Evolving practice in nutrition for patients with neurological disease: **the role of the gut-brain axis**

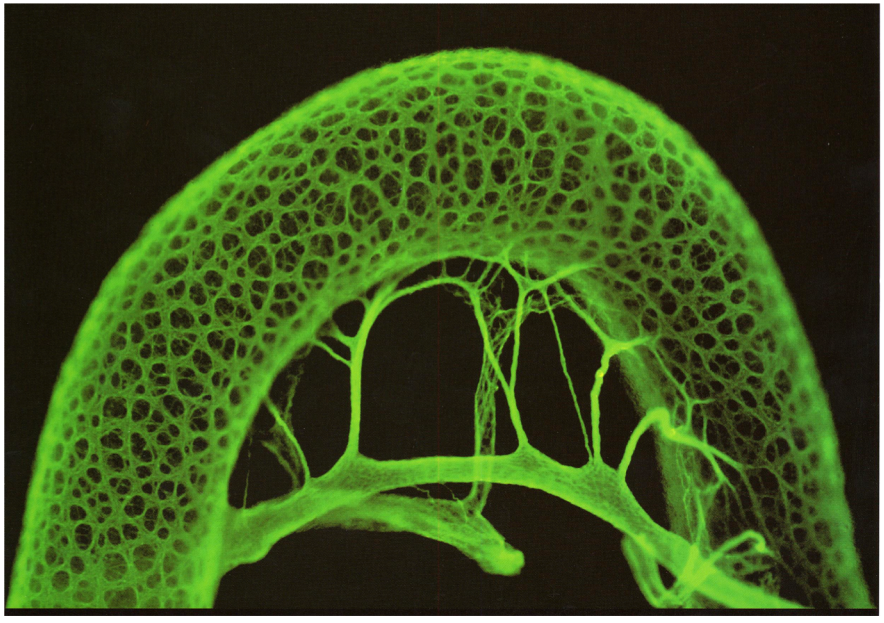
Anton Emmanuel

April 2019

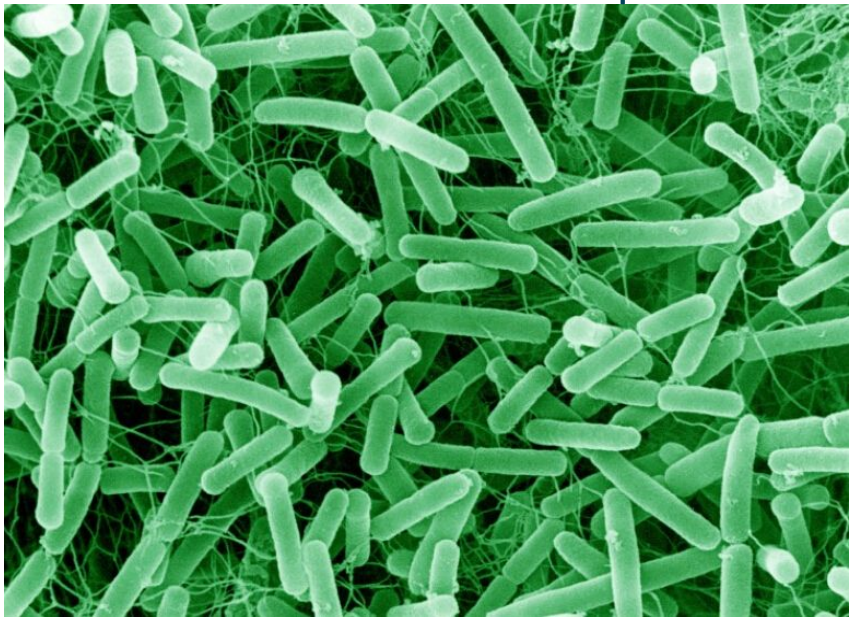
National Hospital for Neurology & Neurosurgery

The human gut

More bacterial cells than human cells



More neurones than the spinal cord



Neuro-gastroenterology

Update on understanding of brain-gut axis

- current understanding of physiology

Types of gut dysfunction

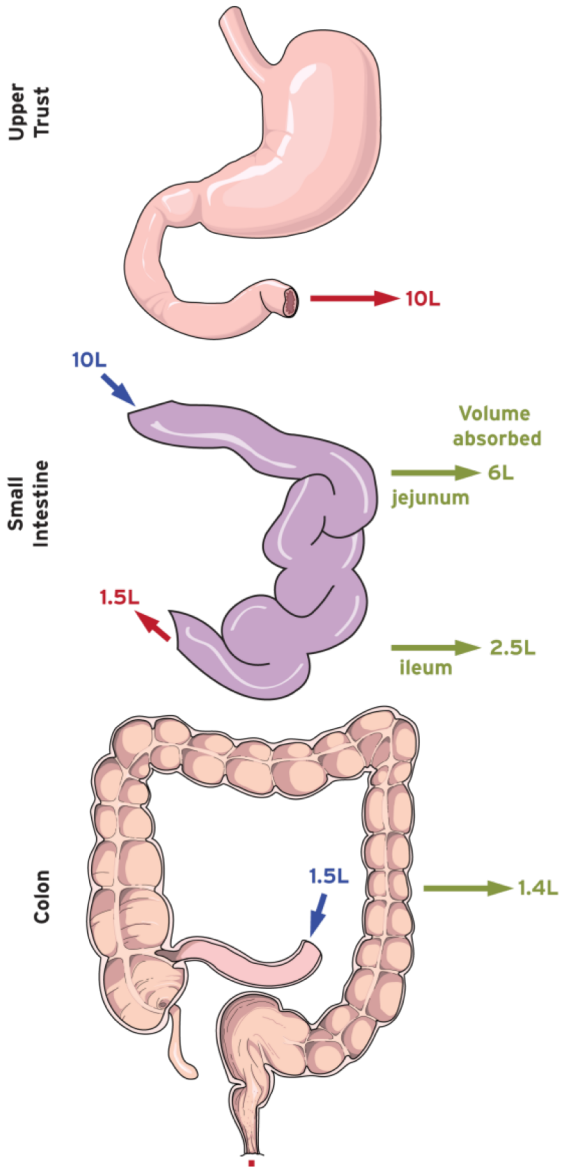
- understanding pathophysiology to target treatment

Microbiome involvement in control of gut function

Water fluxes through the intestine

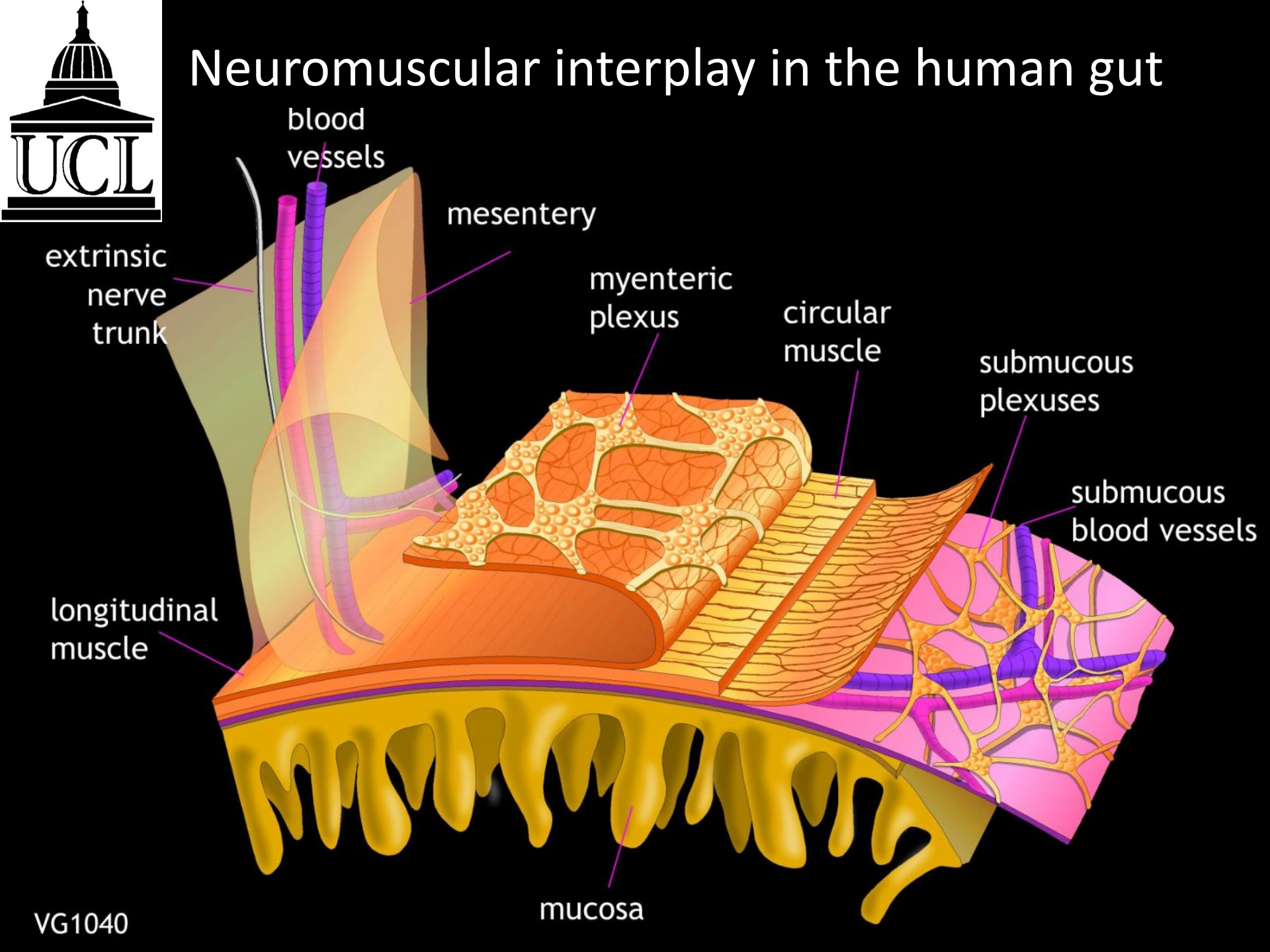
Water influx	
Food and drink	2.0 l
Saliva	1.5 l
Gastric juice	2.5 l
Bile	1.5 l
Pancreatic juice	2.5 l
Total	10.0 l

Extreme control



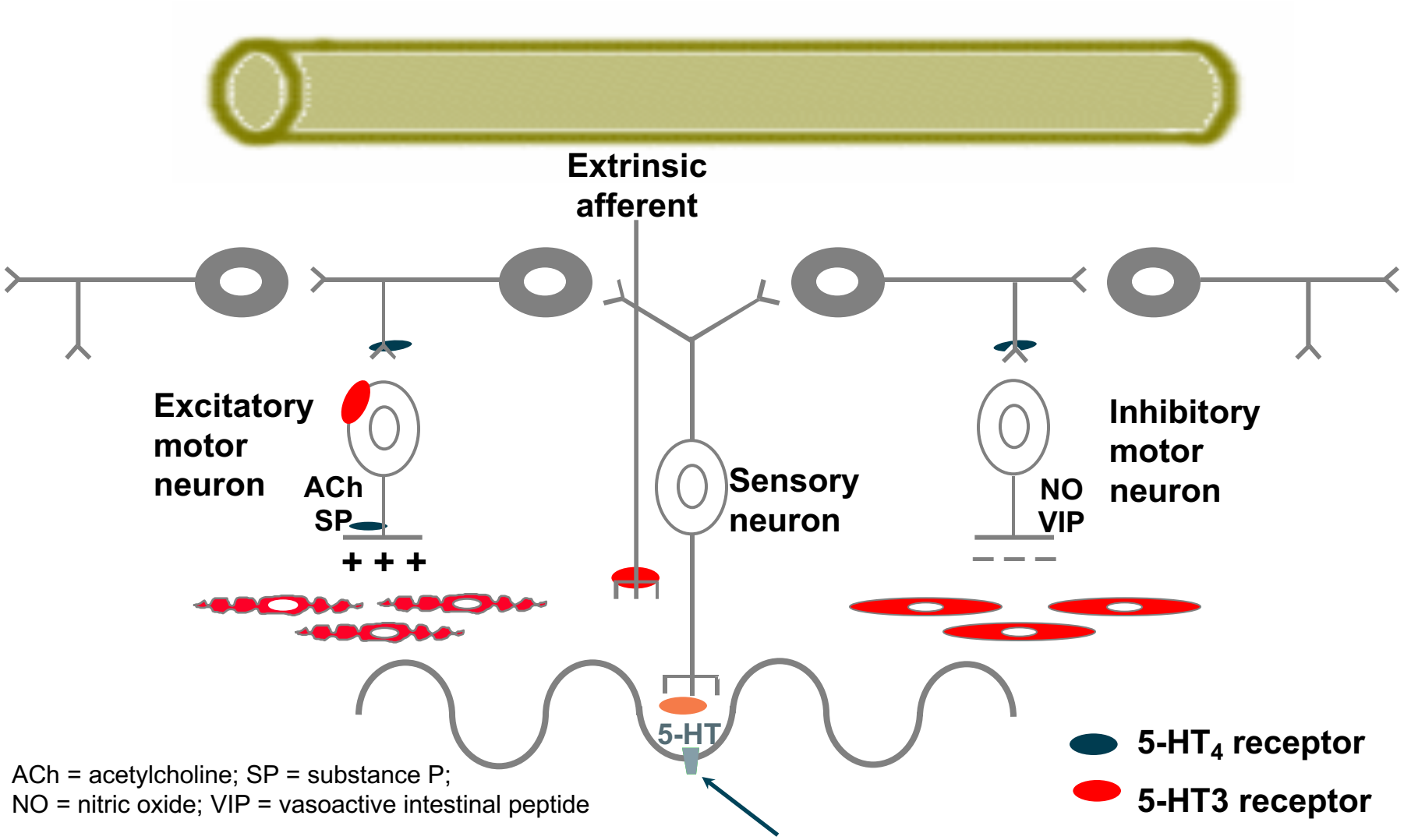
Chang and Rao. In: Johnson LR, eds. Physiology of the digestive tract. New York: Raven Press;1994;2027–2081.

Neuromuscular interplay in the human gut



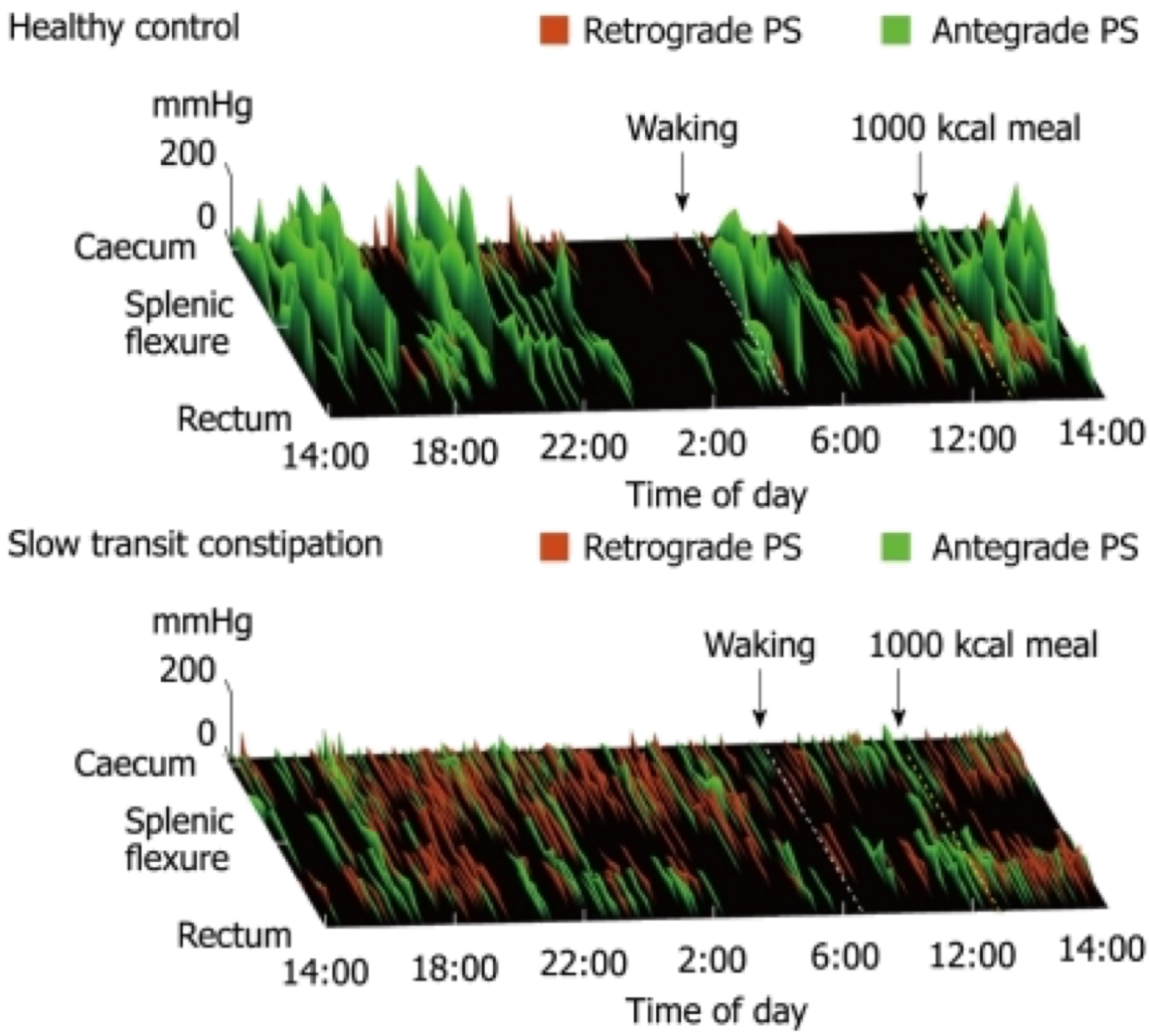
VG1040

Colonic 5-HT receptors



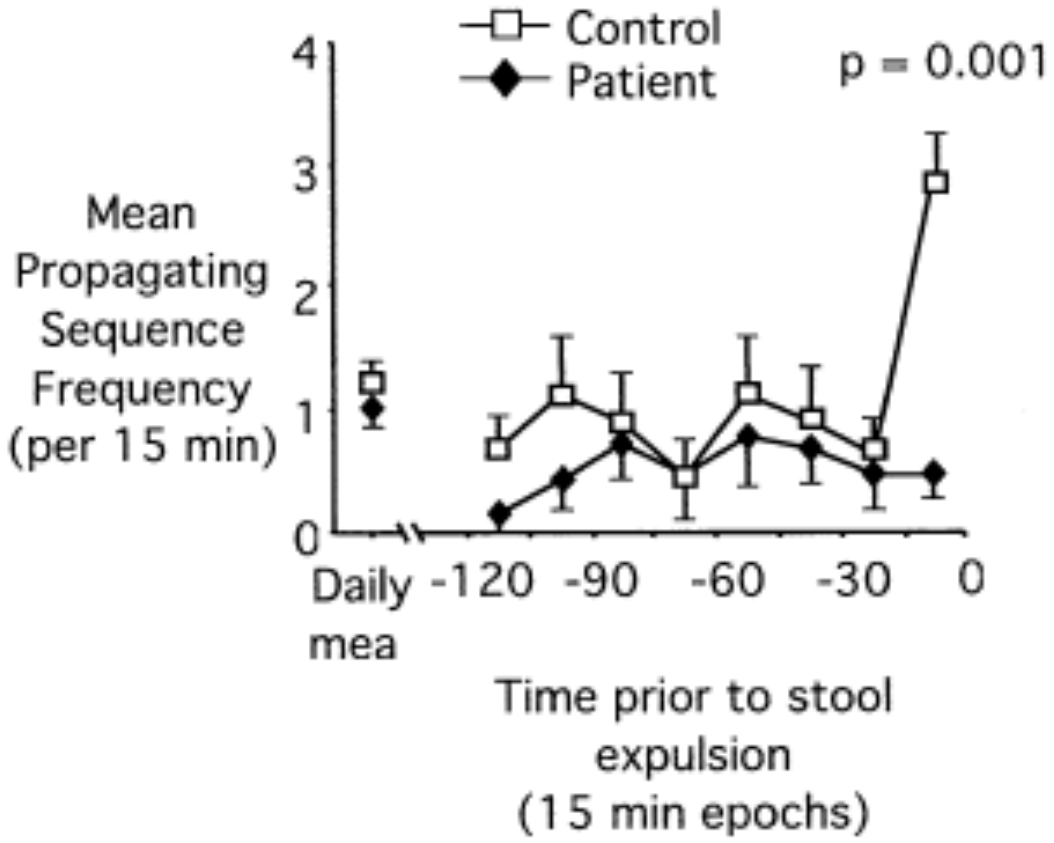
ACh = acetylcholine; SP = substance P;
NO = nitric oxide; VIP = vasoactive intestinal peptide

