# Pain and opioids

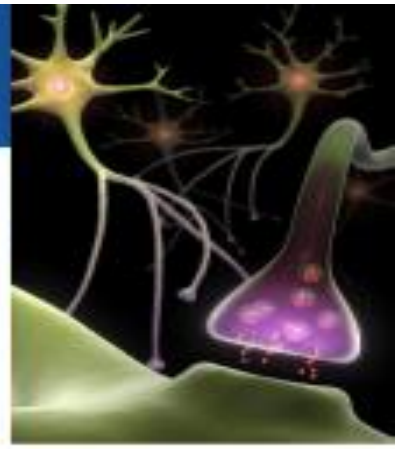
National Institute of Neurological Disorders and Stroke

## Pain and Opioids

*NCI Integrative Medicine Course*

February 27, 2020

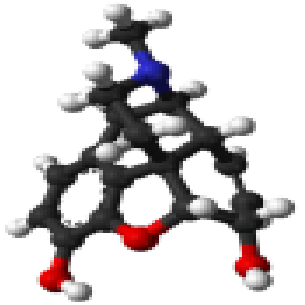
Walter J. Koroshetz, MD
Director, NINDS
DP Mohapatra, PhD
Program Director, NINDS



# Opiate history

## How did we get here?

- 1805: Friedreich Sertuerner isolates morphine from tarry poppy seed juice
  - Physicians believe opium has been tamed
  - Morphine dubbed "God's own medicine" for long-lasting effects and safety
- 1827: Merck starts commercial manufacture of morphine
- 1843: Dr. Alexander Wood discovers intravenous injection is more powerful and quick
- 1895: Bayer company purifies heroin and used to wean morphine addicts
- 1905: US Congress bans opium
- 1914: US requires doctors prescribing narcotics to register



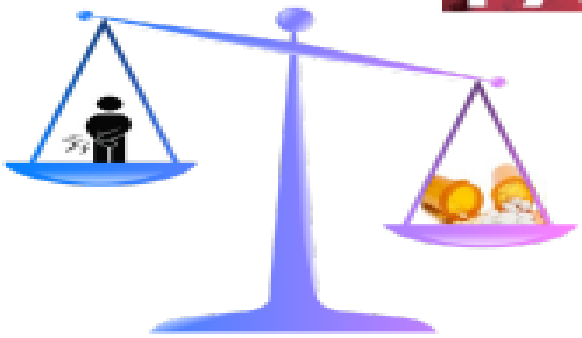
*Morphine molecule*

# Treating pain

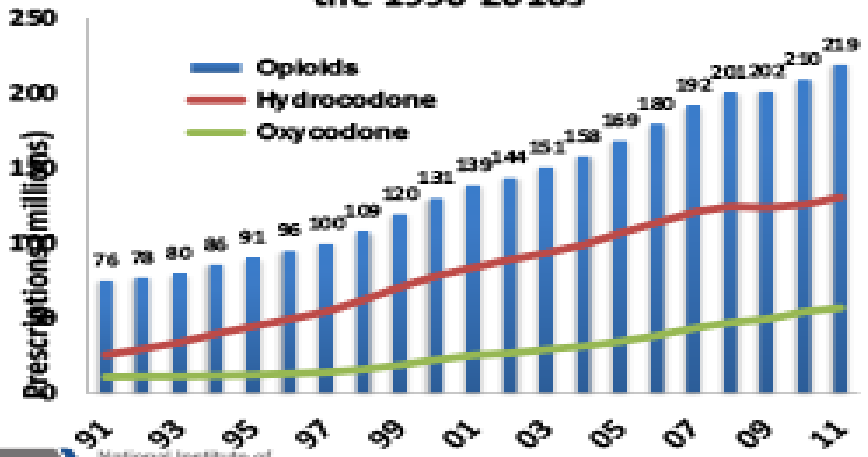
## Balancing act of treating pain

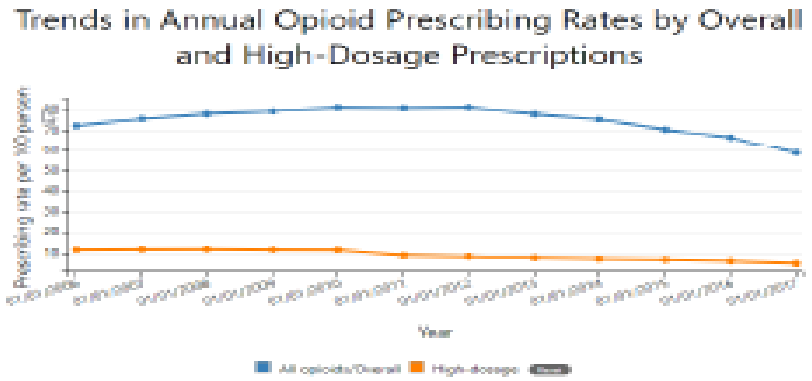

100 million American adults have pain

- 40 million have severe pain
- 25 million report daily pain
- 8 million have pain that interferes with lifestyle



**Opioid prescriptions increased through the 1990-2010s**

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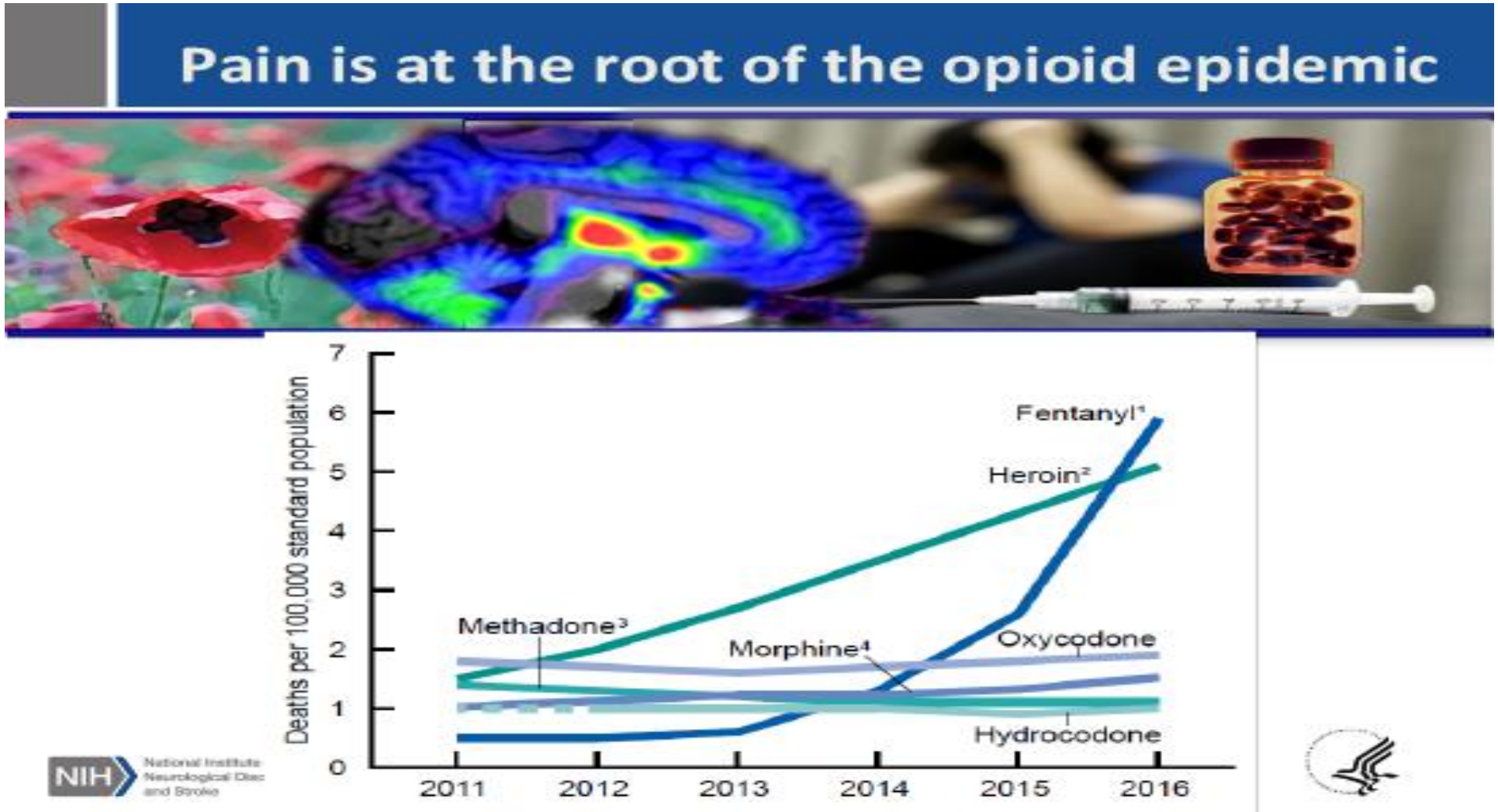
Source: NIDA, IMS Health, National Prescription Audit, years 1997-2011

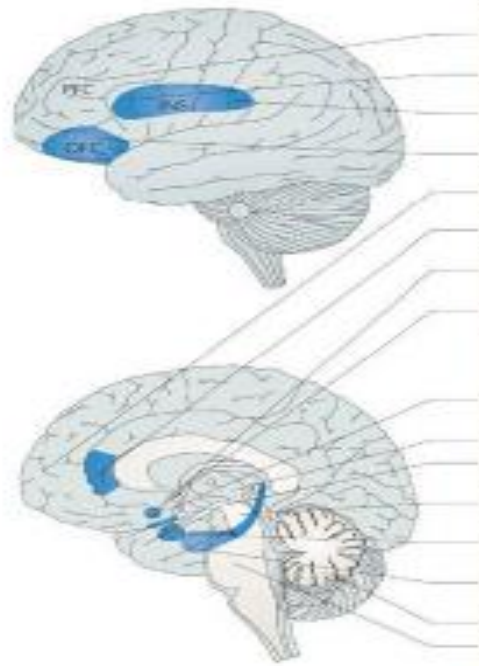
# Opioid epidemic



# Pain and pleasure

**"Nature has placed mankind under the governance of two sovereign masters, Pain and Pleasure" - Jeremy Bentham**

Brain regions implicated in pain and reward processing show striking overlap in neuroimaging and electrophysiology studies




| Region | Pleasure/reward | Pain |
|---|---|---|
| Lateral prefrontal cortex | • Humans, fMRI, taste reward[69] | • Humans, $H_2O$ PET, hyperalgesic pain[70]<br>• Humans, fMRI, pain[71] |
| Anterior insula | • Humans, fMRI, food cravings[69]<br>• Humans, $H_2O$ PET, chocolate reward[71] | • Humans, fMRI, pain[72]<br>• Humans, fMRI, placebo analgesia[69] |
| Posterior insula | • Humans, fMRI, hypothetical reward[69] | • Humans, direct brain stimulation[68]<br>• Humans, fMRI, pain[72] |
| Orbitofrontal cortex | • Humans, fMRI, pleasant touch[73]<br>• Humans, fMRI, chocolate reward[71] | • Humans, fMRI, pain[74]<br>• Humans, fMRI, placebo analgesia[69] |
| Medial prefrontal cortex | • Humans, $H_2O$ PET, pleasurable music[34]<br>• Humans, fMRI, monetary reward[69] | • Humans, fMRI, pain[75,76] |
| Anterior cingulate gyrus | • Monkeys, electrophysiology[77]<br>• Humans, $H_2O$ PET, chocolate reward[71] | • Humans, fMRI, pain[71]<br>• Humans, opioid PET[71] |
| Dorsal striatum | • Humans, fMRI, fruit juice[78]<br>• Humans, fMRI, monetary reward[79] | • Humans, dopamine ligand PET, pain[71]<br>• Humans, fMRI, pain[78] |
| Nucleus accumbens/ ventral striatum | • Humans, fMRI and dopamine ligand PET, monetary reward[69]<br>• Rodents, hedonic hotspot, taste reactivity<br>• Humans, dopamine ligand PET, drug reward | • Humans, dopamine ligand PET[71]<br>• Humans, fMRI, expectation of pain[80]<br>• Rodents, pain-induced analgesia[81] |
| Ventral pallidum | • Rodents, taste reactivity[82,83] | • Rodents, tracing, pain affect[84]<br>• Humans, μ-opioid PET, sustained pain[85] |
| Thalamus | • Humans, $H_2O$ PET, chocolate reward[71] | • Humans, fMRI, placebo analgesia[69] |
| Hypothalamus | • Humans, $H_2O$ PET, pleasurable music[34] | • Rodents, tracing of nociception pathway[86]<br>• Humans, direct brain stimulation[87] |
| Midbrain | • Humans, $H_2O$ PET, chocolate reward[71]<br>• Humans, $H_2O$ PET, pleasurable music[34] | • Humans, fMRI, anticipation of pain[88]<br>• Humans, fMRI, pain[72] |
| Amygdala | • Humans, $H_2O$ PET, pleasurable music[34]<br>• Primates, reward anticipation/learning[89] | • Humans, fMRI, pain[90,91] |
| Hippocampus | • Humans, fMRI, unexpected reward[92]<br>• Humans, $H_2O$ PET, pleasurable music[34] | • Humans, fMRI, pain[93]<br>• Humans, fMRI, anticipation of pain[94] |
| Cerebellum | • Humans, fMRI, unexpected reward[92] | • Humans, fMRI, pain[71] |
| Brainstem | • Rodents, taste reactivity[95]<br>• Rodents, conditioned place preference[96] | • Humans, fMRI, pain[72]<br>• Rodents, pain[97] |

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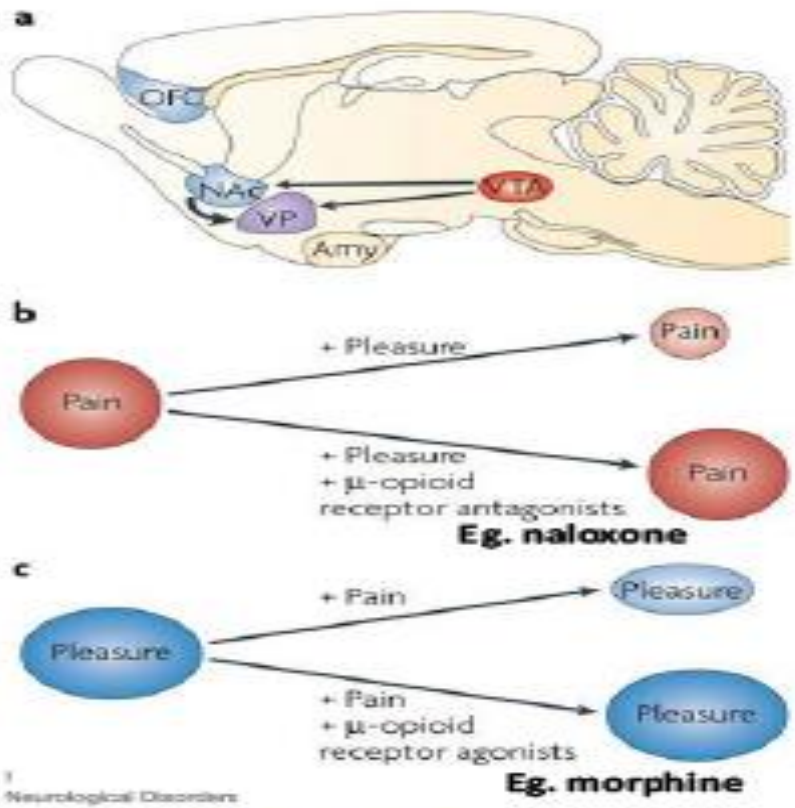
Nature Reviews | Neuroscience
Nat Rev Neurosci. 2008 Apr;9(4):314-20

# Pain versus reward

## Pain versus reward

### Shared pathway

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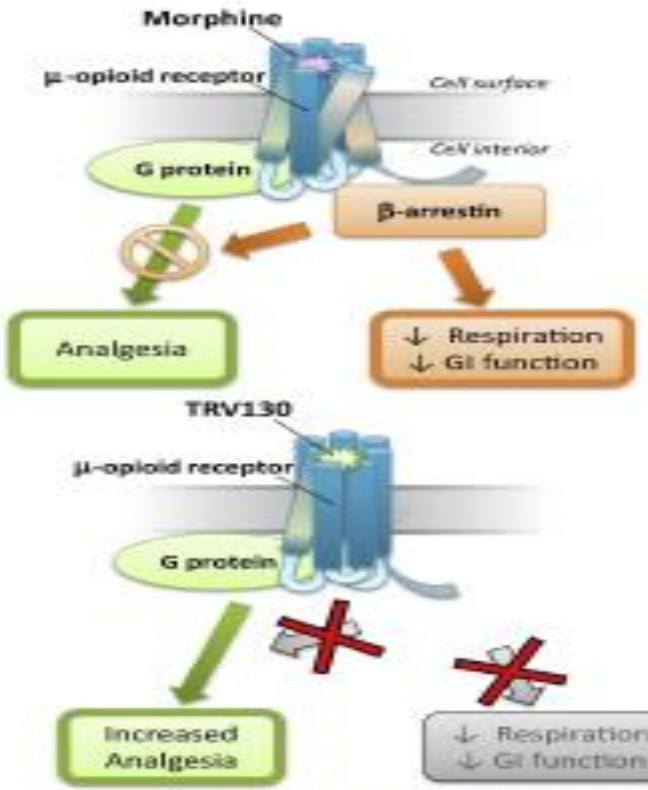
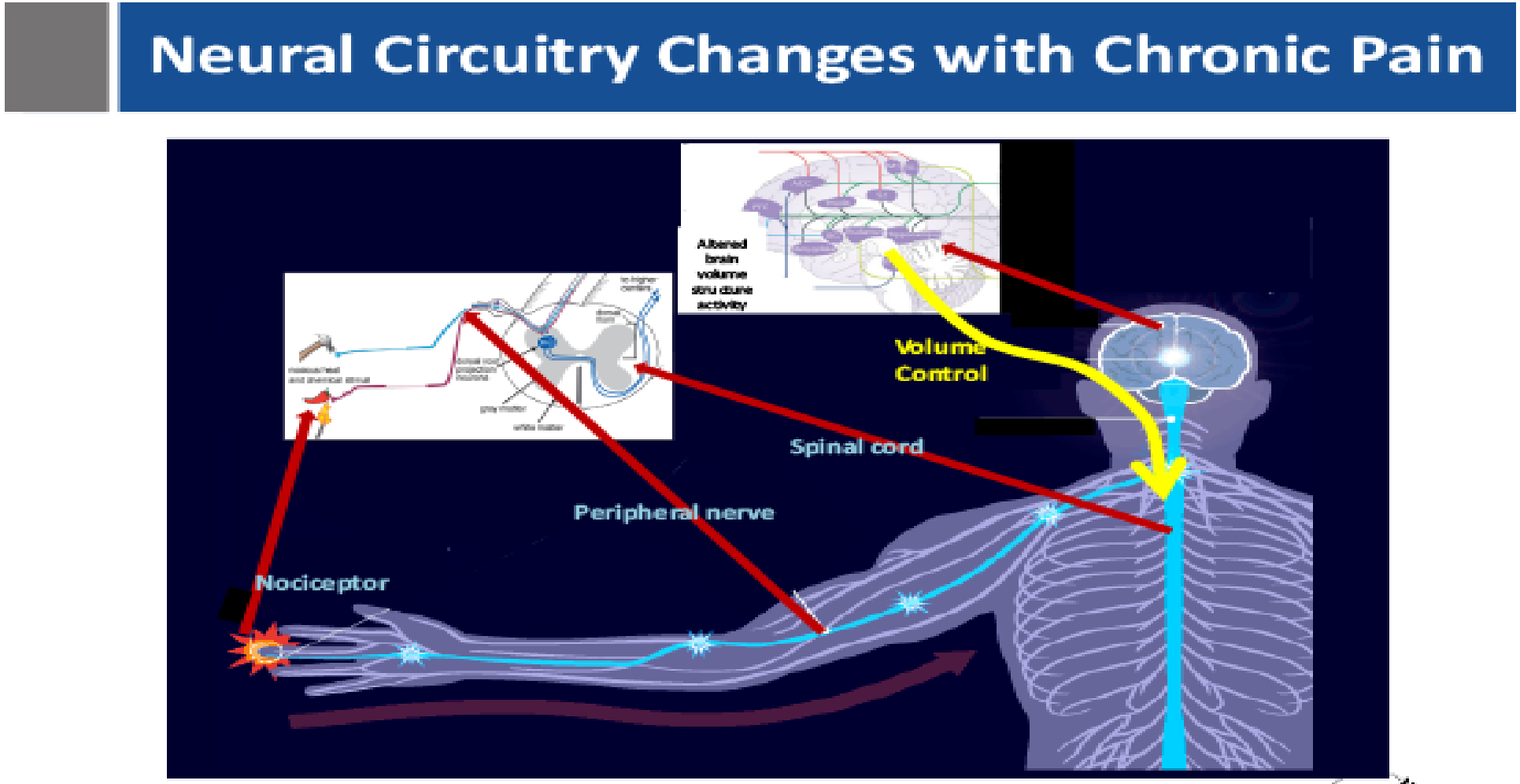
Nat Rev Neurosci. 2008 Apr;9(4):314-20

