Biosemiotics as a theoretical framework to approach the human gut-microbiota-brain-axis

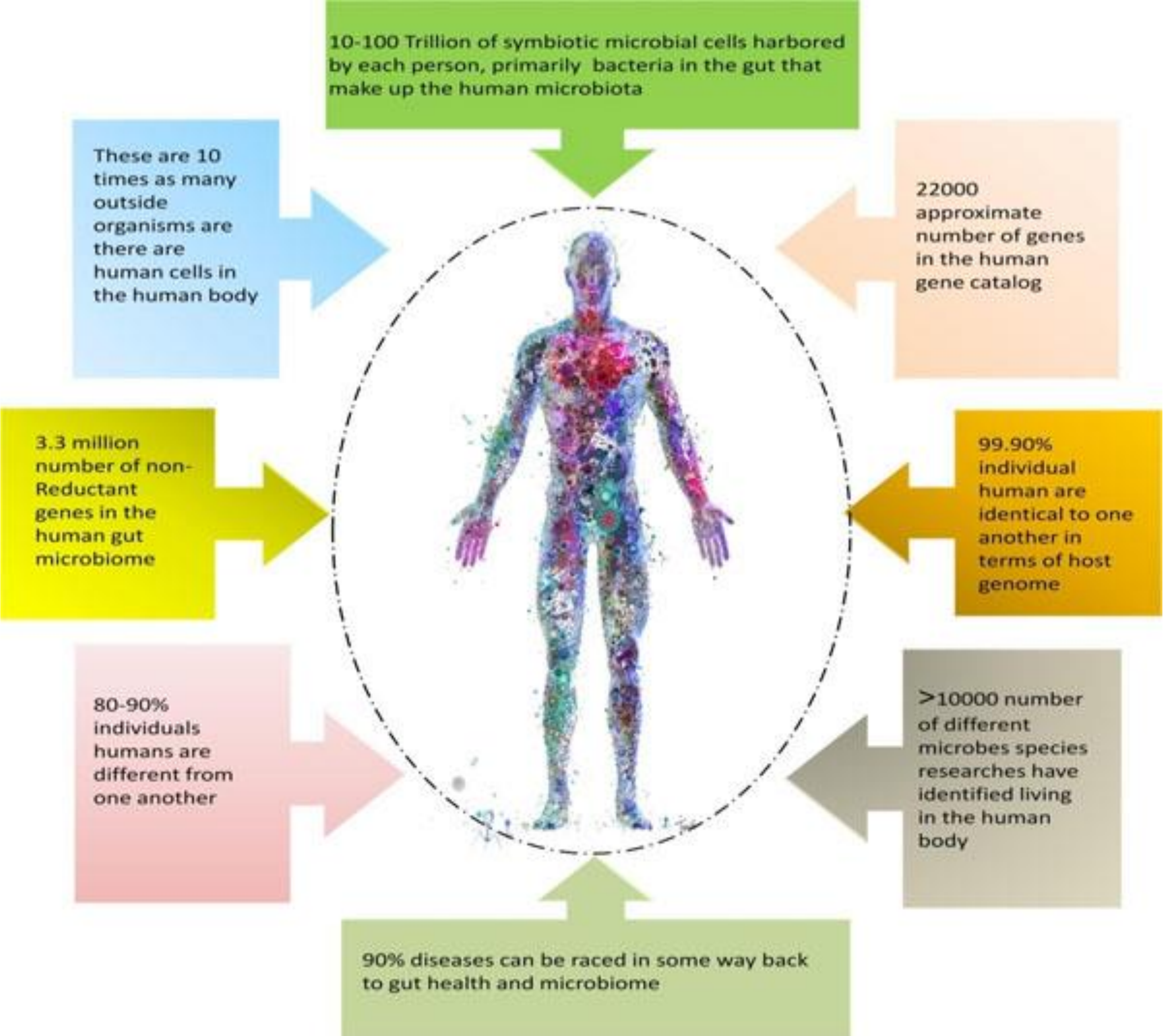
Rebeca Méndez-Veras

Universidad Mariano Gálvez de Guatemala

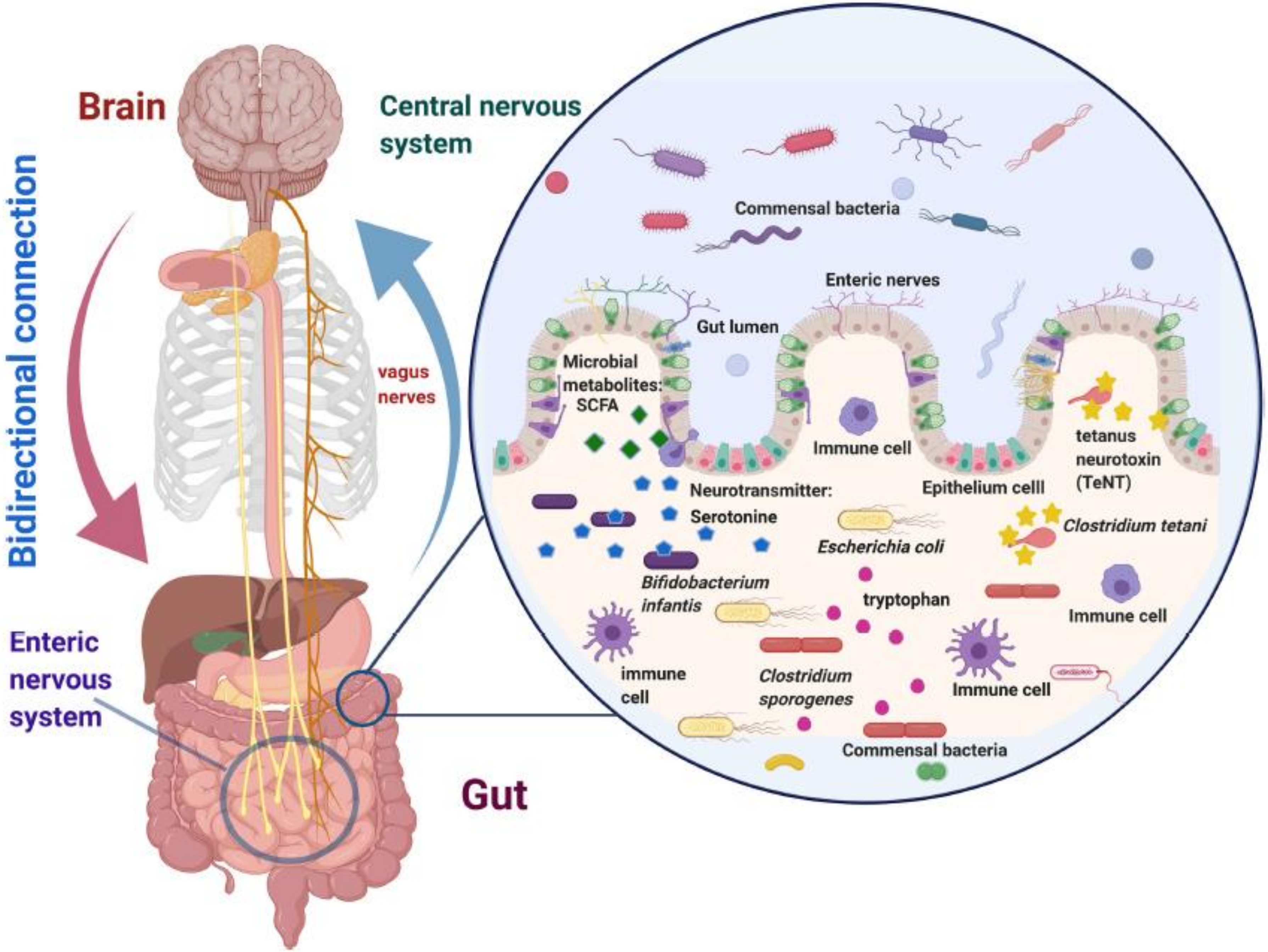
Óscar Castro

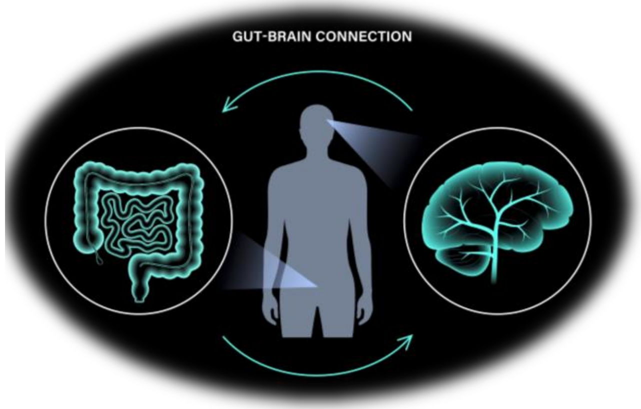
Universidad Autónoma de Barcelona

Last year…

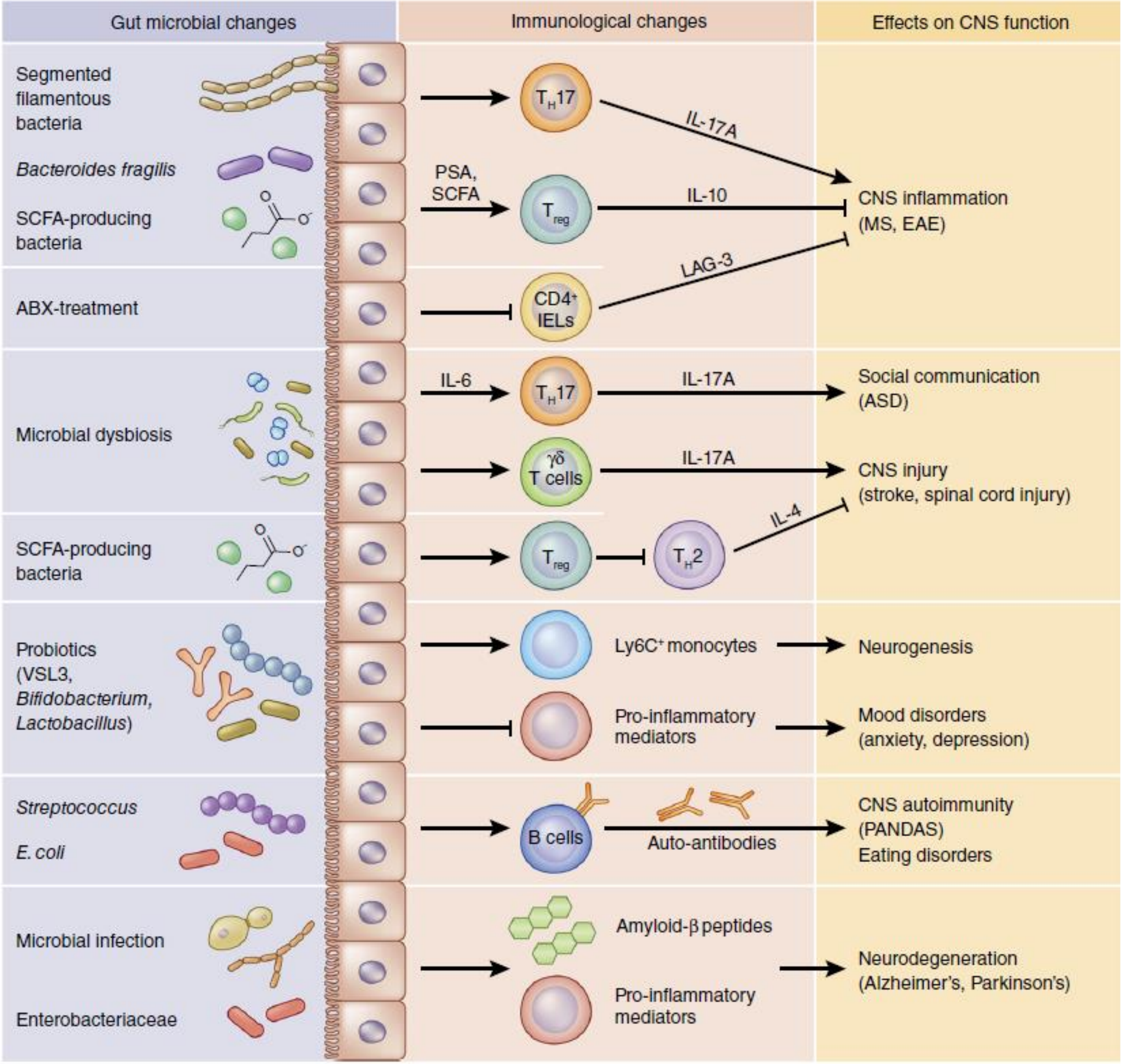


Krishna, et al., 2019





Taniya, et al, 2023



Fung, et al., 2017

Microbial influences in behaviour

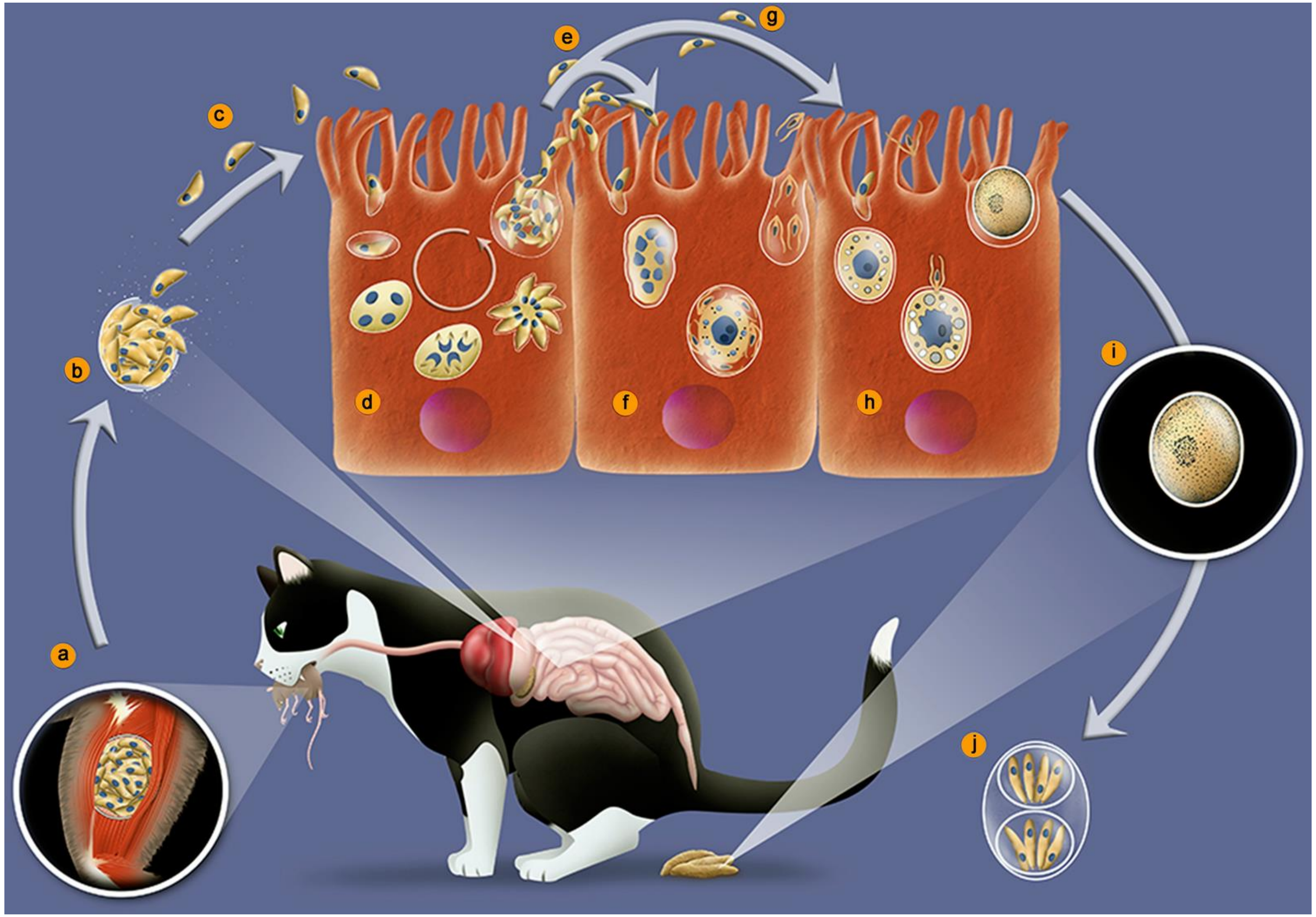


Fig. 4 Life-cycle of *Toxoplasma gondii* in cat. **a** Ingestion of prey containing tissue cysts. **b** The cyst wall is digested in the stomach and intestines, liberating bradyzoites. **c** Bradyzoites invade epitelial cells of the intestine. **d** In the enterocytes bradyzoites divide by schizogony giving rise to merozoites. **e** Merozoites differentiate into microgamonts, or macrogametes (**f**). **g** Fertilization gives rise to an unsporulated oocyst excreted with cat feces (**h**). **i** Sporulation occurs and generates two sporocysts with four sporozoites each (**j**)

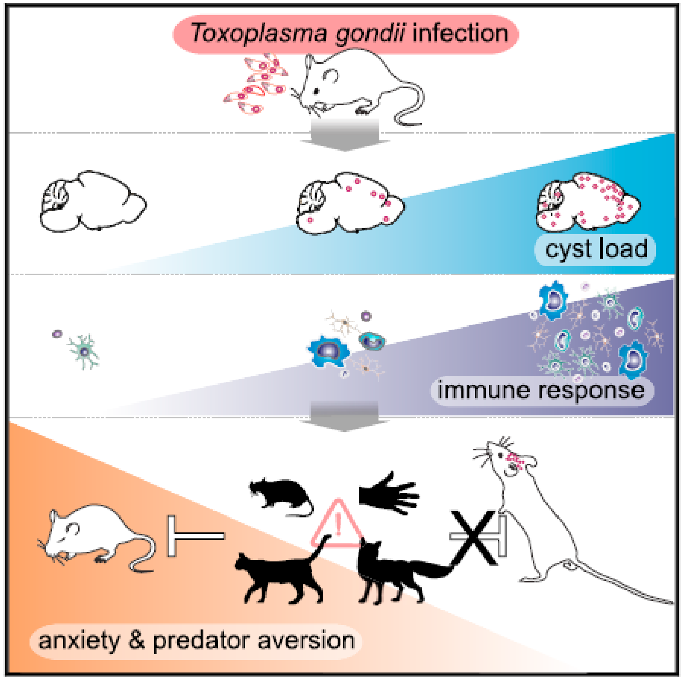
Attias, et al., 2020.

