, is this going to hurt?" I told him that if at any time the treatment hurt too much, he could tell me to stop—and I would. I opened the boil with a very sharp scalpel. He did not make a sound for some time. "When are you going to start?" he finally asked. "It's done," I said. "How did you do that?" he replied. "I didn't feel anything."

Most people think of pain as resulting from physical injury or disease, but psychological factors play a huge role in pain perception. In the case of my elderly patient, my reassurance that the treatment would not significantly worsen his pain—because he could stop me if it did—produced an analgesic effect. In addition, reducing the man's fear enabled him to look forward to pain relief instead, and that positive expectation also eased his pain.

The importance of mind-set to pain perception should come as no surprise. Pain is a warning sign of injury, but for such a sign to be useful, pain must influence human behavior in a way that increases survival. Thus, pain must be intimately tied to brain functions that govern behavior and decision making, including expectation, attention and learning. By way of these links, a painful blister on your foot can motivate you to stop walking or to protect the area with moleskin. It may also teach you to shop for more comfortable shoes or wear thicker socks in the future.

The interaction between the pain message and the brain centers that mediate motivation and learning accounts for the powerful effect of a person's state of mind on the severity of pain he or she experiences with any injury. It explains the placebo effect: the expectation that a sugar pill will relieve pain reduces the extent of the agony even though the pill has no pharmacological effect. Conversely, if you are convinced that an injection, say, will be very painful, you are likely to unwittingly amplify the sting. Mood also interacts with agony. Depressed people, for example, may feel more pain as a result of their sour state of mind. In fact, worsening of a long-standing

pain problem, such as headache, often is the first sign of depression or at least the complaint that first brings a depressed patient to the attention of a physician.

Recent investigations are unraveling the mystery of how and when factors such as expectation of reward or punishment, fear, stress and mood alter perceived pain intensity and affect our daily decisions. Some of these psychological factors also influence the risk of developing a chronic pain condition. The research not only reveals just how far pain reaches into our psyches but also may lead to better ways of controlling pain and hastening recovery from painful injuries.

Mind over Matter

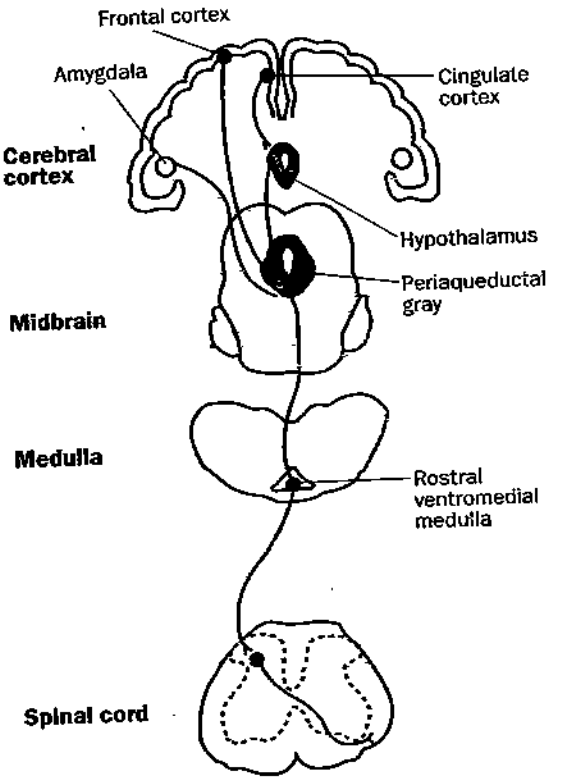
In the classic view of pain perception, a stimulus to the body excites pain-sensitive sensory neurons in the body's periphery; these neurons then transmit information in the form of electrical signals that eventually activate parts of the brain that enable us to perceive pain [see "When Pain Lingers," by Frank Porreca and Theodore Price, on page 34]. But for decades doctors have noted that a person's mental state can also dramatically affect pain perception.

For example, Harvard University anesthesiologist Henry K. Beecher noted in an article published in 1956 that soldiers who had been wounded in battle complained of much less pain than did patients with similar injuries in a civilian hospital. Beecher reasoned that in the context of having survived a battle and heading for home, an injury has a different meaning than it does for people hurt in the course of ordinary life. In the war scenario, a wound has honorable connotations, and such a positive spin on pain can lessen the sensation, Beecher speculated. Doctors have also long known about the analgesic powers of traumatic stress and of dummy pills that patients believe to be painkillers.

How could cognitive and emotional influences affect how much agony we feel? Over the past few decades researchers have uncovered a circuit in the brain and spinal cord that functions as a kind of volume control for pain, adjusting the amount a person perceives depending on the circumstances. In the early 1970s scientists at the University of California, Los Angeles, discovered that excitation of a small area in the midbrain of the rat produced profound pain relief. When they sent electricity through small wires implanted into that region of the brain, the rodent would no longer respond to intense, tissue-damaging stimuli that otherwise would make it squeak and flee. Later in the decade scientists showed that patients with severe chronic pain obtain significant, though temporary, relief from electrical stimulation of the same midbrain site, the periaqueductal gray.

Mind Control

A circuit in the brain and spinal cord acts as a volume control for pain, adjusting its perception depending on circumstances. This pathway contains two classes of neurons: off cells, which are activated by endorphins and morphine and inhibit pain transmission, and on cells, which facilitate pain signals and are stimulated by noxious stimuli and certain psychological factors.



FAST FACTS

Mentality of Misery

1» Most people think of pain as resulting from physical injury or disease, but psychological factors play a huge role in pain perception. Pain is intimately tied to brain functions that govern behavior and decision making, including expectation, attention and learning.

2» Recent investigations are unraveling how factors such as expectation of reward or punishment, fear, stress and mood alter perceived pain intensity and affect our choices.

3» Scientists are not only revealing just how far pain reaches into our psyches but are also using their findings to devise ways of better controlling pain and hastening recovery from painful injuries.

FROM "PAIN MODULATION: EXPECTATION, OPIOID ANALGESIA AND VIRTUAL PAIN," BY HOWARD L. FIELDS, IN [illegible] FROM ELSEVIER

Since then, researchers have mapped other parts of the body's pain-control circuit [*see box on opposite page*]. It stretches from the brain's cerebral cortex in the frontal lobes through underlying brain structures, including the periaqueductal gray, to the spinal cord, where pain-sensitive nerve fibers connect to neurons that transmit pain signals from the rest of the body. Neurons in this pathway synthesize peptides known as endorphins that have pharmacological properties identical to the powerful opioid morphine. Endorphins, the body's natural painkillers, and opioids (which also include opium and heroin) act at the same receptors, called mu opioid receptors, along this pain modulatory pathway to produce their analgesic effects.

