



DROSSMANCARE



Understanding IBS and FGIDs: Disorders of Gut-Brain Interaction

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“Organic” disorder

Functional GI Disorder (Gut-Brain Interaction)

Primary domain

Organ morphology

Illness experience

Criterion

Pathology (disease)

Symptoms

Measurement

**Histology
Pathology
Endoscopy
Radiology**

**Motility
Visceral sensitivity
Symptom criteria (Rome)
Psychosocial**

Treatment options

**Medications
Surgery
Ther. endoscopy**

**Pro / anti-kinetics
Antinociceptives
Antidepressants
Behavioral**

Examples

**Esophagitis
Peptic ulcer
IBD
Colon cancer**

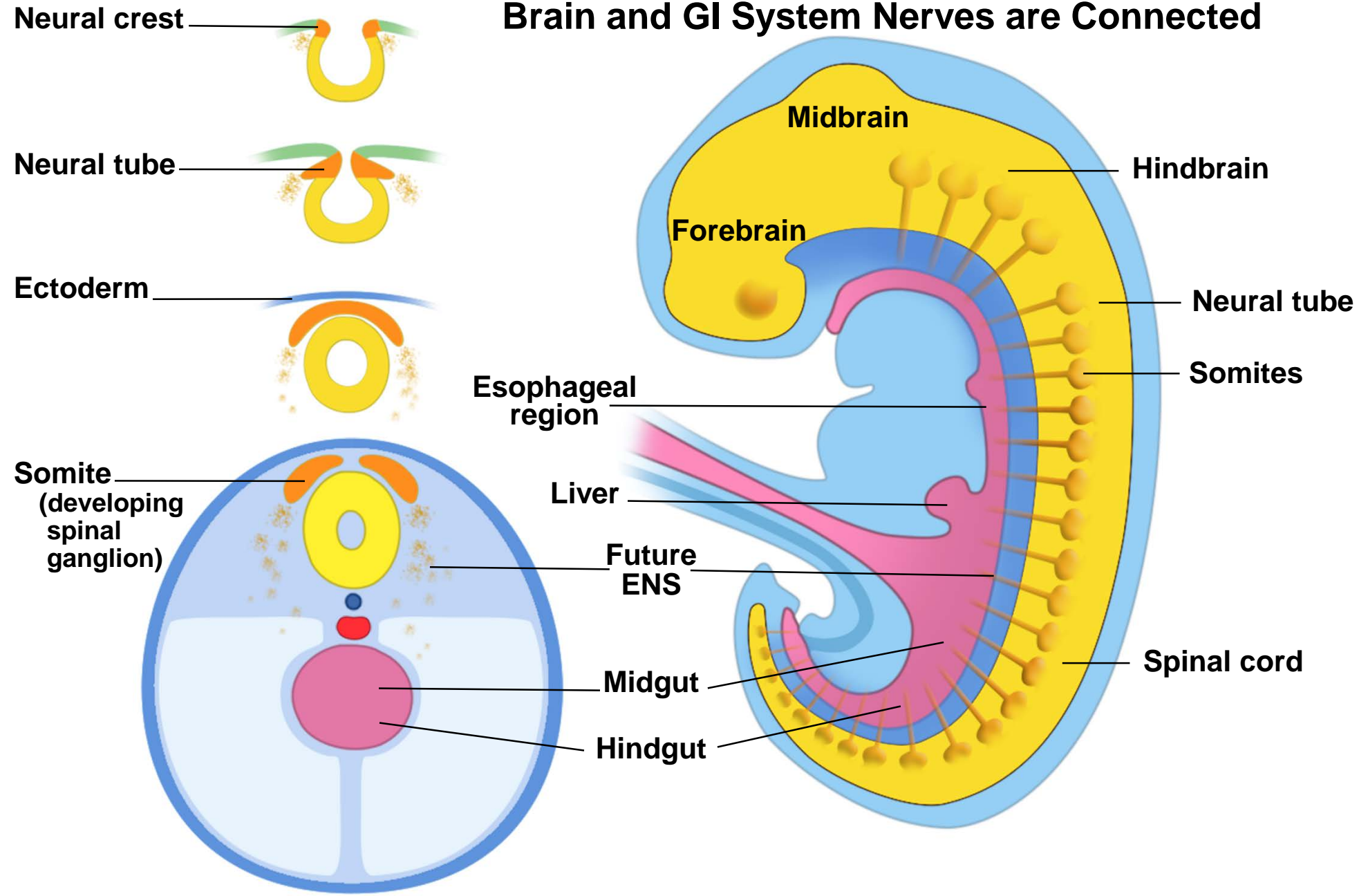
**Esophageal chest pain
Functional dyspepsia
IBS
Funct. abdominal pain**

Rome IV: Functional GI Disorders: Disorders of Gut-Brain Interactions

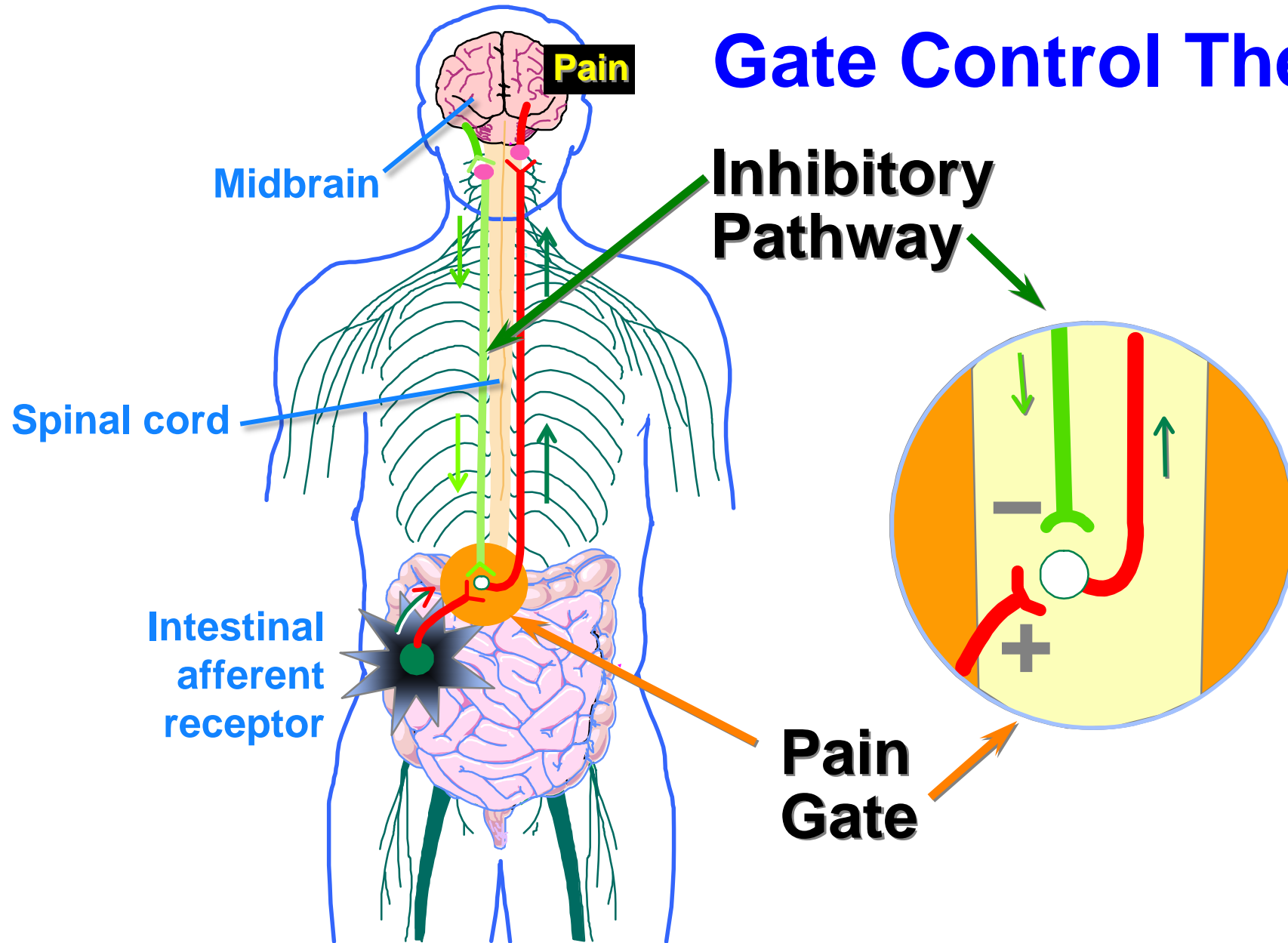
A group of disorders classified by gastrointestinal symptoms related to any combination of:

- **Motility disturbance**
- **Visceral hypersensitivity**
- **Altered mucosal and immune function**
- **Altered gut microbiota**
- **Altered central nervous system processing**

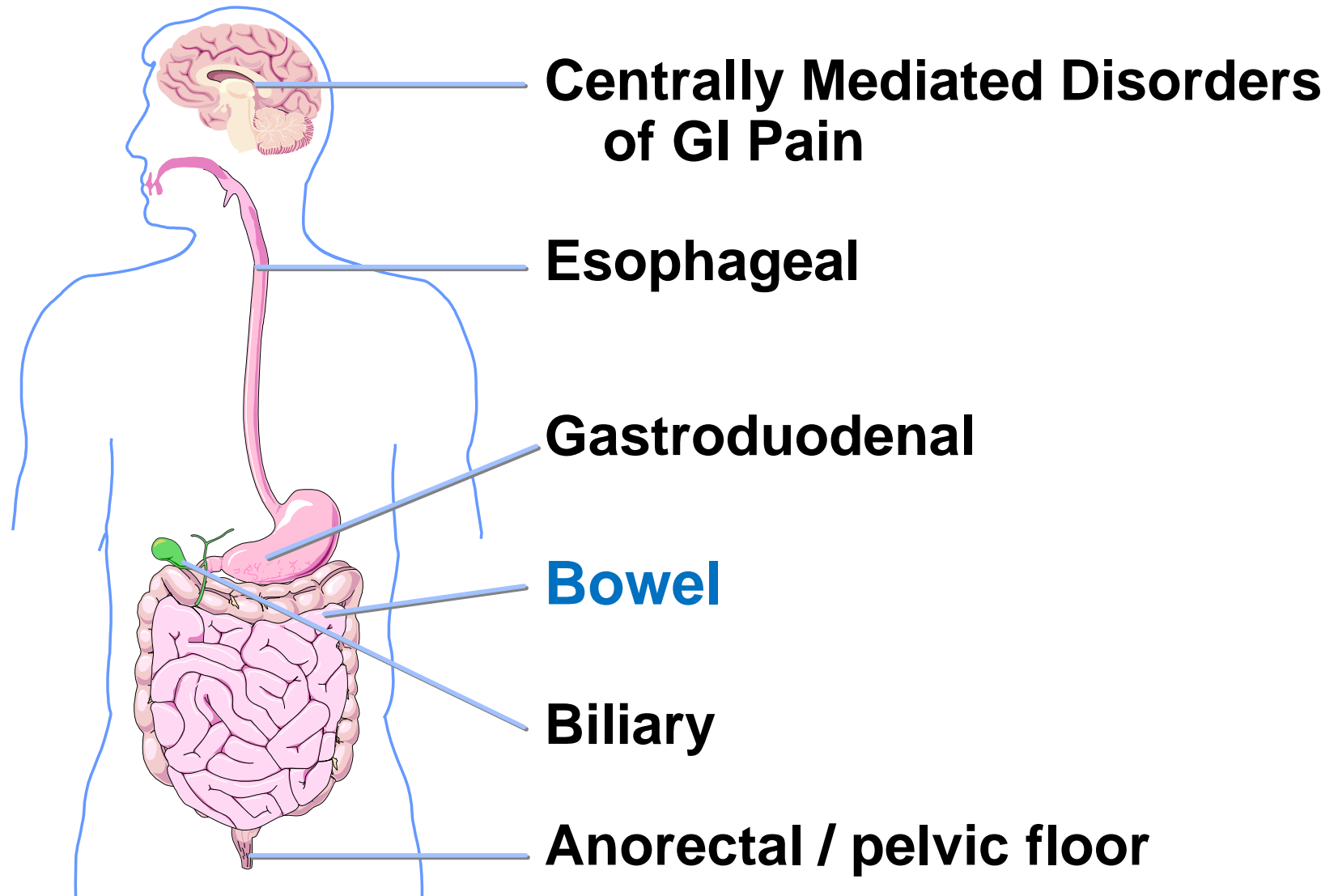
Brain and GI System Nerves are Connected



Gate Control Theory



Rome IV – Disorders of Gut-Brain Interaction



Rome IV Criteria* Irritable Bowel Syndrome

Recurrent abdominal pain at least 1 day/week
in the last 3 months associated with 2 or more :



**Related
to
defecation**

and

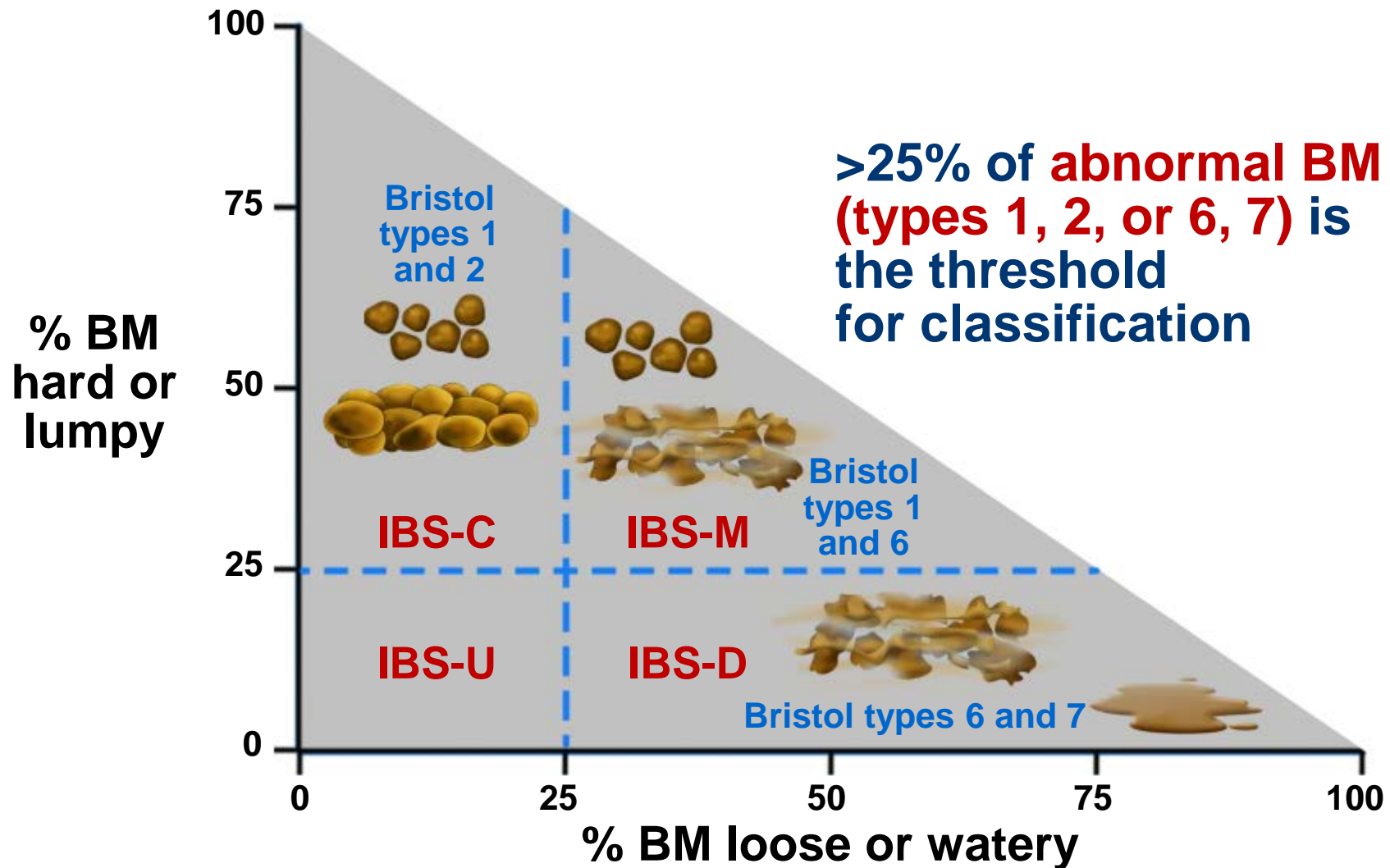
**Onset
associated
with a
change in
frequency of
stool**

and

**Onset
associated
with a change
in form
(appearance)
of stool**

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis.

Rome IV IBS Subtypes: Stool Form



What Patients Tell Me (IBS and FGIDs)

“Doctor’s don’t believe me”

“There MUST be something wrong”

“I know it’s real”

“I just want you to open me up and find out the problem”

“You don’t think it’s in my head do you?”

“Sometimes I feel like I’m going crazy”

“Nobody really knows what I’m going through”

“I feel like I’m not the person I used to be”

“I feel so alone with this”

“I feel like such a burden to my family”

“I have no control over this”

“ I feel I may have caused some damage”

“I feel like a failure”

“I feel ashamed”

International Survey of Patients with IBS: Symptom Features and their Severity, Health Status, Treatments and Risk Taking to Achieve Clinical Benefit

Douglas A. Drossman MD, Carolyn Morris MPH, Susan Schneck MA, Nancy J Norton BS, William F Norton, Stephan Weinland PhD, Christine Dalton PA-C, Jane Leserman PhD, Srikant Bangdiwala PhD

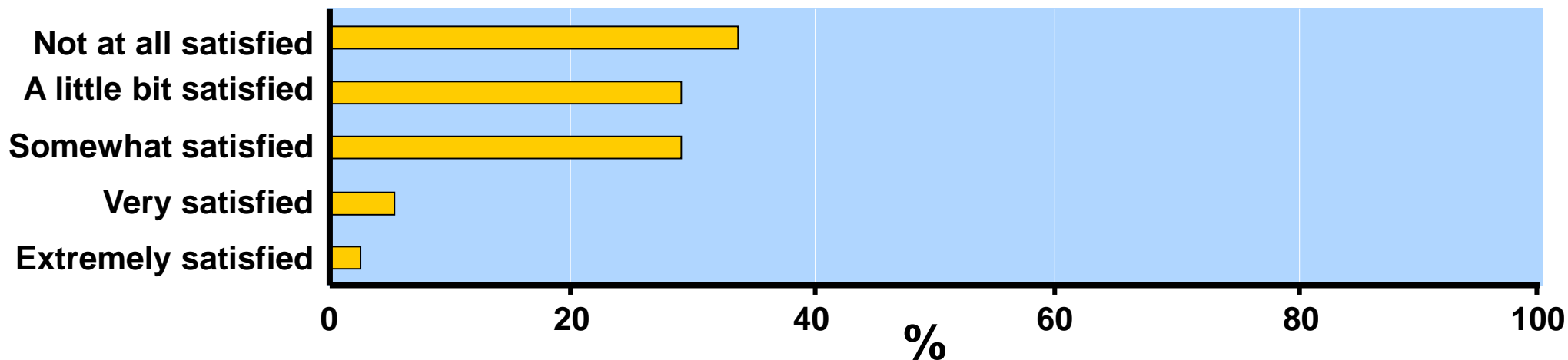
From the UNC Center for Functional GI and Motility Disorders, University of North Carolina and the International Foundation for Functional GI Disorders, Milwaukee

Results – Health Status

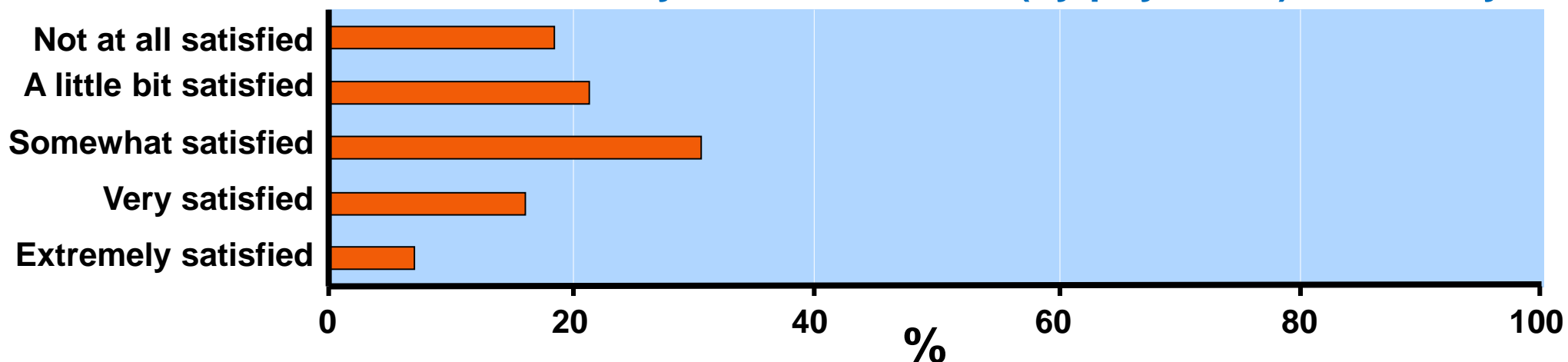
- **77% report moderate-severe symptoms (43.3% FBDSI)**
- **Days restricting activities: 73_±98 days (20% of year)**
- **Out of work due to health: 12.8%**
- **Times seen MD in past 6 months: 2.7_±4.5**
- **Times hospitalized in past 2 years: 3.0_±1.9**
- **Risk: 13% would take 1/1000 chance of death to take a medication to be in perfect health**
- **Time Trade Off: Would give 15.1 years (25% of remaining life) to be in perfect health**

