Inflammation The “Gut Brain Axis” and Schizophrenia

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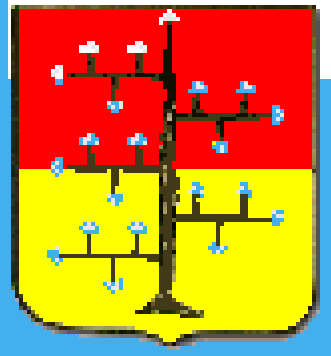


I have no conflicts of interest to disclose

Mount Sinai

Schizophrenia-related psychosis is increasing in prevalence, incidence, and its disability-related burden

From 1990 to 2019, estimates show dramatically increased:

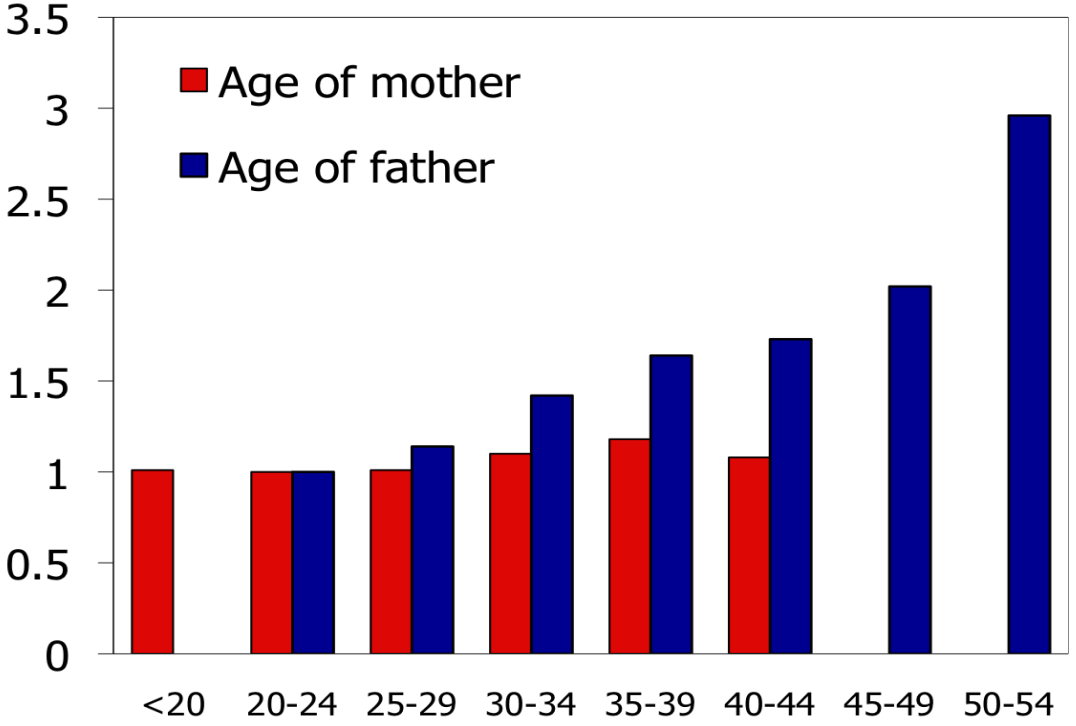
prevalence increased by over 65% (14.2 to 23.6 million).

incidence increased by 37% (941,000 to 1.3 million)

disability burden increased by 65% (DALYs 9.1 to 15.1)

How can we understand these worsening statistics ?

Paternal age introduces novel and rare gene variants for schizophrenia into the population. Maternal age is related to increased inflammatory states.

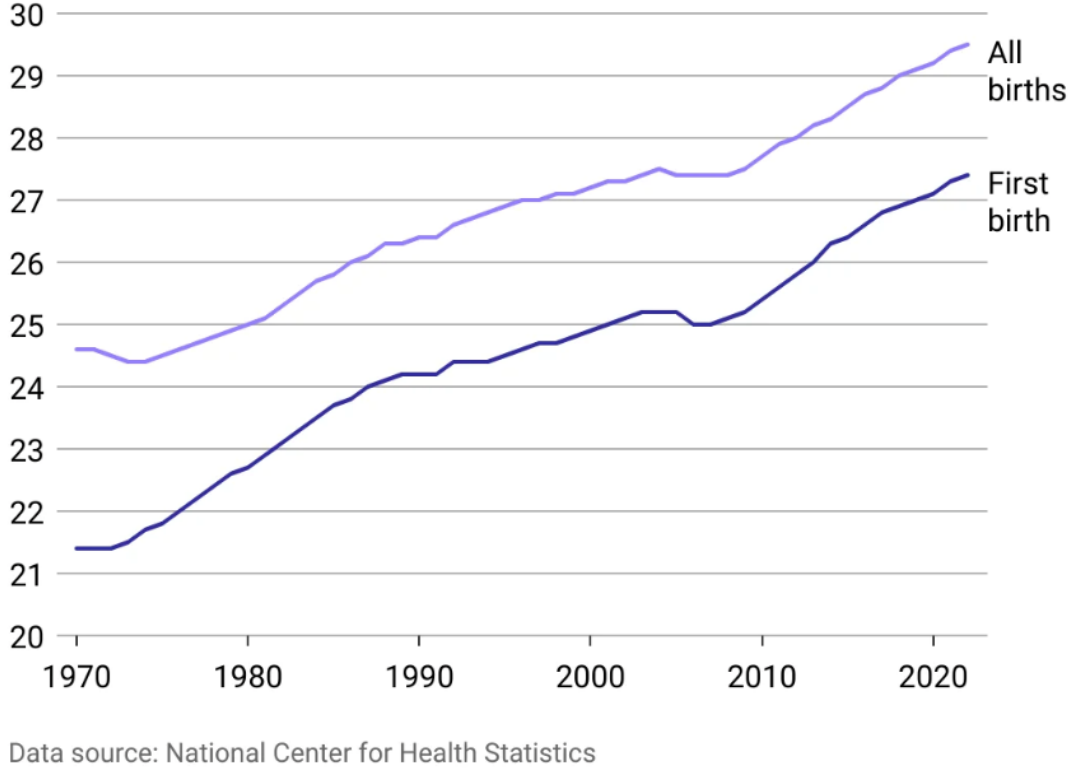


Paternal aging & offspring risk for schizophrenia

1.34: p = 0.0001 per 5 years; beginning age 25-34

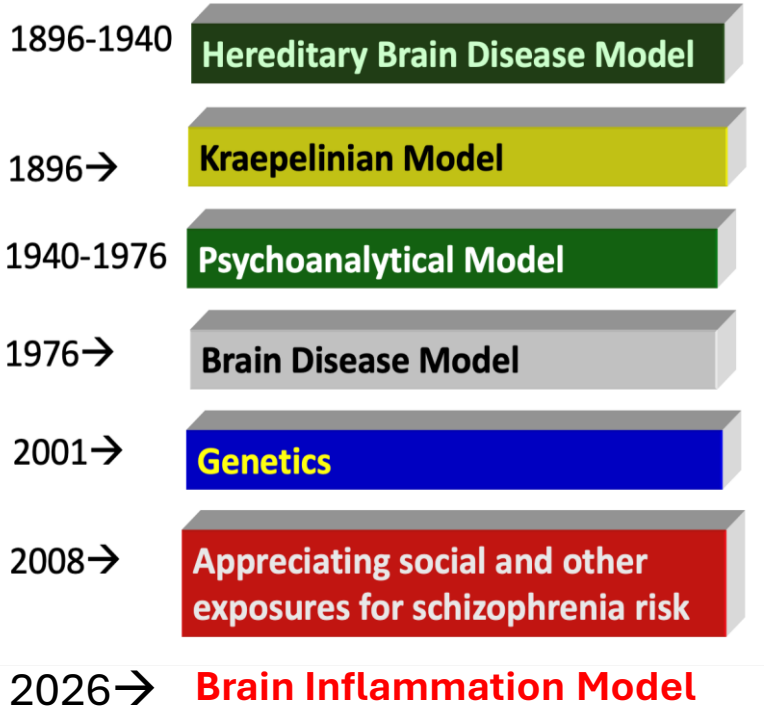
Malaspina et al, 2001; 2019

Advancing Maternal and Paternal Ages in the US: 5 years from 1970-2022



Kranz TM, Harroch S, Manor O, ..Chao MV, Malaspina D. De novo mutations from sporadic schizophrenia cases highlight important signaling genes in an independent sample. Schizophr Res. 2015 Aug;166(1-3):119-24. doi:

We need new models to advance understanding and treatment



Inflammation, GBA and Schizophrenia

To explain the etiology and/or contribute to a poor course

Lecture to feature:

1. Evidence that inflammation relevant to SZ
2. What are Inflammatory/immune pathways
3. Why inflammation is increasing now.
3. The microbiome as anti-inflammatory
4. The gut brain axis and schizophrenia

1923 – a century ago!!!

