

Mind Body Interactions:

The Microbiota-Gut-Brain Axis

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Summary

- Review of my last (2019) presentation on this topic
- Update on more recent research
- Question: Are we in the middle of a 'paradigm shift'? (Kuhn, 1962)
- Where might this be going next?
- ...and what are the implications for Artificial Intelligence?

Definitions

'Microbiota' vs 'Microbiome'

- Microbiota: The microbes living within us
- Microbiome: The collective genome of the Microbiota
- Reason for the confusion: Many of these organisms cannot be cultured and are identified through their genomes

Clarifications

- Microbiota/Microbiome: All parts of the body including the skin
- Enteric (or gut) Microbiota/Microbiome: The microbiota within the digestive system

The Human Microbiota

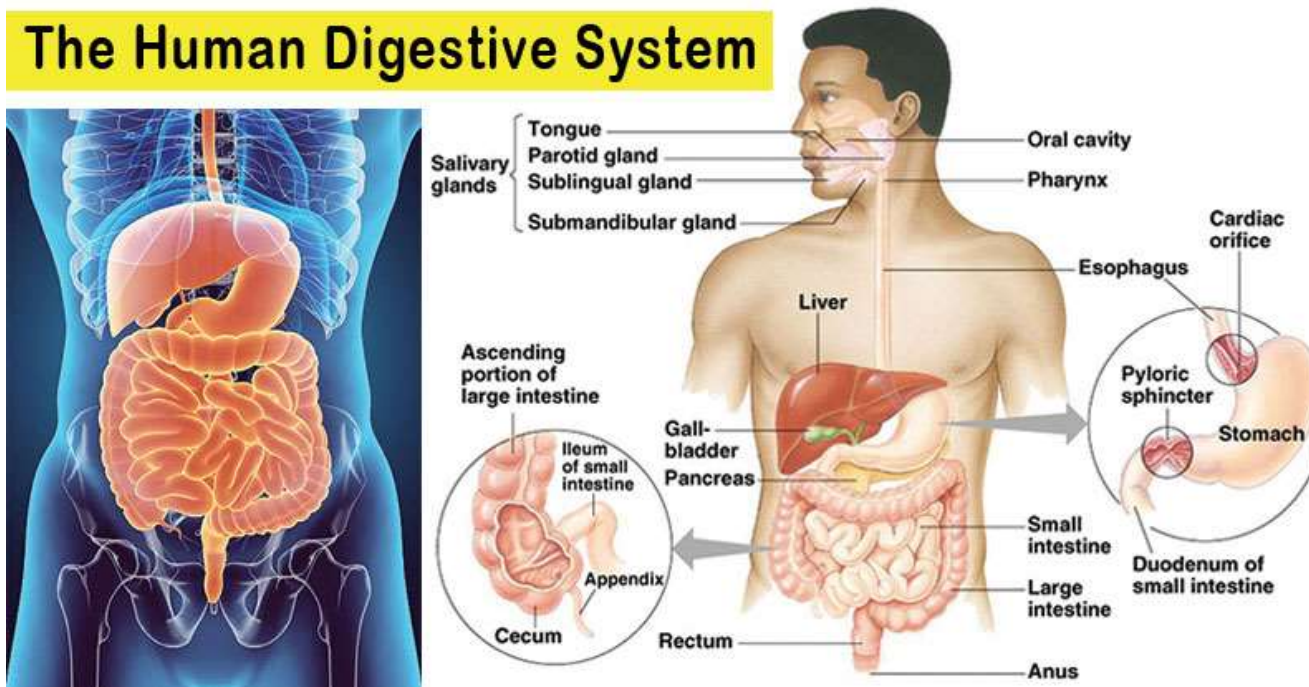
- 39 trillion microbes (*cf* Human cells in the body: 30 trillion) – *ie* we are outnumbered by 30%
- Enteric microbiota: 2,000 species
- Total mass: approx. 2kg
- Comprise approx. 55% of human faeces

Composition of Human Microbiota

- **Bacteria** – all animal life depends on bacteria as they possess the genes & enzymes necessary to synthesise Vitamin B12
- **Viruses**
- **Single-celled Eukaryotes**
- These microbes can be detrimental to health but most are beneficial – they are *commensal*

