

2018 CAPER

Collaborative Alliance for
Pancreatic Education and
Research

PANCREAS ACADEMY



Jointly provided by the New Mexico Medical Society (NMMS) through the joint providership of Rehoboth McKinley Christian Health Care Services (RMCHCS) and the Collaborative Alliance for Pancreatic Education and Research.

Why Does it Hurt So Bad?: Understanding Mechanisms of Pain in Chronic Pancreatitis

2018 CAPER Pancreas Academy
Pittsburgh, PA
July 25, 2018

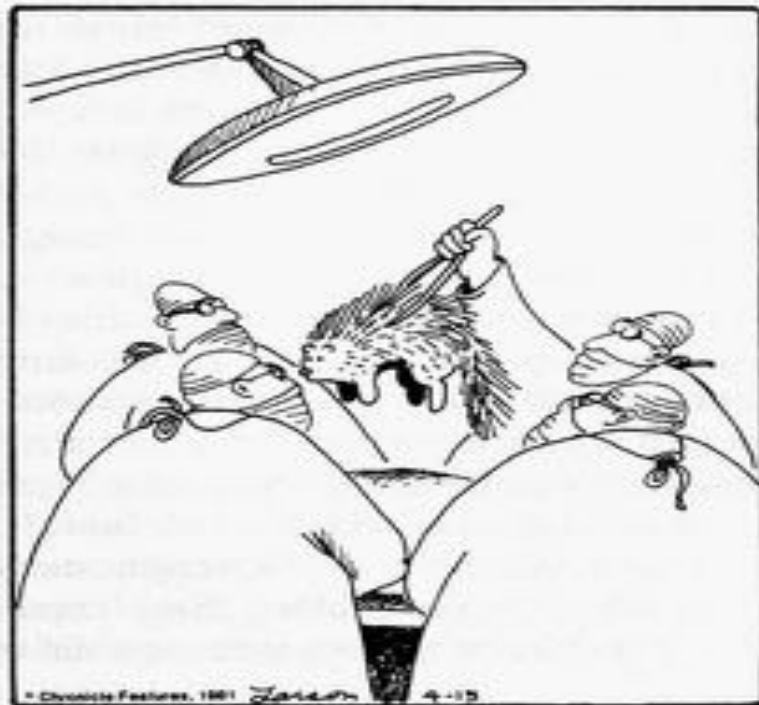
Vikesh K. Singh, MD, MSc
Associate Professor of Medicine
Director of Endoscopy, Johns Hopkins Hospital
Director, Pancreatitis Center
Medical Director, Islet Autotransplantation Program
Johns Hopkins University School of Medicine

Disclosures

- Consultant to Abbvie, Akcea Therapeutics and Ariel Precision Medicine

THE FAR SIDE

By GARY LARSON



"Well, I guess that explains the abdominal pains."

Snapshots at jasonlove.com



"I'm afraid that your irritable bowel syndrome has progressed. You now have furious and vindictive bowel syndrome."

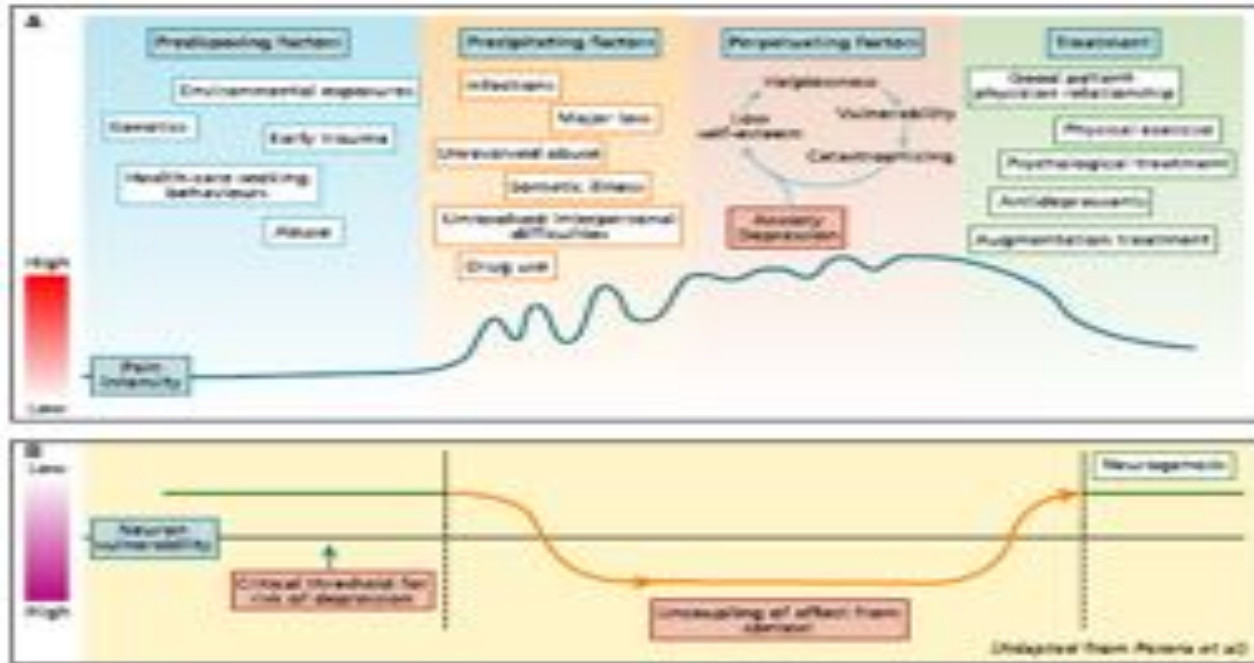
How do Pain and Nociception Differ?

- Pain: A subjective unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage
- Nociception: Response of sensory nervous system to harmful or potentially harmful stimuli
- Due to the subjective nature and emotional aspect of pain, there will never be a biomarker for pain but more likely for nociceptive activation

What is Chronic Abdominal Pain?

- Intermittent or continuous abdominal pain
- Duration of 2 months, ≥ 3 months or ≥ 6 months have all been used in the literature
- Organic and functional etiologies

Complex Interplay between Psychosocial and Somatic Disease Leads to Reduced Pain Thresholds and Chronic Abdominal Pain



Chronic Abdominal Pain



Visceral

Functional
Chronic
Pancreatitis
IBD
Diverticulitis
Infectious/Ischemic
Colitis



Abdominal Wall

Postsurgical
Postherpetic
Myofascial



Central

Depression
Anxiety
PTSD
Substance Abuse
Catastrophizing

Chronic pancreatitis is rare compared to functional gastrointestinal disorders and both cause chronic abdominal pain

Functional Gastrointestinal Disorders are FAR More Prevalent than Chronic Pancreatitis

FGID

- Prevalence of 10-13.5% of the population
- 33,000,000-44,550,000 in the U.S. if population is approximately 330,000,000

Chronic Pancreatitis

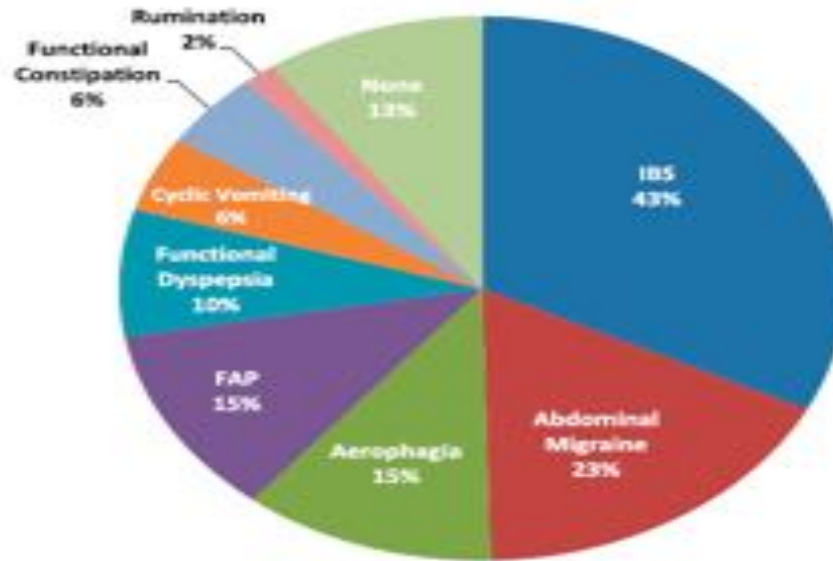
- Prevalence of 3-42 per 100,000
- 9,900-138,600 in the U.S. if population is approximately 330,000,000

