BM Systems

PREDICTIVE INTEGRATIVE BIOLOGY

Les besoins fonctionnels de la biologie intégrative pour construire des modèles intégrés de pathologies impactées par la dynamique des microbiotes: Autisme & Schizophrénie

The functional needs of integrative biology to construct integrated models of pathologies impacted by microbiota dynamics : Autism & Schizophrenia

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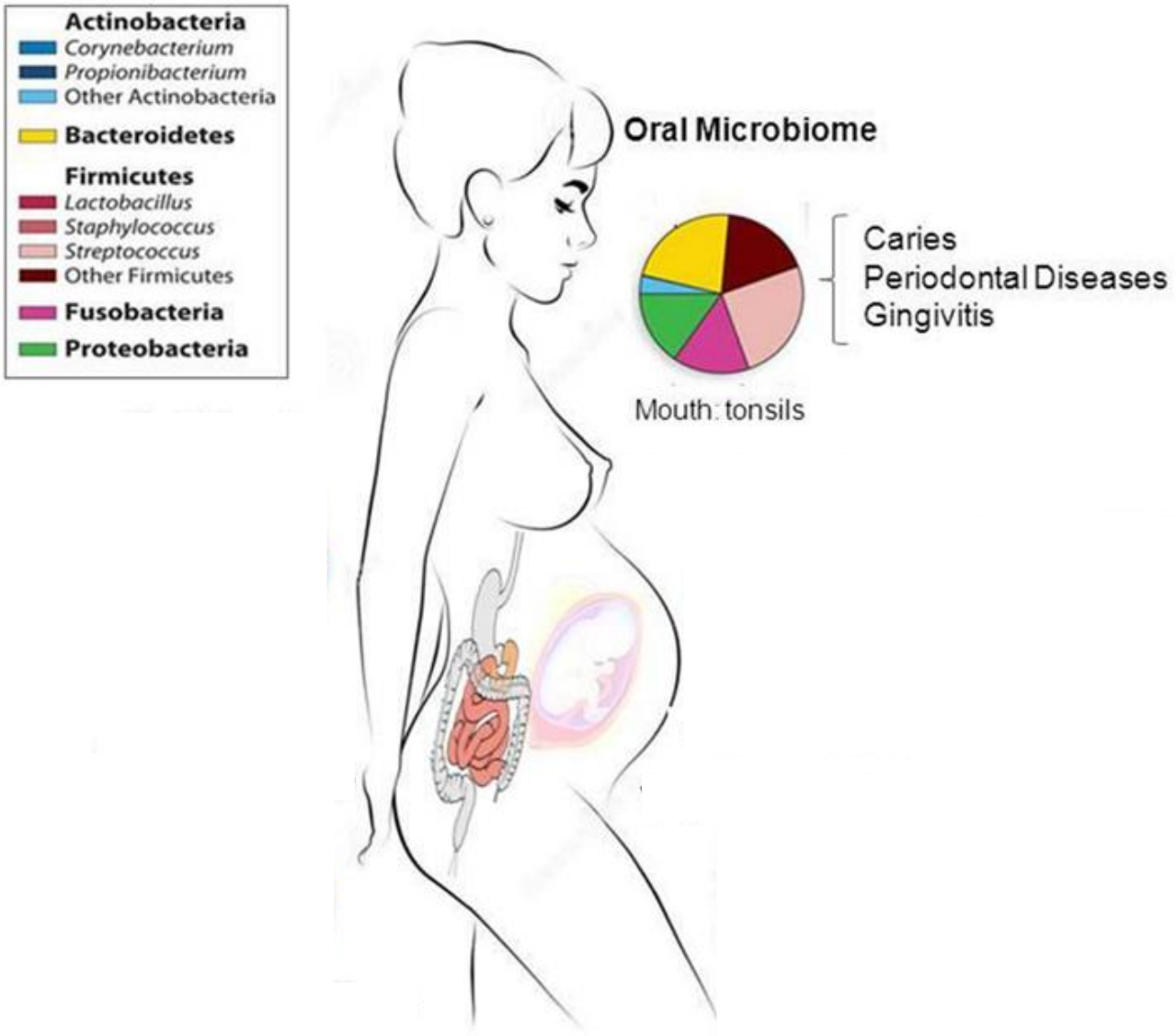
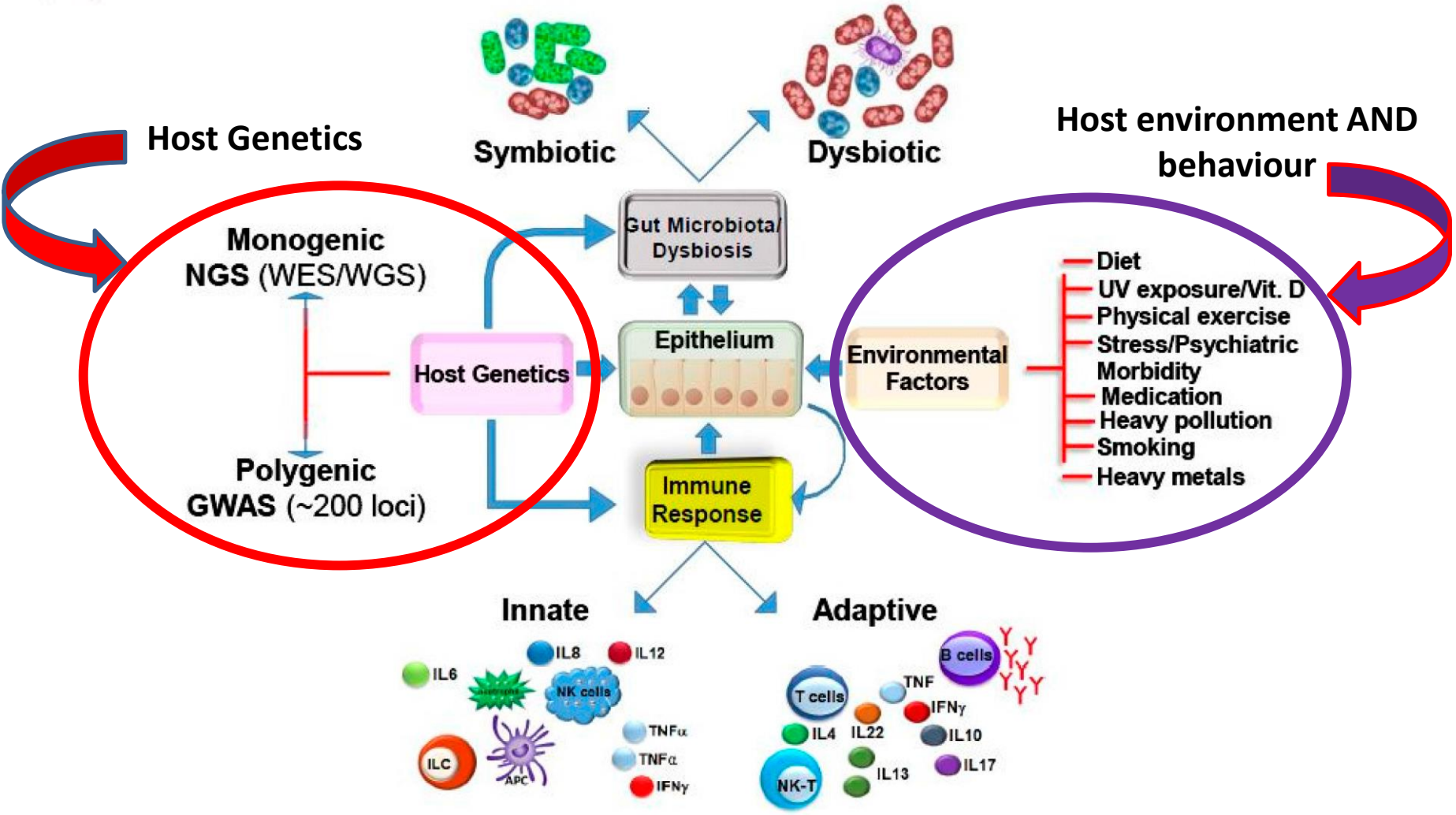
We are walking zoos and inmates of the zoo affect us



