

Gut Pain & Vagal Nerve Stimulation

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Director of Motility & Cyclic Vomiting Syndrome Programs
Children's Wisconsin Hospital
Medical College of Wisconsin

Disclosures

- **Consultant: Takeda Pharmaceuticals**

Objectives

- Review chronic pain mechanisms in relation to functional GI disorders
- Non-invasive vagal nerve stimulation therapies

What are Functional GI Disorders (FGIDs)?

- Persistent or recurring GI symptoms caused by abnormal *functioning* of the GI tract
- No structural or biochemical abnormality
- Medical tests are normal
- Prevalence: 10-20%
- *Not* psychiatric disorders
  - Stress may worsen symptoms



Disorders of Gut-Brain Interaction: Rome IV

Functional Abdominal Pain Disorders

- IBS
- Functional Dyspepsia
- Abdominal Migraine
- Functional Abdominal Pain-NOS

Functional Nausea & Vomiting Disorders

- Cyclic Vomiting Syndrome
- Functional Nausea & Functional Vomiting
- Rumination
- Aerophagia

FGIDs: pathophysiology

"aberrant brain-gut"

"visceral hyperalgesia"

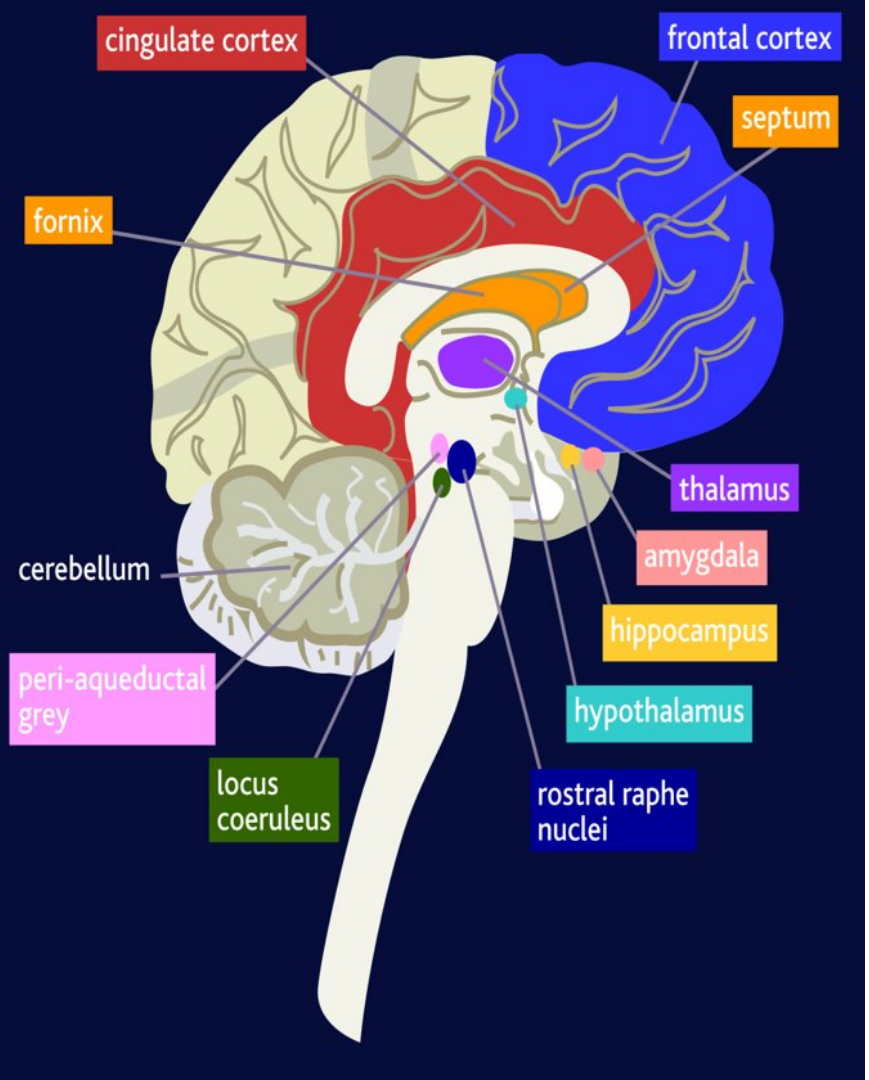
"genetically susceptible"