Motility: Healthy vs. constipated motor activity[1]



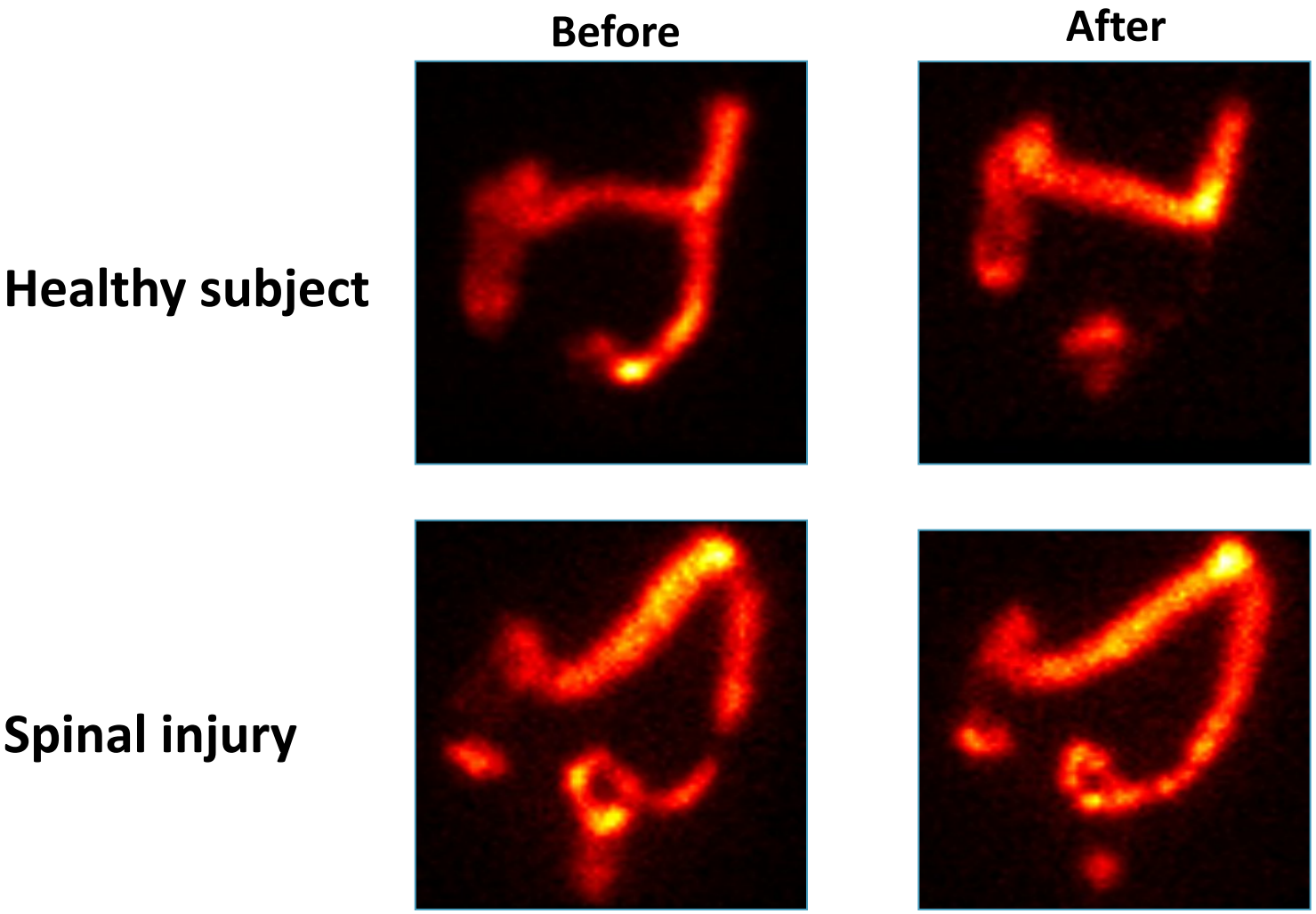
1. Dinning et al. World J. Gastroenterol 2010;16(41):5162-5172.

Relationship of synchronising defaecatory effort with colonic mass movements



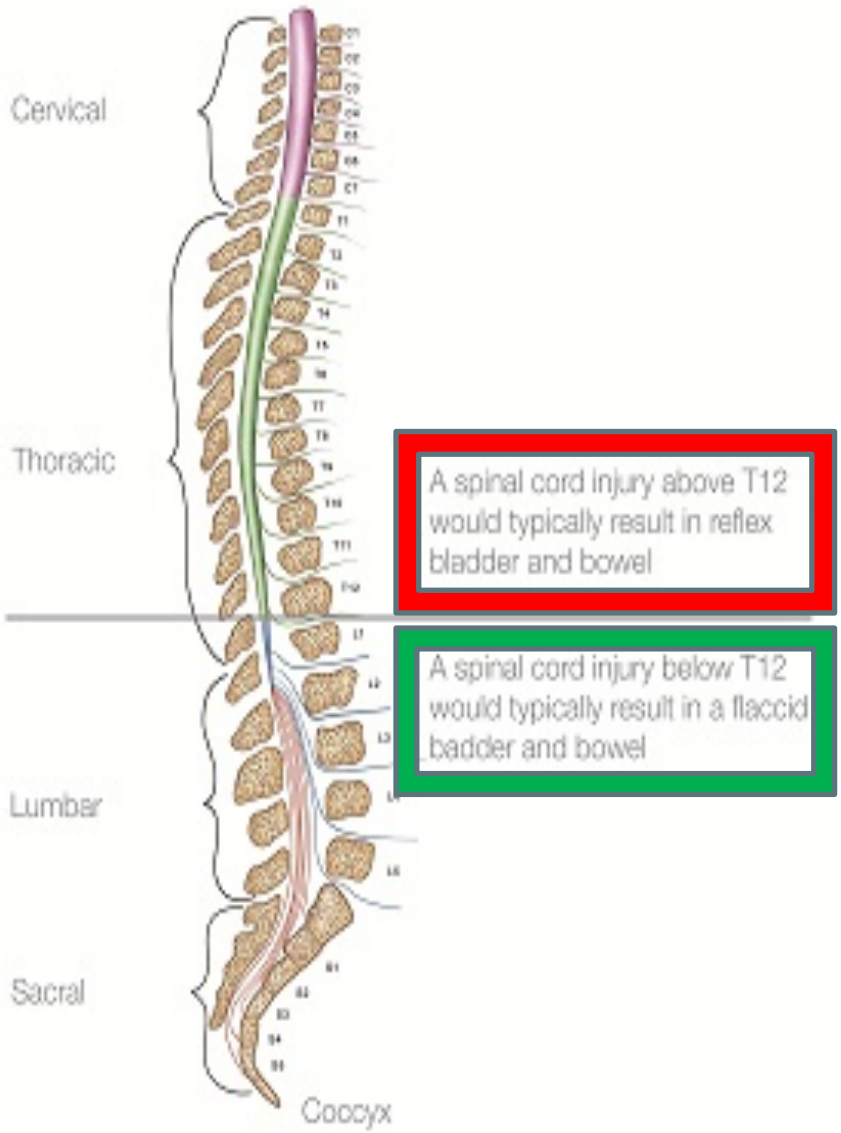
Dinning et al *Gastroenterology* 2004;**127**(1):49-56

Scintigraphic study showing defaecation produces a complete emptying of the left colon in healthy subjects, but not in SCI



Rasmussen MM et al. Spinal Cord 2013; 51: 683- 7

Pathophysiology



Reflex bowel:

Loss of sensation of fullness

Rectal pressure **high**

Anal sphincter **high pressure** opens as a reflex when the rectum is full

Predisposes to inappropriate emptying

Flaccid bowel:

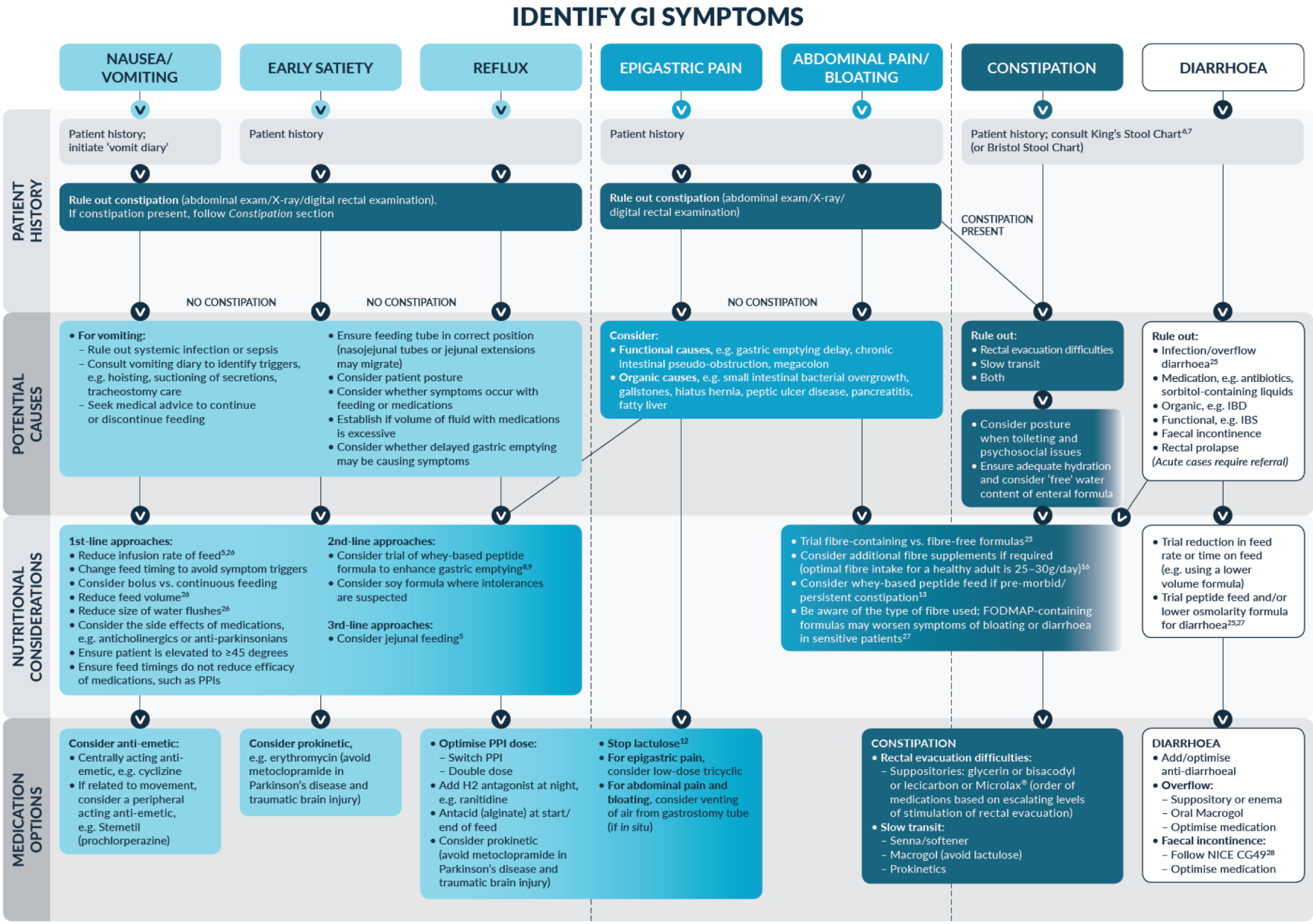
Loss of sensation of fullness

Rectal pressure **low**

Anal sphincter at **low pressure**

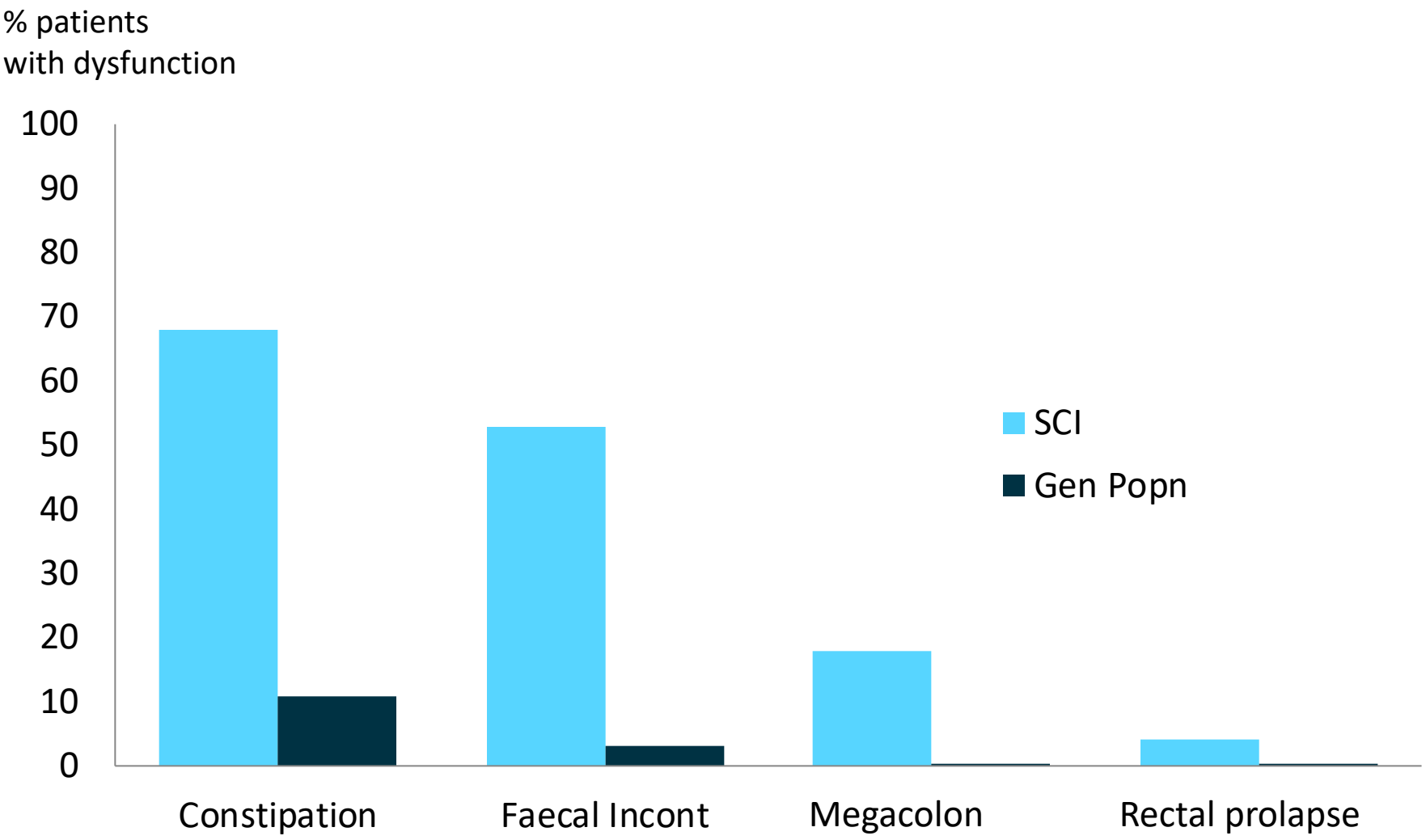
Predisposes to bowel soiling

Involvement goes beyond the bowel



FODMAP = fermentable oligosaccharides, disaccharides, monosaccharides and polyols; GI = gastrointestinal; IBD = inflammatory bowel disease; IBS = irritable bowel syndrome; PPI = proton pump inhibitor

Prevalence of neurogenic bowel symptoms



Bowel dysfunction ruins quality of life

Spinal Cord Injury

Limitation	Impact (0-6)
Mobility	4.8
Bowel	4.3
Sexual	3.5
Bladder	3.4
Sensation	2.7

Glickman & Kamm, Lancet 1998

Multiple Sclerosis

Limitation	Impact (0-6)
Bowel	4.4
Bladder	3.9
Sexual	3.5
Mobility	3.1
Sensation	3.1