But we also affect the components of the zoo

The cross-talks between microbiota, host and environment



NGS: next-generation sequencing;
WES/WGS: whole-exome (mRNA)/whole-genome sequencing;
GWAS: genome-wide association study

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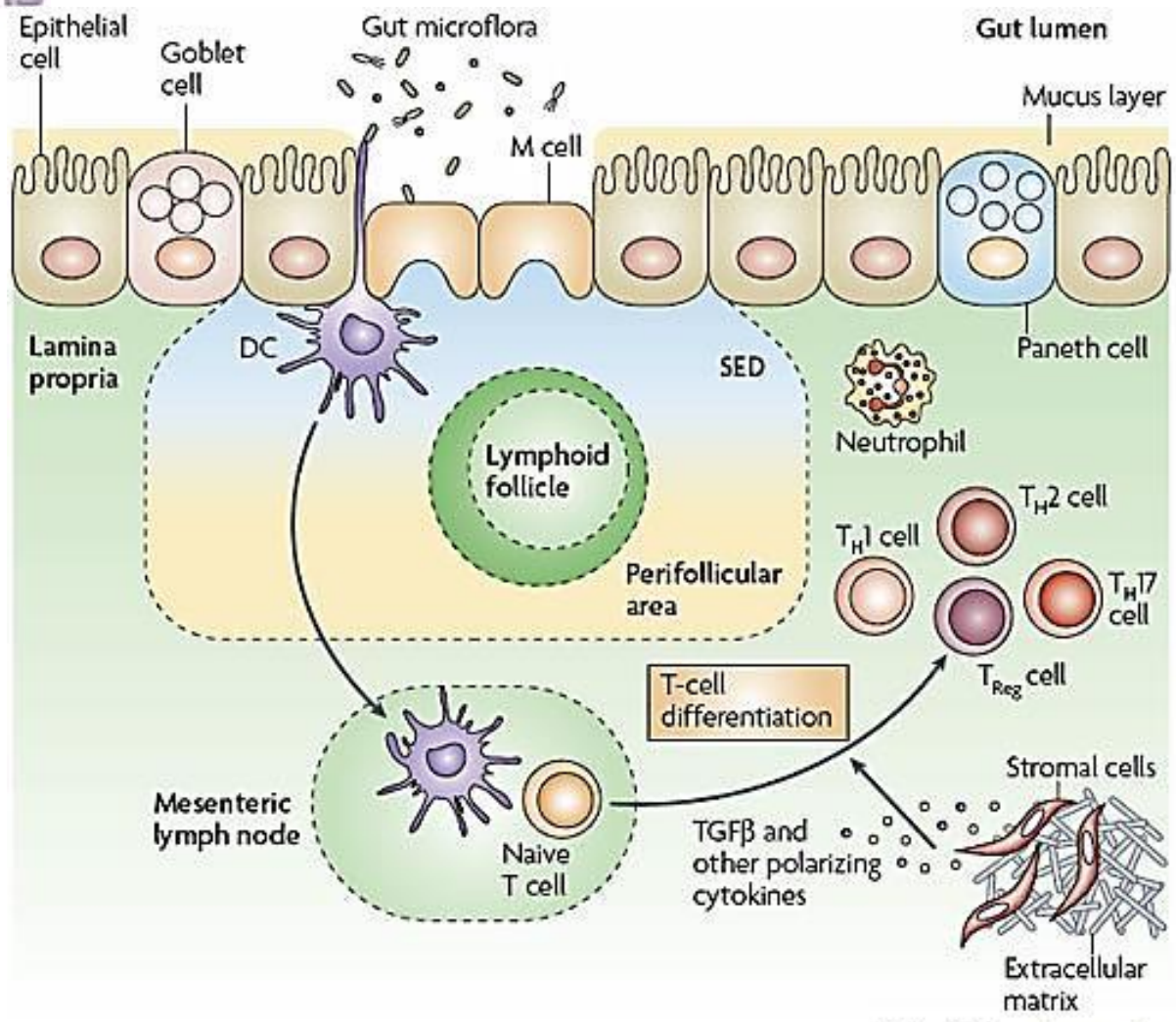
Immunological environment of the intestine



