Microbiota-Gut-Brain Axis


microbiota
microbial
intestinal
bacteria
bacterial
gut
human
species
analysis
study
samples
different
metagenomic
using
community
composition
disease
diversity
gene
genes
immune
dna
rrna
communities
microorganisms
levels
mucosal
function
isolates
soil
mice
including
factors
resistance
populations
based
showed
probiotics
molecular
growth
present
well
significant
methods
detected
effect
coli
diet
production
environmental
among
pcr
role
presence
potential
population
model
higher
infection
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two
studies
patients
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development
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periodontal
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lactobacillus
associated
pathogens
strains
gastrointestinal
health
cell
effects
protein
group
results
high
cells
changes
known
significantly
related
identified
strain
system
tract
genetic
isolated
bowel
increased
new
sequence
complex
differences
intestine
control
also
healthy
within
mechanisms
major
novel
inflammation
metabolic
groups
found
treatment
use
metagenomics
fecal
subjects
host
sequences
inflammatory
probiotic
diseases
expression
three
clinical
acid
conditions
functional
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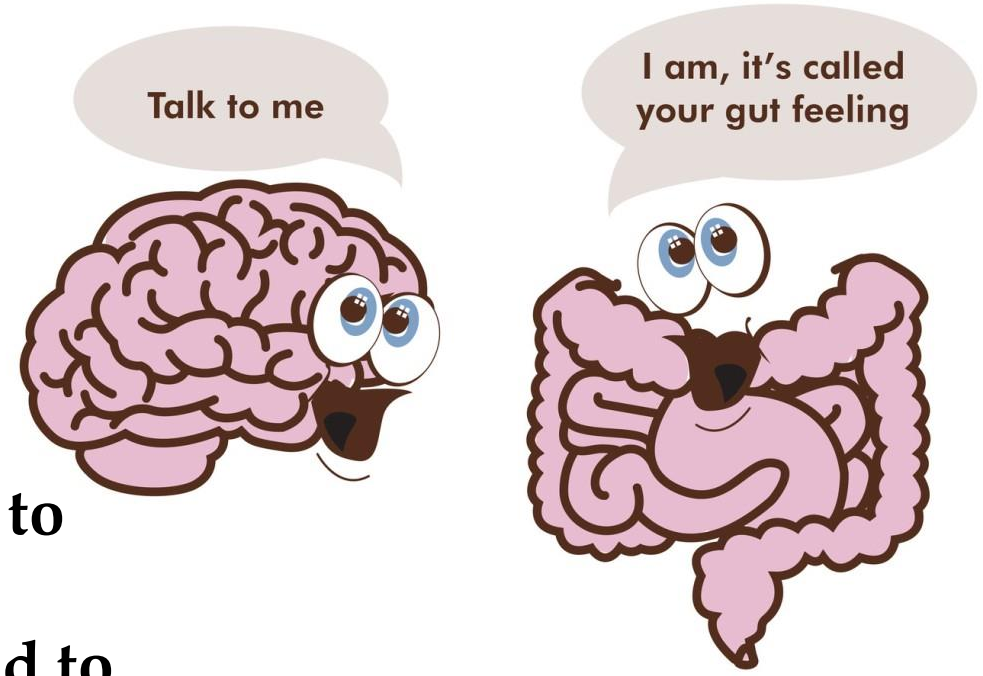
16s
data
revealed
oral
total
first
number
observed
colonization
addition
colonic
response
microbes
used

Learning Objectives



- Explain the concept and significance of the microbiota-gut-brain axis (MGBA)
- Describe key mechanisms linking gut microbes to brain function and behavior
- Critically evaluate experimental approaches used to study the MGBA
- Discuss the clinical relevance of the MGBA in mental, neurological, and gastrointestinal disorders
- Analyze current research and identify open questions in the field

What is the Microbiota-Gut-Brain Axis?

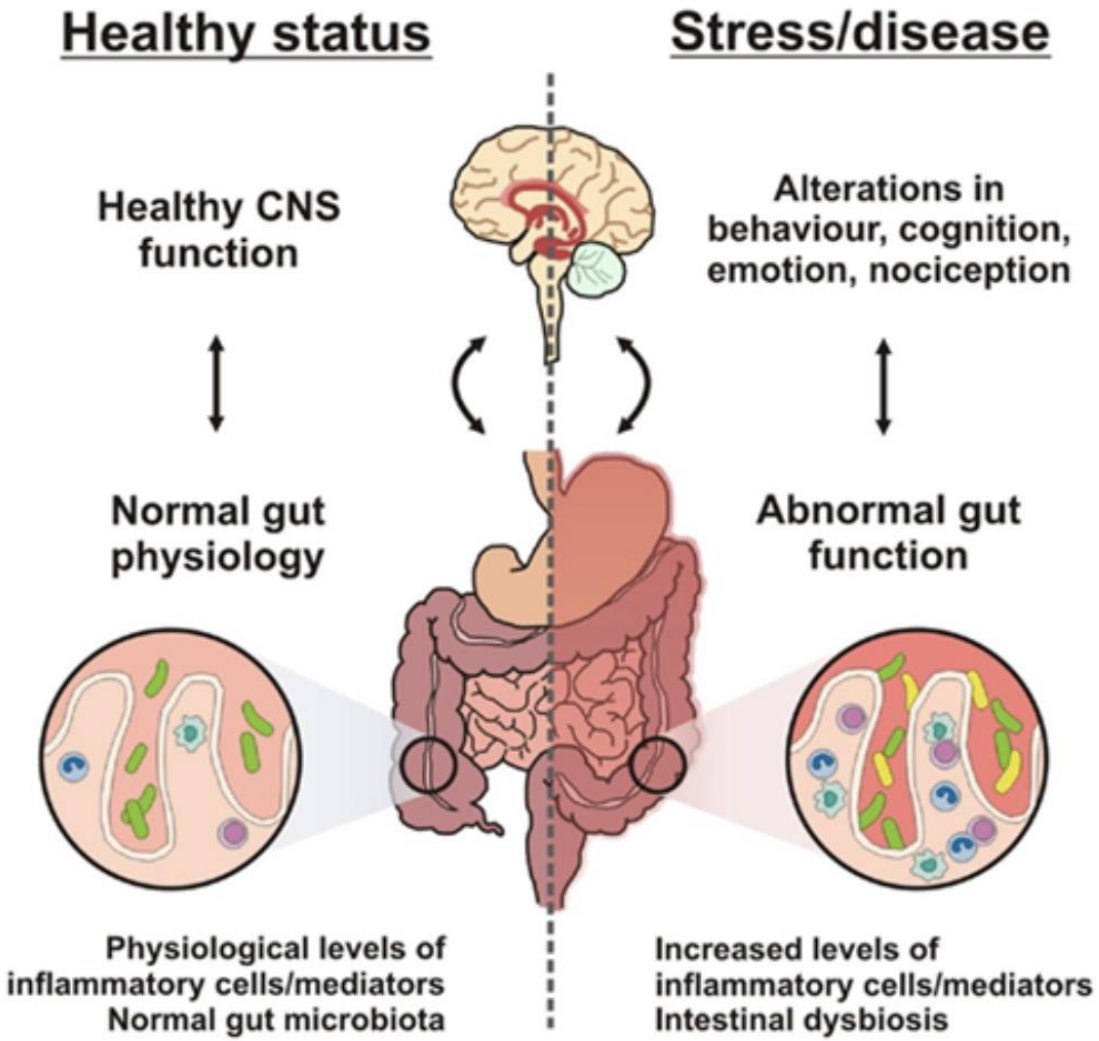
The microbiota-gut-brain axis is a bidirectional communication network connecting the gut microbiota, the gastrointestinal tract, and the brain.

- **Signals travel via neural (vagus nerve, enteric nervous system), immune, endocrine, and metabolic pathways.**

- **Gut microbes influence brain function, mood, and behavior by producing neuroactive compounds and modulating inflammation.**

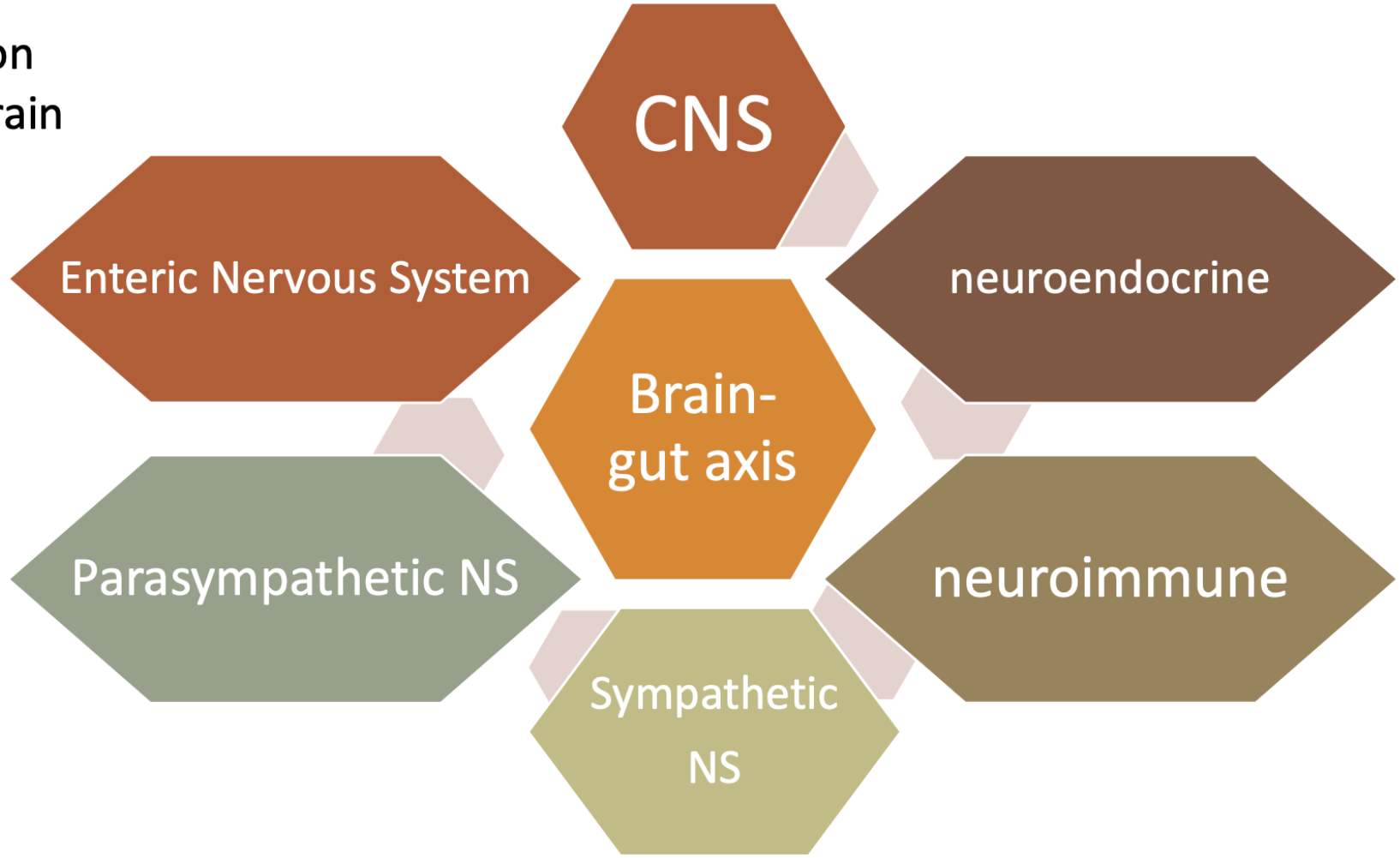
- **The brain also affects gut physiology and microbiota composition through stress and hormonal responses.**

- **Disruptions in this axis are linked to neurological and psychiatric disorders, highlighting its importance for health and disease.**



What is the Microbiota-Gut-Brain Axis?

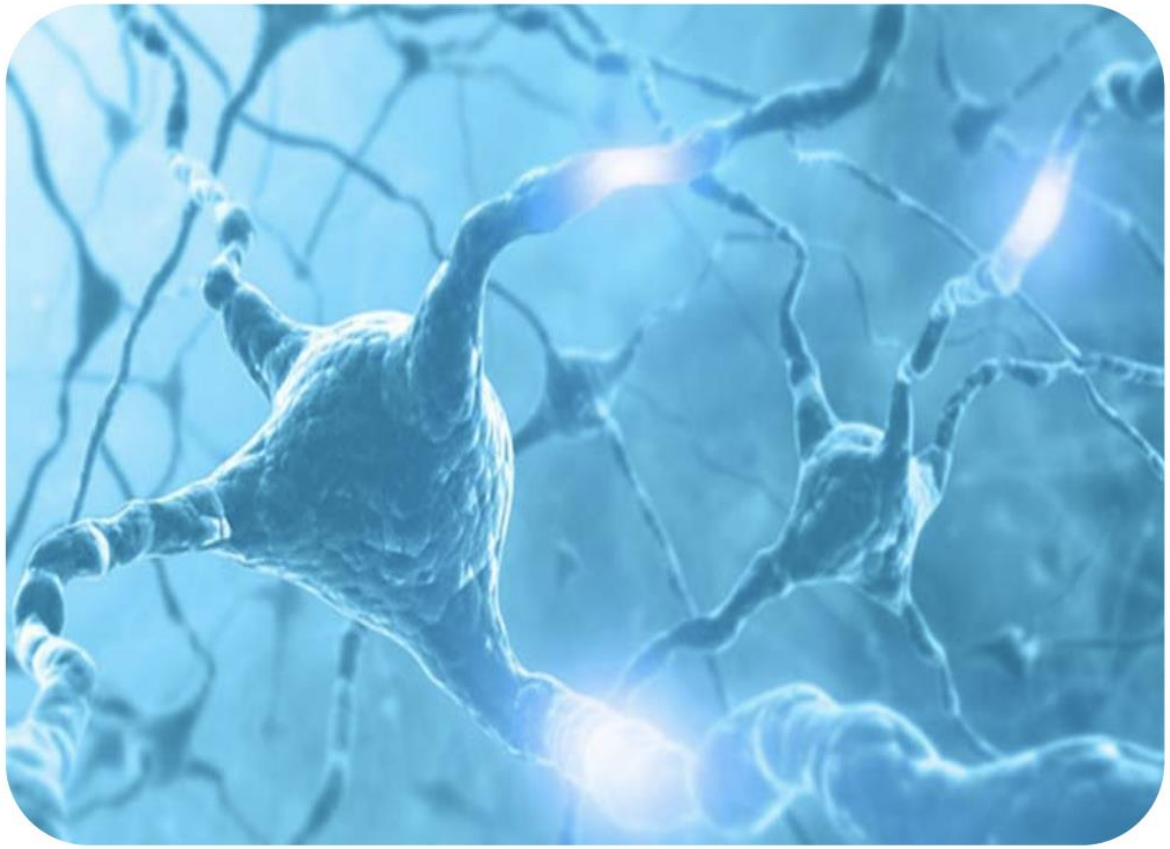
"Bidirectional communication network, signals from the brain can influence the motor, sensory, and secretory modalities of the GIT and conversely, visceral messages from the GIT can influence brain function."

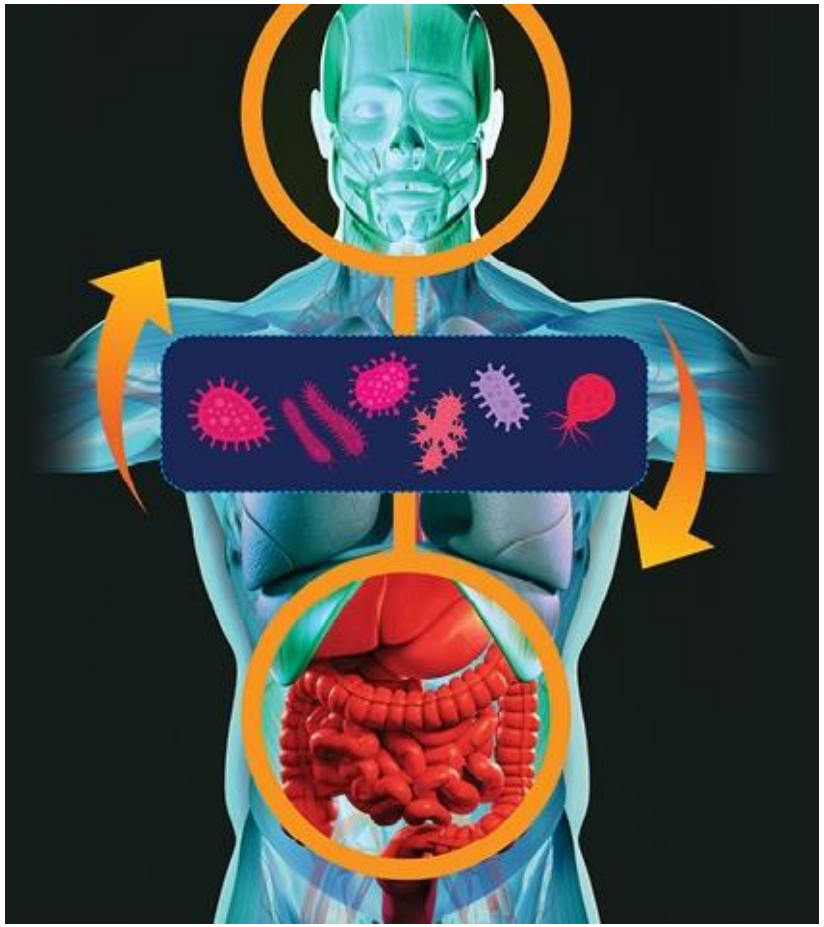


O'Mahony et al., 2011

Gut Bacteria May Manipulate Your Mind

Certain species of gut bacteria can interact with our nervous system in ways that appear to affect our stress responses – and stress response can affect the gut bacteria too!





Think Twice: How the Gut's "Second Brain" Influences Mood and Well-Being

The emerging and surprising view of how the enteric nervous system in our bellies goes far beyond just processing the food we eat

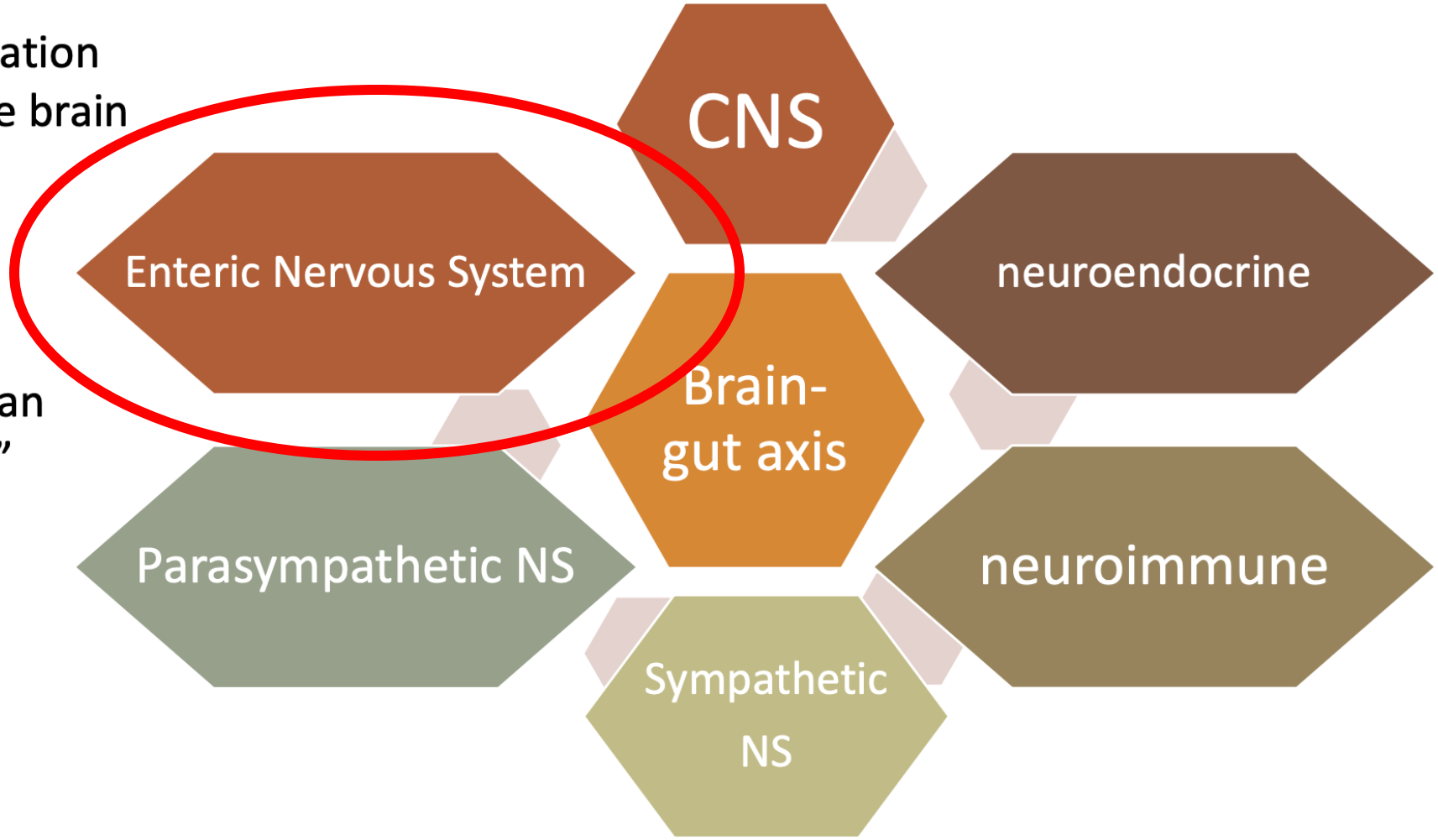
By Adam Hadhazy

Scientific American

GUT CHECK: A complex, independent nervous system lines the gastrointestinal tract that has been dubbed the "second brain".

What is the Microbiota-Gut-Brain Axis?

