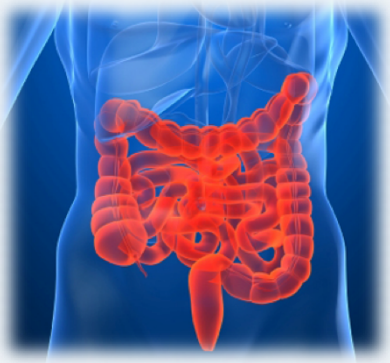
Pathophysiology of Visceral Pain

Etiologies of Visceral Pain

Source	Examples
Inflammation	• Appendicitis • Diverticulitis • Colitis • Gastric ulcer
Distention of a organ	• Bowel obstruction • Block of bile duct by gallstones • Tumour invasion
Swelling of liver capsule	• Hepatitis • Tumors
Ischemia	• Ischemic colitis • Tumor invasion of blood supply • Mesenteric artery syndrome

Causes of Irritable Bowel Syndrome

- Brain-gut signal problems
- Gastrointestinal motor problems – hyper- or hypomotility
- Hypersensitivity – lower pain threshold for bowel stretching
- Mental health problems - anxiety, depression
- Bacterial gastroenteritis
- Small intestinal bacterial overgrowth (SIBO)
- Body chemicals – neurotransmitters, hormones
- Genetics
- Food sensitivity – trigger foods

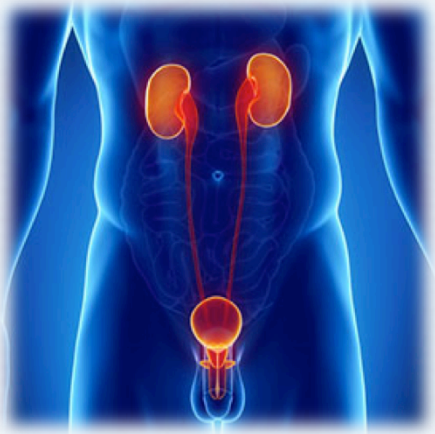


It is believed that a combination of physical and mental health problems can lead to irritable bowel syndrome

National Digestive Diseases Information Clearinghouse. Irritable Bowel Syndrome. Available at:http://www.niddk.nih.gov/health-information/health-topics/digestive-diseases/irritable-bowel-syndrome/Documents/ibs_508.pdf. Accessed March 24, 2015.

Causes of Interstitial Cystitis (IC)

- Exact causes are unknown
- Likely involves many factors
- Patients with IC may also have a defect in bladder epithelium
- Factors may include autoimmune reaction, genetics, infection, or allergy
- May be a bladder manifestation of a more general inflammatory condition

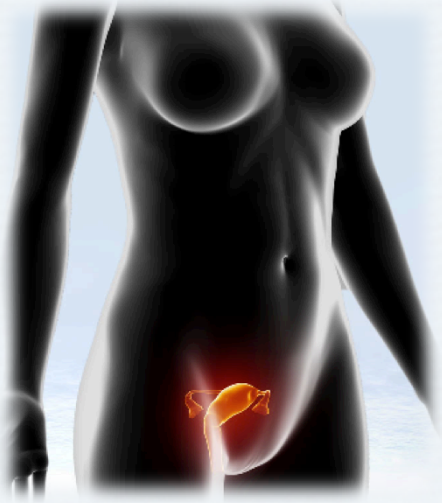


Some IC symptoms resemble those of bacterial infection but urine cultures indicate no infection

Mayo Clinic. Interstitial Cystitis. Available at: http://www.mayoclinic.org/diseases-conditions/interstitial-cystitis/basics/causes/con-20022439. Accessed March 24, 2015; National Kidney and Urologic Diseases Information Clearinghouse. Interstitial Cystitis/Painful Bladder Syndrome. Available at: http://kidney.niddk.nih.gov/kudiseases/pubs/interstitialcystitis/IC_PBS_T_508.pdf. Accessed March 24, 2015.

Causes of Vulvodynia

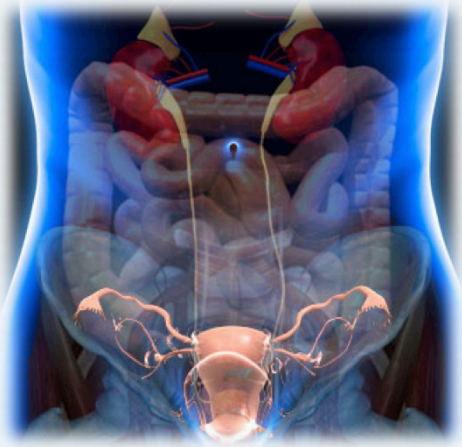
- Exact causes unknown
- Possible contributors:
  - Injury to or irritation of nerves of vulvar region
  - Past vaginal infections
  - Allergies or sensitive skin
  - Hormonal changes
- Some women with vulvodynia have a history of sexual abuse



Most women with vulvodynia have no known causes

Mayo Clinic. Vulvodynia. Available at: http://www.mayoclinic.org/diseases-conditions/vulvodynia/basics/causes/con-20020326. Accessed March 24, 2015.

Causes of Endometriosis



- Retrograde menstruation
- Most likely cause
- Embryonic cell growth
- Surgical scar implantation
- Endometrial cells transport – transport of endometrial cells to other parts of the body
- Immune system disorder – inability to recognize and destroy endometrial tissue growing outside uterus

Mayo Clinic. Interstitial Cystitis. Available at: : http://www.mayoclinic.org/diseases-conditions/vulvodynia/basics/causes/con-20020326. Accessed March 24, 2015.

Causes of Acute and Chronic Pelvic Pain in Women

Gynecological Causes	Other Causes
• Pelvic inflammatory disease • Ectopic pregnancy • Adnexal torsion • Ruptured ovarian cyst • Adhesions	• Endometriosis • Gynecologic malignancies • Residual ovary syndrome • Pelvic congestion syndrome • Pelvic inflammatory disease • Adhesions • Leiomyomata • Adenomyosis • Ovulatory pain • Adnexal cysts • Cervical stenosis • Chronic endometritis • Intrauterine contraceptive device • Uterine prolapse

Karnath BM, Breitkopf, DM. *Hospital Physician*. 2007;July:41-8.

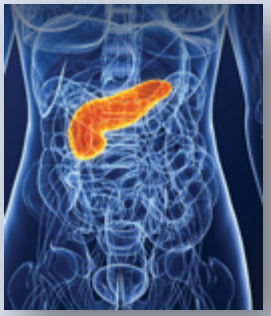
Non-gynecologic Causes of Pelvic Pain

Acute	Chronic
• Diverticulitis	• Diverticular disease
• Bowel obstruction	• Irritable bowel syndrome
• Adhesions	• Inflammatory bowel disease
• Hernia	• Hernia
• Urinary tract infection	• Colorectal cancer
• Urolithiasis	• Interstitial cystitis
• Musculoskeletal	• Musculoskeletal

Karnath BM, Breitkopf, DM. *Hospital Physician*. 2007;July:41-8.