Cell Reports

Article

Neuroinflammation-Associated Aspecific Manipulation of Mouse Predator Fear by *Toxoplasma gondii*

Graphical Abstract



Authors

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Maged Goubran, Ivan Rodriguez,
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In Brief

Contradicting the prevailing model of a selective loss of cat fear in *Toxoplasma gondii*-infected rodents, Boillat et al. show in a multiparametric analysis of host behavior, physiology, and brain transcriptome that the loss of predator fear is not specific to felids and that the severity of behavioral alterations correlates with neuroinflammation.

Boillat, et al., 2020

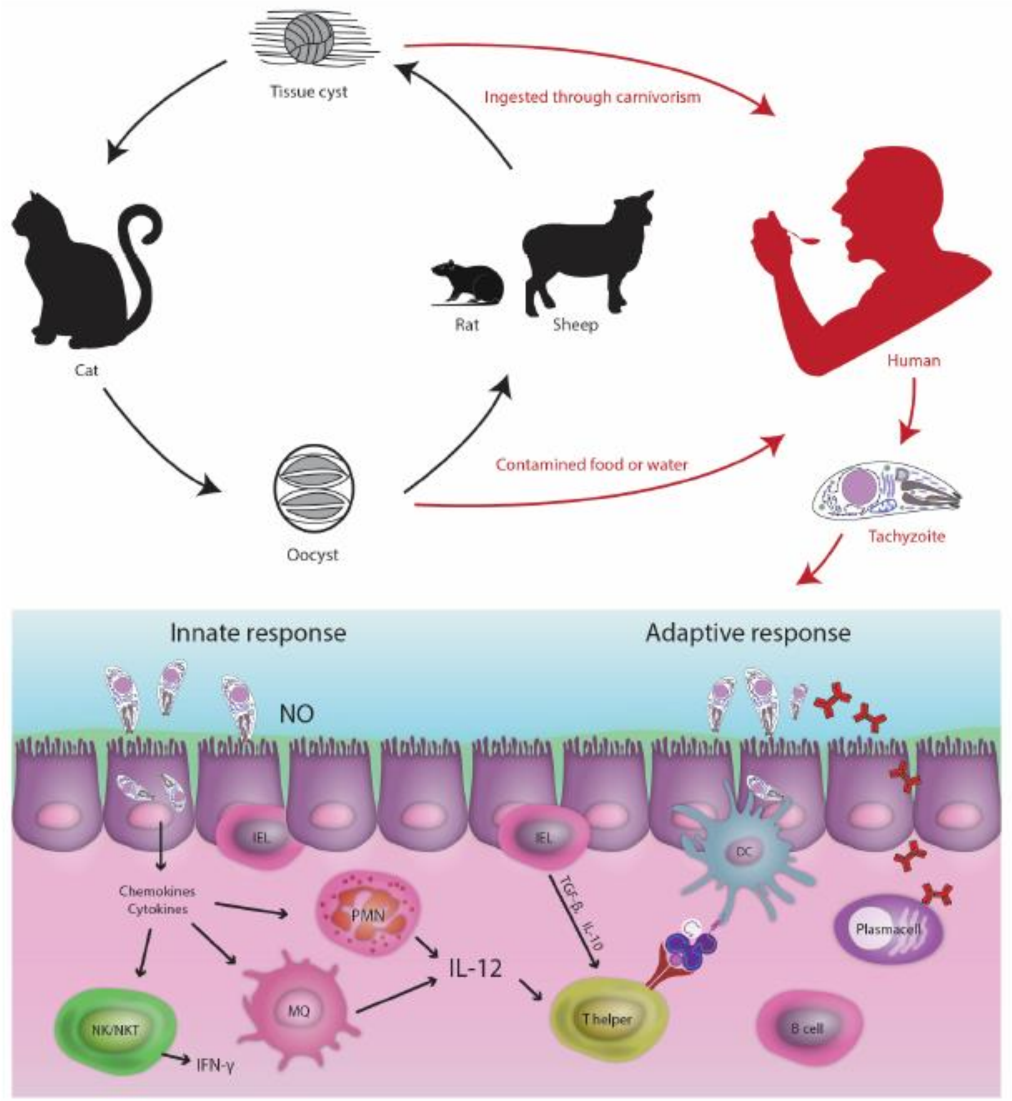
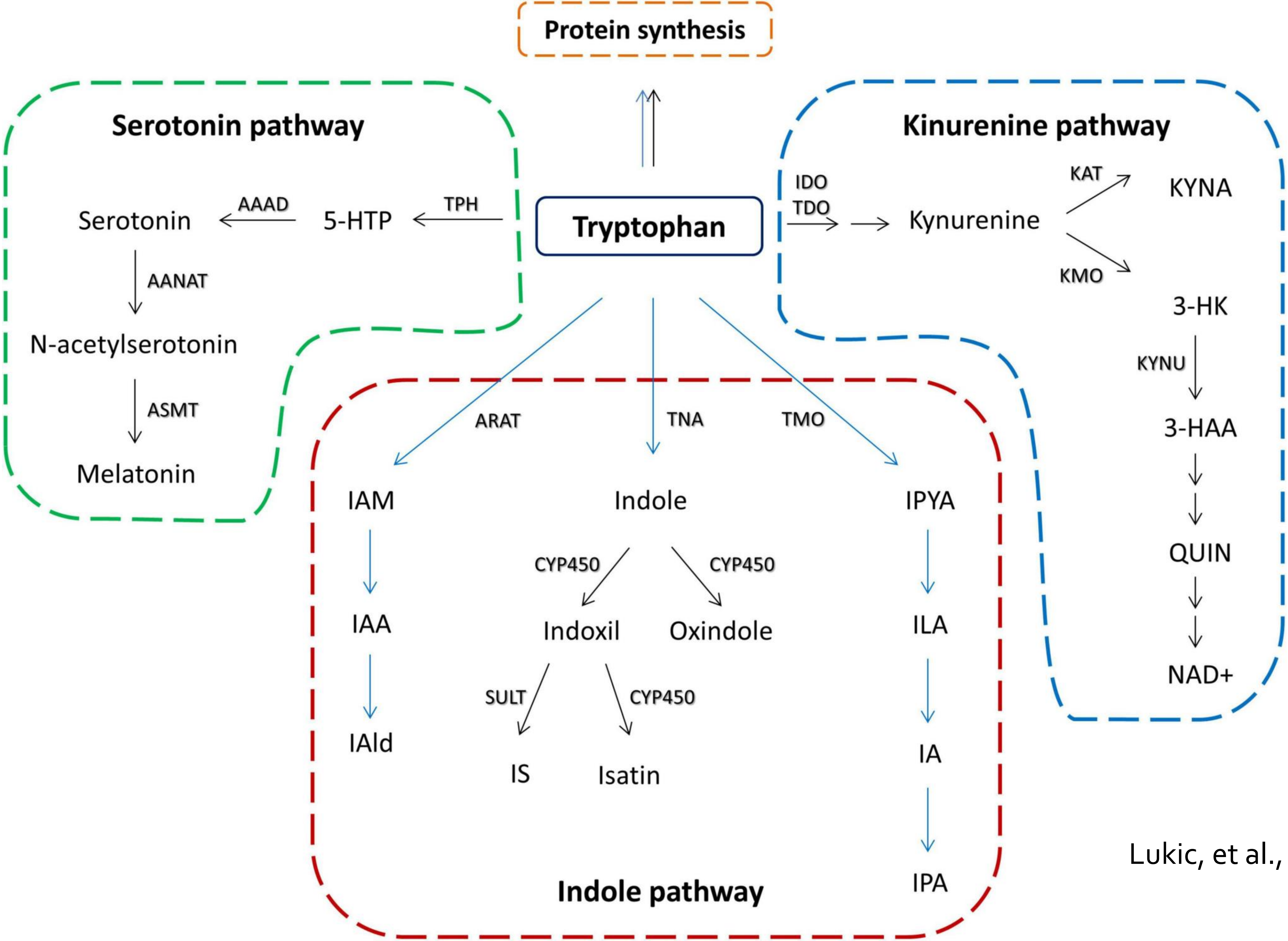
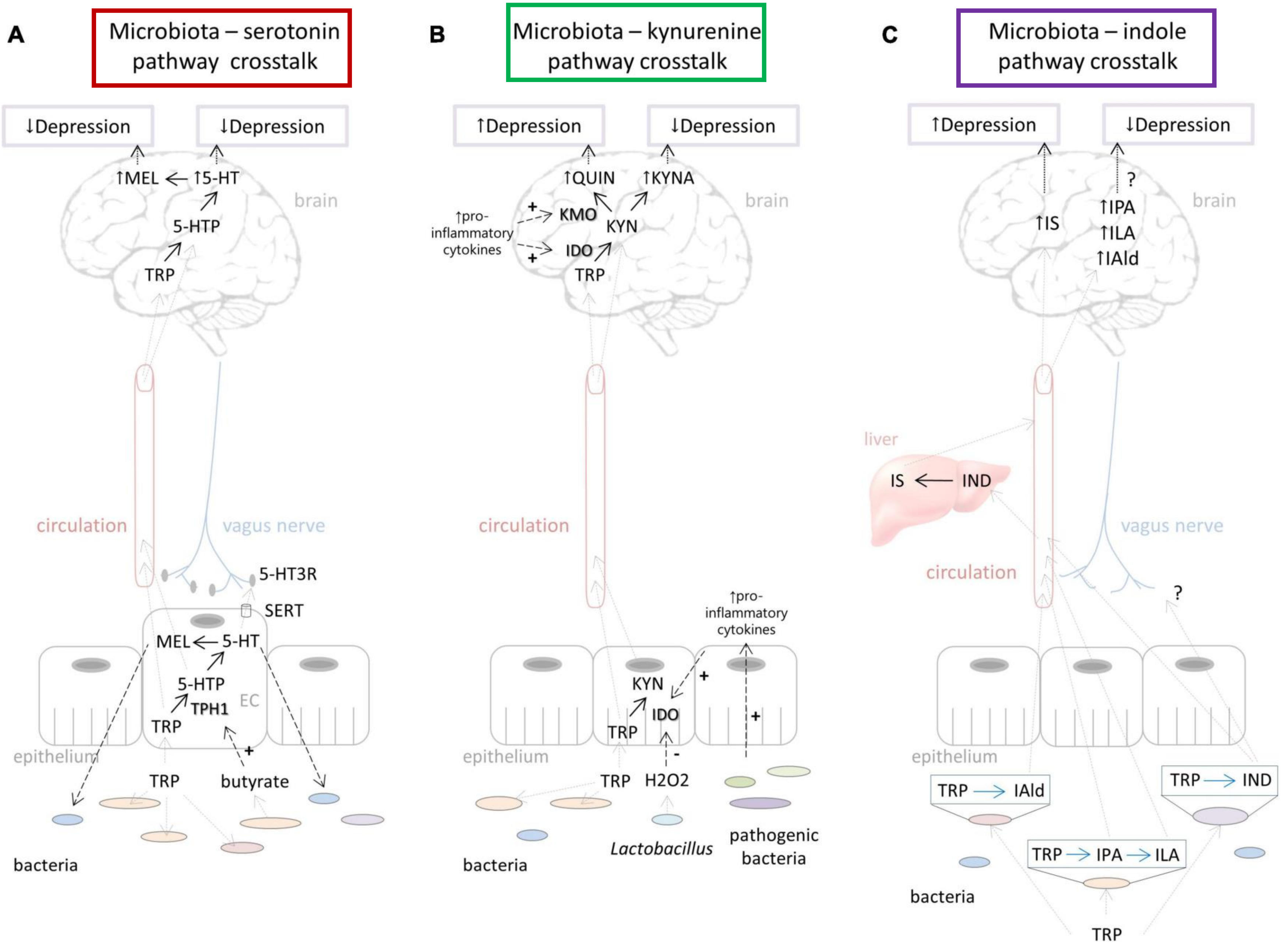


Figure 1. Life cycle of *T. gondii*. Schematic representation of the three virulence stages, main infection routes, and host innate and adaptive immune responses to toxoplasmosis.

Ahmadpour, et al., 2023



Lukic, et al., 2022.



