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A new paradigm for pain?

A new way of thinking about pain that occurs in the absence of a pathophysiologic process or injury may alter our approach to conditions like fibromyalgia.

The care of people with pain has been wrought with ineffective and unnecessary treatment, including the misuse of opioids, largely because we do not have an accurate conceptualization of pain. The absence of animal and human models of central nervous system (CNS) pain processing ensures that our understanding of pain will remain incomplete for the foreseeable future, but enough evidence exists to help family physicians develop an understanding of pain that goes beyond what we learned in medical school and that can help us more effectively treat patients with pain.

In this review, we will briefly discuss the established concepts of nociceptive and neuropathic pain. And then, with those concepts in mind, we will explore a third type of pain that for lack of a better term, we will call “pain for psychological reasons.” We hypothesize that this pain may be the consequence of changes in nervous system function that arise from developmental trauma, other traumatic experiences in a patient’s life, or mental health disorders. It is this third type of pain that may offer us insights into conditions such as fibromyalgia.

While we do not yet have validated diagnostic criteria for this third type of pain, we believe that there is enough information to present initial criteria so that one may distinguish it from nociceptive and neuropathic pain.

Nociceptive and neuropathic pain:

The current paradigm

Nociceptive pain. The sensory pain experience, or nociceptive pain, is produced by noxious stimuli that either damage, or are

capable of damaging, tissues (eg, burns, cuts, fractures, inflammation, and increased pressure in a hollow viscus). Noxious stimuli are detected at the molecular level by specific pain sensory receptors embedded in our tissues called nociceptors.

The process by which noxious stimuli lead to the experience of sensory pain consists of 4 steps—transduction, transmission, modulation, and perception—which are described in “From periphery to brain: The process of nociceptive pain,”¹⁻⁴ on page 600.

■ **Neuropathic pain.** While nociceptive pain can be easily traced from a peripheral nociceptive fiber to the brain and typically resolves when the nociceptive stimulus stops, neuropathic pain (NPP) results from changes to the function of the nervous system and is typically caused by injury to the nerves. Such changes, referred to as neuronal sensitization, may not quickly resolve, as is the case with postherpetic neuralgia. In fact, the changes can become permanent. NPP fundamentally differs from nociceptive pain because it results from changes in the central processing of pain that can lead a person to perceive pain sensations even in the absence of tissue pathology.

Common causes of NPP that persists even after tissue damage has healed include trauma (eg, amputation of a limb), ischemia (eg, pressure palsy), disease (eg, the metabolic injury of diabetes or the injury caused by a shingles infection), and drug treatment (eg, chemotherapy). The underlying mechanisms of NPP and the neuronal plasticity (the ability of the nervous system to rewire itself)



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that initiate and then maintain NPP are important areas of active research that may eventually lead to the development of more effective treatments.

■ **Timing is critical.** Neuroplastic changes in the nervous system following nerve injury are time-dependent. Synaptic plasticity can occur within seconds to minutes, while cellular plasticity occurs within hours to days. Synaptic and cellular plasticity happen relatively fast and may be reversible.

In contrast, systems plasticity (when new CNS neuronal connections are formed in response to nerve injury) takes place over the months and years following nerve injury and is often irreversible. When we recognize NPP and intervene before system neuroplastic changes occur, it may be possible to prevent pain from becoming chronic (TABLE 1³). In cases of nerve injury, researchers have long suspected that early and aggressive pain treatment within the first few months that may include sympathetic and peripheral neural blockade reduces the likelihood that the patient will have chronic pain.^{6,7}

From this discussion, one can understand why pharmacotherapeutic agents such as antiepileptic drugs and some antidepressants

are effective for treating the changes in nervous system pain processing that cause NPP, and why nerve blocks and neural stimulation—treatments that alter peripheral and central pain processing—might be effective for neuropathic but not acute or chronic nociceptive pain.

It's time to update our understanding of pain

The International Association for the Study of Pain (IASP)—a group of health care providers, scientists, and policymakers seeking to improve pain relief worldwide—notes in its definition of pain that the complaint, “I hurt” does not necessarily imply that there is a painful stimulus in the form of tissue injury.⁸ Yet most of us have been taught to think of pain solely as the result of tissue pathology, and we assume that emotional factors merely modify how the physical damage is perceived. This traditional concept of pain is incomplete. It leads clinicians to misdiagnose the cause of pain, initiate expensive and unnecessary treatment, engage in well-meaning but misguided prescribing behavior, and miss opportunities to help patients.

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For more on pain care in primary care, see **“When to consider an interventional approach to pain management,”** the first video in a new *JFP* series that is available at: <http://ow.ly/tihZ303mQHP>.

