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Your System Has Been Hijacked: The Neurobiology of Chronic Pain

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Pain insists upon being attended to. God whispers to us in our pleasures, speaks in our consciences, but shouts in our pains. It is his megaphone to rouse a deaf world.

—C.S. Lewis

Mr. M., an Iraq war veteran, is admitted to the hospital for intractable pain in his left arm. He suffered an acute crush injury 2 years ago while in combat. He has had multiple surgeries to repair damage but still suffers from chronic, unrelenting pain. He states that if a surgeon does not agree to amputate his arm, he has purchased a gun and is planning to kill himself.

It may be hard to imagine a pain that is so severe that it would lead someone to consider suicide but, in fact, it is not an uncommon occurrence. Chronic pain affects 100 million people in the United States and has an estimated economic burden of \$560 to \$635 billion per year, including both the cost of health care and loss of productivity (1). It affects more people than diabetes, heart disease, and cancer combined (2).

Pain processing is one of the most vital functions of our body and is biologically required for survival. When all is well, we become immersed in our regular thoughts and experiences, unaware that a system for pain processing even exists. But when something goes awry, pain emerges. It invades our consciousness and transcends all other perceptual experiences. Pain signals danger. When severe, pain triggers a well-coordinated biological response that prioritizes escape over all other basic functions. In contrast to the glorified film and literature portrayals of superheroes or villains who feel no pain, we cannot live without it: children born with congenital insensitivity to pain (a rare disease caused by a mutation affecting voltage-gated sodium channels) usually die in childhood (3).

The perception of pain, under ordinary circumstances, begins with a signal from peripheral nociceptors on A-delta and C fibers that synapse onto the dorsal horn of the spinal cord. From there, there is a fast reflex response and also a separate signal that ascends and synapses in the thalamus. The signal is then relayed to higher cortical regions (including the

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somatosensory cortex, the cingulate, and the insula). A separate descending system, coordinated by the periaqueductal gray in the midbrain (and likely mediated by the release of serotonin and norepinephrine from the raphe nucleus and locus coeruleus), has the ability to inhibit the perception of pain by blocking the signal at the level of the spinal cord with enkephalin, a powerful endogenous opioid. Details of this pathway can be found in Figure 1A and are illustrated in Supplemental Video A (4,5).

Under ideal circumstances, pain signals an acute threat and, after resolution and recovery, it resolves. Unfortunately, as was the case for Mr. M., sometimes things go wrong. Mr. M. was still suffering and became progressively more debilitated, losing his ability to work, cook for himself, and even tie his shoes. He was now experiencing chronic pain, defined in the literature as a pain condition that lasts longer than 3 months, may or may not be related to injury, persists beyond expected healing time, and is often resistant to treatment. It can be seen as the byproduct of a biological system that has been hijacked and/or remodeled and no longer serves its intended purpose.

How does a once elegant and functional neural system become so dysregulated? Basic science and neurobiology are beginning to elucidate how the transition from acute pain to chronic pain is largely dependent upon neural plasticity, with changes occurring at multiple levels in the pathway.

Peripherally, after an acute injury, cytokines summon macrophages that release growth factors (including brain-derived neurotrophic factor) to help regrow damaged nerve fibers and synapses. These growth factors, however, are not selective. Nonpain (A-beta) fibers can grow alongside the pain fibers. Sympathetic fibers may also sprout in the dorsal root ganglia of injured nerves and become responsive to catecholamine. Abnormal connections can then develop between adjacent axons so that pain, nonpain, and sympathetic fibers all synapse on a cell body that used to only respond to pain. As a result, nonnoxious stimuli, such as a feather or anxiety, can trigger pain, a syndrome called allodynia [Figure 1B and Supplemental Video B (4–6)].

Plasticity can also be seen at the level of the dorsal horn synapse. Under conditions of consistent and severe injury, C fibers fire repetitively and dorsal horn neurons become more easily stimulated, a phenomenon called wind up. This process—essentially a form of classic Hebbian learning via long-term potentiation—is illustrated in Figure 1C and Supplemental Video C. Evidence of this “learning” is seen in hyperalgesia, where a mild injury produces pain out of proportion to the stimulus. In essence, mundane, nonthreatening, nondangerous, and even formerly pleasurable sensory experiences can become crippling (4–6).

Central plasticity also occurs, and the article by Zhang *et al.* in this issue of *Biological Psychiatry* sheds light on one fascinating aspect of this process (7). Historically, there has been a conflict in the literature about the role of the mesolimbic reward circuitry as it relates to chronic pain. The ventral tegmental area, a group of neurons in the midbrain that contain dopamine-synthesizing neurons, is known to be activated in chronic pain and was initially thought to reflect reward from the relief of pain. In an elegant set of experiments, the authors demonstrate that the firing of the ventral tegmental area may instead be the signal of chronic

pain, propagated via projections to the nucleus accumbens. Similar to the previously described peripheral plasticity, the authors show that brain-derived neurotrophic factor may help the nucleus accumbens “learn” to be hypersensitized to pain signals.