Visceral Pain Conditions

Inflammatory-related Conditions
Pancreatitis
Cholecystitis
Diverticulitis
Appendicitis
Peritonitis
Crohn's Disease
GERD



Functional Visceral Pain Disorders
IBS
Non-ulcer dyspepsia
Non-cardiac chest pain

Neuropathic Visceral Pain
Surgery/Trauma
Birth

Gynecological Pain
Endometriosis
Dysmenorrhea
Interstitial cystitis (pelvic pain syndrome)

Urological Pain
Renal/urethral calculosis

Post-operative Pain
Major surgery

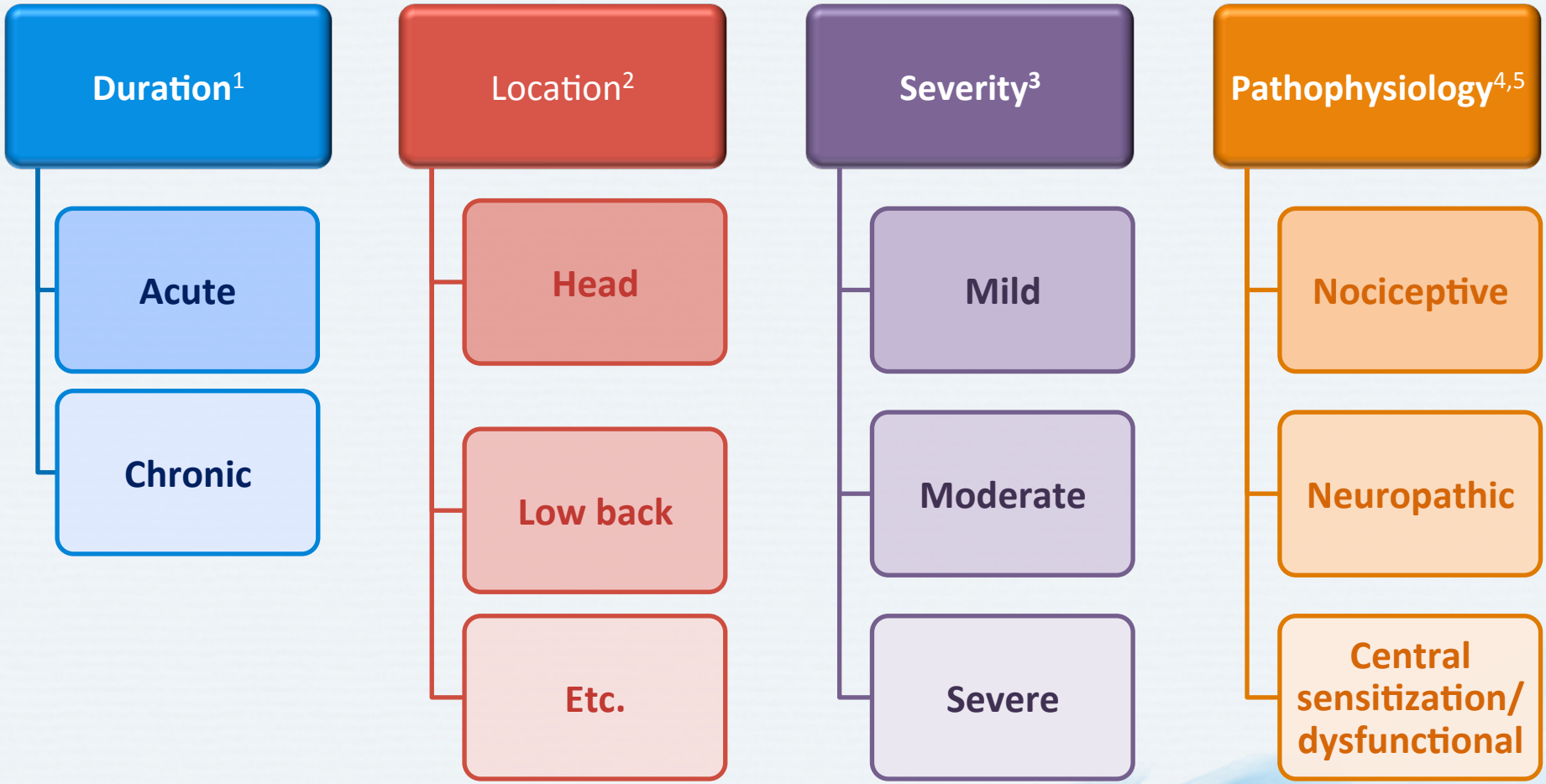
Hypoperfusion/Ischemia

Visceral Cancer Pain

Ileus

GERD = gastro-esophageal reflux disease; IBS = irritable bowel syndrome

Pain Classification



1. McMahon SB, Koltzenburg M. In: McMahon SB, Koltzenburg M (eds). *Wall and Melzack's Textbook of Pain.* 5th ed. Elsevier; London, UK: 2006;
2. Loeser D *et al* (eds). *Bonica's Management of Pain*. 3rd ed. Lippincott Williams & Wilkins; Hagerstown, MD: 2001;
3. Hanley MA *et al. J Pain* 2006; 7(2):129-33; 4. Jensen TS *et al. Pain* 2011; 152(10):2204-5; 5. Woolf CJ. *Pain* 2011; 152(3 Suppl):S2-15.

Characteristics of Nociceptive Pain

Type of pain	Nociceptor location	Potential stimuli	Pain localization
Superficial somatic pain	• Skin • Subcutaneous tissue • Mucous membranes	• External mechanical, chemical or thermal events • Dermatologic disorders	Well localized
Deep somatic pain	• Muscles • Tendons • Joints • Fasciae • Bones	• Overuse strain • Mechanical injury • Cramping • Ischemia • Inflammation	Localized or diffuse and radiating
Visceral pain	• **Visceral organs***	• **Organ distension Muscle spasm** • **Traction** • **Ischemia** • **Inflammation**	**Well or poorly localized**

*Visceral organs include the heart, lungs, gastrointestinal tract, pancreas, liver, gallbladder, kidneys and bladder

American Pain Society. *Pain: Current Understanding of Assessment, Management, and Treatments.* Available at: http://www.npcnow.org/system/files/research/download/Pain-Current-Understanding-of-Assessment-Management-and-Treatments.pdf. Accessed March 24, 2015.

Examples of Nociceptive Pain

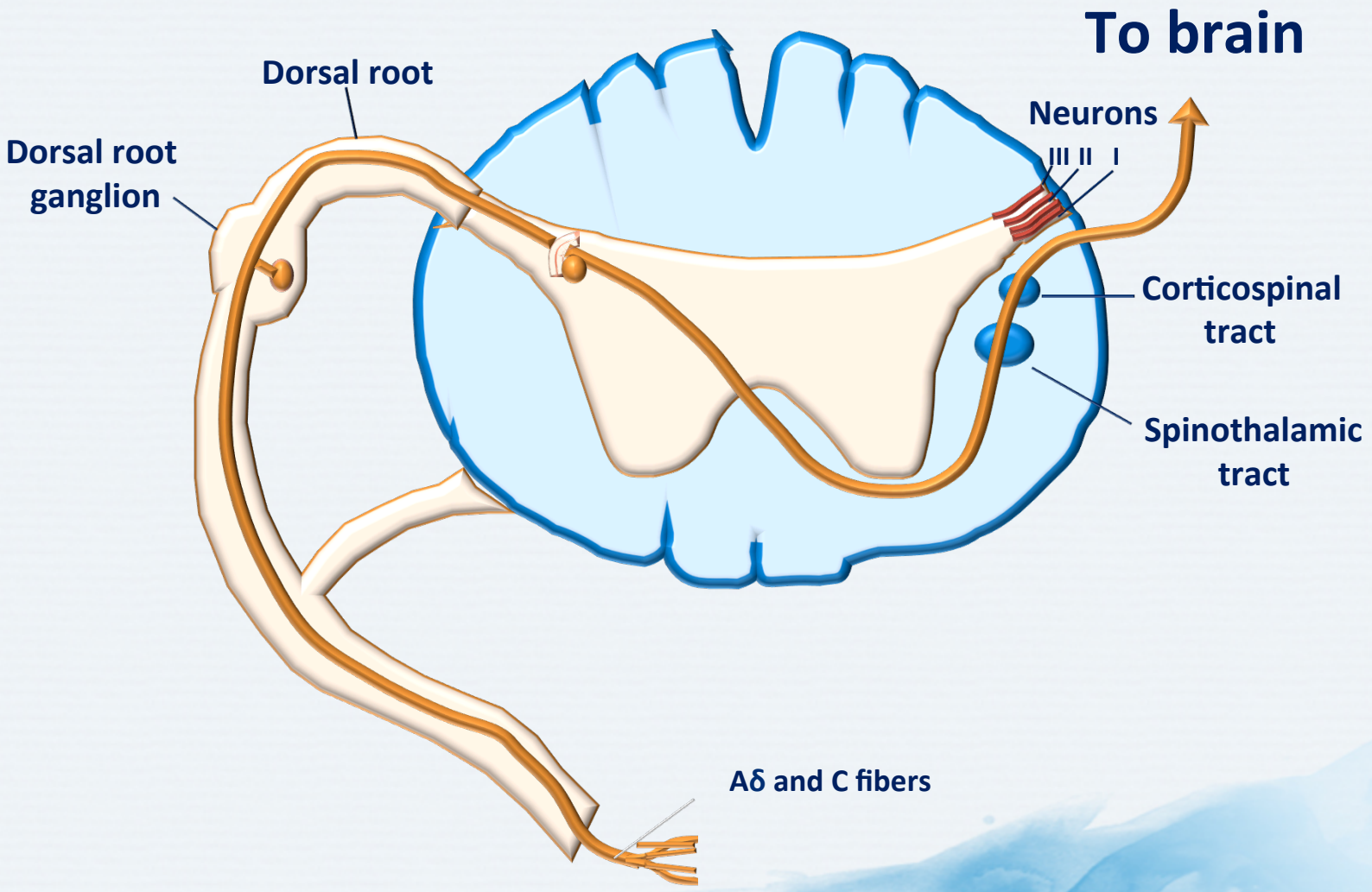
Type of Pain	Pain Quality	Signs and Symptoms	Examples
Superficial somatic pain	• Sharp, pricking or burning sensation	• Cutaneous tenderness Hyperalgesia Hyperesthesia Allodynia	• Sun, chemical or thermal burns • Skin cuts and contusions
Deep somatic pain	• Usually dull or aching, cramping	• Tenderness • Reflex muscle spasm • Sympathetic hyperactivity†	• Arthritis pain • Tendonitis • Myofascial pain
Visceral pain*	• **Deep aching or sharp stabbing pain, which is often referred to cutaneous sites**	• **Malaise** • **Nausea** • **Vomiting** • **Sweating** • **Tenderness** • **Reflex muscle spasm**	• **Colic** • **Appendicitis** • **Pancreatitis** • **Peptic ulcer disease** • **Bladder distension**