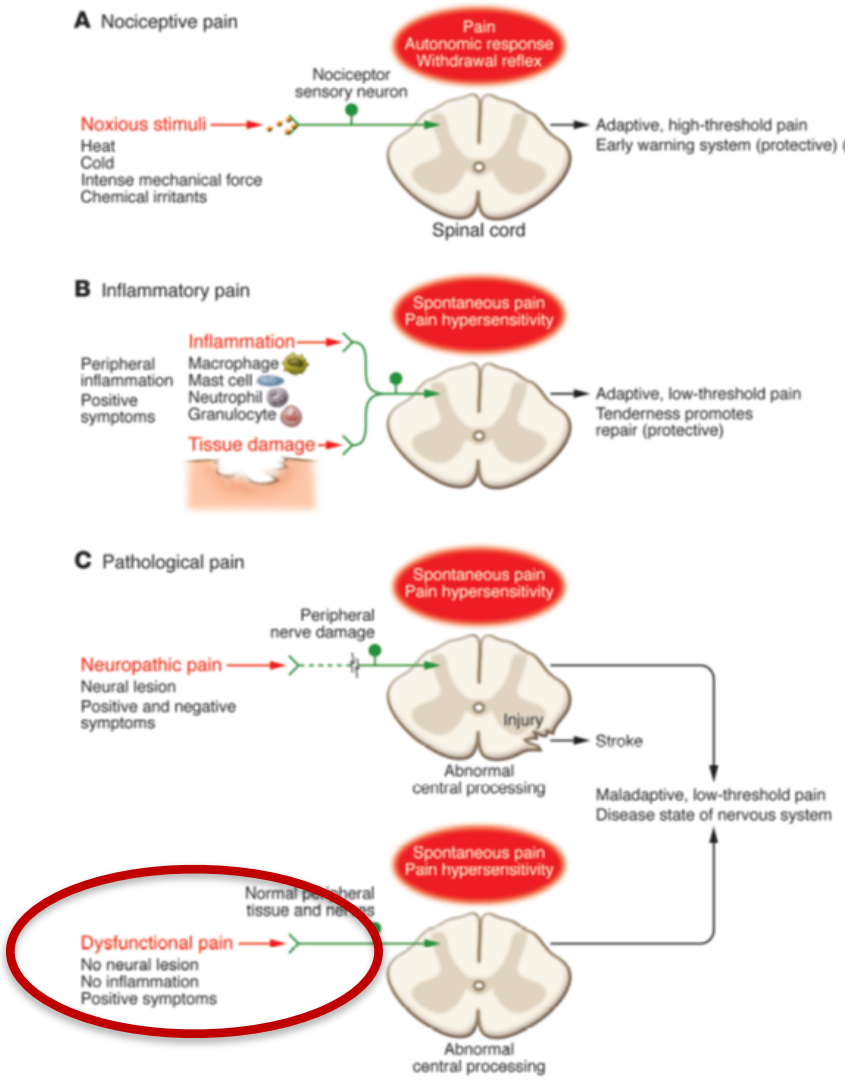
"coping

Message: "*absence of identifiable disease*"

Anxiety stress style gains history

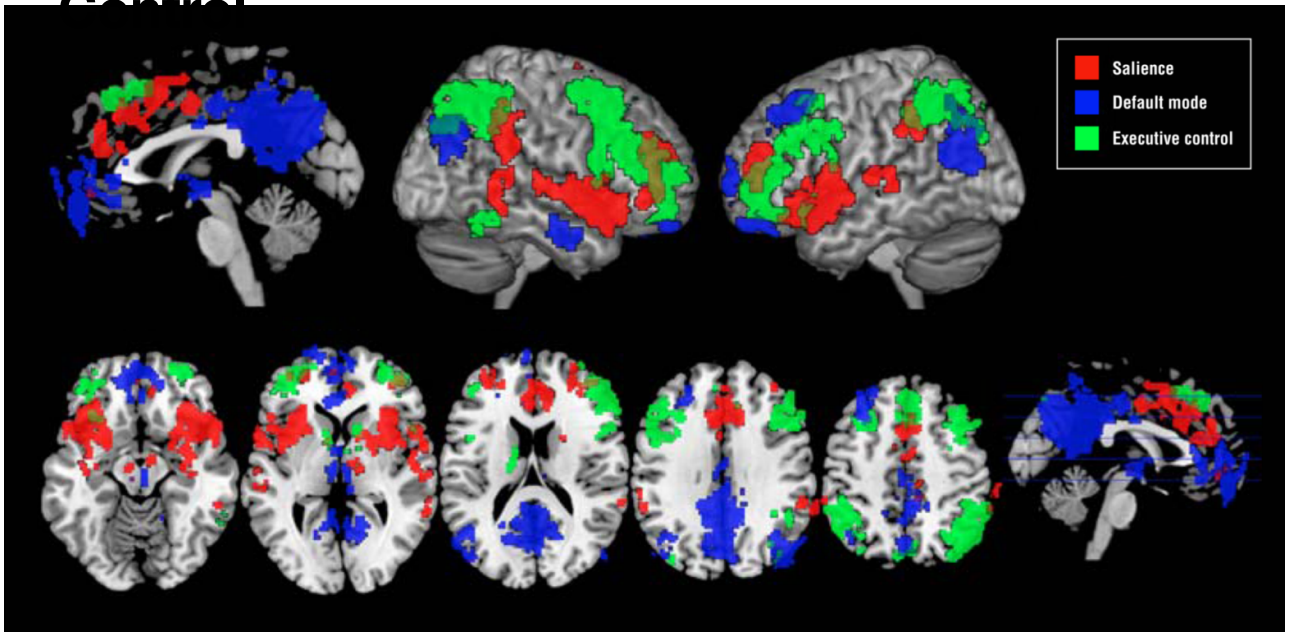
Is there absence of identifiable disease?

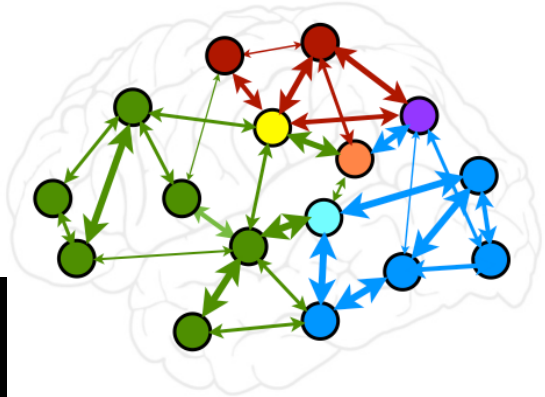

cingulate cortex
frontal cortex
septum
fornix
thalamus
amygdala
cerebellum
hippocampus
peri-aqueductal grey
hypothalamus
locus coeruleus
rostral raphe nuclei