### Opioid receptor mediates reward and analgesia and other critical functions



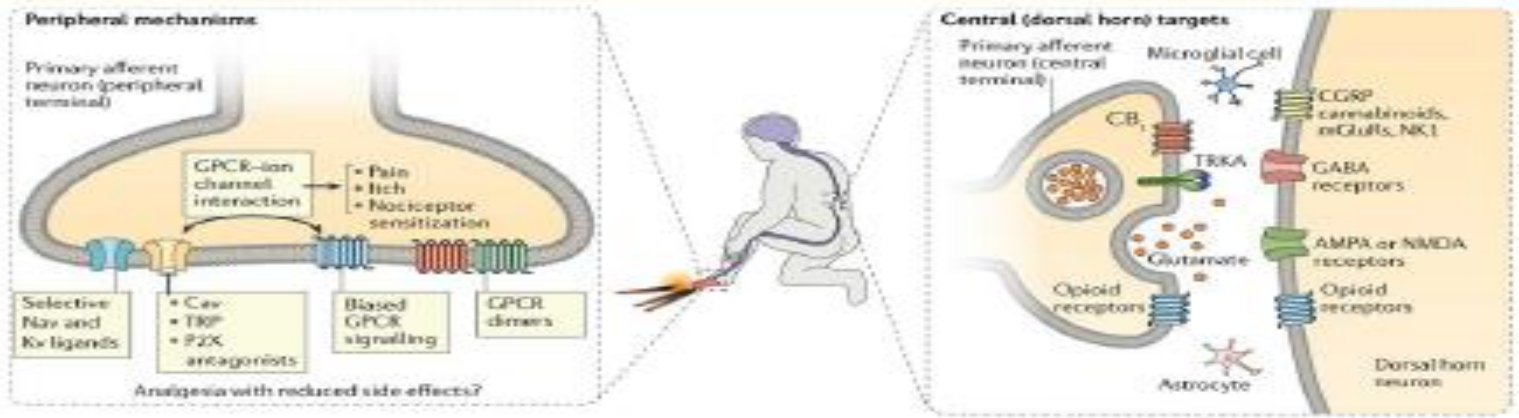

Pain. 2014 Sep;155(9):1829-35.

# Neural circuitry changes



# New targets for pain

## Advances in pain research: New Targets for Pain




- HSV vector driven expression of analgesic signals in DRG
- Transient receptor potential channels (TRPA1/4)
  - TRPA1 gain of function mutation causes familial episodic pain syndrome
- Voltage activated Ca++ channel blockers
- K+ channels blockers
- Chemokine receptor antagonists
- Tetrahydropbiopterin from GTP release from injured neurons, polymorphisms in BCH1 enzyme linked to pain vulnerability
- Alpha2 adrenergic agonist
- Bivalent MOR with linked mGluR5 antagonist, CCR5 antagonist, delta OR antagonist,
- Epigenetic mechanisms involved in chronic pain
- microRNA cluster 183

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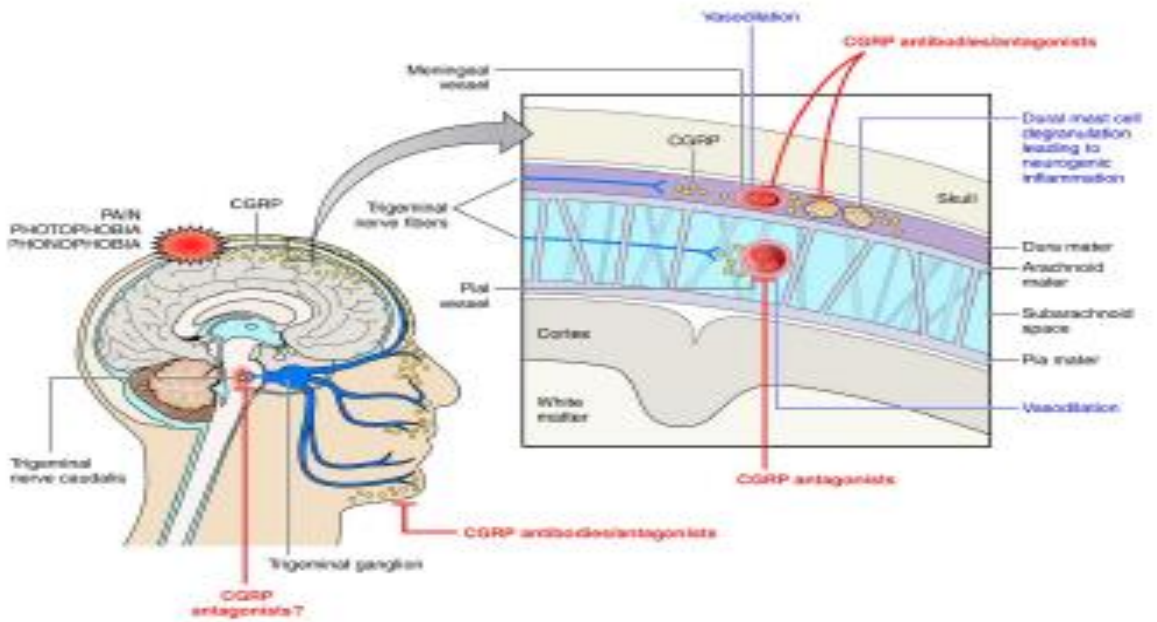
Nat Rev Drug Discov. 2017 Aug;16(8):545-564

# cGRP for migrane

## Advances in Pain Research: cGRP for Migraine

- Calcitonin gene-related peptide (cGRP) levels:
  - rise during spontaneous migraine attacks
  - Increased levels in serum in chronic migraine patients
  - decrease in response to triptans in parallel with symptomatic relief
- Kappa Opioid Receptor (KOR) antagonists block increased cGRP
- Anti-cGRP Monoclonal antibodies are in phase 3 clinical trials for migraine prevention




Curr Treat Options Neurol. 2017 Aug;19(8):27.
Cephalalgia. 2017 Jul;37(8):780-794.

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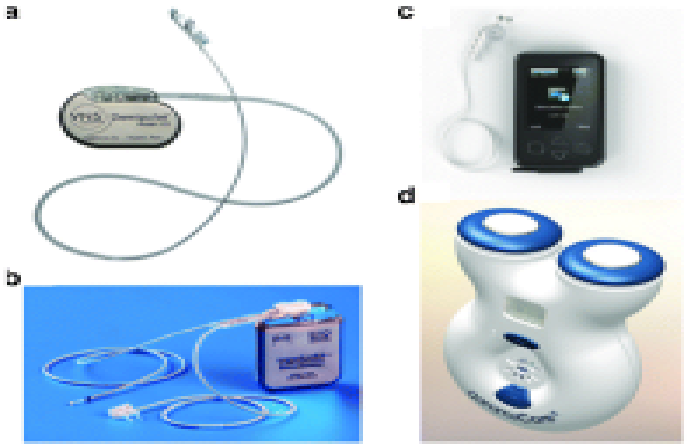
# Vagus nerve stimulation

## Advances in Pain Research: FDA Approval for Vagus Nerve Stimulation in Headache




Curr Pain Headache Rep. 2015 Dec;19(12):54.

gammaCore® Receives FDA Clearance for the Acute Treatment of Pain Associated with Migraine Headache in Adult Patients

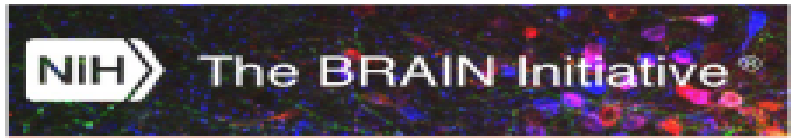
First non-invasive vagus nerve-stimulation therapy applied at the neck provides new option for Americans living with migraine

electroCore

FDA Releases gammaCore®, the First Non-Invasive Vagus Nerve Stimulation Therapy Applied at the Neck for Acute Treatment of Pain Associated with Episodic Cluster Headache in Adult Patients

# Brain initiative

## Translating the BRAIN Initiative to address pain and the opioid crisis



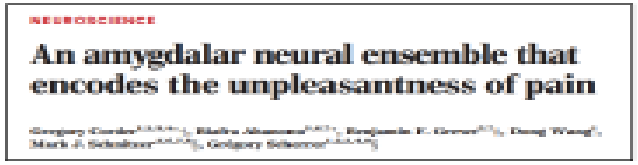

**FIRST FIVE YEARS** → **SECOND FIVE YEARS**

Emphasize technology development

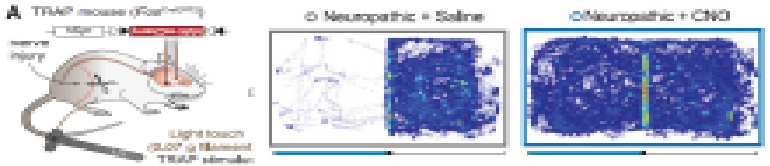
Emphasize discovery driven science

**Molecular/Structural Pathology** → **Circuit Dysfunction** → **Neuro/Mental/Substance Abuse Functional Disability**

- One example of BRAIN-funded scientists contributing to understanding of pain as a circuit disorder
- Silencing Basal Lateral Amygdalar (BLA) neurons alleviates pain affective-motivational behaviors without affecting detection of pain stimuli
- **Would silencing these BLA neurons in people with chronic pain limit their suffering without affecting their nociceptive sensitivity?**


NEUROSCIENCE

An amygdalar neural ensemble that encodes the unpleasantness of pain




Corder et al., *Science*, 2019

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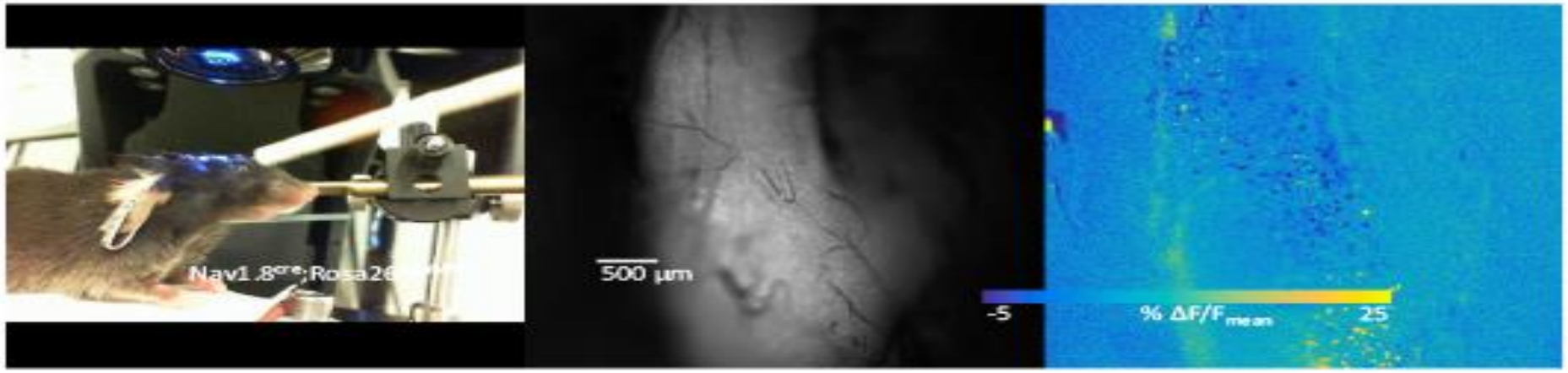
# Neural circuit activity

Tools from the NIH BRAIN Initiative enable precise monitoring and modulation of neural circuit activity

Live cell imaging of GCaMP responses in Nav1.8+ trigeminal ganglion neurons



# NIH pain consortium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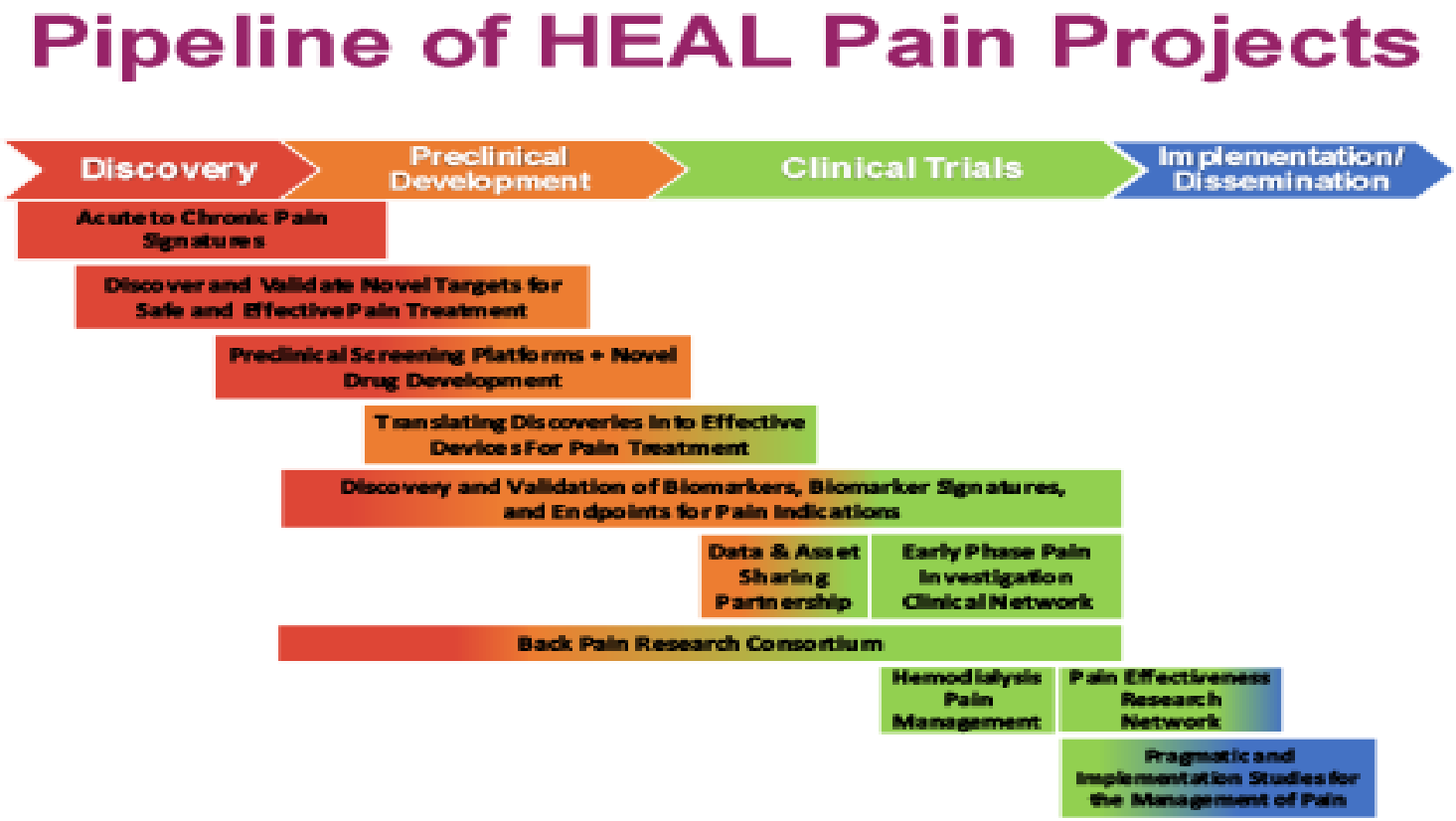
# Helping end addiction

## NIH Helping End Addiction Long-term (HEAL) Initiative

- Mission: scientific solutions to the opioid crisis
- $500M/year Trans-NIH effort
  - Over $945M obligated in FY2019
- 12 NIH Institute and Centers currently leading 26 HEAL research projects
  - Over 20 collaborating Institutes, Centers and Offices
  - From prevention, basic and translational research, clinical trials, to implementation science
- Released 40+ funding announcements in FY2019, issued over 400 awards