Aziz I et al. Lancet Gastroenterol Hepatol 2018; 3: 252-62

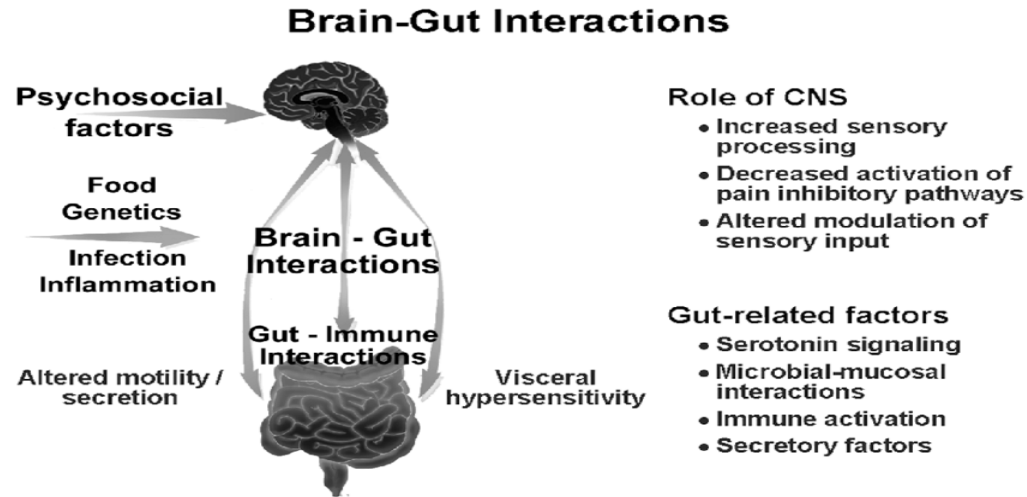
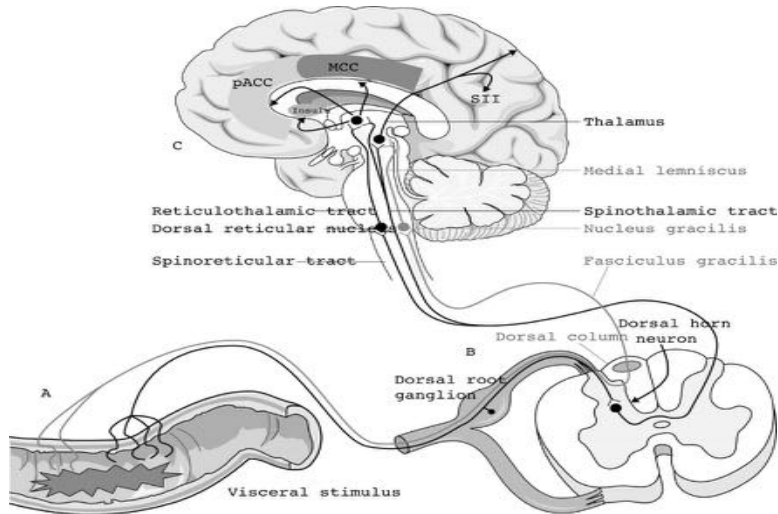
Rajindrajith S et al. Expert Rev Gastroenterol Hepatol 2018; 12: 369-90

Levy P et al. United European Gastroenterol J 2014; 2: 345-54

Functional Gastrointestinal Disorders in 87% of Children with Abdominal Pain



Functional Gastrointestinal Disorders are due to Brain Gut Interactions

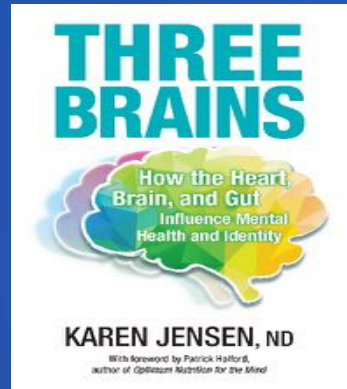
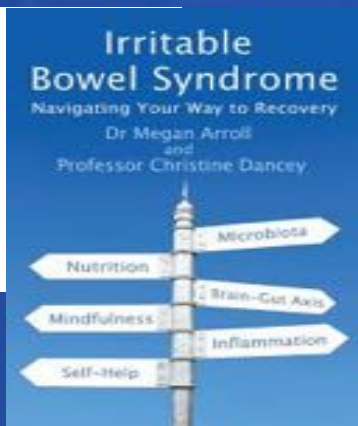
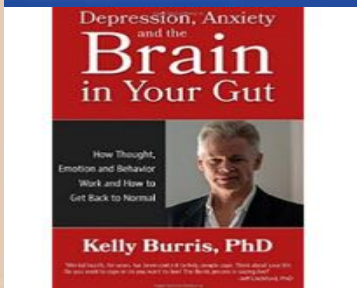
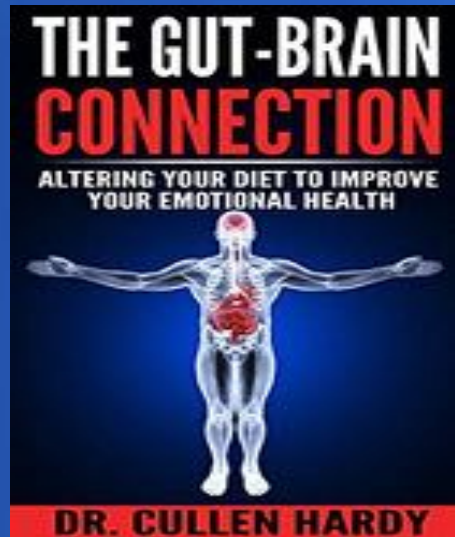
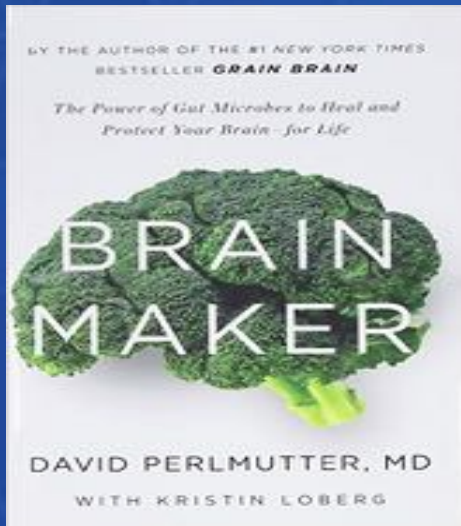
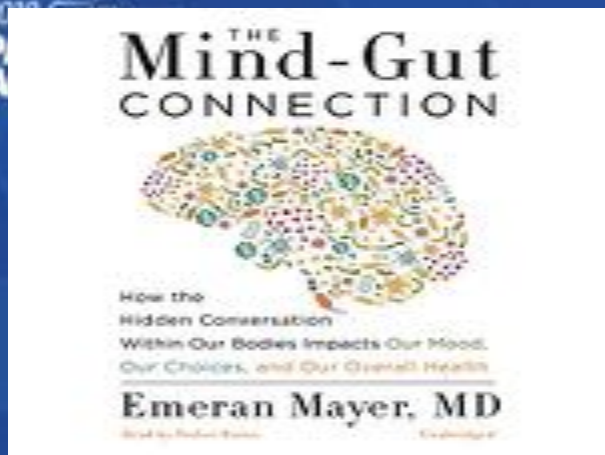




Rome IV

Functional Gastrointestinal Disorders:
Disorders of Gut-Brain Interaction



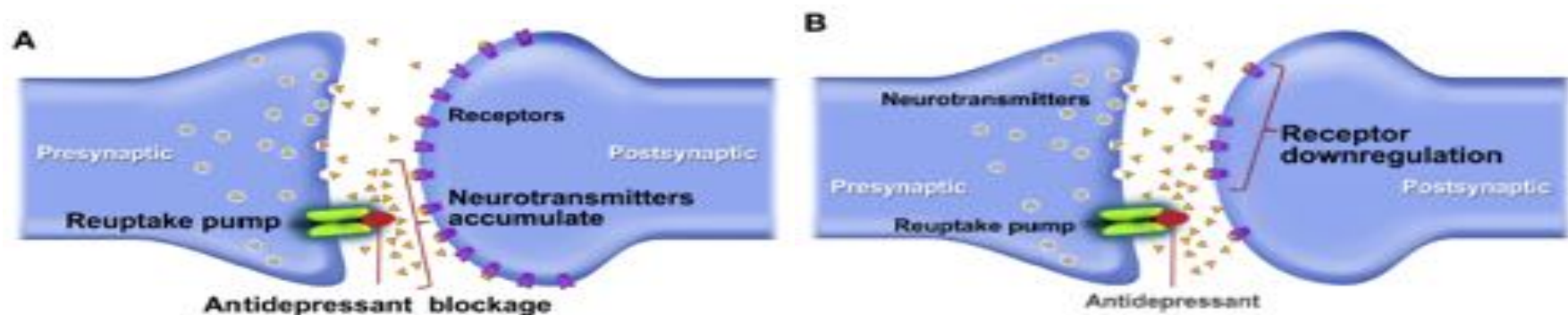


SPECIAL REPORT

Neuromodulators for Functional Gastrointestinal Disorders (Disorders of Gut – Brain Interaction): A Rome Foundation Working Team Report



Douglas A. Drossman,^{1,2} Jan Tack,³ Alexander C. Ford,^{4,5} Eva Szigethy,⁶ Hans Tömbli,⁷ and Lukas Van Oudenhove⁸



AGA CLINICAL PRACTICE UPDATE: EXPERT REVIEW

Best Practice Update: Incorporating Psychogastroenterology Into Management of Digestive Disorders



Laurie Keefer,¹ Olafur S. Palsson,² and John E. Pandolfino³

¹Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, New York; ²University of North Carolina Chapel Hill, North Carolina; and ³Northwestern University Feinberg School of Medicine, Chicago, Illinois

Early chronic pancreatitis can be difficult to differentiate from functional disorders and other conditions that cause chronic abdominal pain



Morphological and functional changes of chronic pancreatitis in patients with dyspepsia: A prospective, observational, cross-sectional study

José Lariño-Noia ^{a, *}, Daniel de la Iglesia ^a, Julio Iglesias-García ^a, Fernando Macías ^a,
Laura Nieto ^a, Iria Bastón ^a, Carmen Villalba ^b, J. Enrique Domínguez-Muñoz ^a

^a Department of Gastroenterology and Hepatology, Health Research Institute (IDIS), University Hospital of Santiago de Compostela, Spain

^b Department of Radiology, University Hospital of Santiago de Compostela, Spain

Chronic pancreatitis like changes on EUS, MRI, and/or ePFT in 21% of Functional Dyspepsia patients!