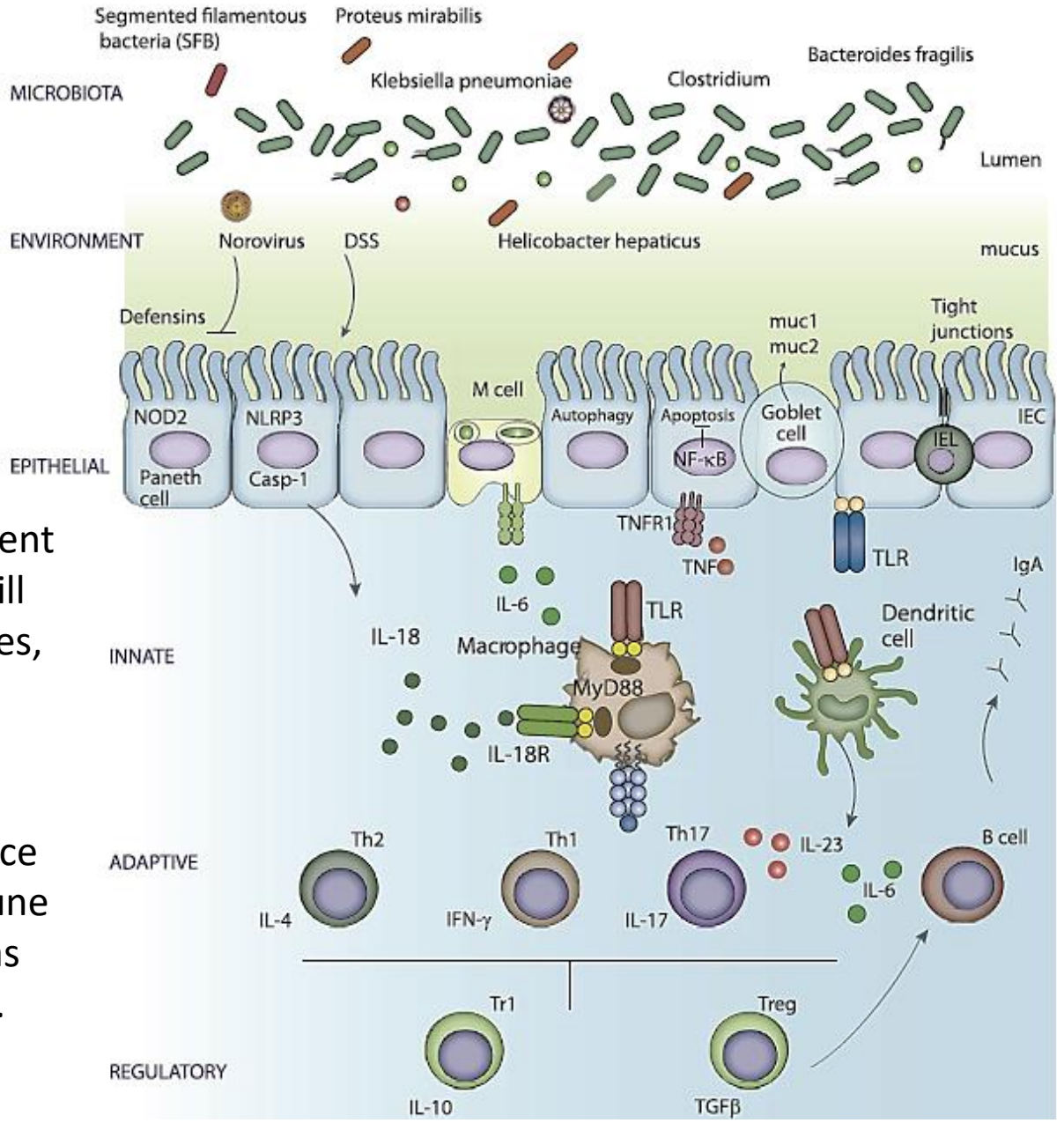
Local microbiota (gut, skin, airways, etc.) are in direct contact with resident immune components of the host.

Intestinal immunological homeostasis

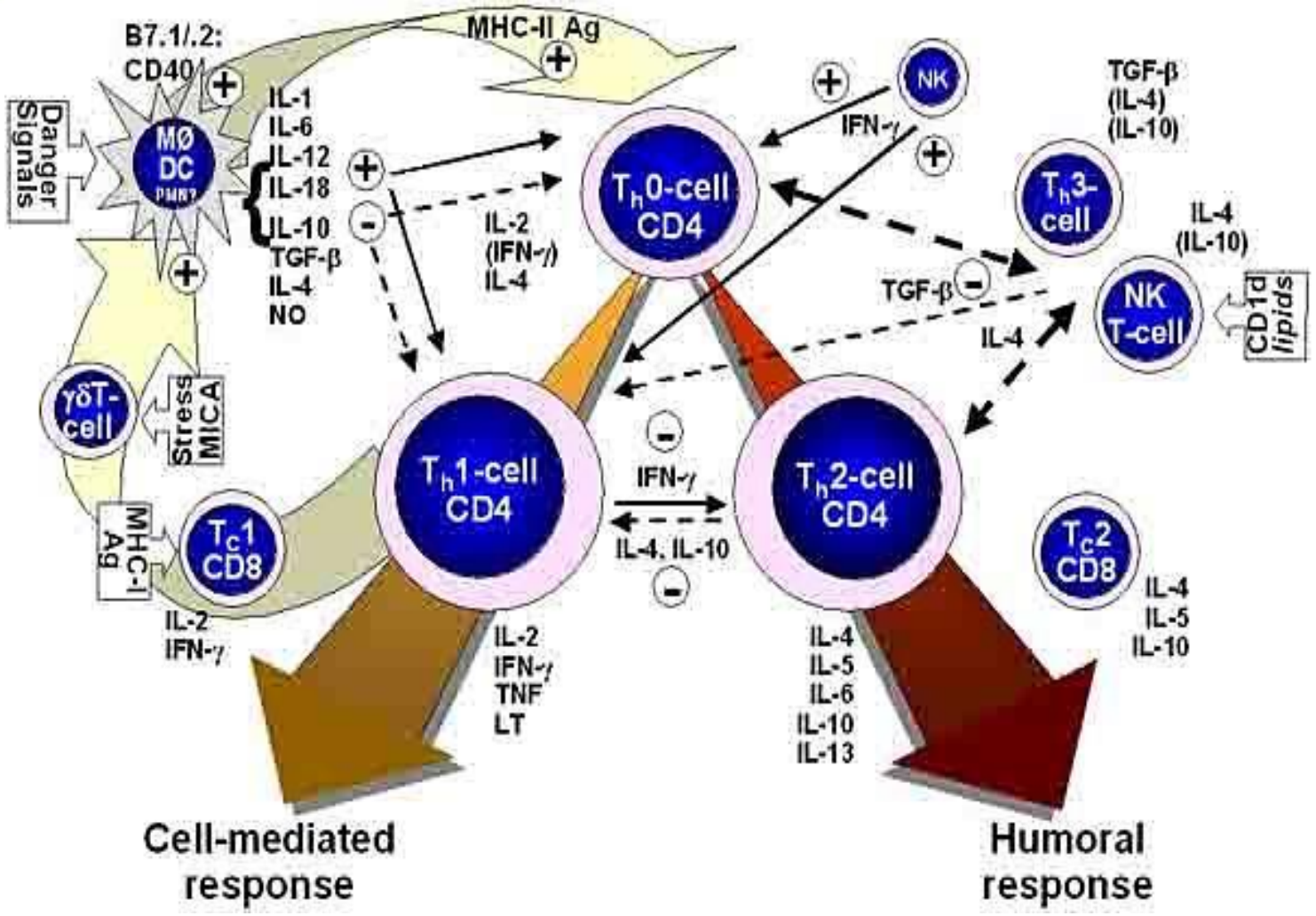
The local dynamics of our microbiota literally shapes

The responsiveness of the resident innate immune system (what will results in inflammations, allergies, etc. & in which contexts) ;

As well as the degree of tolerance of the attendant adaptive immune system (what will be accepted as innocuous & in which contexts).



