Sorrow, 1882
V. Van Gogh

Seconda Lezione: Interpretare il dolore

14 / 03 / 2018

Levis est dolor qui loquitur, magnus muta

Lieve è il dolore che parla…Il grande dolore è muto.

Lucio Anneo Seneca (Corduba 4 a.C. – Roma 65 d. C)

Pain

"An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage"

IAPS, APS, 2003

- Pain is always a subjective experience;
- Everyone learns the meaning of "pain" through experiences (usually injuries) in early life;
- Pain is a significant cause of stress

Various types of pain

Somatic pain: caused by the activation of **pain receptors** in the skin or deeper tissues (musculoskeletal tissues)

Visceral pain: caused by activation of **pain receptors** (e.g., infiltration, compression, stretching) of the thoracic, abdominal or pelvic viscera

Neuropathic pain: caused by **injury to the nervous system** (e.g., a tumor compressing nerves or the spinal cord, or cancer actually infiltrating into the nerves or spinal cord)

Acute vs. chronic pain

Acute pain:

-short-lasting (up to 'several days')

-clinically associated with diaphoresis and tachycardia

-increasing in intensity over time, or it can occur intermittently (episodic or intermittent pain)

-usually related to a discreet event for onset: e.g., post-operative, post-trauma, etc…

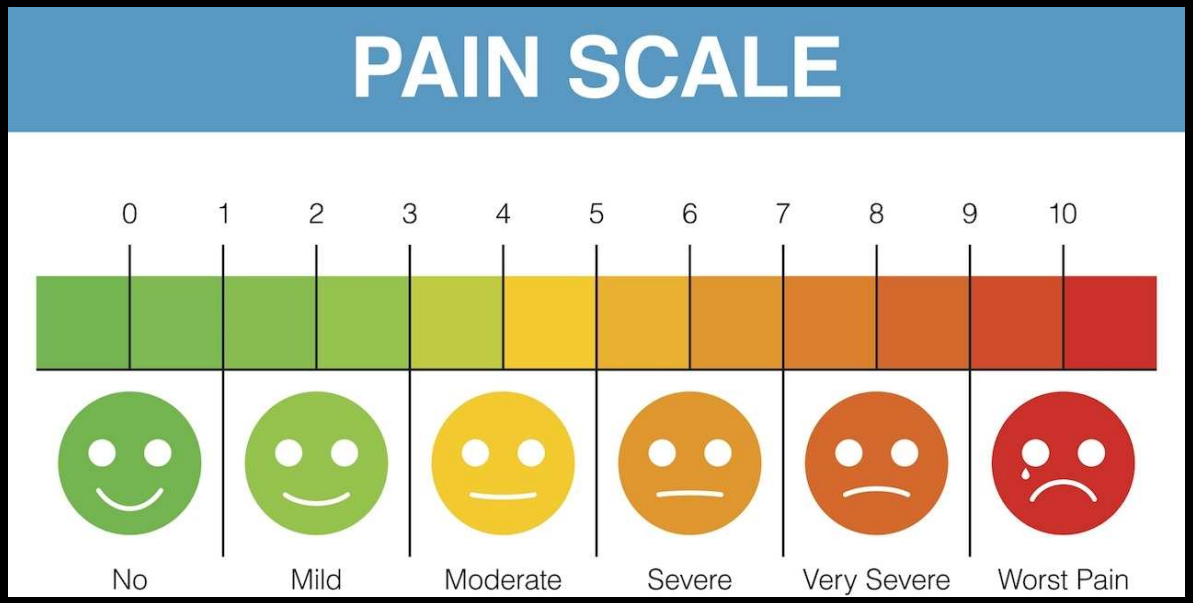
Chronic pain:

- long-term (> 3 months)
- more subjective (less characterized than acute pain)
- more commonly associated with psychological distress
- usually affects a patient's quality of life

Pain: How do we measure it ?