A Nociceptive pain
Pain
Autonomic response
Withdrawal reflex
Nociceptor sensory neuron
Noxious stimuli
Heat
Cold
Intense mechanical force
Chemical irritants
Adaptive, high-threshold pain
Early warning system (protective)
Spinal cord
B Inflammatory pain
Spontaneous pain
Pain hypersensitivity
Inflammation
Peripheral inflammation
Positive symptoms
Macrophage
Mast cell
Neutrophil
Granulocyte
Tissue damage
Adaptive, low-threshold pain
Tenderness promotes repair (protective)
C Pathological pain
Spontaneous pain
Pain hypersensitivity
Peripheral nerve damage
Neuropathic pain
Neural lesion
Positive and negative symptoms
Injury
Stroke
Abnormal central processing
Maladaptive, low-threshold pain
Disease state of nervous system
Spontaneous pain
Pain hypersensitivity
Dysfunctional pain
No neural lesion
No inflammation
Positive symptoms
Abnormal central processing

Brain connectivity & networks

1) Salience 2) Default Mode 3) Executive Control





- Earlier studies: whole brain/regional activation
- MRI modalities: maps of brain connectivity
- Resting state fMRI, task fMRI, diffusion MRI

Complex Cocktail



Anxiety

Emotions

Disordered sleep

Depression

Coping

Peer Relationships

Functional GI disorder

Trauma

Early Life Events

Genetics

Microbiome

How is this constant aberrant emotional reactivity and repeated signaling re-structuring brain

Gut feelings: the emerging biology of gut–brain communication

Emeran A. Mayer
Center for Neurobiology of Stress, Division of Digestive Diseases, Departments of Medicine, Physiology and Psychiatry, David Geffen School of Medicine at University of California, Los Angeles, CHS 47-122 10833 Le Conte Avenue, Los Angeles, California 90095-7378, USA

- **Repeated aberrant brain-gut signaling can induce chronic brain functional connectivity changes**

Increased attentional network functioning related to symptom severity measures in females with irritable bowel syndrome

C. S. HUBBARD, *,†,‡,§ J. HONG, *,†,¶,** Z. JIANG, * B. EBRAT, *,† B. SUYENOBU, *,† S. SMITH, *,†
N. HEENDENIYA, *,† B. D. NALIBOFF, *,†,**,††,§§ K. TILLISCH, *,†,** E. A. MAYER*,†,**,‡‡,§§ & J. S. LABUS*,†,**,§§

- Efficiency of attentional network functioning during fMRI in IBS vs healthy controls
- IBS: **abnormalities in attentional network** functioning
  - Symptom-related anxiety, pain catastrophizing and fear of uncertainty
  - →hypervigilance and visceral hypersensitivity…

Abnormal Amygdala Resting-State Functional Connectivity in Irritable Bowel Syndrome

R. Qi, C. Liu, J. Ke, Q. Xu, Y. Ye, L. Jia, F. Wang, L.J. Zhang, and G.M. Lu

Neurobiology of Disease

Sex and Disease-Related Alterations of Anterior Insula Functional Connectivity in Chronic Abdominal Pain

Jui-Yang Hong,[1,5,8] Lisa A. Kilpatrick,[1,2,3,5] Jennifer S. Labus,[1,2,3,4,5] Arpan
Cody Ashe-McNalley,[1,2,3,5] Jean Stains,[1,3,5] Nuwanthi Heendeniya,[1,3,5] S
Bruce Naliboff,[1,2,3,4,5] and Emeran A. Mayer[1,2,3,4,5,6,7]

Neurogastroenterology & Motility NGM

Neurogastroenterol Motil (2016) **28,** 127–138 doi: 10.1111/nmo.12710

Altered brain responses in subjects with irritable bowel syndrome during cued and uncued pain expectation

J.-Y. HONG,*,†,‡ B. NALIBOFF,*,†,§,¶ J. S. LABUS,*,†,§,¶ A. GUPTA,*,† L. A. KILPATRICK,*,†,§
C. ASHE-McNALLEY,*,†,§ J. STAINS,*,† N. HEENDENIYA,*,† S. R. SMITH,*,† K. TILLISCH*,†,§ &
E. A. MAYER*,†,§,¶,**,††

MEDICAL COLLEGE OF WISCONSIN knowledge changing life

Pharmacological neuromodulation

Psychological therapies, hypnotherapy…

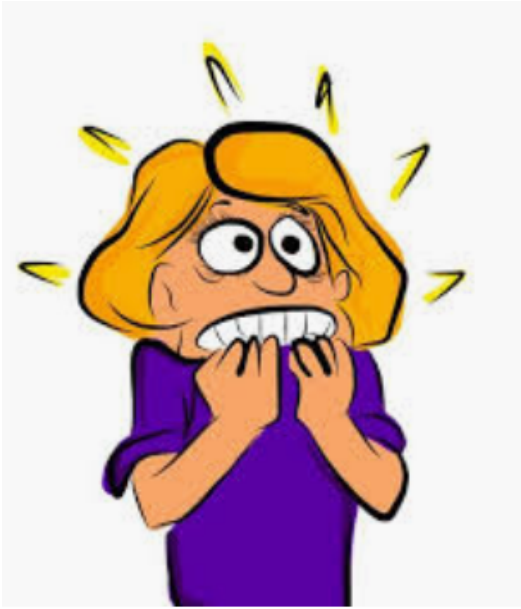
Cognitive therapy for irritable bowel syndrome is associated with reduced limbic activity, GI symptoms, and anxiety

Jeffrey M. Lackner[a,*], Mary Lou Coad[b], Howard R. Mertz[c], David S. Wack[b], Leonard A. Katz[a], Susan S. Krasner[d], Rebecca Firth[a], Thomas C. Mahl[a], Alan H. Lockwood[b,e]

A few diagnoses we may see…

Intractable migraine
Gastroparesis
Chronic constipation
Functional Nausea
GERD
Chronic neck and muscle pain
Anxiety
Raynaud's
Sleep disorder
Restless Leg syndrome
Fibromyalgia
Chronic fatigue
POTS
Joint hypermobility

GASTROINTESTINAL Multisystem Disorders!