# HEAL initiative

# Projects

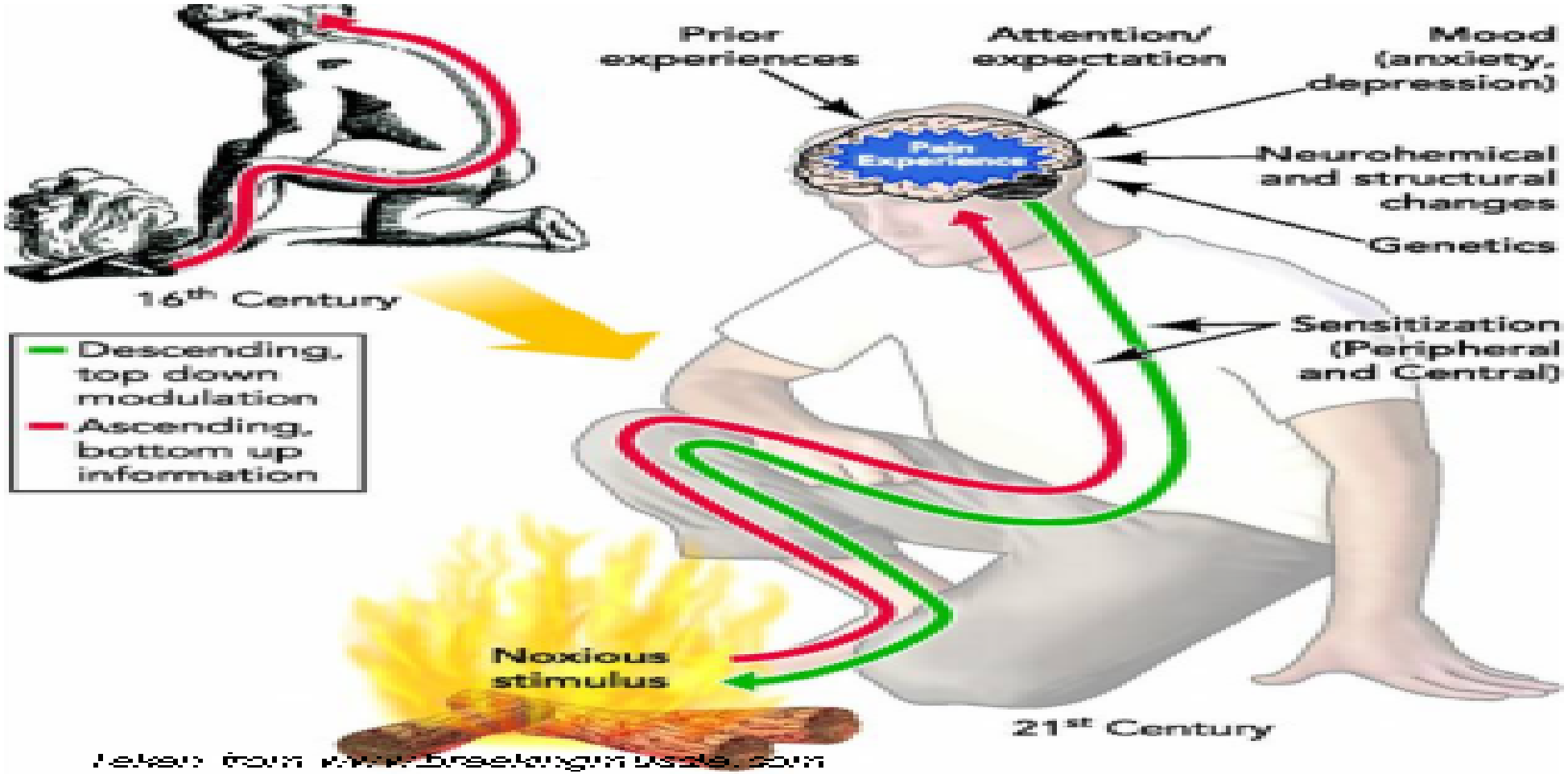

Pipeline of HEAL Pain Projects
Discovery
Preclinical Development
Clinical Trials
Implementation/ Dissemination
Acute to Chronic Pain Signatures
Discover and Validate Novel Targets for Safe and Effective Pain Treatment
Preclinical Screening Platforms + Novel Drug Development
Translating Discoveries into Effective Devices For Pain Treatment
Discovery and Validation of Biomarkers, Biomarker Signatures, and Endpoints for Pain Indications
Data & Asset Sharing Partnership
Early Phase Pain Investigation Clinical Network
Back Pain Research Consortium
Hemodialysis Pain Management
Pain Effectiveness Research Network
Pragmatic and Implementation Studies for the Management of Pain

# DP Mohapatra


NIH National Institute of Neurological Disorders and Stroke

# Human pain

# What is pain?


Prior experiences
Attention/ expectation
Mood (anxiety, depression)
Pain Experience
Neurochemical and structural changes
Genetics
Sensitization (Peripheral and Central)
16th Century
Descending, top down modulation
Ascending, bottom up information
Noxious stimulus
21st Century

# Why do I have pain?


A protective mechanism / alarm system in our body to warn about infection/injury and pathological conditions


# Nociception versus pain

## Nociception vs Pain

**Nociception** - The activation of nociceptors by noxious stimuli. *Nociception may or may not be accompanied by the perception of pain.*

**Nociceptor:** Sensory nerve/neuron that responds to damaging or potentially damaging stimuli by sending electrochemical signals to the spinal cord and brain.

**Pain** - The perception of actual or impending tissue damage. In certain pathological conditions, Pain may not be associated with nociception.

# Classes of Pain

## Classes of Pain

### Nociceptive Pain

**Pain originating as a results of activation of nociceptors in response to tissue injury**

### Neuropathic Pain

**Pain originating due to a lesion or disease of the somatosensory, sympathetic or central nervous system**

### Nociplastic Pain (new class – 2017)

**Pain originating from altered nociception despite no clear evidence of**

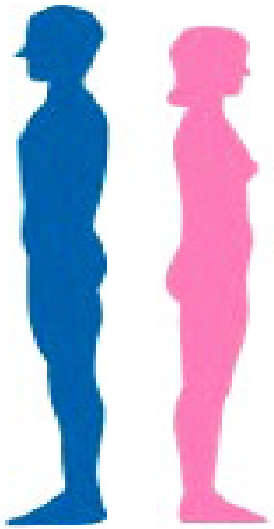
- actual or threatened tissue damage causing activation of peripheral nociceptors or
- disease or lesion of the somatosensory system causing the pain

# Cancer cases

## Incidences of Major Cancers in the US
## Facts & Figures – New Cases Predicted for 2019

### Males

| | | |
|---|---|---|
| Prostate | 174,650 | 22% |
| Lung & bronchus | 116,440 | 14% |
| Colo-rectum | 78,500 | 9% |
| Urinary bladder | 61,700 | 7% |
| Melanoma of the skin | 57,220 | 8% |
| Non-Hodgkin lymphoma | 41,090 | 5% |
| Kidney & renal pelvis | 44,120 | 5% |
| Oral Cavity & pharynx | 38,140 | 4% |
| Leukemia | 35,920 | 4% |
| Liver & hepatic bile duct | 29,480 | 3-4% |
| Pancreas | 29,940 | 3-4% |
| Bone & joints | 2,030 | 0.21% |
| All Sites | 870,970 | 100% |



### Females

| | | |
|---|---|---|
| Breast | 268,600 | 30% |
| Lung & bronchus | 111,710 | 12% |
| Colo-rectum | 67,100 | 8% |
| Uterine corpus and cervix | 74,050 | 6% |
| Thyroid | 37,810 | 6% |
| Non-Hodgkin lymphoma | 33,110 | 4% |
| Melanoma of the skin | 39,260 | 5% |
| Pancreas | 26,640 | 3% |
| Leukemia | 25,860 | 3% |
| Kidney & renal pelvis | 29,700 | 3% |
| Ovary | 22,530 | 2-3% |
| Bone & joints | 970 | 0.11% |
| All Sites | 891,480 | 100% |

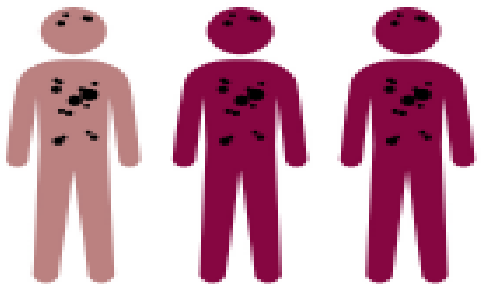
Metastatic bone cancers account for >97% of all bone cancers

Source - American Cancer Society. *Cancer Facts & Figures 2019*. Atlanta: American Cancer Society; 2019

# Chronic pain

## The Problem(s) of Chronic Pain

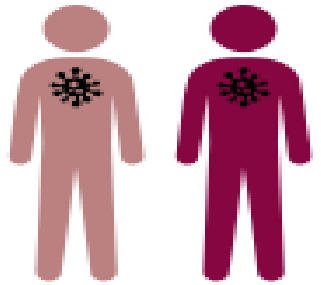
- Over **100 million** Americans suffer from **chronic pain**



**66%**

of patients who have advanced **metastatic** or **terminal cancer** experience pain

6-8 out of 10 patients with advanced cancers express major fear of dying due to excruciating/unbearable PAIN



**55%**

of patients undergoing **treatment for cancer** experience pain

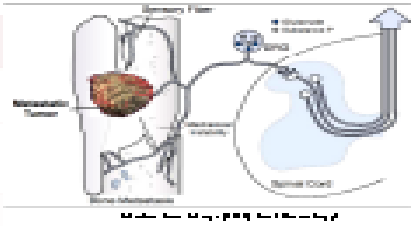
- Associated with multiple chemoRx
  - Platinum drugs (oxaliplatin, cisplatin)
  - Taxanes (paclitaxel, docetaxel)
  - Proteasome inhibitors (bortezomib)
  - Plant alkaloids (vincristine); IMDs (thalidomide)
- Mainly lead to peripheral neuropathy and associated chronic pain
- **Annual financial impact of chronic pain in the US**
  - **$560-635 billion**

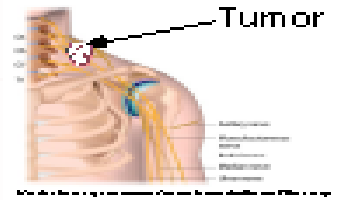
*Source: Institute of Medicine Report (2011); WHO guidelines for the management of cancer pain in adults and adolescents (2019)*

# Types of cancer pain

## Types of Cancer Pain

| TYPE | | | NEURAL MECHANISM | EXAMPLE |
|---|---|---|---|---|
| *Nociceptive* | Visceral | | Stimulation of pain receptors on normal sensory nerve endings | Hepatic capsule stretch |
| | Somatic | | | Bone metastases |
| *Neuropathic* | Nerve compression | | Stimulation of *nervi nervorum* | Sciatica due to vertebral metastasis with compression of L4, L5 or S1 nerve root |
| | Nerve injury | Peripheral | Lowered firing threshold of sensory nerves (deafferentiation pain) | Tumour infiltration or destruction of brachial plexus |
| | | Central | Injury to central nervous system | Spinal cord compression by tumour |
| | | Mixed | Peripheral and central injury | Central sensitization due to unrelieved peripheral neuropathic pain |
| | Sympathetically maintained | | Dysfunction of sympathetic system | Chronic regional pain syndrome following fracture or other trauma |

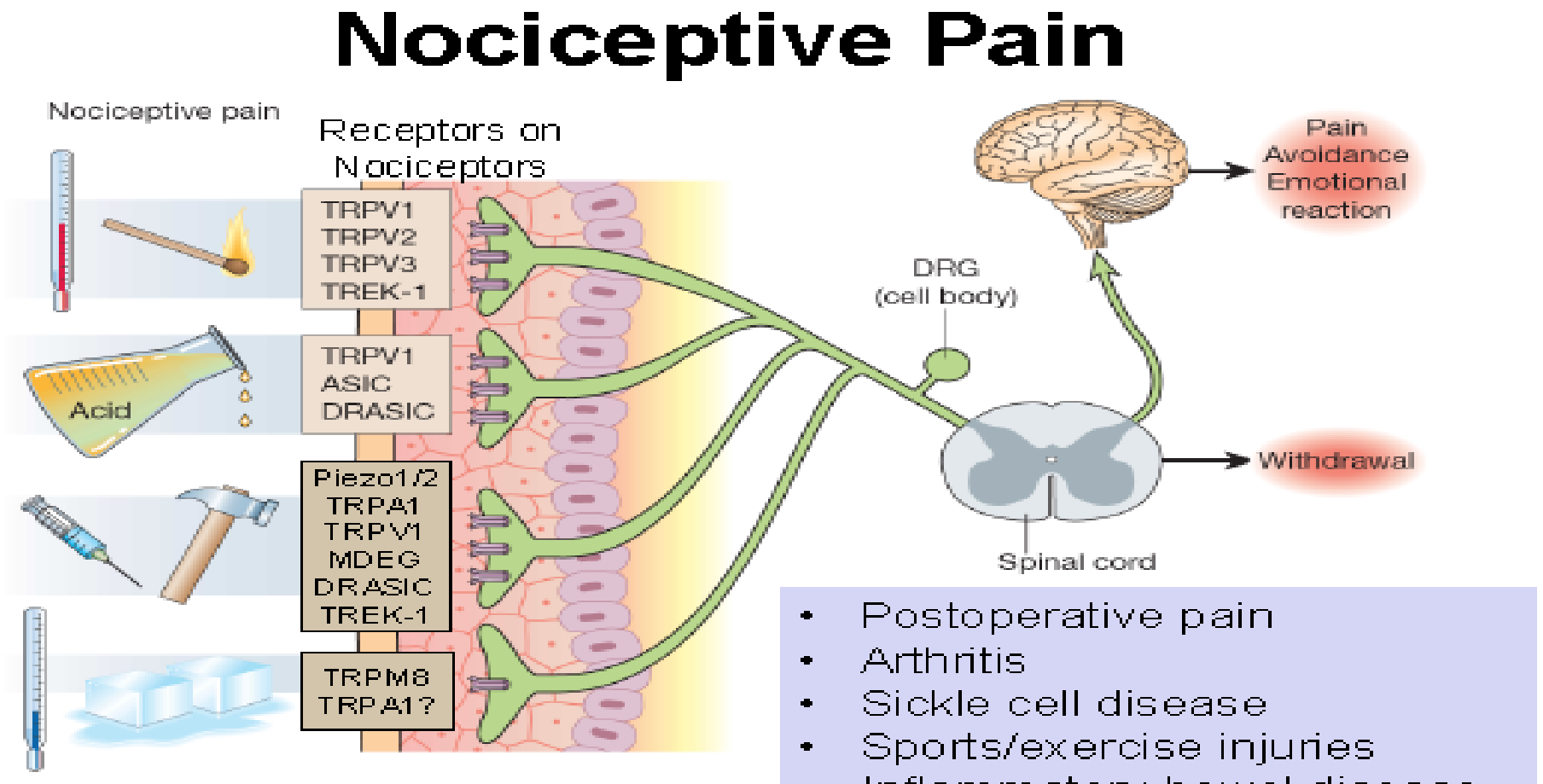






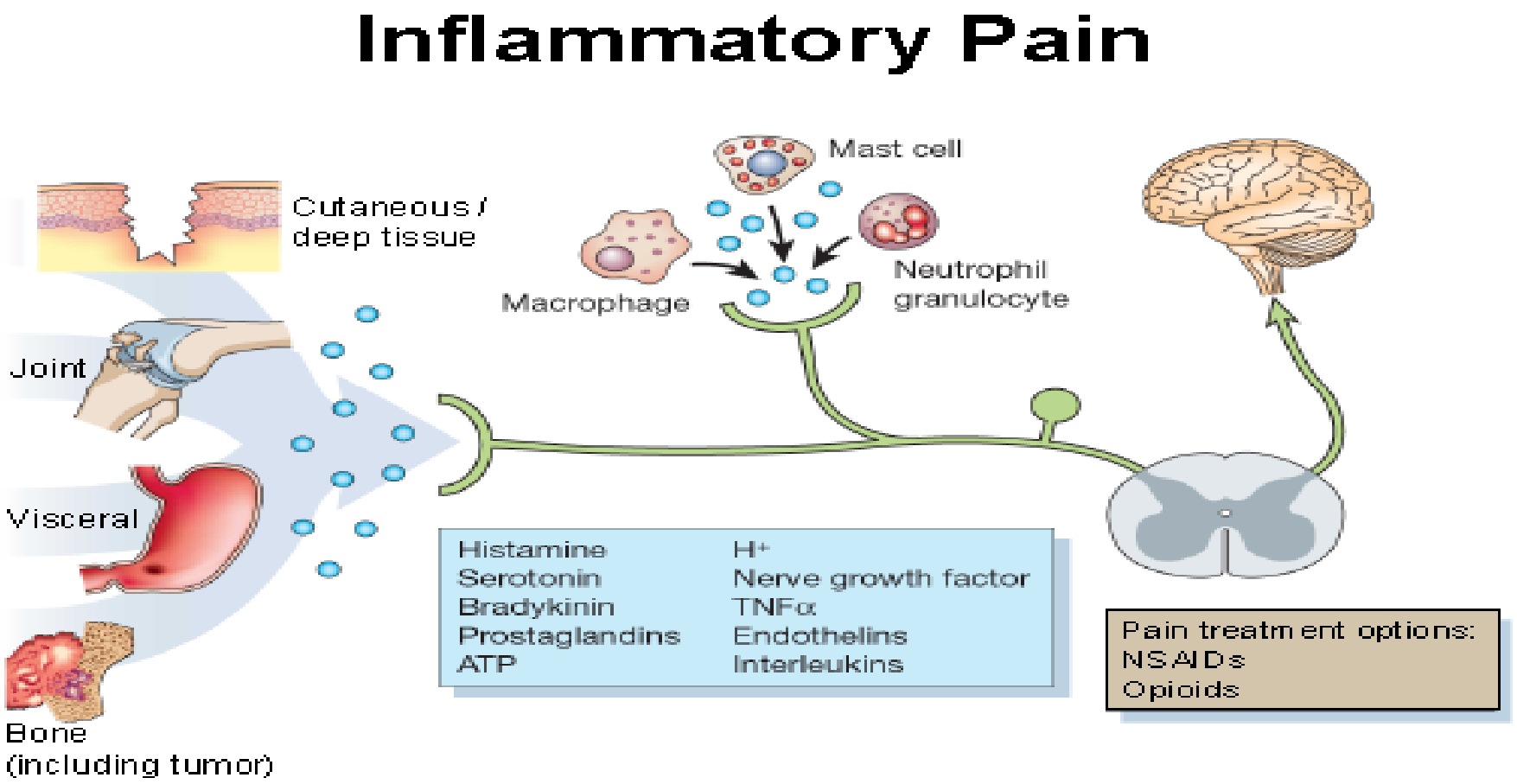
*Source : WHO guidelines for the management of cancer pain in adults and adolescents (2019)*

