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Breinwijzer vzw

De ‘microbiota-gut-brain axis’

Tussen hype en revolutie?

- Prof. Dr. Lukas Van Oudenhove
- Laboratory for Brain-Gut Axis Studies (LaBGAS)
- Translational Research Center for Gastrointestinal Disorders (TARGID)
- KU Leuven

Introduction

anatomy & physiology of the ‘brain-gut axis’

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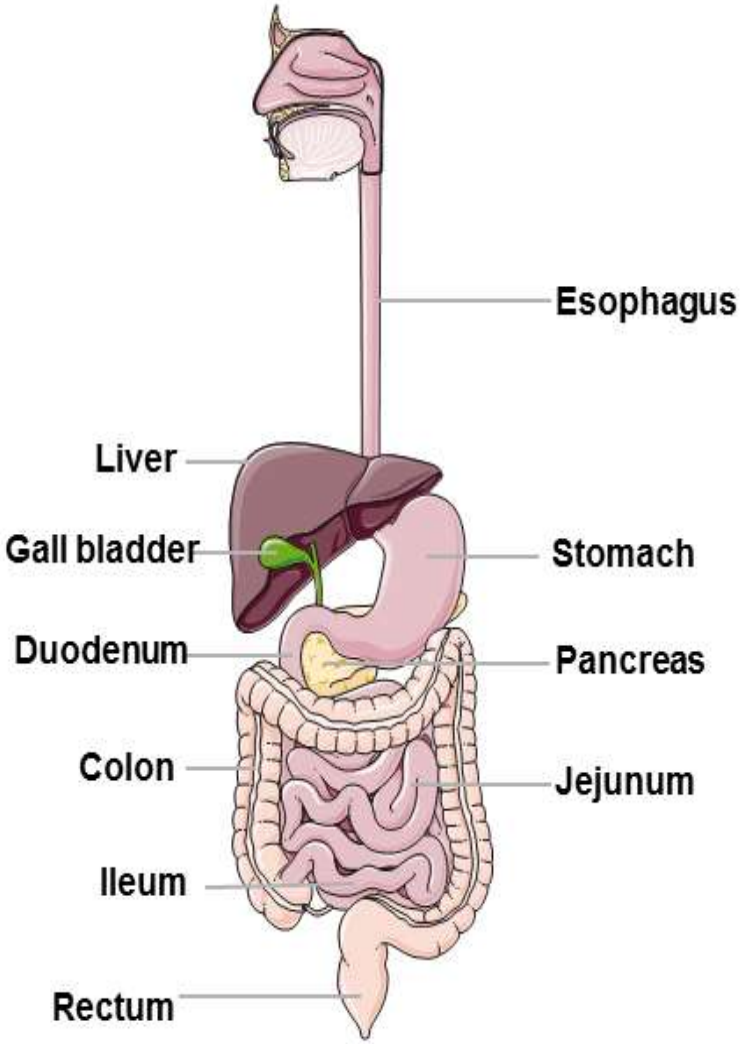
Gastrointestinal Tract



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Gastrointestinal Tract
an extremely complex organ system

- **surface** ~ 300 m^2
  - absorption
- **nervous organ**
  - 100 million nerve cells
    - “intrinsic”
    - “extrinsic”
  - most complex interaction with the brain
- **hormonal organ**
  - largest hormone production (> 30 hormones)
- **immune organ**
  - 60-70% of our immune cells
- 10^{14} **bacteria**

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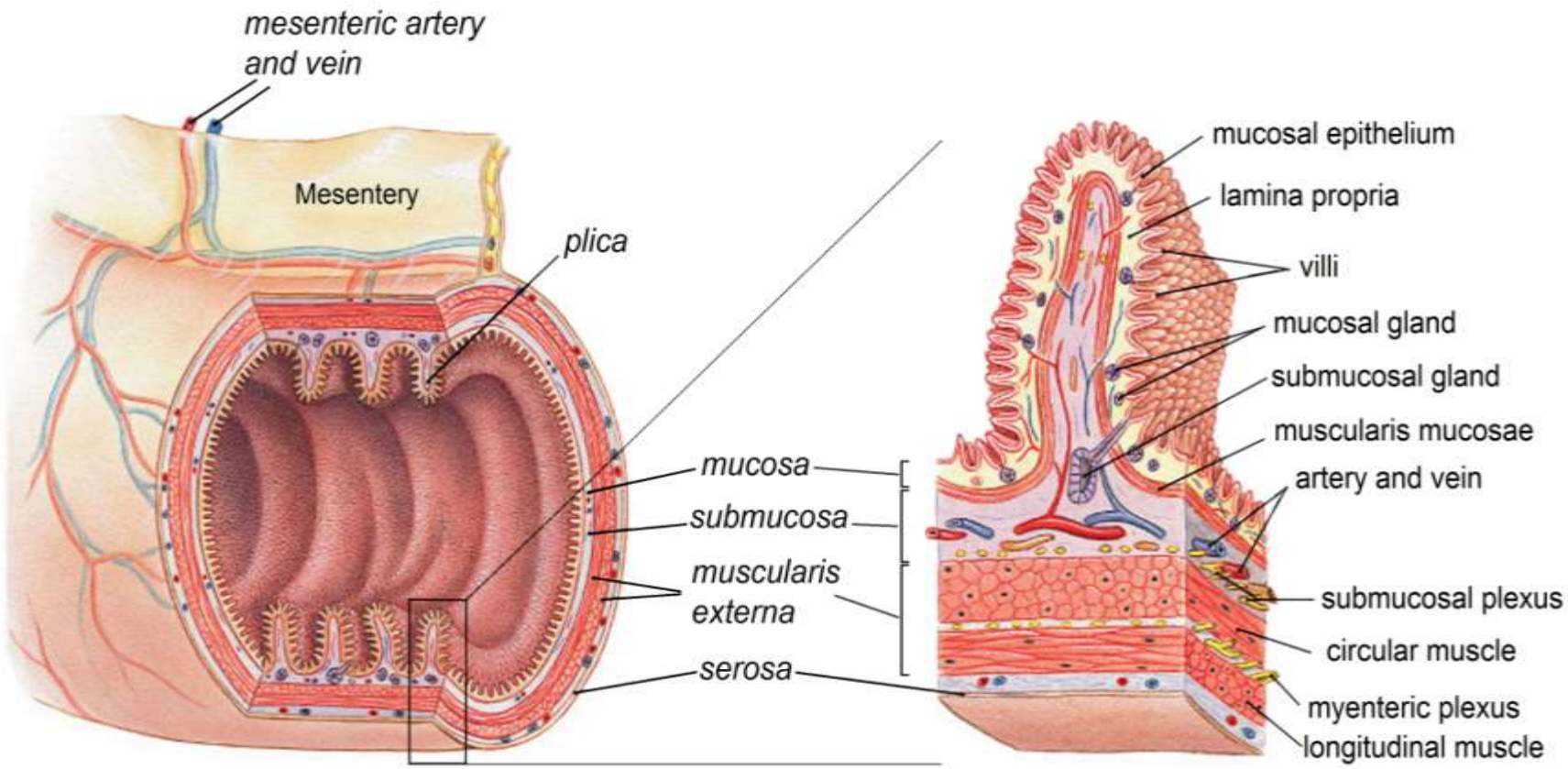
Gastrointestinal Tract



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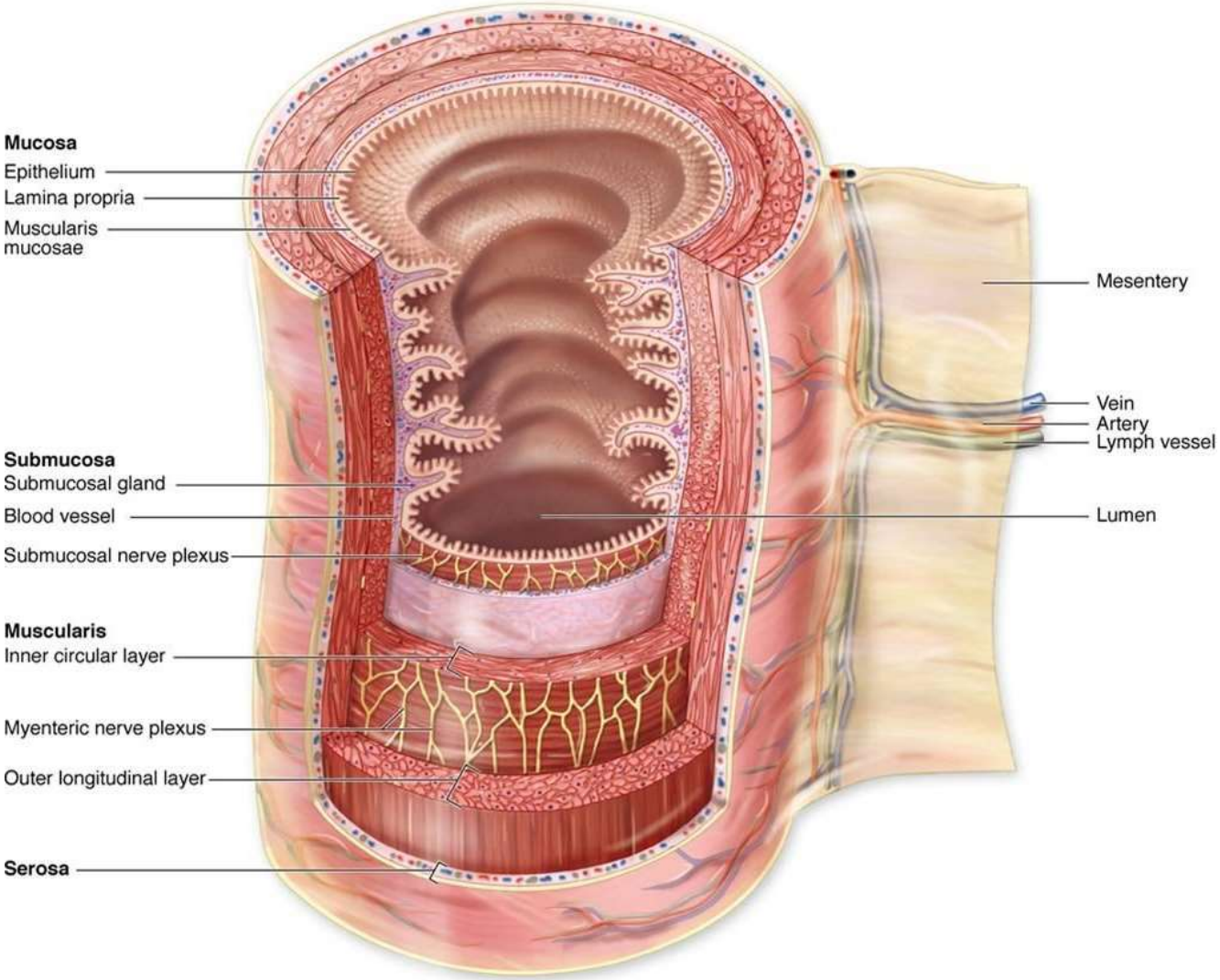
Enteric Nervous System (ENS)



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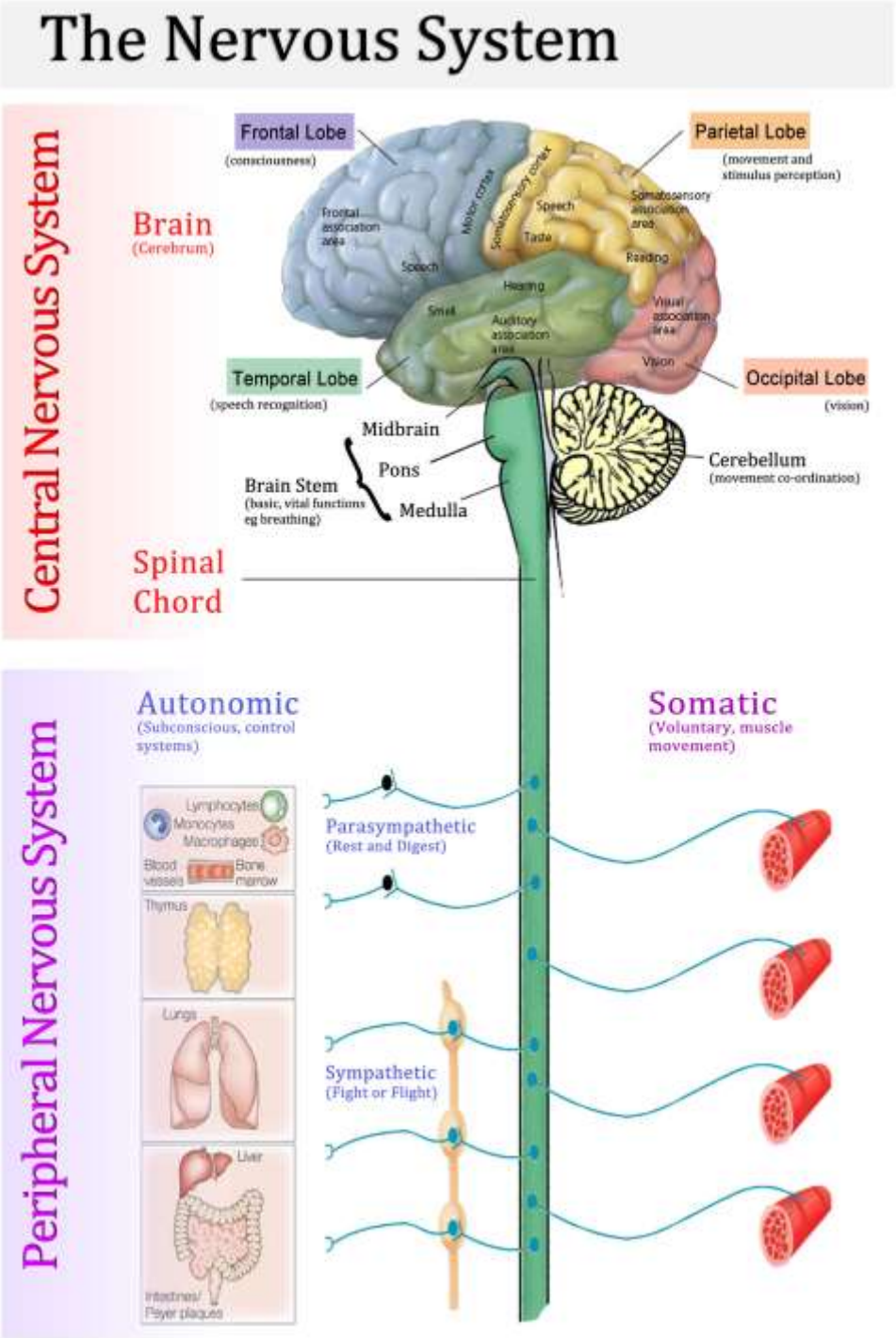
Brain
Nervous Systems



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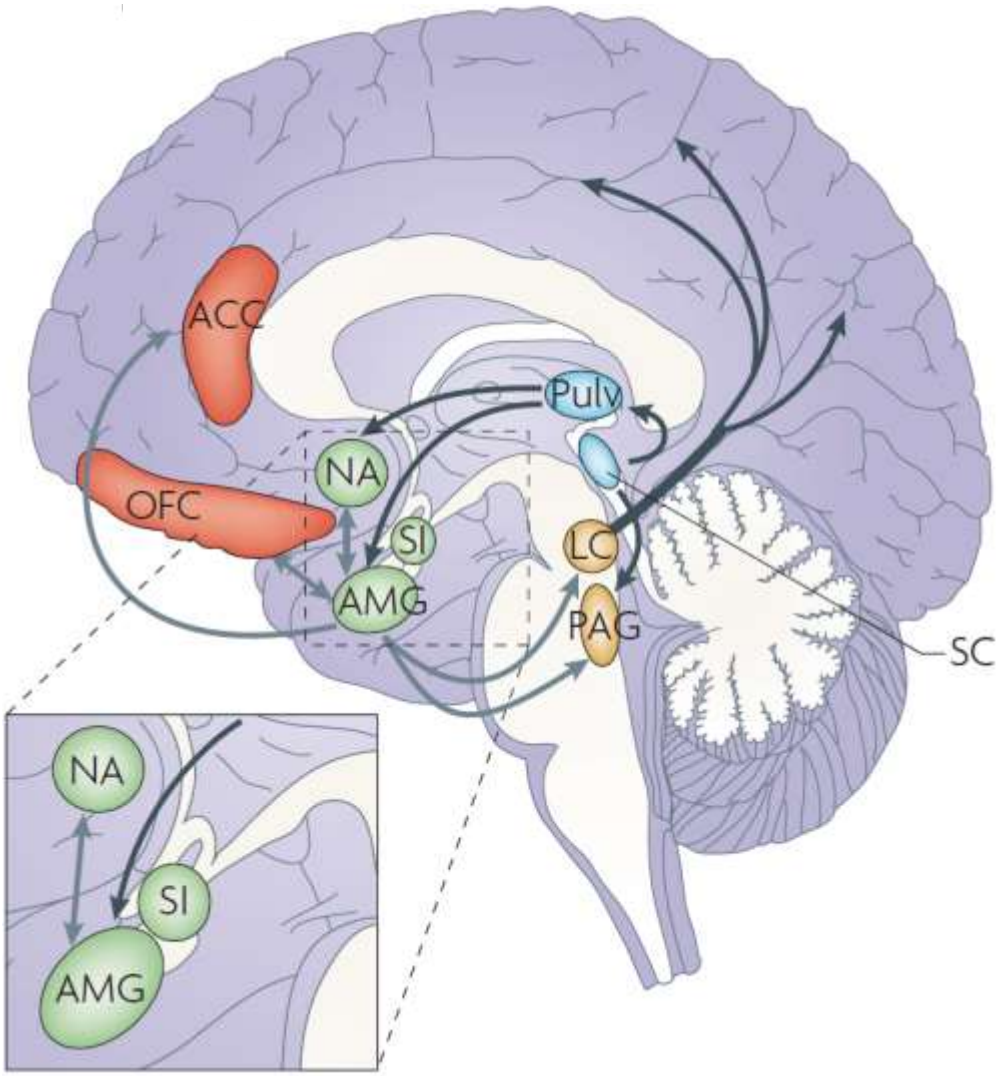
Emotional Brain



- Brainstem
  - PAG, periaqueductal gray
  - LC, locus coeruleus
- Subcortical
  - NA, nucleus accumbens
  - AMG, amygdala
- Cortical
  - ACC, anterior cingulate cortex
  - OFC, orbitofrontal cortex