*Visceral organs include the heart, lungs, gastrointestinal tract, pancreas, liver, gallbladder, kidneys and bladder

†Symptoms and signs of sympathetic (autonomic) nervous system hyperactivity include increased heart rate, blood pressure, and respiratory rate; sweating pallor; dilated pupils; nausea; vomiting dry mouth; and increased muscle tension

American Pain Society. *Pain: Current Understanding of Assessment, Management, and Treatments.* Available at: http://www.npcnow.org/system/files/research/download/Pain-Current-Understanding-of-Assessment-Management-and-Treatments.pdf. Accessed March 24, 2015.

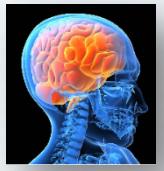
Nociception



Dubin AE, Patapoutian A. *J Clin Invest* 2010; 120(11):3760-72; Fields HL *et al. Neurobiol Dis* 1998; 5(4):209-27; Williams SJ, Purves D. Neuroscience. Sinauer Associates; Sunderland, MA: 2001..

Sensitization and Visceral Pain

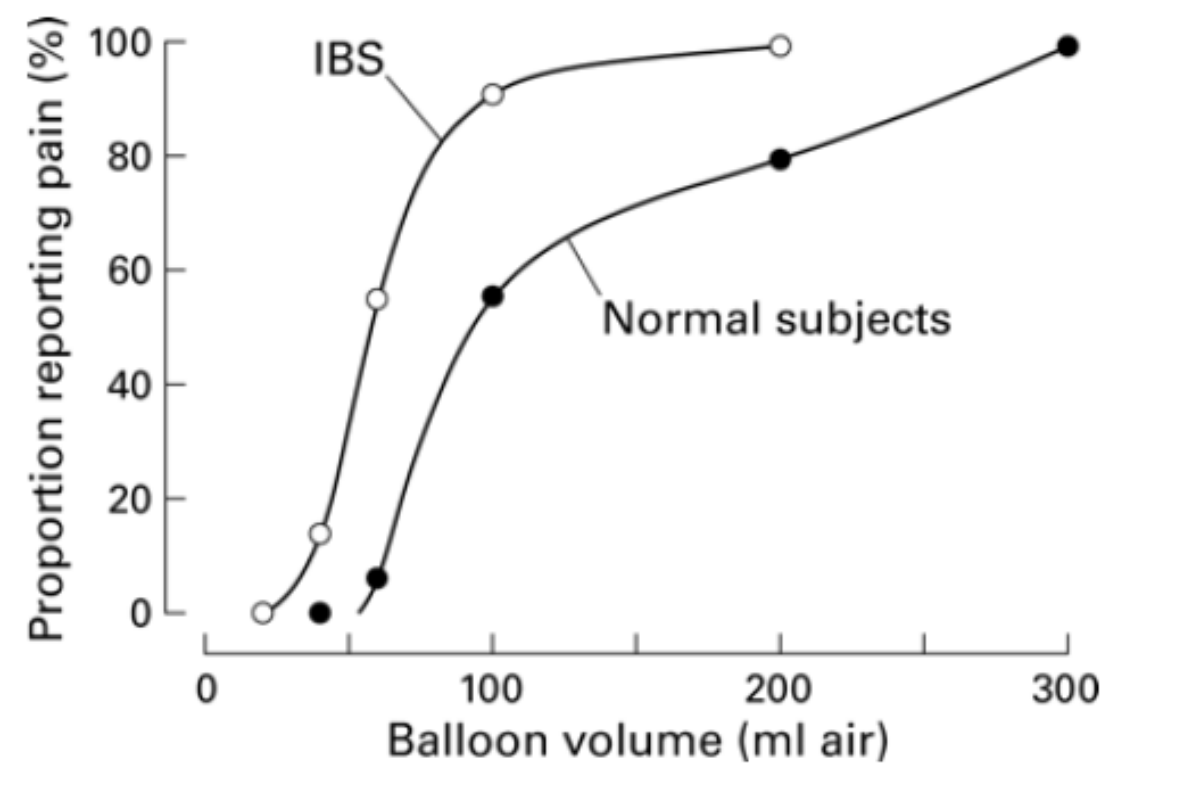
- Visceral pain involves **visceral hyperalgesia**
- Increased sensitivity has **two causes**
  1. A change of sensory neurons in the viscera; they respond more intensely to naturally occurring stimuli
     and
  2. An enhanced sensitivity of the sensory pathways in the brain that mediate sensations from the viscera
- Both processes are known as "sensitization"
  - **Peripheral sensitization** occurs in the viscera
  - **Central sensitization occurs** in the brain



Both types of sensitization are thought cause the pain produced by the inflammatory disease/injury and the hyperalgesia that occurs without an identifiable cause

Cervero F. Available at: http://www.wellcome.ac.uk/en/pain/microsite/science3.html. Accessed 8 January, 2015.

Visceral Hyperalgesia in Irritable Bowel Syndrome



Patients with IBS report pain at lower distension volumes of the colon than normal subjects

IBS = irritable bowel syndrome

Gebhart GF. *Gut*. 2000;47:iv54-iv55.

What is central sensitization/ dysfunctional pain?

