I. Nociceptors

A noxious stimulus is high intensity, may damage tissue, and may be life threatening if not terminated. 

Nociception is any process in the PNS or CNS associated with a noxious stimulus. Pain is the conscious experience associated with noxious stimuli. Since we are not conscious of PNS, spinal cord and much brainstem activity, it is incorrect to refer to nociceptive processing in the cord and brainstem as pain processing. Pain processing refers to the conscious experience of noxious stimulation and this occurs in the cerebral cortex, although an argument can be made for involvement of the thalamus in the conscious experience of noxious stimulation (pain).

Nociceptors are cutaneous and visceral receptors that respond to noxious and not innocuous stimuli. Mechanical nociceptors respond to crushing pressure (high threshold) and are surrounded by keratinocytes. Thermal nociceptors appear to be free nerve endings and respond optimally above 45°C or below 15°C.

Figure 1 shows responses of a single axon to different types of stimulation in its peripheral sensory receptive field. Only acute noxious mechanical stimuli activate it. Notice that the response habituates during the prolonged and high intensity squeezing.

Distinguish between Nociceptors and Innocuous Cutaneous Receptors

1. Receptive field size

Receptive fields of nociceptors are about an order of magnitude larger than those of other cutaneous receptors. While the low threshold receptors can be 1-2 to 30 mm² (depending on where they are located), those of nociceptors are usually greater than 1 cm².

2. Multiple energies can drive a single nociceptor

Polymodal nociceptors respond to both noxious pressure and thermal stimuli.

3. Nociceptor action potentials are very broad to enhance response duration over other inputs.

Two ionic channels account for particularly long action potential duration; TTX-resistant Na⁺ and high voltage activated (HVA) Ca²⁺.
4. Substance P (SP): Neurotransmitter and Tissue Repair

SP is a peptide in nociceptors (not other sensory receptors) and plays a critical role in long-latency responses to nociceptor stimulation of spinal cord neurons. Noxious stimuli do not only damage the skin and supporting cells they also damage the nociceptor and cause the release of substance P into the surrounding tissue. SP causes vasodilation, activates macrophages to secrete interleukin-1; SP and interleukin-1 together stimulate fibroblast proliferation. Thus, in addition to transmitting the message to the CNS that the skin, joint, or viscera has received a noxious stimulus, the nociceptor mediates wound healing at the site of injury. SP triggers tissue repair.

5. Nociceptor (Peripheral) Sensitization

Mechanical and thermal receptors respond in the same way to numerous presentations of the same amplitude stimulus. Of what value is reproducible coding (like innocuous receptors) of a stimulus that may destroy the skin? If a noxious stimulus was not detected the first time, nociceptors increase their rate of discharge to the same stimulus on a second presentation. This assures that an avoidance response will be made. Enhanced nociceptor responsiveness to the same amplitude stimulus is termed peripheral sensitization and it follows damage to nociceptor nerve terminals in the tissue or nerve bundles.

5. Hyperalgesia

Hyperalgesia is enhanced nociception resulting from elevated spike activity in nociceptors particularly following burns to the skin (low threshold receptors do not undergo hyperalgesia-like changes). Allodynia is noxious activity associated with previously innocuous stimuli such as light touch as often happens in the periphery of a burn to the skin.
Figure 4 shows a series of thermal nociceptor responses to the same noxious temperature. Although the stimulus does not change, the response increases to a plateau level. This produces a state of hyperalgesia; intense and ongoing pain.

Nav1.8 (Na\(^+\) channel)-null mouse mutant mice show normal nociceptive behavior to acute noxious stimulation of abdominal viscera (intracolonic saline) but showed no hyperalgesia following intracolonic capsaicin. Nav1.8 is essential for mediating spontaneous activity in sensitized nociceptors (Laird et al., J Neurosci 2002, 22:8352-56).

**Know the mechanisms of peripheral sensitization**

Peripheral sensitization accounts for hyperalgesia including reduced thresholds to somatic stimuli (above) and spontaneous pain (i.e., spontaneous activity in nociceptors in the absence of a stimulus). Prostaglandins PGD\(_2\) and PGI\(_2\) likely mediate sensitization and hyperalgesia.

Figure 5 shows that tissue damaging stimuli (star) cause the release of arachidonic acid into the cytoplasm of fibroblasts, Schwann cells, keratinocytes (damaged) and other cells.

1. Cyclooxygenase 1 and 2 convert arachidonic acid into prostaglandins that are released from the supporting cell and bind to prostaglandin receptors on the nociceptor terminal in the injured skin or joint. Second messengers activate protein kinases that elevate intracellular Ca\(^{2+}\) and Na\(^+\) and block the release of K\(^-\). Each of these events leads to a hyperexcitable terminal that spontaneously generates receptor potentials and action potentials without exogenous stimuli. Nonsteroidal anti-inflammatory drugs (NSAID) can block peripheral sensitization.
Figure 6 shows frequency dependent phosphorylation of extracellular signal-regulated protein kinase (pERK) (Dai et al., J Neurosci 2002, 22:7737-45).

