

Somatosensory System II: Pain

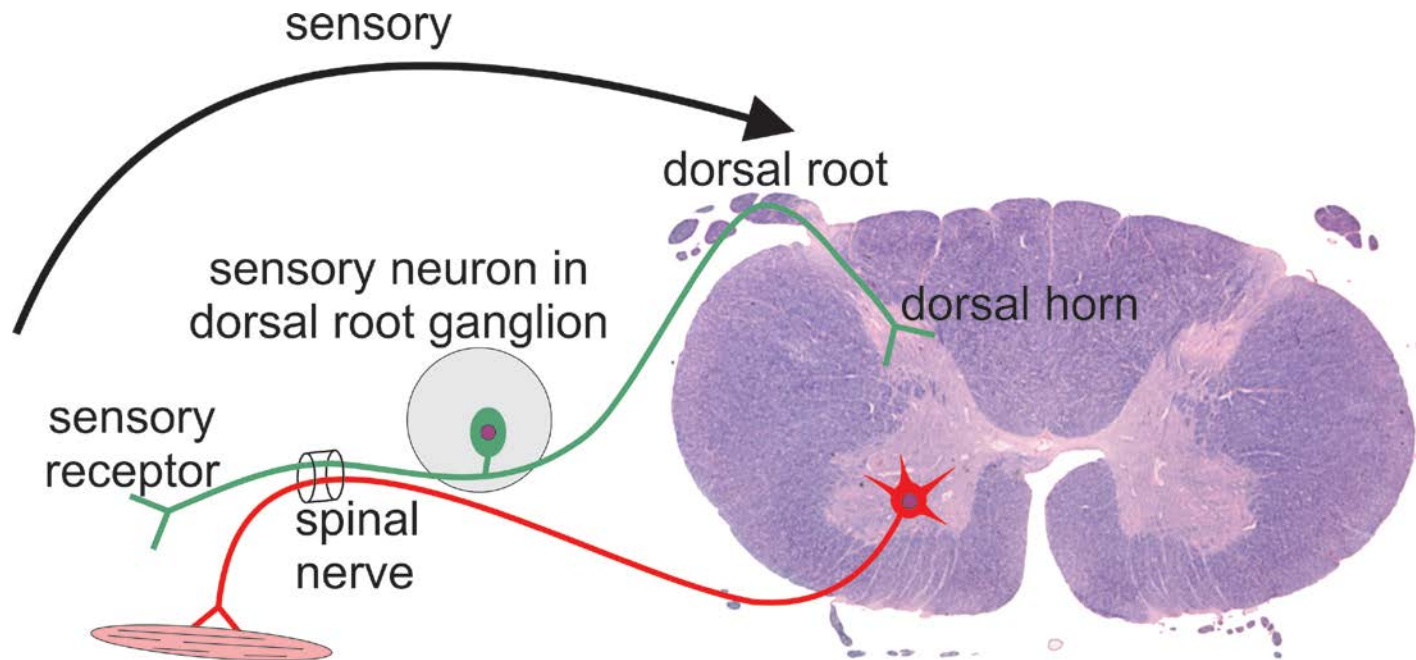
Martin Wessendorf

Department of Neuroscience

University of Minnesota

Somatosensory Primary Afferent Neurons

- The somata of somatosensory primary afferent neurons are in:
 - dorsal root (spinal) ganglia
 - cranial nerve sensory ganglia



The somatosensory system detects multiple sensations.

- Touch
 - fine touch
 - pressure
 - Vibration
 - hair movement
 - movement against the skin
- Proprioception
 - limb & trunk position
 - limb movement
 - load
- Thermoception (temperature)
 - heat
 - cold
- Nociception (pain – tissue damage)
- Pruriception (itch)

Pain

- “An unpleasant sensory and emotional experience associated with actual or potential tissue damage.” (International Association for the Study of Pain)

Pain

- Carried into CNS by small primary afferent axons with slow conduction velocities
 - Myelinated: <10 meters/sec
 - Unmyelinated: < 2 m/sec
- Sensations are carried to the thalamus by spinothalamic tract neurons

Pain can be provoked by activation of **nociceptors**

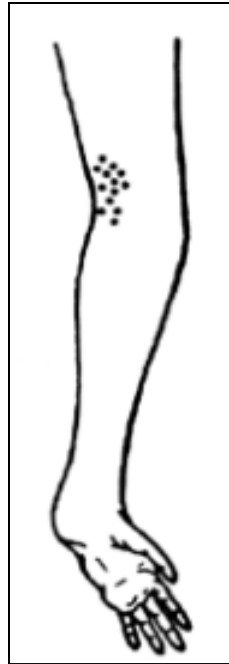
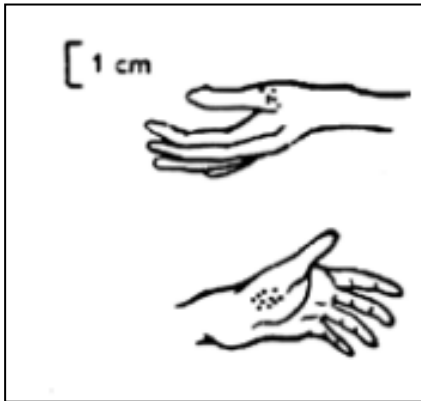
- Nociceptors signal ***tissue damage or threat of tissue damage***
 - Mechanical injury (e.g., cutting, scraping, etc.)
 - Heat injury (burning)
 - Cold (frost-bite)
 - Gut distension (e.g., gas pains)
 - Chemical injury (e.g., acid)
 - Etc.

