



Salute mentale e benessere dell'intestino: ruolo del Microbiota

Fabio Pace

Gastroenterologia ed Endoscopia Digestiva,
Ospedale Bolognini, Seriate (Bg)
fabio.pace@unimi.it

Outline della lettura

- Cenni introduttivi sul Microbiota Umano
- Il Microbiota-brain-gut axis
- Studi preclinici
- Dati sull'uomo
- Il ruolo dello stress

REVIEW ARTICLE

Elizabeth G. Phimister, Ph.D., *Editor*

The Human Intestinal Microbiome in Health and Disease

Susan V. Lynch, Ph.D., and Oluf Pedersen, M.D., D.M.Sc.

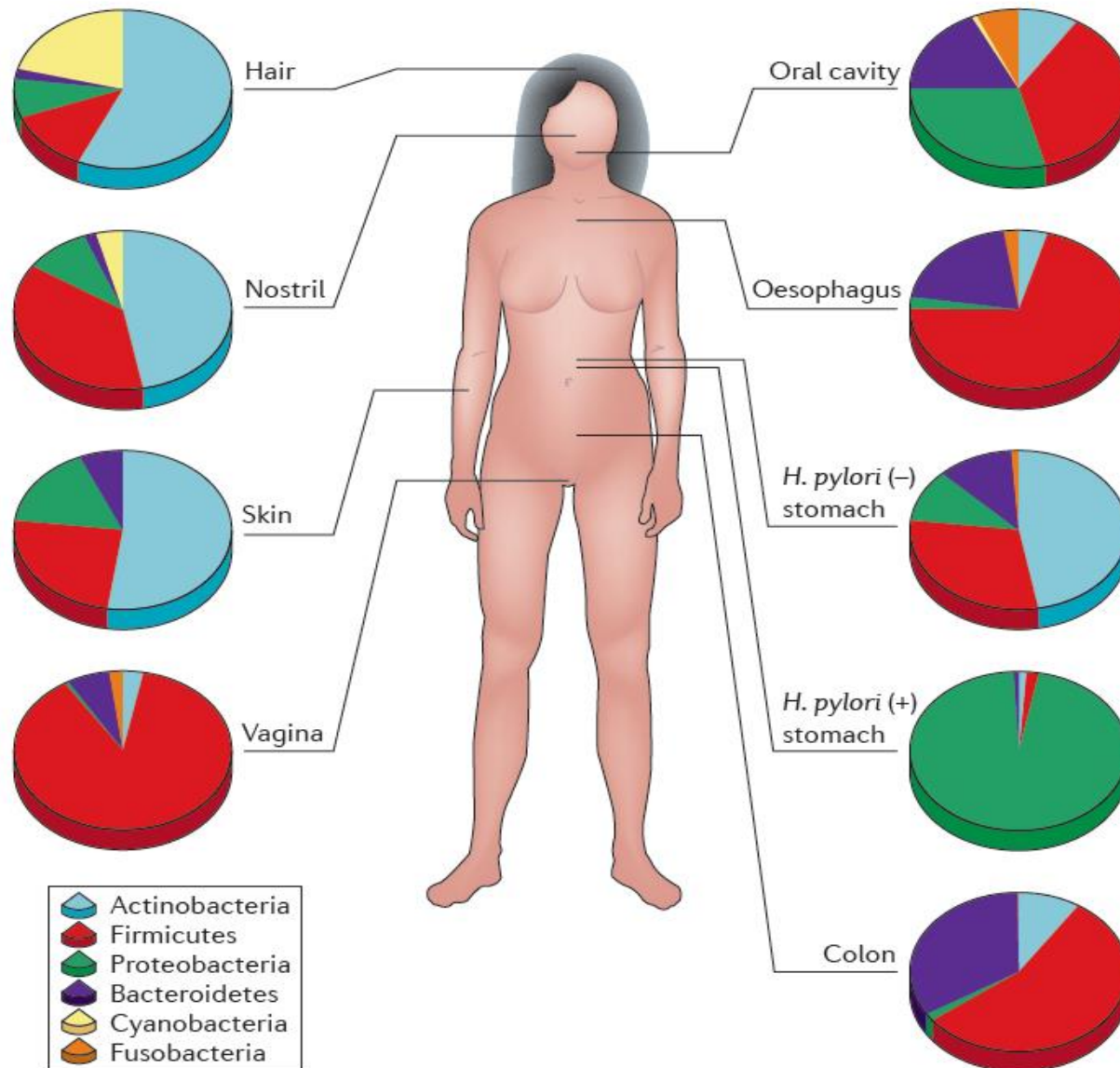
La “Rivoluzione” del Microbiota Umano

La tradizionale visione antropocentrica del microbiota intestinale come essenzialmente patogeno e minaccia per il sistema immune è stata sostituita dal riconoscimento che esso ha prevalentemente un effetto benefico per la salute umana.

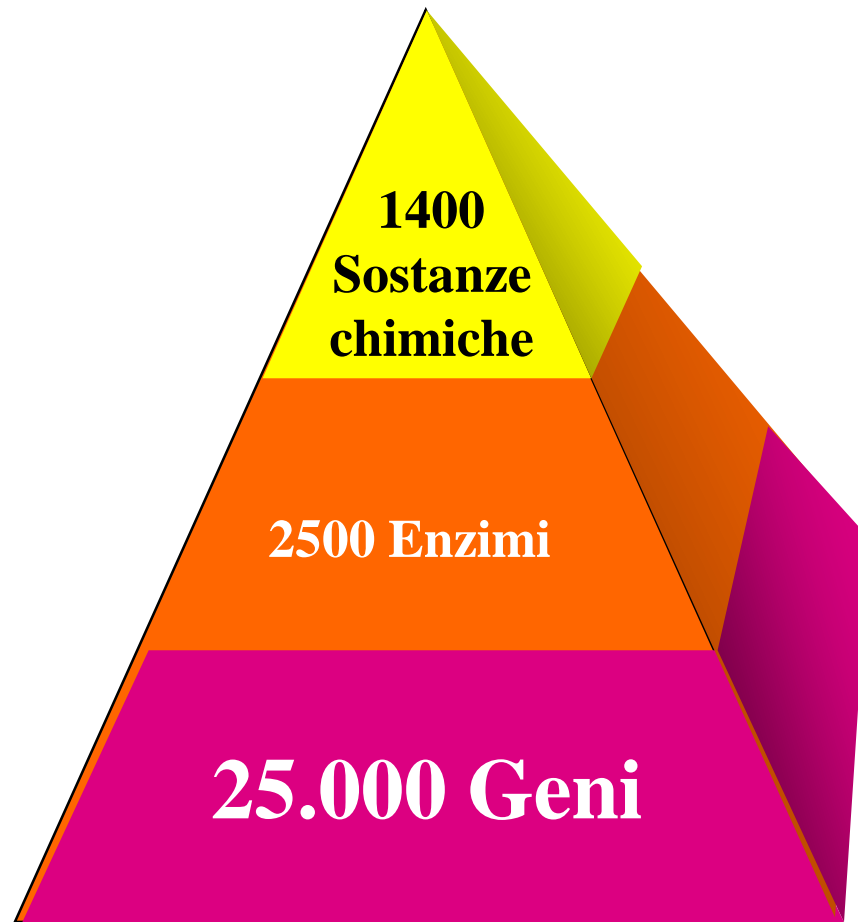
Definizione di microbiota umano

- Il microbiota umano è costituito dalla comunità dei microrganismi (*con i relativi genomi = microbioma*) che colonizzano varie regioni anatomiche dell'organismo, interne o superficiali.