"Most people who go insane are victims of bad heredity....or.....unable to bear the strain of the struggle of existence (psychic shocks), ...or infection or intoxication" " There can be little doubt that that the latter depend on (brain) structural alterations too fine to recognize by current methods". Lewellys Barker

Components of the inflammatory / immune system

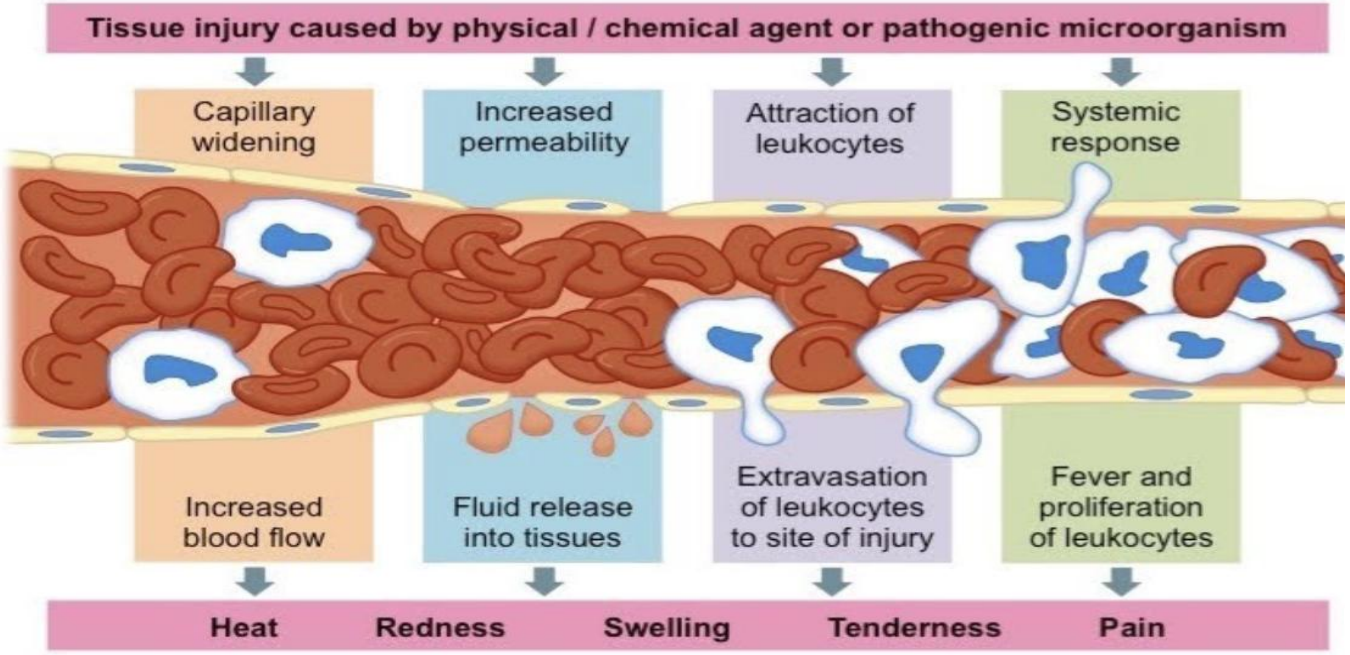
Triggered by immune system when it detects:

1. Infection
2. Tissue injury
3. Harmful stimuli

Response to injury, infection, toxin:
Innate Inflammatory Response:

Involves coordinated activation:

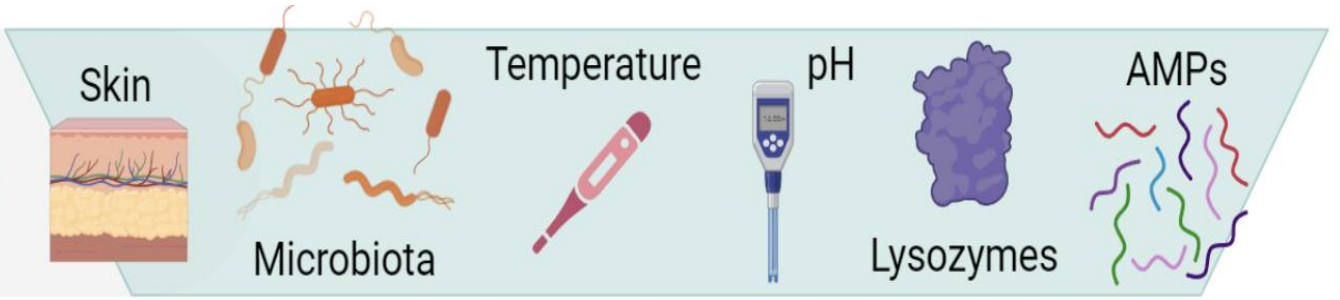
- Immune cells detect a pathogen or tissue damage by special receptors; no memory of past
- Blood vessel widen & become leaky- then redness; swelling, leucocytes and systemic response
- Mediators block threats & promote tissue repair (cytokines chemokines, acute-phase proteins)