Results – Satisfaction with Treatment for IBS

Satisfaction with all types of treatments

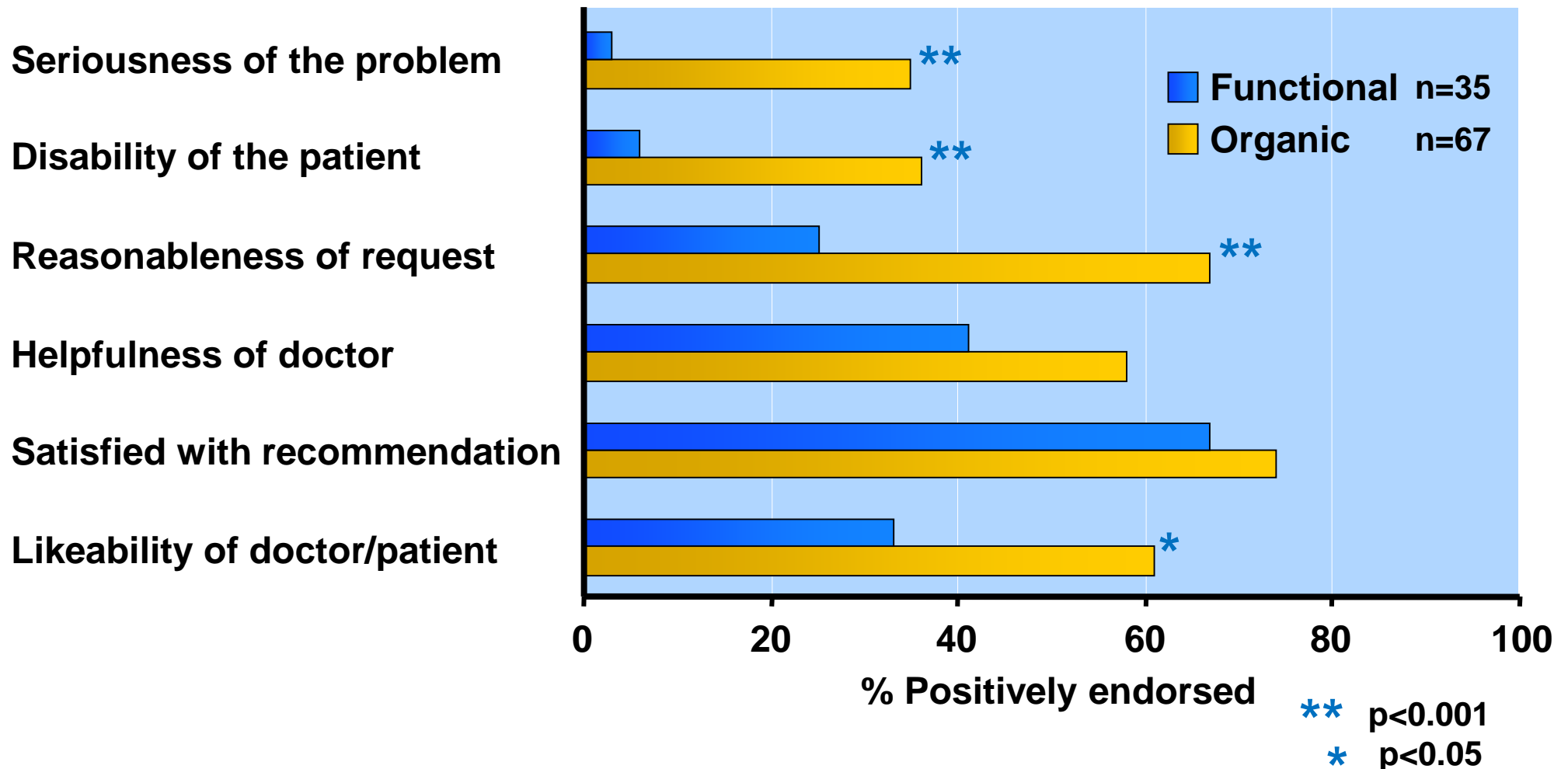


Satisfaction with your medical care (by physician) over last year



Off-hours Phone Calls

MD Perceptions of Patients: Organic vs. Functional





“The concept of the separation of mind and body is dominant and pervasive in Western thinking. This has had profound negative effects on research, patient-care and the patient-physician relationship.”

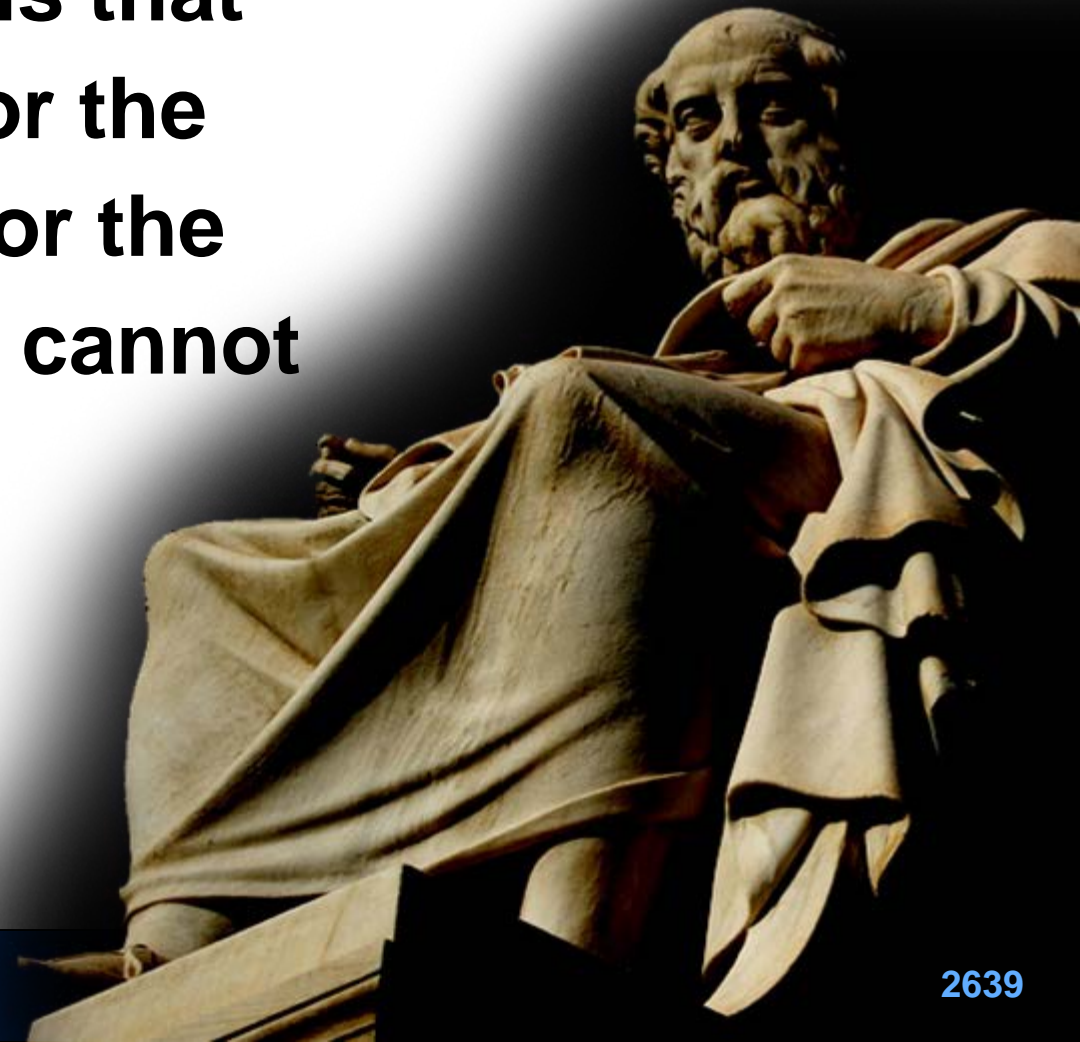
Drossman DA, IFFGD Meeting 2011



“The greatest mistake in the treatment of diseases is that there are physicians for the body and physicians for the soul, although the two cannot be separated.”

Plato

400 BC





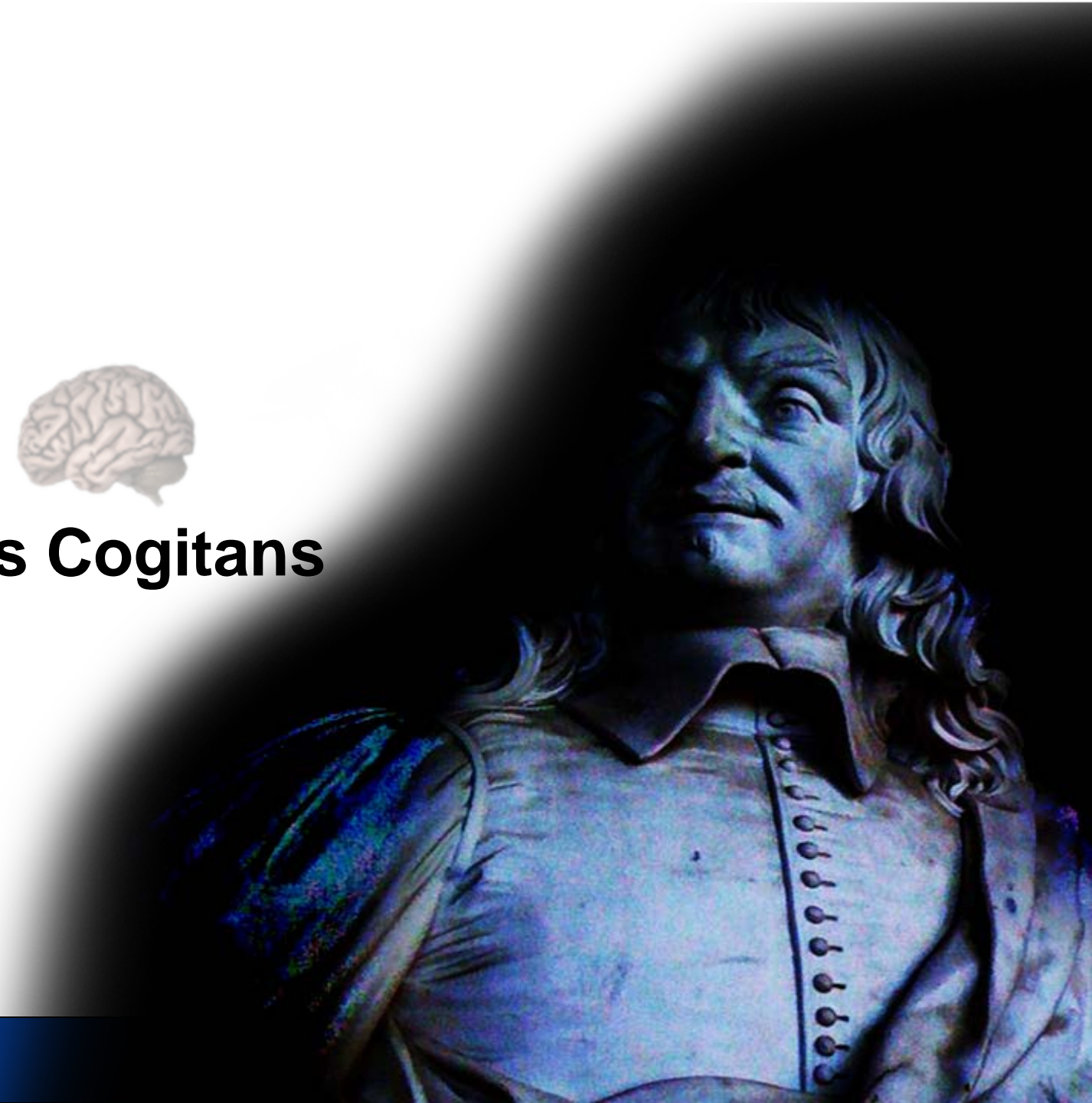
Res Extensa



Res Cogitans

Descartes

1637 CE

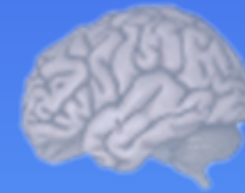
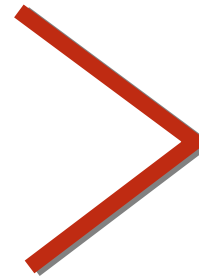




Disease

Verifiable

“Organic”

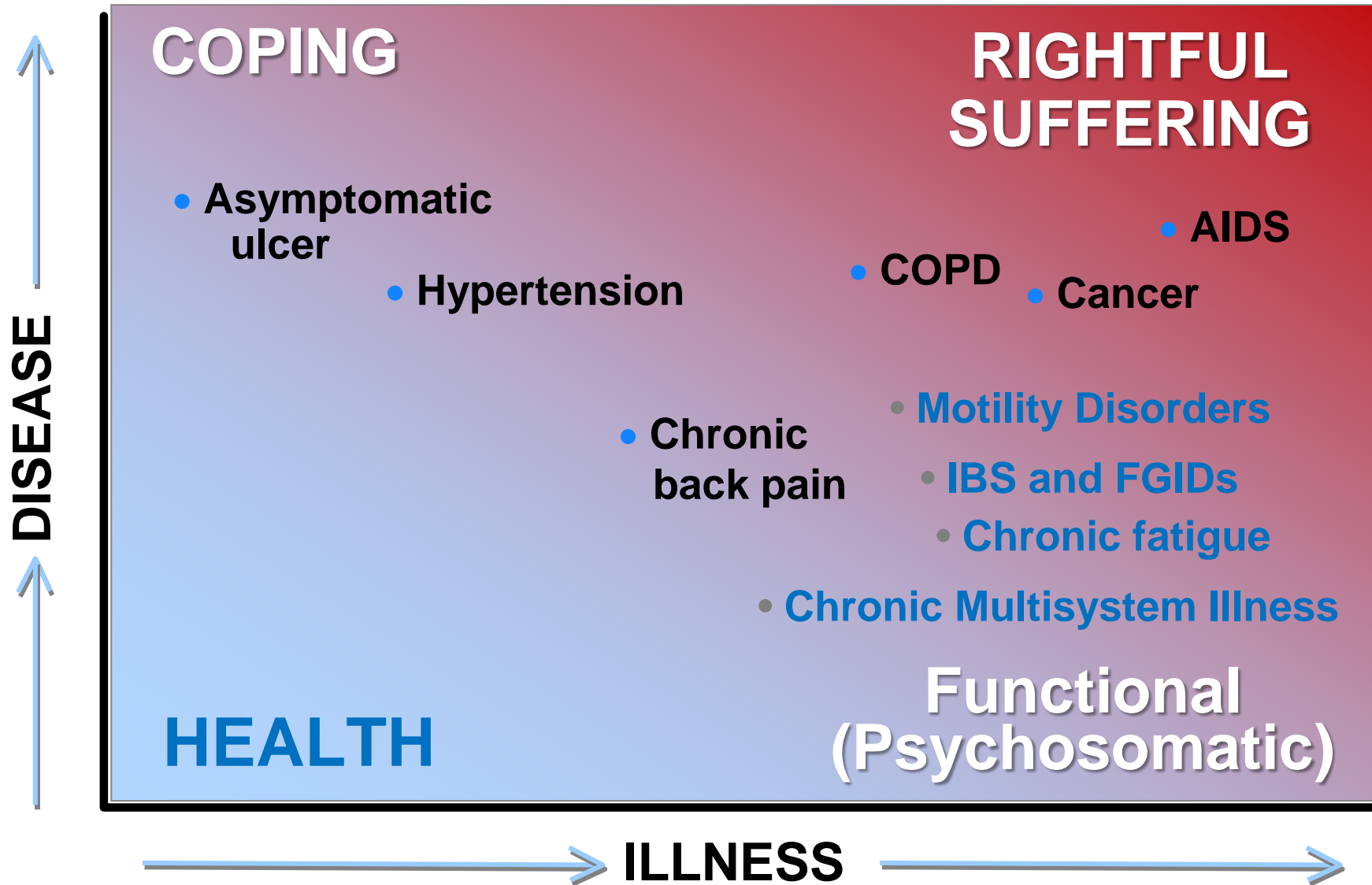


Illness

Perception

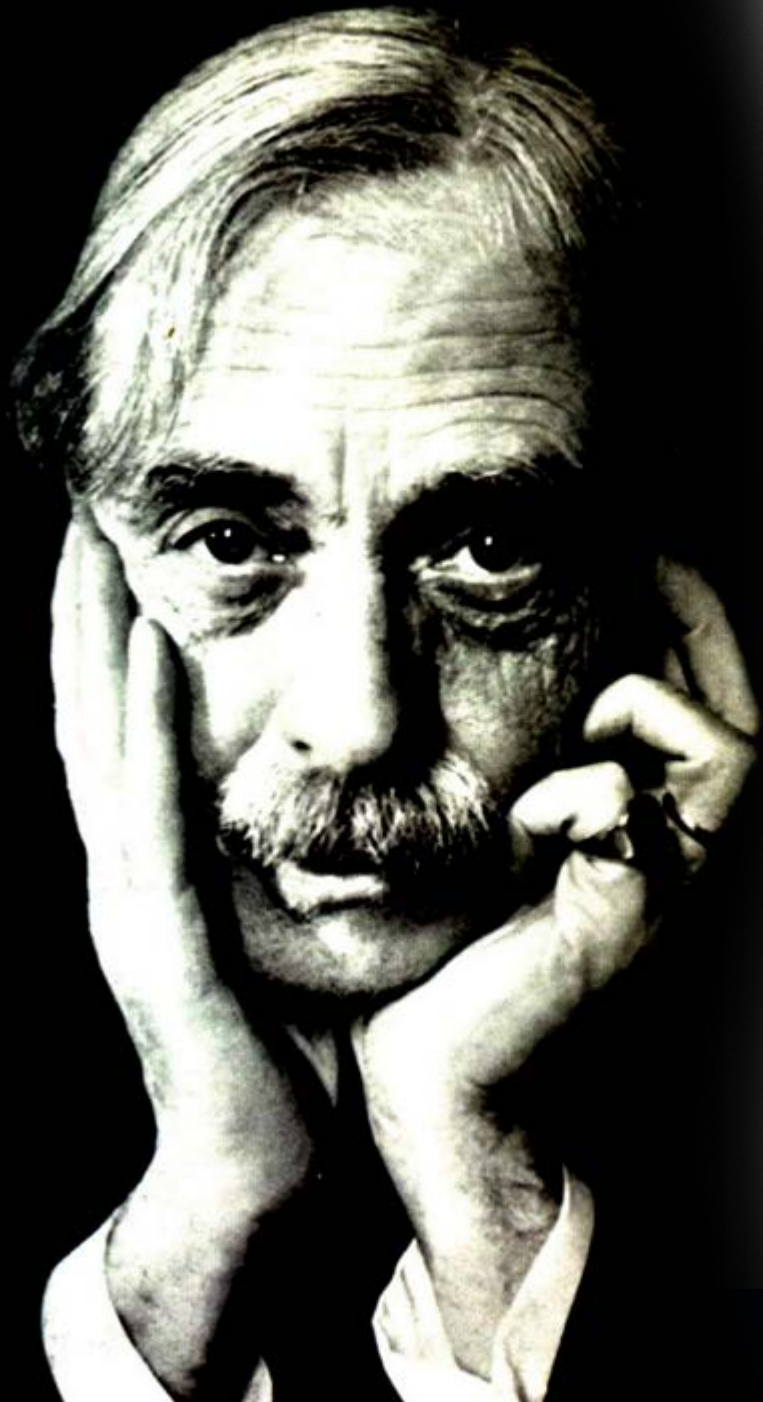
“Functional”

Illness - Disease Continuum and Physician Attitudes





“Well, the old body checks out. Now let’s see what Doc Atkins here makes of the old mind.”



**“To see is to forget
the name of the
thing one sees.”**

Paul Valéry

Stress Is Not Just Psychological

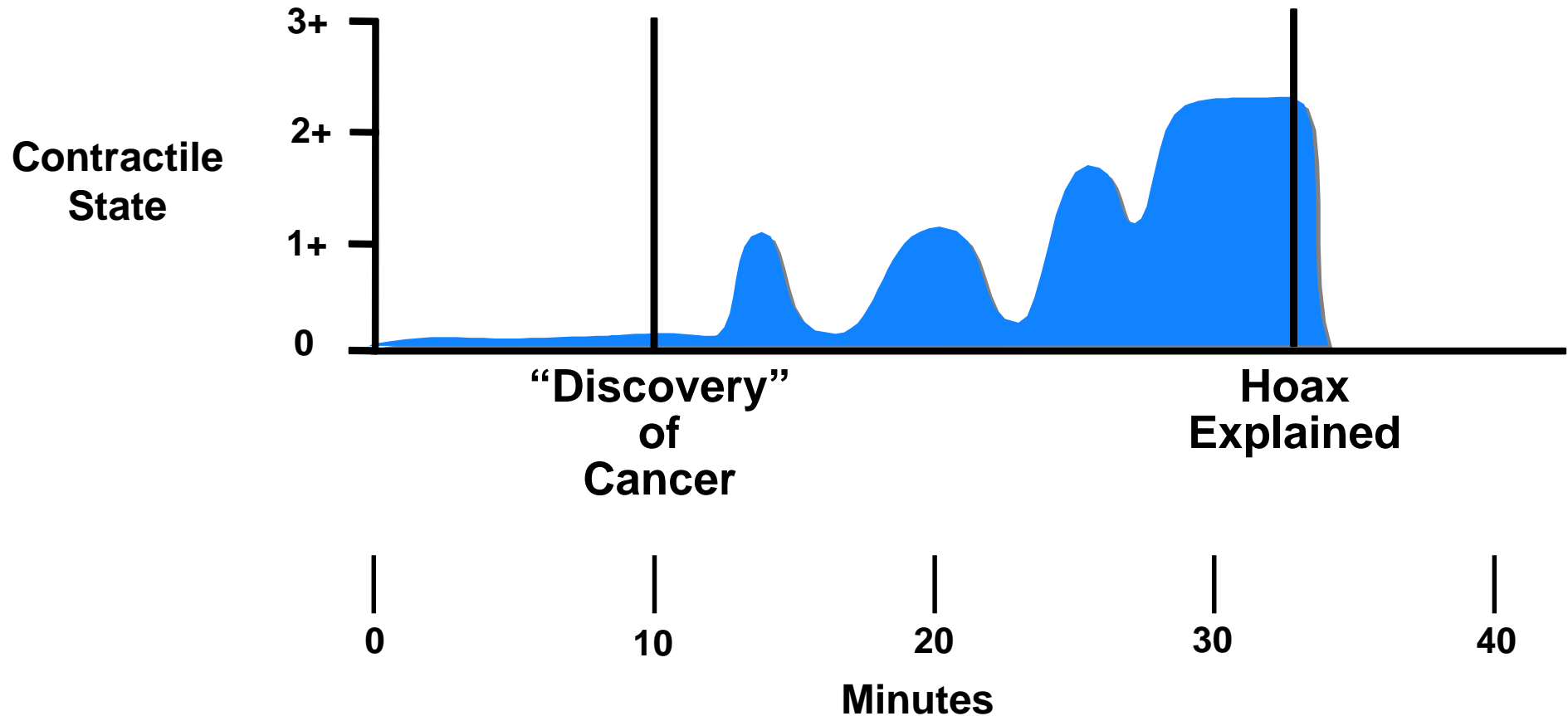
- Any influence that requires adjustment or adaptation to the person's steady state (concept of homeostasis) is stress
- Stress encompasses the *stimulus* (stressor) and the *response*
- The *stimulus* can vary and is non-specific (injury, disease, pain, psychological stress, temperature change, infection, overeating, etc.)
- The *response* may be predictable and consistent (e.g., to pain, threat of injury, major loss), or can vary depending on the unique psychological features of the person (e.g., divorce, change of job)
- The person's interpretation of events as stressful or not and his or her response depend on prior experience, attitudes, coping, culture, personality and biological susceptibility (e.g., to disease)