I diversi Microbiota umani



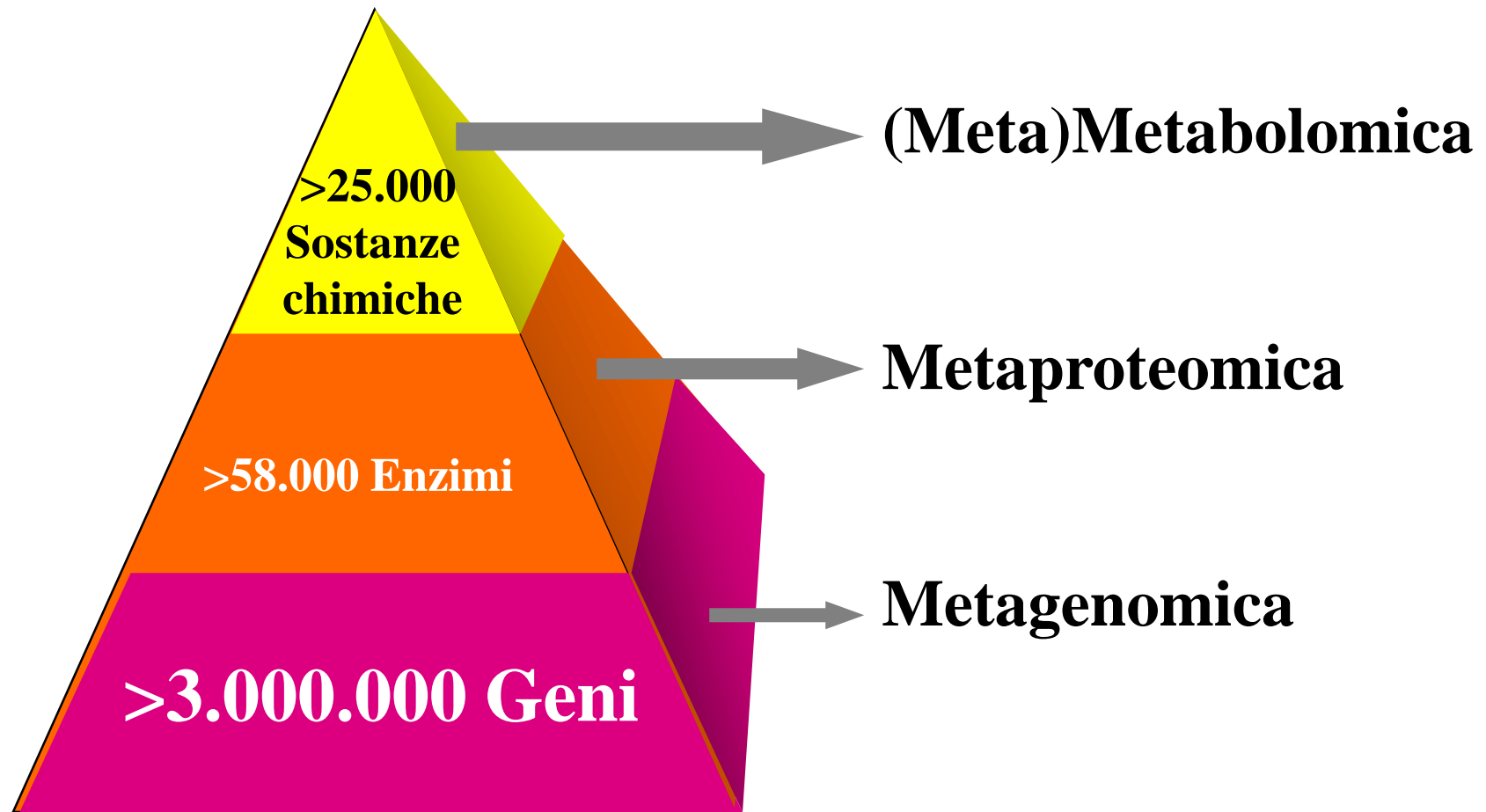
Piramide della vita: *homo sapiens*



Kau et al, Nature 2011

Qin et al, Nature 2011

Piramide della vita: il super-organismo (*homo sapiens* + microbiota)