The Human Digestive System

The Human Digestive System



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The Human Nervous System

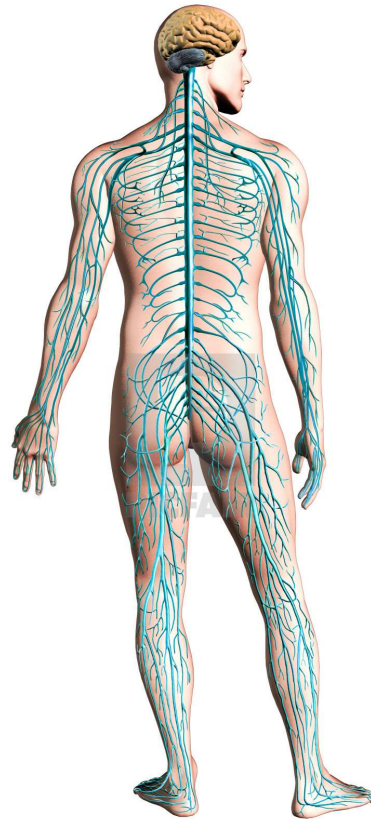
- The Central Nervous System
- The Somatic (Voluntary) Nervous System
- The Autonomic Nervous System
 - The Sympathetic Division ('Fight or Flight')
 - The Parasympathetic Division ('Rest & Digest')
 - The Enteric Nervous System

The Human Nervous System

Anatomically:

- Spinal Nerves (31 pairs)
- The Vagus Nerve

Spinal Nerves



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The Vagus Nerve



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The Endocrine System

- Made up of glands that produce and secrete hormones
 - chemical substances produced in the body that regulate the activity of cells or organs
- These hormones regulate:
 - Growth
 - Metabolism
 - Sexual development and function

The Endocrine System

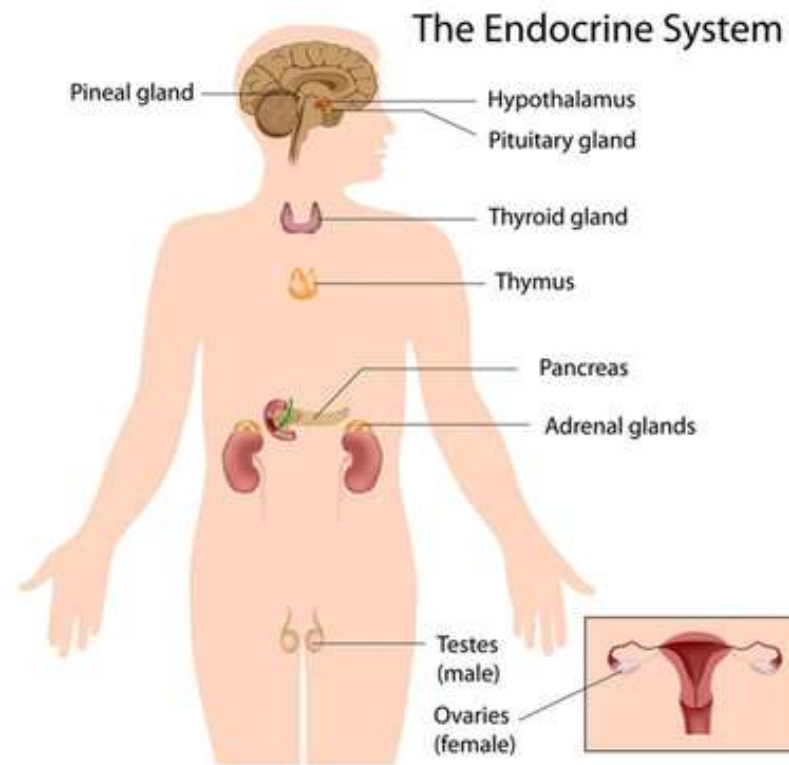
Stress Reaction

- Initiated by the Hypothalamus in the Brain
- Mediated by the Pituitary Gland
- Controls the Adrenal Glands