2. Aβ (innocuous receptors) Convert to C Fiber Phenotype with Chronic Noxious Stimulation

Peripheral sensitization and allodynia follow acute noxious stimuli due to the altered responsiveness in C fibers. When stimulation is burning and/or involves inflammation Aβ fibers convert their phenotype and express SP. This phenotype change results greater levels of substance P release during innocuous stimulation and accounts for some of the allodynia following inflammation. The exact steps that lead to changes in the expression of preprotachykinin A are known but not worth enumerating in this forum.

II. Compound Action Potential and Conscious Perceptions

Axons in peripheral nerves conduct at different velocities (meters/sec) because of differences in diameter and myelin sheath thickness (larger axons with more myelin conduct faster because they have lower overall resistance to current flow between distally placed nodes of Ranvier). Different axon conduction velocities are associated with different stimulus activation properties, terminations in the spinal cord, and conscious perceptions. Since large diameter axons also have a lower threshold for activation, electrical stimulation of the skin or nerve provide a precise means of defining functional differences. Stimulation that activates many axons in one or more size classes evokes the compound action potential (vs action potential of a single neuron).
Figure 7 shows an example of a compound action potential recorded with electrodes in the trigeminal roots following two levels of electrical stimulation through electrodes in the cheek. (Note: largest myelinated A-α fibers are associated with muscle spindles and Golgi tendon organs that are not stimulated in this preparation.) Large Aβ fiber activity (6-12 μm diameter; 35-70 m/sec conduction velocity) is evoked with the lowest level stimulation (10 mA) and is associated with "tingling, tapping, or fluttering" sensations. These are associated with activation of mechanoreceptor nerve endings in the skin. Aδ activity (1-5 μm diameter; 5-30 m/sec) evokes the same sensations as well as "stinging" sensations. C fiber (0.2-1.5 μm diameter; 0.5-2 m/sec) report intensely painful sensations including burning and the stimulator must be turned off. The Aδ and C fiber activity, therefore, is associated with small myelinated and "unmyelinated" nociceptors and the rate of conduction is associated with conduction velocity; fast stinging and slow burning.

III. Animal Models of Neuropathic Pain

The common feature of all models is degeneration of some but not all sensory fibers in a major peripheral nerve so the target is partially denervated. For example, Seltzer et al. (A.) tightly ligated one-third to one-half of the sciatic nerve with a silk suture. Multiple branches of the sciatic nerve (B.), multiple loose ligations (C.; creates more inflammation), and ligation of two nerves (D. leaves virtually all somata in DRG either axotomized or intact).

The virtue of these models are the clinical parallels; animals guard and avoid placing weight on affected paw, escape to innocuous stimulation (allodynia), noxious cold evokes exaggerated responses (cold allodynia). Figure 8 summarizes each of the strategies for generating chronic pain in experimental animals.

Schematic illustration of different experimental models of neuropathic pain. In each case the sciatic nerve and its projection through dorsal root ganglia (DRG) are shown. In (A), a portion, typically about 50%, of the sciatic nerve is tightly ligated. In (B) ligatures are loosely tied around the sciatic nerve. In (C) one or more branches of the sciatic nerve are tightly ligated and cut. In (D) one or more spinal nerves are ligated and cut.
IV. Spinal Cord Organization and Central Sensitization

A. Nociceptor Termination in Spinal Cord

Mechanical and thermal, low threshold receptors are glutamatergic and terminate mainly in Rexed's laminae III, IV, and V, while nociceptors terminate in different layers of the spinal cord and use both SP and glutamate as shown in Figure 9. C-fiber nociceptors terminate mainly in laminae I and II, while Aδ nociceptors terminate mainly in laminae I and V and express the neurokinin-1 receptor that binds SP. Since nociceptors contain Substance P, they initiate healing in the damaged region (see above) and transmit to the CNS that a stimulus has occurred. SP excites neurons in laminae I, II, and V. Blocking nociception with neurokinin-1 antagonists has not been very successful.

Neurons in laminae I and II are nociceptor specific, i.e., selective for mechanical, thermal, or polymodal nociception. In lamina V there is an additional neuron termed the Wide Dynamic Range (WDR) neuron. This latter cell is the result of convergence of innocuous and nociceptor axon terminals on neurons in lamina V as modeled in Figure 10. Notice there are μ-opioid receptors expressed on the terminals of Aδ and C fibers for modulation of these axons by opioids.