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Gut-Brain Axis

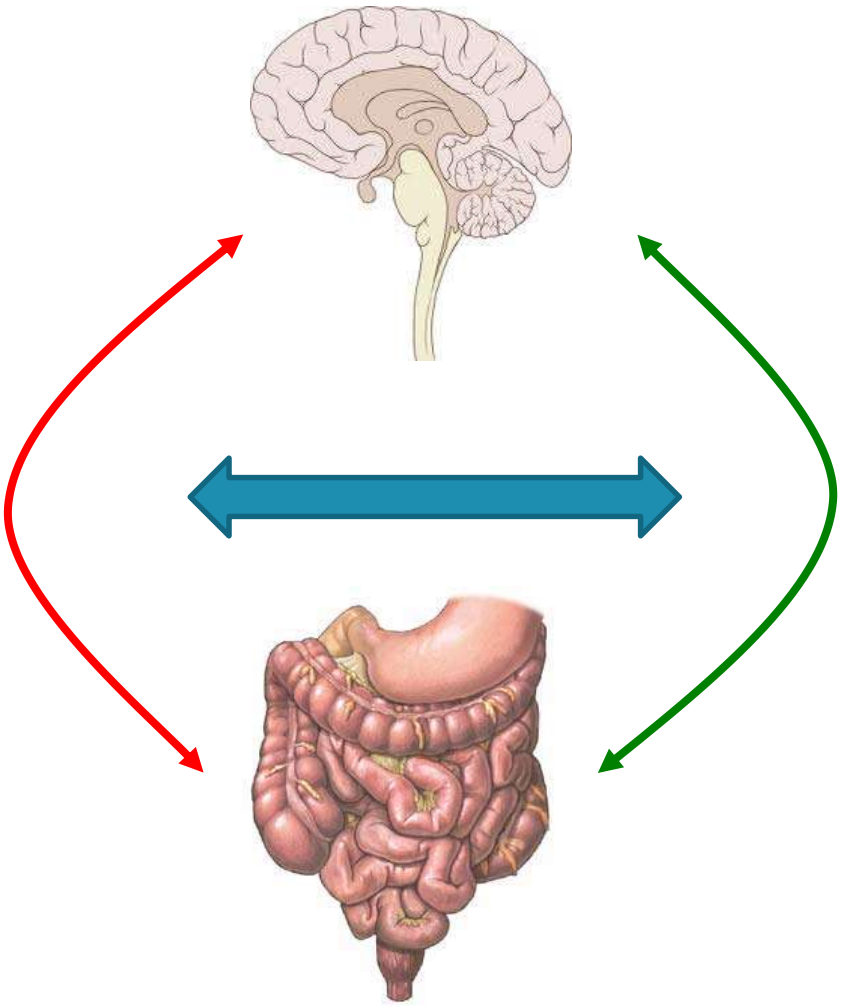
HUMORAL

GUT-BRAIN

gastrointestinal hormones
inflammatory mediators

BRAIN-GUT

Hypothalamo-Pituitary-Adrenal Axis



NEURAL

Autonomic Nervous System

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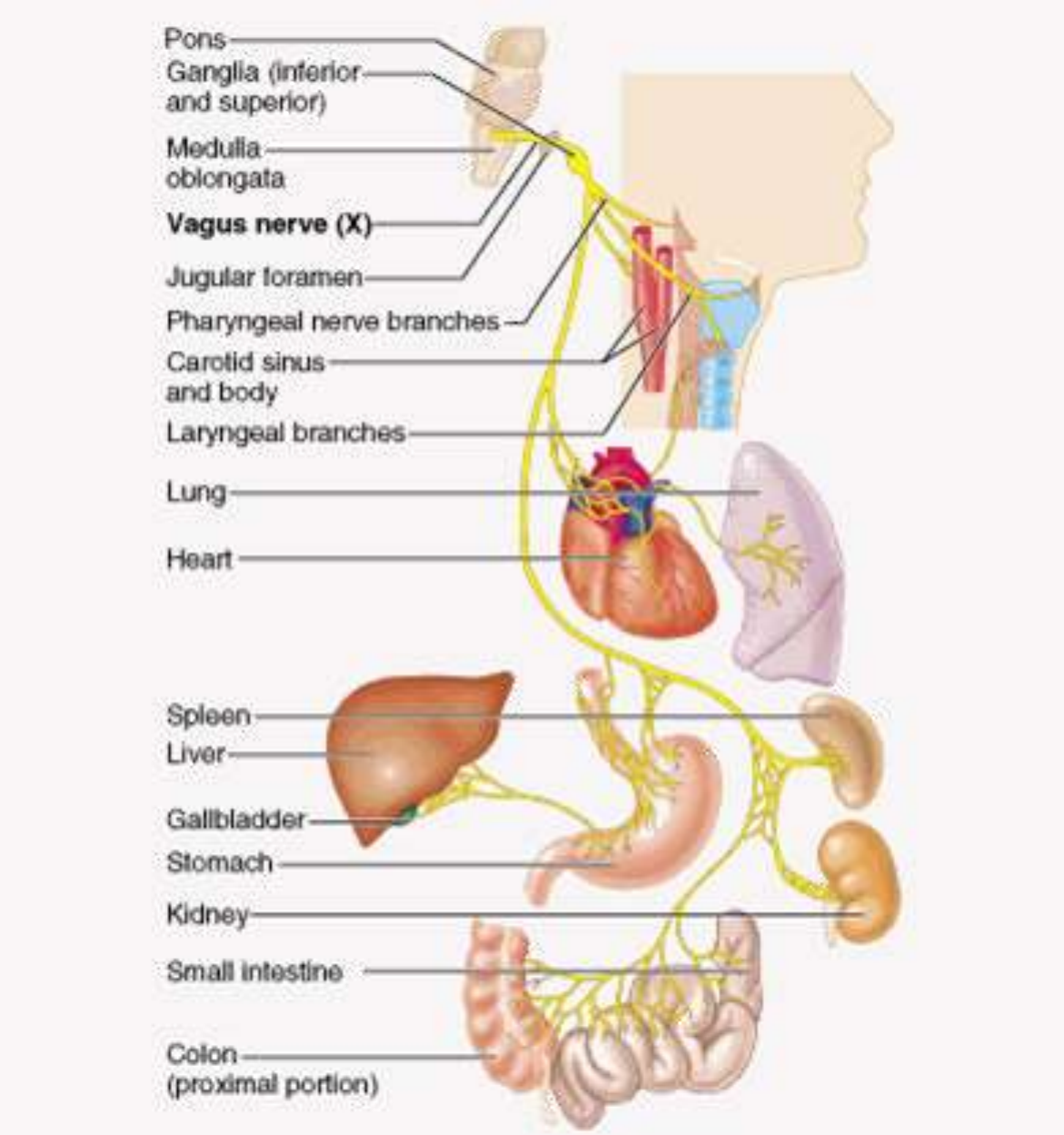
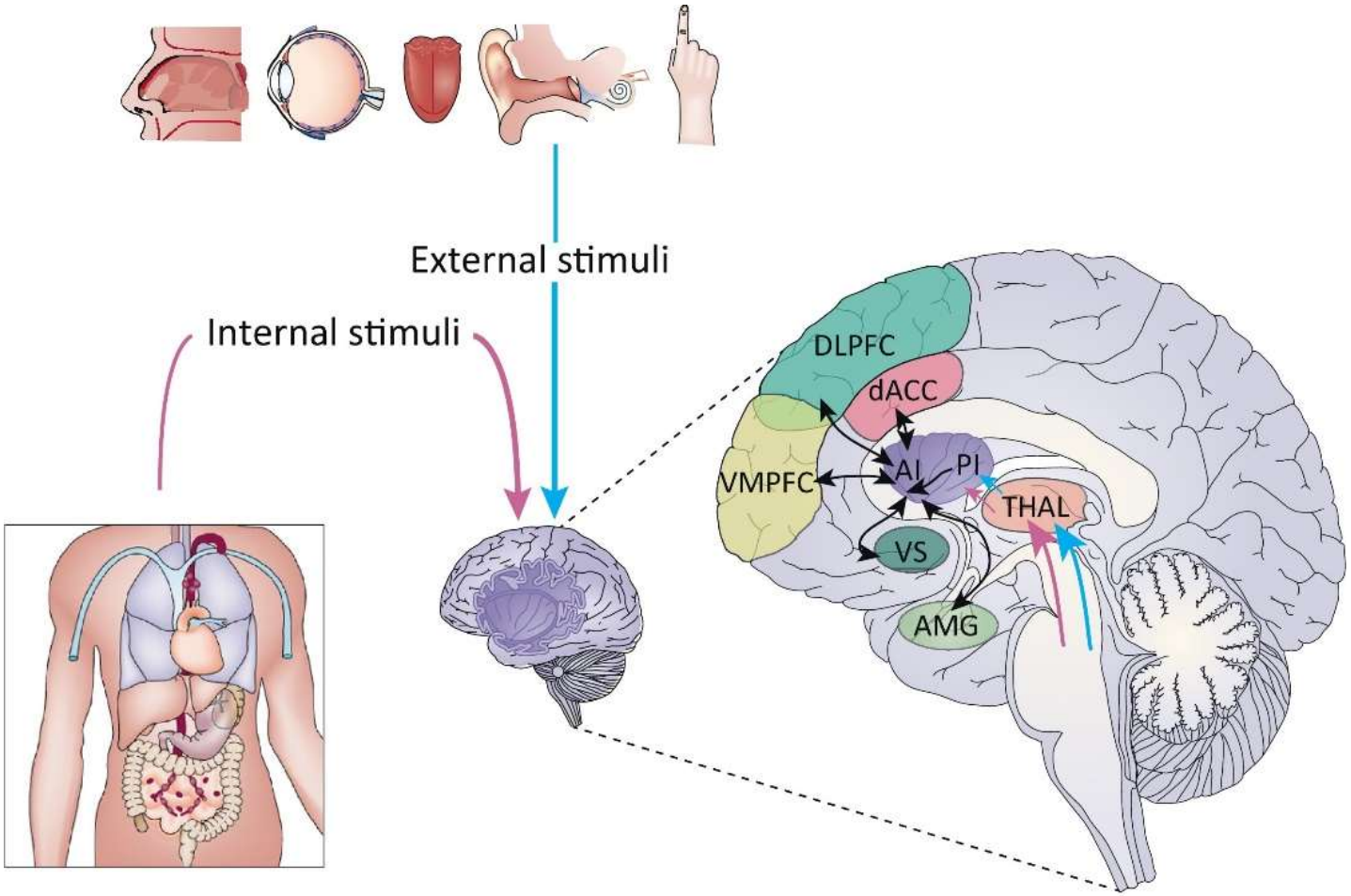
Vagus nerve


Pons
Ganglia (inferior and superior)
Medulla oblongata
Vagus nerve (X)
Jugular foramen
Pharyngeal nerve branches
Carotid sinus and body
Laryngeal branches
Lung
Heart
Spleen
Liver
Gallbladder
Stomach
Kidney
Small intestine
Colon (proximal portion)

Insula
Linking sensory & emotional information



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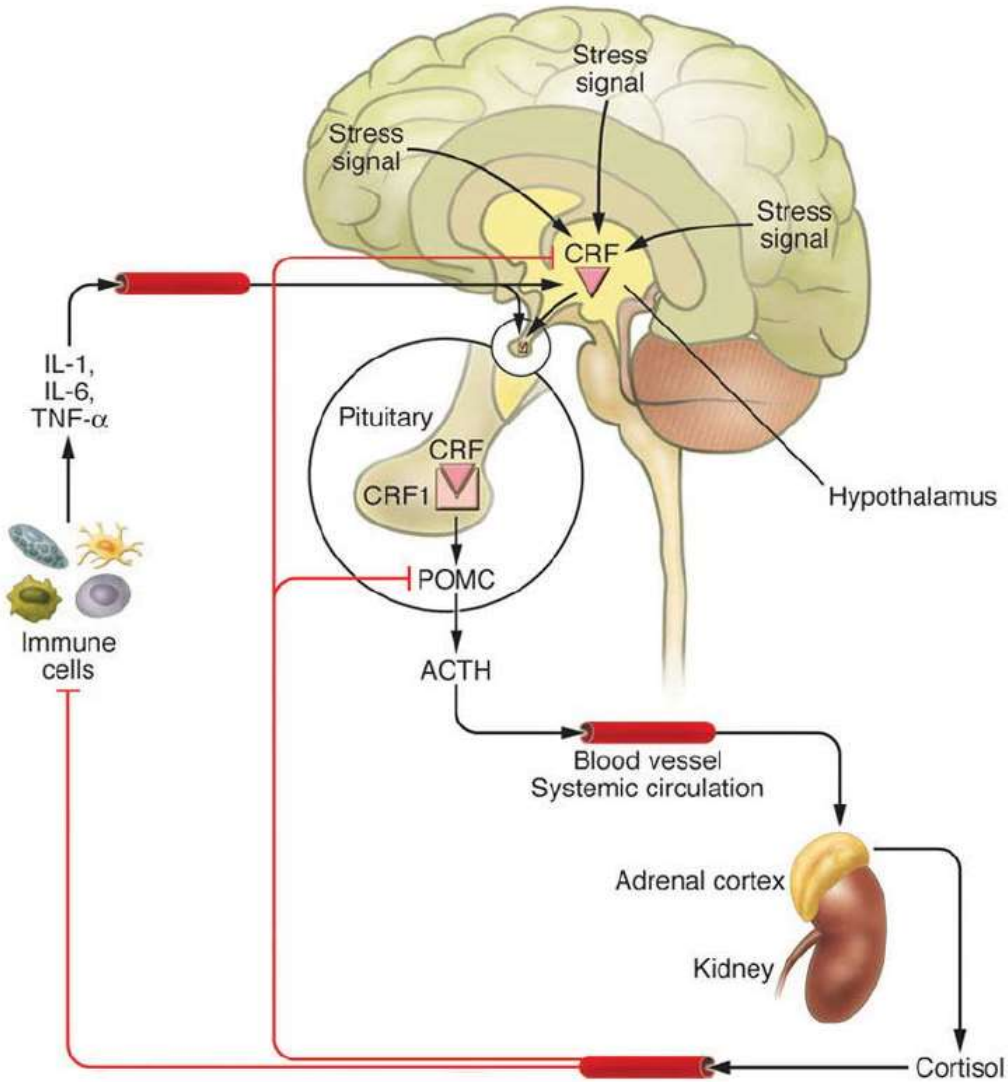
Hypothalamo-Pituitary-Adrenal (HPA) axis



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1. The link between psychological & gastrointestinal symptoms

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‘stress-related’ gastrointestinal symptoms
normality to functional gastrointestinal disorders

- **normality**
  - gastrointestinal symptoms during stress
    - stomach problems
    - diarrhea
  - “butterflies in the stomach”

- **“functional gastrointestinal disorders”**
  - irritable bowel syndrome, functional dyspepsia,…
  - symptom-based diagnosis, no organic cause
  - associated with stress, fear/anxiety, depression,…

irritable bowel syndrome (IBS)
Rome IV definition

C1. Diagnostic Criteria[a] for Irritable Bowel Syndrome

Recurrent abdominal pain, on average, at least 1 day per week in the last 3 months, associated with 2 or more of the following criteria:

1. Related to defecation
2. Associated with a change in frequency of stool
3. Associated with a change in form (appearance) of stool

[a]Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis.

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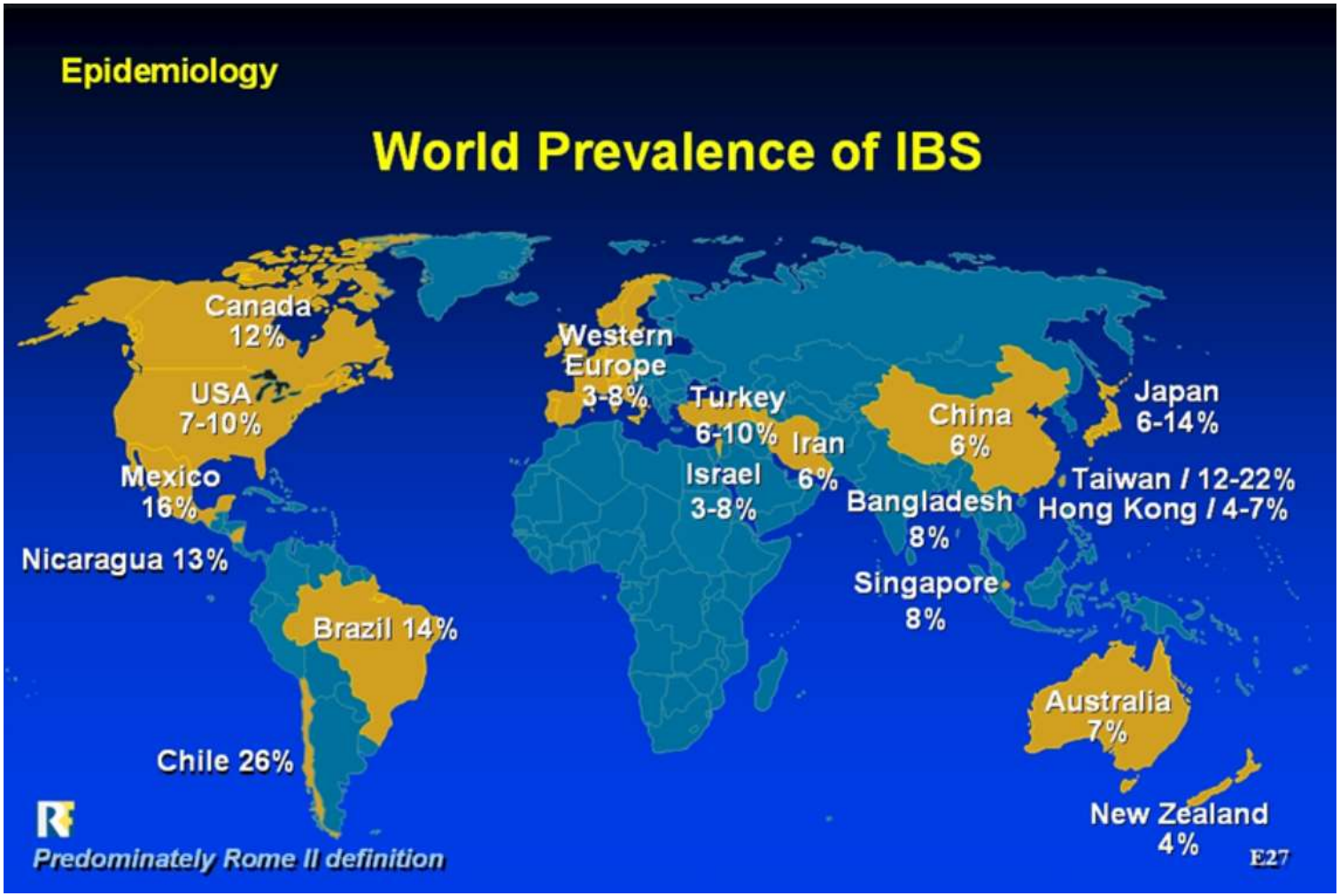
irritable bowel syndrome world prevalence



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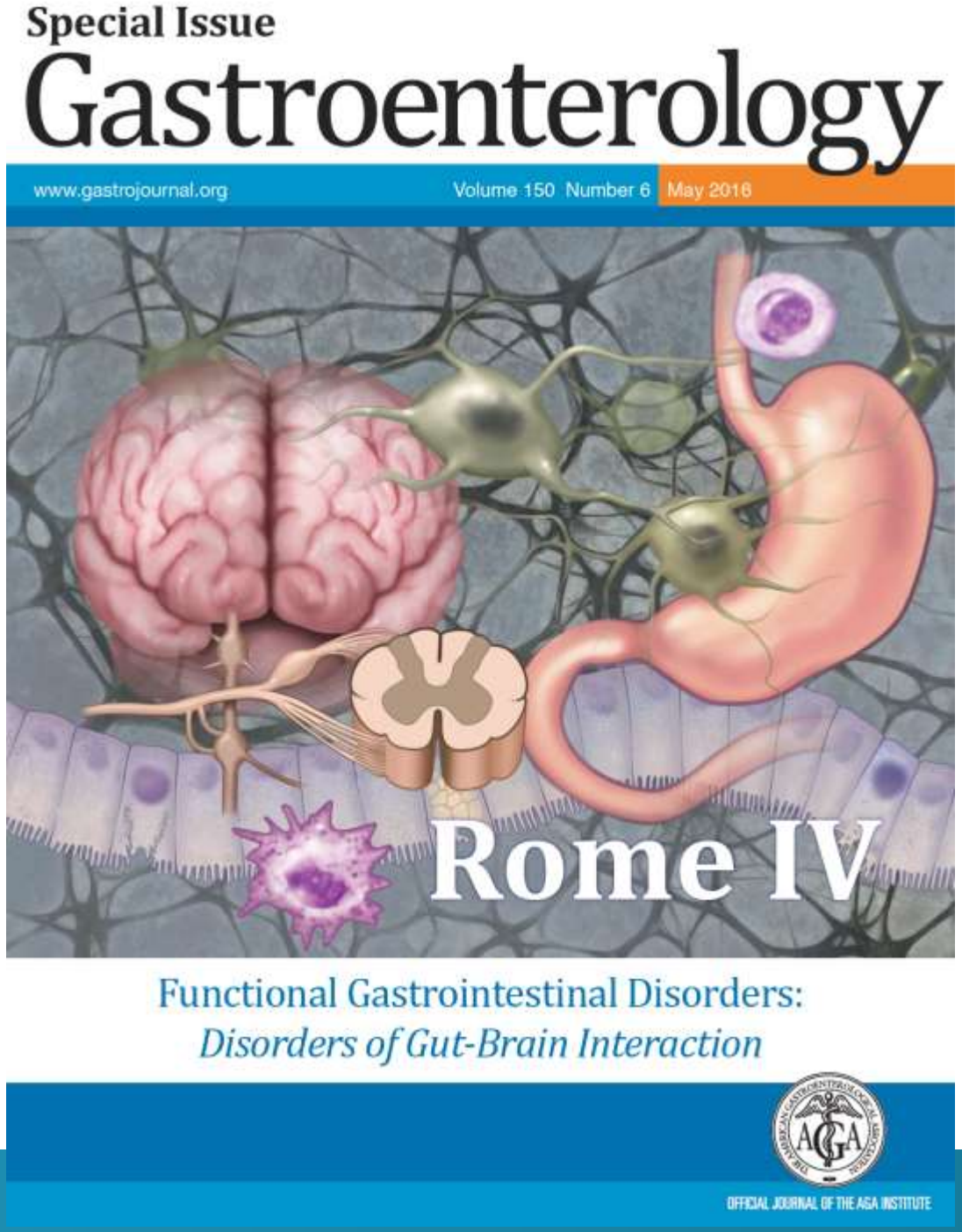

Douglas A. Drossman

William L. Hasler

Special Issue Editors

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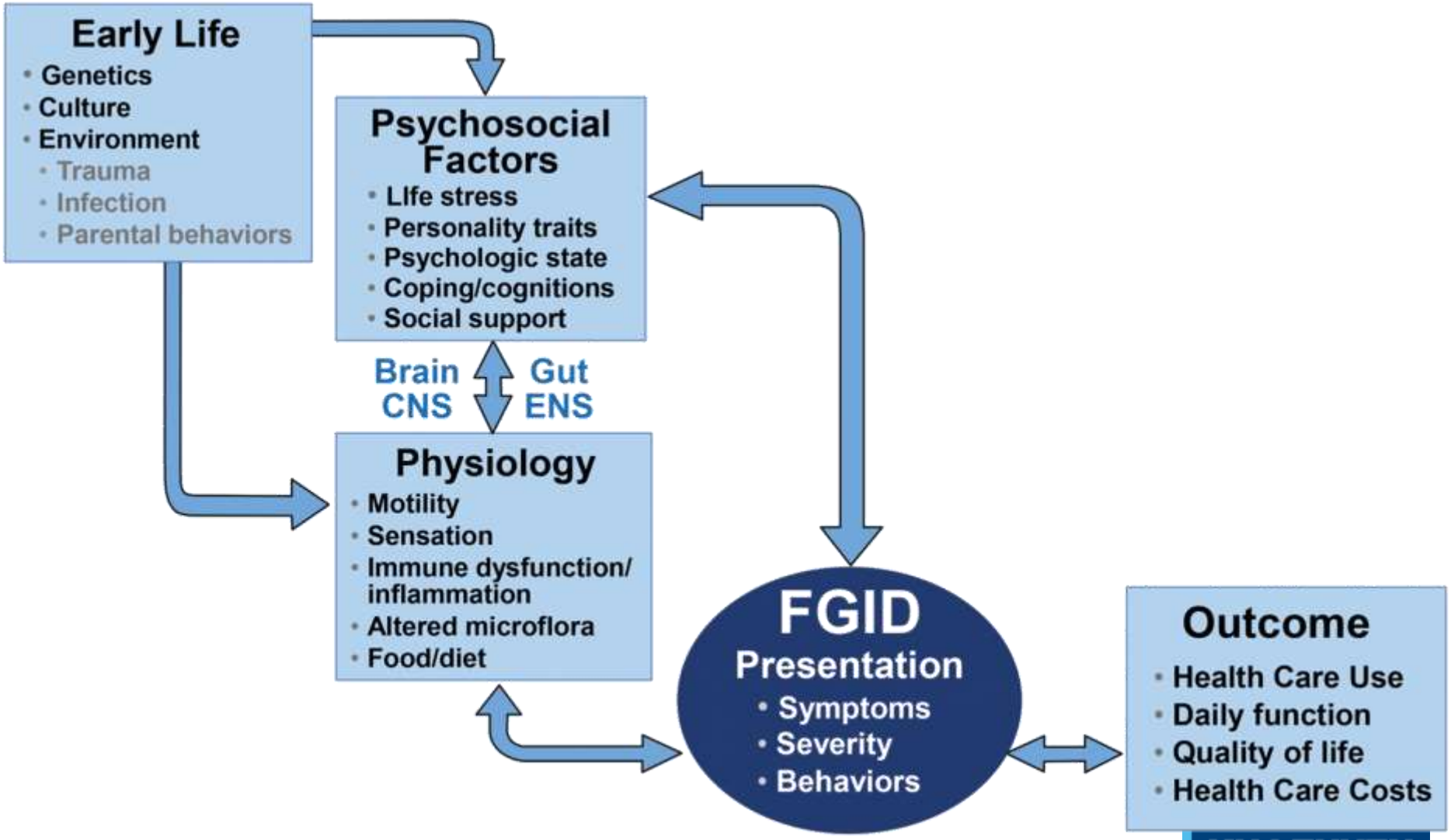
functional gastrointestinal disorders
biopsychosocial model