Definition

- Amplification of neural signaling within the CNS that elicits pain hypersensitivity

Examples

- Fibromyalgia
- Irritable bowel syndrome
- Interstitial cystitis
- Temporomandibular joint pain
- May be present in many patients with chronic low back pain, osteoarthritis and rheumatoid arthritis

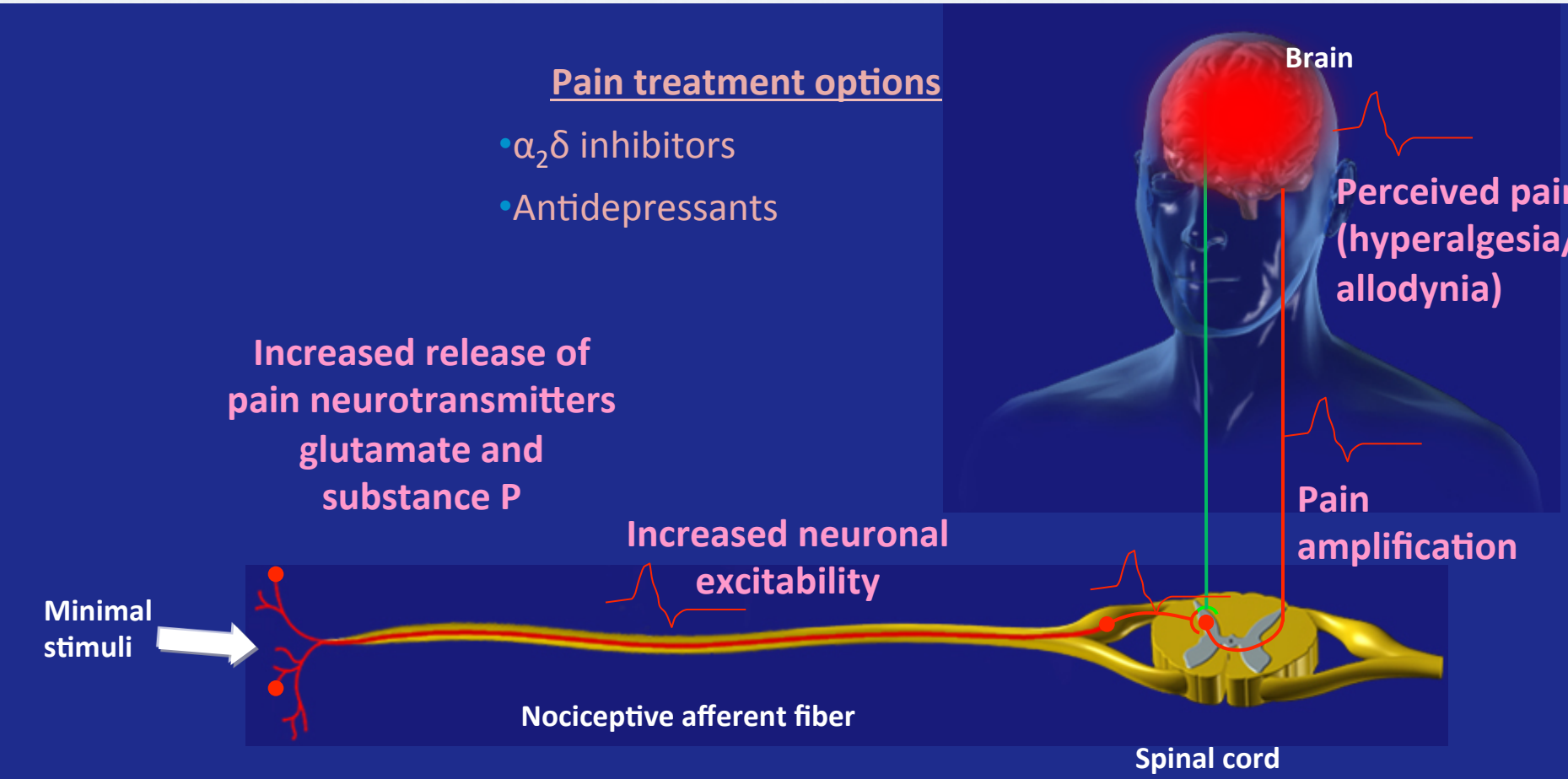
Pain Quality

- Burning
- Lancinating
- Electric shock-like
- Often diffuse
- Frequently with allodynia and/or hyperalgesia

CNS = central nervous system

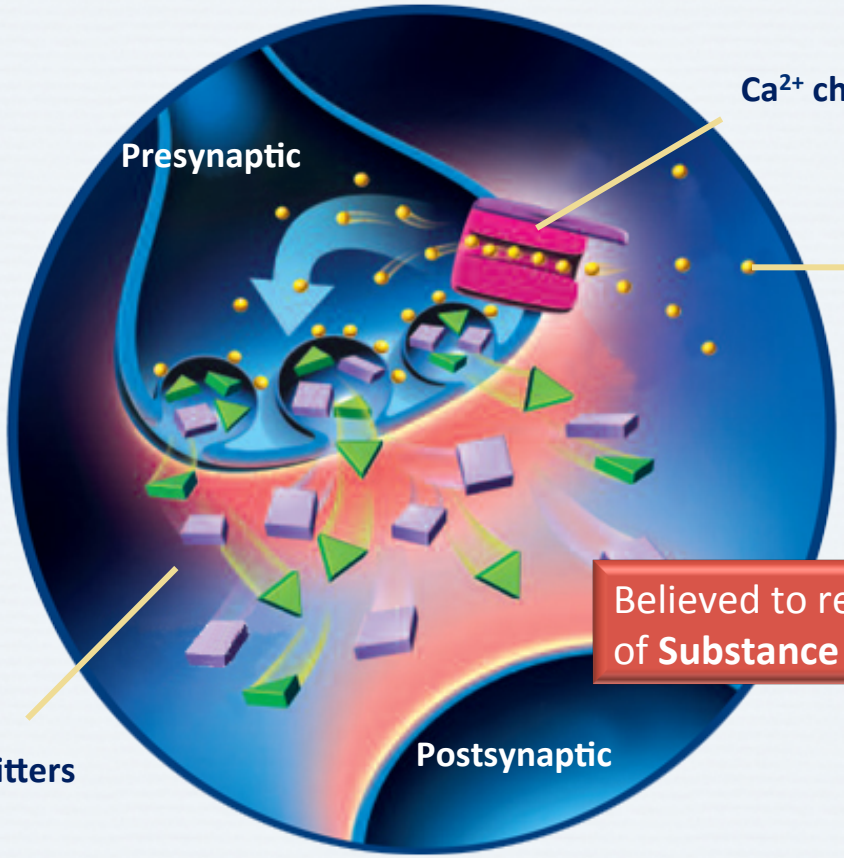
Woolf CJ. *Pain* 2011; 152(3 Suppl):S2-15.

Central Sensitization Produces Abnormal Pain Signaling



Adapted from: Campbell JN, Meyer RA. *Neuron* 2006; 52(1):77-92; Gottschalk A, Smith DS. *Am Fam Physician* 2001; 63(10)1979-86; Henriksson KG. *J Rehabil Med* 2003; 41(Suppl):89-94; Larson AA *et al. Pain* 2000; 87(2):201-11; Marchand S. *Rheum Dis Clin North Am* 2008; 34(2):285-309; Rao SG. *Rheum Dis Clin North Am* 2002; 28(2):235-59; Staud R. *Arthritis Res Ther* 2006; 8(3):208-14; Staud R, Rodriguez ME. *Nat Clin Pract Rheumatol* 2006; 2(2):90-8; Vaerøy H *et al. Pain* 1988; 32(1):21-6; Woolf CJ *et al. Ann Intern Med* 2004; 140(6):441-51.