IBS

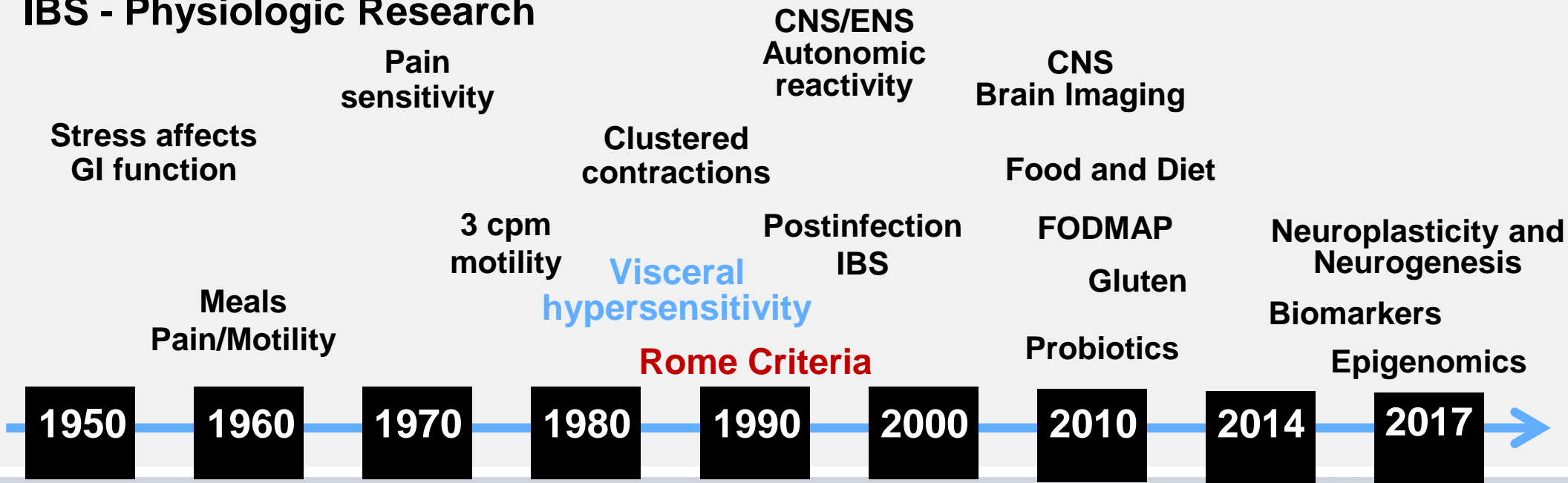
Pathophysiology in

Evolution

Normal Colonic Response to Stress



IBS - Physiologic Research



Mechanisms

Food and Diet

Brain-Gut Interactions

Motility

Myoelectrical Marker

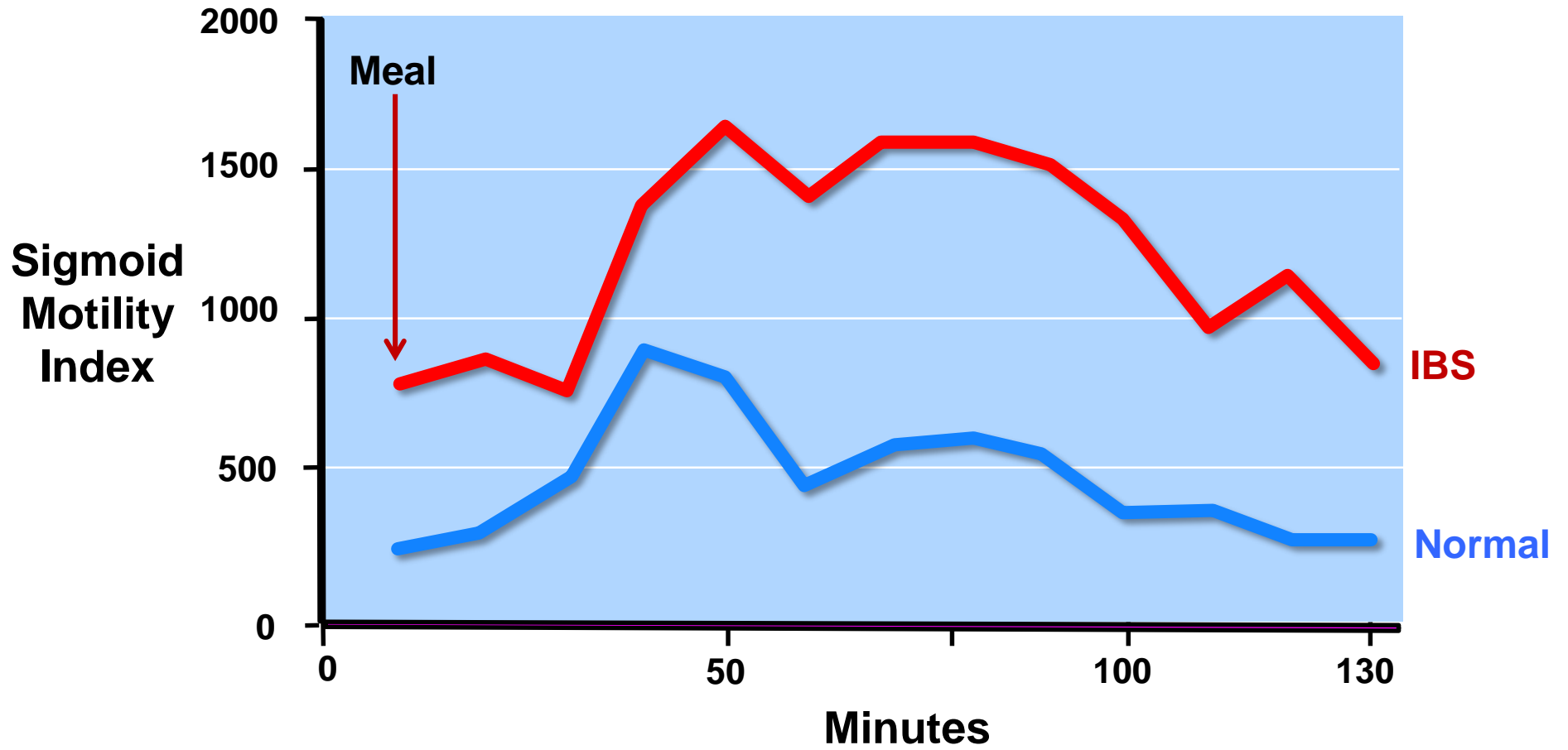
Microflora

Inflammation

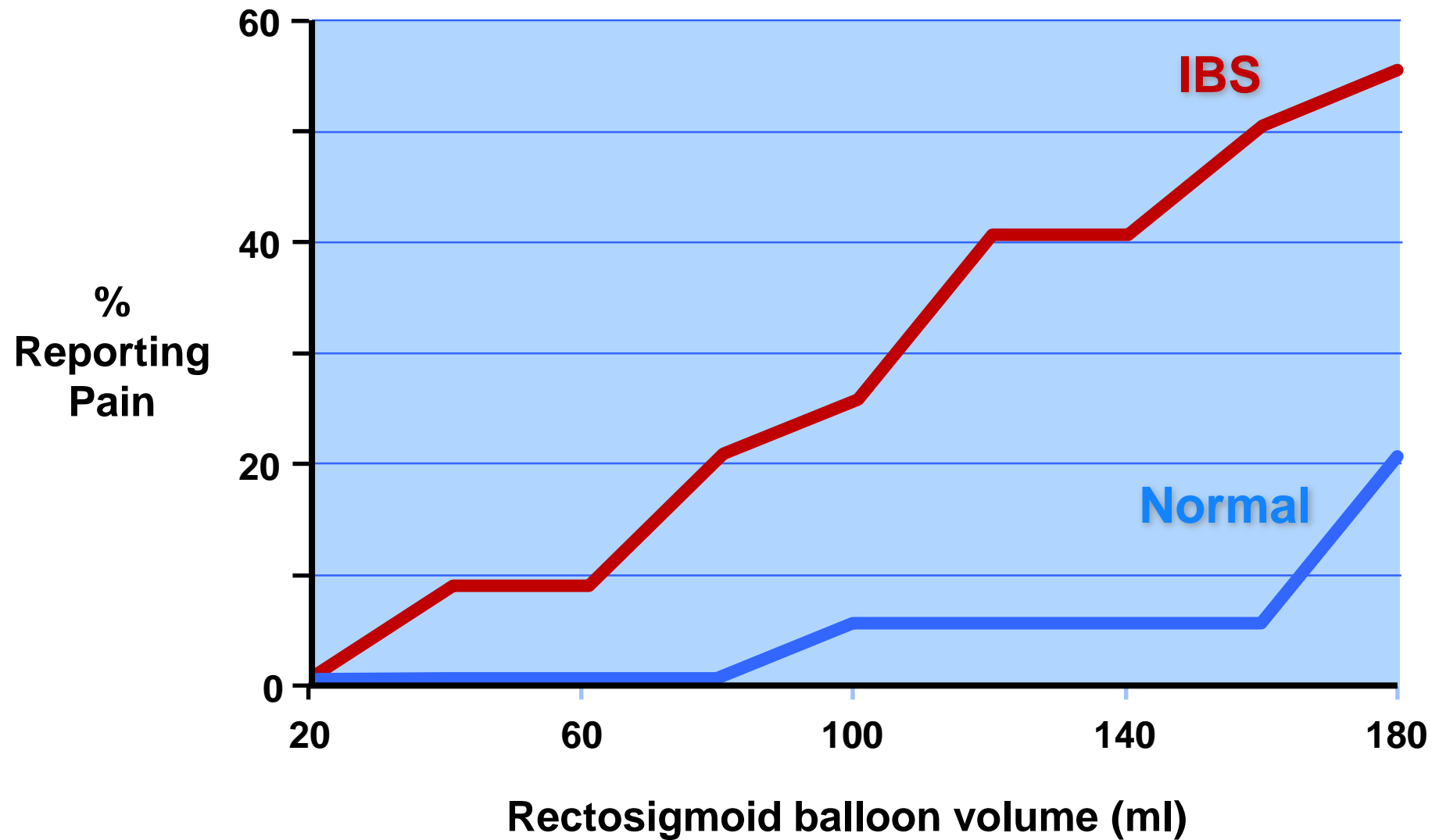
Mucosal Immune Dysfunction

Visceral Hypersensitivity

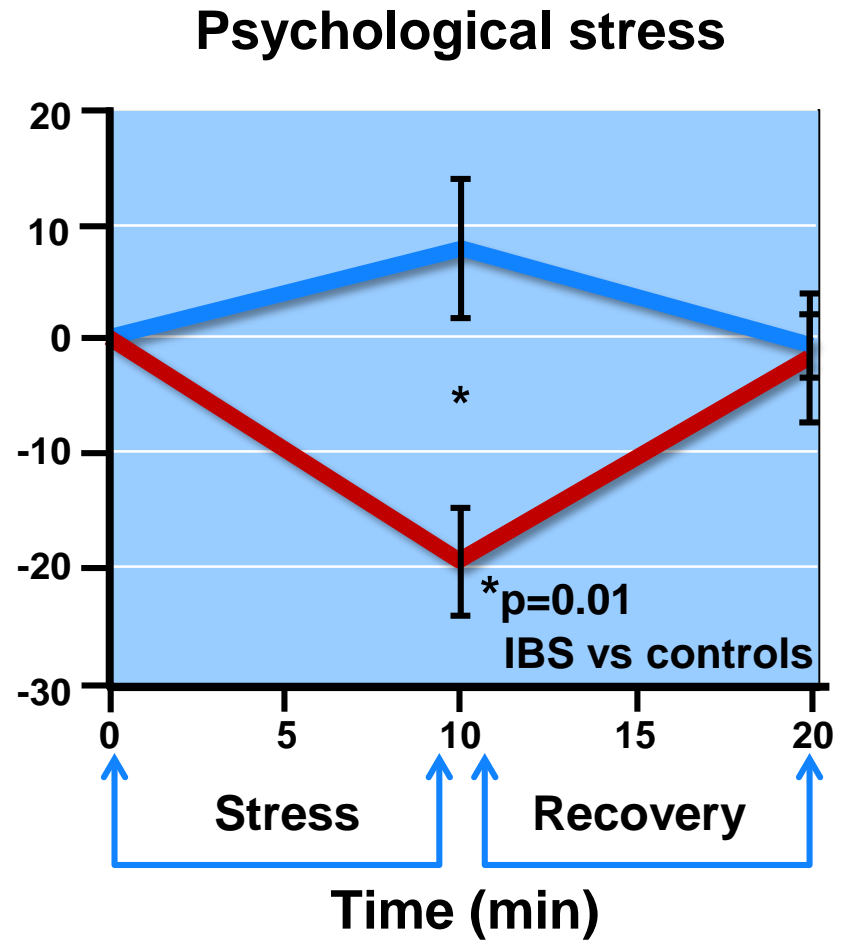
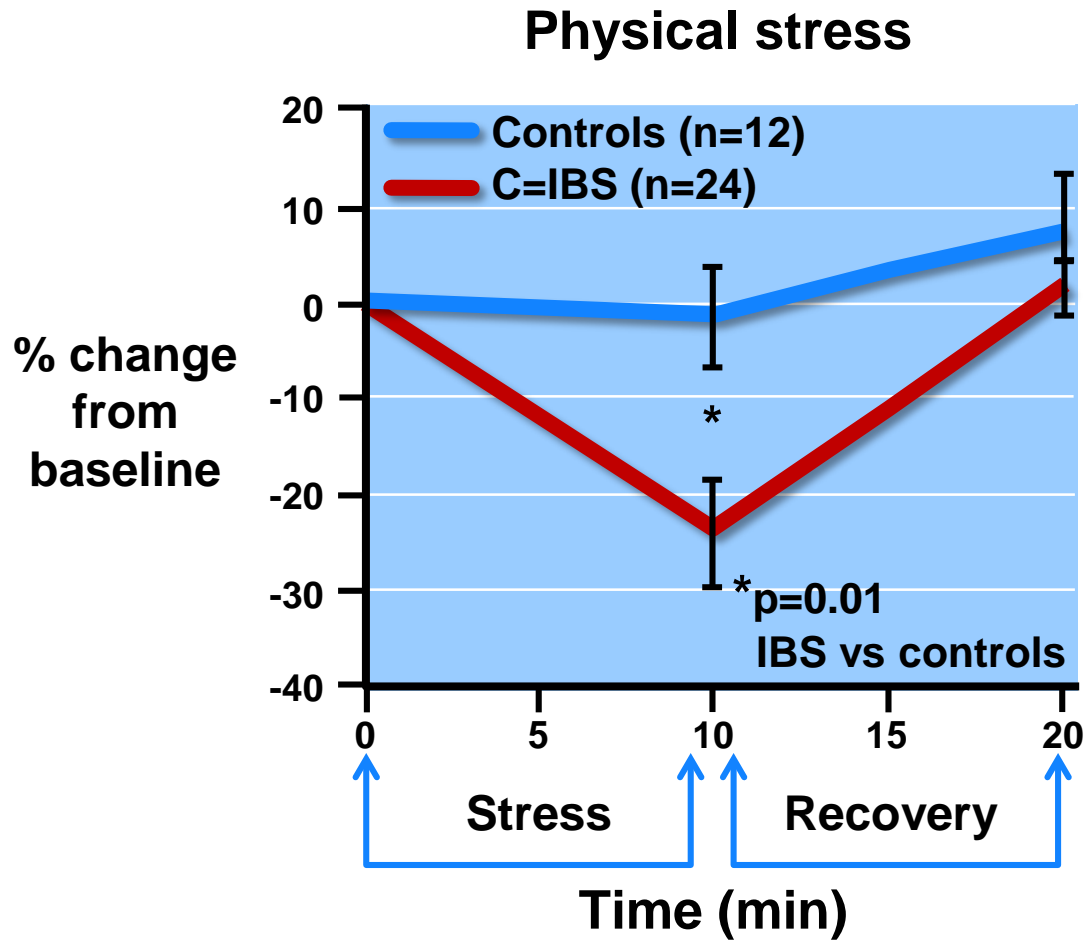
IBS - Physiology



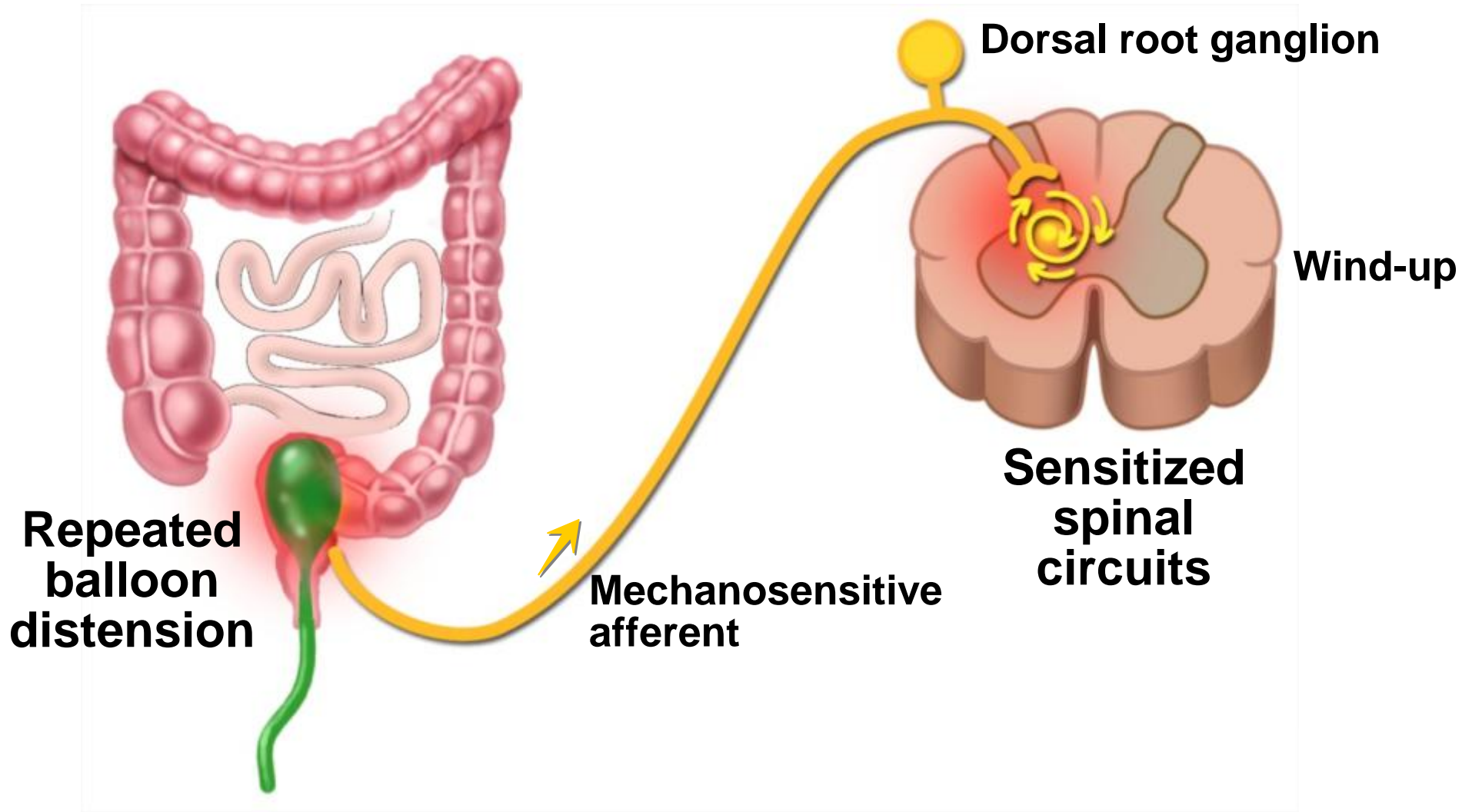
IBS – Visceral Hypersensitivity



Effect of Stress on Rectal Perception Threshold



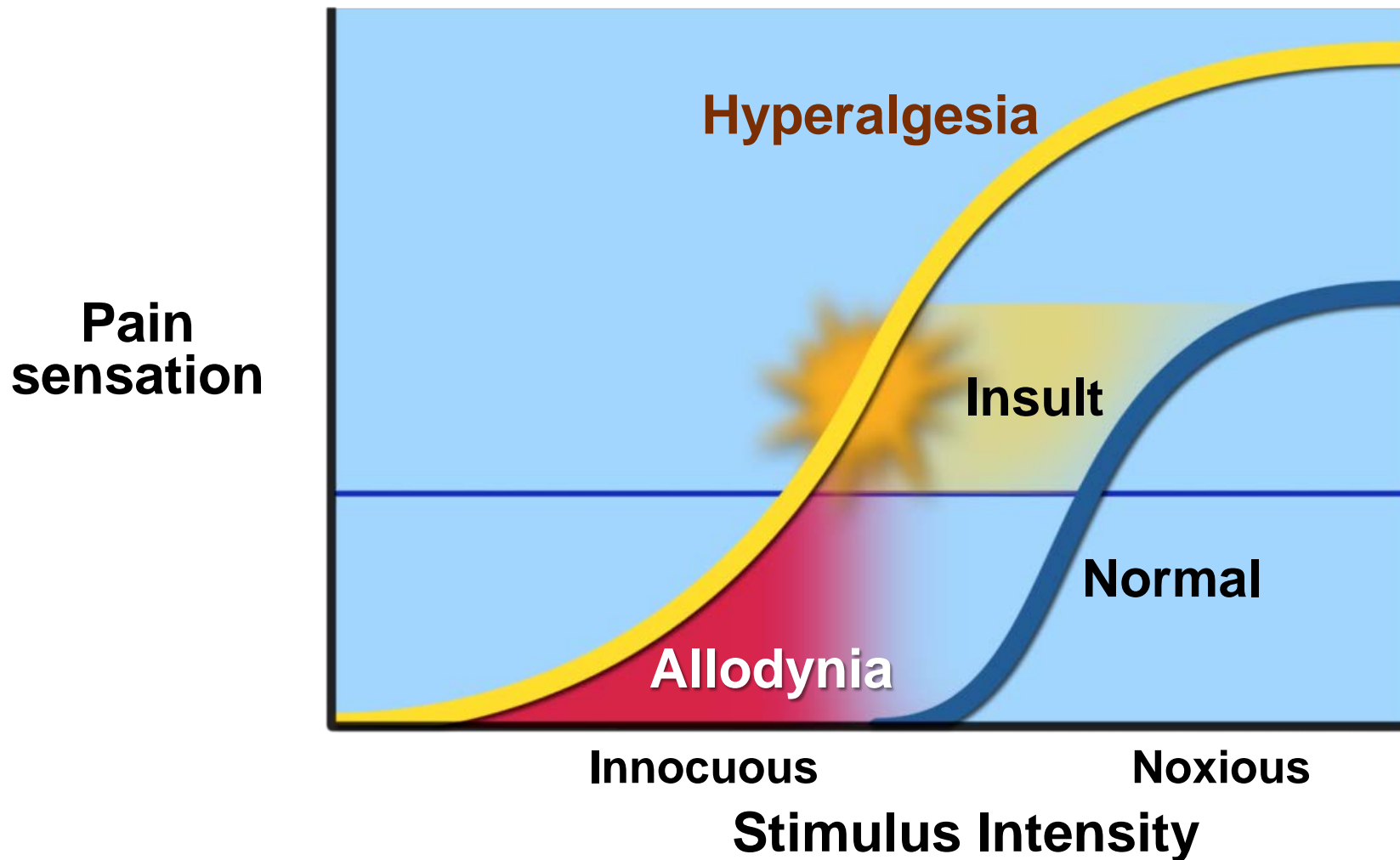
Repetitive Mechanical Stimulation Sensitizes the Spinal Cord