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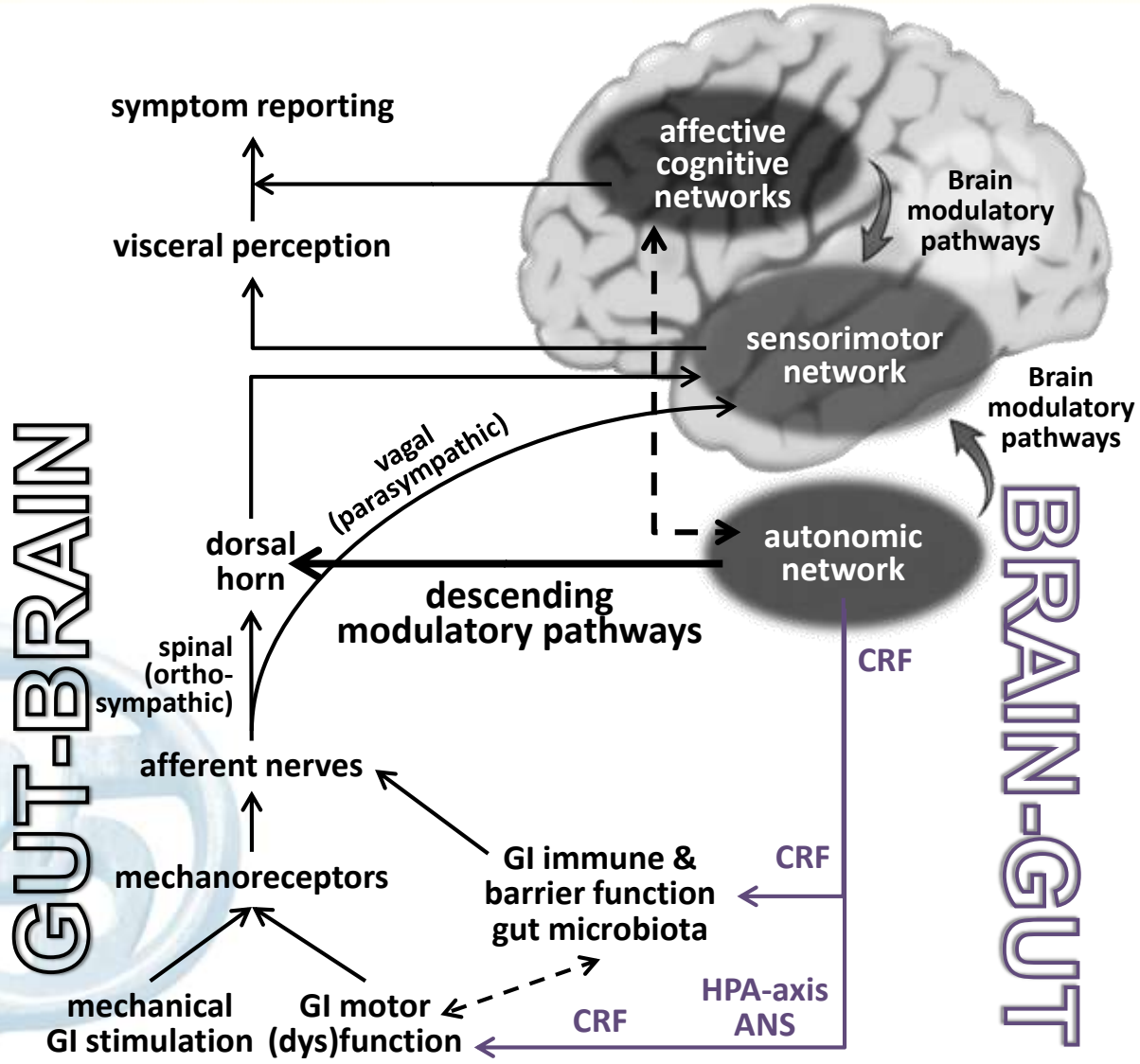
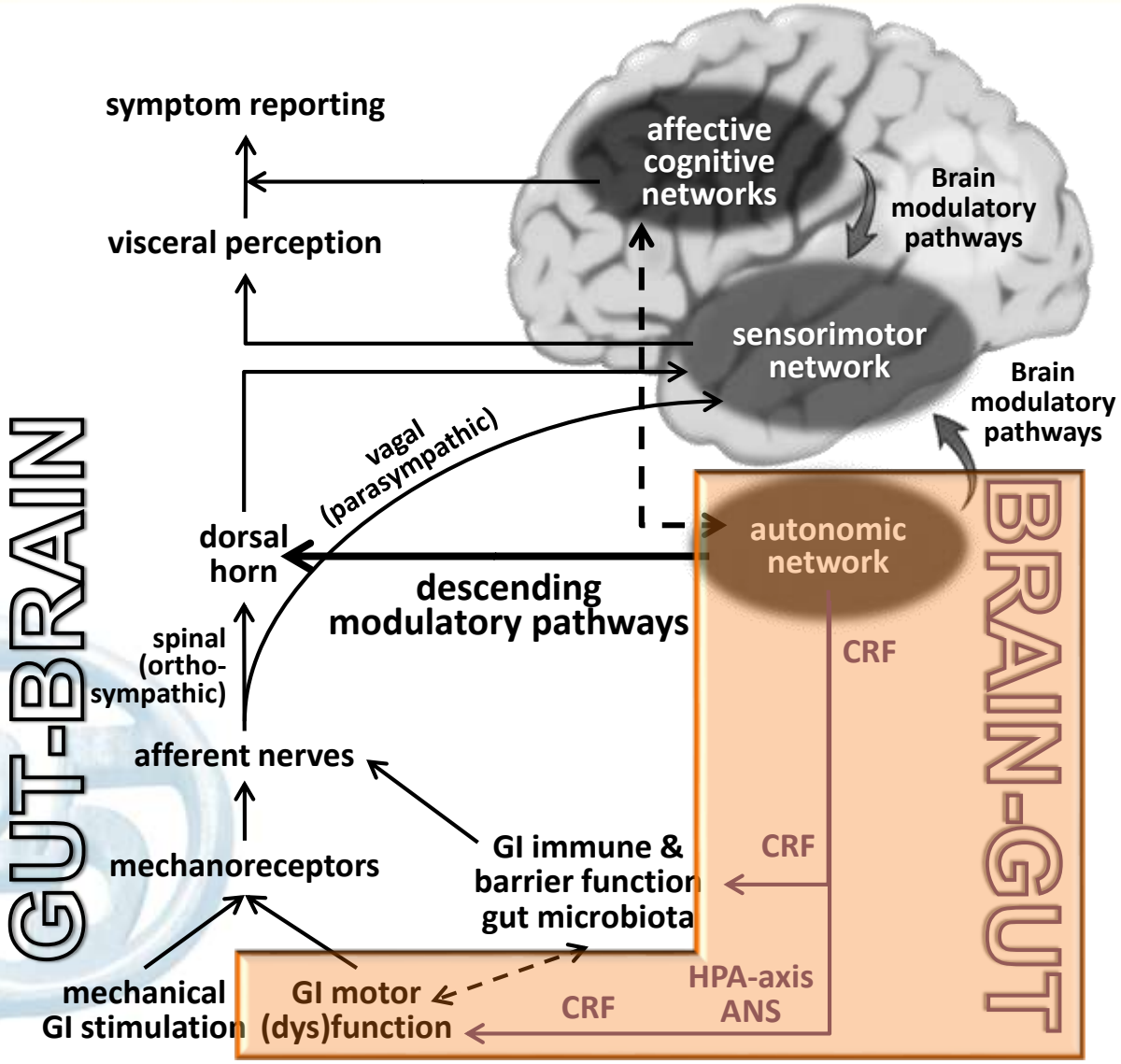
Functional Gastrointestinal Disorders
disorders of gut-brain interactions

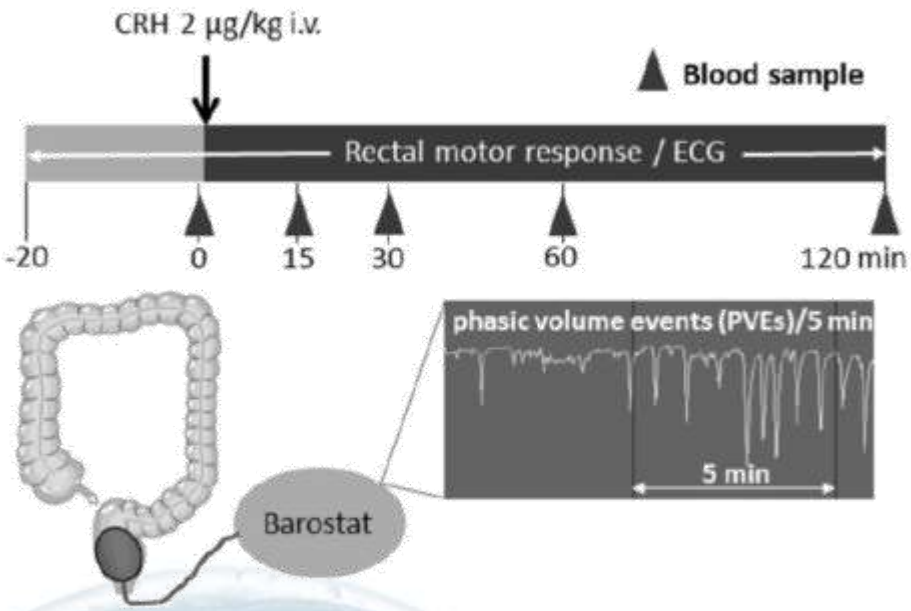


Psychological impact on GI symptoms
overview



HPA-axis & gastrointestinal responses to CRH injection in IBS

Experiment 1

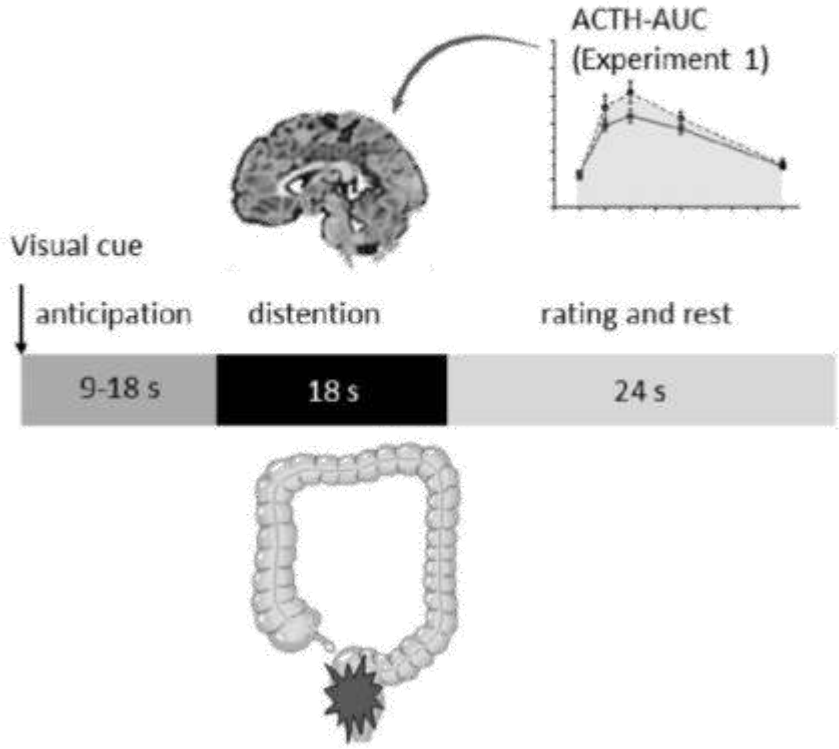


Parameters

- **HPA axis:** ACTH & cortisol
- **Colonic motor responses:** number of PVEs/ 5 min
- **Autonomic function:** HRV/ 5 min

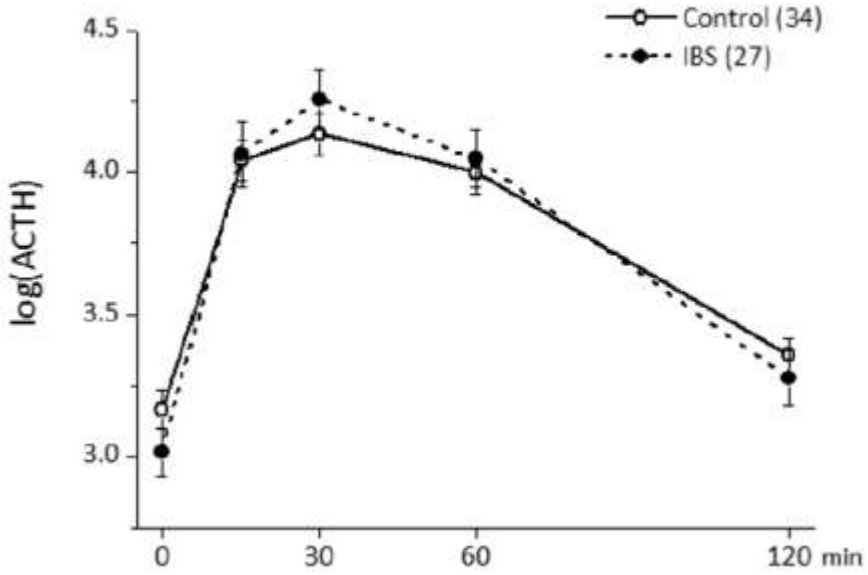
Experiment 2

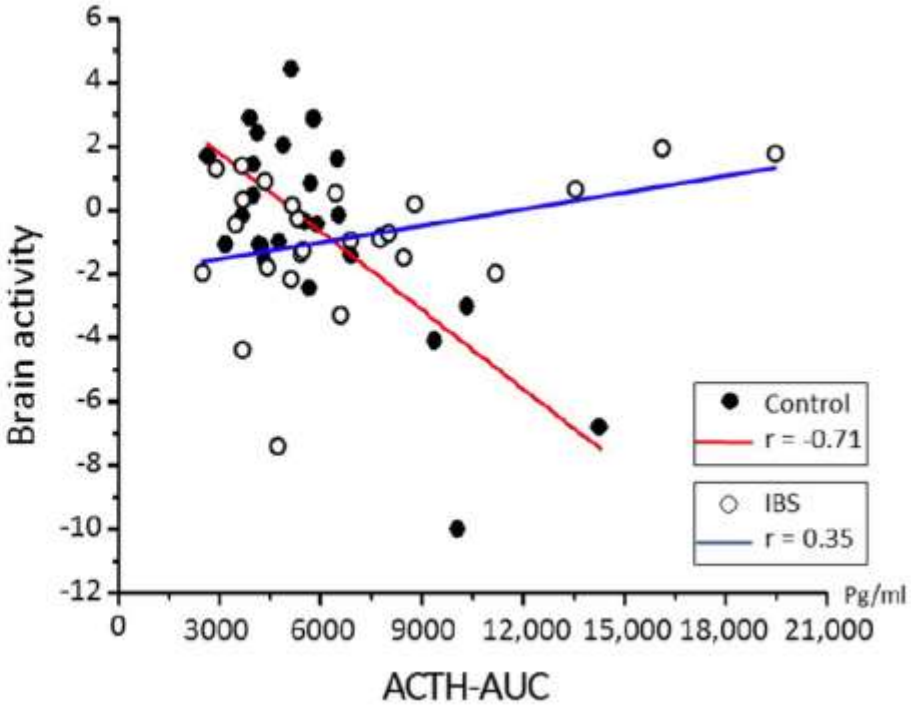
Brain activity during rectal distension correlated with the ACTH-AUC

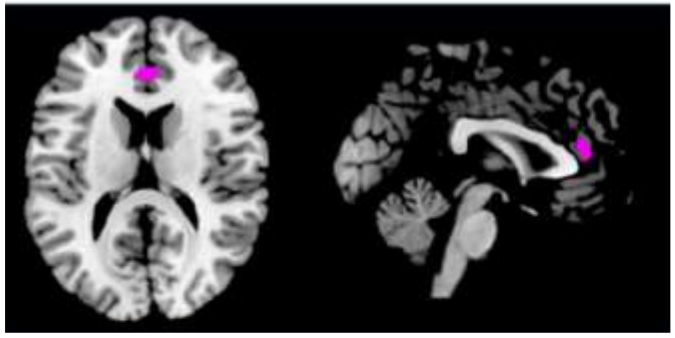


Kano, …, Van Oudenhove, …, Fukudo, Sci Rep 2017

Increased ACTH response to CRH injection in IBS

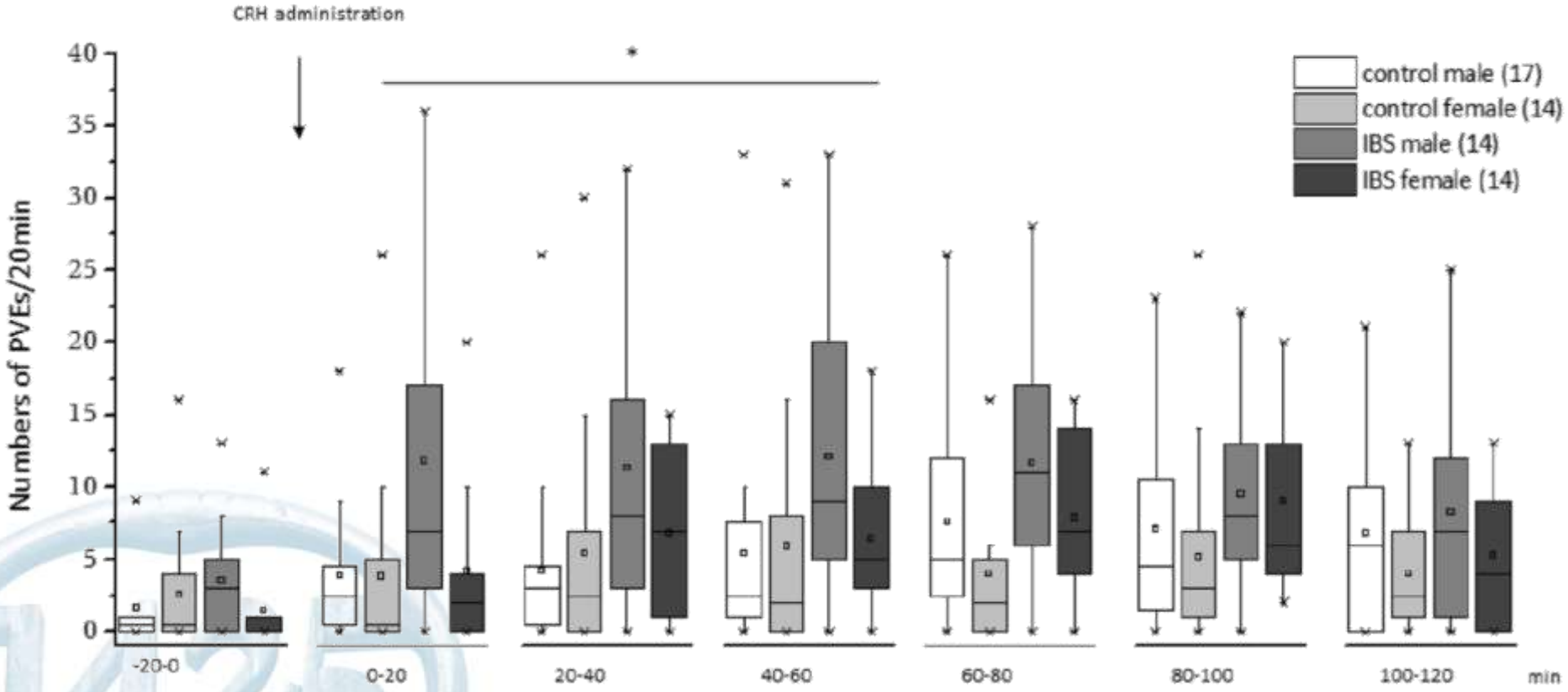






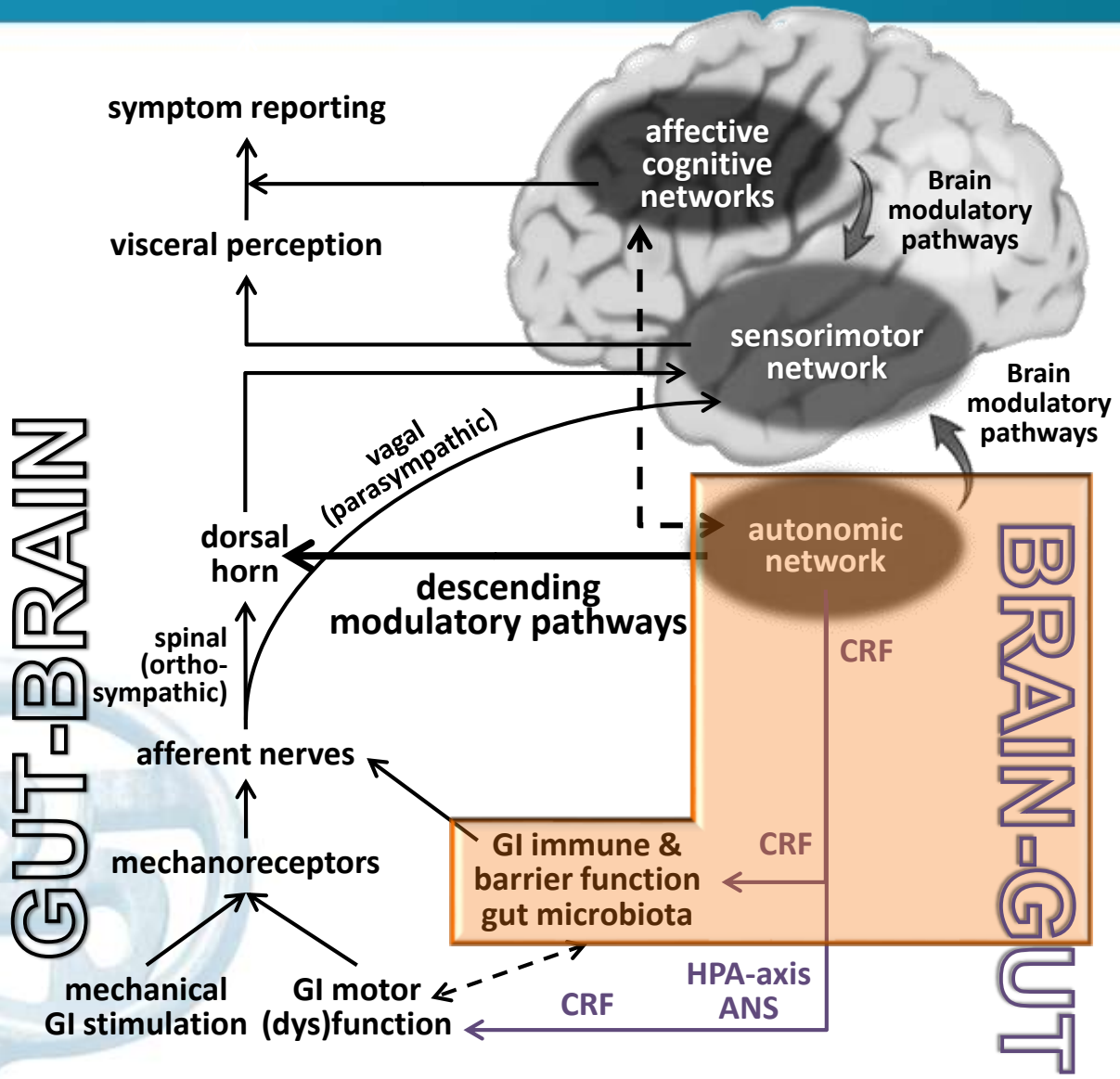
Kano, …, Van Oudenhove, …, Fukudo, Sci Rep 2017

Increased colonic motility response to CRH injection in male IBS patients

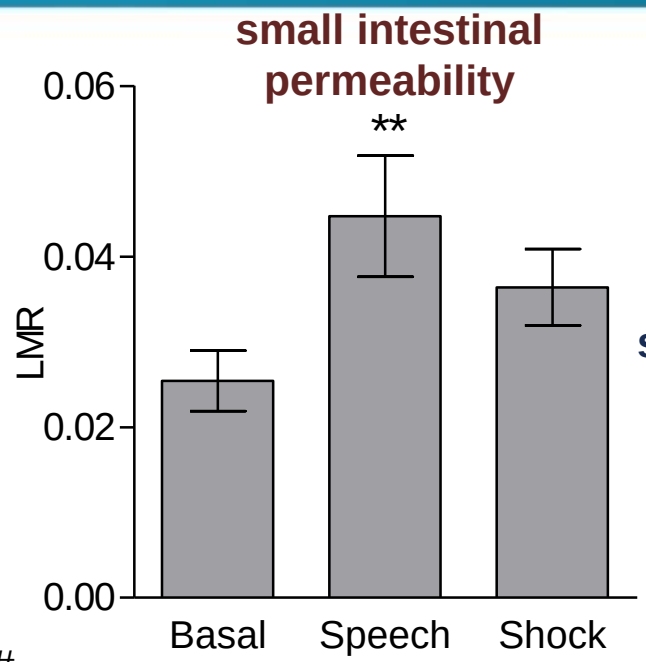


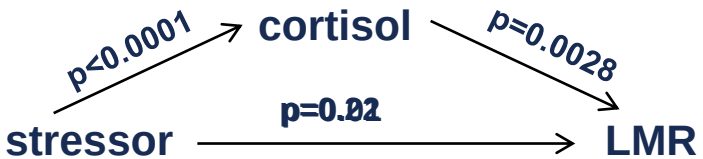
Kano, …, Van Oudenhove, …, Fukudo, Sci Rep 2017