Preziosi et al, DDW 2011

Hospitalisations twice as frequent in SCI patients with bowel symptoms

Sonnenberg et al, Am J Gastro 2004

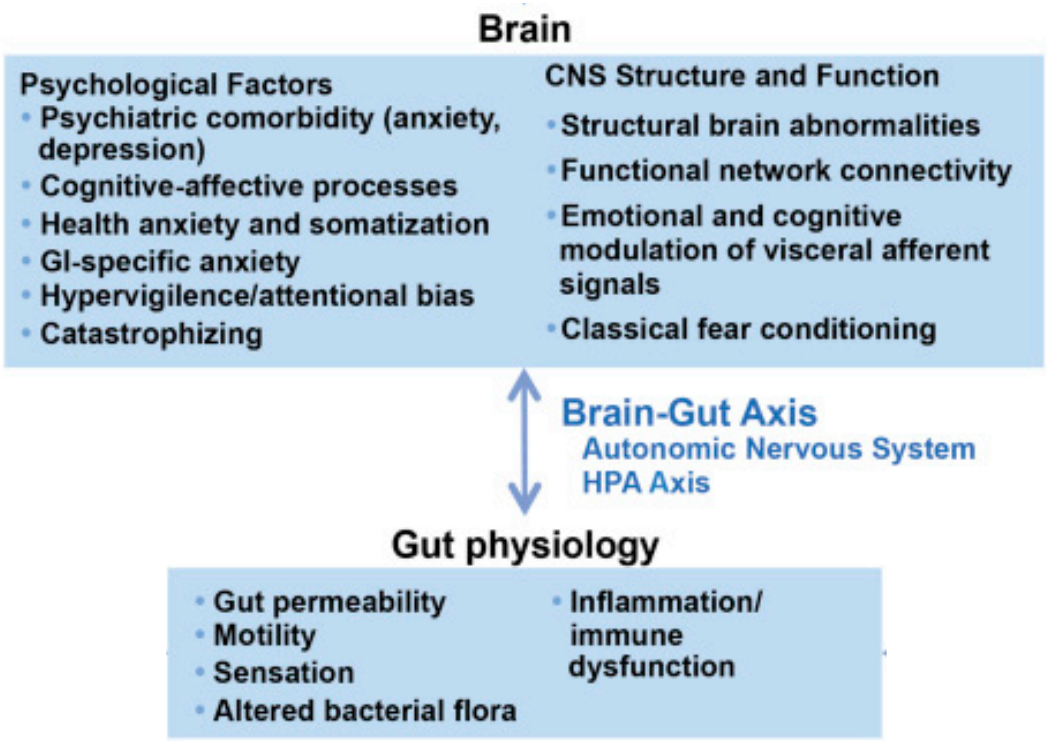
The bi-directional brain-gut axis

Incidence Ψ disorders in FGIDs

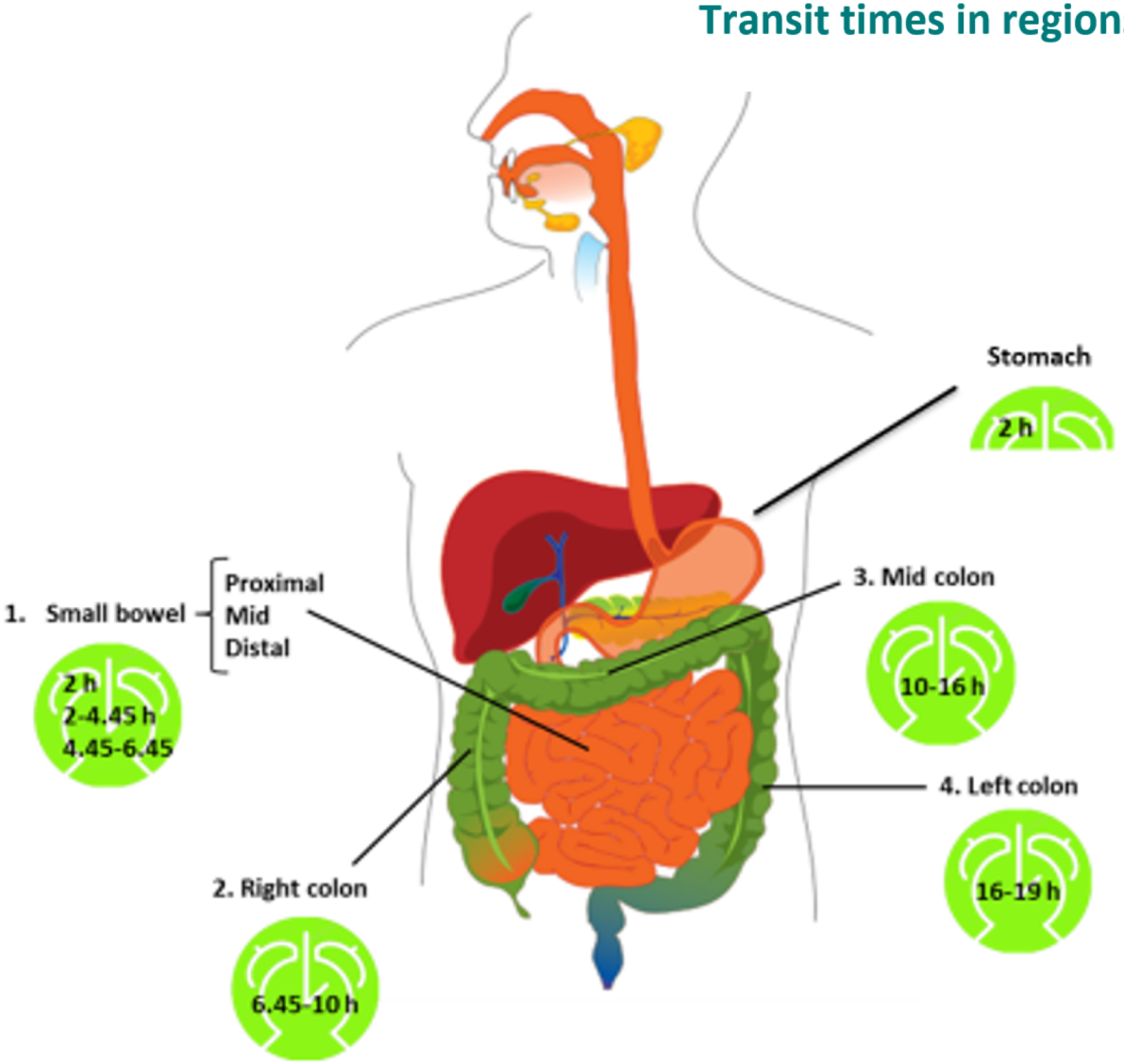
Use of tricyclics in FGIDs

Overlap of neurotransmitters in brain & gut

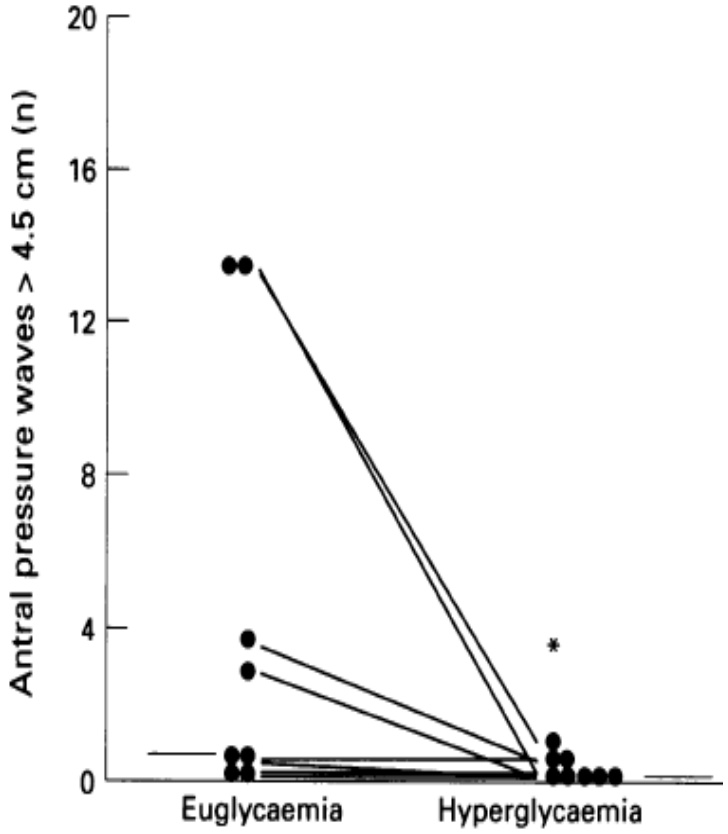
Stress exacerbation of FGIDs



Transit times in regions of the gut

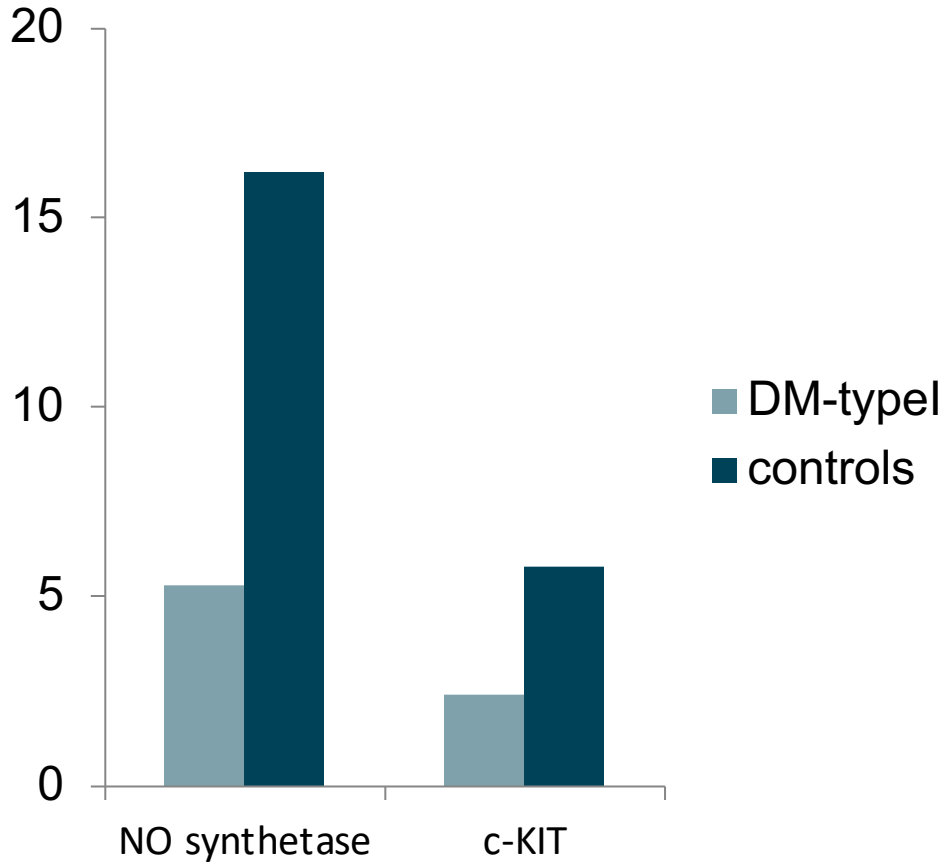


Gastric Emptying and Blood Sugar



Hyperglycaemia delays gastric emptying

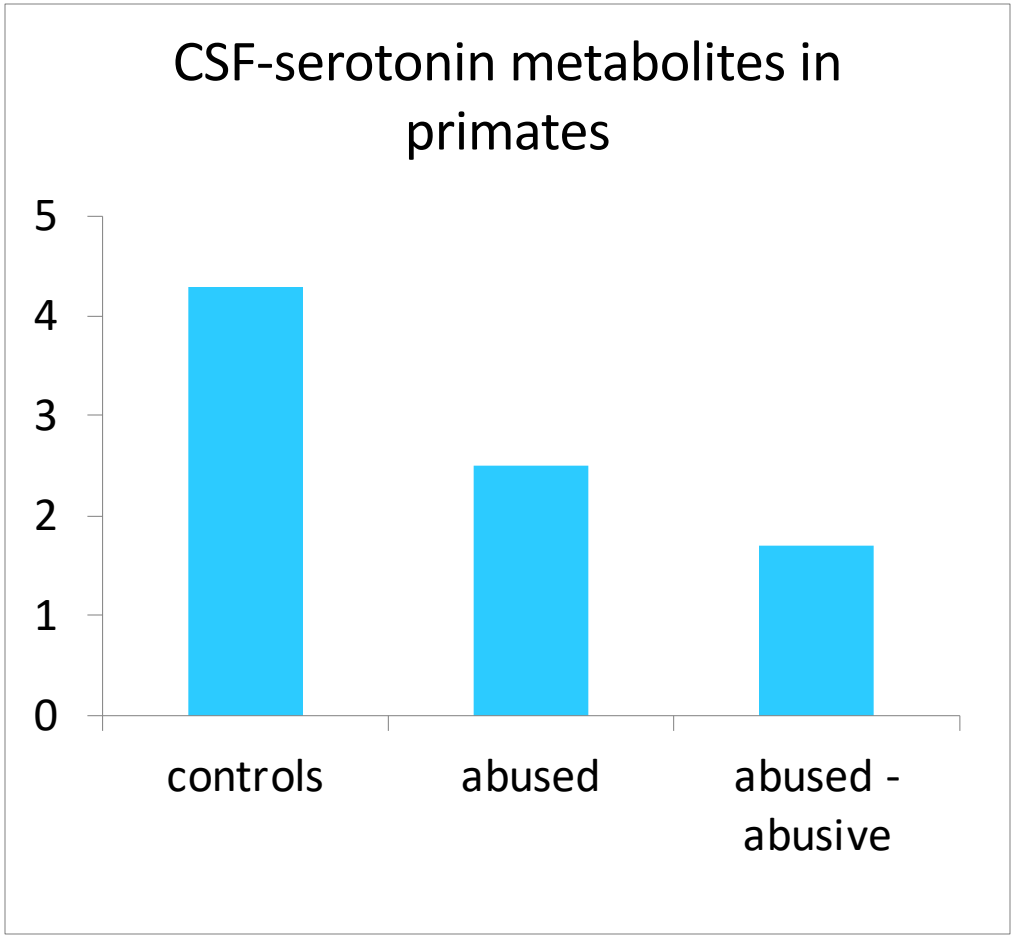
Samsom et al, Gut 1997



Abnormal neural networks in diabetes

Russo et al, J Clin Endocrin & Metab 2005

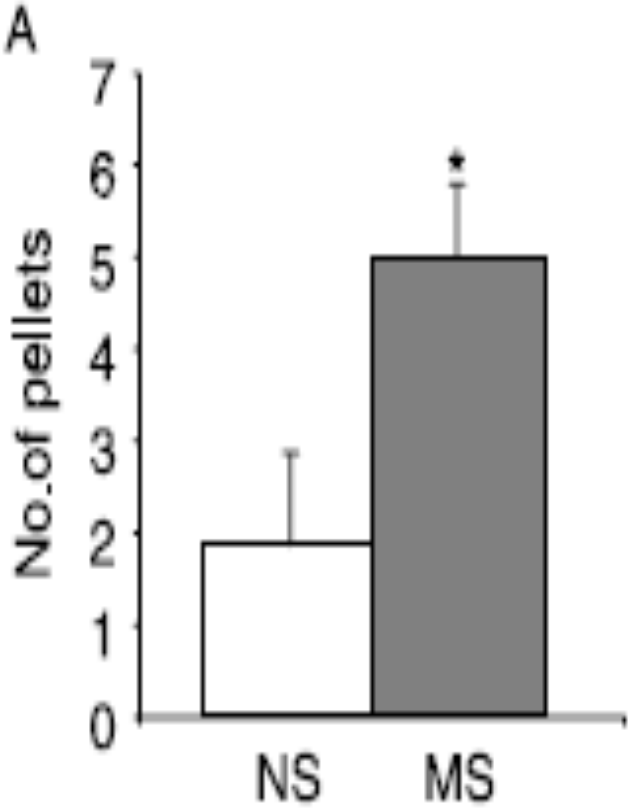
Serotonin: gut derived, brain active
Abuse and chronic stress



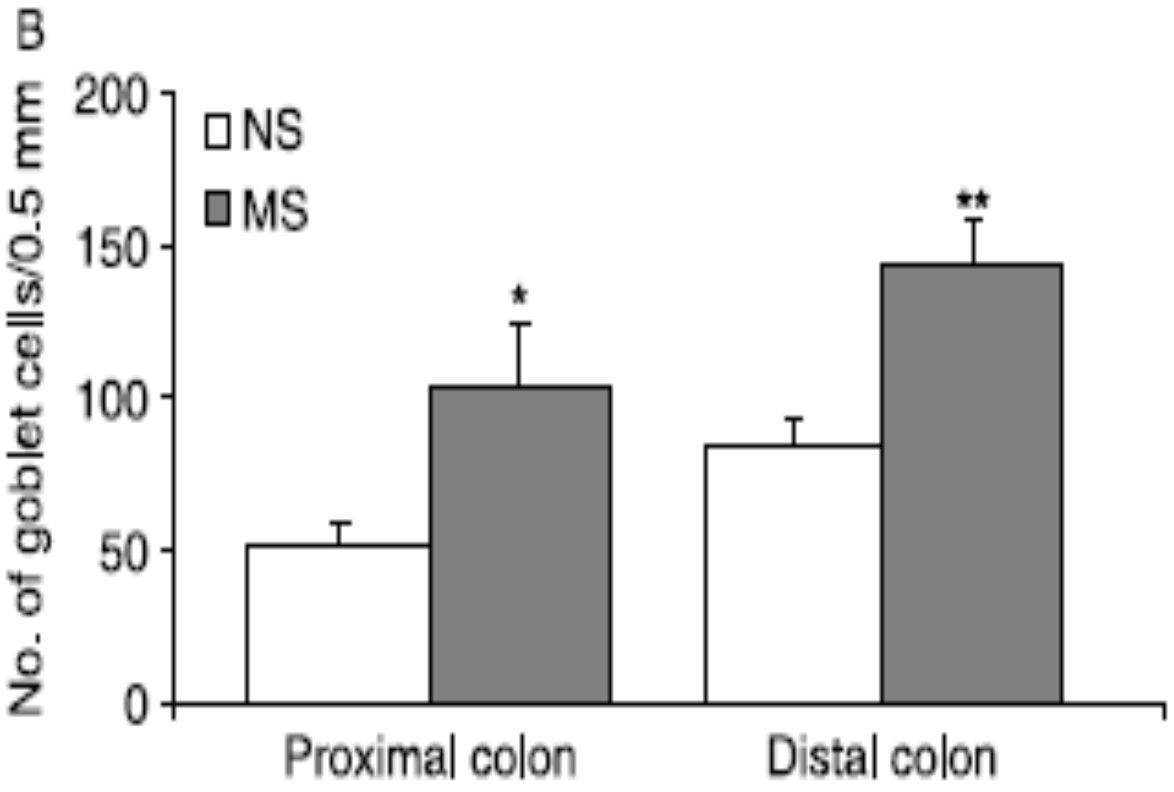
Maestripieri et al Prog Neurophysiol 2011