Lukic, et al 2022

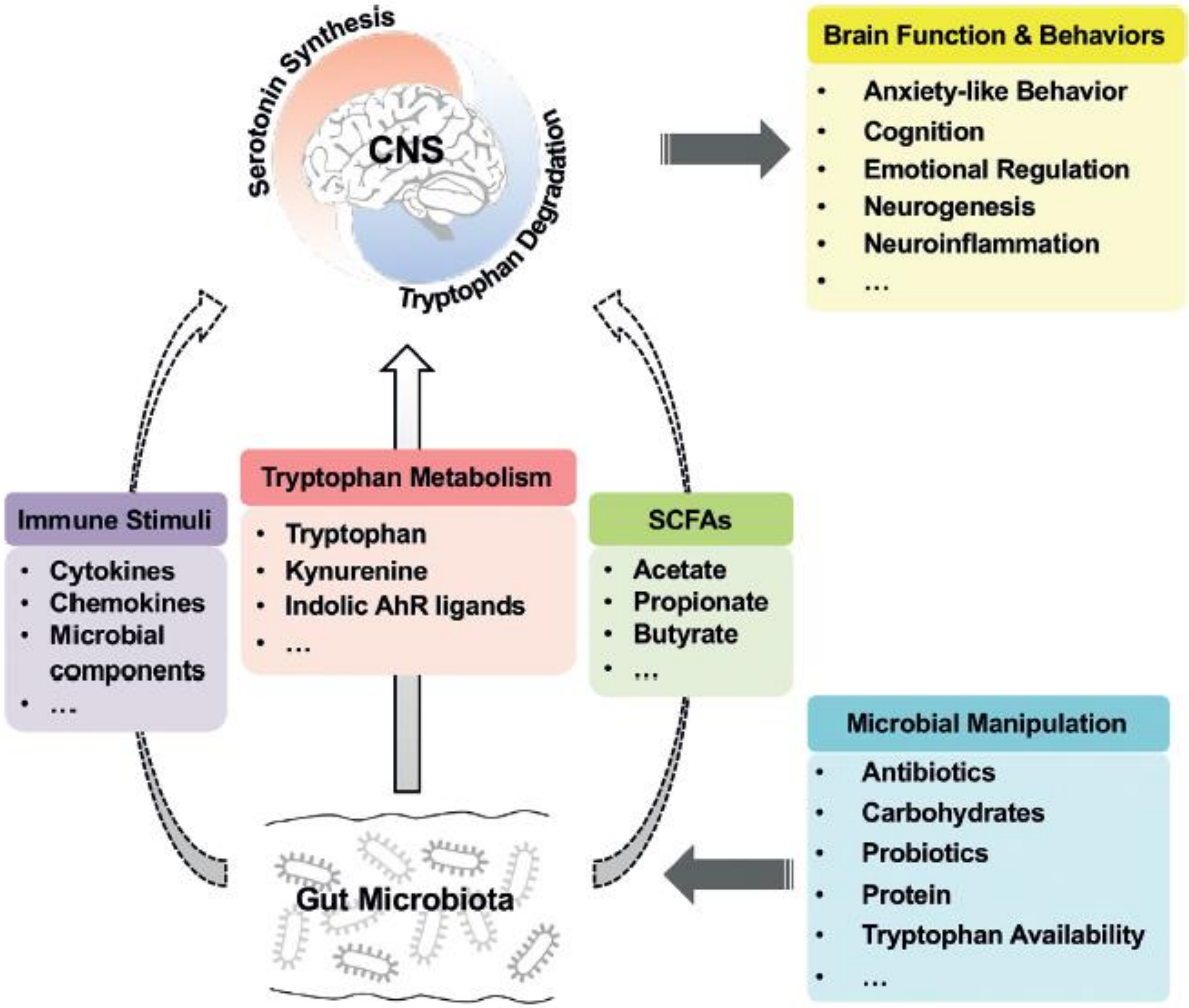
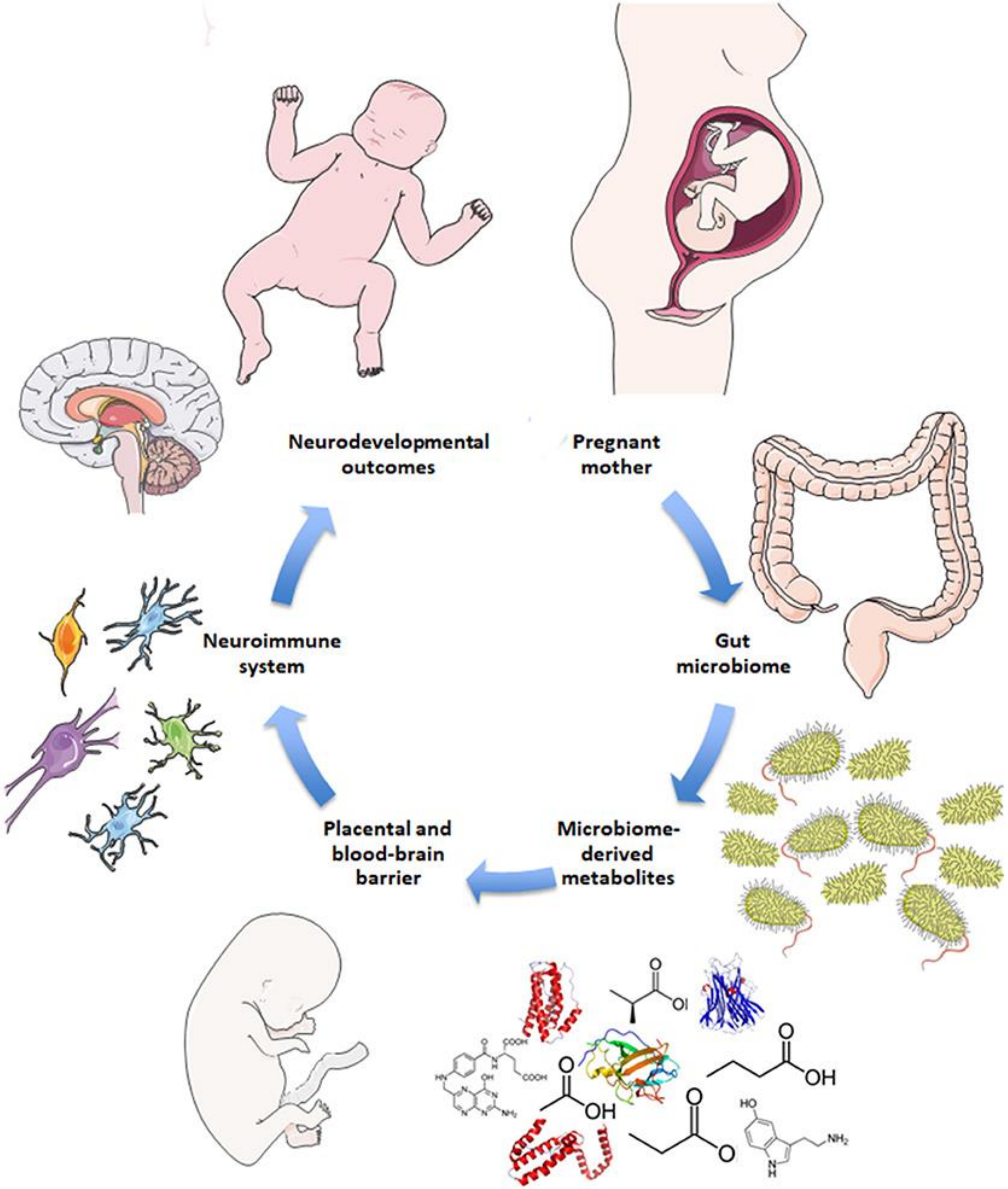


FIGURE 3 The potential role of tryptophan metabolism in the gut microbiota-brain axis. Manipulations of gut microbiota composition and metabolism by various ways (e.g., antibiotics and probiotics) contribute to the shifts in the central tryptophan metabolism between serotonin synthesis and tryptophan degradation pathways, which thereby influence the brain function and behaviors. The solid arrow indicates the tryptophan metabolism–dependent effects of alterations in gut microbiota on the central tryptophan metabolism; the dashed arrow indicates the tryptophan-independent effects on the central tryptophan metabolism. AhR, aryl hydrocarbon receptor; CNS, central nervous system; SCFA, short-chain fatty acid.

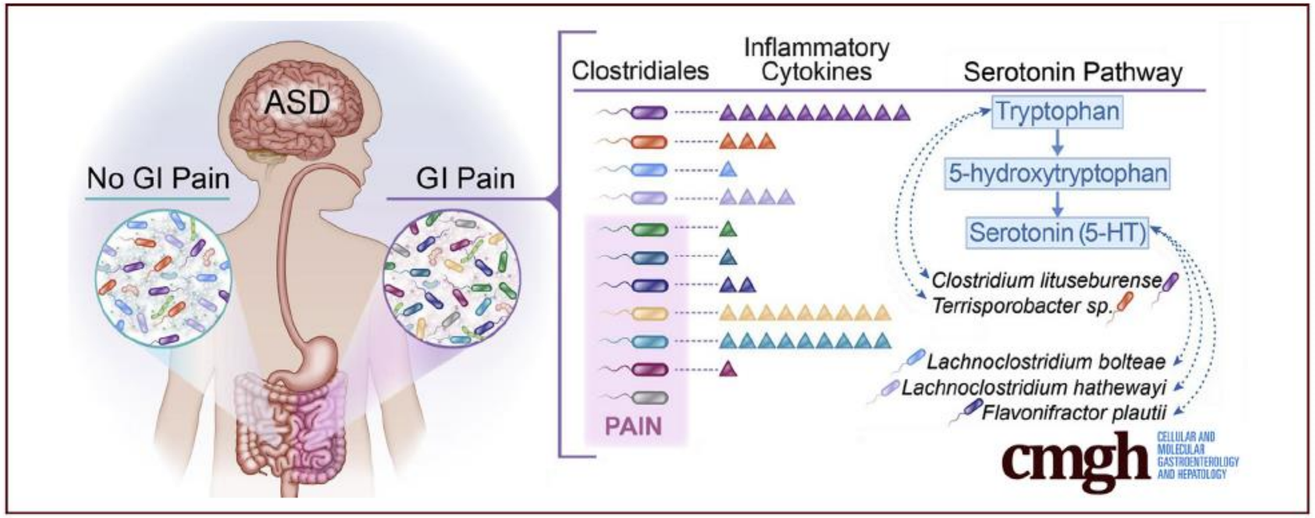
Gao, et al., 2020.

Autism Spectrum Disorder (ASD)

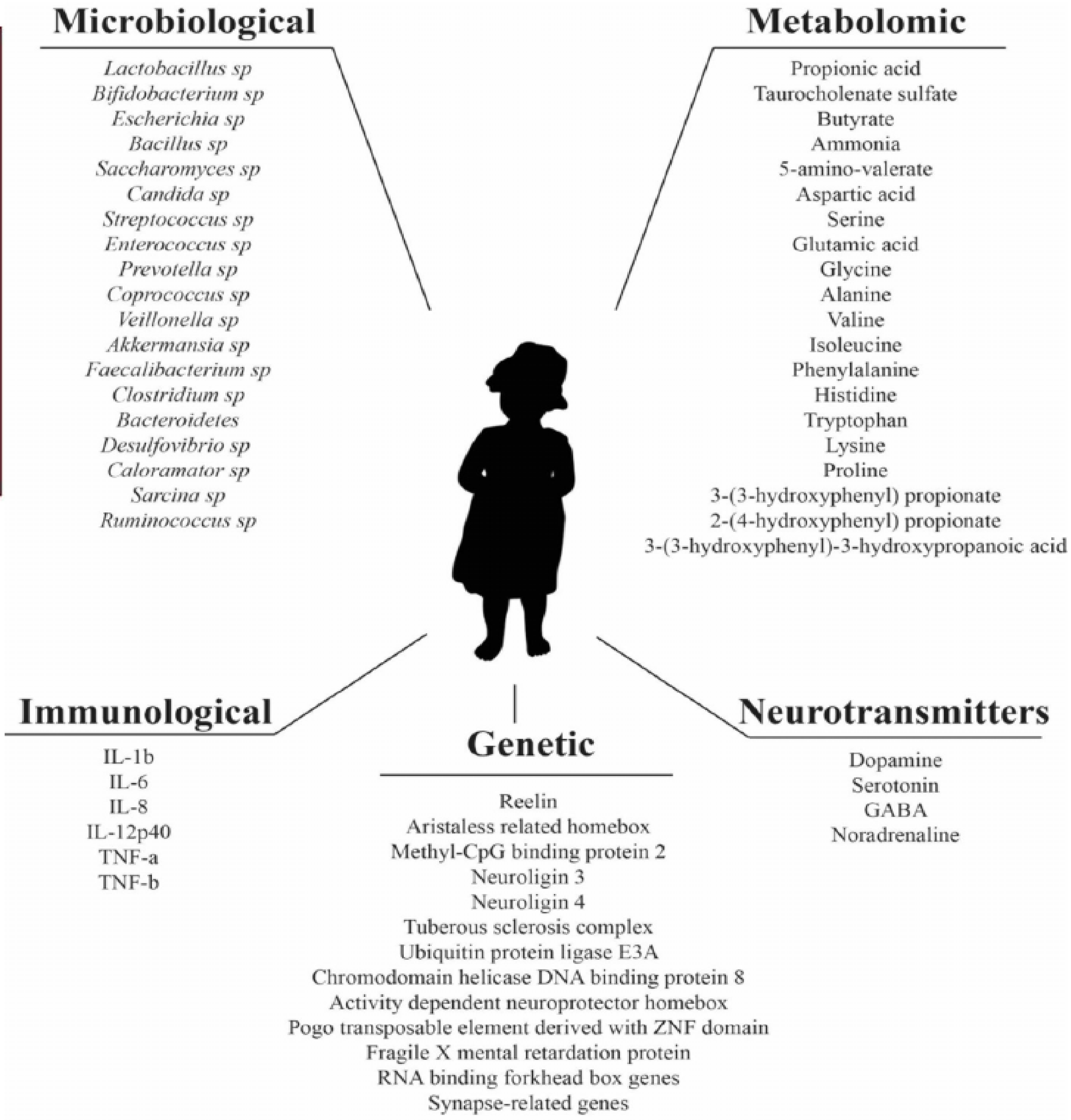


https://neurosciencenews.com/autism-microbiome-gut-23527/

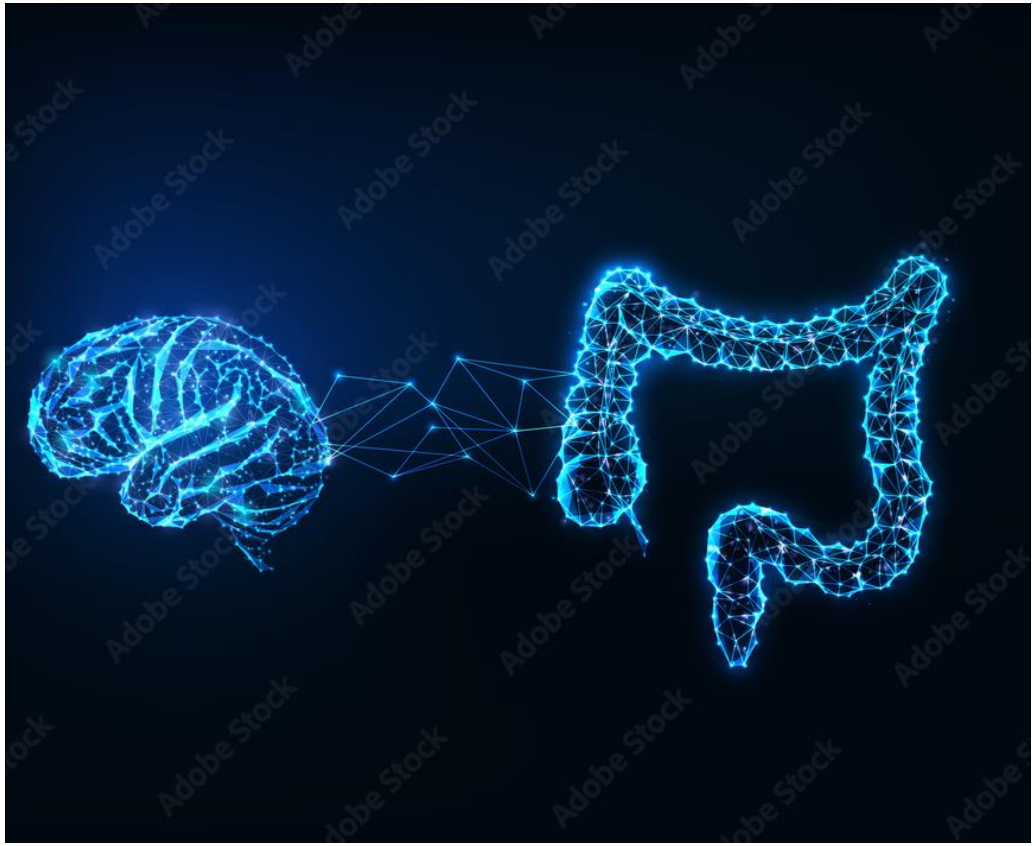
Lebovitz, et al., 2018.



Ann Luna, et al., 2017



García-Gutiérrez, et al., 2020



Can biosemiotics help in the understanding of the gut-microbiota-brain dialogue?

Can Biosemiotics help in developing personalized healthcare interventions?

frontiers in Psychology

PERSPECTIVE
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The *Holobiont Blindspot*: Relating Host-Microbiome Interactions to Cognitive Biases and the Concept of the "*Umwelt*"

Jake M. Robinson[1,2,3] and Ross Cameron[1]*

[1] Department of Landscape Architecture, The University of Sheffield, Sheffield, United Kingdom, [2] In vivo Planetary Health, Worldwide Universities Network (WUN), West New York, NJ, United States, [3] The Healthy Urban Microbiome Initiative (HUMI), Adelaide, SA, Australia

Cognitive biases can lead to misinterpretations of human and non-human biology and behavior. The concept of the *Umwelt* describes phylogenetic contrasts in the sensory realms of different species and has important implications for evolutionary studies of cognition (including biases) and social behavior. It has recently been suggested that the microbiome (the diverse network of microorganisms in a given environment, including those within a host organism such as humans) has an influential role in host behavior and health. In this paper, we discuss the host's microbiome in relation to cognitive biases and the concept of the *Umwelt*. Failing to consider the role of host–microbiome (collectively termed a "*holobiont*") interactions in a given behavior, may underpin a potentially important cognitive bias – which we refer to as the *Holobiont Blindspot*. We also suggest that microbially mediated behavioral responses could augment our understanding of the *Umwelt*. For example, the potential role of the microbiome in perception and action could be an important component of the system that gives rise to the *Umwelt*. We also discuss whether microbial symbionts could be considered in System 1 thinking – that is, decisions driven by perception, intuition and associative memory. Recognizing *Holobiont Blindspots* and considering the microbiome as a key factor in the *Umwelt* and System 1 thinking has the potential to advance studies of cognition. Furthermore, investigating *Holobiont Blindspots* could have important implications for our understanding of social behaviors and mental health. Indeed, the way we think about *how* we think may need to be revisited.

Keywords: *Umwelt*, cognition, microbiome, system one thinking, *Holobiont Blindspot*, cognitive bias

OPEN ACCESS

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Special Issue: Chilean 4E cognition

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Adaptive Behavior
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DOI: 10.1177/10597123211053071
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The holobiont mind: A bridge between 4E cognition and the microbiome

Ismael Palacios-García[1,2,]* and Francisco J Parada[2,]*

Abstract

All life on earth is intrinsically linked. At the very foundation of every evolutionary interaction are microorganisms, integral components in the composition of both organisms and ecosystems. The available data and this perspective on the order of life challenge the traditional conception of *monogenetic biological individuals*, suggesting living beings are actually *composite multi-species complexes: holobionts*. In the present article, we introduce our perspective on the concept of the *holobiont mind*, a biogenic conception of cognition compatible with the 4E approach and the holobiont theory. We furthermore expand on the idea of the mind as the emerging product of multi-genomic morphology of a composite animal-agent, in ever-changing interaction with its ecological niche. We thus briefly review recent evidence on the brain–gut–microbiome axis and the *Microbiome of the Built Environment* in order to provide a bridge between the *Holobiont Mind* and the *4E approach to Cognition*, two complementary lines of evidence that have not been linked before, opening novel venues for research with direct impact on health and disease.