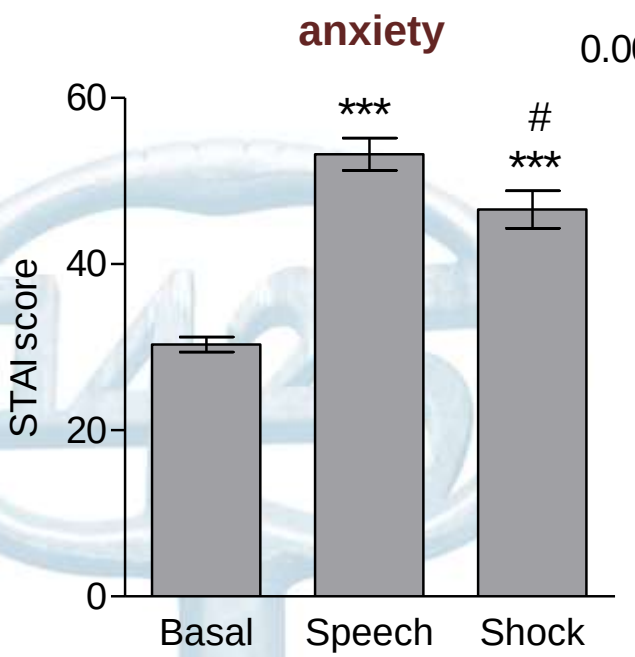
Psychological impact on GI symptoms
overview



Psychosocial stress increases small intestinal permeability in healthy subjects







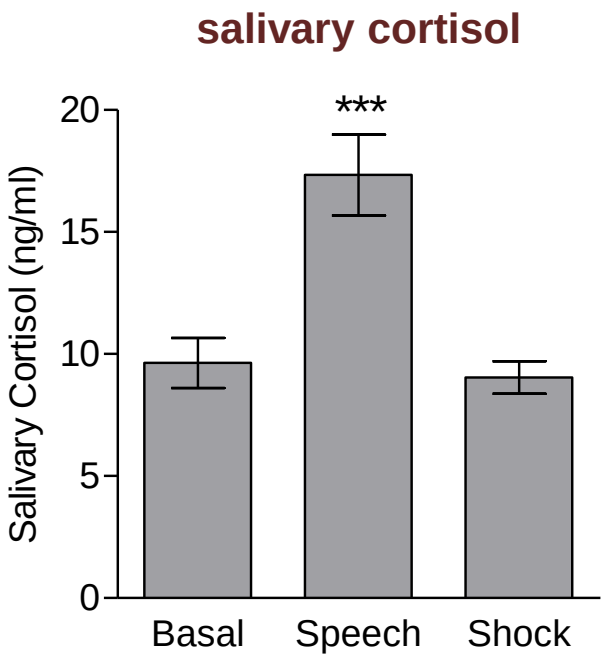
mixed models + Bonferroni:

** P<0.01 vs. basal

*** P<0.001 vs. basal

# P<0.05 vs. speech

Vanuytsel et al, Gut 2013



Psychological impact on GI symptoms
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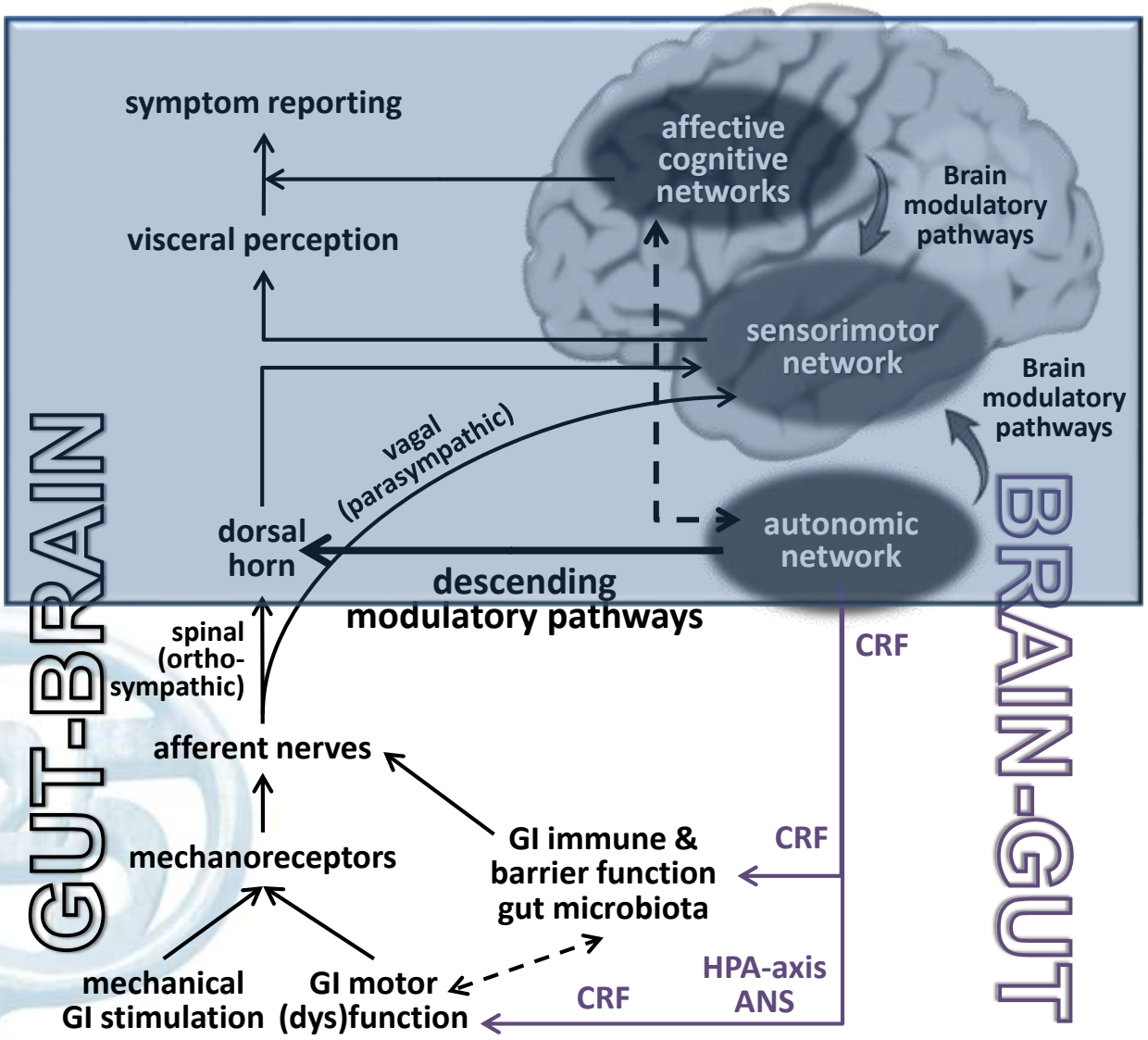
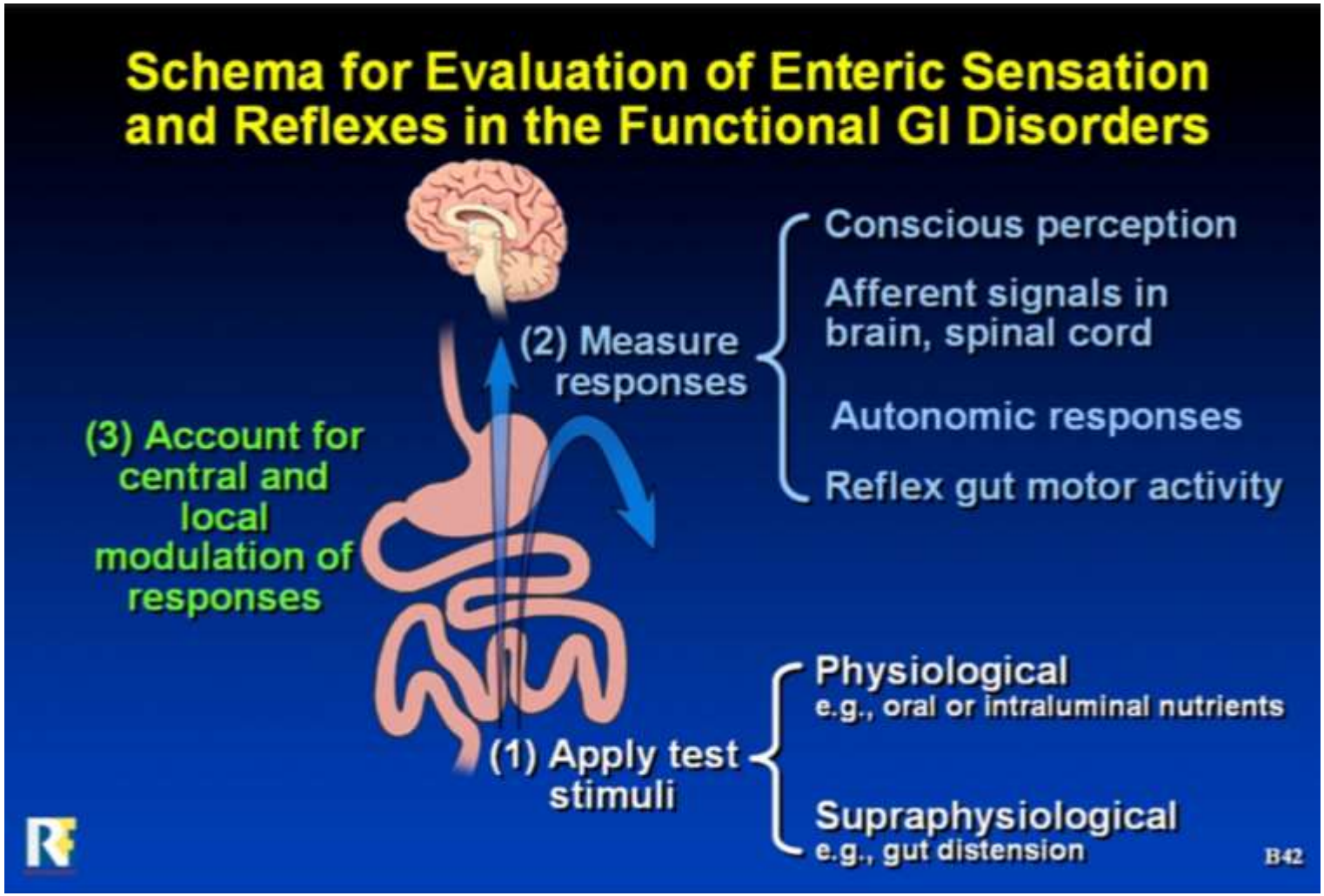


gastrointestinal sensitivity testing



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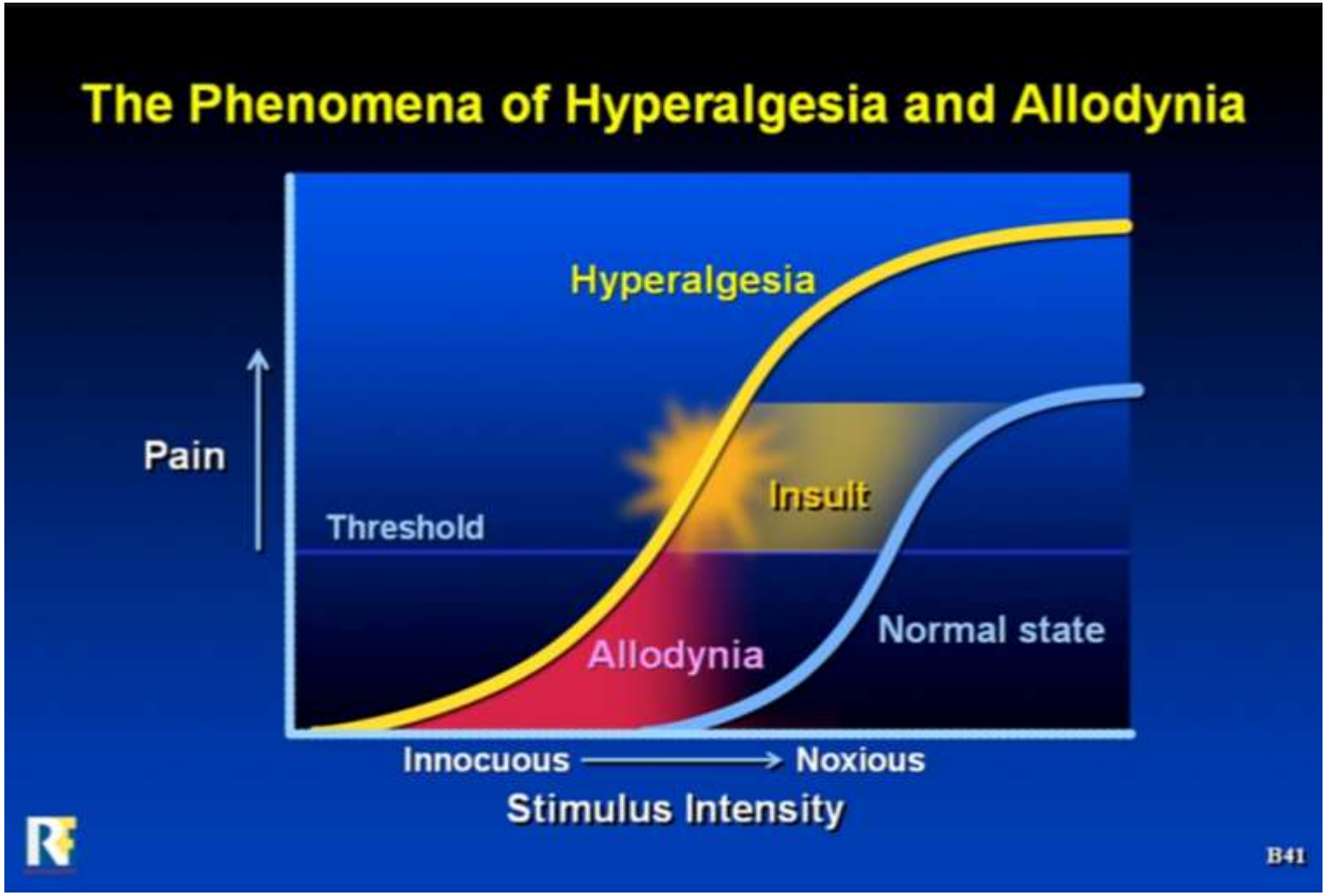
gastrointestinal hypersensitivity



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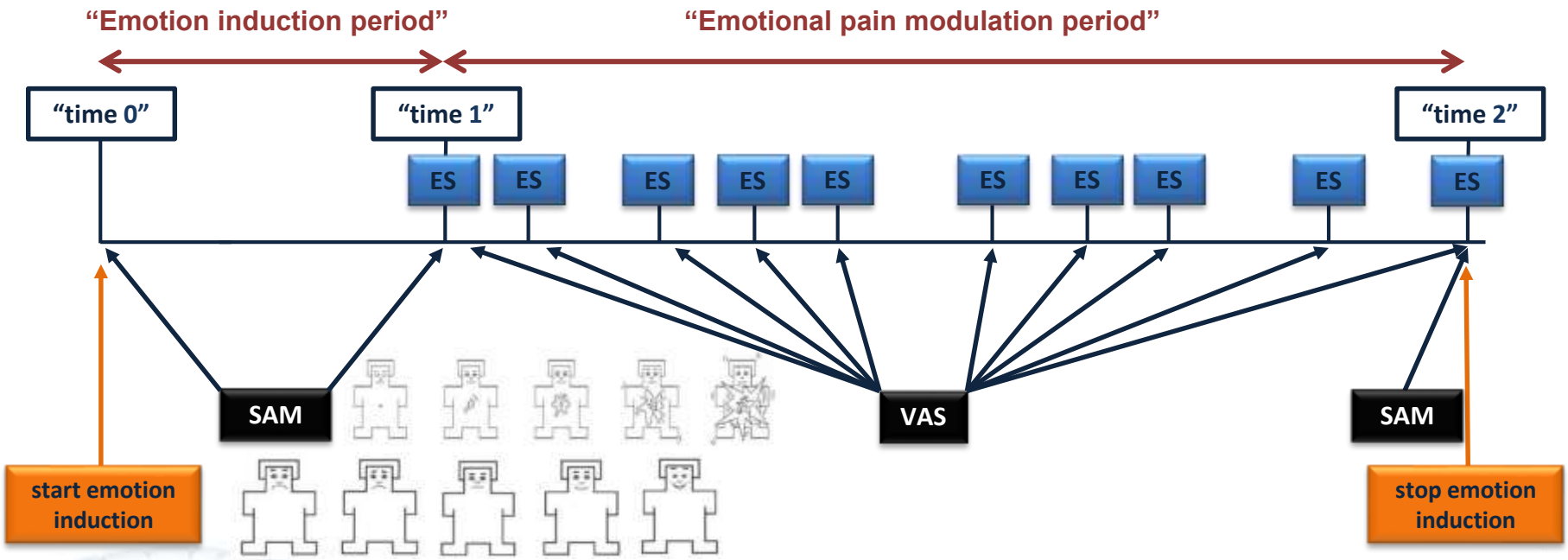
Emotional modulation of visceral pain paradigm



Emotion induction

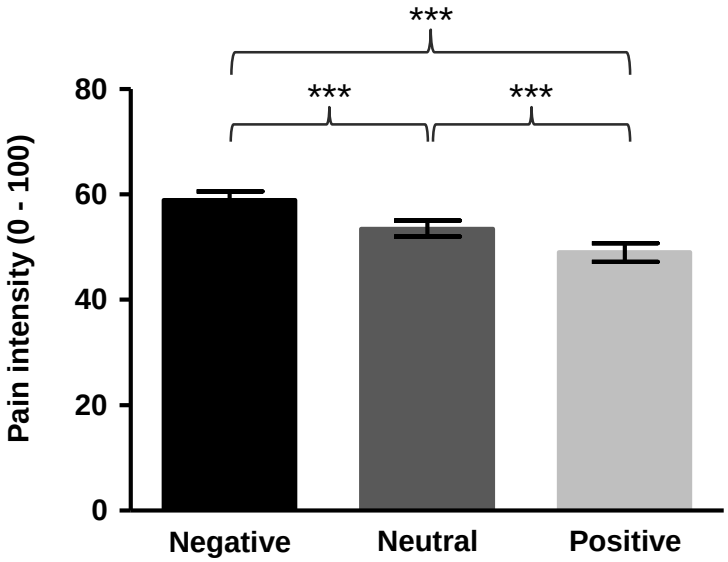
- Validated classical music
- Velten mood induction statements
- IAPS pictures

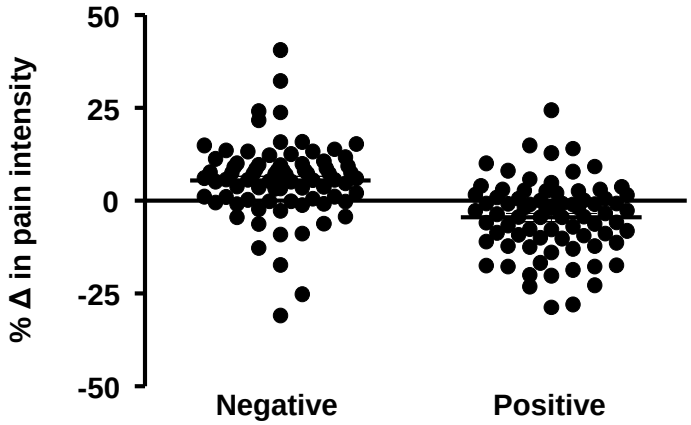
Weltens, Schaub, Aziz, Tack, Van Oudenhove & Coen*, submitted*