(Hypothalamic, Pituitary, Adrenal (HPA) Axis)

- To produce Cortisol, which circulates in the bloodstream and produces the fight/flight response

The Endocrine System



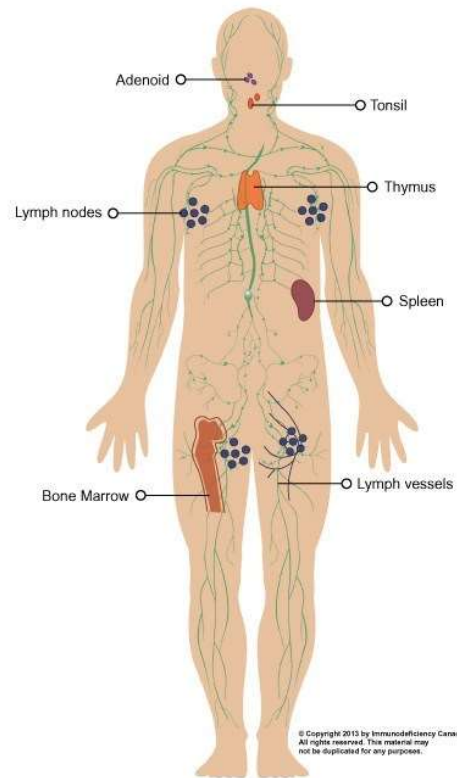
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The Immune System

- Phagocytes in pursuit of Pathogens
- Carried through the network of lymphatic vessels in lymph fluid
- Broken down in the Lymph Nodes...
- ...and removed by the Spleen

The Immune System



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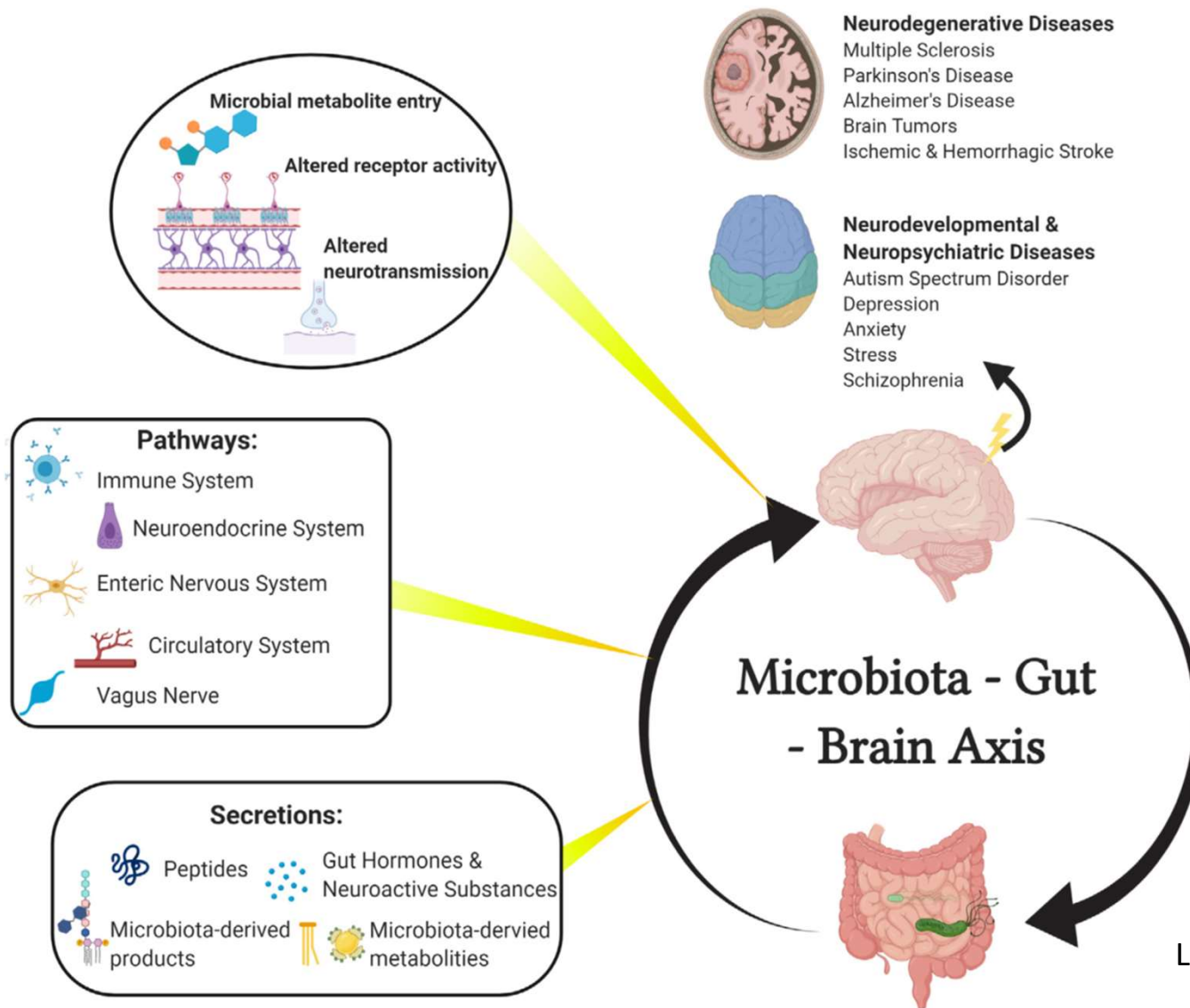
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The Enteric Nervous System