There is also an adaptive immune system with memory

Stage 1

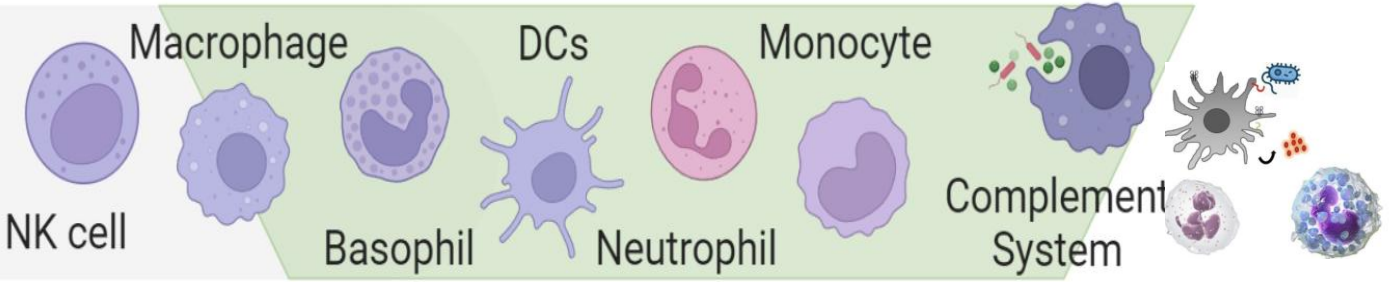
Externals and Interns Barriers



Stage 2

Innate Immune System

Nonspecific, fast, no memory

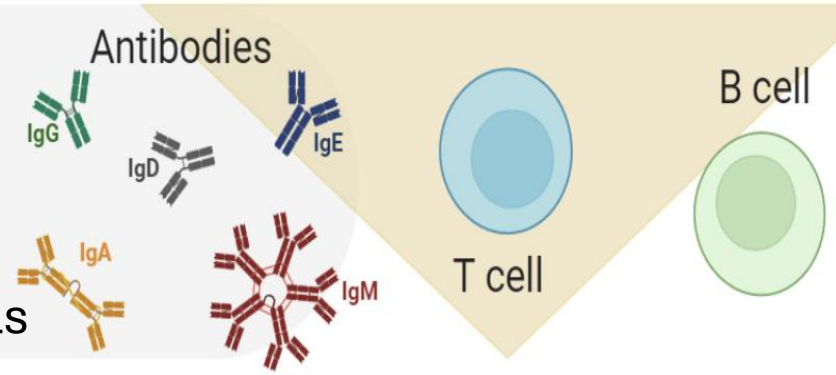


Stage 3

Adaptative Immune System

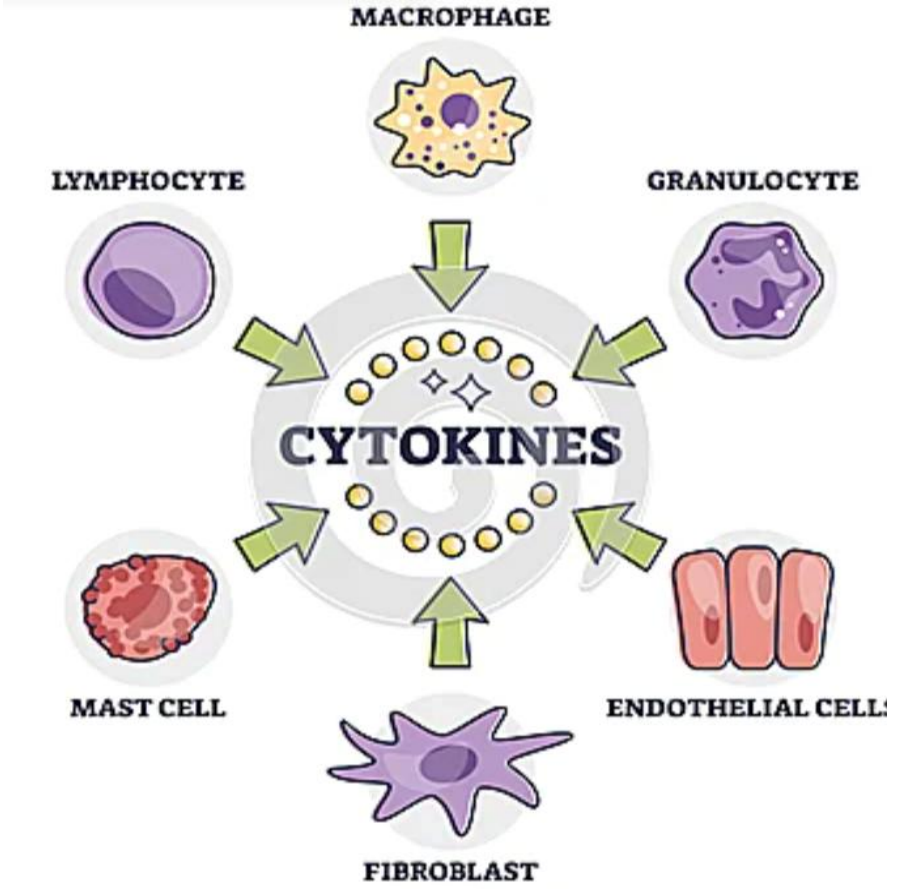
Memory: Vaccines; Autoimmunity

Humoral: B Cells; Cell-mediated T-Cells



Cytokines

- Small proteins that communicate between cells
- Regulates immunity, inflammation, and hematopoiesis
- Maintain physiological homeostasis in inflammation
- Essential for learning and memory.
- Cause cell activation, proliferation, differentiation



Also Produced in the brain

Microglia: Brain immune cells-promote & stop inflammation
Astrocytes: Support cells- especially during stress or injury.
Neurons: Can produce cytokines- contribute to cell signaling.
Endothelial Cells: Blood-brain barrier (BBB) and pericytes .
Meningeal Cells: Immune cells in membranes around the brain

Example of Cytokine Function and Production

Inflammation:

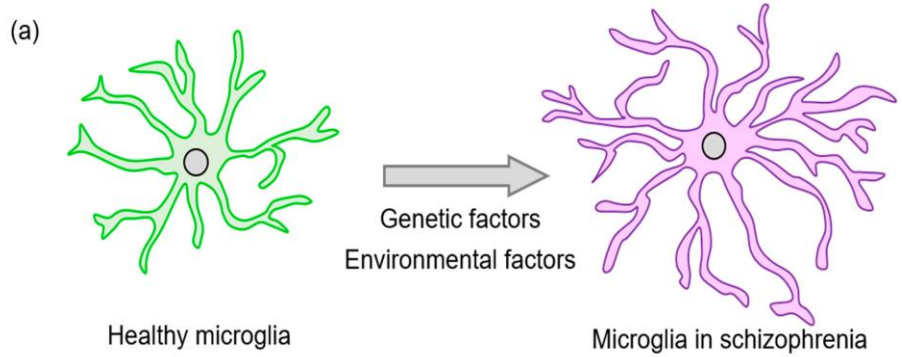
Macrophages secrete proinflammatory cytokines like TNF-α, IL-1, and IL-6 when exposed to stimuli, causing fever and recruiting more immune cells.

Immune Regulation:

T cells produce cytokines like IL-2 to promote their own growth and activate other immune cells.

Microglia

The brain's gardeners, weeding out infection and "pruning" unwanted connections between brain cells. But over-pruning synapses in SZ risk!



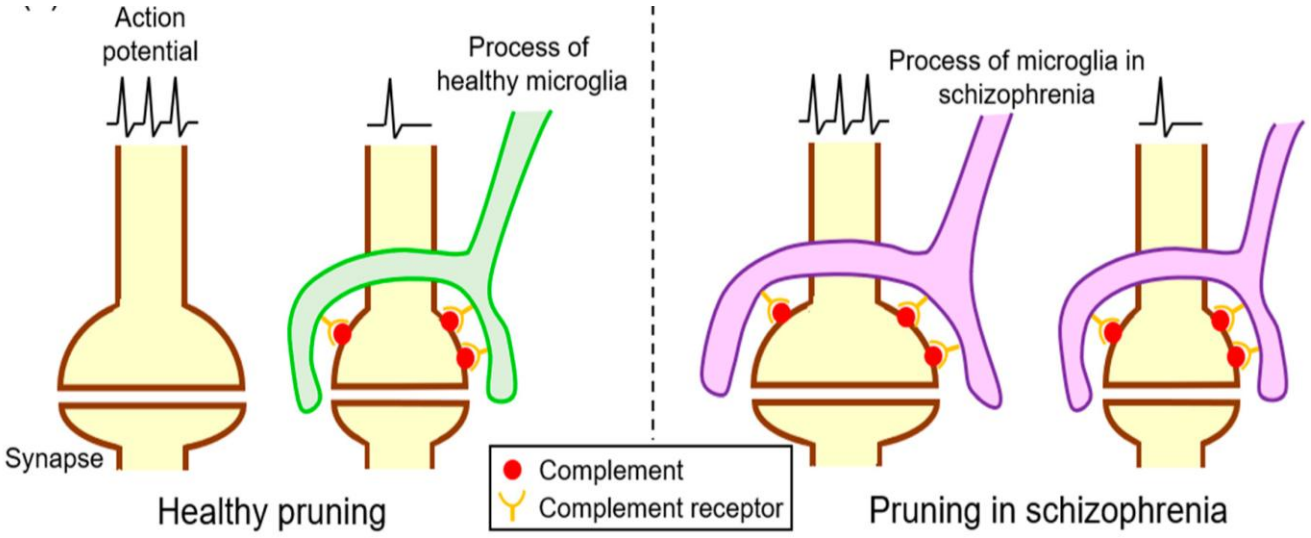
The Brains Resident Immune Cells:

- Regulating brain development and maintaining neuronal networks
- Eliminating microbes, dead cells, redundant synapses, & protein aggregates
- Modulating neuronal proliferation, differentiation, and synaptic connections
- Primary source of proinflammatory cytokines when activated
- Promoting neurogenesis and tissue repair

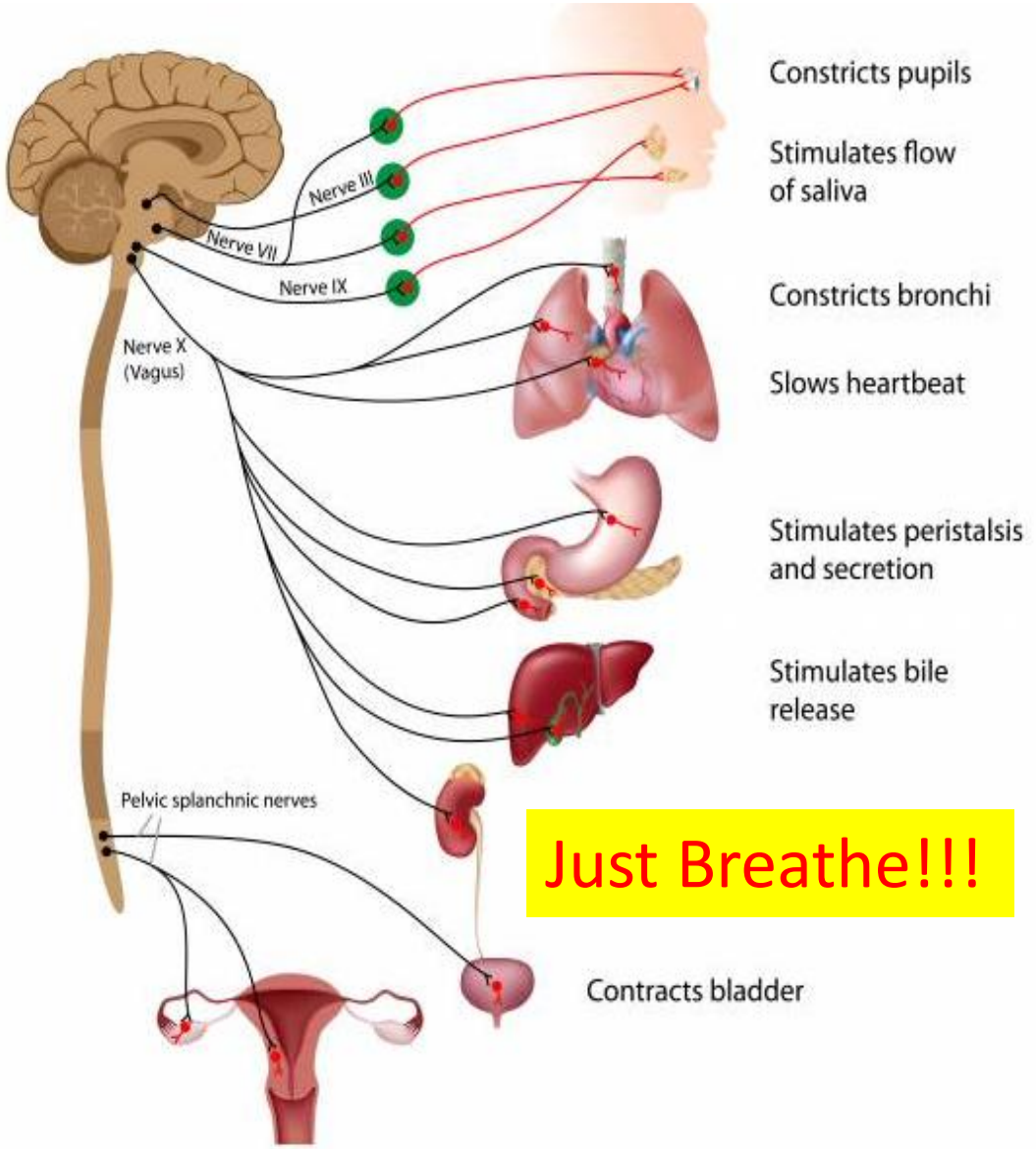
Microglia are over-active before illness onset. Could reducing their activity prevent or treat psychiatric disorders?