Gut Influences on Visceral Sensitization

- **Bowel inflammation or mucosal disruption**
 - **Bowel infection**
 - **Inflammatory bowel disease**
 - **Increased bowel permeability**
 - **Altered bacterial composition in gut**
- **Trauma to intestines**
 - **Operations**
 - **Colonoscopy**

Hyperalgesia and Allodynia



FODMAPs



Excess Fructose

Honey, apples, pears, peaches, mangos, fruit juice, dried fruit



Fructans

Wheat (large amounts), rye (large amounts), onions, leeks, zucchini



Sorbitol

Apricots, peaches, artificial sweeteners, artificially sweetened gums



Raffinose

Lentils, cabbage, brussels sprouts, asparagus, green beans, legumes

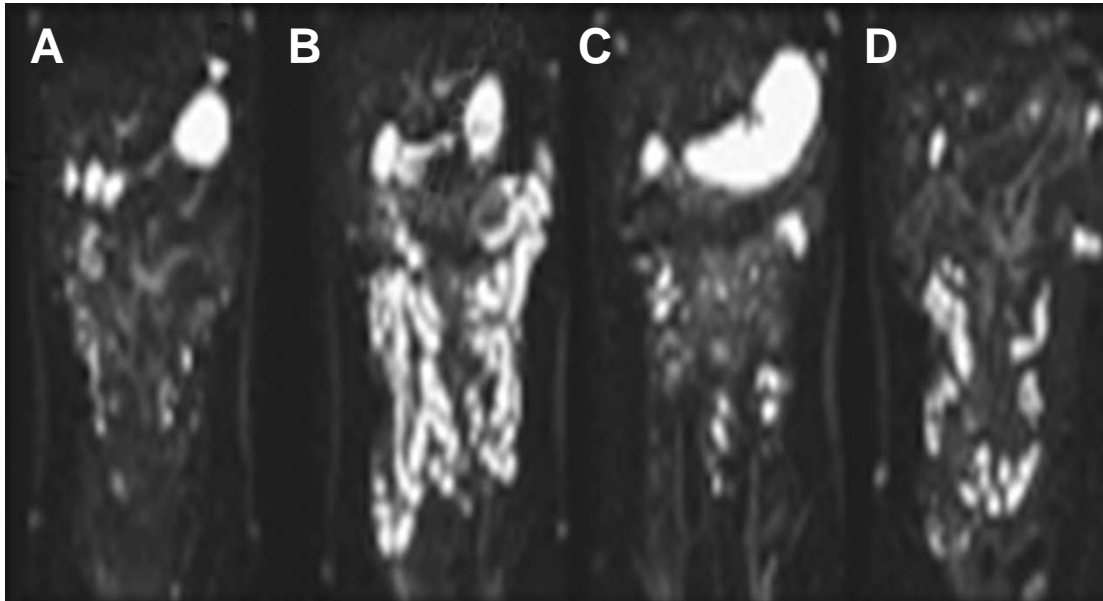
FODMAPs = Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols

¹ Somers SC, Lembo A. *Gastroenterol Clin North Am.* 2003; 32:507

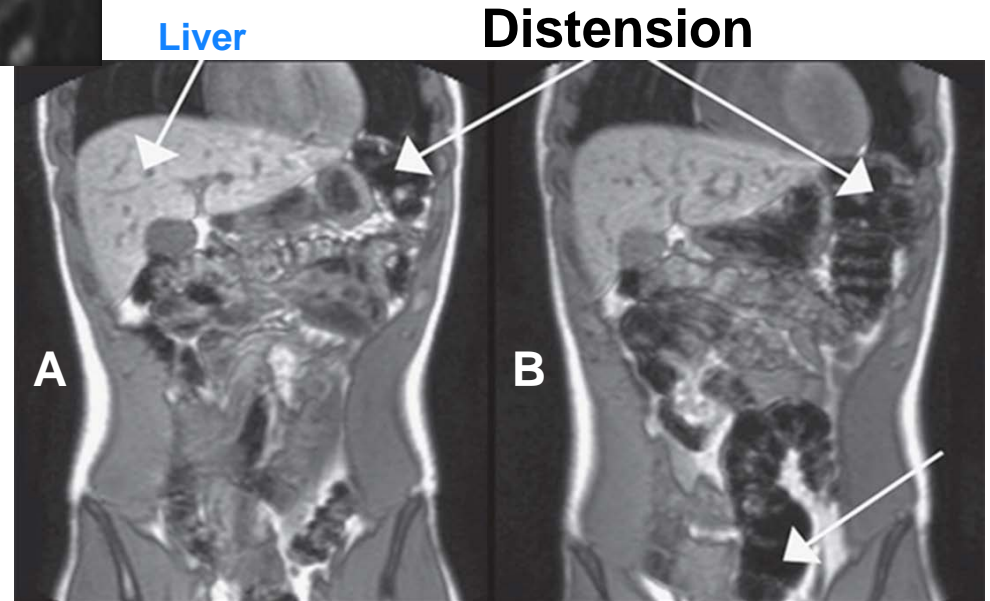
² Shepherd SJ, et al. *Clin Gastroenterol Hepatol.* 2008; 6:765

³ Shepherd SJ, Gibson PR. *J Am Diet Assoc.* 2006; 106:1631

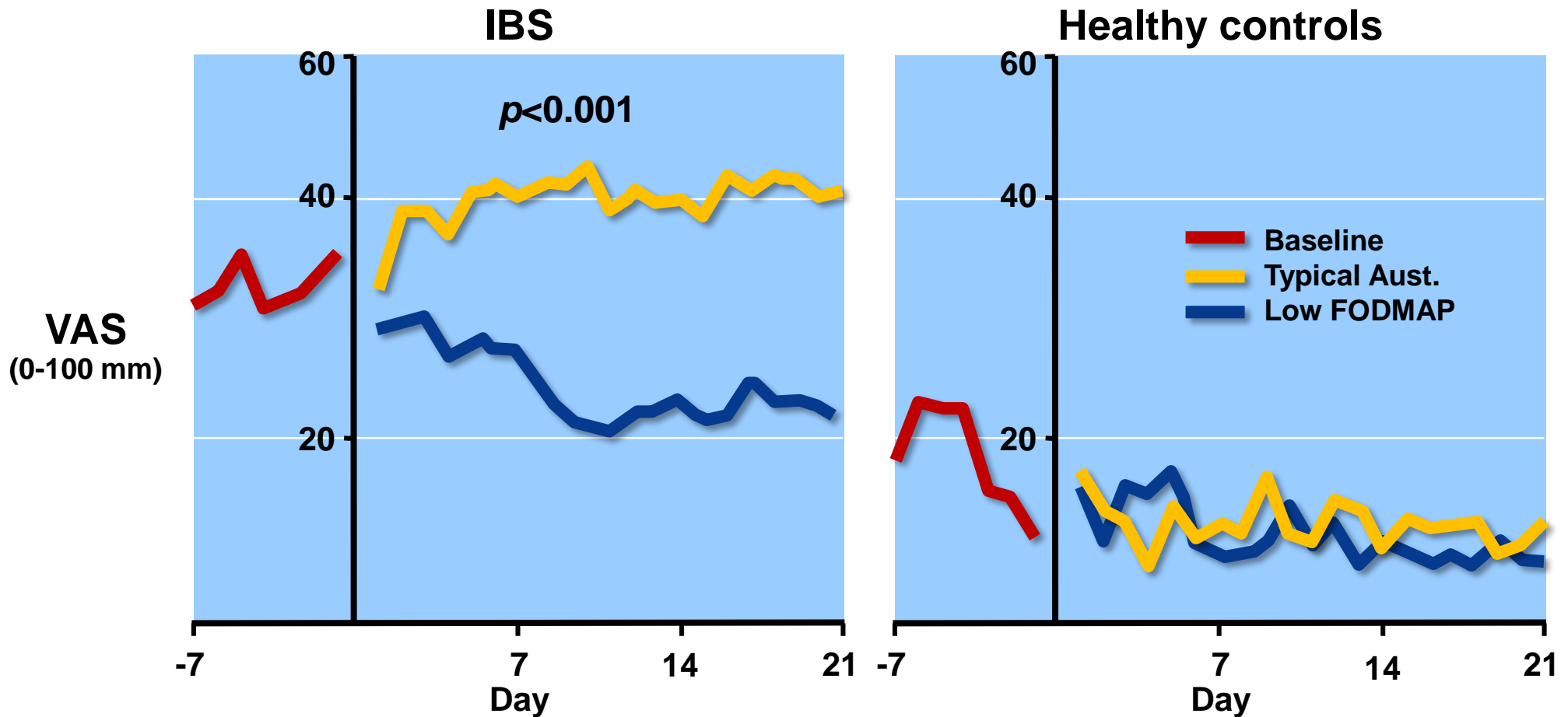
Differential Effects of Gas Production with FODMAPs



Different test meals

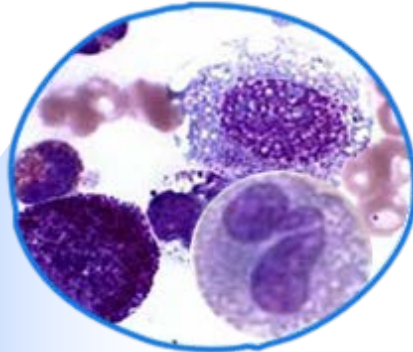
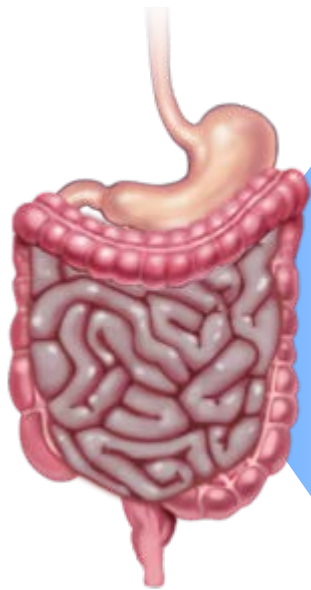


A Low-FODMAP Diet Reduces Symptoms in IBS



30 IBS patients and 8 HVs: 1 week baseline followed by 21 days of low-FODMAP diet or typical Australian diet before crossing over to other diet. Significant benefits for overall IBS symptoms, bloating, pain, and wind ($p < 0.001$). Benefits for King's Stool Chart only for IBS-D ($p < 0.04$)

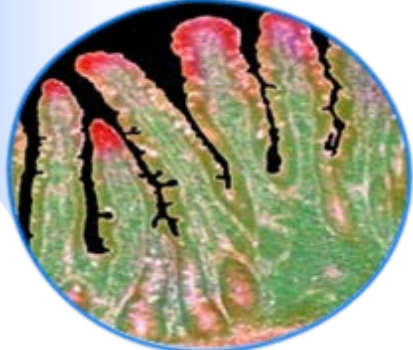
Interrelated Enteric Factors Associated with Visceral Sensitization and FGIDs