Effect of acute stress on bowel function

Symptoms and Histology



Maternally separated rats have ↑ bowel frequency

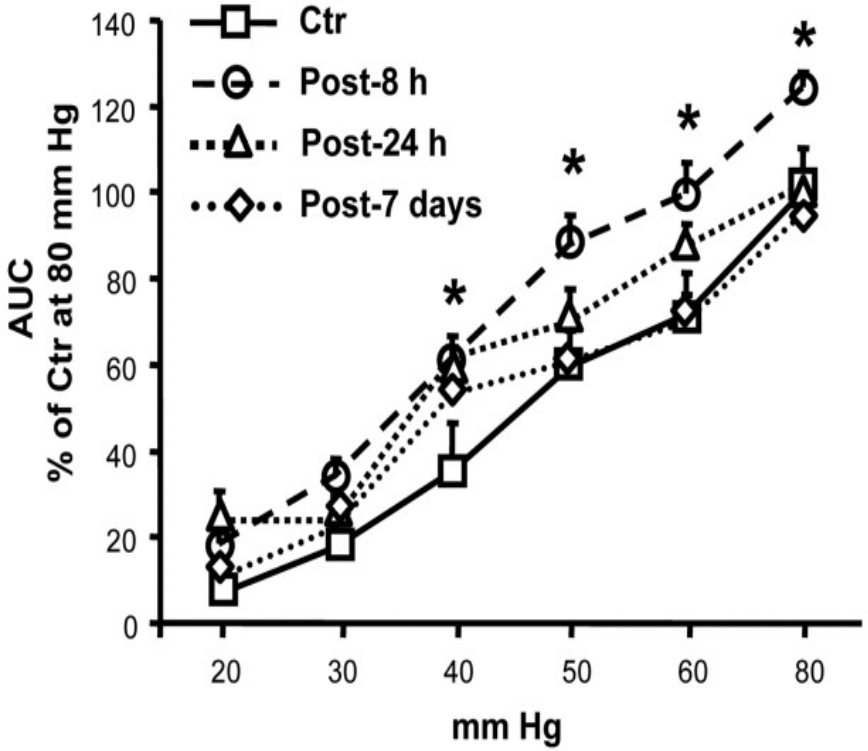


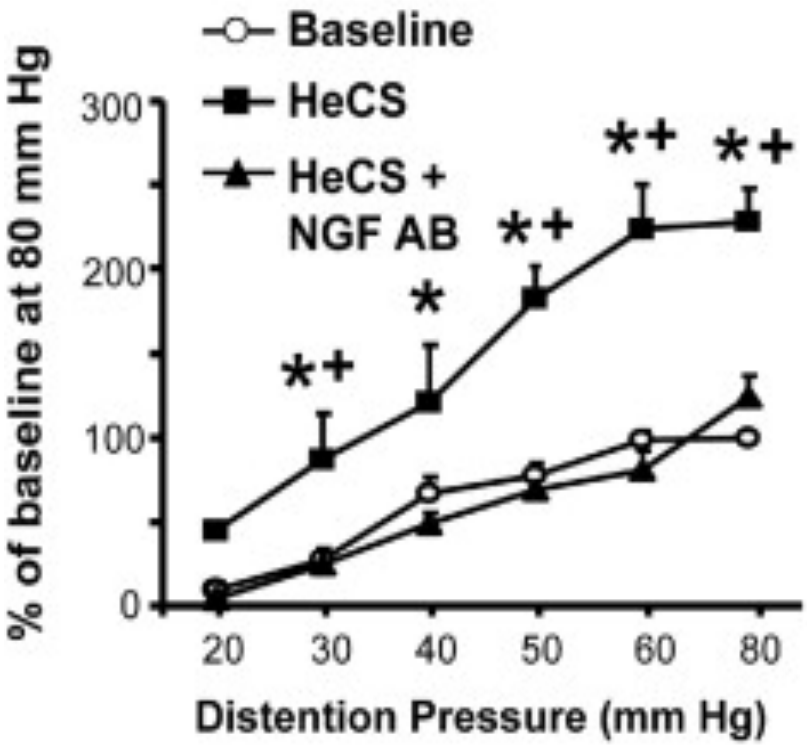
Maternally separated rats have ↑ goblet cells

O'Malley et al Gastroenterol 2010

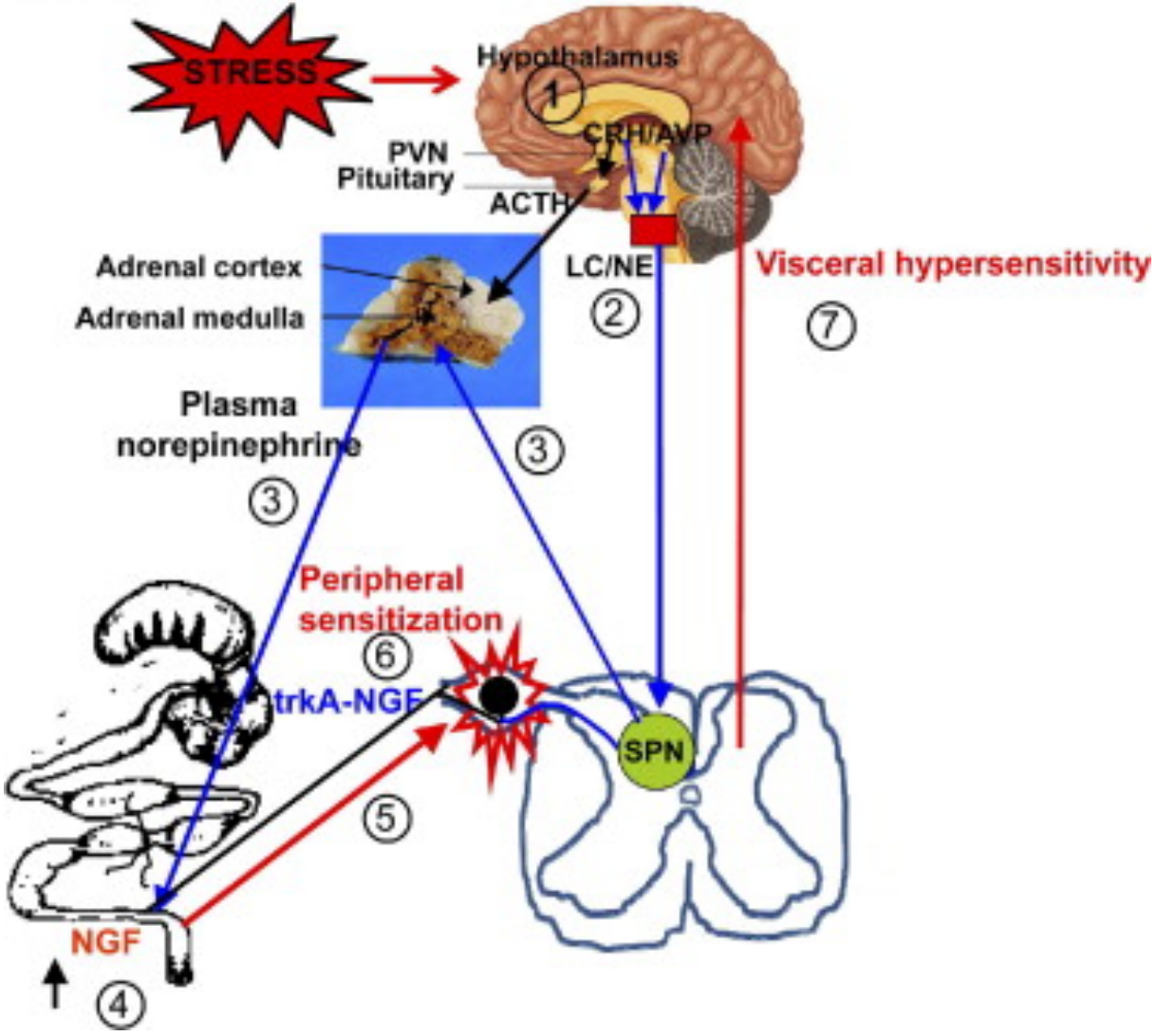
Stress causes pain through an adrenergic mechanism

Rat model of stress (Winston et al 2010)





Putting it together



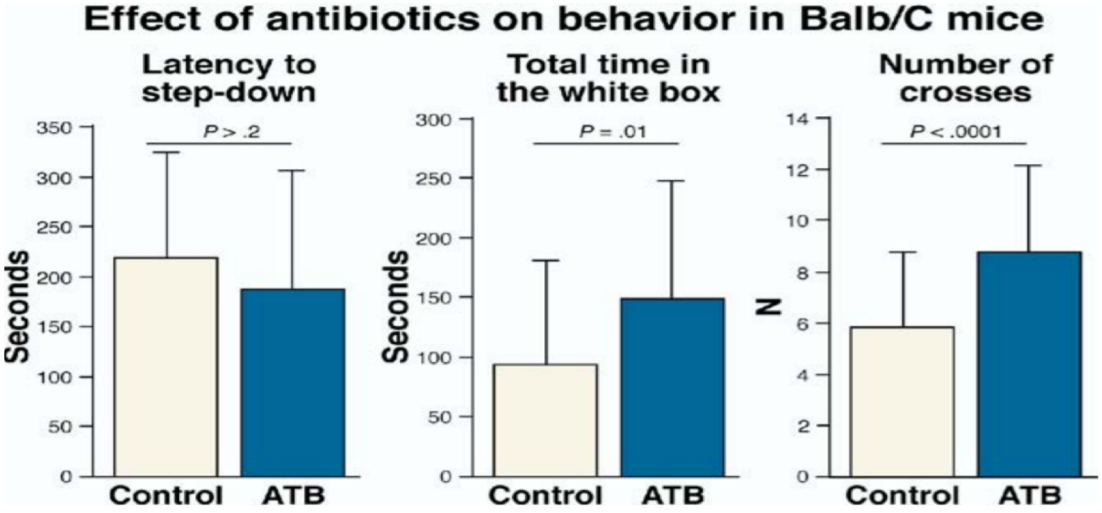
Evidence of microbiome-gut-brain axis: antibiotics

	≥1 Additional Symptoms		≥2 Additional Symptoms	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Antibiotic use	3.29 (1.25–8.62)	0.02	6.18 (1.3–29.41)	0.02
Female gender	1.31 (0.43–3.93)	0.63	0.27 (0.06–1.22)	0.09
Age (per yr)	1.03 (0.97–1.09)	0.28	0.97 (0.90–1.05)	0.50
GP visits group	0.93 (0.47–1.85)	0.83	2.34 (0.86–6.37)	0.10
Anxiety score (per unit)	1.00 (0.87–1.15)	0.97	1.06 (0.88–1.28)	0.55
Depression score (per unit)	1.01 (0.82–1.24)	0.92	0.88 (0.63–1.23)	0.45
Hypochondriasis score (per unit)	1.12 (0.83–1.53)	0.46	1.04 (0.68–1.59)	0.87
Disease phobia score (per unit)	0.91 (0.68–1.23)	0.55	0.96 (0.66–1.38)	0.81
Bodily preoccupation score (per unit)	1.06 (0.80–1.41)	0.69	1.24 (0.82–1.85)	0.30

GP = general practitioner; OR = odds ratio.

Effect of antibiotics on FGID symptoms

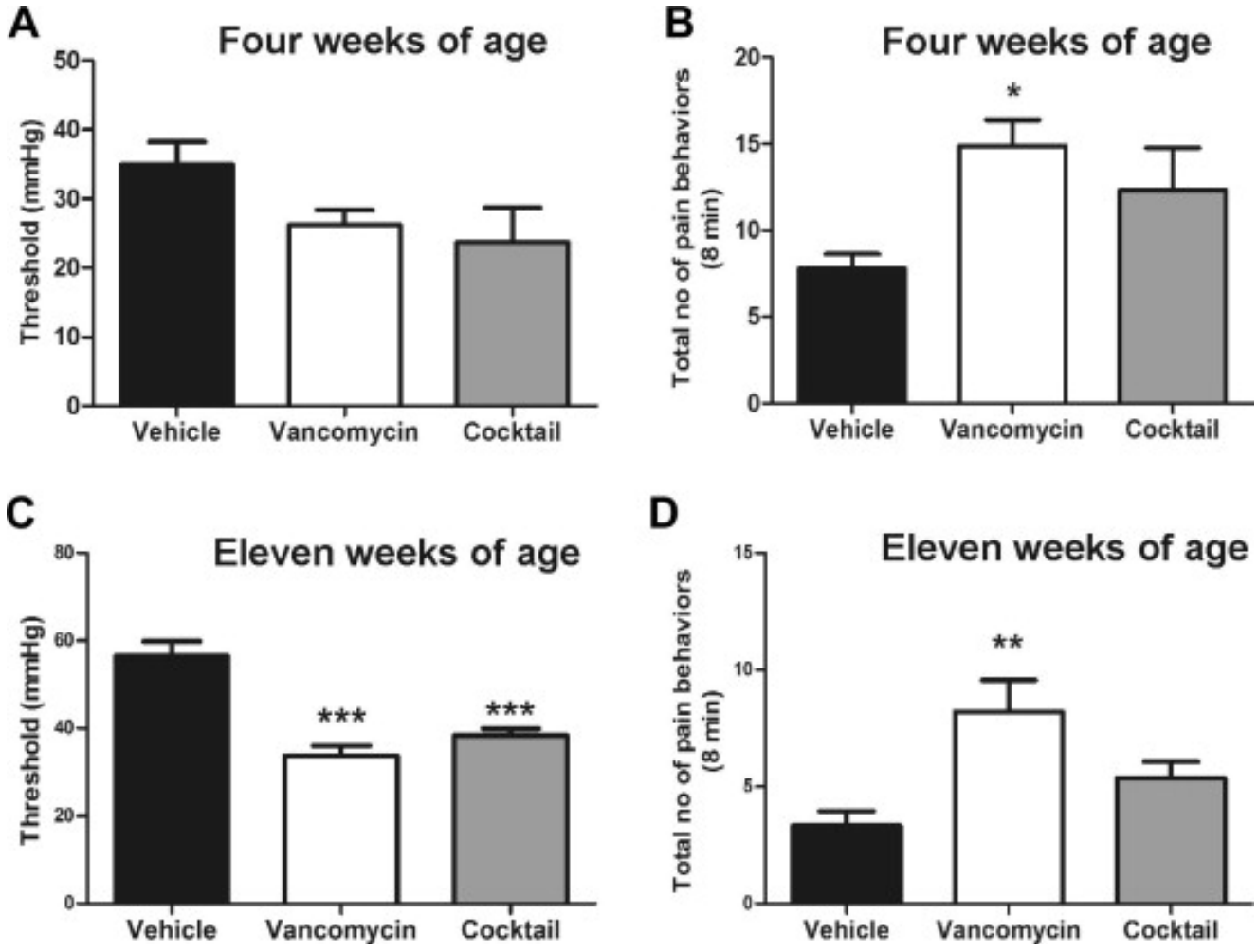
Maxwell et al Am J Gastro 2002



Effect of antibiotics on behaviour (mouse)