Keywords

Microbiome, holobiont, brain–gut, built environment, 4E cognition

Received: 19 October 2021 | Accepted: 15 March 2022

DOI: 10.1002/bies.202100249

BioEssays

HYPOTHESIS

Insights & Perspectives

The 4E approach to the human microbiome: Nested interactions between the gut-brain/body system within natural and built environments

Ismael Palacios-García[1,2] | Gwynne A. Mhuireach[3] | Aitana Grasso-Cladera[1] | John F. Cryan[4,5] | Francisco J. Parada[1]

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Abstract

The complexity of the human mind and its interaction with the environment is one of the main epistemological debates throughout history. Recent ideas, framed as the *4E perspective to cognition*, highlight that human experience depends causally on both cerebral and extracranial processes, but also is embedded in a particular sociomaterial context and is a product of historical accumulation of trajectory changes throughout life. Accordingly, the human microbiome is one of the most intriguing actors modulating brain function and physiology. Here, we present the *4E approach to the Human Microbiome* for understanding mental processes from a broader perspective, encompassing one's body physiology and environment throughout their lifespan, interconnected by microbiome community structure and dynamics. We review evidence supporting the approach theoretically and motivates the study of the global set of microbial ecosystem networks encountered by a person across their lifetime (from skin to gut to natural and built environments). We furthermore trace future empirical implementation of the approach. We finally discuss novel research opportunities and clinical interventions aimed toward developing low-cost/high-benefit integrative and personalized bio-psycho-socio-environmental treatments for mental health and including the brain-gut-microbiome axis.

KEYWORDS

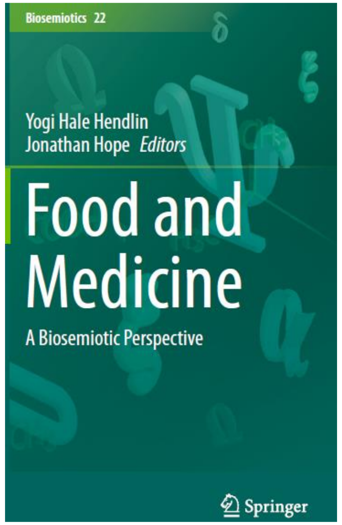
4E cognition, built environment, gut-brain axis, mental health, microbiome

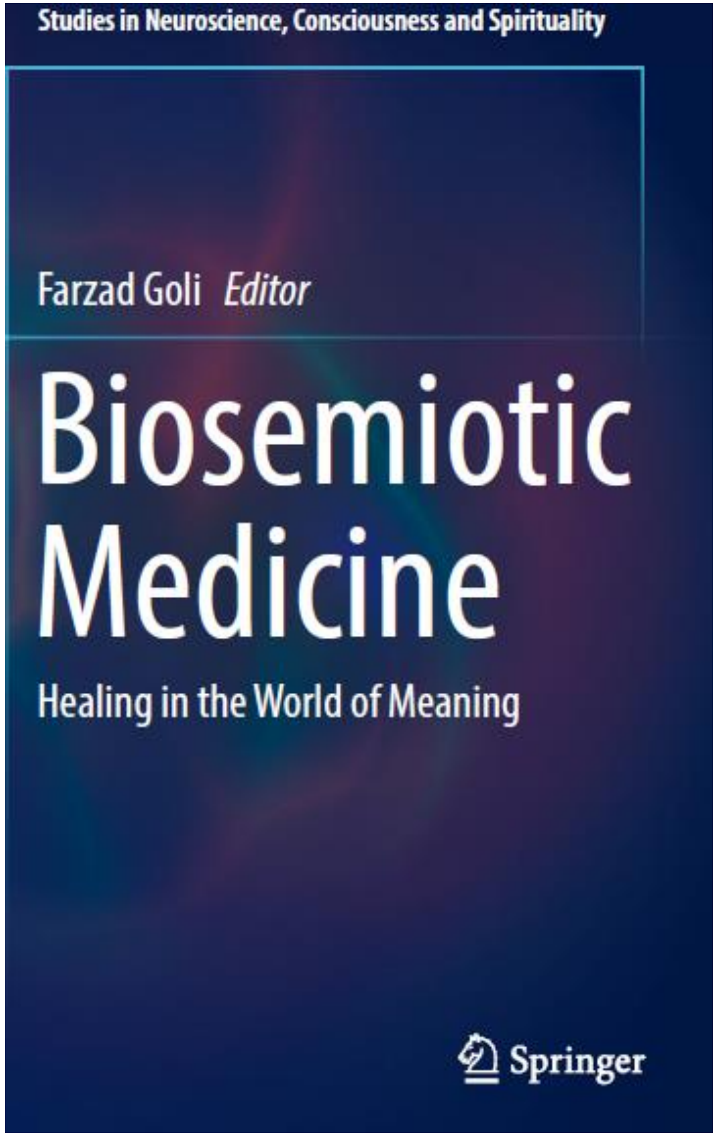
Biosemiotics (2016) 9:417–433
DOI 10.1007/s12304-016-9273-4

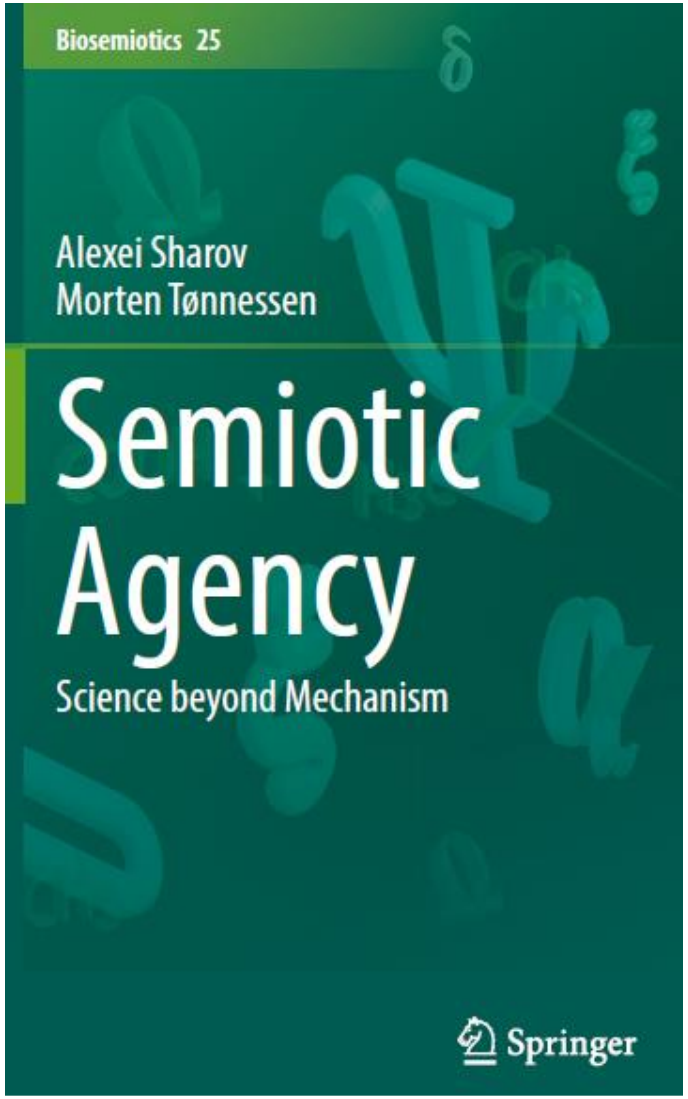
CrossMark

Semiosis as Individuation: Integration of Multiple Orders of Magnitude

Vefa Karatay[1] · Yagmur Denizhan[2] ·
Mehmet Ozansoy[3]







CHAPTER 6

SEMIOTIC SCAFFOLDING OF LIVING SYSTEMS*

JESPER HOFFMEYER
Department of Biological Chemistry, University of Copenhagen, Denmark jhoffmeyer@mail.dk

Abstract: The apparently purposeful nature of living systems is obtained through a sophisticated network of semiotic controls whereby biochemical, physiological and behavioral processes become tuned to the needs of the system. The operation of these semiotic controls takes place and is enabled across a diversity of levels. Such semiotic controls may be distinguished from ordinary deterministic control mechanisms through an inbuilt anticipatory capacity based on a distinct kind of causation that I call here "semiotic causation" to denote the bringing about of changes under the guidance of interpretation in a local context. Anticipation through the skilled interpretation of indicators of temporal relations in the context of a particular survival project (or life strategy) guides organismic behavior towards local ends. This network of semiotic controls establishes an enormously complex semiotic scaffolding for living systems. Semiotic scaffolding safeguards the optimal performance of organisms through semiotic interaction with cue elements which are characteristically present in dynamic situations. At the cellular level, semiotic scaffolding assures the proper integration of the digital coding system (the genome) into the myriad of analogical coding systems operative across the membranes of cells and cell organelles

Biosemiotics
DOI 10.1007/s12304-015-9231-6

ORIGINAL PAPER

Semiotic Scaffolding of Multicellularity

Jesper Hoffmeyer

Received: 8 October 2014 / Accepted: 26 January 2015

Abstract The threshold from unicellularity to multicellularity has been crossed only in three major living domains in evolution with any lasting success. The hard problem was to create a multicellular self. Such a self is vulnerable to breakdown due to the unavoidable appearance of mutant anarchistic cells, and stringent semiotic scaffoldings had to emerge to prevent this. While a unicellular self may go on to live practically forever, the multicellular self most often must run through an individuation process ending in the death of the individual. Due to basic differences in cells of plants, fungi and animals this

Green Letters: Studies in Ecocriticism, 2015
http://dx.doi.org/10.1080/14688417.2015.1058175

Routledge
Taylor & Francis Group

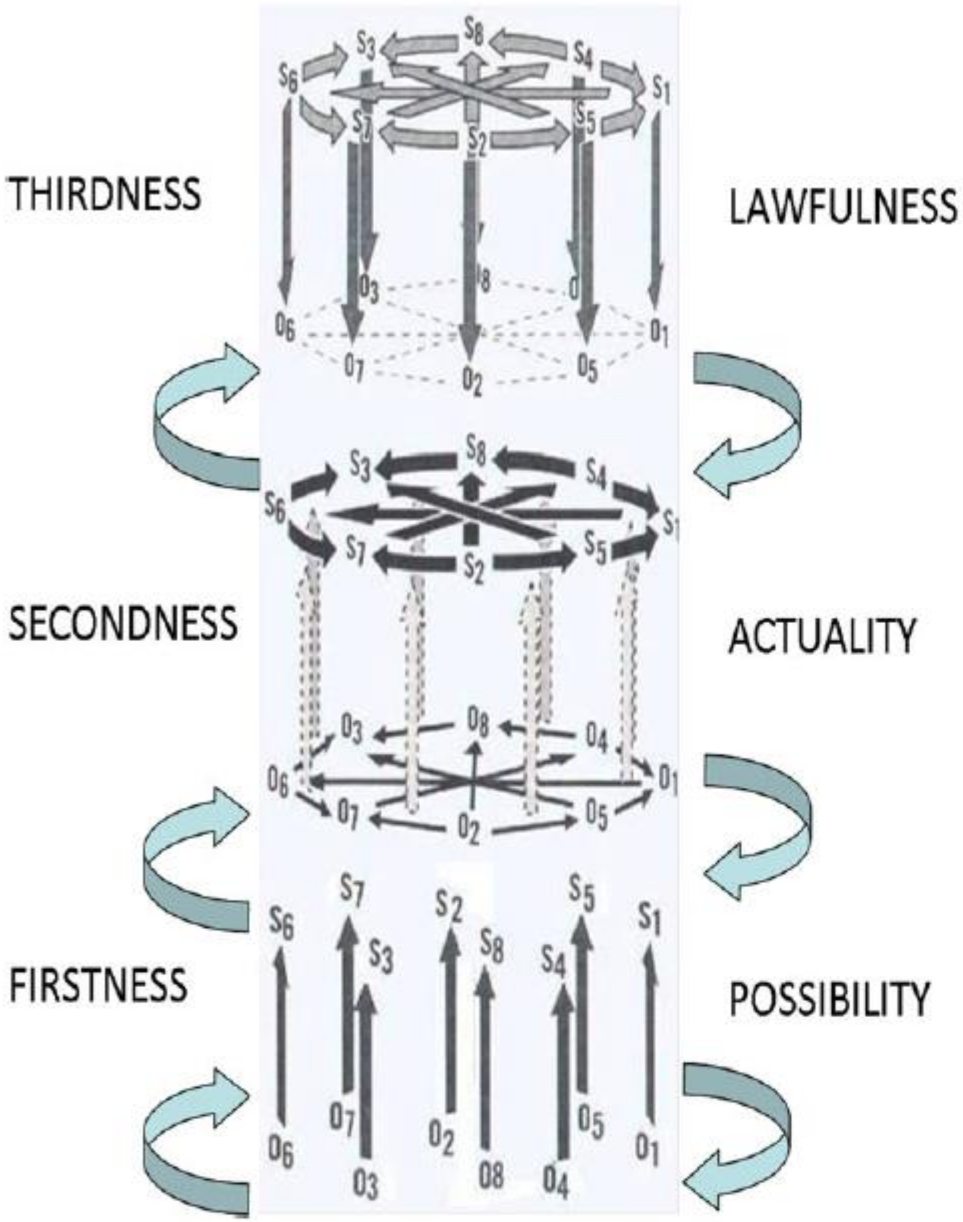
Semiotic scaffolding: a unitary principle gluing life and culture together

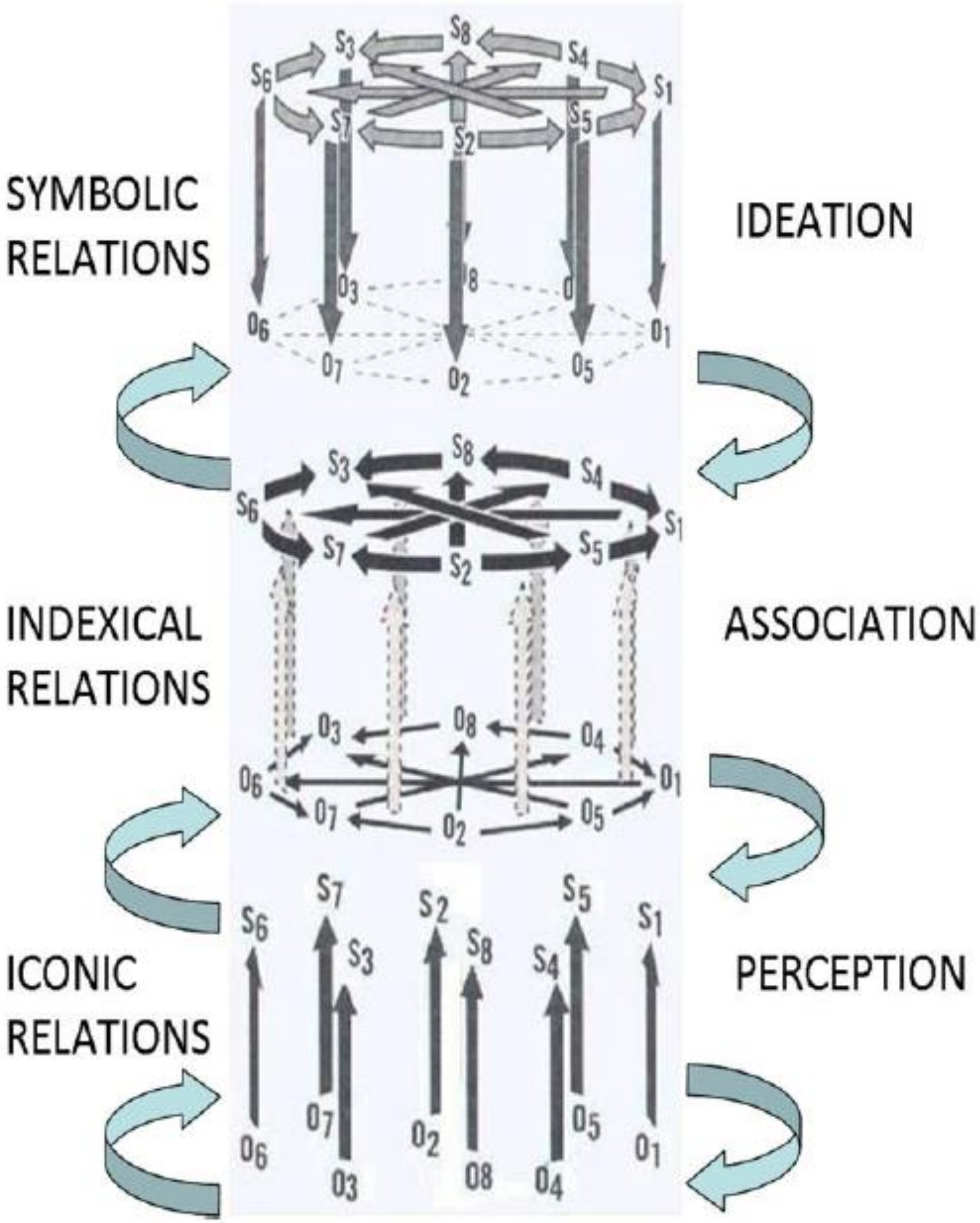
Jesper Hoffmeyer*

Biological Institute, University of Copenhagen, København, Denmark

(*Received 15 April 2015; accepted 15 May 2015*)

Life processes at all levels (from the genetic to the behavioral) are coordinated by semiotic interactions between cells, tissues, membranes, organs, or individuals and tuned through evolution to stabilize important functions. A stabilizing dynamics based on a system of semiotic scaffoldings implies that genes do not *control* the life of organisms, they merely *scaffold* it. The nature-nurture dynamics is thus far more complex and open than is often claimed. Contrary to physically based interactions, semiotic interactions do not depend on any direct causal connection between the sign





Favareau, 2015.