Systemic immunological homeostasis



Cumulatively, these local effects modulate individual-specific systemic immunological patterning.

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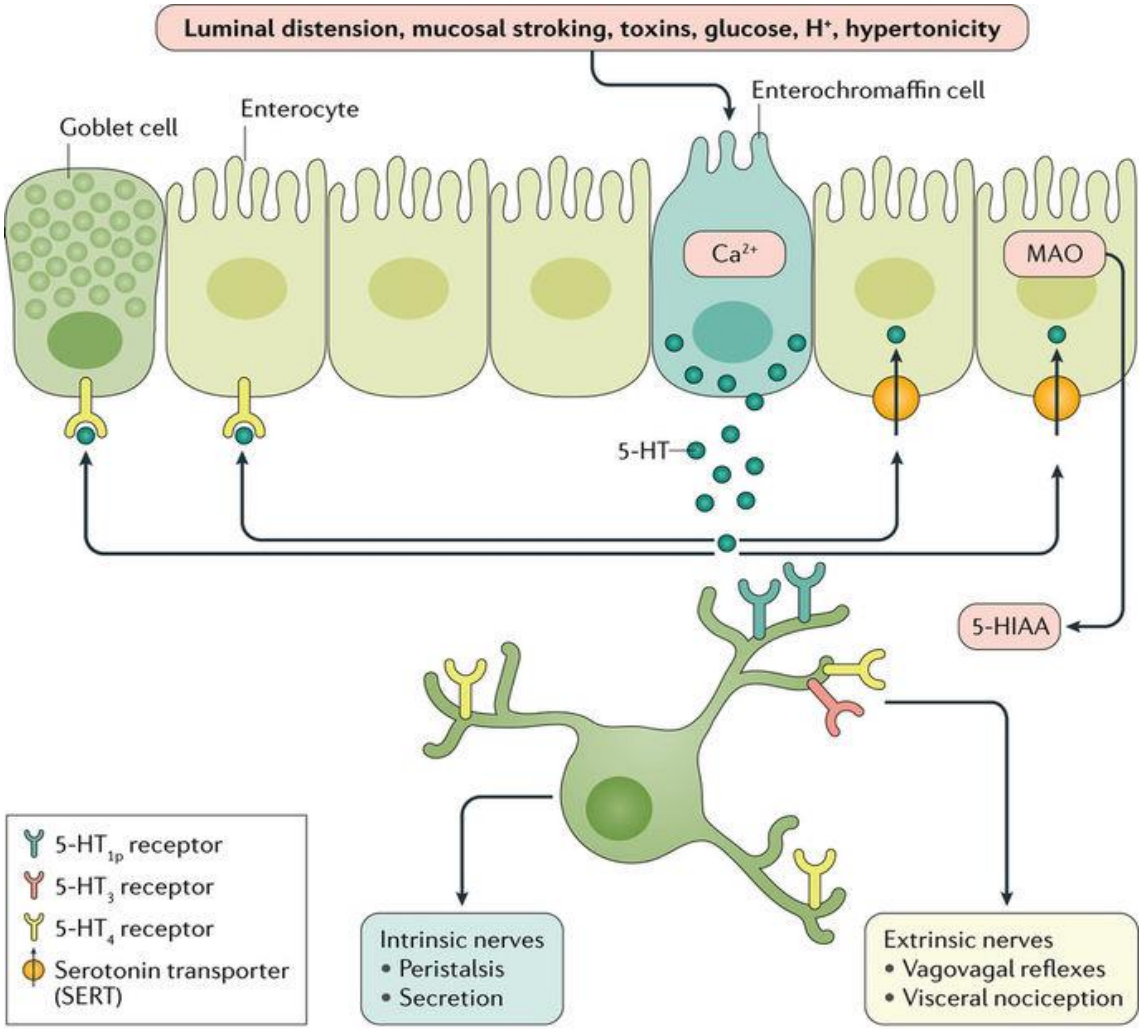
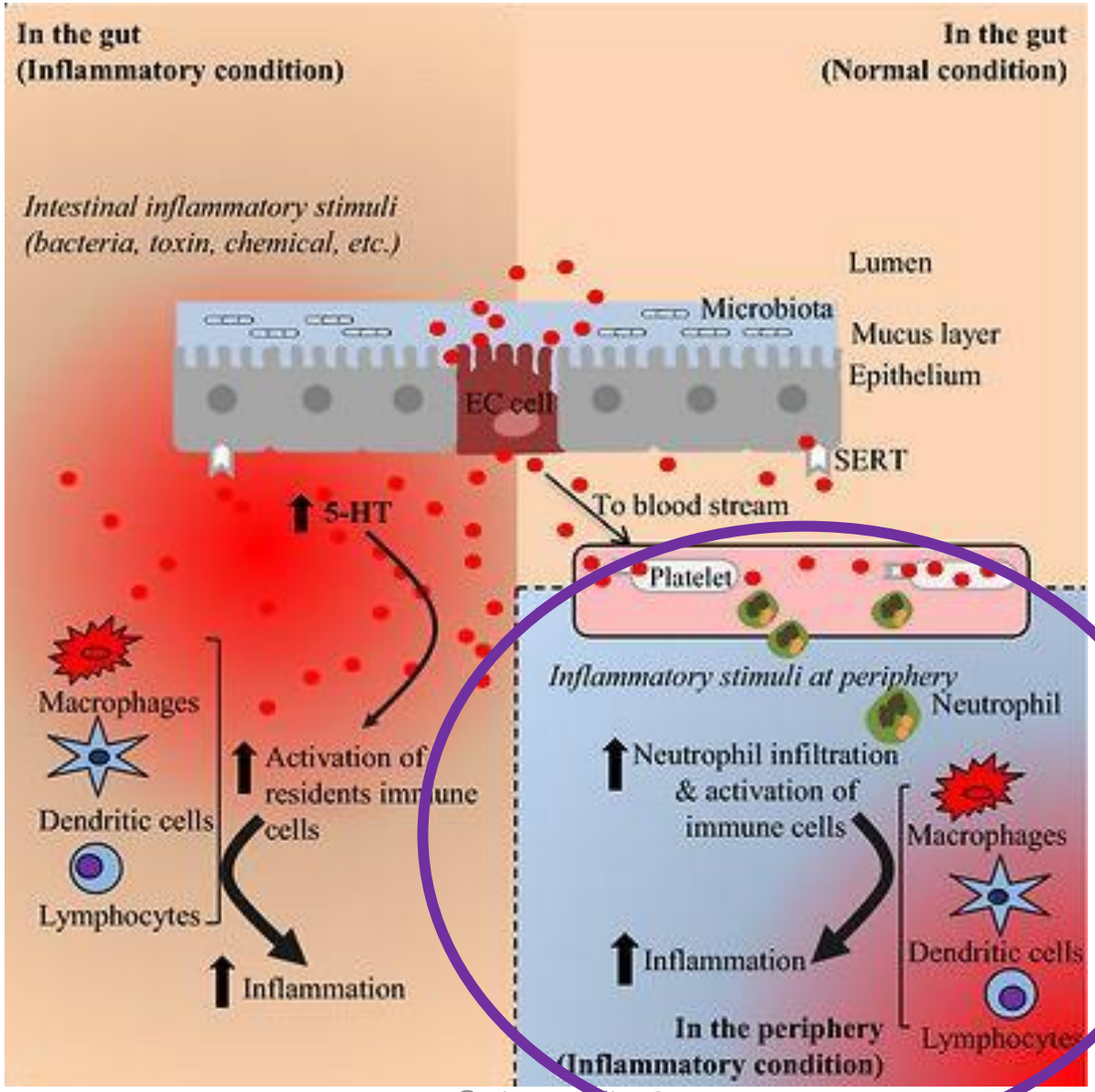
Additionally, the cells in contact with a microbiota also signal changes in its metabolic dynamics