"Bidirectional communication network, signals from the brain can influence the motor, sensory, and secretory modalities of the GIT and conversely, visceral messages from the GIT can influence brain function."



O'Mahony et al., 2011

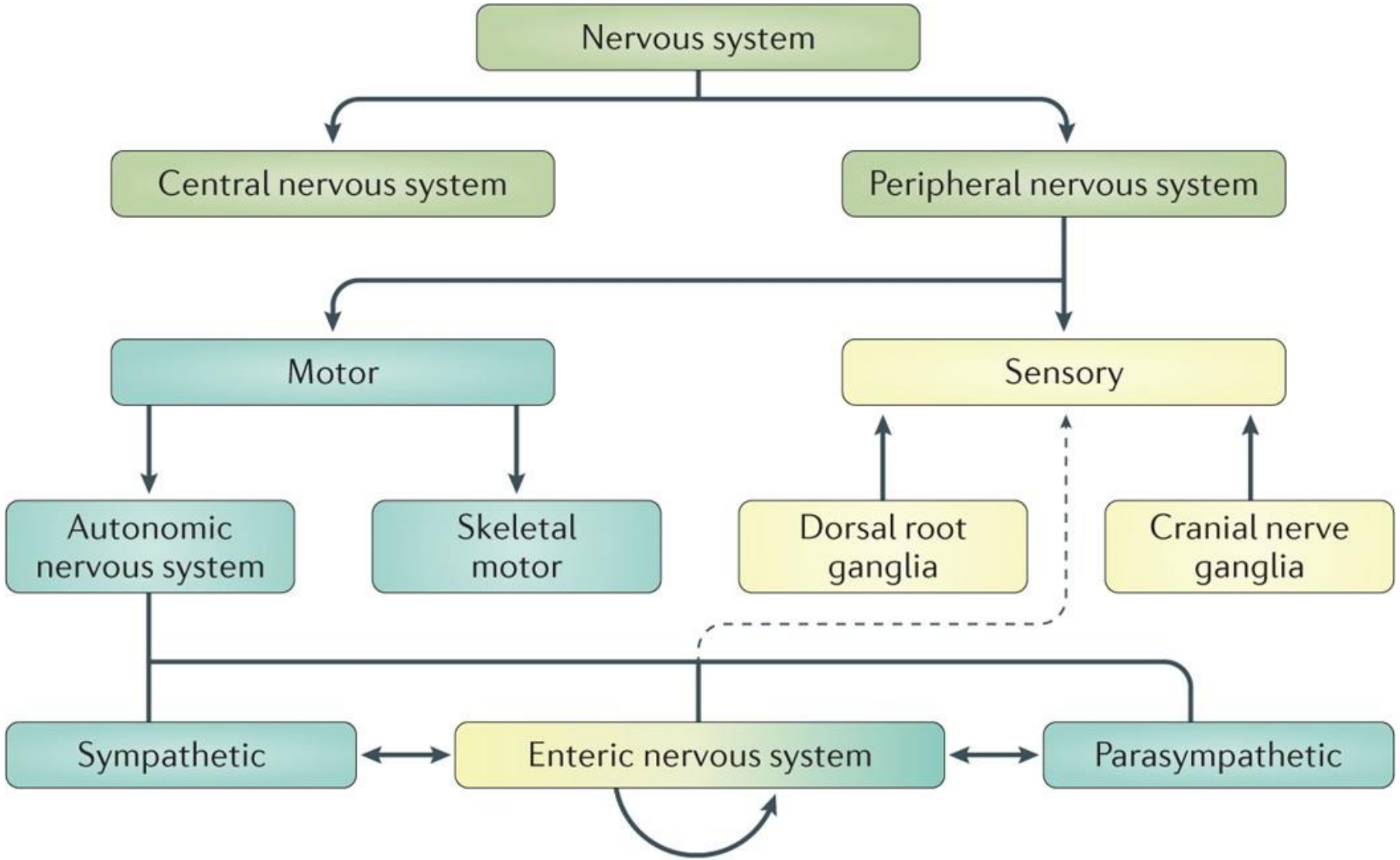
Enteric Nervous System

Enteric Nervous System
(not discovered until late 1900's is part of the autonomic nervous system.)

500 million neurons yet has no conscious thoughts.	With reflexes and senses can have 'on site' control of gut behavior – what else does it control?	No thought processes (religion, philosophy, or poetry) yet it can alert you to danger – & influences your response!	90% of vagus nerve information flow is *from* the gut to the brain – how much of that is conscious?

Recall, the autonomic nervous system is the network of peripheral nerves that control visceral functionality.

Enteric Nervous System



Nature Reviews | Gastroenterology & Hepatology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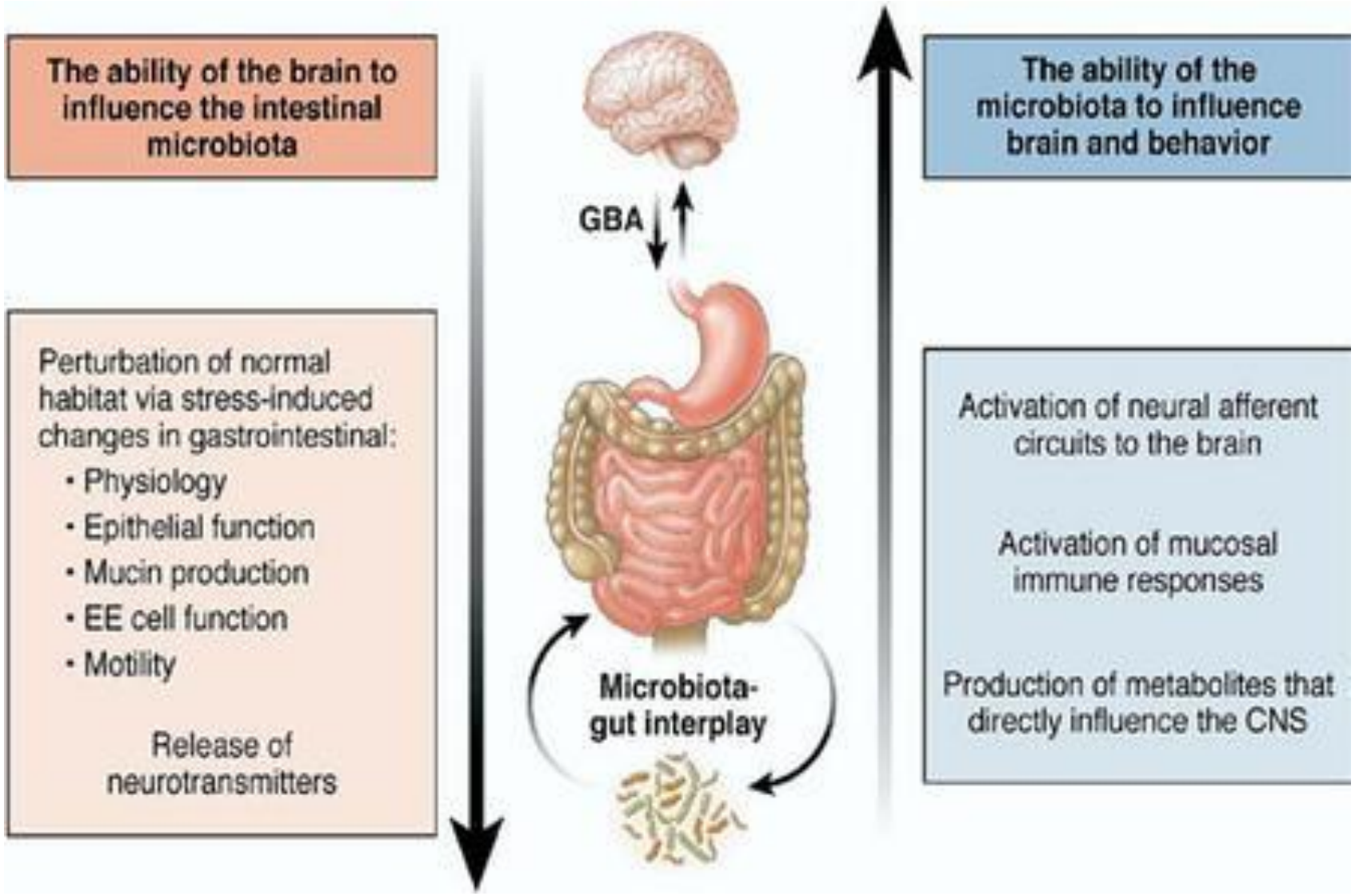
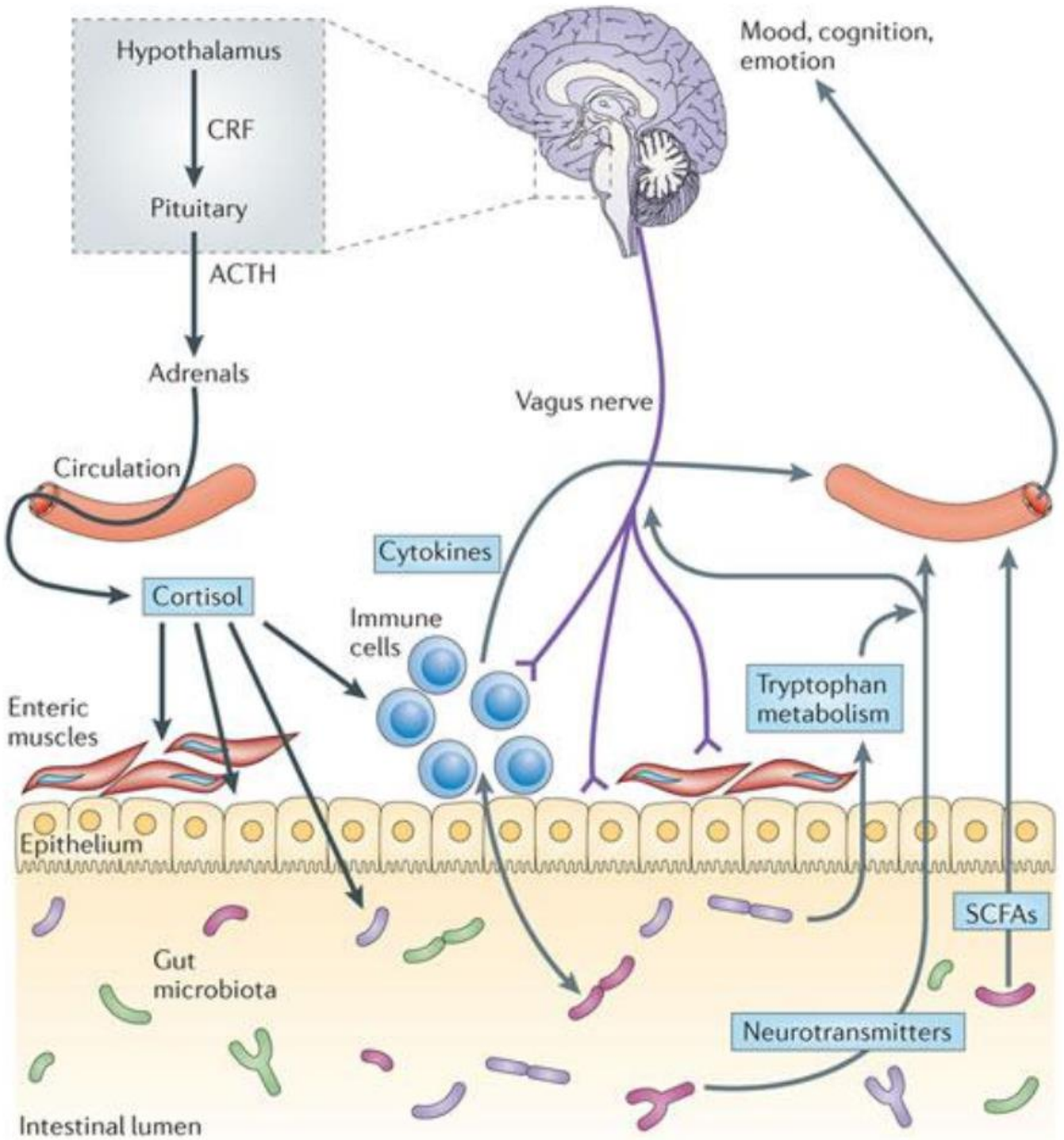
Microbiota Gut Brain Axis



Microbiota Gut Brain Axis

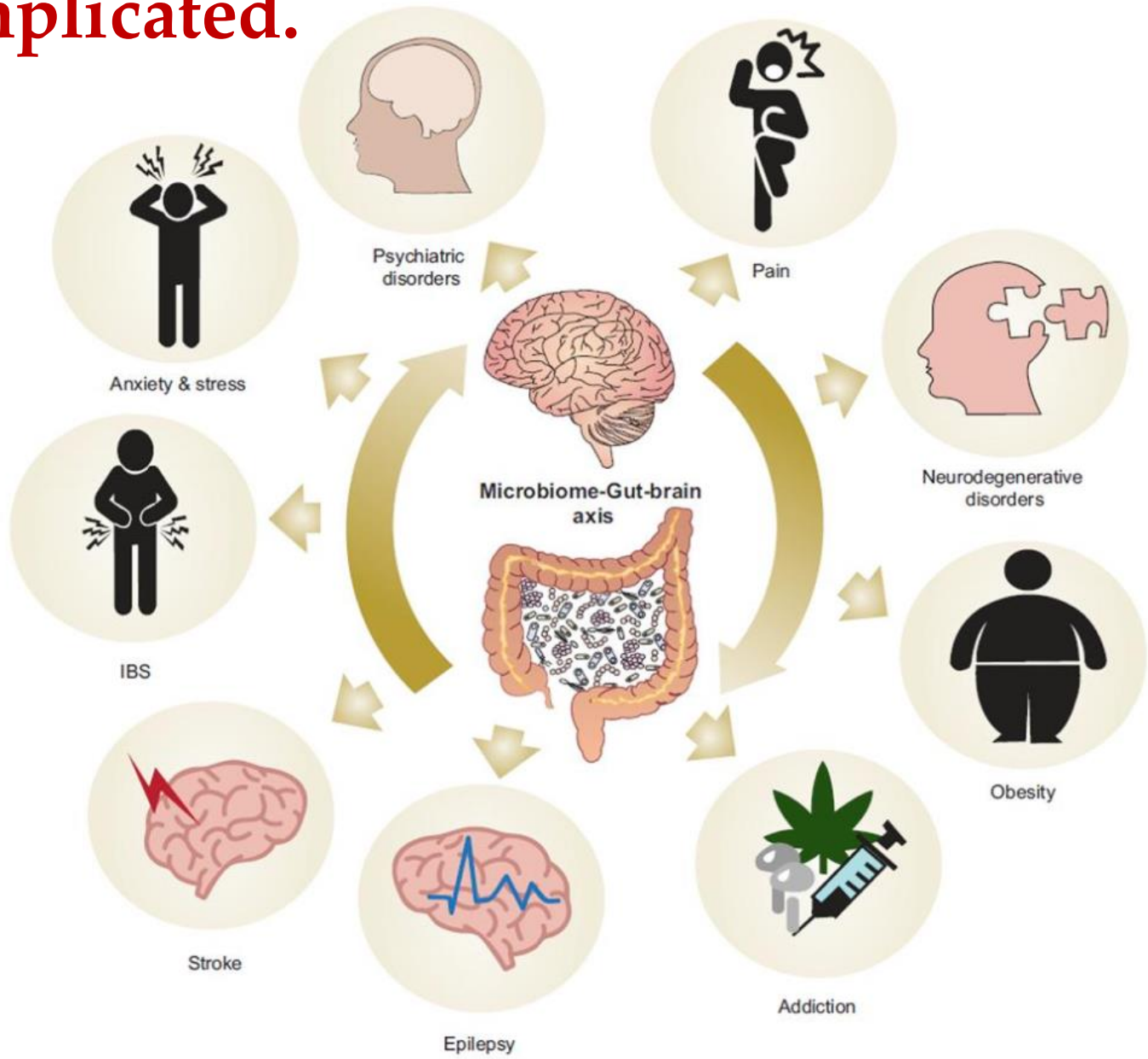
Bidirectional communication between the brain and the digestive system.



MGB axis

(Cryan & Dinan 2012)

Pathological processes in which the microbiota–gut–brain axis has been implicated.



MICROBIOTA

- The human intesti… …at are essential f…
- Th…
- …ance of gut microbiota to …mal

MICROBIOTA

The human intestine harbors nearly 100 trillion bacteria that are essential for health. The largest microbial component of the human microbiome is located in the large intestine of the gastrointestinal (GI) tract.

- critical contributions to metabolism by helping to break down complex polysaccharides
- critical to the normal development of the immune system.

Recent studies reveal the importance of gut microbiota to the function of the CNS.

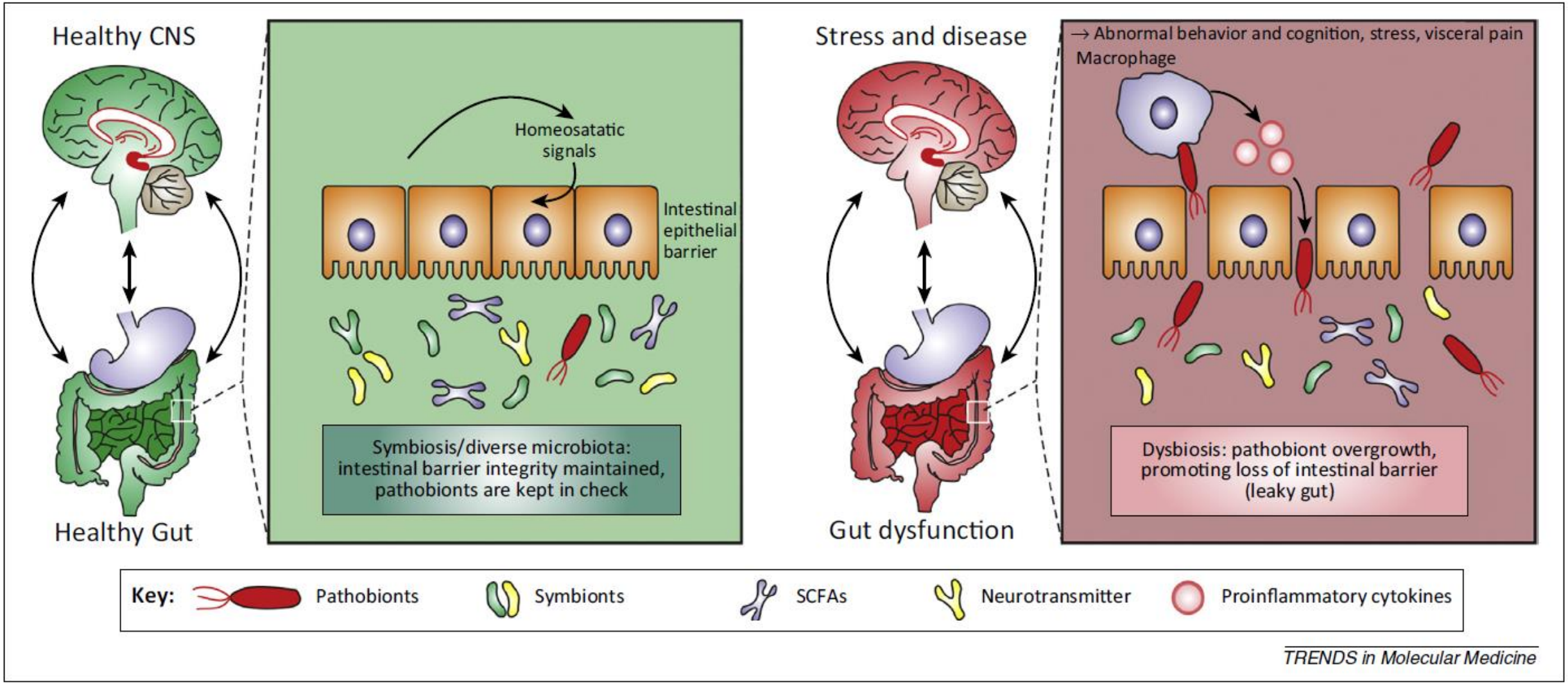
MICROBIOTA–GUT–BRAIN AXIS:

A complex network of communication between the gut, the intestinal microbiota, and the brain, modulating

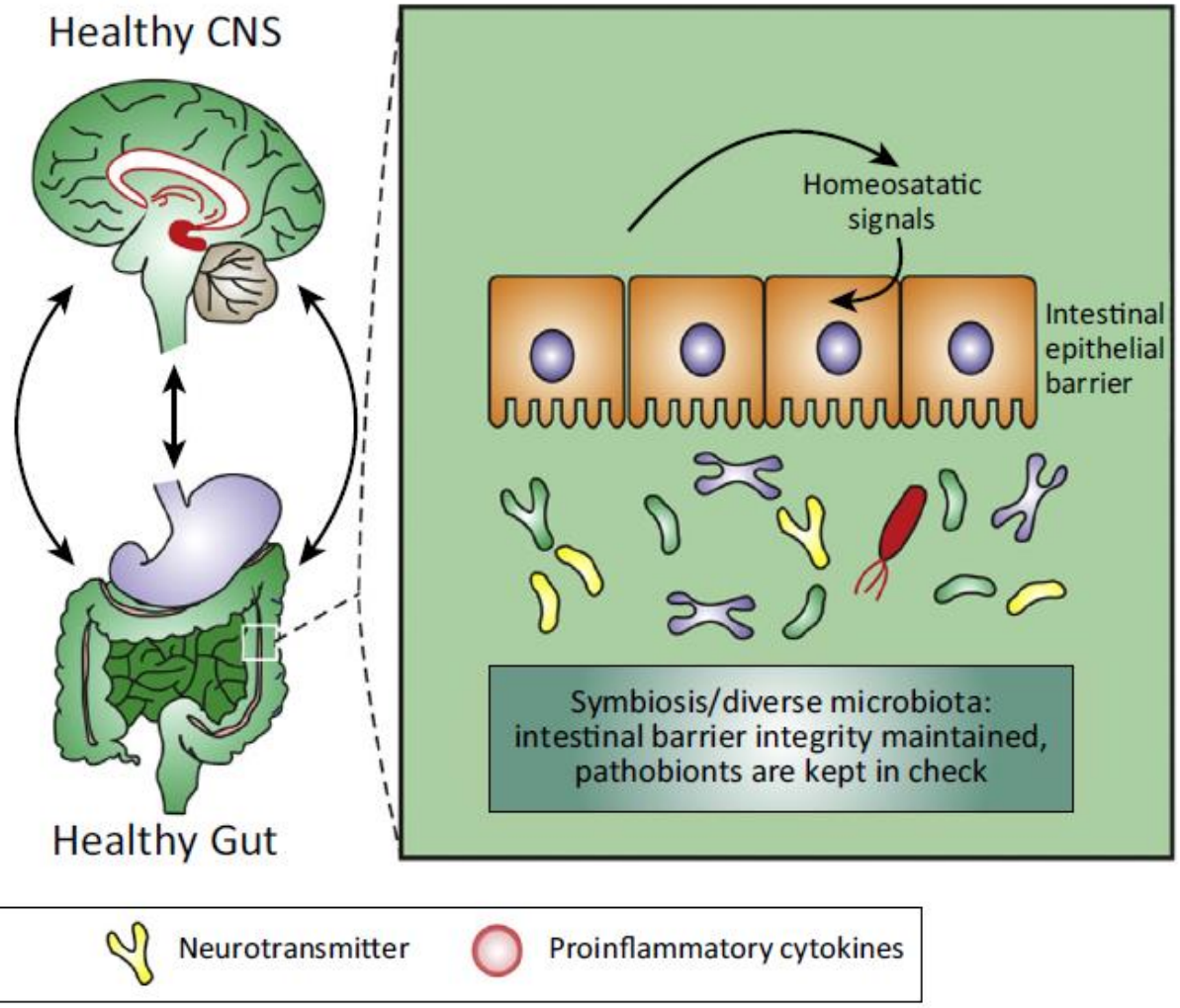
- immune
-GI
-and CNS functions.