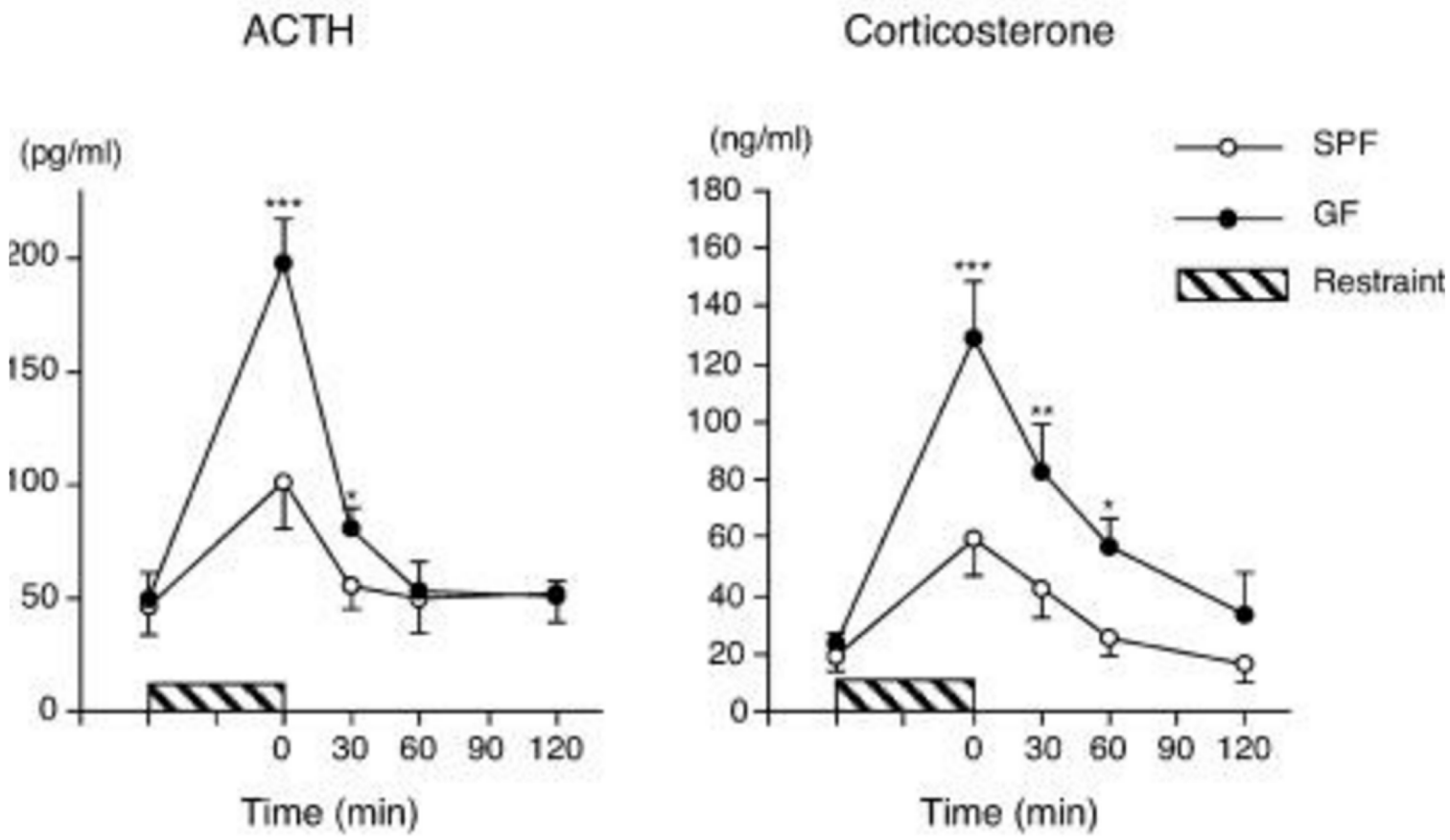
Collins & Bercik Gastroenterol 2009

Evidence of microbiome-gut-brain axis: early life



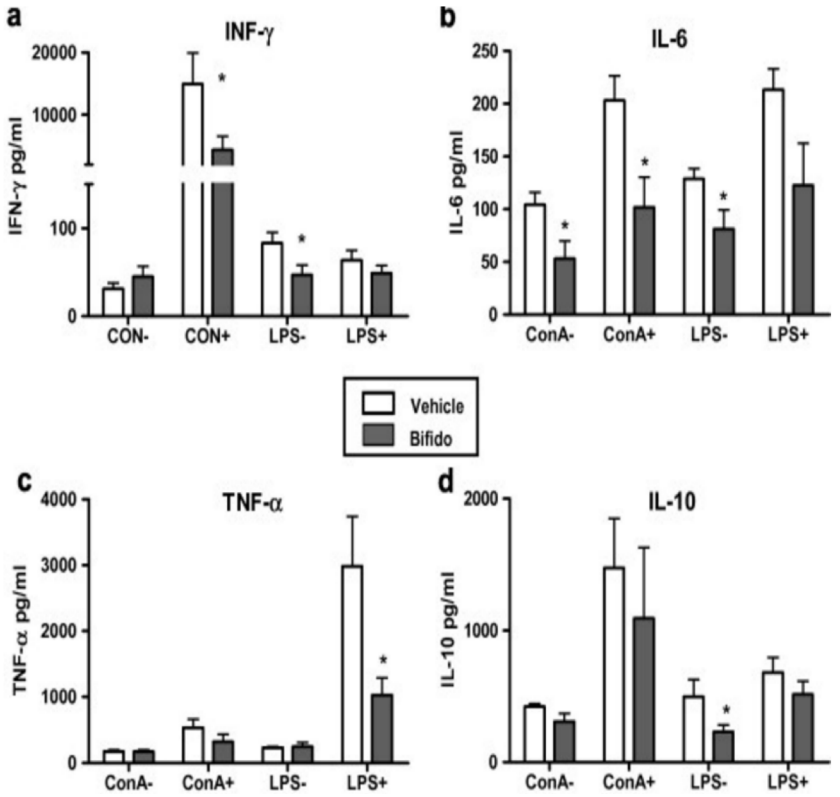
O'Mahony et al Neuroscience 2014

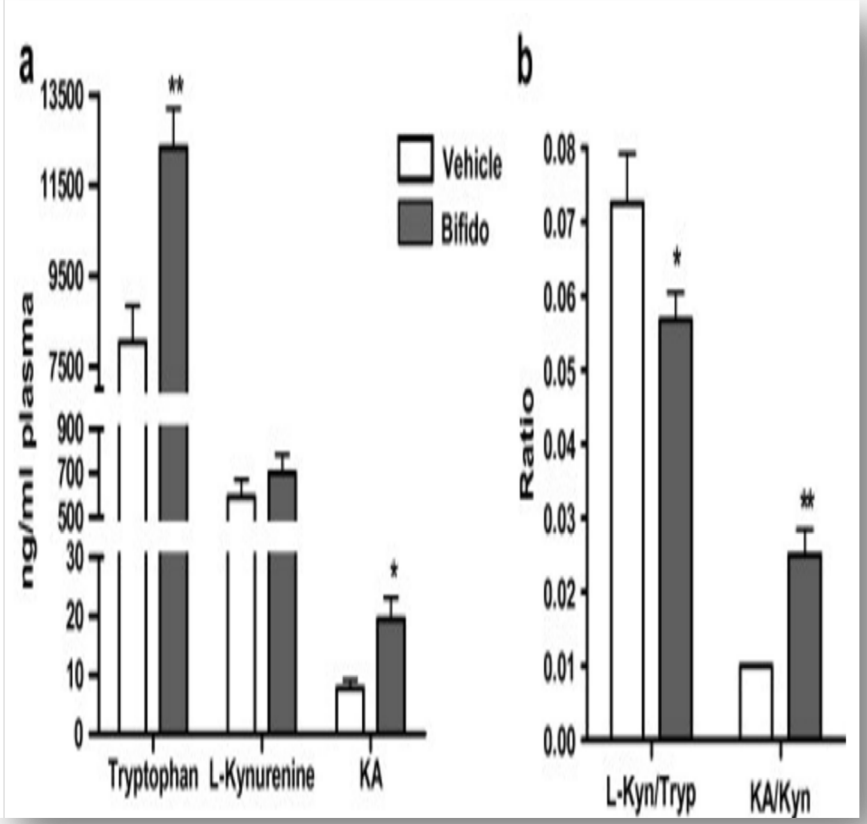
Evidence of microbiome-gut-brain axis: germ-free model



Sudo et al J Physiol 2004

Evidence of microbiome-gut-brain axis: probiotic effect

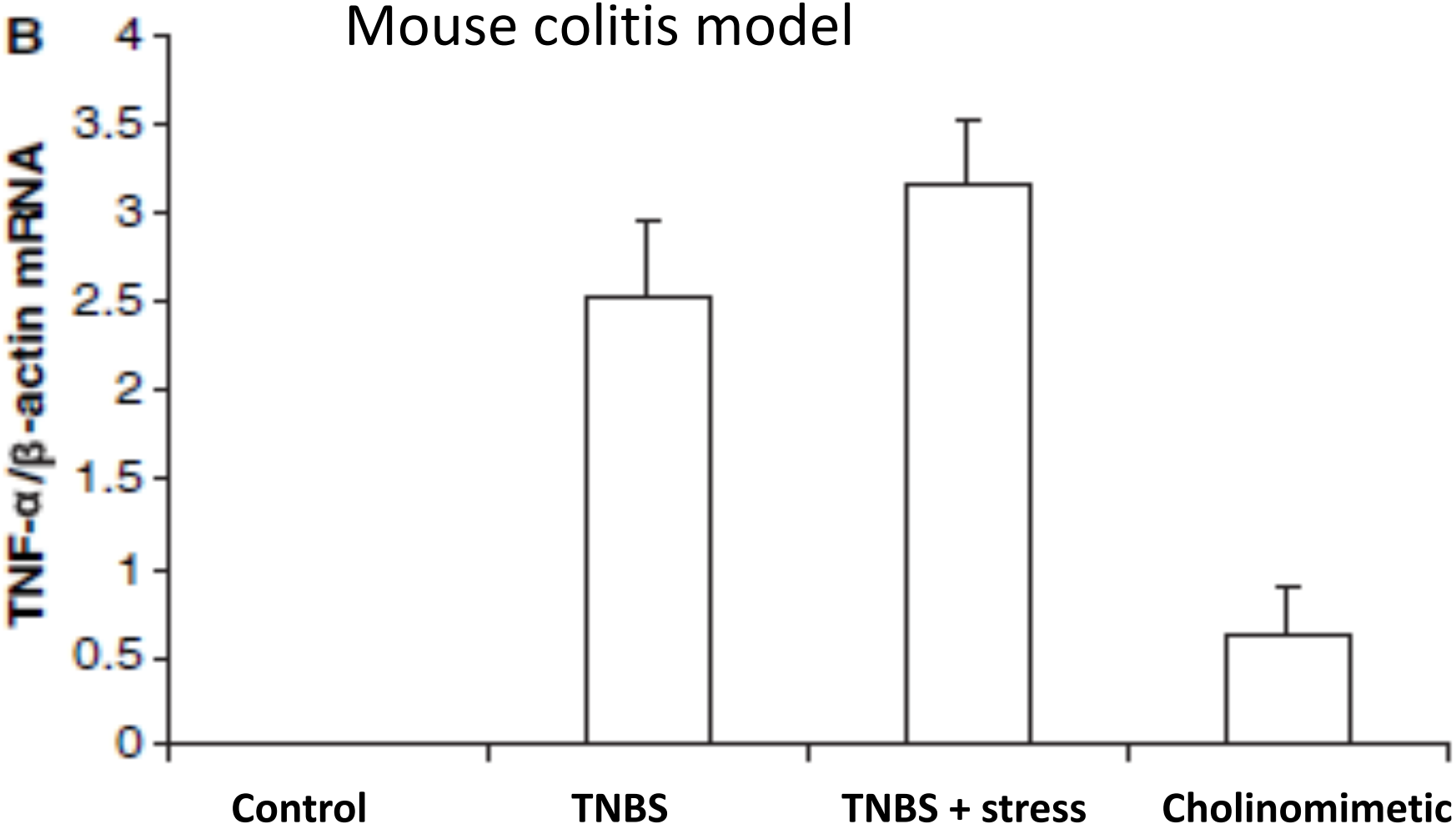




Desbonnet et al J Psych Res 2008

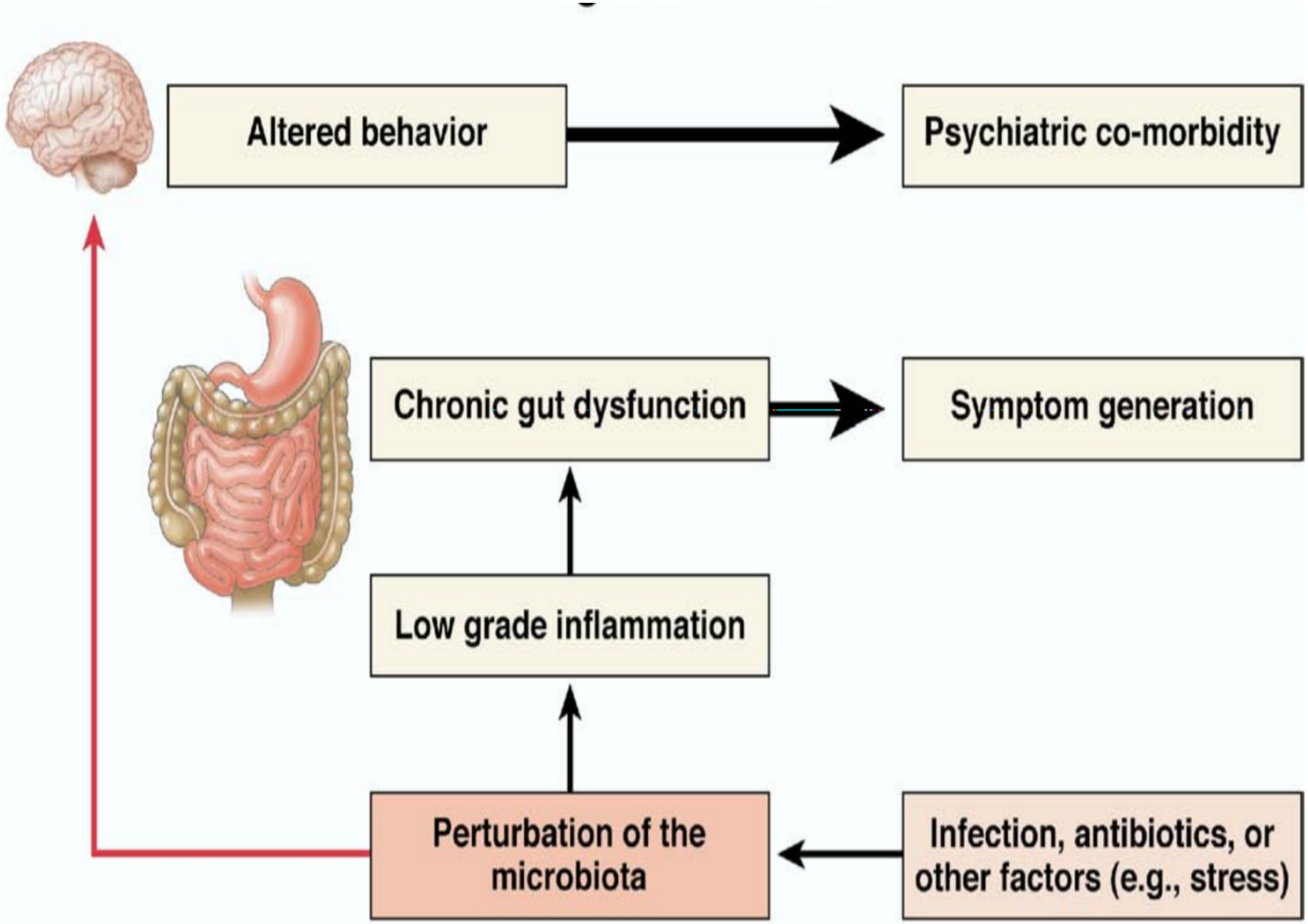
Modifying the cholinergic stress anti-inflammatory pathway

Mouse colitis model

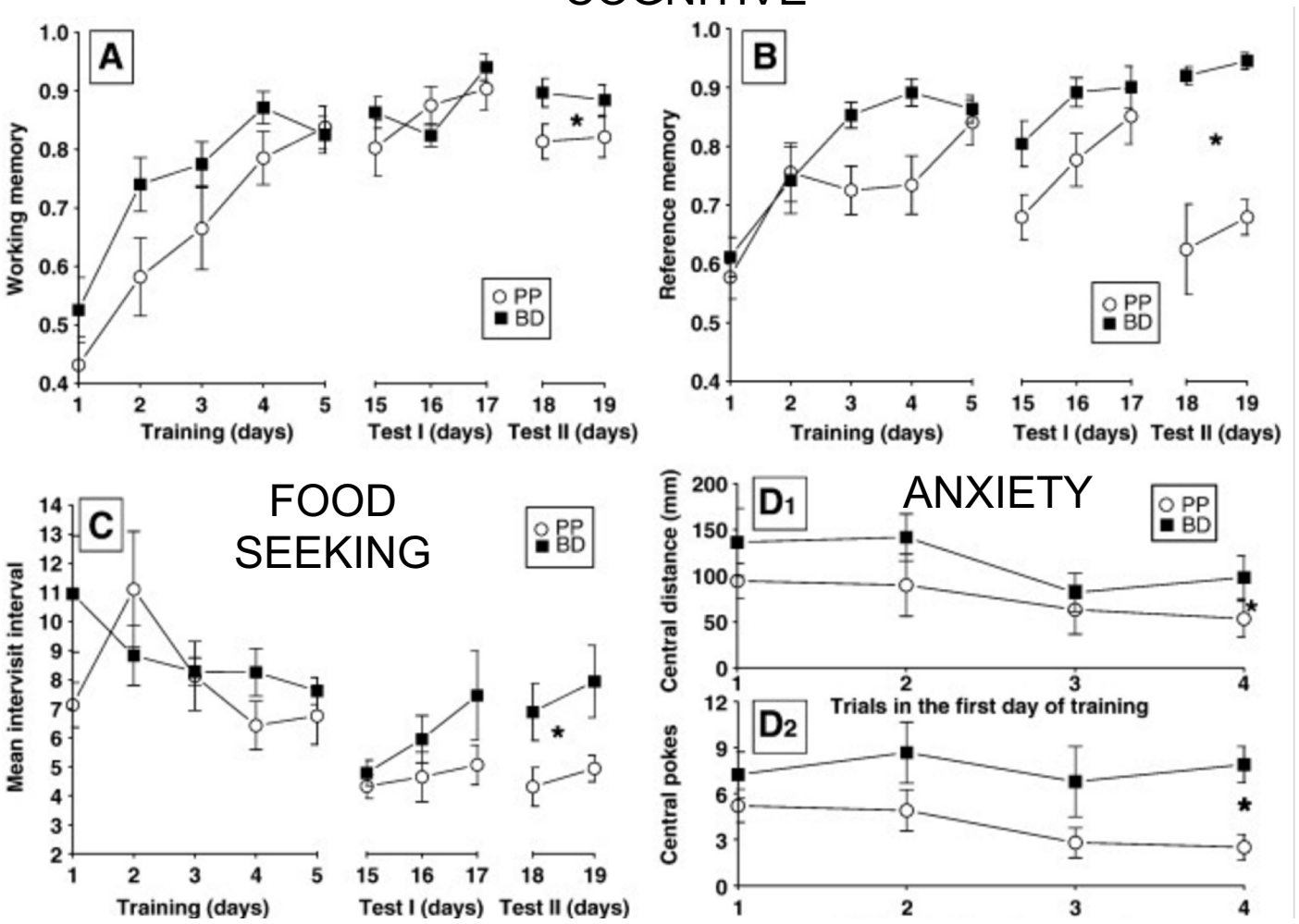


Bai et al Scan J Immunol 2007

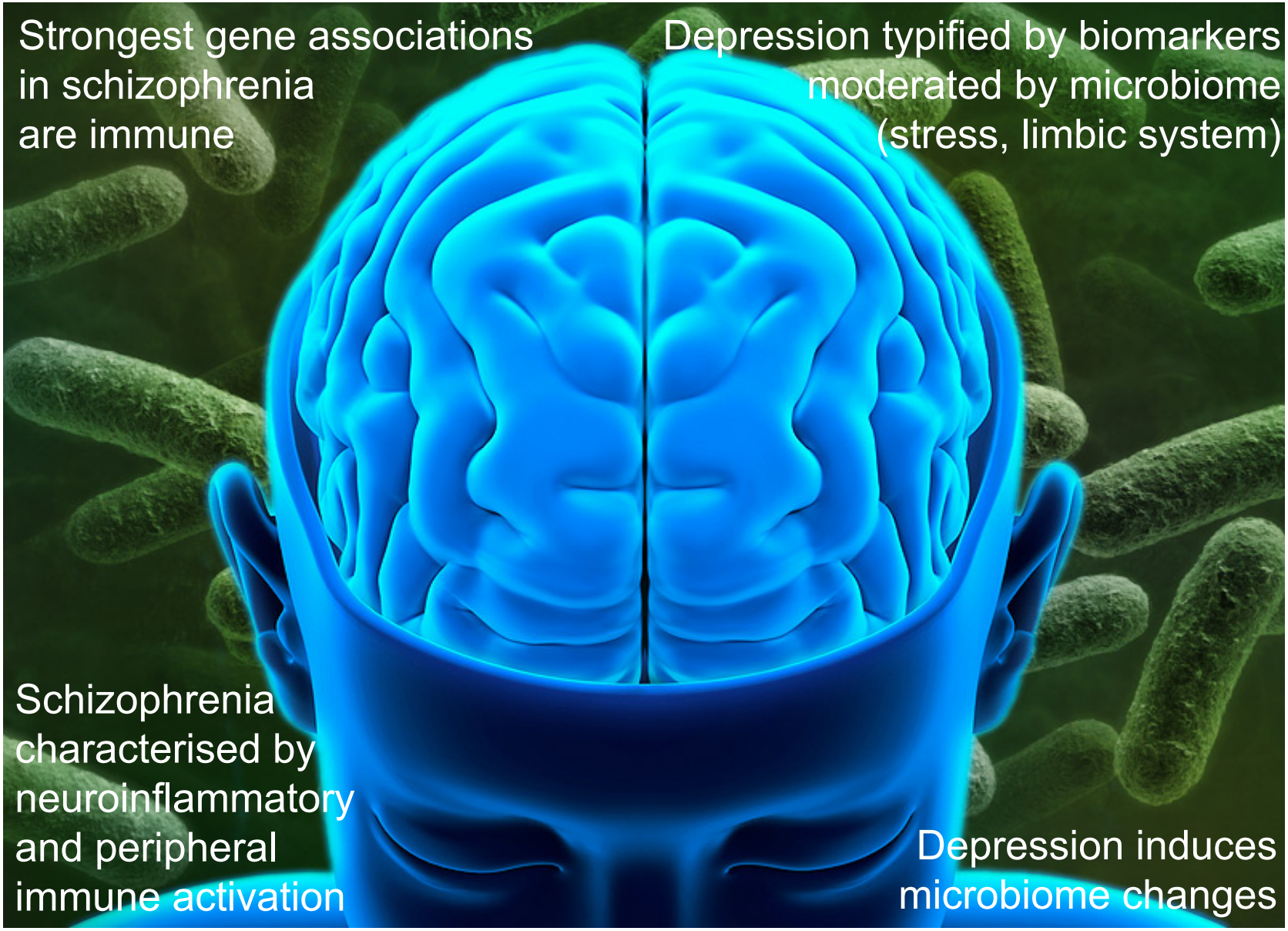
Putting it together: a hypothetic model



Diet modifies this cortical effect



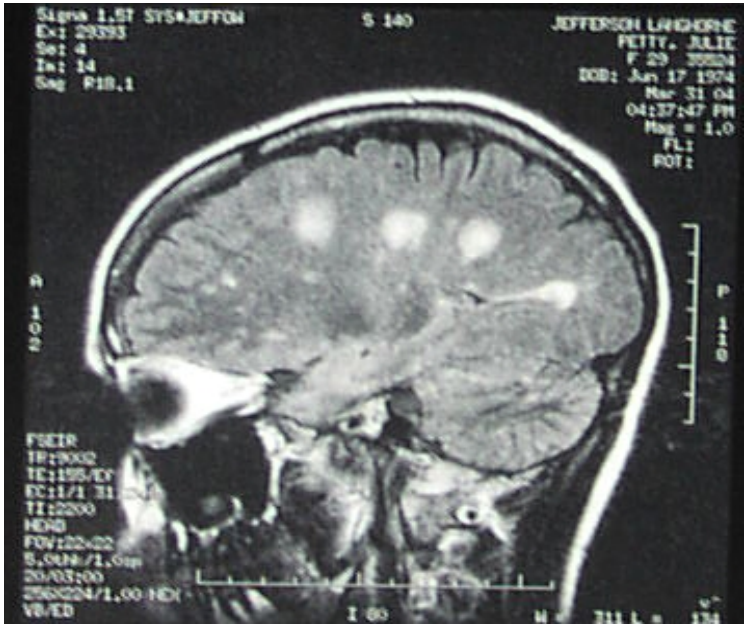
Li et al Physiol Behav 2009


Strongest gene associations in schizophrenia are immune
Depression typified by biomarkers moderated by microbiome (stress, limbic system)
Schizophrenia characterised by neuroinflammatory and peripheral immune activation
Depression induces microbiome changes