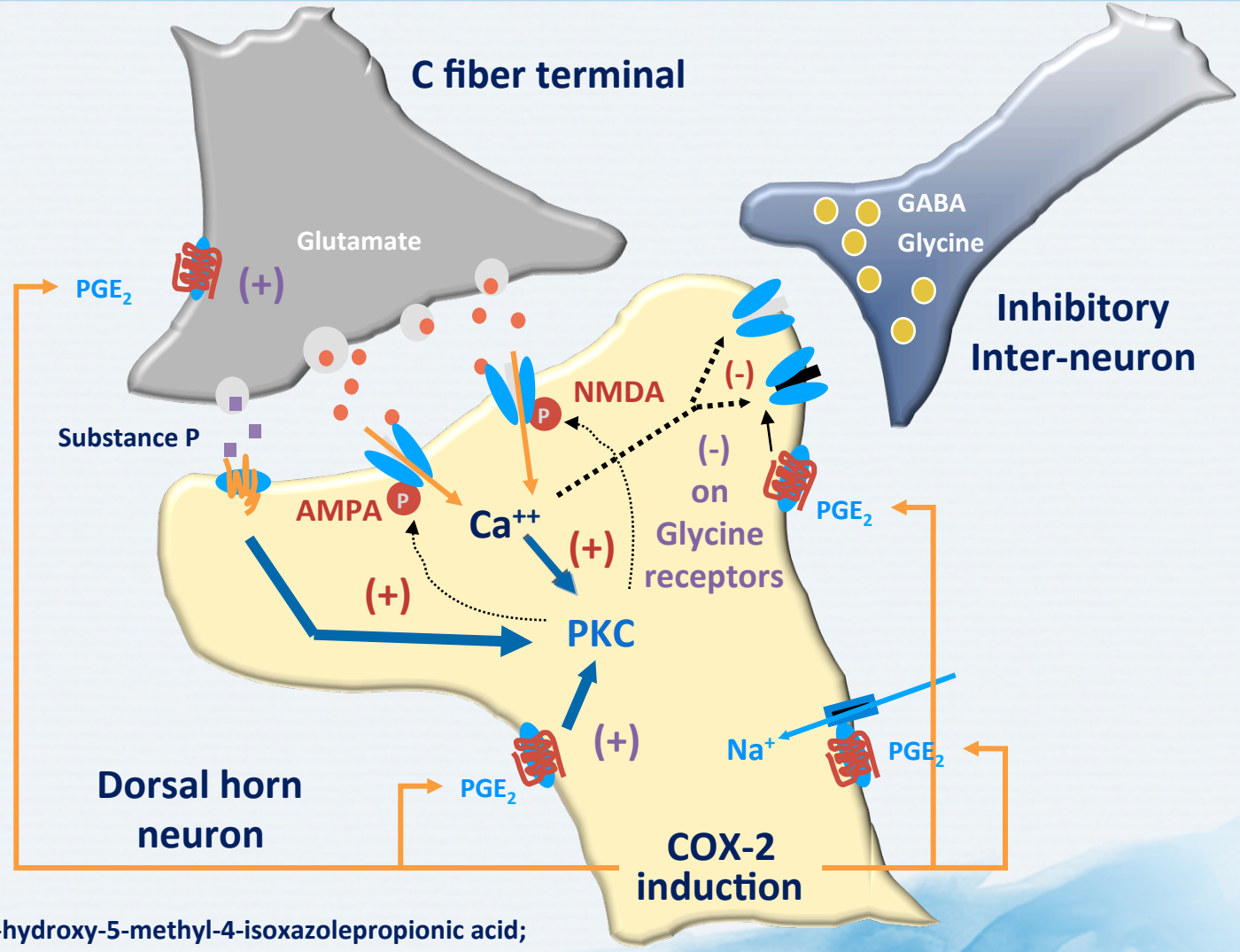
Central Sensitization



Believed to result from excessive release of **Substance P** and **glutamate**

Costigan M *et al. Annu Rev Neurosci* 2009; 32:1-32; Costigan M *et al.* In: Siegel GJ *et al* (eds). *Basic Neurochemistry: Molecular, Cellular and Medical Aspects*. 7th ed. Elsevier Academic Press; Burlington, MA: 2006; Staud R. *Arthritis Res Ther* 2006; 8(3):208-14.

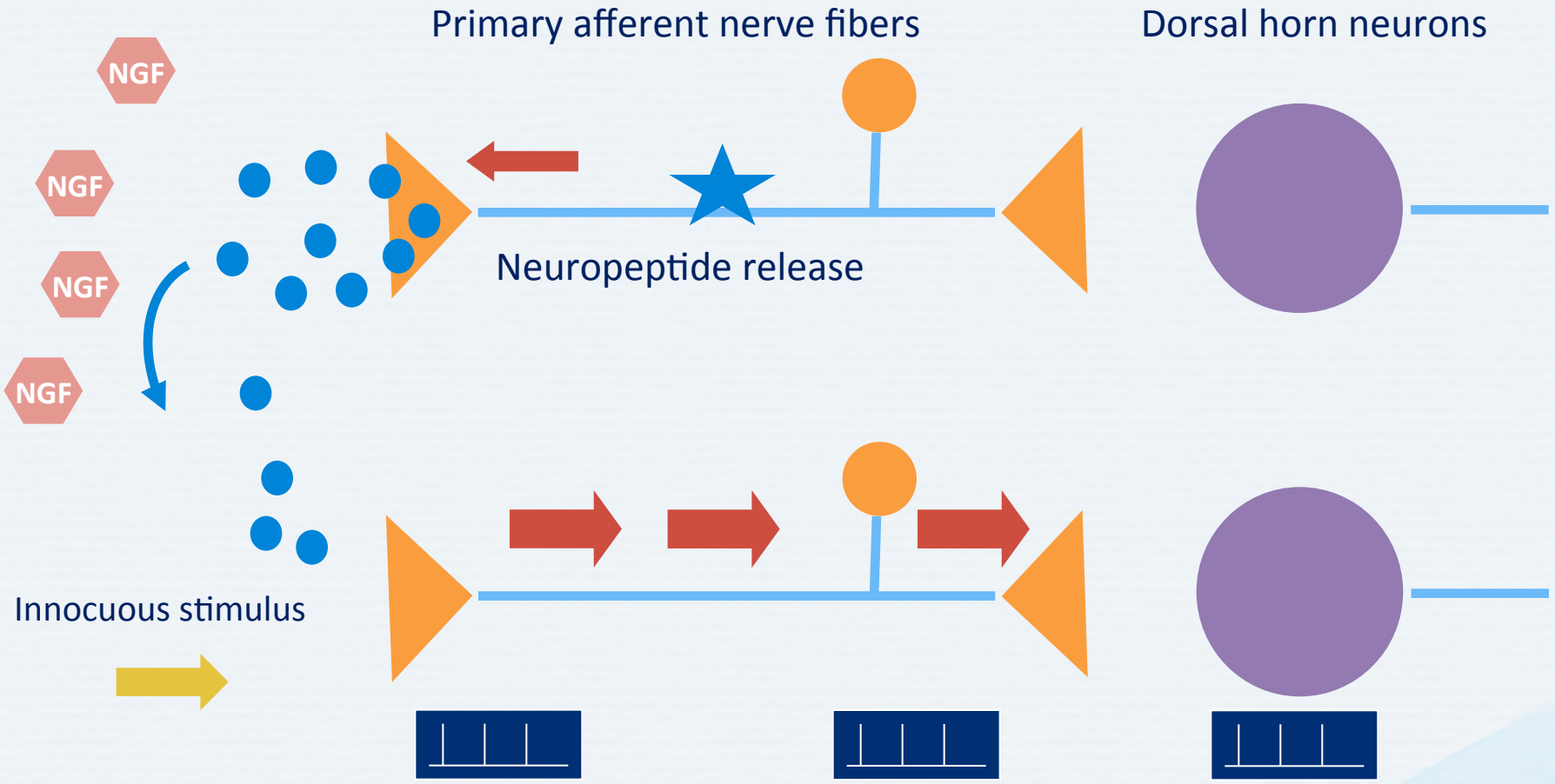
Central Sensitization



AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid;
GABA = γ-aminobutyric acid; NMDA = N-methyl-D-aspartate; prostaglandin E; PKC = protein kinase C