It encompasses the CNS, the sympathetic and parasympathetic branches of the autonomic nervous system, as well as the enteric nervous system and the neuroendocrine and neuroimmune systems.

Impact of the gut microbiota on the brain–gut axis.



Impact of the gut microbiota on the brain–gut axis.



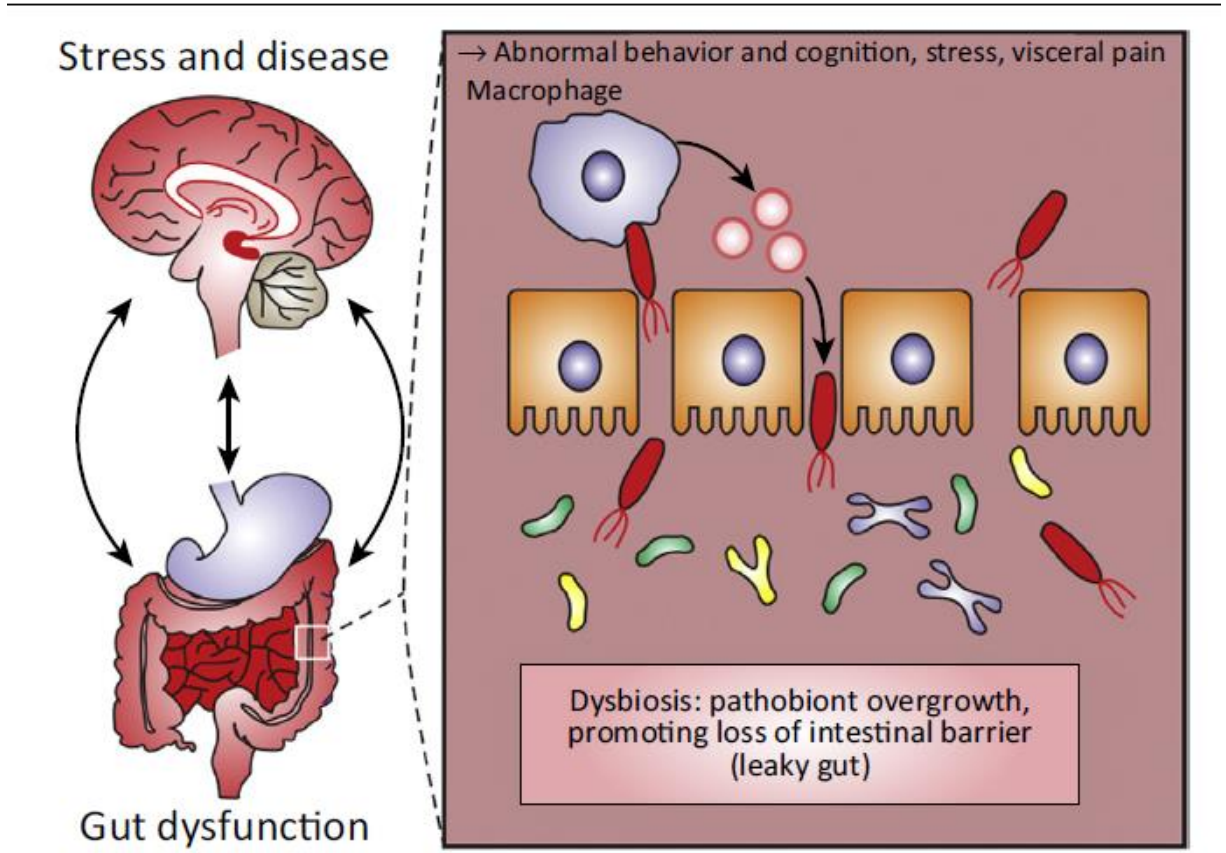
In healthy individuals:
the normal dominant microbiota is relatively stable and forms a mutually beneficial rapport with the host.

Impact of the gut microbiota on the brain–gut axis.

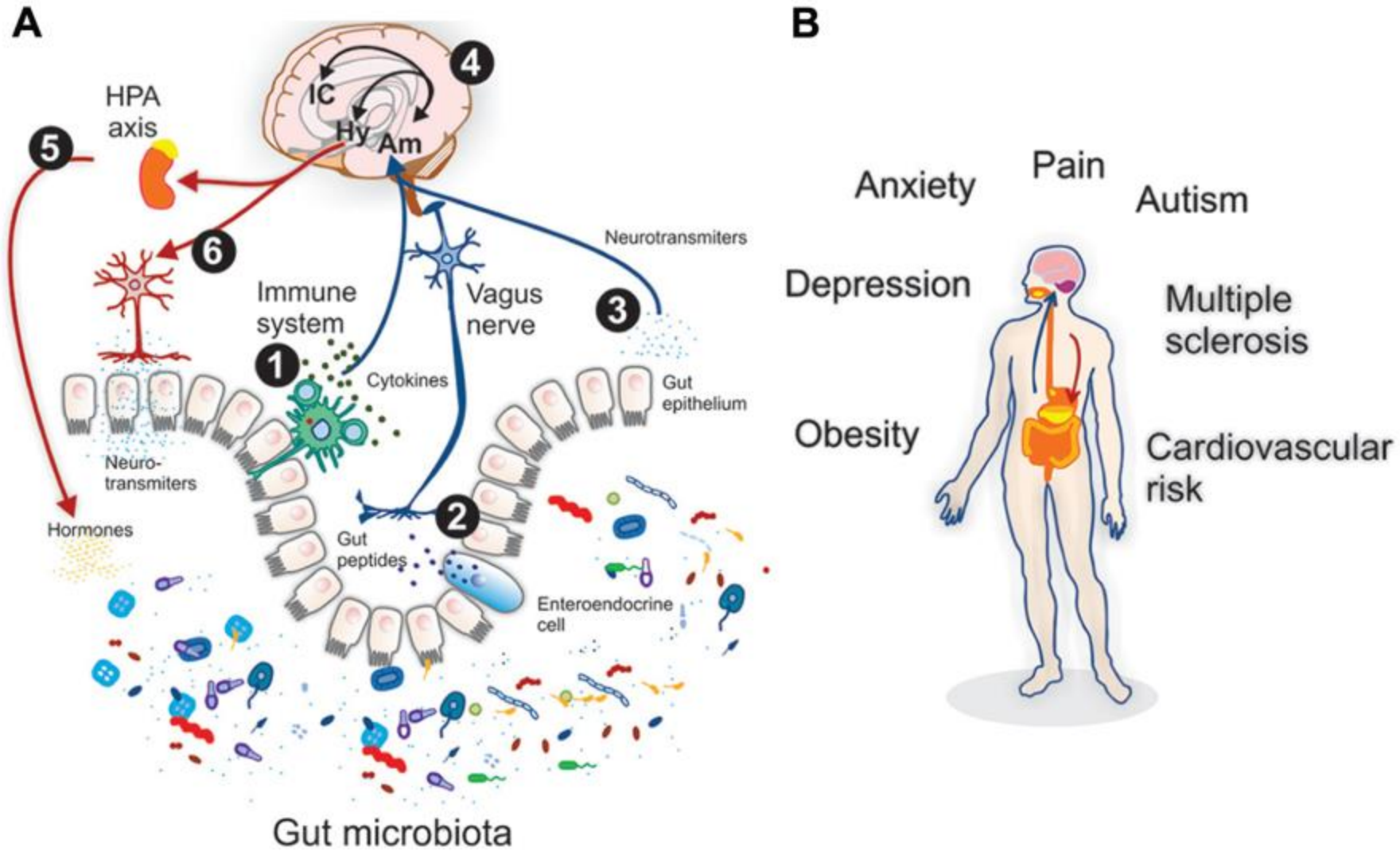
Perturbations may have serious consequences and has the potential to exacerbate brain, digestive, and metabolic disorders.

Bidirectional communication between the microbiota and the CNS influences stress reactivity, pain perception, neurochemistry, and several brain– gut axis disorders.

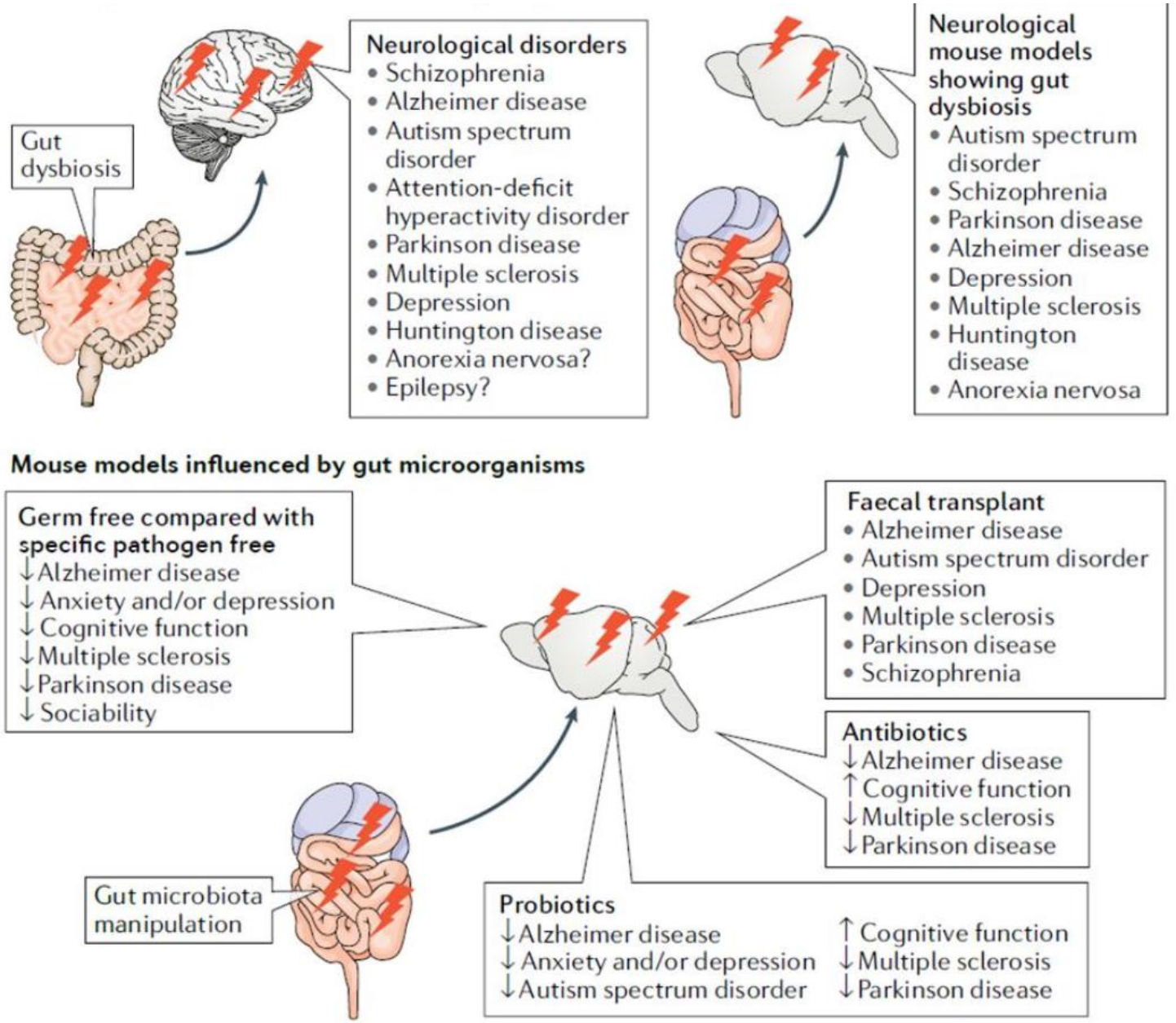
The composition of the gut microbiota during critical periods of CNS development is affected by a broad range of factors. Perturbation of any of these factors can lead to host stress or disease.



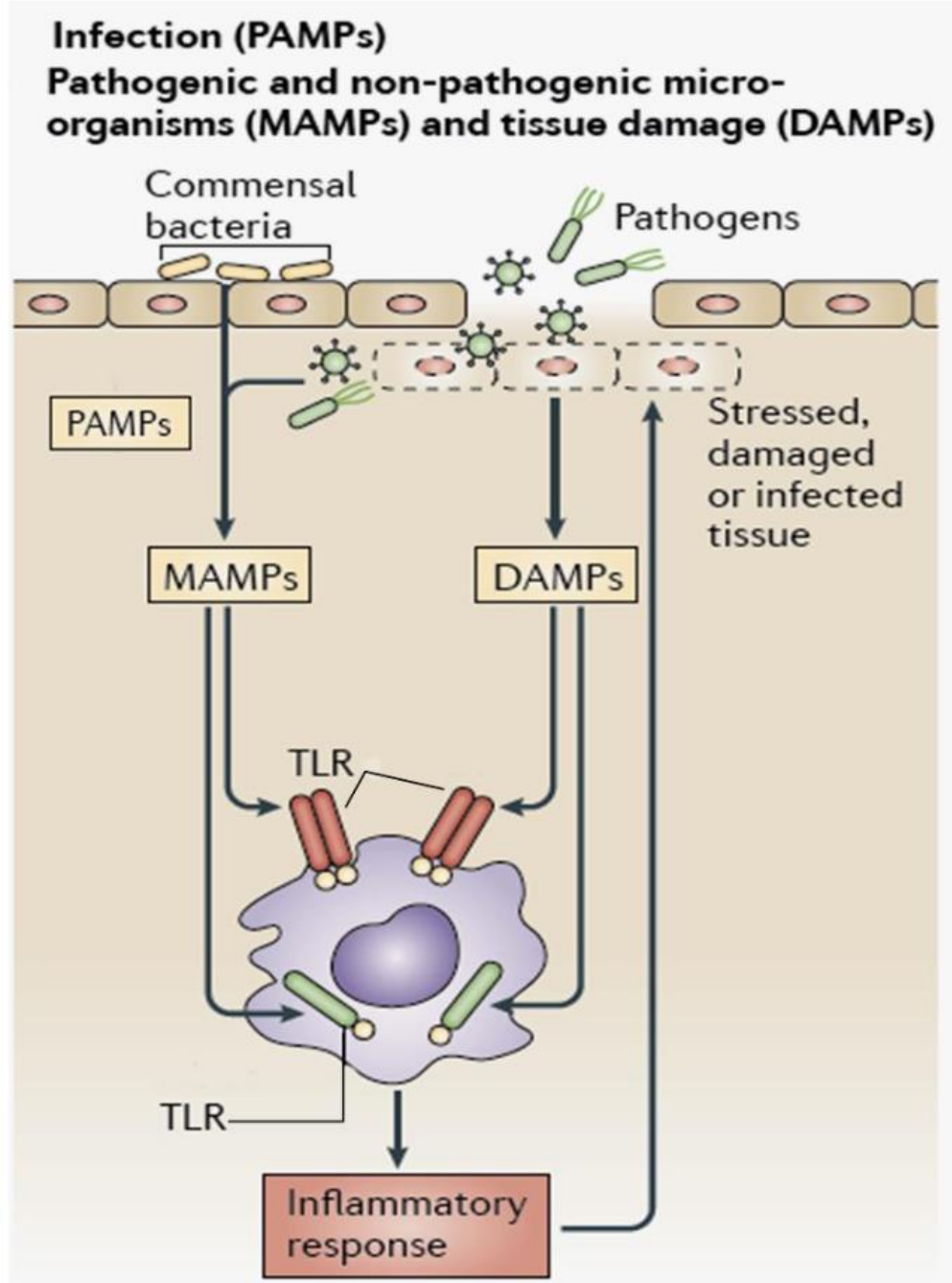
Pathologies with associated dysbiosis.



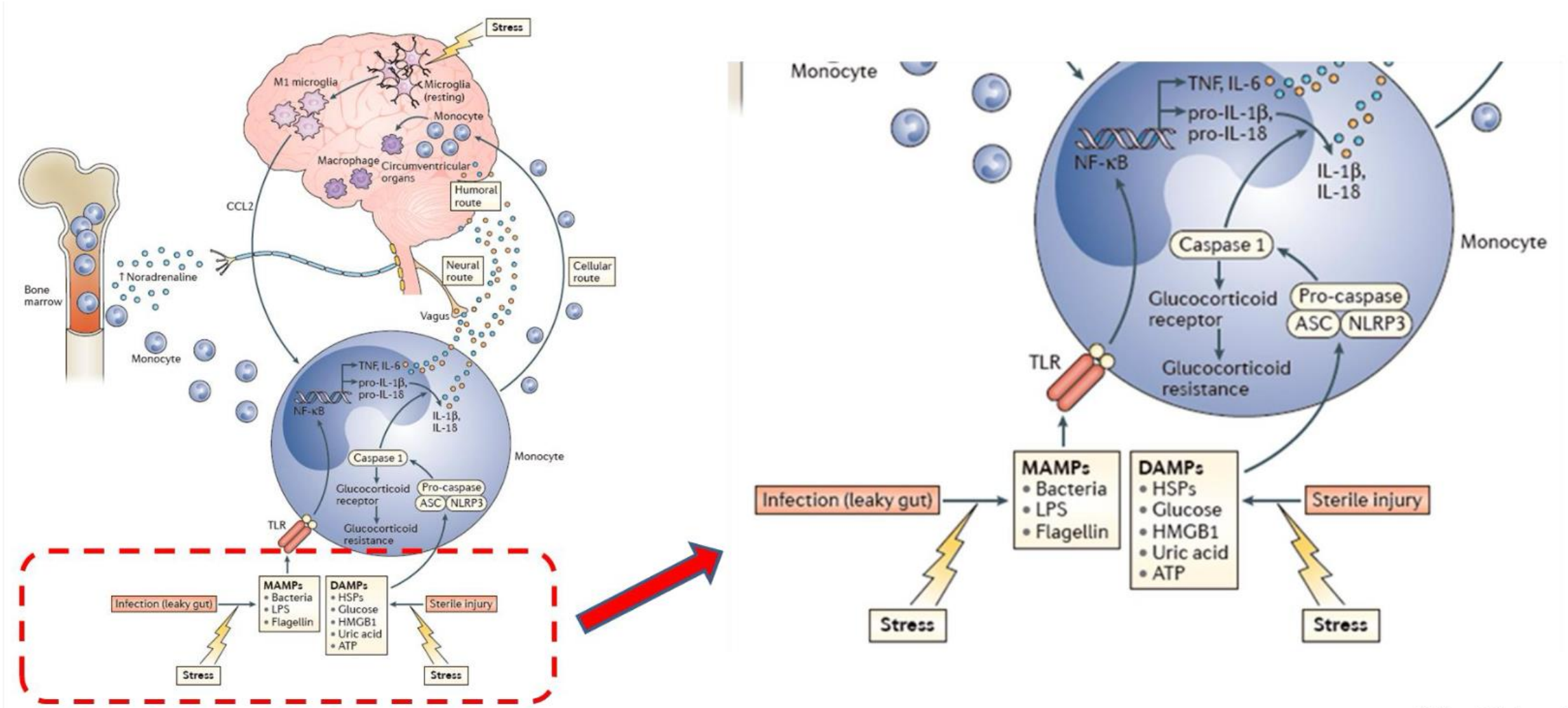
Neurological disorders with associated dysbiosis.