B. Ventral Root Afferents!

Although most axons in the ventral roots are efferent from motor neurons in the ventral horn, about 13% are small, lightly myelinated axons that are afferents conducting nociceptive information (mechanical and polymodal nociceptors). Some texts make the silly observation these are "aberrant" fibers. The "law" of Bell (1811) and Magendie (1822) states that sensory afferents enter the spinal cord through the dorsal roots and motor efferents exit via the ventral roots. Ventral root nociceptor afferents assure that even after section of the dorsal roots, nociception will be preserved. The system is built to avoid noxious/tissue damaging/life threatening stimulation. Complete section of the dorsal root afferents (dorsal rhizotomy, below) does not remove these neurons and residual nociceptor afferents remain to report noxious stimulation in the periphery.

C. SP projections terminate on Lamina I and III-V neurons that express SP receptors: NK1
Figure 11 below is from Mantyh et al. (Science 1997, 278:275-78) who removed all neurons expressing NK1 receptors with SP coupled to saporin (SP-SAP; a mRNA disrupting cytotoxin). Notice the changes in pain behavior (withdrawal reflexes) that are associated with the loss of neurons in laminae I and II.

D. Central Sensitization

Acute noxious stimuli, such as pin prick, produce a painful sensation that outlasts the stimulus but is brief (minutes). When tissue is severely damaged as with cutaneous burns, cardiac ischemia, or chronic block of nerve conduction (nerve compression; e.g., carpel tunnel syndrome), a cascade of events is initiated that has long-term (days, months, years) implications for nociception in the spinal cord and brainstem, pain processing in the cerebral cortex, and treatment strategies.

Central sensitization is the enhanced excitability of dorsal horn neurons characterized by increased spontaneous activity, enlarged receptive fields, and response increases to large and small caliber primary afferents. Sensitized nociceptors contribute to central sensitization. They are more active and release SP in the spinal cord leading to long periods of abnormal depolarization in spinal cord neurons. This releases the Mg++ block of the NMDA (N-methyl-D-aspartate) receptor, elevated Ca++ entry, elevation of Ca++-dependent kinases and later actions in second messenger transduction systems as shown in Figure 12.
V. Staging Pain Therapeutics (strategies to treat pain)

Pain treatment involves alleviating the conscious perceptions of noxious stimuli. Before treatment begins, the site and source of noxious stimulation must be identified and treated along with the pain.

1) Where no clear etiology can be identified (e.g., atypical facial pain), psychotherapy, meditation, biofeedback, and hypnosis can be used. These approaches address cognitive and affective processes in the cerebral cortex.

2) When pain is moderate and well localized, modification of peripheral nerve activity with electrical stimulation and acupuncture may be appropriate.

3) Pain can be a consequence of cardiac ischemia, bowel disease, various cancers, peripheral nerve damage, stroke, and infection. In these conditions, the pain sensation is simply a notification from the primary site of damage that treatment is needed. Once the disease etiology is identified, non-opiate drugs are usually employed first and include non-steroidal anti-inflammatory drugs or opiate compounds may be administered. These drugs are avoided too often because of the false belief that addiction follows the use of morphine and related compounds.

4) Neurosurgery is the last line of defense because it is permanent and the outcomes are not assured.

VI. Opiates, Opioids, and Opioid Receptors

Morphine and other opiate compounds like meperidine (Demerol) are effective in alleviating pain because they mimic the actions of endogenous substances that modulate nociception throughout the PNS and CNS. Although meperidine is a drug of choice for moderate to severe pain, it has a shorter time of action, and it cannot be used chronically because it forms the metabolite normeperidine which has a half life of about 20 hrs and is secreted through the kidneys. Young and old patients with renal conditions are susceptible to its toxic effects. Of course, opiates are not effective with all pain including lack of efficacy in central pain (post-stroke & spinal cord injury pain).

Morphine binds to the μ-opioid receptor on both presynaptic and postsynaptic locations and blocks formation of hyperalgesia. Once hyperalgesia is established, the μ-opioid receptor agonists (e.g., Fentanyl, meperidine) still produce analgesia. In contrast, NK1 and NMDA antagonists can block onset of thermal or mechanical hyperalgesia and attenuate neuropathic thermal hyperalgesia by blocking SP and glutamate binding, respectively. However, they are less effective once hyperalgesia is established. Opiates are preferable for established neuropathic and inflammatory pain syndromes.

A. Endogenous Opioids and Their Receptors
The endogenous opioids are the product of prohormone cleavage of proopiomelanocortin to produce enkephalins, dynorphins, and endorphins. As the actions of morphine most closely mimic that of methionine-enkephalin, we focus on this compound and the μ-opioid receptor.

There are four classes of opioid receptors and met-enk binds preferentially to the μ-opioid receptor. Morphine is an agonist at the μ-opioid receptor because it mimics the actions of met-enk. The actions of both compounds are blocked by naloxone and naloxone is used as a blocker in overdose cases.