Kau et al, Nature 2011

Qin et al, Nature 2011

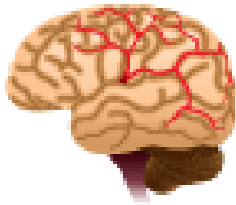
Organi del nostro corpo a confronto

Cuore



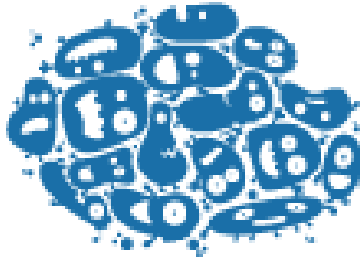
360 g

Cervello



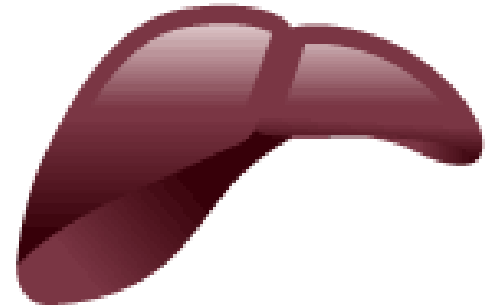
1360 g

**Microbiota
intestinale**



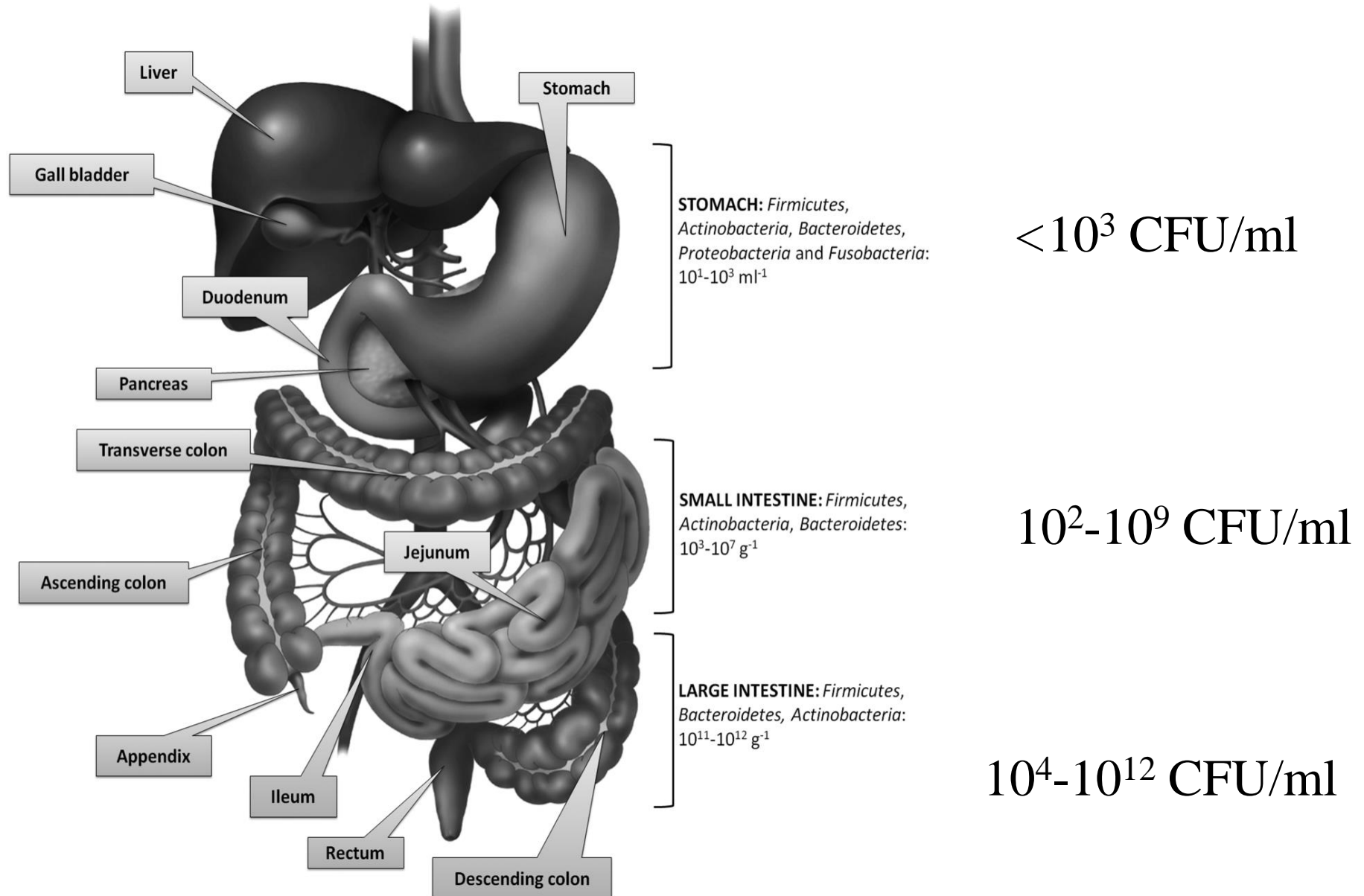
1600 g

Fegato



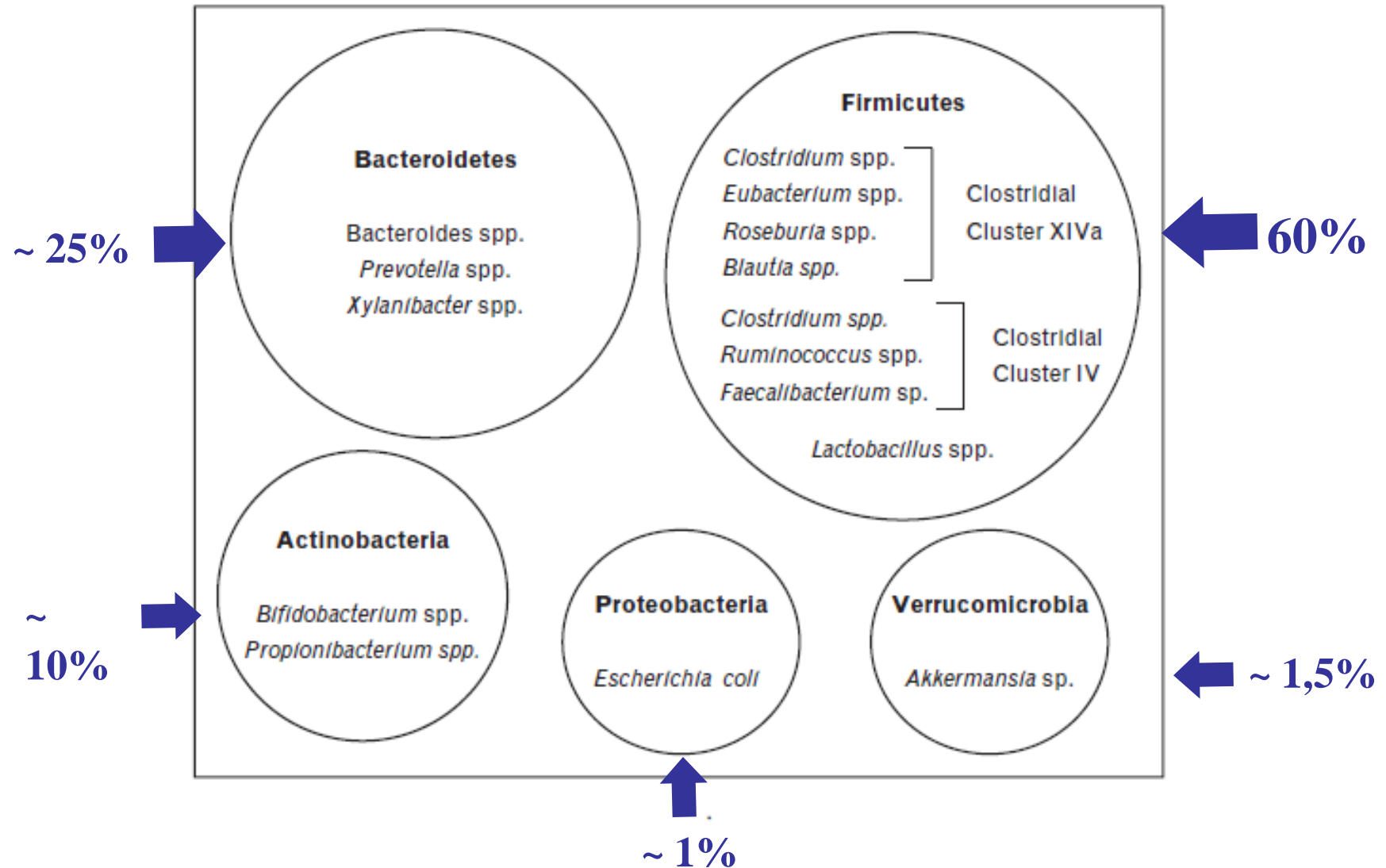
1800 g

Distribuzione qualitativa e quantitativa del microbiota intestinale umano

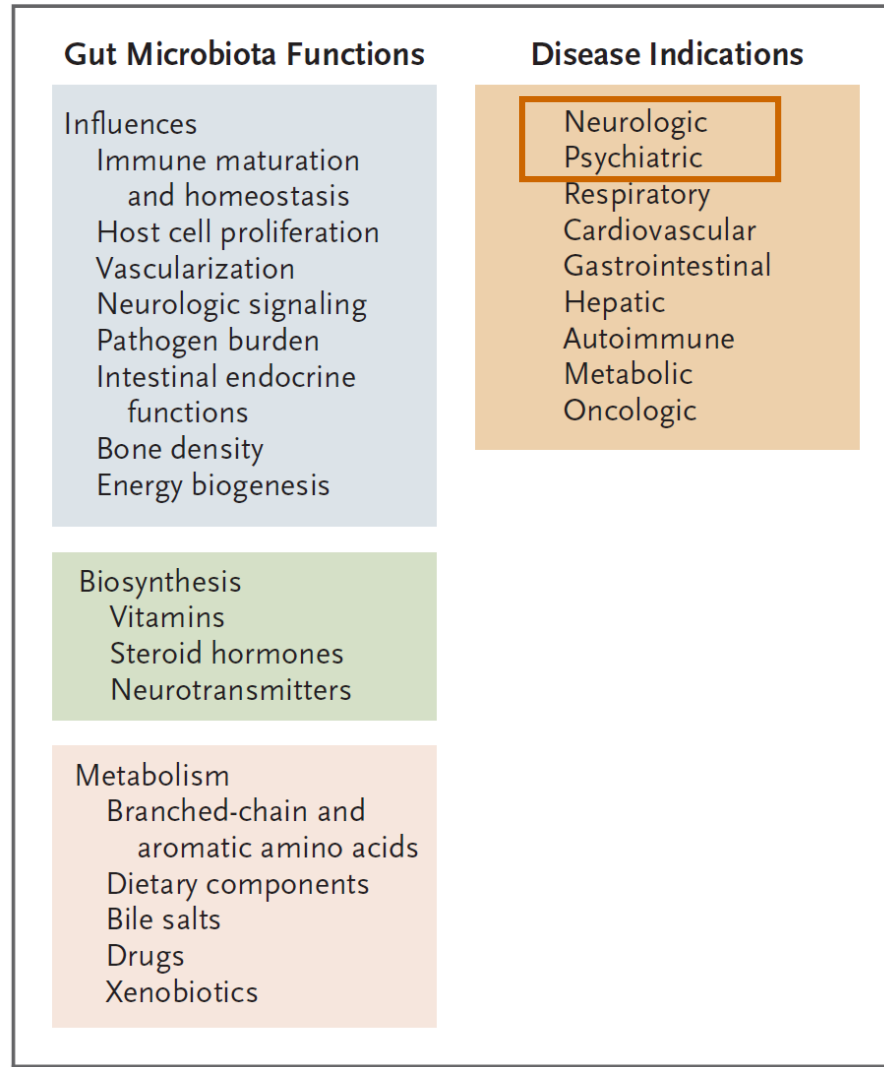


Il microbiota intestinale (MI) adulto umano

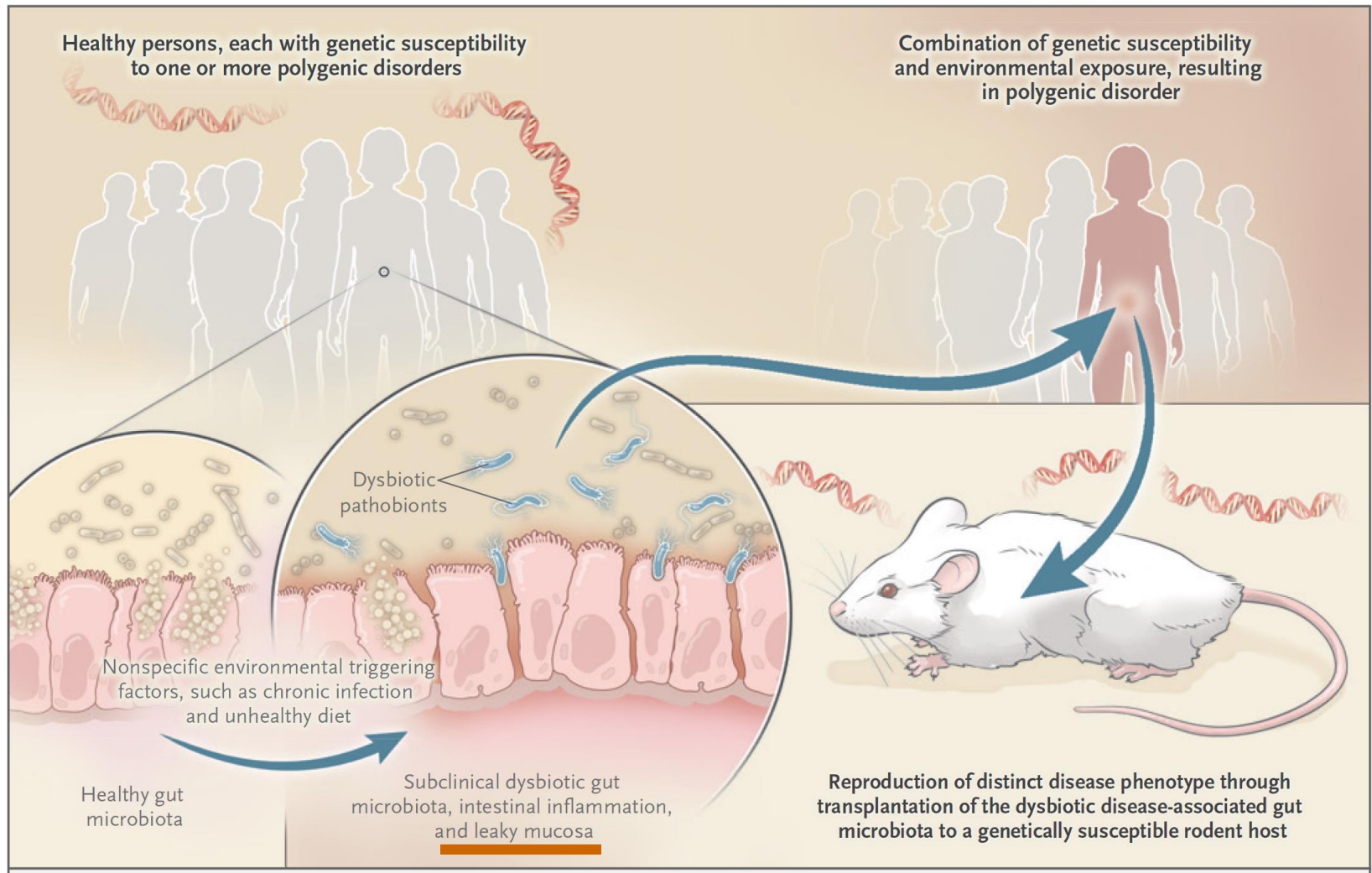
Phyla principali



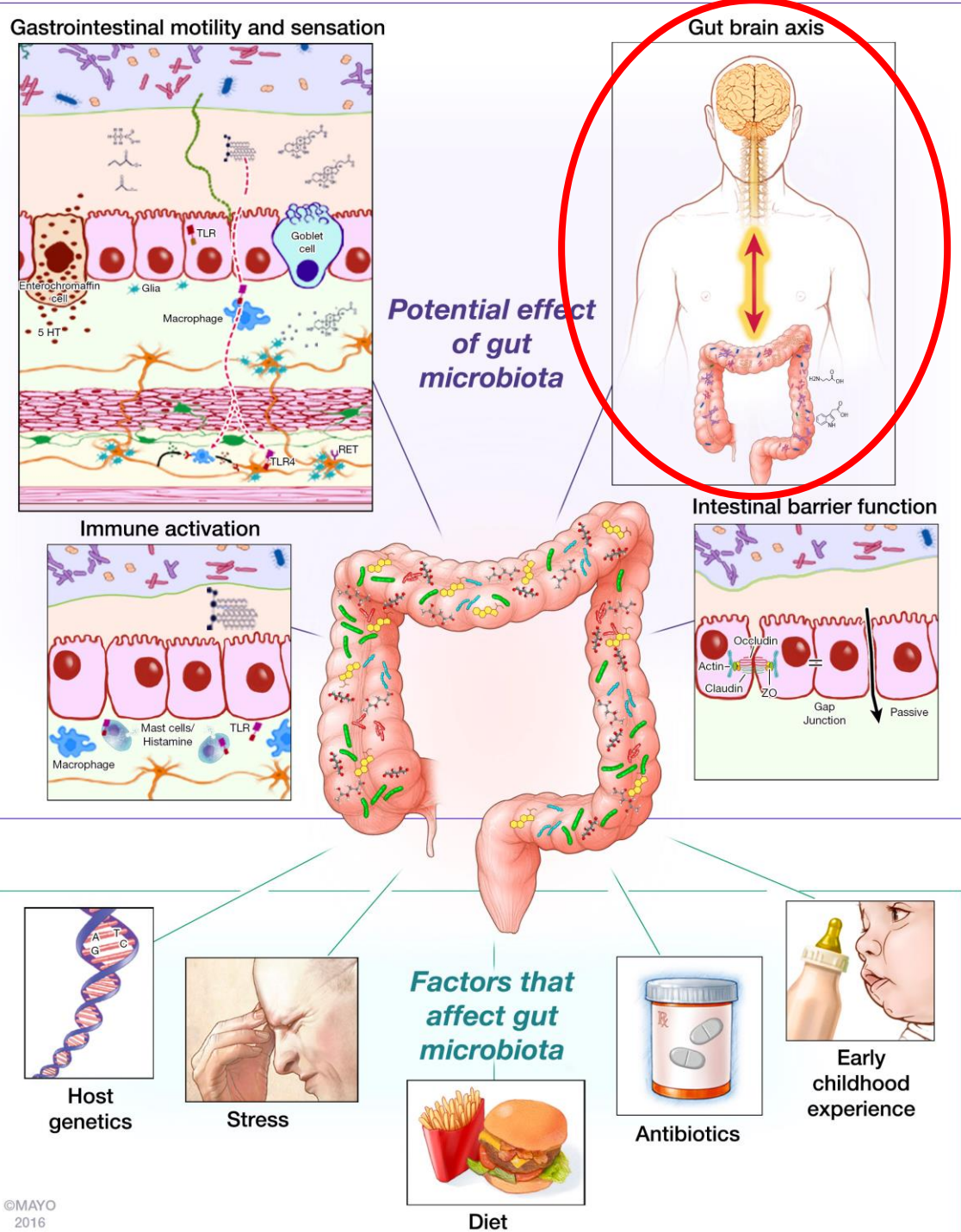
Alcune funzioni del MI e patologie associate a disbiosi



Dalla disbiosi alla patologia umana: ipotesi patogenetica unificante “Common Ground”