- The ***Enteric Nervous System*** consists of a mesh-like network of nerves along the whole length of the digestive system with its own reflexes independent of the brain or spinal cord
- It is now considered to be a third division of the Autonomic Nervous System – a 'second brain'

The Gut-Brain Axis

- There is two-way connection between the Central Nervous System and the Enteric Nervous System
- The mechanisms involve neural, immune system & endocrine mediators
- The gut microbiota influence these interactions
- The emotional & cognitive functions of the brain connect with our intestinal functions



Neurodegenerative Diseases

Multiple Sclerosis
Parkinson's Disease
Alzheimer's Disease
Brain Tumors
Ischemic & Hemorrhagic Stroke



Neurodevelopmental & Neuropsychiatric Diseases

Autism Spectrum Disorder
Depression
Anxiety
Stress
Schizophrenia

Liu, Huh & Shah (2022)

Main Source

Cryan, J *et al* (2019) 'The Microbiota–Gut–Brain Axis'. *Physiol Rev* vol.99, pp 1877–2013.

- 34 Authors
- 137 pages
- 1,694 References

Significant Developments

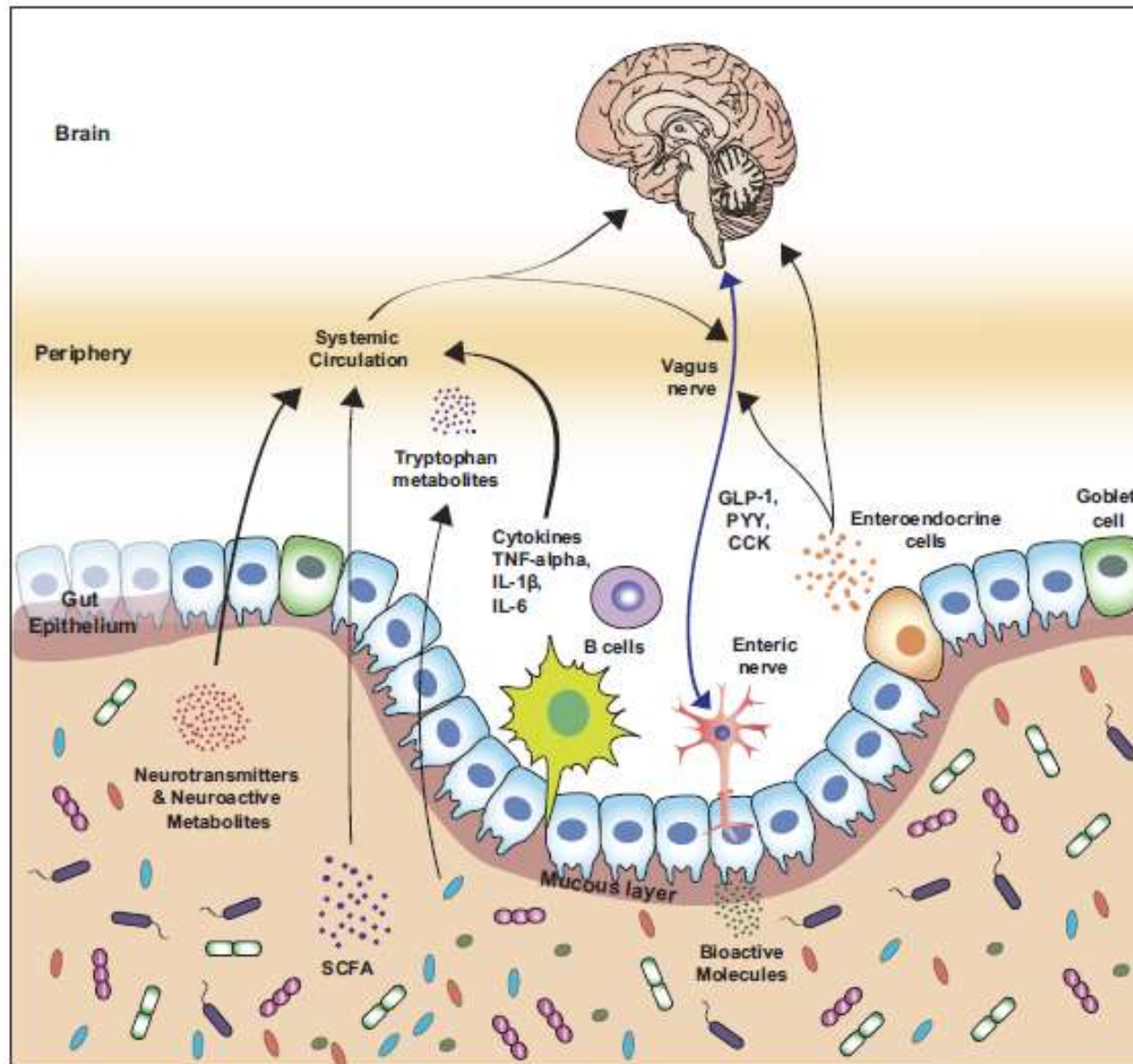
- Increase in knowledge base
- Significant Paradigm Shift?
 - *Previously*: Host organism 'entire into itself' + symbiotic microbiota
 - *New Paradigm*: 'Holobiont' with a 'Hologenome'
 - 'Holobiont' – an integrated unit of *evolutionary* selection
 - 'Hologenome' – the collective genome of the holobiont
- 'The idea of 'holobionts' represents a paradigm shift in biology' (*The Economist*, 14 June 2023)

Research Methods

- Germ Free Models – especially mice
- Antibiotics
- Faecal Microbiota Transplant (+antibiotic control)
- Faecal Sampling (+sequencing)
- Prebiotics and Fermented Foods
- Probiotics and Psychobiotics
- Brain Imaging

Pathways of Communication

- Autonomic Nervous System
- Enteric Nervous System
- Immune System
- Enteroendocrine Signalling
- Neurotransmitters
- Branched Chain Amino Acids
- Bile Moieties
- Short Chain Fatty Acids
- Spinal Mechanisms
- HPA Axis
- Peptidoglycans



From:
Cryan *et al* (2019)