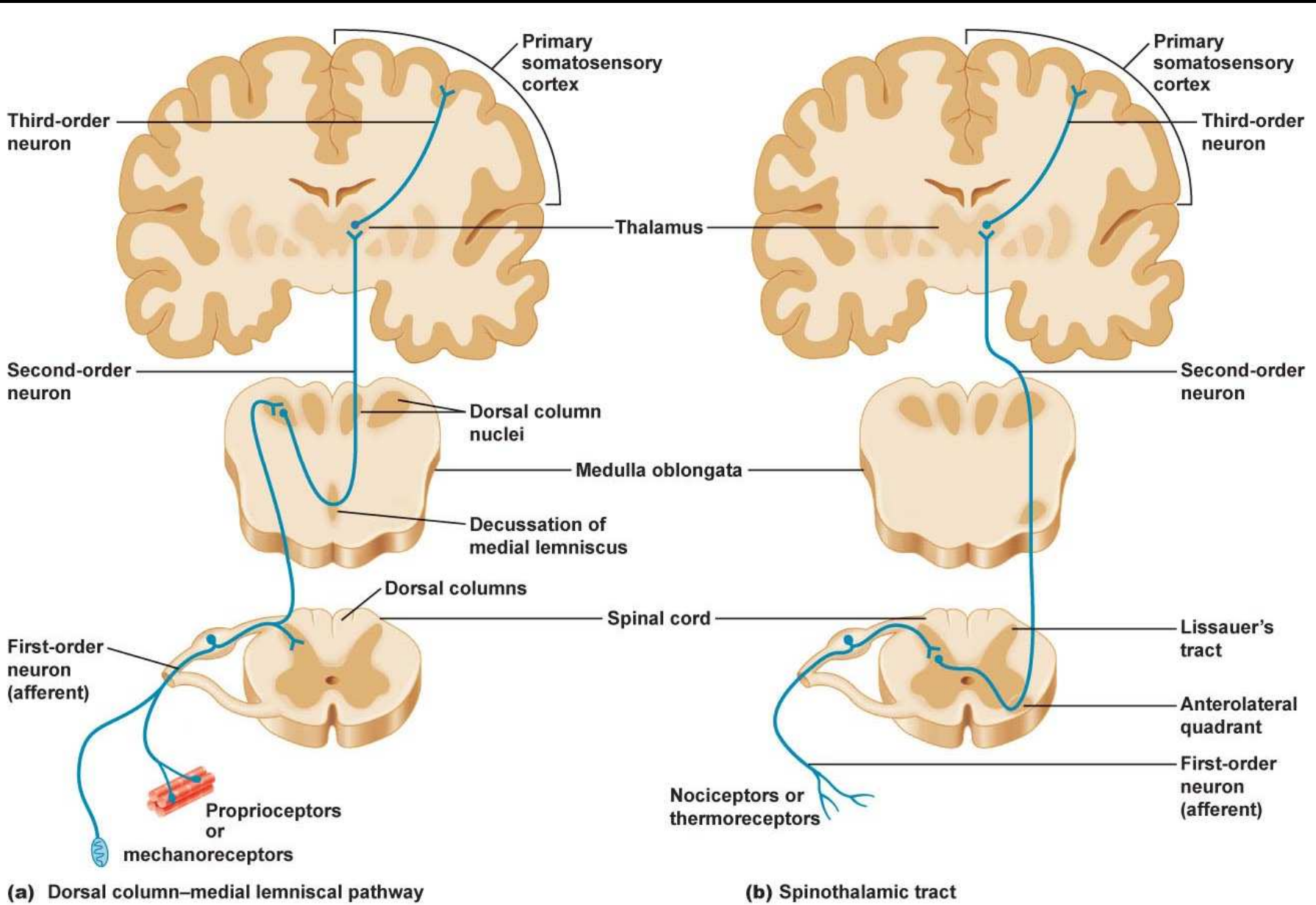
Mild Moderate Severe

zero max

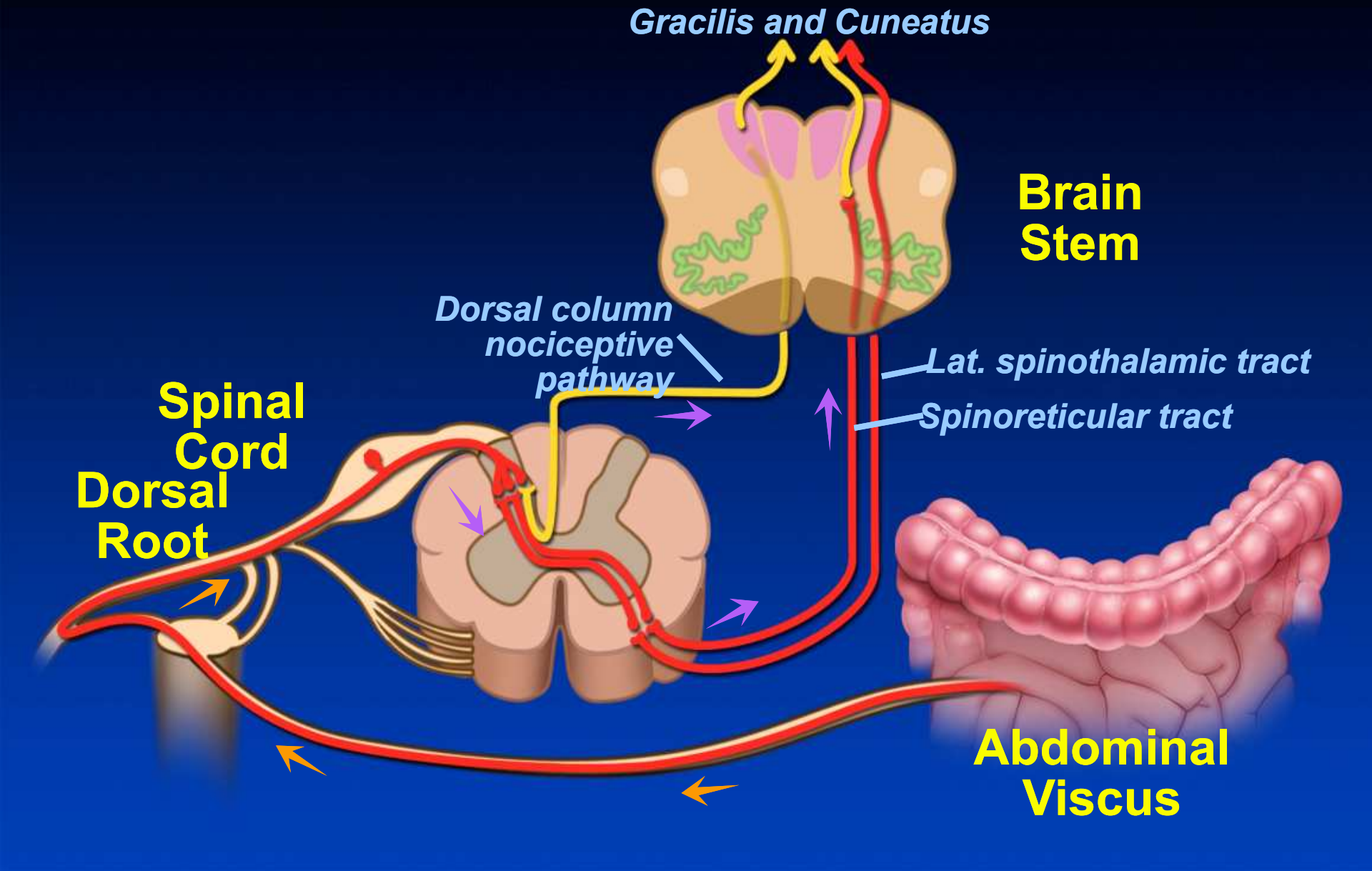


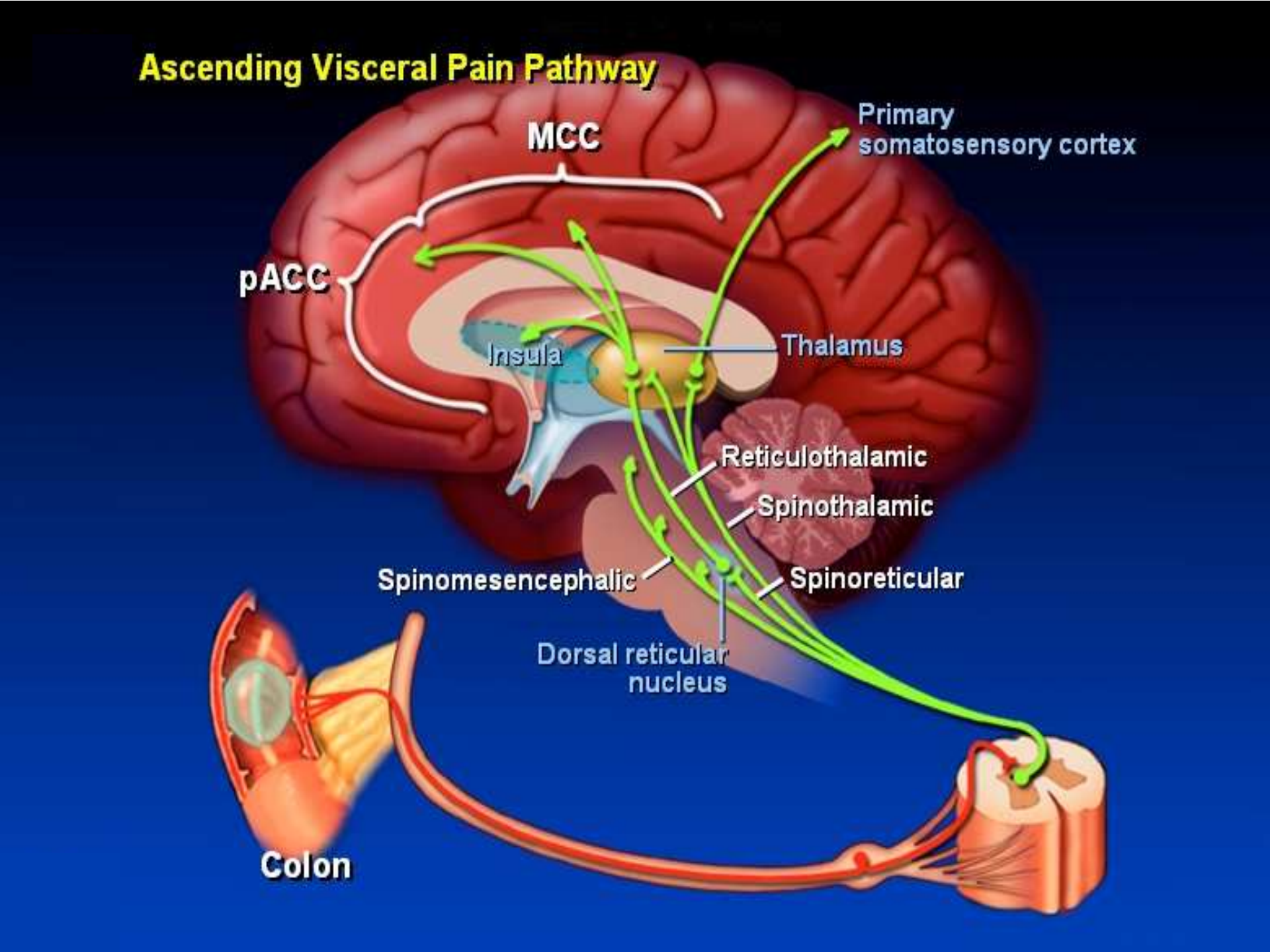
General features

Somatic and visceral pain pathways

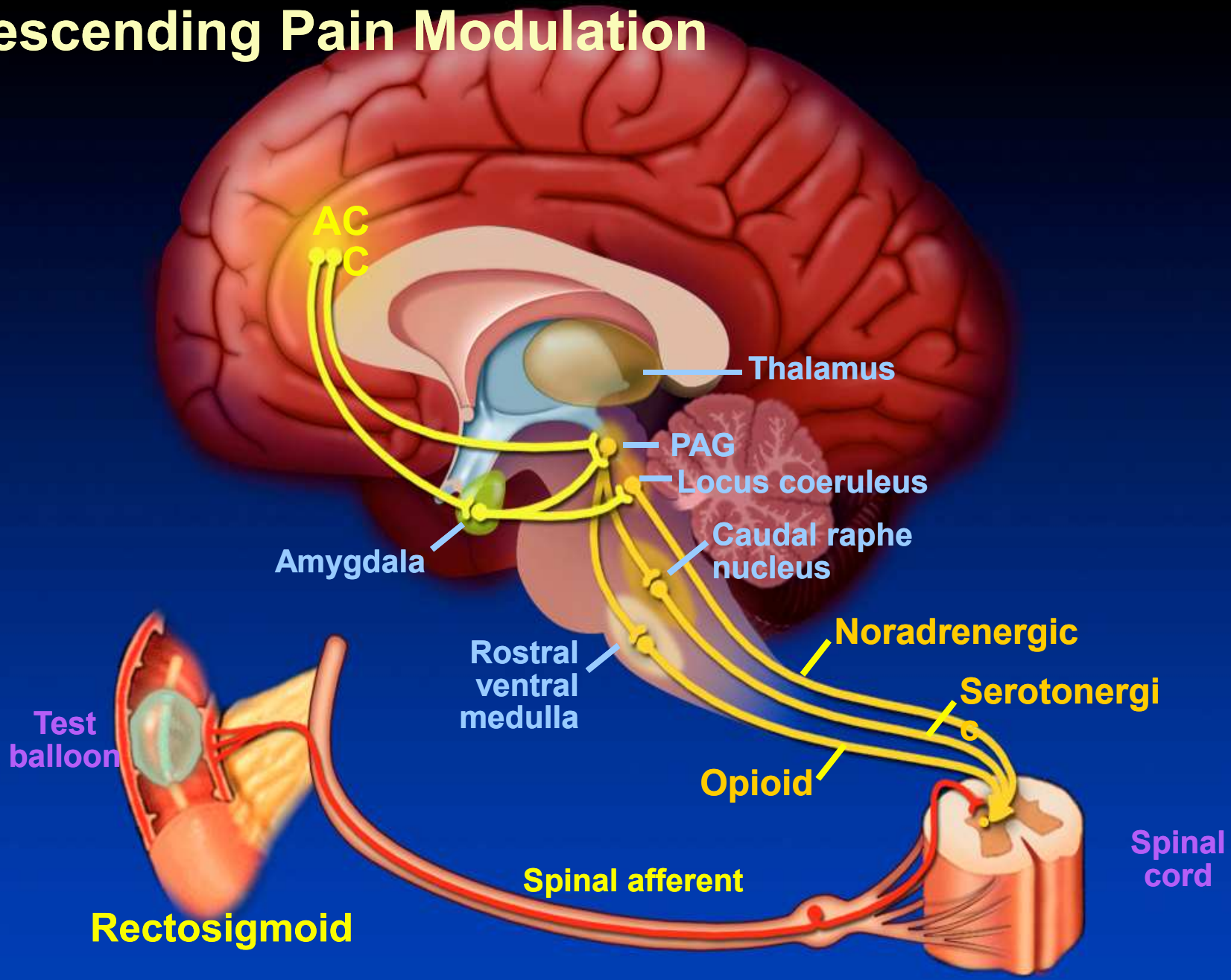


Processing of Sensory Signals in Spinal Cord, Brain Stem, and Brain

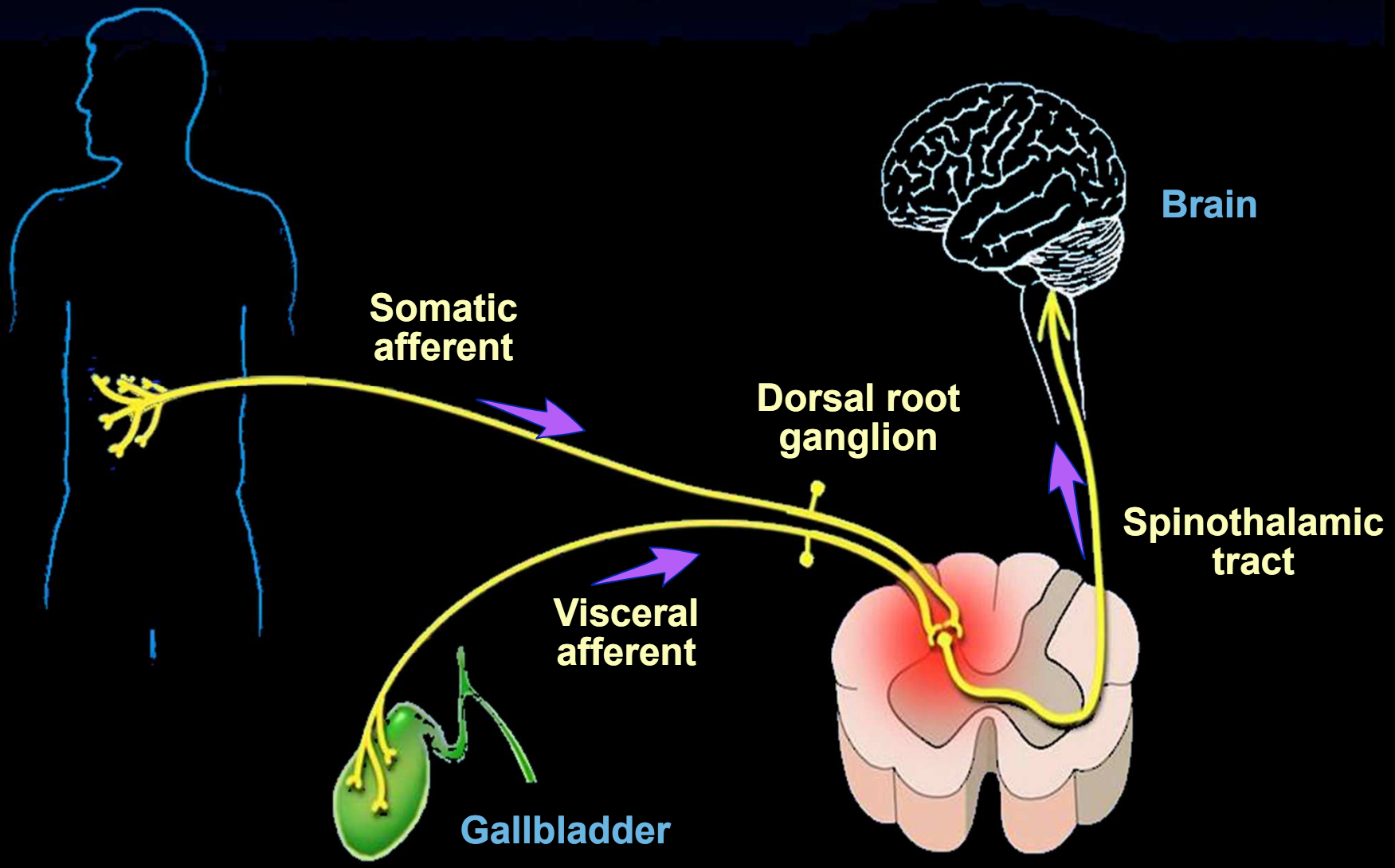



Ascending Visceral Pain Pathway
MCC
Primary somatosensory cortex
pACC
Insula
Thalamus
Reticulothalamic
Spinothalamic
Spinomesencephalic
Spinoreticular
Dorsal reticular nucleus
Colon

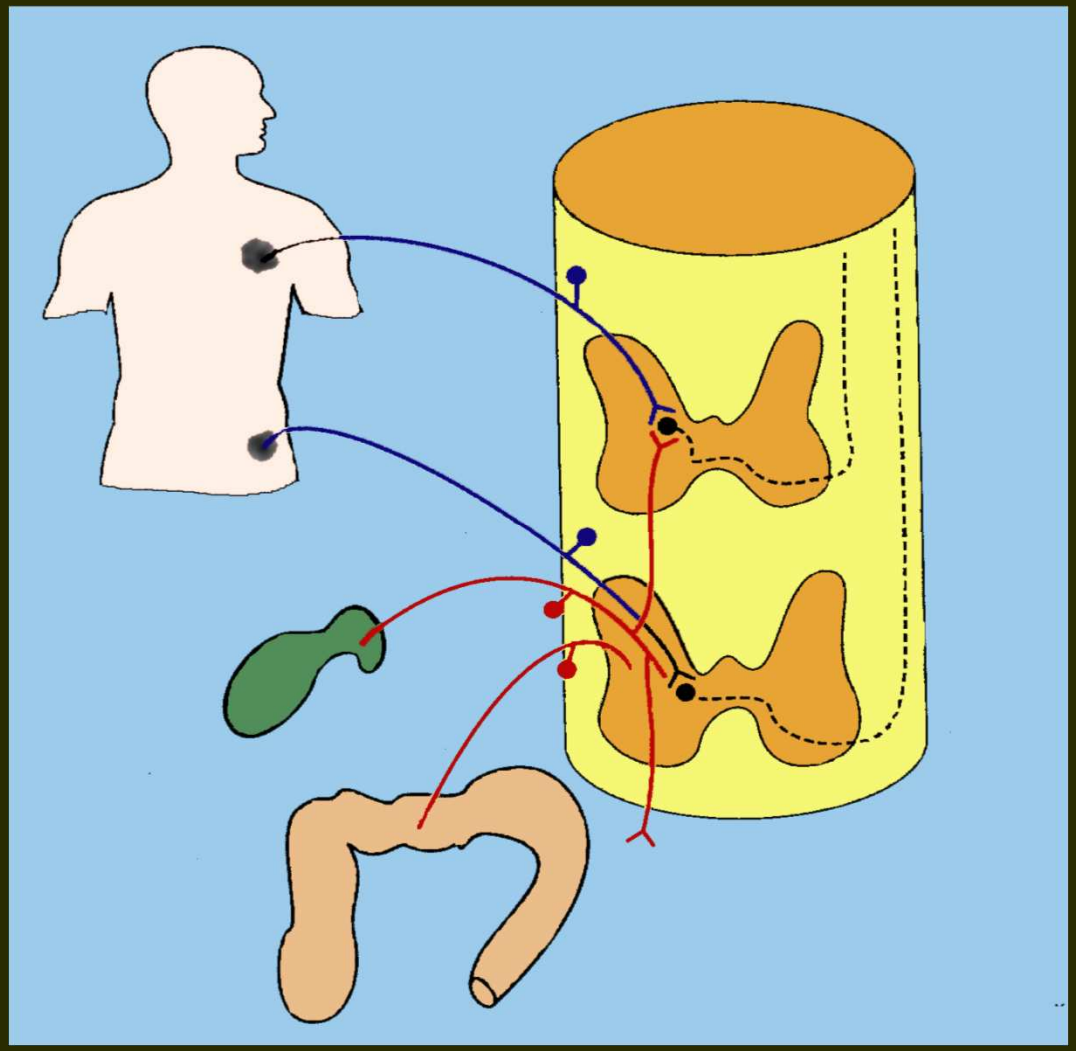
Descending Pain Modulation



Convergence of Somatic and Visceral Afferents in the Spinal Cord

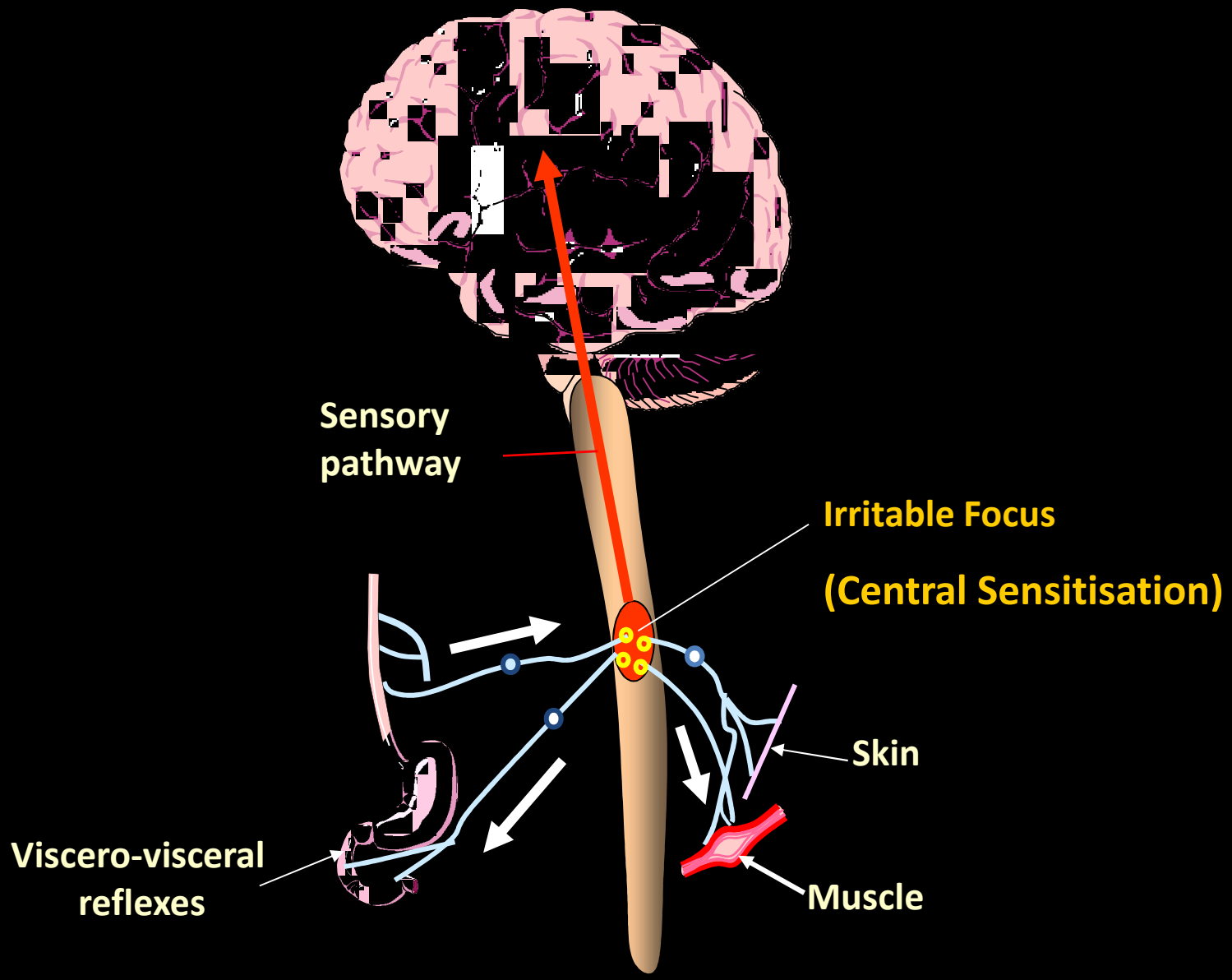


Divergence of Somatic and Visceral Afferents in the Spinal Cord

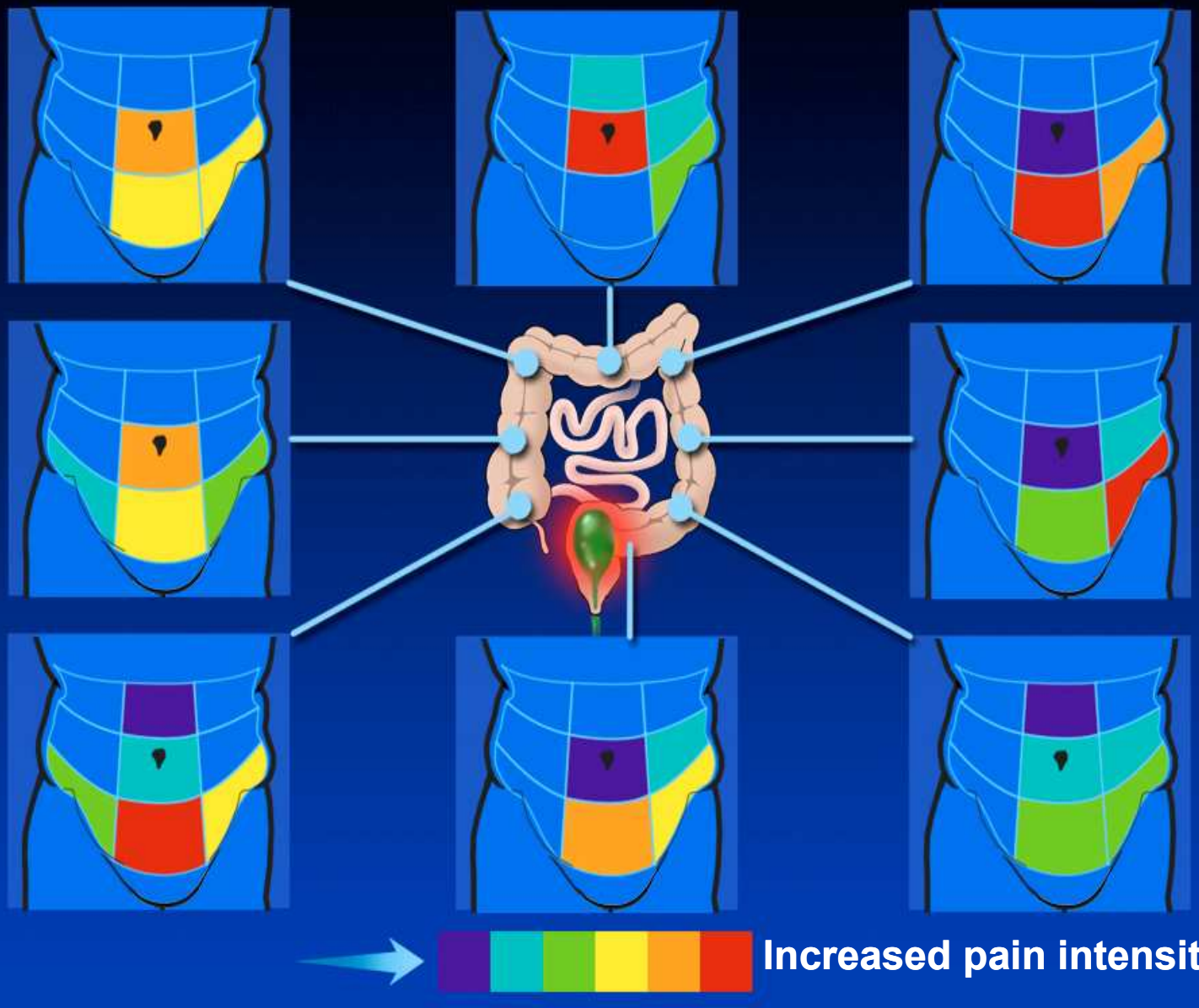


(Wolf et al. 1965)

Mackenzie's Interpretation of the mechanisms of visceral pain and related reflexes (1909)