(Needham et al., 2020)

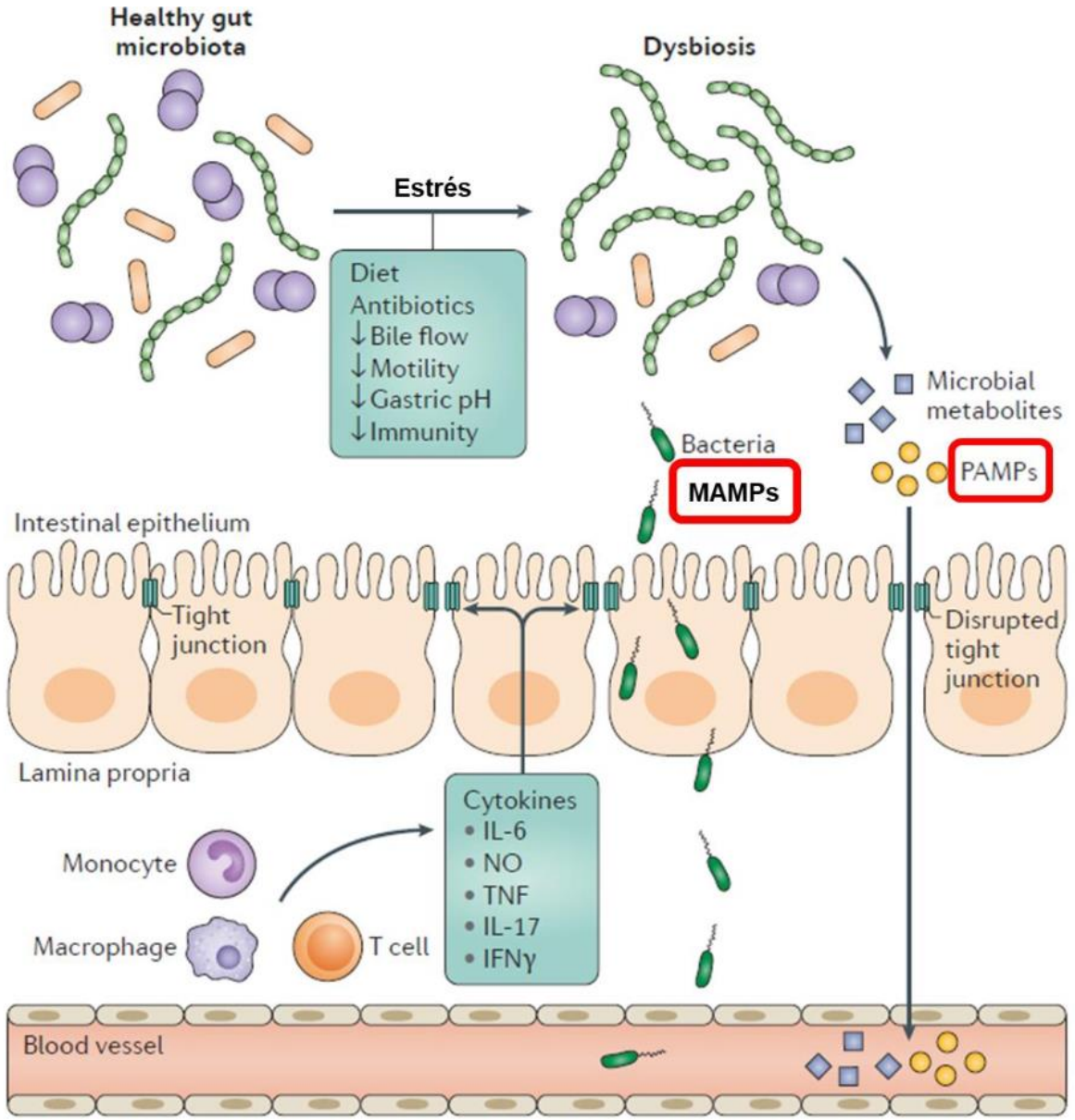

Infection (PAMPs)
Pathogenic and non-pathogenic micro-organisms (MAMPs) and tissue damage (DAMPs)
Commensal bacteria
Pathogens
PAMPs
Stressed, damaged or infected tissue
MAMPs
DAMPs
TLR
TLR
Inflammatory response

Transmitting stress-induced inflammatory signals to the brain.



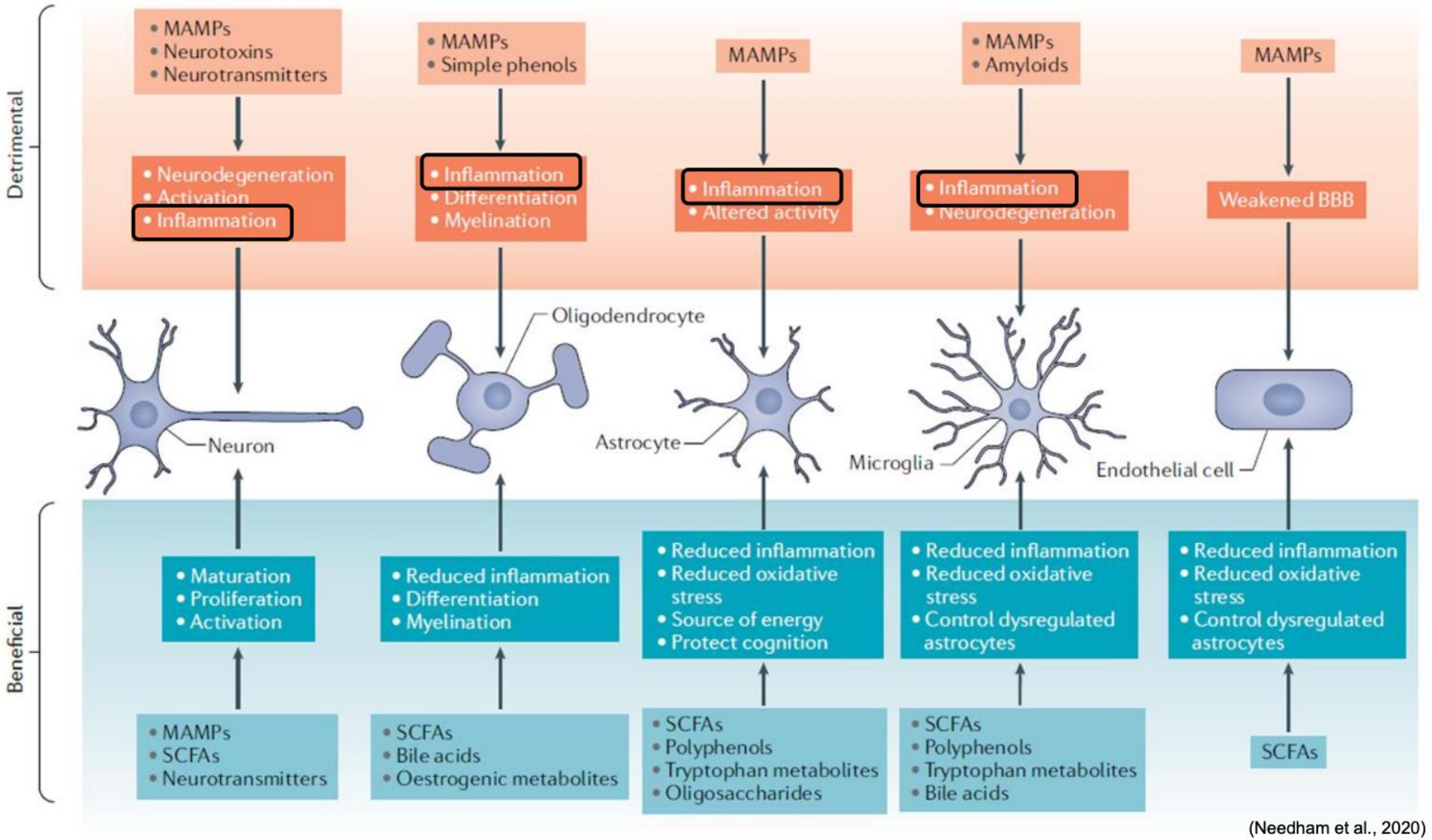
(Miller & Raison, 2016)

Transmitting stress-induced inflammatory signals to the brain.



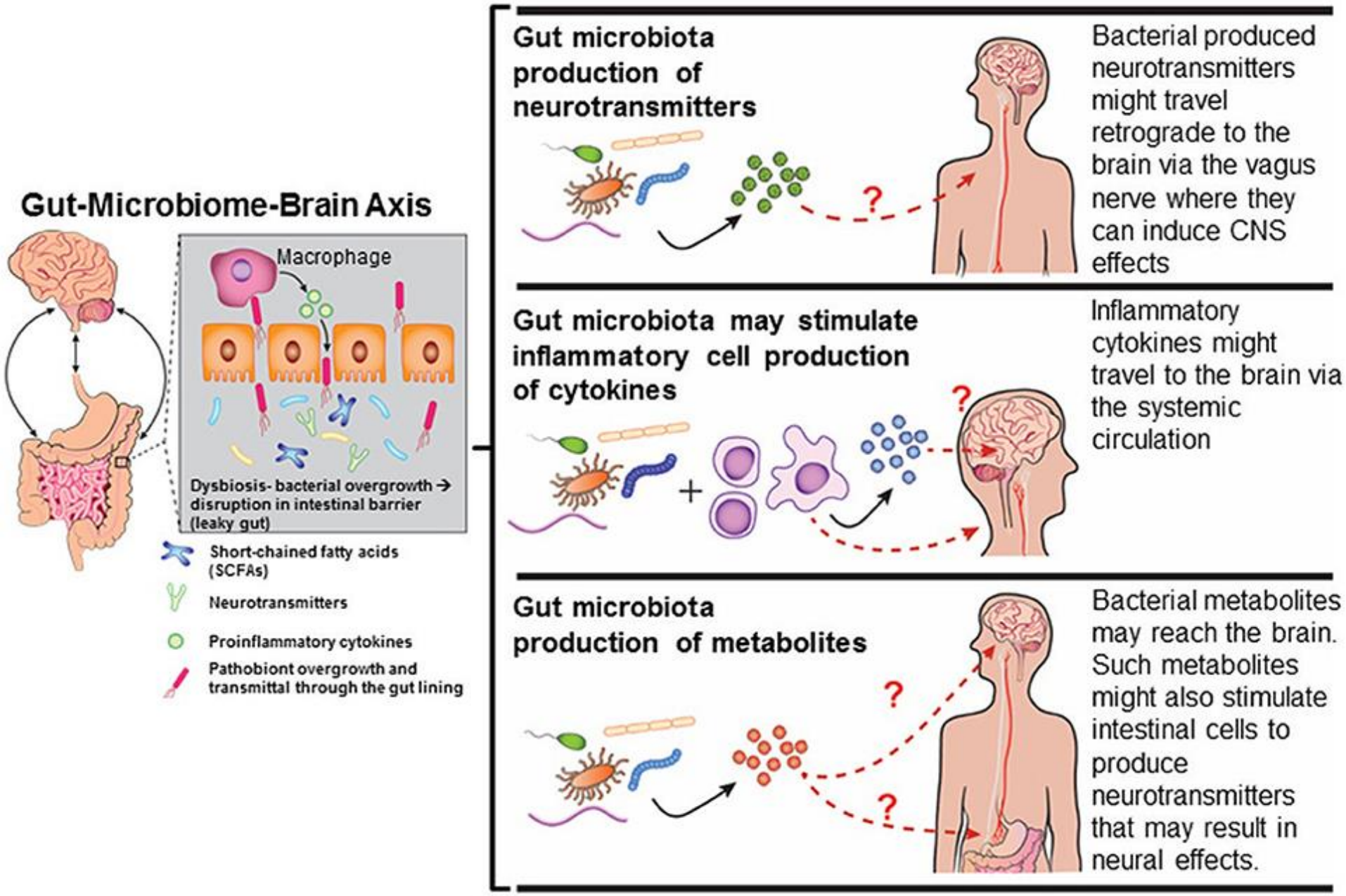
(Arroyo et al. 2016)

Microbiota Gut Brain Axis at cellular level

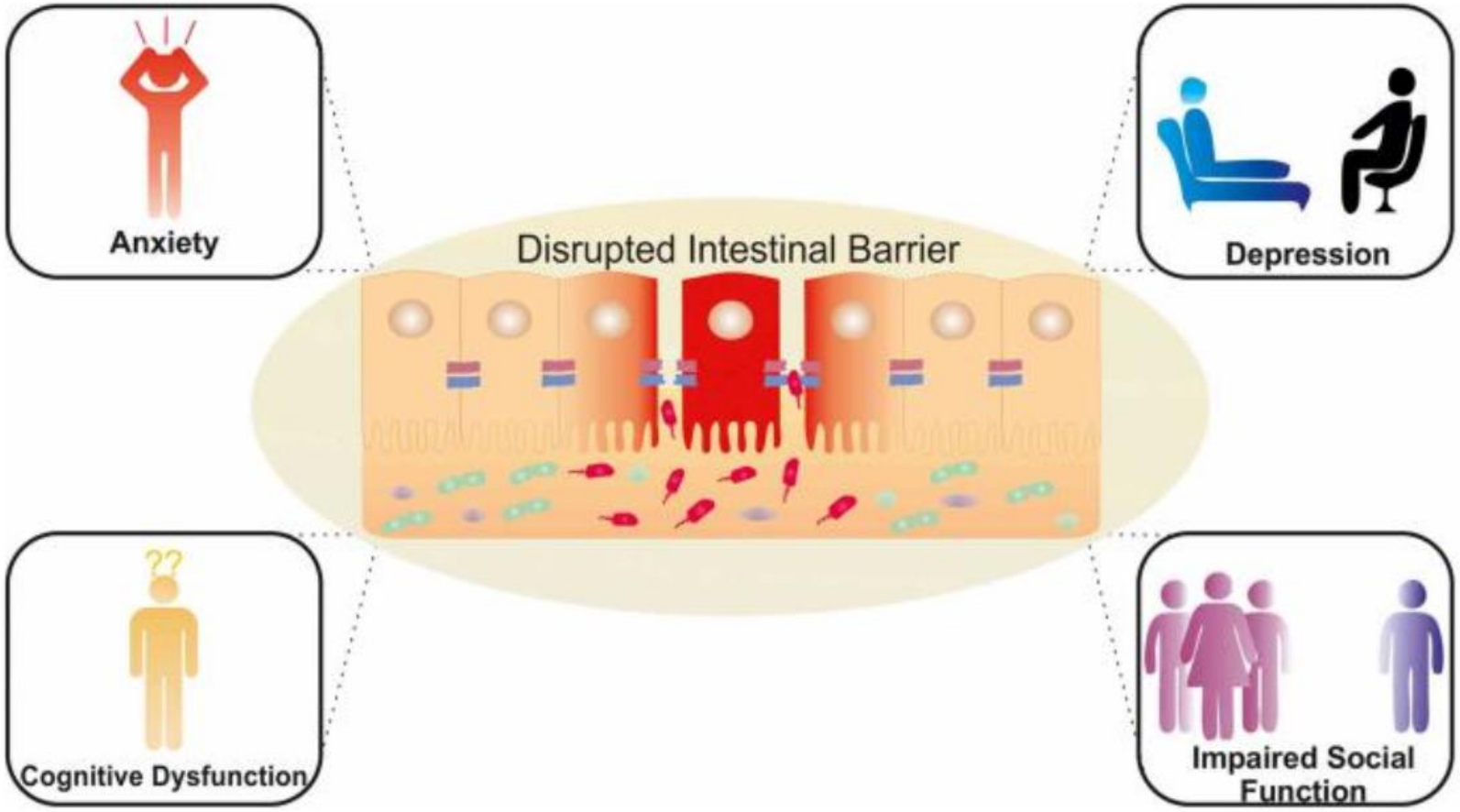


(Needham et al., 2020)

Microbiota Gut Brain Axis



Intestinal barrier and neuropsychiatric diseases



| Potential neuropsychiatric consequences of a dysregulated intestinal barrier. Activation of brain-gut-microbiota Axis signaling pathways via a compromised intestinal barrier with potential effects on mood, anxiety, cognition and social interaction.

(Kelly et al. 2015)

Microbiota Development

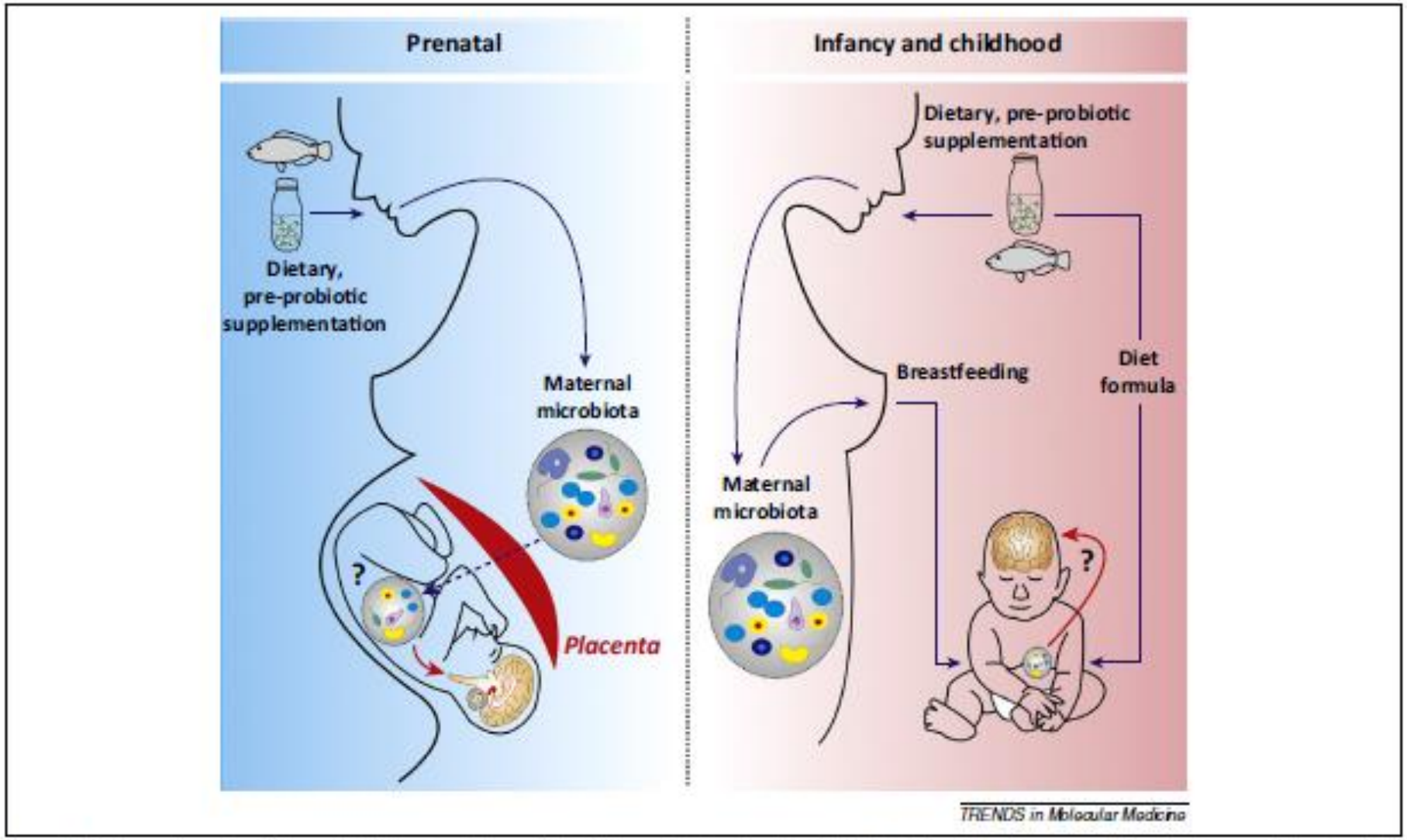


Figure 3. Windows of opportunity to modulate the microbiome of the infant prenatally and postnatally. Microbiota–gut–brain communication during prenatal and postnatal development is shown. Although still controversial, some evidence suggests that the microbiota of the infant before birth is not sterile, but may be influenced by the maternal immune state and nutrition. Prenatal and postnatal development undergoes vigorous neurodevelopmental phases and it is possible that it may be indirectly influenced by the fetal microbial population (via microbiota of the mother). This opens avenues for the development of novel dietary and microbe-modulating therapies, which may directly and indirectly alter the composition of the microbiota and neurodevelopment of the infant.