Pain is CENTRAL

BENIGN???

Ehlers-Danlos Syndrome

	Maneuver
A	Passive dorsiflexion of fifth metacarpophalangeal joint to >=90^{O}
B	Opposition of thumb to volar aspect of ipsilateral forearm
C	Hyperextension of elbow >= 10^{O}
D	Hyperextension of knee >= 10^{O}
E	Place hands flat on floor without bending knees



Ehlers–Danlos Syndrome, Hypermobility Type: A Characterization of the Patients' Lived Experience

Brittney Murray,[1*] Beverly M. Yashar,[2] Wendy R. Uhlmann,[2,3] Daniel J. Clauw,[4] and Elizabeth M. Petty[5]

[1]Division of Cardiology, Johns Hopkins Hospital, Baltimore, Maryland

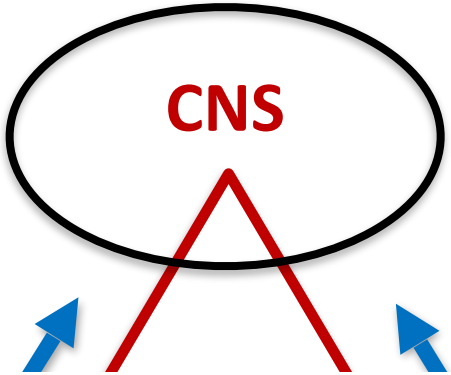
[2]Department of Human Genetics, University of Michigan Medical School, Ann Arbor, Michigan

[3]Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan

[4]Departments of Anesthesiology, Medicine (Rheumatology) and Psychiatry, University of Michigan Chronic Pain and Fatigue Researcl Ann Arbor, Michigan

[5]Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin

96% GI symptoms!



..and then there is the GUT!

CNS and ANS are connected…via VAGUS…



Dig Dis Sci.

Eviden
irritabl

Heitkempe

children
ain:
GN.
nterology & Motility NGM

ntestinal

ELSEVIER

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Journal of
Digestive Diseases

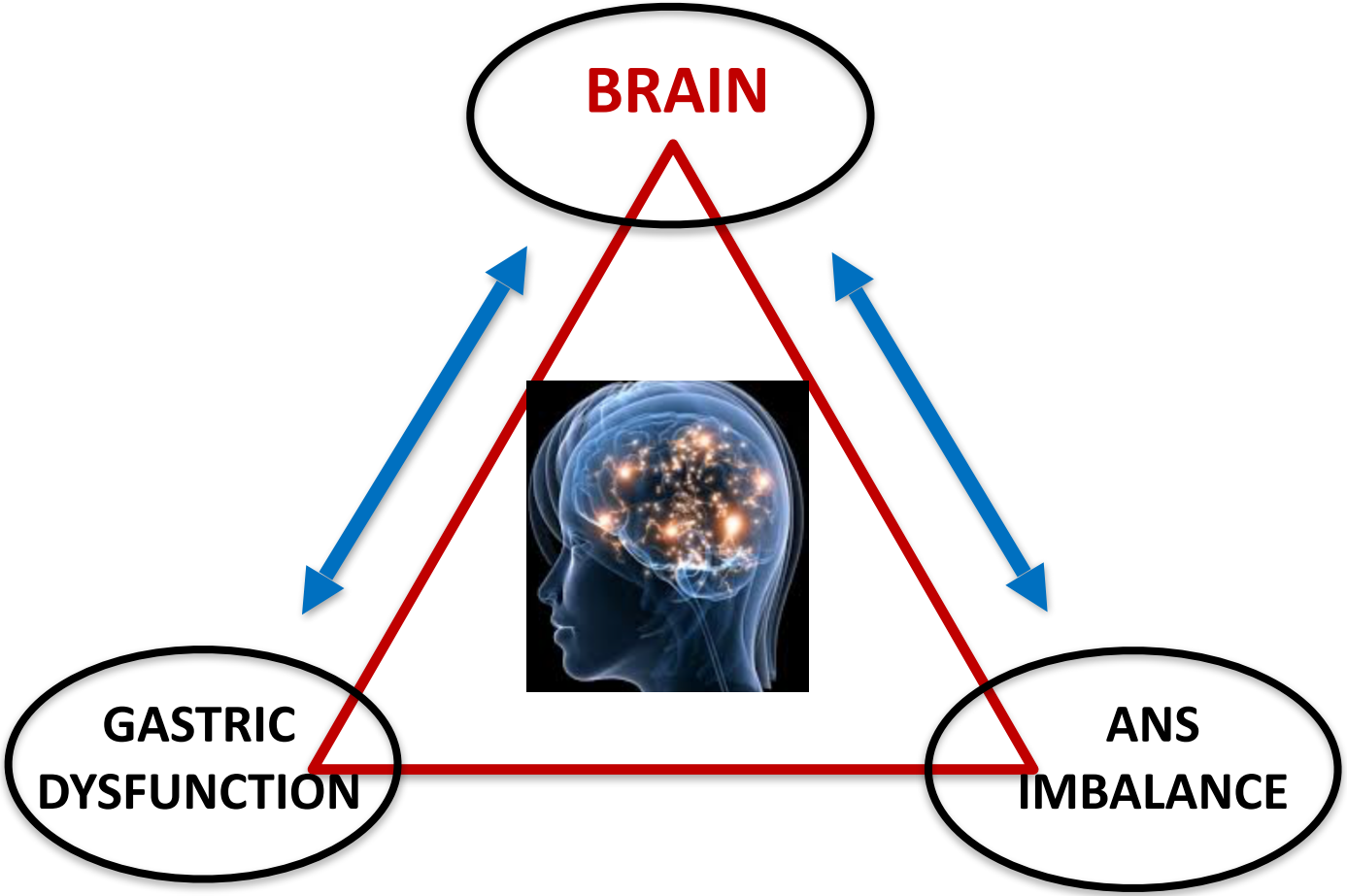
Journal of Digestive Diseases 2013; 14; 638–646