Great Expectations

Neuroscientists are finding that cognitive influences on pain operate through this modulatory pathway. The circuit is the conduit for a variety of expectation effects, including the prospect of pain relief from a placebo pill. In 2004, for example, neuroscientist Tor D. Wager, now at Columbia University, and his colleagues found that a placebo produced increased activity in this pain-control circuit. Endorphins seem to be important in transmitting the pain-suppressing signal: my colleagues and I found that blocking mu opioid receptors with the drug naloxone erases the placebo effect in patients experiencing pain from a recent surgery. [For more on placebos, see "Cure in the Mind," by Maj-Britt Niemi; SCIENTIFIC AMERICAN MIND, February/March 2009.]

Recent data from my laboratory implicate the same circuit in other forms of expectation while underscoring their power over pain. In a study published in 2006 my research team showed volunteers color cues generated on a computer monitor just before exposing them to a painful stimulus through a metal probe taped to their hand. The words "low temperature" against a blue background were followed by mildly painful heat, and the words "high temperature" against a red background by more intense heat. Afterward subjects were placed in a magnetic resonance imaging scanner and randomly shown the red-high and blue-low cues beginning just before the mild or intense painful stimuli were applied.

EROS HOAGLAND *Redux Pictures*

Soldiers injured in battle may feel less pain than those hurt in other contexts because war wounds have psychological upsides.

The pain we experience is a synthesis of what happens in our body and what we expect, which depends on what we are told or have otherwise learned.

We found that the blue-low temperature cue, which had previously preceded milder discomfort, reduced the reported pain to the intense stimulus. In contrast, the red-high temperature cue, which had been paired with greater pain, amplified the discomfort of the mild stimulus. When the red-high cue preceded the intense stimulus, the pain magnitude was greatest. The brain sites known to be part of the pain transmission system in the thalamus and cortex were fully activated only when both stimulus intensity and high pain cues were given together. Thus, the pain we experience is a synthesis of what happens in our body and what we expect, which depends on what we are told or have otherwise learned.

We isolated the brain regions involved in the expectation effect by subtracting activity in the brain areas that lit up when the stimulus was intense and a person anticipated more pain from those excited by the same painful peripheral stimulus given when a person expected less pain. The net result was activation in cortical and brain stem regions that we now know are involved in the control of pain.

In addition to predictions about the pain itself, the expectation of a reward—say, from food or drugs—can profoundly affect pain intensity. In a classic 1984 ex-

(The Author)

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Looking forward to eating a delicious dessert can reduce pain.

periment pharmacologists J. Dum and Albert Herz of the Max Planck Institute for Psychiatry in Munich fed rats every day while the rodents were standing on a metal plate, which was at room temperature. Some of the rats ate regular rat chow, whereas the others feasted on chocolate-covered biscuits. After two weeks, the researchers placed the rats on the plate, which they then gradually heated to a painful temperature. The rats that had previously consumed their regular chow responded to the pain after four seconds; the rats that expected to receive chocolate endured the heat for twice as long. When the rats received a drug that prevents endorphins from relieving pain, however, the animals would no longer wait twice as long for their chocolate treat. Thus, the anticipation of the food reward had served as an analgesic, effectively raising the rats' tolerance for pain.

Food, sex and other natural enticements—and even the mere anticipation of such pleasures—activate the brain's reward circuitry in both rodents and humans. In doing so, they can also produce pain relief. The effects of opioid drugs further suggest that reward and pain relief have a partially shared neural basis. After all, the most powerful of these drugs, such as morphine and oxycodone (OxyContin, a prescription painkiller that has been widely abused), can relieve severe pain but also unleash a "high"—leading to their addictive potential.

Food, sex and other natural enticements—and even the mere anticipation of such pleasures—activate the brain's reward circuitry. In doing so, they can also produce pain relief.

Painful Choices

Pain and reward interact at mu opioid receptors. Mice engineered to lack a functioning mu receptor experience neither pain relief nor reward from morphine. In addition, rats given naloxone (which blocks opioid receptors) no longer experience pain suppression when they are expecting a food reward such as chocolate. Thus, when a person anticipates a reward such as a delicious dinner, the body releases endorphins, activating the mu receptors along the descending pain-control pathway and controlling pain signals as they enter the central nervous system.

A brain region called the nucleus accumbens plays a critical role in both signaling reward and controlling pain. Inactivating this region, which contains mu receptors, prevents animals from experiencing pleasure from either recreational drugs or natural rewards such as food and sex. What is more, injecting rewarding substances into this region can suppress pain responses.

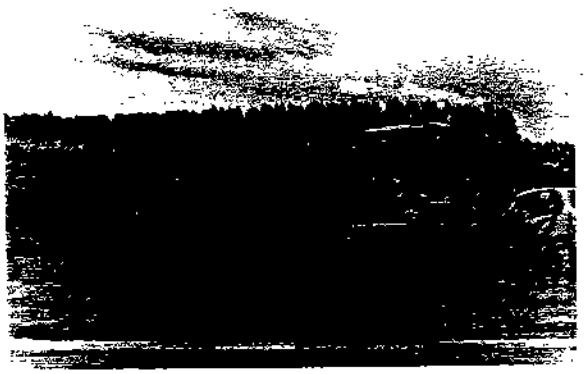
The ability of an imminent prize to suppress pain can influence decision making in situations in which reward seeking and escape from pain are in conflict. An athlete, for example, may face a choice between giving in to physical discomfort and enduring it in hopes of winning a race or a game. A person with a painful blister on his foot might have to choose between resting the injury and going out for pizza and a movie. Such decisions depend on a cost-benefit analysis inside the brain. How painful is the injury, and how much do you expect to enjoy the victory, movie or pizza? These expectations influence your decisions, in part through the pain-control circuit.

If you are a highly motivated athlete

or you expect the pizza or movie to be extremely good, your expectation will—through the release of endorphins and their stimulation of mu receptors—not only enhance the predicted enjoyment of the victory, food or film but also suppress pain. The overall effect biases you toward tolerating the pain to reach your goal or reward. In addition, you will actually *feel* less pain as you compete or head to town.

Similarly, rats that anticipate chocolate subconsciously "decide" to bear the pain of a hot plate to get the chocolate, both because they expect it to taste delicious and because that expectation alone reduces their pain. Such a resolution of pain-reward conflicts may have survival value. Animals often must endure pain to fight off a competitor for food or for a desirable mate.

