

Uncovering Visceral Hyperalgesia



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I have no financial relationships with any commercial entity to disclose



A brief word about abdominal pain prevalence

Demographics	AP prevalence
Male	29%
Female	36%
Average age (range), years	11.8 (8-15)
Average age of boys	11.7
Average age of girls	11.9
African-American	33%
Latino	22%
Caucasian	33%
Other	16%
Asian	8%

*278 subjects with weekly questionnaires for 1 year

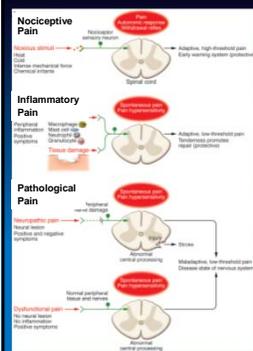
Saps M et al., 2009

"What is this thing called love (*pain*)?
 This funny thing called love (*pain*), just
 who can solve its mystery?"

Cole Porter's famous song 1926

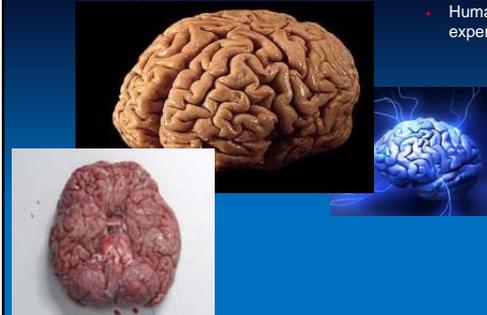


Pain from a Neurobiological Perspective



1. Early-warning physiological protective system
2. Adaptive and protective (*inflammatory pain*)
3. Pathological pain not protective, but maladaptive, abnormal functioning of the nervous system.

Why so complex?



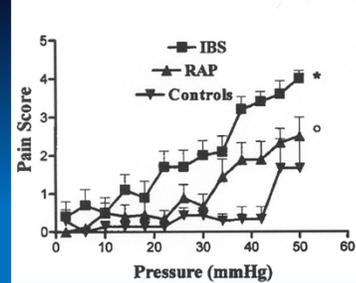
- 100 billion nerve cells
- Each makes 1,000 to 10,000 contacts with other neurons
- Human pain experience

Important Definitions

Allodynia: Pain due to a stimulus that does not normally provoke pain

Hyperalgesia: Increased pain from a stimulus that normally provokes pain

Hyperalgesia to mechanical distension



Di Lorenzo, Youssef, Wald et al. Journal of Pediatrics 2001;139:838-843

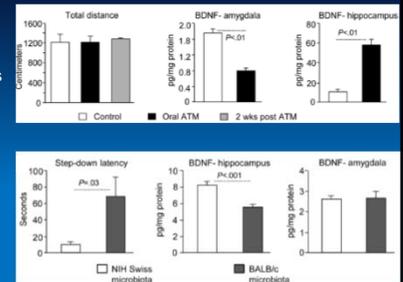
Microbiota-gut-brain axis

- 1-2kg of bacteria in the gut
 - 10 x more bacteria than cells in the body
- Vital for maintaining homeostasis and is regulated by neural, hormonal, and immunologic levels.



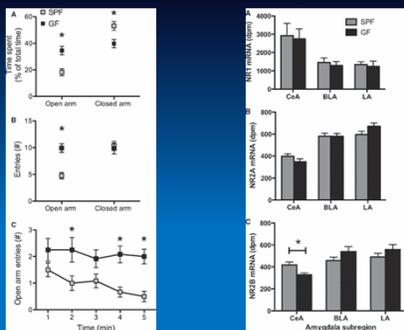
Microbiota-gut-brain axis influences brain biochemistry and modulates behavior

- Brain derived neurotrophic factor (BDNF)
- Increases in hippocampal BDNF is associated with anxiolytic and antidepressant behavior