Serotonin signalling in the gut



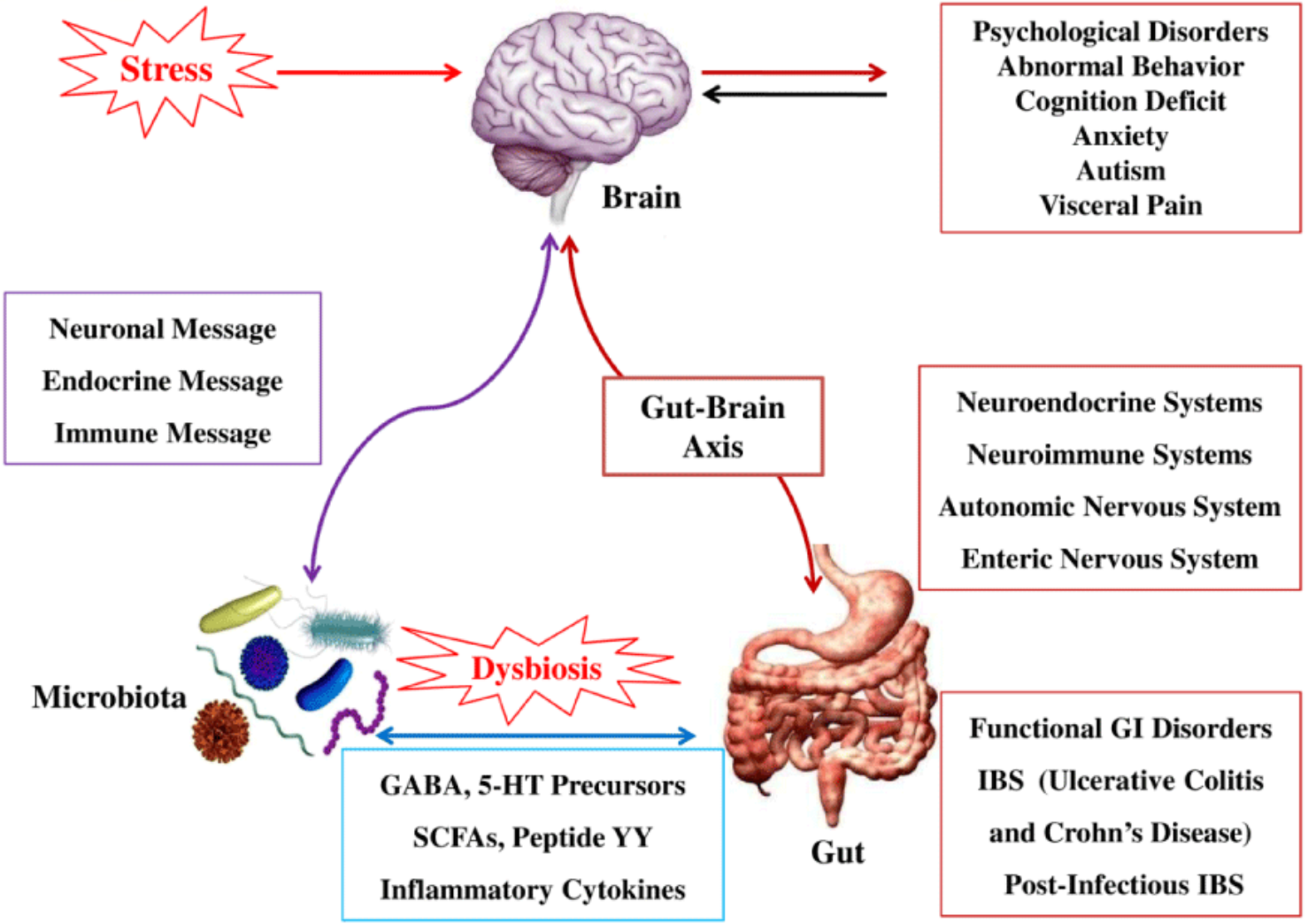
This form of signalling has systemic consequences

The role of gut-derived 5-HT in systemic inflammation.



Subthreshold (low grade) systemic inflammation

There are well established links between microbiota and psychiatry



Microbiota dysbiosis is a primary source of low grade systemic inflammation.