The analgesic properties of anticipated rewards are consistent with the placebo effect. If relief of pain is rewarding, then a placebo pill is a sign of a forthcoming reward, leading to pain suppression. Thus, the expectation of relief becomes a self-fulfilling prophesy. Conversely, predicting pain has the opposite effect, amplifying activity in the pain transmission pathway and leading to greater pain perception.

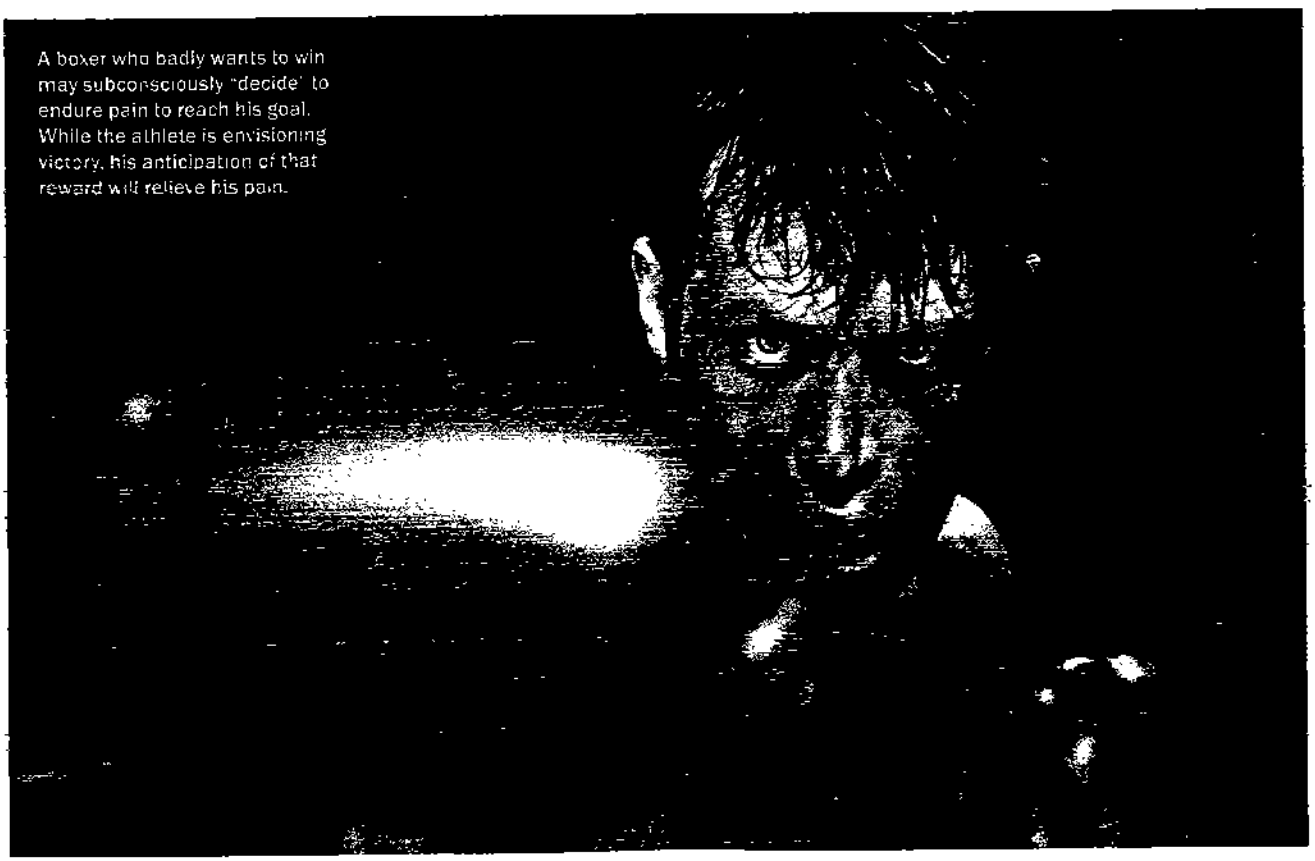


Victims of traffic-related whiplash injuries who expected to return to work recovered faster than those who were less optimistic.

Positive expectations for healing from painful injuries can lead to faster actual recovery from those wounds. In 2009 epidemiologist J. David Cassidy of the University of Toronto and his colleagues reported that among 2,335 Saskatchewan residents who endured traffic-related whiplash injuries, which are a major source of neck pain, those who expected to get well enough to return to their regular job reported recovering 42 percent faster than did those who were less positive. Previous studies have also shown that expectations for recuperating are consistently associated with going back to work among patients who have lower back pain, suggesting that a person's outlook on the future can strongly influence how much pain impinges on his or her life.

Skirting Danger

In addition to expectations of recovery or reward, a sense of danger can squelch pain. Researchers, including psychologists Fred. J. Helmstetter of the University of Wisconsin–Milwaukee and Michael S. Fanselow of U.C.L.A., have



A boxer who badly wants to win may subconsciously "decide" to endure pain to reach his goal. While the athlete is envisioning victory, his anticipation of that reward will relieve his pain.