Microbiota Development

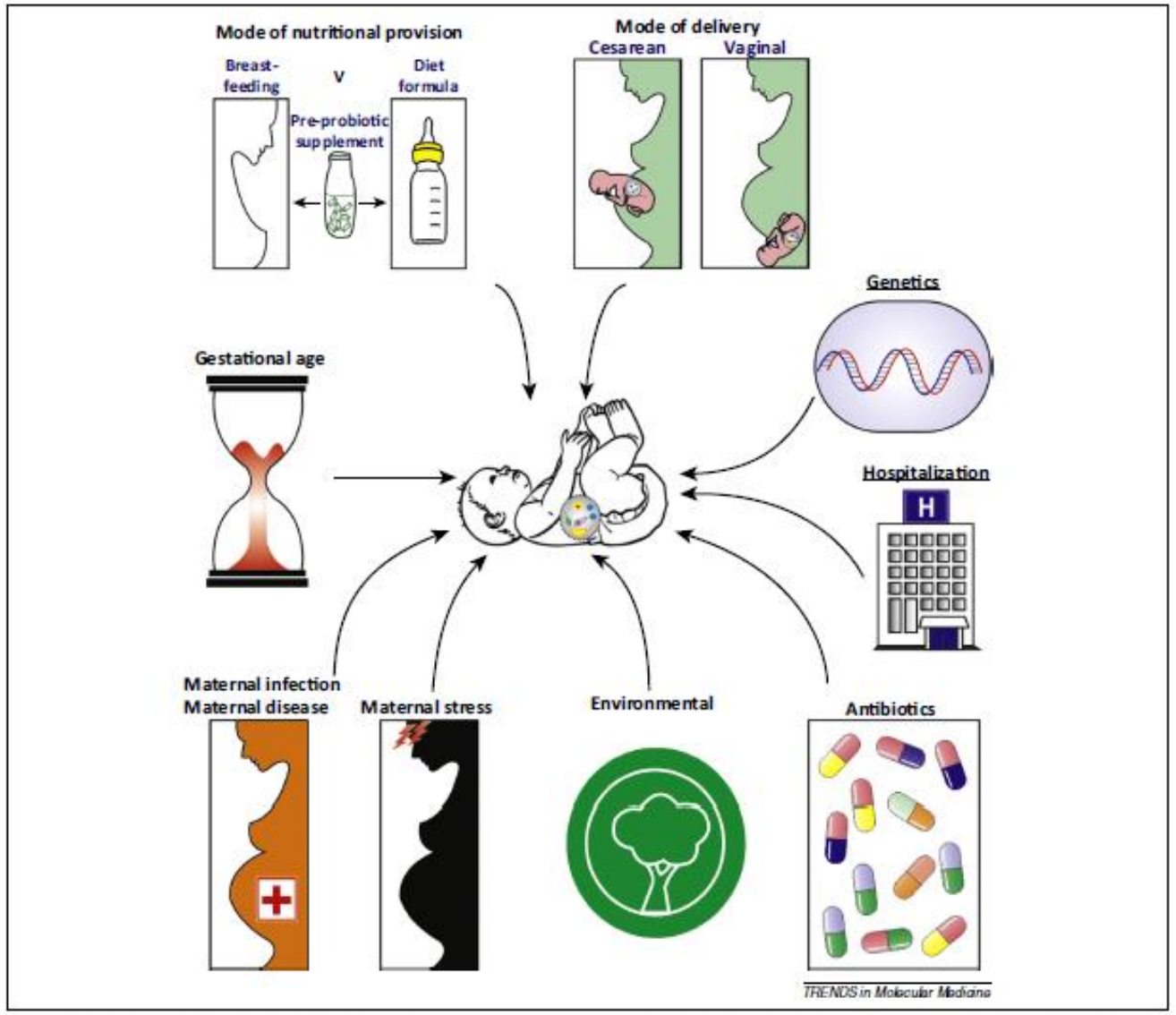
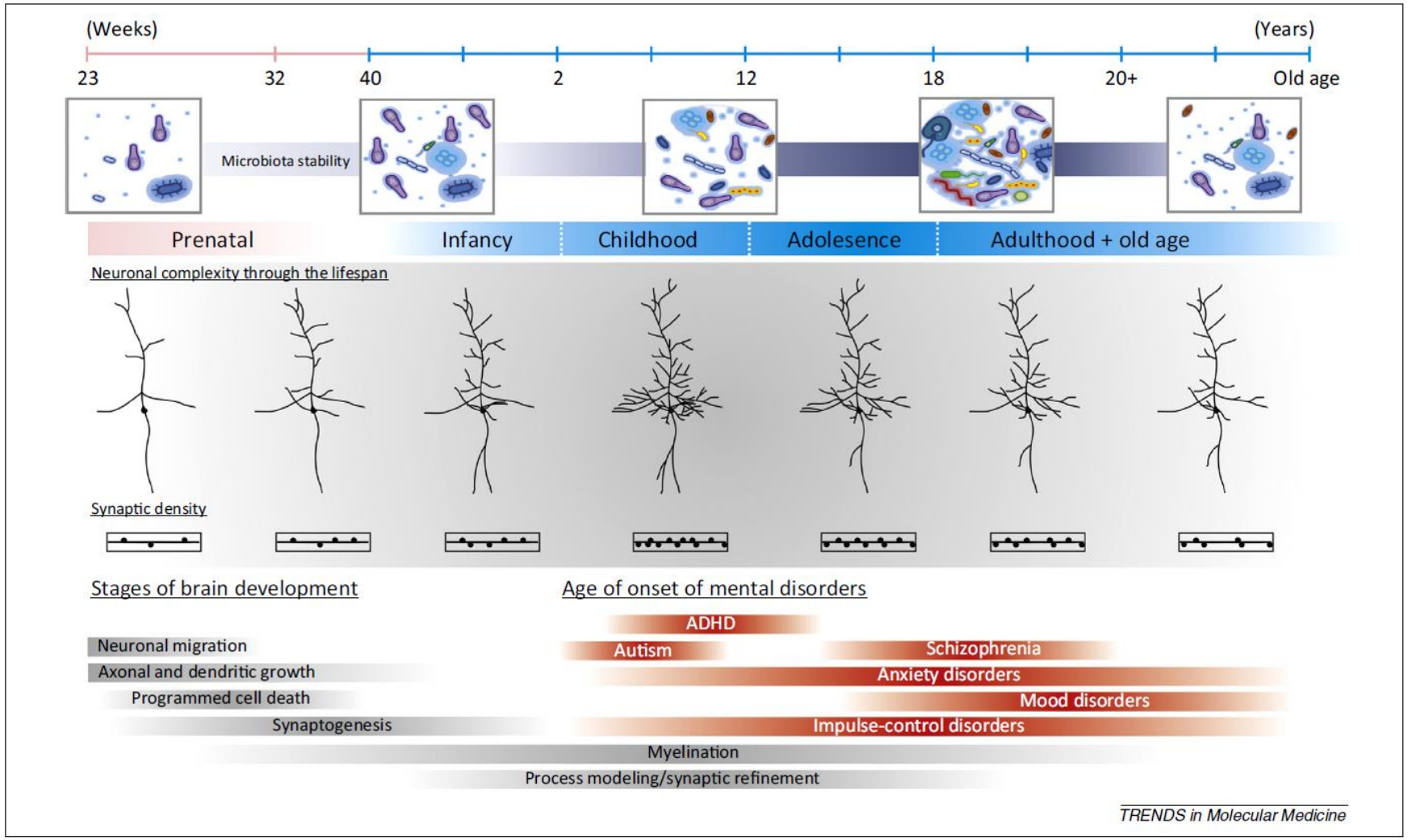


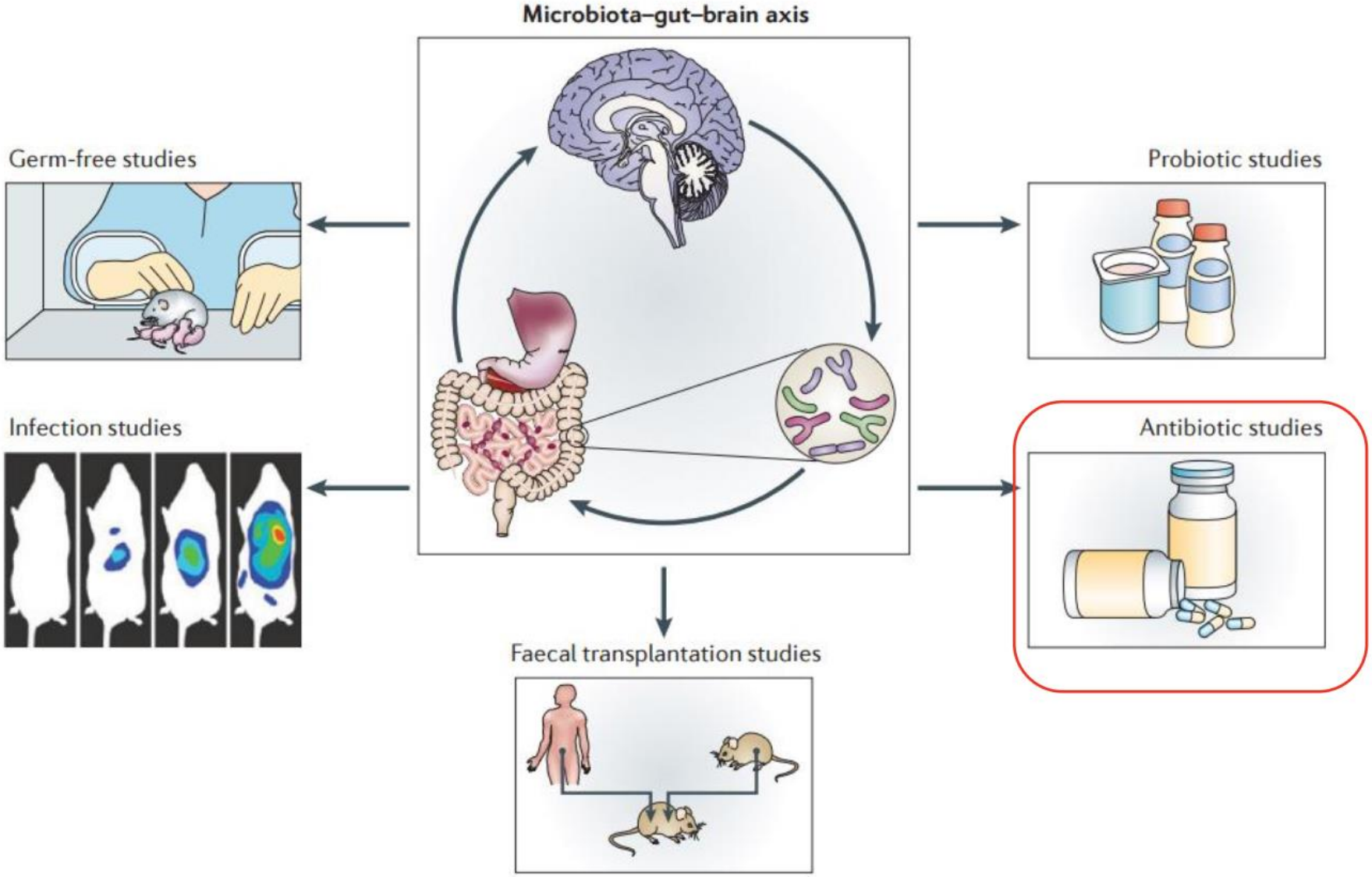
Figure 4. Factors influencing the development of the infant microbiota. Several factors play a role in shaping of the bacterial landscape in the development of the infant microbiota. In addition to mode of birth, mode of early nutrition, environment, other factors such as gestational age, genetics, and hospitalization, also influence the microbial composition of the infant. Infections (both maternal and infant) and antibiotic usage influence the trajectory of the developing microbiota as does the selective transient enrichment by probiotics and prebiotics. Taken together, such a plethora of factors with the ability to modulate the microbiota development suggest the importance of environmental influence superimposed over genetics in the establishment of a core microbiome.

Microbiota And Brain Development



Childhood and adolescence are critical developmental windows sensitive to damage. Disruptions of dynamic microbiota increase the risk of (or lead to) neurodevelopmental disorders.

Strategies used to investigate the role of the MGB axis in health and disease.



(Cryan & Dinan 2012)

Review

Gut–brain axis: how the microbiome influences anxiety and depression

The Journal of Neuroscience, July 29, 2015 • 35(30):10821–10830 • 10821

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Neurobiology of Disease

Probiotics Improve Inflammation-Associated Sickness Behavior by Altering Communication between the Peripheral Immune System and the Brain

Charlotte D'Mello,[1] Natalie Ronaghan,[2] Raza Zaheer,[2] Michael Dicay,[2] Tai Le,[1] Wallace K. MacNaughton,[2] Michael G. Surrette,[3] and Mark G. Swain[1]

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Institutet, 171 76 Stockholm, Sweden

Edited by Arturo Zychlinsky, Max Planck Institute fc
review August 11, 2010)

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Brain, Behavior, and Immunity

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

Altered gut microbiota and activity in a murine model of autism spectrum disorders

Caroline G.M. de Theije [b,1], Harm Wopereis [a,c,1], Mohamed Ramadan [a,b], Tiemen van Eijndthoven [a], Jolanda Lambert [a], Jan Knol [a,c], Johan Garssen [a,b], Aletta D. Kraneveld [b], Raish Oozeer [a,*]

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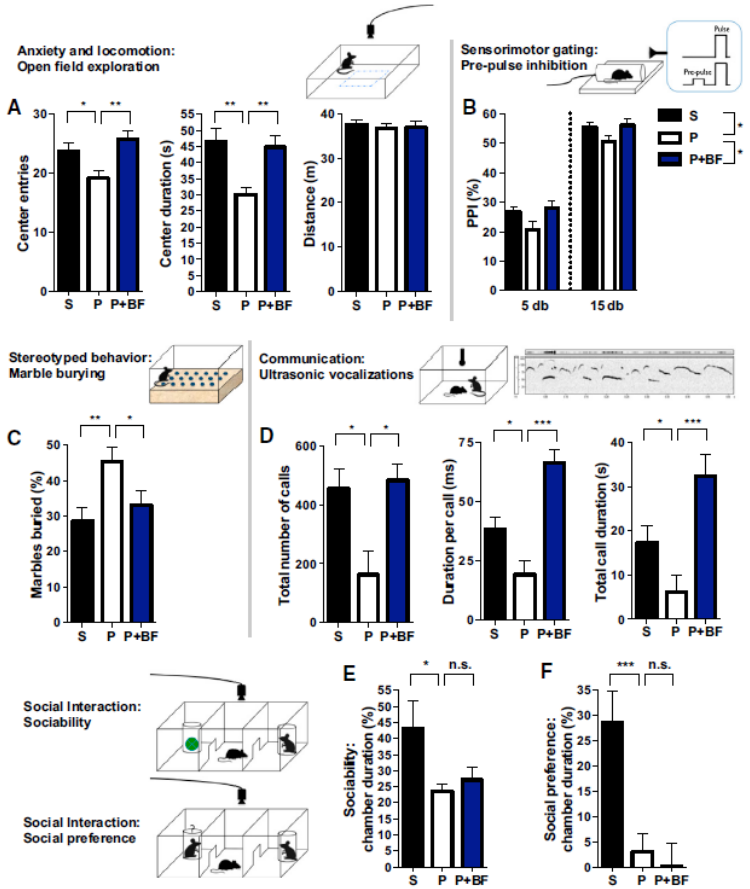
[c] Laboratory of Microbiology, Wageningen University, Wageningen, The Netherlands

Microbiota And Neurodevelopmental Disorders

B. fragilis Treatment Corrects ASD-Related Behavioral Abnormalities



Cell

Microbiota Modulate Behavioral and Physiological Abnormalities Associated with Neurodevelopmental Disorders

Elaine Y. Hsiao,[1,2,*] Sara W. McBride,[1] Sophia Hsien,[1] Gil Sharon,[1] Embriette R. Hyde,[3] Tyler McCue,[3] Julian A. Codelli,[2] Janet Chow,[1] Sarah E. Reisman,[2] Joseph F. Petrosino,[3] Paul H. Patterson,[1,4,*] and Sarkis K. Mazmanian[1,4,*]
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[4]These authors contributed equally to this work
*Correspondence: ehsiao@caltech.edu (E.Y.H.), php@caltech.edu (P.H.P.), sarkis@caltech.edu (S.K.M.)
http://dx.doi.org/10.1016/j.cell.2013.11.024

Microbiota And Neurodevelopmental Disorders

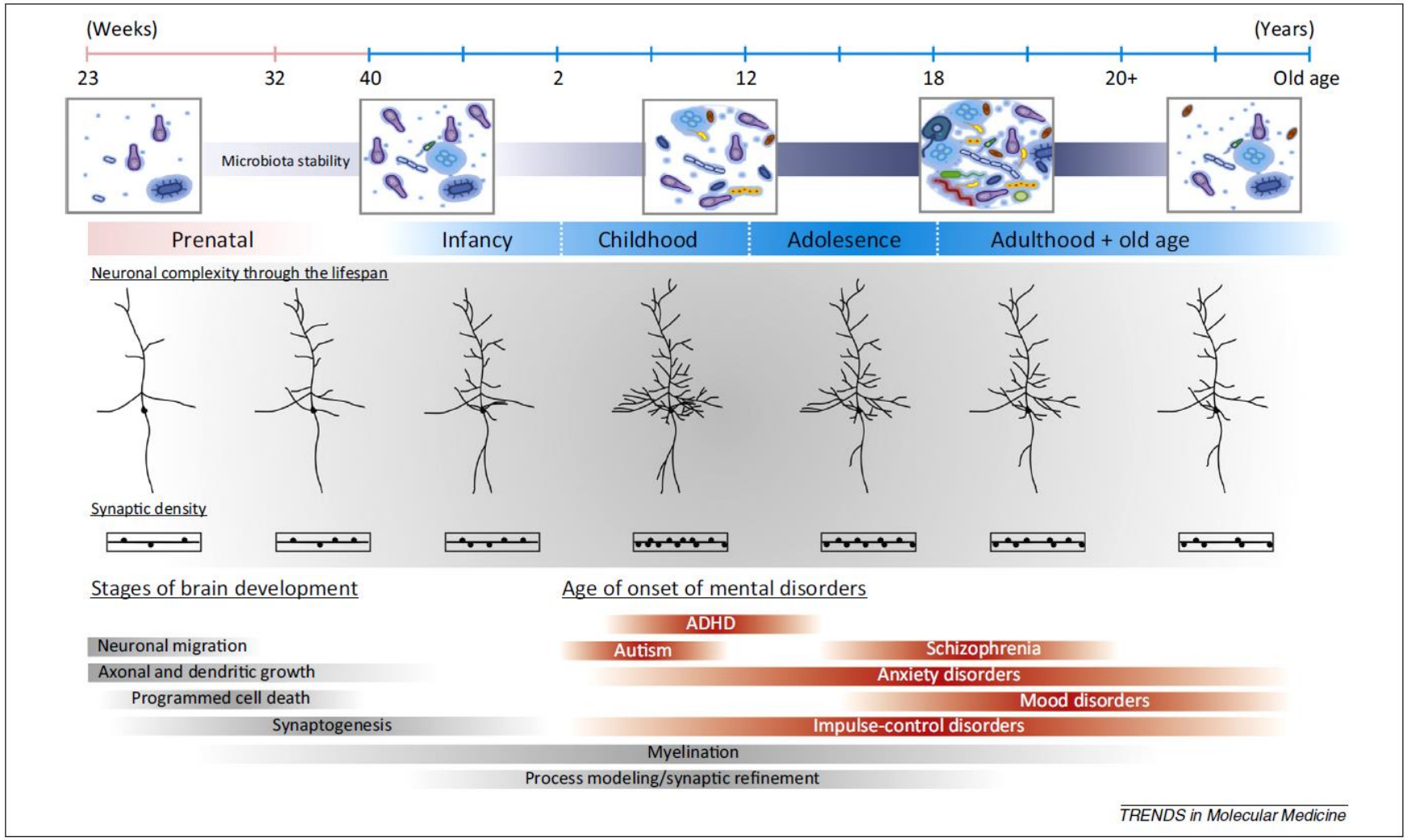
Both clinical and preclinical studies

Important role for the gut microbiota in the pathogenesis of ASDs,
novel therapeutic strategies in managing neurodevelopmental disorders via microbiome-based treatment.

Bacteroides fragilis given in early adolescence has been shown to ameliorate some, but not all, of the behavioral dysfunctions

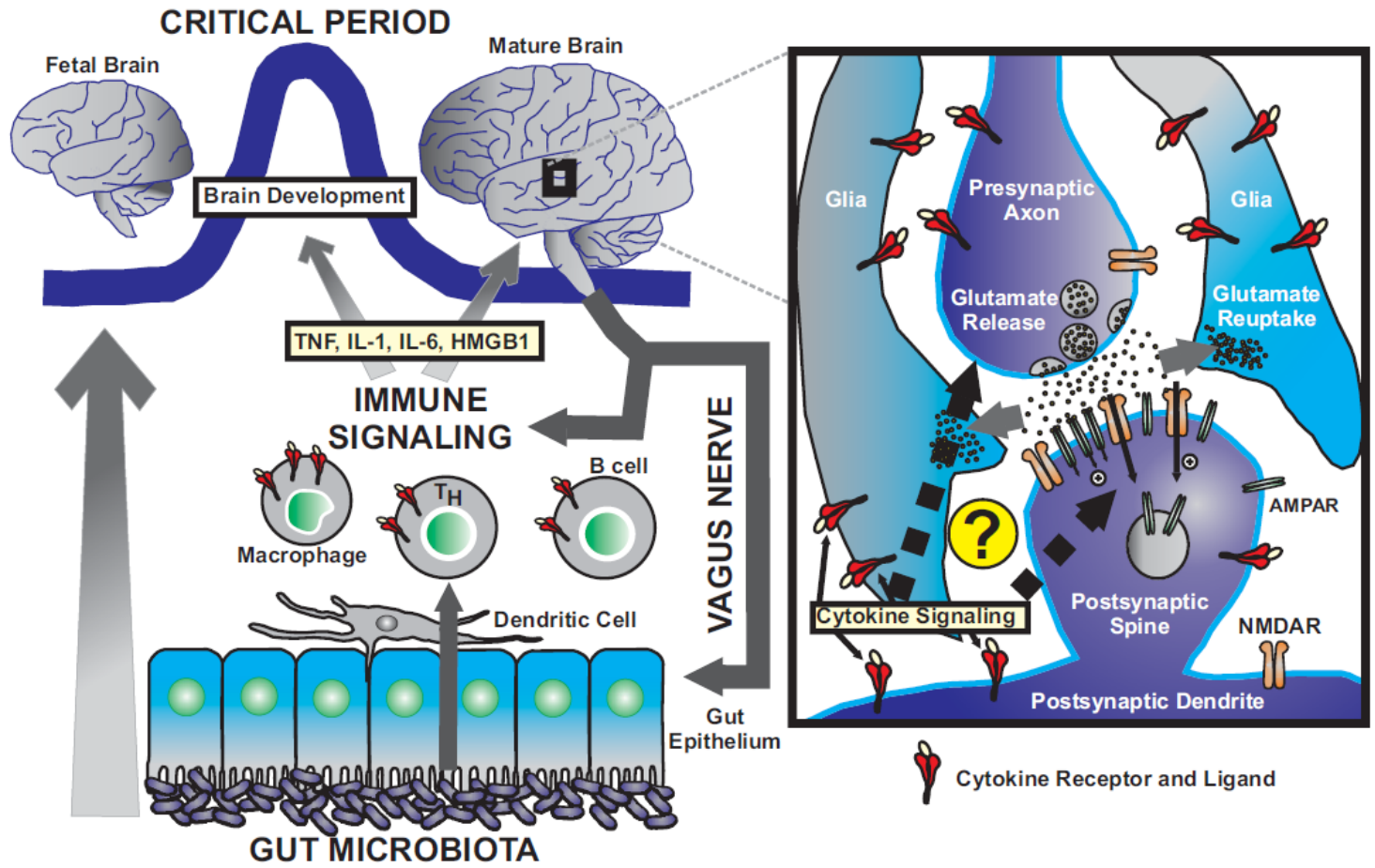
The gut microbiota may be modified in throughout life and possibly pregnancy.
Early preweaning and adolescence periods appear to be critical periods for modifying enteric microbiota with the potential to prevent the development of abnormal behaviors.
Consequently, it is becoming clear that understanding the early interaction between the intestinal microbiota and the host opens novel avenues for nutritional/therapeutic interventions in at-risk populations, particularly for infants and young children.