Other brain disorders with microglial abnormalities Include:

Major depressive disorder, bipolar disorder, autism, obsessive-compulsive disorder, Alzheimer's disease, and more



Vagal nerve (parasympathetic) links gut and brain



Just Breathe!!!

Key regulator in brain-body communication

Can suppress inflammation in the CNS and periphery

It is a target for treating inflammatory CNS disorders like epilepsy, depression, and stroke.

Neuro-immune Reflex:

It is the parasympathetic nervous system that interacts with sympathetic nervous system in a reflex arc to control systemic & brain inflammation.

Mechanisms

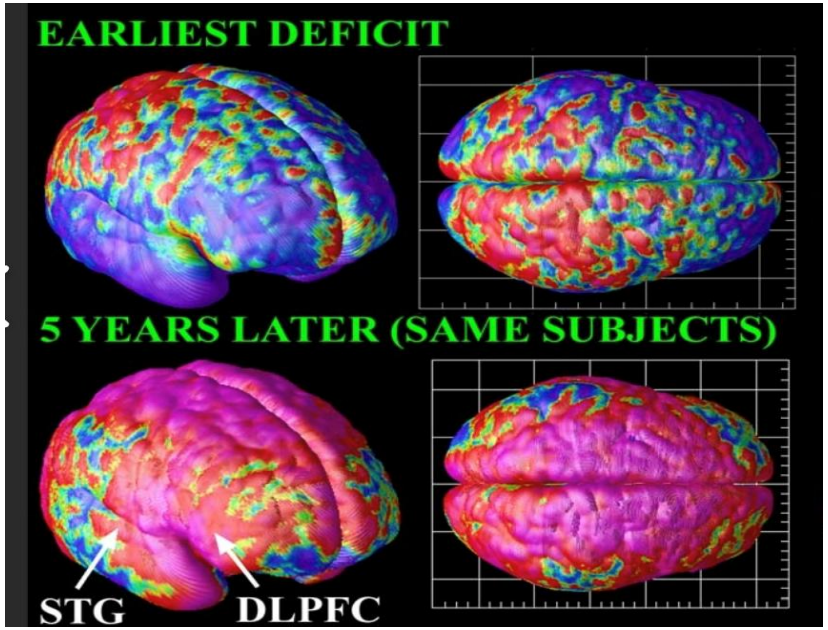
Cholinergic Anti-inflammatory Pathway:

Binds to receptors on immune cells (macrophages) to inhibit release of inflammatory cytokines (like TNF-α, IL-1β).

Biomarker Evidence that inflammation is significant for schizophrenia

Peripheral Immune molecules are Biomarkers

Cytokines - proteins for cell signaling



Neuroimaging

Loss of synapses over maturation; microglia

Epidemiology

Longitudinal studies of immune dysfunction and risk
Prenatal infections, cytokines in childhood→ SZ

Genetics

Associates SZ risk to C6p22.1 region (HLA) an immune region. Complement Component C4 gene region, over-prunes synapses in a SZ pathway.

Treatment response trials

Meta-analyses demonstrate advantageous effects of COX-2 inhibitors, particularly in early-stage; others in trials. Antipsychotic medications have intrinsic anti-inflammatory and immunomodulatory properties.

Why are Immune-mediated inflammatory diseases increasing ?

"Bubonic Plague" (Black Death) of the 1600's was the last great plague in Europe, which began in 1350 (killing 50-80% of European population).

Plagues put selective pressure on human allele frequencies for adaptive immune responses, including HLA & genes responding to pathogens.

Genes: Survivors of plagues are more inflammatory; Loss of healthy gut microbes

Socioeconomic status- Environmental stressors in low-income areas

Low to high gradients for autoimmune diseases further support environmental causation.

Lifestyle - Environmental factors:

Psychosocial stressors change gene expression, promote autoantibody production, smoking, sleep patterns, and occupational exposures.

Climate change - Environmental factors:

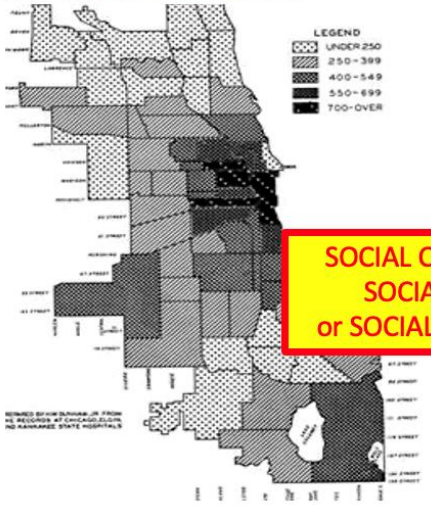
heat, storms, floods, wildfires, droughts, UV radiation,, malnutrition, Shifting infections

Air Pollution- Environmental factors:

Systemic inflammation, oxidative stress: Autoimmune diseases, lupus (SLE), RA, psoriasis

Urbanization

SZ in Chicago 1922-31
By zip code
(<250→ 700+)
(Farris & Dunn 1939)



SOCIAL CAUSATION ?
SOCIAL DRIFT?
or SOCIAL SELECTION?

Fox, John W. (1990) Social Class, Mental Illness, Social Mobility: Social Selection-Drift Hypothesis for SMI. J Health & Social Behavior. 31 (4): 344–353. doi:10.2307/2136818. JSTOR 2136818..

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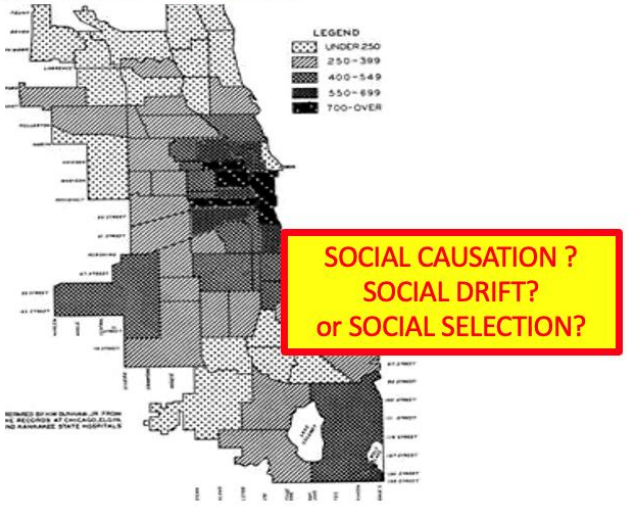
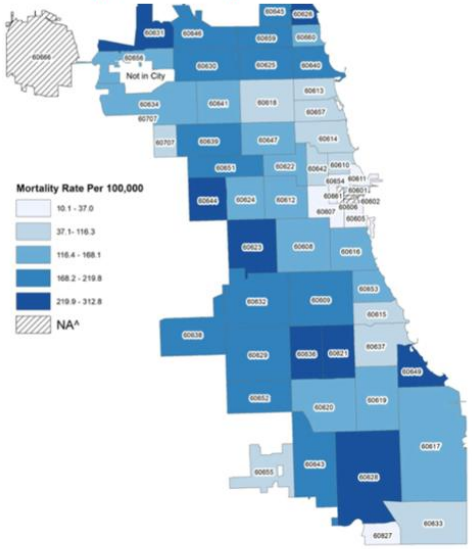


