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Anatomy And Neurobiology Of Pain

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Chapter 2: Anatomy and Neurobiology of Pain
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"Champagne for my real friends, and real pain for my sham friends."
~~Tom Waits

This chapter examines some of the basic human anatomy and neurobiology related to the perception of pain. In this context we will discuss how the nervous, endocrine, and musculoskeletal/fascial systems all contribute to our experience of this important sensation. We will look at some of the pathologic changes that occur when short-term pain becomes a long-term problem, and how stress can exacerbate pain perception. Finally, we will discuss how manual therapies may access peripheral nervous system structures in order to address some of the factors that can contribute to chronic pain patterns.

<h1>What is pain?
The concept of pain has many definitions, but for the purposes of this chapter, this one is a good fit:

> *Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.* (Merskey et al., 2012)

This description introduces several important points. First is the term "unpleasant:" who decides if an experience is unpleasant? Only the person experiencing it can make this judgment. Pain is a completely subjective phenomenon. (Coghill, 2010) While we can empathize with another person's pain, it is not possible to feel or interpret it in comparison to any other person's experience.

Also, according to this definition, pain has both sensory and emotional components. The interconnectedness of our emotional state to our physical state cannot be overemphasized. For many people whose pain is long-lasting, these two aspects of experience become inextricably entangled, to the extent that physical pain often cannot be successfully treated without addressing emotional pain, and vice versa. (Deligianni et al., 2010)

Finally, pain may occur in association with actual or potential damage. The perception of pain may occur with anticipation alone, separate from that caused by tissue damage. All of these ideas figure prominently in this chapter, but we will

begin with pain that begins from an environmental, rather than an emotional trigger.

<h1>Pain as Part of the Sensory System

The great art in life is sensation, to feel that we exist, even in pain.

~~Lord Byron

Pain serves a vital function to healthy people: it lets us know when we are at risk for injury. If we lose this function, then ordinary normal interactions with our environment can quickly lead to tissue damage. Imagine not knowing that the oven rack is hot, that you have a blister on your toe, or that you broke a bone. The threat of invading infection and challenging complications is significant, which is why we need an effective reaction to this type of stimulus (see sidebar, "Numbness is Dangerous").

<Sidebar> Numbness is Dangerous

Leprosy, nowadays known as Hansen's disease, is a collection of bacterial infections of nerve endings in the skin and mucous membranes where the temperature is relatively low. Unlike other nerve infections, Hansen's disease leads to dangerous numbness rather than pain. The result is a gradual atrophy of healthy skin and small muscles, accrual of minor injuries, and tissue-destroying secondary infections coupled with poor healing. These accumulate to the point that extremities like fingers, toes, ears and the nose appear to simply "fall off."

</Sidebar>

At its most elemental, pain is simply a signal of real or potential damage. It is often classified by the source of that damage. Examples include mechanical injury (caused by impact, pressure, or swelling); temperature-related injury (for instance, frostbite or burns that can range from a mild sunburn to extreme of 3rd degree charring); or chemical injuries (various toxins, infection, or ischemia).

Pain is often multifactorial: it is rarely only one type of damage that creates this perception.

Many of us learned in elementary school that we have five senses: seeing, hearing, smelling, tasting, and touch. Vision, hearing, taste, and smell are called special senses because their receptors are located in isolated, specialized areas. But the

sensation of touch is called a general sense because our touch receptors are located all over the body, in our skin, connective tissue, and internal organs. For more on the general senses of heat and cold, see sidebar.

In fact, the term "touch" covers several distinct senses, including light and deep pressure, texture, hot, cold, and pain. Each of these sensations has a dedicated type of receptor neuron.

<Sidebar> Fun Facts About Food and Sensation
Imagine eating a minty breath freshener. Now imagine taking a sip of water—even warm water. Feels colder than usual, right? The reason for this is that menthol in mint hyper-sensitizes our receptors to cold, so everything feels colder.

The opposite is true of capsaicin, the substance that puts the "heat" in hot peppers: it hyper-sensitizes our receptors to heat, so that everything, even the cold beer that you gulped after your 5-Alarm chili verde, feels hot.
</Sidebar>

It is critically important to understand the definitions of the language used in the study of pain. These definitions are regularly updated by groups of scientists and clinicians and published by the International Association for the Study of Pain. For our discussion, the most important definitions are those of pain and nociception.

- *Pain*, a sensation that integrates multiple pathways of nerve transmission, has been defined above.
- *Nociception* describes the neural processes of encoding and managing noxious, or potentially painful stimuli.

Not all pain requires nociception, and not all nociception leads to pain. Nociceptors are sensory neurons in the peripheral or central nervous system (CNS) that carry signals. Nociceptors convert, or transduce, various stimuli (energy forms), such as might occur from a cut or other injury, into electrical impulses that communicate with the CNS, where we interpret the information. No single chain of neurons leads to the perception of pain; it takes many neurons in multiple pathways to create this awareness.