Bowel Dysfunction in MS

60-70% of MS patients

25% regular incontinence



Neurological:

- Cortical involvement (frontal lobe)
- Hypothalamic autonomic dysfunction
- Spinal Cord
- Conus Medullaris

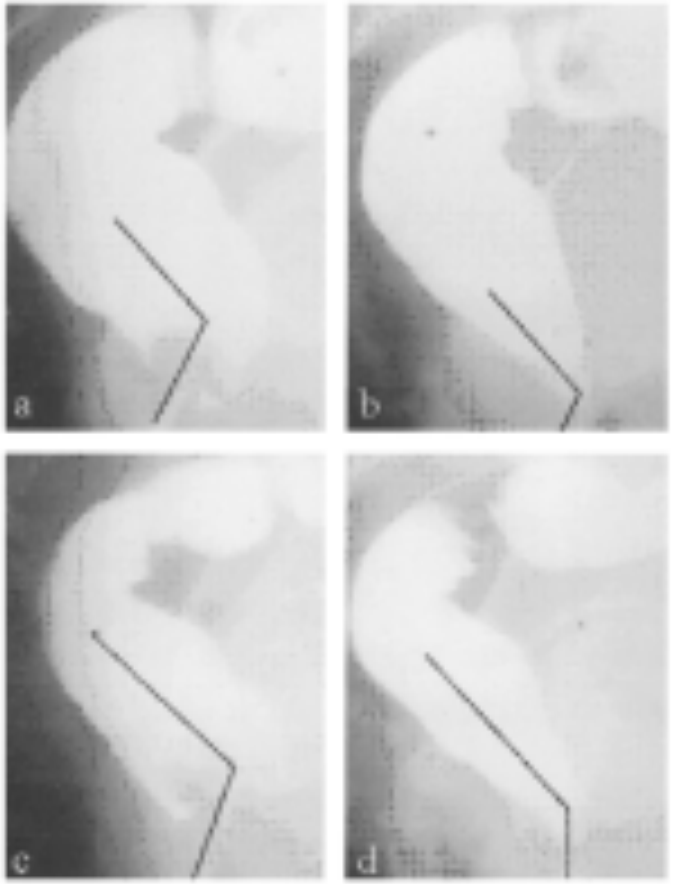
Non-Neurological:

- Polypharmacy
- Reduced mobility
- Coeliac
- Others (cancer, IBD, IBS, pre-existing condition)

Constipation in Parkinson's Disease

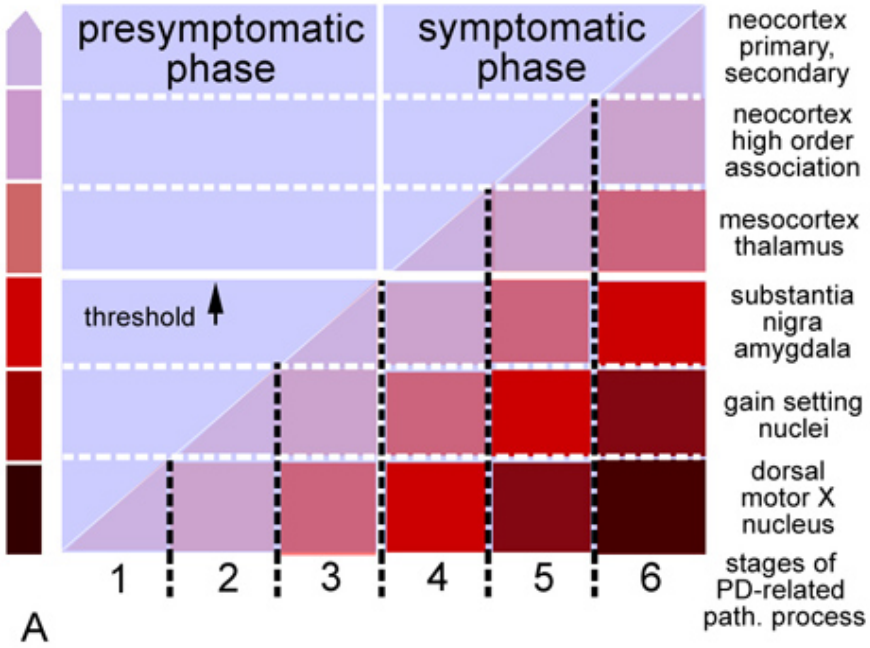
Pathophysiology

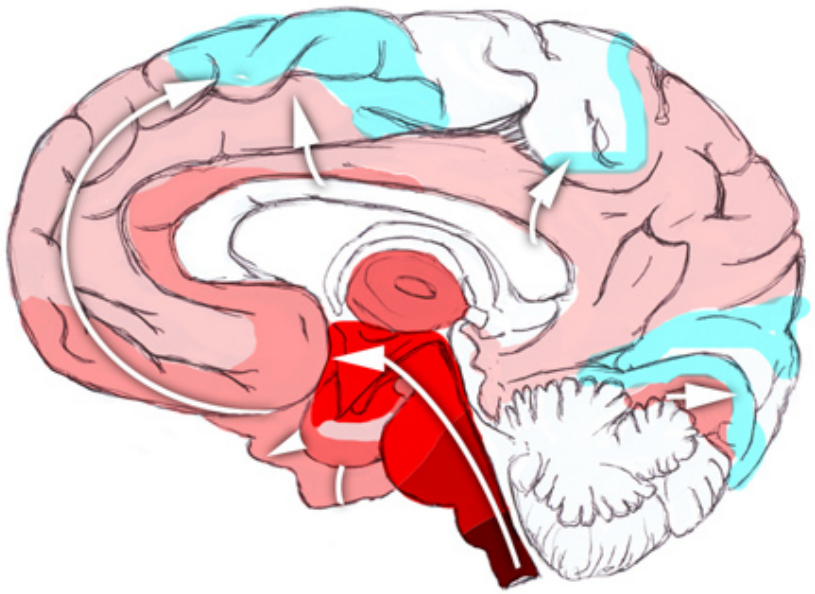
1. Slow transit due to disturbed parasympathetic tone
    - Commonest cause
    - Constipation predates treatment
2. Rectal outlet dysfunction: rare
    - Dyssynergic anal sph. contraction on attempted voiding
    - Probably related to loss of rectal sensation
3. Medication related: probably not dominant factor
    - No dose-relationship with gut transit
    - Drugs may potentiate prior constipation



Parkinson's Disease

The Braak Hypothesis and Bowel Function





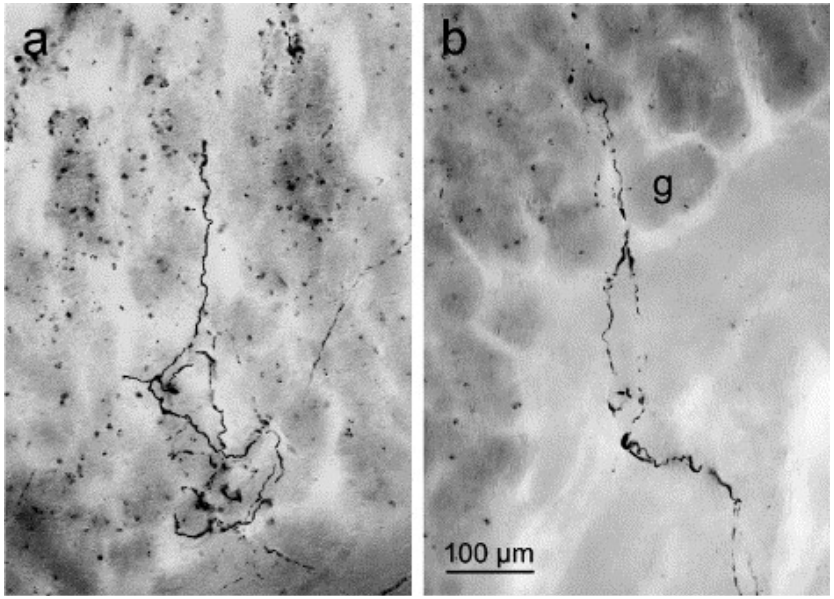
Vagal innervation of gut from oesophagus to colon

⇨ ascending path of neurodegeneration

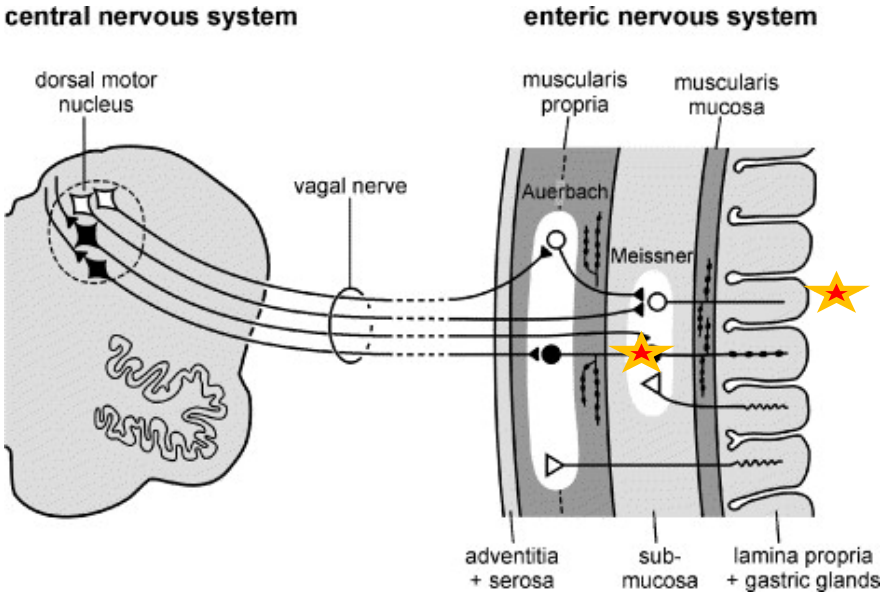
Dorsal motor nucleus of vagus as "departure point" of the disease

Parkinson's Disease

The Braak Hypothesis and Bowel Function

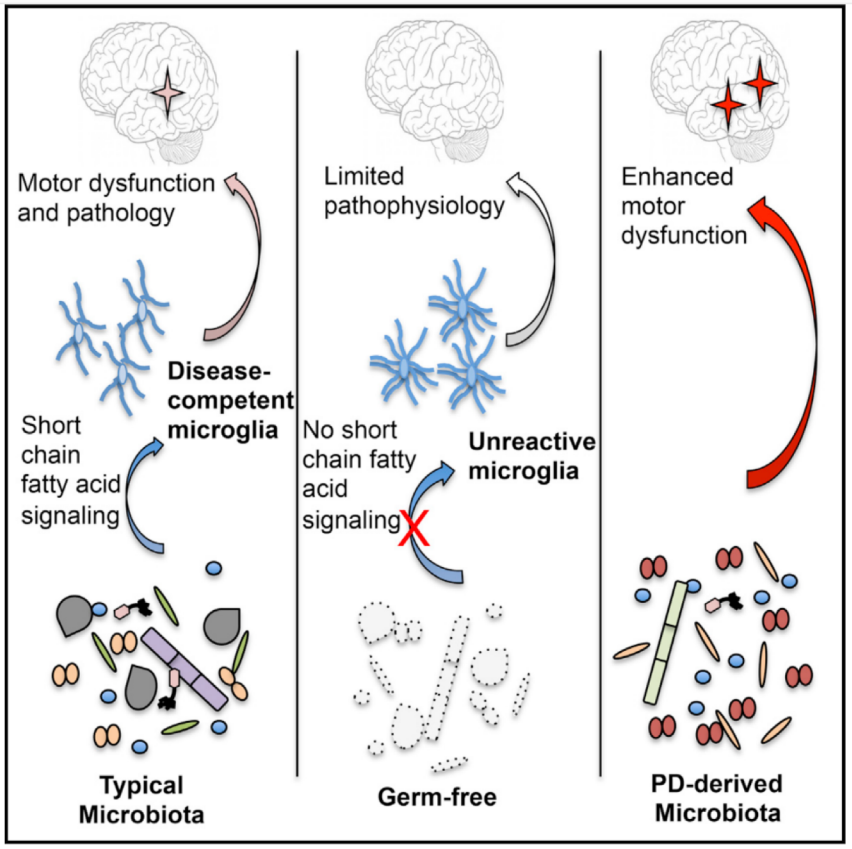


Aggregated axonal α-synuclein inclusions in the colonic Meissner plexus



Schematic diagram showing the interconnections between the enteric nervous system and brain.

Human gut microbiota from PD patients induce enhanced motor dysfunction in mice



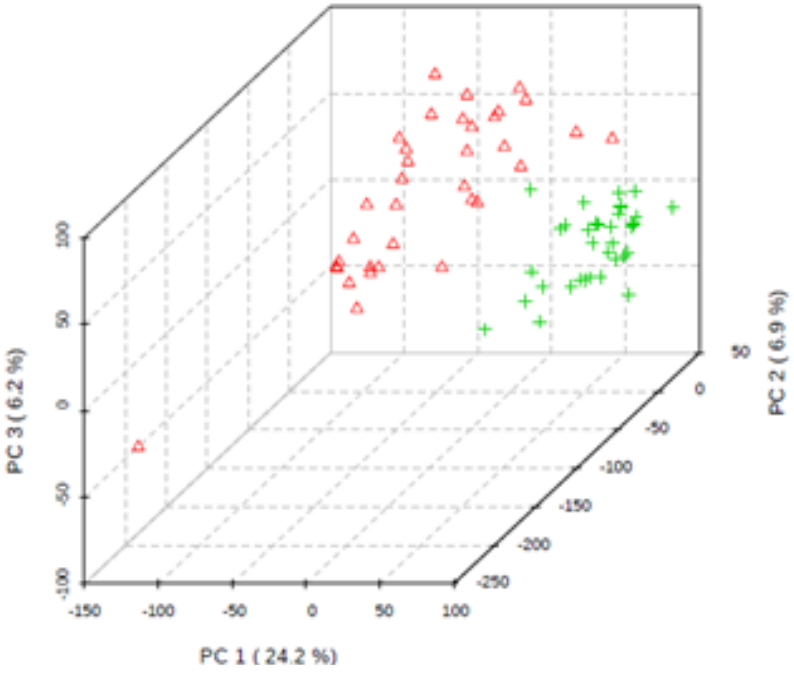
Gut microbes promote a-synuclein-mediated motor deficits and brain pathology

Depletion of gut bacteria reduces microglia activation

SCFAs modulate microglia and enhance PD pathophysiology

Sampson et al Cell 2017

Volatile organic compounds in healthy controls (red) and Parkinson's Disease (green)



De Pablo Fernandez, current data

Gastroparesis

Definition: impaired gastric emptying 2^0 autonomic failure, occurs >70% people living with PD (Tanaka et, al, 2011; Marrinan et al, 2014; Heetun et al, 2012)

Symptoms: abdominal distention; bloating; N&V; early satiety

Consequences:

Delays L-dopa in transit to the ileum for absorption (Müller et al, 2006)

Reduced oral intake and lead to unintentional weight loss

Dehydration

Electrolyte imbalance

Gastroparesis is associated with impaired quality of life

Nutritional management (Gastroparesis)

Outcome is to focus on maintaining or improving nutritional status

Aims:

Reduce symptoms, such as nausea, vomiting, diarrhoea, early satiety, bloating and pain

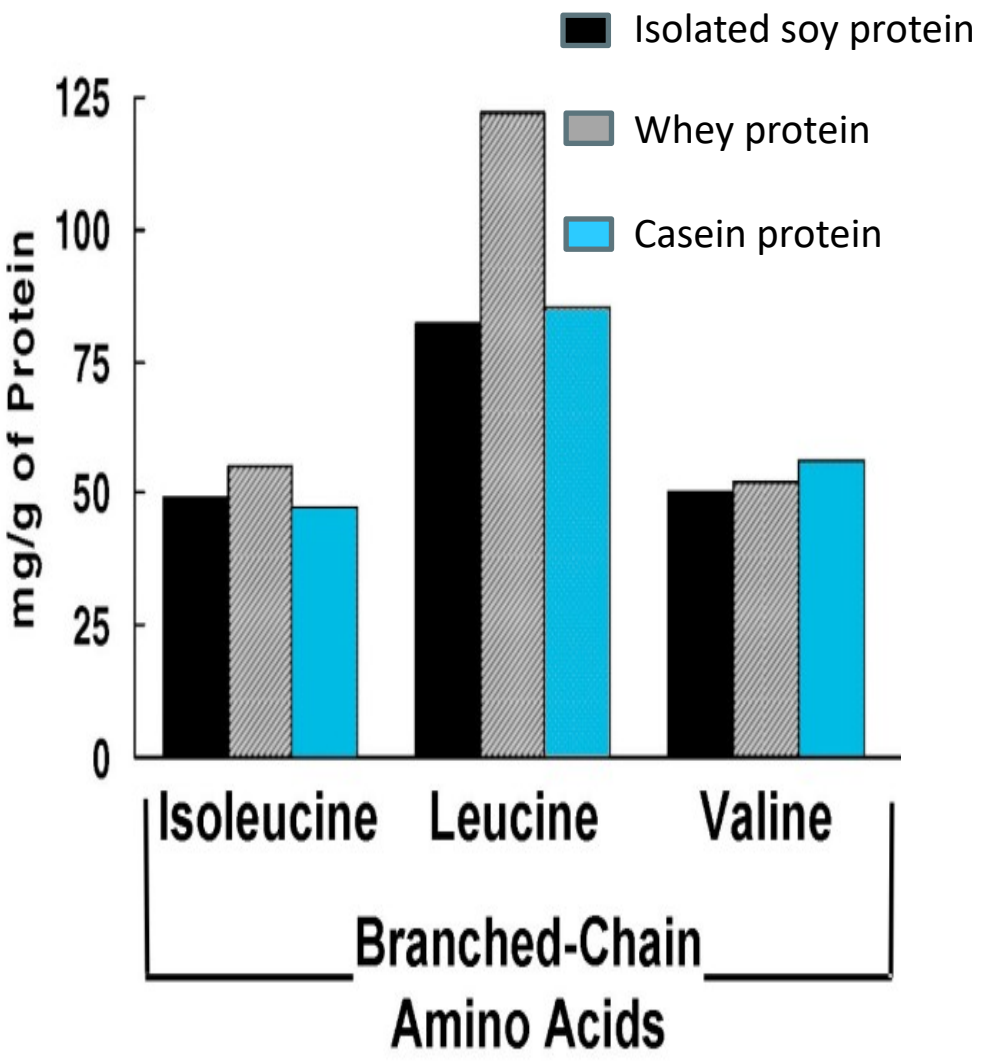
Correct fluid, electrolyte and nutrition deficiencies