Colonic Referred Pain

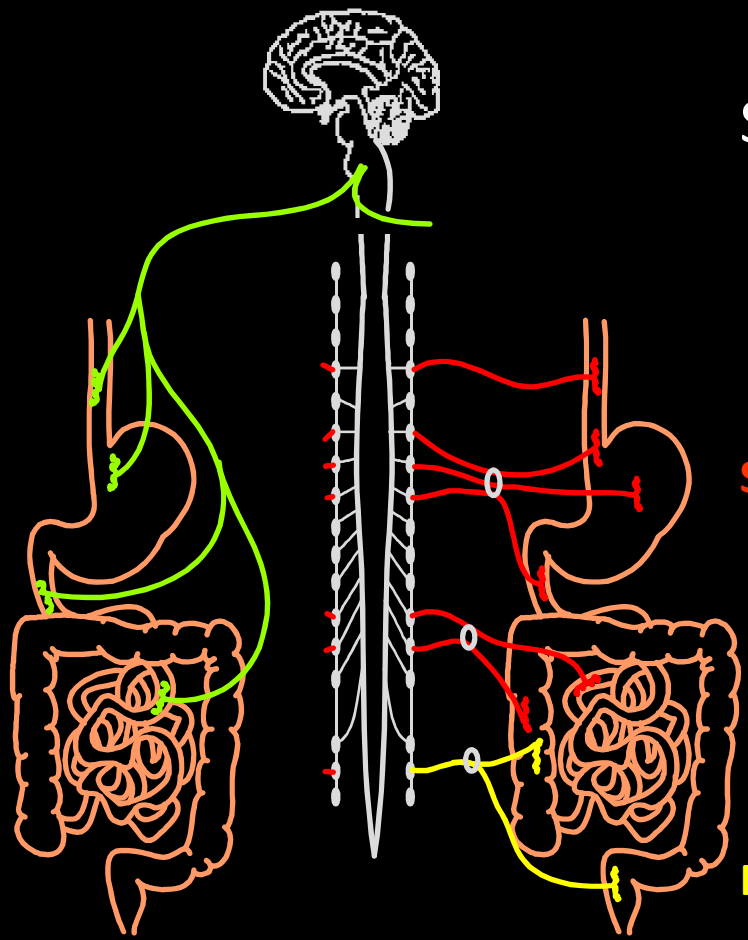


Mechanism(s) of visceral pain

Pathways of visceral sensations

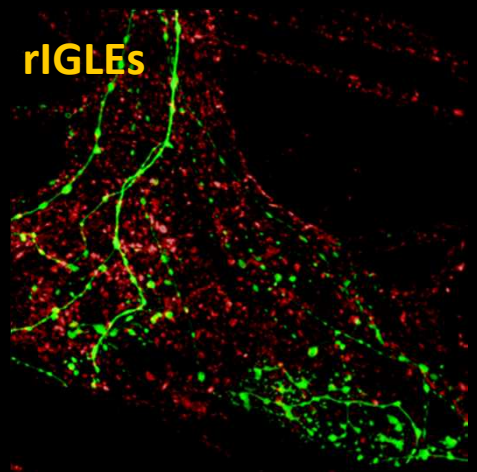
VAGAL

SPINAL

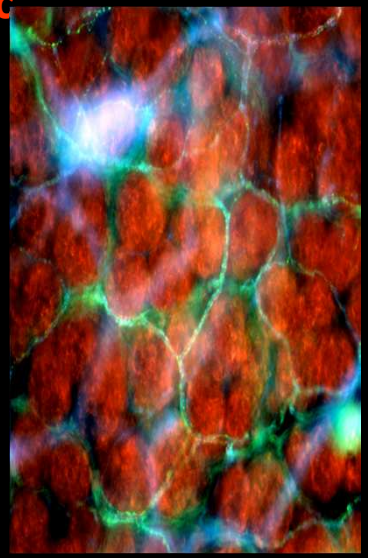


Splanchnic

Pelvic

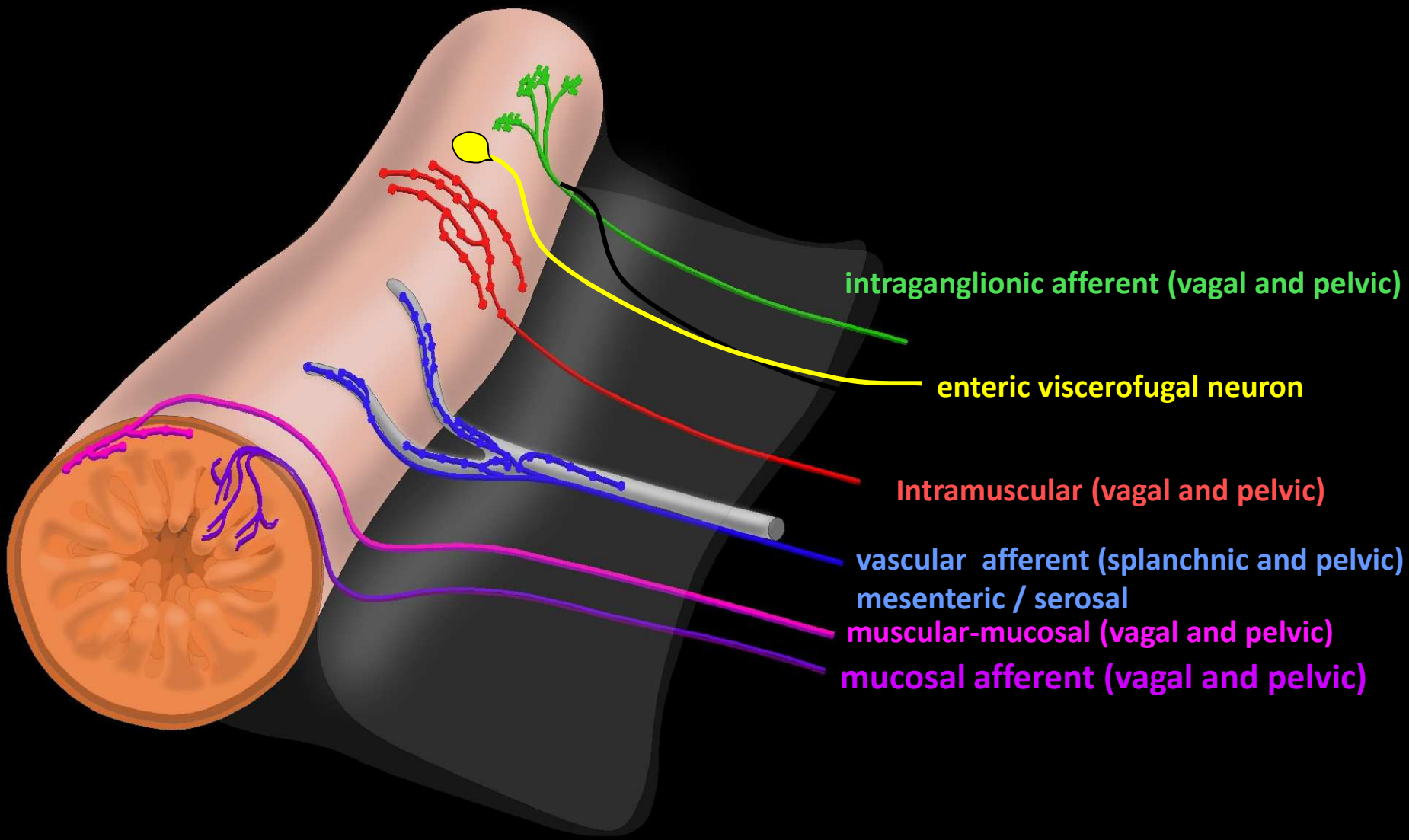


Low-threshold vagal mechanoreceptor



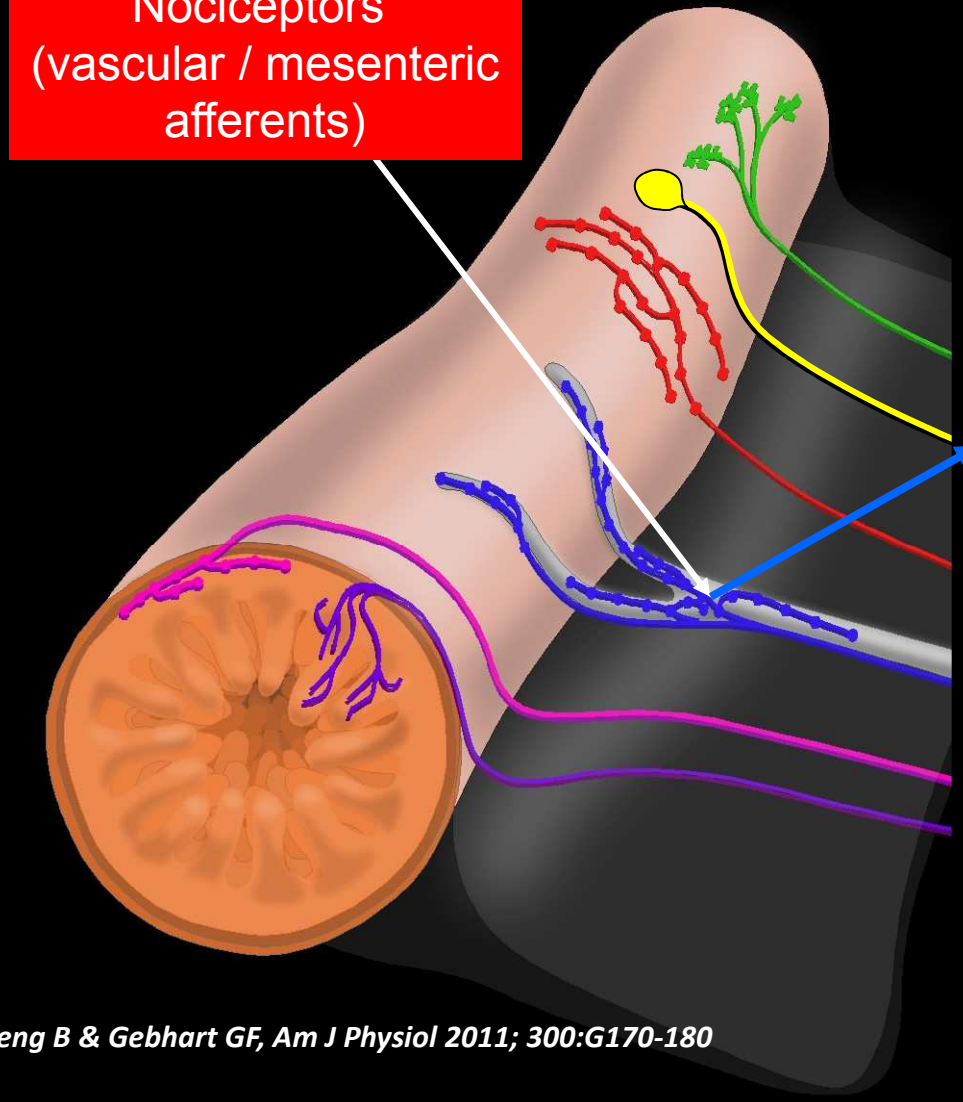
Muscular-mucosal afferen

Types of afferents in the gut

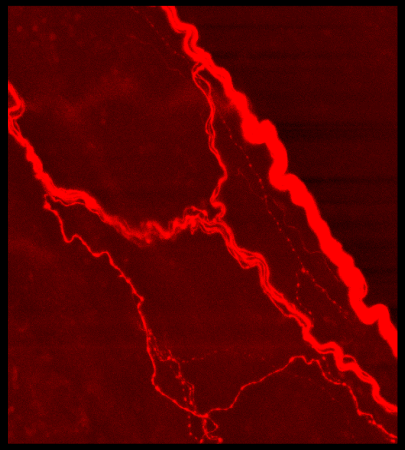


Vascular / mesenteric afferents act as nociceptors of the gut

Nociceptors (vascular / mesenteric afferents)



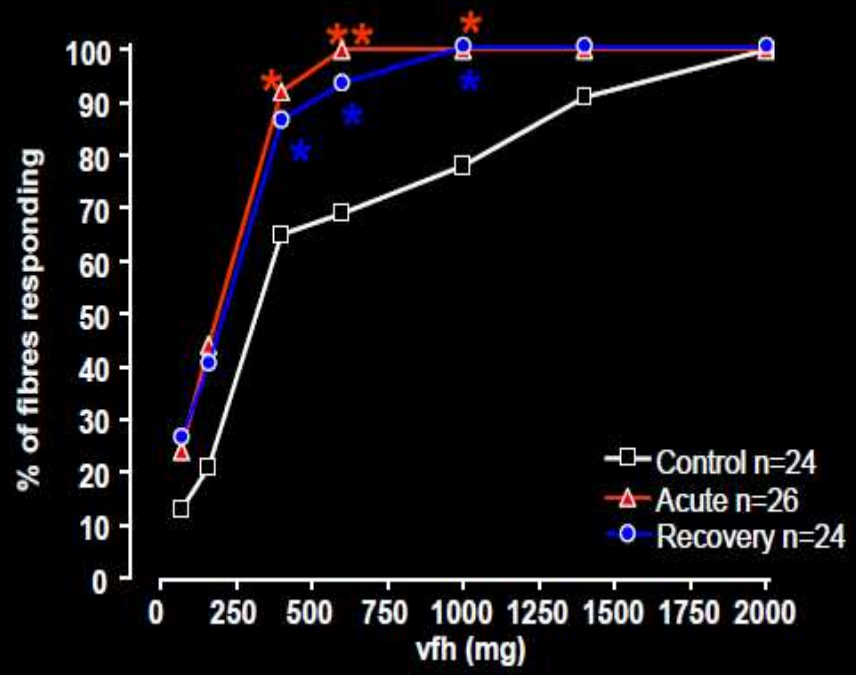
- Many are 'silent nociceptors'
- Modulated by inflammation
- Activation evokes vasodilation



Feng B & Gebhart GF, Am J Physiol 2011; 300:G170-180

Song X et al., Gastroenterology 2009; 137:274-284

Visceral hypersensitivity evoked by serosal (splanchnic) afferents in a mouse model of colitis

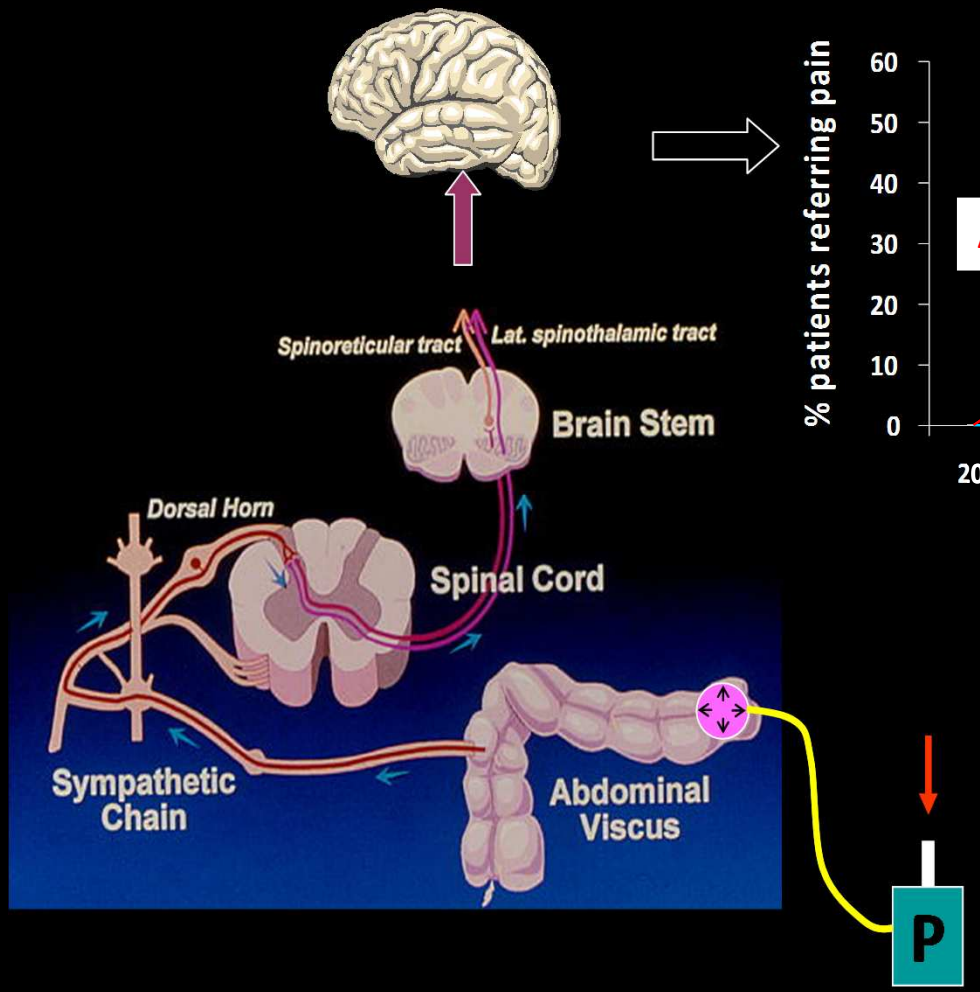


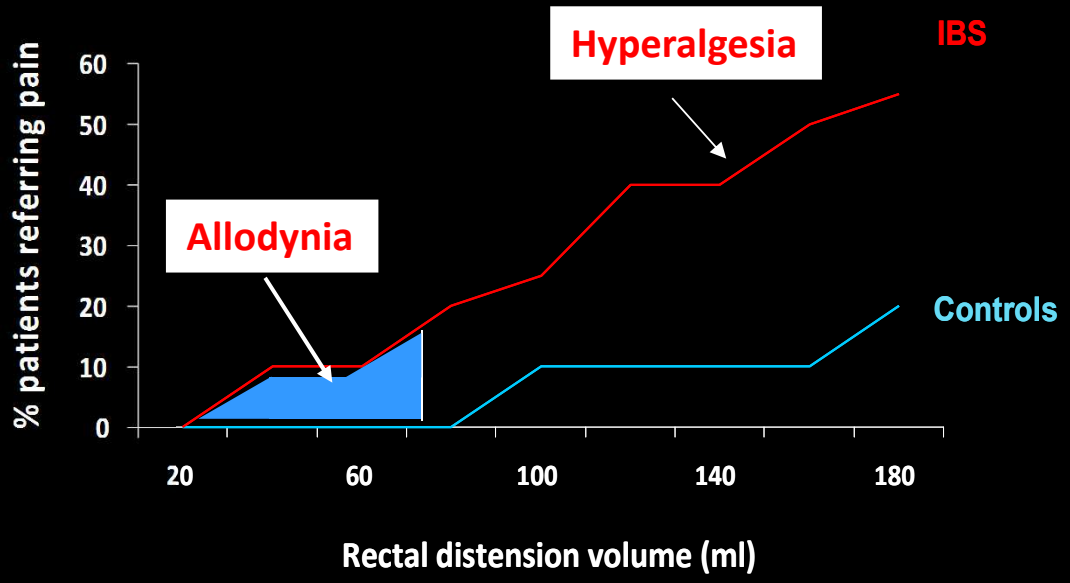
- Low-threshold mechanosensory fibers → not involved
- High-threshold (nociceptors) → acute and chronic (recovery) hepersensitivity