By contrast, nociceptor discharge, or nociception, happens regardless of whether we interpret pain as the outcome of the nerve transmission. It can be measured directly by recording from the neuron, even if the neuron is disconnected from the body.

Once a noxious stimulus begins, the signals travel through complex pathways within the CNS. Signals can be amplified or suppressed in several places along the way. The details of these pathways and interactions are far beyond the scope of this chapter. We will focus on the part of the system with which we most often directly interact: the nociceptors of the peripheral nervous system.

<h1>Pain Pathways: from Outside to Inside

The process of turning an environmental trigger into pain perception takes several discrete steps.

<h2>Transduction

The first step, transduction, occurs when nociceptors are activated by a trigger, like pressure, high or low temperature, or chemical irritation. The stimulus is converted into an action potential by specialized receptor channels in the cell membrane. It is important to remember that activated nociceptors also simultaneously secrete pro-inflammatory chemicals, which helps to sustain the inflammatory response at the site of injury.

<h2>Transmission

After transduction, the axon transmits the message from the body to the spinal cord's dorsal horn through the dorsal root. Here the axon branches to multiple segments and to multiple levels. If the input is sufficient to propagate at this level, it crosses to the contralateral side of the spinal cord and travels to the thalamus. (See Figure 2.1)

<Insert Figure 2.1 approximately here>

<h2>Perception

The thalamus, which functions somewhat like an old-fashioned switchboard, transmits incoming signals to the appropriate cerebral cortical centers for consciousness and interpretation. Unlike our other senses, we have no specific area in the brain to receive information about pain or tissue damage. Instead, the thalamus sends these messages toward the reticular center for autonomic motor responses; the somatosensory cortex for interpretation, evaluation and memory; and the limbic system: the source of our emotional and behavioral responses.

<h2>Modulation

While the major part of messages in sensation travel from the peripheral nervous system up to the brain, at each step of the way the transmission can be either amplified or depressed, by activity in descending pathways. These interactions are

all neurochemical; excitatory neurotransmitters make our pain sensation more intense, while inhibitory neurotransmitters act as organic analgesia, subduing our perception of pain. (For more on organic analgesics, see sidebar, Fun Facts About Neuromodulation) All of this happens below levels of consciousness, even before we may become conscious of ongoing pain signals.

<Sidebar> Fun Facts About Neuromodulation

It is no surprise that opium and marijuana are such popular drugs. Our bodies produce very powerful versions of both, and both can have profound suppressing influences on pain.

Opium poppies secrete morphine in their "milk," the base for heroin, morphine, and codeine. Oxycodone and similar drugs are synthesized versions of the same chemicals. Endorphins are endogenous opiates, and they all inhibit critical pain pathways.

The active ingredient in marijuana is a *cannabinoid.* We produce anandamide, (based on a Sanskrit word for bliss), and many other cannabinoids. While these affect many systems, in relation to pain, these chemicals are powerful pain suppressants. Acetaminophen works in the cannabinoid pathways as well.
</Sidebar>

Understanding the steps in the transmission of signals that are eventually interpreted and consciously perceived as pain provides important treatment strategies, because different types of analgesics act at different sites in the transmission process. Over-the-counter anti-inflammatories, for instance, act at the tissue level by working to reduce the mechanical pressure and chemical irritation that may trigger pain signals at the site of an injury. Anti-seizure drugs, by contrast, are powerful pain modulators because they suppress the secretion of excitatory neurotransmitters in the central nervous system. Antidepressants are sometimes used as pain treatments because they do exactly the opposite: they promote the secretion and uptake of inhibitory neurotransmitters, which leads to the same result: the reduced perception of pain.

Pain is sometimes called the "fifth vital sign" because a patient's report of pain must inform the priorities for his or her treatment. This is a complicated issue, however, because when a patient reports acute or severe pain, treatment is often limited to opioid drugs, which is fraught with problematic side effects and undesired consequences, (Morone et al., 2013) and have little effect on the primary afferent nociceptor. That said, the experience of being in pain gives rise to several stress-

related reactions that can increase the risk of serious health problems. Increased potential for blood clots, hypertension, and insomnia (which deprives us of sleep, our best opportunity for tissue repair) comprise a short list of the consequences of long-term pain. All of this points to a need to develop more and better strategies for dealing with pain in acute and chronic settings.