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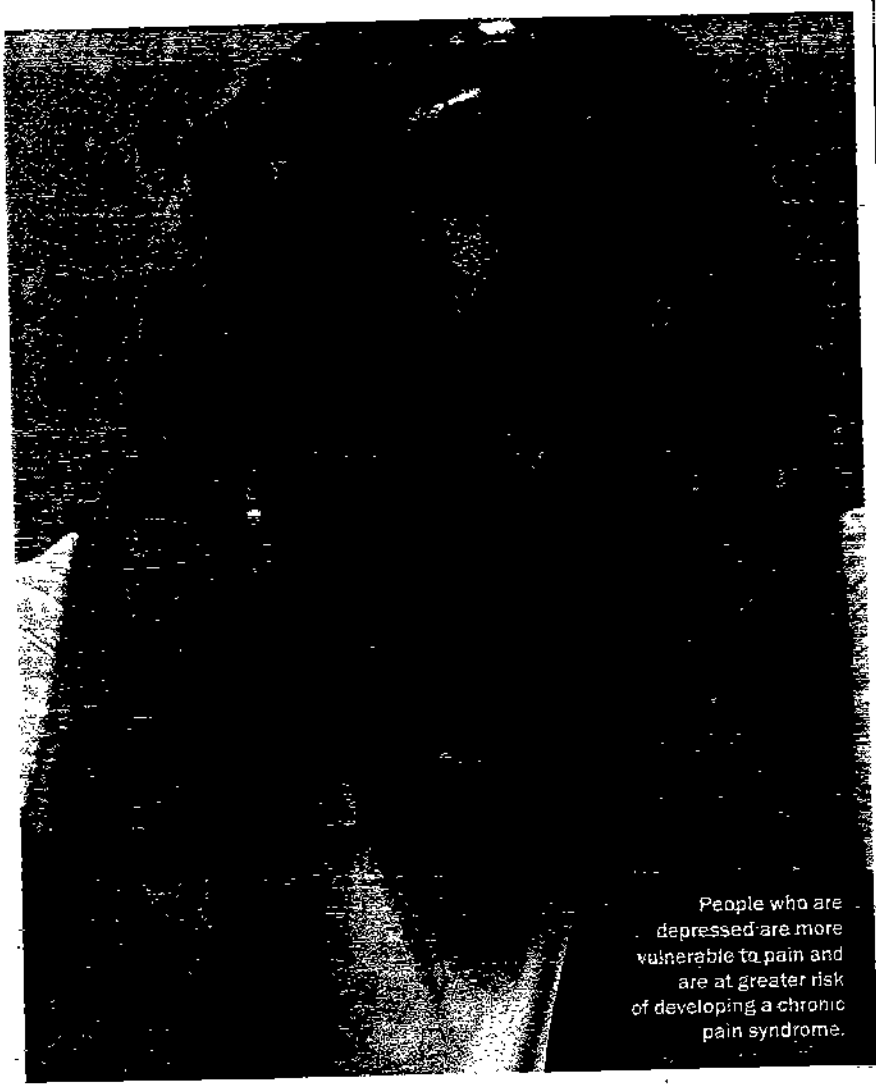
shown that rats do not respond to painful stimuli in the presence of a predator or when the rats are in an environment that provokes fear because, say, they had previously experienced a painful stimulus in it. Naloxone blocks this analgesic effect of fear in rats, indicating that the presence of imminent danger suppresses the experience of pain through release of an endogenous opioid.

People will often feel no pain during or immediately after severe trauma—say, a traffic accident or incident on a battlefield or during an athletic contest. Situations that produce acute tissue injury may signify an ongoing hazard and thus unleash fear or acute stress in humans and animals. The resulting suppression of pain may enable a person or animal to get to safety before being hobbled by agony.

Although acute stress can suppress pain, if stress persists and becomes chronic, pain usually intensifies. A bad mood may also increase pain. People who suffer from depression, for instance, may be more vulnerable to or less tolerant of pain. A 2007 study of 131,500 Canadians showed that among chronic pain patients, 11.3 percent had major depressive disorder as compared with just 5.3 percent of individuals who did not experience chronic pain. Being in pain may be depressing, and depression itself is also thought to affect pain perception. Neurochemical changes associated with depression—such as the depletion of the neurotransmitters serotonin and norepinephrine—may reduce normal inhibition or increase facilitation within the descending pain pathway.



People who are depressed are more vulnerable to pain and are at greater risk of developing a chronic pain syndrome.

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Catastrophizing, or interpreting pain as unbearable and likely to worsen, tends to intensify pain. People who catastrophize feel greater discomfort after surgery.

In addition, catastrophizing, or interpreting pain as unbearable and likely to worsen, tends to increase the experience of pain. Patients who score high on catastrophizing on a standard questionnaire tend to experience more severe pain after surgery and show more sensitivity to experimentally induced pain than do those who score low on the questionnaire. Catastrophizing may worsen pain by making a person concentrate on it and attach additional emotion to it. In a study published in 2004 rheumatologist Daniel J. Clauw of the University of Michigan at Ann Arbor and his colleagues tested 29 fibromyalgia patients for their tendency to catastrophize and then measured their brain responses to blunt pressure on a thumbnail. They linked pain catastrophizing to increased activity in brain areas related to the anticipation of pain, attention to pain and emotional aspects of pain perception.

Psychological distress of various forms raises a person's risk of developing a pain syndrome. In a study published in 2007 neurobiologist William Maixner of the University of North Carolina at Chapel Hill and his colleagues tracked 244 initially pain-free women for up to three years to see who developed temporomandibular joint disorder, a condition characterized by persistent jaw pain, to determine the traits that foretell its development. They linked being depressed and feeling stressed, for example, with a twofold to threefold rise in the chance of getting the disorder. In earlier work, scientists at the University of Washington tied somatization—a ten-

The **Empathy** Effect

Among the more intriguing psychological effects on pain perception is empathy, a sense of knowing and even sharing the experience of another person. In 2006 a team led by neuroscientist Jeffrey S. Mogil of McGill University showed that mice respond more readily to pain when they see cage mates, but not strangers (of the rodent variety), in pain. In 2008 Mogil, along with McGill pain researchers M. Catherine Bushnell and Marco L. Loggia, reported that empathy similarly heightens pain perception in humans.

The researchers exposed volunteers to a painful heat stimulus before and after showing them a video designed to evoke either empathy or distaste for an actor, depending on the version the viewer watched. When the participants felt the heat a second time, they watched the same actor being exposed to painful and nonpainful stimuli. The viewers who felt empathetic toward the actor rated their own pain as more intense and unpleasant than did those who felt negatively toward the actor (no matter whether or not they perceived the actor to be in pain). In fact, the more a person said he or she identified with the actor, the more pain the individual reported having,

supporting the idea that empathy itself alters pain perception.

The scientists theorize that activation of the brain areas associated with vicarious emotional distress from the high empathy video may have boosted the stimulation of the neuronal pathways that govern pain, because physical pain and distress activate similar brain regions. They also speculate that the empathy effect may be greater in more established relationships; it may, for example, help explain why the spouses of chronic pain patients so often say they are also in pain.

—Ingrid Wickelgren, staff editor

dency to report numerous symptoms in excess of that expected from a physical injury—with more than a doubling of the incidence of the disorder and less improvement after five years.

Parting with Pain

Research into the psychology of pain may lead to new ways of helping people overcome or cope with pain caused by injury, medical treatment or disease, whether minor or significant. Already, increased knowledge of the brain circuits that mediate the interaction of reward and pain relief is beginning to provide clues for strategies to dissociate the addictive potential of drugs from their pain-relieving power. The findings may lead to effective painkillers that are significantly less addictive than opiates.

In addition, understanding the powerful effects of mood, expectation and other psychological factors on pain is important for helping friends, patients or loved ones deal with their pain. Telling people in pain about individuals who have done well can often ease their distress and discomfort, whereas informing them of others who have had serious illnesses with similar symptoms will very likely worsen their suffering.