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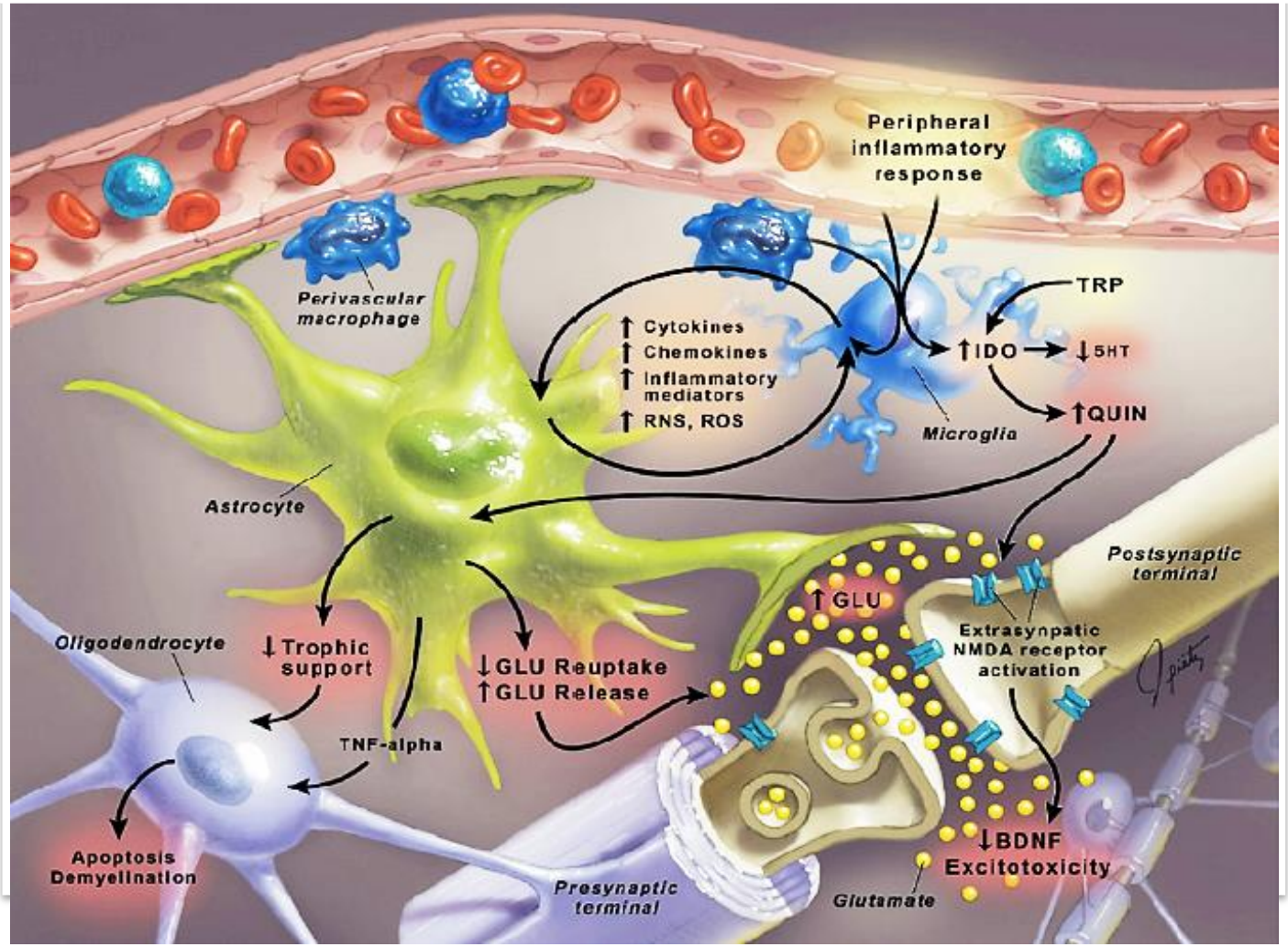
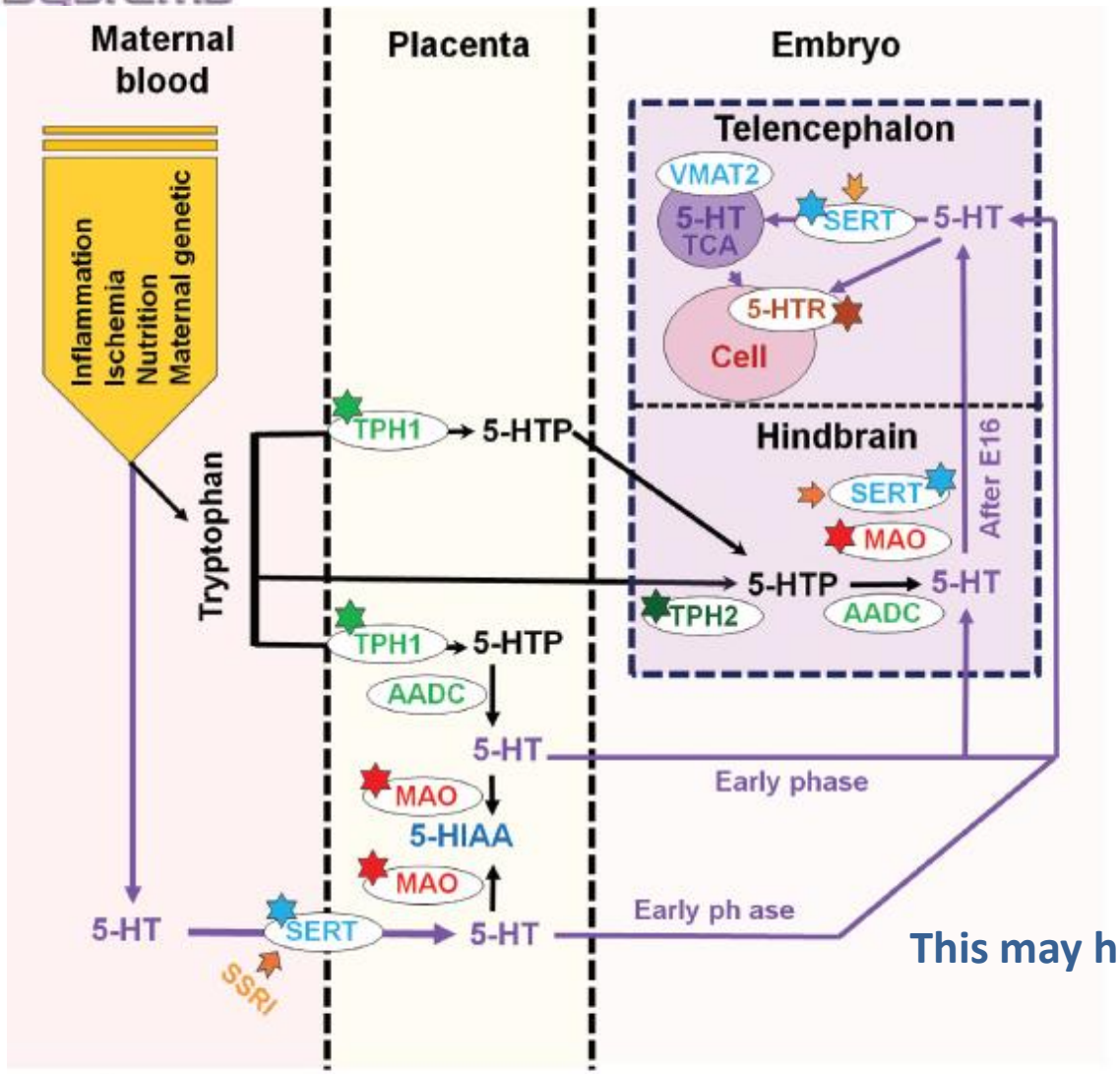
Systemic sub-threshold pro-inflammatory conditions dysregulate CNS functions