Il microbiota intestinale è un modulatore della fisiologia intestinale, ma influenza anche attività cognitive e l'umore



Bhattarai et al, *Am J Physiol Gastrointest Liver Physiol* 2017;312:G52–G62

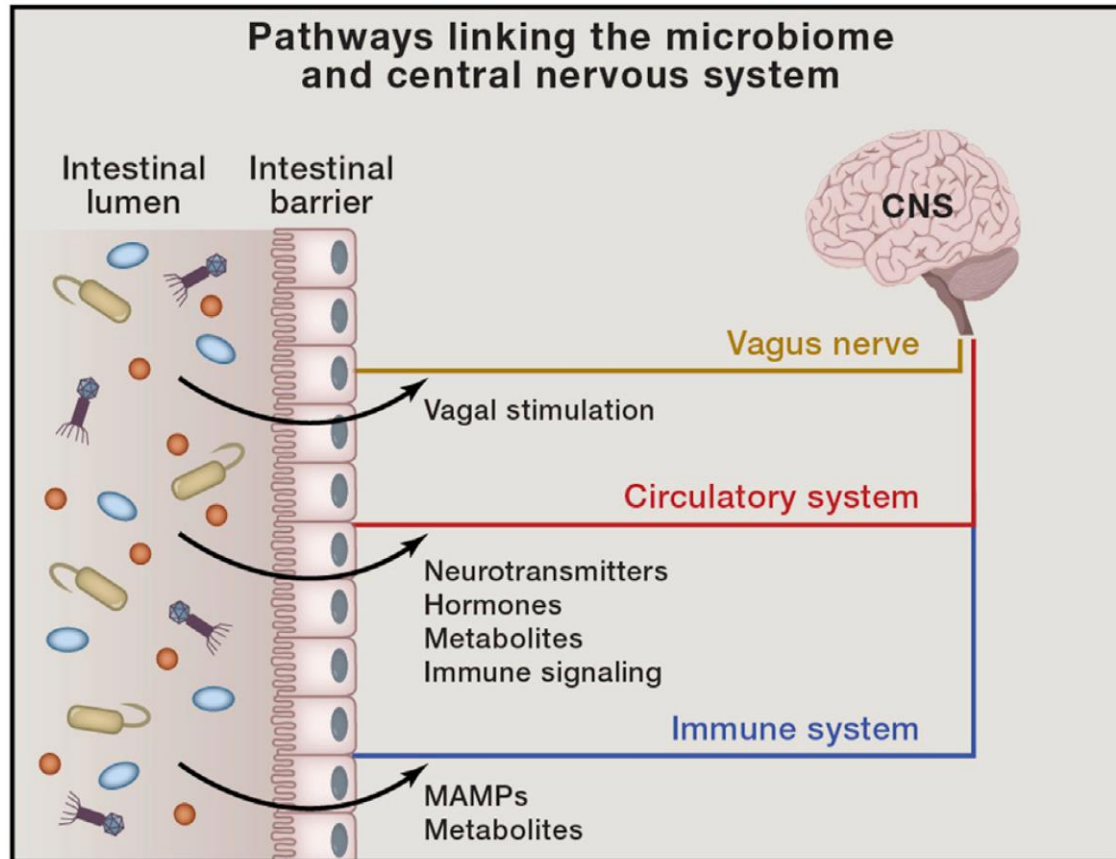
Definizione di *Microbiota-brain-gut axis*

- E' un sistema bidirezionale di comunicazione che consente ai microbi intestinali di comunicare col cervello e al cervello di comunicare con l'intestino¹
- Tale sistema, non del tutto esplorato, si basa su vie neurali, endocrine, immunologiche e metaboliche ²

¹ Rhee SH, et al. Nat Rev Gastroenterol Hepatol 2009;6:306–14

² El Aidy S, et al. Clin Ther 2015;37:954–67

Vie di comunicazione tra il microbiota intestinale e il cervello



General efferent function:

- Motor reflexes
- Neuroendocrine
- Pain patterns
- Immune system regulation

General afferent function:

- Food intake
- Visceral pain
- Gut homeostasis

MAMP: microbe associated molecular patterns (es. LPS)

Un elenco di patologie neuro-psichiche associate a disbiosi, e in cui sono presenti disturbi digestivi

Diseases	
→	Parkinson's disease
→	Autism spectrum disorder
	Amyotrophic lateral sclerosis
	Alzheimer diseases
	Prion diseases
	Creutzfeldt-Jakob disease
	Transmissible spongiform encephalopathies
→	Depression
	Anxiety
	Behavior
	Cognition
→	Mood
	Stress
	Fatigue
	Aging

Evidenze sull'uomo

Depressione

- Riduzione del numero di Bifidobatteri e Lattobacilli in soggetti depressi
- Correlazione negativa tra *Faecalibacterium* spp. e sintomi depressivi
- Alcuni probiotici (Bifidobatteri e Lattobacilli) attenuano ansia, depressione e stress → **Psicobiotici**

Psicobiotici

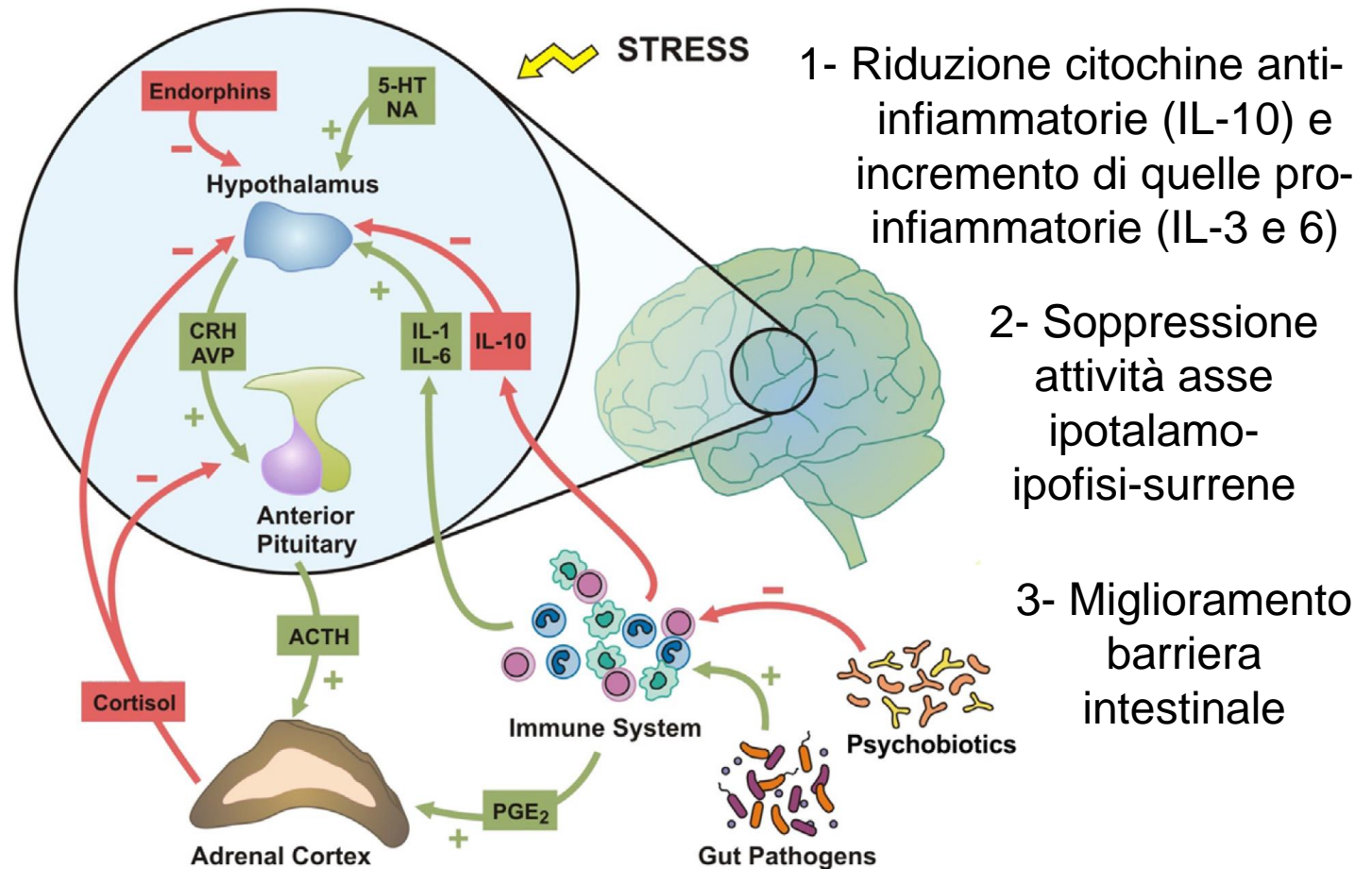
REVIEW

Psychobiotics: A Novel Class of Psychotropic

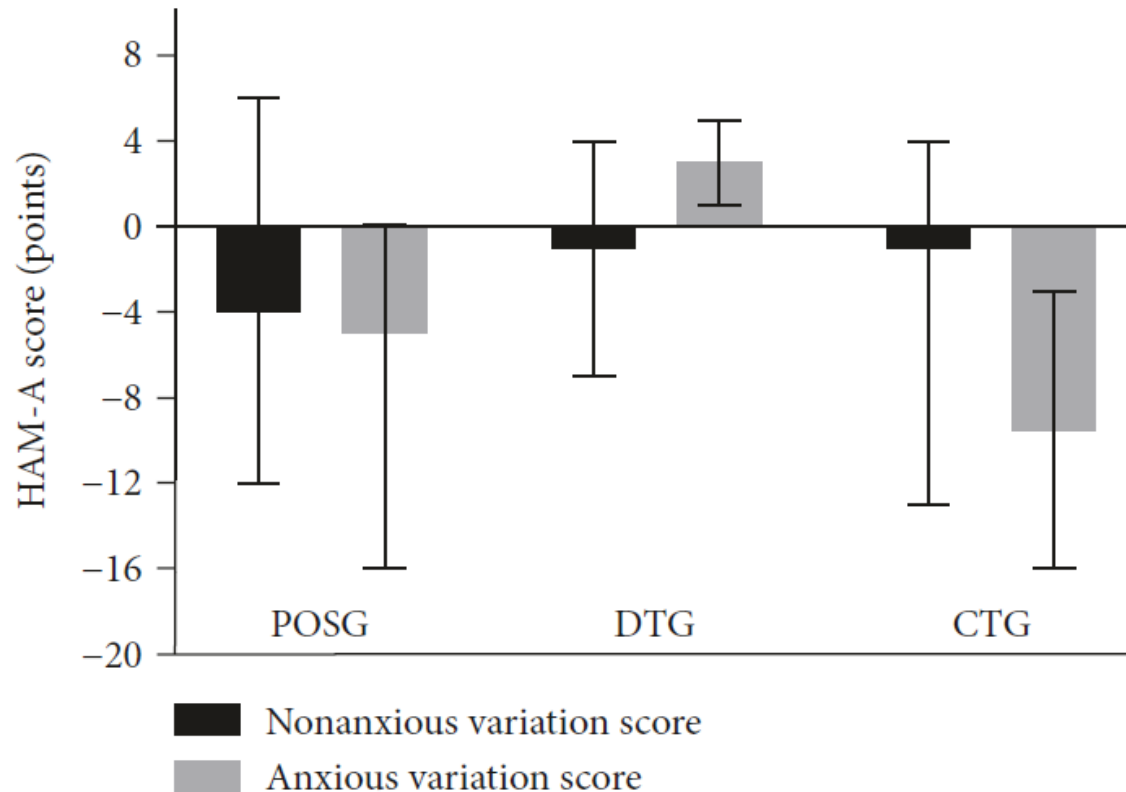
Timothy G. Dinan, Catherine Stanton, and John F. Cryan

Here, we define a psychobiotic as a live organism that, when ingested in adequate amounts, produces a health benefit in patients suffering from psychiatric illness. As a class of probiotic, these bacteria are capable of producing and delivering neuroactive substances such as gamma-aminobutyric acid and serotonin, which act on the brain-gut axis. Preclinical evaluation in rodents suggests that certain psychobiotics possess antidepressant or anxiolytic activity. Effects may be mediated via the vagus nerve, spinal cord, or neuroendocrine systems. So far, psychobiotics have been most extensively studied in a liaison psychiatric setting in patients with irritable bowel syndrome, where positive benefits have been reported for a number of organisms including *Bifidobacterium infantis*. Evidence is emerging of benefits in alleviating symptoms of depression and in chronic fatigue syndrome. Such benefits may be related to the anti-inflammatory actions of certain psychobiotics and a capacity to reduce hypothalamic-pituitary-adrenal axis activity. Results from large scale placebo-controlled studies are awaited.