<h1>Nociceptors: Pain Signal Initiators

Nociceptors are the first sensors in the pathways to pain. The neuronal cell bodies are located in the dorsal root ganglia, which lay in the intervertebral foramina. The cell bodies extend one axon, which splits into two branches before leaving the ganglion. One branch goes to the spinal cord through the dorsal root, and the other one extends to the peripheral structures through the spinal nerve. Nociceptors innervate almost every structure and tissue type in the body (exceptions include the nucleus pulposis of intervertebral discs and hyaline cartilage). (See Figure 2.2)

When nociceptors reach their target, they branch into numerous very fine processes, and are called "nerve endings." Unlike other sensory neurons, nociceptor processes have no obvious capsule or structure around them, so they are often referred to as "free" nerve endings. However, nociceptors are not nerves, they are single neurons. Further, functionally these are not endings; they are beginnings, in that the impulses begin here. Nociceptor processes are sensitive specifically to the types of stimuli that lead to the brain's interpretation of pain. In the skin, these include mechanical, thermal, and chemical triggers. In the deeper structures, the nociceptors respond to these stimuli as well, but thermal stimuli may be less important, as the body keeps internal temperature relatively constant.

Nociceptors that supply the skin look like a spray of flowers; these define the "receptive field" for the individual neuron. Receptive fields are usually relatively small, but can be discontinuous, and may or may not overlap with other neurons' receptive fields. In fact, the skin has some areas that are not innervated at all, where a needle can pierce without pain.

The receptive fields of the skin are relatively well established, but we know less about the receptive fields of muscle and other deep nociceptors. It is clear that they can be larger, and involve multiple tissue types (Bove and Light, 1995). This means that a nociceptor innervating a muscle might also innervate the tendon associated with that muscle, and also the nerve sheath in which it is encased (see Figure 2.2). This may explain the generally poor spatial localization of pain from deep structures compared to that of skin.

<Insert Figure 2.2 approximately here>

<h2>Types of Nociceptors

The nomenclature that scientists currently use to describe nociceptors is a bit clumsy. The distinctions between types of nociceptors are described here for completeness, but are by no means critical to the understanding of pain anatomy. However, these terms frequently appear in the literature, so it can be helpful to have a basic idea of their characteristics.

- C-fibers
  Afferent or sensory axons within a peripheral nerve are various sizes (See Figure 2.3). The smallest diameter axons, C-fibers, are about 1-2 μ diameter, they are unmyelinated, and they conduct action potentials very slowly (under 2.5 m/sec). These are typically associated with nociceptor function, although not all C-fiber axons are nociceptive. In skin, nociceptors with C-fiber axons are called C-nociceptors. In muscle and other deep structures, nociceptors with C-fiber axons are called Group IV nociceptors.

- A-delta nociceptors
  A-delta axons are slightly larger than C-fibers. These axons have a thin myelin sheath, and conduct action potentials at 2.5 – 10 m/sec. In skin, nociceptors with A-delta axons are called A-delta nociceptors, while in muscle and other tissues they are called Group III nociceptors.

The sensations associated with A-delta fiber stimuli are highly localized, and often described as “sharp,” “stinging,” or “pricking.” C-fibers, by contrast, are slow conductors, and several different types of stimuli can trigger them. Mechanical distortion, thermal injury, and chemical irritations can all activate C-fibers, hence the common term “polymodal nociceptor.” Descriptors of C-fiber related pain include “diffuse,” “dull,” and “aching;” these also reflect the slower nature of C-fiber stimulation.

<Insert Figure 2.3 approximately here>

<h2>Nociceptor activation

When an event such as pressure, thermal injury, or chemical imbalance causes tissue damage, a flood of pro-inflammatory substance is released into the local tissues (See Figure 2.4). Prostaglandin behaves like a localized hormone, promoting

pain sensitivity and vasodilation; bradykinin, serotonin, potassium and histamine all prolong and reinforce the inflammatory response. When these chemicals activate nociceptors, they release two substances that are key to inflammation. Calcitonin gene related peptide (CGRP) causes blood vessels to dilate, and Substance P (SP) causes the fenestrations in the blood vessels to open. This allows immune cells to cross from the blood to the extracellular matrix to do their job of cleaning up the damage. This essential endocrine function of nociceptors is referred to as neurogenic inflammation, and occurs whenever nociceptors are activated.

The need for nociceptors in acute pain is not controversial, but their involvement in chronic pain is hotly debated. All pain scientists recognize that pain can exist without any peripheral input. However, data are accumulating that even in the most reticent chronic pain cases, a source of peripheral nociception often maintains the centrally mediated pain processes (Gracely et al., 1992, Staud, 2011). This means that a client who has long-term pain related to central nervous system hypersensitivity probably also has some external sources of irritation that contribute to the problem. This is good news, because if a manual therapist can identify and help to resolve those external irritants, then at least some contributors to the pain cycle can be interrupted.

<Insert Figure 2.4 approximately here>

<h1>Good Pain, Bad Pain
While the experience of pain is not something we generally look forward to, pain processes can be highly useful, or dangerously dysfunctional.