Hughes PA, et al., Gut 2009; 58:1333-41

Hypersensitivity in the clinical setting

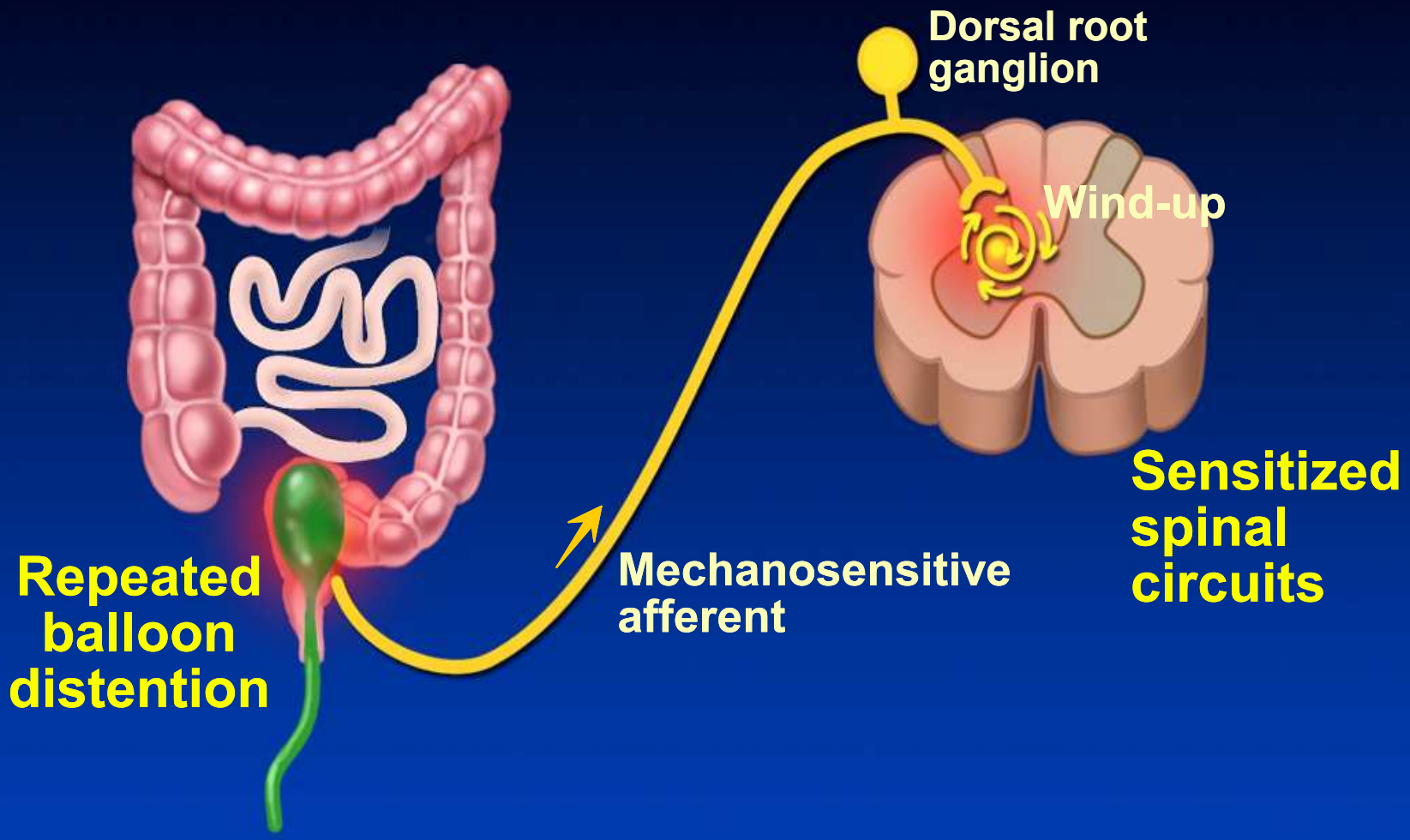
Visceral hypersensitivity in IBS



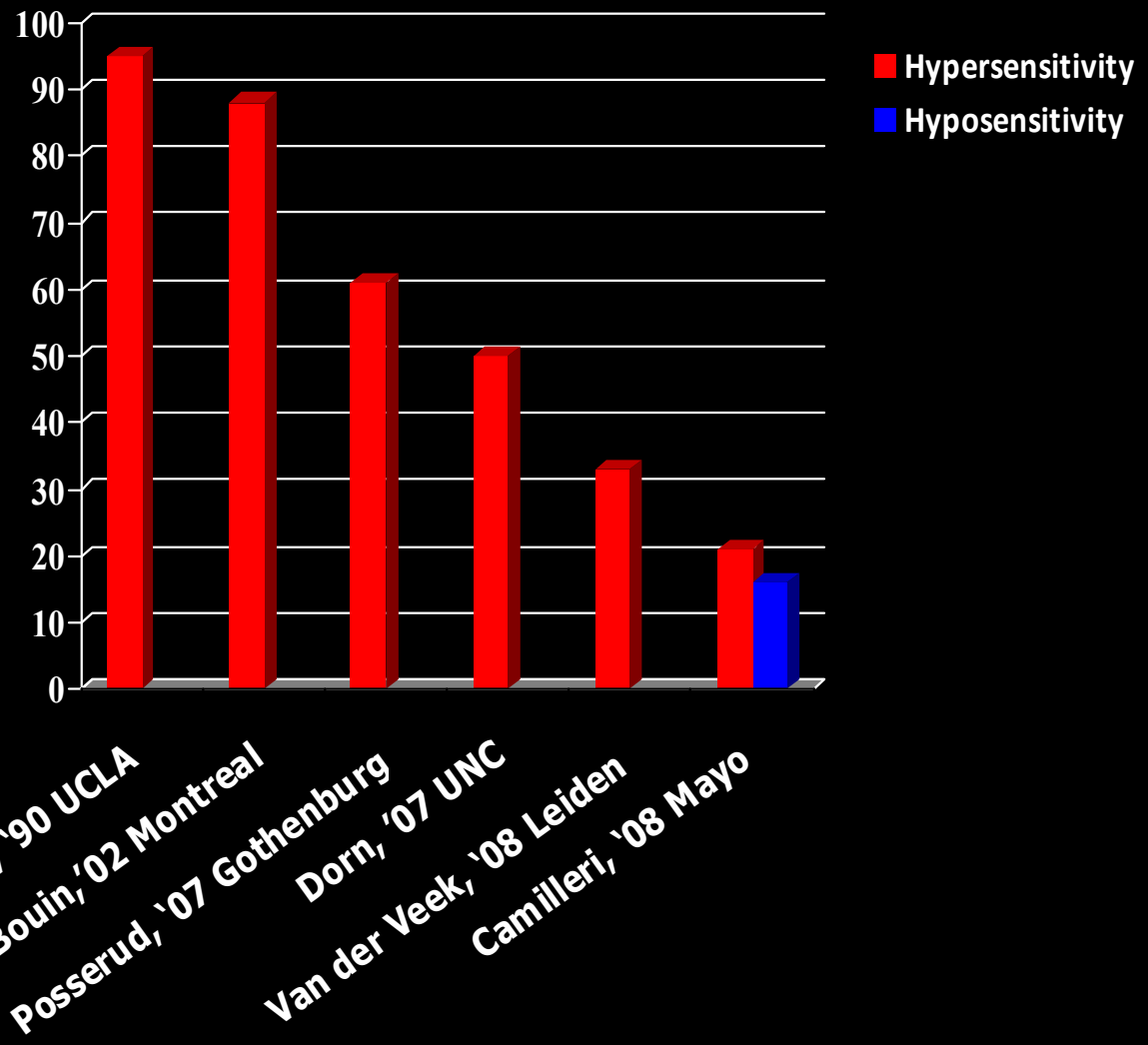


Whitehead W.E., et al., Dig Dis Sci 1980; 25(6):404-1

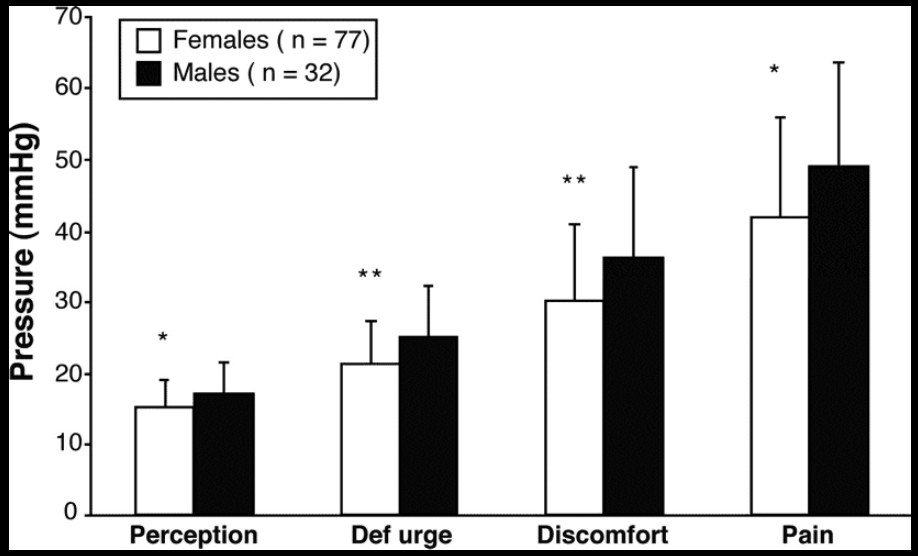
Repetitive Stimulation Sensitizes the Spinal Cord



Prevalence of rectal hypersensitivity in IBS

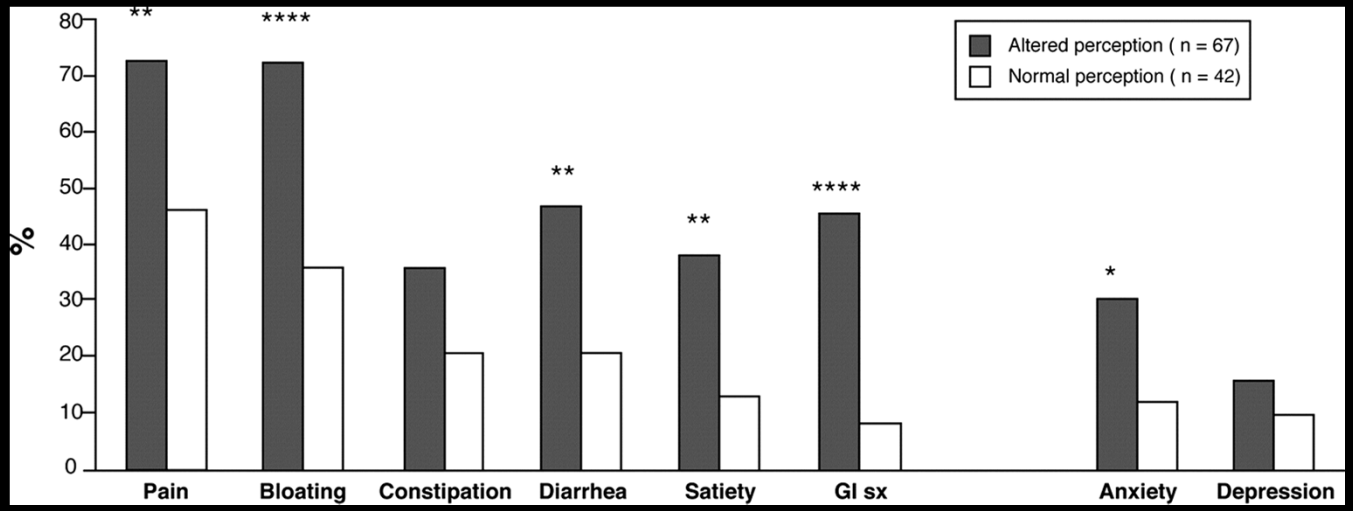


Female with IBS show more hypersensitivity than male pts



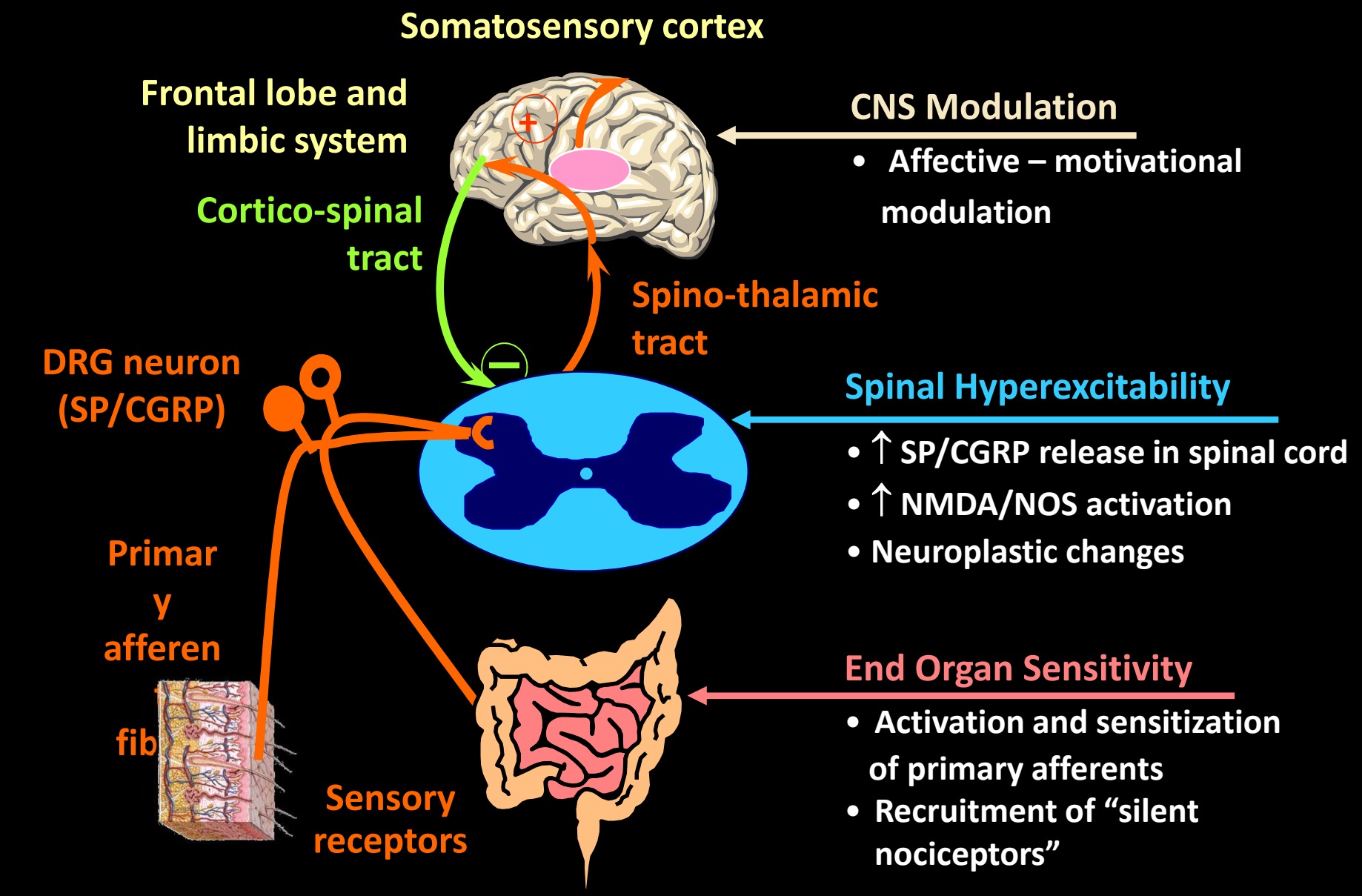
Posserud I., et al., Gastroenterology 2007;133: 1113-23