Meccanismi d'azione degli Psicobiotici (Sul SNC e sull'intestino)



Variazione della scala HAM con psicobiotici (POSG), dieta (DTG) o terapia combinata (CTG) in soggetti ansiosi



Evidenze sull'uomo - 2

Autism

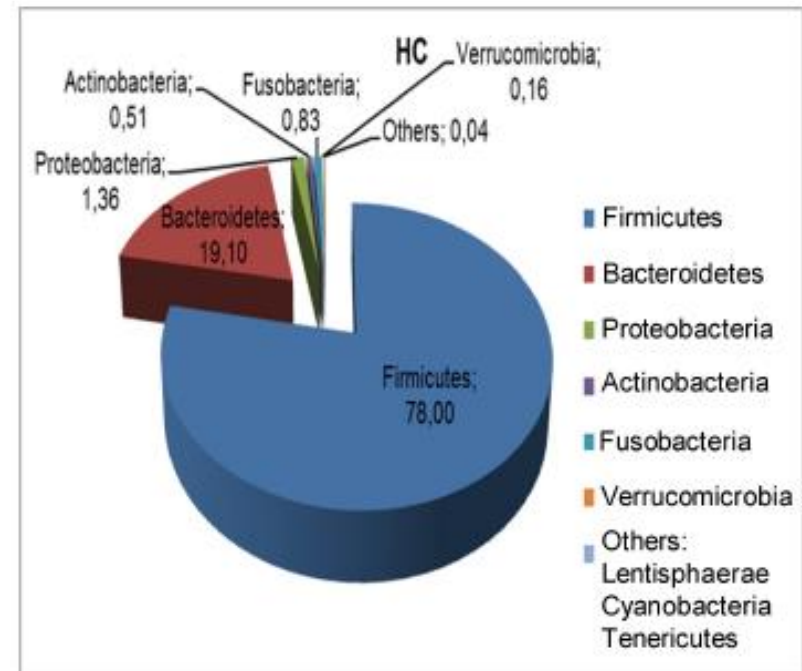
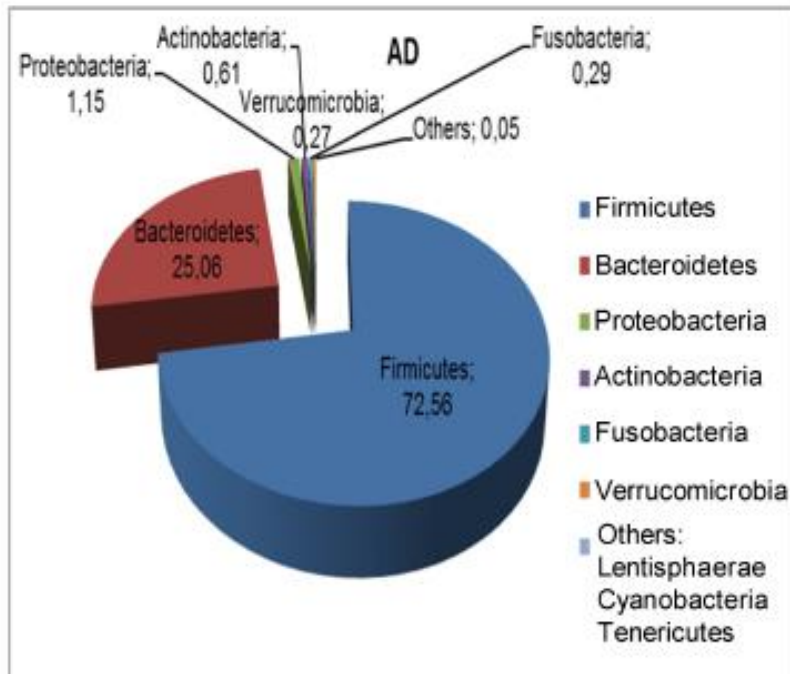
Increase in microbiota diversity is associated with autism^[43]

Abundance of Bacteroidetes has found to be linked with severe autistic cases^[43]

Increase in short chain fatty acids has been found in fecal samples from autistic children^[44]

A specific strain of the species *Lactobacillus reuteri* has shown to modulate oxytocin levels and reverse autism-related behavior^[41]

Abbondanza batterica relativa (phylum) in soggetti con autismo (AD) e controlli (HC)



Evidenze sull'uomo - 3

Parkinson's disease

Alterations in bowel function, mainly constipation, often precede the onset of motor symptoms associated with PD^[76]

Reduction in the levels of Prevotellaceae has been found in PD patients^[80]

Positive correlation between levels of Enterobacteriaceae and the severity of postural instability and gait difficulty was proven in PD patients^[80]

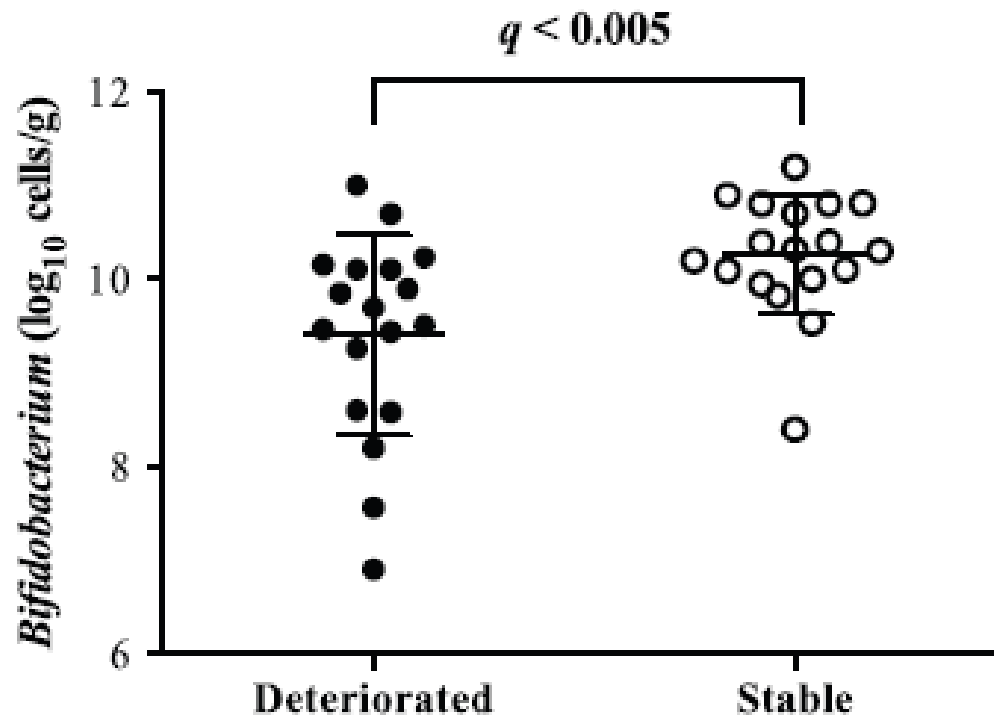
Reduction in short chain fatty acids^[78] and butyrate-producing bacteria (*Blautia*, *Coprococcus*, *Faecalibacterium spp* and *Roseburia*)^[79] were found in fecal samples from PD patients

GF mice overexpressing human α -synuclein (α Syn) display reduced microglia activation, α Syn aggregates and motor deficits (treatment with short chain fatty acids restored all major features of PD in GF mice)^[77]