Microbiota And Brain Development



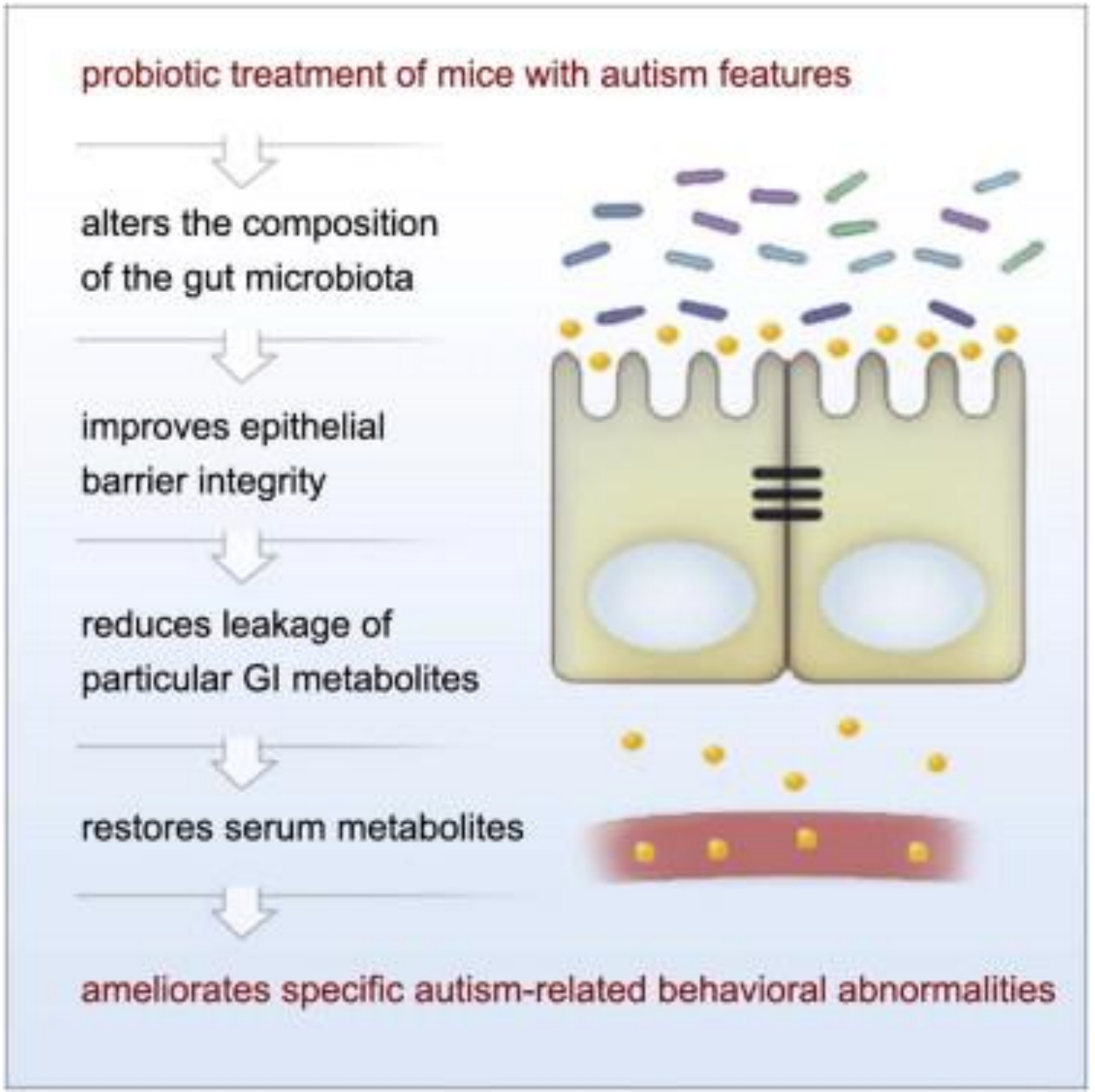
Childhood and adolescence are critical developmental windows sensitive to damage. Disruptions of dynamic microbiota increase the risk of (or lead to) neurodevelopmental disorders.

Microbiota And Neurodevelopmental Disorders: Critical period



there is a ‘‘critical period’’ that is a developmental window during which the gut flora can influence the developing brain.

Microbiota And Neurodevelopmental Disorders



Microbiota And Neurodevelopmental Disorders

Cell

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[4]These authors contributed equally to this work
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http://dx.doi.org/10.1016/j.cell.2013.11.024

Animals and MIA

Pregnant C57BL/6N mice (Charles River; Wilmington, MA) were injected i.p. on E12.5 with saline or 20 mg/kg poly(I:C) according to methods described in Smith et al. (2007). All animal experiments were approved by the Caltech IACUC.

B. fragilis Treatment

Mice were selected at random for treatment with *B. fragilis* NCTC 9343 or vehicle, every other day for 6 days at weaning. 10^{10} CFU of freshly grown *B. fragilis*, or vehicle, in 1.5% sodium bicarbonate was administered in sugar-free applesauce over standard food pellets. The same procedure was used for mutant *B. fragilis* PSA and *B. thetaiotaomicron*.

Offspring of Immune-Activated Mothers Exhibit GI Symptoms of Human ASD

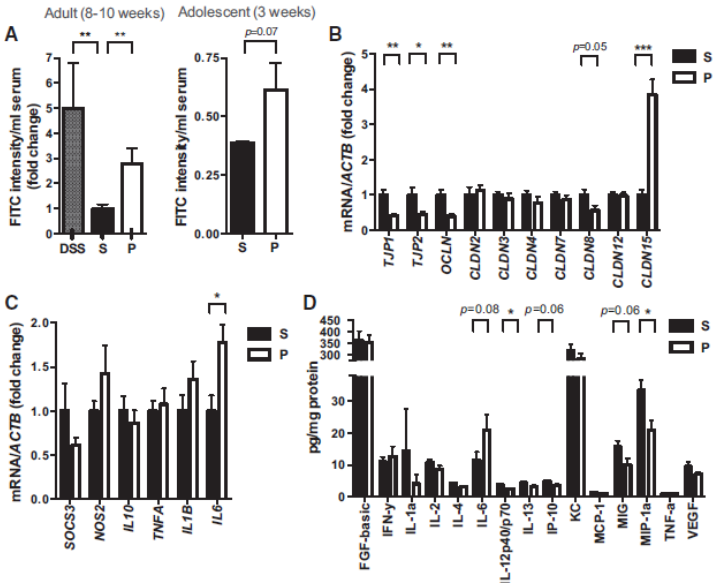


Figure 1. MIA Offspring Exhibit GI Barrier Defects and Abnormal Expression of Tight Junction Components and Cytokines

(A) Intestinal permeability assay, measuring FITC intensity in serum after oral gavage of FITC-dextran. Dextran sodium sulfate (DSS): n = 6, S (saline+vehicle): adult n = 16; adolescent n = 4, P (poly(I:C)+vehicle): adult n = 17; adolescent n = 4. Data are normalized to saline controls.

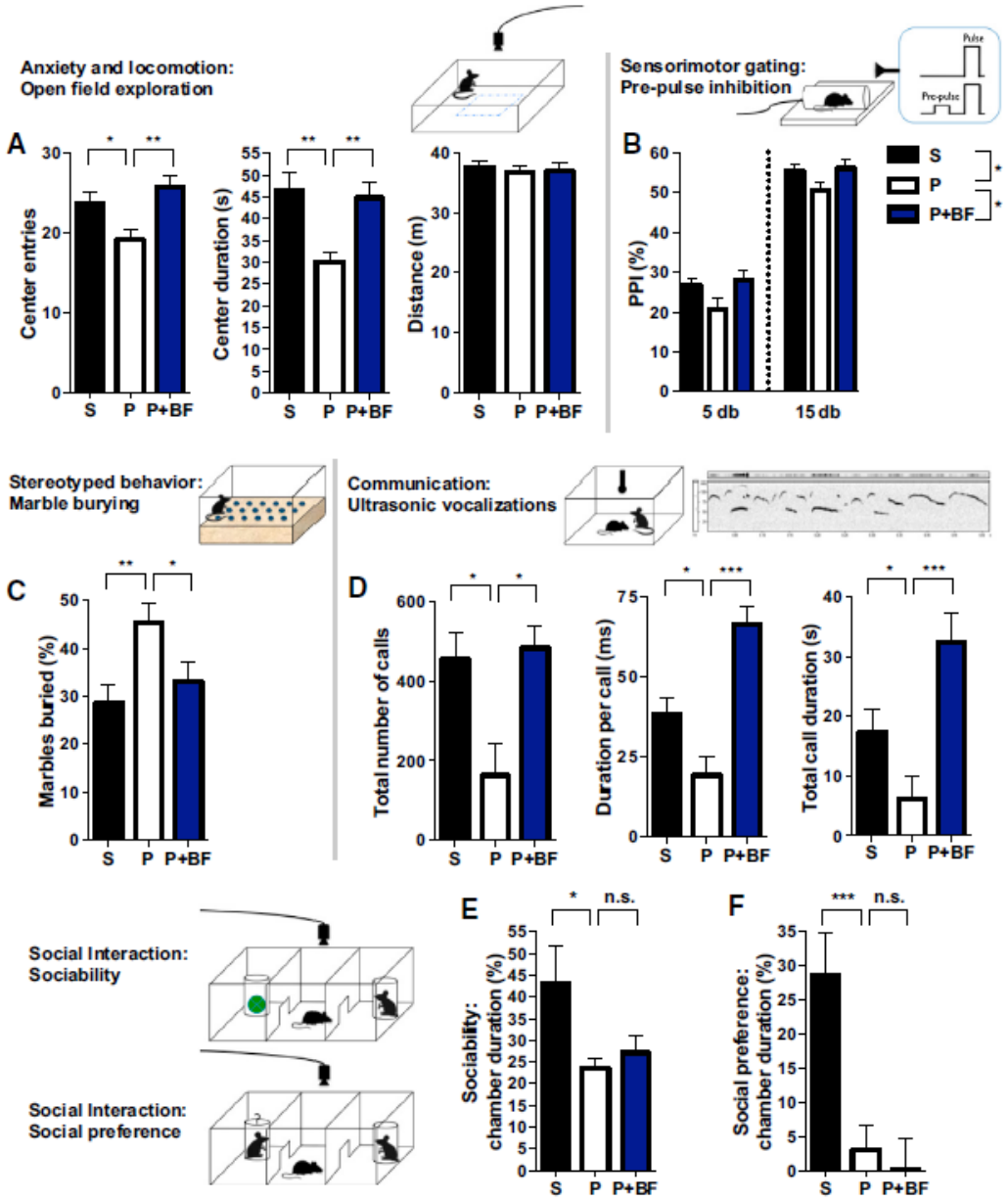
(B) Colon expression of tight junction components relative to β-actin. Data for each gene are normalized to saline controls. n = 8/group.

(C) Colon expression of cytokines and inflammatory markers relative to β-actin. Data for each gene are normalized to saline controls. n = 6–21/group.

(D) Colon protein levels of cytokines and chemokines relative to total protein content. n = 10/group.

For each experiment, data were collected simultaneously for poly(I:C)+*B. fragilis* treatment group (See Figure 3). See also Figure S1.

Microbiota And Neurodevelopmental Disorders



B. fragilis Treatment Corrects ASD-Related Behavioral Abnormalities

Figure 5. *B. fragilis* Treatment Ameliorates Autism-Related Behavioral Abnormalities in MIA Offspring

(A) Anxiety-like and locomotor behavior in the open field exploration assay. n = 35–75/group.

(B) Sensorimotor gating in the PPI assay. n = 35–75/group.

(C) Repetitive marble burying assay. n = 16–45/group.

(D) Ultrasonic vocalizations produced by adult male mice during social encounter. n = 10/group.

S = saline+vehicle, p = poly(I:C)+vehicle, P+BF = poly(I:C)+*B. fragilis*. Data were collected simultaneously for poly(I:C)+*B. fragilis* ΔPSA and poly(I:C)+*B. thetaiotaomicron* treatment groups (See also Figures S3 and S4).

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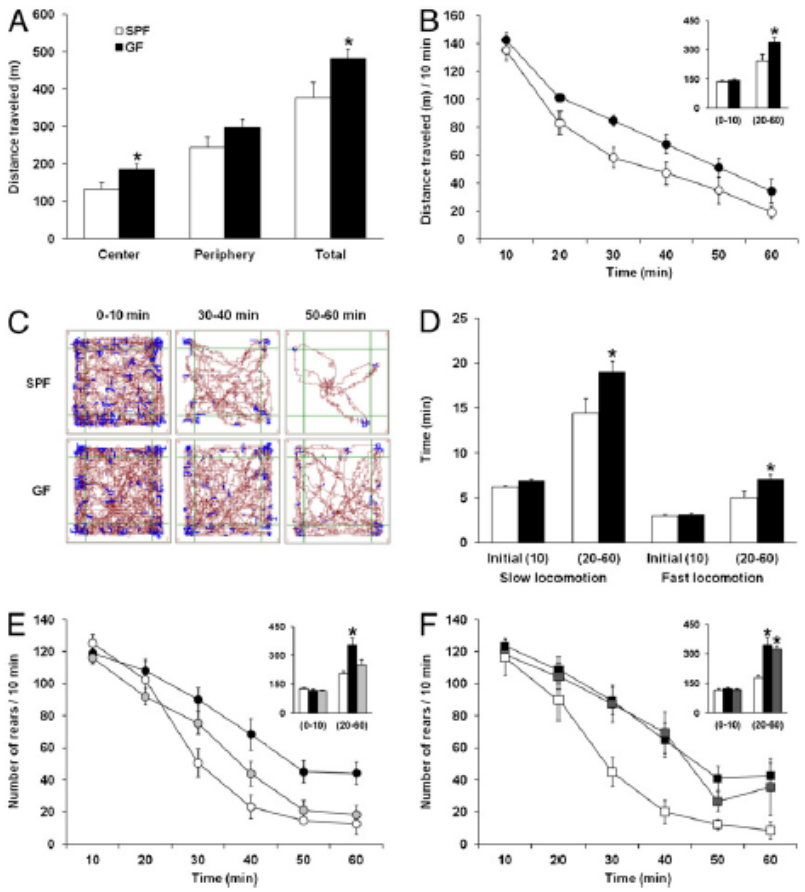

Fig. 1. GF mice display increased spontaneous motor activity. (*A*) Bars show cumulative distance traveled (meters) per zone and in the entire box (total) during the 60-min open field test session by SPF (open bars) and GF (filled bars) mice. (*B*) Average distance traveled (meters) measured in 10-min time bins across a 60-min session in an open field box. (*Inset*) Bars show cumulative distance traveled (meters) during the initial 10 min and the 20- to 60-min time interval of open field testing. (*C*) Representative tracks of movement patterns of SPF and GF mice at the 0–10, 30–40, and 50–60 min time intervals of the 60-min open field test session; distance traveled and rearing activity is shown in dark red and blue colors, respectively. (*D*) The time that SPF and GF mice spent in slow (>5 cm/s) or fast (>20 cm/s) locomotion during the initial 10 min of testing and the 20–60 min time interval. (*E*) Rearing activity of SPF (white), GF (black), and conventionalized (CON; light gray) mice. Circles show the average number of rears measured in 10-min time bins across a 60-min session in an open field box. (*F*) Rearing activity of SPF, GF, and adult CON mice (dark gray); lines connecting cumulative data in *B*, *E*, and *F* were drawn for clarity only. All data (*A*, *B*, and *D*–*F*) are presented as means (± SEM; $n = 7$–14 per group). $^*P < 0.05$ compared with SPF mice.

PNAS

Normal gut microbiota modulates brain development and behavior

Rochellys Diaz Heijtz[a,b,1], Shugui Wang[c], Farhana Anuar[d], Yu Qian[a,b], Britta Björkholm[d], Annika Samuelsson[d], Martin L. Hibberd[c], Hans Forssberg[b,e], and Sven Pettersson[c,d,1]

Departments of [a]Neuroscience, and [d]Microbiology, Cell and Tumor Biology, Karolinska Institutet, 171 77 Stockholm, Sweden; [b]Stockholm Brain Institute, 171 77 Stockholm, Sweden; [c]Genome Institute of Singapore, 02-01 Genome 138672, Singapore; and [e]Department of Women's and Children's Health, Karolinska Institutet, 171 76 Stockholm, Sweden

Edited by Arturo Zychlinsky, Max Planck Institute for Infection Biology, Berlin, Germany, and accepted by the Editorial Board January 4, 2011 (received for review August 11, 2010)

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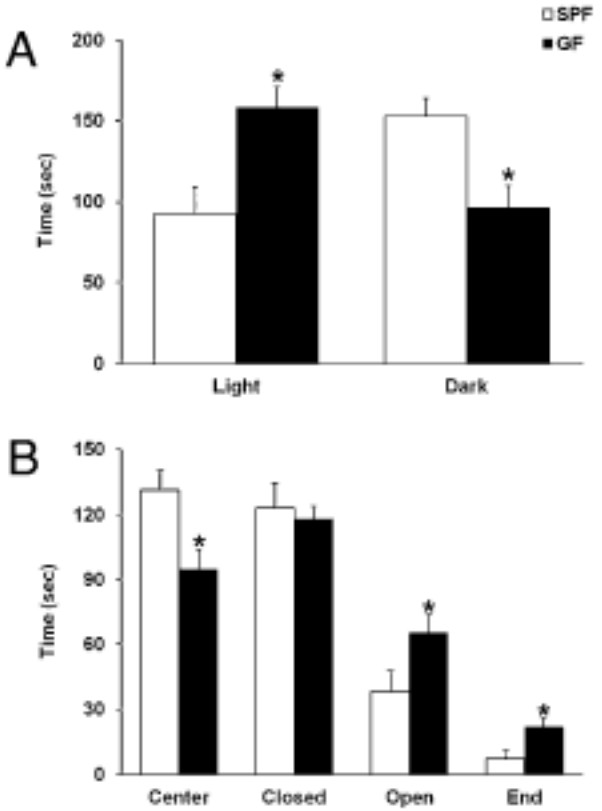

Fig. 2. GF mice display reduced anxiety-like behavior. (*A*) Bars show time (seconds) spent in the light and dark compartments during a 5-min light–dark box test by the SPF and GF mice. (*B*) Bars show time (seconds) spent in each area of the elevated plus maze by the SPF and GF mice during a 5-min test session. All data (*A* and *B*) are presented as means (±SEM; $n = 7–9$ per group). $*P < 0.05$ compared with SPF mice.

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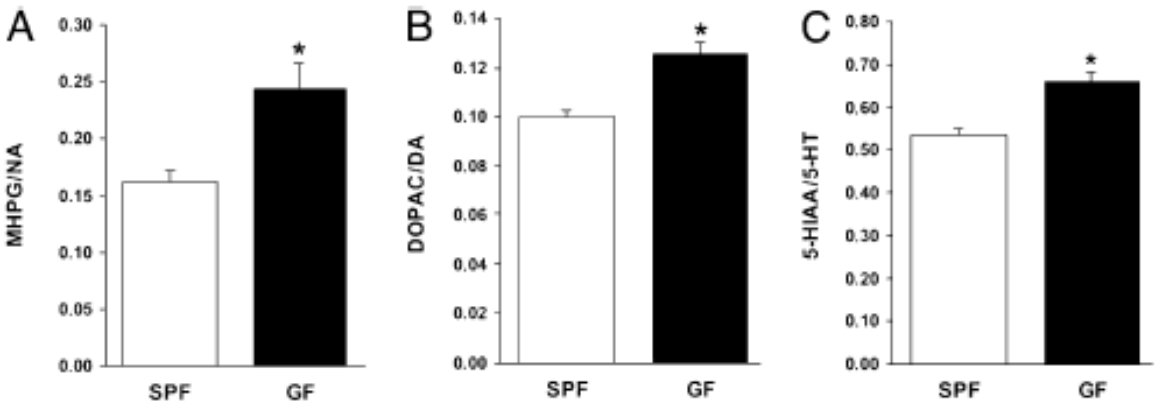

Fig. 3. GF mice show elevated NA, DA, and 5-HT turnover in the striatum. The histograms depict the mean ratios (± SEM; $n = 6$ per group) for MHPG/NA (*A*), DOPAC/DA (*B*), and 5-HIAA/5-HT (*C*) in the striatum of male GF and SPF mice. Asterisks denote where GF mice differ significantly ($P < 0.01$) from SPF mice.

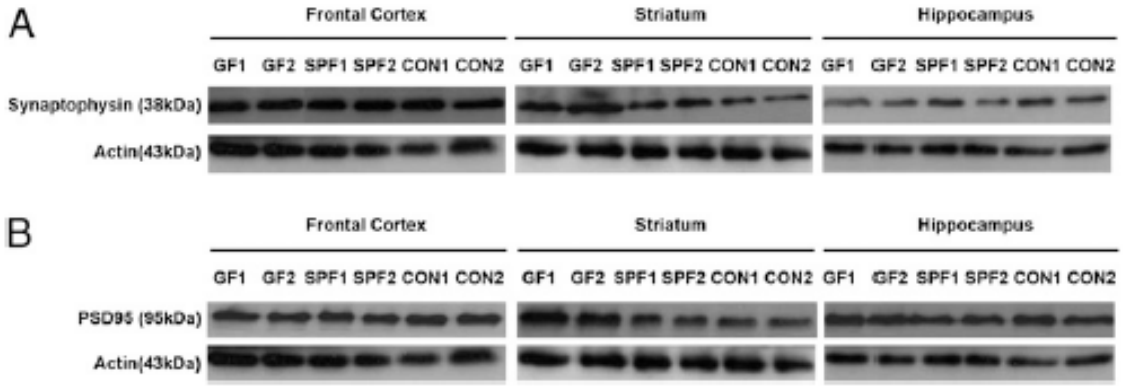

Fig. 6. GF mice show higher expression of synaptic-related proteins in the striatum compared with SPF mice. Representative Western blot films for synaptophysin (*A*) and PSD-95 (*B*) protein expression in the frontal cortex, striatum, and hippocampus of two male GF, SPF, and CON mice (for further details, see Table 1).