Functional Gastrointestinal Disorders: History, Pathophysiology, Clinical Features, and Rome IV



Douglas A. Drossman

Center for Education and Practice of Biopsychosocial Care, Drossman Gastroenterology; Center of Functional GI and Motility Disorders, University of North Carolina; and Rome Foundation, Chapel Hill, North Carolina

	Organic GI disorder	Motility disorder	Functional GI disorder
Primary domain	Organ morphology	Organ function	Illness experience
Criterion	Pathology (disease)	Altered motility	Symptoms
Measurement	Histology Pathology Endoscopy Radiology	Motility Visceral sensitivity	Motility Visceral sensitivity Symptom criteria (Rome) Psychosocial
Examples	Esophagitis Peptic ulcer IBD Colon cancer	Diffuse esophageal spasm Gastroparesis Pseudo-obstruction Colonic inertia	Esophageal chest pain Functional dyspepsia IBS Functional constipation

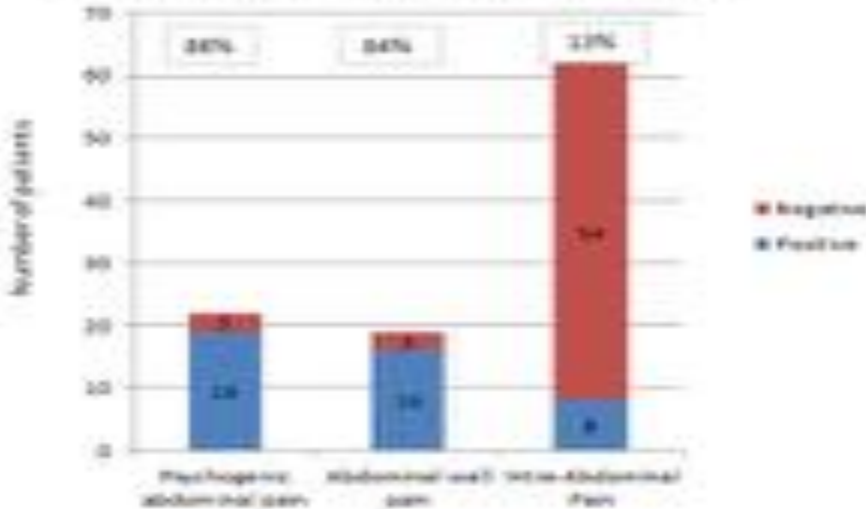
IBD, inflammatory bowel disease.

Chronic Abdominal Wall Pain: A Frequently Overlooked Problem

Practical Approach to Diagnosis and Management

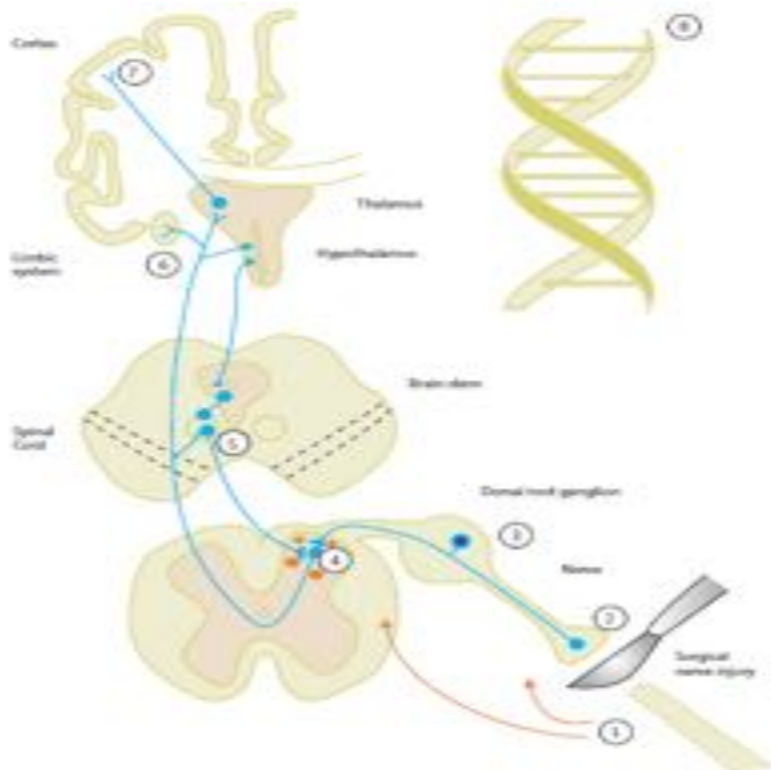


Carnett's test for abdominal pain



Srinivasan R. Am J Gastroenterol 2002; 97: 824-30
Takada T et al. Internal Medicine 2011; 50: 213-7

Chronic Postsurgical Abdominal Pain



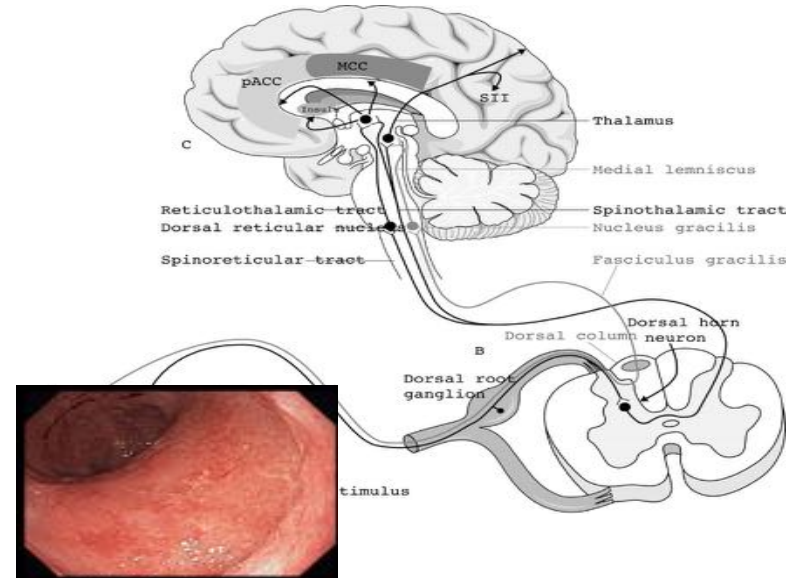
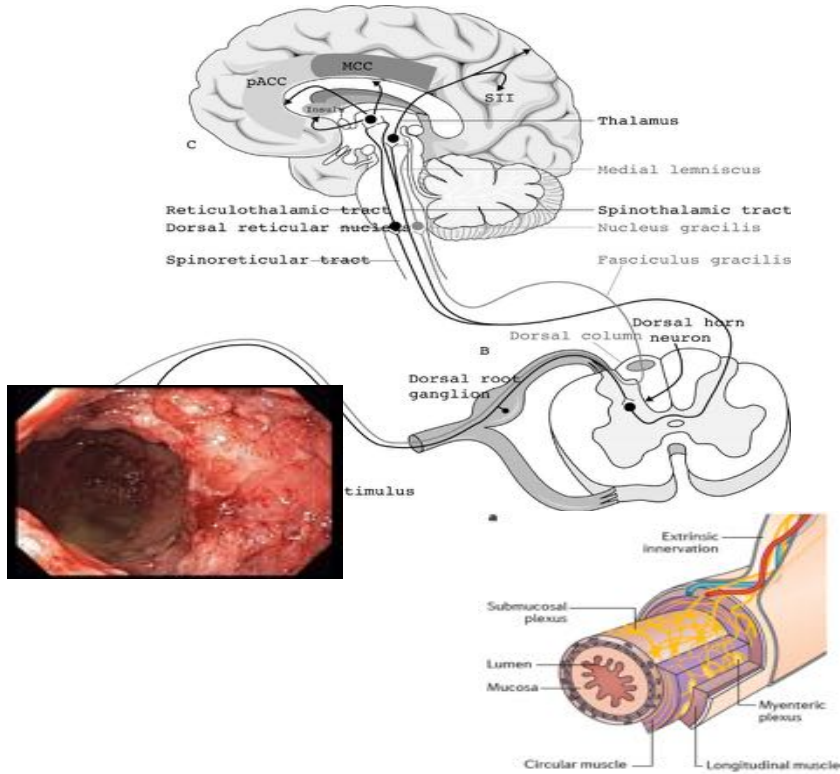
	Estimated incidence of chronic pain	Estimated chronic severe (disabling) pain (>5 out of score of 10)	US surgical volumes (1000s)†
Amputation ²	30–50%	5–10%	159 (lower limb only)
Breast surgery (lumpectomy and mastectomy) ³	20–30%	5–10%	479
Thoracotomy ^{4,7}	30–40%	10%	Unknown
Inguinal hernia repair ^{8–10}	10%	2–4%	609
Coronary artery bypass surgery ^{11–15}	30–50%	5–10%	598
Caesarean section ¹⁴	10%	4%	220

*Gall bladder surgery not included, since preoperative diagnosis of pain specifically from gall bladder is difficult and persistent postoperative pain could therefore be related to other intra-abdominal disorders. †National Center For Health Statistics, Ambulatory and Inpatients Procedures, USA, 1996.