<h2>Nociceptive Pain
The most highly functional form of pain is sometimes called *nociceptive pain*, referring to the perception of something noxious. This is a normal, healthy process: a signal of tissue damage is modulated by inflammatory responses, including the secretion of pro-inflammatory chemicals at the site of injury. These chemicals tend to reinforce and prolong the pain messages. Pain helps us make appropriate accommodations to limit further damage: we limp, taking pressure off our sprained ankle, or we avoid re-injuring our hurt finger by using other fingers instead. As the tissue heals, inflammatory chemicals subside, and pain sensation diminishes.

<h2>Ectopic Nociceptive Pain
Under normal circumstances, axons are not sensitive to normally encountered stimuli along the length of the fiber; they only pick up messages at their “flower

spray" end points. This is good, because it provides spatial specificity for the sensation: we need to be able to tell exactly where a signal comes from. This is easily demonstrated: If you pinch your little finger on the palmar side, you will feel the nociception as coming from the pinched spot. However, if you press moderately hard on the ulnar nerve as it passes behind your ulnar medial epicondyle, you should not feel any sensation into your fingers, even though you are pressing on the axons that were carrying the previous message of "pinch." That said, we have all banged our "funny bone" and felt pain and tingling in our fingers, through mid-axonal activation of the ulnar nerve. Although the axons are being activated in their middle, the impulses going to the CNS are perceived as coming from the fingers (See Figure 2.5). This activation of the axons is *ectopic*, meaning that our interpretation of the source of pain is in the wrong place, like an ectopic pregnancy, which may occur in a uterine tube rather than in the uterus.

<Insert Figure 2.5 approximately here>

Ectopic nociceptive pain is a term coined by Geoffrey Bove and David Seaman (Bove and Seaman, 2010), based on observations of the effects of inflammation of nociceptor axons. As axons wind through nerves and between various structures, they can be exposed to inflammation when they pass through an injured or damaged area. For instance, a deep bruise of the posterior thigh can affect the sciatic nerve and create symptoms that seem to come from the leg, or a constricted carpal tunnel may compress the median nerve, causing pain that appears to come from the hand. The nerve, which may be otherwise normal, then becomes an "innocent bystander" of the local inflammation. (See sidebar, Inflamed Axons and Cutaneous vs. Deep Pain)

<sidebar>
Inflamed Axons and Cutaneous vs. Deep Pain
Inflammation alone does not damage axons. Inflammation has been found to evoke sensitivity only from nociceptor axons that go to deep structures (Bove et al., 2003). When inflamed, deep nociceptor axons display sensitivity to mechanical and chemical stimuli. Nociceptors to the skin do not show these sensitivities. This is a critical difference between the innervation of the skin and that of other structures. Think about it: how many of our clients in pain describe that pain as being just in their skin? Patients with radiculopathy (radiating or distal pain that is due to dorsal and/or ventral root pathology, including inflammation) do not usually report cutaneous pain (Bove et al., 2005).
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Using our previous example, if the ulnar nerve was inflamed, pressing on it could cause pain to be felt into the hand. This radiating pain would be appropriately called ectopic nociceptive pain. Likewise, leg pain from the sciatic nerve or hand pain from the median nerve is ectopic nociceptive pain. This phenomenon is the basis of positive nerve provocation tests, where the nerve is stressed along its length, but the symptoms are reported distal to the stimulus.

Inflamed axons can also generate action potentials without any other stimulus (Bove, 2009). This is called "ongoing activity", and it results in the sensation of pain at rest or with no identified trigger. But again, the site of action potential generation is not the site of symptom perception, so the whole situation can be very confusing. In this situation a thorough knowledge of nociception patterns allows manual therapists to untangle some of these confusing symptoms, and to get at the root of their clients' problems.

<h2>Nerve Trunk Pain

The term "nerve trunk" describes any large section of a peripheral nerve. When you palpated your ulnar nerve (a nerve trunk) at the medial elbow, you may have felt pain at that site. To feel something and be able to localize it, a receptor must be tuned to the stimulus and located appropriately. For nerve trunks, these receptors are called the nervi nervorum, or the "nerves on the nerves." Like other structures, nerves have their own sensory innervation, which includes nociceptors (Bove and Light, 1997). These nociceptors run within the connective tissue of the nerves and neurovascular bundle, and -- at least in rats -- branch and innervate relatively long stretches of the nerve. Clinical examination often identifies sections of nerves that are locally tender: this sensation is mediated by the nervi nervorum, and appropriately called nerve trunk pain.