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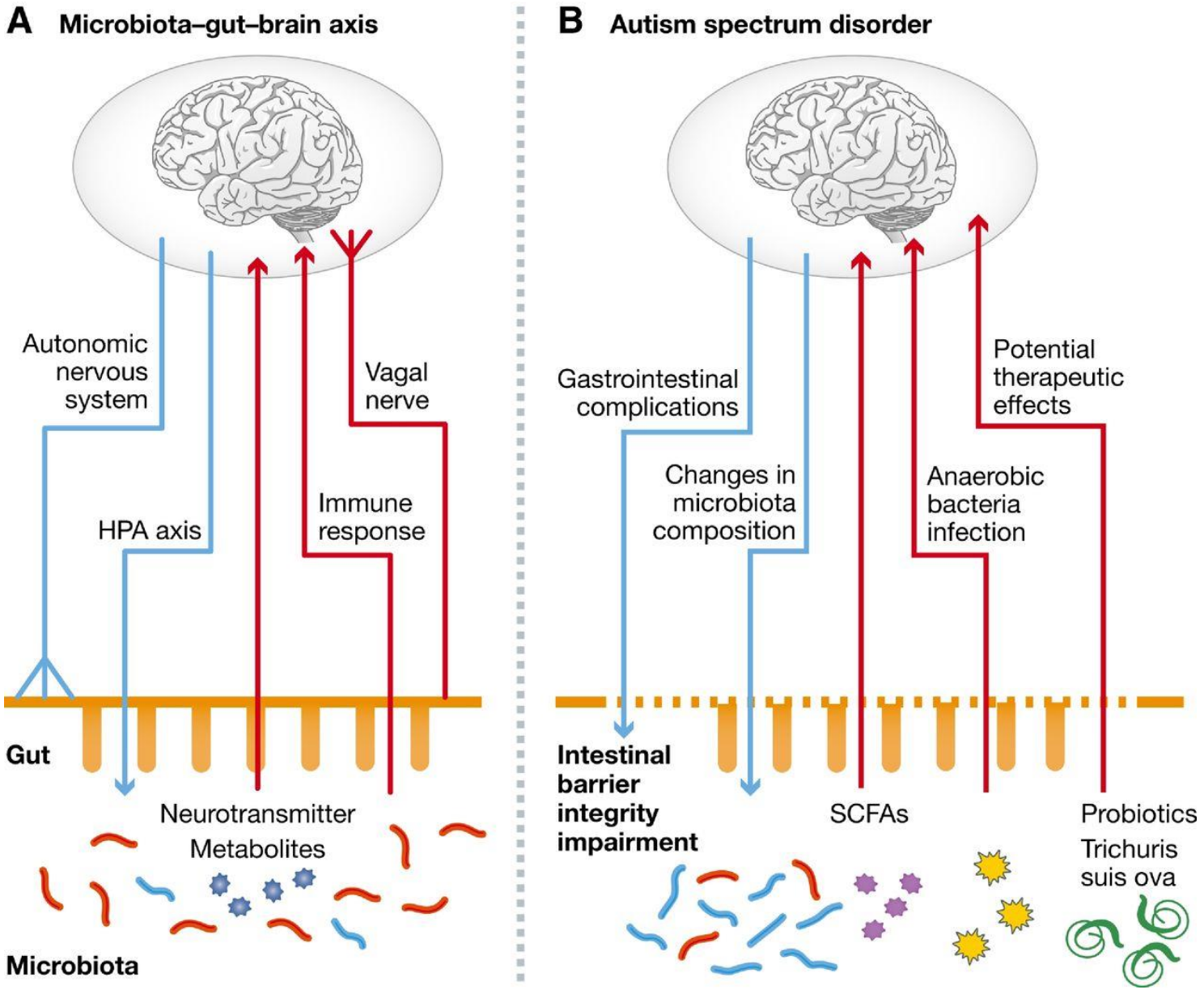

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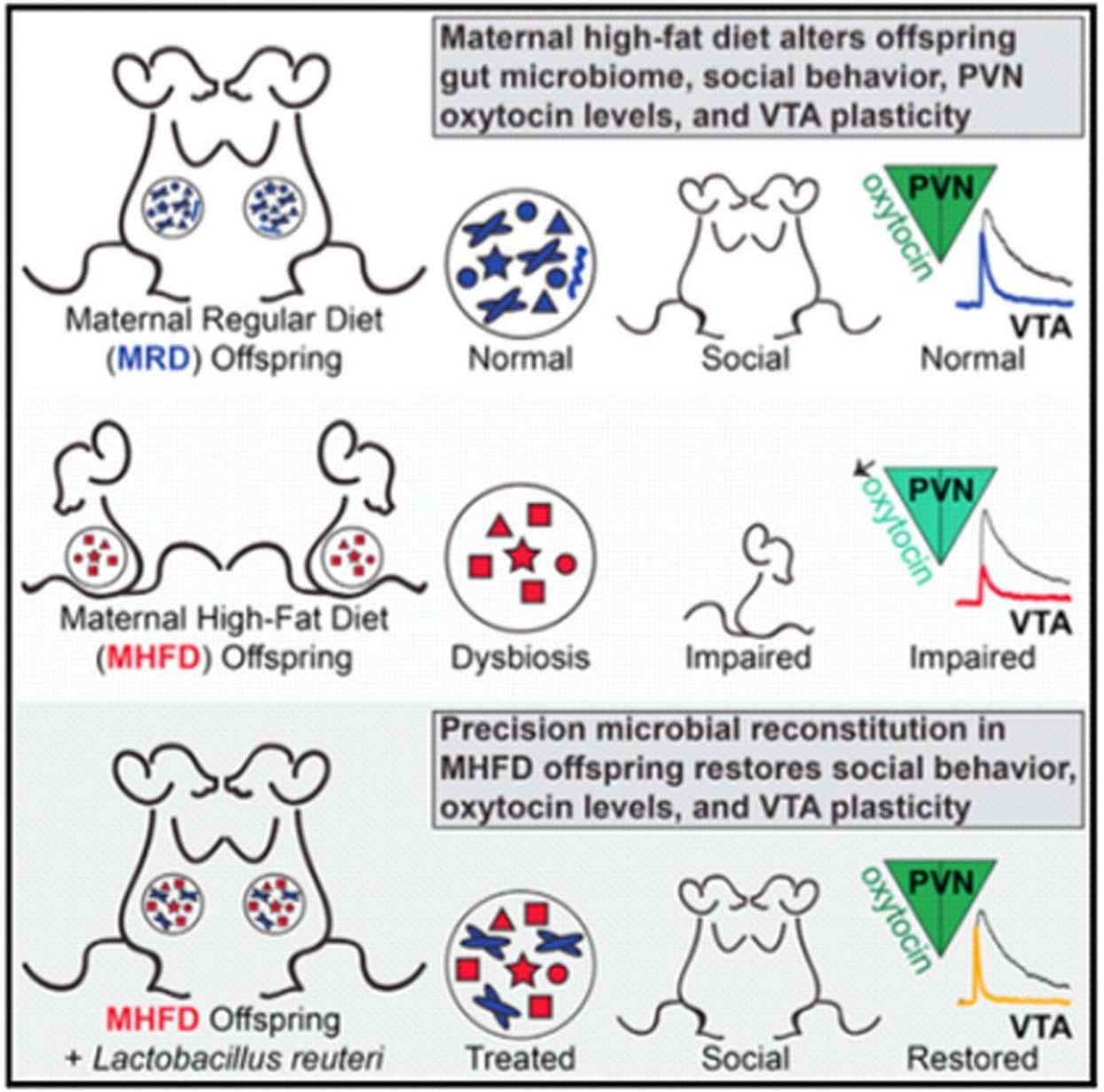
RESCUE?



CREDIT: BUFFINGTON ET AL./CELL 2016

Microbiota And Neurodevelopmental Disorders

Fig 6- www.deviantart.com

Schizophrenia

Fig 7-www.hindustanlink.com

- Lack of microbiota and elevated pro-inflammatory cytokines is seen in schizophrenic patients compared to controls. (Francesconi et al., 2011, and Song et al., 2013)

- Side effects associated with Schizophrenia such as metabolic syndrome and autoimmune disorders could be attributed to changes in microbiota. However no theories are proven.

Microbiota And Adult Neurogenesis

Correspondence

Biological Psychiatry

Adult Hippocampal Neurogenesis Is Regulated by the Microbiome

To the Editor:

Biological Psychiatry

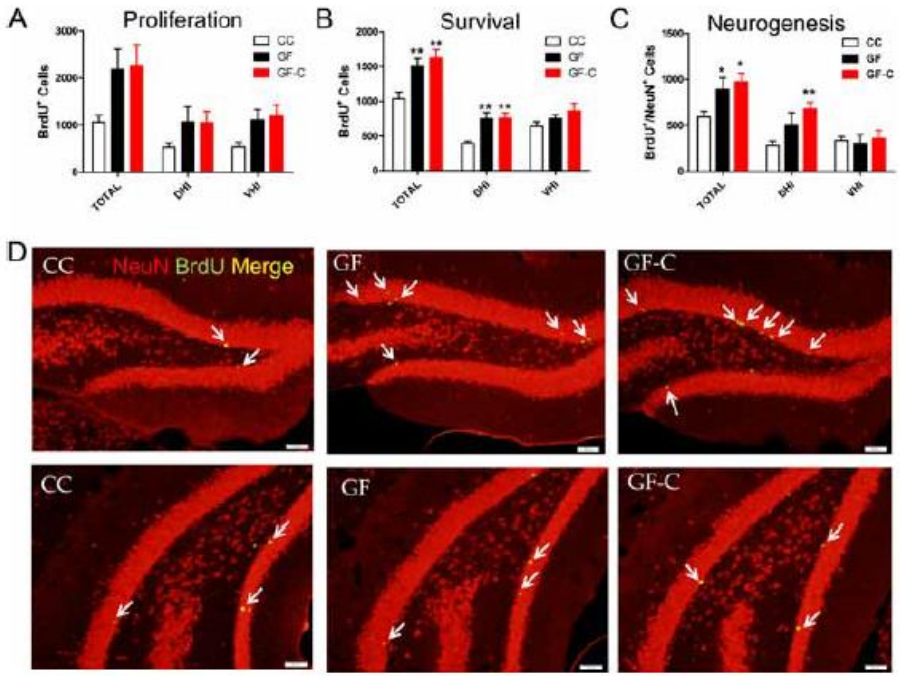
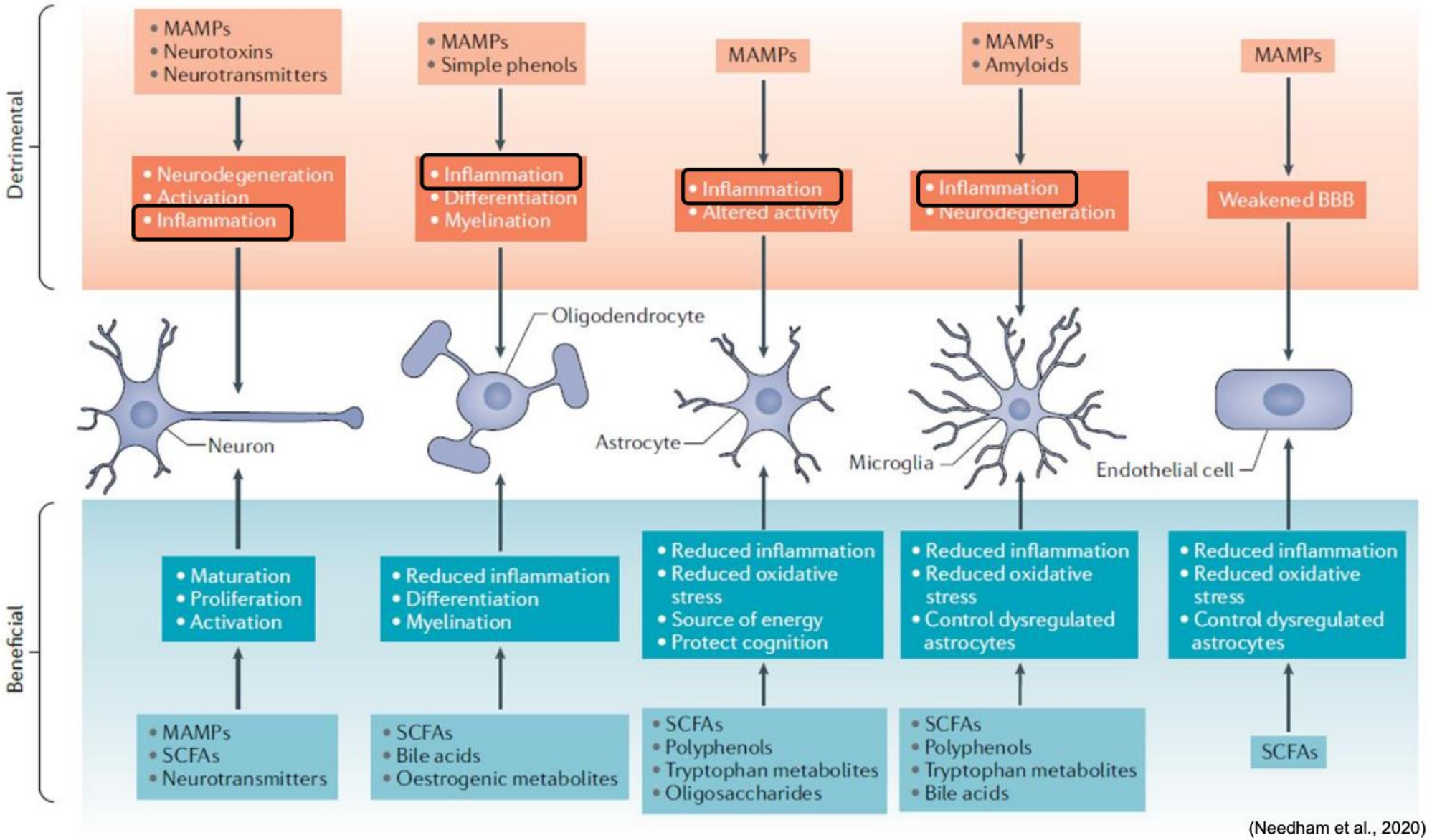


Figure 1. Germ-free mice exhibit increased adult hippocampal neurogenesis. Germ-free and germ-free–colonized mice exhibit a trend for increased cell proliferation as measured by bromodeoxyuridine immunohistochemistry **(A)**. The survival of newly born cells is significantly increased in the dorsal, but not ventral, hippocampus of germ-free and germ-free–colonized mice **(B)**. The survival of newly born neurons is increased in germ-free and germ-free–colonized mice **(C)**, and this effect occurs preferentially in the dorsal hippocampus **(C, D**—upper panels) and not the ventral hippocampus **(C, D**—lower panels). $^{*}p < .05$, $^{**}p < .01$ significantly different from conventionally colonized control mice. BrdU, bromodeoxyuridine; CC, conventionally colonized; DHI, dorsal hippocampus; GF, germ-free; GF-C, germ-free colonized; NeuN, neuronal nucleus; VHI, ventral hippocampus.

least significant difference post hoc test for group-wise comparisons.

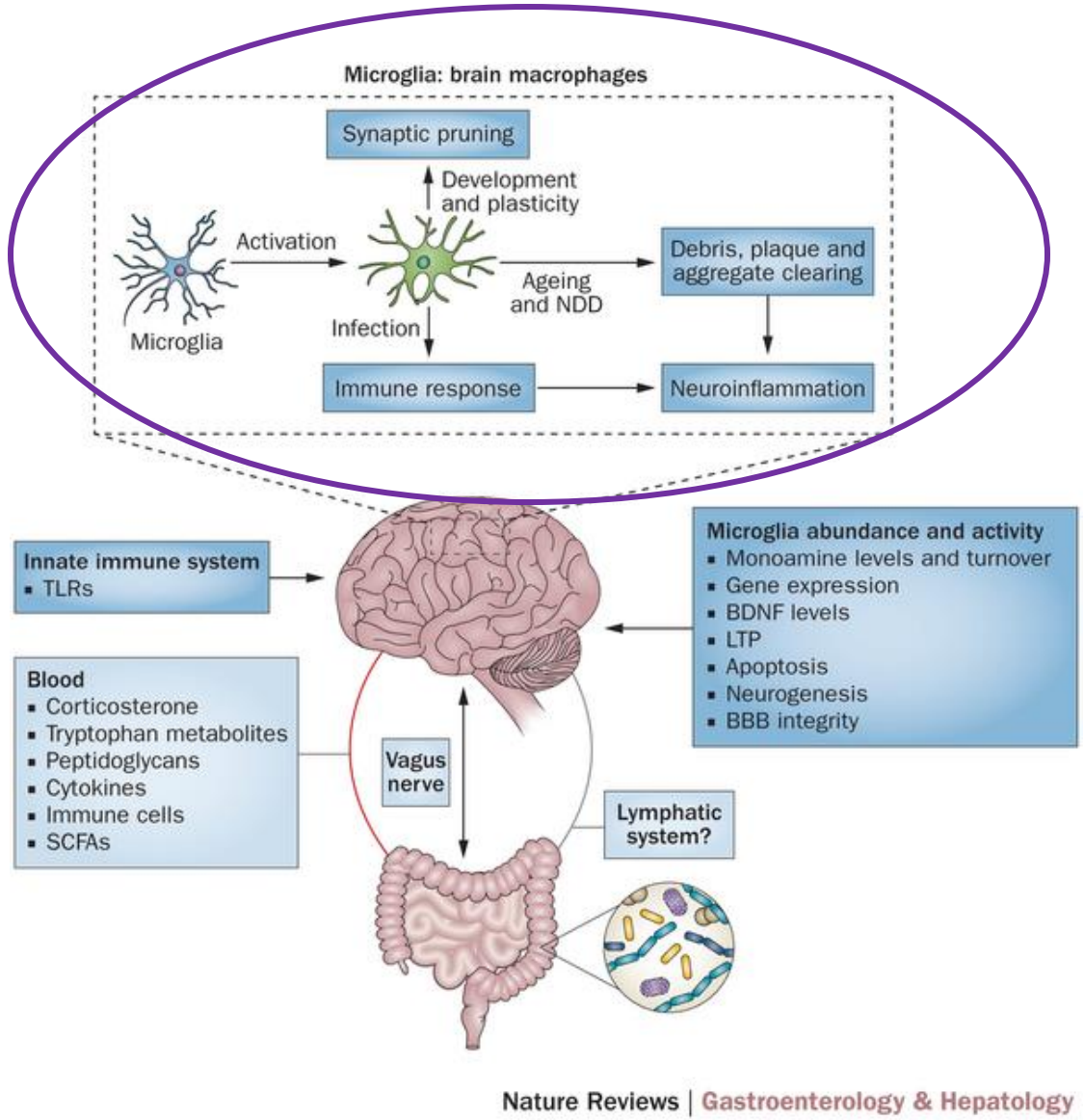
Across the total SGZ, cell proliferation (Figure 1A) was increased in GF and GF-C mice, although the effect did not

Microbiota Gut Brain Axis at cellular level



(Needham et al., 2020)

The Microglial Side Of The Microbiota–gut–brain Axis



The Microglial Side Of The Microbiota–gut–brain Axis

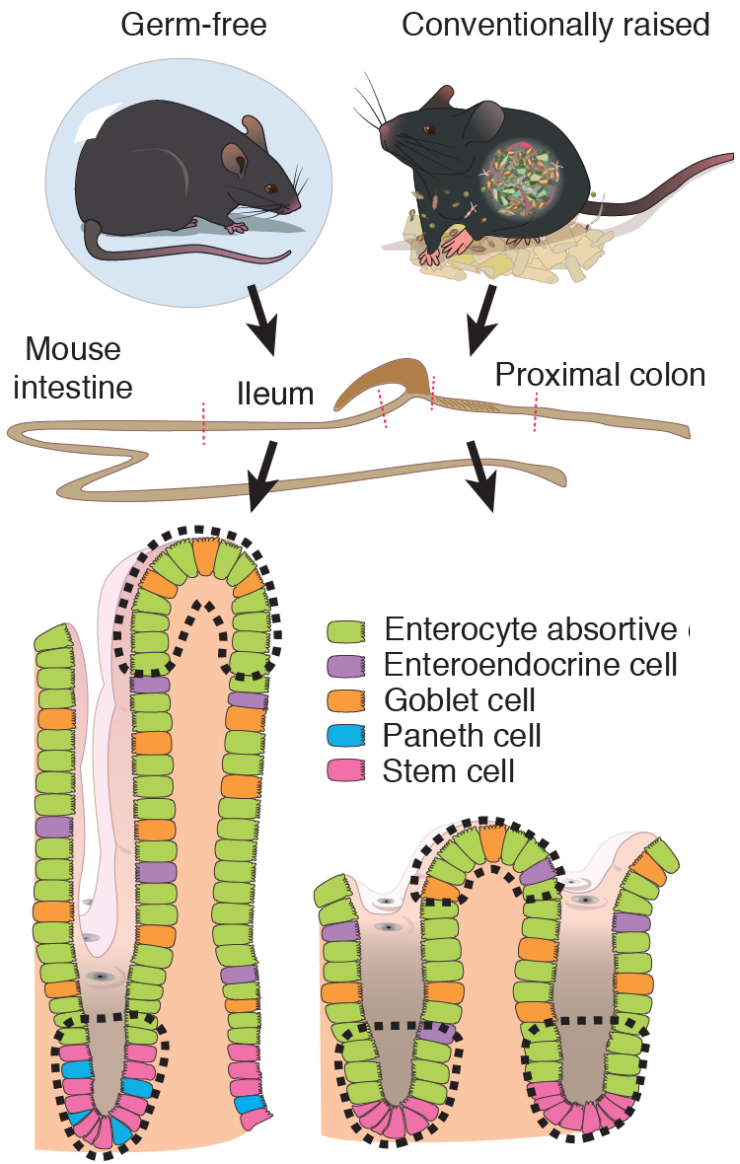
nature neuroscience

ARTICLES

Host microbiota constantly control maturation and function of microglia in the CNS

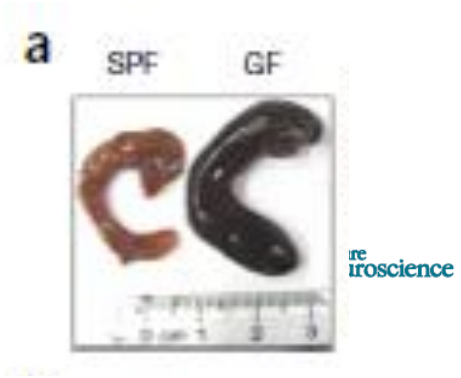
Daniel Erny[1,12], Anna Lena Hrabě de Angelis[1,12], Diego Jaitin[2], Peter Wieghofer[1,3], Ori Staszewski[1], Eyal David[2], Hadas Keren-Shaul[2], Tanel Mahlakoiv[4], Kristin Jakobshagen[5], Thorsten Buch[6], Vera Schwierzeck[7], Olaf Utermöhlen[5], Eunyoung Chun[8], Wendy S Garrett[8], Kathy D McCoy[9], Andreas Diefenbach[7], Peter Staeheli[4], Bärbel Stecher[10], Ido Amit[2] & Marco Prinz[1,11]

The Microglial Side Of The Microbiota–gut–brain Axis



GF animals display global defects in microglia:

- Increased expression of maturation and activation marker in GF microglia.
- M1- and M2-related genes were only marginally changed, whereas most differently regulated genes were found to localize in the M0 cluster, indicating that microglia steady-state condition was severely altered in the absence of microbiota.