Nociceptors

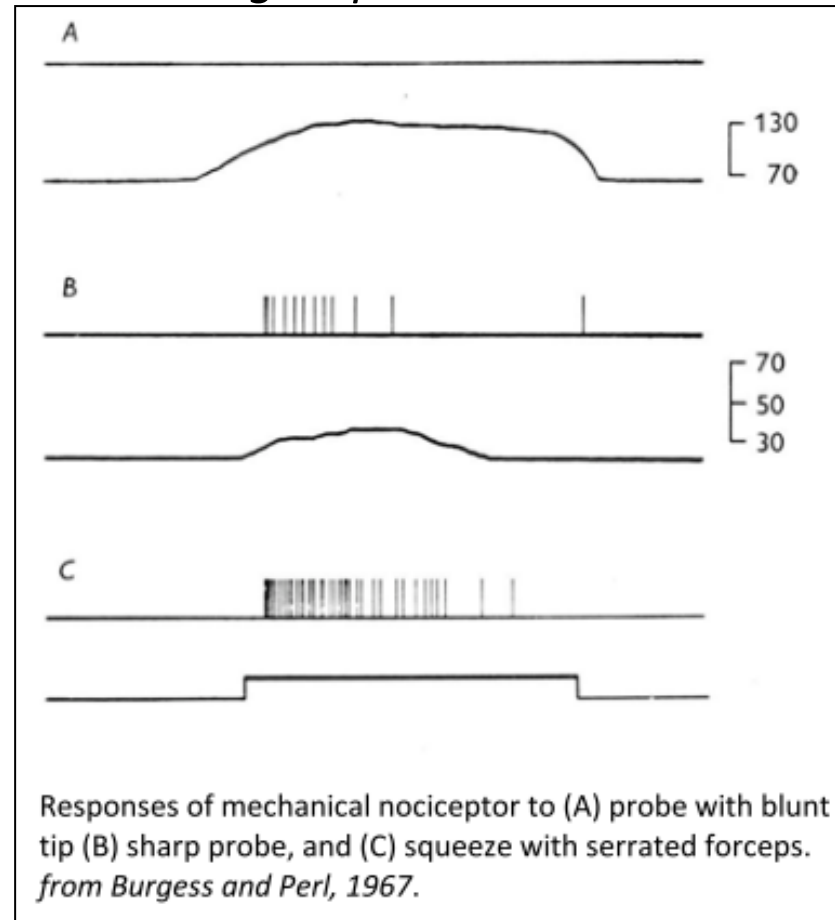
- Free nerve endings
- Thresholds are usually HIGHER than most other sensory receptors
 - Light-touch receptor threshold: <1 g
 - Painful touch threshold: ~70 g

Nociceptors

- Mechanical nociceptors:
 - High threshold
 - Fire more with increased force
 - Small, point-like receptive fields

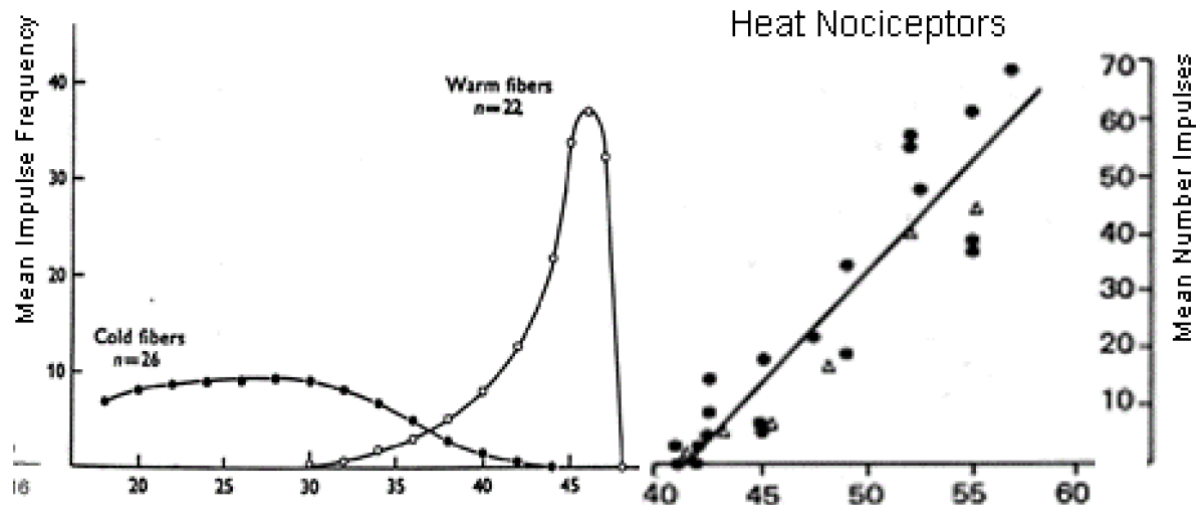


Firing responses to stimuli



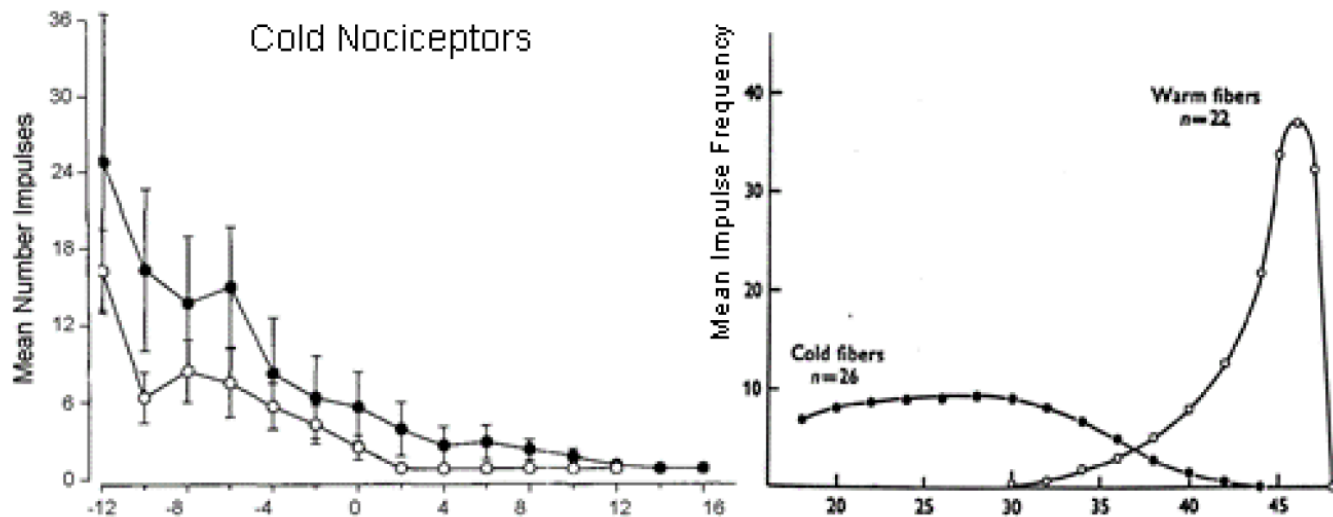
Nociceptors

- Polymodal nociceptors:
 - Respond to mechanical, heat, & chemical stimuli
 - Thermal thresholds 43-45° C
 - High mechanical thresholds
 - Respond to algesic agents, e.g., acid