While these (and other) changes illustrate core neurobiological processes, chronic pain remains a quintessentially biopsychosocial illness: patients are unable to distinguish between pain that signals imminent danger and pain that results from a disease of aberrant connectivity and dysregulated learning; this can lead to a cascade of thoughts, anxieties, and avoidant behaviors that cause even more profound suffering and lead to immense societal burden. To treat pain effectively, a robust and multimodal treatment plan is essential.

A range of medications can be used to treat chronic pain based on the systems described above. Tricyclic antidepressants and serotonin–norepinephrine reuptake inhibitors are thought to act by increasing serotonin and norepinephrine in the nervous system (similar to the action of the periaqueductal gray), thereby leading to an increased release of endogenous opioids. Medications that block sodium channels or alter nerve conduction through the gamma-aminobutyric acid system (e.g., gabapentin and other antiepileptic medications) can decrease pain by slowing down or dampening signal transmission (8). Mu opioid agonists, though useful for the treatment of acute pain, are not recommended for chronic pain. Taken over the long term, they interfere with the descending pathway, our endogenous opioid system, and our ability to self-regulate pain. There is also, of course, the risk that chronic use could lead to addiction or overdose. Hopefully, the research described above may inform the development of new interventions that can act centrally and/or by new mechanisms (such as by targeting plasticity).

Cognitive behavioral therapy has also emerged as a powerful tool to help patients like Mr. M. who are suffering from chronic pain. It teaches patients that common automatic thoughts surrounding the seriousness and interminability of pain can lead to emotions of depression, anxiety, hopelessness, and helplessness. These may result in patients developing avoidant behaviors, such as not getting out of bed, dropping out of work, and not participating in activities that could bring pleasure and distraction—behaviors that are not only impairing unto themselves but may also worsen the underlying pain condition. Cognitive behavioral therapy encourages exercise, behavioral activation, cognitive reframing, and relaxation. Its strength lies in helping the patient break the cycle of negative reinforcement and allows patients to learn that many of their fears—while understandable—may prove to be both unwarranted (i.e., feared situations are not as bad as they imagine they will be) and counterproductive to their long-term recovery (9).

Mr. M. noted a substantial improvement in his pain and his functional status with a comprehensive treatment approach that integrated cognitive behavioral therapy, physical therapy, relaxation techniques, engagement of his family, and a serotonin–norepinephrine reuptake inhibitor. Appreciating that what was once a simple stimulation of a free nerve ending had evolved into a complex interaction of neuronal plasticity, thoughts, mood, and behaviors allowed Mr. M. to decatastrophize his thoughts relating to pain perception and to reengage in his life. Unfortunately, because of a range of systems issues—including, most notably, the lack of access to comprehensive, multimodal treatment resources—most

patients struggling with chronic pain do not do as well. Many have fallen victim to the opioid epidemic (10) as our health care systems are structured to provide “quick fixes” rather than the long-term, comprehensive, and effortful work required to meaningfully effect change. The future of our field needs to think holistically and creatively, integrating the biological, the psychological, and the social aspects of patients’ lives in order to provide them with the best possible chance at recovery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

The human body is designed to experience pain that is a response to a direct threat, like a blow from a hammer. **(A)** We first experience a fast, unconscious reflex, then we become aware of pain as the sensory fiber synapses on a second neuron in the dorsal horn, the second neuron crosses the midline, ascends in the spinothalamic tract, synapses in the thalamus, from which the signal is relayed to the cortex, and lastly, we can dampen the pain through a descending pathway that leads to the release of enkephalins at the level of the dorsal horn. Pain experienced over a long period of time can cause rewiring and remodeling of the nervous system, leading to the chronic pain syndrome. **(B)** When a pain fiber is damaged, growth factors released by macrophages at the site of the injury cause nonspecific sprouting of other axon types that can become aberrantly connected to the same cell body in

the dorsal horn, allowing nonpainful stimuli to be interpreted as pain. (C) At the level of the synapse, prolonged stimulation of the C fiber leads to increased release of presynaptic glutamate, activation of the postsynaptic AMPA receptors, depolarization of the postsynaptic neuron, expulsion of Mg^{2+} that was previously blocking the NMDA receptor channel, calcium flux into the cell triggering the activation of second messengers and gene transcription, and ultimately the docking of more AMPA receptors on the postsynaptic cell membrane. This increase in AMPA receptors strengthens the connection between the peripheral and central nervous system and enhances future signal transmission. AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; NMDA, *N*-methyl-D-aspartate.