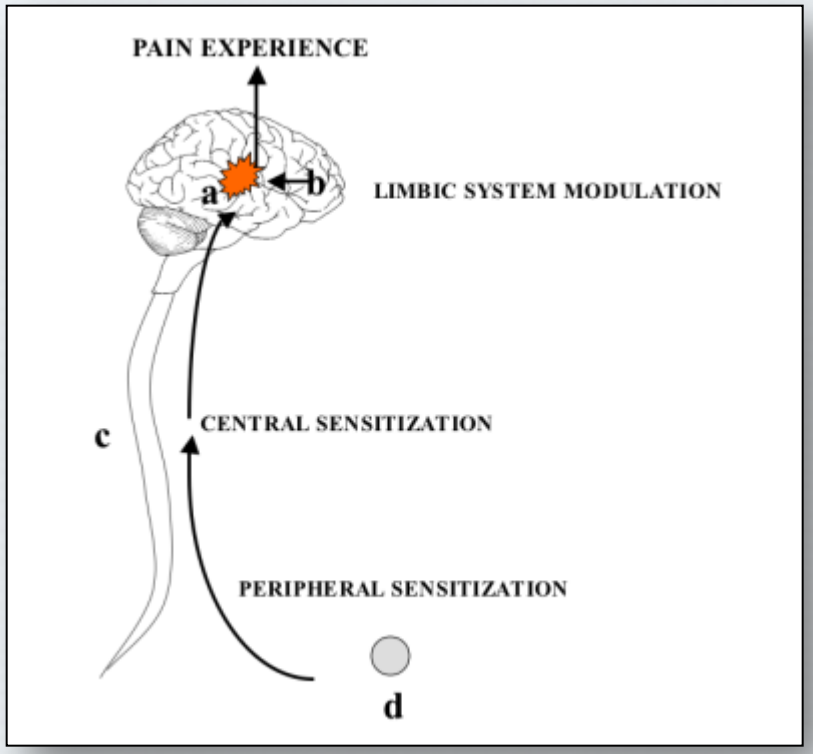
Woolf CJ, Salter MW. *Science* 2000; 288(5472):1765-9.

Peripheral Sensitization



Ørstavik K *et al*. *Brain* 2003; 126(Pt 3):567-78; Woolf CJ, Mannion RJ. *Lancet* 1999; 353(9168):1959-64.

Pathway of Pain from Peripheral Receptors to Cortical Areas



a = secondary somatosensory area
b = limbic areas including the cingulate cortex
c = spinal cord
d = peripheral receptors

Patrizi F *et al. The Scientific World J.* 2006;6:472-90.

Pathophysiology of Visceral Pain

- Correlated with excitation of spinal visceral afferents and (in general) not with the excitation of vagal afferents
- Spinal visceral afferents are polymodal
  - Can be excited by physical and chemical stimuli
- All groups of visceral afferents can be sensitized
- Normally silent visceral afferents are recruited by inflammation
- Individual visceral afferent neurons project in laminae I and V of the dorsal horn over several segments
  - Medio-lateral over entire width of dorsal horn and to contralateral side
  - Activity is synaptically transmitted to viscero-somatic convergent neurons, which receive additional afferent synaptic input from skin and deep somatic tissues of the corresponding dermatomes, myotomes, and sclerotomes

Jänig W, Häbler HJ. Physiology and pathophysiology of visceral pain. *Schmerz.* 2002;16(6):429-46.

Pathophysiology of Visceral Pain

- Usually felt around midline because visceral organs are supplied with afferents bilaterally
  - Exceptions due to unilateral or predominantly unilateral innervation:
    - Cecum, ascending colon, descending colon, sigmoid colon, kidneys, ureters

- Poorly localized and diffuse pain is due to low density of sensory innervation of viscera and extensive functional divergence of visceral input within CNS
- Viscerovisceral convergence at central level contributes to relative difficulty in pinpointing the source of visceral pain

CNS = central nervous systemGiamberardino MA, Vecchiet L. *Curr Pain Headache Reports.* 1997;1:23-33.

Visceral Afferent Fibers and Visceral Pain

- Sensory fibers in viscera are constituents of spinal and cranial nerves
  - Cell bodies are in posterior root ganglia of spinal nerves or ganglia of cranial nerves
- Distal processes occur via sympathetic and parasympathetic nerves to reach viscera
- Central processes pass via the dorsal (and sometimes the ventral) roots
- Size range of fibers is comparable to that of cutaneous fibres
  - However, there is a considerably **higher proportion of small fibers**
- A-δ predominates among A fibers
  - Ratio of A to C fibers differs in dorsal root and visceral nerves:
    - A:C in dorsal root = 1:2 A:C in visceral nerves = 1:8 or 1:10
    - Density of innervation of viscera by spinal afferents is low vs. density of afferent innervation in skin, deep somatic tissues
    - However, visceral afferent terminals are widely distributed in spinal cord

A few visceral afferent fibers can activate many neurons in the spinal cord through extensive functional divergence

Giamberardino MA, Vecchiet L. *Curr Pain Headache Reports.* 1997;1:23-33.

Viscerosomatic Convergence

- Most second-order neurons receiving visceral inputs are in laminae I and V of dorsal horn
  - Also located in the ventral horn of the spinal cord
- Fewest neurons in the superficial dorsal horn
  - Limited ipsilateral input and a cutaneous output
  - Subjected to descending inhibitory control
  - Project to the brain via spinothalamic pathways
- Most neurons are in the deep dorsal and ventral horn
  - Have a diffuse and bilateral visceral and somatic input
  - Subjected to descending excitatory and inhibitory control
  - No evidence for the existence of neurons that are exclusively concerned with visceral afferents
  - Therefore, viscerosomatic convergence is the norm

Visceral sensations can be mediated only through convergent signals via somatosensory pathways

Giamberardino MA, Vecchiet L. *Curr Pain Headache Reports.* 1997;1:23-33.

Viscerosomatic Convergence and Referred Pain

- Neurophysiological convergence of visceral and afferent inputs to CNS is thought to underlie referred pain
  - Noxious stimulation of viscera triggers pain referred to somatic sites
- May be due to scarcity of visceral afferent fibers with spinal cord terminations
- Relative contribution of visceral afferent fibers to total spinal cord afferent input is <10%
- Visceral afferent terminals show extensive divergence and intraspinal distribution vs. cutaneous afferents

CNS = central nervous system

Sikandar S, Dickenson AH. *Curr Opin Support Palliat Care.* 2012;6(1):17-26.

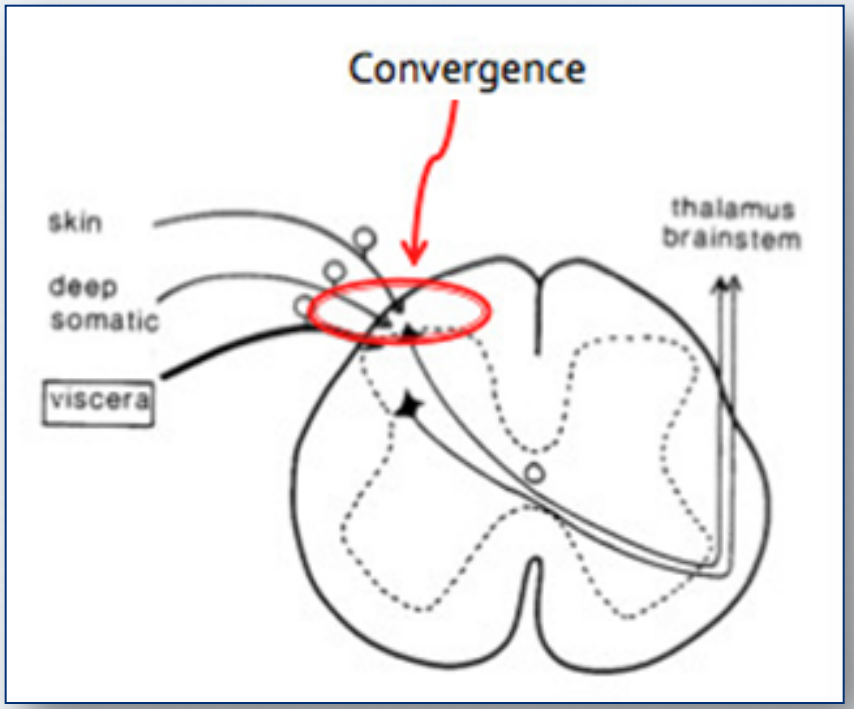
Viscerosomatic Convergence in the Central Nervous System

Spinal Cord	Supraspinal Centers
• Superficial dorsal horn (neurons with visceral and superficial somatic input) • Deep dorsal horn and ventral horn (neurons with visceral and deep somatic input)	• Brain stem • Thalamus • Cortex

Visceral sensations can be mediated only through convergent signals via somatosensory pathways

Giamberardino MA, Vecchiet L. *Curr Pain Headache Reports.* 1997;1:23-33.