COVID mortality, Chicago, zip code
(10→ 2199-3128)
By January 2021



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Social determinants of health & mental health

World Health Organization

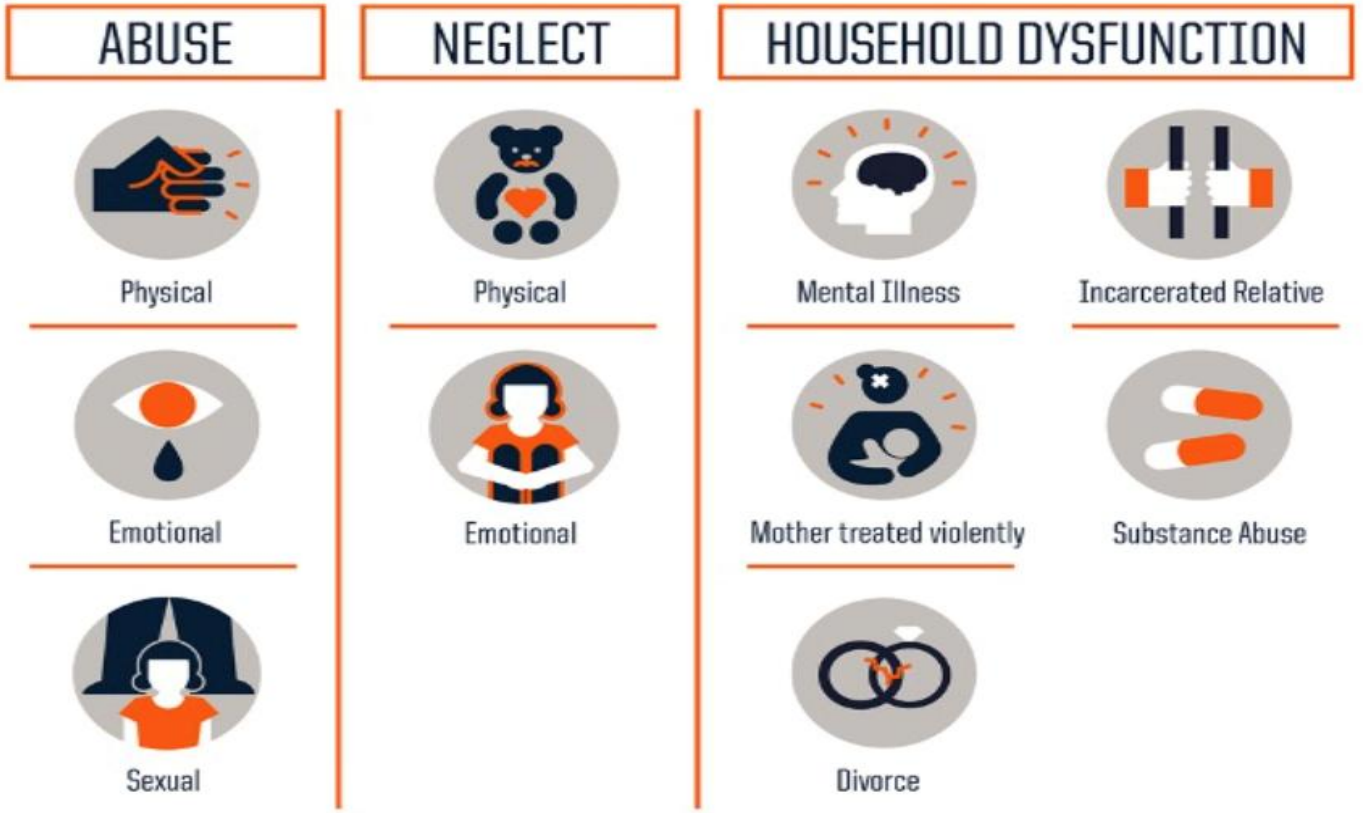
1) Income, social protection
2) Education
3) Unemployment, underemployment
4) Working life conditions
5) Food insecurity
6) Housing, Environmental toxins
7) Childhood trauma, development
8) Social exclusion, discrimination
9) Access to health services.

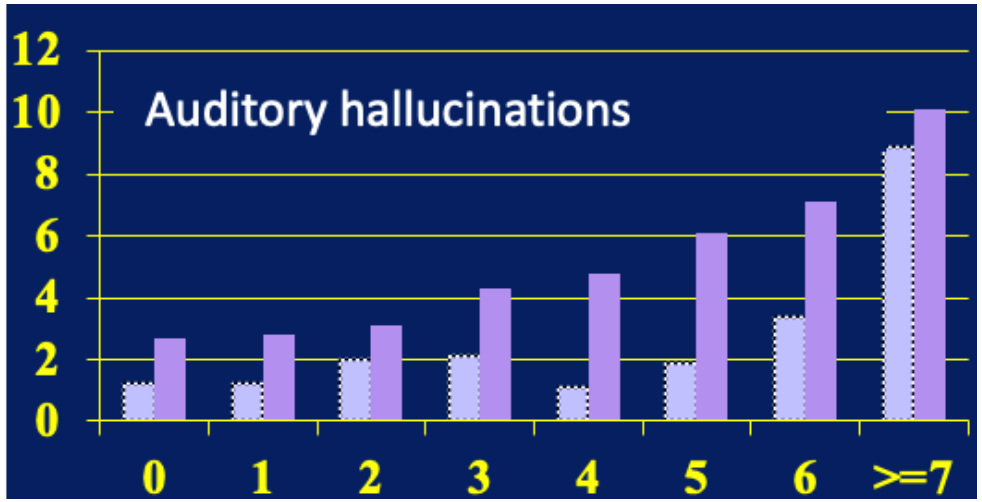
Center for Disease Control

1) Housing, transportation, neighborhood
2) Racism, discrimination, and violence,
3) Income, Education, job opportunities
4) Nutritious food, physical activity access
5) Polluted air and water
6) Language and literacy skills.

Adverse Childhood Experiences through age 18 years. (ACES) highly predict schizophrenia, other psychiatric and medical conditions and mortality

Ten adversities in ACE's



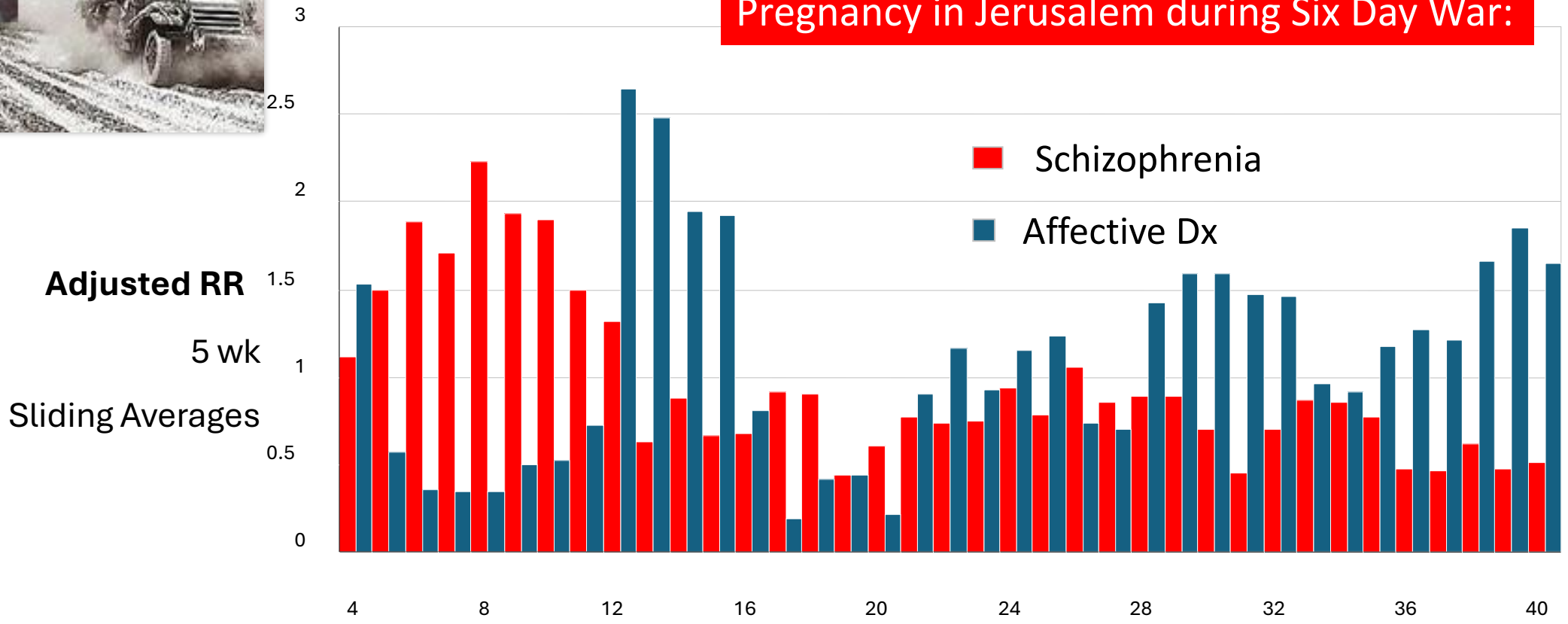


Ace Score	Prevalence
0	33%
1	25%
2	15%
3	10%
4	6%
5->	11%

If any one ACE *category* is present, there is an 87% chance of at least one other category of ACE and a 50% chance of 3->