The location of opioid receptors can be observed in sections through the brain using radioactive opioid compounds either in vitro or in vivo. Mu-opioid receptors are particularly abundant in laminae I, II, and V of the spinal cord as shown in Figure 13. This is a darkfield photomicrograph of an autoradiograph of ligand binding where the white grains are linked to the density of binding which is highest in the superficial layers of the spinal cord. These binding sites are on the axon terminals of nociceptors and on the cell bodies of neurons which are nociceptive in the spinal cord and nucleus caudalis as diagrammed in Figure 18. Release of met-enk in these regions by interneurons which then binds to the μ-opioid receptor. Activation of the μ-opioid receptor inhibits release of SP from the nociceptor axon terminals and inhibits neuronal activity in nociceptive neurons in the spinal cord and nucleus caudalis. Thus, met-enk shuts down responses to noxious stimuli as does morphine as shown in Figure 14.

VII. Peripheral Nerve Interventions

Peripheral neuropathies such as sciatica due to herniated discs are encountered in as many as 40% of adult patients. Epidural steroids provide short-term improvement in leg pain but no functional improvement and does not reduce the need for surgery. Analgesics can provide temporary relief; they have side effects with chronic use. Non-pharmacologic strategies are particularly effective in this instance.

A. Transcutaneous Electrical (Nerve) Stimulation (TENS)

Electrical stimulation provides a noninvasive method for modulating nociception when localized to a single nerve distribution. Electrodes are placed on the surface of the skin so as to stimulate a nerve bundle in the proximal part of the appropriate dermatome. A low amplitude burst of electrical stimuli (tetanus) is administered by the patient when in pain and subsequent analgesia outlasts the tetanus by many hours. Low-amplitude stimulation is used to prevent stimulation of Aδ and C fibers which would evoke pain directly. Figure 15 shows an experimental arrangement similar to that for patient treatment. Notice the reduced neuronal discharges in the spinal thermal nociceptor after a period of stimulating large, i.e., low threshold axons. Notice the black neuron in the spinal cord. This is a met-enk secreting interneuron. Met-enk binds to mu-opioid receptors on nociceceptor terminals and
nociceptive neurons in the spinal cord and inhibits nociceptive processing in the spinal cord, thus, blocking nociceptive transmission to structures in the telencephalon. The prolonged time-course of the analgesia is due to the prolonged binding and second messenger actions of met-enk.

B. Acupuncture

Acupuncture may act via a mechanism similar to that for TENS. It appears that meridians into which needles are placed are closely aligned with branches of many cutaneous nerves. It is thought that optimal anesthesia requires stimulation of Aβ axons in the nerve trunk either by turning the needles or by application of electrical current to the needles. Cross circulation studies have shown that analgesia in one patient can be "transferred" to another implicating a circulating factor such as met-enk.

C. Percutaneous Electrical Nerve Stimulation

PENS involves electrical stimulation through needles in the soft tissues along the distribution of a nerve such as the sciatic shown in Figure 16; i.e., it is a combination of TENS and acupuncture. A recent study with placebo controls (no electrical stimulation) showed better pain relief and functional recovery (physical activity and sleep) in the management of sciatica than that produced by TENS.

XIII. Surgical Block of Nociception

After all non-invasive and drug strategies have been attempted and pain persists, as in chronic cancer pain, neurosurgical routes “permanently” block nociception from passing to the forebrain. These operations do not produce consistent results and can impair function.
A. Dorsal Rhizotomy

DR relieves pain by complete section of the dorsal roots, as shown in Figure 17, and results in loss of mechanoreceptor and thermoreceptor sensations and much nociceptor-induced sensations. Since nociceptor afferents also course through the ventral roots, DR does not usually produce complete and persistent pain relief. To avoid the “aberrant” ventral root afferents, a dorsal root ganglionectomy is performed to include some of the ventral root afferents because some are dorsal root ganglion neurons with axons displaced to the ventral root. Unfortunately there are still some nociceptor cell bodies displaced along the ventral roots and residual pain can persist. Indeed, spinal posterior rhizotomy often results in anesthesia dolorosa which is intense pain in the area of the deafferentation.

B. Nucleus Caudalis of Trigeminal System

Just as termination in the spinal cord is according to dermatomal organization, mechanical and thermal receptors terminate in the trigeminal nuclei in a somatotopic manner. The ophthalmic, maxillary, and mandibular branches terminate in segregated parts of the principal sensory nucleus of the trigeminal nerve and most neurons respond to light touch and temperature. The termination of nociceptors for the face, however, are segregated to nucleus caudalis. The nucleus caudalis is the main component of the nucleus of the spinal tract of the trigeminal nerve in the lower medulla and upper spinal cord. Nucleus caudalis is at the level of the obex. It is composed of only three laminae as shown in Figure 18. These laminae contain neurons with properties similar to those in spinal cord laminae I, II, and V. Since all nociceptor afferents associated with the face and head terminate in nucleus caudalis, this provides a target for neurosurgical intervention for treatment of trigeminal neuralgia. (most pain in the face to the nuc. caudalis).