Can biosemiotics help in the understanding of the gut-microbiota-brain dialogue?

- Certain terms may be insufficient in conveying a comprehensive concept or might become overlooked in subsequent research so, **biosemiotics emerges as a potent approach to encompass entire concepts within this context.**

- A more appropriate definition for a host would be a **"bio<u>semiont</u>"** since it qualifies as a semiotic organism.

- Similarly, the microbiota warrants the term **"micro<u>biosemiota</u>"** as microorganisms function as semiotic agents.

- The holobiont then, can be more accurately described as a **"holo<u>biosemiont</u>,"** signifying its role as an interactive entity within the **"holo<u>biosemiont</u>sphere."**

Opinion TRENDS in Microbiology Vol.12 No.8 August 2004
Full text provided by www.sciencedirect.com

Bacterial linguistic communication and social intelligence

Eshel Ben Jacob[1], Israela Becker[1,2], Yoash Shapira[1] and Herbert Levine[3]

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[2]Tel-Aviv Academic College of Engineering, 218 Bney Efraim Rd., Tel-Aviv 69107, Israel
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Opinion TRENDS in Microbiology Vol.13 No.4 April 2005
Full text provided by www.sciencedirect.com

Bacterial observations: a rudimentary form of intelligence?

Klaas J. Hellingwerf

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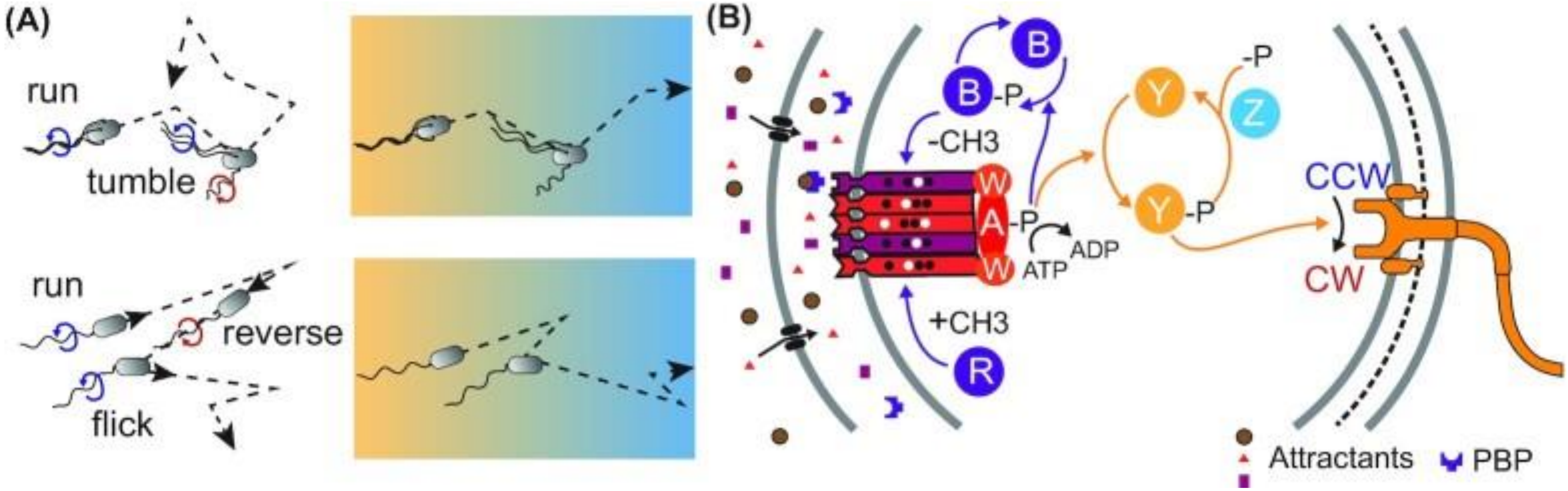
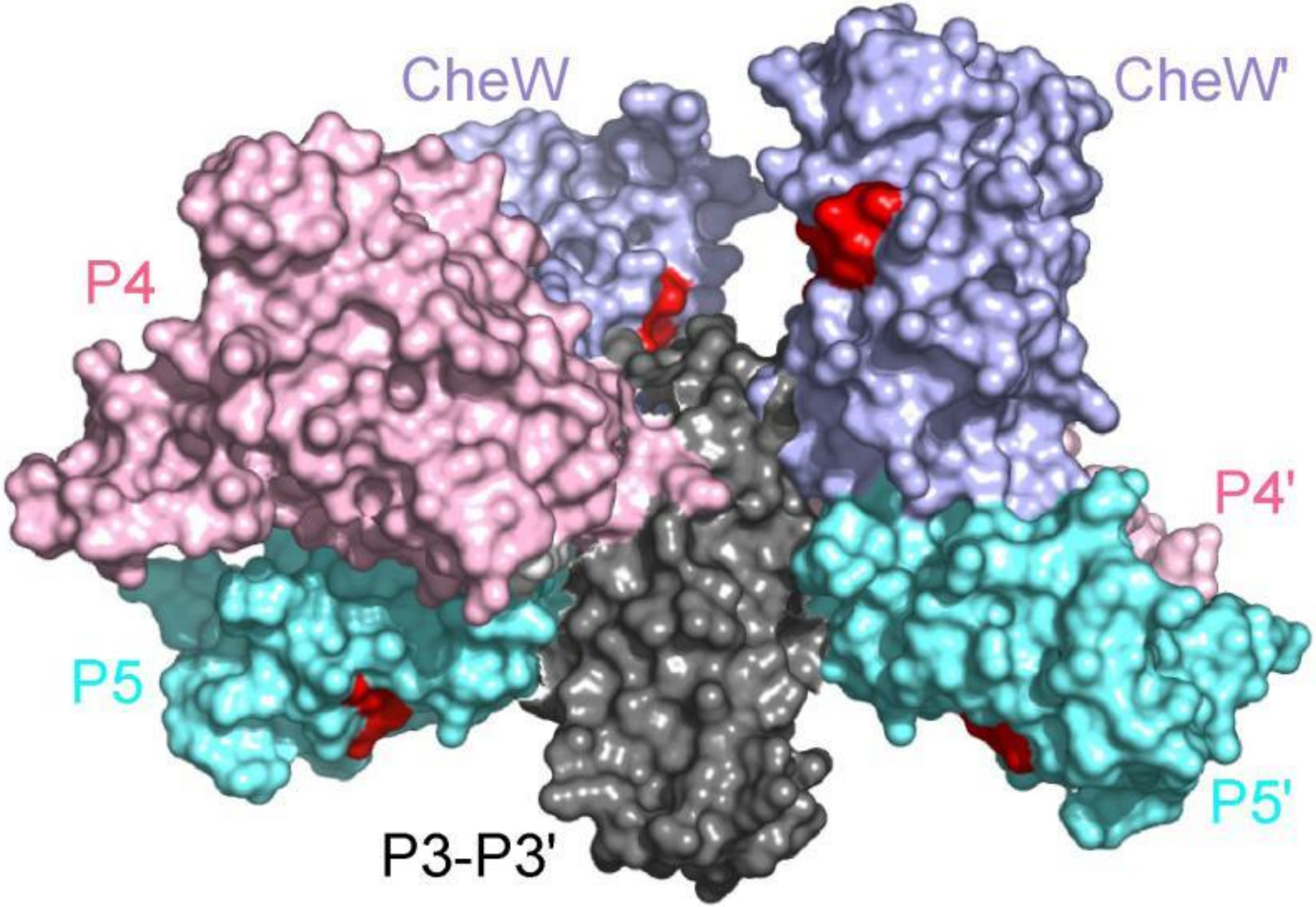


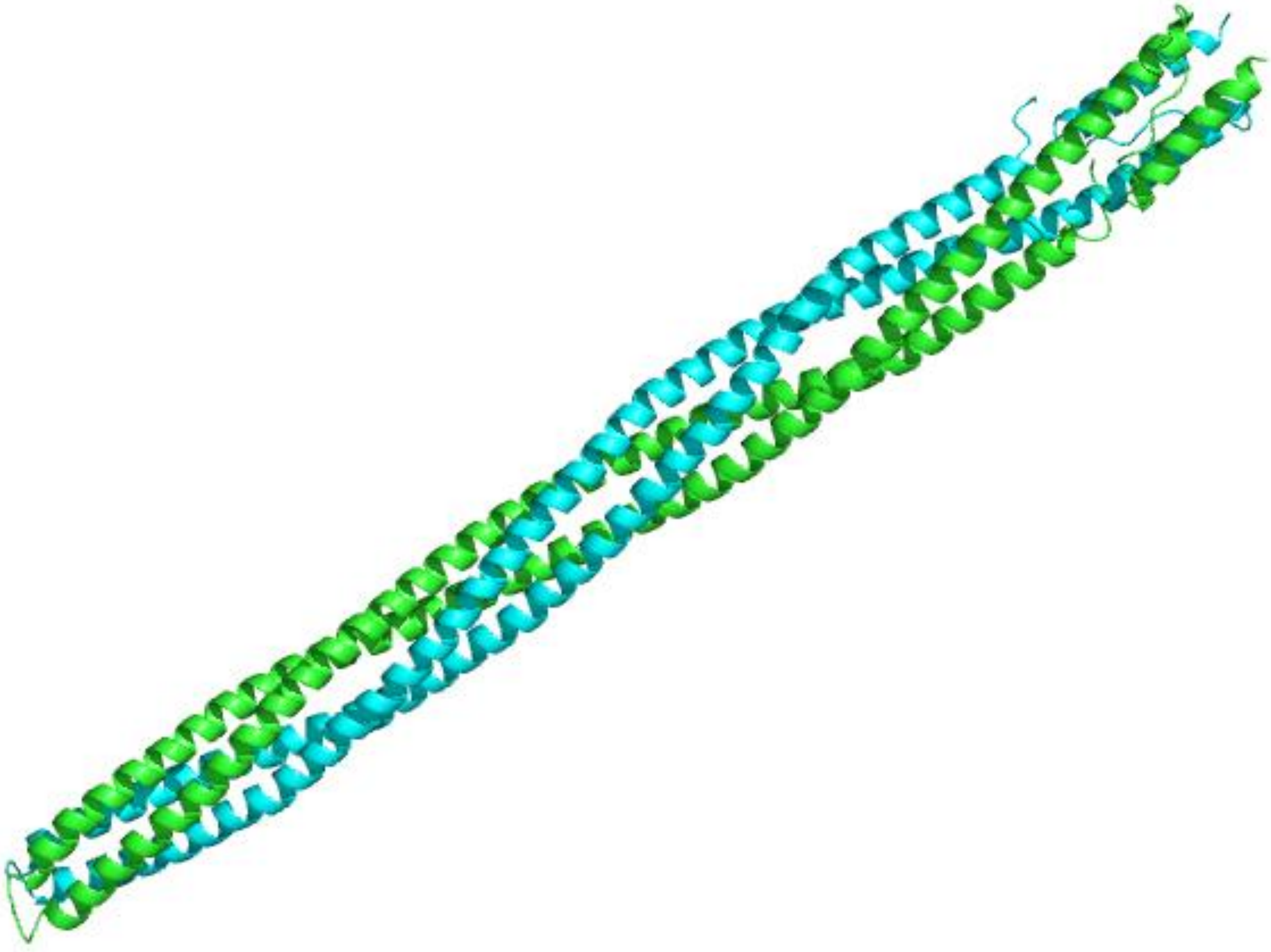
Chemotactic behavior and signaling pathway. (A), Two prominent types of bacterial flagellar motility patterns, run-tumble and run-reverse-flick swimming. (B), Schematic representation of the chemotaxis pathway of E. coli, featuring clustered chemosensory complexes formed by receptors bound to histidine kinase CheA and adaptor protein CheW.

Colin, R., Ni, B., Laganenka, L., & Sourjik, V. (2021). Multiple functions of flagellar motility and chemotaxis in bacterial physiology. *FEMS microbiology reviews*, 45(6), fuab038.

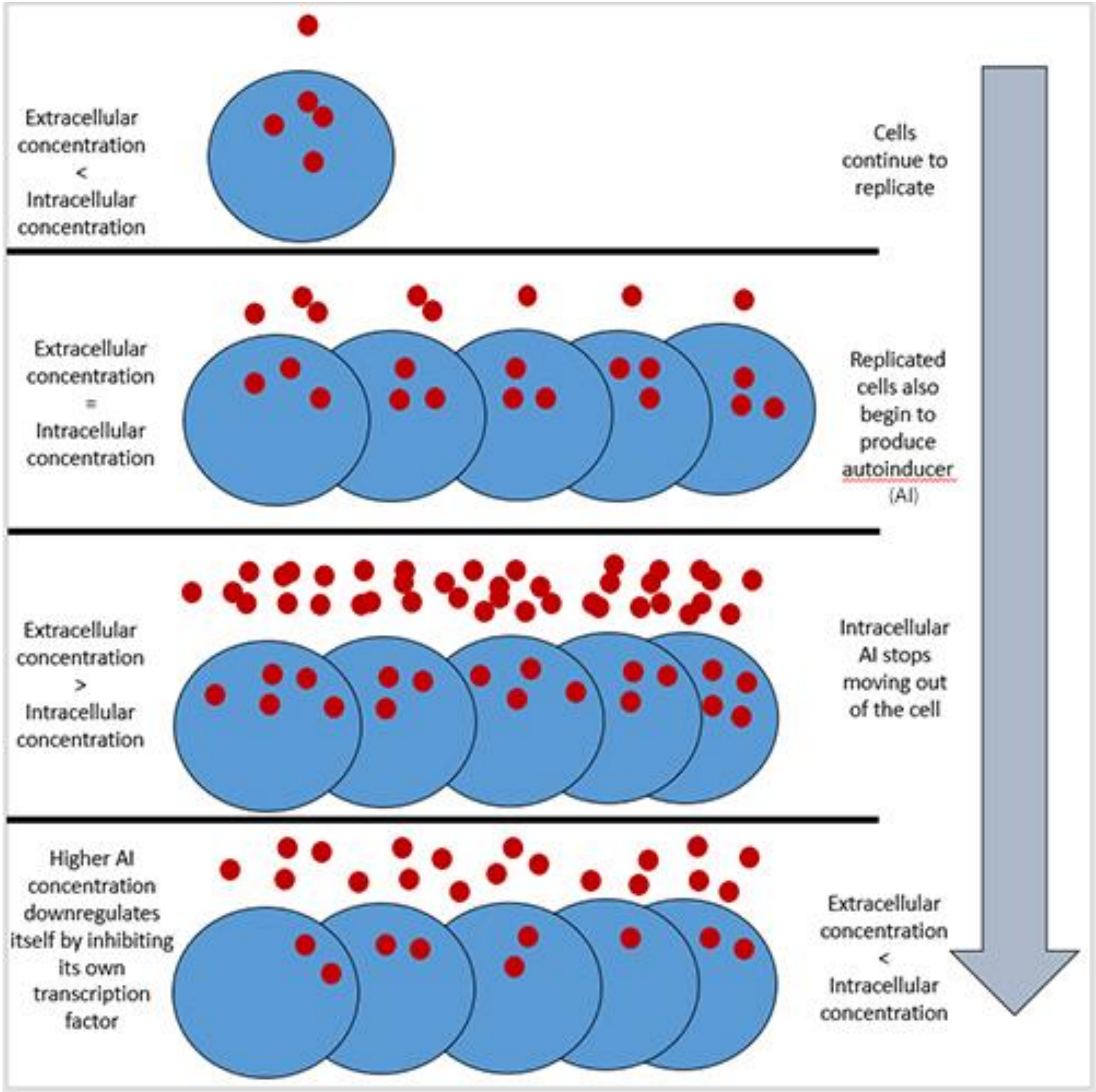


Receptor binding sites of the CheA–CheW complex. The binding sites determined by NMR are shown in red.