Viscerovisceral Convergence



Both viscerosomatic and viscerovisceral convergence are maintained at the supraspinal level (*e.g.*, brain stem, thalamus, cerebral cortex)

Giamberardino MA, Vecchiet L. *Curr Pain Headache Reports.* 1997;1:23-33.

Brain-Gut Axis in Visceral Pain

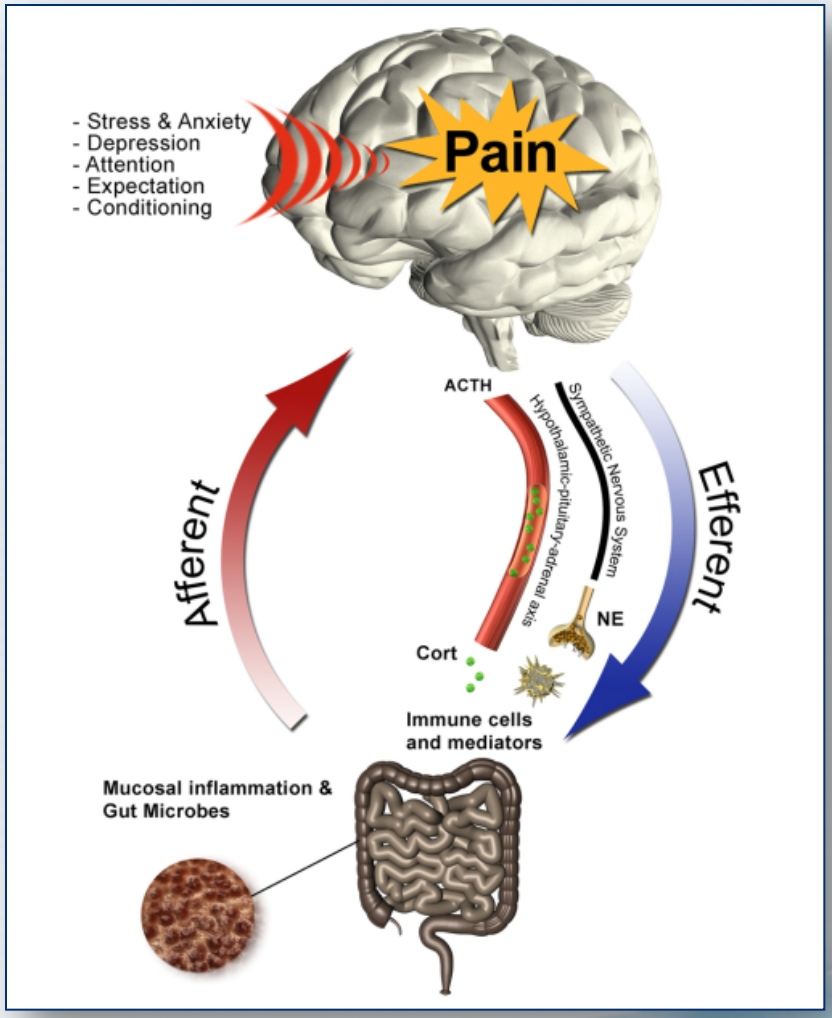
- Gut and brain communicate by multiple means
- Alterations in secretion of corticotropin-releasing factor (CRF) and expression of its receptor implicated in pathology stress-related illnesses, anxiety, depression, changes in GI motility, changes in visceral sensation
  - CRF-receptor agonists can block increased colonic activity and painful sensations induced by acute or chronic stress
- Gut sends information to brain via ascending fibers in vagus nerve
  - Central amygdala transforms noxious and stressful signals into behavioral and autonomic responses, including anxiety and depression
  - Electrical modulation of vagus nerve approved by FDA to treat depression

The vagus nerve can modulate emotional responses to GI stimulation

GI = gastrointestinal

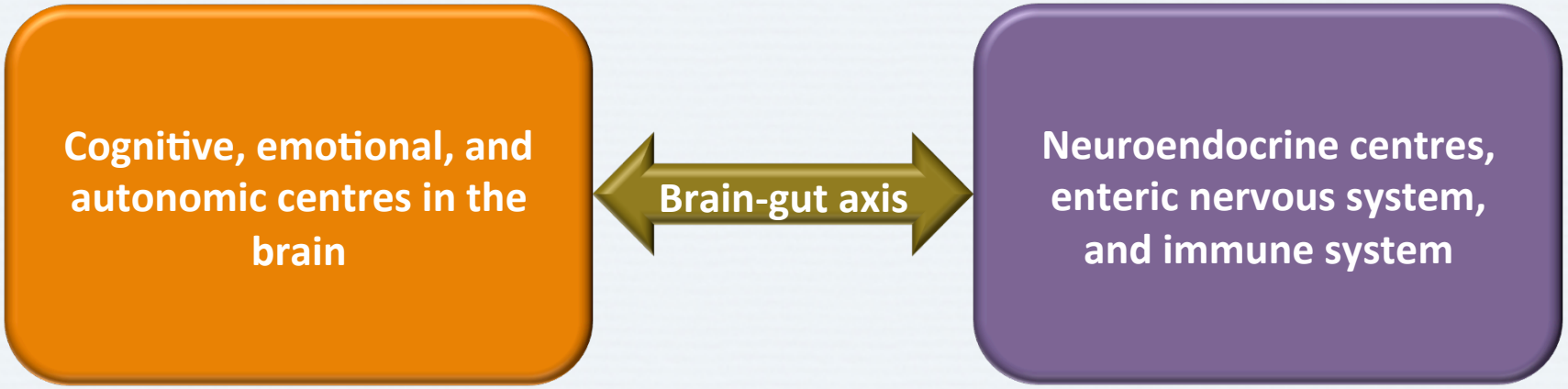
IASP. Painful functional bowel disorders: psychological factors. Available at: http://www.iasp-pain.org/files/Content/ContentFolders/GlobalYearAgainstPain2/VisceralPainFactSheets/4-Psychological.pdf. Accessed 13 January 2015.

Central and Peripheral Pathways of the Brain-Gut Axis



Elsenbruch S. *Brain Behav Immun.* 2011;25(3):386-94.

Brain-Gut Axis in Visceral Pain

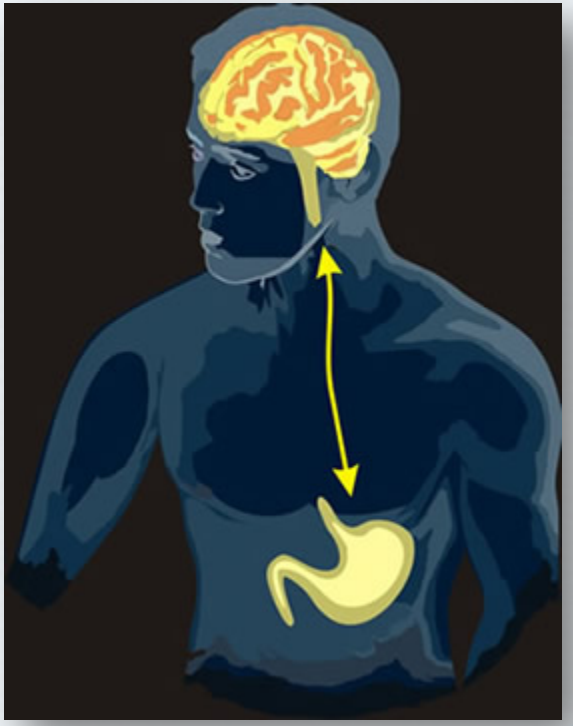


Altered brain-gut interactions can contribute to autonomic dysregulation of the gut and associated pain and perceptual changes in visceral disorders

Sikandar S, Dickenson AH. *Curr Opin Support Palliat Care*. 2012;6(1):17-26.