# Nociceptive pain




- Postoperative pain
- Arthritis
- Sickle cell disease
- Sports/exercise injuries
- Inflammatory bowel disease
- Primary & metastatic cancers

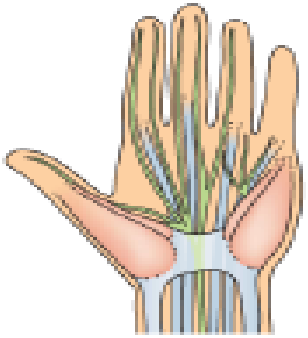
# Inflammatory pain



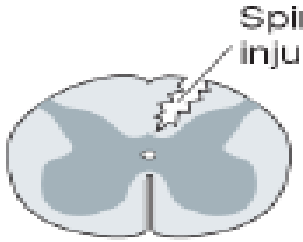

Modified from Schaible and Woolf, 2002, Nature Neuroscience

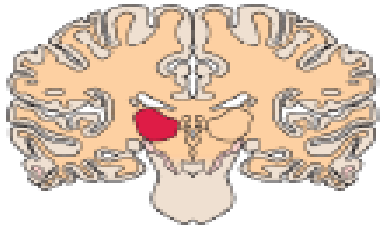
# Neuropathic pain

## Neuropathic Pain



Carpal tunnel syndrome



Thalamic stroke

- Trigeminal neuralgia
- Central post-stroke pain
- Distal polyneuropathy (eg. Diabetic, HIV, CIPN)
- Spinal tumor-induced nerve compression
- Spinal cord injury-induced pain
- Postherpetic neuralgia / Shingles
- Neuropathic low back pain

Pain treatment options:
Tricyclic antidepressants
Anticonvulsants
$Na^+$ channel blockers
NMDA receptor antagonists
Opioids

*Modified from Sehgal and Woolf, 2002, Nature Neuroscience*

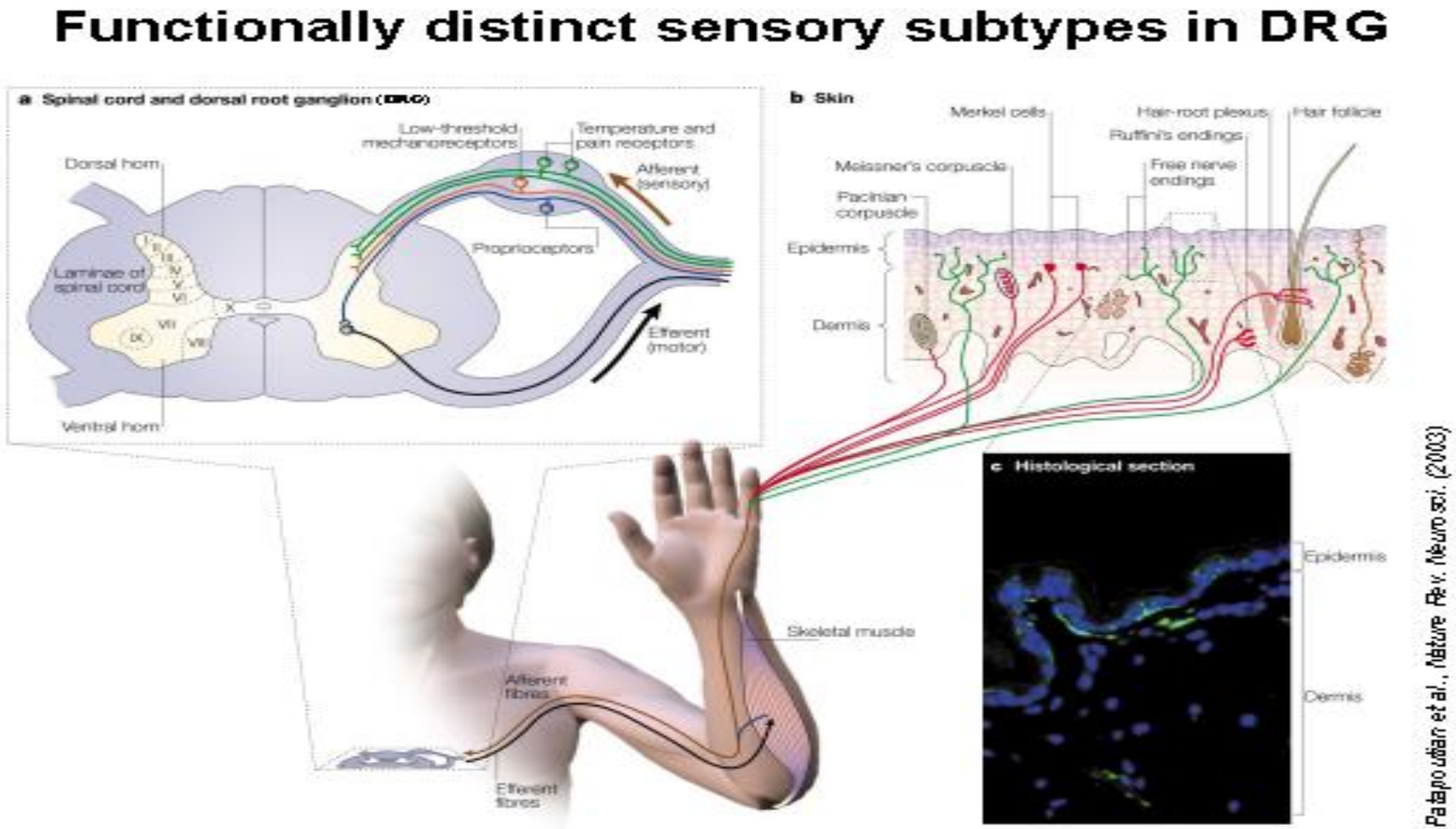
# Nociplastic pain

## Nociplastic Pain

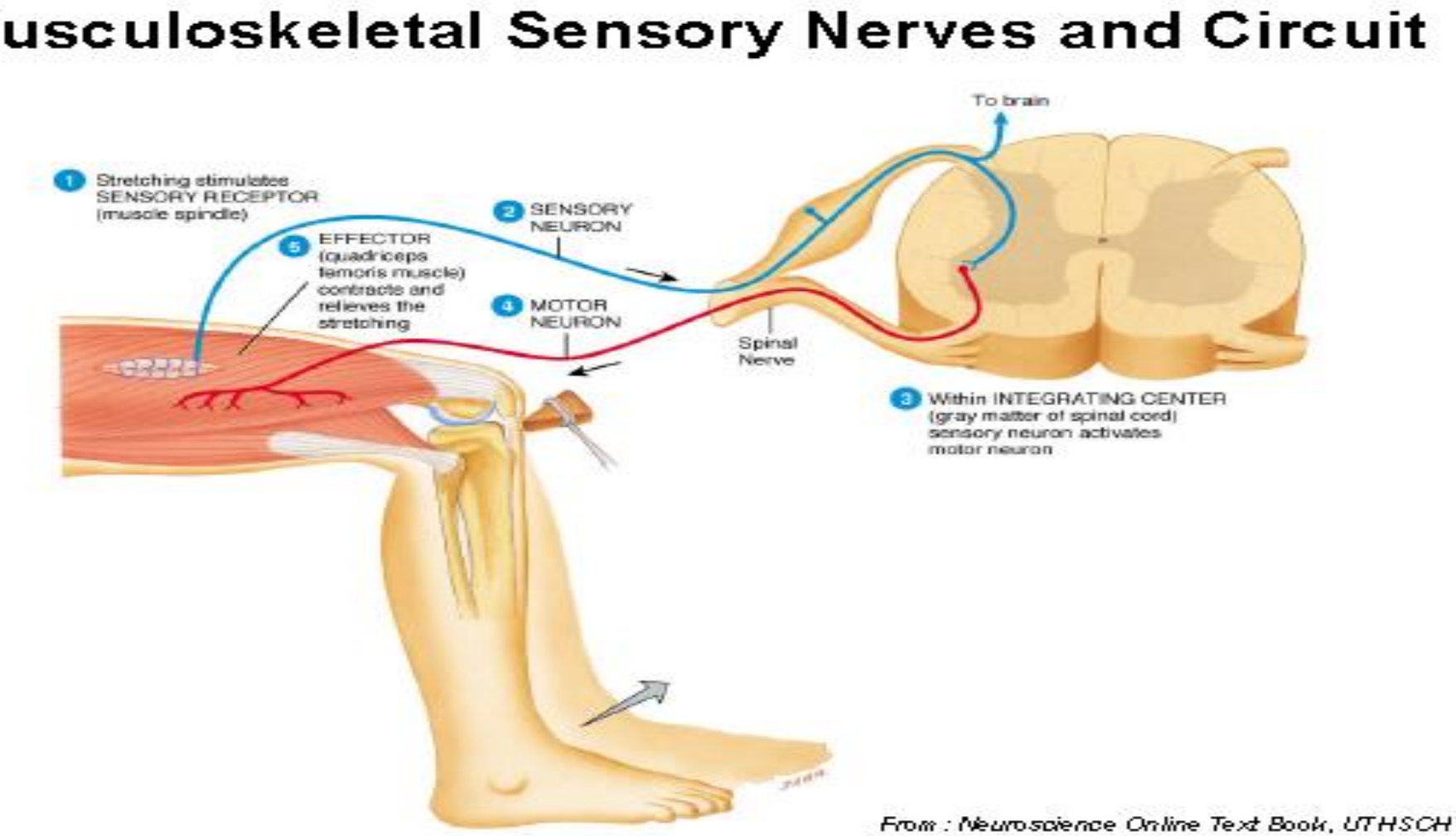


- Fibromyalgia
- Complex regional pain syndrome (CRPS)
- Pain in irritable bowl syndrome
- Chronic low back pain
- Bladder pain syndrome
- Spinal tumor-induced nerve compression

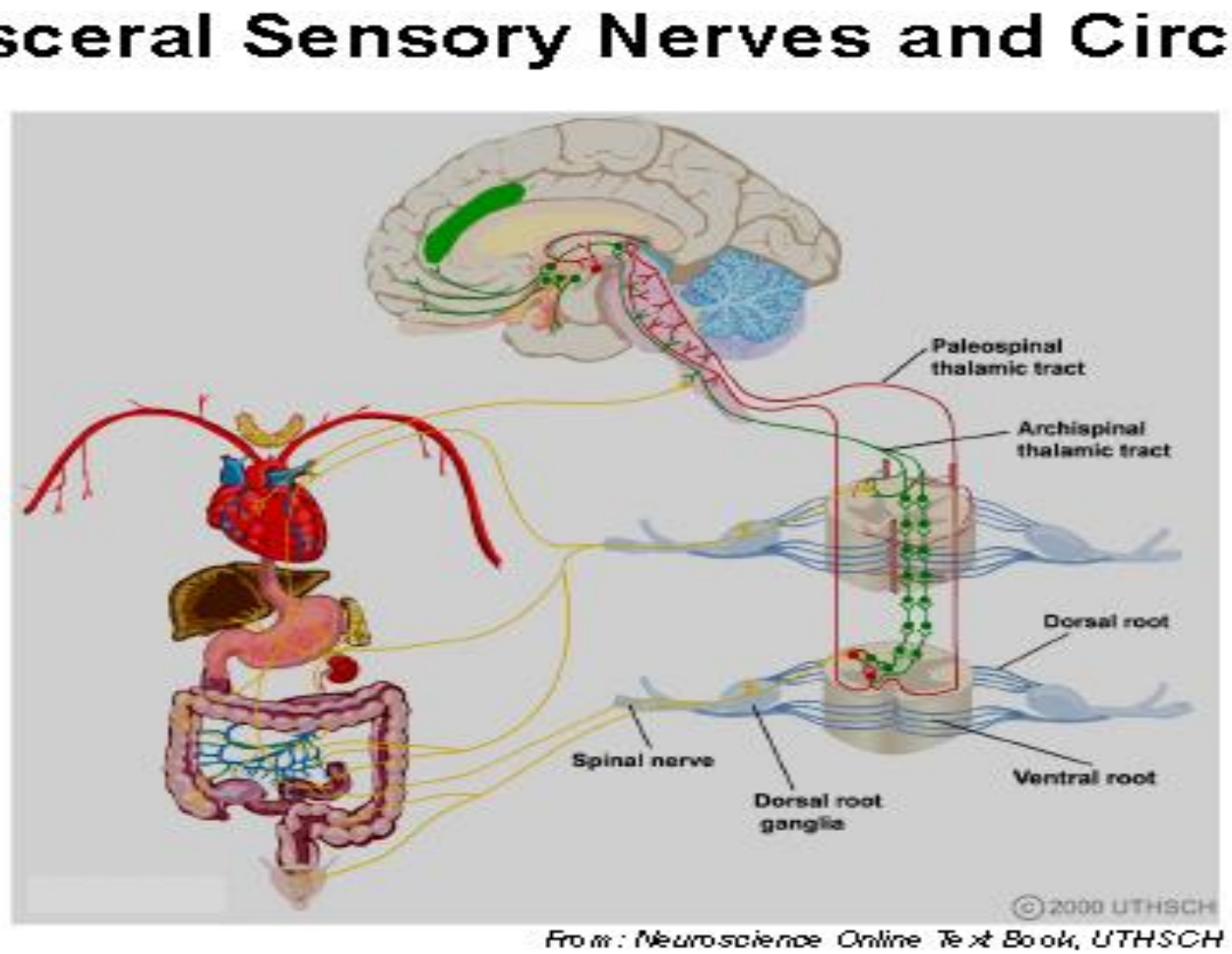
# Sensory subtypes



# Musculoskeletal sensory nerves



# Visceral sensory nerves




From: Neuroscience Online Text Book, UTHSCH

# Classification of sensory fibers

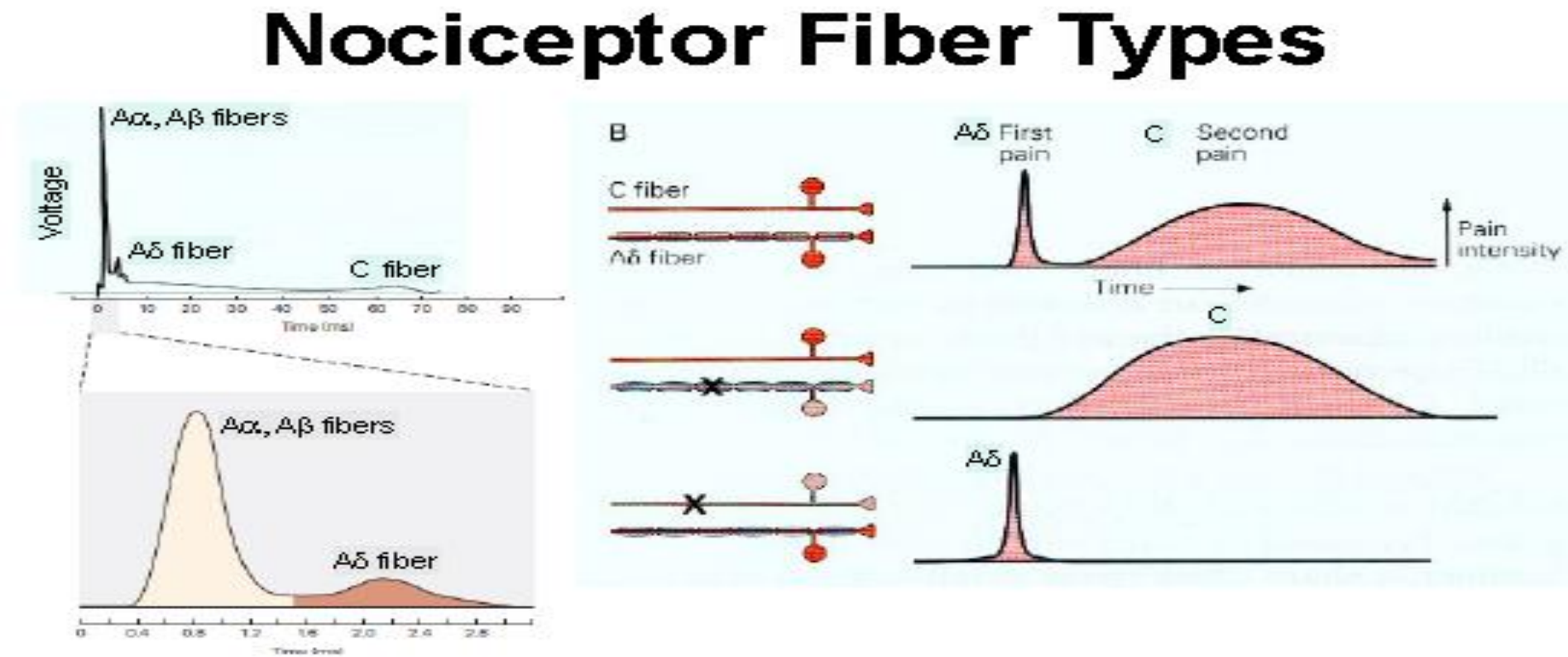
**Classification of Peripheral Afferent Sensory Fibers**

| 1º Axon to skin | Aα | Aβ | Aδ | C |
|---|---|---|---|---|
| 1º Axon to muscle | Group-I | Group-II | Group-III | Group-IV |
| Diameter (µm) | 12 – 22 | 6 – 12 | 1 – 6 | 0.2 – 1.5 |
| Speed (m/sec) | 70 – 170 | 30 – 70 | 5 – 30 | 0.5 – 2.0 |
| Sensory receptors | Proprioceptors of Skeletal Muscle | Mechanoreceptors of Skin | Temperature, Pain, Itch(?) | Temperature, Pain, Itch |

From: Neuroscience Online Text Book, UTHSCH

- A fibers – myelinated (multiple extent) → High conduction velocity.
- C fibers – unmyelinated → low conduction velocity.