doi: 10.1111/1751-2980.1209

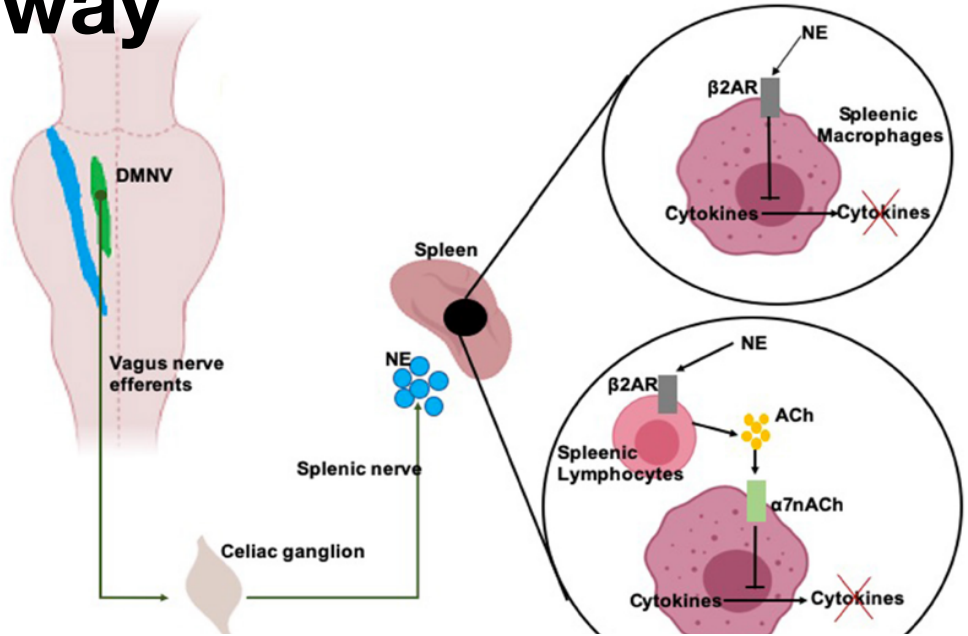
Meta analysis

Autonomic functioning in irritable bowel syndrome measured by heart rate variability: A meta-analysis