C. Interventions into Spinal and Trigeminal Nociceptive Systems

1) Nerve blocks. Combinations of tetracaine and other anesthetics into peripheral nerves (such as the infraorbital nerve) can alleviate trigeminal neuralgia (TN) for up to 3 months.

2) Trigeminal cistern glycerol injection. Injection of glycerol into the trigeminal cistern is surprisingly effective in alleviating trigeminal neuralgia without producing commensurate deficits in other somatic sensations. In a patient from which the recordings in Figure 19 were made, glycerol injection abolished the Aδ and C fiber components of the compound action potential. The patient did not suffer from pain subsequent to surgery. One explanation for glycerol effectiveness is it causes osmotic destruction of axons that are demyelinated and are the source of ectopic discharges and associated nociceptive responses.

3) Trigeminal rhizotomy. Trigeminal neuralgia can be caused by vascular anomalies, small tumors, and multiple sclerosis. One method of treating this type of pain is to cut the trigeminal roots just as they enter the brainstem. This can result, however, in complete anesthesia of the head.

4) Trigeminal tractotomy. Another method of treating trigeminal neuralgia is to cut the descending tract of V below the obex. Since other facial sensations are transmitted rostral to the principal sensory nucleus of V, this operation usually abolishes nociceptive responses without producing a general anesthesia in the head.
5) Anterolateral spinothalamic tractotomy. Since nociceptive and temperature connections pass from the spinal cord to the thalamus via the anterolateral spinothalamic tract, neurosurgeons can cut this bundle of axons to alleviate pain, while leaving other components of body sensation intact including the dorsal column system. Localized and unilateral sites of nociceptive tissues are best alleviated with this surgery.

IX. Sympathetic Nociceptors, Reflex Sympathetic Dystrophy, Sympathectomy

A. Sympathetic Nociceptors (sympathetic neurons are nociceptive)

There are small diameter, nociceptive sympathetic axons in the heart that are activated by ischemia and bradykinin released from ischemic cardiac muscle (mechanical nociceptors are disputed). There are no uniform rules for the distribution of nociceptors in the viscera. For example, the intestines do not have mechanisms for responding to burning or cutting pains but do for distention. In order to state the strongest case for sympathetic involvement in nociception, we consider the heart.

Neither electrical stimulation of the sympathetic chain nor arterial injection of norepinephrine excites C-fiber nociceptors. When the tissue is inflamed, however, about half have elevated discharges to both conditions. Yohimbine, an $\alpha_2$ antagonist, blocks this effect in inflamed tissue suggesting that $\alpha_2$ adrenoceptors are up-regulated in C fibers and this confers their sympathetic sensitivity. Infusion of norepinephrine into inflamed tissue induces pain.

B. Angina Pectoralis

Chemosensitive sympathetic nociceptors are activated by bradykinin via the B2 receptor, serotonin from activated platelets; adenosine, and $K^+$, however, none of these stimuli appear to work independently. Each of these substances are likely released during ischemia. (None alone will activate nociceptors, but 2 together will.) Angina pectoralis is mediated primarily by sympathetic axons. It has long been known that thoracic sympathectomy or destruction of upper thoracic dorsal root ganglia (i.e., location of somata of sympathetic sensory neurons innervating the heart) are valuable treatments for angina. Their removal, however, relieves 50-60% of the pain, 40% of patients experience only partial relief and 10-20% no relief. One explanation is that sympathetics innervate the anterior surface of the heart, while vagal afferents may innervate the posterior ventral surface.

C. Causalgia/Complex Regional Pain Syndrome type II: Sympathetics Modulates Nociception

In 1872 Mitchell introduced the term causalgia for the burning pain of his wounded Civil War soldiers. Causalgia or CRPSII is also termed sympathetically maintained pain because of its sensitivity to various interventions into the sympathetic nervous function. Destruction of the noradrenergic sympathetic innervation to a region of the body abolishes causalgia because of removal of chemosensitive sympathetic nociceptors, removal of noradrenergic release in the periphery including innervation of nociceptors, and removal of sympathetics in dorsal root ganglia where vascular sympathetics may sprout. Scientific basis for causalgia:

* Elevated sympathetic activity enhances generator potentials in the somatosensory receptors including nociceptors.
* In sympathectomized tissue following the relief of causalgia, NA evokes causalgia
* Preganglionic upper thoracic sympathectomy alleviates causalgia in most cases.
* Yohimbine, alpha 2 receptor antagonist, abolishes hyperalgesia. Also, phenoxybenzamine (nonselective $\alpha$ adrenoceptor antagonist) administered for 6 weeks provides permanent relief for post-burn hyperalgesia.

X. Referred Pain Syndromes

A. Referred or Heterotopic Pain
This is pain that is perceived to arise from one part of the body but actually originates in another. The best known, but by no means only, heterotopic pain is that of cardiac origin referred to the left arm, shoulder, neck and/or face. The anatomic basis for this pain is well understood. Identification of a referred pain is crucial for proper and immediate therapy. For example, tooth extractions will be performed to relieve pain when the pain actually follows a myocardial infarction. Tooth extraction in this situation is not only contraindicated but requires time that should be applied to treating the infarction.