# Nociceptor fiber types



# Classes of nociceptors

## Classes of Nociceptors

### Thermal Nociceptors

→ Respond to extreme temperatures (>43°C or <5°C)

→ Thin, sparsely myelinated Aδ fibers that conduct at 5-30m/s

### Mechanical Nociceptors

→ Respond to intense pressure

→ Also Aδ fibers

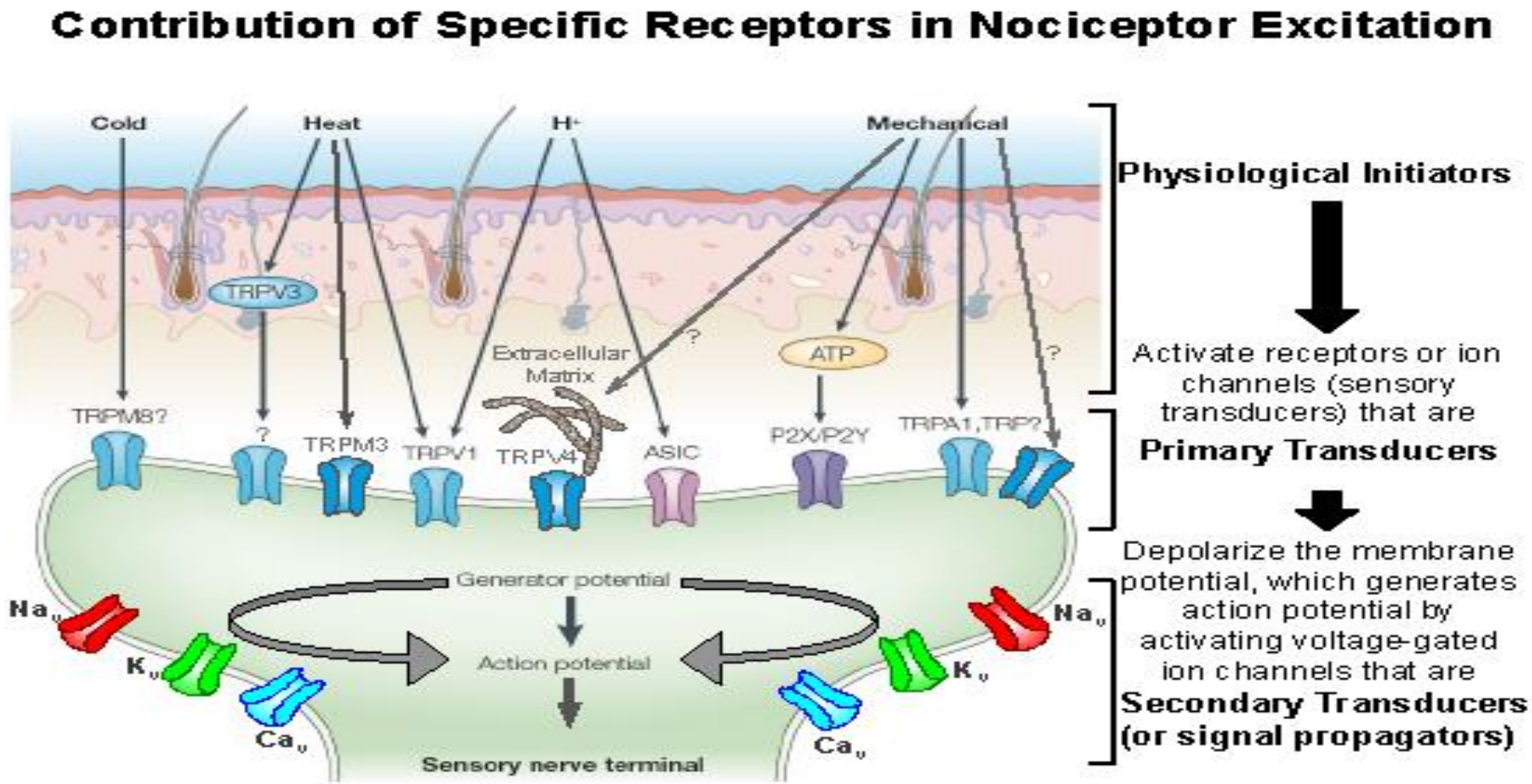
### Polymodal Nociceptors

→ These fibers respond to extreme temperatures, pressure, and noxious chemicals

→ Aδ and C fibers that conduct at ~1m/sec

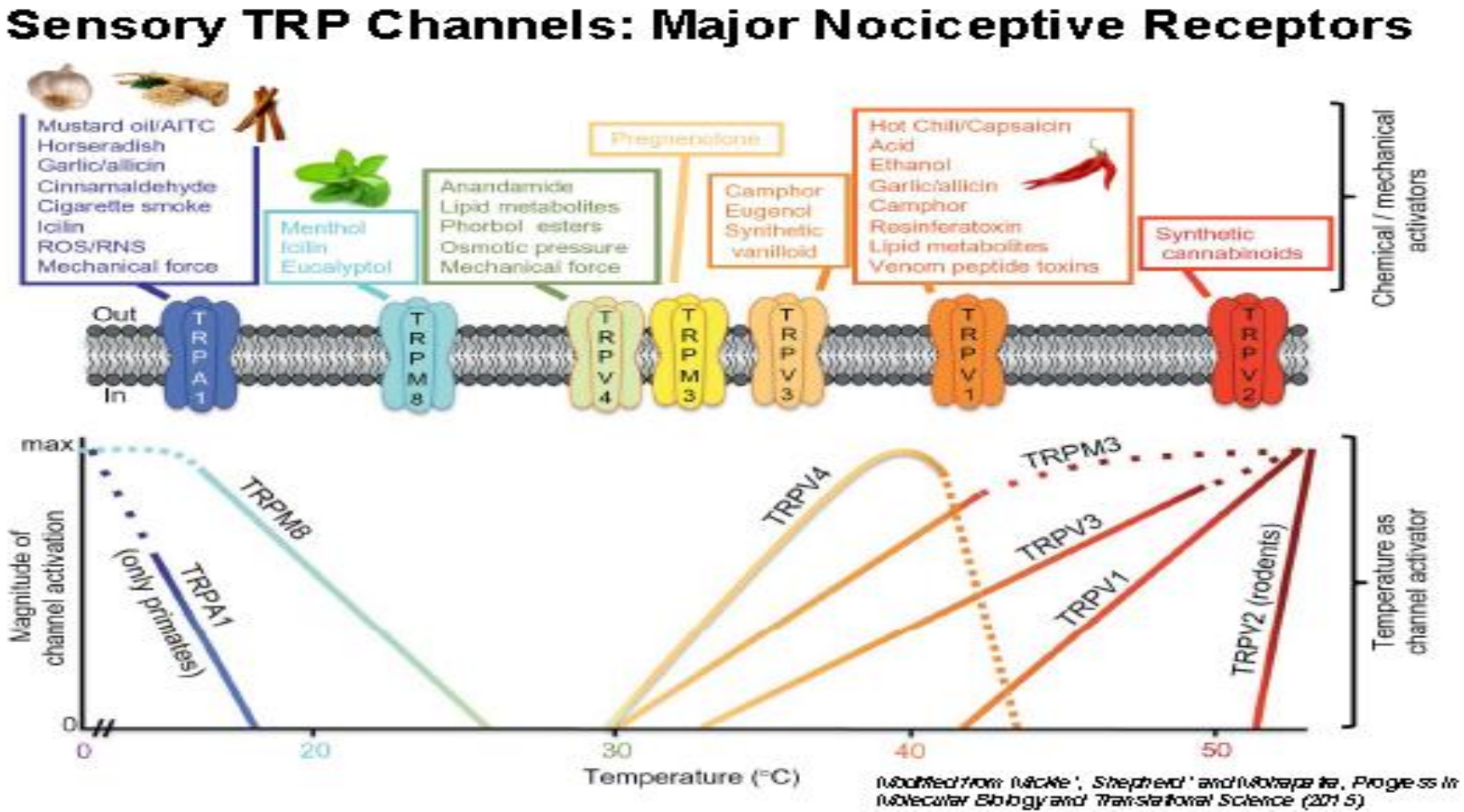
| Modality | Sub Modality | Sensory Fiber |
|---|---|---|
| Temp. | Warm/Hot | C |
| | Cool/Cold | Aδ/C |
| Pain | Sharp cutting pain | Aδ |
| | Dull burning pain | C, Aδ(??) |
| | Deep aching pain | C, Aδ(??) |
| | Chemical pain (acid) | C |