ARTICLES

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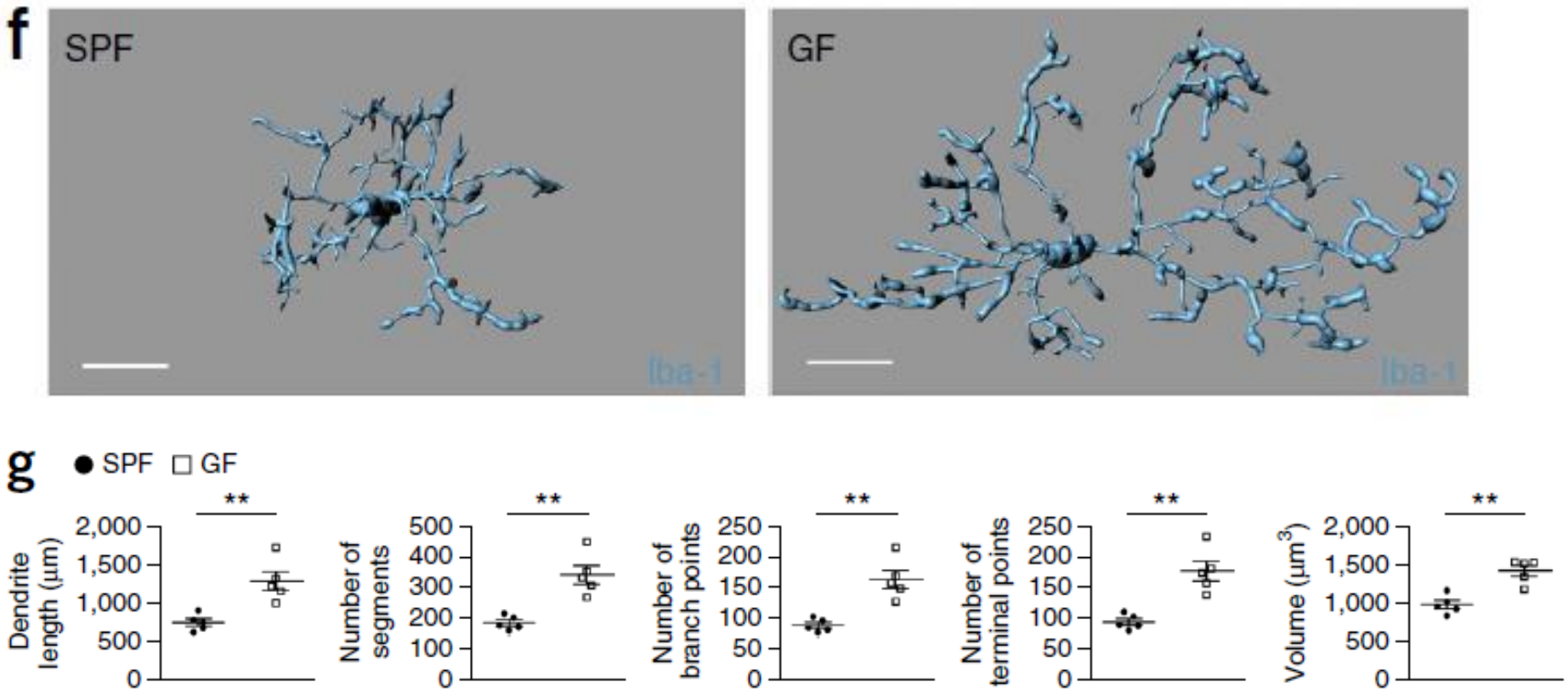
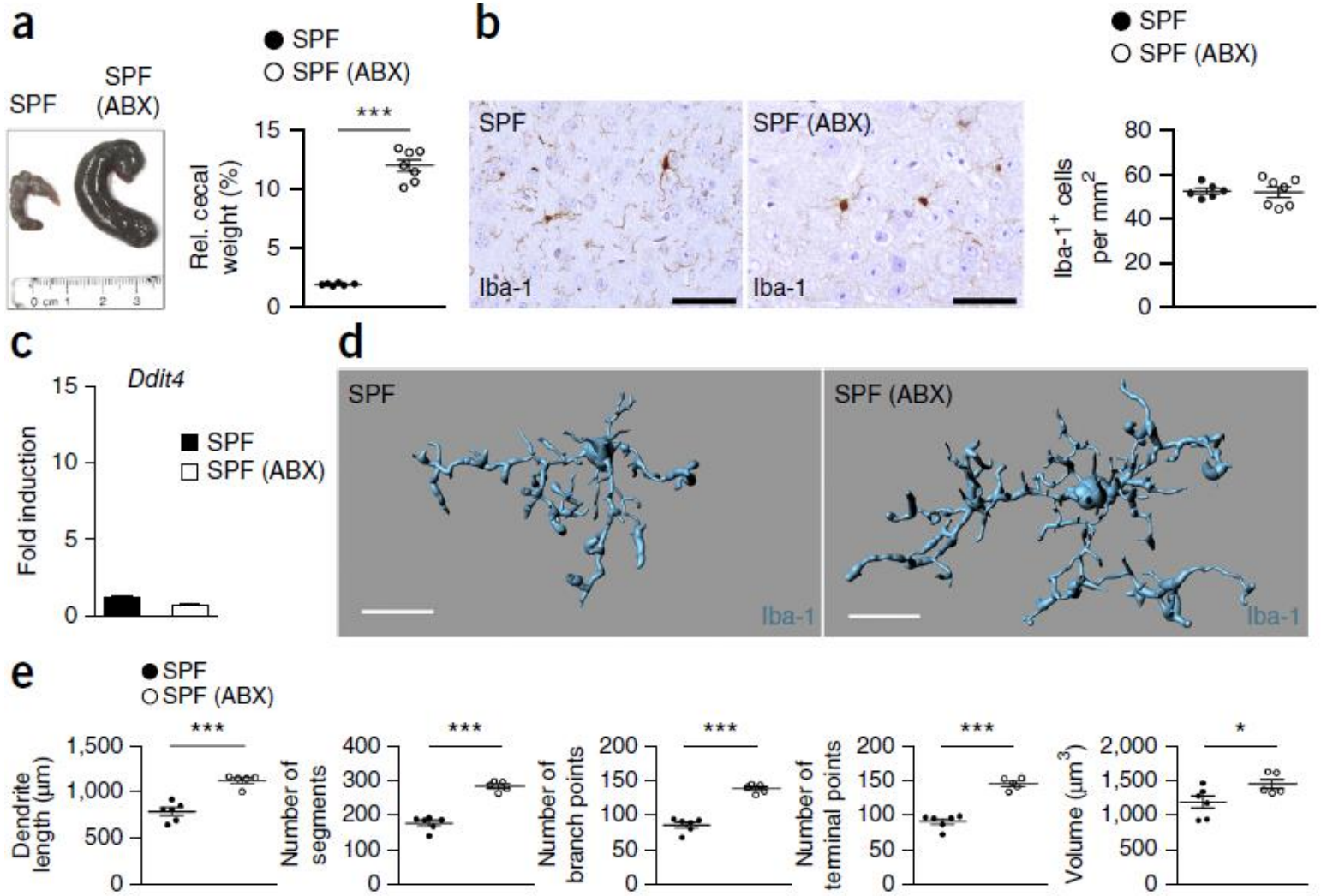
Lack Of Microbes Impairs Microglia Morphology

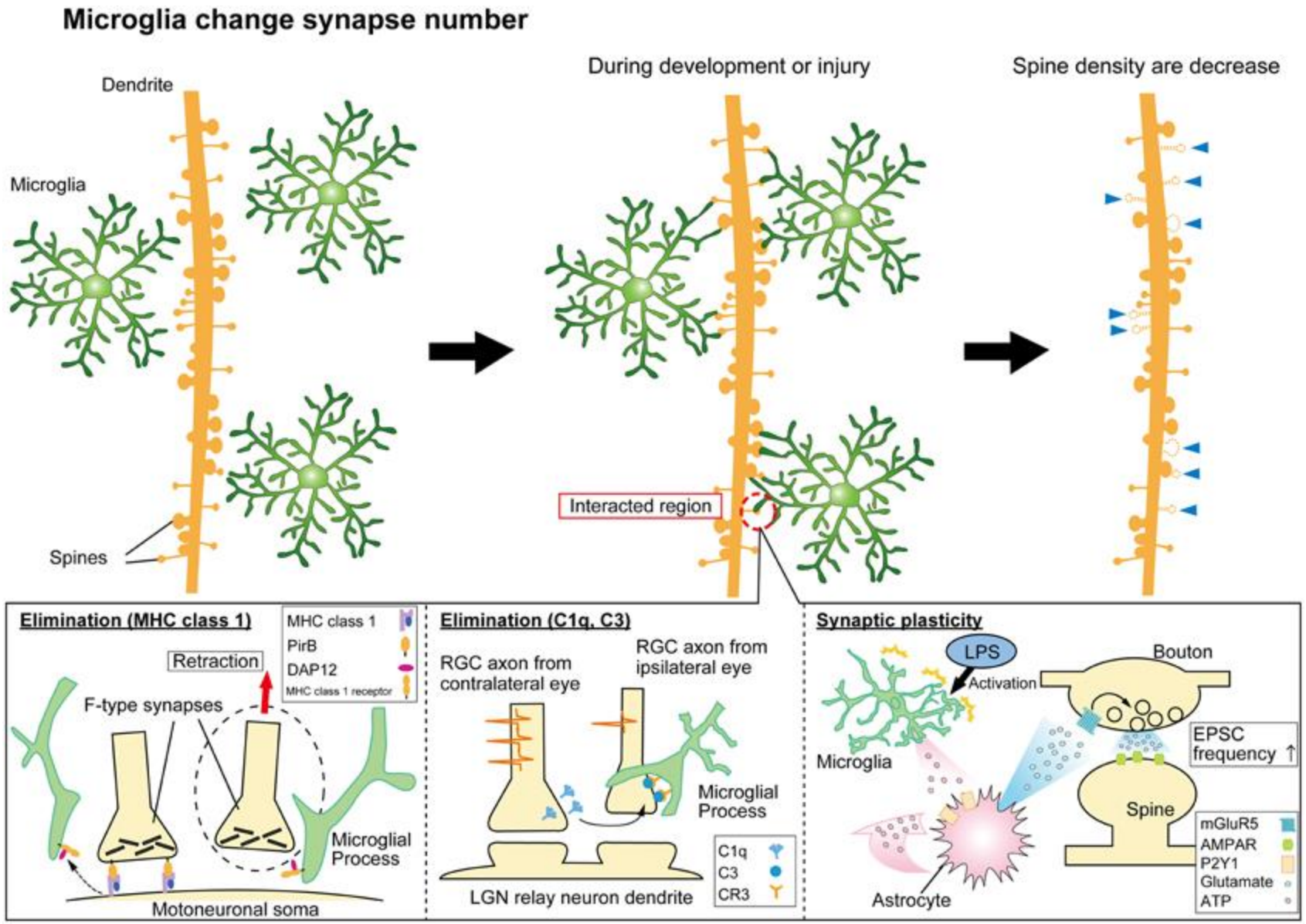


Increased microglia cell numbers with significantly longer processes and increased numbers of segments, branching and terminal points.

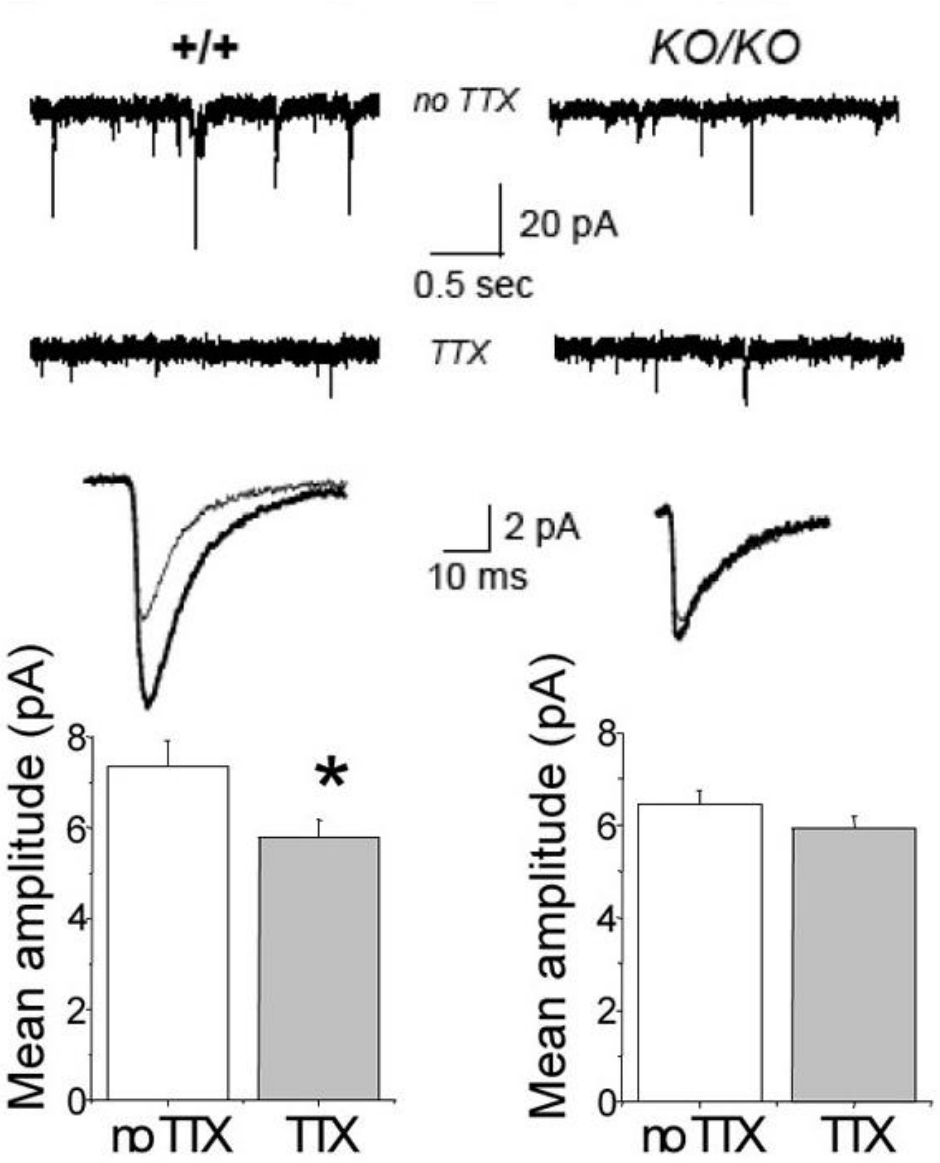
Antibiotic Treatment Induces Immature And Malformed Microglia That Can Be Restored By SCFA Administration



Microglial Control Of Synaptic Development



Developing CC3CR1 KO Mice Display Immature Synaptic Features



REPORTS

Science
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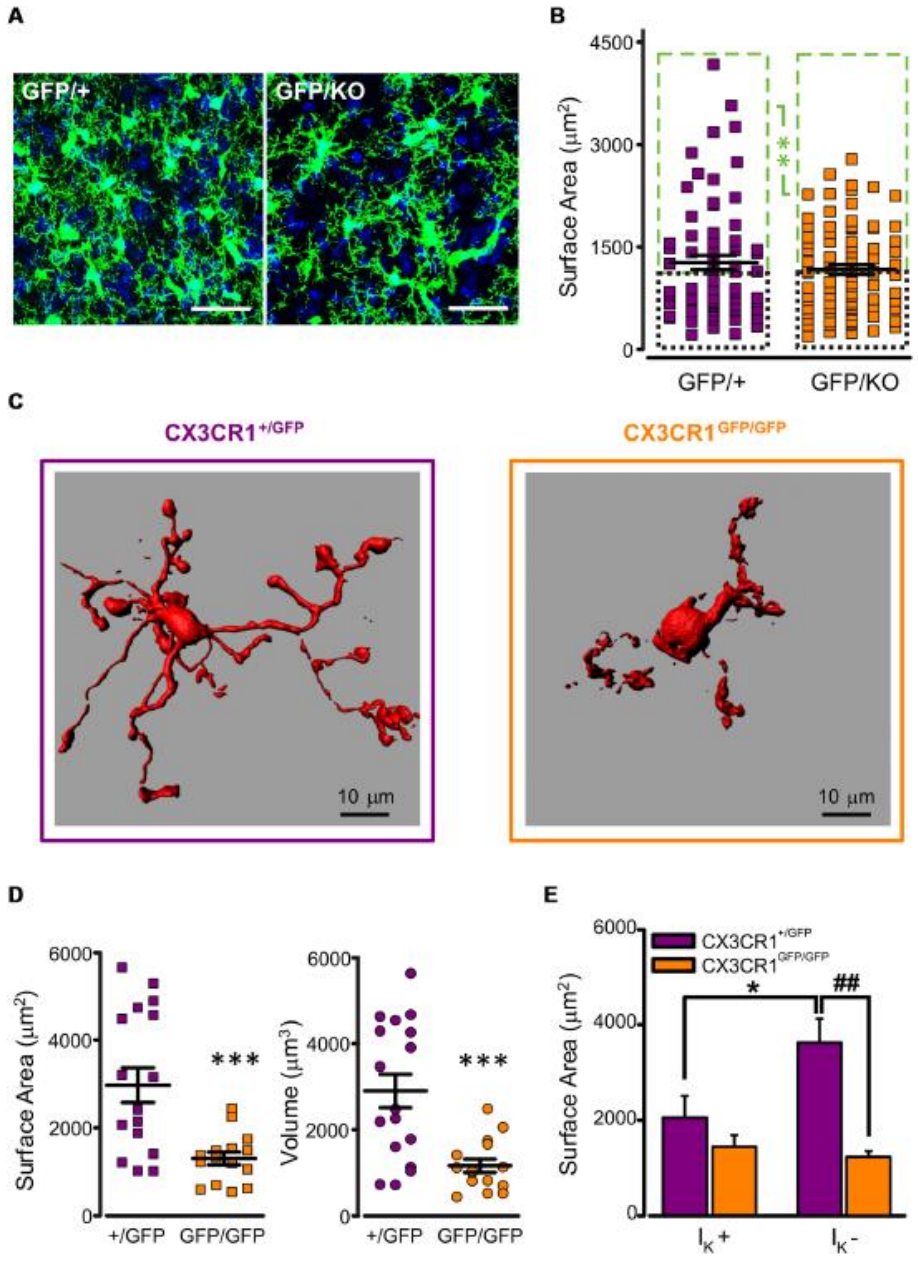
Synaptic Pruning by Microglia Is Necessary for Normal Brain Development

Rosa C. Paolicelli,[1] Giulia Bolasco,[1] Francesca Pagani,[2] Laura Maggi,[2] Maria Scianni,[2] Patrizia Panzanelli,[3] Maurizio Giustetto,[3,4] Tiago Alves Ferreira,[1] Eva Guiducci,[1] Laura Dumas,[1] Davide Ragozzino,[2] Cornelius T. Gross[1]*

Defective Microglial Development In CX3CR1 KO Mice



frontiers in Cellular Neuroscience

ORIGINAL RESEARCH
published: 31 March 2015
doi: 10.3389/fncel.2015.00111

Defective microglial development in the hippocampus of *Cx3cr1* deficient mice

Francesca Pagani[1], Rosa C. Paolicelli[2,3], Emanuele Murana[4], Barbara Cortese[5], Silvia Di Angelantonio[1,4], Emanuele Zurolo[6], Eva Guiducci[3], Tiago A. Ferreira[3], Stefano Garofalo[4], Myriam Catalano[4,7], Giuseppina D'Alessandro[4,7], Alessandra Porzia[8], Giovanna Peruzzi[1], Fabrizio Mainiero[8], Cristina Limatola[4,7], Cornelius T. Gross[3] and Davide Ragozzino[4,7]*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