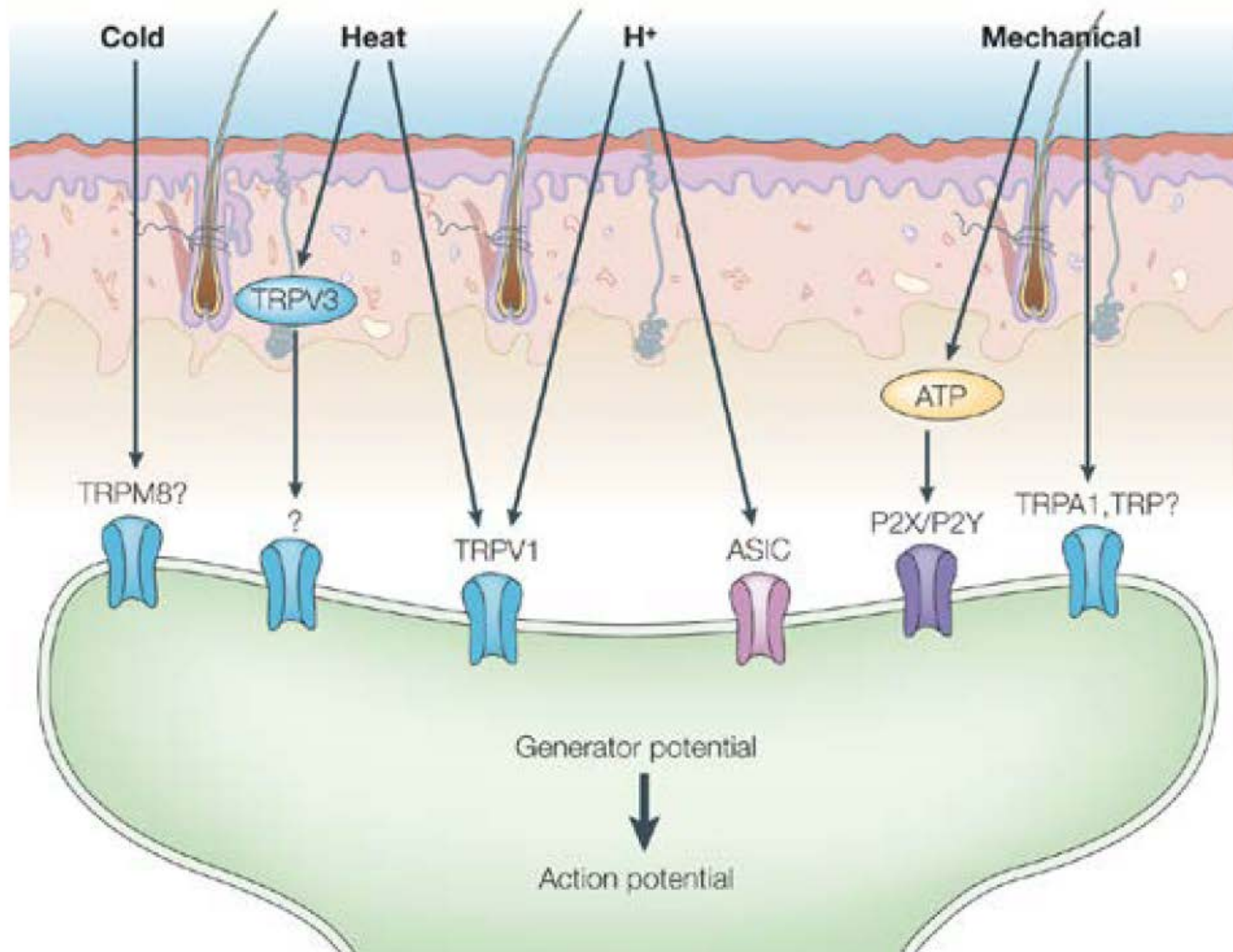


Nociceptors

- Cold nociceptors:
 - Thresholds $\sim 0^\circ\text{C}$
 - No overlap with cooling receptors

