A brief word about abdominal pain prevalence

<table>
<thead>
<tr>
<th>Demographics</th>
<th>AP prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>43%</td>
</tr>
<tr>
<td>Female</td>
<td>57%</td>
</tr>
<tr>
<td>Average age (range), years</td>
<td>11.8 (8-15)</td>
</tr>
<tr>
<td>Average age of boys</td>
<td>11.7</td>
</tr>
<tr>
<td>Average age of girls</td>
<td>11.9</td>
</tr>
<tr>
<td>African-American</td>
<td>33%</td>
</tr>
<tr>
<td>Latino</td>
<td>22%</td>
</tr>
<tr>
<td>Caucasian</td>
<td>21%</td>
</tr>
<tr>
<td>Other</td>
<td>16%</td>
</tr>
<tr>
<td>Asian</td>
<td>8%</td>
</tr>
</tbody>
</table>

*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

Why so complex?

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

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.

Uncovering Visceral Hyperalgesia

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I have no financial relationships with any commercial entity to disclose
**Important Definitions**

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

**Hyperalgesia:** Increased pain from a stimulus that normally provokes pain

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**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.

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

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**Development of chronic pain**

- Microbiome
- Genetics
- Early life stress
- Psychological stress
- Triggers
- Risk Factors
- Re-injury, infection, inflammation, pain, surgery

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**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

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**Hyperalgesia to mechanical distension**

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

- Bercik et al., Gastroenterology 2011

- Neufeld et al., Neurogastroenterol Motil. 2011
Vagal Afferents

- Project directly to hypothalamus, amygdala, peri-aqueductal 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

Visceral hyperalgesia following a neonatal somatic stimulus

- Adult rats following acid injections during the neonatal period
- Adult rats with following acid injections in ON muscle

No alteration in visceral sensitivity
Miranda et al., Gastroenterology 2004
Miranda et al., Journal of Physiology 2006

Spinal sensitization or decrease descending tone

Conditioned Pain Modulation

- Neurons in RVM receive input from pain regions (ACC, PAG, hypothalamus and medial thalamus)
- Electrical stimulation of RVM produces biphasic modulation responses of lumbo-sacral neurons to colorectal distension
- Activation of this system occurs through endogenous opioids


Descending Inhibitory Control
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

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

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

Salivary amylase as marker of adrenergic activity

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.

Which brain regions are involved?

5
Why sleep?
- Sleep deprivation activates sympathetic activity
- Activation related to disruption or discontinuity, not amount of sleep lost
- Documented in children with chronic pain
- Shift workers have higher prevalence of abdominal pain compared to day shift

Sleep restriction augments pain ratings in healthy volunteers

Can we link it all together?

Brain areas that control pain, wakefulness, and cardiovascular activation
1) Periaqueductal gray
2) Locus coeruleus
3) Rostro-ventromedial medulla
4) Nucleus tractus solitarius

Ventral PAG stimulation

NOT YET!!
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.


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

Analgesic effect of dextromethorphan in neuropathic pain and IBS
Acta Anaesthesiologica Scandinavica. 2004

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.