B. Anatomical basis for referred pain: Convergence of Cardiac & Somatic Nociceptors

Figure 20 shows that terminations of the C2 DRG and trigeminal ganglion overlap in the C1-C3 segments of the spinal cord. Half of the spinothalamic tract neurons in C1-3 are excited by electrical stimulation of cardiopulmonary afferent and vagal nerve stimulation. Most of these activated neurons also receive somatic nociceptive input (97% WDR and 88% nociception specific). The somatic nociceptor receptive fields are most often in the neck, jaw, ear and upper arm. An example of a STT neuron discharge to overlapping cardiopulmonary and somatic noxious stimulation is shown in Figure 21.

C. Manifestations of Heterotopic Pain
The relationships between cardiac ischemia and shoulder, arm and/or neck pain referred from the heart are well known by patients at risk for such events and the mechanisms are clear from the previous two figures. Less well known, are the production of headaches referred from cervical origins and toothaches that can be referred from the heart. Imagine having your teeth removed because you are suffering from a heart attack! This actually happens and these patients are in serious danger because of lost time to treatment of the heart disease. There are symptoms that provide clues to avoid such mistakes. Although there may not be an overt heart attack (“silent ischemia”), there may be some radiating pain in the neck and shoulder, pain onset occurs during exercise but not during sleep (perform a stress test and evoke toothache), there may be a history of cardiac disease and arteriographic analysis may show coronary artery obstruction. Indeed, if the latter is true, a coronary bypass or angioplasty will alleviate the facial pain. Referred pain = anatomical overlap of receptive fields of visceral and somatic nociceptors.

XI. Medullary Subnucleus Reticularis Dorsalis (SRD): PRONociception

The medullary DRN/SRD is located in the caudal and dorsal part of the medulla as shown in Figure 22. Neurons in the DRN are activated mainly by nociceptive stimulation, have large receptive fields (sometimes the entire body), ablations of DRN depresses nociceptive responses to acute and inflammatory pain, while electrical stimulation produces the inverse effect. DRN block with lidocaine decreases nociceptive activity of spinal dorsal horn neurons, while stimulation with Glu has the opposite effect. This is a pronociceptive system in that it alerts the midbrain and spinal cord for reflex responses before the nociceptive stimulus produces a conscious/painful response.

One of DRN/SRD major outputs is to ON-neurons in the rostral ventral medulla (RVM) that drives escape responses via the spinal cord. It also has a number of ascending projections that transmit nociceptive information to limbic regions involved in avoidance behaviors. Finally, there are descending projections that provide for some negative feedback in the spinal cord. A summary of this circuitry is provided in Figure 23 below. The nucleus of the solitary tract (NTS) is associated with visceral functions and receives inputs from the autonomic nervous system associated with noxious stimulation including angina pectoralis and infectious irritation of the bowel.
XII. Supraspinal Nociceptive Projections

Figure 24: Spino-tegmento-thalamic tract to

Nuc ambiguous; breathing
PGi; paragigantopyramidal nucleus of reticular formation; autonomic/sympathetic
PB; visceral integrative center
LC; locus coeruleus
Much of midline and intralaminar thalamus
Somatosensory thalamus (VPL/VPM)

Figure 25:
Although small spinal nociceptive input to the LC, most comes from the PGi which acts to integrate autonomic output via descending projections to intermediolateral nucleus of the spinal cord as shown in Figure 26 (below left).

Figure 27 (below right) Shows the actual termination of lamina I spinal input (PHAL) input to aa caudal part of the cat thalamus and include projections to parafascicular (Pf) and subparafascicular (SPf) nuclei

Nociceptive Driving of PGi & LC Neurons

1. PGi & LC receive spinal lamina I nociceptive input
2. Electrical stimulation of C fibers nociceptors drive PGi & LC
3. PGi Lidocaine Blocks LC output

PGi Mediates Nociceptive Responses & Sympathetic Output
LC Drives HPA Axis

HPA Axis
PVN
CRH
ACTH
Cortisol

Locus Coeruleus

Rostral Pons

IML
Sympathetics

Spinal Nociceptive Inputs

Pul

Spino-tegmento-thalamic tract

Medial thalamus to
1. Hypothalamus
2. Amygdala
3. MCC
4. ACC
5. Ant. Insula

PGi
PB
LC
A1/Nuc Ambiguus

Pre-Lidocaine
Post-Lidocaine
Barrington’s nucleus is a key intermediate for rest-and-digest autonomic systems; e.g., visceral digestive systems. It interfaces with autonomic outputs of the spinal cord such as Onuf’s nucleus as shown in the circuit below in Figure 28. Notice parallel with PGi and sympathetic system above.