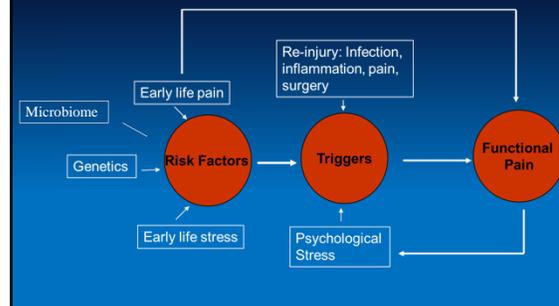
Bercik et al., Gastroenterology 2011

Decrease in anxiety and alteration in central NR2B in germ free mice

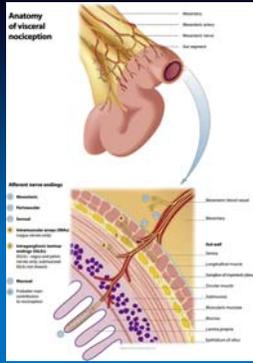


Neufeld et al., Neurogastroenterol Motil. 2011

Development of chronic pain



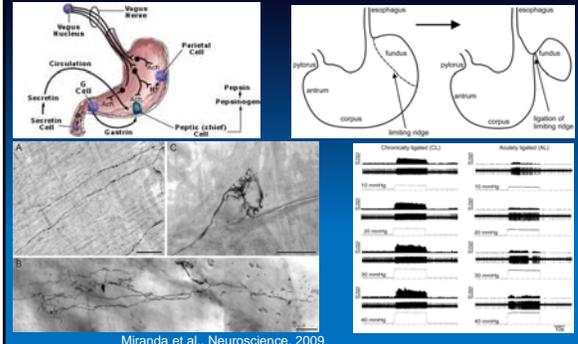
Vagal Afferents



- Project directly to hypothalamus, amygdala, periaqueductal grey (PAG) and locus coeruleus (LC)
- Regulate emotional, autonomic and behavioral responses.

C.H. Knowles, Q. Aziz. PAIN 2009

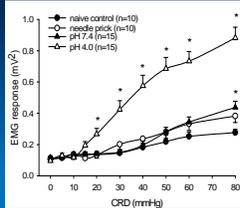
Fundus ligation changes enteric nerves and vagal response



Miranda et al., Neuroscience, 2009

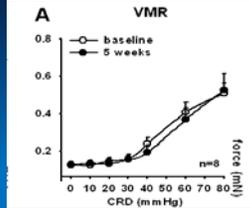
Visceral hyperalgesia following a neonatal somatic stimulus

Adult rats following acid injections during the neonatal period



Visceral hyperalgesia

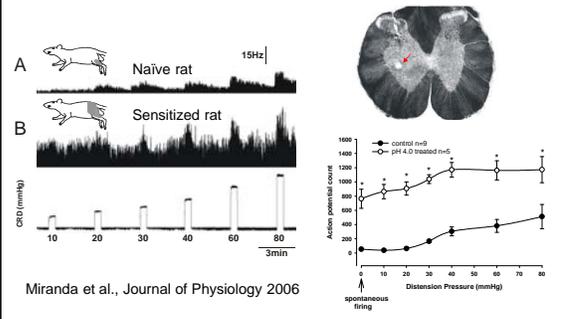
Adult rats with following acid injections in GN muscle



No alteration in visceral sensitivity

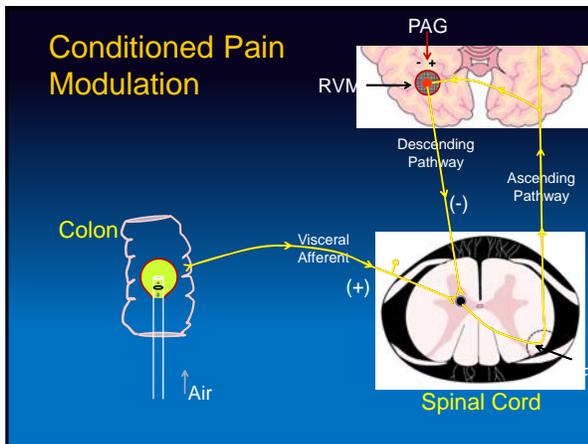
Miranda et al., Gastroenterology 2004
Miranda et al., Journal of Physiology 2006