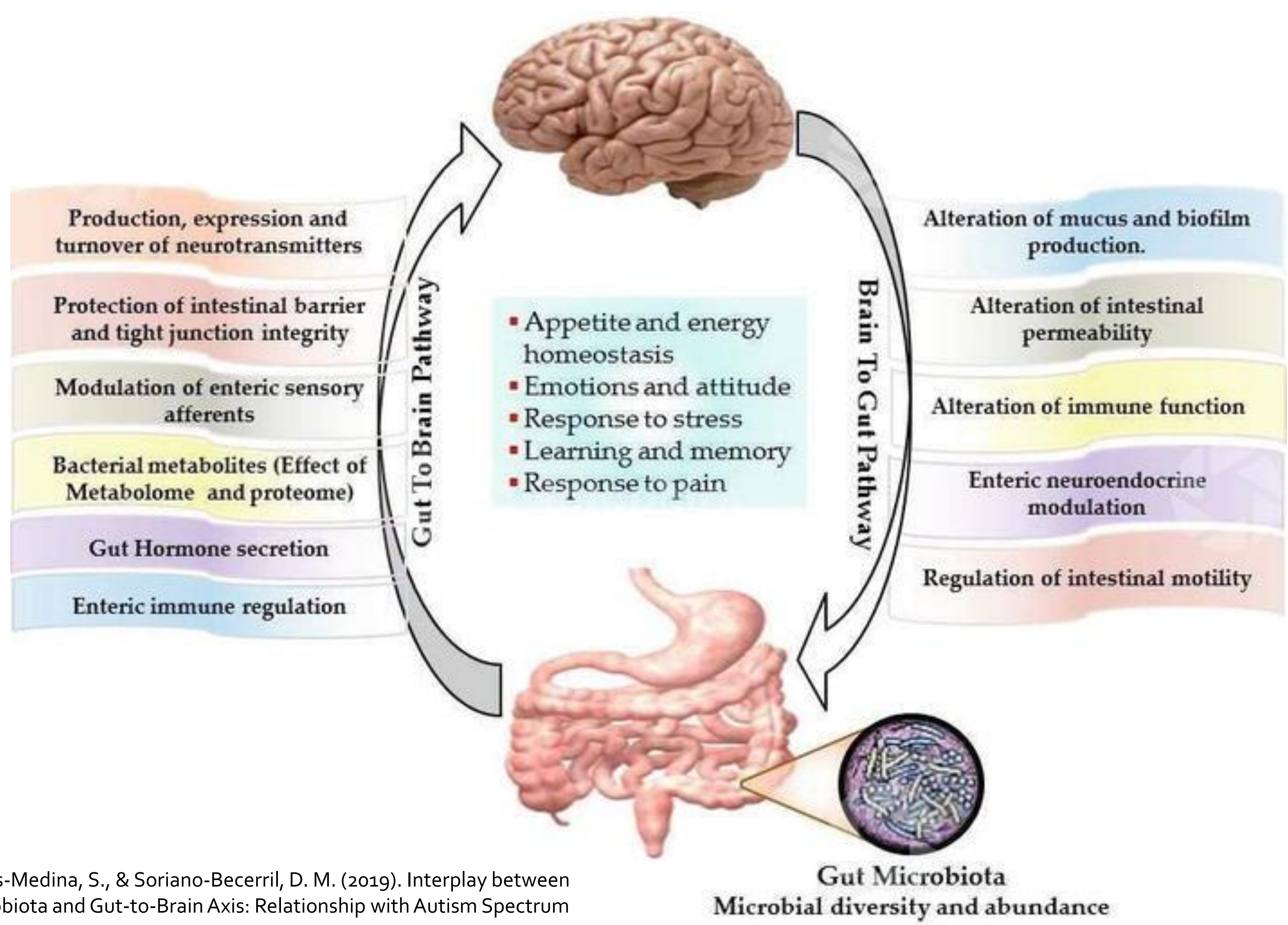
Wang, X., Vu, A., Lee, K., & Dahlquist, F. W. (2012). CheA-receptor interaction sites in bacterial chemotaxis. Journal of molecular biology, 422(2), 282–290.



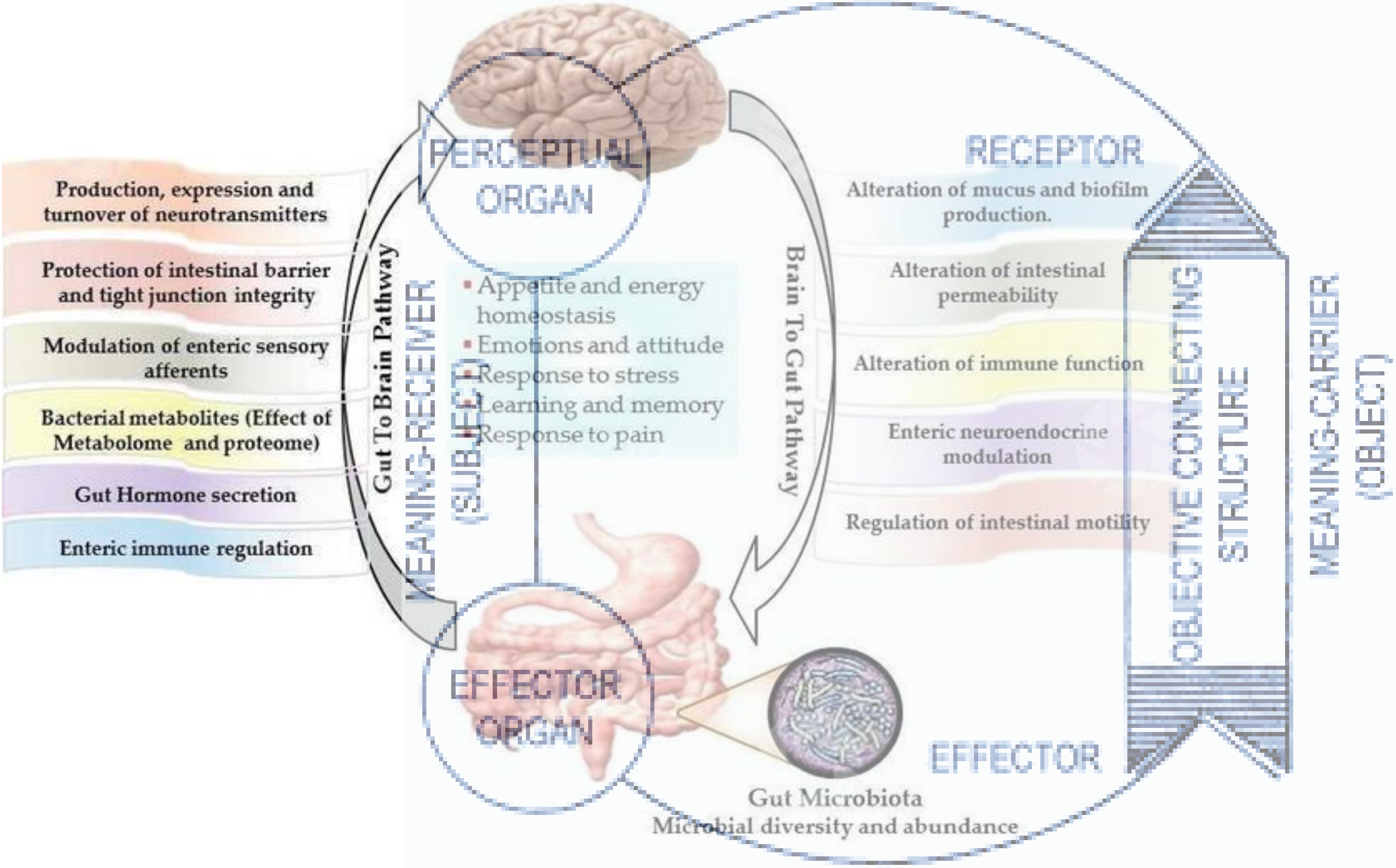
Methyl-accepting chemotaxis protein I. PDB



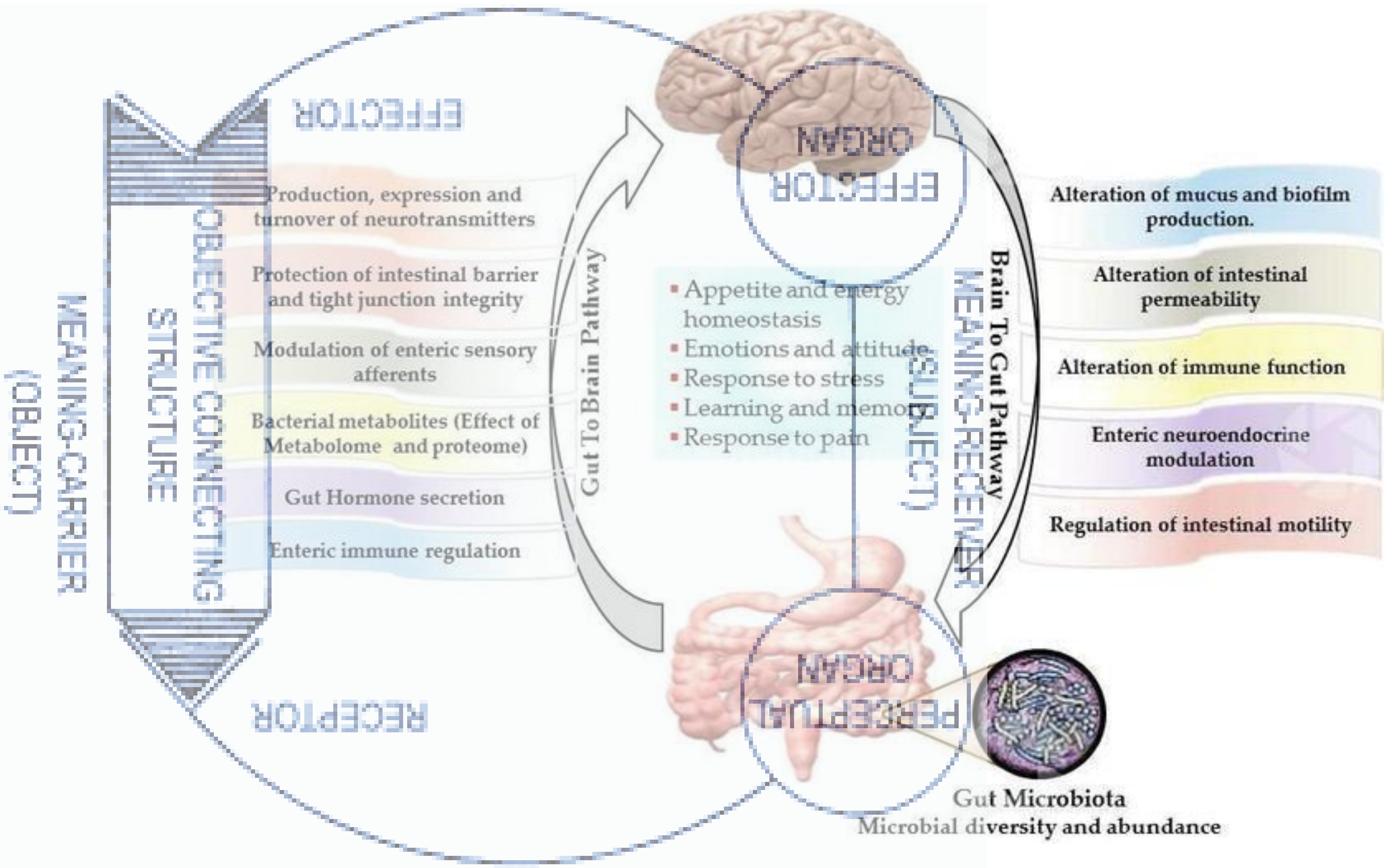
Overview of how quorum sensing works in bacteria. Source: W. Jon Windsor



Díaz-García, F. J., Flores-Medina, S., & Soriano-Becerril, D. M. (2019). Interplay between Human Intestinal Microbiota and Gut-to-Brain Axis: Relationship with Autism Spectrum Disorders. In Microorganisms. IntechOpen.



Production, expression and turnover of neurotransmitters
Protection of intestinal barrier and tight junction integrity
Modulation of enteric sensory afferents
Bacterial metabolites (Effect of Metabolome and proteome)
Gut Hormone secretion
Enteric immune regulation
Gut To Brain Pathway
MEANING-RECEIVER (SUBJECT)
PERCEPTUAL ORGAN
Appetite and energy homeostasis
Emotions and attitude
Response to stress
Learning and memory
Response to pain
Brain To Gut Pathway
EFFECTOR ORGAN
RECEPTOR
Alteration of mucus and biofilm production.
Alteration of intestinal permeability
Alteration of immune function
Enteric neuroendocrine modulation
Regulation of intestinal motility
OBJECTIVE CONNECTING STRUCTURE
MEANING-CARRIER (OBJECT)
EFFECTOR
Gut Microbiota
Microbial diversity and abundance