Inflammation/immune reactivity
Cytokines
Lymphocytes
Mast cells

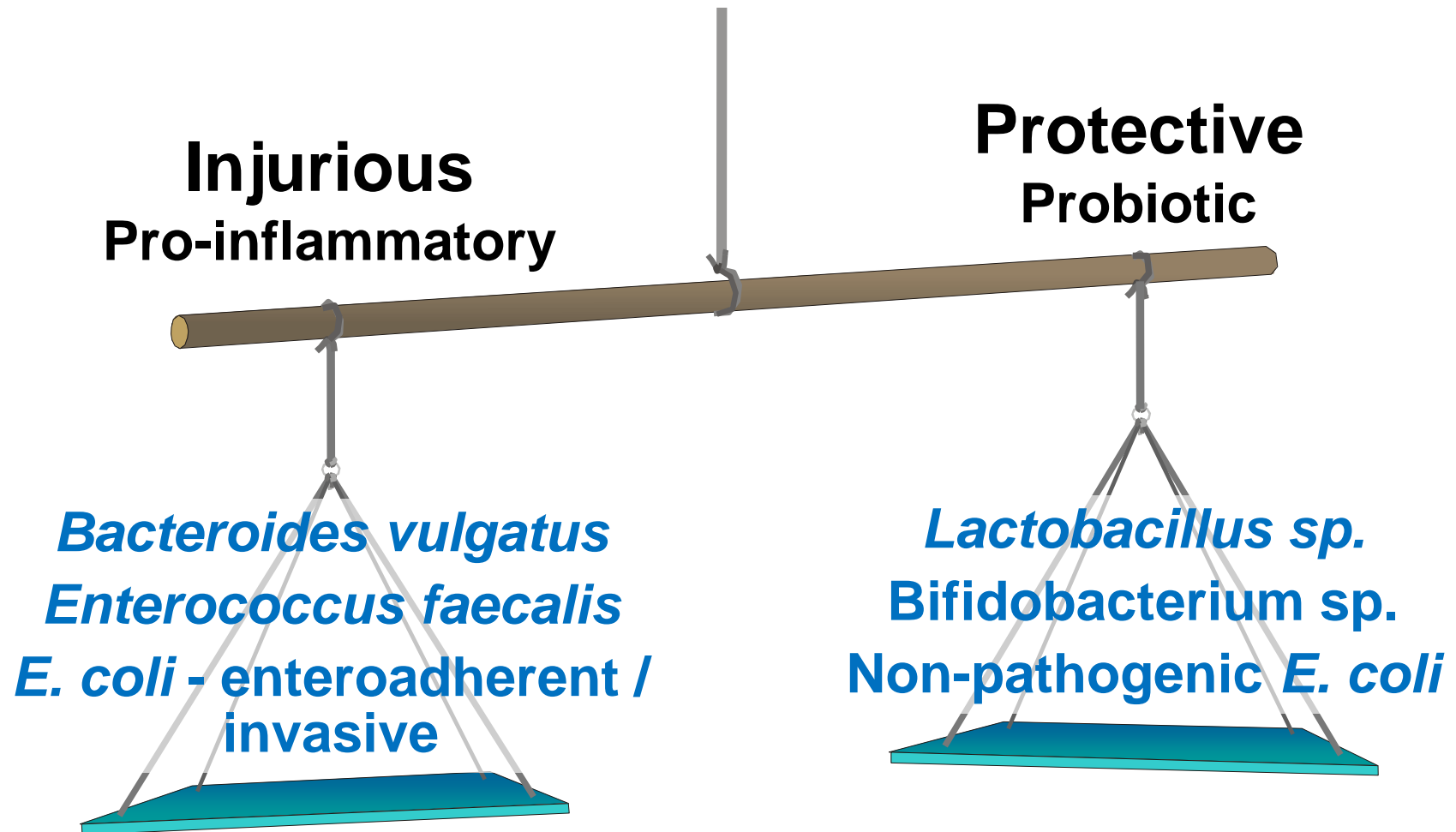


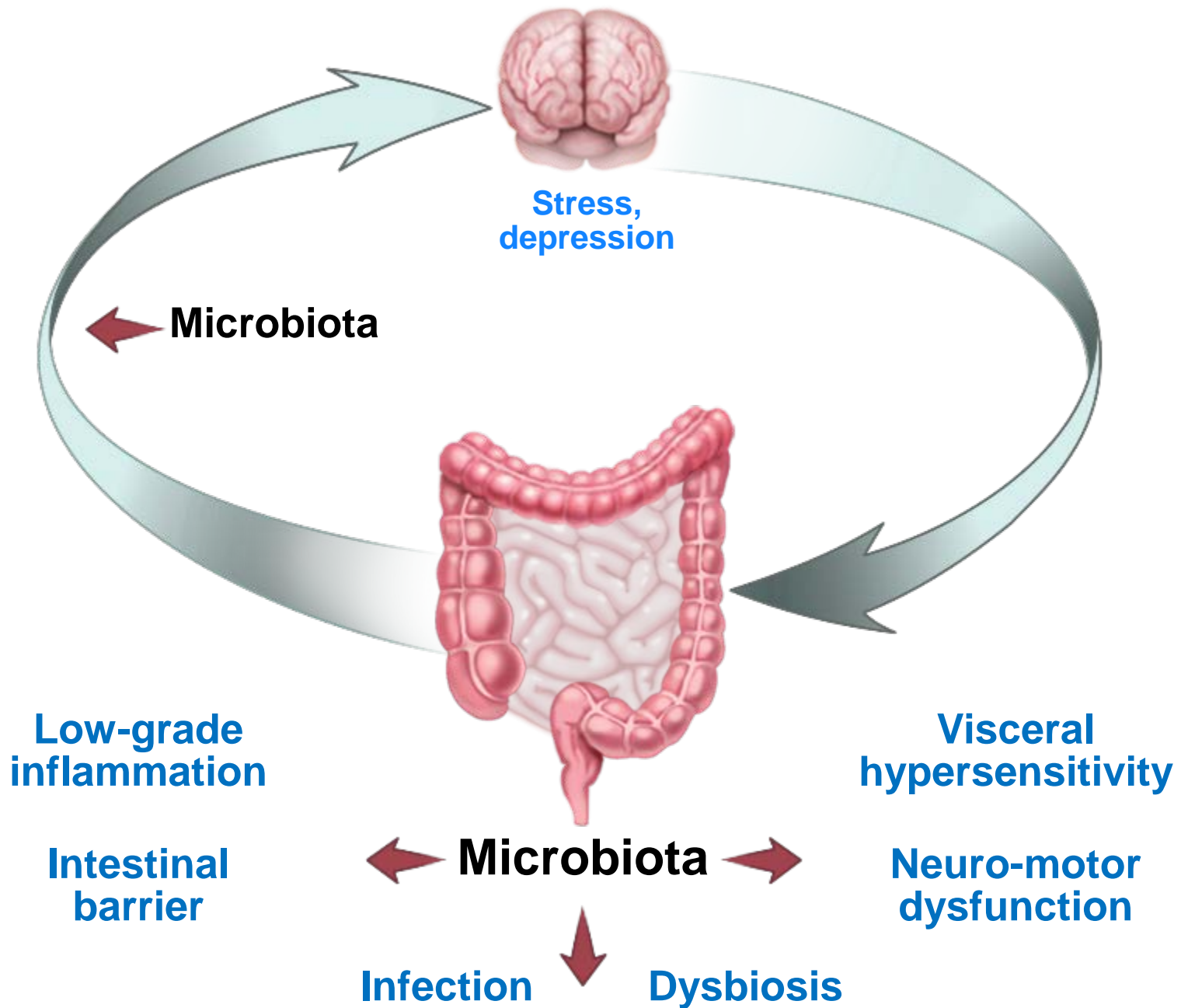
Gut flora
Altered microbiome



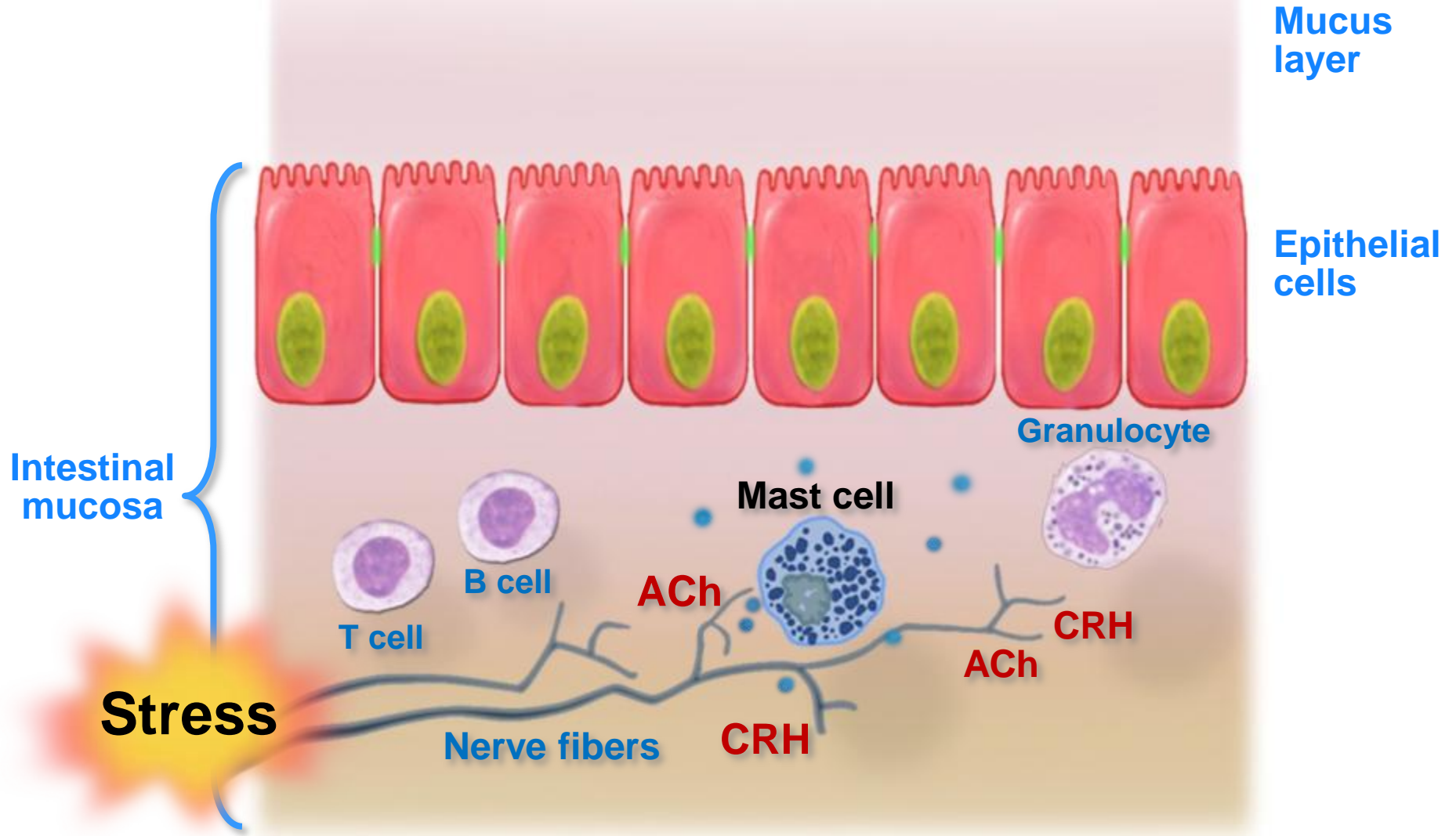
Increased Intestinal
Permeability

Luminal Microbial Environment

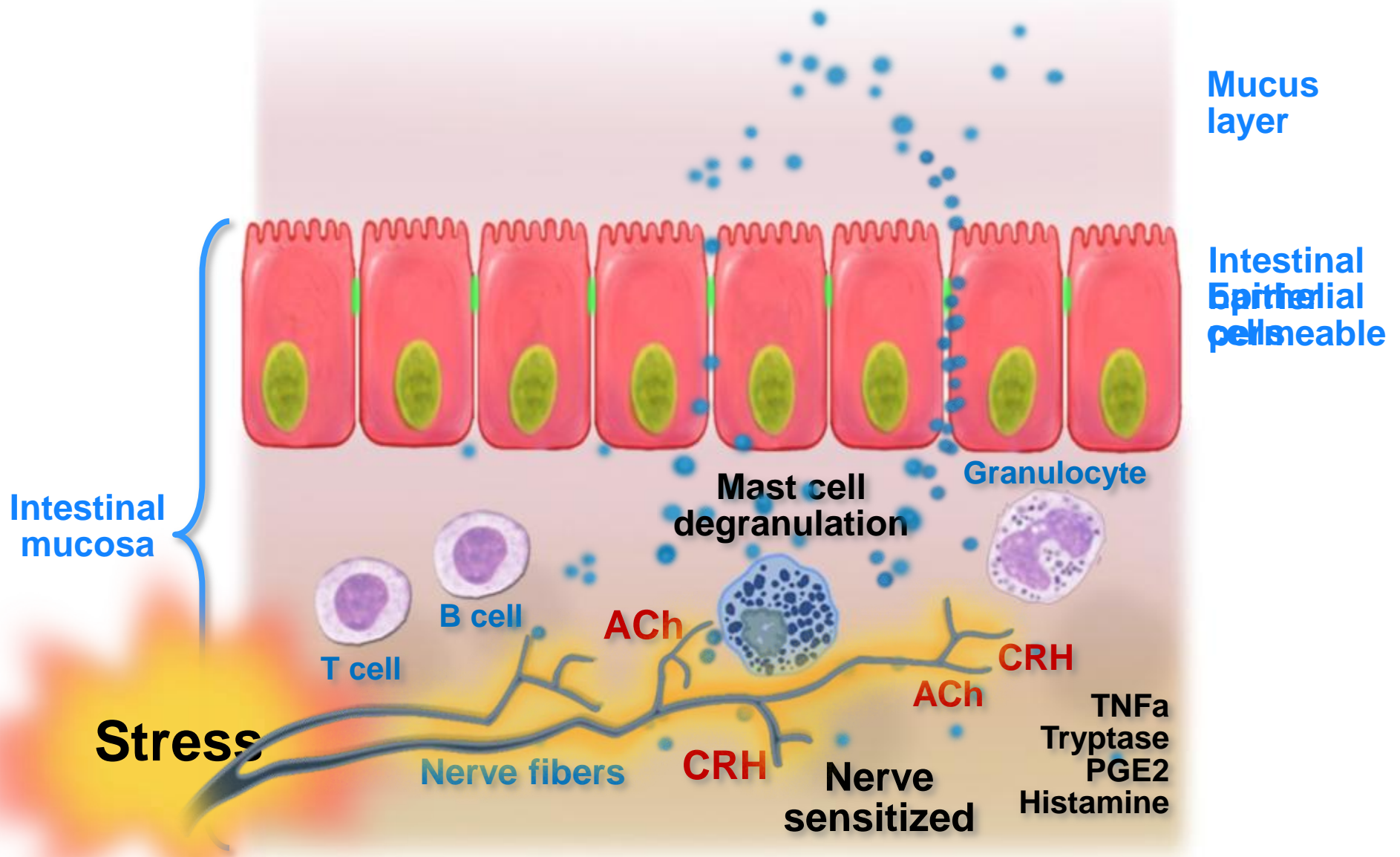




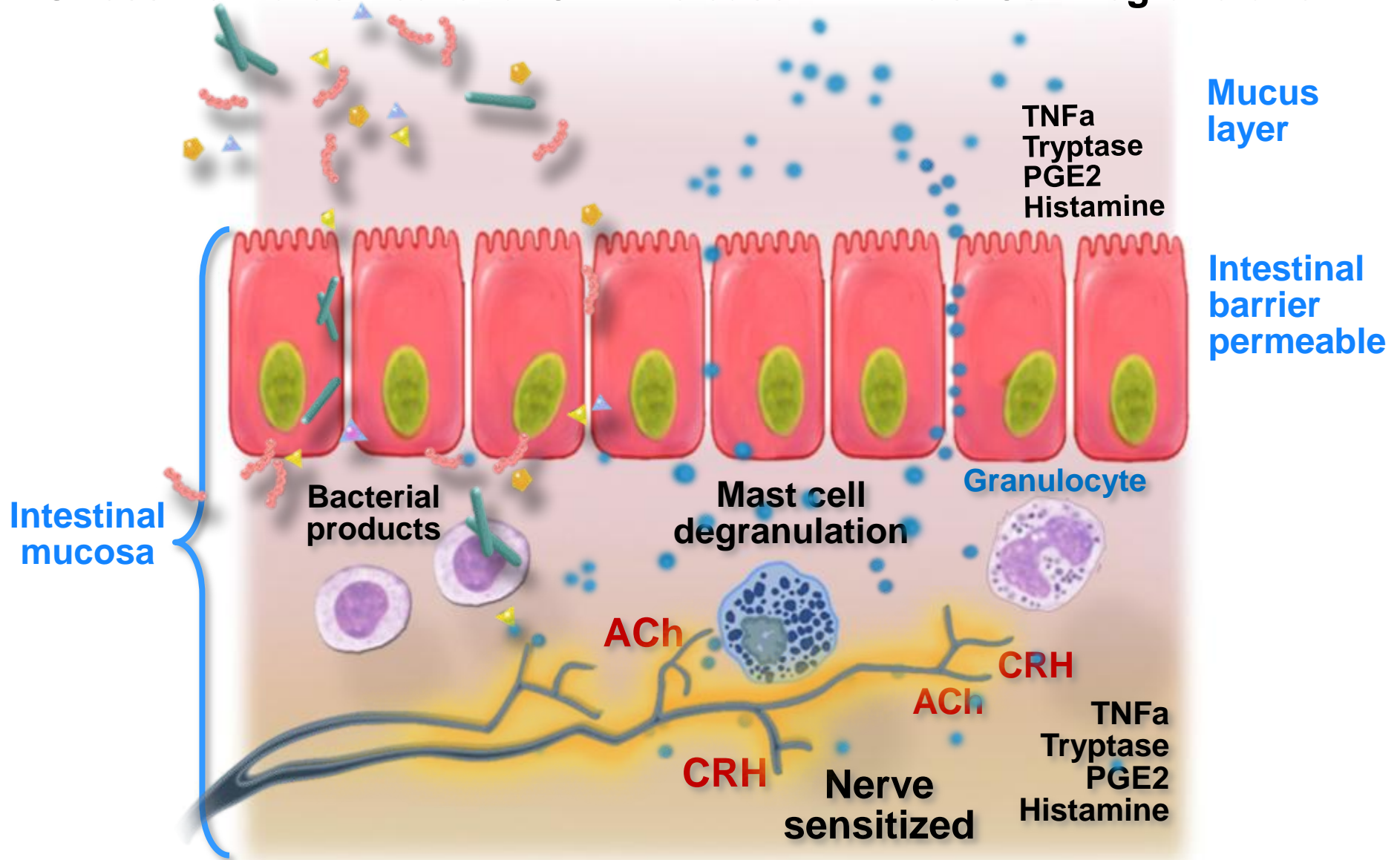
Stress Activates Neuronal CRH Release with Mast Cell Degranulation



Stress Activates Neuronal CRH Release with Mast Cell Degranulation



Stress Activates Neuronal CRH Release with Mast Cell Degranulation

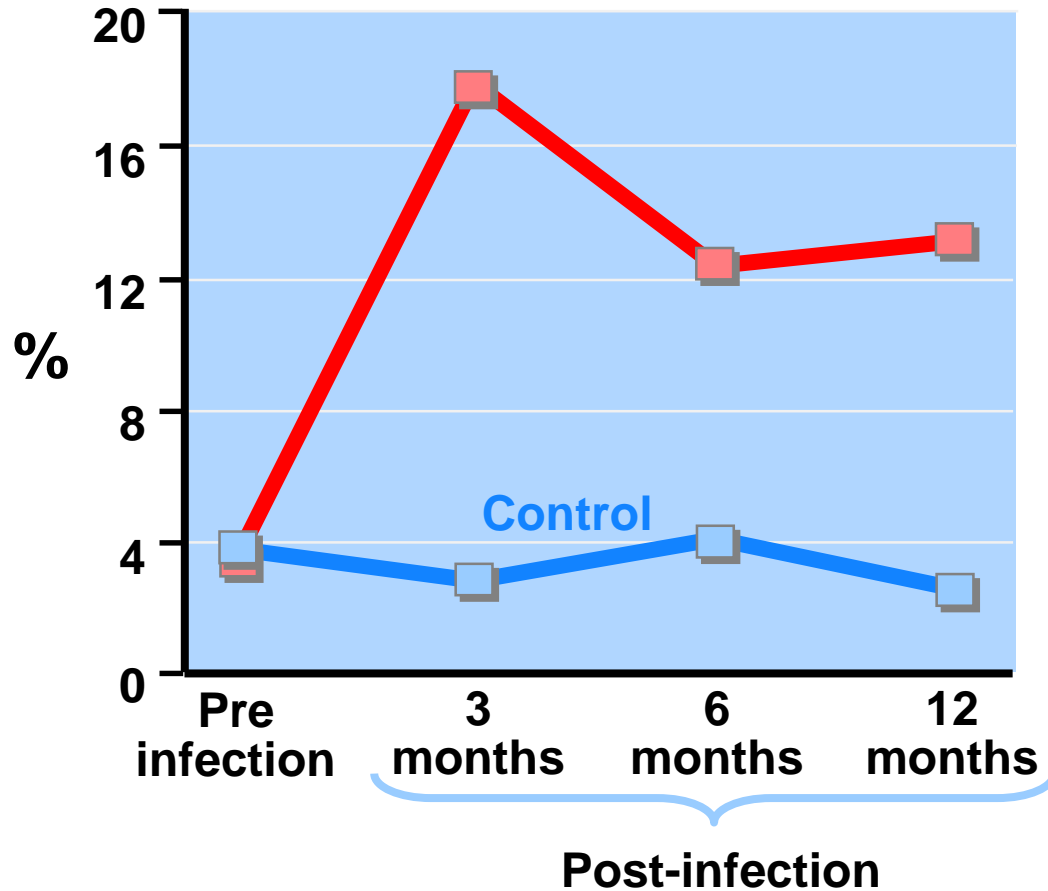


Post Infection IBS

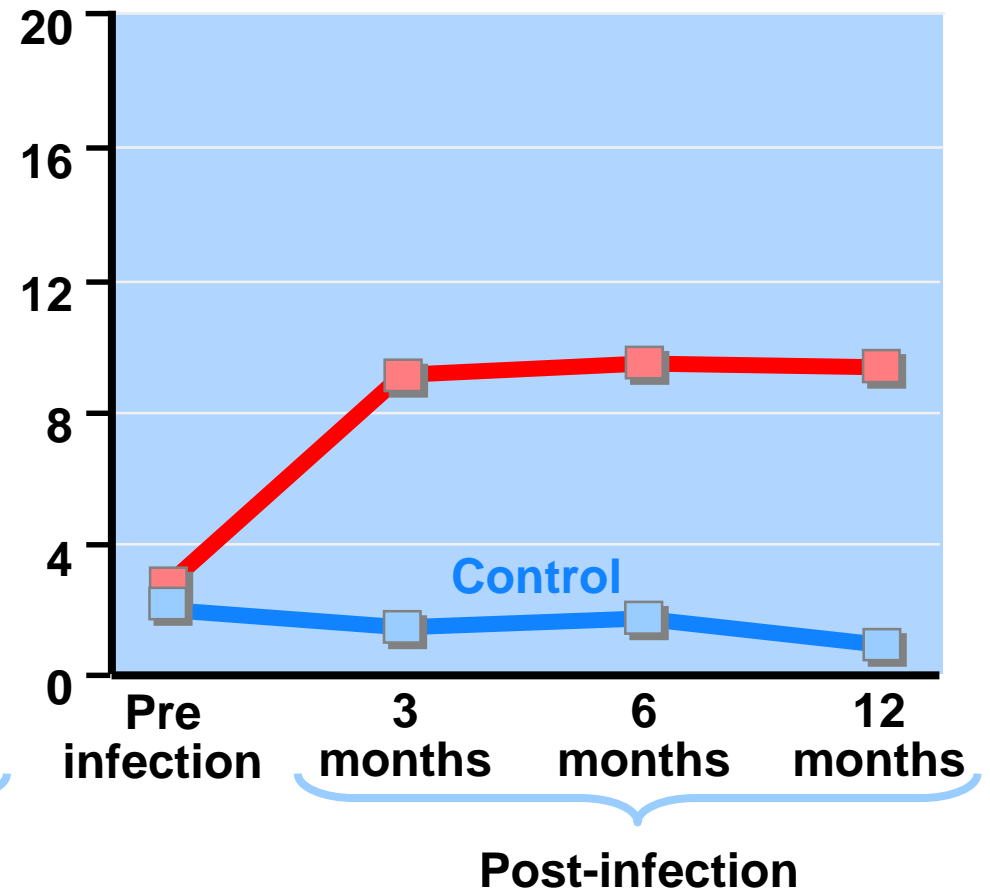
- **About 25% of patients who meet criteria for IBS**
 - **Initiated by an infection**
 - **Increased mucosal immune dysfunction (T-lymphocytes, enterochromaffin cells)**
 - **Altered microbial flora**
 - **Normal colonoscopic appearance**
 - **Increased psychosocial distress at time of infection**

Prevalence of Dyspepsia and IBS Post-Infection

Dyspepsia



IBS



Committee on Gulf War and Health

Health Effects of Serving in Gulf War, Update 2009-10

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES



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Jennifer D. Peck
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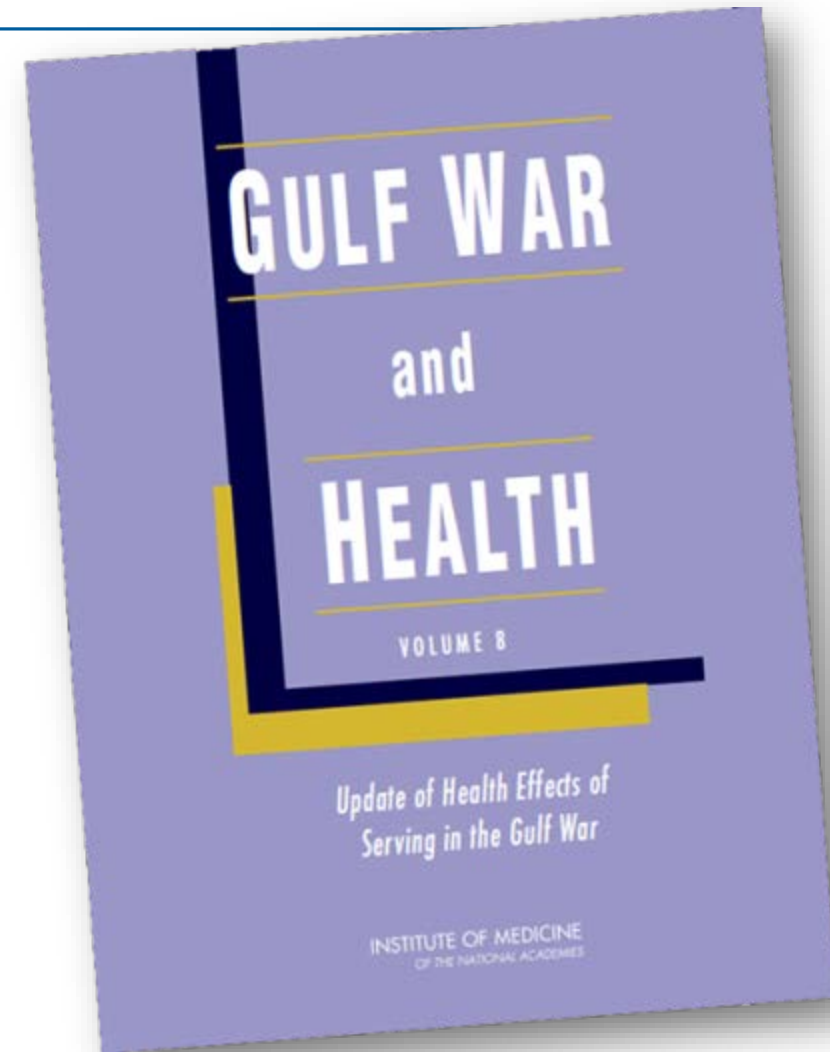
Francine Laden
Brigham & Women's Hospital

Ezra S. Susser
Columbia University

Christina M Wolfson
McGill Univeristy

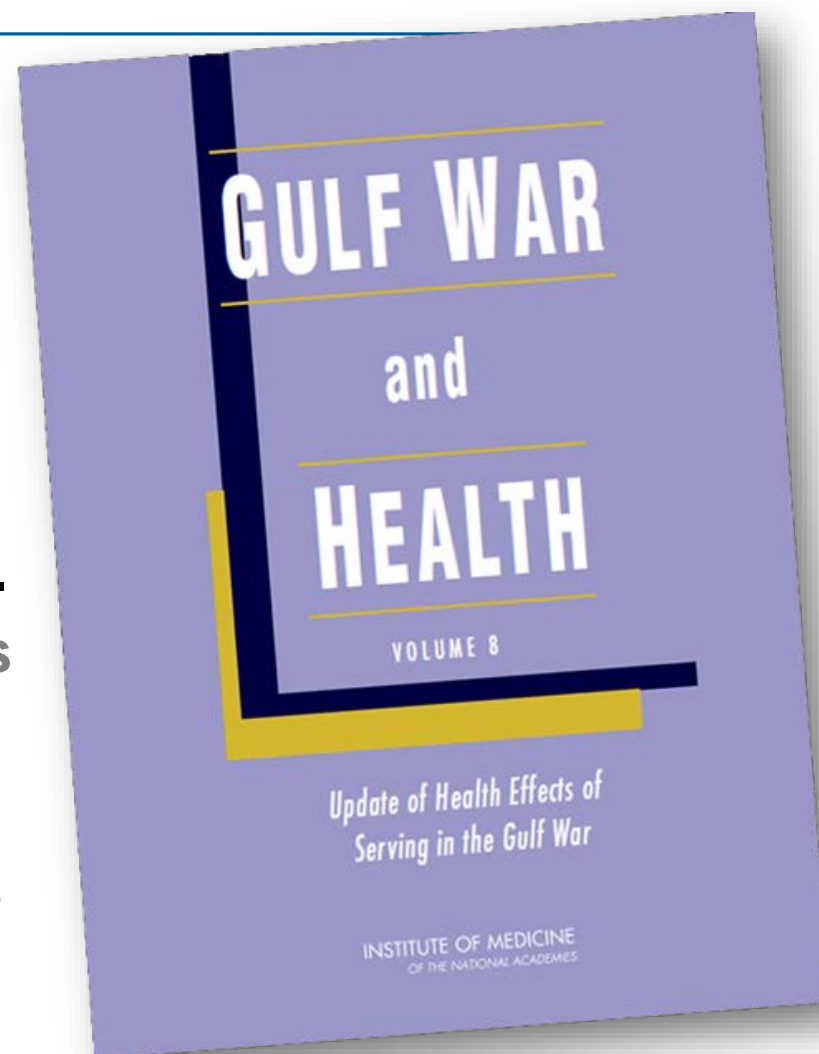
Health Effects of Serving in Gulf War Vol. 8

- **Causal Relationship**
 - PTSD
- **Sufficient Evidence for an Association**
 - Other Psychiatric – Anxiety, Depression, Substance/alcohol abuse
 - **GI symptoms consistent with FGIDs**
 - Multisymptom Illness
 - Chronic fatigue Syndrome
- **Limited/Suggestive Evidence for an Association**
 - ALS
 - Fibromyalgia and Chronic Widespread Pain
 - Sexual difficulties
 - Mortality from external causes (e.g., MVA)