From periphery to brain: The process of nociceptive pain¹⁻⁴

The process by which noxious stimuli lead to the experience of sensory pain consists of 4 steps:

In **transduction**, nociceptors containing special molecular proteins respond to noxious modalities, such as thermal, mechanical, or chemical stimuli, and trigger nerve impulses in the nociceptive nerve fibers (nerves dedicated to pain sensation).

During **transmission**—the second stage of the process—information from the nociceptors in the periphery (skin, muscle, viscera) is relayed to the spinal cord mainly by 2 types of nociceptive neurons: C-fibers and A delta (A δ) fibers. Both approach the spinal cord in a peripheral nerve and then enter the spinal cord in the dorsal root entry zone. Because A δ fibers are thinly myelinated, they send impulses faster than unmyelinated C fibers. This is why when injury occurs, we first feel sharp, acute pain that then slowly diffuses into a duller ache.

Once the incoming signal is transmitted to the CNS at the spinal cord, primary afferent neurons synapse on second order neurons. From there, information travels on to the thalamus via multiple neurons that have the capacity to change their response patterns when activity of nociceptive fibers is sustained (as occurs in the setting of a tissue or nerve injury and perhaps in the setting of psychological trauma). This is known as **modulation** of the incoming nociceptive stimulus. During this step of the process, stimuli can be amplified, suppressed, or even transformed from one type to another (eg, a light touch can be modulated in such a way that it will be perceived as a burning sensation). Also, it is this step that is affected by many medications, by intrathecal drug infusions, and by spinal neurostimulators.

In **perception**, the thalamus then directs the pain sensation to multiple brain centers. At this step, the stimulus is finally consciously perceived as pain by the individual.

Cortical pain circuits can be activated without physical input (ie, no tissue damage, noxious stimuli, or nerve injury). This becomes important in understanding pain syndromes, such as fibromyalgia.

Pain in the absence of any pathophysiologic cause or injury

The clinician's search for a pain diagnosis is typically predicated on the notion that there must be an underlying tissue injury of severity equal to the severity of the patient's pain complaints. This approach to a pain evaluation rests on 2 assumptions that are not true for all patients:

1. Pain is simply a sensory experience that is always caused by tissue damage of some type.
2. The severity of the pain experienced by a patient should be tightly bound

to the severity of the pain stimulus (ie, tissue damage).

These assumptions are true of acute nociceptive pain, they may or may not be true for NPP, but they do not apply to the third type of pain—pain for psychological reasons. While tissue pathology in humans and animals with nociceptive pain is usually visible, measurable, and correlates with observed pain behaviors, the damage to nerve tissue and the ensuing changes in nervous system function with NPP are not always visible or able to be imaged. These changes produce pain that can appear more severe than expected based on a brief exam. Some of the time, however, characteristic symptoms and physical signs of NPP will be present, and perhaps electrodiagnostic or other tests will be abnormal, thus providing some objective sense of changes in nervous system function.

In contrast, pain behavior due to the third type of pain usually appears very much out of proportion, and unbound to, tissue pathology. Furthermore, the patient's pain behaviors often reflect heightened emotional pain processing (TABLE 2⁹). The resulting emotionally charged presentation can be alarming and suggestive of extreme tissue injury, but there may be absolutely no evidence of tissue injury or pathology.

Functional change in the CNS

There is evidence from experimental studies that psychologic factors change nervous system function. In one review, the authors concluded, "Pain...can vary widely between people and even within an individual depending on...the psychological state of the person."¹⁰ In a second review, the authors concluded that our emotional state has an enormous influence on pain; a negative emotional state increases pain, whereas a positive state lowers pain.¹¹

But can psychological factors induce long-term changes in nervous system function analogous to the systems neuroplasticity responsible for irreversible changes in NPP? And can psychologically induced changes in nervous system sensory processing lead to pain without any tissue or nerve damage?

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Brain activity in response to emotional insult mimics physical pain, and it is difficult to tell from images of brain activity whether a person is experiencing one or the other.

TABLE 1

Early signs and symptoms of neuropathic pain⁵

If at least one sign and one symptom are present together, suspect neuropathic pain.