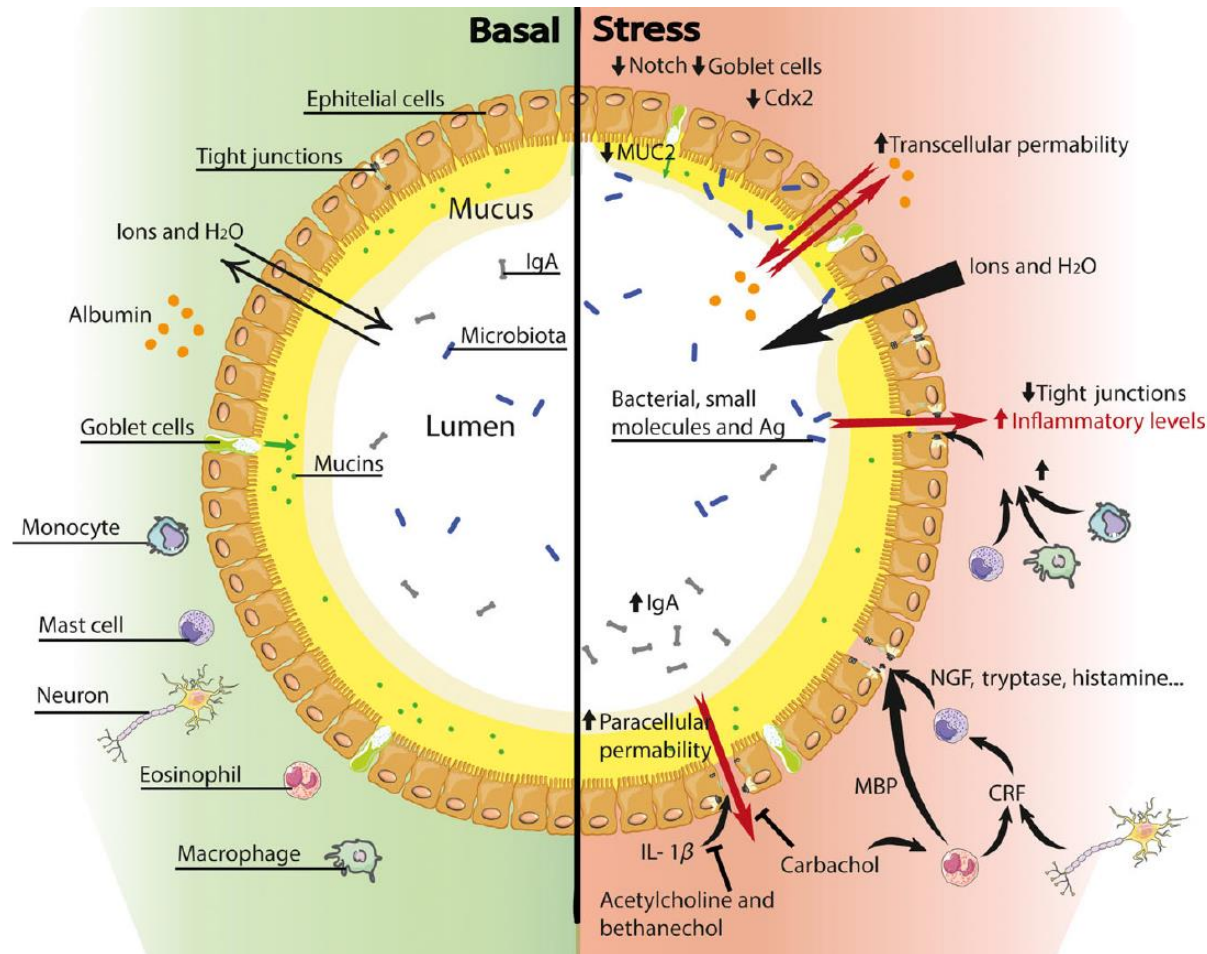
Gut microbiota transfer from PD patients into GF mice overexpressing human α -synuclein (α Syn) enhances physical impairments whereas gut microbiota transfer from healthy human donor does not enhances those deficiencies^[77]

La progressione del m. di Parkinson si associa a disbiosi intestinale.

Uno studio con follow-up di 2 anni



Effetti dello stress sulla funzione di barriera epiteliale intestinale



Probiotic *Lactobacillus casei* strain Shirota relieves stress-associated symptoms by modulating the gut–brain interaction in human and animal models

M. TAKADA,* K. NISHIDA,† A. KATAOKA-KATO,* Y. GONDO,* H. ISHIKAWA,* K. SUDA,* M. KAWAI,* R. HOSHI,‡
O. WATANABE,‡ T. IGARASHI,‡ Y. KUWANO,† K. MIYAZAKI* & K. ROKUTAN†

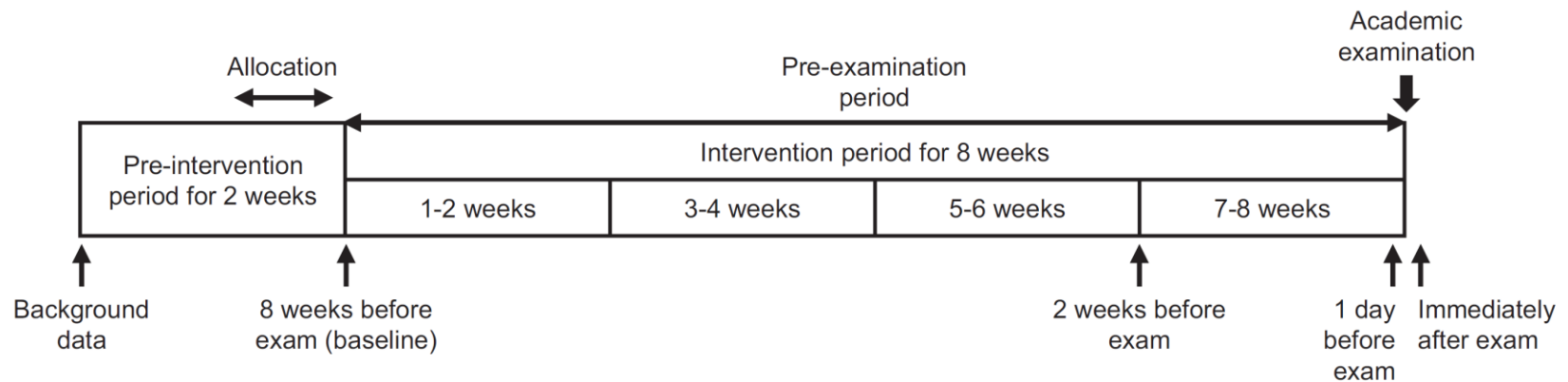


Figure 1 Study schedule.

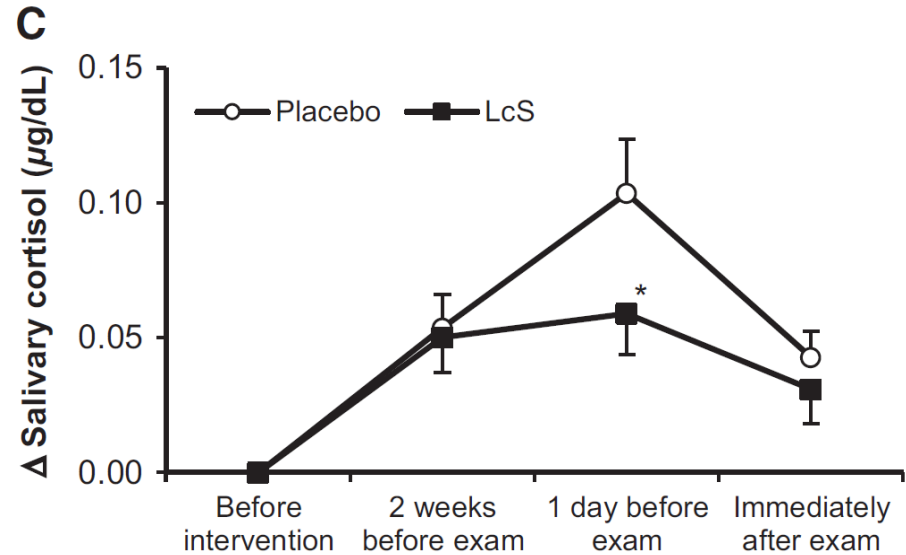
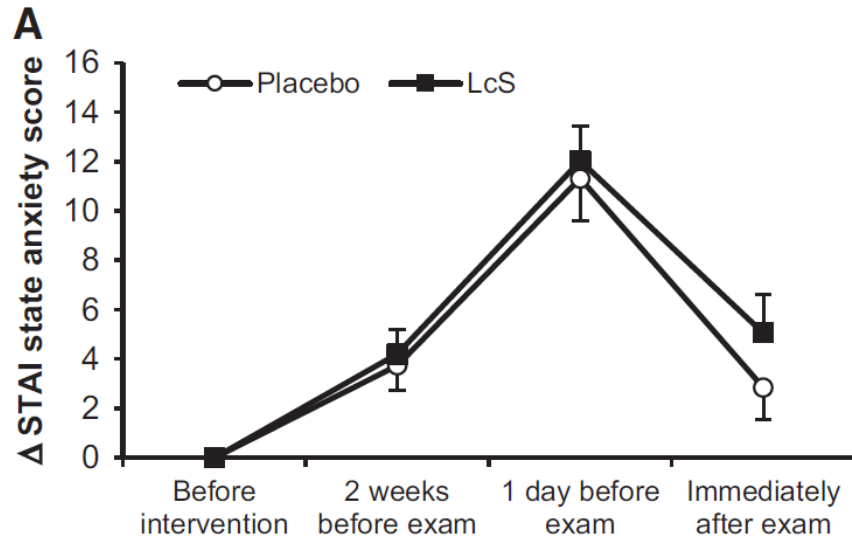
Caratteristiche clinico-demografiche nei due gruppi

Table 1 Background data of subjects and their compliance during the intervention period