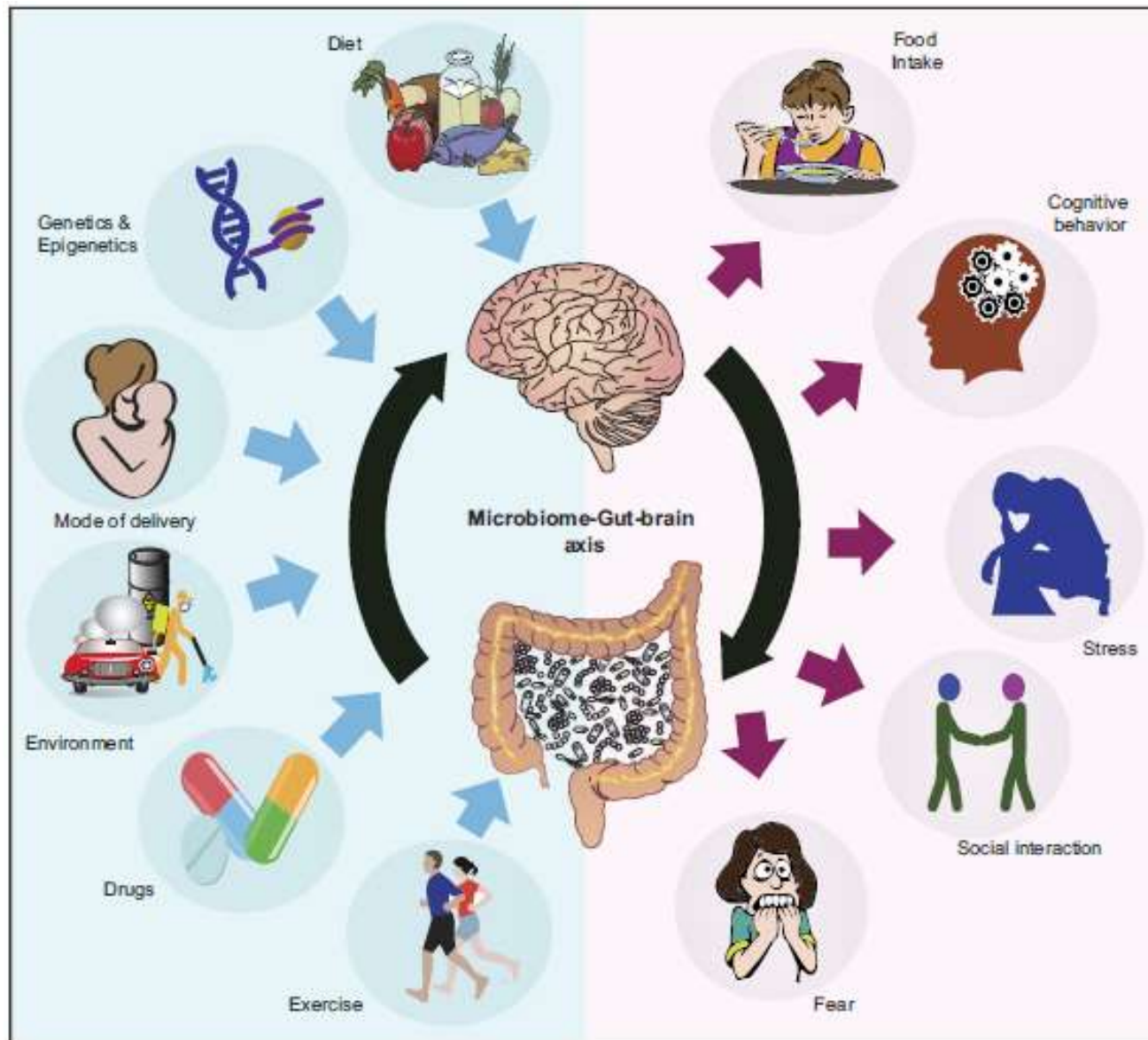
Factors Influencing the MGBA

- Genetics & Epigenetics
- Mode of Delivery at Birth
- Diet
- Environment
- Exercise
- Medications and the Microbiome
- Stress
- Circadian Rhythm

From: Cryan et al (2019)