Chronic pain after common surgical procedures occurs in 10-50% with severe pain in 2-10%

Kehlet H et al. Lancet 2006; 367: 1618-25

“Irritable Bowel Syndrome” in IBD



Centrally Mediated Disorders of Gastrointestinal Pain

Laurie Keefer,¹ Douglas A. Drossman,² Elspeth Guthrie,³ Magnus Simrén,⁴ Kirsten Tillisch,⁵ Kevin Olden,⁶ and Peter J. Whorwell⁷

D1. Diagnostic Criteria^a for Centrally Mediated Abdominal Pain Syndrome^b

Must include all of the following:

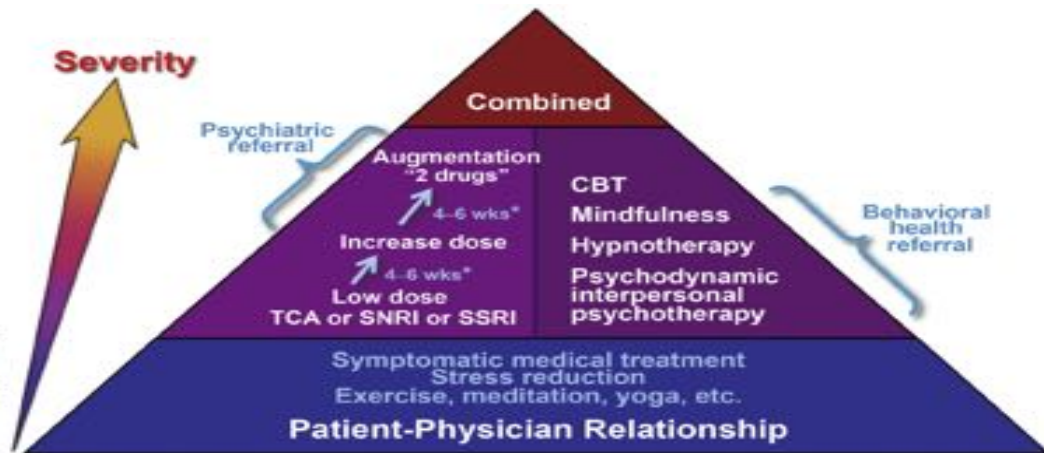
- Continuous or nearly continuous abdominal pain
- No or only occasional relationship of pain with physiological events (eg, eating, defecation, or menses)^c
- Pain limits some aspect of daily functioning^d
- The pain is not feigned
- Pain is not explained by another structural or functional gastrointestinal disorder or other medical condition

^aCriteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

^bCAPS is typically associated with psychiatric comorbidity, but there is no specific profile that can be used for diagnosis.

^cSome degree of gastrointestinal dysfunction may be present.

^dDaily function could include impairments in work, intimacy, social/leisure, family life, and caregiving for self or others.

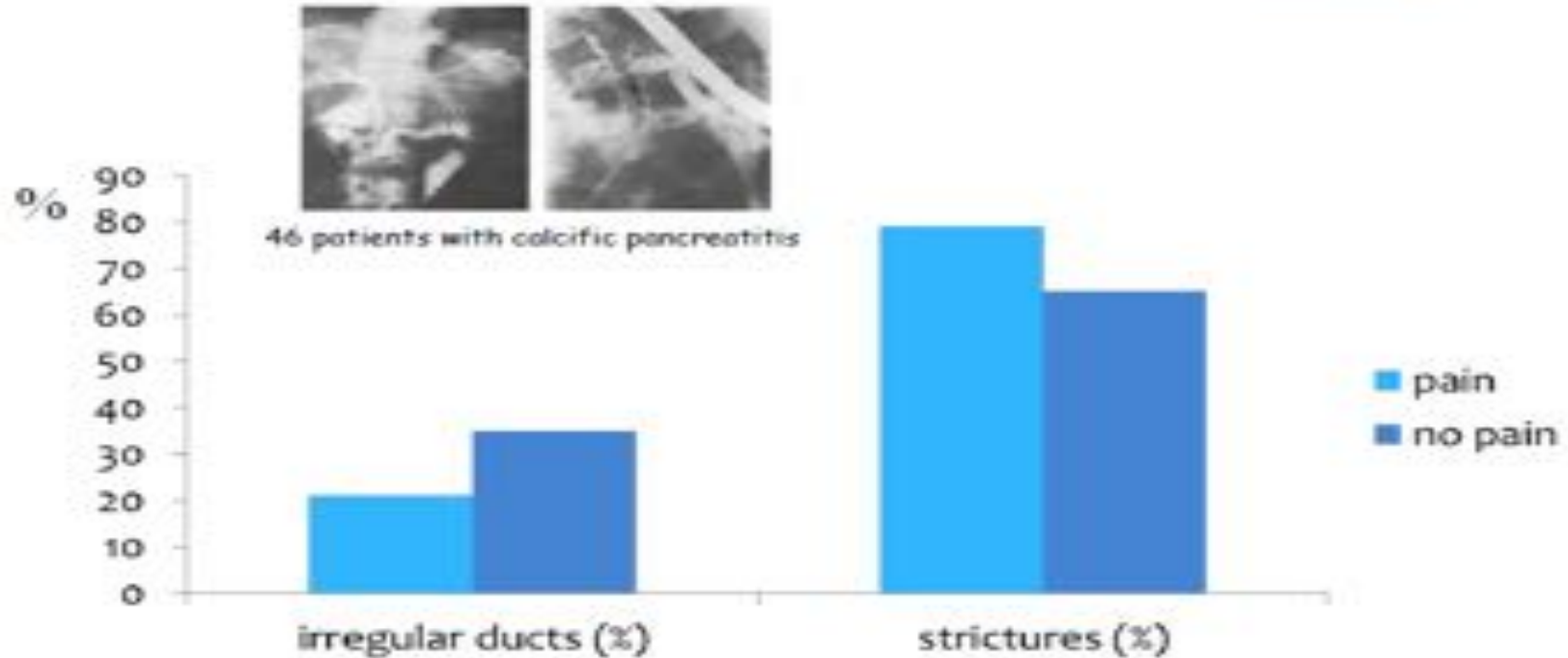


*Monitor side effects.

Keefer L et al. Gastroenterology
2016; 150: 1408-1419

Some patients with advanced chronic
pancreatitis have no pain!

Irregularity and Strictures of the Pancreatic Duct do not Correlate with Pain in Chronic Calcific Pancreatitis



Bornman PC et al. Br J Surg 1980; 67: 425-8

Pain Does not Correlate with Radiographic and Imaging Findings Even in Advanced Chronic Pancreatitis!

Variable	All patients (n = 518)	Pain pattern					P value	
		No pain (n = 81)	A (n = 67)	B (n = 23)	C (n = 98)	D (n = 229)		E (n = 19)
Calcification	276 (53.3)	49 (60.5)	37 (55.2)	12 (52)	58 (59.2)	107 (46.7)	13 (68.4)	.11
Calcification*	286 (55.2)	51 (63)	41 (61.2)	12 (52)	59 (60.2)	109 (47.6)	14 (73.7)	.0324
Atrophy	281 (54.3)	50 (61.7)	37 (55.2)	16 (69.7)	48 (49)	121 (52.8)	9 (47.4)	.41
Atrophy*	297 (57.3)	53 (65.4)	38 (56.7)	18 (78)	50 (51)	128 (55.9)	10 (52.6)	.21
PD dilatation	317 (61.2)	50 (61.7)	44 (65.7)	14 (58.3)	64 (65.3)	135 (59)	10 (52.6)	.79
PD dilatation*	350 (67.6)	52 (64.2)	49 (73.1)	15 (62.5)	70 (71.4)	151 (65.9)	13 (68.4)	.76
PD stricture/obstruction	103 (19.9)	10 (12.4)	16 (23.9)	2 (8.3)	26 (26.5)	46 (20.1)	3 (15.8)	.13
PD stricture/obstruction*	142 (27.4)	17 (21)	22 (32.8)	3 (12.5)	30 (30.6)	63 (27.5)	7 (36.8)	.24
Pseudocyst	137 (26.5)	16 (19.8)	24 (35.8)	5 (20.8)	18 (18.4)	70 (30.6)	4 (21.1)	.0544
Pseudocyst*	167 (32.2)	19 (23.5)	28 (41.8)	5 (20.8)	24 (24.5)	86 (37.6)	5 (26.3)	.0229
PD irregularity	266 (51.4)	34 (42)	38 (56.7)	14 (58.3)	57 (58.2)	115 (50.2)	8 (42.1)	.25
Inflammation	176 (34)	23 (28.4)	19 (28.4)	4 (16.7)	37 (37.8)	82 (35.8)	11 (57.9)	.0497
Pancreatic mass	30 (5.8)	6 (7.4)	3 (4.5)	1 (4.2)	9 (9.2)	9 (3.9)	2 (10.5)	.31
Abnormal side branches	213 (41.1)	27 (33.3)	35 (52.2)	11 (45.8)	36 (36.7)	97 (42.4)	7 (36.8)	.24
CBD stricture	61 (11.8)	9 (11.1)	10 (14.9)	3 (12.5)	19 (19.4)	19 (8.3)	1 (5.3)	.0911
CBD dilatation	92 (17.8)	16 (19.8)	17 (25.4)	4 (16.7)	20 (20.4)	32 (14)	3 (15.8)	.31
Changes of cirrhosis and/or portal hypertension	64 (12.4)	7 (8.6)	9 (13.4)	2 (8.3)	11 (11.2)	30 (13.1)	5 (26.3)	.40