Altered perception is associated with symptom severity in IBS



Mechanisms and sites of hypersensitivity

Mechanisms of visceral hypersensitivity



CNS Modulation

- Affective – motivational modulation

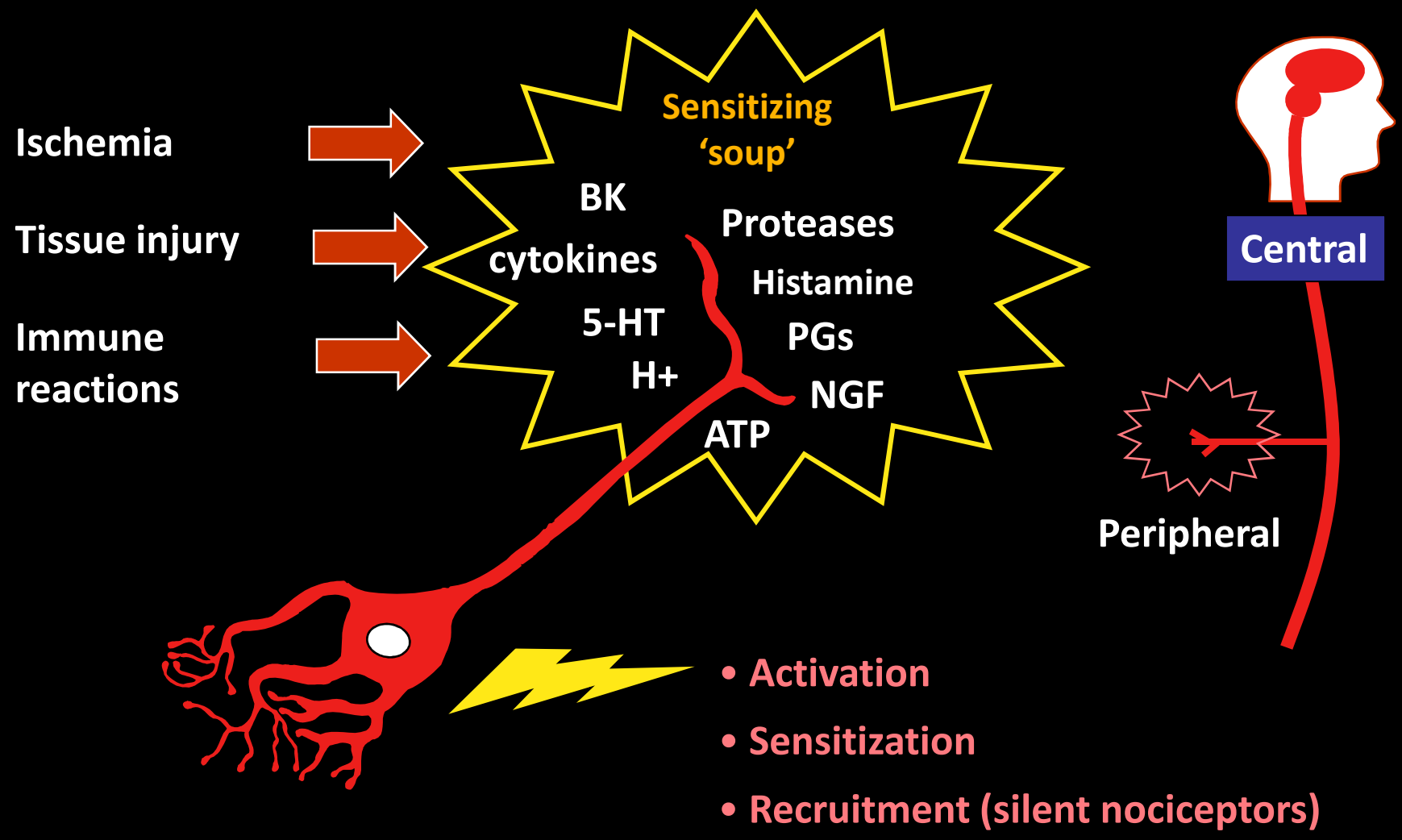
Spinal Hyperexcitability

- ↑ SP/CGRP release in spinal cord
- ↑ NMDA/NOS activation
- Neuroplastic changes

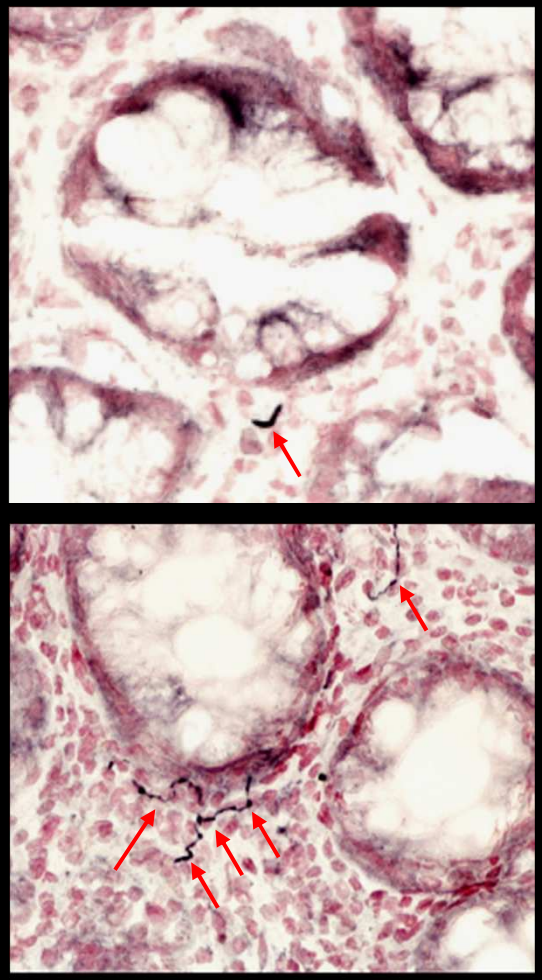
End Organ Sensitivity

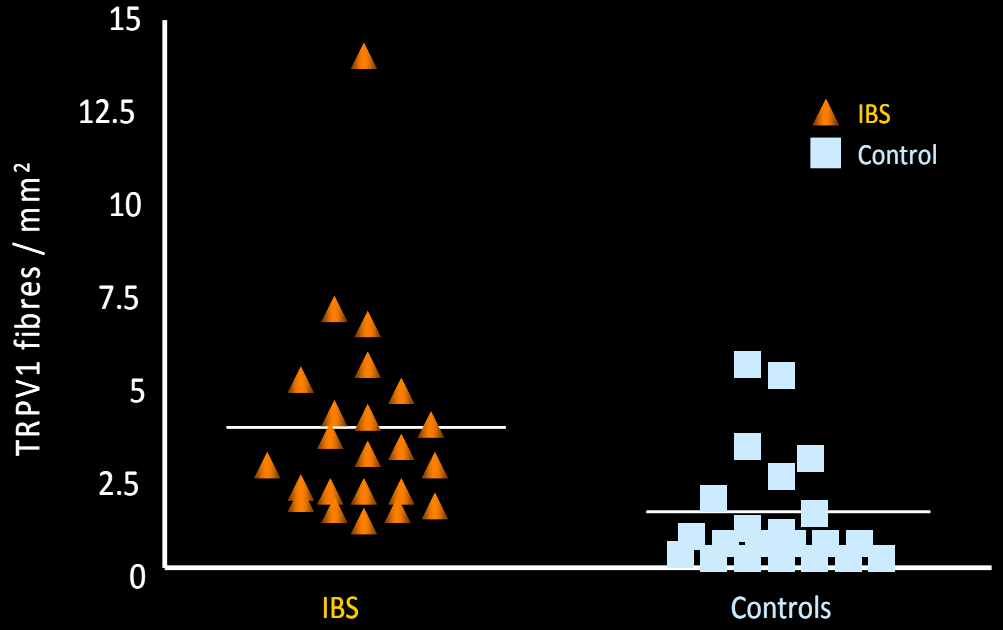
- Activation and sensitization of primary afferents
- Recruitment of “silent nociceptors”

Mechansims of Altered Afferent Sensitivity



Increased TRPV1-immunoreactive sensory fibres in IBS

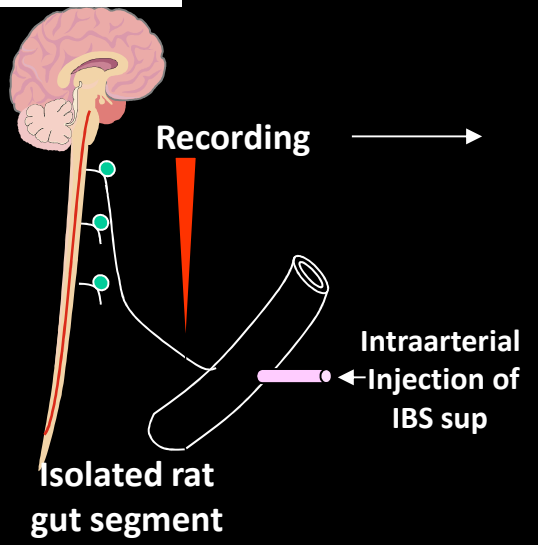


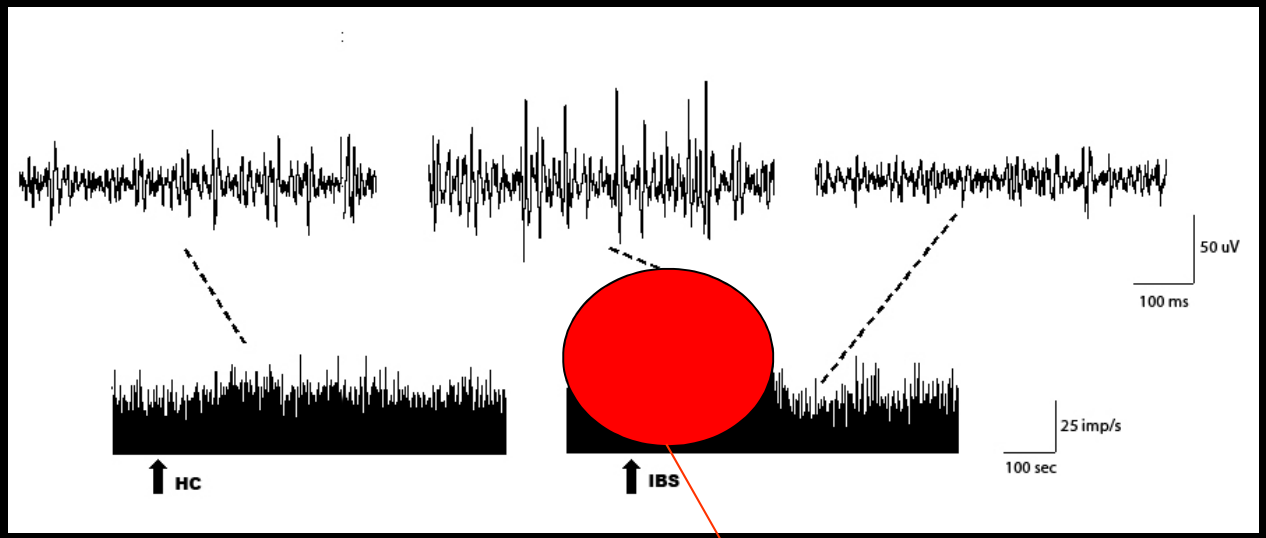


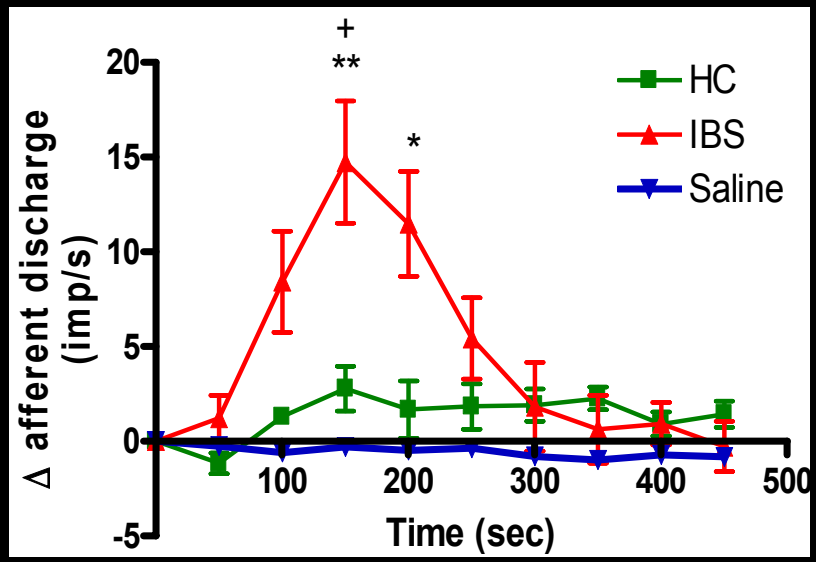
- 23 IBS pts; ~ 2/3 with non-D-IBS
- Low-grade inflammation
- Only TRPV1-IR nerves and MCs correlated with pain

Akbar A. et al., Gut 2008;57:923–929

Colonic mucosal mediators of IBS patients excite rat mesenteric sensory neurons







Proteases mainly involved in the firing of sensory neurons in IBS

Barbara G., et al. Gastroenterology 2007;132(1):2

CNS: visceral hypersensitivity

IBS hypersensitive (n=15)

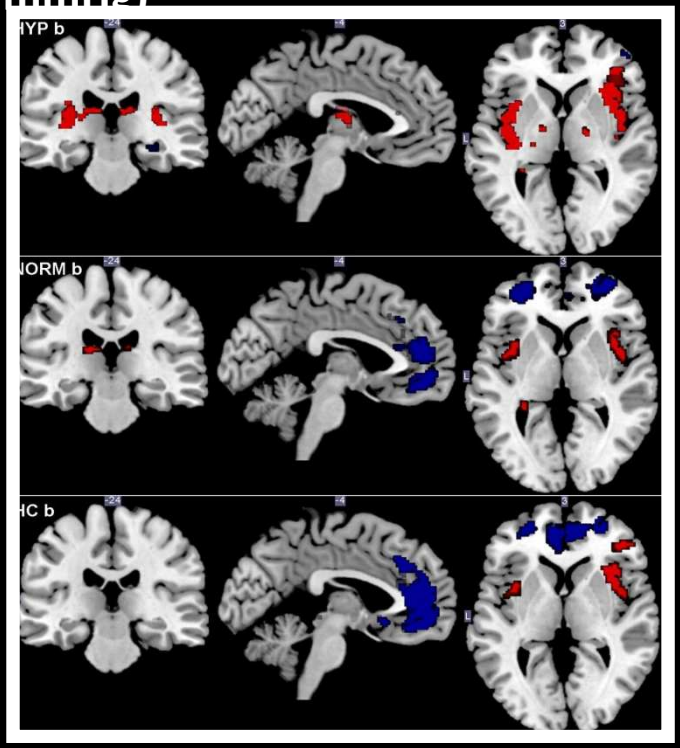
IBS normosensitive (n=18)

controls (n= 18)