Doctors should be on the lookout for mood-related factors such as depression or chronic stress that might be abetting a patient's pain. They also need to carefully query patients about, or otherwise assess, their expectations regarding their discomfort. If a patient is overly pessimistic, a physician can reassure him or her by providing more accurate information, as I did with the man I treated for the abscess. Ultimately, the new understanding of the effects of mind-set on pain promises to revolutionize our approach to pain treatment. **M**

JUPITERIMAGES

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- **A Motivation-Decision Model of Pain: The Role of Opioids.** Howard L. Fields in *Proceedings of the 11th World Congress on Pain*. Edited by Herta Flor, Eija Kalso and Jonathan O. Dostrovsky. IASP Press, 2006.
- **Depression and Pain.** CME Institute of Physicians Postgraduate Press, Inc. (from a teleconference with John H. Greist, John F. Greden, James W. Jefferson and Madhukar H. Trivedi), in *Journal of Clinical Psychiatry*, Vol. 69, No. 12, pages 1970–1978; December 2008.
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I DO NOT FEEL YOUR PAIN

Researchers are unraveling why some people are more sensitive to pain than others. Their efforts could lead to more accurate diagnoses, better pain prevention and safer, more powerful painkillers

■ BY INGRID WICKELGREN

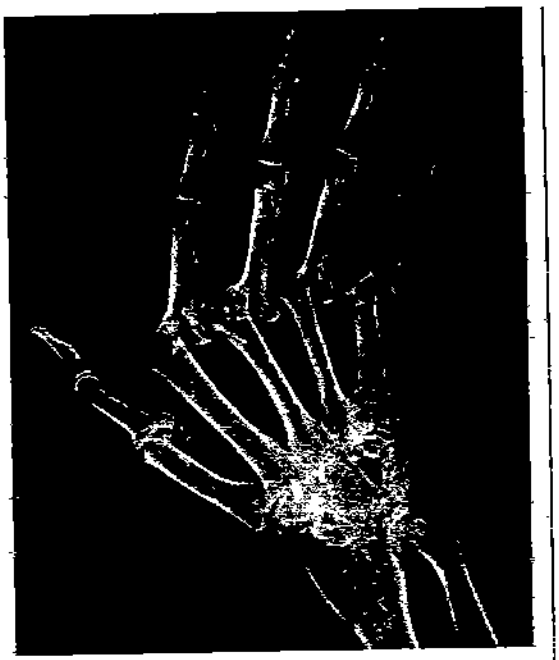
One day as a child Billy Smith (not his real name), a resident of Newfoundland, could not take off his shoe. No amount of twisting or tugging would loosen its grip on his foot. The reason for his struggle eventually surfaced: a nail had pierced the sole and entered Smith's flesh, tightly binding the two. Removing the nail freed the foot, but solving that problem only underscored a bigger one: Smith had not noticed.

Smith is among a tiny cluster of people, fewer than 30 in the world, who harbor a genetic quirk that renders them incapable of perceiving pain. "These humans are completely healthy, of normal intelligence, but don't know what pain is," says clinical geneticist C. Geoffrey Woods, who studied a group of such patients from northern Pakistan. They can sense touch, heat, vibration and their body's position in space. Yet for them, root canals are painless, as are falls, fires and whacks on the head with a baseball bat. One woman with so-called congenital indifference to pain (CIP) delivered a baby without discomfort.

"The children have lots of bruises, cuts and scalds from exploring like kids do, but with no pain to restrict their activities," Woods says. One Pakistani boy entertained others by sticking knives in his arms and leaping out of trees. Before Woods could see the child, he died jumping off a roof. The kids who survive are often deformed and disabled by self-mutilation or broken bones that they failed to notice or refused to rest. When Smith was three, he fractured a bone in his foot but kept walking on it as if nothing had happened.

Although such cases are exceptional, doctors and scientists have known for decades, if not centuries, that human beings at large differ greatly in how sensitive they are to pain. Much of the variation is apparently random. But gender matters. Women tend to hurt more than men do. Ethnicity can also interface with ache; some ethnic groups are more tolerant of discomfort than others are.

In the past few years, as technological advances have eased the deciphering of the human genome, researchers have begun unearthing the genetic roots of these differences. They are also pinpointing social, cultural and psychological factors that play parts in pain sensitivity. The multitude of influences on pain refutes the conventional conception of this sensation as an index of tissue damage. Thus, assessing patients' vulnerability to anguish may be essential to accurately judging the severity of their condition. It is also critical to deciding how to treat their pain. Revealing the molecular causes of individual variation in pain perception is already helping to



Pain does not always parallel injury. The amount of pain a person has may not correspond to the degree of damage displayed on an x-ray.

unravel the biology of agony and providing targets for novel pain medications.

Spectrum of Suffering

Physicians have long noticed wide disparities in the pain tolerance of the people they treat. Among patients with the same condition, pain ratings typically range from "no pain" to "the worst pain imaginable." And although some disorders are more painful than others, the variation in distress among individuals with the same physical malady is far greater than the difference in the discomfort people feel, on average, from one condition to the next. "Two soldiers may be shot in the same nerve," says Stephen G. Waxman, a neurologist at Yale University and the Veterans Administration Connecticut Health Care Center. "One has sensory loss but is otherwise okay; the other has intractable burning pain."

Objective indicators of physical harm often correspond poorly to perceived pain. In one study the amount of inflammation in rheumatoid arthritis patients did not parallel the degree of suffering they reported. In people with osteoarthritis, the tissue damage shown on an x-ray often bears little relationship to the amount of discomfort a patient feels. Even when a scientist carefully controls the intensity of a painful procedure—say, a cold bath or compression of a limb—people significantly differ in how much they say it stings. (On the other hand, an individual's evaluations of agony are surprisingly consistent. If you ask someone to hold an object that becomes increasingly hot to tell you when the pain starts, that moment will be the same—within 0.2 degree Celsius—every time you repeat the procedure, even a few years later.)

What a person says about pain does jibe with changes in the brain if not the body. In a 2003 investigation neurobiologist Robert C. Coghill of the Wake Forest University School of Medicine and his colleagues asked 17 adults to evaluate the pain they felt from a hot metal device touching their lower leg. At the same time, the researchers scanned the volunteers' brains using functional magnetic resonance imaging. Pain-related regions of the brain were more active in the individuals who judged the twinge as more intense than they were in less sensitive subjects, Coghill and his colleagues found.