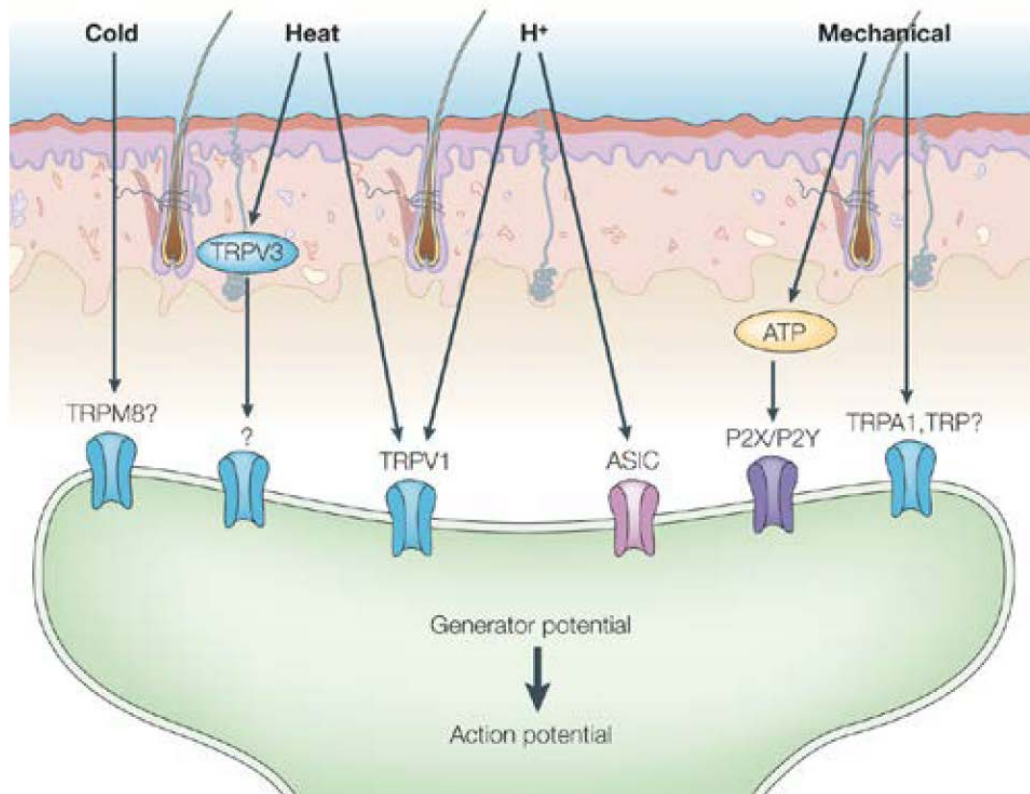


Anatomy of nociceptors: free nerve endings



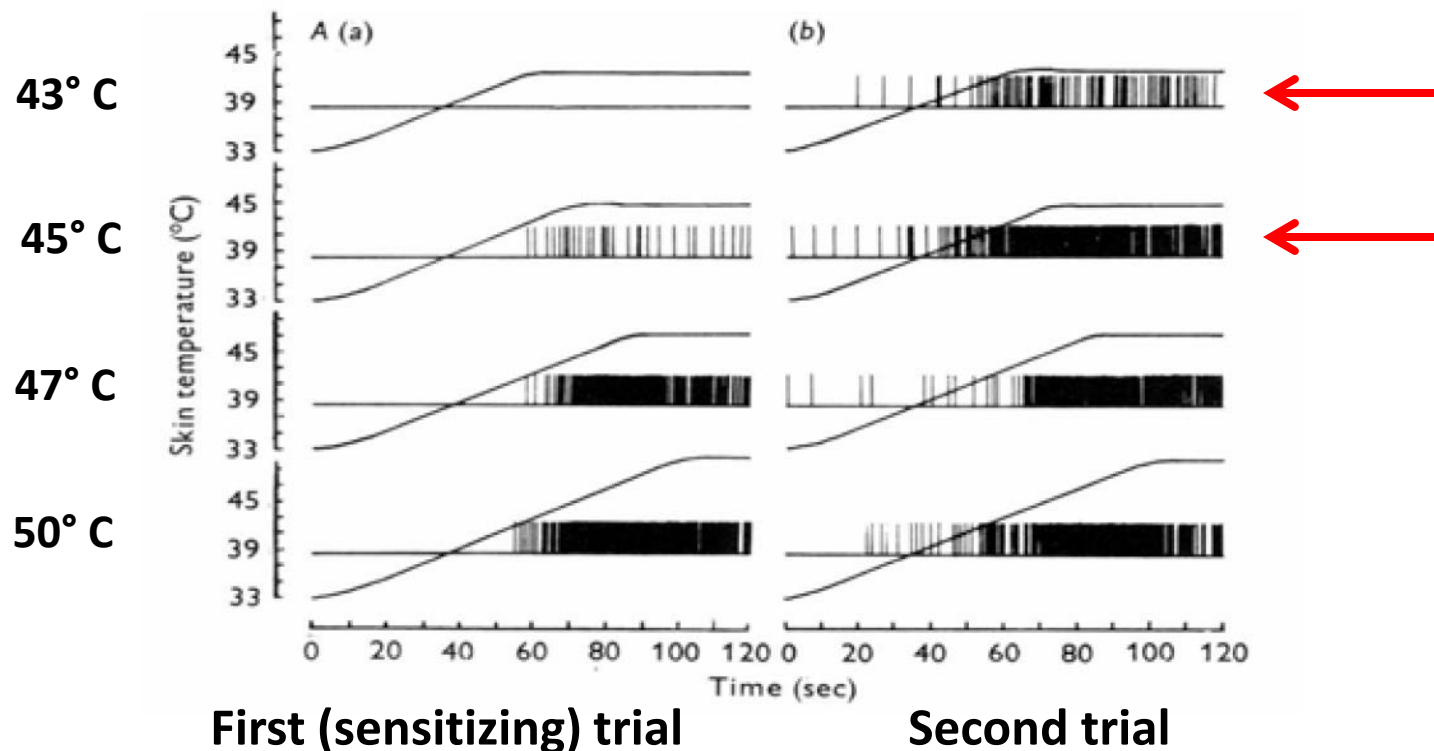
Anatomy of nociceptors

- Free nerve endings in superficial skin
- Terminals have transduction proteins sensitive to
 - Heat
 - Cold
 - Acid
 - Pressure
 - ATP



Sensitization of nociceptors

- Causes decreased threshold & larger response
- Contributes to increased pain after injury



Sensitizers

- Activity
 - Heat
 - Mechanical stimulation
 - Chemical stimulation
- Inflammatory agents
 - Prostaglandins
 - Bradykinin, serotonin, cytokines
- Etc.

Types of pain

- Acute pain (“normal pain”)
 - In response to injury or threat of injury
 - Lasts as long as the stimulus
 - Sets boundaries: what’s safe to explore?
- Persistent pain
 - Outlasts the injury or threat of injury
 - Related to healing
 - Protective during healing process
- Chronic pain
 - Outlasts duration of healing

Inflammatory pain

- Most common persistent pain (e.g., sunburn)
- Accompanies all injuries: skin, joints, muscle, bones, post-surgery
- Paradox :
 - inflammation promotes healing
 - inflammation causes more pain
- Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
 - blocks production of prostaglandins → reduced inflammatory pain
 - Effect on healing is uncertain

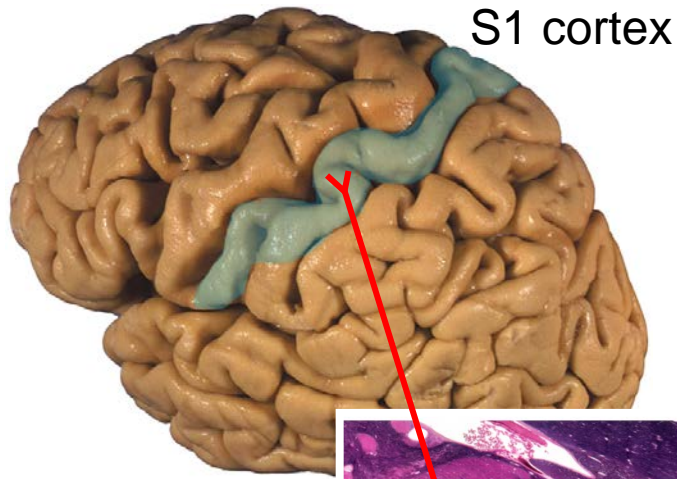
Chronic pain

- **Huge public health issue**
 - More than 50% of Americans will experience chronic (> 3 months) pain during lives
 - Chronic pain can lead to helplessness, depression, suicide
 - Cost roughly \$600 billion annual (> heart disease, cancer, and diabetes)
 - Cost of treatment
 - Lost productivity
- **Chronic pain remodels brain**
 - Difficult to reverse
 - May underlie long-lasting nature of chronic pain