Health Effects of Serving in Gulf War Vol. 8

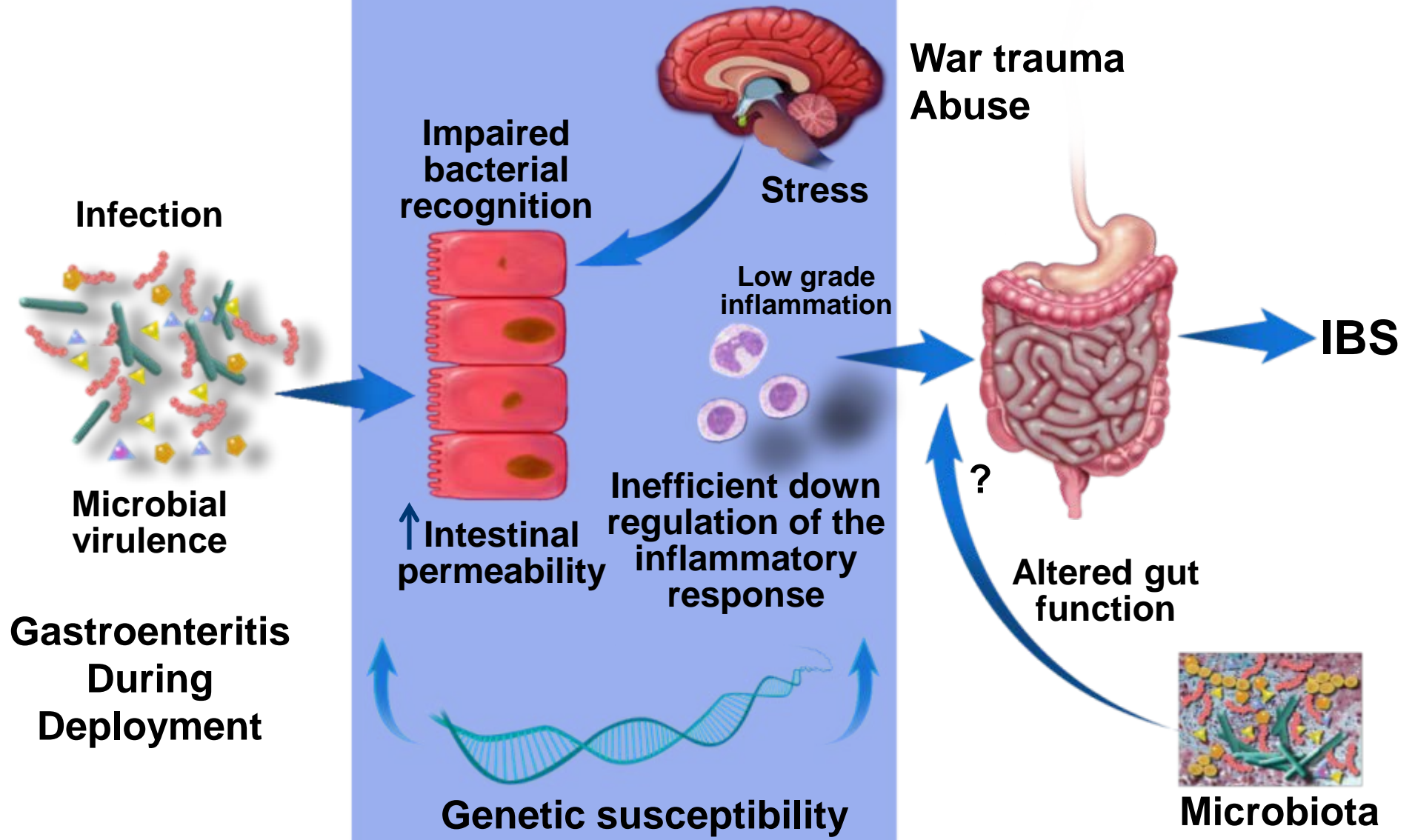
The committee concludes that there is sufficient evidence for an association between deployment to the Gulf War and gastrointestinal symptoms consistent with functional GI disorders such as irritable bowel syndrome and functional dyspepsia. The committee also concludes that there is inadequate/insufficient evidence to determine whether an association exists between deployment to a war zone and the development of structural gastrointestinal diseases.



Summary – GI Health Effects for Serving in War

- Incidence of acquiring an acute gastroenteritis during deployment is >50%
- Deployed vets experiencing war trauma who are exposed to a gastroenteritis are at greater risk to later develop IBS
- Deployed vets with IBS symptoms have increased microscopic inflammatory changes in the bowel mucosa
- Microscopic inflammation in IBS is associated with increased cytokine activity → visceral sensitivity and abdominal pain
- Postinfectious IBS symptoms are facilitated by psychological distress via CNS (HPA axis), effects on mucosal inflammation and enhanced pain via anterior cingulate cortex activation

Conceptual Model – Postinfectious IBS



Pain Is a Modifiable Experience

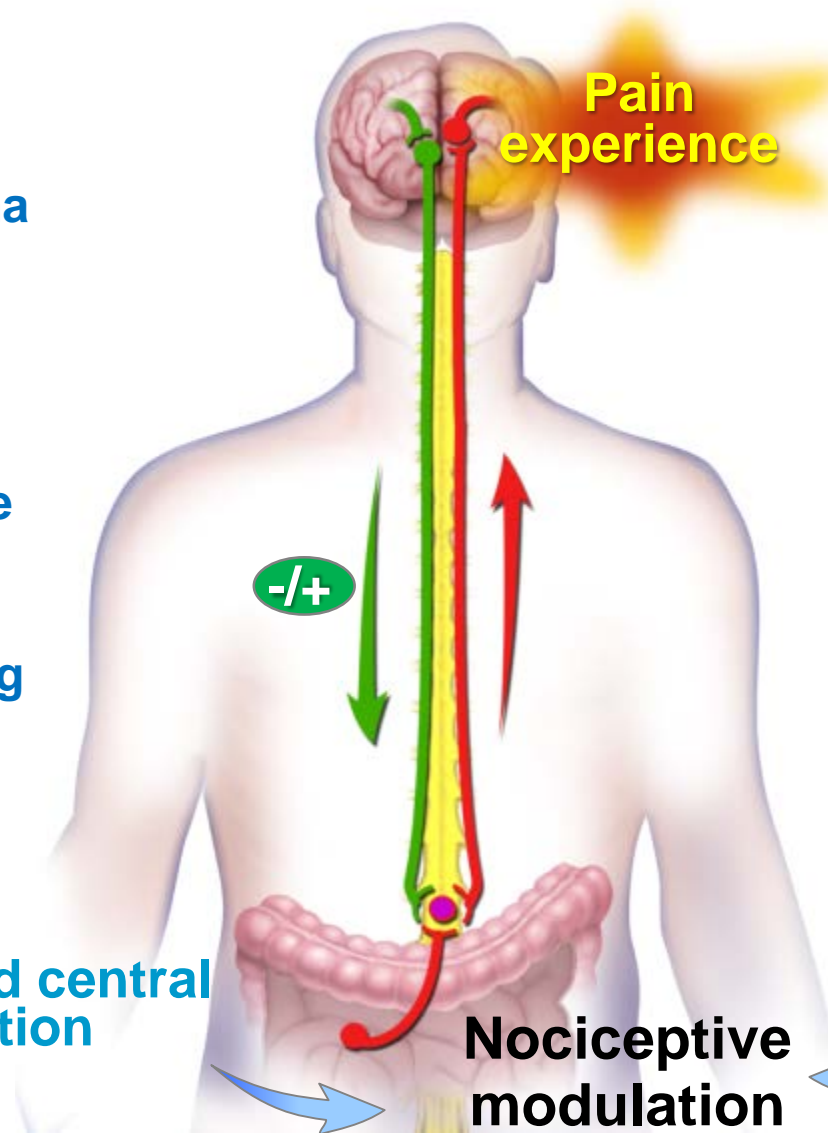
Psychosocial context

- Pain beliefs
- Cultural schema
- Expectation
- Conditioning

Cognitions

- Hypervigilance
 - Attention
 - Distraction
- Catastrophizing

Peripheral and central sensitization



Pain experience

Chemical/Structural

- Neurodegeneration
- Metabolic (opioidergic, dopaminergic)
- Maladaptive plasticity

Mood

- Depression
- Anxiety

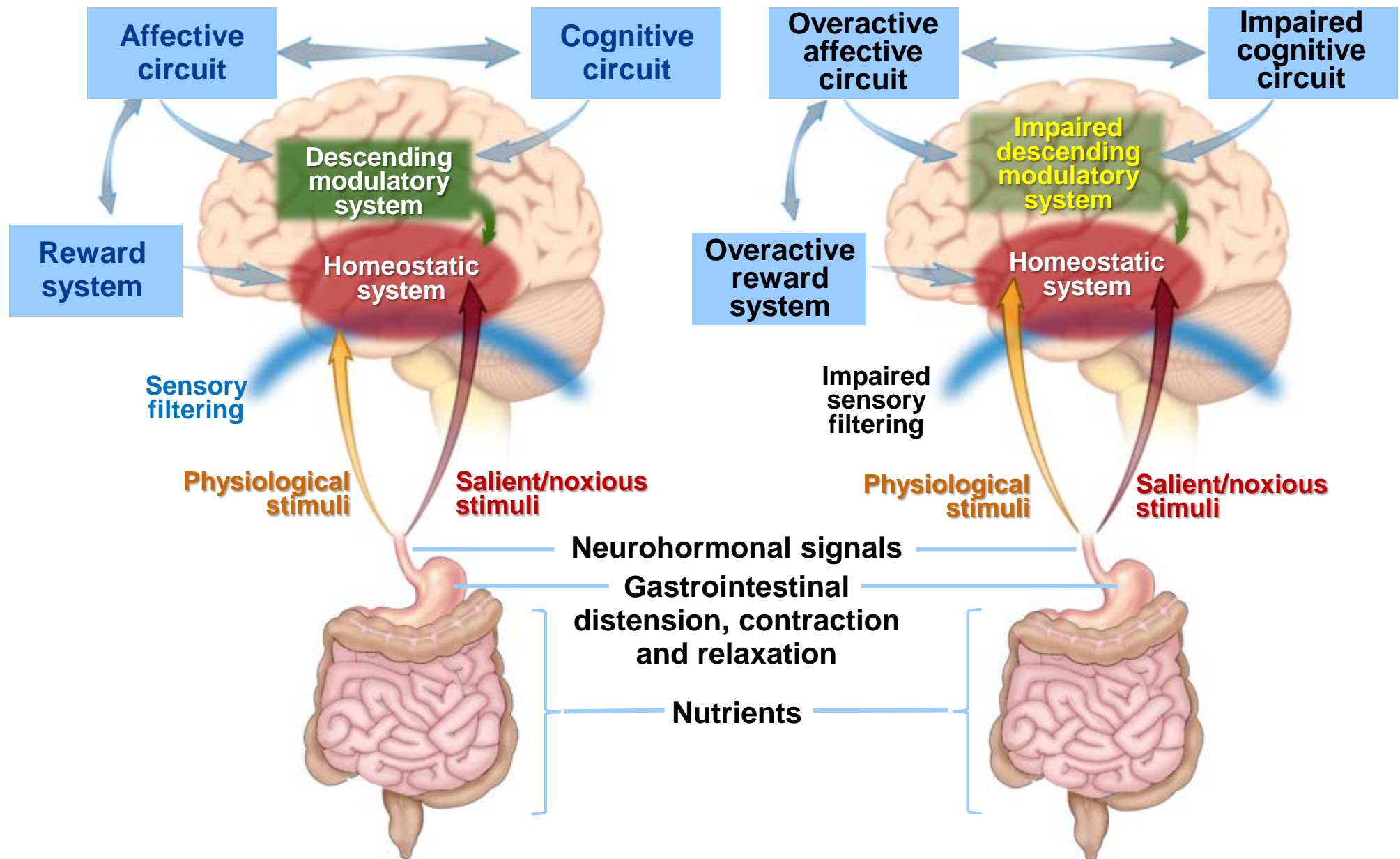
Genetics

Amplified input

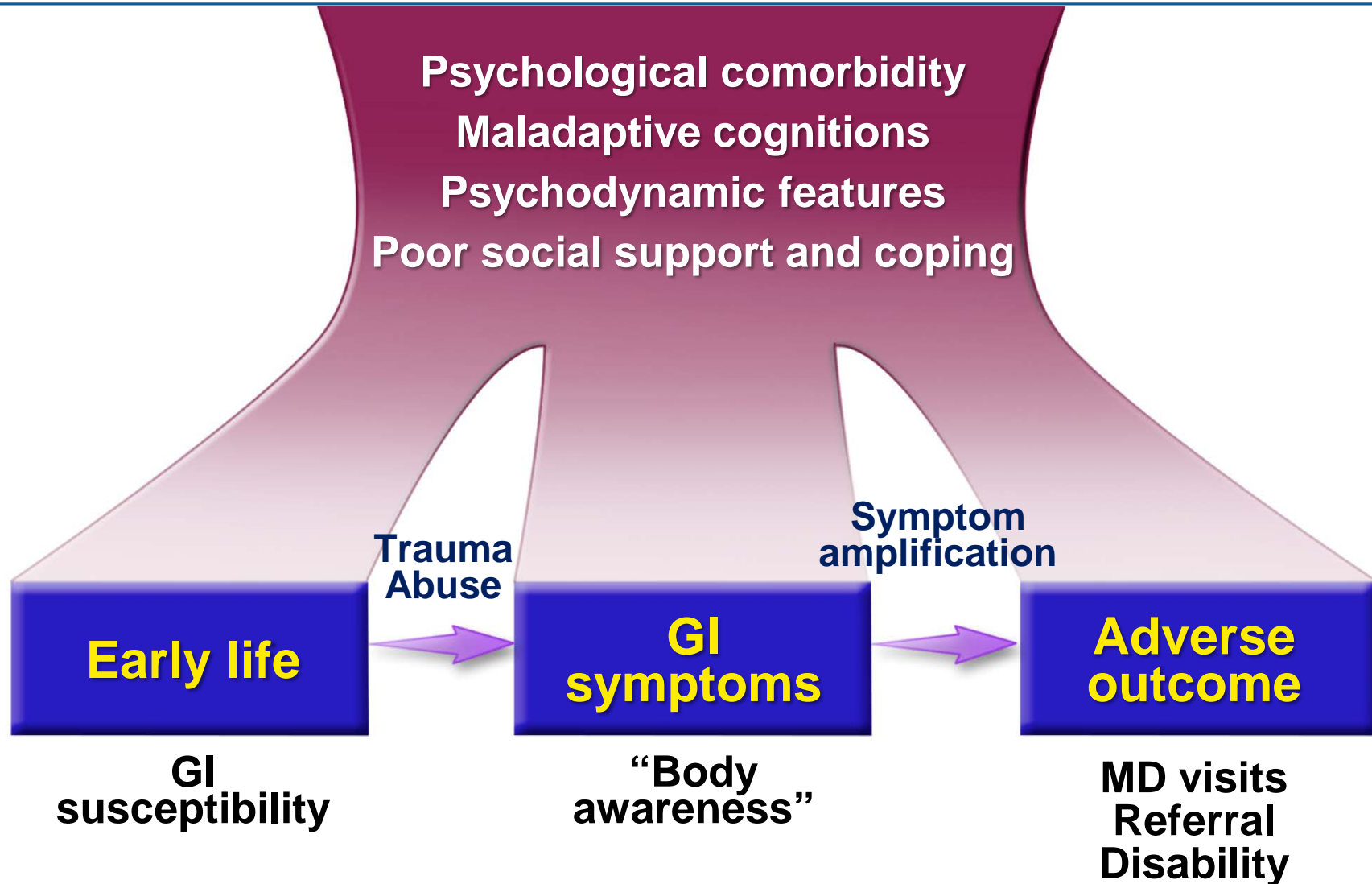
Nociceptive modulation

Health

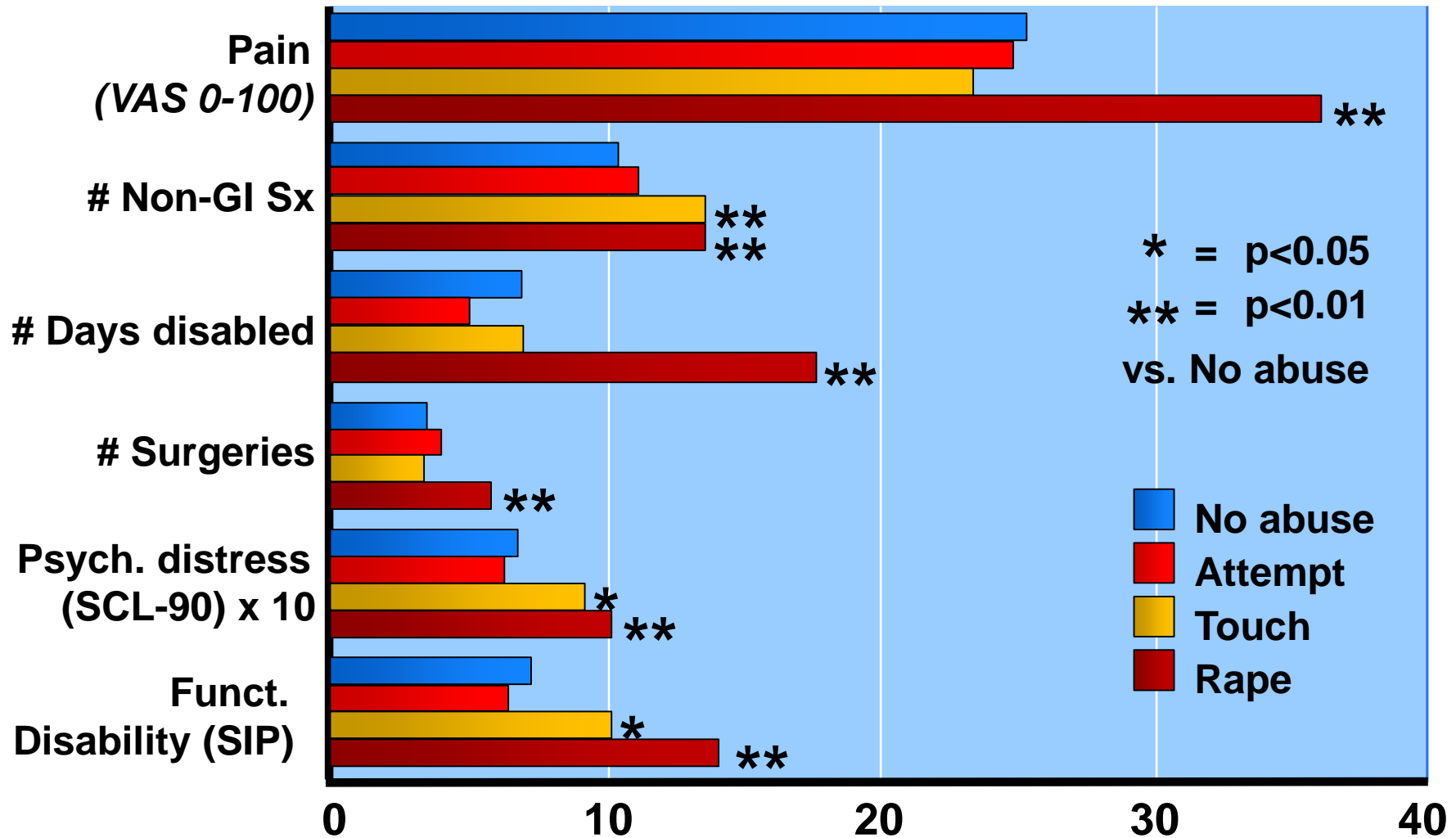
Functional Gastrointestinal Disorders



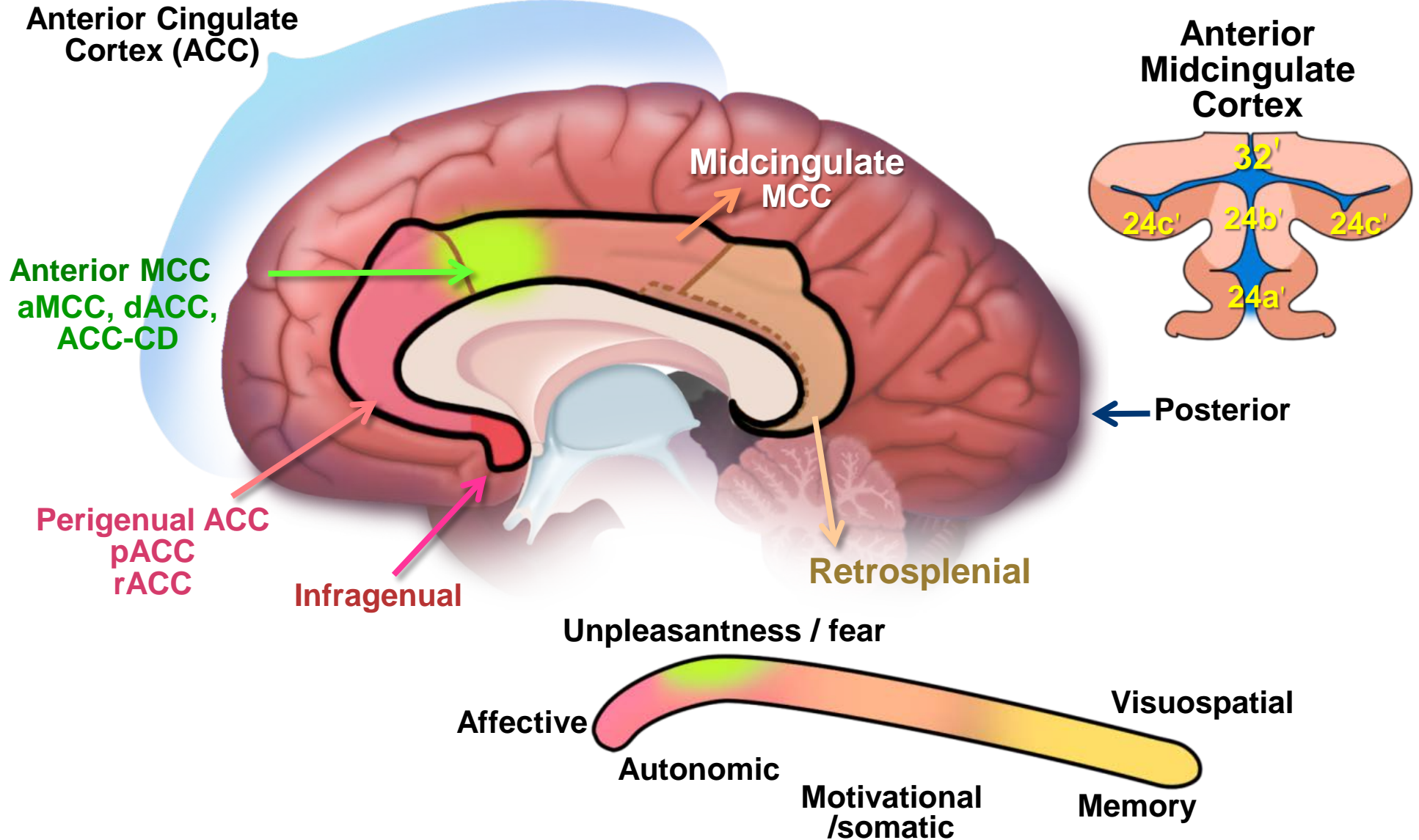
Relationship of Abuse/Trauma History and Psychological Comorbidities on GI Symptoms and Adverse Health Outcomes