Neuroglial cross-talk dysregulations are typically associated with psychiatric disorders such as schizophrenia, major depression, bipolar disorder, etc..

Maternal placental conditions determine the amount of serotonin (5-HT) supply to the developing brain

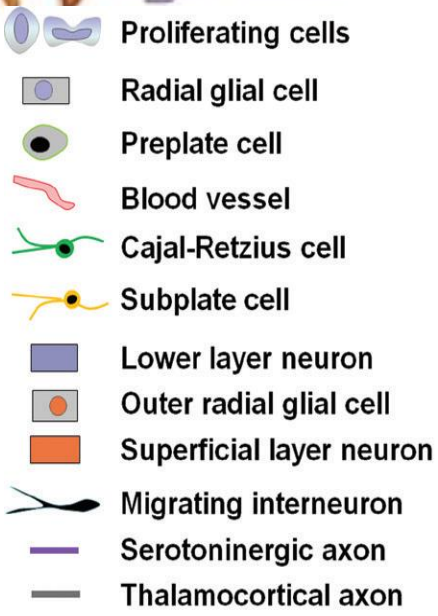


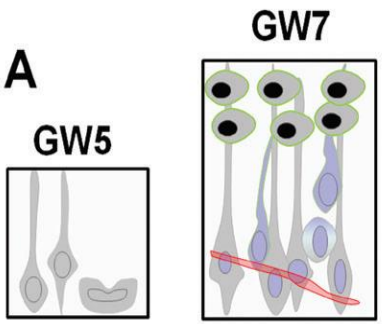
Maternal chronic subthreshold systemic inflammation during early pregnancy will result in an oversupply of 5-HT to the developing embryo.

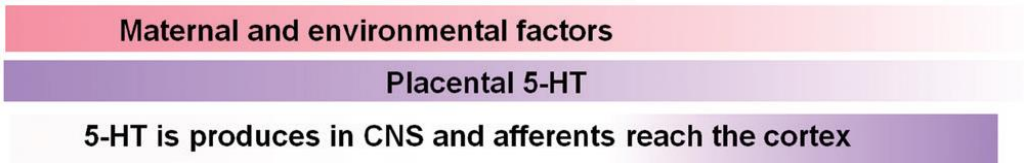
This may have dramatic consequences!

Serotonin literally sculpts the cerebral cortex

Development of the human cerebral cortex in relation to 5-HT







MZ

CP

SP

IZ

OSVZ

VZ

- In human, intense proliferation of neuro-epithelium and the formation of the preplate (PP) take place around GW5 and GW 6-7.
- By GW 8-10, PP is split by the migration of the first pyramidal neurons.
- Around GW 10, another source of progenitors arises: the outer radial glial (oRG) cells that do not maintain contacts with the apical surface.
- By GW 16 most glutamatergic neurons are generated and 5-HT axons run in the apical (MZ) and deep layers (IZ). SP neurons occupy a large proportion of the cortical space and oRG cells are still producing a high amount of neurons.
- At this time, interneurons first migrate tangentially and later radially to the cortical surface.

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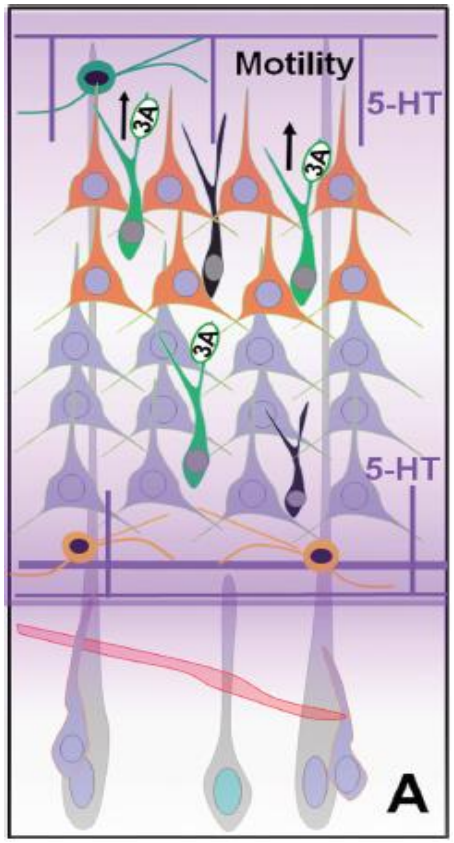
Serotonin literally sculpts the cerebral cortex

Modulation of cerebral circuit formation by 5-HT



Excessive 5-HT supply at this stage results in positioning & connectivity alterations affecting numerous neuronal populations.

Positioning & connectivity alterations leads to loss of control over pruning regulation resulting in aberrant, excessive pruning (an anatomical hallmark of autism)**.**

Physiological concentration of serotonin (5-HT), induce an acceleration of radial migration of 5-HT3A+ interneurons during the 20th gestational week.

At early **postnatal** stage, Cajal-Retzius cells (C-R) respond to 5-HT by releasing reelin, inducing pruning of apical dendrites of pyramidal neurons (Pyr).

Such cortical alterations are typically associated with Autism Spectrum Disorders.