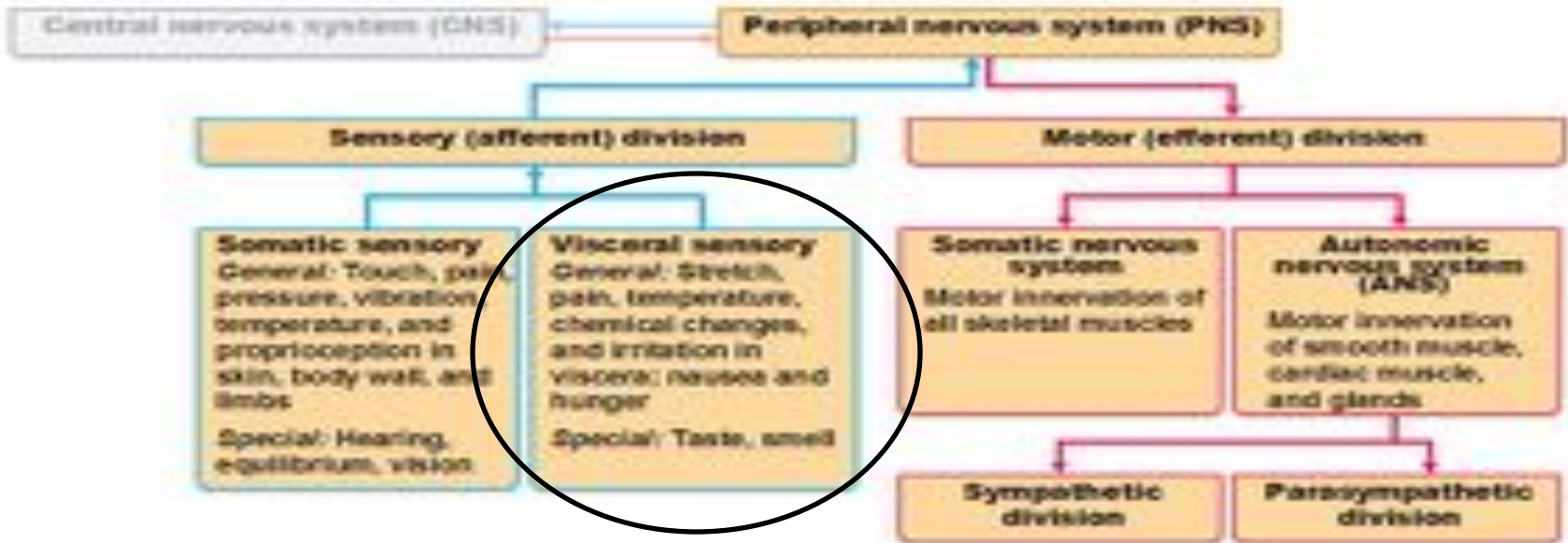
There is no easy way to differentiate visceral and central pain in chronic pancreatitis
[Is pain coming from pancreas or it is now in the central nervous system?]

Characteristics of Visceral Pain

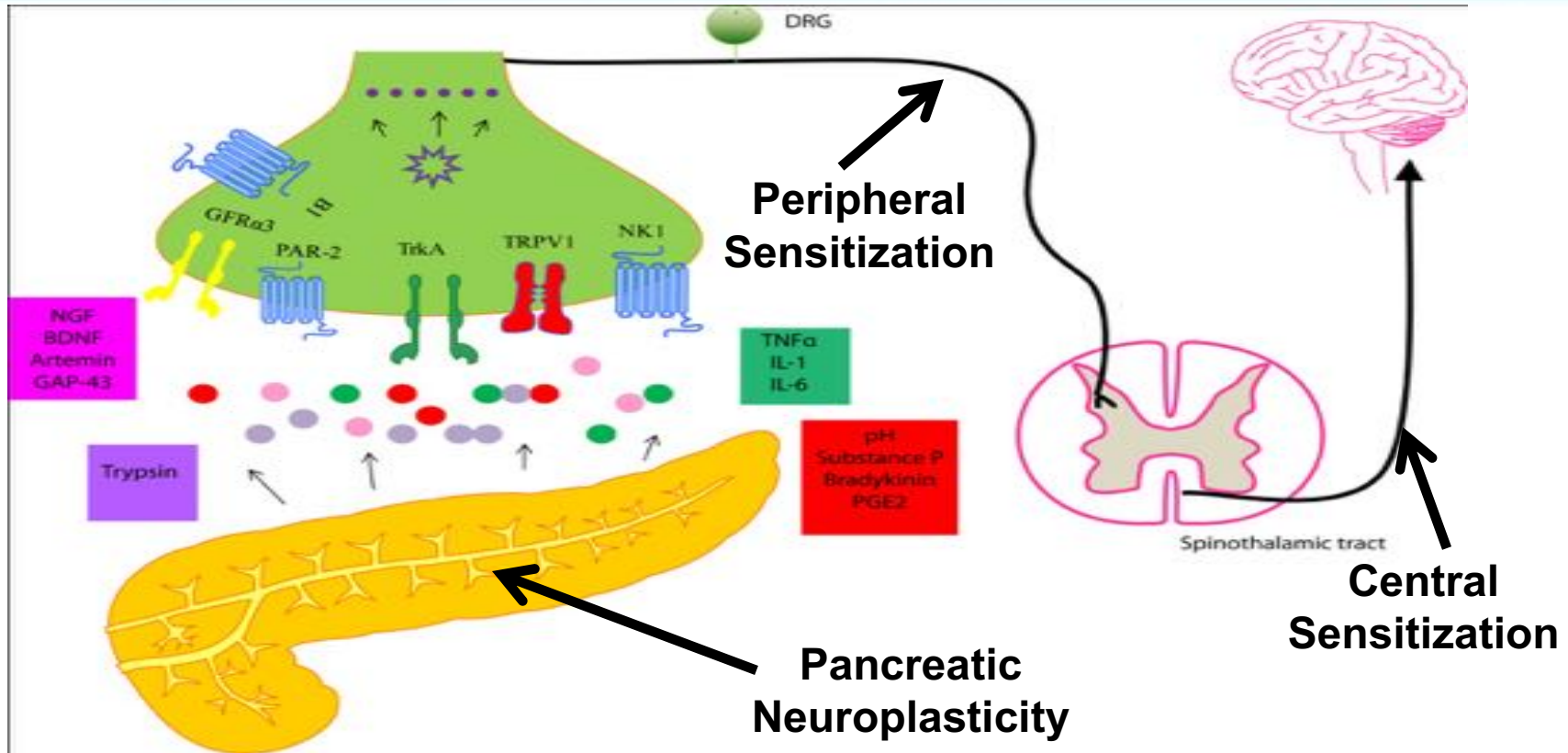
- Not all viscera have sensory innervation (e.g. liver, lung, kidney)
- Not always due to visceral injury
 - Distension (e.g. bladder), obstruction (e.g. bile duct), ischemia and inflammation (e.g. pancreatitis) often lead to pain but cutting (e.g. intestine) and burning do not
- Referred to other locations
- Diffuse and poorly localized
- Accompanied by motor and autonomic reflexes (e.g., nausea, vomiting, diarrhea)

Sensory Nerves Mediate Nociception between Viscera and CNS

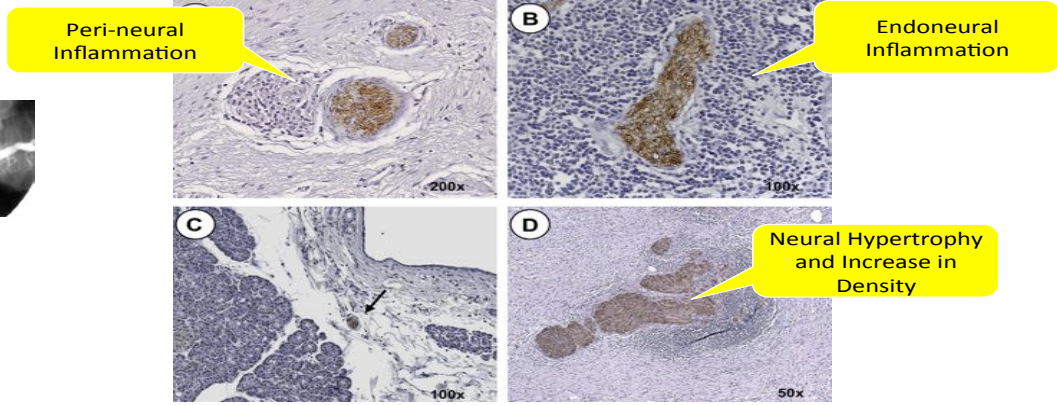
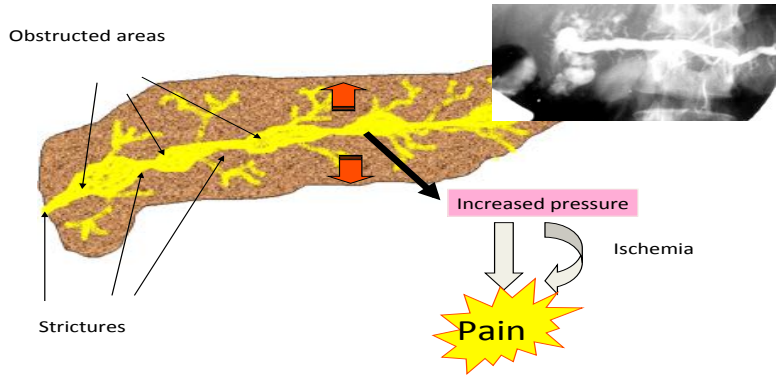
Functional Organization of the PNS



