Understanding IBS and FGIDs: Disorders of Gut-Brain Interaction

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<th>Primary domain</th>
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<td>Colon cancer</td>
<td>Funct. abdominal pain</td>
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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
Neural crest

Neural tube

Ectoderm

Somite (developing spinal ganglion)

Brain and GI System Nerves are Connected

Midbrain

Hindbrain

Forebrain

Neural tube

Somites

Esophageal region

Liver

Future ENS

Midgut

Hindgut

Spinal cord
Gate Control Theory

Midbrain

Inhibitory Pathway

Pain Gate Control Theory

Spinal cord

Intestinal afferent receptor

Pain Gate

Drossman DA. Rome IV Gastroenterology 2016 150:1262
Rome IV – Disorders of Gut-Brain Interaction

- Centrally Mediated Disorders of GI Pain
- Esophageal
- Gastroduodenal
- Bowel
- Biliary
- Anorectal / pelvic floor
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
- Onset associated with a change in frequency of stool
- 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.

Lacy BE, Mearin F, Gastroenterology 2016; 150:1393
Rome IV IBS Subtypes: Stool Form

>25% of abnormal BM (types 1, 2, or 6, 7) is the threshold for classification.
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”
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

- Not at all satisfied
- A little bit satisfied
- Somewhat satisfied
- Very satisfied
- Extremely satisfied

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

- Not at all satisfied
- A little bit satisfied
- Somewhat satisfied
- Very satisfied
- Extremely satisfied

Off-hours Phone Calls

MD Perceptions of Patients: Organic vs. Functional

Seriousness of the problem
Disability of the patient
Reasonableness of request
Helpfulness of doctor
Satisfied with recommendation
Likeability of doctor/patient

% Positively endorsed

Functional n=35
Organic n=67

** p<0.001
* p<0.05

“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

- Asymptomatic ulcer
- COPD
- AIDS
- Hypertension
- Cancer
- Chronic Multisystem Illness
- Chronic back pain
- Motility Disorders
- IBS and FGIDs
- Chronic fatigue

COPING

RIGHTFUL SUFFERING

Health

Disease

Illness

Functional (Psychosomatic)
“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

Contractile State

“Discovery of Cancer”

Hoax Explained

Minutes

0 10 20 30 40

Almy TP et al. Gastroenterology 1949;12:425
IBS - Physiologic Research

- Stress affects GI function
- Meals Pain/Motility
- Pain sensitivity
- Motility

Mechanisms

- CNS/ENS Autonomic reactivity
- Brain-Gut Interactions
- Myoelectrical Marker
- Visceral Hypersensitivity
- Inflammation
- Microflora
- Food and Diet
- CNS Brain Imaging
- Probiotics
- FODMAP
- Gluten
- Postinfection IBS
- Nutritional/Biochemical 
- Pain
- Visceral hypersensitivity
- Rome Criteria
- CNS
- Brain Imaging
- Neuroplasticity and Neurogenesis
- Biomarkers
- Epigenomics
- IBS - Physiologic Research
- Stress affects GI function
- Meals Pain/Motility
- Pain sensitivity
- Motility

IBS - Physiology

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Rogers J, Gut 1989;30:634
IBS – Visceral Hypersensitivity

Whitehead et al., Gastroenterology 1990;98:1187
Effect of Stress on Rectal Perception Threshold

**Physical stress**

- Controls (n=12)
- C=IBS (n=24)

% change from baseline

- Stress
- Recovery

Time (min)

- *p=0.01 IBS vs controls

**Psychological stress**

- Stress
- Recovery

Time (min)

- *p=0.01 IBS vs controls

Murray CDR, Gastroenterology 2004; 127:1695
Repetitive Mechanical Stimulation Sensitizes the Spinal Cord

- Dorsal root ganglion
- Wind-up
- Sensitized spinal circuits
- Repeated balloon distension
- Mechanosensitive afferent
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

Pain sensation

Hyperalgesia

Insult

Normal

Alldynia

Innocuous

Stimulus Intensity

Noxious
### FODMAPs

<table>
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<tr>
<th><strong>Excess Fructose</strong></th>
<th>Honey, apples, pears, peaches, mangos, fruit juice, dried fruit</th>
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<tbody>
<tr>
<td><strong>Fructans</strong></td>
<td>Wheat (large amounts), rye (large amounts), onions, leeks, zucchini</td>
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<tr>
<td><strong>Sorbitol</strong></td>
<td>Apricots, peaches, artificial sweeteners, artificially sweetened gums</td>
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<tr>
<td><strong>Raffinose</strong></td>
<td>Lentils, cabbage, brussels sprouts, asparagus, green beans, legumes</td>
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FODMAPs = **Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols**

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Differential Effects of Gas Production with FODMAPs

Different test meals

Liver
Distension

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

**Injurious**
- Pro-inflammatory
- *Bacteroides vulgatus*
- *Enterococcus faecalis*
- *E. coli* - enteroadherent / invasive

**Protective**
- Probiotic
- *Lactobacillus sp.*
- Bifidobacterium sp.
- Non-pathogenic *E. coli*
Low-grade inflammation
Intestinal barrier
Microbiota
Visceral hypersensitivity
Neuro-motor dysfunction
Infection
Dysbiosis
Stress, depression
Microbiota
Stress Activates Neuronal CRH Release with Mast Cell Degranulation