Bi-directionality of the Brain-Gut Pathway in FGIDs

- Evidence indicates a brain-to-gut pathway may account for GI symptoms in some FGIDs
- Other evidence indicates the gut may be the primary driver of symptoms
  - Via gut to brain connections, possibly via cytokines
- It has been shown that both brain-gut and gut-brain pathways may occur in FGIDs
- In IBS and FD, it appears the brain-gut pathway is dominant



FGID = functional gastrointestinal disorder; GI = gastrointestinal; IBS = inflammatory bowel disease

Koloski NA *et al. Gut.* 2012;61(9):1284-90.

Literature cited

American Pain Society. (n.d.-b). Pain: Current Understanding of Assessment, Management, and Treatments - Pain-Current-Understanding-of-Assessment-Management-and-Treatments.pdf. Retrieved June 24, 2015, from http://www.npcnow.org/system/files/research/download/Pain-Current-Understanding-of-Assessment-Management-and-Treatments.pdf

Campbell, J. N., & Meyer, R. A. (2006). Mechanisms of neuropathic pain. *Neuron*, *52*(1), 77–92. http://doi.org/10.1016/j.neuron.2006.09.021

Cervero, F. (n.d.). Visceral pain. Retrieved June 24, 2015, from http://www.wellcome.ac.uk/en/pain/microsite/science3.html

Elsenbruch, S. (2011). Abdominal pain in Irritable Bowel Syndrome: a review of putative psychological, neural and neuro-immune mechanisms. *Brain, Behavior, and Immunity*, *25*(3), 386–394. http://doi.org/10.1016/j.bbi.2010.11.010

Gebhart, G. F. (2000). Visceral pain-peripheral sensitisation. *Gut*, *47 Suppl 4*, iv54–55; discussion iv58.

Gottschalk, A., & Smith, D. S. (2001). New concepts in acute pain therapy: preemptive analgesia. *American Family Physician*, *63*(10), 1979–1984.

Literature cited

Hanley, M. A., Masedo, A., Jensen, M. P., Cardenas, D., & Turner, J. A. (2006). Pain interference in persons with spinal cord injury: classification of mild, moderate, and severe pain. *The Journal of Pain: Official Journal of the American Pain Society*, *7*(2), 129–133. http://doi.org/10.1016/j.jpain.2005.09.011

Henriksson, K. G. (2003). Fibromyalgia--from syndrome to disease. Overview of pathogenetic mechanisms. *Journal of Rehabilitation Medicine*, (41 Suppl), 89–94.

iasp-pain.org. (n.d.). Painful Functional Bowel Disorders: Psychological Factors. Retrieved June 25, 2015, from http://www.iasp-pain.org/files/Content/ContentFolders/GlobalYearAgainstPain2/VisceralPainFactSheets/4-Psychological.pdf

Jänig, W., & Häbler, H. J. (2002). [Physiology and pathophysiology of visceral pain]. *Schmerz (Berlin, Germany)*, *16*(6), 429–446. http://doi.org/10.1007/s00482-002-0187-5

Jensen, T. S., Baron, R., Haanpää, M., Kalso, E., Loeser, J. D., Rice, A. S. C., & Treede, R.-D. (2011). A new definition of neuropathic pain. *Pain*, *152*(10), 2204–2205. http://doi.org/10.1016/j.pain.2011.06.017

Koloski, N. A., Jones, M., Kalantar, J., Weltman, M., Zaguirre, J., & Talley, N. J. (2012). The brain--gut pathway in functional gastrointestinal disorders is bidirectional: a 12-year prospective population-based study. *Gut*, *61*(9), 1284–1290. http://doi.org/10.1136/gutjnl-2011-300474

Literature cited

Larson, A. A., Giovengo, S. L., Russell, I. J., & Michalek, J. E. (2000). Changes in the concentrations of amino acids in the cerebrospinal fluid that correlate with pain in patients with fibromyalgia: implications for nitric oxide pathways. *Pain*, *87*(2), 201–211.

Marchand, S. (2008). The physiology of pain mechanisms: from the periphery to the brain. *Rheumatic Diseases Clinics of North America*, *34*(2), 285–309. http://doi.org/10.1016/j.rdc.2008.04.003

Mayo Clinic. (n.d.). Interstitial cystitis Causes - Mayo Clinic. Retrieved June 24, 2015, from http://www.mayoclinic.org/diseases-conditions/interstitial-cystitis/basics/causes/con-20022439

McMahon, S. B. (Ed.). (2013). *Wall and Melzack's textbook of pain* (6th ed). Philadelphia, PA: Elsevier/Saunders.

(2009). *Bonica's Management of Pain* (Fourth edition). Baltimore, MD: LWW.

National Institute of Diabetes and Digestive Kidney Diseases. (n.d.). Irritable Bowel Syndrome. Retrieved June 24, 2015, from http://www.niddk.nih.gov/health-information/health-topics/digestive-diseases/irritable-bowel-syndrome/Documents/ibs_508.pdf

Ørstavik, K., Weidner, C., Schmidt, R., Schmelz, M., Hilliges, M., Jørum, E., … Torebjörk, E. (2003). Pathological C-fibres in patients with a chronic painful condition. *Brain: A Journal of Neurology*, *126*(Pt 3), 567–578.

Literature cited

Pain: Current Understanding of Assessment, Management, and Treatments - Pain-Current-Understanding-of-Assessment-Management-and-Treatments.pdf. (n.d.-b). Retrieved from http://www.npcnow.org/system/files/research/download/Pain-Current-Understanding-of-Assessment-Management-and-Treatments.pdf

Patrizi, F., Freedman, S. D., Pascual-Leone, A., & Fregni, F. (2006). Novel therapeutic approaches to the treatment of chronic abdominal visceral pain. *TheScientificWorldJournal*, *6*, 472–490. http://doi.org/10.1100/tsw.2006.98

Purves, D. (2008). *Neuroscience, Fourth Edition* (4th edition). Sunderland, Mass: Sinauer Associates, Inc.

Rao, S. G. (2002). The neuropharmacology of centrally-acting analgesic medications in fibromyalgia. *Rheumatic Diseases Clinics of North America*, *28*(2), 235–259.

Siegel, G. J. (2006). *Basic neurochemistry molecular, cellular and medical aspects*. Amsterdam; Boston: Elsevier. Retrieved from http://site.ebrary.com/id/10169920

Literature cited

Sikandar, S., & Dickenson, A. H. (2012). Visceral pain: the ins and outs, the ups and downs. *Current Opinion in Supportive and Palliative Care*, *6*(1), 17–26. http://doi.org/10.1097/SPC.0b013e32834f6ec9

Staud, R. (2006). Biology and therapy of fibromyalgia: pain in fibromyalgia syndrome. *Arthritis Research & Therapy*, *8*(3), 208. http://doi.org/10.1186/ar1950

Staud, R., & Rodriguez, M. E. (2006). Mechanisms of disease: pain in fibromyalgia syndrome. *Nature Clinical Practice. Rheumatology*, *2*(2), 90–98. http://doi.org/10.1038/ncprheum0091

Vaerøy, H., Helle, R., Førre, O., Kåss, E., & Terenius, L. (1988). Elevated CSF levels of substance P and high incidence of Raynaud phenomenon in patients with fibromyalgia: new features for diagnosis. *Pain*, *32*(1), 21–26.

Vulvodynia Causes - Mayo Clinic. (n.d.). Retrieved June 24, 2015, from http://www.mayoclinic.org/diseases-conditions/vulvodynia/basics/causes/con-20020326

Woolf, C. J. (2011). Central sensitization: implications for the diagnosis and treatment of pain. *Pain*, *152*(3 Suppl), S2–15. http://doi.org/10.1016/j.pain.2010.09.030

Woolf, C. J., American College of Physicians, & American Physiological Society. (2004). Pain: moving from symptom control toward mechanism-specific pharmacologic management. *Annals of Internal Medicine*, *140*(6), 441–451.

Literature cited

Woolf, C. J., & Mannion, R. J. (1999). Neuropathic pain: aetiology, symptoms, mechanisms, and management. *Lancet (London, England)*, *353*(9168), 1959–1964. http://doi.org/10.1016/S0140-6736(99)01307-0