Qing LIU, Er Man WANG, Xiu Juan YAN & Sheng Liang CHEN

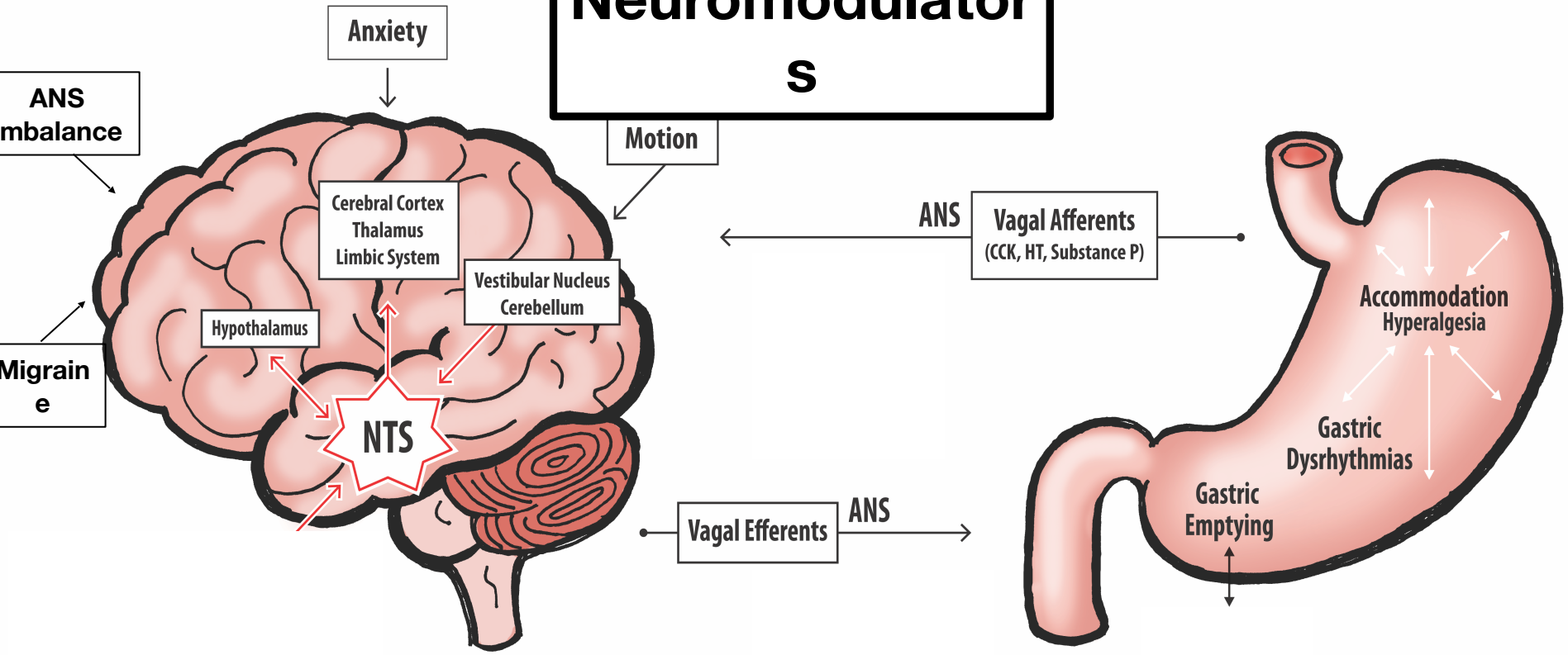

BRAIN
GASTRIC DYSFUNCTION
ANS IMBALANCE

Cholinergic Anti-inflammatory Pathway



Therapeutics to inhibit immune cell activation?

Neuromodulators

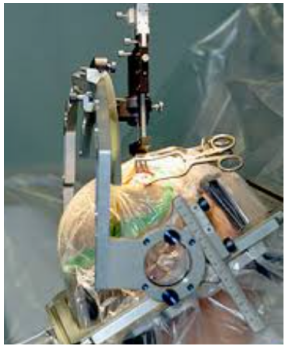


Centrally Mediated Therapies: Neuromodulation

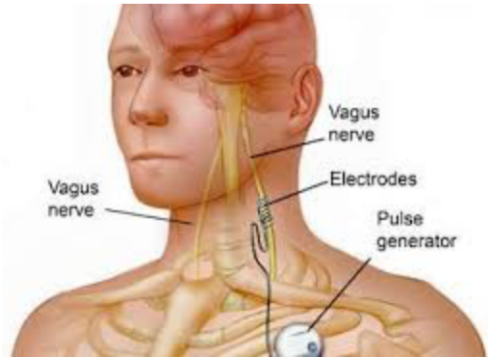
Spinal cord stimulation



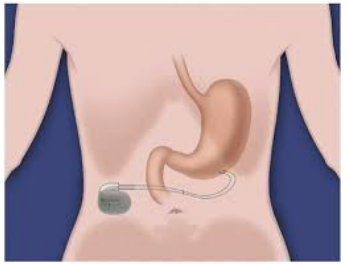
Deep brain stimulation



Vagus nerve stimulation



Gastric electrical stimulation



How could we target both ANS and CNS non-invasively?

Mechanism: Percutaneous Electrical Nerve Field Stimulation (PENFS)

- CNS effects via the ***AURICULAR BRANCH OF VAGUS NERVE***
- Brainstem nuclei: NTS & DMNV
- Vagal nerve stimulation?
- CNS effects?



Efficacy over placebo; RCT in complex FAPDs

THE LANCET
Gastroenterology & Hepatology

Articles

Neurostimulation for abdominal pain-related functional gastrointestinal disorders in adolescents: a randomised, double-blind, sham-controlled trial

Katja Kovacic, Keri Hainsworth, Manu Sood, Gisela Chelimsky, Rachel Unteutsch, Melodee Nugent, Pippa Simpson, Adrian Miranda

Summary

Background Development of safe and effective therapies for paediatric abdominal pain-related functional gastrointestinal disorders is needed. A non-invasive, US Food and Drug Administration-cleared device (Neuro-Stim, Innovative Health Solutions, IN, USA) delivers percutaneous electrical nerve field stimulation (PENFS) in the external ear to modulate central pain pathways. In this study, we evaluated the efficacy of PENFS in adolescents with abdominal pain-related functional gastrointestinal disorders.