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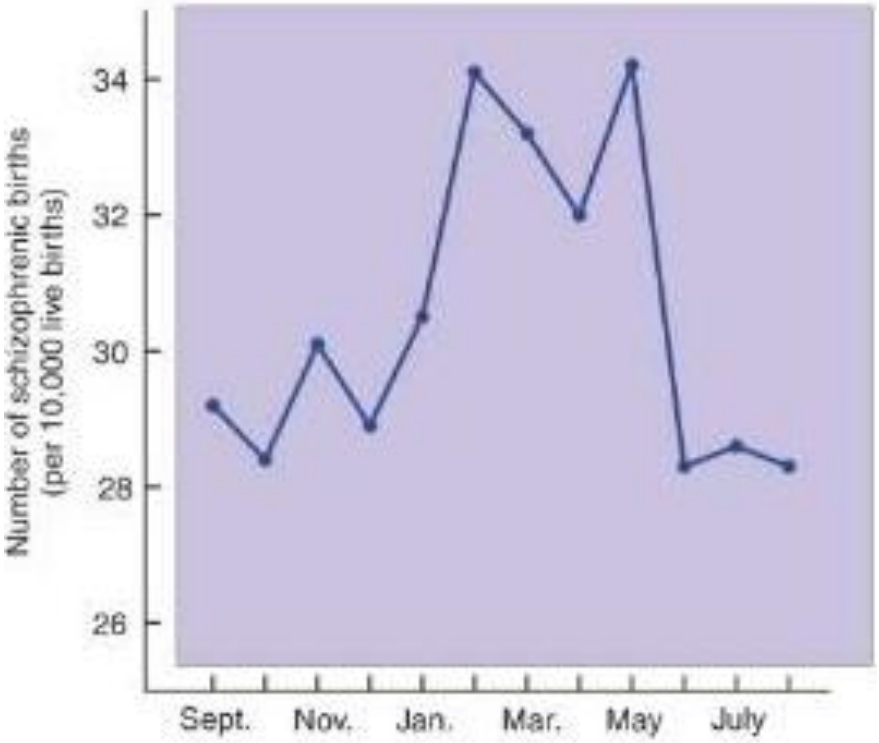
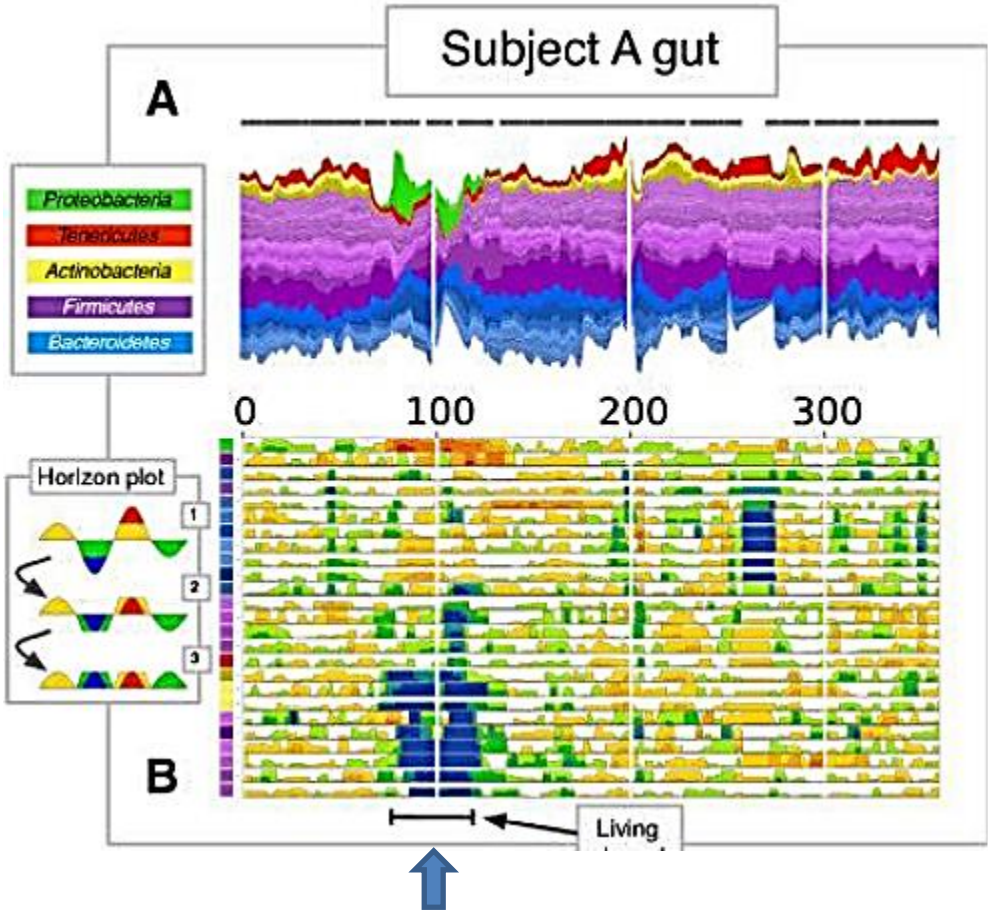
In a same environment different psychiatric disorders show different seasonal incidence characteristics

Relative Risk for **Schizophrenia** depending upon Month of Birth



Whereas the risk for SZ is greatest for children born between January and May, that for ASD is greatest for births between May and September (conceptions between May & August and between August & December respectively).

Although over a year human-associated microbial communities appear relatively stable, they can be quickly and profoundly altered by common human actions and experiences



Travel episode

Furthermore, microbial communities composition and populations dynamics differ significantly not only between subjects but also seasonally within the same subject.

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The problems in terms of integrative biology

Because of well installed CNS functional alterations, successful treatment of psychiatric disorders is particularly difficult to achieve by the time they become clinically evident.

Prevention is thus highly desirable.

- **Given the impact of alterations in microbiota metabolic and populations dynamics upon the development of subthreshold systemic inflammation,**
- **The impact of subthreshold systemic inflammation upon CNS function and architecture, particularly during early pregnancy,**
- **The significant seasonal differences in microbial communities composition and populations dynamics observed not only between different subjects but also within a same individual, together with**
- **The different seasonal incidence characteristics that distinguish different psychiatric disorders,**

Solid data addressing the forms of microbial dysbiosis and the conditions under which they could provoke significantly increased risks of clinically relevant psychiatric alterations becomes an inescapable prerequisite to the construction of any integrated model capable of suggesting valid preventive actions.

Hence, so long as we remain ignorant of which forms of alterations in microbial populations AND metabolic dynamics could constitute clinically relevant "dysbiosis", designing preventive measures against pathogenesis of psychiatric disorders shall remain an unattainable goal.