EFFECTOR
Production, expression and turnover of neurotransmitters
Protection of intestinal barrier and tight junction integrity
Modulation of enteric sensory afferents
Bacterial metabolites (Effect of Metabolome and proteome)
Gut Hormone secretion
Enteric immune regulation
RECEPTOR
MEANING-CARRIER (OBJECT)
OBJECTIVE CONNECTING STRUCTURE
Gut To Brain Pathway
ORGAN
EFFECTOR
Appetite and energy homeostasis
Emotions and attitude
Response to stress
Learning and memory
Response to pain
MEANING-RECEIVER (SUBJECT)
Brain To Gut Pathway
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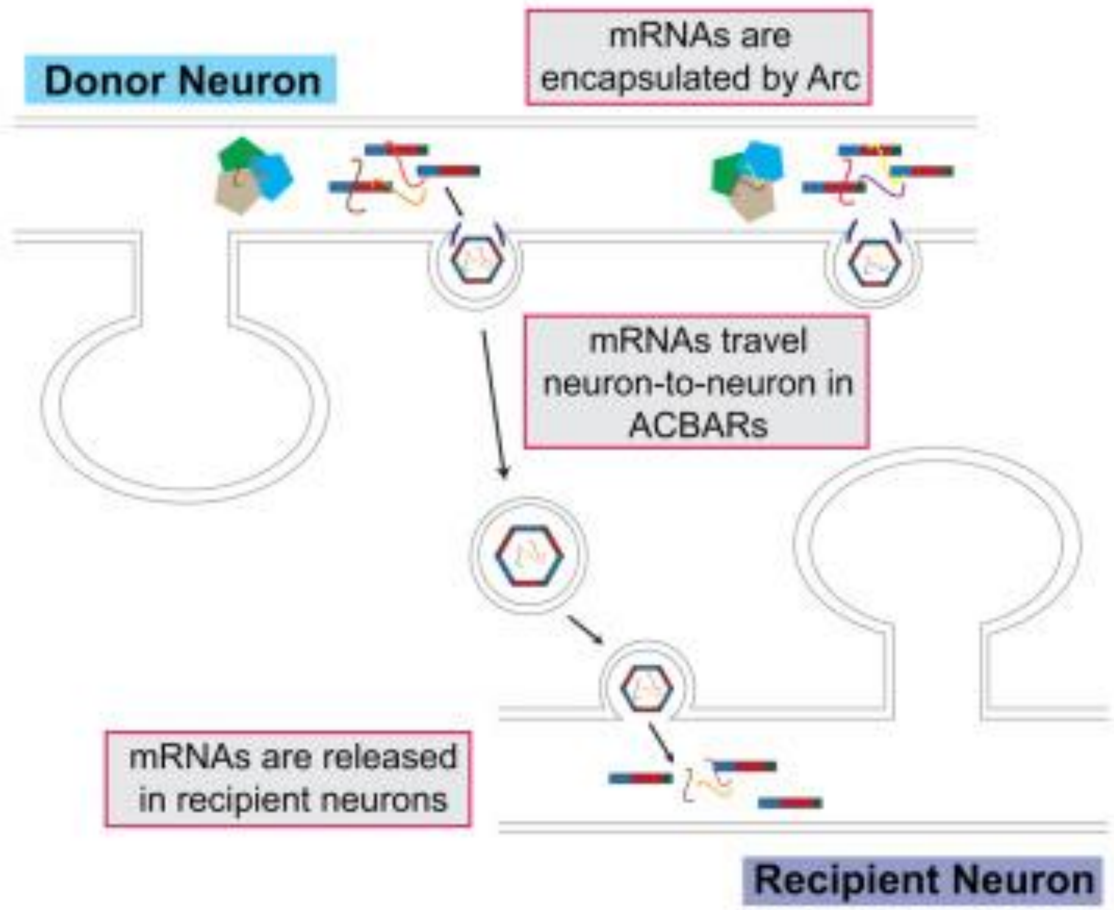
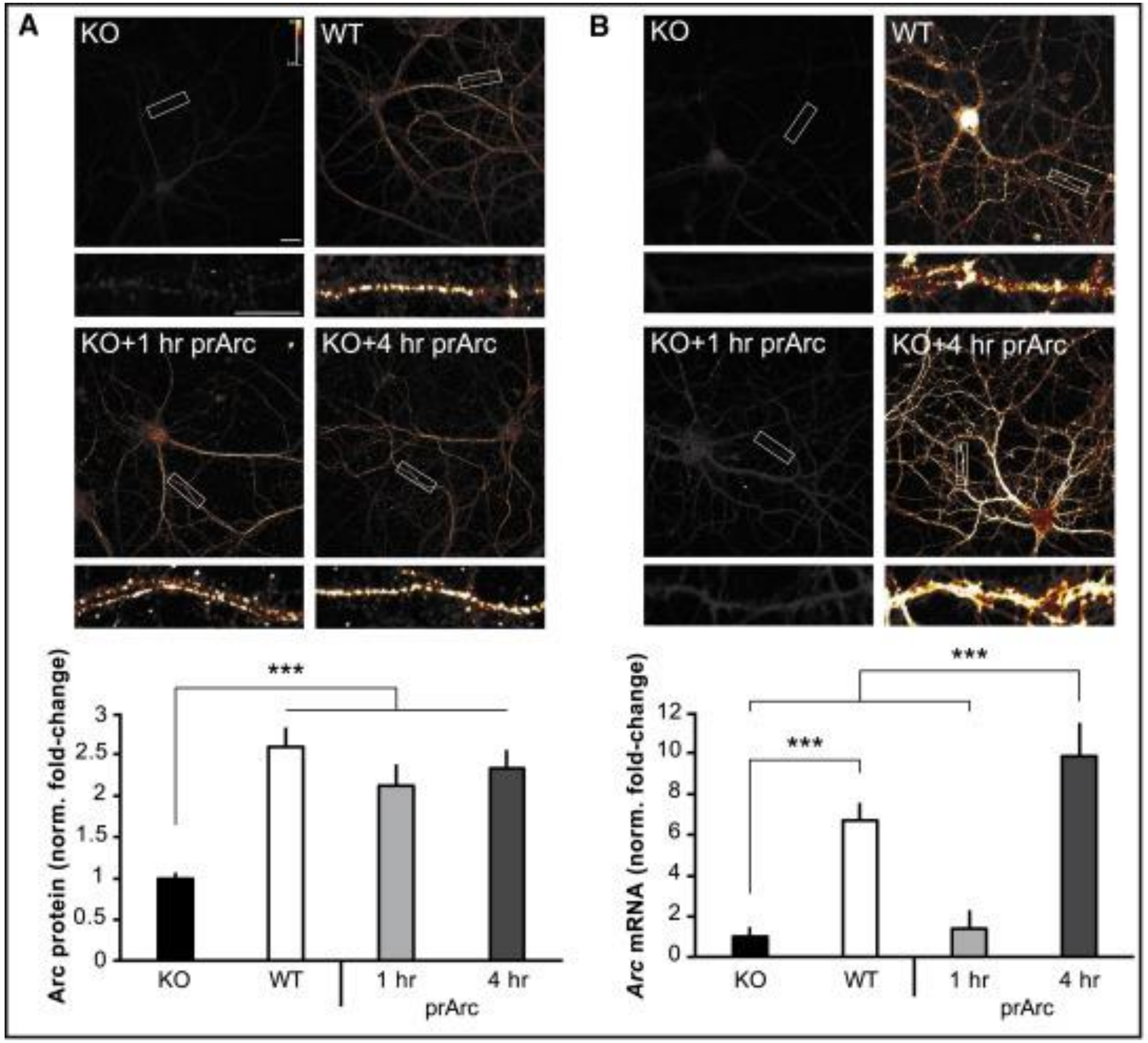
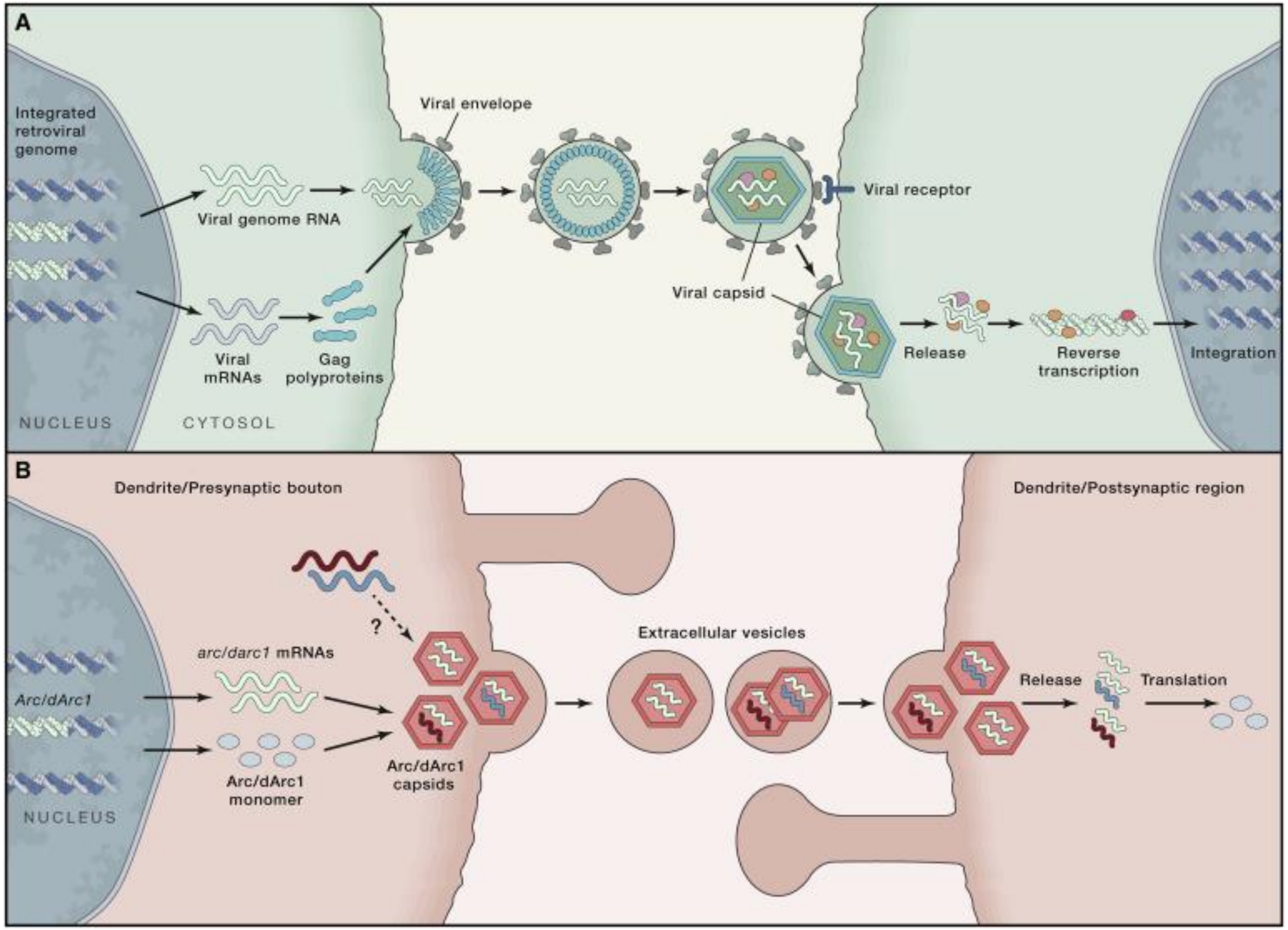
PERCEPTUAL
Alteration of mucus and biofilm production.
Alteration of intestinal permeability
Alteration of immune function
Enteric neuroendocrine modulation
Regulation of intestinal motility
Gut Microbiota
Microbial diversity and abundance





Arc Capsids Transfer Arc mRNA into Neurons

Pastuzyn, E. D. et al. (2018). The neuronal gene arc encodes a repurposed retrotransposon gag protein that mediates intercellular RNA transfer. *Cell*, 172(1-2), 275-288.



Gypsy-like Gag Arc/dArc1 Proteins Assemble a Virus-like Capsid to Transfer arc/darc1 mRNAs into Postsynaptic Sites.

Parrish, N. F., & Tomonaga, K. (2018). A viral (Arc) hive for metazoan memory. *Cell*, 172(1-2), 8-10.

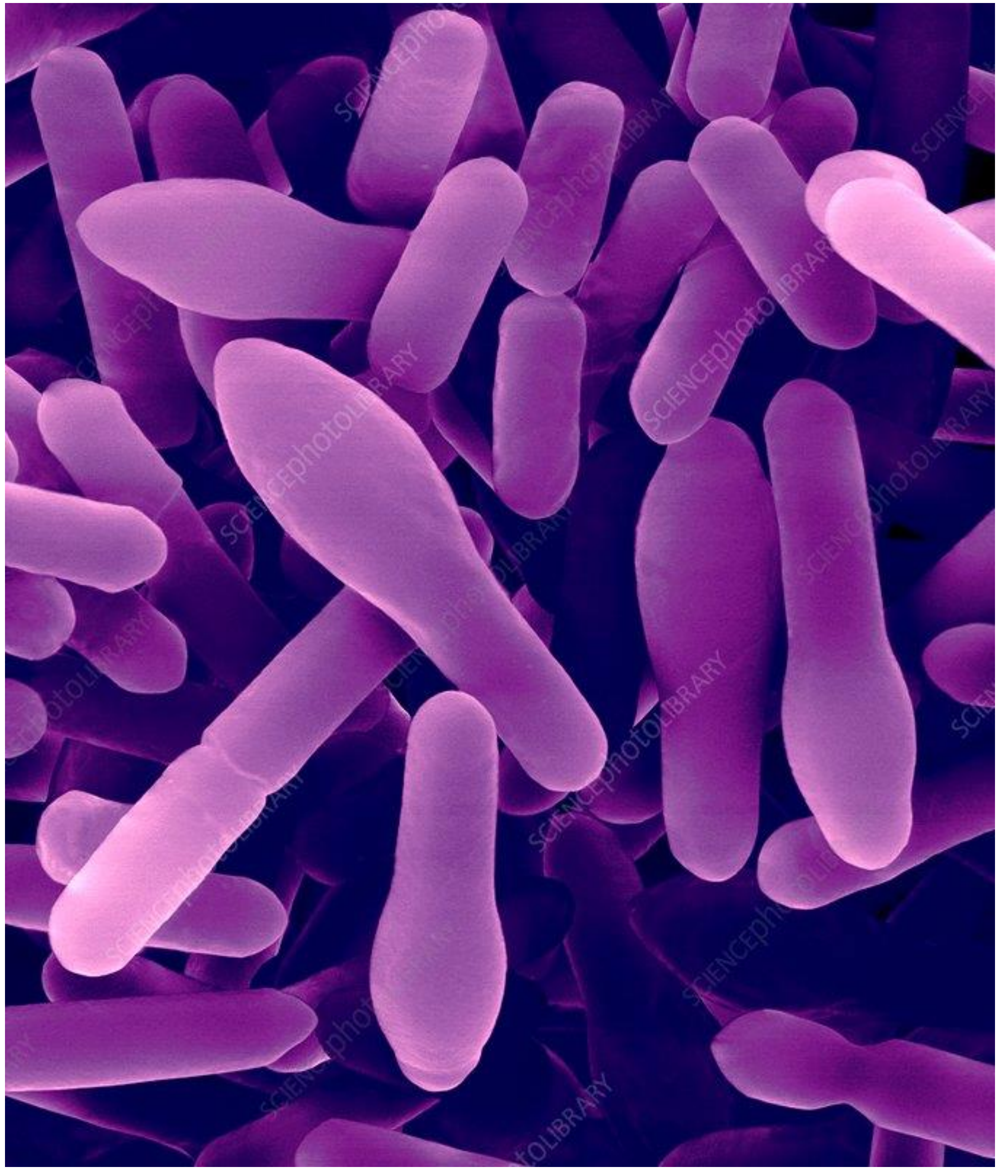
"Nature is everywhere gothic, not classic. She forms a real jungle, where all things are provisional, half-fitted to each other, and untidy."

William James

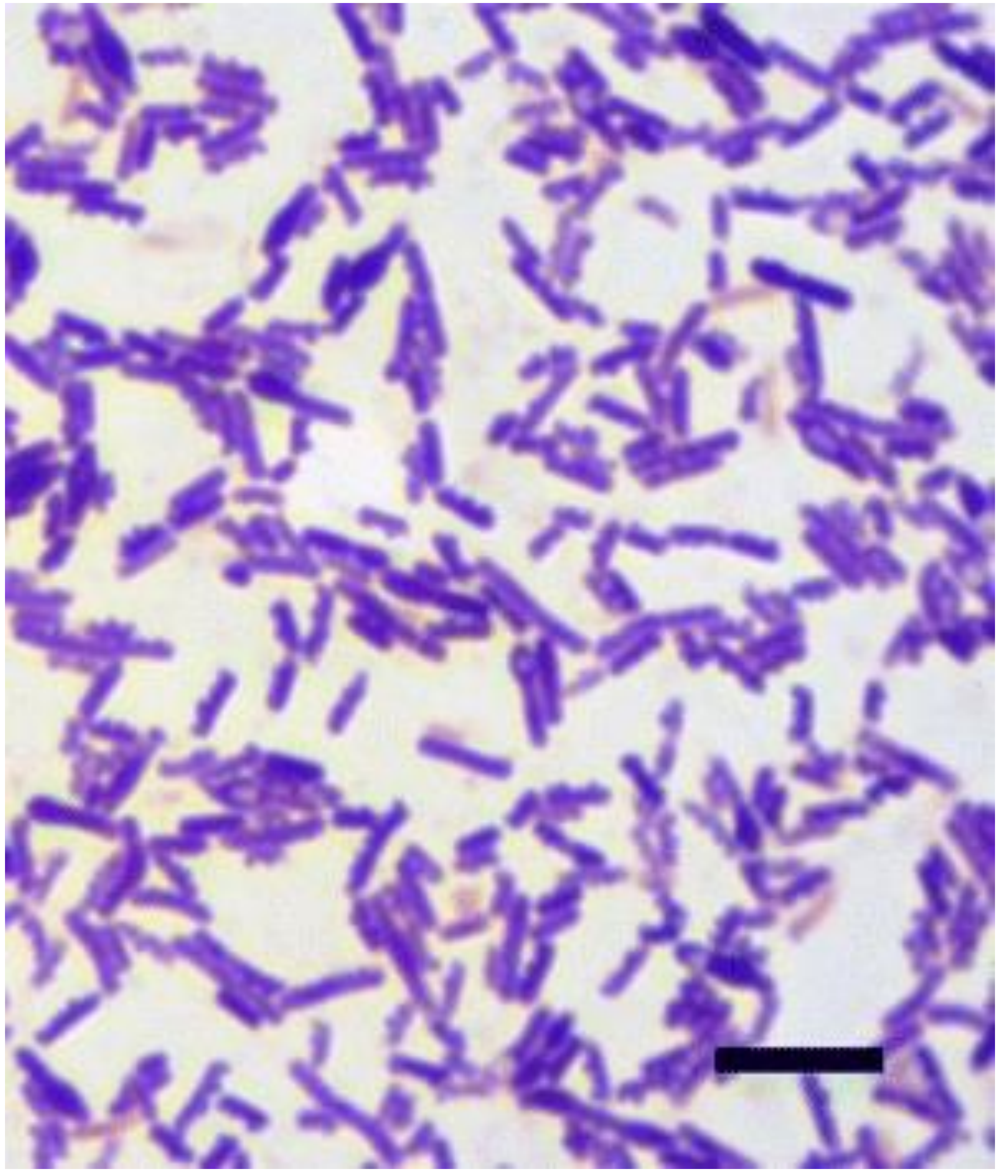
"Frederic Myers's Service to Psychology". *Proceedings of the Society for Psychical Research*, 200–201.