Barrington’s Nucleus (BN)
1. Lies medial to LC
2. Receives NTS input; bladder/colon distention
3. Regulates micturition via projections to Onuf’s N. in sacral spinal cord
4. Projects CRH to LC

VIII. Diffuse Noxious Inhibitory System

Reflex limb and head withdrawal from noxious stimuli are mediated by spinal cord and medullary neurons and are considered to be part of motor system function as discussed elsewhere in the course. An important component of nociceptive processing and conscious intermediation of pain processing is the subconscious and conscious modulation of pain through the DNIS. Electrical stimulation of the periaqueductal gray (PAG) inhibits noxious-evoked activity in the spinal cord as shown in Figure 29.
Figure 30 activation of SP-containing nociceptors (P in figure) leads to activation of nociceptive-specific neurons in the spinal cord including WDR neurons (shown in Fig. 25 only for simplicity). Axons of the WDR neurons pass via the anterolateral spinothalamic tract to the midbrain before completing their course to the thalamus. This tract should be termed the spinal-midbrain-thalamic tract rather than the spinothalamic tract. In the PAG there are met-enk interneurons (E in figure) that are excited and release met-enk onto projection neurons that are thereby inhibited (sold triangles in figure are for inhibitory terminals). Inhibition of inhibitory PAG projection neurons (G= GABA in figure) results in disinhibition of serotonergic neurons in the raphe nuclei. This allows raphe neurons to discharge spontaneously and so release serotonin in the spinal cord and nucleus caudalis. Serotonin is an inhibitory transmitter and so turns off nociceptive neurons and reduces transmission of nociception from the cord and caudalis. This system is not selective for particular dermatomes. It shuts down nociception throughout the cord and nucleus caudalis; hence the term diffuse noxious inhibitory system. Produces generalized analgesia throughout the spinal cord (therefore can treat headache with repeated pinching of arm). Analgesia induced by intracranial stimulation is a method of therapeutically intervening into the DNIS. Electrodes placed into the PAG or midline thalamus which projects to the PAG can be stimulated and results in the release of serotonin in the spinal cord and nucleus caudalis and abolishes responses to noxious stimuli. Side effects from PAG stimulation, however, include nausea, vertigo, and sensation of smothering (not an ideal outcome). Electrode placed in the periventricular thalamus can also produce analgesia but without the side effects

IX. Supraspinal Dichotomy in Pain Systems
A. Lateral and Medial Pain Systems

The spinomesothalamic tract divides into lateral and medial branches as it enters the posterior thalamus. The lateral division terminate in the ventroposterior nucleus, while the medial division terminates in the midline and intralaminar thalamic nuclei. Figure 30 shows projections of the spinothalamic tract in the medial thalamus (e.g., parafascicular nucleus, Pf) and the VPL and VPM nuclei.

Figure 31 summarizes the nociceptive properties of neurons in the lateral and medial thalamic nuclei. Neurons in the VPL/VPM project to primary somatosensory cortex in the postcentral gyrus and the second somatosensory area in the anterior insula. Neurons in the medial/intralaminar thalamic nuclei project to limbic areas including the cingulate cortex. Neurons in both systems code for stimulus intensity as shown for thermal nociceptors.

<table>
<thead>
<tr>
<th>THALAMUS</th>
<th>Medial (CI/Pf)</th>
<th>Lateral (VPL/VPM)</th>
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<tbody>
<tr>
<td>Nociceptive fields</td>
<td>very large</td>
<td>somatotopic</td>
</tr>
<tr>
<td>Stimulus coding</td>
<td>weak</td>
<td>high fidelity</td>
</tr>
<tr>
<td>Mu opioid receptors</td>
<td>high</td>
<td>low</td>
</tr>
<tr>
<td>Neurosurgical removal</td>
<td>relief of chronic pain</td>
<td>no relief</td>
</tr>
<tr>
<td>Cortical projections</td>
<td>cingulate and prefrontal</td>
<td>SI and SII</td>
</tr>
</tbody>
</table>

The midline and intralaminar thalamic nuclei (e.g., Pf) project to ACC as shown below. These nuclei do not project to posterior cingulate cortex. The midline and intralaminar thalamic nuclei provide a direct route for assessment noxious information at the conscious level.

The lateral system is optimally organized for localizing the stimulus on the body surface, while the medial system has no localization information. Figure 32 shows an example of a cortical neuron in the medial system of the rabbit which has the same non-somatotopic organization like medial thalamic neurons. Notice that noxious mechanical stimulation on any part of the body produces a robust response. These neurons do not know where the noxious stimulus is located, although they are well aware that it hurts. Lesions in the medial thalamus and ACC can abolish pain sensations without impairing localization; "I know the pain is on my foot but I do not care." In contrast, lesions in the ventroposterior nucleus and somatosensory cortex do not reduce pain perceptions.
Injections of retrograde tracers (Figure 33; above; red hatch injection of horseradish peroxidase and red dots are 3-5 labeled neurons) into ACC labels neurons in the midline and intralaminar thalamic nuclei; one example of these is the Pf nucleus (i.e., this is the only nucleus of the 15 midline nuclei you need to remember). This nucleus receives spinothalamic inputs, has nociceptive neurons with large receptive fields and it projects to cingulate cortex. Blocking activity in this region of thalamus with lidocaine blocks nociceptive ACC responses.