Verbal pain ratings also predict a person's vulnerability to chronic pain. In 2007 neurobiologist William Maixner of the University of North Carolina at Chapel Hill and his colleagues tested healthy female volunteers for pain sensitivity and psychological functioning. The researchers then tracked them for three years to determine who would acquire temporomandibular joint disorder (TMJD), which causes persistent discomfort in the joints on either side of the ear where the upper and lower jaw meet. Sixteen of 243 women came down with classic TMJD, and the disorder was three times more likely if a woman was very sensitive to pain than if she was relatively insensitive, Maixner says. His

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FAST FACTS

Diversity in Discomfort

1» Human beings at large differ in how sensitive they are to pain. Much of the variation is apparently random. But gender matters. Women tend to hurt more than men do. Ethnicity can also interface with ache; some ethnic groups are more tolerant of discomfort than others are.

2» In the past few years researchers have begun unraveling the genetic roots of these differences. They are also pinpointing social, cultural and psychological components that play parts in pain sensitivity.

3» Assessing patients' vulnerability to anguish may be essential to accurately judging the severity of their condition. It is also critical to deciding how to treat individuals' pain. Revealing the molecular causes of individual variation in pain perception is already providing potential targets for novel pain medications.

team has also associated elevated sensitivity to painful stimuli with other persistent pain syndromes such as fibromyalgia.

Gender Bias

For a decade or longer, researchers have known that women are at greater risk than men for a number of chronic pain conditions, including rheumatoid arthritis, lupus and fibromyalgia. Women are also more sensitive to noxious stimuli: in laboratory experiments the average woman exhibits a lower pain threshold (the point at which she first feels pain) and less pain tolerance (the degree or duration of pain she can stand) than the average man.

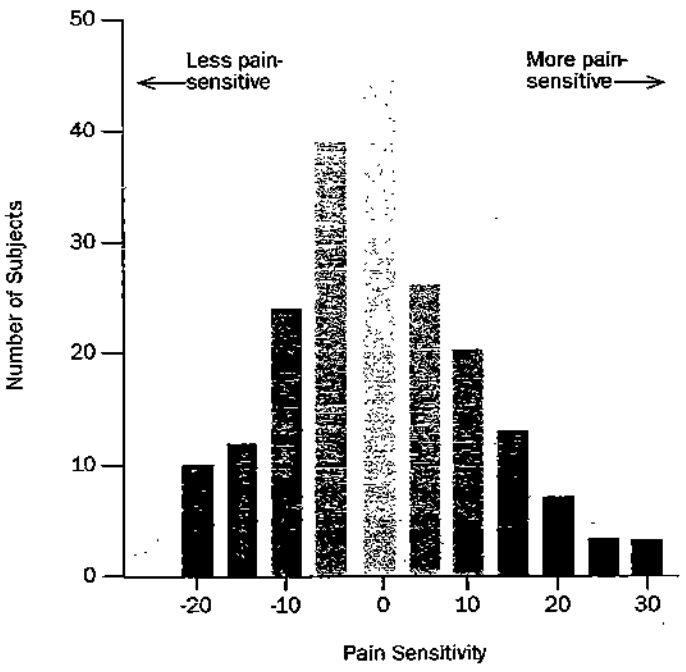
Sex hormones may contribute to this gender difference. Estrogen, for example, can often increase pain, in part by acting at receptors that sit on pain nerves. During her menstrual cycle, a woman perceives more pain after ovulation when progesterone—and to a lesser extent, estrogen—levels are high, consistent with the idea that female hormones intensify pain. In addition, hormone replacement therapy increases pain sensitivity in women, whereas drugs that stymie estrogen's actions provide long-term pain relief in certain situations. (In other circumstances, such as pregnancy, high levels of female hormones are accompanied by diminished pain perception; scientists do not fully understand why.)

Very pain-sensitive women were three times more likely to develop a common persistent pain syndrome than women who were relatively indifferent to pain.

Male and female brains seem to register discomfort differently. In 1999 Coghill's team reported that women perceived the same painful stimulus as more intense than men did and showed more activity in brain regions involved in processing pain. This excess excitement may stem in part from a weaker network for blocking pain. In 2002 psychiatrist Jon-Kar Zubieta, now at the University of Maryland, and his colleagues gave 14 men and 14 women an excruciating injection of saline into their cheeks while scanning their brains, focusing on parts of a "descending" pain-thwarting pathway in which endorphins, the body's natural painkillers, bind to mu opioid receptors to squelch the pain signal after acute injury [see "The Psychology of Pain," by Howard L. Fields, on page 42]. In the males this pain-curbing network was flooded with more endorphins and activity at mu opioid receptors than it was in females—a sign of a more powerful pain-control system.

Other evidence points to weaker pain inhibition in women. Intense or long-lasting pain applied to one part of the body, say, an arm, can suppress pain at another site, such as a tooth. The initial pain is thought to invoke the body's descending pain suppression system. In 2003 neuroscientist Donald D. Price of the University of Florida College of Dentistry and his colleagues showed that this phenomenon was less pronounced in women: in men, dunking one hand into a painfully hot bath diminished the discomfort of a scorching object touching the other hand, but the women felt no such relief.

Emotional and social factors may also contribute to women's enhanced pain sensitivity. For instance, women tend to engage in



Pain perception varies among people. Researchers gave 202 healthy women 16 pain sensitivity tests, subjecting them to heat, pressure and constriction, and reported a range of overall sensitivity scores (*above*).

SOURCE: "GENETIC BASIS FOR INDIVIDUAL VARIATIONS IN PAIN PERCEPTION AND THE DEVELOPMENT OF A CHRONIC PAIN CONDITION," BY LUDA DIATCHENKO ET AL., IN *HUMAN MOLECULAR GENETICS*, VOL. 4, NO. 4; 2005

Pain is not necessarily a sign of weakness. Women's tendency toward discomfort might enable females to better detect threats and thereby protect their offspring.

Women are more sensitive to painful stimuli than men are. Female hormones, weaker pain inhibition in women, and emotional as well as social factors may explain this gender difference.

pain-related catastrophizing—that is, expecting that pain will be awful and unbearable—more than men do. On the other hand, men are typically less willing than women to admit to being in pain because men want to appear tough and strong.

But pain is not necessarily a sign of weakness. In fact, women's tendency toward discomfort might be adaptive. Women are generally more attuned to bodily sensations than men are and have a greater capacity to sense all environmental stimuli, such as light, noise and odor, which may improve their ability to detect threats. Some scientists argue that evolutionary pressures may have promoted such a trait in women to enable them to better protect their offspring.

Not only are women more prone to pain, so are certain ethnicities. African-Americans display greater sensitivity to painful stimuli in the laboratory and report more negative emotional responses to pain than Caucasians do.