Lancet Gastroenterol Hepatol 2017

Published Online August 18, 2017

http://dx.doi.org/10.1016/S2468-1253(17)30253-4

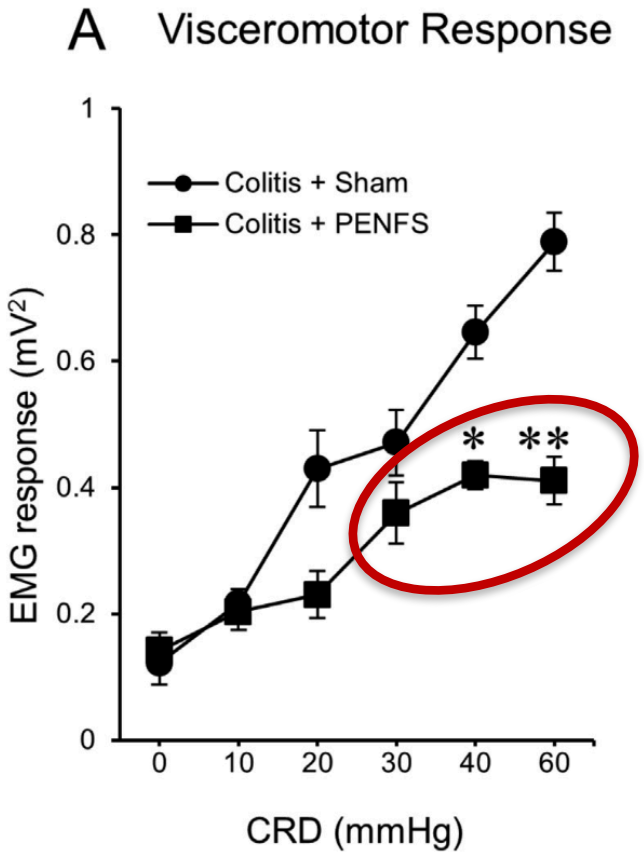


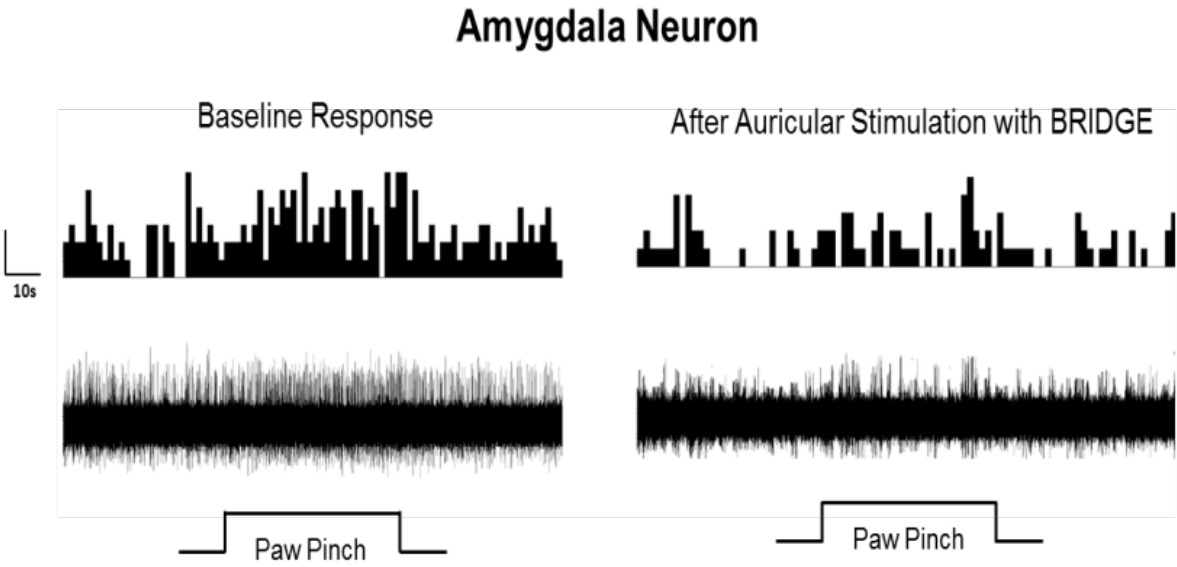
Animal & Human Studies



ANIMAL MODEL

- Intracolonic TNBS → PENFS vs sham
- Visceromotor response (VMR) to colon distention
  - Baseline/post-TNBS/post-PENFS
- Recordings from single neurons in amygdala and lumbar spinal cord
  - Baseline firing and responses to paw compression pre and post therapy


A
Visceromotor Response
Colitis + Sham
Colitis + PENFS
EMG response (mV²)
CRD (mmHg)
0
0.2
0.4
0.6
0.8
1
0
10
20
30
40
60
*
**


Amygdala Neuron
Baseline Response
After Auricular Stimulation with BRIDGE
10s
Paw Pinch
Paw Pinch

Received: 10 August 2018 | Revised: 29 November 2018 | Accepted: 16 December 2018

DOI: 10.1111/nmo.13546

REVIEW ARTICLE

WILEY Neurogastroenterology & Motility NGM

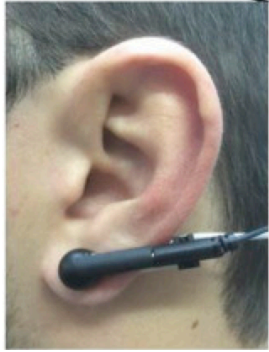
Advances in the physiology of gastric emptying

Raj K. Goyal | Yanmei Guo | Hiroshi Mashimo

- Brainstem mediates gastric function
- Gastric inhibitory and excitatory vagal motor circuits

Transcutaneous VNS





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Brain Stimulation

journal homepage: www.brainstimjrnl.com

Original Articles

Non-invasive Access to the Vagus Nerve Central Projections via Electrical Stimulation of the External Ear: fMRI Evidence in Humans

Eleni Frangos [a,*], Jens Ellrich [b,c,d], Barry R. Komisaruk [a]

Contents lists available at SciVerse ScienceDirect

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Brain Stimulation

journal homepage: www.brainstimjrnl.com

Transcutaneous Vagus Nerve Stimulation Modulates Default Mode Network in Major Depressive Disorder

Jiliang Fang, Peijing Rong, Yang Hong, Yangyang Fan, Jun Liu, Honghong Wang, Guolei Zhang, Xiaoyan Chen, Shan Shi, Liping Wang, Rupeng Liu, Jiwon Hwang, Zhengjie Li, Jing Tao, Yang Wang, Bing Zhu, and Jian Kong

utaneous Electrical Nerve
Pilot Study

in [c], Johannes Kornhuber [a],

Children's Wisconsin

Impaired Vagal Efficiency Predicts Auricular Neurostimulation Response in Adolescent Functional Abdominal Pain Disorders