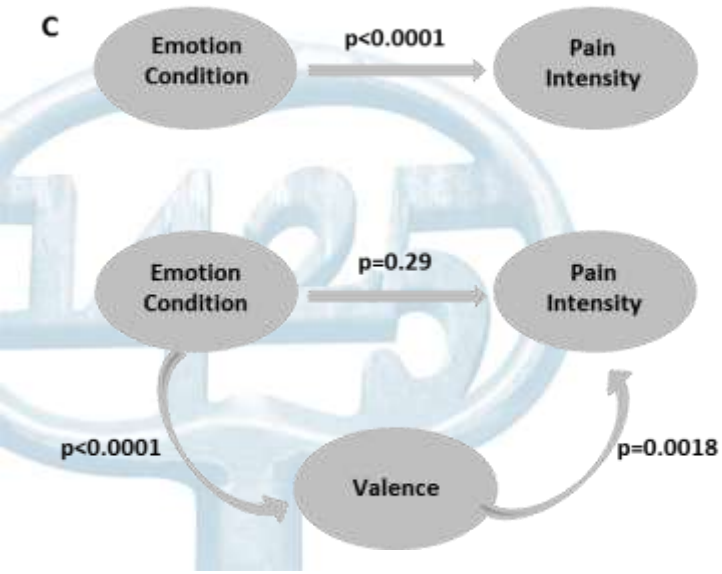
Emotional modulation of visceral pain

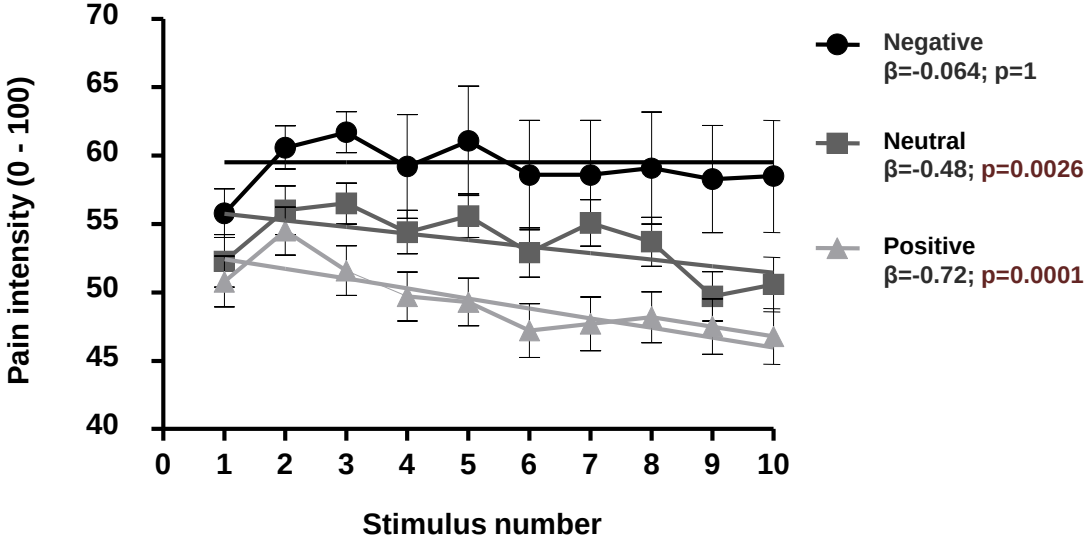
sad emotion induction

Emotional modulation of visceral pain
effect on esophageal pain ratings



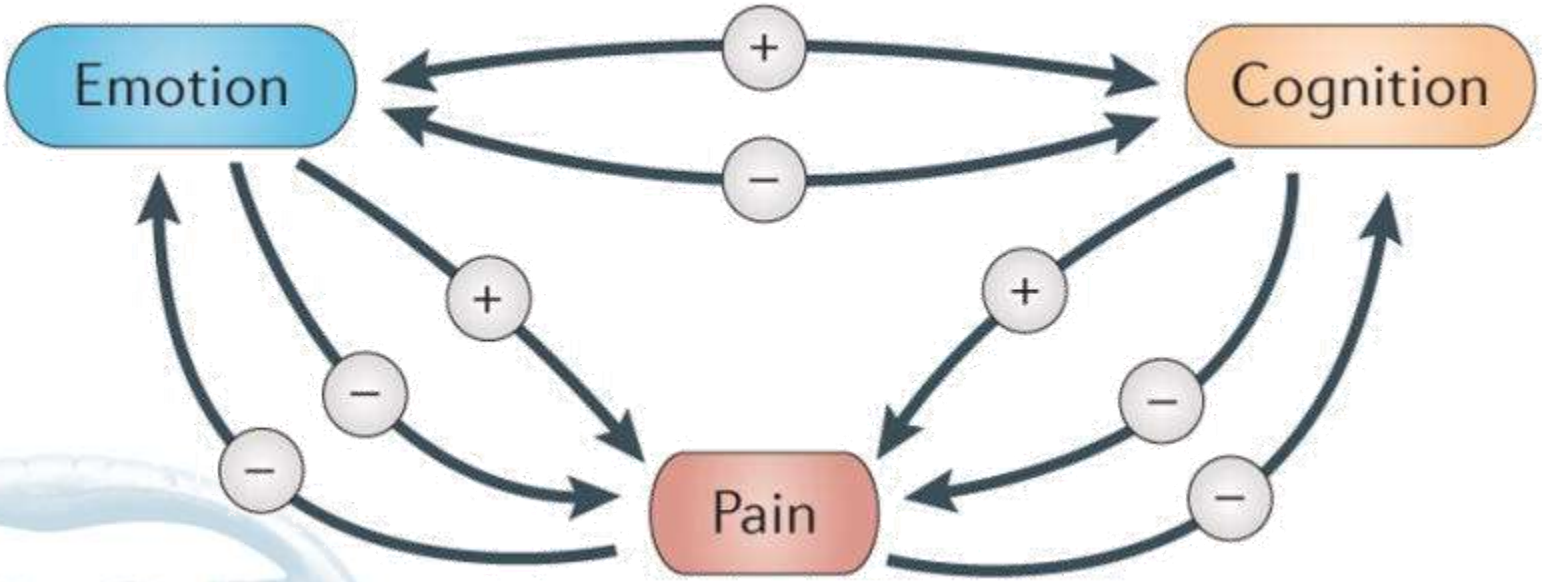






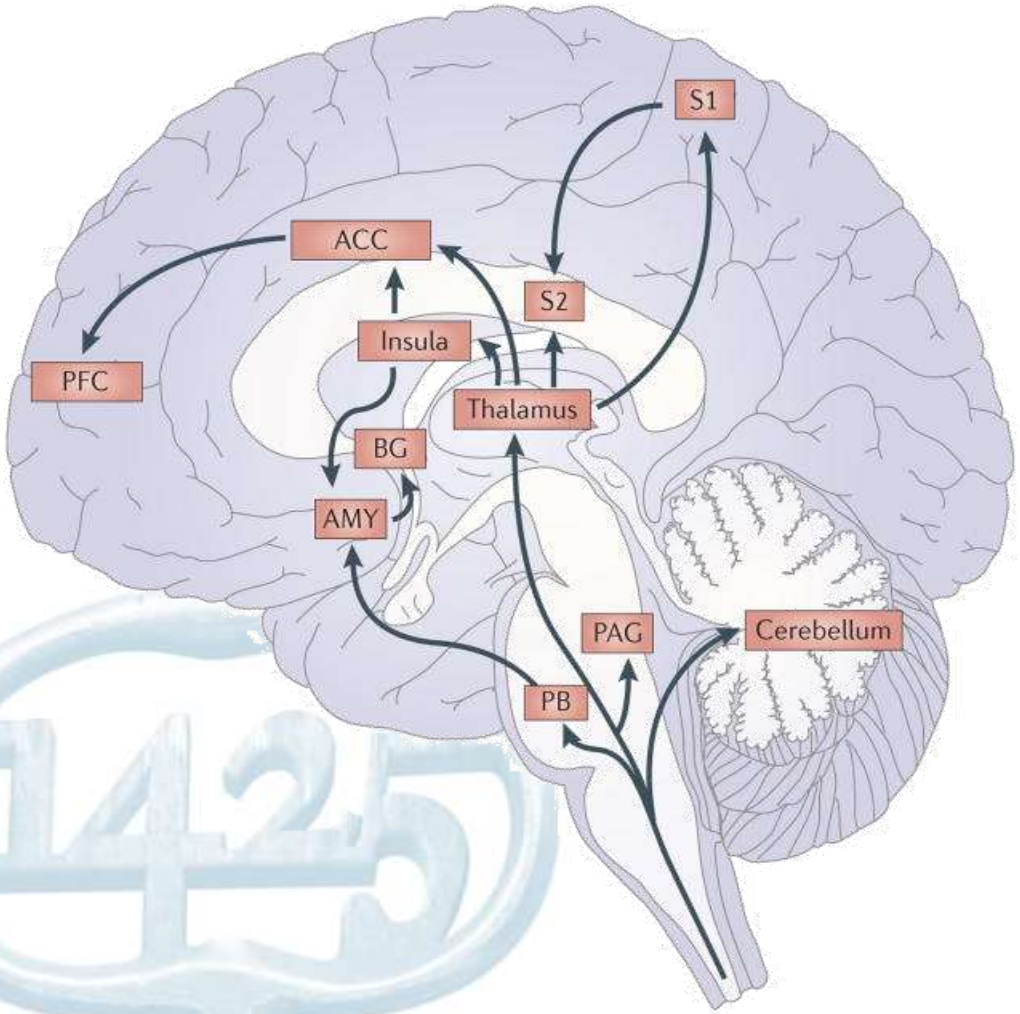
Weltens, Schaub, Aziz, Tack, Van Oudenhove & Coen*, submitted*

Emotion, cognition & pain



Bushnell et al, Nature Reviews Neuroscience 2013

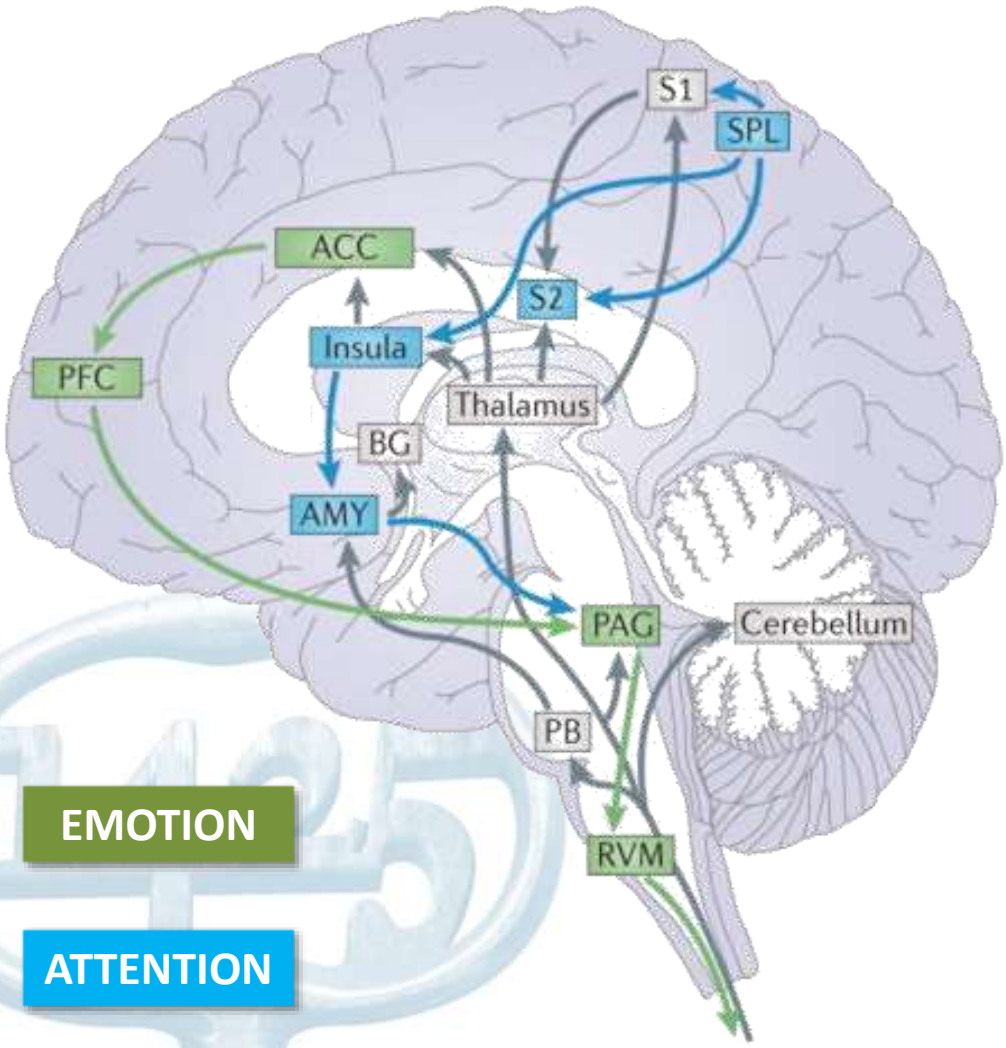
Emotion, cognition & pain



- PAG: periaqueductal gray
- PB: parabrachial nucleus
- AMY: amygdala
- BG: basal ganglia
- S1, S2: somatosensory cortex
- ACC: anterior cingulate cortex
- PFC: prefrontal cortex

Bushnell et al, Nature Reviews Neuroscience 2013

Emotion, cognition & pain



EMOTION

ATTENTION

- PAG: periaqueductal gray
- PB: parabrachial nucleus
- AMY: amygdala
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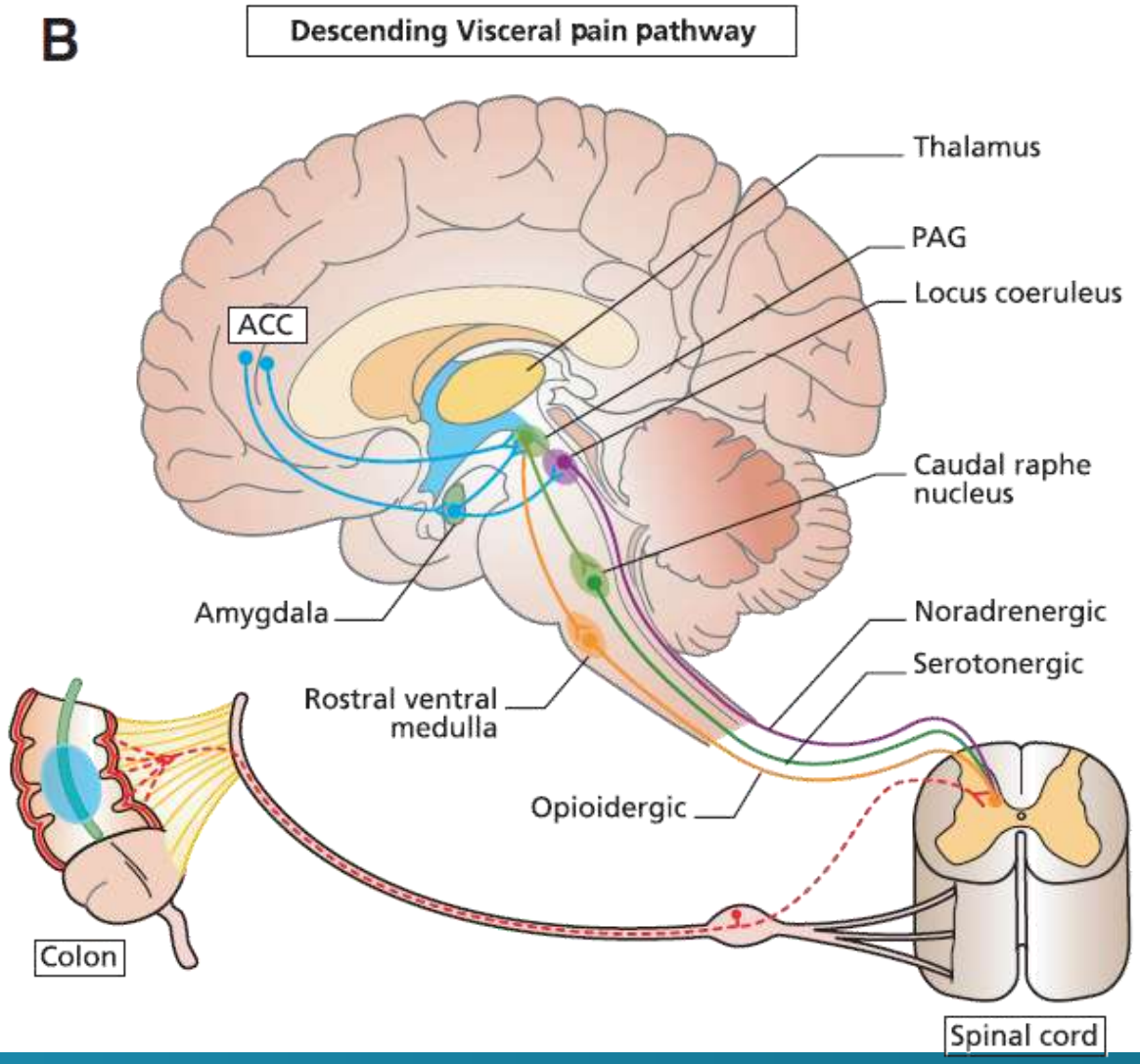
- ACC: anterior cingulate cortex
- PFC: prefrontal cortex
- SPL: superior parietal lobule

Bushnell et al, Nature Reviews Neuroscience 2013

descending pain modulatory pathways



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3. impact of the gut microbiota on psychological & brain function

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Microbiota-Gut-Brain Axis
The hype of the day?

KATHOLIEKE UNIVERSITEIT LEUVEN

Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour

John F. Cryan[1,2] and Timothy G. Dinan[1,3]

Gut Microbes and the Brain: Paradigm Shift in Neuroscience

Emeran A. Mayer,[1] Rob Knight,[2] Sarkis K. Mazmanian,[3] John F. Cryan,[4] and Kirsten Tillisch[1,5]

REVIEW

Psychobiotics: A Novel Class of Psychotropic

Timothy G. Dinan, Catherine Stanton, and John F. Cryan

Review

What's bugging your teen?—The microbiota and adolescent mental health

Karen-Anne McVey Neufeld[a], Pauline Luczynski[a], Clara Seira Oriach[a,b], Timothy G. Dinan[a,b], John F. Cryan[a,c,*]

THE Mind-Gut CONNECTION

How the Hidden Conversation Within Our Bodies Impacts Our Mood, Our Choices, and Our Overall Health

Emeran Mayer, MD

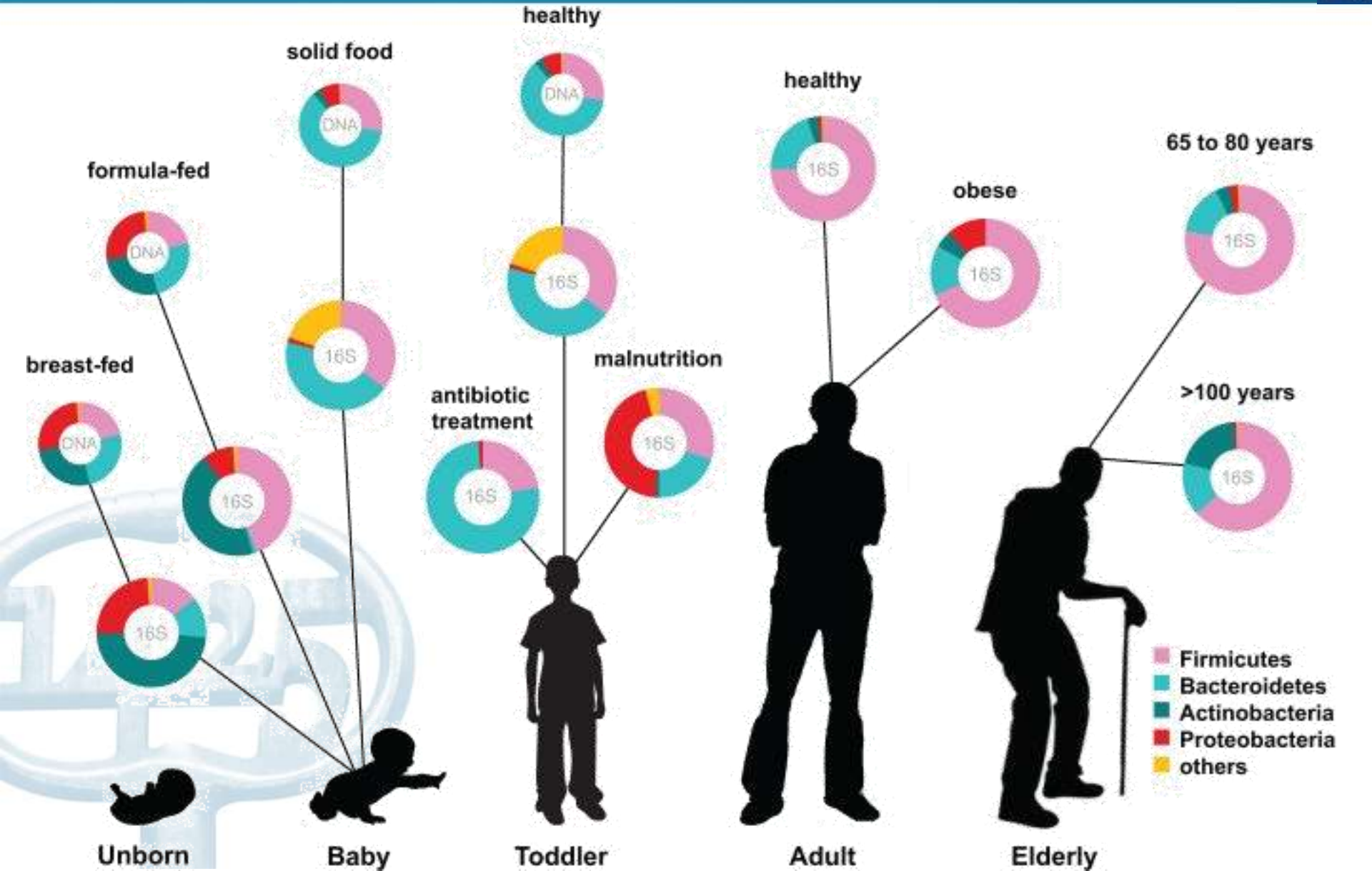
Gut microbiota

- **collection of micro-organisms** in our gastrointestinal tract
- **bacteria**
  - 10^{14} in the colon (~ 10 x human cells in the entire body)
  - > 1000 species (but ~ 200 in each individual)
  - 3 x 10^{6} genes (~ 100 x human genes)
  - 1 – 2 kg weight
- **variability** between individuals
  - host genetics
  - birth mode (caesarian section versus vaginal delivery)
  - breastfed versus bottle-fed
  - antibiotics
  - diet, diet, diet!
  - stress
  - age

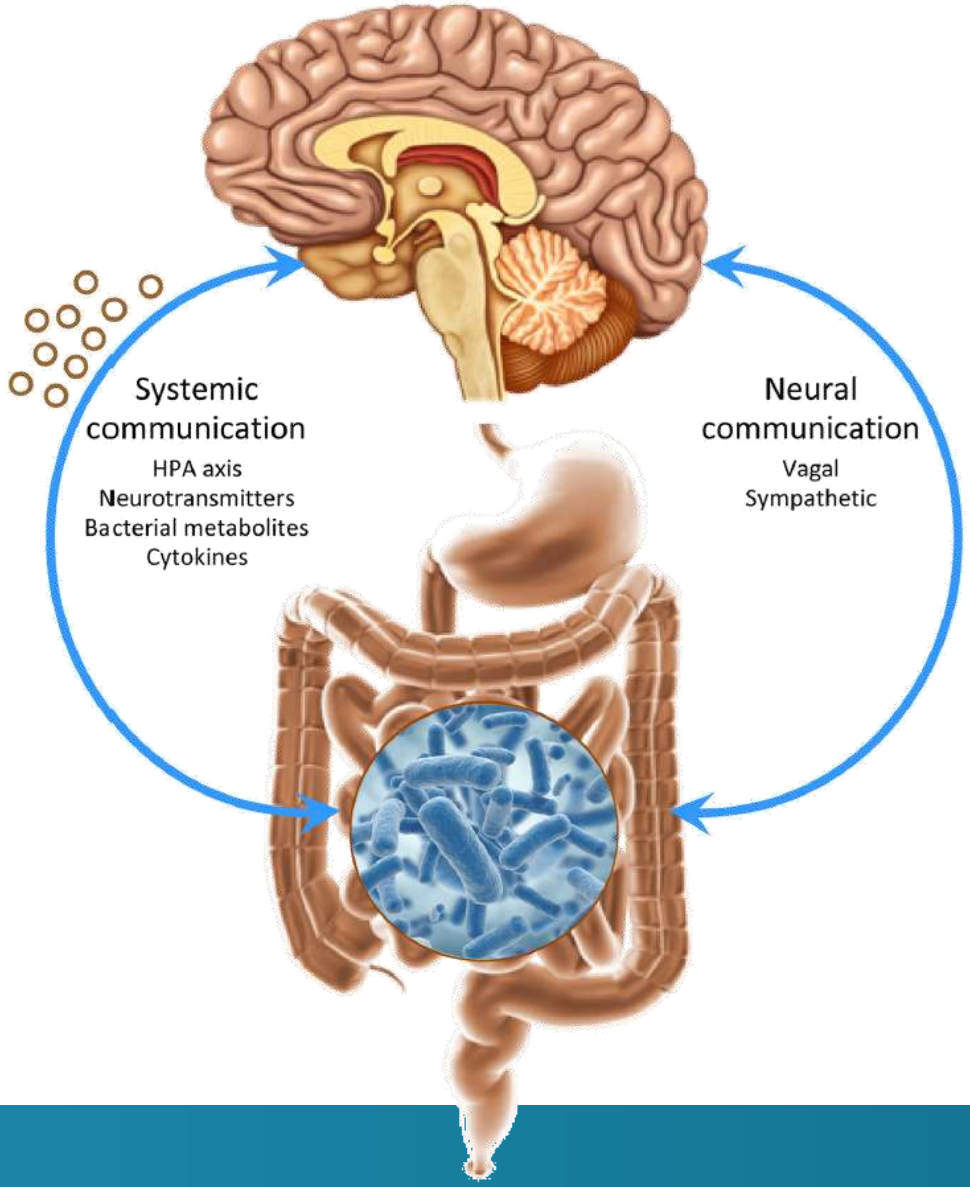
Gut microbiota

Firmicutes		**64%**
	Lactobacillus	
	Streptococcus	
	Staphylococcus	
	Enterococcus (E. faecalis)	
	Faecalibacterium prausnitzii	
	Clostridia (C. difficile)	
Bacteroidetes		**23%**
	Bacteroides	
	Prevotella	
	Alistipes	
Proteobacteria		**8%**
	Enterobacteriaceae (Salmonella, E. coli, Klebsiella, Shigella)	
	Campylobacter (C. jejuni)	
Actinobacteria		**3%**
	Bifidobacteria	
TOTAL		**98%**

Gut microbiota



Microbiota-Gut-Brain Axis
What?