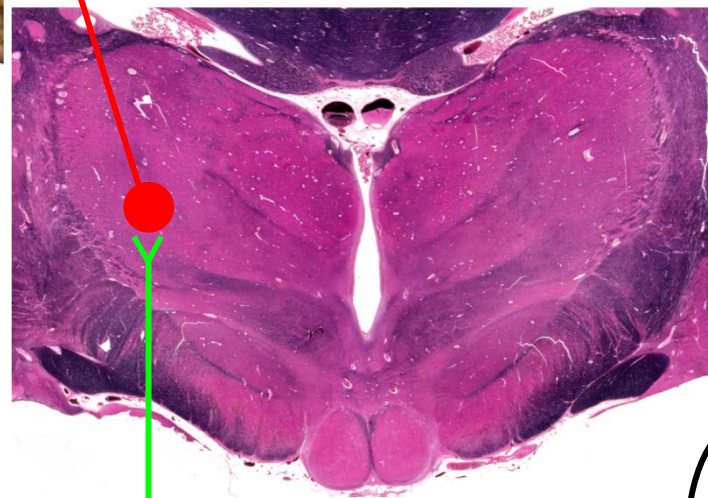
Neuropathic pain

- Type of chronic pain caused by nerve compression, nerve injury, chemotherapy, diabetes, etc.
- Loss of innervation → anesthesia in affected area
- Loss of growth factors released by cut nerves → adjacent nerves behave abnormally
- Thus light touch can cause pain
- Example: Carpel tunnel syndrome