A review of many studies looking at acute pain (A) or simple emotions (B) in an effort to link these events. The conclusions are considered in detail in Vogt (2005).

B. Cingulotomy for Chronic Pain Relief

Chronic back pain and atypical facial pain elevate neuronal activity in ACC and the anterior insula. If pharmacological or neurosurgical interventions in the spinal cord do not produce relief in chronic pain patients, ACC is a potential target as shown in Figure 34. Pain relief is not associated with general anesthesia as is the case for other procedures; however, it usually lasts for only 2-5 years.

C. Opiate Binding: PAG, Medial Thalamus & Cortex

Diprenorphine is a non-specific opioid receptor antagonist that is a potent analgesic and has been used to localize the opioid receptors with positron emission tomography ($^{11}$C-diprenorphine with corrections for blood flow and metabolites). Binding is very high in the PAG, medial thalamus, medial cortex including prefrontal cortex and ACC (Figure 35). Thus, the actions of opiate compounds are due to binding to nociceptors, nociceptive neurons in the spinal cord, medial thalamus, and cingulate and prefrontal cortices.

D. Human Pain Processing & Links to Emotion

Plotting responsive sites in cingulate gyrus from all pain studies in Talairach and Tournoux standardized coordinates shows activate of mainly midcingulate cortex. Structural and functional analyses show the rostral pACC region is involved in affect/happiness/sadness, while the aMCC is involved in fear and pMCC has no specific role in affect as shown by the analysis of simple emotion in Figure 33 (above).

Activation of pACC does occur in pain studies but is more likely when activity is correlated with heart rate. Thus, the thermal grill illusion is associated with pain affect and autonomic reactions, while most other pain studies explore a caudal cingulate region involved in fear and skeletomotor avoidance responses.

X. Placebo Analgesia
Since pain is a conscious experience, neuron activity during consciousness must be identified to explain pain processing and therapeutics. The concept of the placebo effect is viewed with disdain by some that view this as a mentalistic and non-physical approach to pain relief. This view impedes efforts to develop non-invasive and non-pharmaceutical treatments for pain such as hypnosis and acupuncture. The placebo effect is a physical reality based on medial surface neuronal activity and it can be harnessed to regulate pain and reduce the need for analgesics.

A. Placebo Effect

A placebo is defined as any treatment or aspect of treatment that does not have a specific action on the patient’s symptoms or disease; any therapy used for nonspecific psychological effect but is devoid of any specific activity for the condition being treated. The placebo is influenced by patient and/or physician beliefs or expectations and the quality of the patient/physician interaction. These views of the placebo view beliefs and expectations as though they are not a physical reality and can be overlooked as “subjective.” Beliefs are expectations and they are stored in parts of the brain. Importantly, the placebo effect has a physical basis. The notion that treating psychological activity in pain is irrelevant to the symptom’s is absurd. Pain processing in the forebrain is as important as it is at the nociceptor and in the spinal cord.

A study of 97 patients about to receive intra-abdominal surgery had an anesthetist visit the patient the evening before surgery. One half of the patients (Special Care) were counseled about time, duration, and other aspects of the surgery/recovery, the role of muscle spasms in pain and how to relax, orient their body, and use a sling to help relieve the pain. The other half of the patients were simply visited and told about the procedure without pain counselling. Both groups were told that pain medication was available if needed. Neither surgeons or nurses knew about the study. Figure 34 shows the Special Care Group used 50% less morphine than patients without insight into pain management.

B. Placebo Analgesia

Placebo analgesia is very effective in about 30% of patients experiencing pain and cannot be overlooked. If mental activity is high in ACC and this is also where high levels of opioid receptors are located, it is reasonable to expect that conscious mental activity alters function in a region associated with pain perception and possibly in ways that are mimicked by opiate drugs. Placebo analgesia can mimic the dose-response effects of opiates but it is less effective with continued treatment. In placebo nonresponders, opiate drugs are less effective. Placebo effects are improved with extensive counseling, intravenous administration, and under double-blind conditions.

Petrovic et al. (2002; Science 295:1737-40; Figure 35) evaluated placebo analgesia with PET produced by the short acting μ-opioid agonist remifentanly and they colocalized the effect to perigenuan anterior cingulate cortex where it overlapped with the highest level of activity produced by remifentanly only. Notice that the nociceptive response produced by noxious heat to the back of the hand activated an entirely different area.