- Stress
- Intestinal mucosa
- Mucus layer
- Epithelial cells
- Nerve fibers
- CRH
- ACh
- Mast cell
- Granulocyte
- B cell
- T cell

Stress Activates Neuronal CRH Release with Mast Cell Degranulation

- T cell
- B cell
- Mast cell
- Granulocyte
- Intestinal epithelial cells
- Intestinal mucosa
- Nerve fibers
- CRH
- ACh
- Mucus layer
- Permeable

- TNFa
- Tryptase
- PGE2
- Histamine
- Sensitized

Stress Activates Neuronal CRH Release with Mast Cell Degranulation

Intestinal mucosa

Bacterial products

Mast cell degranulation

Granulocyte

CRH

ACh

Nerve sensitized

Intestinal barrier permeable

Mucus layer

TNFa

Tryptase

PGE2

Histamine
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

**IBS - Epidemiology**

**Mearin, et al., Gastroenterology 2005; 129:98**
• 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)
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

Infection
Microbial virulence
Gastroenteritis During Deployment

Impaired bacterial recognition
Intestinal permeability
Inefficient down regulation of the inflammatory response

Genetic susceptibility

War trauma Abuse
Altered gut function
Microbiota

Low grade inflammation

IBS

Collins SM, Am J Gastro suppl 2012:1:2
Pain Is a Modifiable Experience

**Psychosocial context**
- Pain beliefs
- Cultural schema
- Expectation
- Conditioning

**Cognitions**
- Hypervigilance
  - Attention
  - Distraction
- Catastrophizing

**Peripheral and central sensitization**

**Chemical/Structural**
- Neurodegeneration
- Metabolic (opioidergic, dopaminergic)
- Maladaptive plasticity

**Mood**
- Depression
- Anxiety

**Genetics**

**Nociceptive modulation**

**Amplified input**
Health

- Affective circuit
- Cognitive circuit
- Reward system
- Homeostatic system
- Descending modulatory system
- Neurohormonal signals
- Gastrointestinal distension, contraction and relaxation
- Nutrients

Functional Gastrointestinal Disorders

- Overactive affective circuit
- Impaired cognitive circuit
- Overactive reward system
- Impaired descending modulatory system
- Impaired sensory filtering
- Salient/noxious stimuli
- Physiological stimuli

Van Oudenhove L and Aziz Q Nat Rev Gastroenterol Hepatol 2013
Relationship of Abuse/Trauma History and Psychological Comorbidities on GI Symptoms and Adverse Health Outcomes

- Psychological comorbidity
  - Maladaptive cognitions
  - Psychodynamic features
  - Poor social support and coping

Early life

GI symptoms

Adverse outcome

GI susceptibility

“Body awareness” MD visits Referral Disability

Drossman DA, Am J Gastro 2011; 106:14
Sexual Abuse and Health Status

Sexual Abuse Category

- No abuse
- Attempt
- Touch
- Rape

Health Status Indicators

- Pain (VAS 0-100)
- # Non-GI Sx
- # Days disabled
- # Surgeries
- Psych. distress (SCL-90) x 10
- Funct. Disability (SIP)

Significance Levels:
- * = p<0.05
- ** = p<0.01

Comparison:
- vs. No abuse
IBS - Cingulate Cortex - Functional Associations

Anterior Cingulate Cortex (ACC)

Midcingulate Cortex (MCC)

Perigenual ACC
  pACC
  rACC

Infragenual

Retrosplenial

Unpleasantness / fear

Affective

Autonomic

Motivational /somatic

Visuospatial

Memory

Anterior MCC
  aMCC, dACC, ACC-CD

Drossman DA, Gut 2005; 54:569
Severe IBS / Abuse-Psychological Distress

Clinical Recovery (8 months later)
Pain and Psychological Measures

Stress, Coping and Utilization

Drossman et al, Gastroenterology 2003; 124:754
IBS + Abuse (50 mm Hg)

Pain Covariate (50 mm Hg)

Pain ratings

IBS / Abuse
n=5

All others
n=14

p=0.004

Ringel Y, Drossman DA, Gastroenterology 2008; 134:396
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

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

Weeks after injury

% of time in NOR†

1 Week 2 Weeks 3 Weeks 4 Weeks

TBI-AD
Sham-AD
Sham-saline
TBI-saline

† Novel Object Recognition Task

p<0.05

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

2 weeks

4 weeks

TBI - vehicle  TBI - imipramine

Ki67-positive cells (100x)
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)

After surgery  
n=10 at 4 months  
Increase in gray matter with no pain (relative to pre-surgery)

Physiology
- Motility
- Sensation
- Immune Dysfunction/Inflammation
- Altered microflora
- Food/diet

Psychosocial Factors
- Life stress
- Personality trait
- Psychologic state
- Coping/Cognitions
- Social support

Brain
- CNS

Gut
- ENS

Early Life
- Genetics
- Culture
- Environment
- Trauma
- Infection
- Parental Behaviors

Psychosexual Factors
- LIfe stress
- Personality trait
- Psychologic state
- Coping/Cognitions
- Social support

FGID Presentation
- Symptoms
- Severity
- Comorbidities
- Behaviors

Outcome
- Health Care Use
- Daily function
- Quality of Life
- Health Care Costs
End