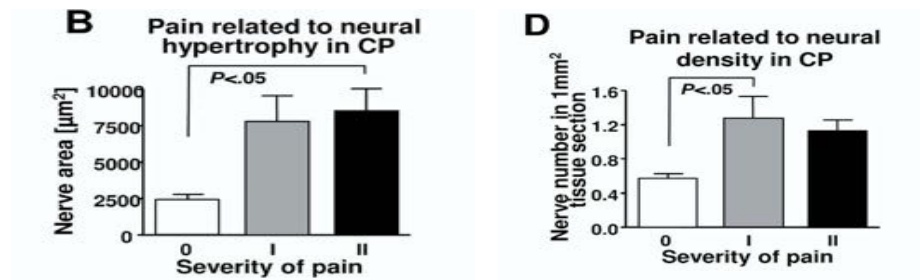
Neurobiological Principles of Pancreatic Pain



Neuropathic changes, but not intraductal pressure, correlates best with pancreatic pain in CP

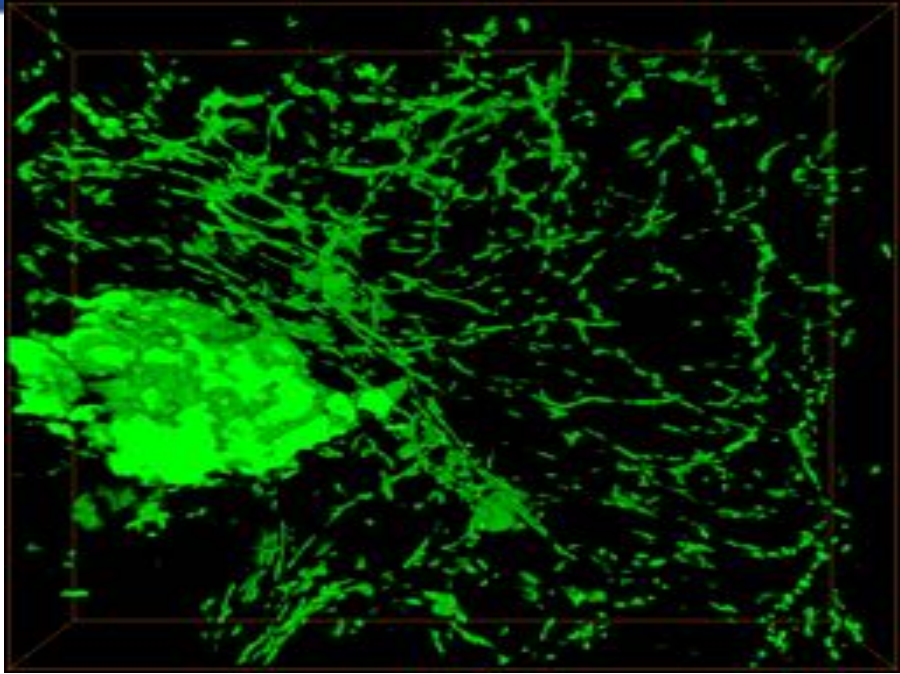


Cehyan et al Best Prac Res Clin Gastroenterol 2008

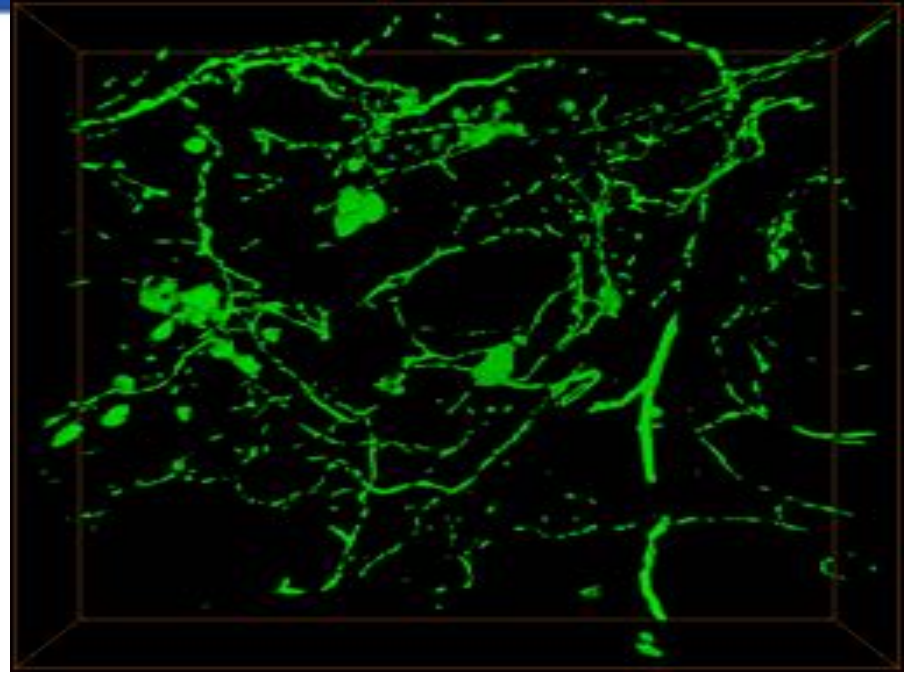


Cehyan et al Gastroenterology 2009

Pancreatic Neuroplasticity



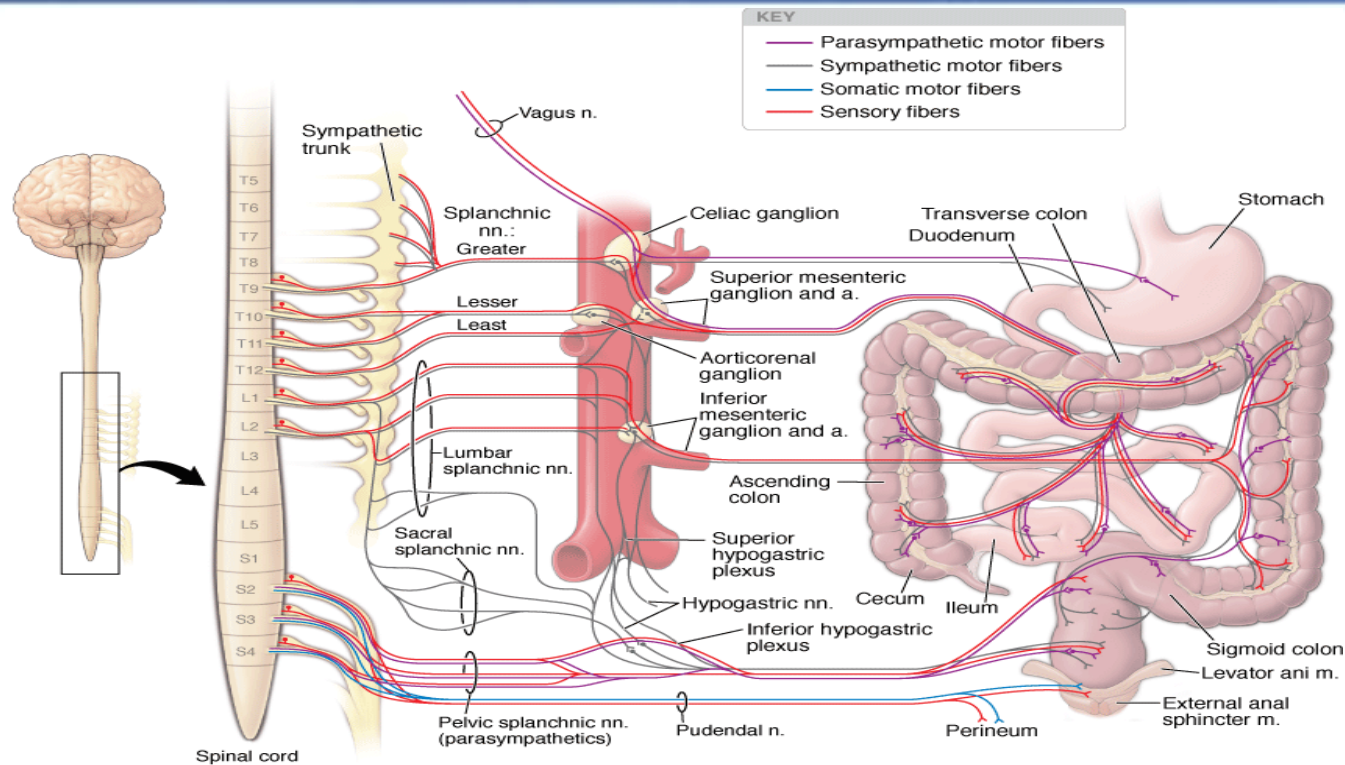
Chronic Pancreatitis



Normal

Courtesy of Dr. Pankaj Pasricha