Adverse Pregnancy Exposures by Month

Pregnancy in Jerusalem during Six Day War:



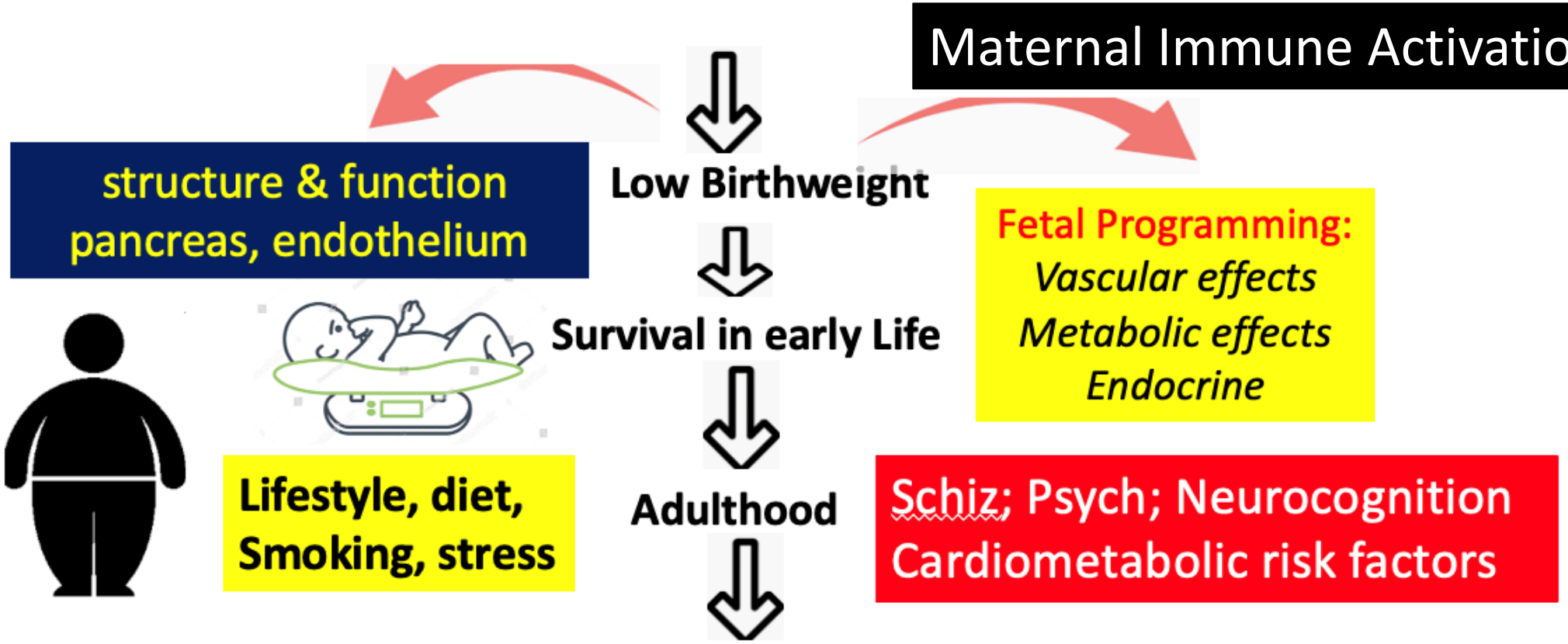
Malaspina et al 2008

Kleinhaus et al 2013

Iaroslav Youssim, in revision

Currently in revision is our study of the offspring of Holocaust survivors showing intergenerational effects of war trauma on risk for schizophrenia and metabolic disorders

Adverse Pregnancy Exposures Program Lifelong Gene Expression

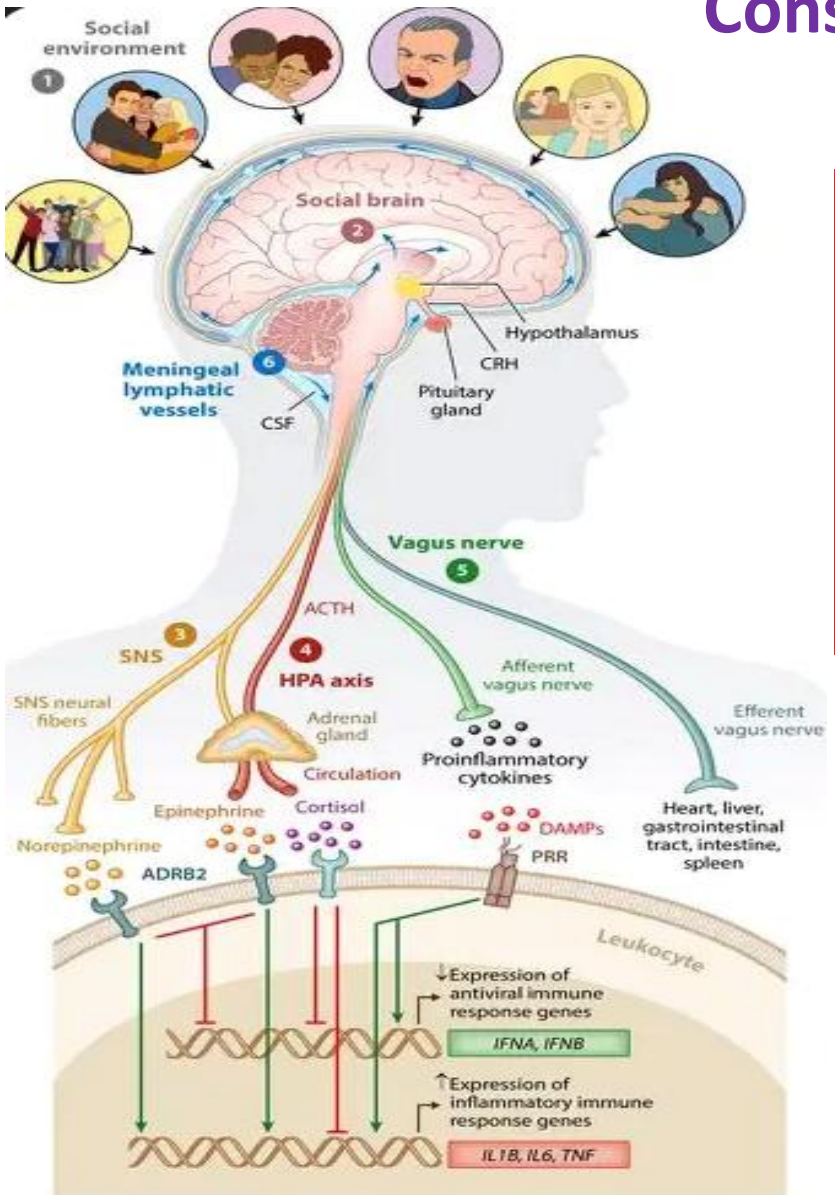


Heat Waves in Pregnancy:

Puthota J, Alatorre A, Walsh S, Clemente JC, Malaspina D, Spicer J. Prenatal ambient temperature and risk for schizophrenia. Schiz Res. 2022 PMC8977400.