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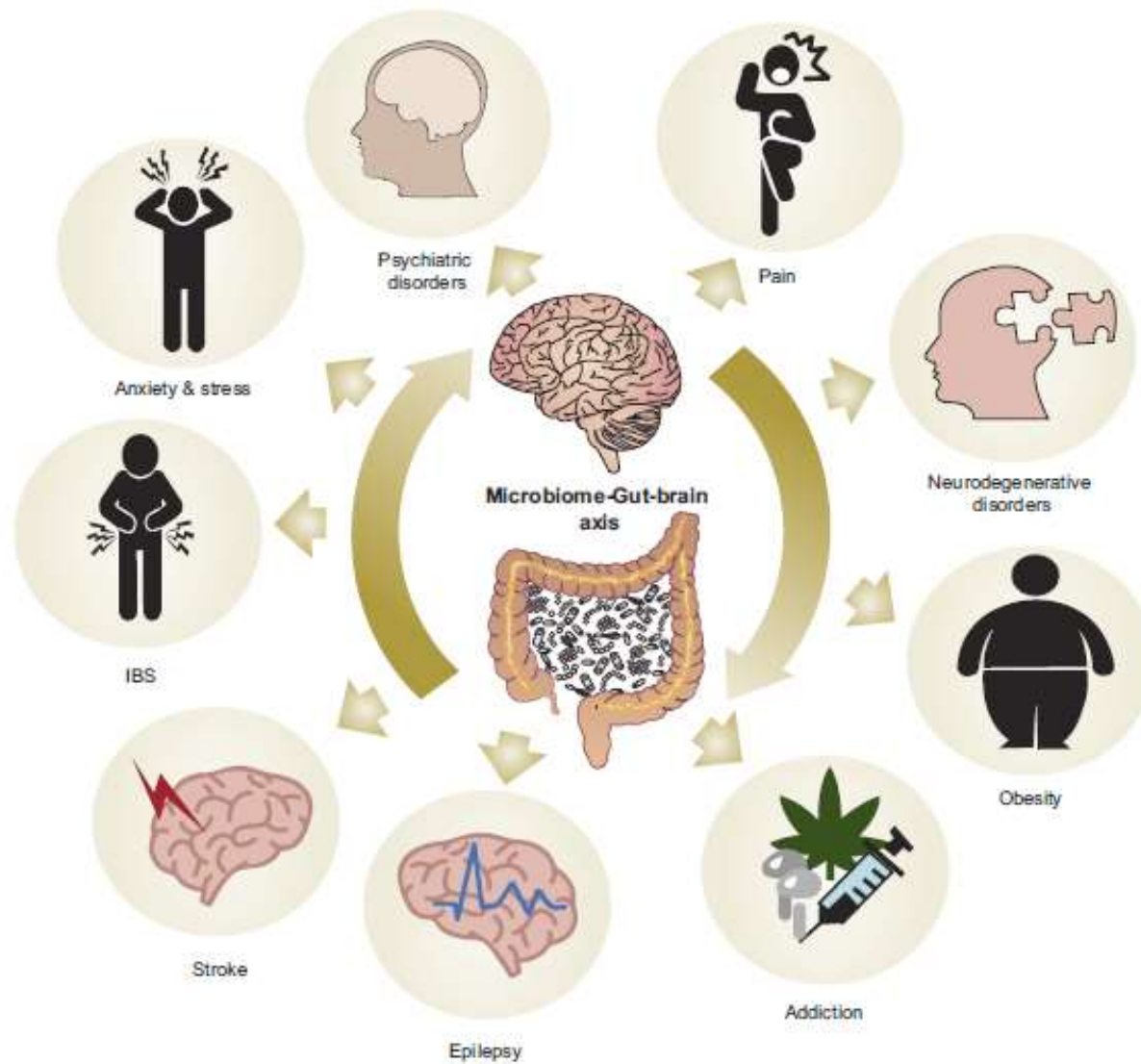
From:
Cryan et al (2019)

Diseases & Disease Processes

- Autism Spectrum Disorder
- Major Depressive Disorder
- Anxiety
- Schizophrenia
- Bipolar Disorder
- Anorexia & Cachexia
- Addiction
- ADHD
- Post Traumatic Stress Disorder
- Obsessive-Compulsive Disorder
- Obesity
- Irritable Bowel Syndrome
- Pain Disorders
- Parkinson's Disease
- Alzheimer's Disease & Dementia
- Stroke & Brain Injury
- Multiple Sclerosis
- Obstructive Sleep Apnoea
- Epilepsy
- Amyotrophic Lateral Sclerosis
- Huntington's Disease
- Infections & the Brain

From: Cryan et al (2019)