Symptoms

- Pain in an extremity, portion of the trunk, or head/face that is out of proportion to any apparent injury
- Non-dermatomal distribution of pain
- Burning sensation in the painful area
- Skin sensitivity to normally non-painful stimuli, such as light touch (bedclothes) or even air conditioning in and around the painful area
- Numbness or tingling in the painful area
- Edema, skin color change, and temperature change in the affected area

Signs

- Loss of light touch or pinprick skin sensation in the painful area
- Hypersensitivity to light touch, cold, or pinprick sensation in the painful area
- Signs of autonomic instability, such as an affected limb that is cooler or warmer than the contralateral normal side; edema in the painful area

We theorize that a functional change in the CNS can occur in response to certain emotional states or traumatic experiences (eg, child abuse, assault, accidents). (More on this in a bit.) When such changes occur, mildly painful stimuli are amplified and processed through overly sensitized, dysregulated, ramped-up emotional and somatosensory pain circuits in the brain. This is analogous to the functional changes in the nervous system that occur with NPP; however, when the nervous system changes are due to psychological factors, there may be no tissue or nerve injury.

■ **Childhood trauma influences adult pain.** One of the more compelling narratives emerging in health care has to do with the influence that childhood developmental trauma can have on health, including pain. In his chapter on the impact of early life trauma on health and disease, Lanius states:¹²

“Women were 50% more likely than men

TABLE 2

When to suspect ramped-up emotional pain processing⁹

- Patient reports disability that seems out of proportion to physical pathology.
- Pain behaviors seem out of proportion to the physical pathology (eg, grimacing, groaning, crying out with light palpation, protected movement).
- Patient uses emotionally charged language to describe the pain. (Patient says, “I cry in pain.”)
- Patient uses emotionally charged pain descriptors such as “sickening,” “fearful,” and especially “punishing” or “cruel.” (For more examples, see the Short-Form McGill Pain Questionnaire available at: <https://www.esahq.org/~media/ESA/Files/ClinicalTrial-Network/PLATA/Docs/04A%20Appendix4A-PLATAManuscript%20sfMGPQ%20v10%2025FEB2013.ashx>.)
- The patient complains of diffuse pain without evidence of a systemic cause.
- The patient describes multiple (and often vague) non-painful somatic complaints across several systems that often include irritable bowel and vague neurologic symptoms.

to have experienced 5 or more categories of adverse childhood experiences. We believe that here is a key to what in mainstream epidemiology appears as women’s natural proneness to ill-defined health problems like fibromyalgia, chronic fatigue syndrome, obesity, irritable bowel syndrome, and chronic non-malignant pain syndromes. In light of our findings, we now see these as medical constructs, artifacts resulting from medical blindness to social realities and ignorance of the impact of gender.”

Lanius¹² suggests that adverse childhood experiences¹³ (trauma such as abuse and sexual assault) can lead to long-term changes within the nervous system, including areas of pain processing. My coauthor and I describe these changes here in terms of nervous system sensitization or dysregulation, and we believe that these changes lead to a bias toward hyperactivation of emotional pain circuits, which leads to the emotionally laden

pain behaviors that often seem out of proportion to tissue pathology.

A look at the research

In determining whether a person experiences real pain in the complete absence of physical injury, consider the following research study by Kross et al:¹⁴

Forty patients who had recently endured a breakup of an important relationship underwent functional magnetic resonance imaging (fMRI) during the following 4 tasks:

1. While viewing a headshot of their former partner, they were asked to recall and think about the person who had rejected them.
2. They viewed a headshot of a same-sex friend while they thought about a recent positive experience they had with that person.
3. They experienced noxious thermal stimulation on their left arm using a hot heating pad.
4. They experienced non-noxious thermal stimulation in the same area using a warm heating pad.

The authors found that when the participants thought about being rejected, areas of the brain that support the sensory components of physical pain (the secondary somatosensory cortex and the dorsal posterior insula) became active.

Although the study had numerous limitations, the authors concluded that significant social rejection and physical pain are similar not only in that they are both distressing, but they both activate the same somatosensory brain circuits.¹⁴ In other words, brain activity in response to emotional insult mimics physical pain, and it is difficult to tell from images of brain activity whether a person is experiencing one or the other. The study authors noted that other research in their field has shown that intense emotion is insufficient to activate pain pathways, but that activation requires specific feelings, such as those that arise from social rejection.

■ **Our suspicions.** There is already evidence that adult trauma leads to changes in pain processing,^{15,16} and there is prelimi-

Case study: Were psychological factors driving these symptoms?

Judith B, a 34-year-old single mother of 2, presents to the office after 2 years of fruitless medical, rheumatologic, and neurologic work-ups for diffuse muscle pain, headaches, fatigue, and difficulty falling asleep after a motor vehicle accident (MVA) in which her injuries were not severe. She reports that sleep is difficult "because I cannot shut my mind off."