# Receptors

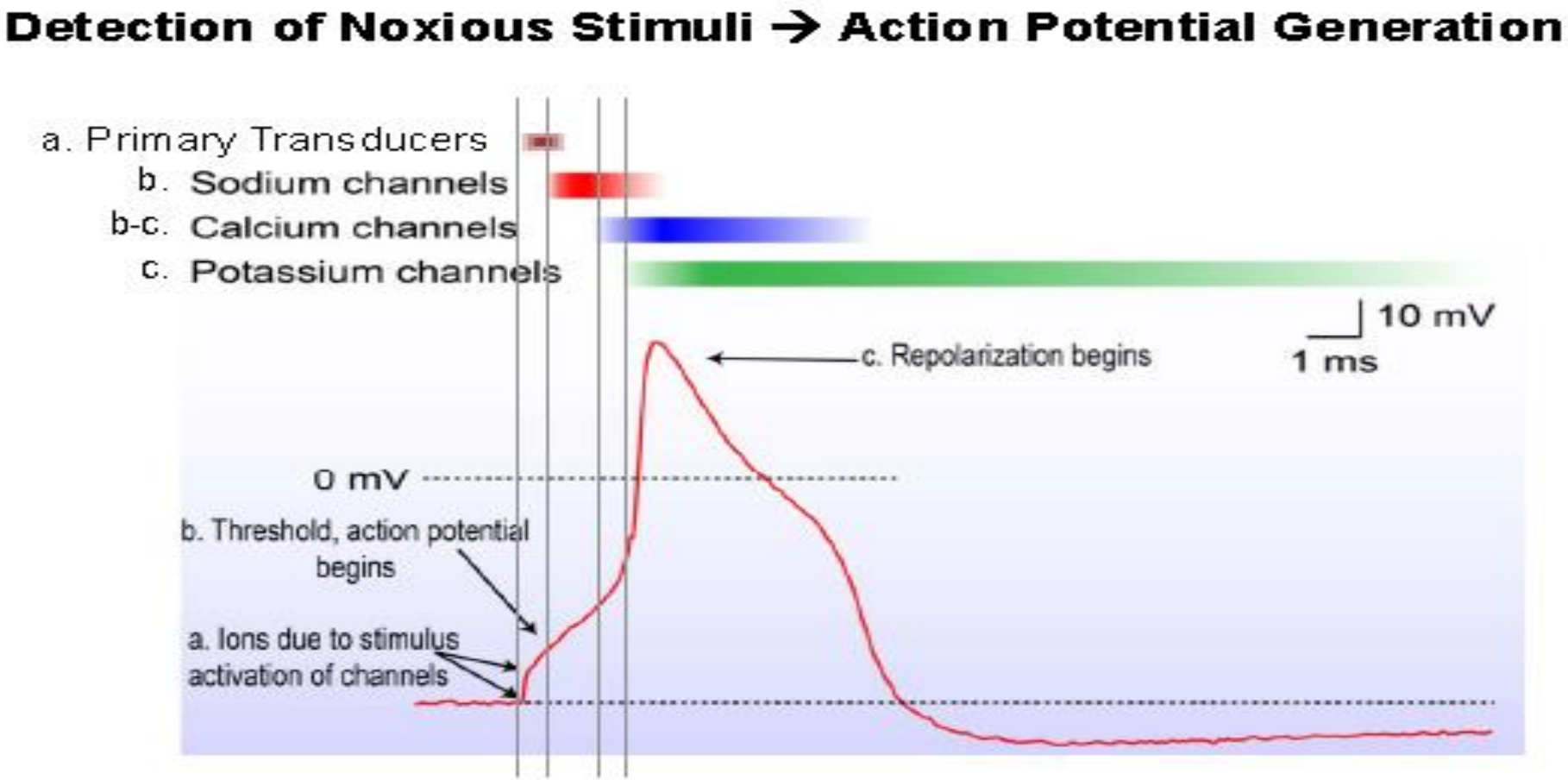



*Modified from Marchand et al., Nat Rev Neurosci (2005)*

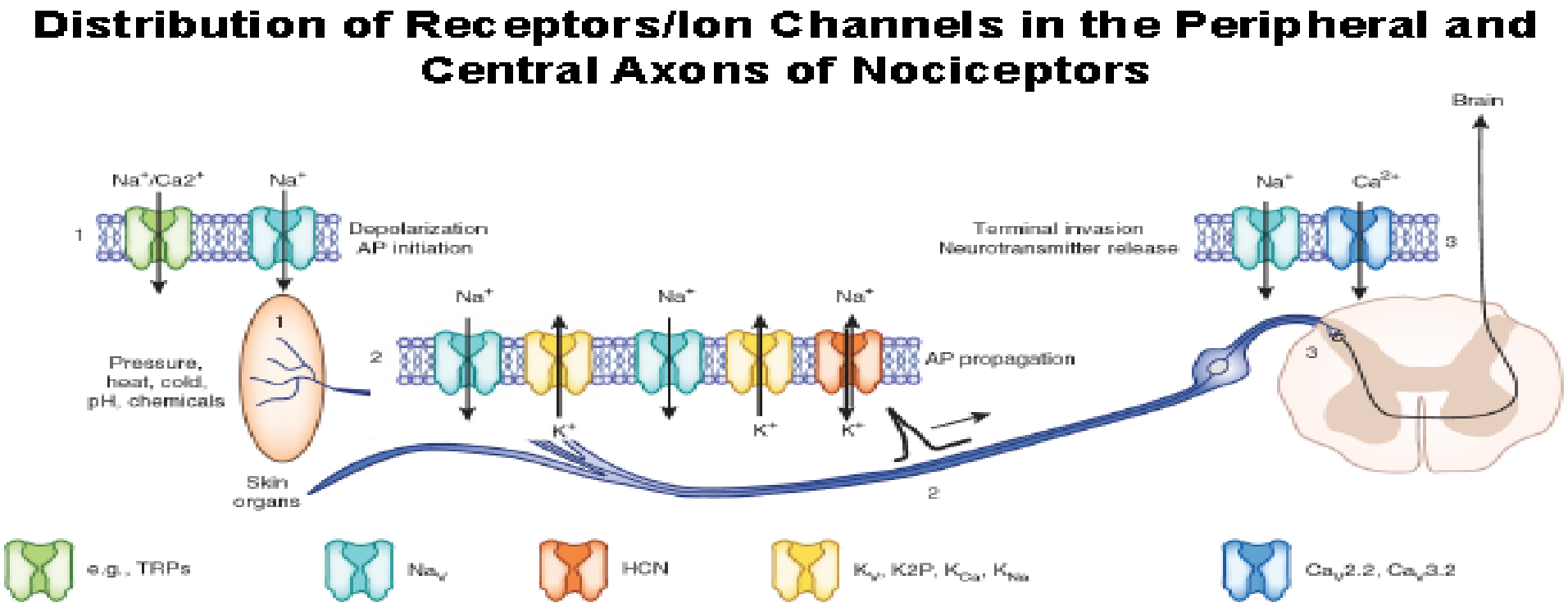
# Sensory TRP channels



# Noxious stimuli

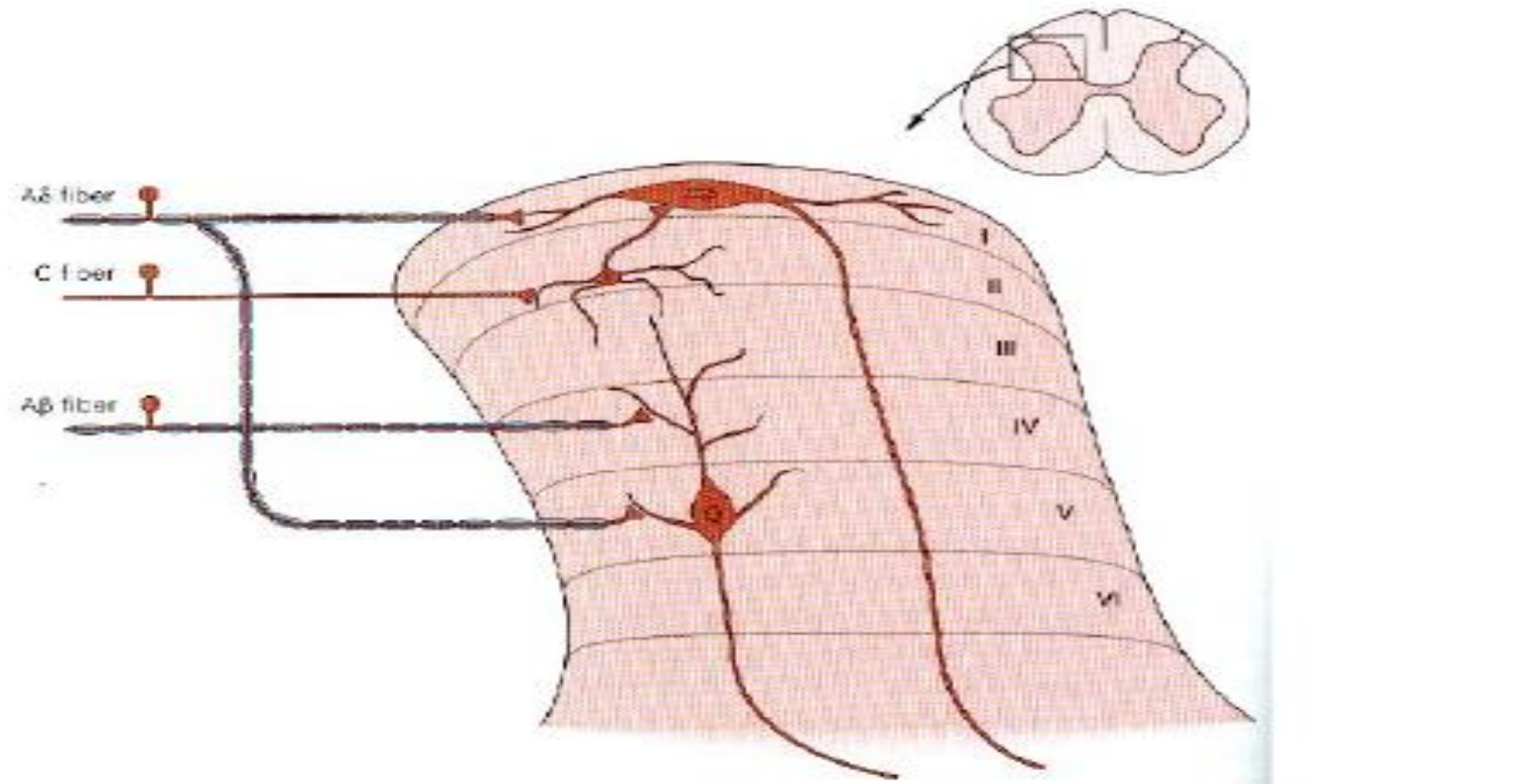


# Nociceptors



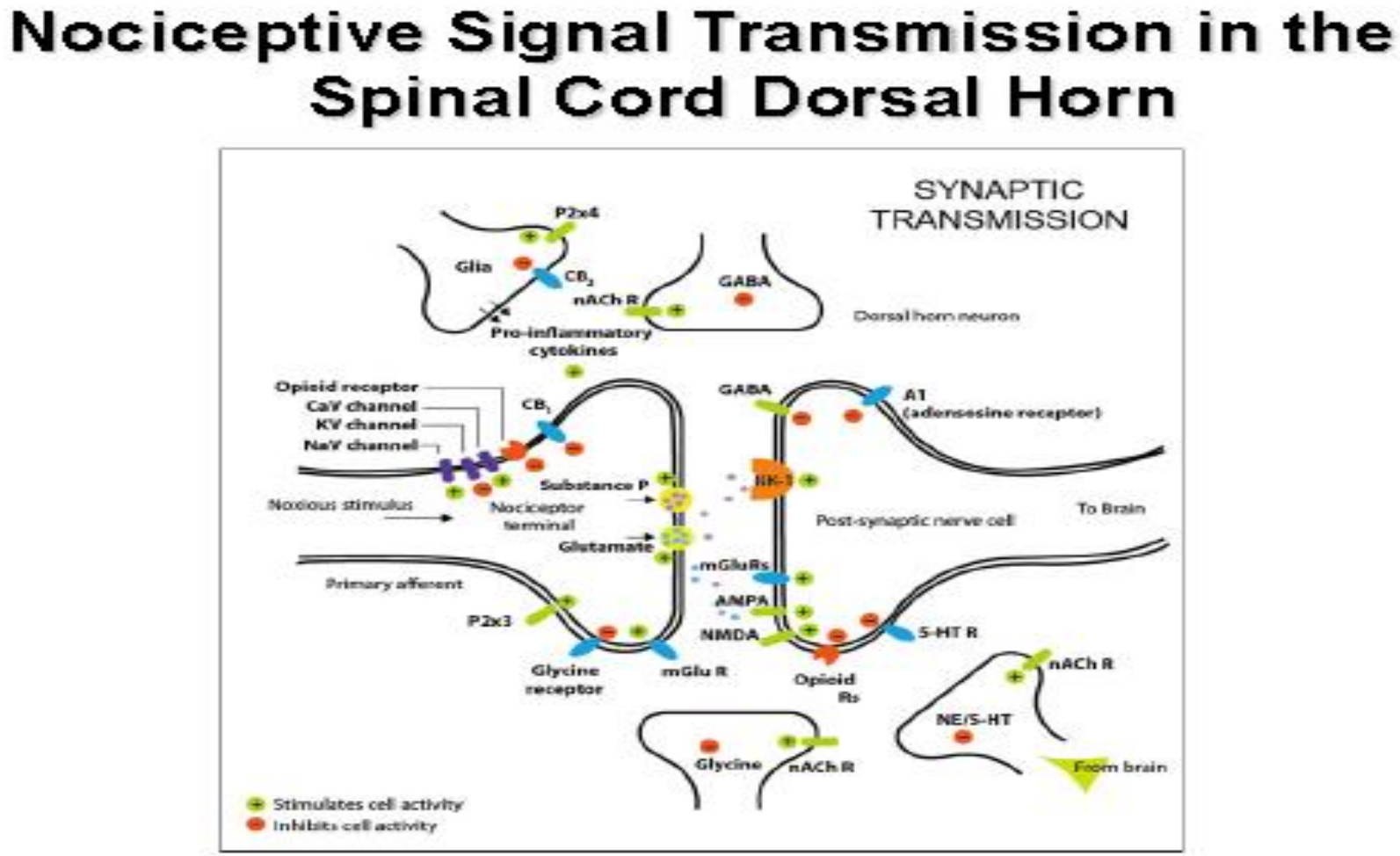

*Waxman and Zamponi, Nature Neuroscience (2014)*

# Nociceptive inputs




*Adapted from Kandel, Schwarz, and Jessell (2012)*

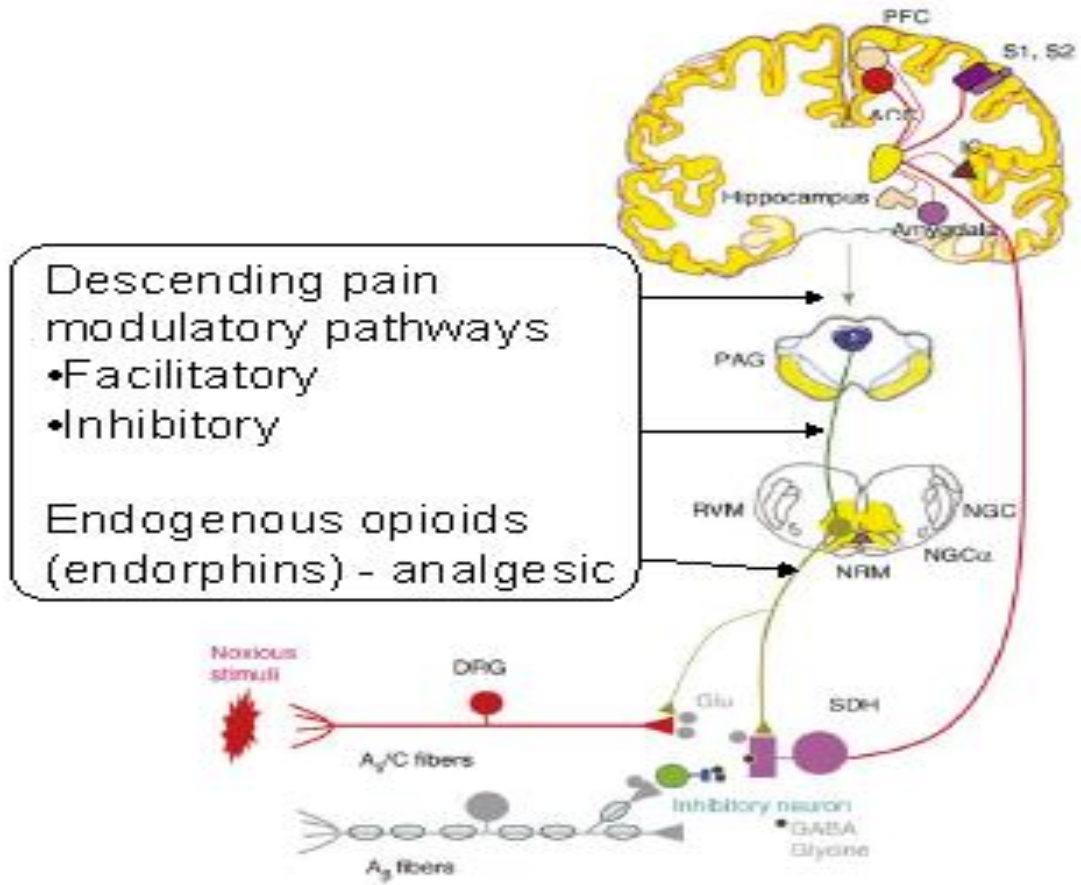
# Nociceptive signal transmission




Adapted from Univ. Wisconsin Pain Management Project

# Nociceptive information

## Multiple areas in the brainstem, mid- and fore-brain process nociceptive information




**Cortical process of pain**
ACC, IC: two major cortical regions responding to physiological and pathological pain, critical for pain perception and unpleasantness
S1, S2: important for pain transmission, information about pain modality, location
PFC: is also activated by pain

**Other related structures**
Hippocampus: pain-related spatial memory and mood disorders
Amygdala: pain-related fear, anxiety and pain modulation

**Endogenous biphasic modulation**
PAG: midbrain analgesic neurons
RVM: exert biphasic descending modulation of spinal pain transmission. It contains NGC, NGCα, NRM and other raphe nuclei

**Spinal dorsal horn**
First central pain synapse in the CNS
Local gating control of pain and descending biphasic modulation; biphasic modulation is mediated by multiple transmitters
Descending modulation may act by presynaptic and postsynaptic mechanisms

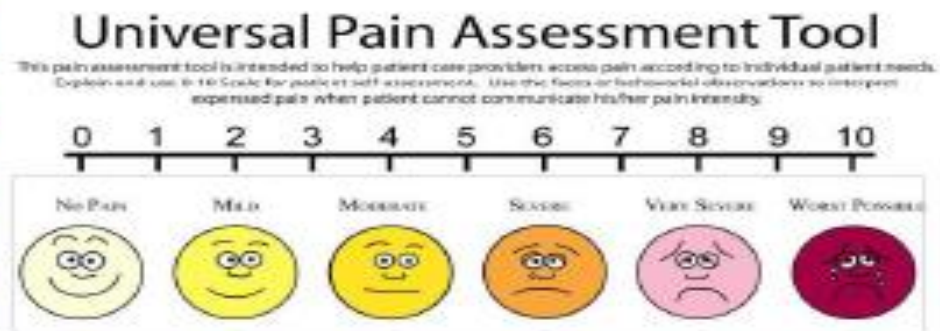
*Adapted from Zhou (2008), Trend Neurosci*

# Pain measurement

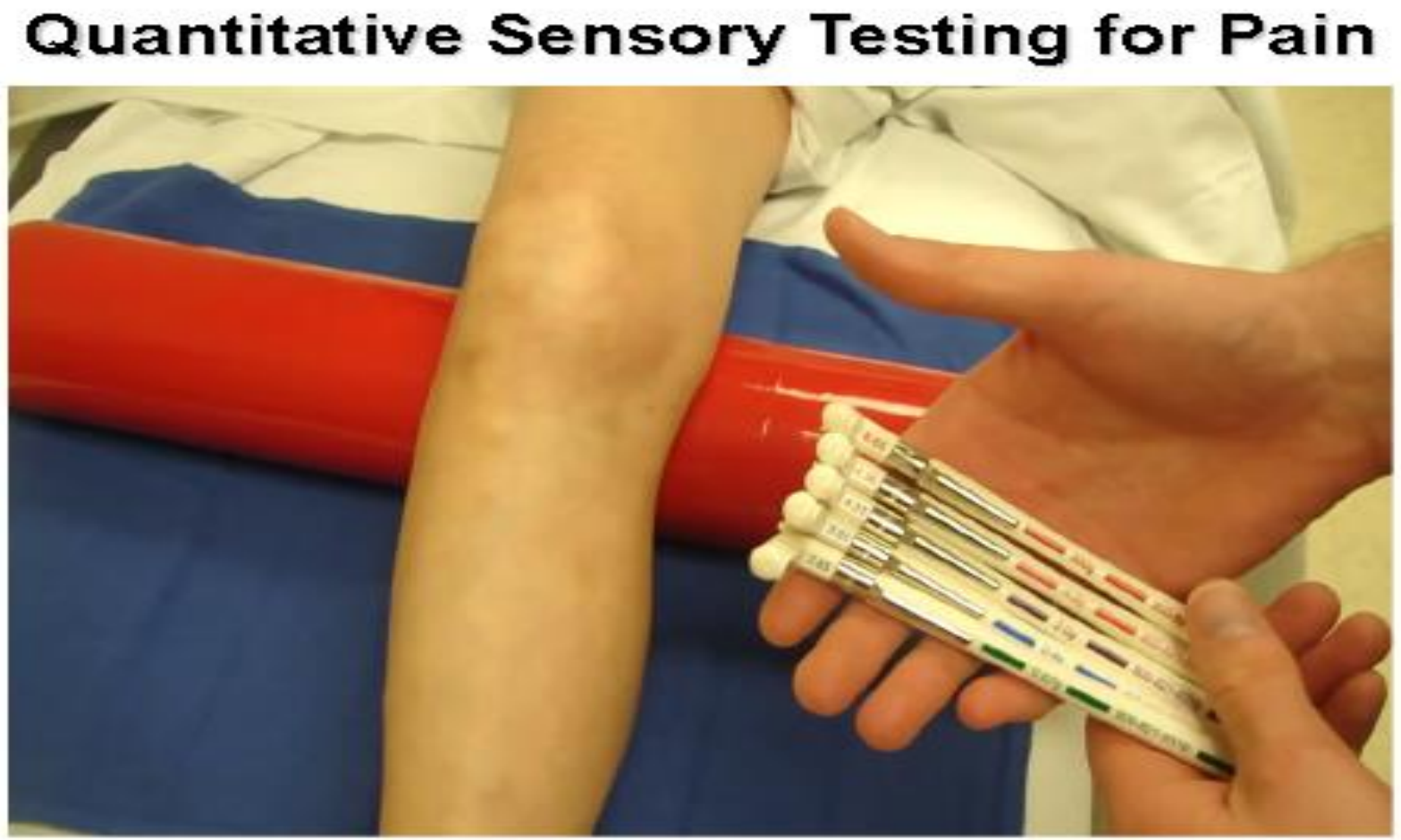
## How Pain is Measured or Assessed?

### 0-10 SCALE OF PAIN SEVERITY

| Severity | | Description of Experience |
|---|---|---|
| 10 | Unable to Move | I am in bed and can't move due to my pain. I need someone to take me to the emergency room to get help for my pain. |
| 9 | Severe | My pain is all that I can think about. I can barely talk or move because of the pain. |
| 8 | Intense | My pain is so severe that it is hard to think of anything else. Talking and listening are difficult. |
| 7 | Unmanageable | I am in pain all the time. It keeps me from doing most activities. |
| 6 | Distressing | I think about my pain all of the time. I give up many activities because of my pain. |
| 5 | Distracting | I think about my pain most of the time. I cannot do some of the activities I need to do each day because of the pain. |
| 4 | Moderate | I am constantly aware of my pain but I can continue most activities. |
| 3 | Uncomfortable | My pain bothers me but I can ignore it most of the time. |
| 2 | Mild | I have a low level of pain. I am aware of my pain only when I pay attention to it. |
| 1 | Minimal | My pain is hardly noticeable. |
| 0 | No Pain | I have no pain. |