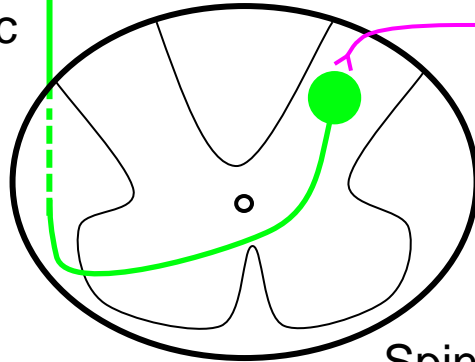
Pain pathways



VPL of thalamus

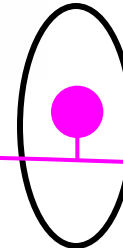


Spinothalamic tract

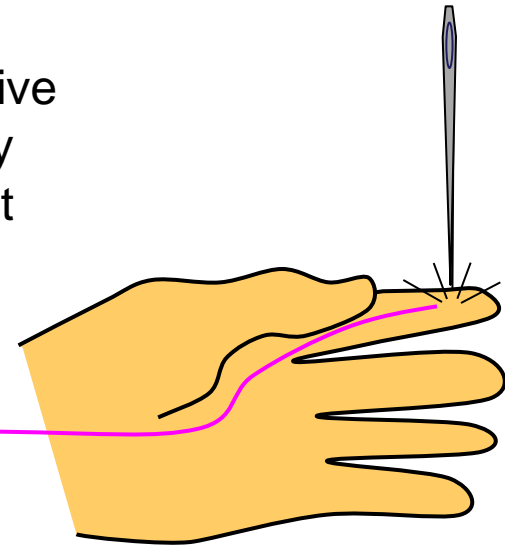


Spinal cord

Dorsal root ganglion



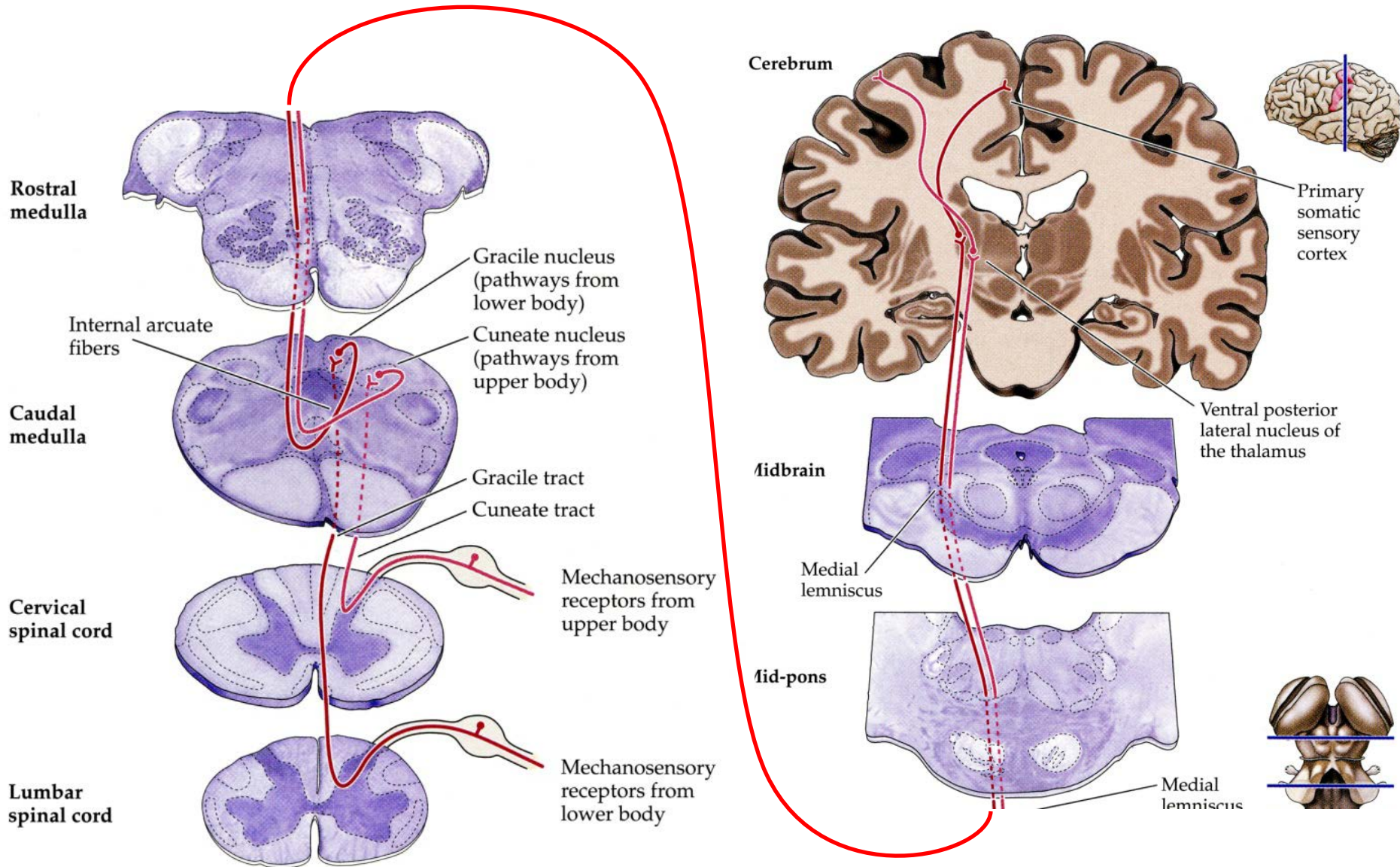
Nociceptive primary afferent axon



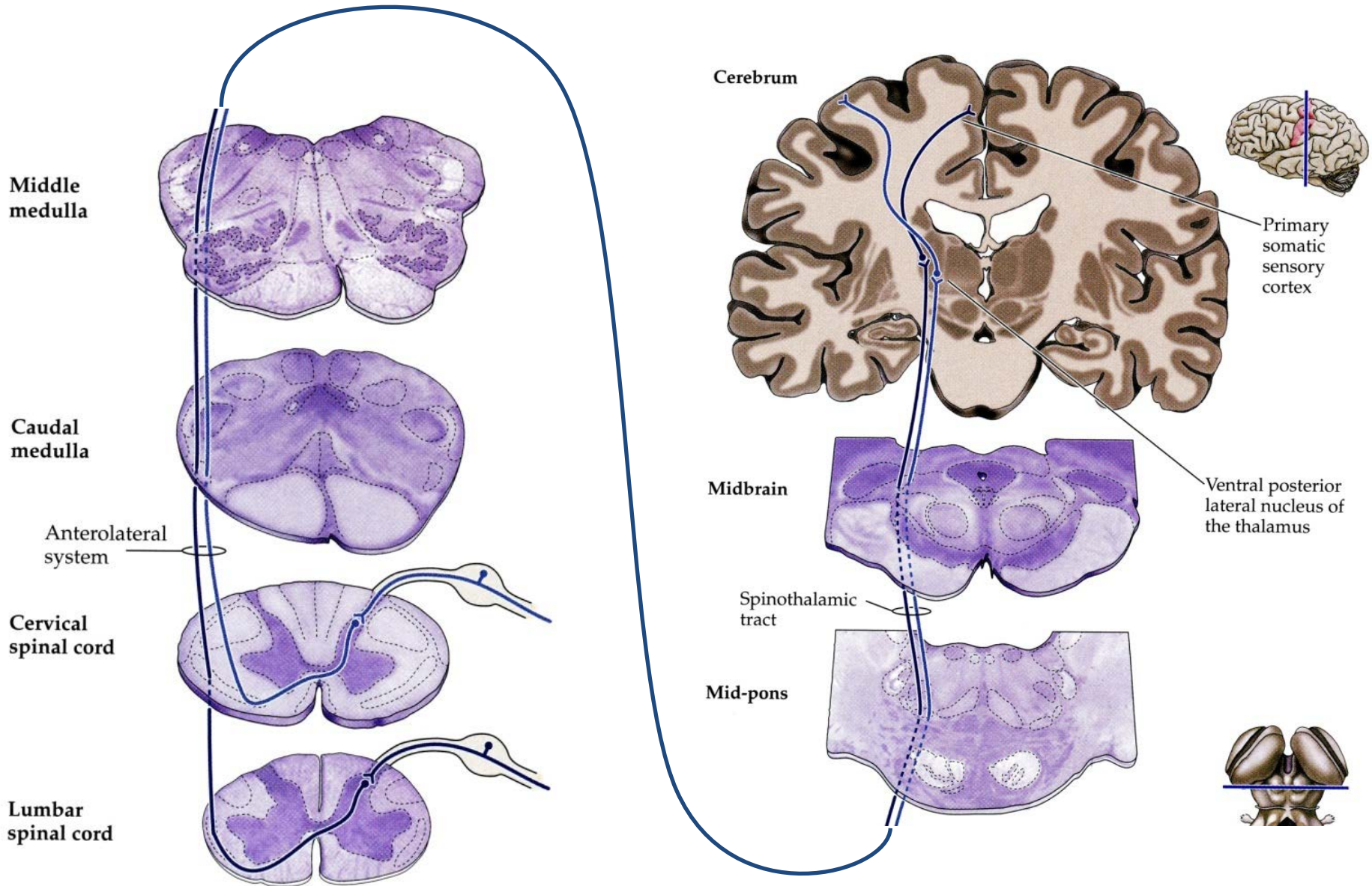
Pain pathway vs. innocuous touch

- Touch/vibration
 - First synapse: dorsal column nuclei (nucleus gracilis or nucleus cuneatus)
 - Point of crossing midline: medulla
- Pain
 - First synapse: spinal cord
 - Point of crossing midline: spinal cord