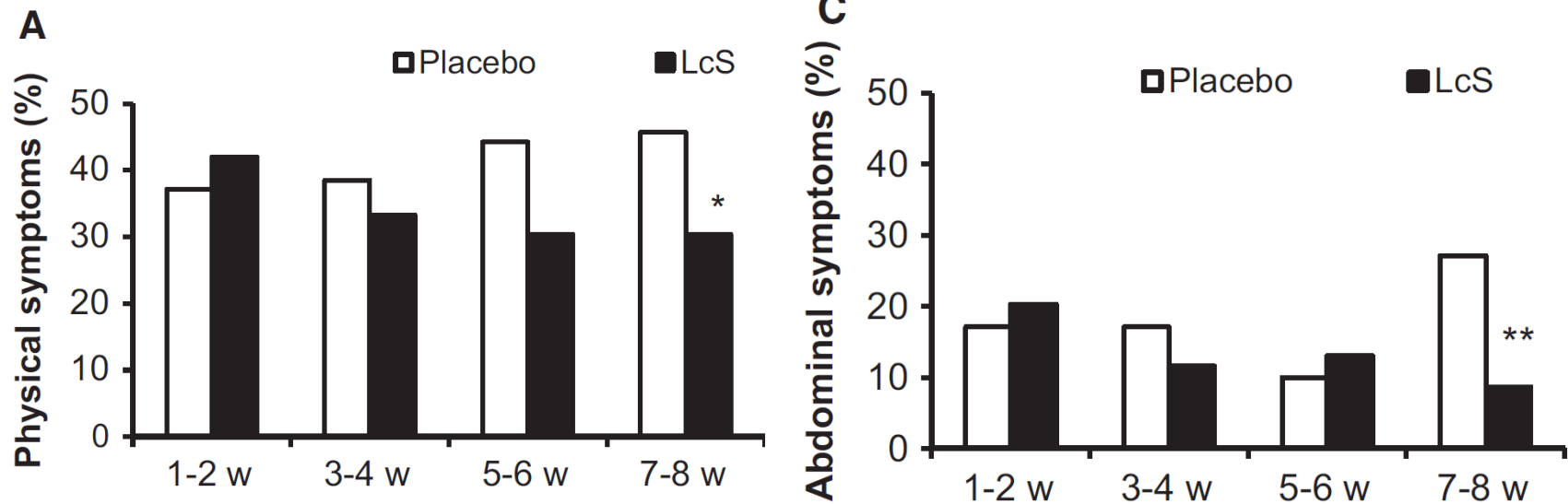
	Placebo	LcS
Male/Female	38/32	38/32
Age (years)	22.8 \pm 0.2	23.0 \pm 0.2
BMI (kg/m ²)	20.7 \pm 0.3	21.0 \pm 0.2
HPI	5.0 \pm 0.2	5.0 \pm 0.1
GHQ	4.5 \pm 0.5	4.8 \pm 0.4
STAI		
Trait anxiety	44.4 \pm 1.1	44.8 \pm 1.2
State anxiety	40.1 \pm 1.1	39.9 \pm 1.0
Salivary cortisol (μ g/dL)	0.15 \pm 0.01	0.15 \pm 0.01
% flu vaccination	63	56
% of daily test beverage consumption	97.3	97.6

BMI, body mass index; HPI, Health Practice Index; GHQ, General Health Questionnaire; STAI, State-Trait Anxiety Inventory; LcS, *Lactobacillus casei* strain Shirota.

Modificazioni nei markers dello stress nei due gruppi



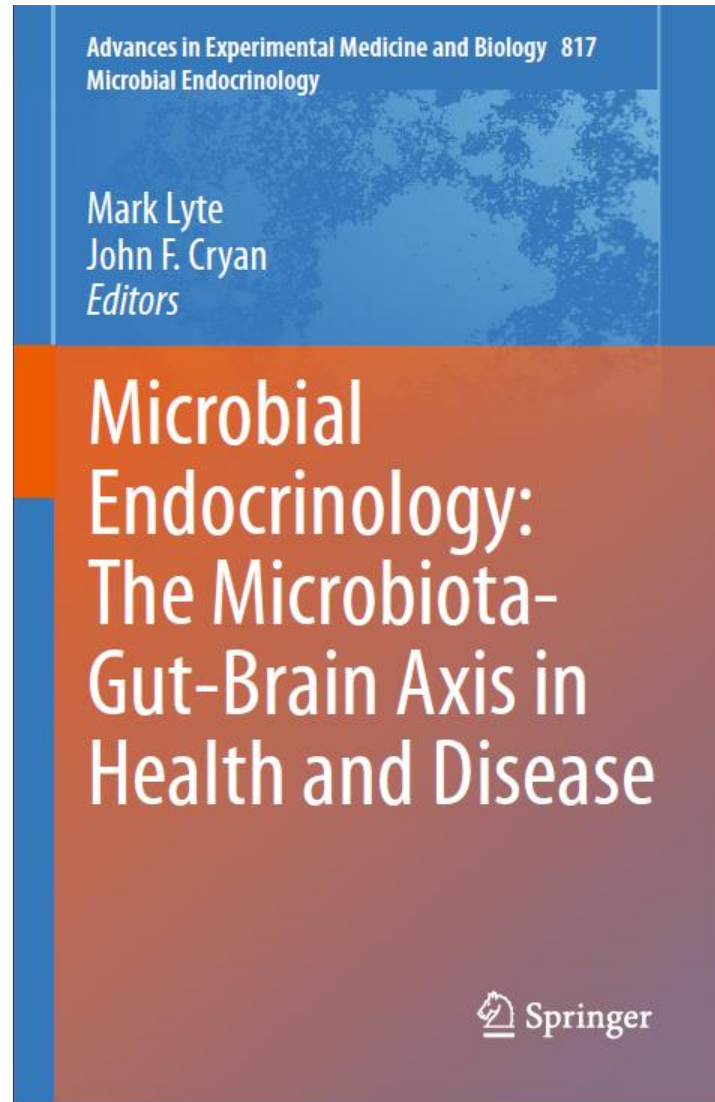
Modificazioni dei sintomi, fisici e addominali, nei due gruppi



Conclusioni

- L'alterazione del microbiota intestinale potrebbe rappresentare il **link patogenetico unificante** (“common ground”) tra i vari fattori fisiopatologici, periferici e centrali, ipotizzati per varie malattie associate a “leaky gut”, e alcune alterazioni neuro-psichiche, come autismo, Parkinson, depressione, stress.
- Modificare la disbiosi (pre-probiotici, antibiotici, trapianto fecale, altro) è l'obiettivo terapeutico prossimo futuro

Per saperne di più sull'asse microbiota-intestino-cervello





Per saperne di più sul microbiota

REVIEW

nature
medicine

Current understanding of the human microbiome

Jack A Gilbert¹⁻³, Martin J Blaser⁴ , J Gregory Caporaso⁵, Janet K Jansson⁶, Susan V Lynch⁷ & Rob Knight⁸⁻¹⁰ 

Nature Medicine 2018;24:392-400

Per ulteriori informazioni sul Microbiota



top
ten

in gastroenterologia

10^a EDIZIONE

8 e 9 MARZO 2019

BERGAMO

HOTEL EXCELSIOR SAN MARCO

Piazza della Repubblica, 6

Responsabile Scientifico: Fabio Pace

SEGRETERIA ORGANIZZATIVA E PROVIDER ECM



via Pagliari, 4 - 26100 Cremona
tel 0372 23310 - fax 0372 569605
info@overgroup.eu - www.overgroup.eu

MICROBIOTA CORNER

- Rapporti bidirezionali tra H. pylori e Microbiota del tratto GE superiore
- Microbiota e IBD: fatti e suggestioni
- Microbiota e preparazione per colonscopia
- Microbiota intestinale e sviluppo di allergopatie
- Microbiota intestinale e cancro del colon
- I probiotici: aspetti normativi, biologici e clinici

TOP TEN

- Nuove terapie nel morbo di Crohn
- Endocrinologia e Intestino
- Come preparare al meglio il paziente per la colonscopia
- Permeabilità intestinale e infiammazione
- La Malattia Diverticolare in Italia: i dati REMAD
- Endoscopia bariatrica e metabolica
- Dalla steatosi al carcinoma epatico: cosa fare per interrompere la sequenza
- Il trattamento endoscopico della malattia da reflusso gastro-esofageo
- Si può fare diagnosi di celiachia senza biopsie intestinali?
- Terapia con protettori mucosali nella MRGE
- Update su Helicobacter pylori

DOCENTI

Bruno Annibale (Roma)
Patrizia Brigidi (Bologna)
Valentina Casini (Bergamo)
Guido Costamagna (Roma)
Antonio Di Sabatino (Pavia)
Edoardo Giannini (Genova)
Enzo Grossi (Milano)
Gianluca Ianiro (Roma)
Peter Malfertheiner (Magdeburgo)
Giampiero Manes (Milano)
Fabio Pace (Bergamo)
Francesca Penagini (Milano)
Franco Radaelli (Como)
Luigi Ricciardiello (Bologna)
Pier Alberto Testoni (Milano)
Roberto Trevisan (Bergamo)
Gian Vincenzo Zuccotti (Milano)