Cultural, social and psychological factors probably contribute to this disparity. In a study published in 2007 clinical psychologist Roger B. Fillingim, also at the University of Florida College of Dentistry, and his colleagues demonstrated that a person's ethnic identity—that is, the degree to which a person relates to a minority group's ancestry, language, physiology and culture—strongly affects his or her pain sensitivity. The researchers tested 63 African-Americans, 61 Hispanics and 82 non-Hispanic whites for their susceptibility to pain from a hot object touching their arm, very cold water surrounding a hand, and constriction of blood flow to an arm. Each person also filled out a questionnaire called the Multigroup Ethnic Identity Measure (MEIM).

The researchers found that the range of temperatures and the time that a person was willing to endure pain were lower for members of the two minority groups than they were for whites. And for the African-Americans and Hispanics, but not the whites, the stronger a participant's ethnic identity as judged by the MEIM, the greater his or her sensitivity to any of the types of pain. "Within a minority group the greater your ethnic identity, the greater your pain sensitivity," Fillingim concludes. Cultural factors related to ethnic identity such as religion, education or social expressiveness might bestow specific meanings on pain or suggest coping strategies, he posits. Such shared beliefs and practices may not only influence people's outward expressions of pain; they may also sculpt the biological infrastructure that underlies the experience of pain.

Some of that physiology apparently differs between African-Americans and whites. In 2008 Fillingim and his colleagues tested the natural pain suppression elicited by a strong or prolonged sensation of pain in 29 African-Americans and 28 whites. They induced ischemic pain, depriving an arm muscle of oxygen, by squeezing the arm with a tourniquet; during that procedure, they electrically shocked each person's ankle. The researchers found that ischemic pain produced greater reductions in

CHRIS RYAN Getty Images (top left); GETTY IMAGES (top right and bottom)

electrical pain ratings in whites than it did in African-Americans, who may have a weaker inhibitory pathway. "This suggests that African-Americans are less effective at controlling pain than whites," Fillingim says.

Spectacular Mutations

Of course, individuals within a gender or ethnic group also vary in their sensitivity. Genes account for 22 to 60 percent of the variance, according to studies comparing the correspondence in this trait between fraternal twins, who share about half of their genes, with that between identical twins, who have virtually the same DNA.

In rare cases, such as those with a congenital indifference to pain, a single gene has a huge effect. Smith and others like him have a mutation in a gene for a tiny molecular gate, or channel, that sits on the endings of nerves that sense pain. The channel ordinarily serves as an amplifier of neural signals and appears to be necessary for all types of pain perception. In patients with the mutation, the channel does not work, knocking out pain perception. "This spectacular observation seals the case, at least in the extreme, that genetics can have profound effects on sensitivity to pain," says Stanford University anesthesiologist David Clark.

Other mutations in the same channel protein make its gate flip open more readily and stay open too long, turning up the amplifier instead of knocking it out. This molecular mishap results in the flip side of Smith's perilous indifference to pain: an existence infused with agony. Patients experience mild warmth as searing or scalding heat. They liken slipping on socks to pouring hot lava on their feet, Waxman says. One teenager's pain gets so severe that he requires anesthesia in an intensive care unit [see "The Pain Gate," by David Dobbs; SCIENTIFIC AMERICAN MIND, April/May 2007].

Subtler genetic tuning of this channel could underlie more ordinary variation in pain sensitivity. Woods has unpublished data fingering a relatively uncommon change in a single base pair that makes the channel more responsive and its bearers feel a moderate amount of additional pain, about the level that could be countered by codeine.

Inherited Ache

Common variants of genes for other proteins, including enzymes, appear to underlie a hardiness to hurt, or the opposite. The enzyme catecholamine-O-methyltransferase (COMT) breaks down the stress hormones adrenaline and noradrenaline (also known as epinephrine and norepinephrine) as well as dopamine, a brain chemical involved in reward and mood. If this enzyme is scarce or not working properly, stress hormone and dopamine levels rise, and that chemical bounty apparently intensifies pain. Fibromyalgia patients and people with facial pain have higher levels of these chemicals. People who are disposed to pain such as females or chronic pain patients also often have relatively sluggish COMT.

Lethargic COMT can result from an alteration in the gene for the enzyme, leading to a threefold to fourfold reduction in its function. In a study published in 2003 Zubieta and his colleagues found that people who had at least one genetic blueprint for the less active enzyme were more sensitive than those with only active COMT to pain from intramuscular injections of saline, requiring less saline to reach the same level of agony.

STEWART TILGER Getty Images

"At the end of the day, there will be scores to hundreds of genes related to explaining individual differences in pain," predicts one behavioral geneticist.

Responses of patients to opioid painkillers vary widely. Some of this variation may stem from differences in the gene for the receptor in the body at which these drugs act.

In recent years Maixner, geneticist Luda Diatchenko, also at the University of North Carolina, and their colleagues linked two other versions of the same gene, along with the one Zubieta studied, with distinct levels of pain sensitivity—low, average and high—as well as with vulnerability to chronic pain. (Zubieta evaluated the "average" version, for the enzyme with lower activity.) The researchers analyzed the gene in 202 healthy women, whom they also tested for sensitivity to 16 types of painful stimuli and followed for three years to determine which ones developed TMJD. Compared with the other versions of the gene, the variant conferring low pain sensitivity gives rise to vastly greater quantities of COMT and lowers a woman's risk for TMJD more than twofold.

These COMT alternatives account for 11 percent of the variability in human pain perception, the largest contributor to pain sensitivity people have found so far, Diatchenko says. COMT type is a better predictor of the risk of developing a chronic pain condition than cholesterol level is for cardiovascular disease risk, Maixner adds.

The link between COMT and pain turns out to involve intermediaries called beta-adrenergic receptors that sit on pain-sensitive nerve endings. Adrenaline stimulates these receptors, whose activation (by drugs) can result in an agonizing arthritislike syndrome. Variation in the genes for these receptors, too, can shape pain perception. Maixner's group has nabbed one version of the gene for the beta-adrenergic 2 receptor, which is especially responsive to epinephrine and thereby sensitizes a person to pain.

Diversity in pain sensitivity may also arise from different forms of the mu opioid receptor, which also influence responses to opioid drugs. Opioids such as morphine and the body's endogenous painkillers exert their pain-suppressing effects by acting on this receptor. Responses of patients to opioid painkillers vary widely. The lowest effective dose may be five to 10 times higher for some patients than for others, and in 25 percent of patients morphine is ineffective or causes intolerable side effects.