Spinal sensitization or decrease descending tone

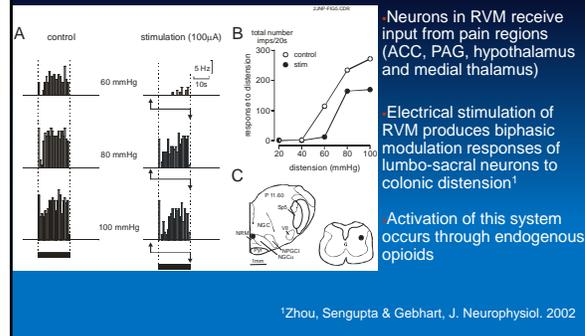


Miranda et al., Journal of Physiology 2006

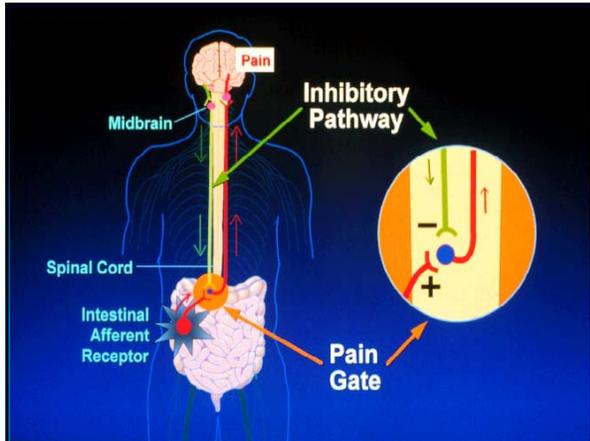
Conditioned Pain Modulation



Descending Inhibitory Control



*Zhou, Sengupta & Gebhart, J. Neurophysiol. 2002



Melatonin influences the release of endogenous opioid peptides in rat periaqueductal gray

Yu CX, Wu GC, Xu SF, Chen CH
 State Key Laboratory of Medical Neurobiology, Department of Neurobiology, Shanghai Medical University, Shanghai 200032, China

Placebo Response Rate

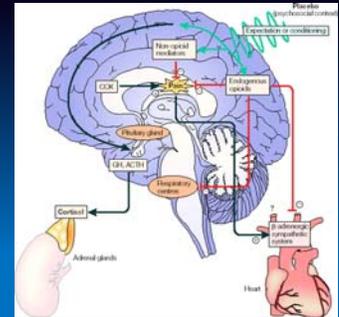
Author	Drug	Placebo Response (%)	DS-AR
Piai '81	Prifinium	65	no
Milo '80	Trimiprimine	60	equivocal
Longstreth '81	Metamucil	71	no
Fielding '81	Timolol	73	no
Fielding '80	Trimebutine	88	no

Multicenter, Randomized, Placebo-Controlled Trial of Amitriptyline in Children With Functional Gastrointestinal Disorders

MIGUEL SAPS,* NADER YOUSSEF,† ADRIAN MIRANDA,§ SAMUEL NURKO,¶ PAUL HYMAN,* JOSE COCJIN,* and CARLO DI LORENZO**

Responding to Placebo Does Not Make You "Crazy"

- Distracting tasks activate PAG, parts of ACC, and orbitofrontal cortex when subjects perform distracting tasks
- Placebo induces mild respiratory depression and decreases adrenergic activity



Benedetti F et al., J.Neurosci. 2005
 Pollo et al., Pain 2003

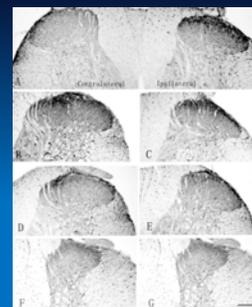
Glial cells, what's that?

Glial cells

Once dismissed as a mere packing material, glia make up 85 percent of the cells in our brain

J Clin Invest. 2010;120:3779-3787

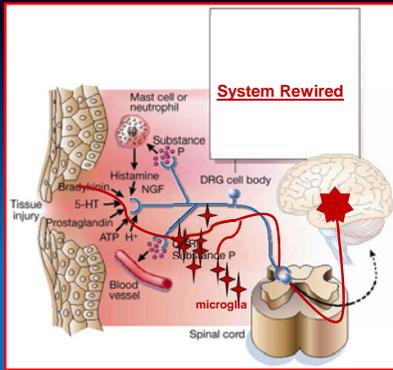
Glia and BDNF



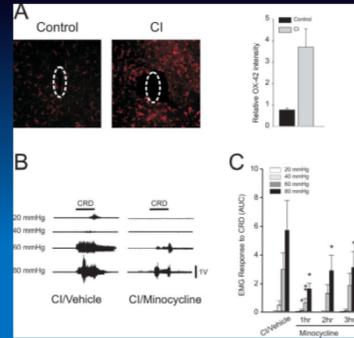
- Brain's defense against disease
- Important role in neuropathic pain and surgical pain
- BDNF is critical for communication between glia and neurons.
- Expression in SDHNs is required for development and maintenance of neuropathic pain

Chang-Qi et al., Molecular Pain 2008

Neuropathic Pain



Glial cells are involved in chronic visceral hyperalgesia



Saab et al. Neuron Glia Biology, 2006

Mechanism gone wrong?