<h2>Peripheral Nerve Damage

The word neuropathy refers to a lesion of part of the nervous system. In the peripheral nervous system (PNS), neuropathy refers to damage to the sensory cell bodies found in the DRG, and to sensory and motor axons within a peripheral nerve, including cranial nerves. The dorsal and ventral roots are usually considered parts of the PNS as well. In the CNS, neuropathy is used to describe damage to CNS structures such as the spinal cord and brain. We need to remember that the autonomic nervous system, consisting of the sympathetic and parasympathetic divisions, also sends axons to peripheral and cranial nerves, and contributes to pain

under certain circumstances. To remain in the scope of this chapter, we will limit our discussion to effects of damage to peripheral nerves.

Peripheral nerves can be damaged in numerous ways, including by trauma, infection, chemotherapy, radiation therapy, fascial entrapment, and pathologies such as degenerative disc disease. It is important to remember that not all nerve injuries are painful, and most heal with no lasting pain. Nerve injury symptoms indicate what types of axons have been damaged. That is, if motor axons are damaged in isolation, the denervated muscle will be paralyzed, but not painful. If the sensory axons are damaged in isolation, the denervated territory will be numb, but moveable. If the sympathetic axons within a peripheral nerve are damaged, symptoms can include decreased blood flow, goose bumps, and/or sweating in the denervated area.

When nociceptor axons within a peripheral nerve are damaged, they develop spurious activity, which can be perceived as pain. They regenerate rapidly, but while most peripheral nerve injuries heal well, in some cases the healing fails and the endings form a neuroma: a tangled mass of axons growing in a ball, or a sort of tumor, with no well-defined receptive field. If the injury was diffuse, and axons were damaged along a length of nerve, the result is often called a "neuroma in continuity." Injuries in which nerves are stretched, like brachial plexus injuries, often lead to neuroma in continuity, which can be devastating. Neuromas can develop and then remain hypersensitive to all kinds of stimuli, becoming a source of strong afferent discharge that causes a more intense, severe experience than most other sources of pain. The signals from damaged nociceptors seem particularly efficient at evoking central sensitization, a potentially serious phenomenon that contributes to neuropathic pain.

> *Neuropathic Pain: a description, not a diagnosis*
> Neuropathic pain is an abnormal sensation, usually caused by a lesion or disease of the somatosensory nervous system; that is, it is often caused by a type of neuropathy, as described above. It is critical to understand that "neuropathic pain" is a *clinical description* rather than a *diagnosis*. It is equally critical to understand that neuropathies do not necessarily cause neuropathic pain, and that neuropathic pain can exist in the absence of neuropathy. The effects of persistent nociceptive pain and ectopic nociceptive pain can include symptoms that qualify as neuropathic pain, but with no true neuropathy. This is why the definition has recently been amended to a clinical description, and is under constant revision as our knowledge base grows.

The complex of symptoms that we call neuropathic pain usually includes the presence of a peripheral generator or initiating trigger, though one cannot always be found. The term peripheral generator describes a source of intense nociceptor discharge. As has been pointed out, neuropathies are often a source of this discharge, but are not requisite.

Intense nociceptor discharge induces and maintains changes in the CNS, most of which have been studied in the dorsal horn of the spinal cord. These changes are currently referred to as central sensitization. It is the combination of the persistent afferent discharge and the effects of central sensitization that comprise neuropathic pain. The qualities of neuropathic pain can be different from other pain sensations. While the perception of typical tissue damage might be described as "dull," "sharp," "achy," or "throbbing," in the context of directly damaged nerve tissue patients often use adjectives like "burning," "electric," "tingling."

Neuropathic pain has several possible causes. For a list of common diagnoses associated with neuropathic pain, see sidebar, Common Descriptors and Diagnoses for Neuropathic Pain.

<sidebar> Common Descriptors and Diagnoses for Neuropathic Pain

- Diabetic neuropathy
- Postherpetic neuropathy
- Entrapment neuropathies (carpal tunnel syndrome, thoracic outlet syndrome, etc.)
- Nerve compression or infiltration by tumor
- Chemotherapy-induced peripheral neuropathy
- Post-radiation plexopathy
- Phantom limb pain
- Acute and chronic dymyelinating polyradiculopathy (e.g., Guillain-Barre syndrome)
- Alchoholic polyneuropathy
- Radiculopathy
- Complex regional pain syndrome
- HIV sensory neuropathy
- Nutritional deficiency neuropathies
- Toxic exposure neuropathies
- Tic douloureux (trigeminal neuralgia)

/sidebar

<h2>Altered Neural Processing, aka Central Sensitization

Central sensitization (CS) refers to a complex change in the CNS induced by abnormal peripheral activation. When painful, CS can be devastating. A perfect example is the too-frequent complication of adult herpes zoster infections (aka "shingles"), called post-herpetic neuralgia. The first appearance of the infection for most people is as a childhood bout with chickenpox, but the virus then goes into dormancy, usually residing in a dorsal root or trigeminal ganglion. Later in adulthood it may reactivate: after a prodromal period usually described as a tingling sensation, painful blisters form on the skin all along the dermatome of the affected nerve. It is thought that the infection causes the degeneration of the nociceptor terminals, causing spurious activation and pain. If the symptoms persist after the visible lesions heal, the condition is called post-herpetic neuralgia. The skin becomes hypersensitive to light touch, and even a slight breeze will cause excruciating pain. Patients often cannot wear clothes or have bed-sheets covering the affected area. These symptoms are not likely to be mediated by nociceptors; sensors that normally carry the sensation of light touch and temperature mediate them. So why do these neurons suddenly relay pain messages? And why can the changes persist, often for the lifetime of the patient?