fMRI activation

fMRI deactivation

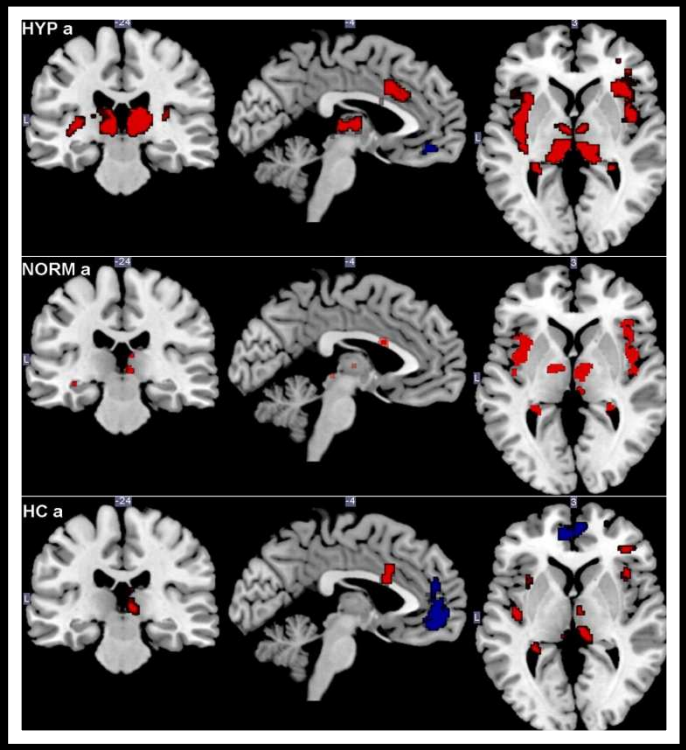
actual **rectal distension (45 mmHg)**



↑activation insula & ACC in

hypersensitive vs normosensitive & controls

expectation **rectal distension**

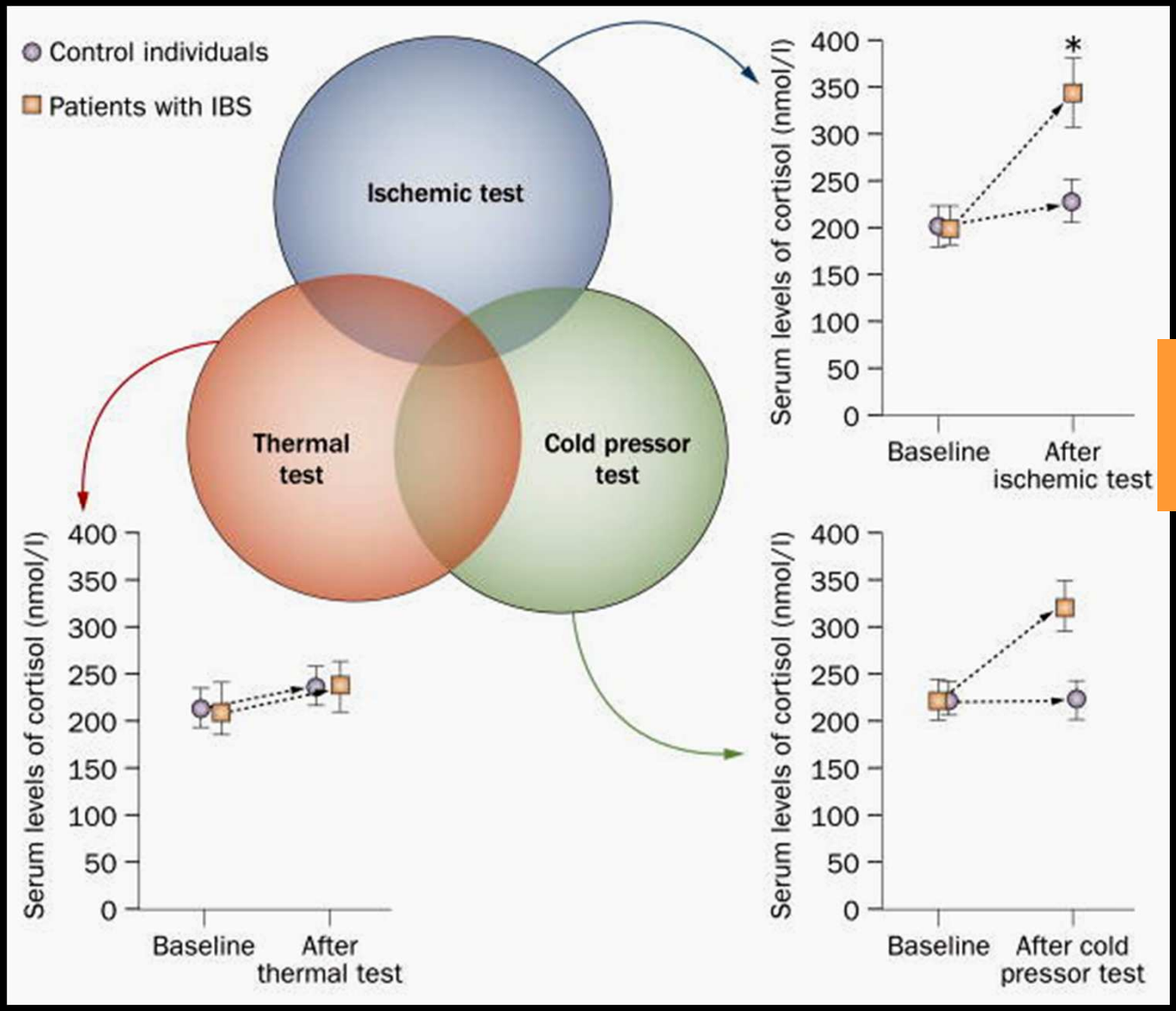


↑ activation insula in hypersensitive vs normosensitive

↑ activation right hippocampus in normosensitive vs controls

Larsson M.B., et al., Gastroenterology 2012;142:463-72

Visceral and somatic hypersensitivity overlap in IBS pts



IBS pts 2fold ↑ of somatic comorbidities e.g. fibromyalgia, CFS, etc.

Riedel A., et al., J Psychosom Res 2008;64:573-582

Zhou Q. & Verne GN, NRGH 2011;8(6):349-55

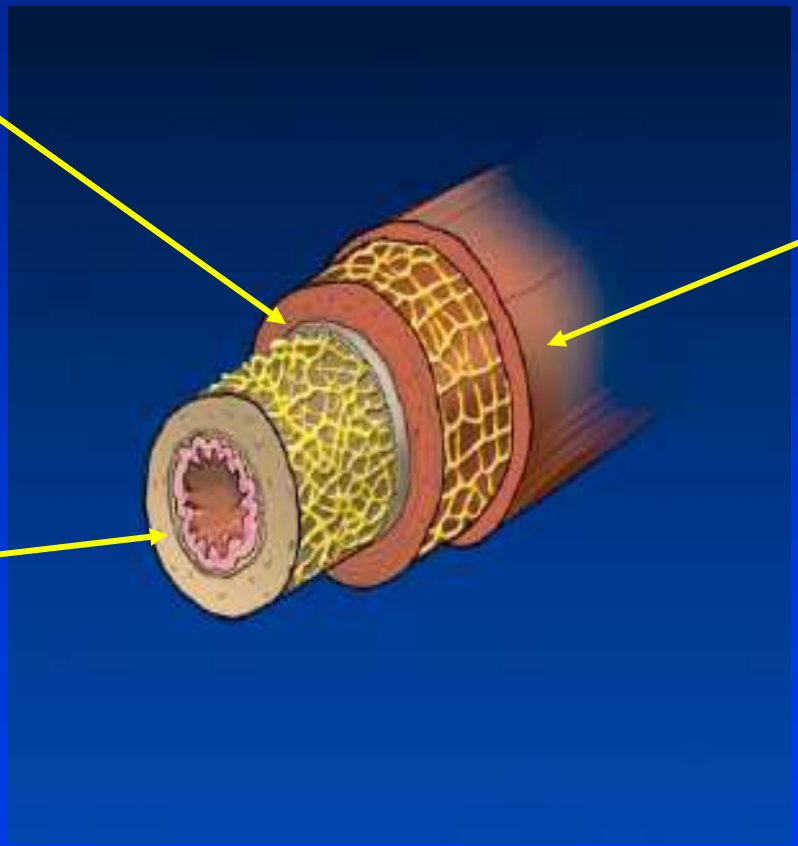
Mechanoreceptors of the Digestive tract - localisation

Vascular
(8/10 high threshold)

Tonic & Phasic distensions

Mucosal
(8/10 low threshold)

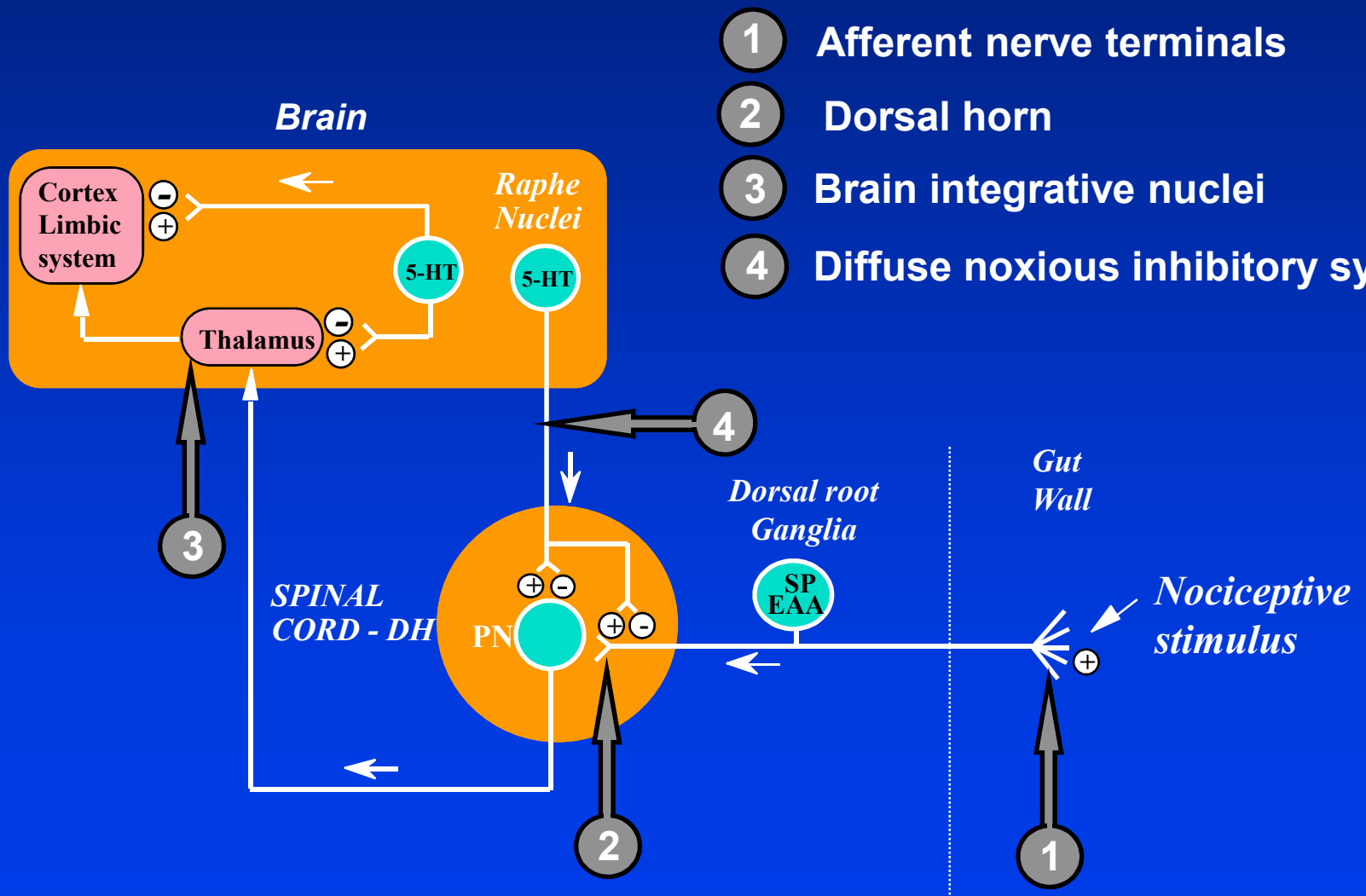
Phasic Distension
(act in parallel)



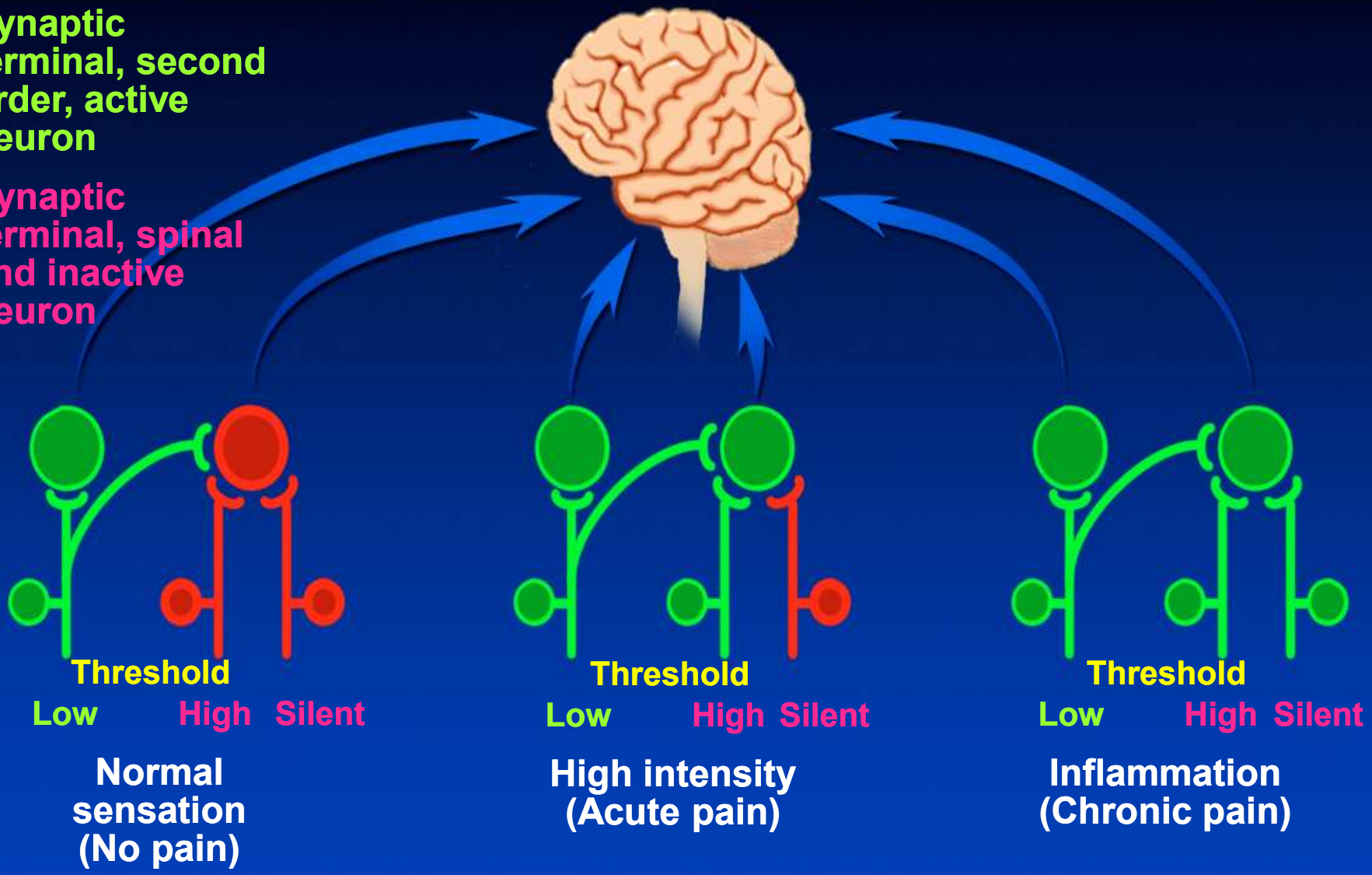
Serosal
(1/3 low threshold)

Tonic Distension
(act in series)

Possible sites of alterations in gut sensitivity



Spinal Gating for Three Classes of Visceral Nociceptors (Low, High and Silent) Account for Normal Regulatory Functions, Acute and Chronic Pain



Pharmacological treatment

Non-opioid antinociceptive drugs

Opioid drugs

Non-opioid antinociceptive drugs

Drug	Dose (mg)	Frequency of administration
Paracetamol (acetaminophen)	1000	Every 6-8 hours
Aspirin	300	Every 8 hours
Diclofenac	75	Every 8 hours
Diflunisal	500	Every 8 hours
Etodolac	400	Every 8 hours
Ibuprofen	200	Every 6-8 hours
Indomethacin	50	Every 6-8 hours
Ketoprophen	75	Every 8 hours
Ketorolac	10	Every 4-6 hours
Naproxen	500	Every 12 hours
Sulindac	200	Every 12 hours
Piroxicam	40	Once a day
Selective COX-2 inhibitors • Celecoxib • Etoricoxib	 200 120	 Every 12 hours Once a day

Paracetamol

- First choice in mild-moderate pain

Dose:

1 g x 4 / day

Hepatopaty / altered hepatic function:

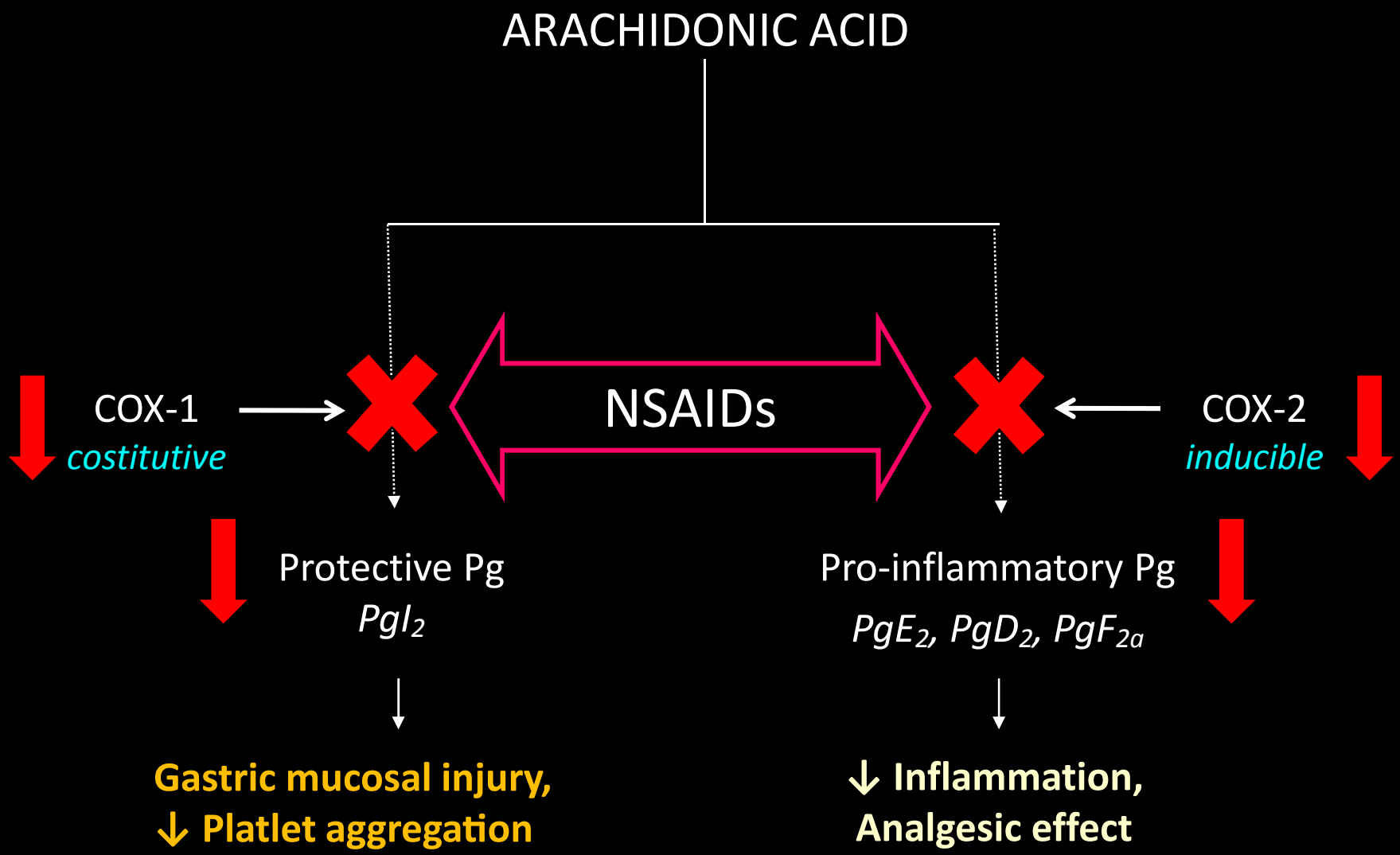
1 g x 3 / day

- No cross-reaction with NSAIDs

NSAIDs

Drug	Dose (mg)	Frequency of administration
Aspirin	300	Every 8 hours
Diclofenac	75	Every 8 hours
Diflunisal	500	Every 8 hours
Etodolac	400	Every 8 hours
Ibuprofen	200	Every 6-8 hours
Indomethacin	50	Every 6-8 hours
Ketoprophen	75	Every 8 hours
Ketorolac	10	Every 4-6 hours
Naproxen	500	Every 12 hours
Sulindac	200	Every 12 hours
Piroxicam	40	Once a day
Selective COX-2 inhibitors • Celecoxib • Etoricoxib	 200 120	 Every 12 hours Once a day

Mechanisms of action of NSAIDs



NSAIDs

- **Pain related to inflammation**

- **DICLOFENAC:** no antiplatelet action
- **IBUPROFEN:** lowest gastrolesivity
- **KETOROLAC**: highest gastrolesivity

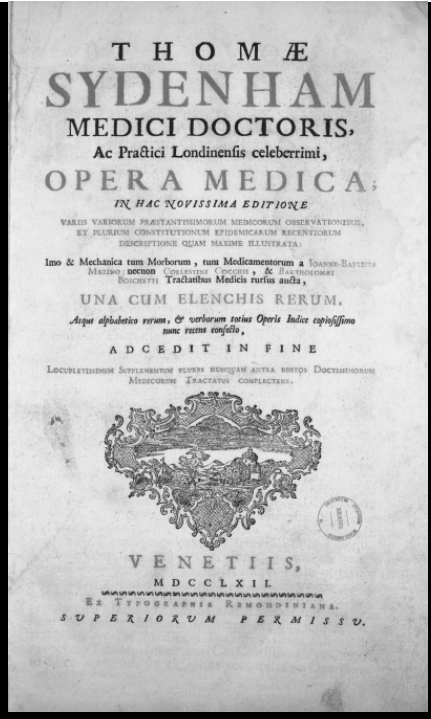
Non-opioid antinociceptive drugs

Drug	Dose (mg)	Frequency of administration
Aspirin	300	Every 8 hours
Diclofenac	75	Every 8 hours
Diflunisal	500	Every 8 hours
Etodolac	400	Every 8 hours
Ibuprofen	200	Every 6-8 hours
Indomethacin	50	Every 6-8 hours
Ketoprophen	75	Every 8 hours
Ketorolac	10	Every 4-6 hours
Naproxen	500	Every 12 hours
Sulindac	200	Every 12 hours
Piroxicam	40	Once a day
Selective COX-2 inhibitors • Celecoxib • Etoricoxib	 200 120	 Every 12 hours Once a day

PPIs to prevent gastropathy

PPIs not strictly necessary; cautiously administered in pts with previous CAD

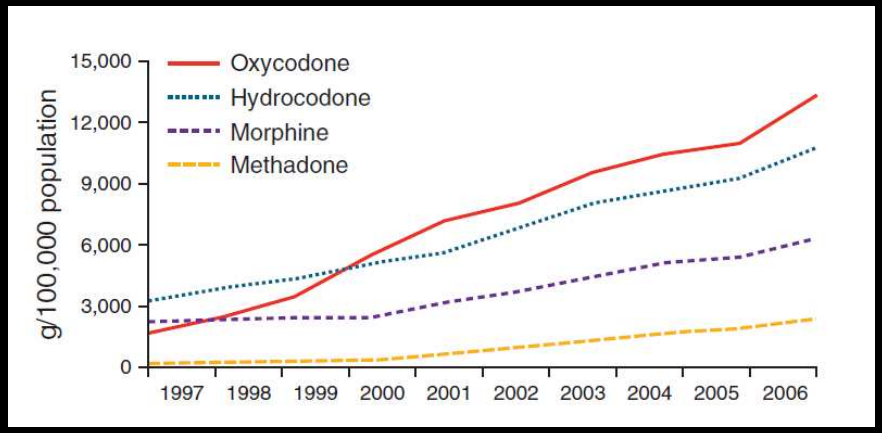
Thomas Sydenham (1624-1689)


THOMÆ
SYDENHAM
MEDICI DOCTORIS,
Ac Practici Londinenſis celeberrimi,
OPERA MEDICA;
IN HAC NOVISSIMA EDITIONE
VARIIS VARIORUM PRÆSTANTISSIMORUM MEDICORUM OBSERVATIONIBUS,
ET PLURIUM CONSTITUTIONUM EPIDEMICARUM RECENTIORUM
DESCRIPTIONE QUAM MAXIME ILLUSTRATA:
Imo & Mechanica tum Morborum, tum Medicamentorum a IOANNE-BAPTISTA
MORGNO: necnon CELESTINO COCCHII, & BARTHOLOMÆO
BOSCHETTI Tractatibus Medicis rurſus aucta,
UNA CUM ELENCHIS RERUM,
Atque alphabetico rerum, & verborum totius Operis Indice copioſiſſimo
nunc recens confecto,
ADCEDIT IN FINE
LOCUPLETISSIMUM SUPPLEMENTUM PLURES HUNQUAM ANTEA EDITOS DOCTISSIMORUM
MEDICORUM TRACTATUS COMPLECTENS.
VENETIIS,
MDCCLXII.
EX TYPOGRAPHIA REMONDINIANA.
SUPERIORUM PERMISSU.

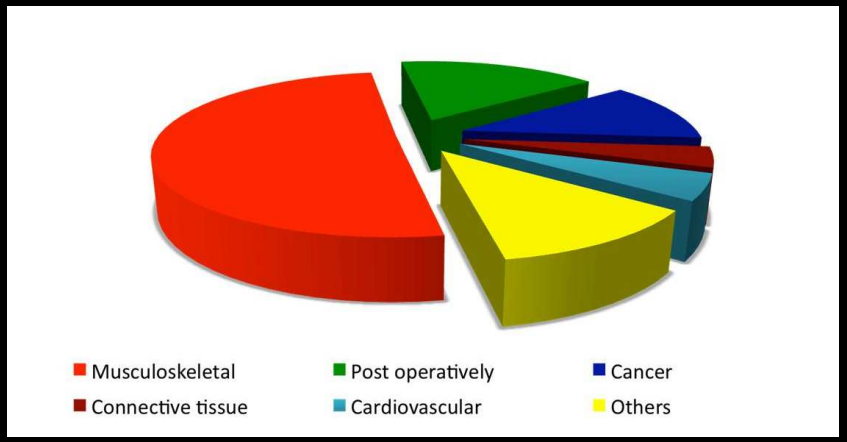
Among the remedies which it has pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium…

Opioid use and prescriptions

Increased use of opioids



Indications for opioid prescribing



- In 2012, >240 million prescriptions for opiate analgesics in the USA
- ~40-80% of pts take opiods for chronic, non-cancer pain
- Up to 94% of patients with advanced illness who take opiods require laxatives
- Standars laxatives are often insufficient for treatment of OIC and fail in ≈50% of cases

Camilleri M., Am J Gastroenterol. 2011;106(5):835-42; IMS Health 2012 (reported by Fauber J. J Sentinel. March 6, 2013);
Holzer P., Eur Rev Med Pharmacol Scl. 2008; 12 (S1): 119-127;6

Opioid System

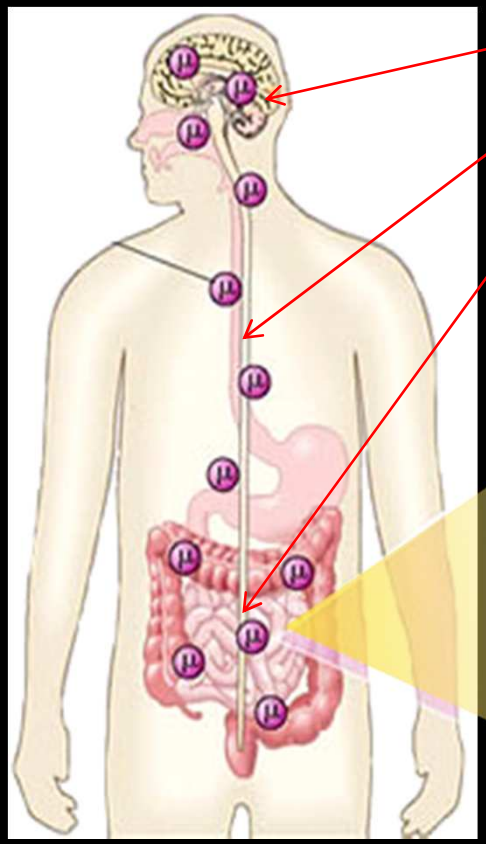
- **Endogenous opioids:**
  - Dynorphins
  - ß endorphins
  - Enkephalins

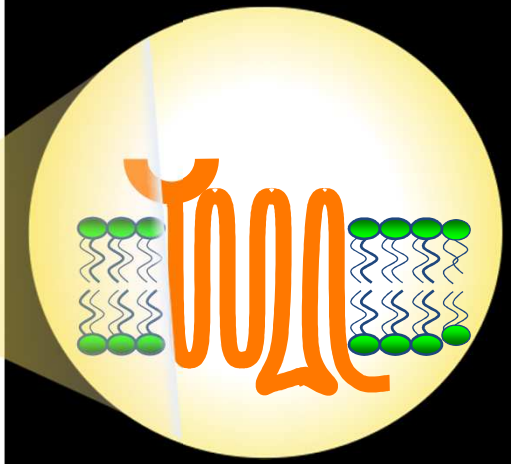
Receptors:
- μ
- δ
- κ
- σ

CNS

PNS

ENS





- **Effects:**
- Euphoria
- Analgesia
- Sedation
- Relief from diarrhea
- Cough suppression

- **Localization & Function in the ENS:**
- **Enteric neurons**
- **Smooth muscle cells**
- **Immune cells**

- **GI motility & secretion**
- **Immune response**

Opioids

Opioid	Half life (h)	Onset (h)	Duration (h)	Relative potency	Initial dose (mg)	Dosing interval (h)
Pethidine / Meperidine (Demerol)	2-3	0.1-0.4	1-3	0.1	50-150	4
Codeine	3	0.25-1.0	3-4	0.15	30-60	4
Hydromorphone (Jurnista)	2-3	0.3-0.5	2-3	4	2-4	4
Oxycodone (Oxycontin)	2-3	0.5	3-6	1.5	5-10	6
Methadone (Dolophine, Eptadone)	15-30	0.5-1.0	4-6	3	20	6-8
Propoxyphene (Darvon, Darvocet)	6-12	1.0-2.0	3-6	0.15	100	6
Tramadol (Contramal, Ultram)	6-7	1.0-2.0	3-6	0.1	50	4-6
Morphine solution (Oramorph)	2-4	0.5-1.0	4	1	10	3-4
Morphine controlled release (MS Contin)	2-4	1.0	8-12	1	15	8-12
Fentanyl (Durogesic)	1-6	12-24	48-72	100	0.025-0.050/hr	48-72

Paracetamol + Codeine

- Mild-moderate pain or severe pain (with controindications for NSAIDs)
- Possible use in association with major analgesic drugs
- Up to 10% of population are poor metabolizers (i.e., little / no analgesia from codeine)
- Rapid metabolizers also may have little analgesic effect

Dose adults / children > 40 kg:

500-30 mg/6 h – 1000 mg-60 mg/8 h (max 3g-180mg)

Dose children 30-40 kg:

500 mg-30 mg /8 h

Morphine

- 10 mg / mL vials for i.v. administration
- Peak in 5 min; half-life: 10 min

Dose adults / children:

1° bolus: 0.1 mg / kg

2° bolus (after 10 min): 0.05 mg / kg

Dose elderly-renal insufficiency-hepatic insufficiency:

1° bolus: 0.05 mg / kg

2° bolus (after 10 minuti): 0.0025 mg / kg

- Oral morphine (tablets): 10 – 30 – 60 – 100 mg PR / oral solution: 10 – 30 – 100 mg / 5 mL
- Histamine release !

Fentanyl-1

- 0.1 mg / 2 mL vials for i.v. administration; rapid onset and very short half-life
- Peak in 5 min; half-life: 10 min

Dose (i.v. = intranasal; adults = children),

NO ADJUSTMENT IN HEPATIC OR RENAL INSUFFICIENCY:

1° bolus: 1.5 mcg / kg

2° bolus (after 10 min): 0.75 mcg / kg

Dose in the elderly:

1° bolus: 0.75 mcg / kg

2° bolus (after 10 min): 0.35 mcg / kg

- Side effects → avoidable with administation of a rapid bolus diluted in 0.9% saline solution

Fentanyl-2

- Transdermal patch for constant analgesia
- Transdermal patch 12 mcg / h – 25 mcg / h – 50 mcg / h – 75 mcg / h - 100 mcg / h
- Titration with adjustment of 12 / 25 mcg / h - change patch every 72 h

Oral Morphine 24 h (mg/day)	Fentanyl t-dermal patch dose (mcg/h)
< 44	12
45 - 89	25
90 - 149	50
150 - 209	75
210 - 269	100
270 - 329	125
330 - 389	150
390 - 449	175
450 - 509	200
510 - 569	225
570 - 629	250
630 - 689	275
690 - 749	300

Oxycodone

- Oral administration (dosing interval 12 h)
- Tablets 5 - 10 - 20 - 40 - 80 mg

Initial dose: 5 mg x 2 / day + on demand theraphy with oral morphine (Oramorph 10 mg) max 4 / day

- Dose adjustment (5 mg) every 24 h if need for Oramorph > 2 / day
- 10 mg oral oxycodone = 20 mg oral morphine

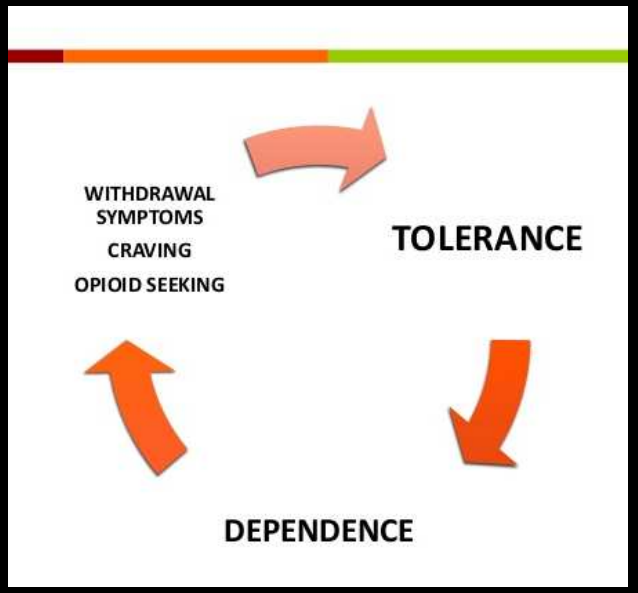
Tolerance and dependence

Tolerance

- Pharmacologic effect characteristic of opioids
- With regular use, opioids become less effective over time and tolerance develops
- Tolerance does not develop to pupil constriction and constipation
- Higher dose are needed to achieve the same effect

Dependence

- Development of physiological / psychological adaptation in response to long term use
- A chronic , relapsing condition associated with physical changes in the brain due to frequent use
- Experience cravings and withdrawal symptoms when the effects of opioids begin to wear off



Side effects

Acute opioid intoxication/overdose

Signs and symptoms

Disruption of central control of peripheral sympathetic activity

- Respiratory depression → apnea
- Circulatory depression → hypotension
- Constricted pupils (maybe dilated with meperidine)
- Convulsions with meperidine and propoxyphene
- Arrhythmias with propoxyphene
- Pulmonary edema
- Reduced reflexes