Early Adversity Evolved to Produce a Pro-Inflammatory Organism

Conserved Transcriptional Response to Adversity

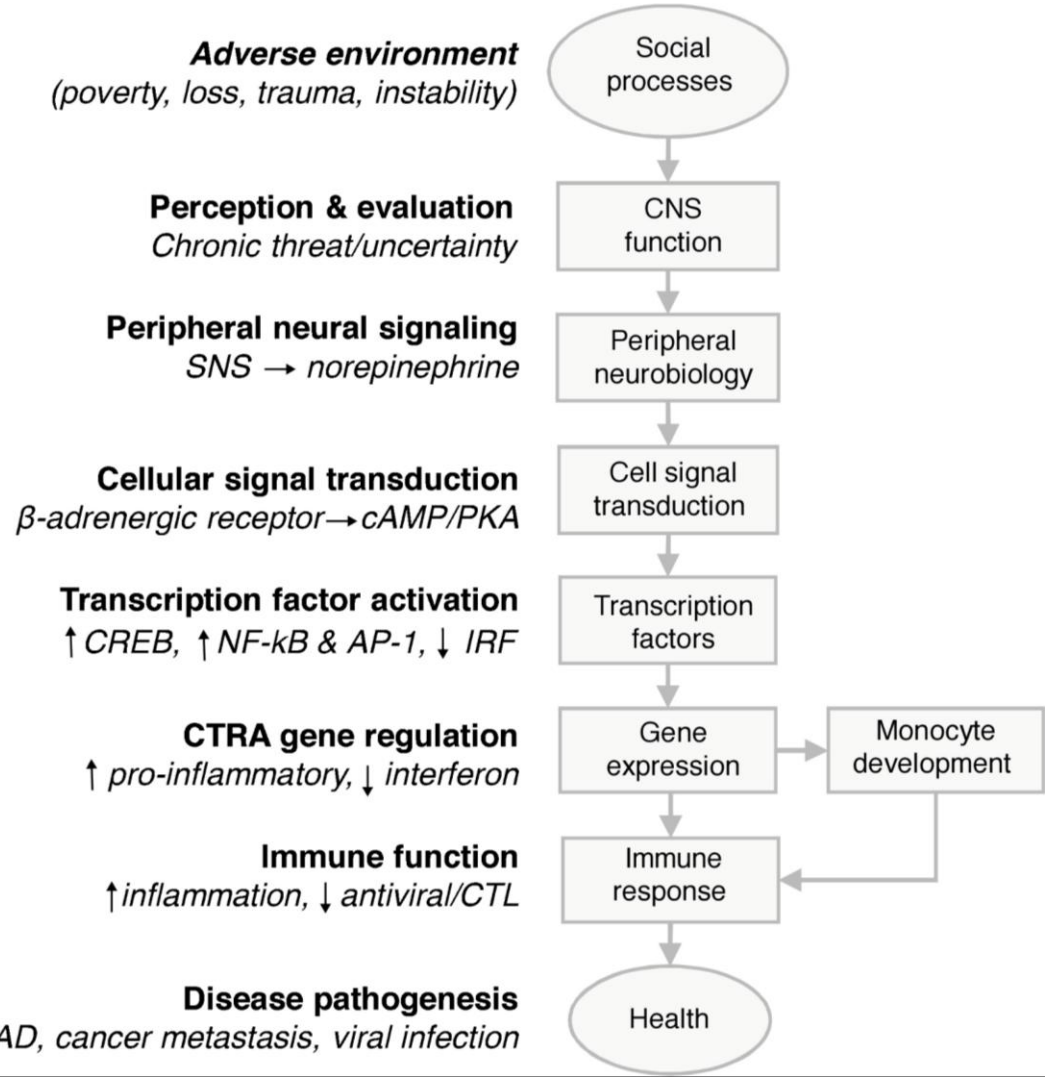


Short term benefits

Proinflammatory
Heightened threat & pain sensitivity
Avoid Physical Danger
Enhance wound healing
Improved physical recovery
More likely to survive

Long term costs

Anxiety, pain, depression
Increased infection
Accelerated aging
Early Mortality



Cole SW. The Conserved Transcriptional Response to Adversity. Curr Opin Behav Sci. 2019. PMCID: PMC6779418.

Is Schizophrenia an Autoimmune Condition

Immune responses against ones own healthy cells, tissues and other body constituents

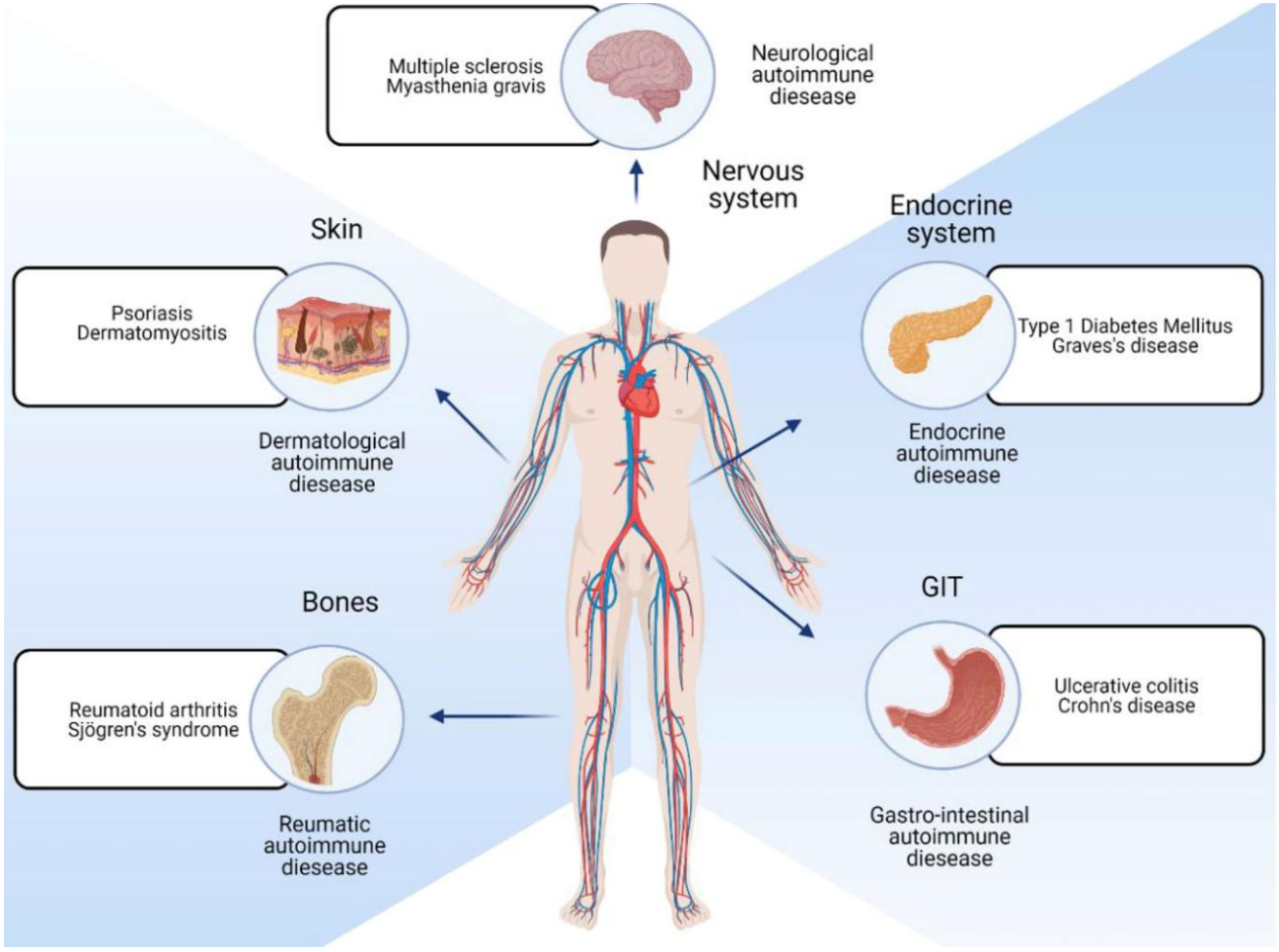
MECHANISMS:

Genetics: Human Leukocyte Antigen (HLA), Variation in immune genes

Environments: Stimulated by infections, tissue injury release of self antigens, stressors, immune activation

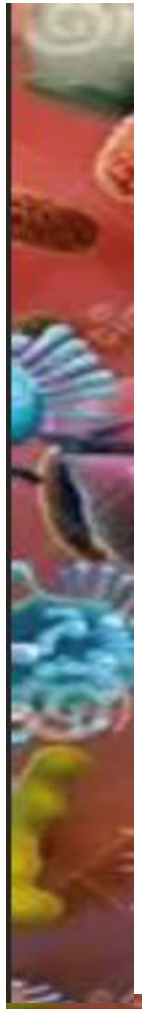
INCREASED RISKS FOR SCHIZOPHRENIA

+ 32 %	Graves Disease
+ 48 %	Psoriasis
+ 71%	Pernicious Anemia
+ 243 %	Celiac Disease
+ 500 %	Hypersensitivity Vasculitis