THE MICROBIOTA-GUT-BRAIN AXIS



From:
Cryan *et al* (2019)

Fear

- Fear is a core symptom of clinical anxiety – and related to stress
- In the CNS, fear is regulated by the amygdala, the hippocampus and the pre-frontal cortex
- All these are modulated by changes in the microbiota
- Studies include functional MRI to investigate linking to brain activity – and the use of fear inducing images
- Research Problem: Profiles between (human) individuals are highly variable

Fear – Two Studies

- In healthy women, intake of a probiotic (fermented milk) reduced the neural response to fear inducing images
- Microbiota composition of healthy women was associated with altered reactivity in the right hippocampus to negative emotional images

Fear – Research Tools

- Administration of Probiotics
- Functional Magnetic Resonance Imaging (fMRI)
- Faecal Sampling (+sequencing)
- Anxiety-Inducing Images

MRI Scanner



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Magnetic Resonance Imaging (MRI)

- The nuclei of atoms in a *strong constant magnetic field*, which is subject to a *weak oscillating magnetic field*, produce electromagnetic signals
- These signals can be resolved into images

MRI vs fMRI (functional MRI)

- 'MRI' creates images of structures
- 'fMRI' provides evidence of metabolic activity over time

Probiotics

- 'Live microorganisms which when administered in adequate amounts confer a health benefit on the host'. (WHO)
- Sources:
 - Live yogurt – and other fermented milk products, eg kefir
 - Sauerkraut
 - Kimchi
- Examples of active organisms:
 - *Lactobacillus bulgaricus*, *Leuconostoc mesentroides*, *Bifidobacterium bifidum*

Anxiety-Inducing Images

- Sets of disturbing images have been devised to research – and to develop therapies for – psychiatric disorders such as:
 - post-traumatic stress disorder
 - other anxiety disorders
 - depression
 - eating disorders
 - psychosis











Another Example: Mediterranean Diet

- Mediterranean Diet: Whole Grain Cereals; Nuts; Legumes; Vegetables; Fruit + Moderate Consumption of Poultry & Fish
- Results in Distinctive Gut Microbiota Characteristics
- Numerous Benefits including: Psychiatric Conditions; Reduction of Depression
- A Randomized Control Trial of Dietary Intervention in Major Depression Showed that Change to a Mediterranean Diet Improved Depression Scores

What's Next?

- Confirm existing findings – including greater use of humans
- Develop greater understanding – especially of the complex interactions between the pathways of communication
- Devise novel treatments for the many diseases implicated (Liu *et al*, (2022))
- Identify MGBA involvement in existing problems – eg effects of pesticides (Matsuzaki *et al*, 2023)
- Re-think psychology? (Liang *et al*, (2018))

Re-think Psychology?

- 'Mental disorders and neurological diseases are becoming a rapidly increasing medical burden. Although extensive studies have been conducted, the progress in developing effective therapies for these diseases has still been slow... Only when we take the human self and its partner microbiota into consideration at the same time, can we better understand these diseases... All of these findings suggest that the existing research has neglected the fact that the human being is a superorganism.'

Liang, S *et al* (2019)

And What Can AI Learn From This?

- Weizenbaum (1976) proposed that for machines to have true human intelligence, they will have to experience the world as humans do. This means through a human body – the brain alone is insufficient.
- We are beginning to understand what this means...

References

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- Kuhn, T (1962) 'The Structure of Scientific Revolutions'. Chicago: University of Chicago Press.
- Liang, S; Wu, X; & Jin, F (2018) 'Gut-Brain Psychology: Rethinking Psychology From the Microbiota-Gut-Brain Axis'. *Front. Integr. Neurosci.*, 11 September 2018, Volume 12.
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- Matsuzaki, R; Gunnigle, E; Geissen, V; Clake, G; Nagpal, J; & Cryan, J (2023) 'Pesticide Exposure and the Microbiota-Gut-Brain Axis'. *The ISME Journal*; <https://doi.org/10.1038/s41396-023-01450-9>.
- The Economist (2023) 'The idea of 'holobionts' represents a paradigm shift in biology'. *The Economist*, 14 June 2023.