Modified from Woolf CJ: Central sensitization: implications for the diagnosis and treatment of pain. Pain. 152:S2-15, 2011.

<Insert Figure 2.6 approximately here>

<h3>Hyperalgesia

Hyperalgesia is increased pain from a stimulus that normally provokes pain, and is a clinical term that does not imply a mechanism (Merskey and Bogduk, 2012). When damaged, nociceptors demonstrate increased sensitivity at their peripheral processes, and this effect can occur in the spinal cord as well. The nociceptors can secrete more neurotransmitter per action potential, and the corresponding spinal cord neuron can also become more responsive. Therefore, less nociceptor input will lead to stronger relaying of the information. Moreover, with persistent stimulation, nociceptors can grow more branches. This has the effect of extending the signal to more neurons. These changes serve to "turn up the volume" of pain.

<h3>Allodynia

More problematic even than increased reactivity to nociceptor activity is the strengthening of a pathway from the low threshold non-nociceptive receptors to the same dorsal horn neurons. This means that normally non-painful or innocuous stimuli such as warmth or light touch can lead to a sensation of pain, in a situation called allodynia. In other words, even very minor, subtle sensory signals create a perception of pain. These light touch neurons are capable of very high frequency discharge, which may account for the very intense nature of pain once this pathway had been established. (See Figure 2.6)

<h3>Neuroplasticity

When peripheral nociceptors enter the spinal cord, they branch to span multiple spinal segments, and they also reach multiple levels of the spinal cord. In response to injury, this branching pattern becomes more extensive. If the new branches reach more nociceptive-specific cells, the expected phenomenon would be an increased pain perception, or hyperalgesia. If the new branches reach more wide dynamic range cells, which respond to many types of input, the expected phenomena include the perception of pain when there was no noxious stimulus, or allodynia. These phenomena, combined with new CNS receptor sites, may account for the perception of an increased "volume" of pain following nerve injury.

<h3>Loss of Pain Filters

The problems carry on within the brain as well as in the spinal cord: in the presence of central sensitization, descending pain modulating pathways in the brain—those innate processes that act as organic analgesia by inhibiting our responses— may become dysfunctional. In other words, we can't filter out the pain sensation. The peripheral neurons become sensitized; the ascending tract becomes sensitized; the brain perceives pain out of proportion to the nature of the damage, and finally our ability to control our perception of pain with internal neurotransmitters is lost as well: we hurt more, because we hurt more.

The good news is that these changes may not be permanent in most people. Theoretically, if the peripheral generators are located and effectively treated, the changes in the CNS leading to neuropathic pain should, and do, revert. If interventions were never successful, all those who have had these injuries and hypersensitivities – which includes most people to some extent—would have chronic pain forever. After all, these phenomena occur without CNS damage; some

would even state that in central sensitization the CNS is behaving exactly as designed. But instead of facing a lifetime of debilitating pain, many people get better, and manual therapies are often listed among the most effective interventions for this population. (Nijs et al., 2010; Courteny, et al., 2011)
As with many other facets of pain, this topic is vigorously debated, and viewpoints continue to change with the publication of new research findings.

The diagnosis of *chronic regional pain syndrome* (CRPS) is given to individuals who have experienced some sort of nerve injury, but who develop a perplexing myriad of painful symptoms that endure long after the tissue seems healed. These vexing disorders were originally identified in gunshot wound patients from the American Civil War, in what may be the first documented cases of central sensitization. In this era it was called "causalgia," from the Greek "kausis," which means burning. This descriptor was derived from patients who talked about how even the gentlest of touch felt like "red hot file, rasping the skin." Since then, the name changed to reflex sympathetic dystrophy, and now to CRPS. Pain in CRPS seems completely out of proportion to the severity of any injury, and it impacted the wellbeing of the patients so that eventually their general health seriously declines. (American RSDHope, 2014) While CRPS begins with a neuropathy, it evolves to include painful central sensitization and autonomic changes, including edema, and/or abnormal trophic findings, such as abnormal fingernail or toenail growth, and keratinization of the skin. The etiology of these symptoms is largely unknown.