Before the accident, she was healthy and working full-time, but now she is thinking about applying for disability because she believes she cannot continue teaching grade school given the severity of her lingering post-accident symptoms. A previous physician prescribed immediate-release oxycodone 5 mg QID and carisoprodol 350 mg tid, which has provided little improvement in function. Her physical exam is relatively unremarkable although she is clearly distressed and moving slowly, with diffuse soft tissue tenderness. A brief psychosocial screening demonstrates an adverse childhood experience score of 3 with a "Yes" to question 3 (sexual abuse) and a high score on the Generalized Anxiety Disorder 7-Item Scale (14 out of 21), indicating significant anxiety.

Given our findings, we referred the patient to a psychologist for a complete psychologic evaluation, explaining that we were looking for answers to the question: "To what degree do psychosocial factors drive this patient's physical complaints?" The psychologist reported that she believed that psychological factors were the main driver of her symptoms, with childhood trauma "reactivated" by the trauma of the MVA.

The patient was initially suspicious that we were simply going to tell her that her symptoms were "all in her head," but the following explanation helped her to understand where we were going with therapy: "Imagine that your muscles are trying to have a conversation with your brain, and your nervous system is the phone line. The phone line is full of static and is distorting the message, so we need to work on the communication system."

Three months of a multi-pronged approach led to improvement in the patient's sleep and fatigue. This approach included cognitive behavioral therapy and somatic experiencing (a method designed to normalize the nervous system changes induced by adverse childhood or adult experiences without requiring patients to recall or think about those events). These efforts were supported by titration of sertraline to 150 mg/day (trials of duloxetine and venlafaxine caused too many adverse effects) and acupuncture. Ms. B returned to teaching and fulfilling relationships with her fiancé and children. She was able to stop the oxycodone and carisoprodol after 2 months of the sertraline and several sessions of somatic experiencing, and she remains pain-free.

Author's note: *This case exemplifies so many of the patients we, as clinicians, see in daily practice and highlights the necessity of vigorously pursuing research in the area of pain due to psychological reasons. This is particularly true when considered in the context of the magnitude of disability due to chronic pain and of pain treatment failures, which have contributed to the current prescription opioid crisis.*

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Reassure patients that the pain is not in their head, but rather in their nervous system.

nary evidence that adverse childhood events change pain processing.¹⁷ We believe that future research will continue to cement a connection between adverse childhood events and changes in pain processing that lead pain pathways, particularly the emotional pain circuits, to be active even in the absence of noxious nociceptive stimuli (ie, in the absence of tissue injury).

We also believe that we must broaden our definition of pain since Kross et al's research demonstrates through objective means that it is possible for a person to feel real pain in response to purely psychological factors that have sensitized the nervous system over weeks and months, in the absence of tissue injury.¹⁴ Perhaps this will explain what is happening with some of our patients who complain of pain "all over" and who are often classified as having fibromyalgia. In addition, we propose that much of the frustration with treating chronic pain over the past 40 years and the failures of physical therapy, various procedures, pharmacotherapy, and surgery occurred because we treated patients with sensitized nervous systems as if they had nociceptive pain due to tissue injury.

Implications for primary care

In our estimation, an evaluation of pain must be based on awareness of the signs and symptoms of all 3 mechanisms of pain perception: nociceptive tissue pathology, nerve injury that alters nervous system processing of sensory stimuli, and/or psychological injury that alters nervous system sensory processing. This approach opens up a whole new menu of treatment options and helps to demystify patients whom we previously regarded as difficult to understand and treat. No longer should we be stumped when we cannot find a traditional cause for pain (ie, tissue injury).

When screening in the primary care clinic reveals signs and symptoms of the third type of pain, the next step should be to look for the presence of psychologically traumatic experiences. Assessments of anxiety, depression, and developmental trauma¹³ should be added to the patient assessment. If pain due to psy-

chological factors is identified, consider:

- counseling
- cognitive behavioral therapy
- therapies such as eye movement desensitization reprocessing and somatic experiencing, both of which are already used to alleviate the stress associated with posttraumatic stress disorder
- pharmacotherapy with a serotonin-norepinephrine reuptake inhibitor (SNRI), such as duloxetine or venlafaxine
- hypnotherapy.

■ **Reassurance goes a long way.** Above all, when you are caring for someone who has pain without clear tissue pathology or who has recognized intensified emotional pain processing, reassure the person that the pain experience is not in his or her head, but rather in his or her nervous system. (See "Case study: Were psychological factors driving these symptoms?" on page 603.)

You can explain that research suggests that emotional, cognitive, or developmental factors may have affected the way his or her nervous system processes sensory information. Such discussions go a long way toward helping patients understand their experience, as well as feel validated. And that can lead to improved compliance with therapy going forward. **JFP**

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