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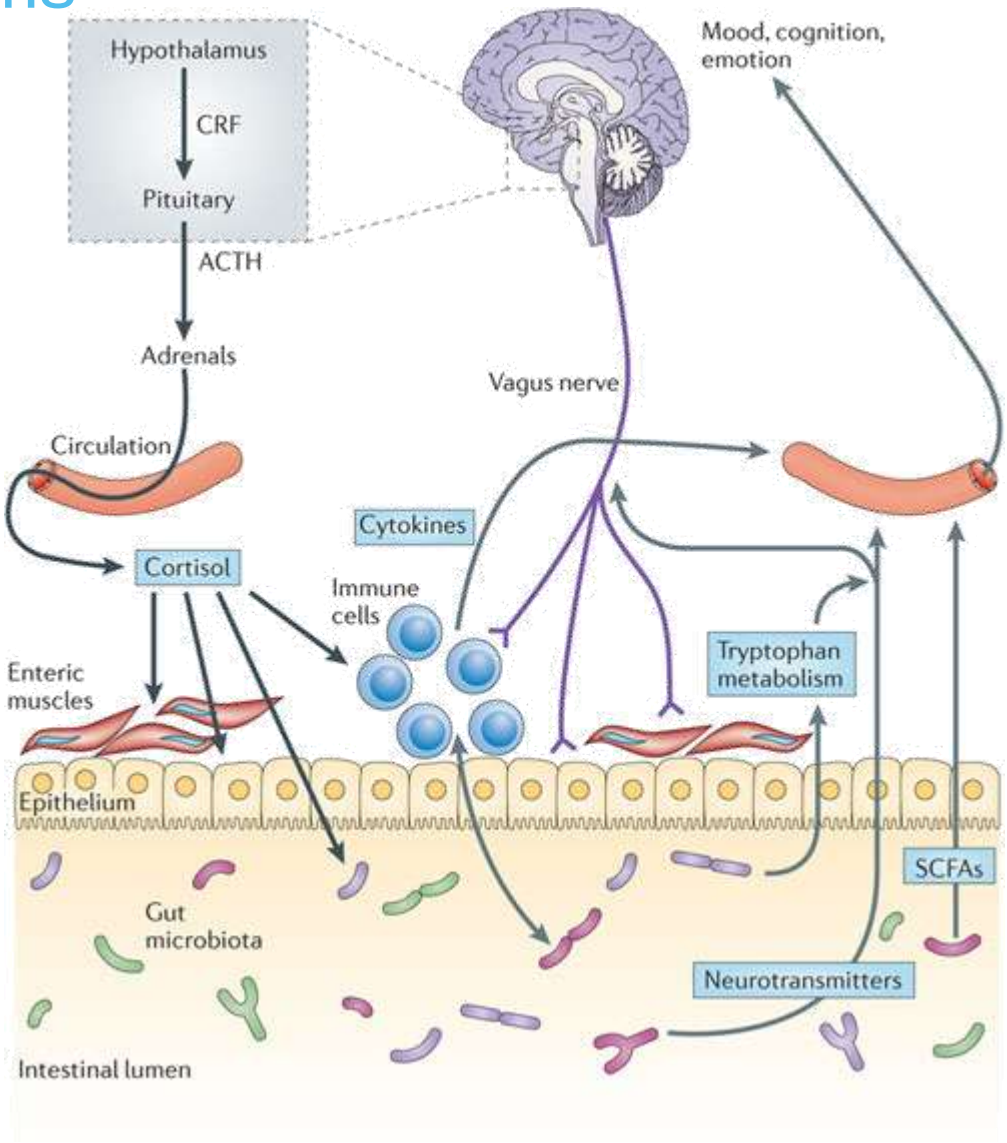
Microbiota-gut-brain axis

Mechanisms



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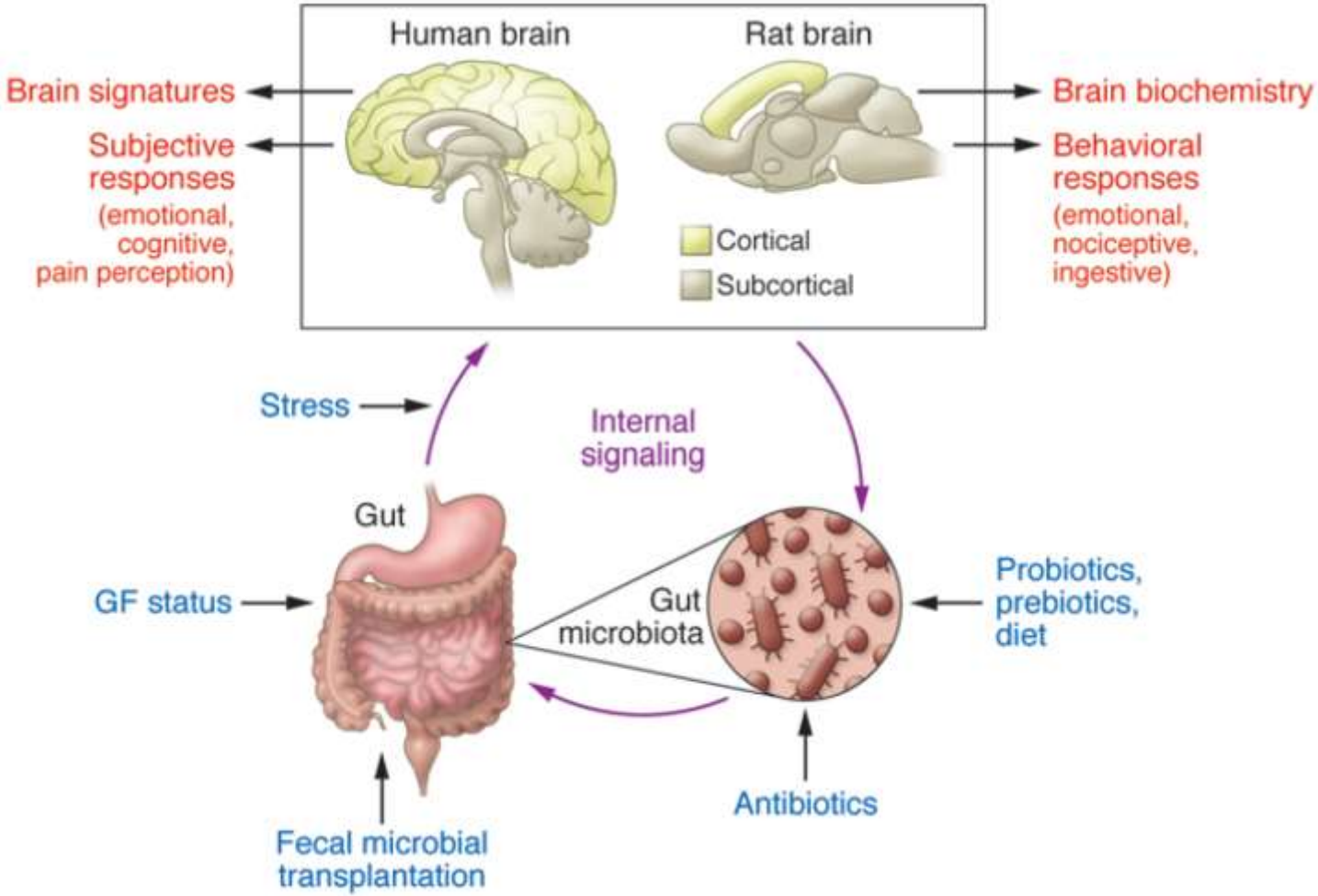
Microbiota-gut-brain axis
How to study?



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Microbiota-gut-brain axis
definitions

- **probiotics**
  - "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host"

- **prebiotics**
  - "a substrate that is selectively utilized by host micro-organisms conferring a health benefit"

- **"psychobiotics"**
  - either of the above conferring a health benefit *in patients with psychiatric illness*

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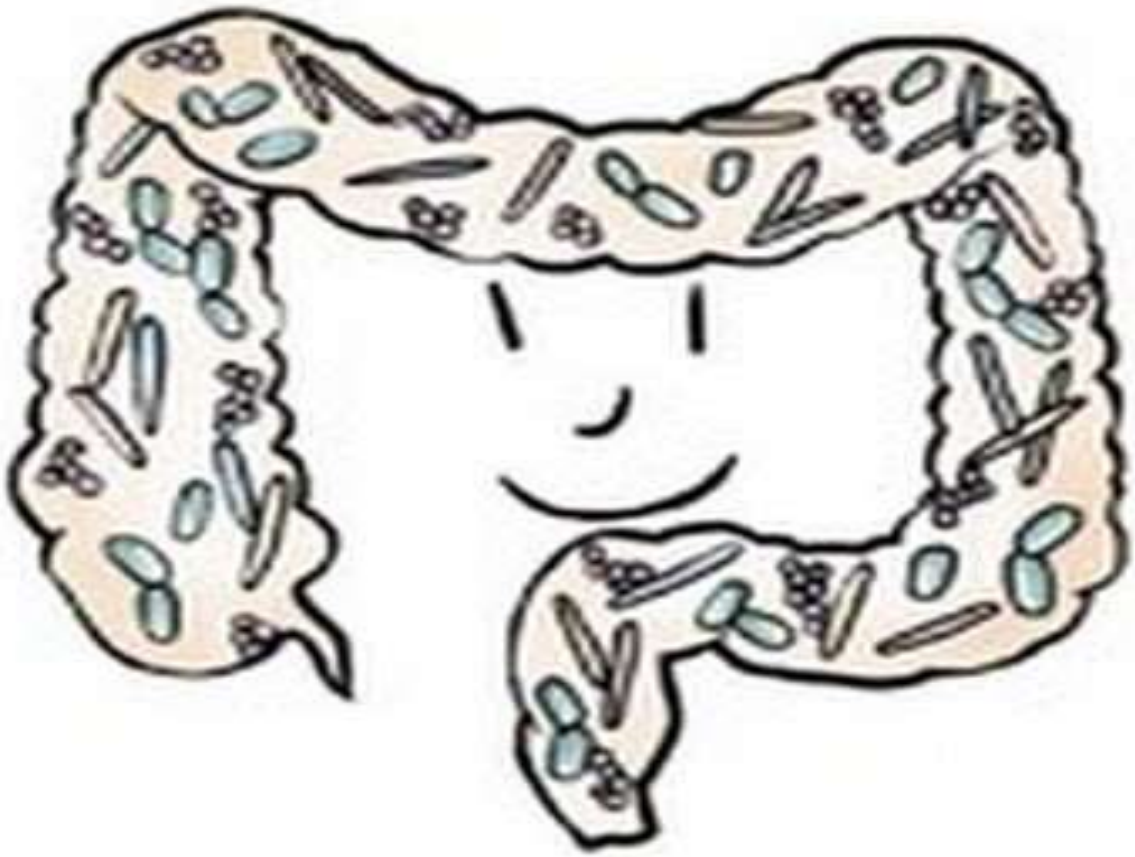
Microbiota-gut-brain axis
fecal microbiota transplantation



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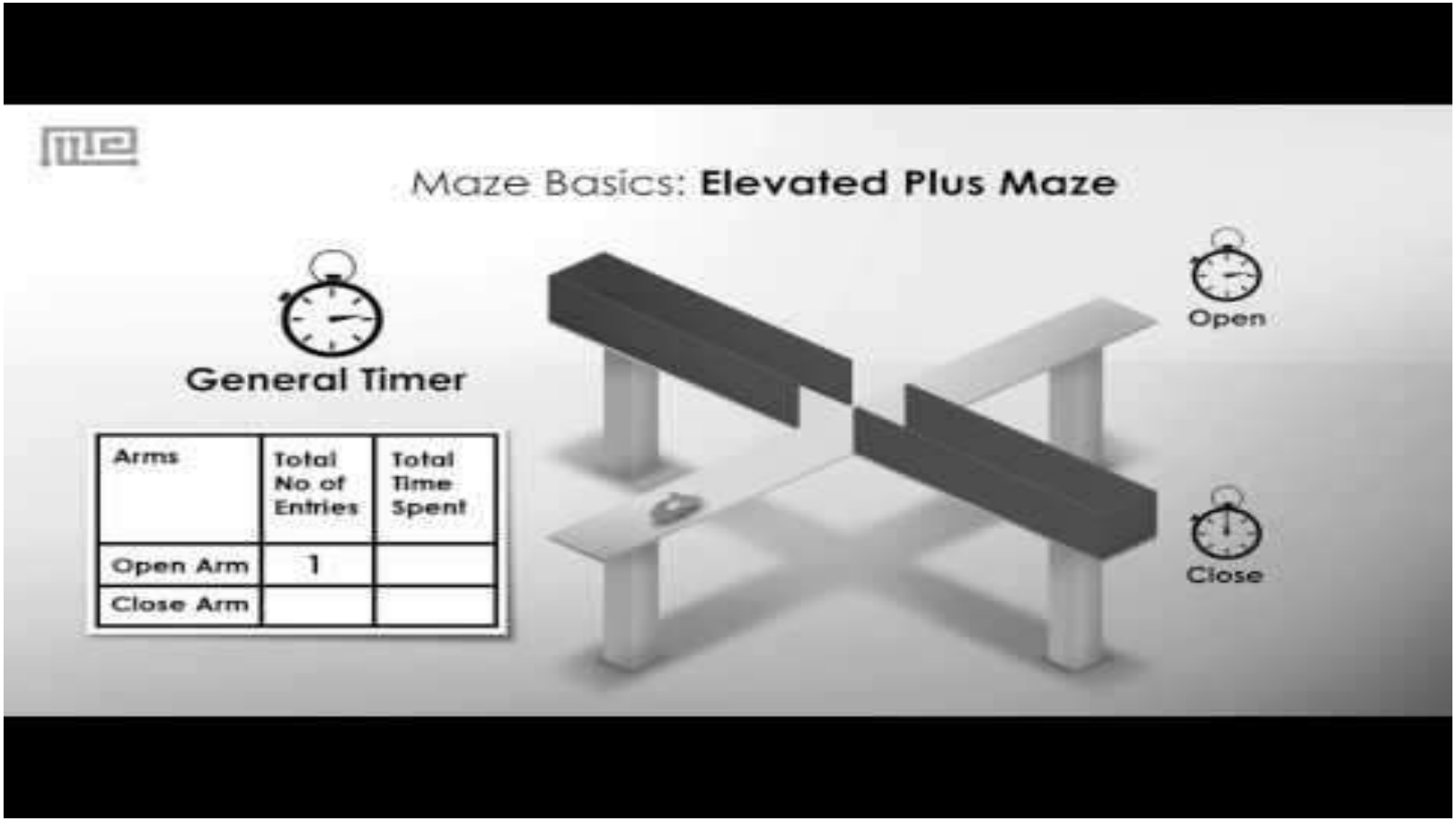
How to test anxious behaviour in mice?
elevated plus maze test



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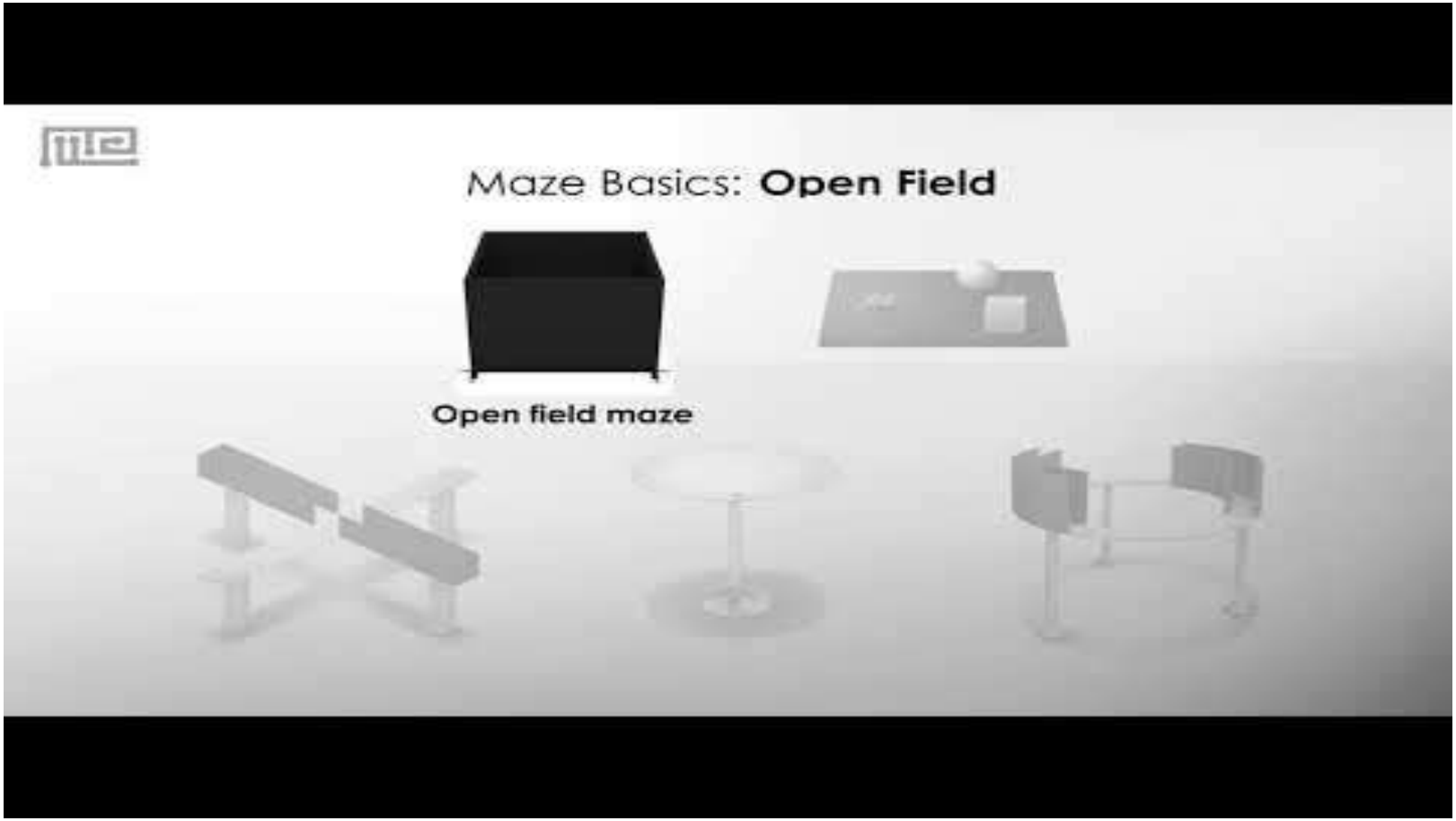
How to test anxious behaviour in mice?
open field test



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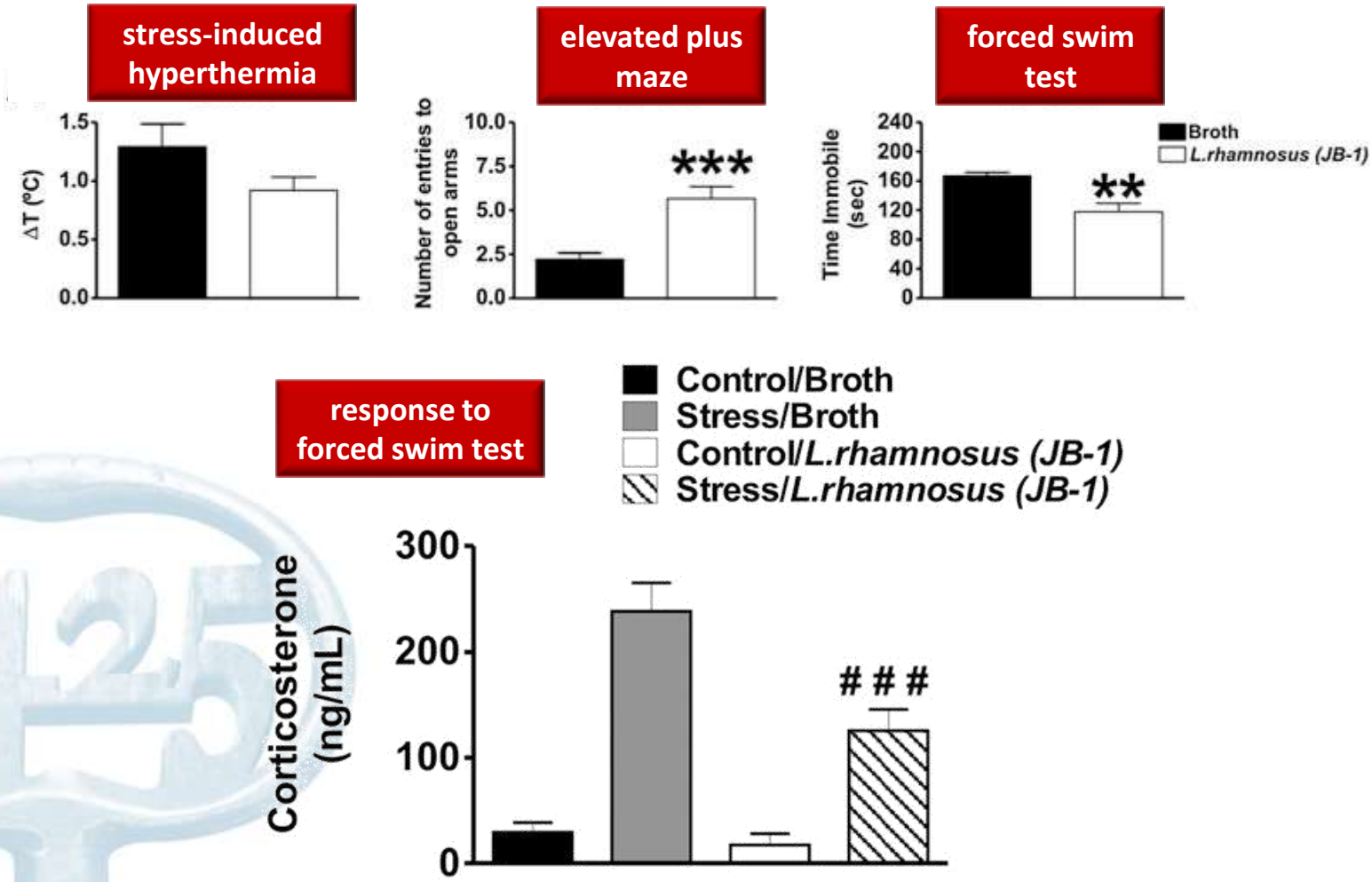
How to test depressive behaviour in mice?
forced swim test

KU LEUVEN

Ingestion of *Lactobacillus* strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve

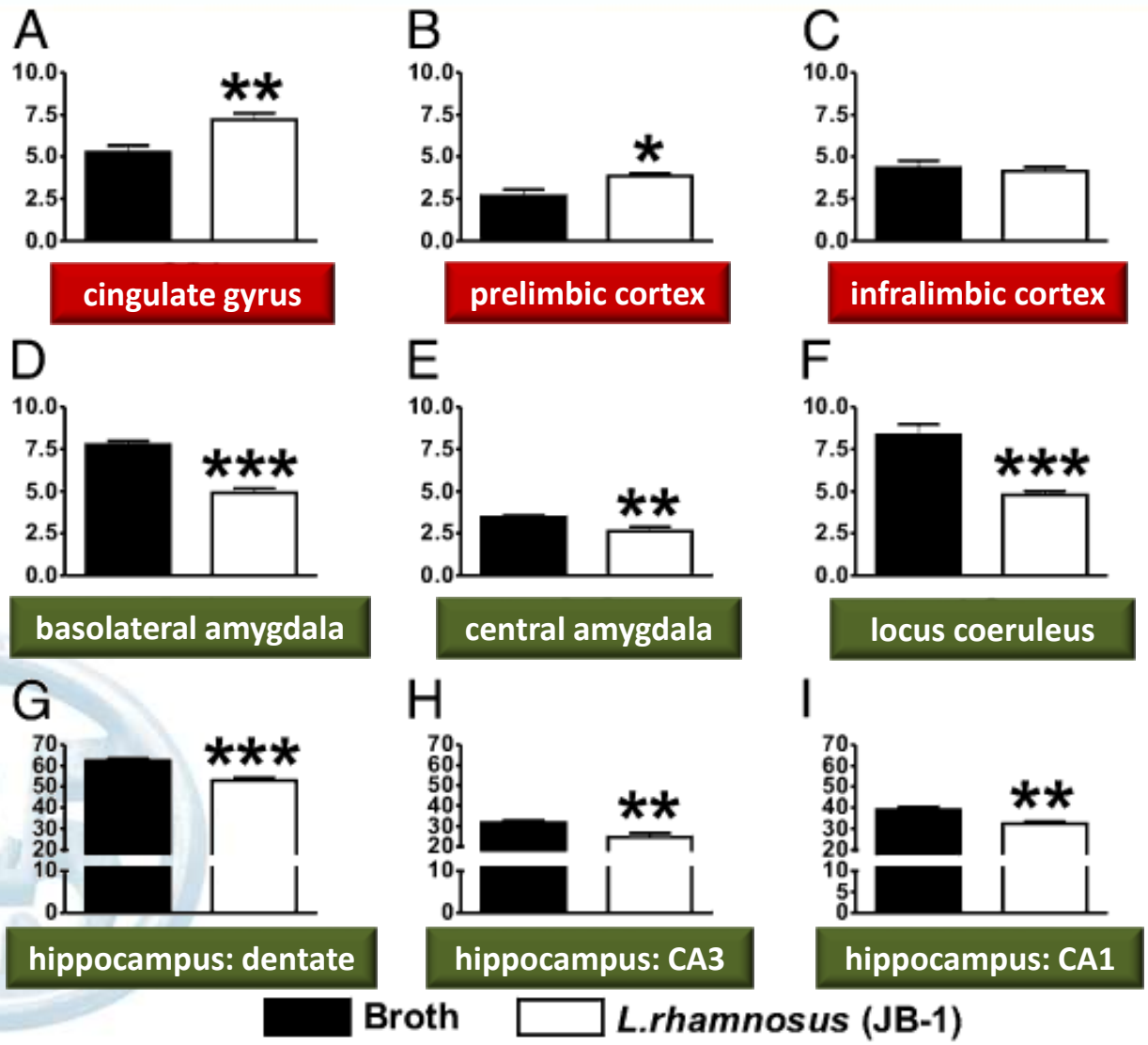
Javier A. Bravo[a,1], Paul Forsythe[b,c,1], Marianne V. Chew[b], Emily Escaravage[b], Hélène M. Savignac[a,d], Timothy G. Dinan[a,e], John Bienenstock[b,f,2], and John F. Cryan[a,d,g,2]

16050–16055 | PNAS | September 20, 2011 | vol. 108 | no. 38



Bravo, Forsythe et al, Proceedings of the National Academy of Sciences USA 2011

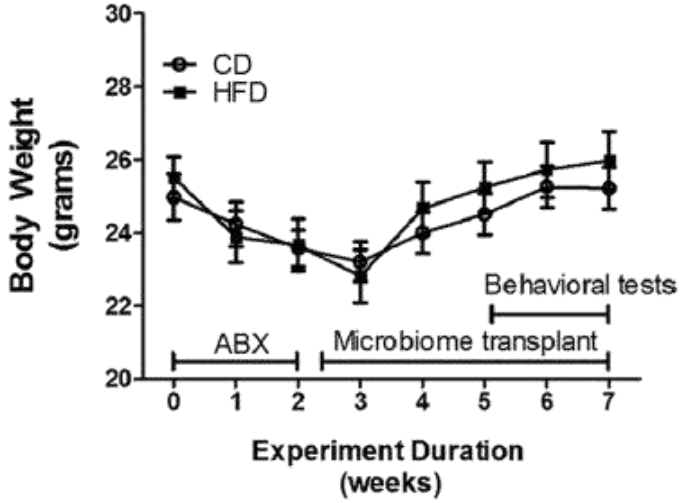
L. Rhamnosus & central GABA receptors



Bravo, Forsythe et al, Proceedings of the National Academy of Sciences USA 2011

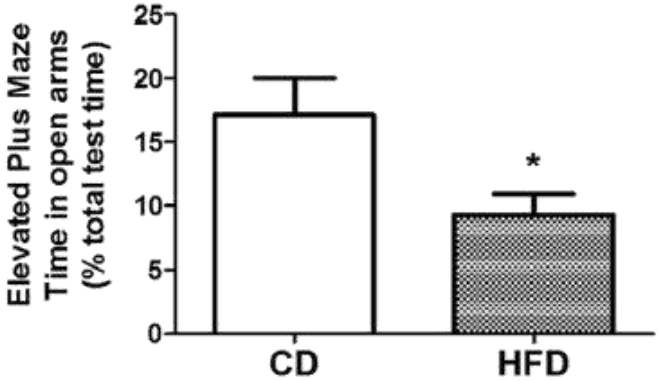
Obese-type Gut Microbiota Induce Neurobehavioral Changes in the Absence of Obesity

A

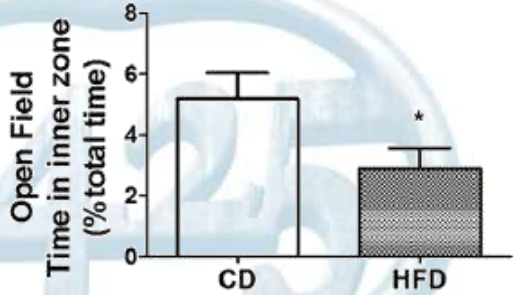


B

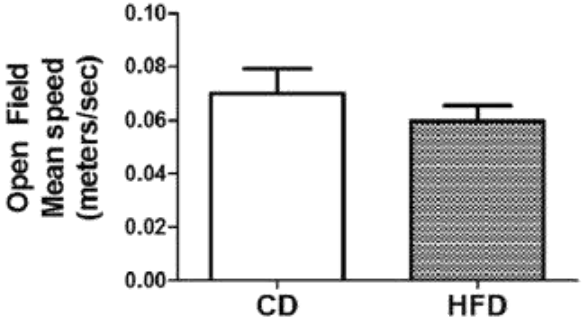
elevated plus maze

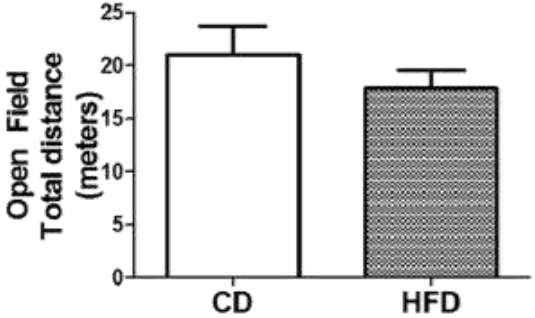


C



open field test



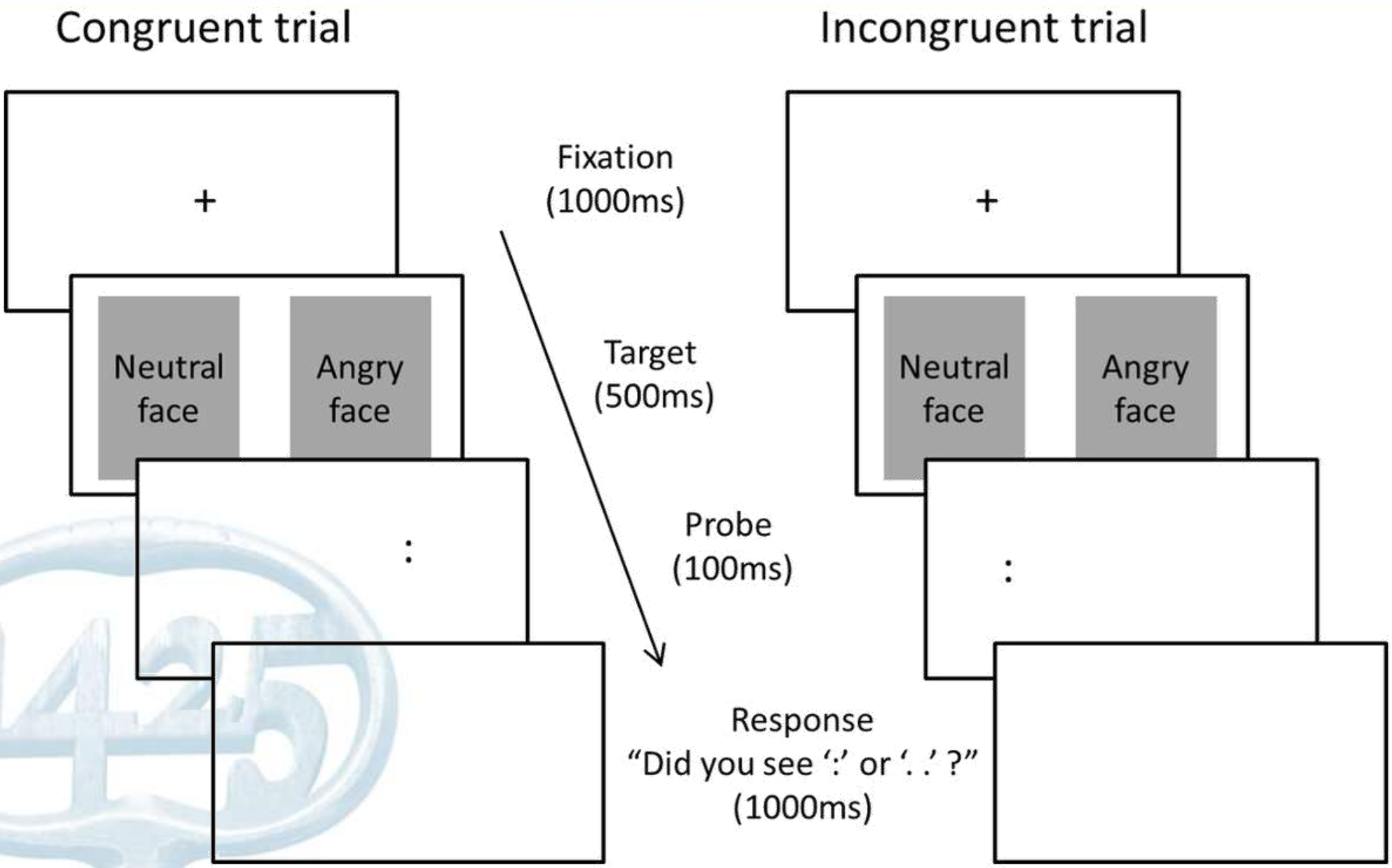


overall locomotor activity

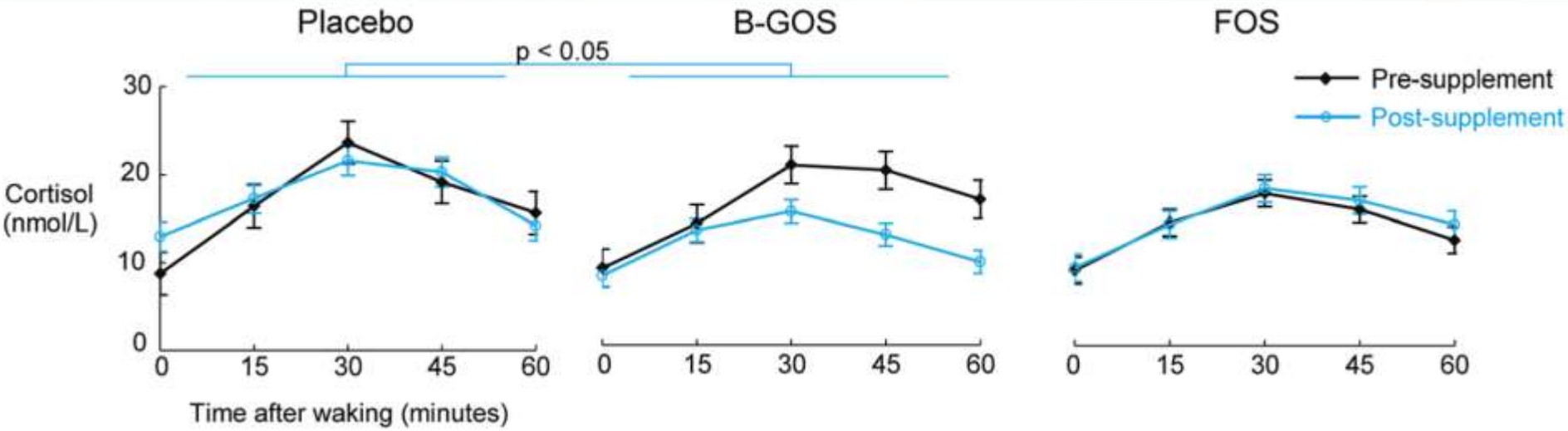
Bruce-Keller et al, Biol Psychiatry 2015

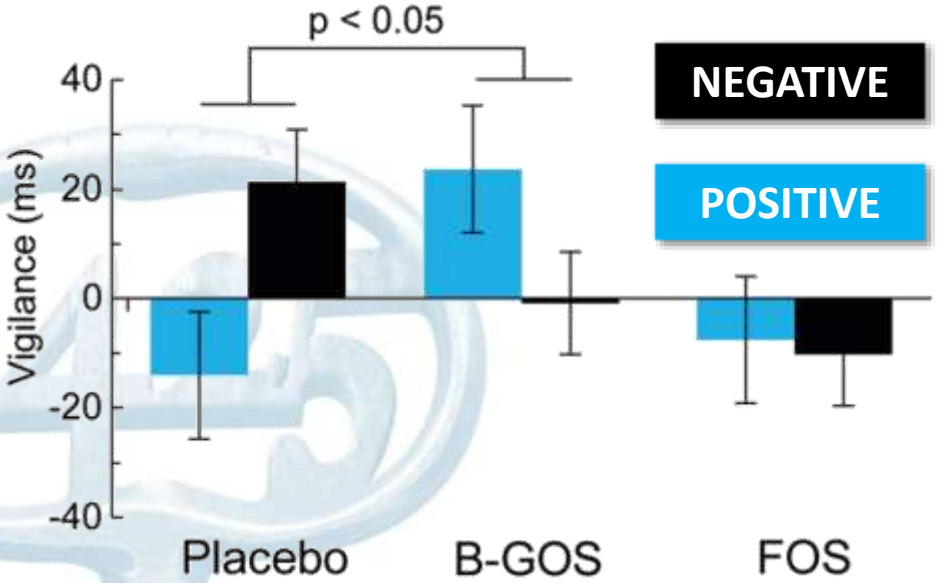
How to measure emotional responses in humans?

Affect labeling/matching task



Prebiotic B-GOS alters cortisol awakening response and emotional bias in health



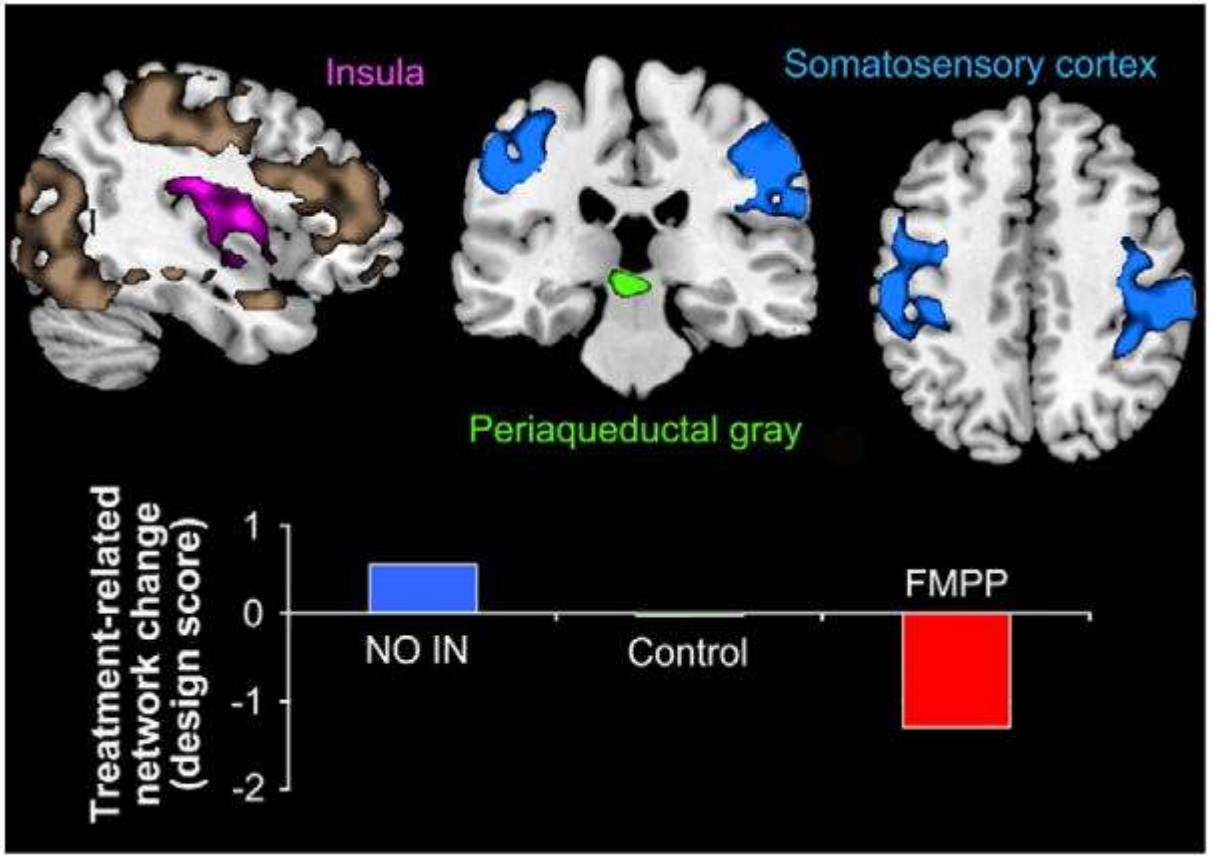


no differences on

- **2 other emotion tasks**
  - facial expression recognition
  - emotional categorization & memory
- **self-report questionnaires**
  - anxiety
  - stress