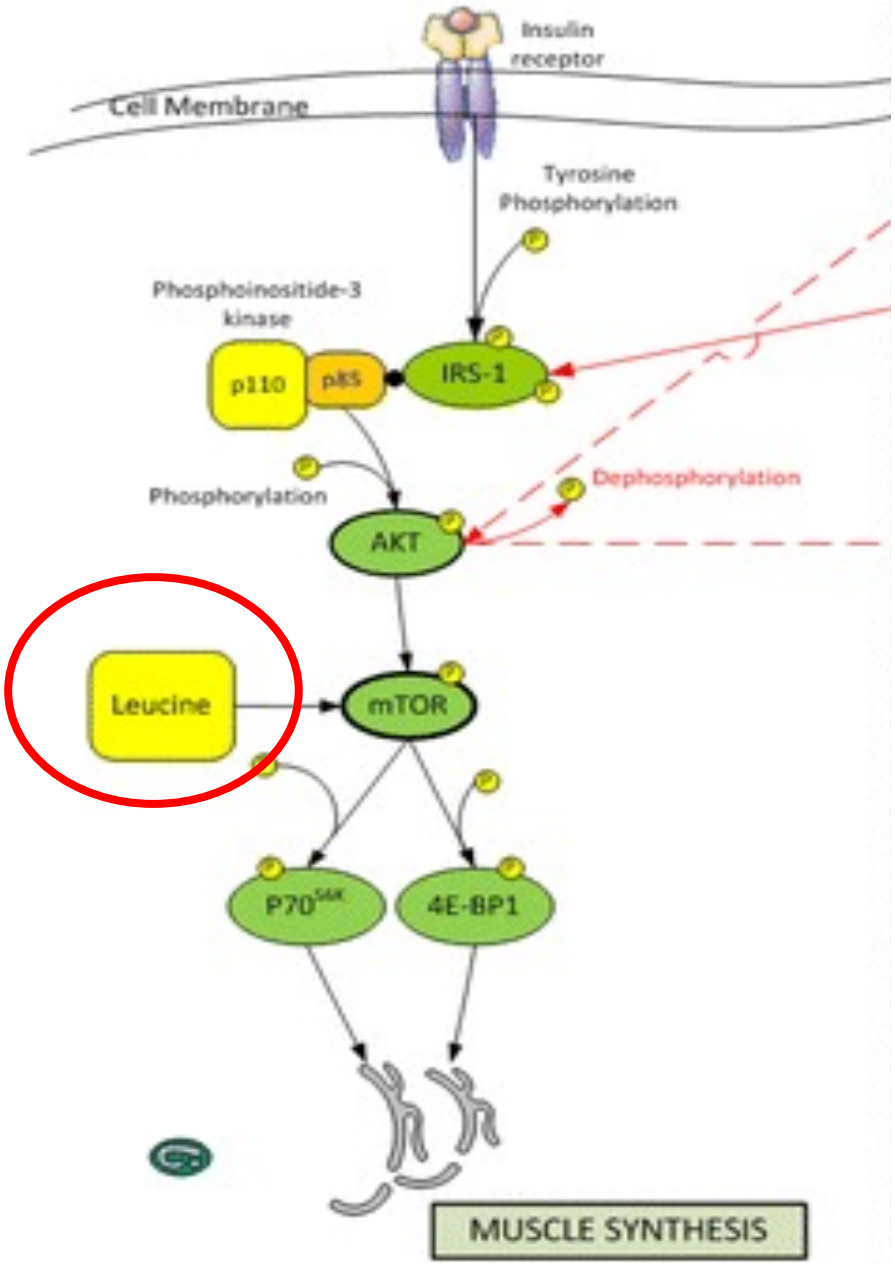
Improve glycaemic control if diabetic

Optimimise protein absorption

Protein absorption

Role of leucine





Paul, J Am Coll Nutr 2009

Dietary strategies

Gastroparesis

4-6 meals per day (PPH)

Low in fat and fibre (PPH)

Modify the texture of foods. Chew very well or pureé.

Offer meal replacement liquids e.g. ready-to-drink or powdered ONS

Varying the form of foods throughout the day (PPH)

Limit ETOH (PPH)

Enteral feeding – polymeric;2kcal/ml

Post-prandial hypotension

500mls H20 on waking (Grobety et al, 2015)

Low CHO meals

Increase salt/salty foods

Reduce caffeine

Usually only shot-style ONS tolerated

Overnight gastrostomy feeding (Young & Mathias, 2006)

Criteria for initiation of enteral supplementation

Severe weight loss, e.g. unintentional weight loss >5–10% of usual BWT over 3–6 months

Repeated hospitalisations for refractory gastroparesis requiring i.v. hydration and/or i.v. medication

Inability to meet weight goals set by dietician and patient

Patient would benefit from gastric venting

Route to absorb medication

Patient has maintained usual BWT, but experiences significant clinical manifestations

Cyclic nausea and vomiting

Overall poor QOL due to gastroparesis symptoms

Multi-strain probiotics in Parkinson's Disease

Randomised double-blind, n=120, 4 weeks

Fermented milk with prebiotic fibre and probiotic

Endpoint	Experimental Group (n = 80)	Placebo Group (n = 40)	*P* Value
Three or more CBMs in week 3 - 4 (%)	58.8	37.5	.03
Mean increase in stool consistency*	0.7	0.1	.018
Mean decrease in use of laxatives, week 3 - 4	0.8	0.1	.018
Satisfied/very satisfied (%)	55.0	17.5	<.001
Likely to continue treatment (%)	56.3	30.0	.008

*Stool consistency, Bristol Stool Form Scale score.

Cereda et al Int Congress PD & Motility 2016

Multi-strain probiotics in Multiple Sclerosis

Randomised double-blind, n=60, 12 weeks

	Placebo group (n = 30)	Probiotic group (n = 30)	P[b]
EDSS	0.05 ± 0.1	−0.4 ± 0.1	0.003
BDI total scores	−1.3 ± 0.8	−5.5 ± 0.8	<0.001
GHQ scores	−3.2 ± 1.1	−8.5 ± 1.1	0.002
DASS scores	−7.6 ± 2.2	−15.0 ± 2.2	0.02
hs-CRP (μg/mL)	0.2 ± 0.4	−1.1 ± 0.4	0.02
NO (μmol/L)	−7.2 ± 0.8	2.1 ± 0.8	<0.001
TAC (mmol/L)	23.7 ± 21.9	21.2 ± 21.9	0.93
GSH (μmol/L)	45.3 ± 14.2	−9.0 ± 14.2	0.01
MDA (μmol/L)	0.3 ± 0.1	−0.006 ± 0.1	0.003
FPG (mg/dL)	2.5 ± 0.9	2.0 ± 0.9	0.70
Insulin (μIU/mL)	1.4 ± 0.7	−2.9 ± 0.7	<0.001
HOMA-IR	0.2 ± 0.2	−0.6 ± 0.2	<0.001
HOMA-B	3.9 ± 2.7	−11.6 ± 2.7	<0.001
QUICKI	−0.005 ± 0.003	0.01 ± 0.003	<0.001
Triglycerides (mg/dL)	3.0 ± 4.8	−5.5 ± 4.8	0.21
VLDL-cholesterol (mg/dL)	0.6 ± 1.0	−1.1 ± 1.0	0.21
Total cholesterol (mg/dL)	7.9 ± 3.3	6.2 ± 3.3	0.71
LDL-cholesterol (mg/dL)	6.4 ± 3.0	4.6 ± 3.0	0.66
HDL-cholesterol (mg/dL)	1.1 ± 0.5	2.6 ± 0.5	0.06
Total-/HDL-cholesterol	0.08 ± 0.05	−0.09 ± 0.05	0.03

Improved neurological symptoms

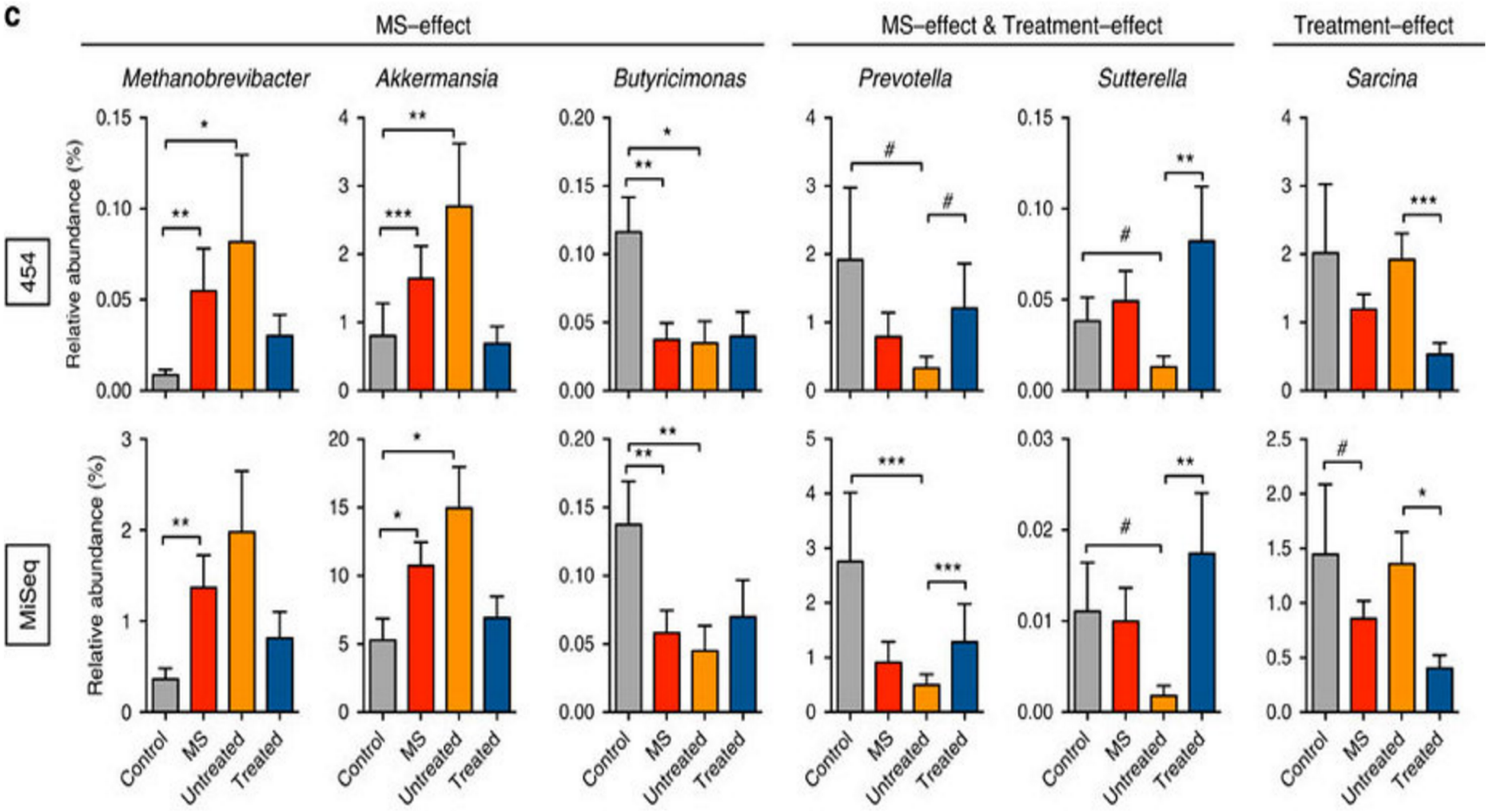
Improved mood

Changes in inflammatory markers

Changes in insulin resistance

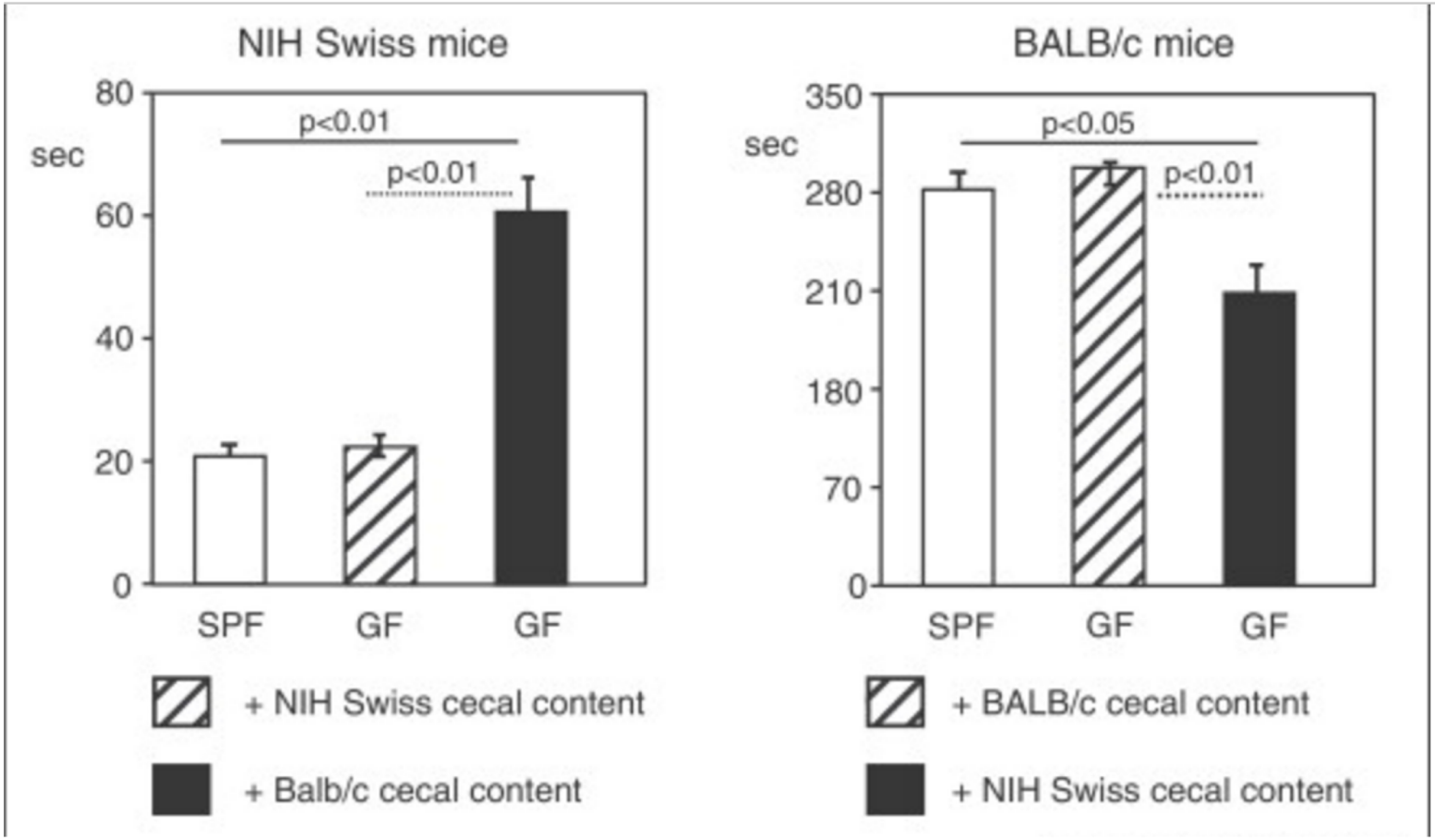
Kouchaki et al J Clin Nutr 2016

Microbiome and multiple sclerosis



Jangi et al Nature 2016

Faecal microbial transplant transfers behavioural traits



Bercik et al Gastroenterol 2011

Neuro-gastroenterology and diet: summary

There is two-way communication between brain and gut

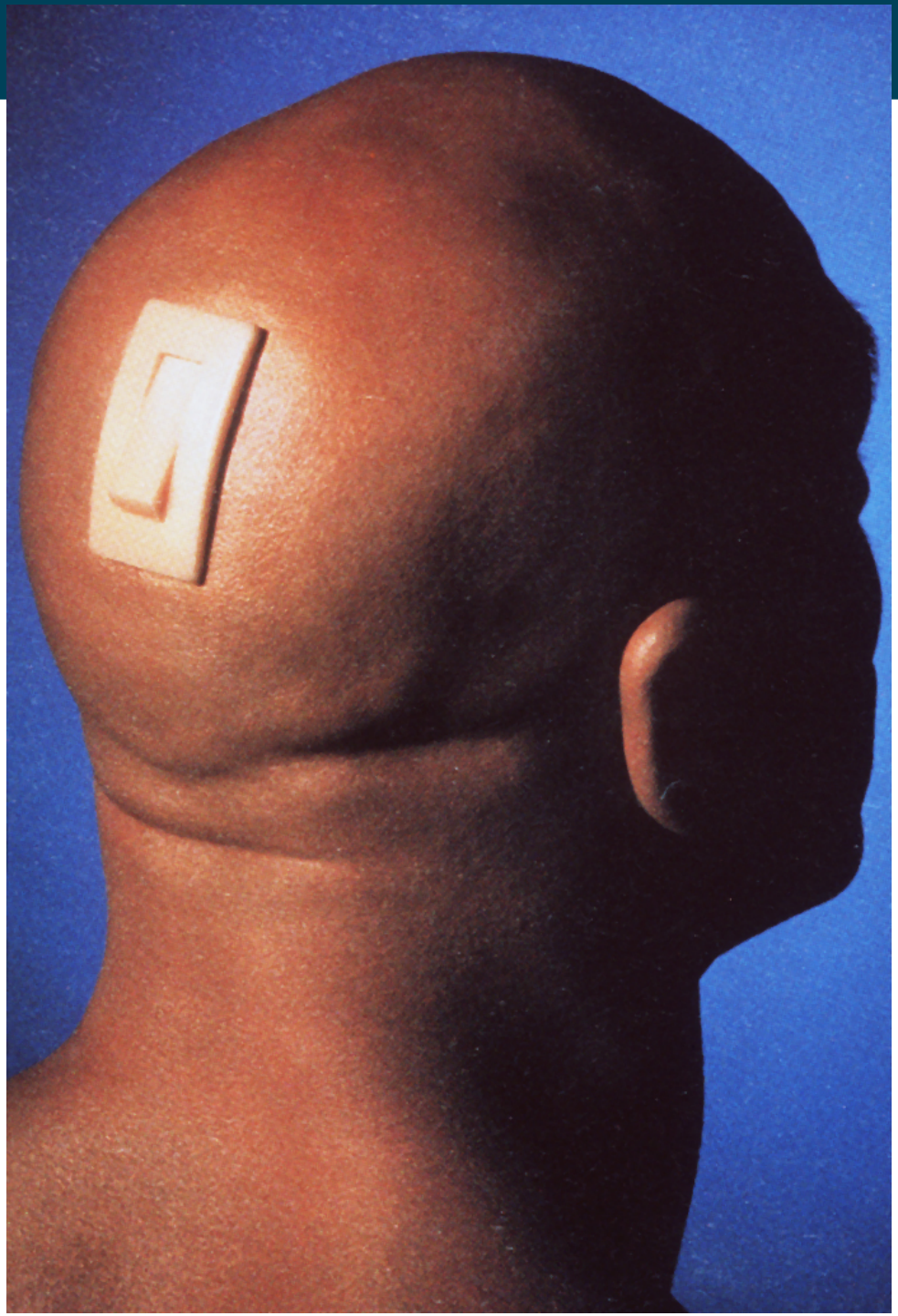
Control is exerted at all levels of gut function

- voluntary and involuntary (stress)

Understanding pathophysiology of GI presentations opens therapeutic options

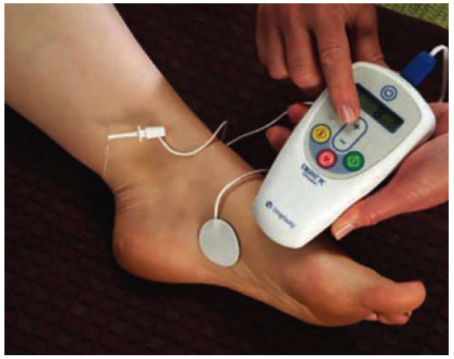
Gut microbes explain some presentations – harder to treat

The future



Posterior tibial nerve stimulation

Improves urgency, consistency…mood



Obstetric anal sphincter injury

Table 3. Measures of Symptom Severity Before and After Treatment in Responders and Nonresponders.