Light touch/vibration pathway



Pain/temperature pathway

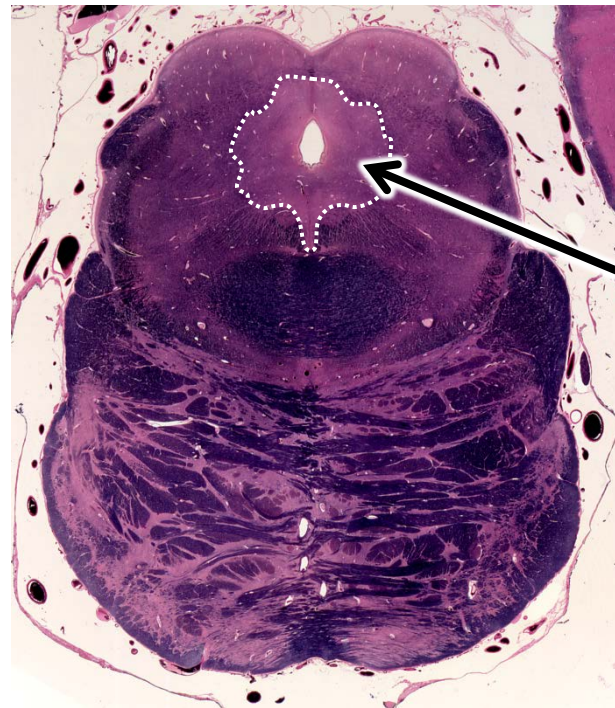


Pain modulation

- Brain circuits exist that can make pain worse or better

Stimulation-produced analgesia

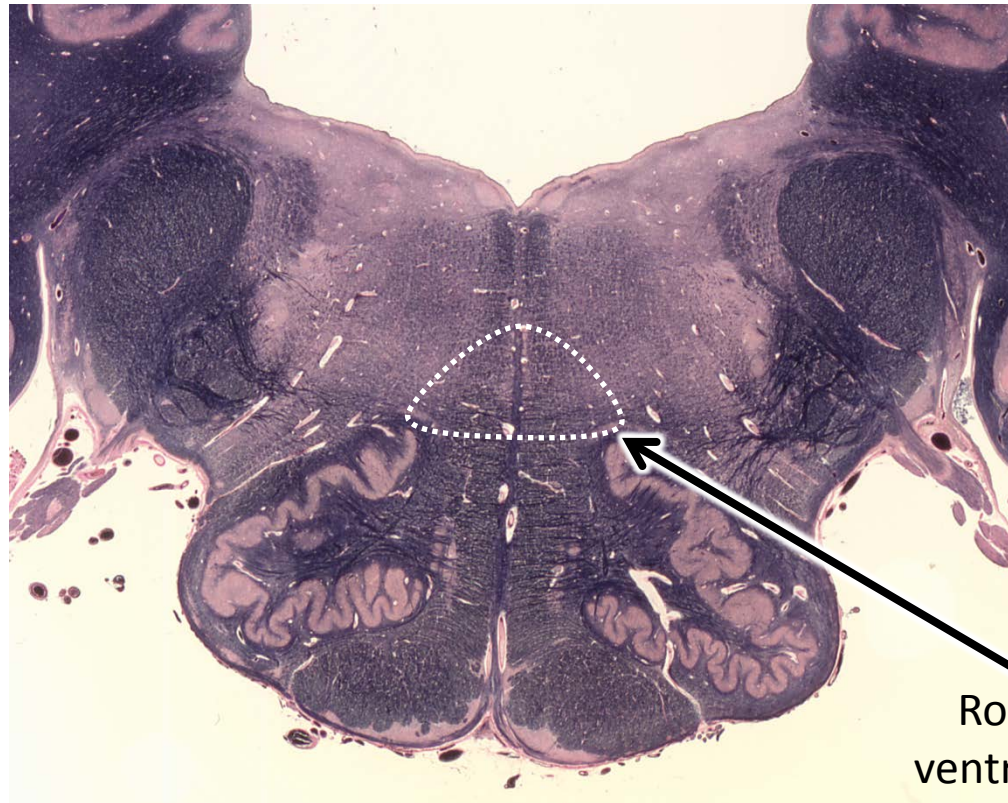
- Stimulation of the region around the cerebral aqueduct (--"central gray" or "periaqueductal gray") produces profound analgesia in rats



periaqueductal
gray

Stimulation-induced pain facilitation

- Stimulation of parts of the rostral portion of the ventromedial medulla can facilitate pain



Rostral portion of
ventromedial medulla

Pain modulation

- These circuits may mediate opiate analgesia as well as withdrawal pain
- Endogenous opioid circuits (“endorphins”) may be involved in analgesic effects

Pain treatment

- Anesthesia
 - Loss of all sensation
- Analgesia
 - Loss of pain sensation

Anesthesia

- General anesthesia
 - ***Causes loss of consciousness: no reaction to pain***
 - Inhalable or injectible
 - Inhalable: isoflurane; nitrous oxide
 - Injectible: propofol
 - Patient is unconscious and may have difficulty breathing and maintaining blood pressure
 - Used mainly for major surgery
 - “Twilight sleep” for more minor procedures

Anesthesia

- Local anesthesia
 - Used for minor or (sometimes) major surgery
 - Injectable
 - E.g., Novocaine
 - Cold temperatures act as a local anesthetic
 - Ice for sprains, burns, etc.
 - ***Blocks action potential generation/propagation at injection site***

Analgesia

- ***Selective decrease or loss of pain sensation***
- Used to decrease suffering from pain
- Major categories:
 - Non-steroidal anti-inflammatory drugs (NSAIDs)
 - Cannabinoids
 - Opioids
 - Drugs for chronic pain
 - Gabapentin, etc.

Non-steroidal anti-inflammatory drugs (NSAIDs)

- Aspirin, ibuprofen
- Inhibit synthesis of inflammatory agents (prostaglandins)
- Effective treatment for many kinds of pain
- Better than opioids for bone cancer pain

Cannabinoids

- Cannabinoid = any drug derived from cannabis
- Analgesic effects of cannabinoids reported for centuries.
- Cannabinoid agonists inhibit nociceptive neurotransmission in animal models
- Nevertheless clinical trials haven't shown consistent benefits to patients

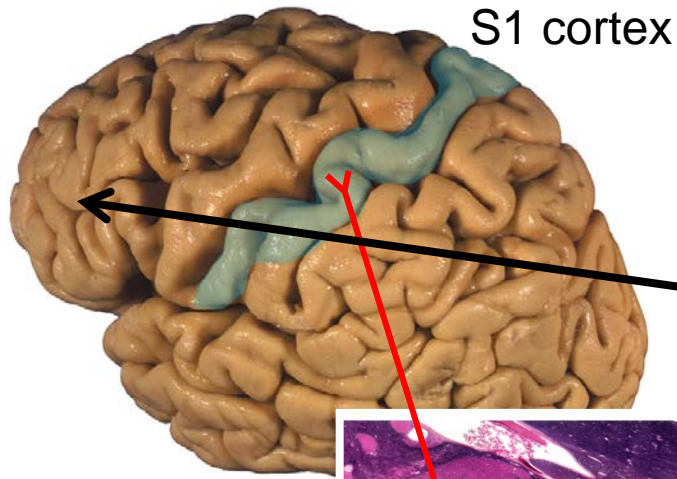
Endocannabinoid system

- Body produces chemicals active at cannabis receptors
 - Anandamide
 - 2-arachidonoylglycerol
- These compounds are broken down by body's enzymes
- Drugs that inhibit those enzymes can increase levels of endocannabinoids and are analgesic in rats