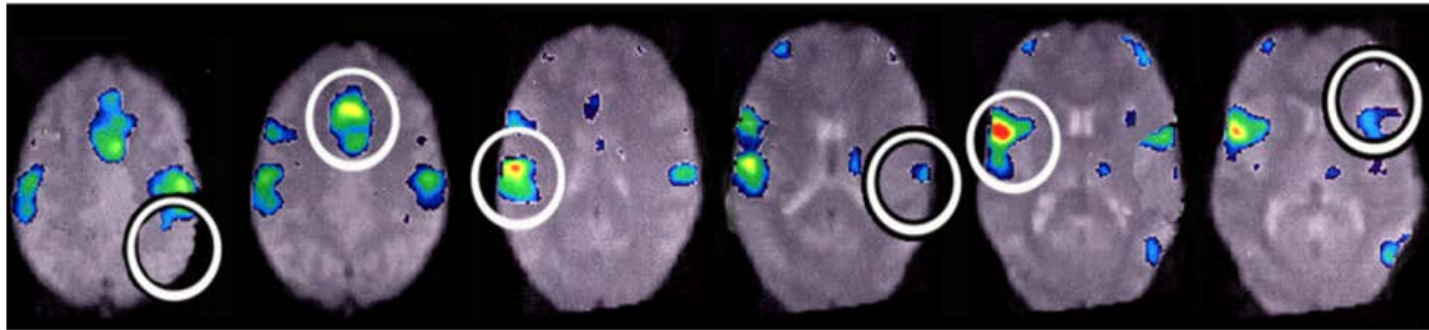
Sexual Abuse and Health Status



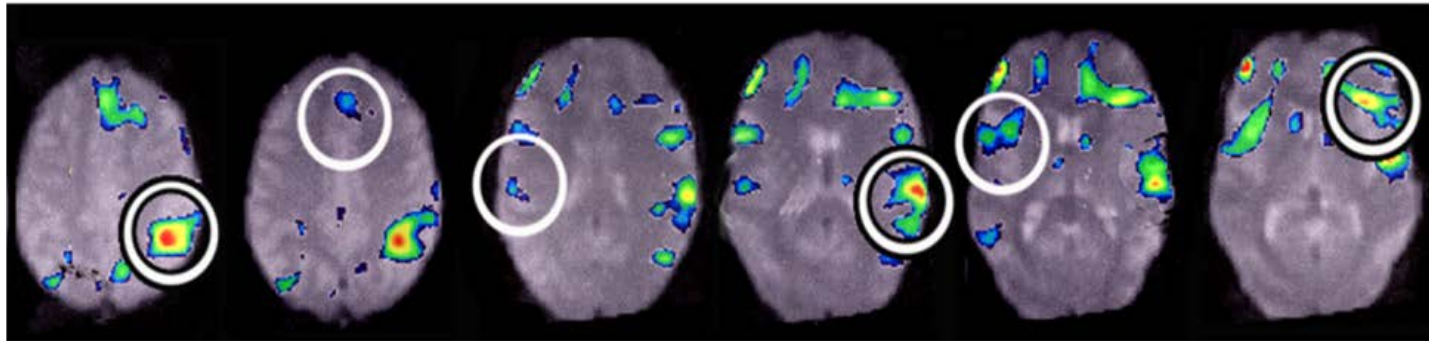
IBS - Cingulate Cortex - Functional Associations



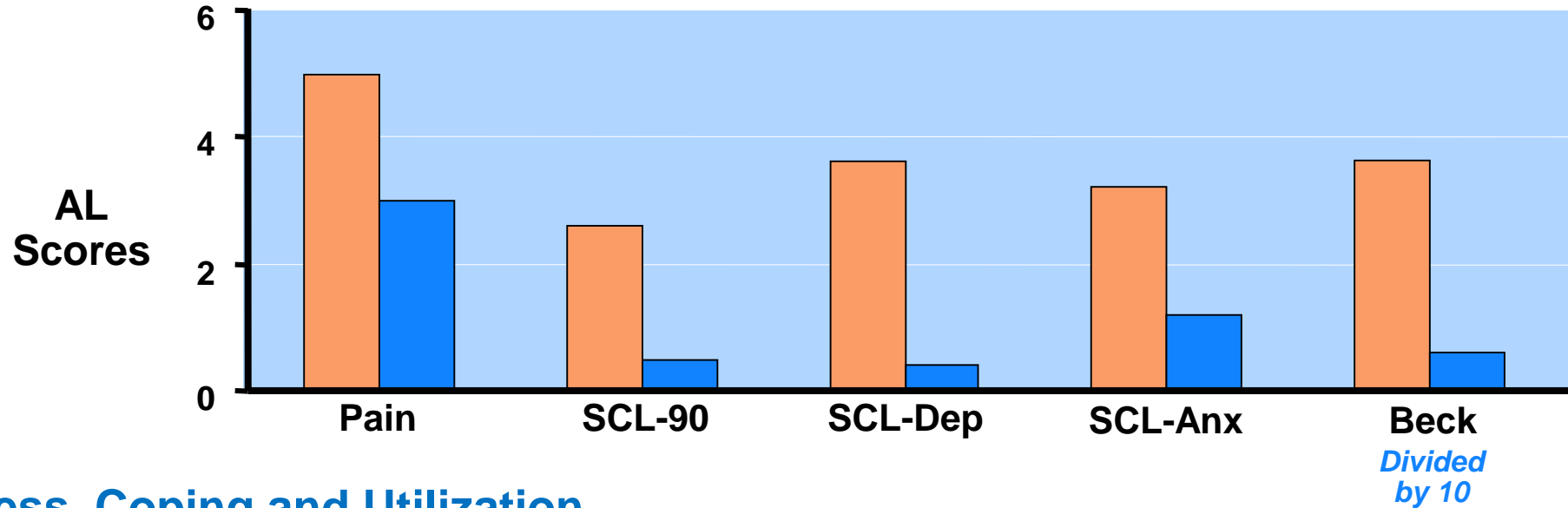
Severe IBS / Abuse-Psychological Distress



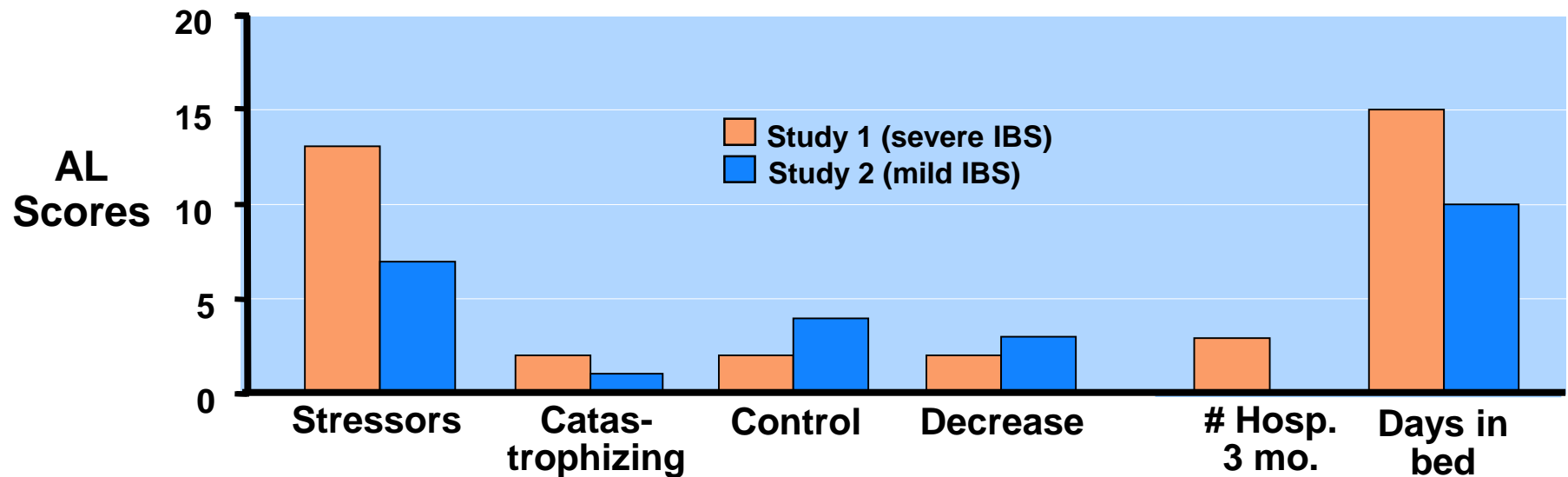
Clinical Recovery (8 months later)



Pain and Psychological Measures

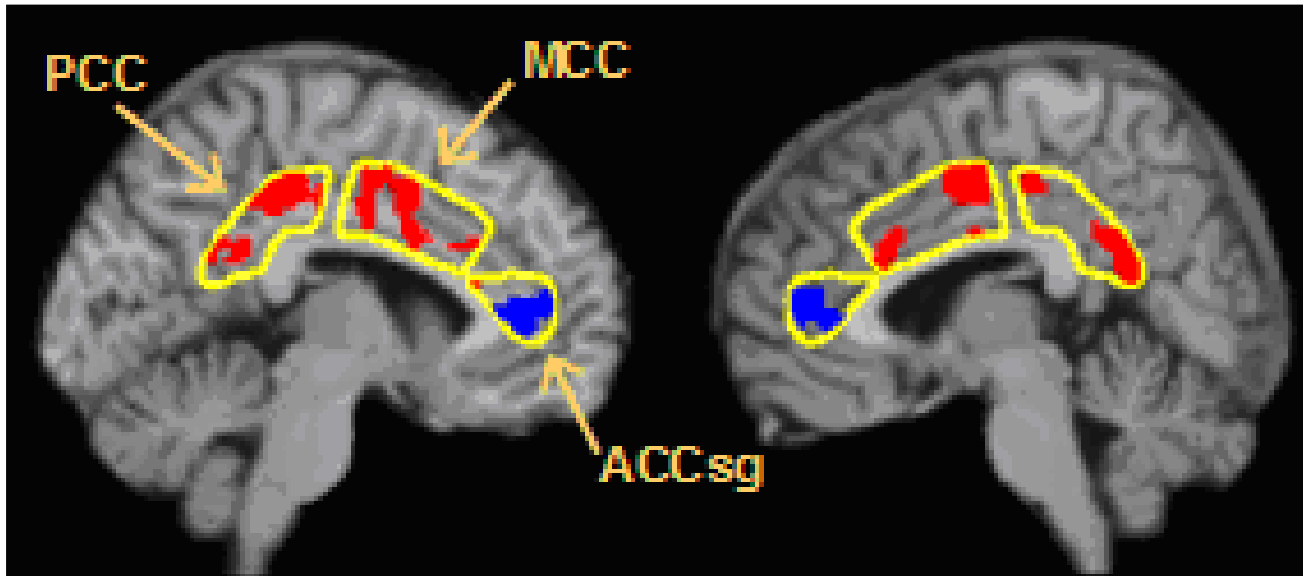


Stress, Coping and Utilization



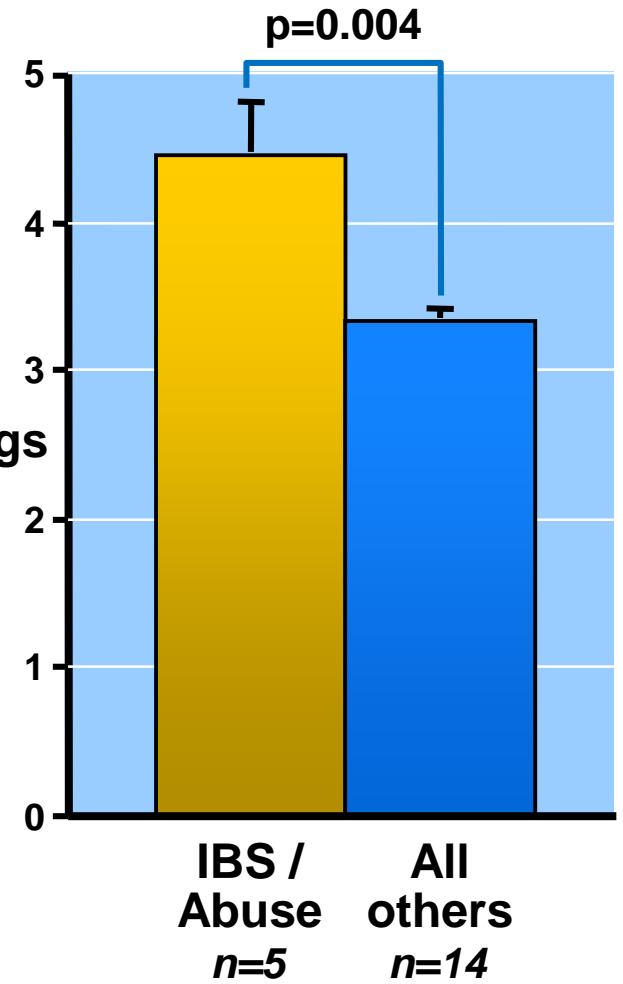
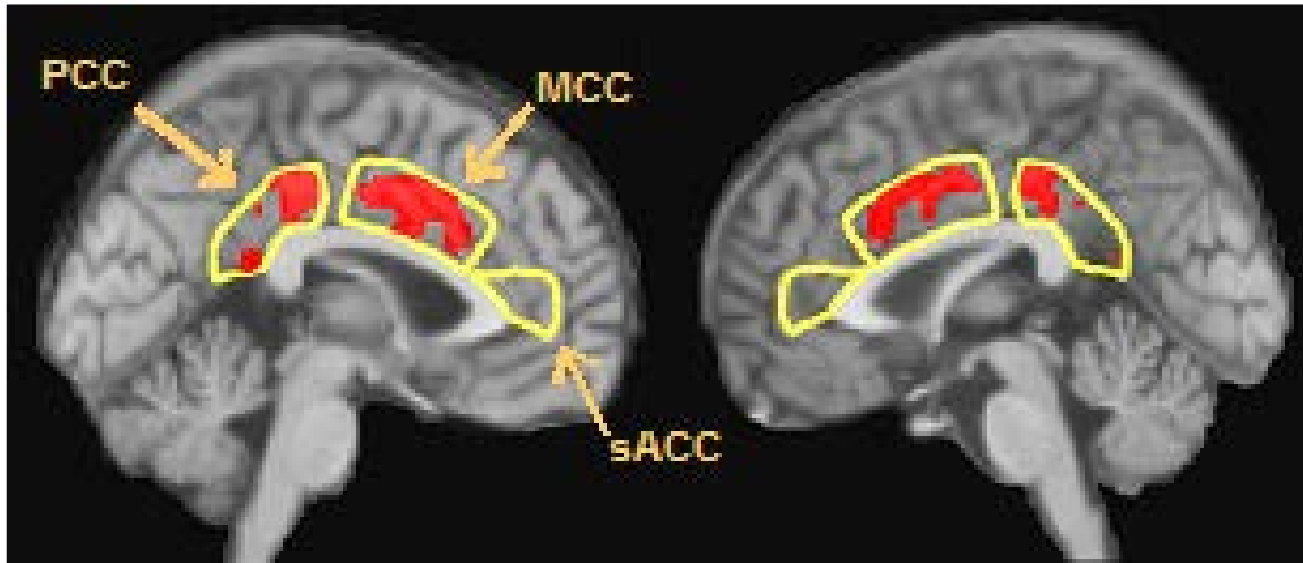
IBS + Abuse

(50 mm Hg)



Pain Covariate (50 mm Hg)

Pain ratings

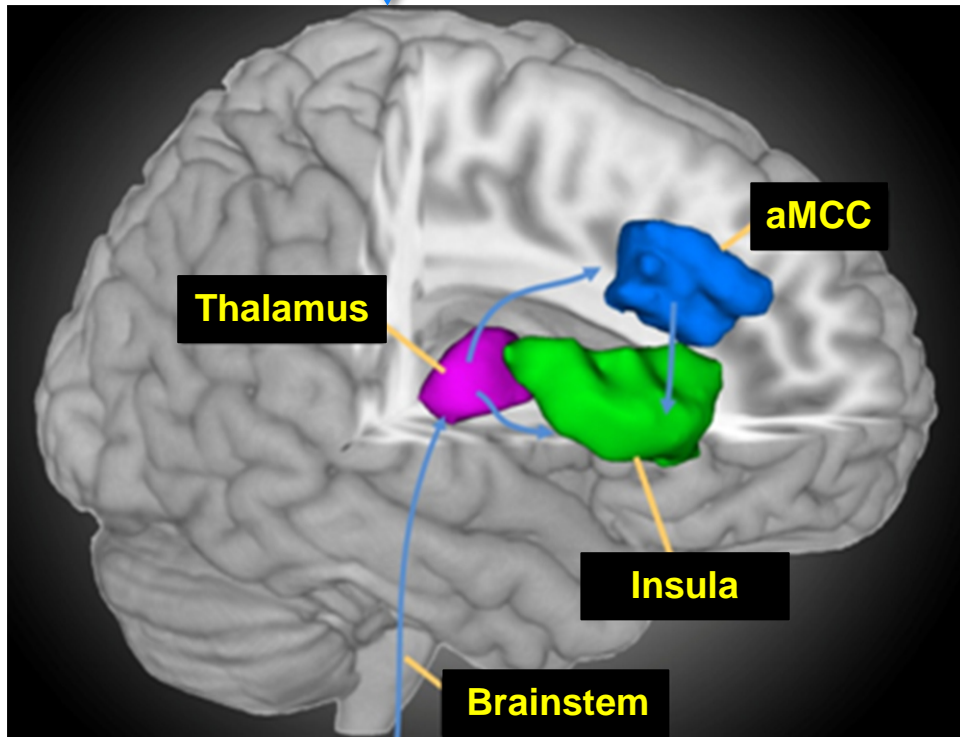


Overlapping Networks in Altered Visceral Sensation

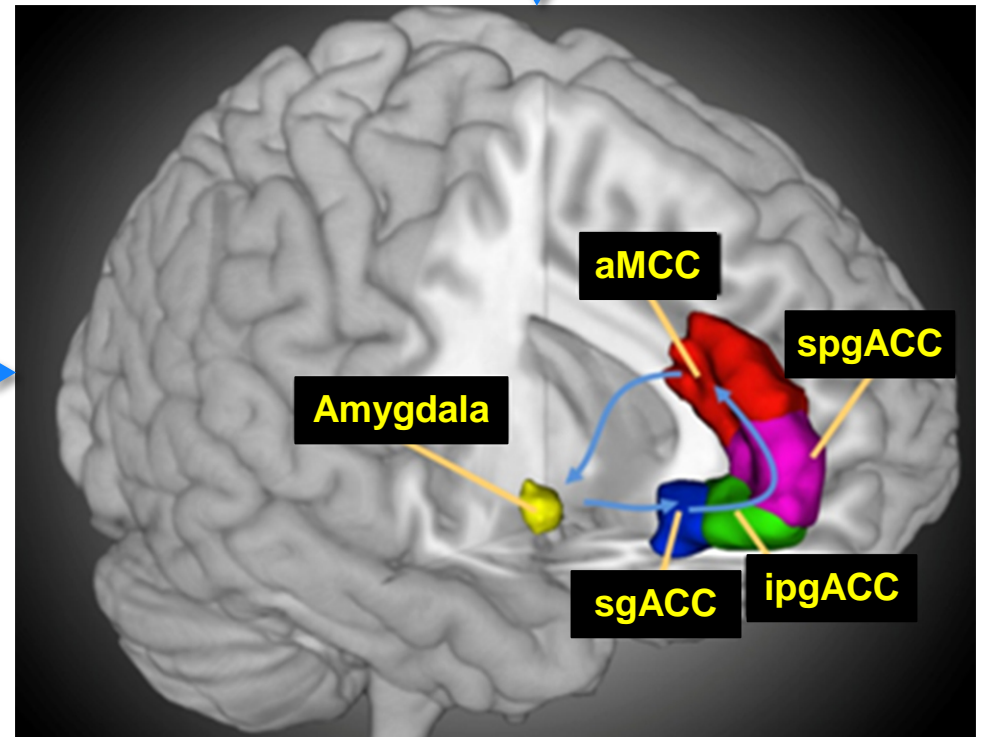
Prefrontal cortical modulatory regions

LPFC, MPFC and BA40

Modulation of response to interoceptive input



Homeostatic-afferent network
Input from the GI tract



Emotional-arousal network
Emotional response to sensation

CNS Neuroplasticity: Reduced Brain Volume/Gray Matter

Major Depression and Bipolar Disorder

- ACC and orbitofrontal cortex

(Konarski JZ et al. Bipolar Disorders 2008; 10:1-37)

Sexual/Physical abuse

- Hippocampus

(Bremner D et al Biol Psychiatry; 1997;41:23-32)

Chronic Somatic Pain

- ACC, PCC, VMPFC

(Valet M et al. Psychos Med 2009;71;49)

Irritable Bowel Syndrome

- dACC (aMCC)