<h1>Responses to Pain
"We cannot be more sensitive to pleasure without being more sensitive to pain."
~~Alan Watts

Regardless of what the trigger might be, when we encounter a stimulus that causes pain, a limited number of things can happen. The fastest response to pain is a reflex action: a stimulus (a hot iron) encounters some skin. Rather than waiting for the scent of burning flesh to reach our nose, we are wired to withdraw from this dangerous and painful trigger. The stimulus activates nerve endings in the skin (transduction); the message is transmitted via sensory neurons to the dorsal root ganglia, and in the spinal cord neurons synapse with both the ascending tract, and with motor neurons at the same level. These transmit the instructions to contract the appropriate muscles in our hand and arm, and we pull away from the iron before much damage can accrue. This is an example of a relatively simple withdrawal reflex. Others can be much more complex with sensory input and motor

responses occurring at multiple levels, but all below our consciousness; we become aware of the stimulus and our responses after they have already taken place.

Pain sensations do not always create a withdrawal reflex. Tissue damage can develop without an initially dangerous trigger (think of a sunburn, for example, or overworking our muscles so that we're sore the next day), and in the best of these circumstances we experience functional nociceptive pain, which is simply the first step of going through a healthy healing process.

When the situation is long-term and frequently repeated, we may become vulnerable to more serious dysfunction and ultimately to painful central sensitization. Conditions ranging from fibromyalgia syndrome to migraine headaches to chronic pelvic pain syndrome for men and women have been described using this model.

What we have described here is a worst-case scenario by which an injury causes changes to nervous system structures, and because of those changes, the sensation of pain becomes self-perpetuating and chronic. The chronification of pain is a leading challenge in health care delivery, as our ability to intervene in these processes is limited at best.

<h1>The Body and the Mind are NOT Separate Entities

Fear is pain arising from the anticipation of evil

~~Aristotle

In our culture we place great value on the power of human cognition, sometimes at the expense of how we view the more primitive experience of sensation. Eighteenth Century philosophy Rene Descartes suggested that our ability to doubt our own existence is in fact proof that we exist; this is the origin of the "I think, therefore I am" philosophical argument (see sidebar, Descartes Joke). Notice that our existence is demonstrated by thinking, not by our perception of feeling. The saying is not, "I *sense*, therefore I am." This foundation for western philosophy and identification of consciousness (which has roots far deeper than Descartes) has given rise to an assumption that what happens in our brain is both separate and superior to what happens in our body.

<sidebar> Descartes Joke

One wet, stormy day in Paris a hungry Rene Descartes visited his favorite restaurant and very much enjoyed a bowl of cassoulet. He ate it to the very

dregs. When his server asked him if he would like some more, he paused for a moment and considered. “I think not,” he replied. And he disappeared.
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This is a false paradigm.

Our physical experiences of pleasure and pain, of hunger and satiety, of energy and fatigue, all have influence on our mood, our cognition, and our ability to function intellectually. Likewise, our emotional state drives many of our motor behaviors. Our posture is a reflection of our habits, and these are influenced by many emotional responses. To suggest that our body and our brains can somehow function separately or be valued differently is a mistake. One of the most important connectors in the loops between the brain and the body is the limbic system.

<h2>The Limbic System
The limbic system is a collection of structures deep in the brain that includes the hypothalamus, the hippocampus, and the amygdala. The hypothalamus, readers may recall, is essentially the mediator of many of our homeostatic processes. It does this in an immediate way through the autonomic nervous system, and in a slower, longer-lasting way through the endocrine system. The hippocampus is a structure mainly understood to assist in the formation of memories, and the amygdala is a center for the interpretation of emotion. (Weinberg and Krebs)

When the limbic system is activated, a response is translated through the motor fibers of the autonomic nervous system. When that reaction is triggered by a perceived threat, our stress response system is recruited.

<h2>Stress response systems: hormonal reactions
Through the limbic system we delineate between the need for two connected-but-distinct stress response loops. The SAM (sympathetic adrenal medulla) axis refers to the activation of the adrenal medulla and the secretion of catecholamines, epinephrine and norepinephrine: the hormones that regulate immediate, short-term, high-grade, *WE'RE ALL GONNA DIE NOW* stress. It has special impact on heart rate and respiratory rate: two mechanisms that help to determine our ability to fight or to run away. The HPA axis, by contrast, refers to the hypothalamus-pituitary-adrenal connection that leads to the secretion of cortisol from the adrenal cortex. This hormone helps us to mobilize our resources to respond to long-term, low-grade, *hold-on-grit-your-teeth-here-it-comes* stress.