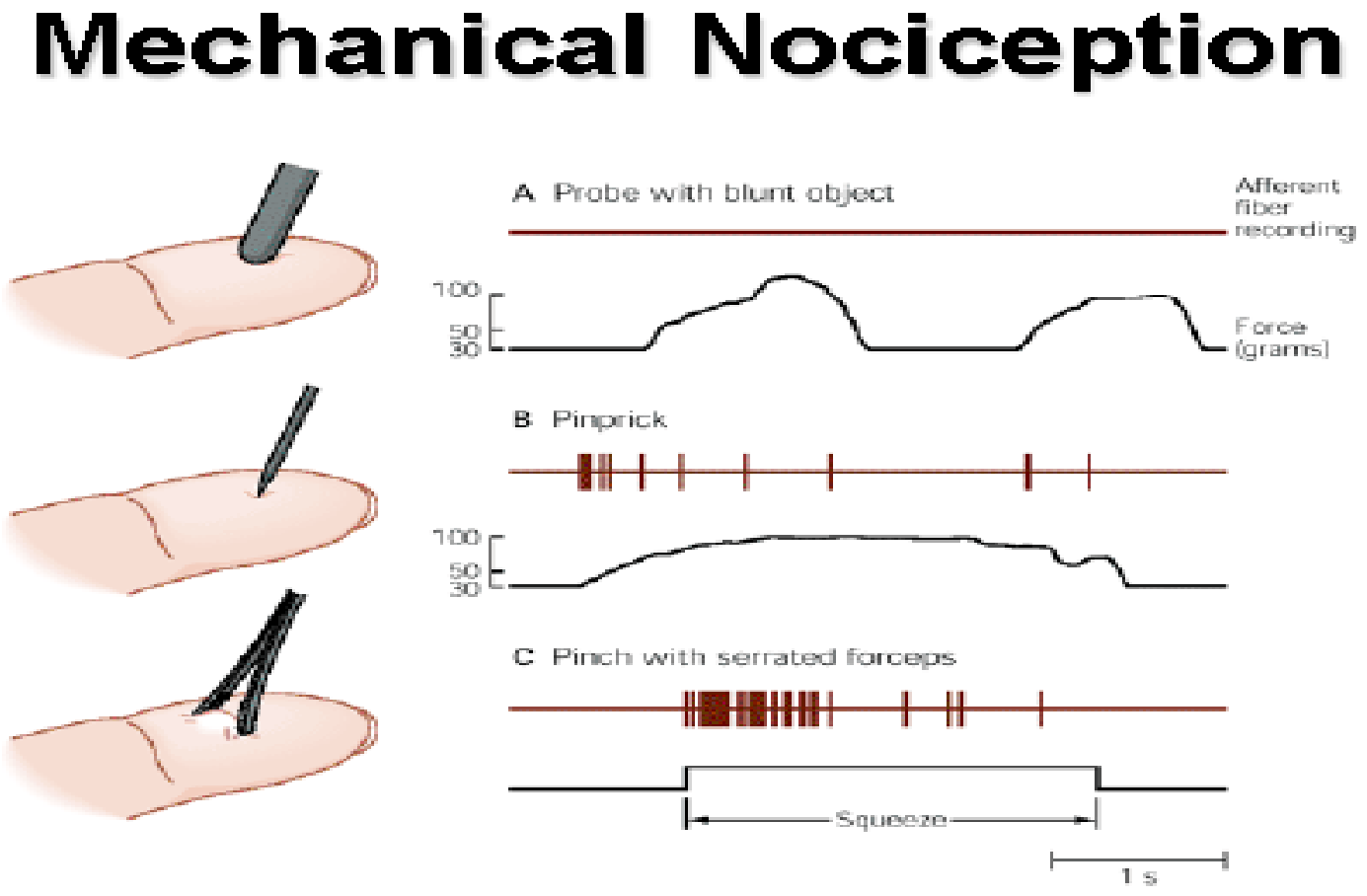


# Sensory testing




https://www.youtube.com/watch?v=jSwcWPYi3Zc

# Mechanical nociception




*Adapted from Kandel, Schwartz, and Jessell (2012)*

# Pain testing

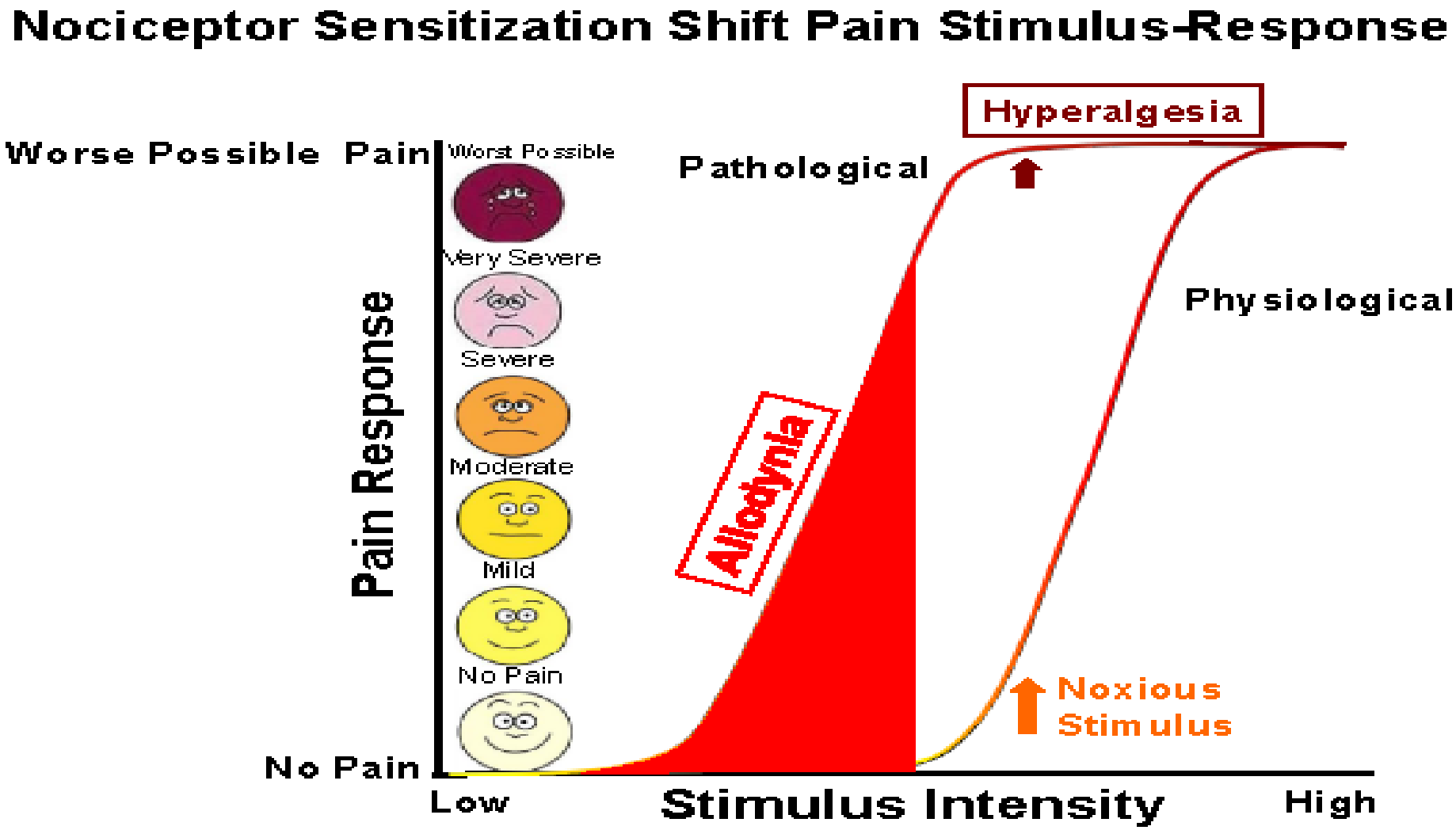
# Quantitative testing


https://www.youtube.com/watch?v=AruMr5N2D0Y

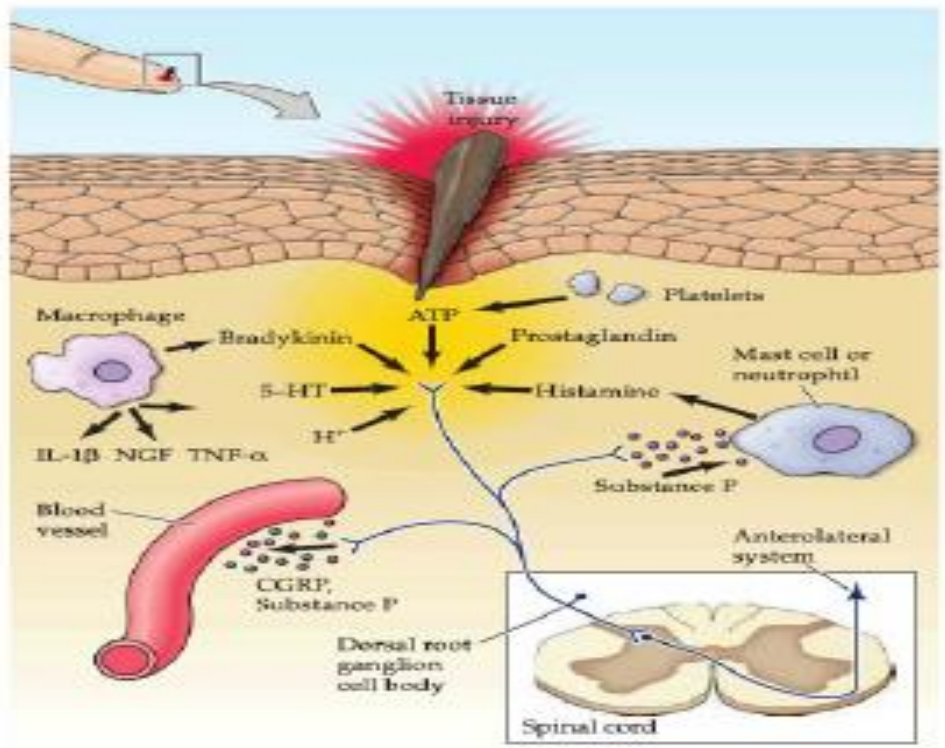
# Animal pain


https://www.youtube.com/watch?v=qWCXySpkVE

# Stimulus-response

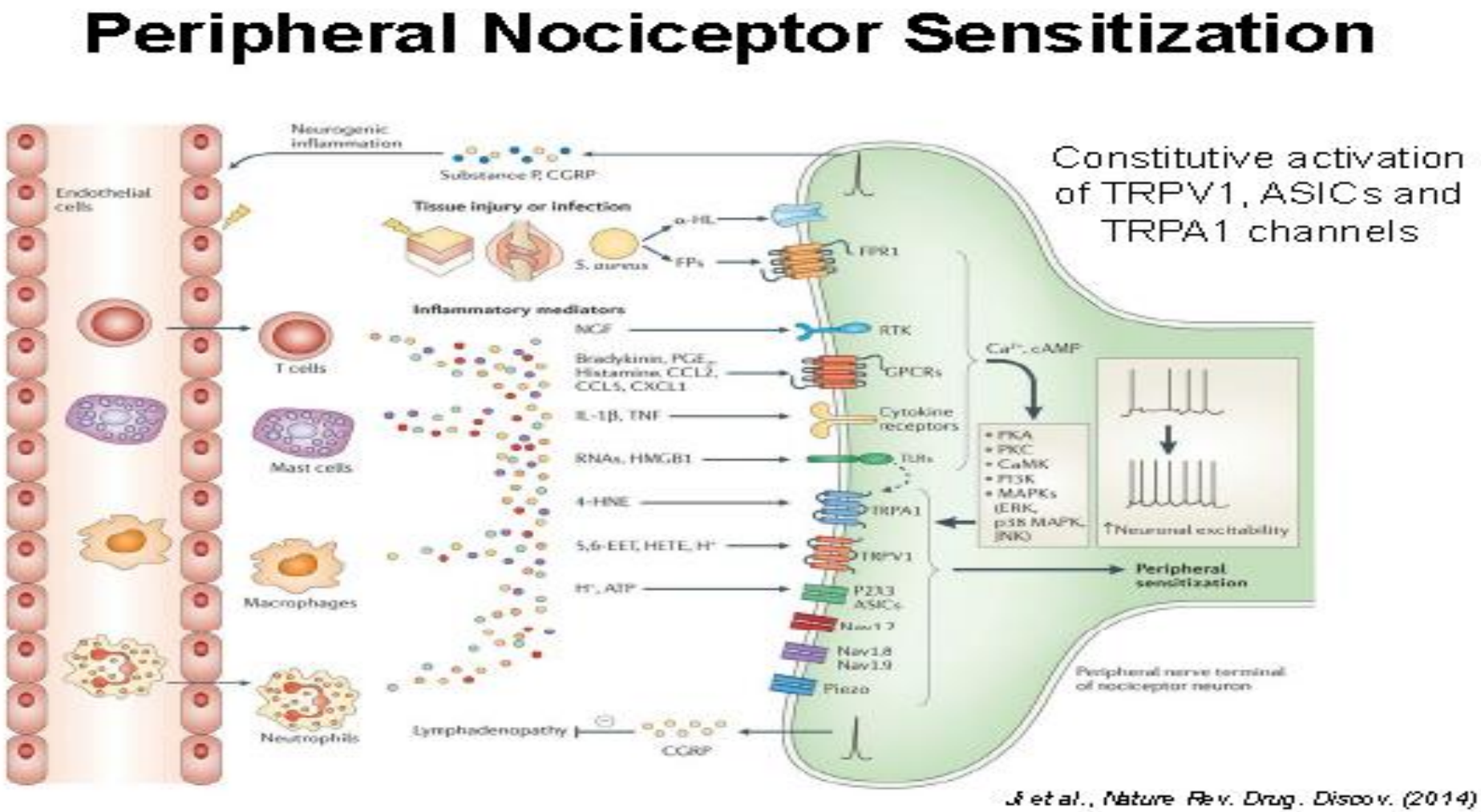


# Peripheral nociceptor




Purves et al., (2013)

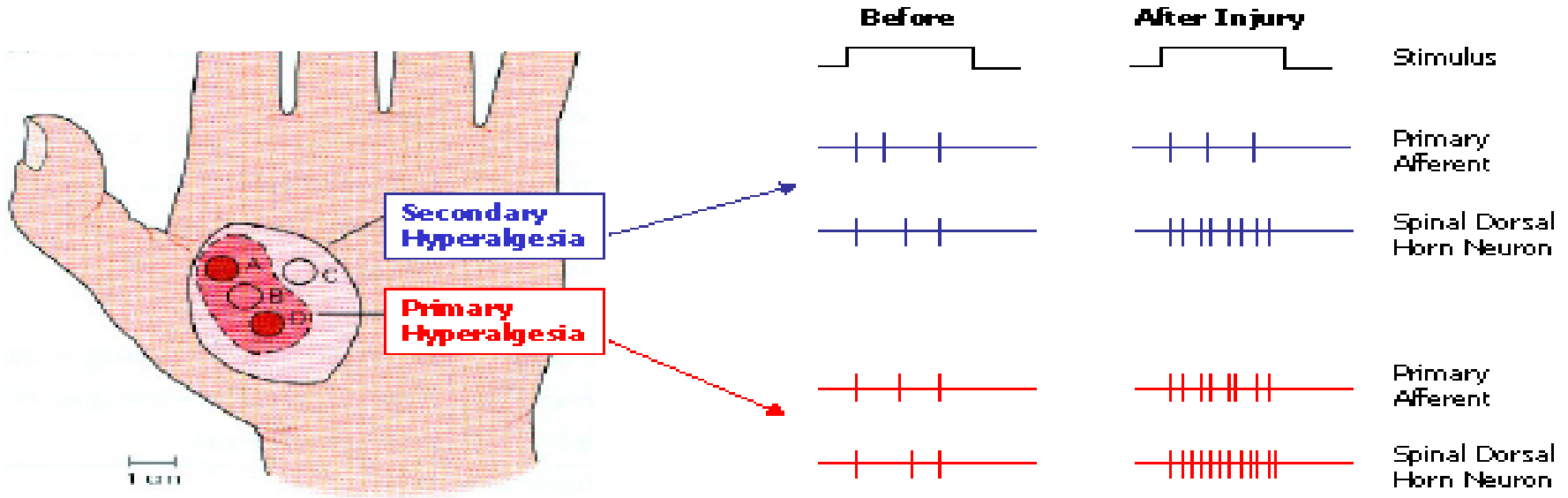
# Nociceptor sensitization




Ji et al., Nature Rev. Drug. Discov. (2014)

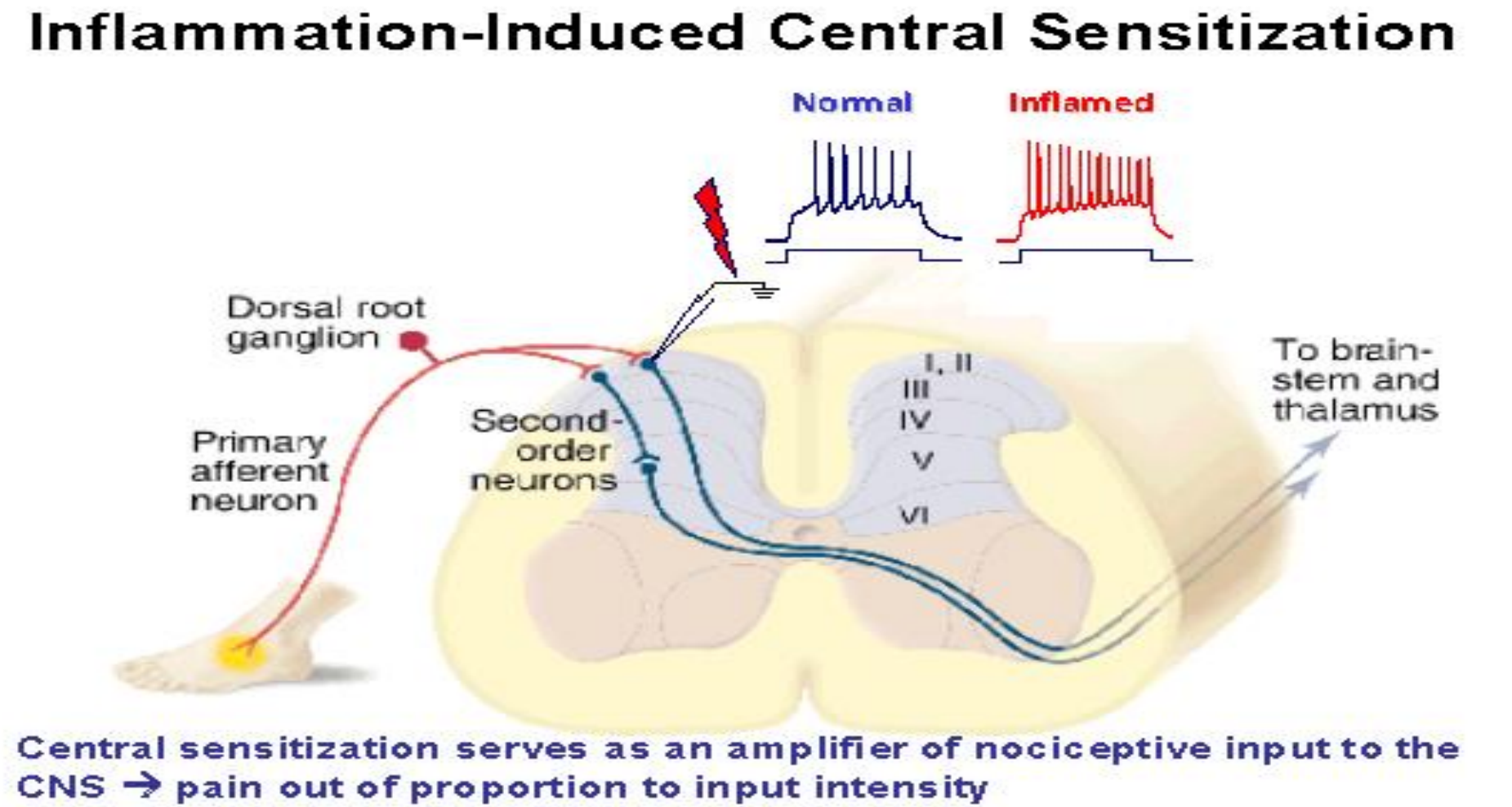
# Central sensitization

**Primary afferents innervating the site of secondary hyperalgesia are not sensitized in response to inflammation. Thus, there must be some change in the spinal cord or brain that mediates secondary hyperalgesia/allodynia. These changes are known as Central Sensitization**