- Living organisms need to be able to sense their immediate environment to withdraw from dangerous situations
- Nociceptive sensitization: the capacity to increase sensitivity following exposure to an injurious stimulus



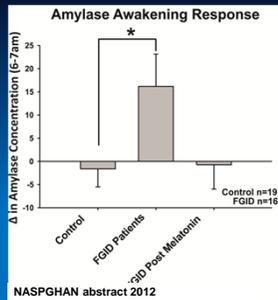
Comparing Pain Modulation and Autonomic Responses in Fibromyalgia and Irritable Bowel Syndrome Patients

Philippe Chalaye, MSc,* Philippe Goffaux, PhD,* Patricia Bourgault, RN, PhD,w Sylvie Lafrenaye, MD, MSc,z Ghislain Devroede, MD, MSc,* Alain Watier, MD,y and Serge Marchand, PhD*

Anxiety and depression are related to autonomic nervous system function in women with irritable bowel syndrome.

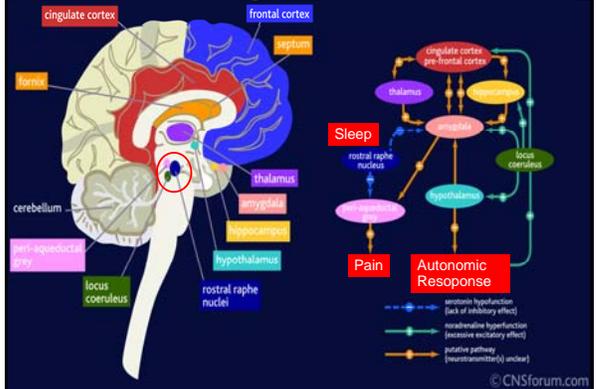
Jarrett ME, Burr RL, Cain KC, Hertig V, Weisman P, Heitkemper MM.

Salivary amylase as marker of adrenergic activity



NASPGHAN abstract 2012

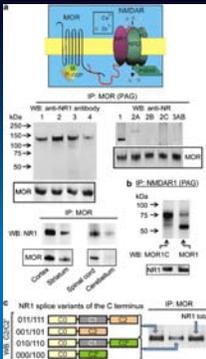
Which brain regions are involved?



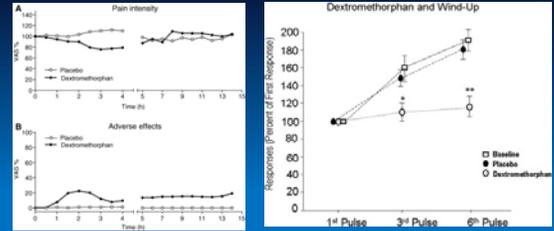
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The mu-opioid receptor and the NMDA receptor associate in PAG neurons: implications in pain control.

Rodríguez-Muñoz M, Sánchez-Blázquez P, Vicente-Sánchez A, Berrocoso E, Garzón J. CIBER of Mental Health (CIBERSAM), ISCIII, Madrid, Spain. Neuropsychopharmacology.



Analgesic effect of dextromethorphan in neuropathic pain and IBS



Acta Anaesthesiologica Scandinavica, 2004

The Journal of Pain, 2011.

Summary

- 1) Early neonatal pain/surgery can influence spinal neurons or primary sensory afferents
- 2) Conditioned pain modulation is an important mechanism involved in descending modulatory control of pain and placebo analgesia
- 3) The microbiota can alter brain chemistry and modulate behavior
- 4) The PAG region is an important structure for control of pain, ANS, sleep and anxiety
- 5) NMDA receptors and opioid receptors likely involved

The way forward for the treatment of functional pain in children lies in our growing understanding of pathogenesis of the disorder- NOT in describing a constellation of overlapping symptoms.