	Responders			Nonresponders			Change in values		
	Baseline	After treatment	*p*	Baseline	After treatment	*p*	Responders	Nonresponders	*p*
Wexner score	13 ± 3	4 ± 2	<0.01	13 ± 5	12 ± 5	0.13	−9	−1	<0.01
Visual analogue scores									
Bowel	63 ± 19*	36 ± 24	<0.01	48 ± 20*	39 ± 23	0.10	−26.8	−20.0	0.05
Bladder	49 ± 30	45 ± 30	0.61	62 ± 30	56 ± 30	0.10	−3.6	−11.1	0.71
Rockwood quality of life scores									
Life	3.2 ± 0.6	3.2 ± 0.6	0.70	2.8 ± 0.8	2.8 ± 0.8	0.61	0	0	0.50
Coping and behavior	2.5 ± 0.8	2.5 ± 0.5	1	2.1 ± 0.7	2.1 ± 0.8	0.80	0	0	0.86
Depression and self perception	1.9 ± 1.0	2.9 ± 0.9	<0.01	2.4 ± 0.9	2.6 ± 0.8	0.10	+1.0	+0.2	0.03
Embarrassment	2.2 ± 1.1	3.0 ± 0.9	0.04	2.4 ± 1.0	2.5 ± 0.9	0.54	+0.8	+0.1	0.09
Bristol stool form score	5 (1)	3 (2)	<0.01	5 (2)	4 (1.5)	0.08	−2	−1	0.06

Underlined values are statistically significant (P ≤ 0.05).
*$p < 0.01$ for responders vs. nonresponders baseline values; higher visual analogue scores correspond to greater severity of symptoms; lower Rockwood scores correspond to greater disability; lower Bristol Stool Form scores correspond to firmer stool consistency; values are means ± SD, medians (IQR).

Sanagapillai et al Neuromod 2018a

Multiple Sclerosis

Table 1. Wexner Score Changes in Responders and Nonresponders to PTNS.

	Responders	Nonresponders
N (%)	26 (79%)	7 (21%)
Baseline Wexner score, mean ± SD	13.5 ± 3.8	13.4 ± 3.9
Post-therapy Wexner score, mean ± SD	7.0 ± 2.8	13.9 ± 3.1

Table 2. Measures of Symptom Severity Before and After Treatment in Responders and Nonresponders.

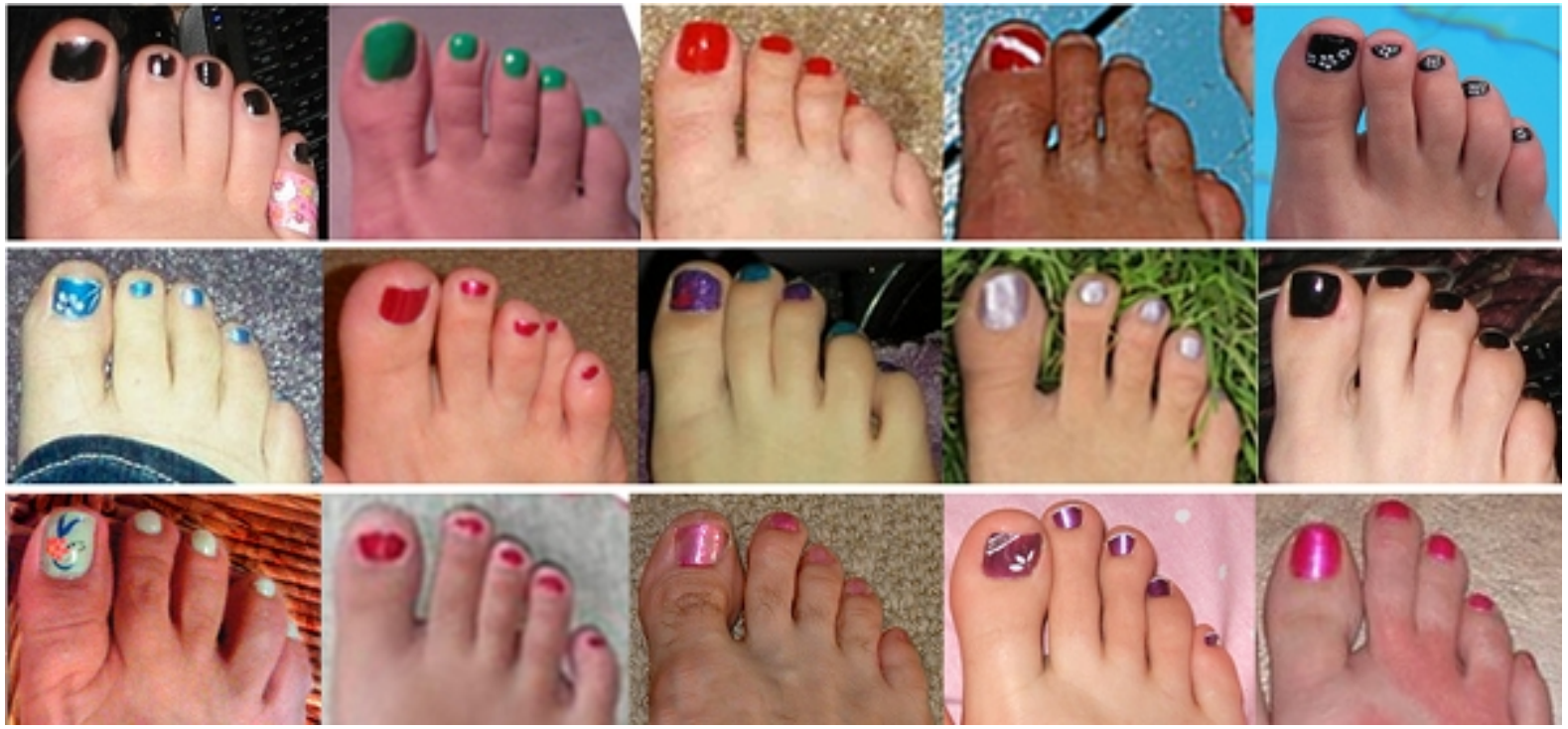
	Responders			Nonresponders			Change in values		
	Baseline	After treatment	*P*	Baseline	After treatment	*P*	Responders	Nonresponders	*P*
Visual analogue scores									
Bowel	58.5 ± 25.4	52.3 ± 24.8	0.28	45.7 ± 22.8	46.4 ± 14.1	0.67	−6.2	+0.9	0.47
Bladder	51.0 ± 26.0	53.1 ± 23.2	0.69	52.9 ± 25.1	50.7 ± 20.1	0.74	+2.1	−2.2	0.91
Rockwood quality of life scores									
Life	2.5 ± 0.9	2.9 ± 0.8	0.11	3.2 ± 0.7	3.1 ± 0.9	0.01	+0.4	−0.1	0.25
Coping and behavior	2.0 ± 0.7	2.4 ± 0.9	0.15	2.6 ± 0.4	2.4 ± 0.8	0.15	+0.4	−0.2	0.20
Depression and self-perception	2.7 ± 0.8*	3.1 ± 0.9	0.01	3.4 ± 0.4*	3.1 ± 0.8	0.18	+0.4	−0.3	0.05
Embarrassment	2.2 ± 0.8	2.6 ± 0.8	0.06	2.5 ± 1.0	2.4 ± 1.0	0.54	+0.4	−0.1	0.21
Bristol stool form score	5 (4–6)	4 (3–4)	0.02	5 (5–5.5)	5 (4.5–5.5)	0.44	−1	0	0.01

Higher visual analogue scores correspond to greater severity of symptoms.
Lower Rockwood scores correspond to greater disability.
Lower Bristol Stool Form scores correspond to firmer stool consistency.
Values are means ± SD, medians (IQR).
*$P < 0.05$ for responders vs. nonresponders baseline values.

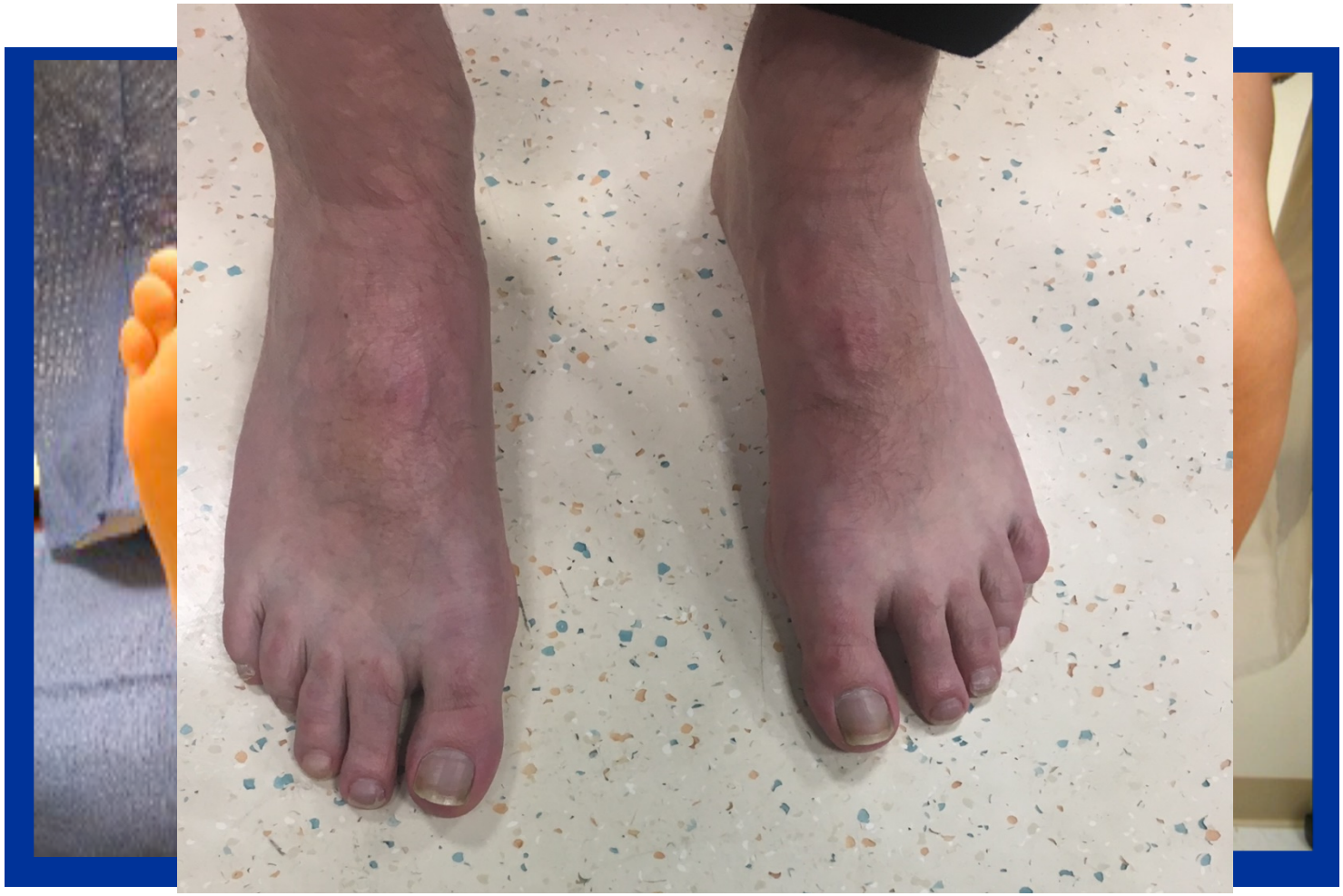
Sanagapillai et al Neuromod 2018b

Patterns of foot variation

It’s easier to fit gloves than shoes

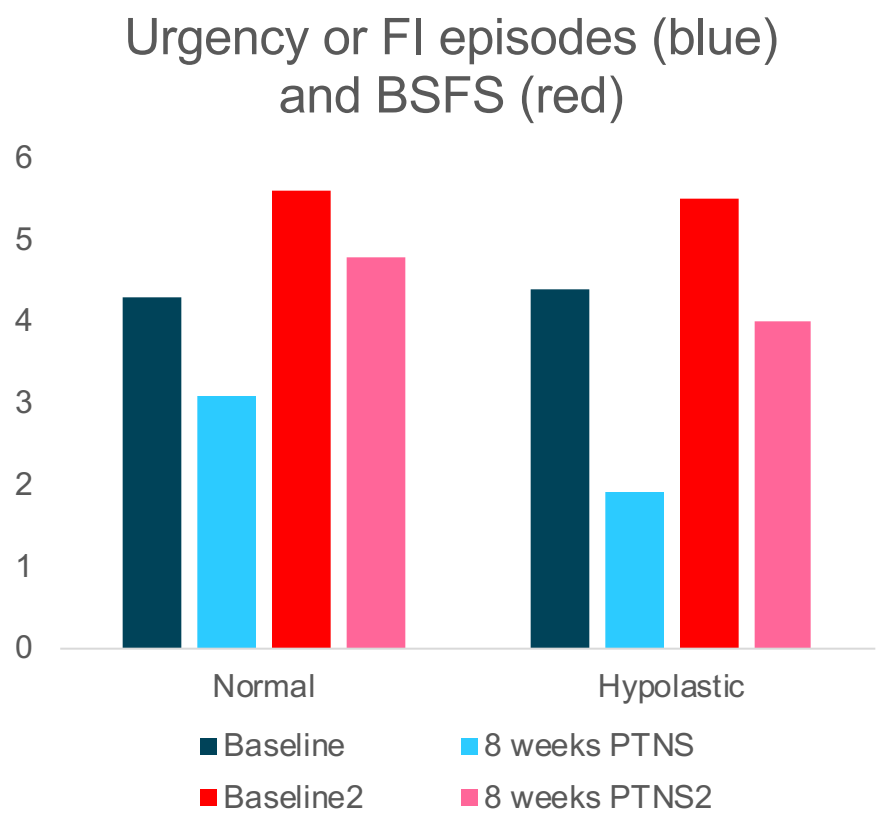


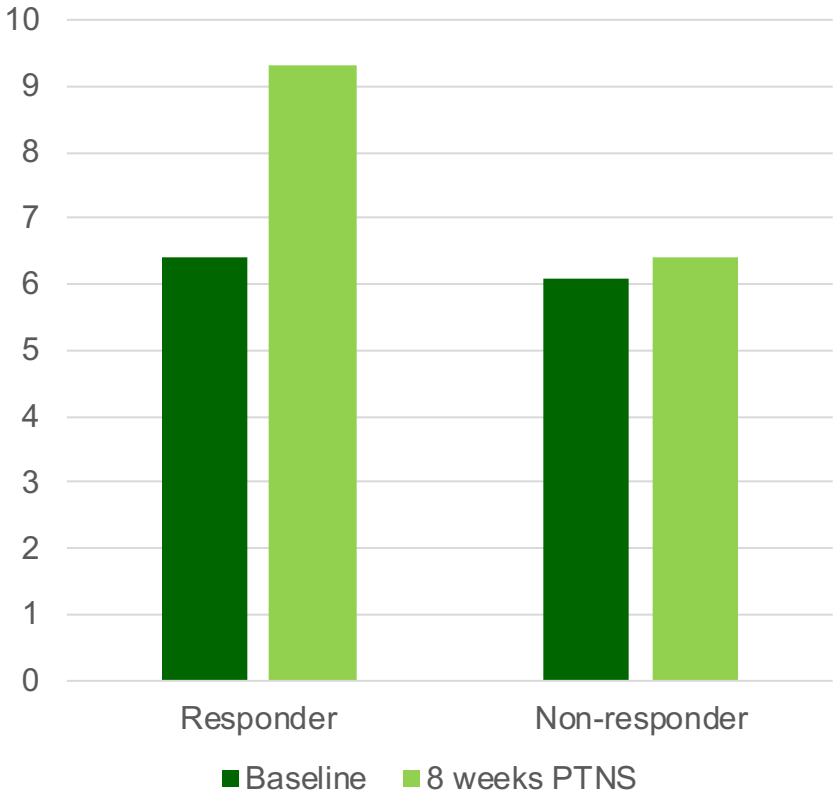
1 in 3 have foot asymmetry
Feet mirror gluteals



PTNS, symmetry and afferent neuromodulation

n=32 idiopathic faecal incontinence (26 female, mean age 46)
All had foot asymmetry
Randomly stimulated in hypoplastic or normal side





Work done by Physiology Unit team

Multiple Sclerosis Society

PARKINSON'S UK
CHANGE ATTITUDES.
FIND A CURE.
JOIN US.

RSA Raynaud's & Scleroderma Association

Aspire
SUPPORTING Spinal Injured PEOPLE

Work done by Physiology Unit team