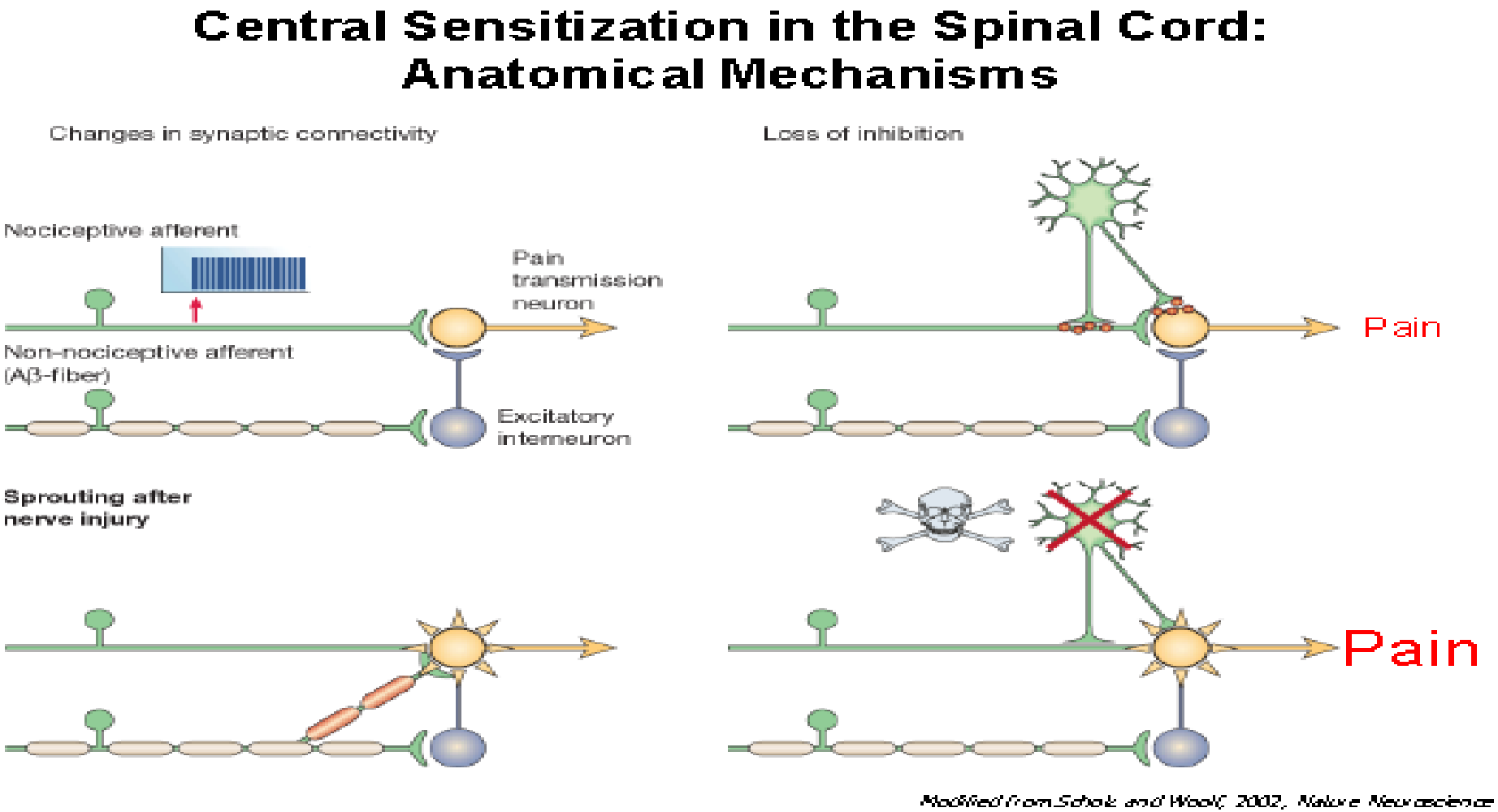



From work by LaMotte and others

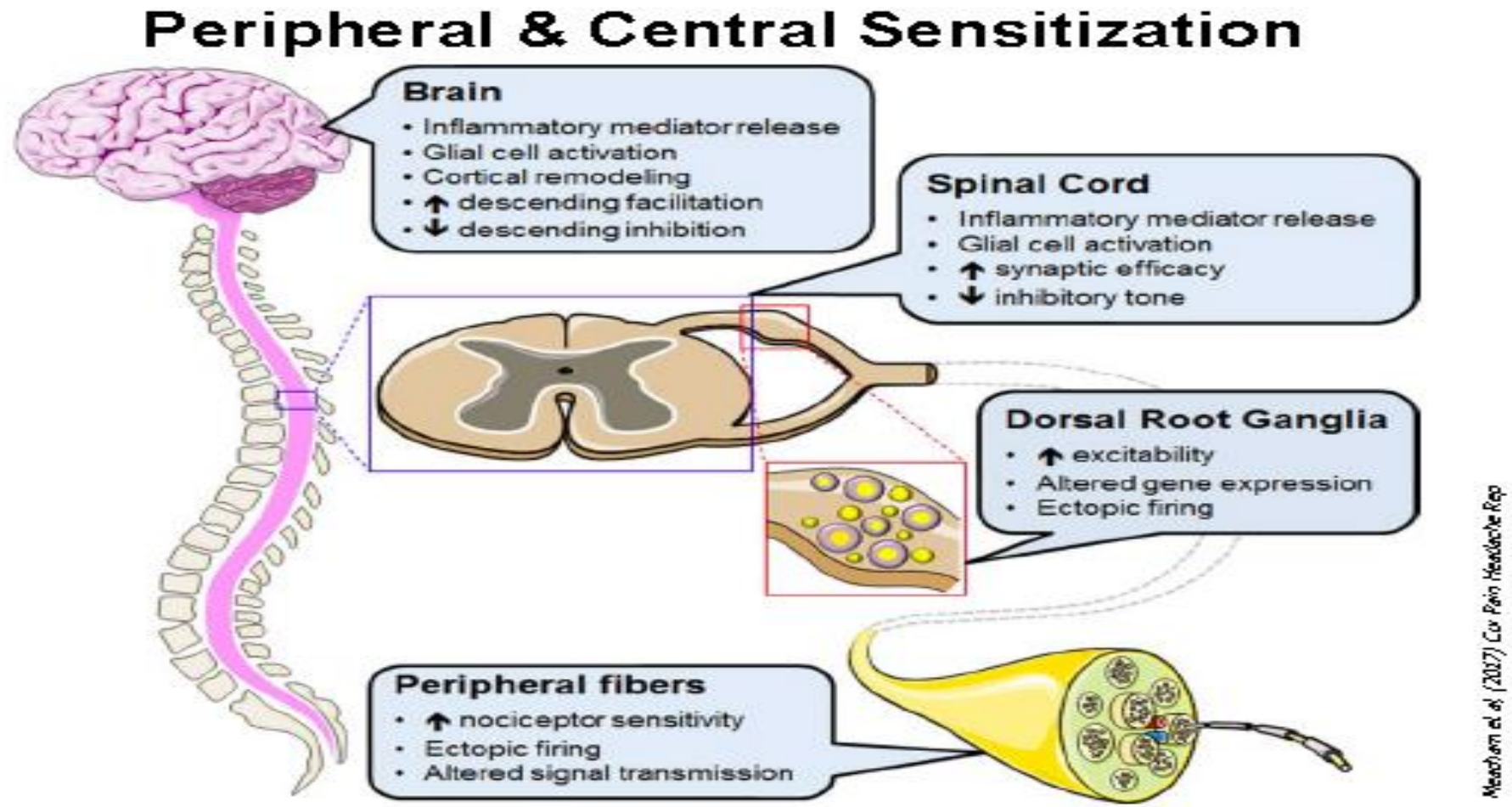
# Central sensitization



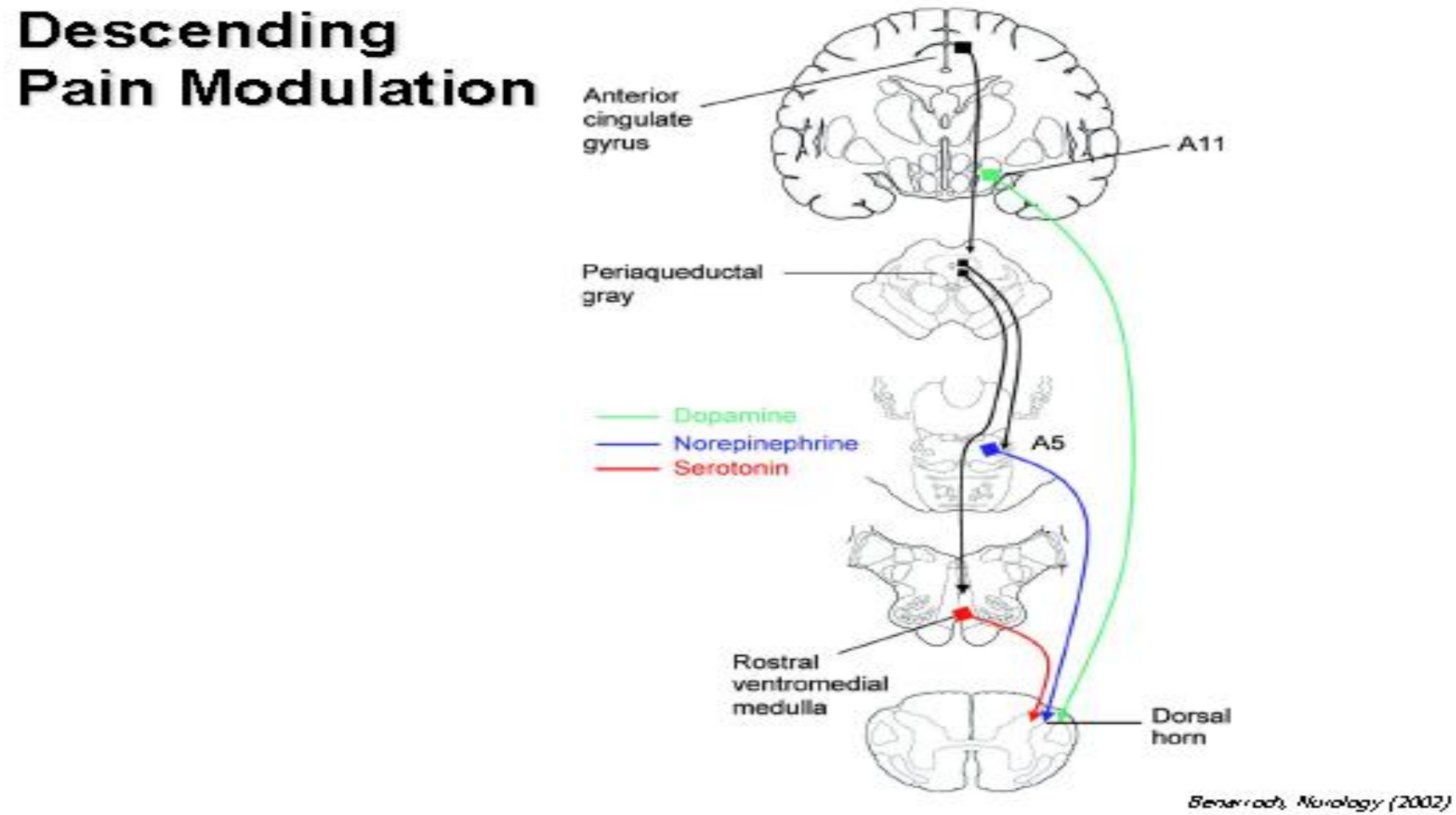
# Spinal cord


Central Sensitization in the Spinal Cord:
Anatomical Mechanisms
Changes in synaptic connectivity
Nociceptive afferent
Pain transmission neuron
Non-nociceptive afferent (Aβ-fiber)
Excitatory interneuron
Sprouting after nerve injury
Loss of inhibition
Pain
Pain
Modified from Sahak and Woolf, 2002, Nature Neuroscience

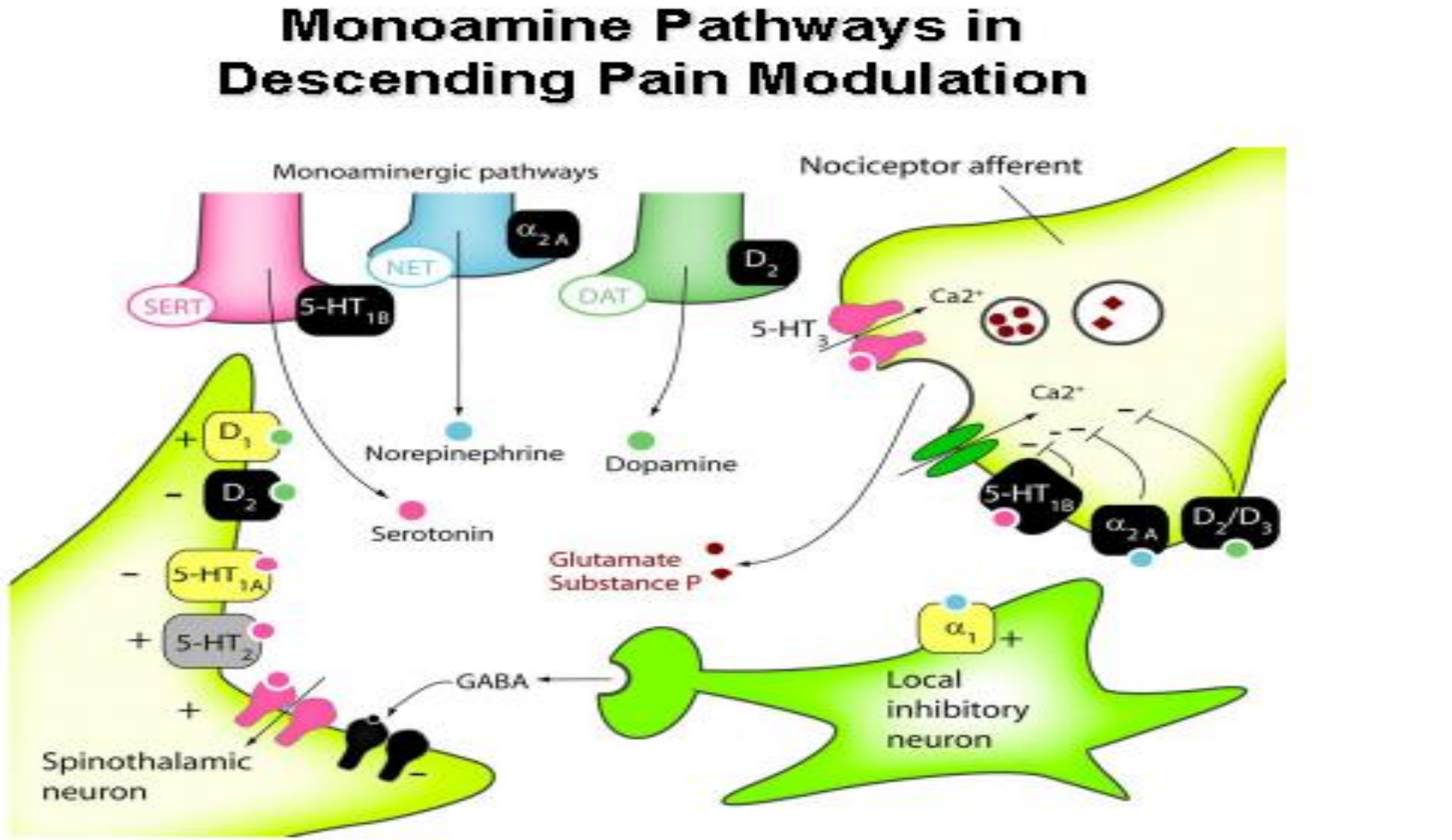
# Central and peripheral sensitization



# Pain modulation



# Monoamine pathways




Besserroch, Neurology (2002)

# Cancer Pain

## Pharmacological Management of Cancer Pain

| MEDICINE GROUP | MEDICINE CLASS | EXAMPLE MEDICINES |
|---|---|---|
| Non-opioids | Paracetamol | Paracetamol oral tablets and liquid. Rectal suppositories, injectable |
| | NSAIDs | Ibuprofen oral tablets and liquid<br>Ketorolac oral tablets and injectable<br>Acetylsalicylic acid oral tablets and rectal suppositories |
| Opioids | Weak opioids | Codeine oral tablets and liquid and injectable |
| | Strong opioids | Morphine oral tablet and liquid and injectable<br>Hydromorphone oral tablets and liquid and injectable<br>Oxycodone oral tablets and liquid<br>Fentanyl injectable, transdermal patch, transmucosal lozenge<br>Methadone oral tablet, liquid, injectable |
| Adjuvants | Steroids | Dexamethasone oral tablet and injectable<br>Methylprednisolone oral tablets and injectable<br>Prednisolone oral tablets |
| | Antidepressants | Amitriptyline oral tablets<br>Venlafaxine oral tablets |
| | Anticonvulsants | Carbamazepine oral tablets and injectable |
| | Bisphosphonates | Zoledronate injectable |

Source: WHO guidelines for the management of cancer pain in adults and adolescents (2018)

# Cancer pain management

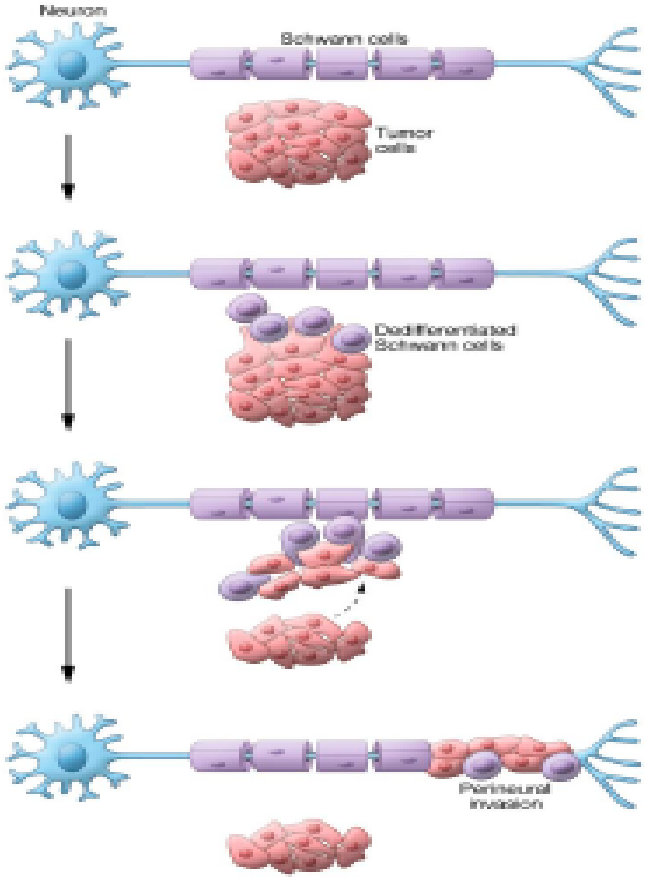
**Non-Pharmacological Management of Cancer Pain**

| Therapy Type | Examples |
|---|---|
| Psychological | • Hypnosis<br>• Relaxation<br>• Cognitive Behavioral Therapy (CBT) |
| Physical | • Acupuncture<br>• Transcutaneous Electrical Nerve Stimulation (TENS)<br>• Healing touch and massage<br>• Yoga<br>• Occupational therapy |
| Clinical Process | • Specific Pain Assessment<br>• Physical Advice and Communication<br>• Education (including family) |

# Other roles

## Other Roles of Nociceptive Sensory System in Cancers

- Perineural Invasion (PNI) High prevalence in prostate and pancreatic cancers
- Cancer cells penetrate inside perineurium and migrate to sympathetic, nodose and dorsal root ganglia, and spinal cord
- Utilize nociceptive sensory neurons for tumor growth, aggression and metastasis
- Ablation of nociceptive afferents in mice → significantly reduced pancreatic tumor growth, and prolonged survival (Saloman et al 2016, PNAS)

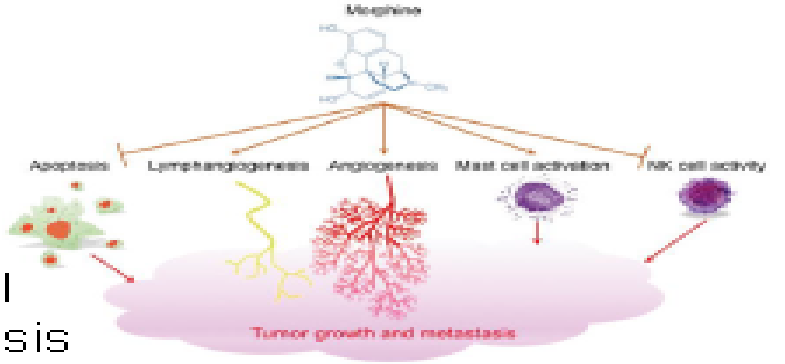



Ayasun and Pecot (2016) J Clin Invest

# Cancer pain

## Cancer Pain: Controversies and Gaps in Knowledge

- Chronic opioid use correlated with cancer aggressiveness (in certain cancers) – only few studies
- In cellular and preclinical studies opioids shown to enhance cancer cell proliferation, tumor growth & metastasis




Aloh et al (2017) Int Anesthesiol Clin

- Mechanisms (clinically-relevant) underlying peripheral & central pain sensitization and central modulation in primary and metastatic cancers
  - A lack in relevant animal models
  - Difficulty in assessing ongoing cancer-related pain in animals
- Neuropathies associated with cancer chemotherapy
  - A lack of relevant animal models of CIPN
  - Difficulties in studying heterogeneous nature of CIPN