In 2009 Diatchenko and her colleagues looked at the mu opioid receptor gene in 196 females who were also scored for their sensitivity to a battery of painful stimuli, including those that were hot, piercing and squeezing. After analyzing the gene at 25 places at which a chemical unit tends to vary between individuals—so-called single nucleotide polymorphisms (SNPs)—the researchers found one site associated with pain sensitivity. The rarer version of this SNP, carried by 6 percent of the population, seemed to make a person pain-prone and relatively unresponsive to opioid medication; its more common counterpart, on the other hand, conferred high pain tolerance and a good morphine response.

Other genetic differences may also impinge on a person's response to opiates. Certain human enzymes metabolize medications, and the results of their actions may be required to make the drugs effective and nontoxic. For example, a liver enzyme known as CYP2D6 converts codeine into morphine, the substance that relieves pain. In 7 to 10 percent of Caucasians, however, codeine does not work, because these individuals' CYP2D6 enzyme cannot accomplish the conversion. On the other hand, 1 to 7 percent of whites have multiple copies of the same gene. These individuals break down codeine extremely quickly, making even low doses of the drug potentially toxic. In one 62-year-old man with this gene duplication, a small dose of codeine nearly killed him, according to a report from Geneva University Hospital in Switzerland.

The genes nabbed so far probably represent just a tiny fraction of the body's Lilliputian conspirators in creating or modulating pain. "At the end of the day, there will be scores to hundreds of genes related to explaining individual differences in pain," predicts behavioral geneticist Jeffrey S. Mogil of McGill University.

Tailoring Treatments

Careful assessment of a patient's pain sensitivity could be invaluable for preventing and treating pain. Pain-sensitive patients are, for example, likely to experience a lot of discomfort after surgery and thus may require a higher-than-average dose of a painkiller. "Even in people who had identical surgeries, there can easily be a severalfold difference in the amount of pain reliever a person will need during recovery," Clark says.

An awareness of such differences may also help doctors better assess the severity of a person's illness. Low pain sensitivity might, for example, mask the true seriousness of a patient's condition. In contrast, an unusually strong reaction to a painful event might exaggerate the degree of physical injury it caused.

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Evaluating the pain tolerance of healthy patients may help doctors identify who is most vulnerable to developing persistent pain syndromes and thus who might want to forgo elective surgeries or take preventive analgesics after accidents or trauma. Genetic tests may further clarify a patient's risk. "Combining a couple of these genes together could give us good predictive value for who is likely to develop several persistent pain syndromes," Maixner says.

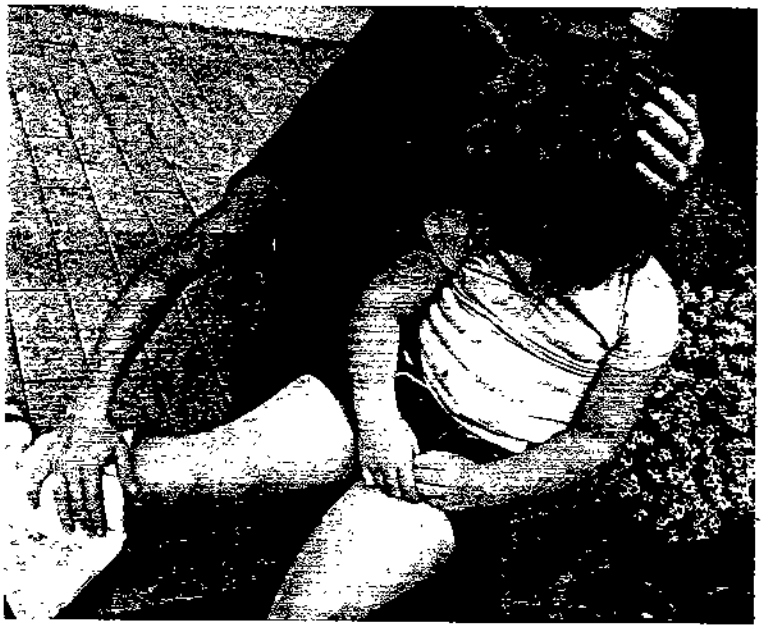
Testing people for variations in the mu opioid receptor or metabolic enzymes might further reveal who will respond well to opioids and at what dose and who might benefit from alternative therapies. Responses to future generations of analgesics might also depend on a patient's genetic makeup. "It's critical to understand the impact of genetics on the treatment of a patient," Clark says.

Unearthing genes involved in pain perception, or lack thereof, can also pave the way toward new therapies. Pharmaceutical and biotech scientists, including those at Xenon Pharmaceuticals in British Columbia, are trying to discover and build molecules that silence the sodium channel that is out of order in congenital insensitivity to pain. "It looks very hopeful that people will have a new generation of painkillers" that target this molecule, Woods says.

Blocking beta-adrenergic receptors may help treat pain conditions stemming from either low COMT activity or high adrenaline levels, or both. In 2007 Maixner's team found that inhibiting beta-adrenergic receptors in rats that had poor COMT function prevented the animals from showing signs of heightened pain sensitivity. In a study published in 2009 Maixner, along with neuroscientist Kathleen C. Light of the University of Utah and colleagues, found that propranolol, which treats high blood pressure by blocking beta-adrenergic receptors, decreased pain in 10 fibromyalgia and 10 TMJD patients as compared with a dummy medication.

Even without genetic tests, doctors may one day base their prognosis and treatments on a person's gender, ethnicity and individual psychology. Some genetic differences seem to be more common among certain genders or races, in accordance with group differences in pain sensitivity. Unpublished work by Fillingim and his colleagues, for example, indicates that a form of the mu opioid receptor associated with stronger natural pain control is far less frequent in African-Americans than it is in whites.

The science of pain peculiarities also helps all of us to gain a better appreciation of pain in those around us. We cannot assume that another person's pain is inconsequential even if the injury looks unimpressive or would not be painful to us. Indeed, the pain perceived, almost by definition, exaggerates or minimizes the damage inflicted, given that pain stems from biological quirks particular to the sensation itself, along with cultural, social and psychological influences.



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Another person may be in a lot of pain even if her wound appears minor.

Of course, extreme cases of pain indifference put the survival value of our aches in stark relief. Despite the unpleasantness of pain and the commercial quest for ever more powerful analgesics, humanity cannot afford to wipe out pain the way it might strive to end cancer or heart disease. "We might joke that we wish we felt no pain, but that would be terrible—and is terrible for those who can't experience pain," Clark says. Aside from their physical injuries, people like Smith must endure a dollop of emotional isolation resulting from their inability to experience a virtually universal sensation. They keep quiet about this void. When they fall, they pretend that it hurts, because they want to be normal. M

(Further Reading)

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