Katja Kovacic, MD[1], Jacek Kolacz, PhD[2,3], Gregory F. Lewis, PhD[2–4] and Stephen W. Porges, PhD[3,5]

Am J Gastroenterol 2020;115:1534–1538. https://doi.org/10.14309/ajg.0000000000000753

- ECG: heart rate variability measurements before and after therapy
- Vagal tone: respiratory sinus arrythmia (RSA)
- RSA: brainstem control of heart

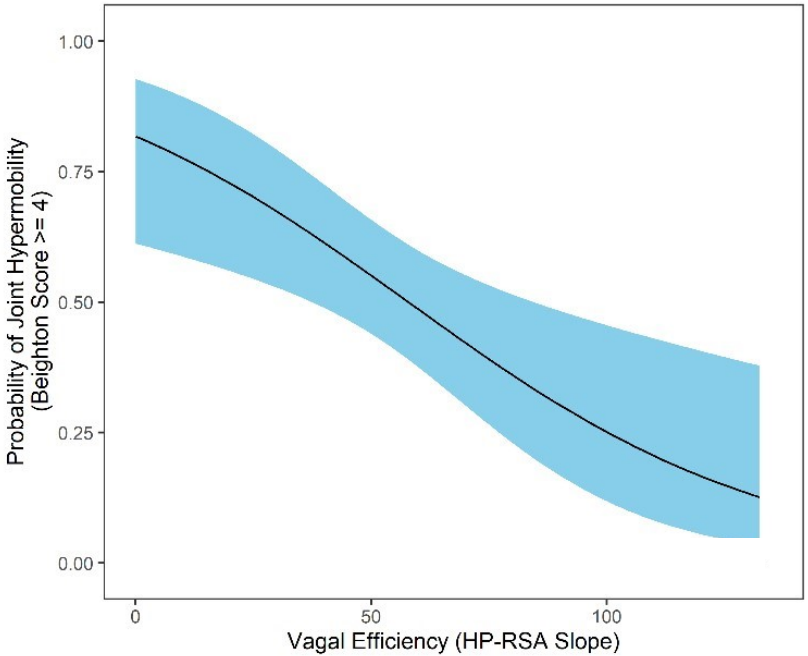
Vagal Efficiency metric

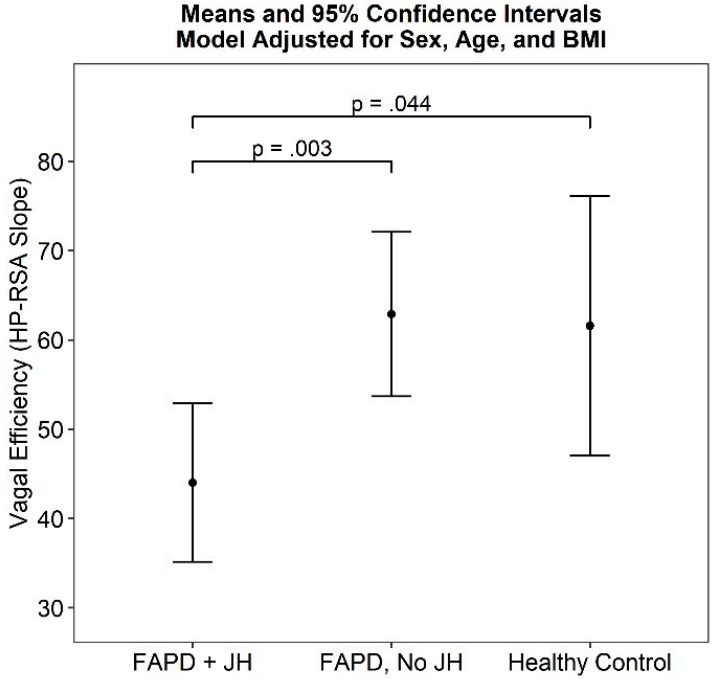


- Effectiveness of the vagal brake in regulating hea rate during posture shifts
- **Low vagal efficiency = predictor of improved pain after neurostimulation therapy**

Vagal neuromodulation is a plausible mechanism

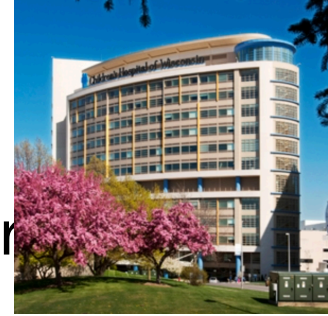
FGIDs, ANS dysfunction & EDS





Higher Beighton score (joint hypermobility) = lower vagal efficiency

Ongoing research at MCW



- NIH: Brain-gut physiology and neuromodulation for chronic nausea
- Multi-center clinical registry
- Pilot study of PENFS for Cyclic Vomiting Syndrome
- Mechanistic studies
- Ehlers-Danlos Syndrome
  - PENFS
  - Acoustic VNS
  - ANS measures, Immune fxn, GI motor function





Summary

- Functional GI disorders= aberrant brain-gut signaling
- Neuroimaging research is expanding our knowledge of abnormal functional connectivity in DGBI
- Aberrant ANS signaling is a key concept
- Brainstem mediates gastric function via vagal pathways
- Ongoing research suggest promising effects of

Thank You

Medical College of Wisconsin

NIH:
1K23DK116969-01

Manu Sood
Reza Shaker
Nita Salzman

Indiana University
Kinsey Institute
Traumatic Stress Research Consortium



Stephen W. Porges, PhD



Jacek Kolacz, PhD