<h2>Stress response systems: motor reactions

The limbic system also connects to the basal ganglia and cerebellum for the translation of a stress response into a behavioral response. (See sidebar, Emotional Body Language.) This can impact our breathing, our muscle tone, our posture, and the efficiency of movement (which, ironically, can influence our risk for injury and more pain). In the context of pain therefore, the limbic system determines our emotional and behavioral responses to a threatening situation. Through electrical and chemical messages it influences our mood, our attention and cognitive function, and our ability to take action—or not—on our own behalf.

<sidebar> Emotional Body Language
Our state of mind and emotion influences every nuance of our motor behavior, even if we don't pay attention. Emotional body language (EBL) refers to the motor expression of emotions, through posture, gestures, and facial expression. Humans innately respond to the EBL of others.
Much of this motor function relies on basal ganglia and the secretion of dopaminergic neurotransmitters. One of the distinguishing features of Parkinson's disease, in which parts of the basal ganglia fail and dopamine is not adequately available, is the "Parkinson's mask": a phenomenon in which a person's facial muscles become rigid and unable to convey expression or EBL. (Weinberg and Krebs) </sidebar>

Many of us live in an ongoing state of perceived threat, and this leads to pain-promoting behaviors like collapsed shoulders, teeth grinding, shallow breathing, and increased general muscle tension. In turn, the physical experience of being in this state can reinforce and prolong the long-term sense of threat or stress. In this way we can enter a particularly vicious circle of pain, stress, motor responses that cause pain, ad infinitum. Add the other stress-related responses that influence blood pressure, heart rate and immune system function, and it is not a stretch to track the relationship between pain, stress, and generalized disease.

<h1>Manual Therapies and Pain
To truly laugh, you must be able to take your pain, and play with it!
~~Charlie Chaplin

What can a manual therapist do in the context of pain? If this sensation is related to triggers that are mostly transmitted via the skin, don't we, even with the best intentions, simply risk exacerbating an already-bad situation?

Fortunately, usually not.

One way to think about debilitating pain is that it is cumulative: enough small things must be wrong to add up to one large, complicated thing. But if that is true, then some of those small things (peripheral generators) can possibly be undone. If some of the contributors to pain can be addressed, then the partnership between a manual therapist and a hurting client yields a virtuous circle: reduced pain leading to improved mood and function, leading to reduced pain-promoting behaviors, and even better function, ad nauseum. The finding that massage has generally positive effect in the context of many pain-experiencing populations (Gelinas et al, 2013; Abdulla et al, 2013; Somani et al., 2013) supports this hypothesis.

The challenge then becomes finding how to unlock the altered patterns.

> "Pain is not just a stimulus or a response, but both together. Hence successful pain practitioners need, oddly, to have a willingness to play in their work. We must guess at the primary drivers of pain…. This approach is greatly aided by a three-dimensional visualization of fascial planes as they relate to nerve trunks and interwoven branches as they transverse throughout the tissues of the body. At the same time, it's important to consider the manifold influence of the central nervous system, often conditioned by years of input. The brainstem, thalamus, limbic system must constantly question the therapist's friendliness, trying to ascertain how much protective stasis is warranted. The more we can convince central and peripheral nervous systems of our essential benevolence, the more the client becomes our ally in the hard-but-rewarding work of creating a pathway toward pain relief." (Michael Hamm, massage therapist)

Manual therapists have a unique role to play with our clients who live in pain: what other health care provider is in a position to offer such prolonged, undivided attention?

> "Pain can be terribly lonely and isolating. Most interventions, however sympathetic, just check in and check out: 'here's a pill, here's an exercise, here's a suggestion, maybe this will help?' But we manual therapists really

want to know: exactly how does it hurt, exactly where? Does this touch "reach" it, or that touch?

It's rare for a massage therapist to be able to fix pain altogether, which can be frustrating, but we can always, always at least recognize it: lay hands on it and be with it. Nobody else in the health care world really does that. When the pain alters mood, as it so often does, the fact that we are willing to be there and stay there with a patient can be profoundly moving and important." (Dale Favier, massage therapist)

The most important take-away ideas about central sensitization and chronic pain are these:

- The pain is common, real, and not imaginary.
- The pain was triggered by some event outside the CNS.
- The pain can be reversible—and manual therapy may help.

Chronic pain and central sensitization take an enormous toll on every affected individual, and on society as a whole with lost productivity and increased disability. Many conventional interventions are extremely expensive, risky (with highly addictive drugs) or invasive (with surgically implanted equipment to alter pain sensation), and many patients report being dissatisfied with these options. (Anderson, et al., 2012; Jouini et al., 2014) Unlike many conventional practitioners, manual therapists have the time and space to patiently and safely approach the body-and-brain as a unified whole, looking for ways to undo some of the contributing factors, and to create an oasis of safety in the midst of the perception unrelenting threat. We may not be able to unpin every tethered neuron, or to reset every hypersensitive synapse, but our contribution to solving the pain puzzle can be valuable and effective.

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