XXIII gatherings in BIOSEMIOTICS

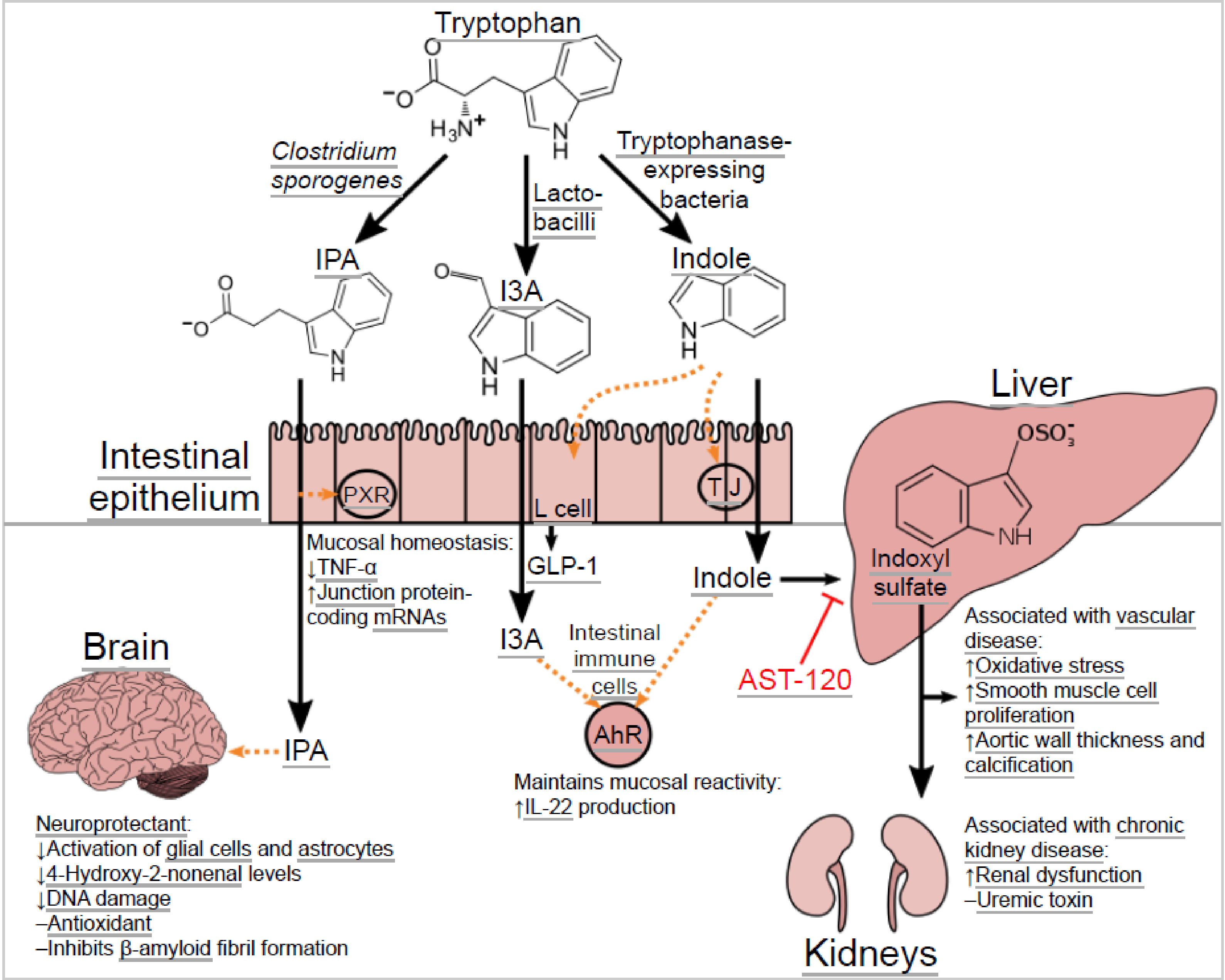
Thank you !!!



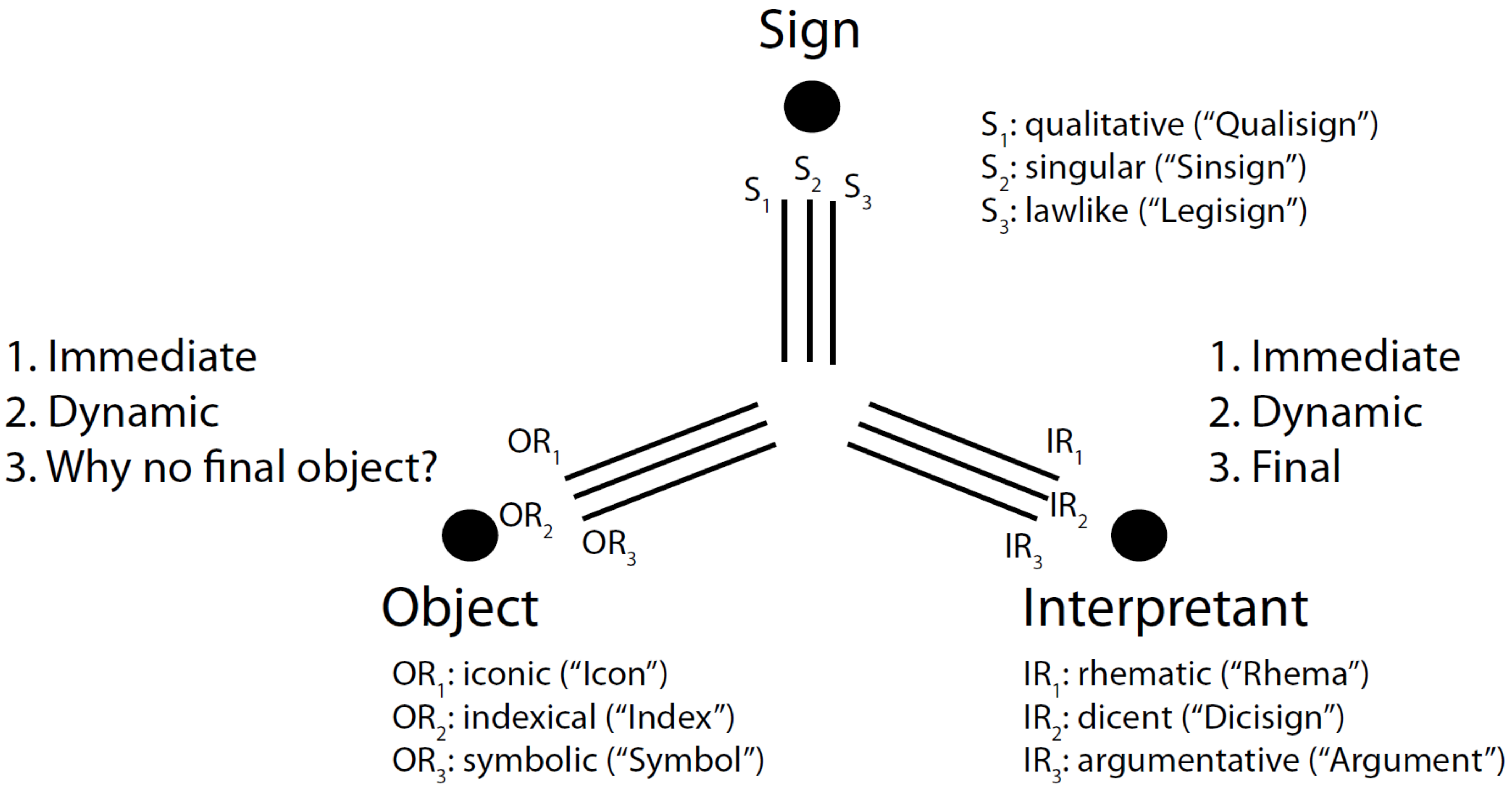
Clostridium sporogenes, spore forming, SEM. Dennis Kunkel Microscopy / Science Photo Library

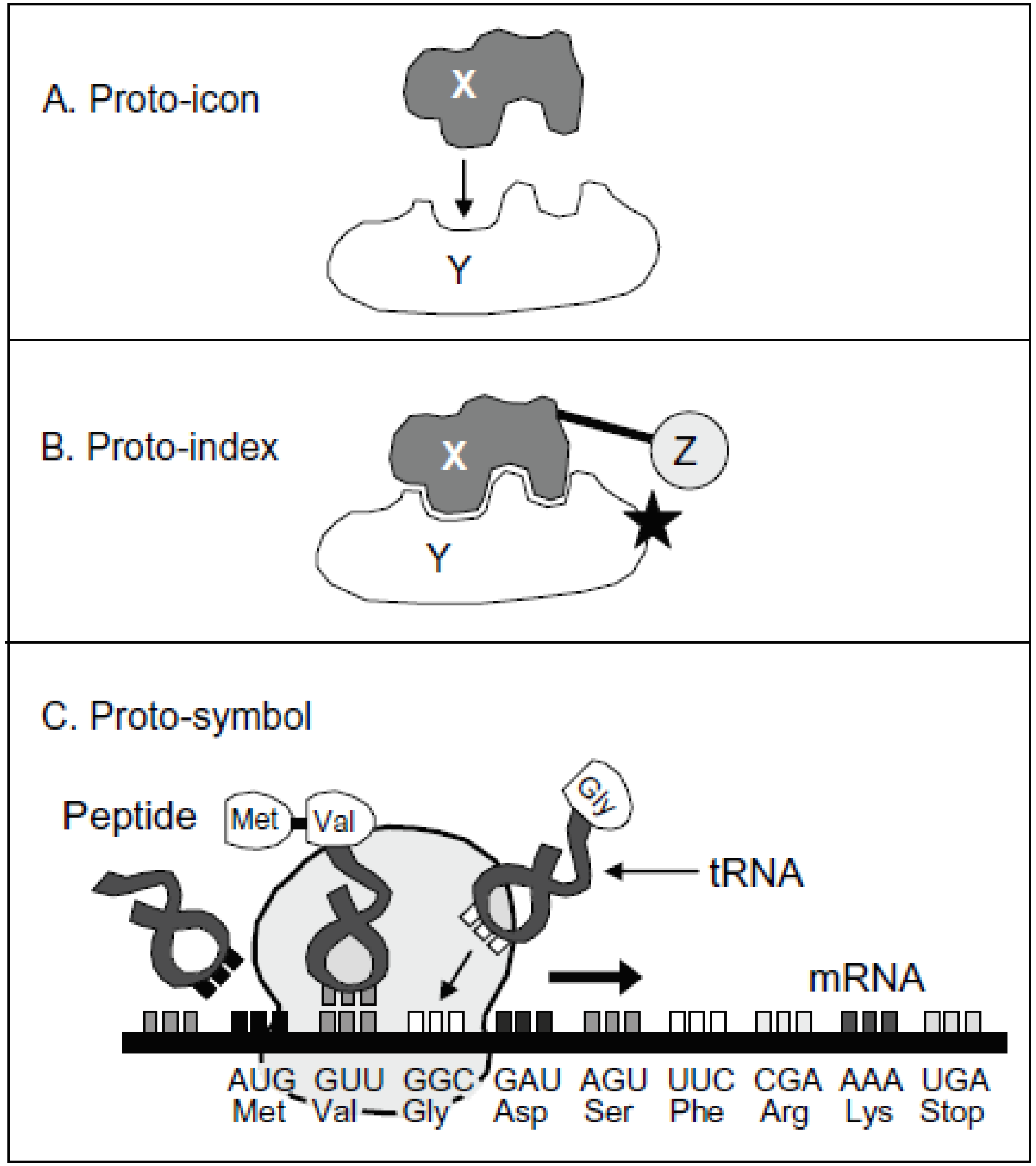


Gram staining of Gram-positive ***C. sporogenes***. Adapted from Figure 1 of Pohlein et al (2015).



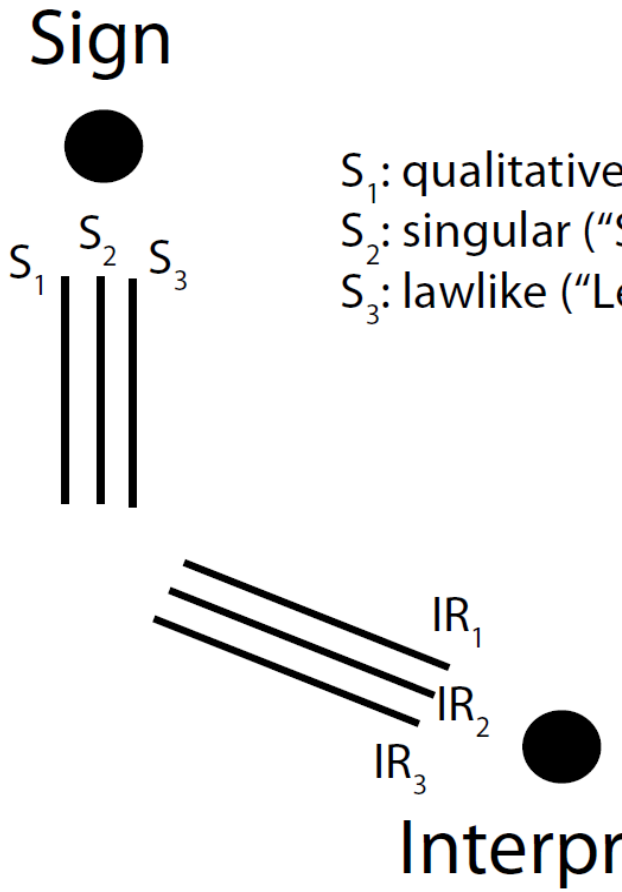
Tryptophan
Clostridium sporogenes
Lacto-bacilli
Tryptophanase-expressing bacteria
IPA
I3A
Indole
Intestinal epithelium
PXR
L cell
TJ
Liver
OSO3-
NH
Indoxyl sulfate
Mucosal homeostasis:
↓TNF-α
↑Junction protein-coding mRNAs
GLP-1
Indole
I3A
Intestinal immune cells
AhR
AST-120
Brain
IPA
Maintains mucosal reactivity:
↑IL-22 production
Associated with vascular disease:
↑Oxidative stress
↑Smooth muscle cell proliferation
↑Aortic wall thickness and calcification
Neuroprotectant:
↓Activation of glial cells and astrocytes
↓4-Hydroxy-2-nonenal levels
↓DNA damage
–Antioxidant
–Inhibits β-amyloid fibril formation
Associated with chronic kidney disease:
↑Renal dysfunction
–Uremic toxin
Kidneys


Sign
S1: qualitative ("Qualisign")
S2: singular ("Sinsign")
S3: lawlike ("Legisign")
S1 S2 S3
1. Immediate
2. Dynamic
3. Why no final object?
OR1
OR2
OR3
Object
OR1: iconic ("Icon")
OR2: indexical ("Index")
OR3: symbolic ("Symbol")
1. Immediate
2. Dynamic
3. Final
IR1
IR2
IR3
Interpretant
IR1: rhematic ("Rhema")
IR2: dicent ("Dicisign")
IR3: argumentative ("Argument")



Types of molecular signs in living cells classified by immediate interaction. Sharov, A. A. (2017). Molecular biocommunication. In R. Gordon & J. Seckbach (Eds.), *Biocommunication. Sign-mediated interactions between cells and organisms* (pp. 3–35). World Scientific.

Quasi-signs : “Proto-signs” (Bennett, 2021; Sharov & Vehkavaara, 2015)



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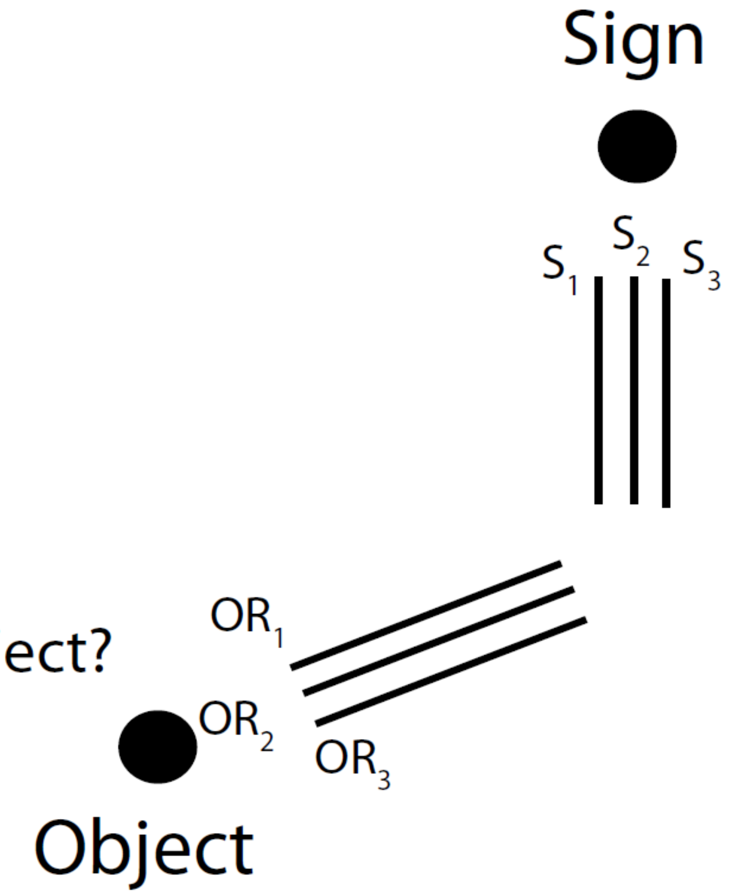
IR_3: argumentative (“Argument”)

Quasi-signs : “Post-signs” or “Tardo-signs” (Bennett, 2021; Sharov & Vehkavaara, 2015)



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