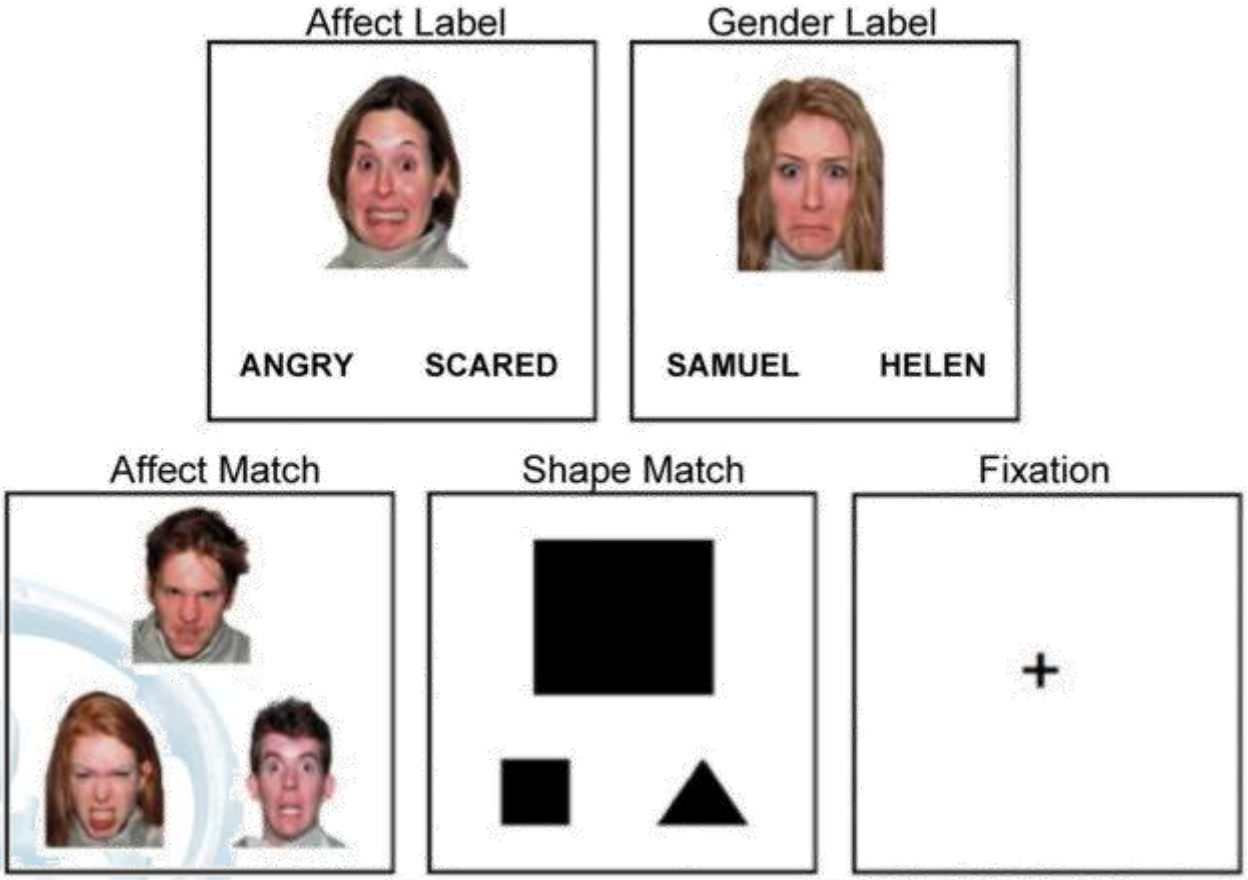
Schmidt et al, Psychopharmacology 2015

Probiotic intake alters resting state brain function in healthy humans

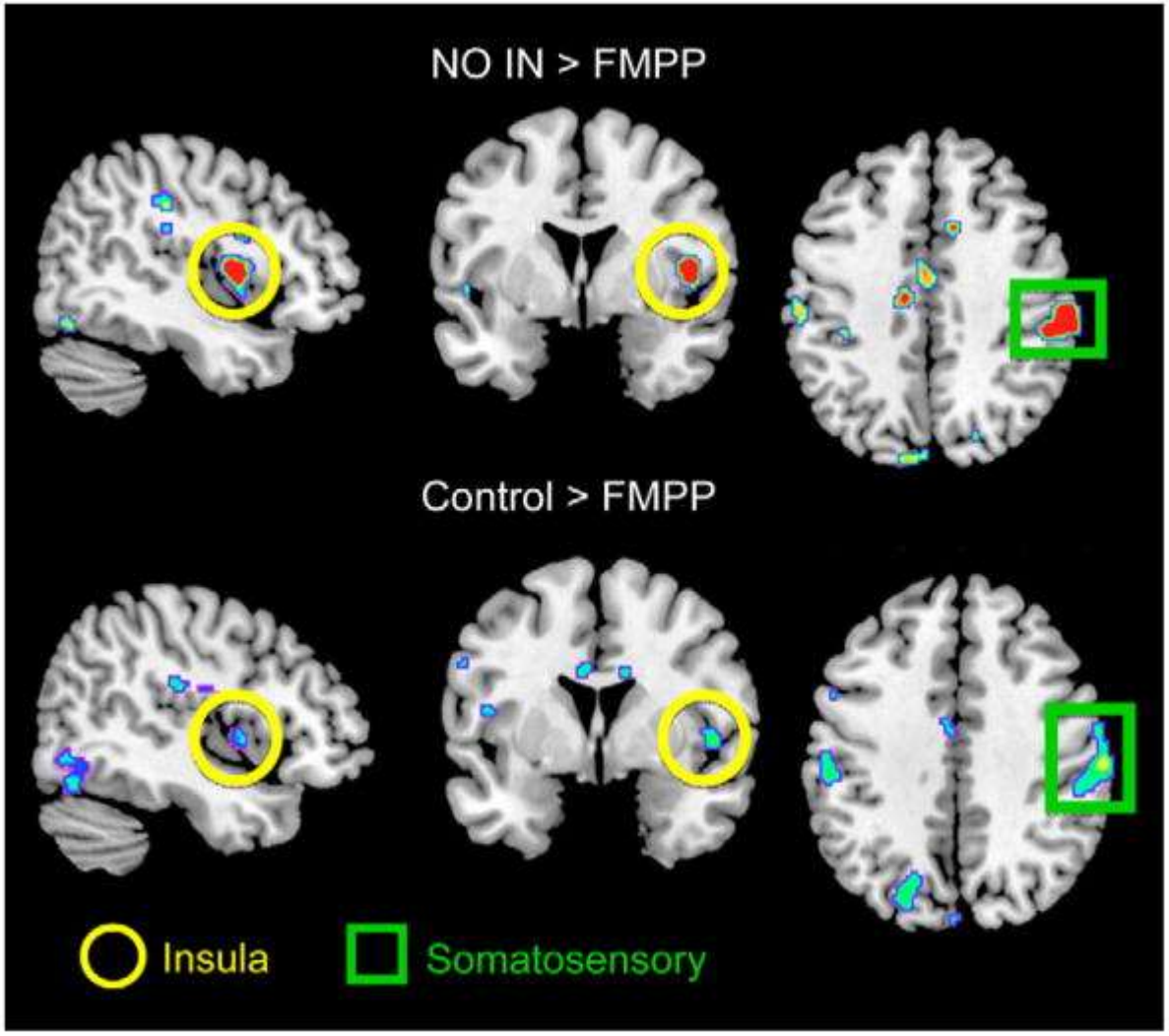


Tillisch,..., Mayer, Gastroenterology 2013

How to measure emotional brain response in humans?
Affect labeling/matching task

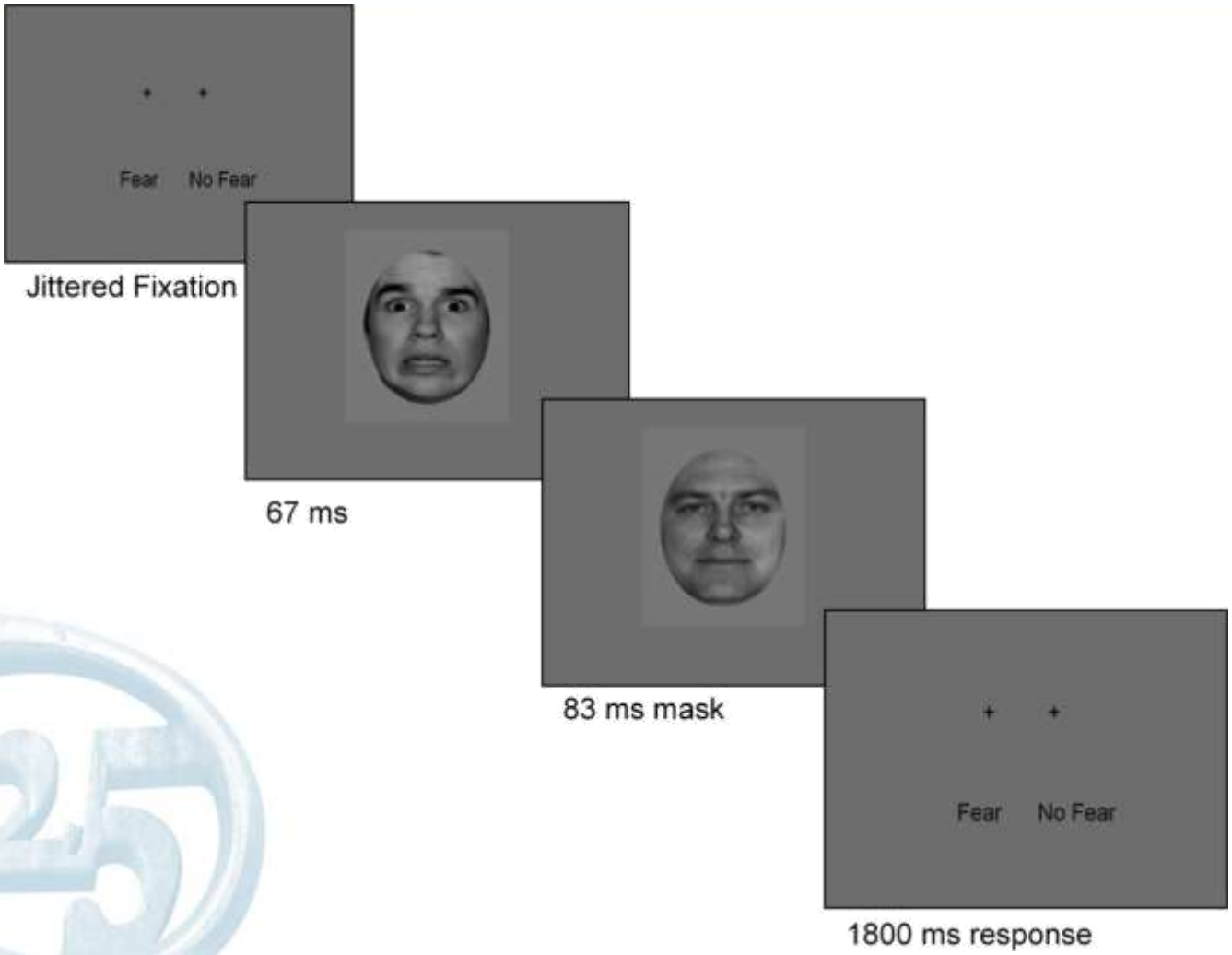


Probiotic intake alters brain responses to emotional attention task in healthy humans

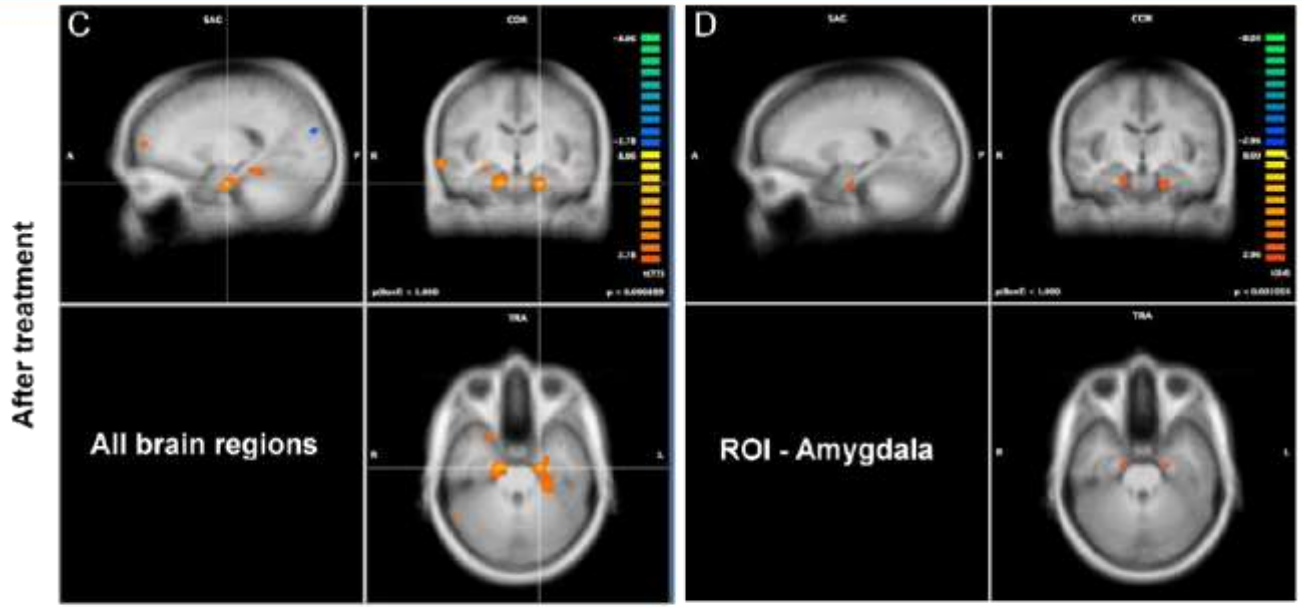


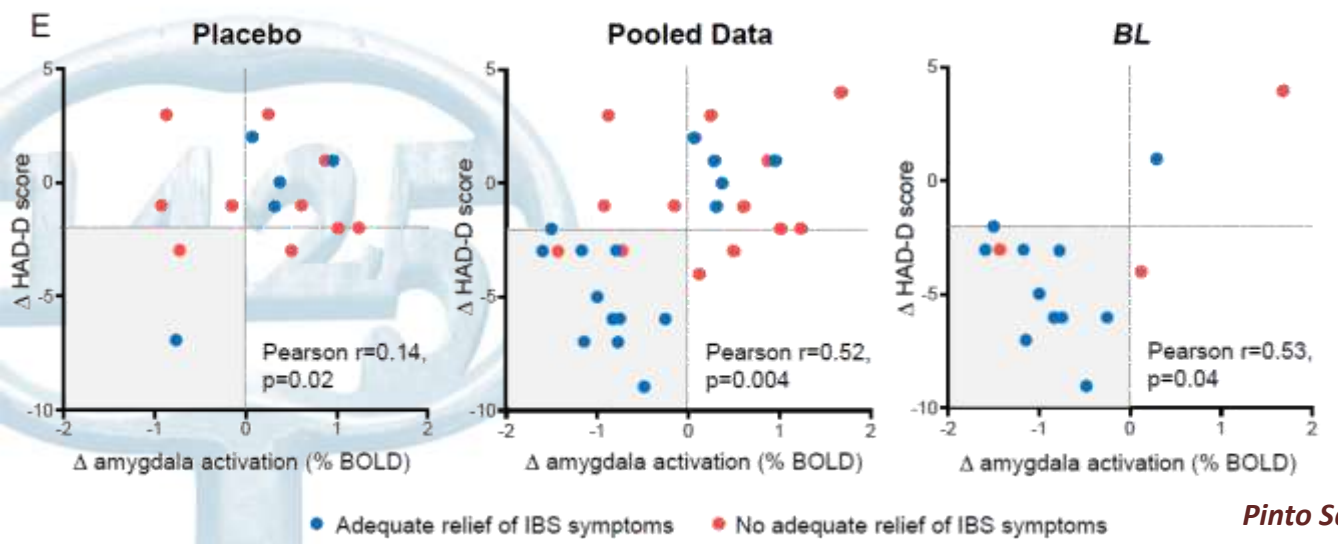
Tillisch,..., Mayer, Gastroenterology 2013

How to measure emotional brain response in humans?
Backward masking paradigm



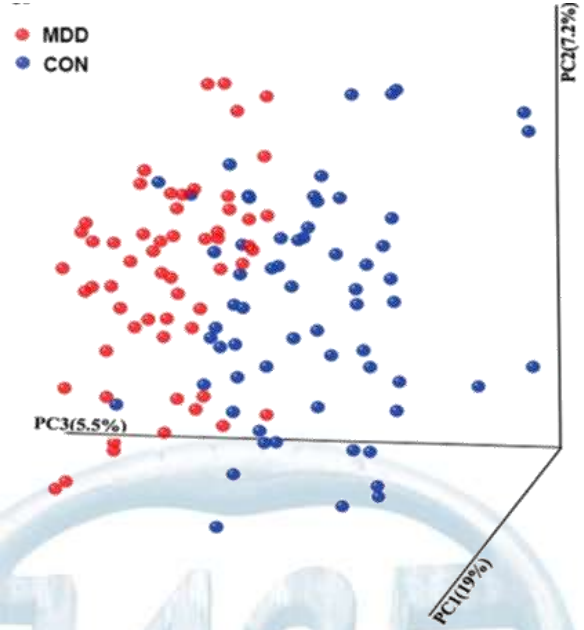
Probiotic treatment decreases depressive symptoms & emotional brain responses in IBS

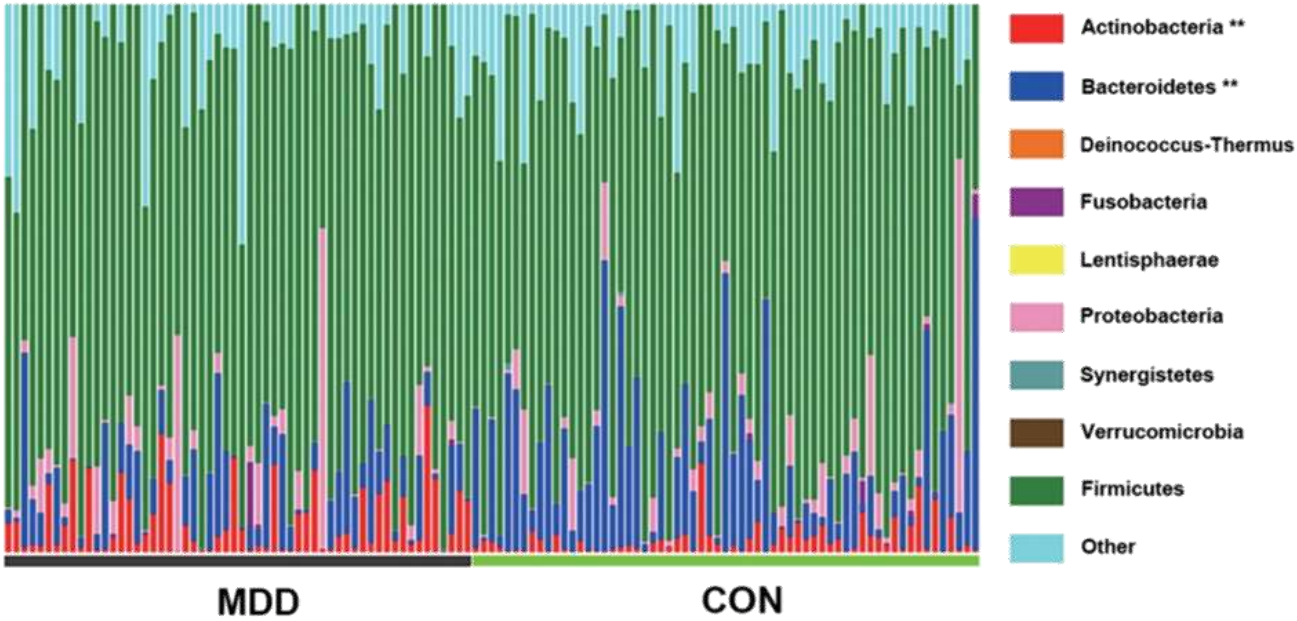




Pinto Sanchez et al, Gastroenterology 2017

Altered microbiota composition in major depressive disorder





Zheng et al, Mol Psychiatry 2016

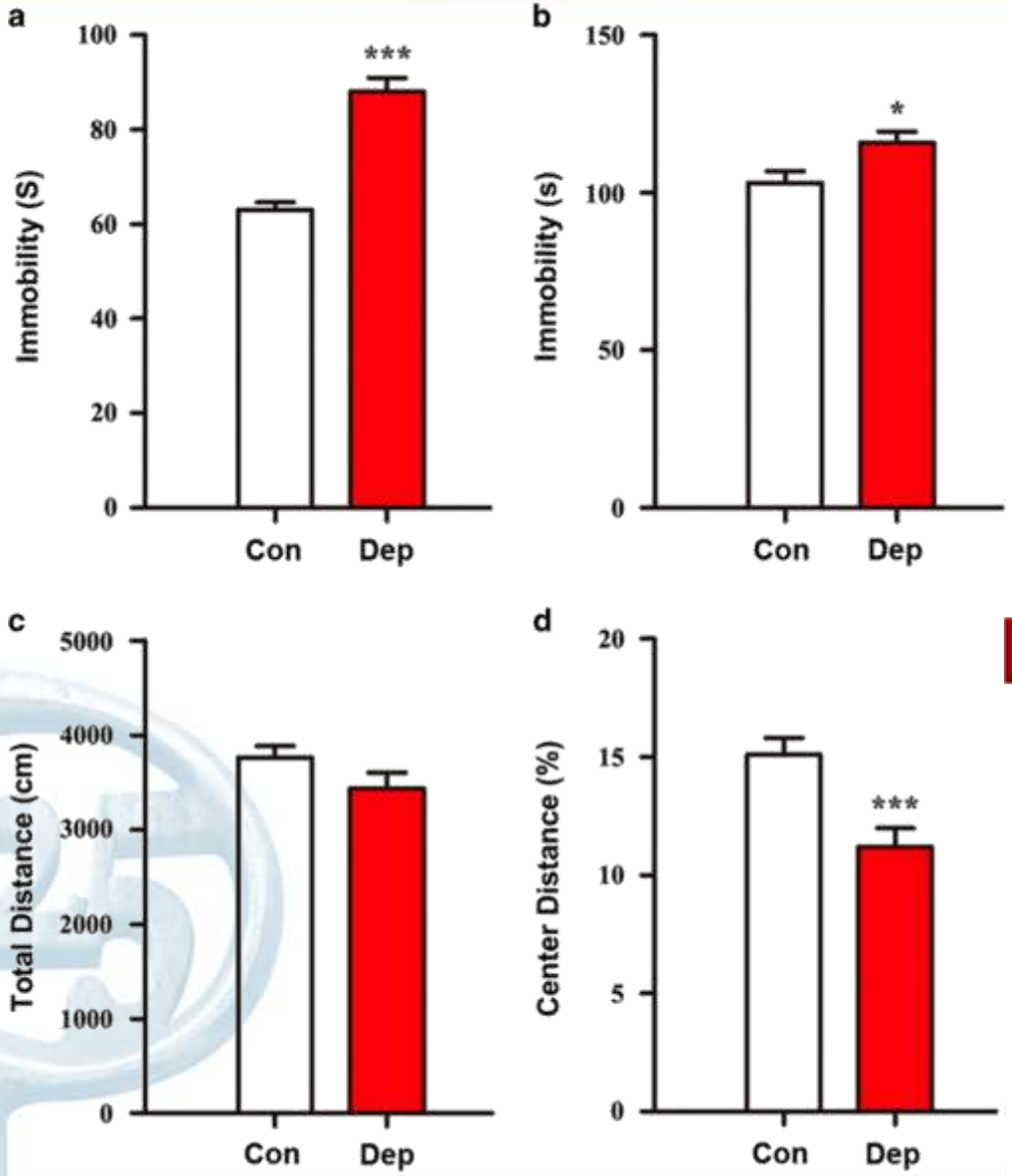
Microbiota from depressed patients induce depressive & anxious behaviour in germ-free mice

forced swim test

tail suspension test

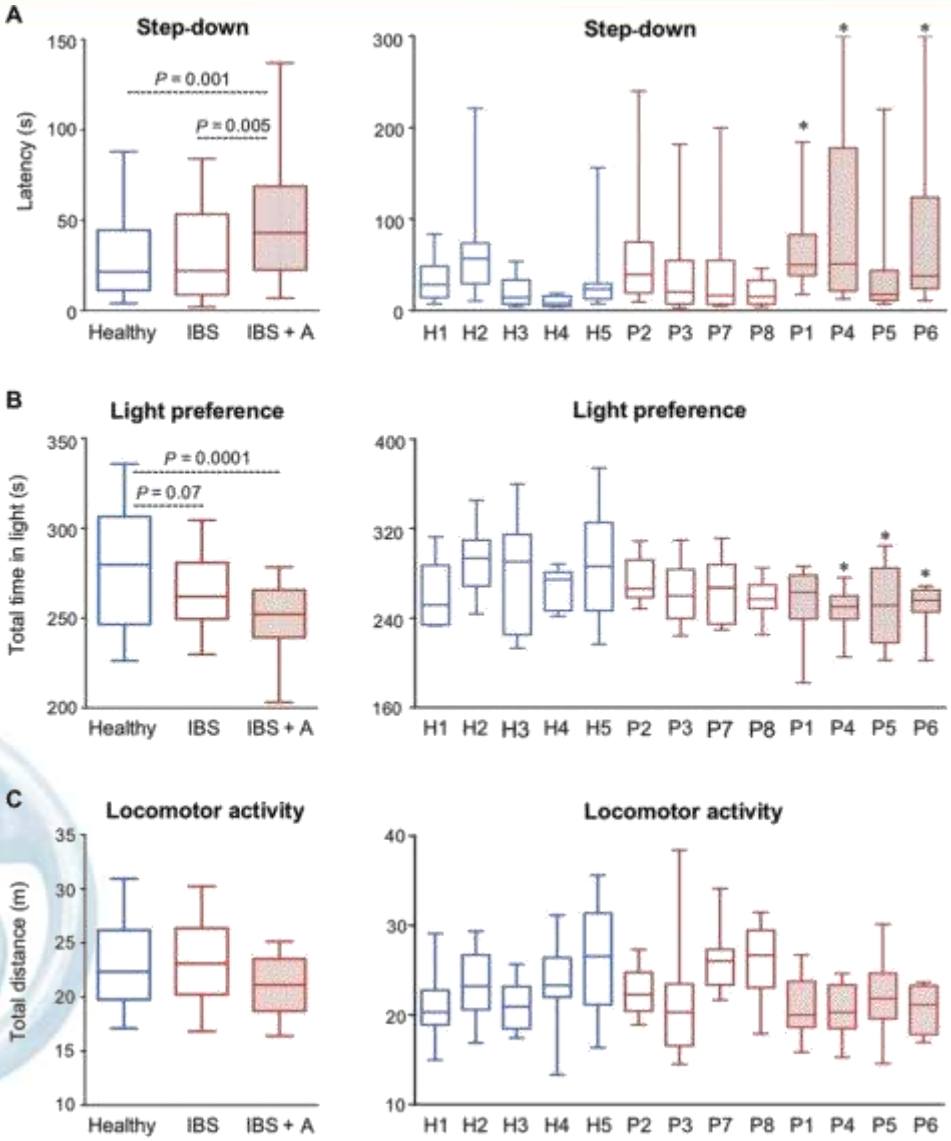
overall locomotor activity

open field test



Zheng et al, Mol Psychiatry 2016

Microbiota from anxious IBS patients induce anxious behaviour in germ-free mice



De Palma et al, Sci Transl Med 2017

Take home messages

- There is intimate **bidirectional communication** between the **gastrointestinal tract** and the **brain**
- This constitutes the **biological basis** of the **link** between **psychological** and **gastrointestinal symptoms**
- The **gut microbiota** have recently been identified as a key **new player** in this **communication**
- Therefore, the **microbiota** could have a strong impact on our **psychological and brain function**, but translation from animals to humans has only just started