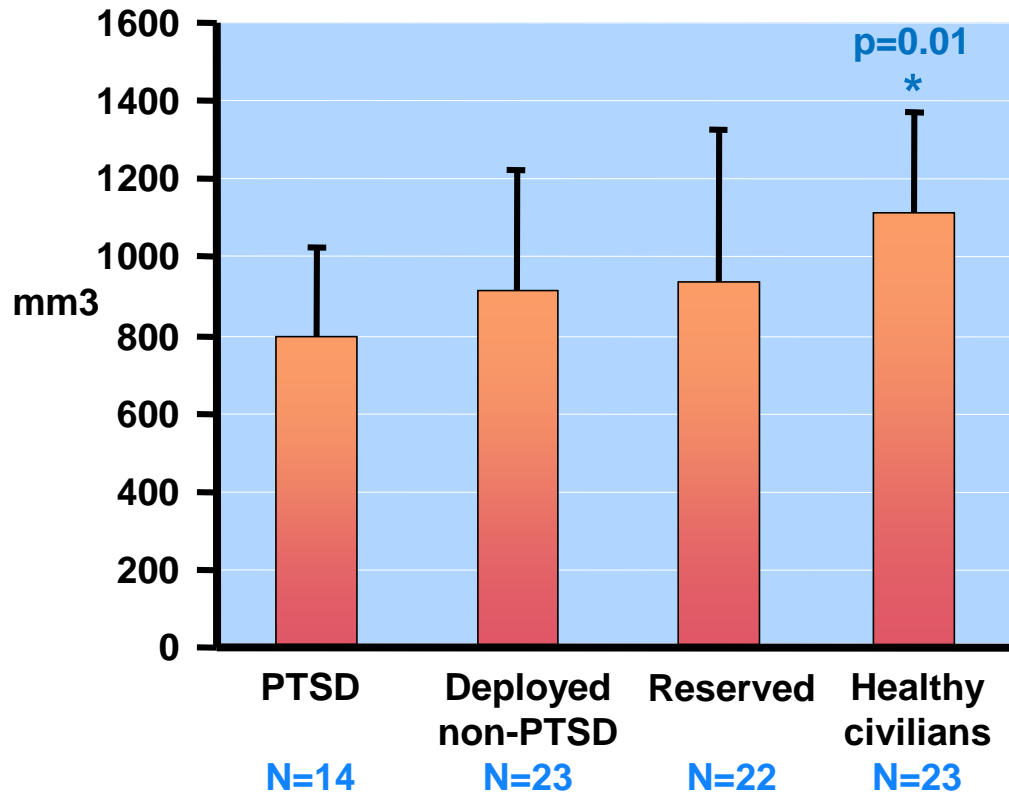
(Blankstein U et al. Gastroenterology 2010;138:1783)

Painful Chronic Pancreatitis

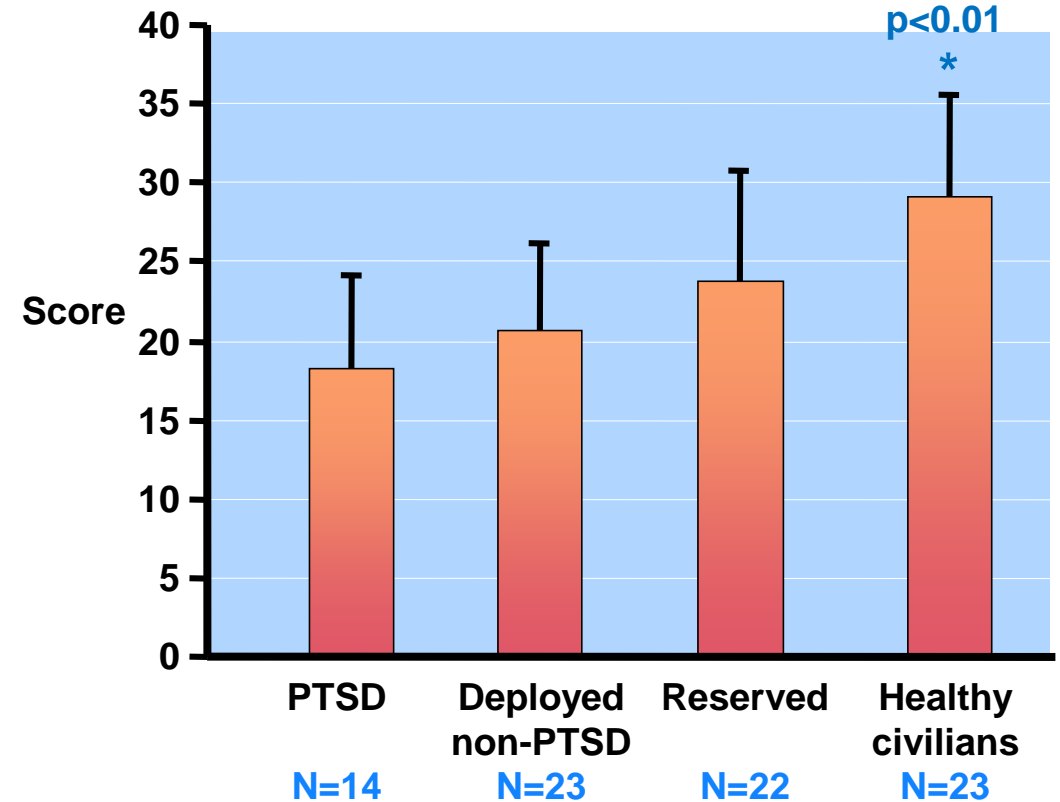
(Frøkjær, Clin Gastroenterol Hep 2012; 10:436)

Hippocampal Volume and Delayed Memory Loss In Gulf War Related PTSD

Hippocampus head volume

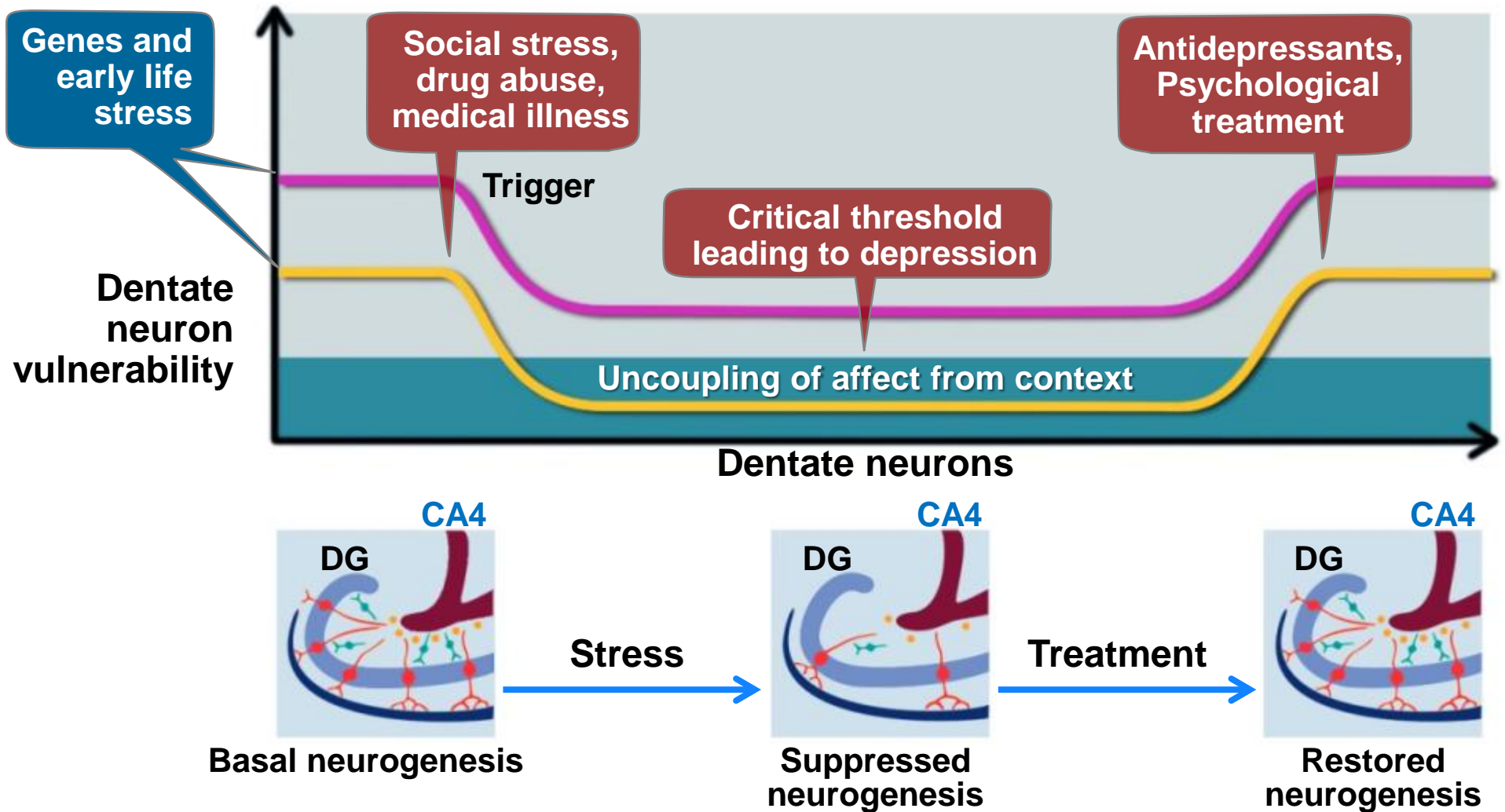


Wechsler delayed verbal memory

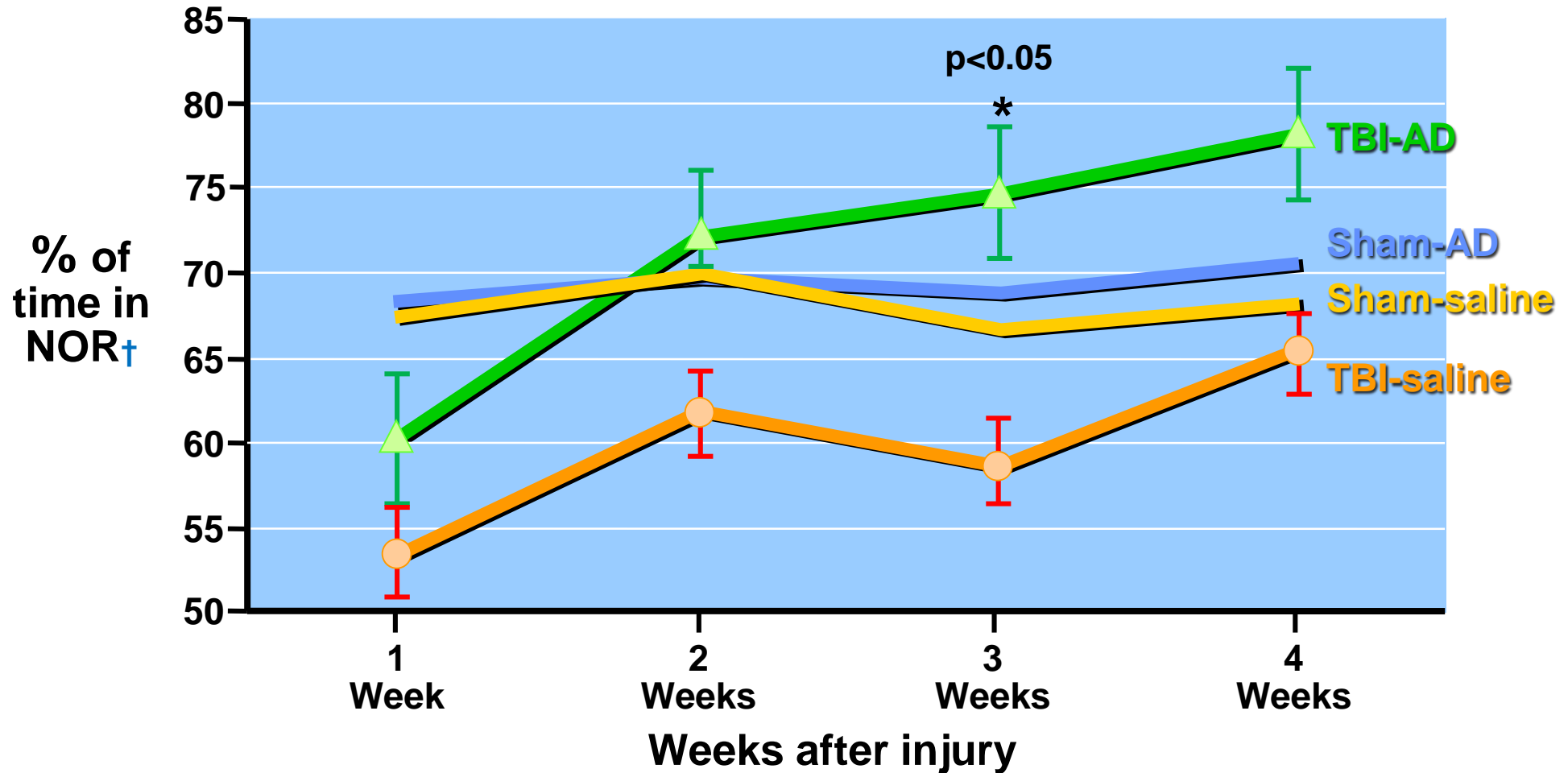


Correlation delayed memory with hippocampal volume $V=0.38$ ($p<0.001$)

Neurogenic Theory of Depression and Antidepressant Treatment

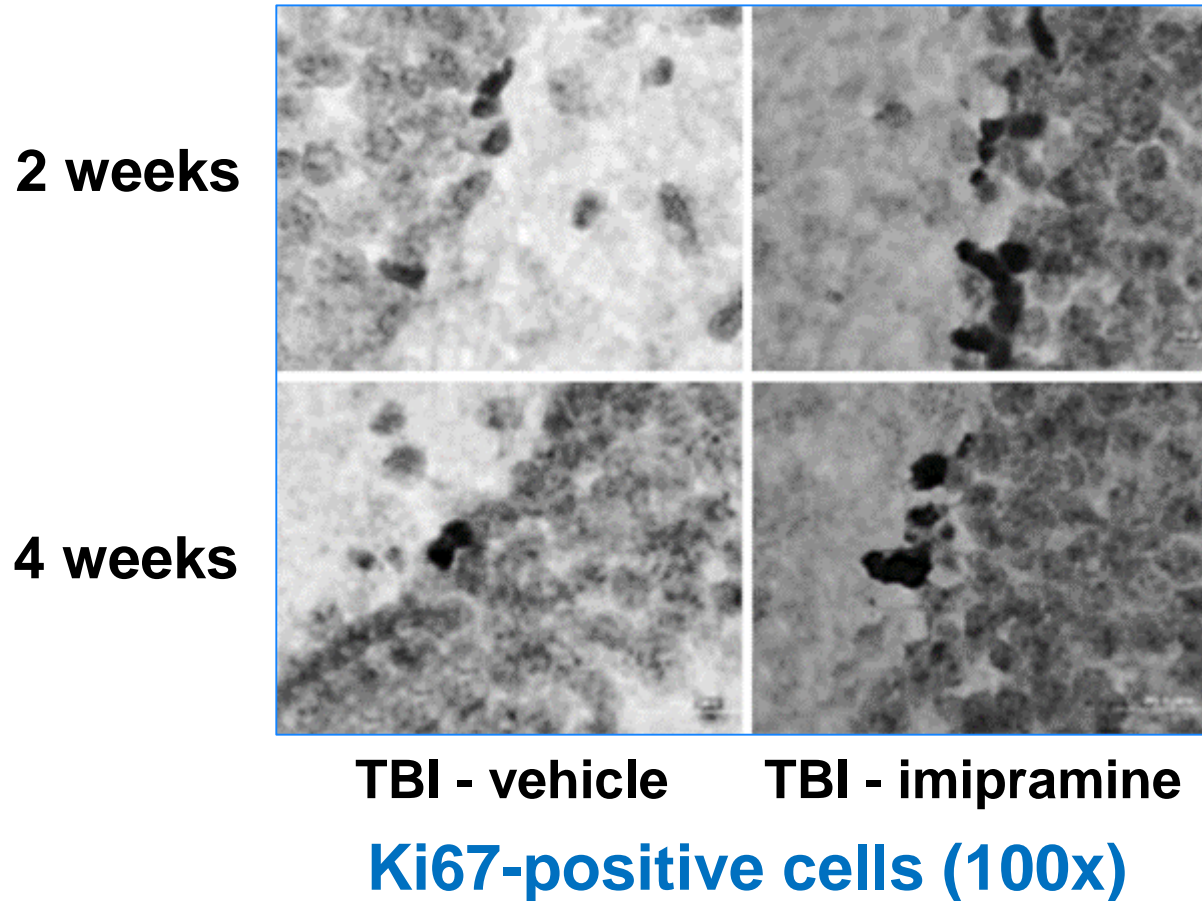


Effect of Imipramine vs. Placebo on Cognitive Function in Traumatic Brain Injured (TBI) Mice



† Novel Object Recognition Task

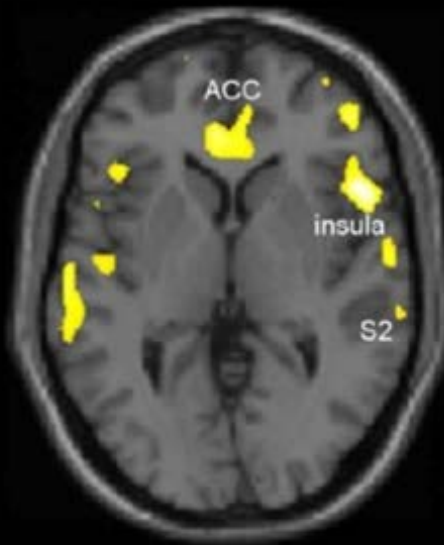
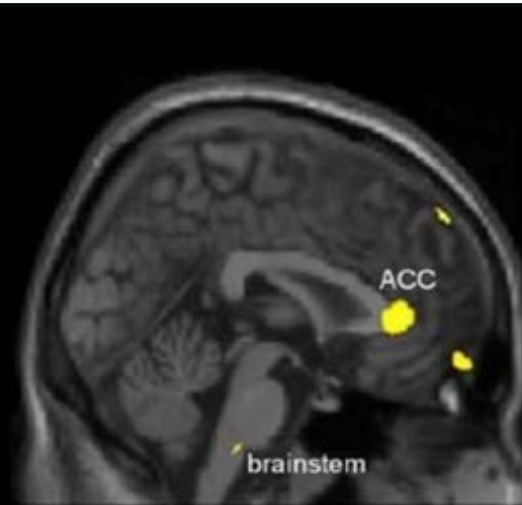
Effect of Imipramine vs. Placebo on Hippocampal Cell Proliferation in Traumatic Brain Injured (TBI) Mice



Changes in Gray Matter of Patients in Pain Before and Without Pain After Hip Surgery

**Before surgery
n=32**

**Decrease in gray matter with pain
(relative to controls)**



5

4

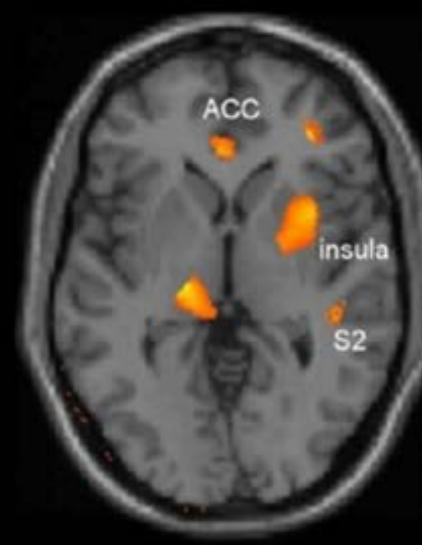
3

2

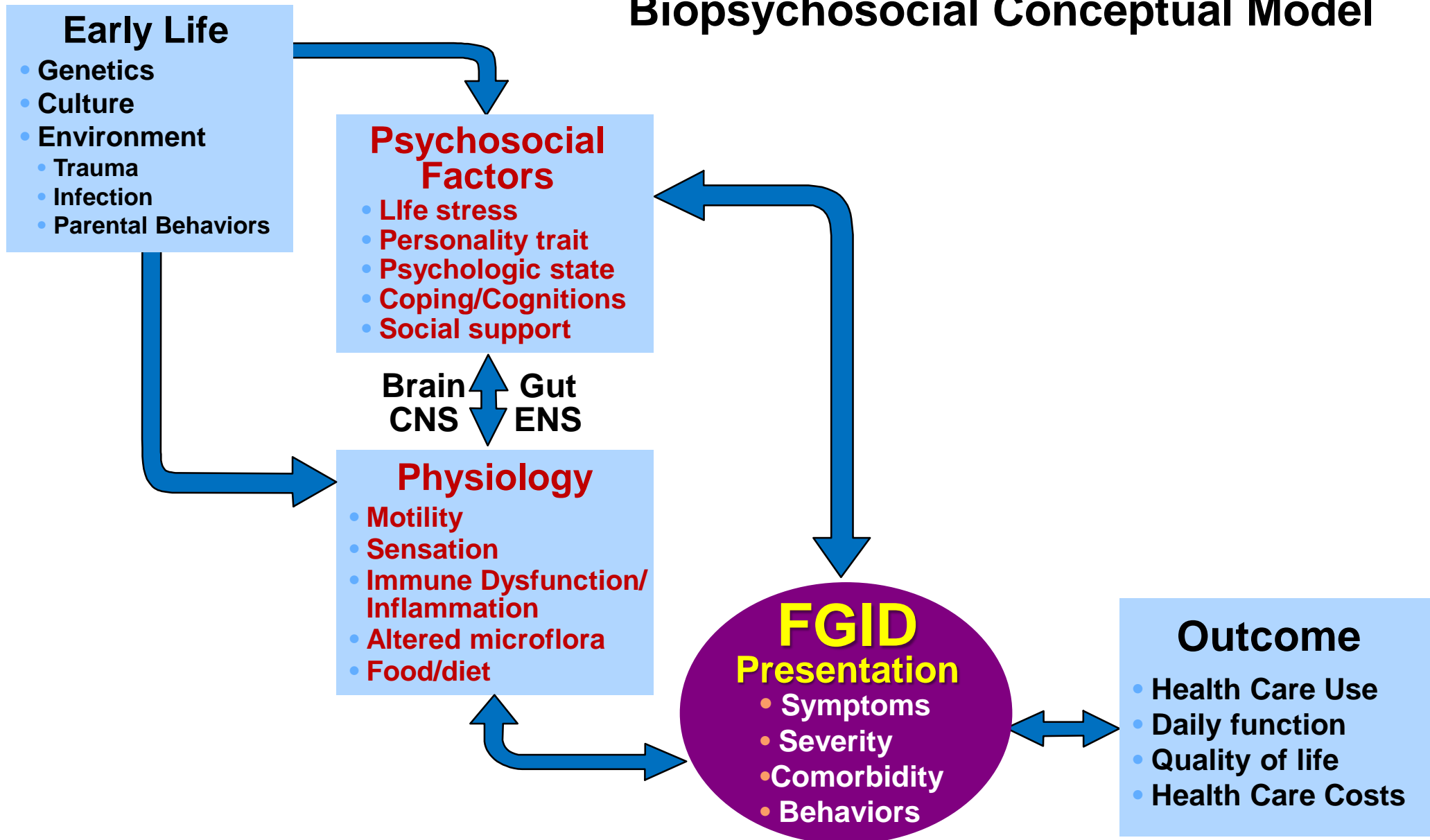
1

**After surgery
n=10 at 4
months**

**Increase in gray matter with no pain
(relative to pre-surgery)**



Biopsychosocial Conceptual Model



End