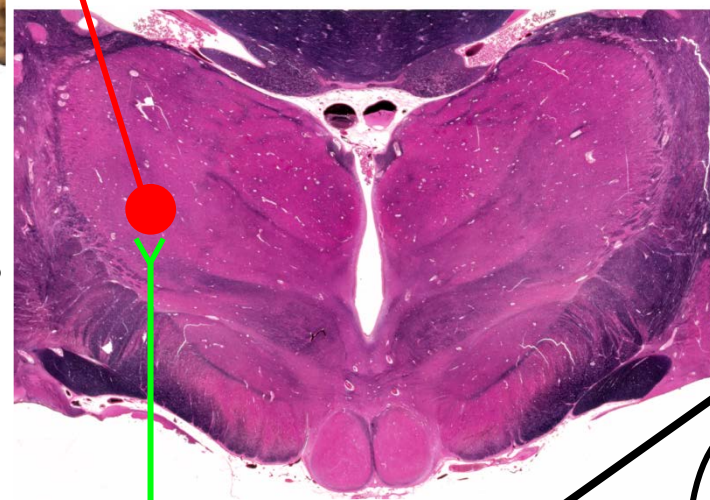
Opioids

- Drugs derived from, or related to, those coming from opium
 - Morphine
 - Heroin
 - Fentanyl
 - Codeine
 - Oxycodone (Percoset, Oxycontin)
 - Hydromorphone (Dilaudid)

Actions of opioids



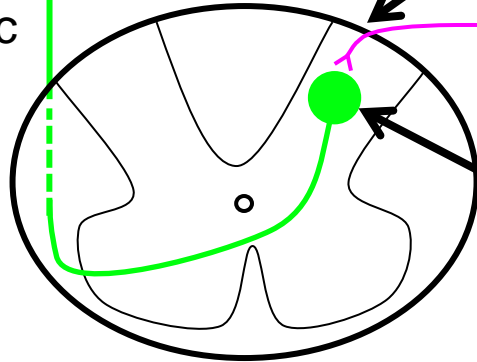
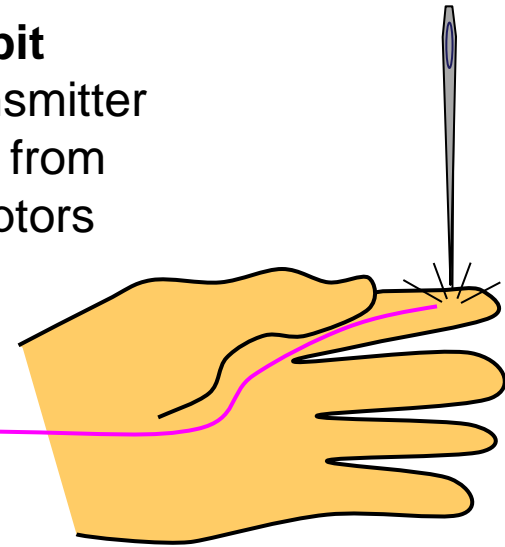
Activate pre-frontal (limbic) cortex



Inhibit neurotransmitter release from nociceptors

Spinothalamic tract

Inhibit spinothalamic tract neurons

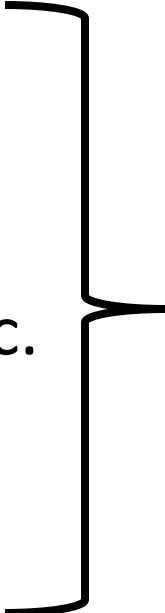


Opioid side-effects

- Constipation
 - Serious problem for chronic users
 - Drugs available for treatment of it
- Tolerance
 - Prolonged drug use → decreased effect
- Dependence
 - Drug abstinence causes pain, diarrhea, etc.
- Addiction
 - A pattern of compulsive drug use

Opioid side-effects

- Constipation
 - Serious problem for chronic users
 - Drugs available to decrease problem
- Tolerance
 - Prolonged drug use → decreased effect
- Dependence
 - Drug abstinence causes pain, diarrhea, etc.
- Addiction
 - *A pattern of compulsive drug use*



***NOT* the
same
things!**

Addiction: two-part mechanism

1. The drug makes you feel good

...But eventually...

2. **Lack** of the drug makes you feel bad (--"I need it to feel normal")

Factors that promote addiction

- Availability
 - Addicts report that it's easier to quit cocaine than it is to quit nicotine (smoking)
- Potency/delivery method
 - Gin > beer; heroin > opium
 - Crack cocaine (smoked) > cocaine (snorted)
- Living where you've used drugs
 - Simply visiting a street where you've often bought heroin, can be sufficient to induce withdrawal

Oxycontin: an addiction flow-chart

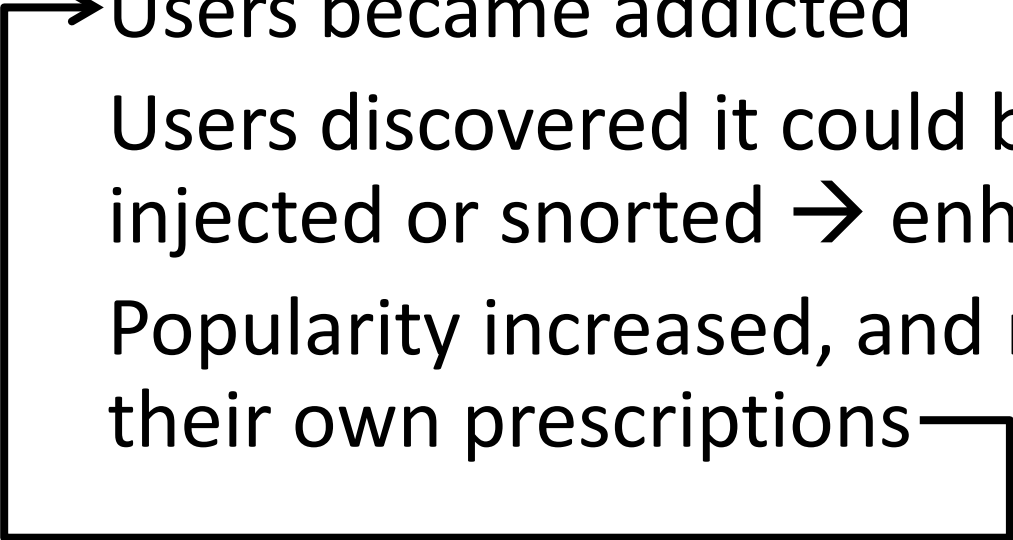
Oxycontin = sustained-release form of oxycodone

Advertised for treatment of chronic pain (i.e. increased availability)

→ Users became addicted

Users discovered it could be crushed, and then injected or snorted → enhanced “rush”

Popularity increased, and new users asked for their own prescriptions



Will cannabinoids be a panacea?

- As potency increases, addictive potential will increase
- Potent cannabinoid drugs may be found to be addictive