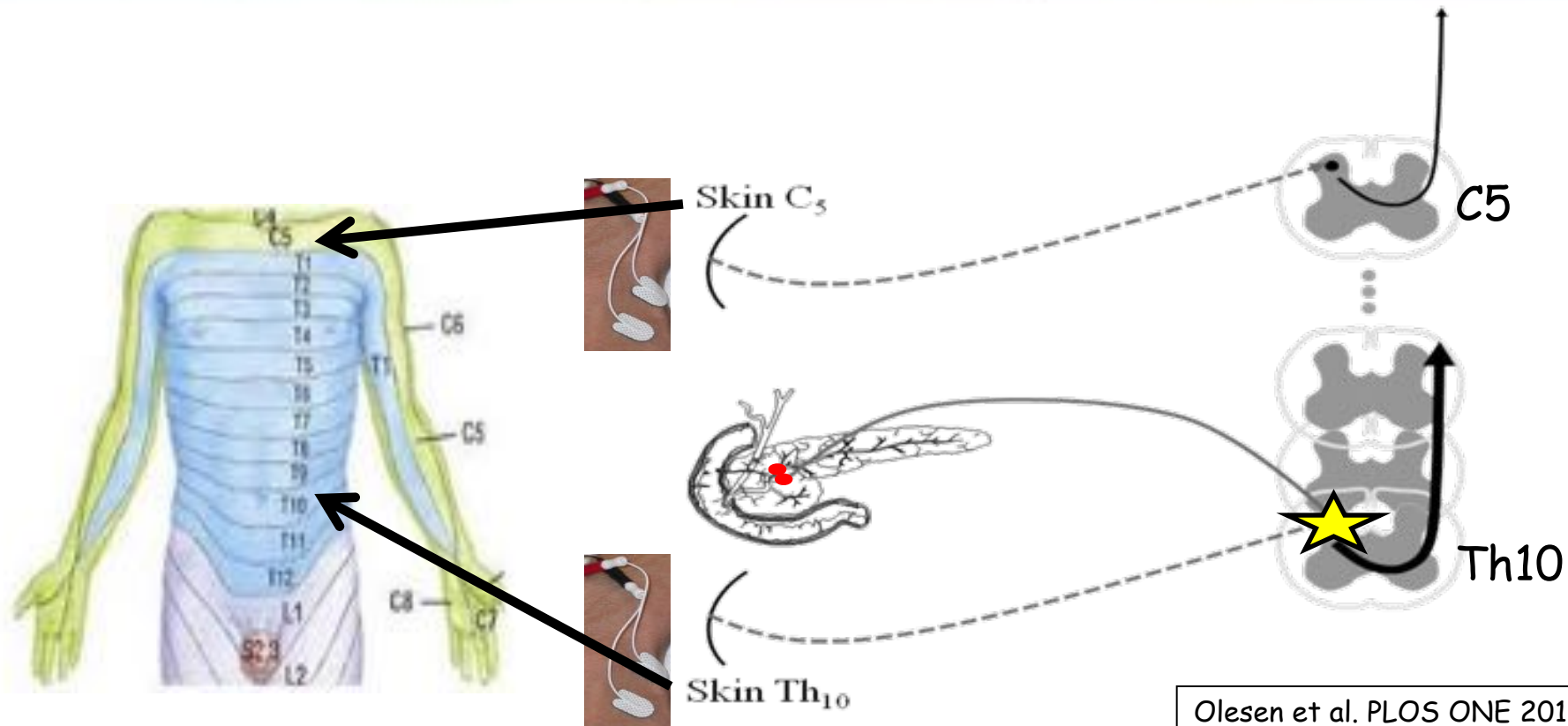
Extensive Nerve Connections Between the Pancreas/Abdominal Organs and Central Nervous System



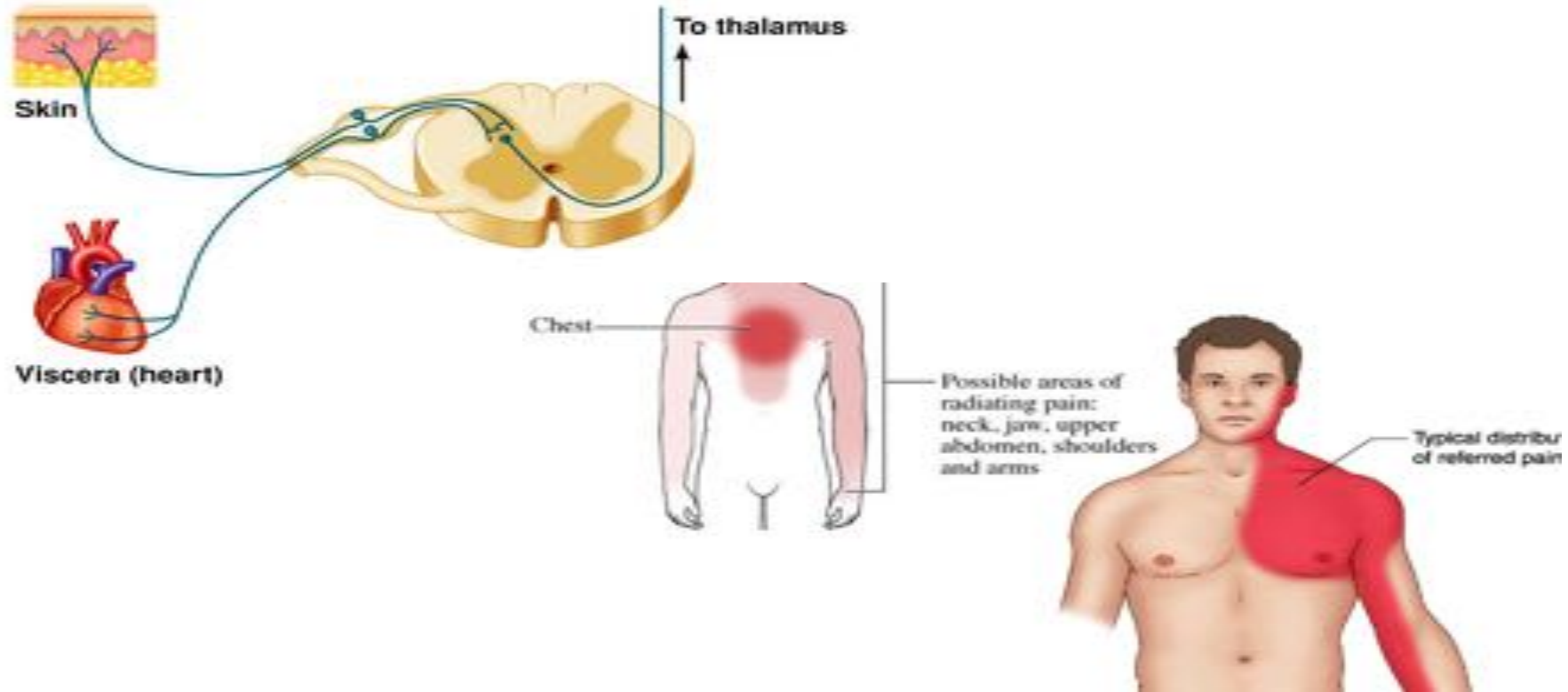
Referred Pain is due to Nerve Connections Between Organs and the Central Nervous System



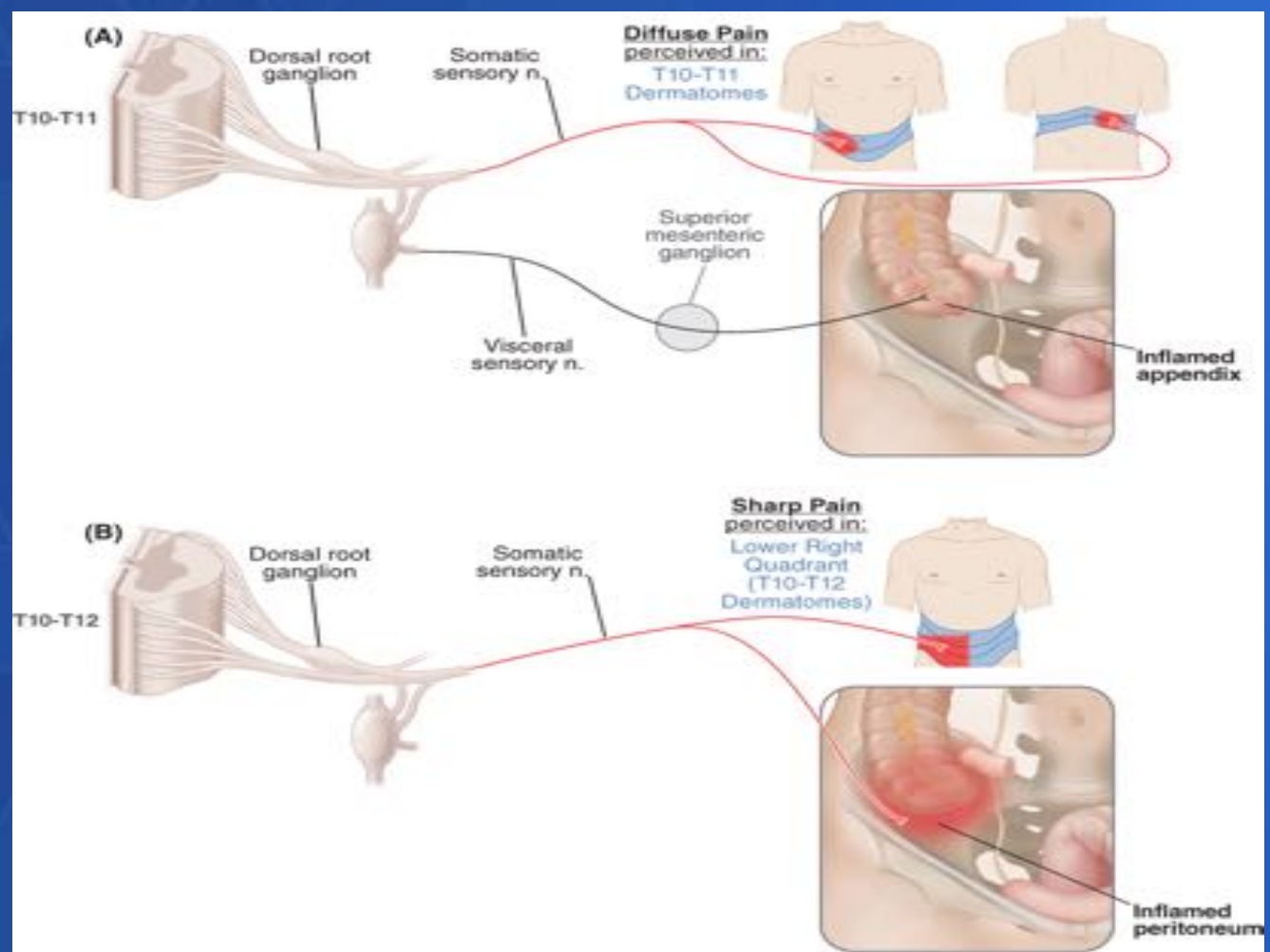
T10 Dermatome and Pancreas Synapse at Same Level in Spinal Cord (This is why we focus on this portion of the abdomen in the history and physical examination)