CNS depression

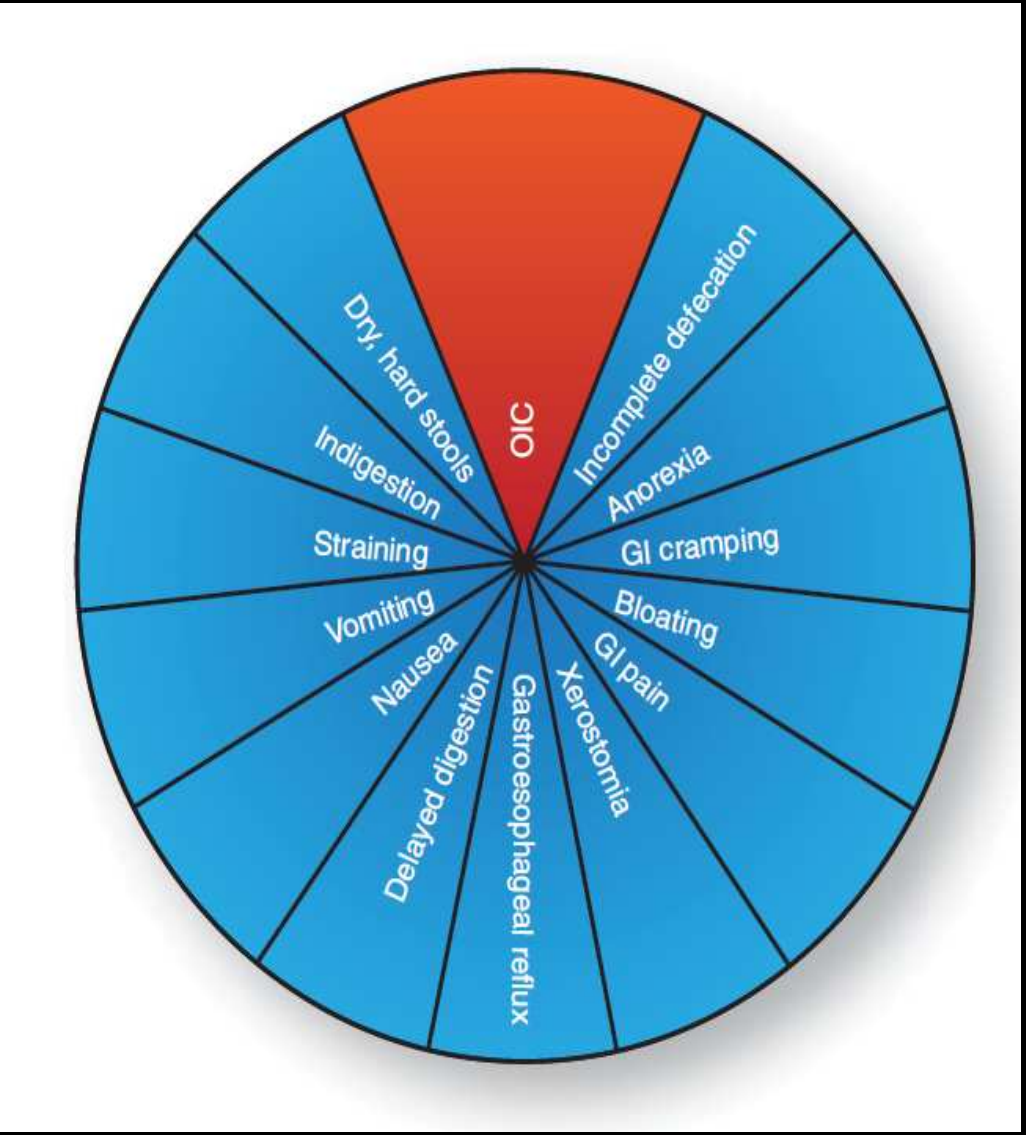
- Drowsiness → sedation → coma

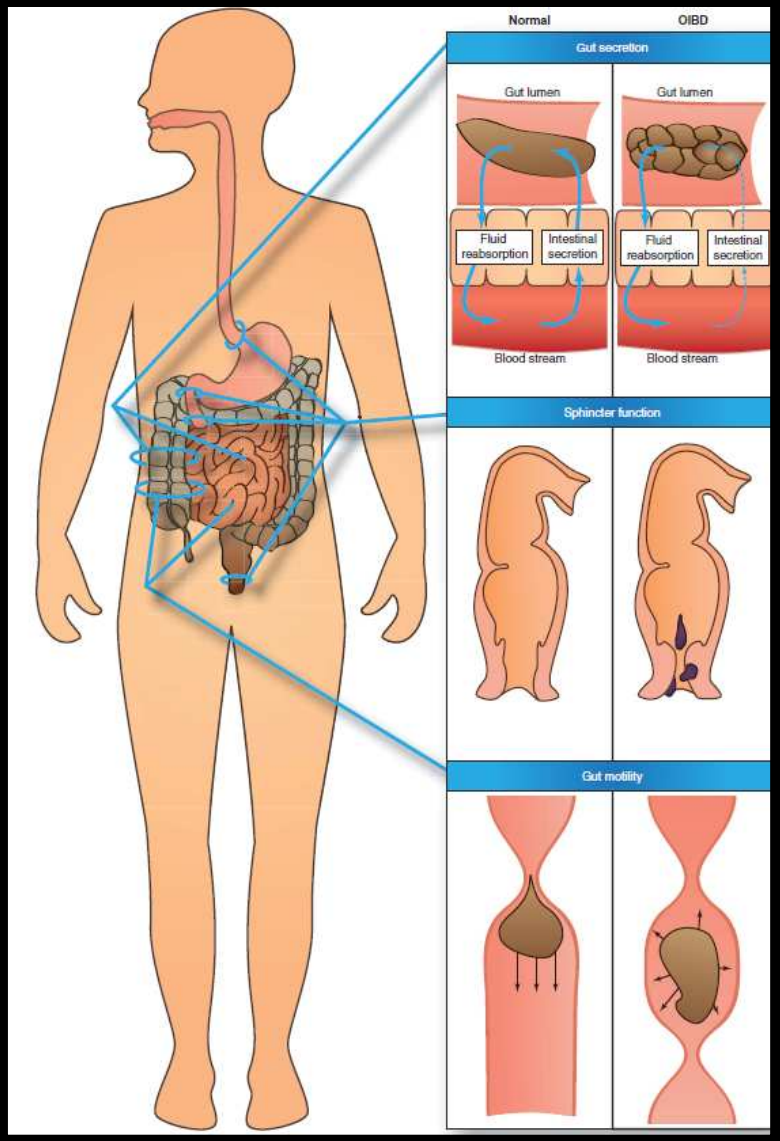
Treatment

Naloxone

- 0.4 mg intravenously and repeated as necessary
- Short duration of action, 1-2hrs
- Give every 30mins until patient is stable

Opioid induced bowel dysfunction

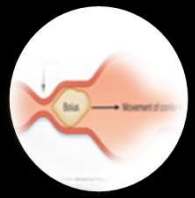




Poulsen J.L., Ther Adv Gastroenterol, 2015; 8(6):360-372

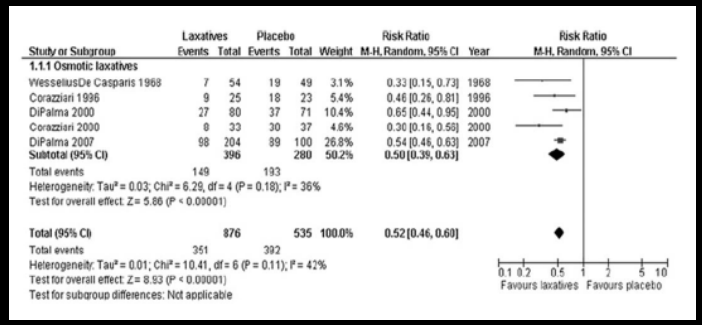
PEG / Macrogol: (Almost) All you wanted to know in…

↓ transit
(> left vs. right colon)



Corazziari E.S., et al., Dig Dis Sci 1996; 41:1636-42

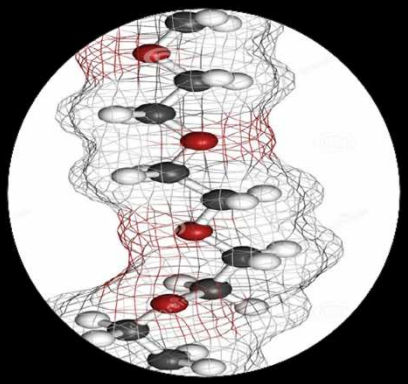
Global, long-term
efficacy in constipation



Ford AC & Suares NC., Gut 2011;60:209-218

Binding water
=
Iso-osmotic effect

Schiller L.R., et al., Gastroenterology 1988;94:933-41



1 st line-therapy in many
patient subtypes

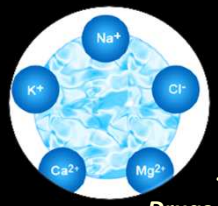
De Giorgio R., et al., Eur Rev Med Pharmacol Sci 2011; 15:960-66

No major adverse events

Well tolerated
(bloating, flatulence
may occur)

Corazziari E.S., et al., Gut 2000; 46: 522-526

PEG no electrolytes =
PEG + electrolytes



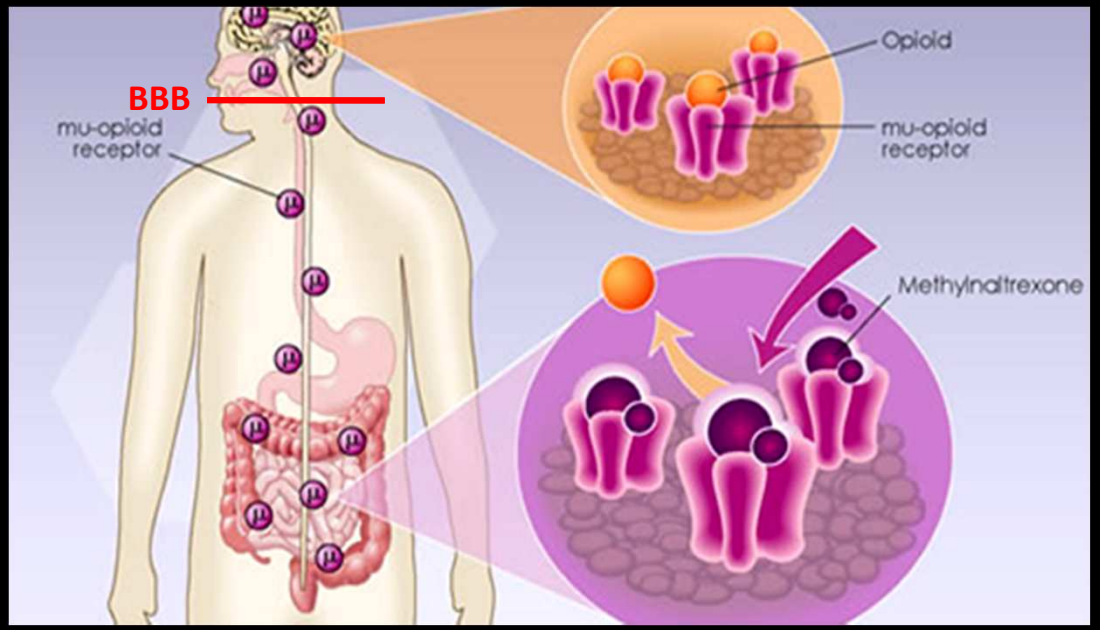
Seinela L., et al., Drugs Aging 2009; 26:703-13

Periferally Acting Mu-Opioid Receptor Antagonists (PAMORAs)

Currently available therapeutics:

Methylnaltrexone (6 trials)*; Alvimopan (4 trials); Naloxone (4 trials); Naloxegol (2 trials)

- Antagonize peripheral constipating effect of opioids
- Restricted ability to cross BBB
- No effect on analgesia



for review see: Camilleri M., et al., Neurogastroenterol Motil 2014;26(10):1386-95

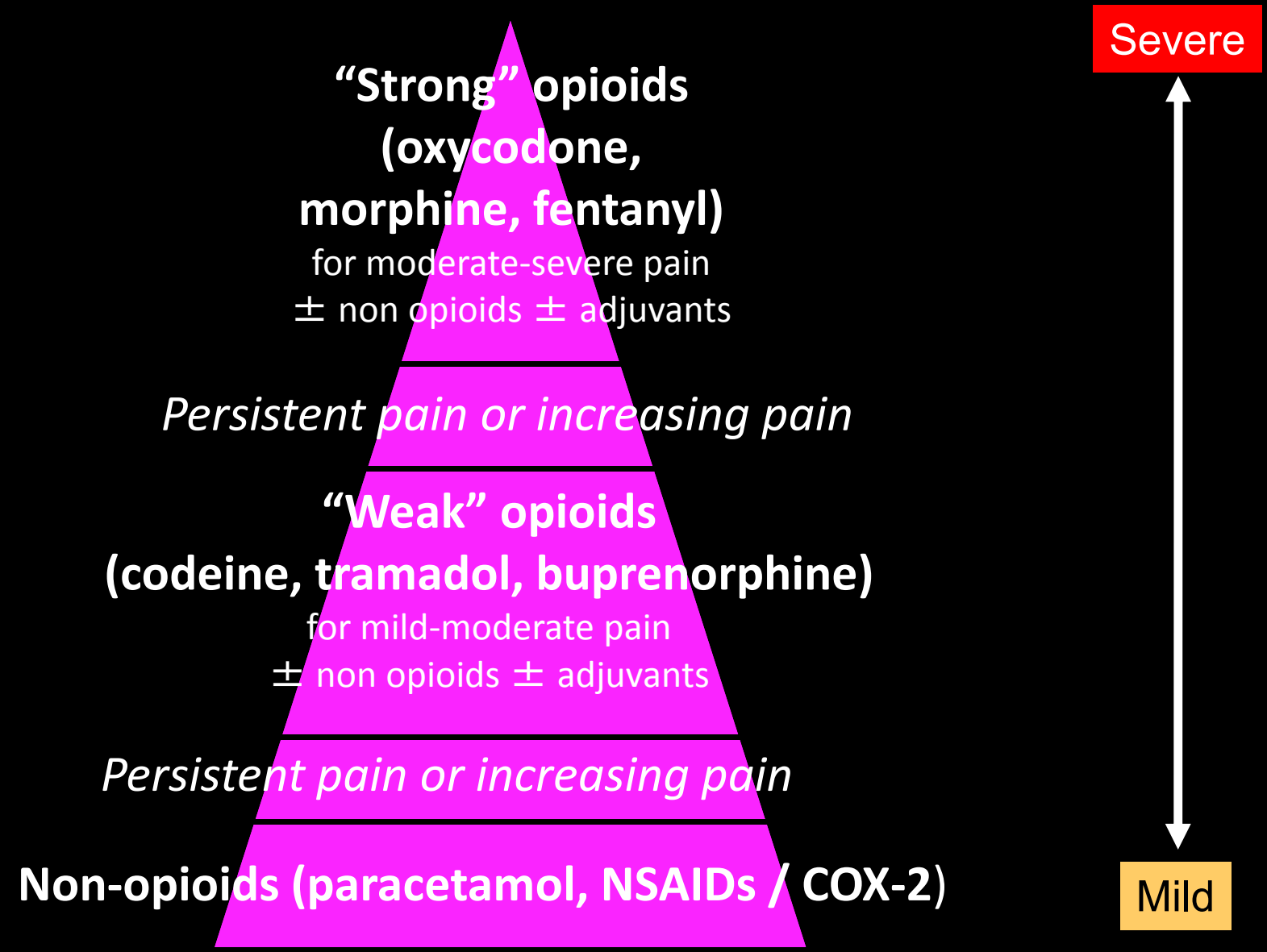
* FDA approved

Types of available prokinetics

Drug	D_2 antag	5-HT_4 ago	5-HT_3 antag	Colinest Inib.	Mot R ago	Dominant Effect(s)
Anticholinesterases						
Neostigmine	-	-	-	+++	-	GI prokinetic
Pyridostigmine	-	-	-	+++	-	
Antidopaminergic*						
Domperidone	+++	-	-	-	-	Antiemetic; prokinetic (UGI)
Antidopaminergic serotoninergic**						
Metoclopramide	+++	+	+	-	-	Antiemetic; prockinetic (UGI)
Sulpiride	+++	+	±	-	-	Antiemetic; prokinetic (UGI)
Clebopride	+++	?	?	-	-	Antiemetic; prokinetic (UGI)
Itopride	+++	-	-	++	-	Prokinetic (UGI)
Serotoninergic						
Prucalopride	-	+++	-	-	-	Enterokinetic

* Butyrophenone derivatives; ** Benzimidazole derivatives

WHO pain ladder



Il valore dell'anamnesi (ανα μνεσισ)…ma quale anamnesi ?

- **Anamnesi patologica prossima:**

Motivo del ricovero in PS, Reparto, della visita ambulatoriale, etc

Non sempre facile stabilire una netta separazione tra APR e APP…
(sintomi direttamente riconducibili alla patologia pregressa)

Sintomi !!!! Fondamentale chiedere: quando ?
come ? Acutamente o più gradualmente ?
caratteristiche ? Continuo…o periodico ?
intensità ?
è in relazione con atti fisiologici ? Postura ?

Se il sintomo è il «dolore»: sede, irradiazione, caratteri, tipologia
quando è comparso ? A digiuno ? Dopo aver mangiato

C'è febbre ?

Acute pain

- AMI
- Trigeminal nevralgia
- Migraine
- Renal colic
- Herpes zooster (VZV)