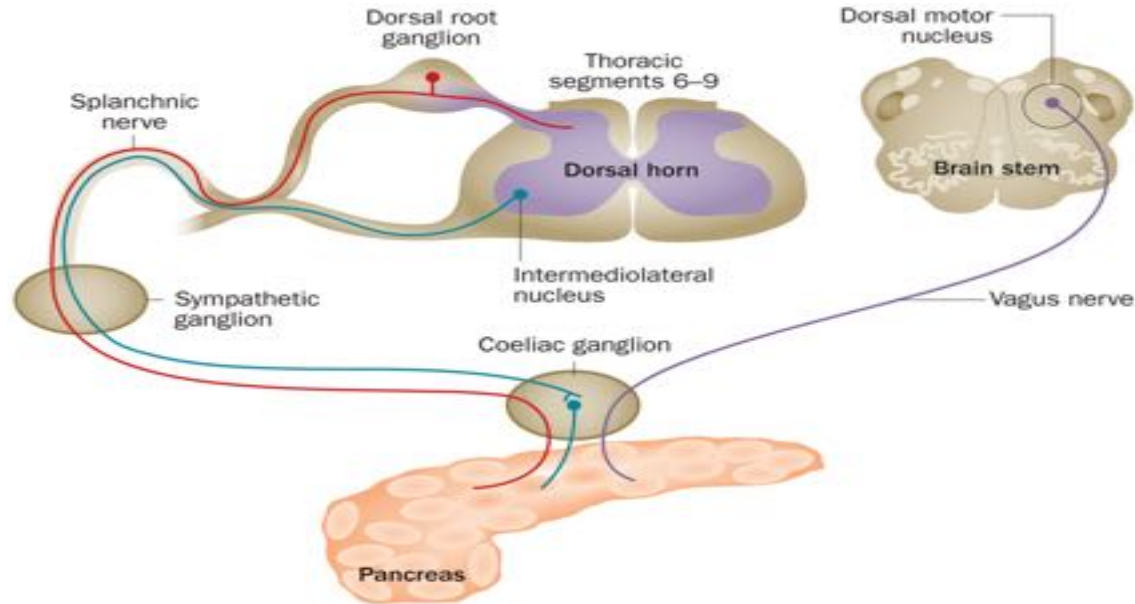
Referred Pain in Myocardial Infarction



Referred Pain in Appendicitis

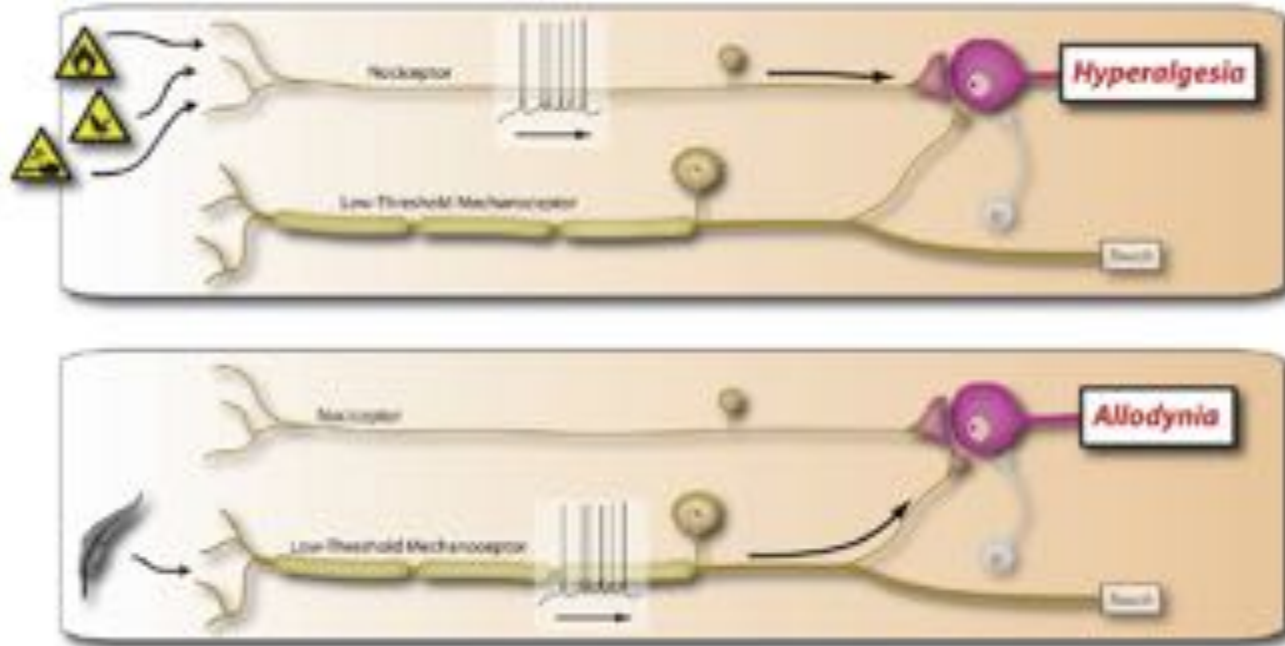


Nerves that carry pain also communicate with nerves that are associated with symptoms such as nausea, vomiting and diarrhea

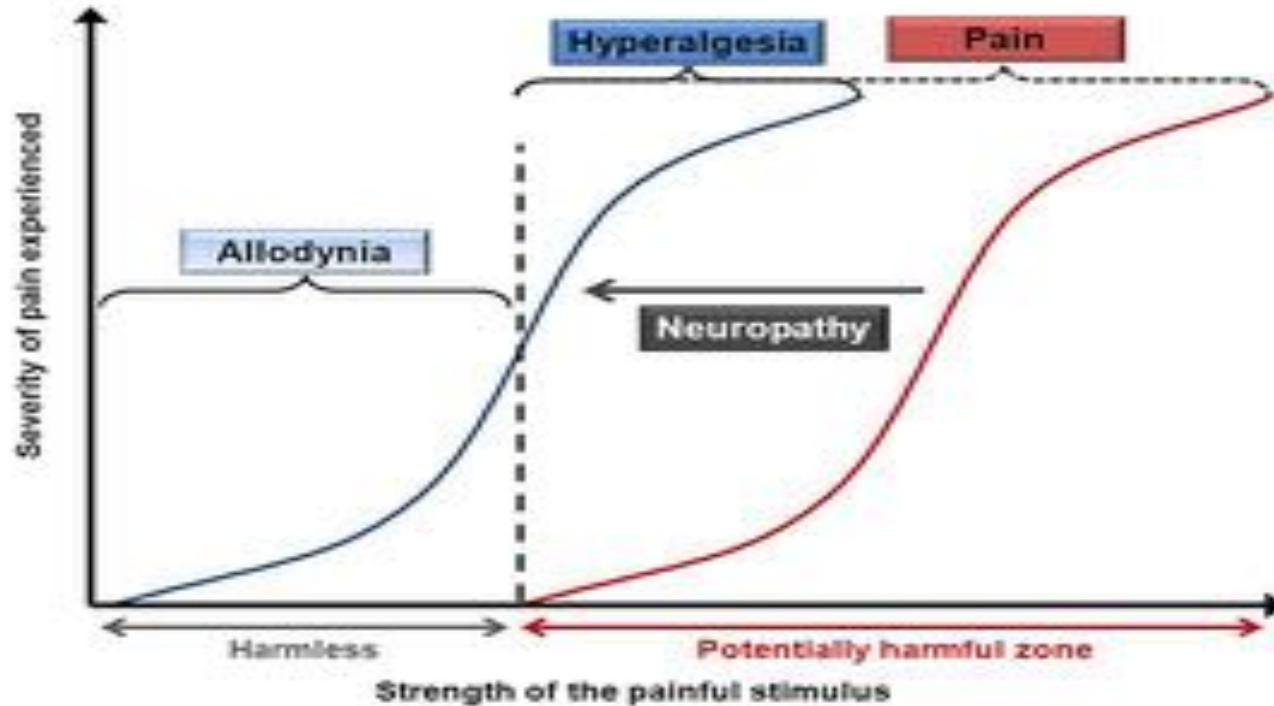


Nature Reviews | Gastroenterology & Hepatology

Central Sensitization Develops over Time in Chronic Pain Conditions



Physical Examination Findings of Sensitization are Hyperalgesia and Allodynia



Key Points

- Chronic pancreatitis is rare compared to functional disorders and both cause chronic abdominal pain
- Early chronic pancreatitis can be difficult to differentiate from functional disorders and other conditions that cause chronic abdominal pain
- Some patients with advanced chronic pancreatitis will have no pain
- No easy way to differentiate visceral and central pain in chronic pancreatitis

Thank You