Chen, 2012

Microbiome: trillions of symbiotic microbes maintain inflammatory tone



The Human Microbiome

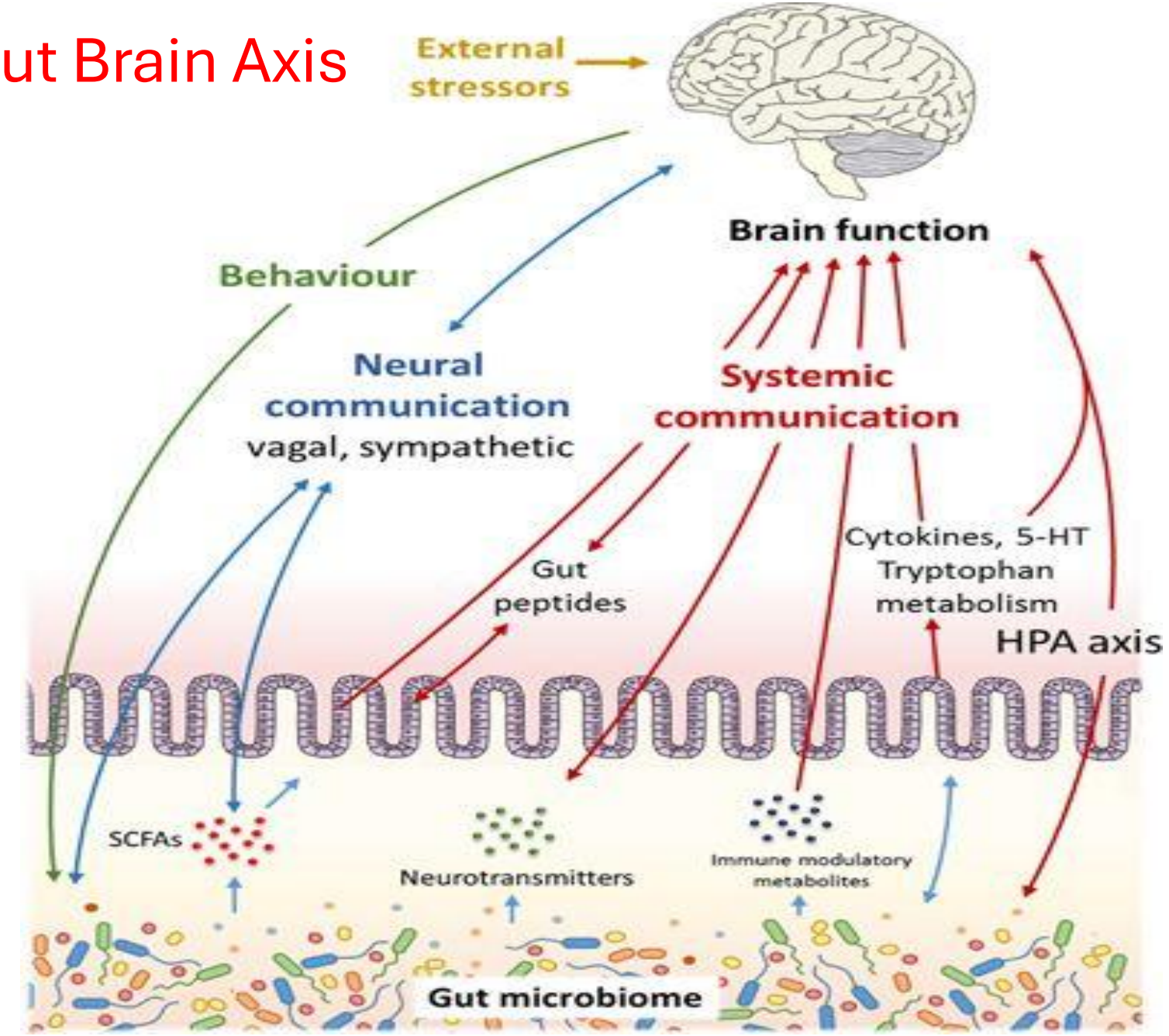
We are a “supraorganism,” a collection of human and microbial cells and genes. We are each a unique blend of human and microbial traits!

- 75 - 200 trillion individual bacterial live in us and on us. Our cells number ½ of these.
- in addition to archaea, fungi, protozoans, noninfective viruses.
- Necessary at birth for CNS maturation & function and immune system development
- The Microbiome is is an anti-inflammatory system at the interface of host and environment, defending against pathogens by strengthening the intestinal barrier[1]
- Supplies nutrients (Vitamin K, B complex), aids their absorption, metabolizes the indigestible agents.

Gut Brain Axis

Short Chain Fatty Acids
Made by friendly gut bacteria via fermentation of fibers in colon. Main source of energy for GI epithelium.

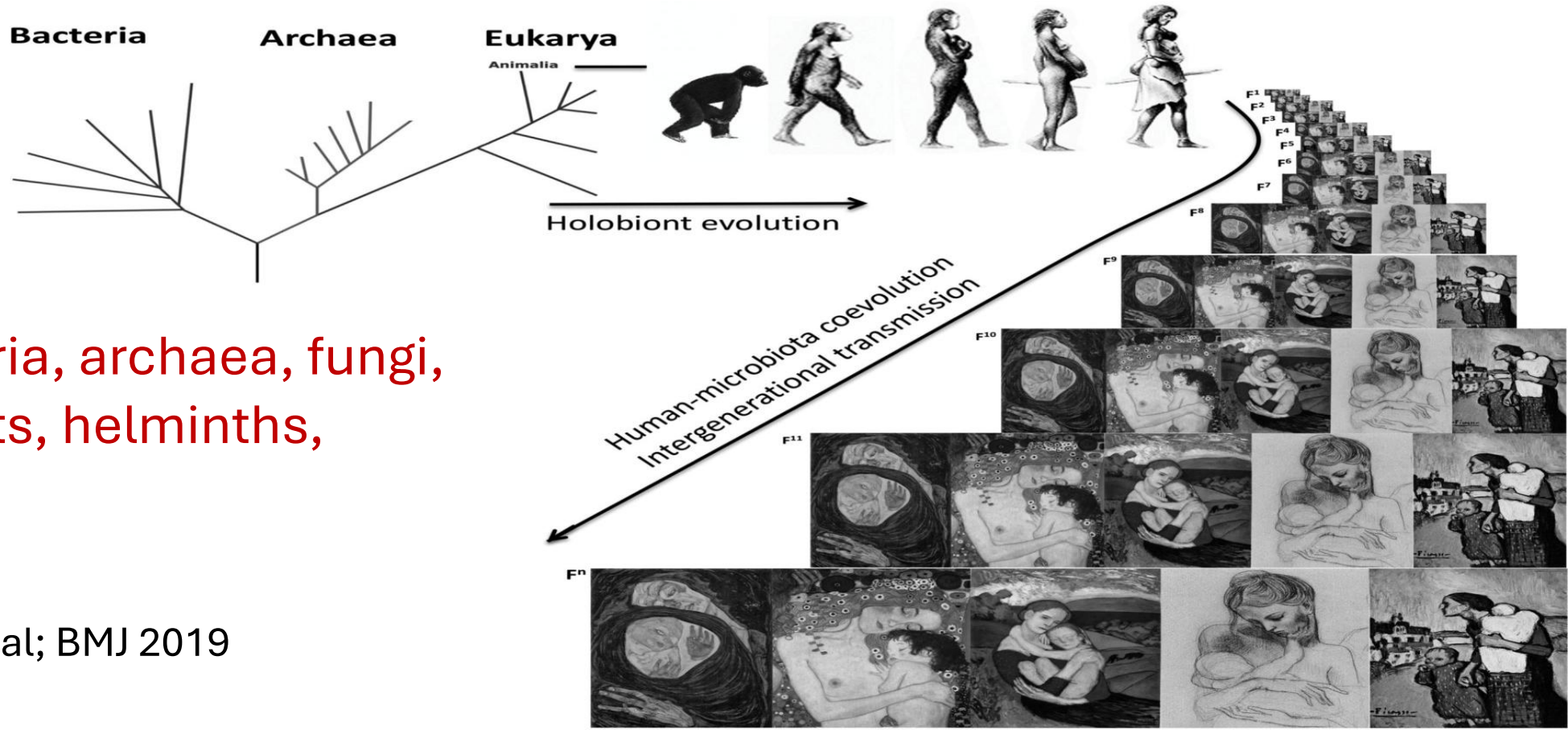
Requires 5 fresh fruit and vegetables daily!



Humans and their microbial community evolved together

The newborns gut is seeded by the maternal vaginal microbiome, which controls the development of the brain and immune system

3.8 billion years ago



bacteria, archaea, fungi, protists, helminths, virus

Dominguez-Bello et al; BMJ 2019

The Healthy gut

Releasing anti-inflammatory metabolites into the blood stream

Fermenting fruit and vegetable fibers by gut bacteria (Firmicutes, Bifidobacterium)

1. Short-Chain Fatty Acids (SCFAs) – butyrate, propionate, and acetate

- Promote the differentiation of regulatory T cells (Tregs), which suppress inflammation
- Inhibit histone deacetylases (HDACs) in immune cells
- Changing gene expression to favor an anti-inflammatory state
- Produce anti-inflammatory cytokine interleukin-10 (IL-10), to suppress inflammatory cytokines (TNF-α, IL-6).

2. Other Metabolites.

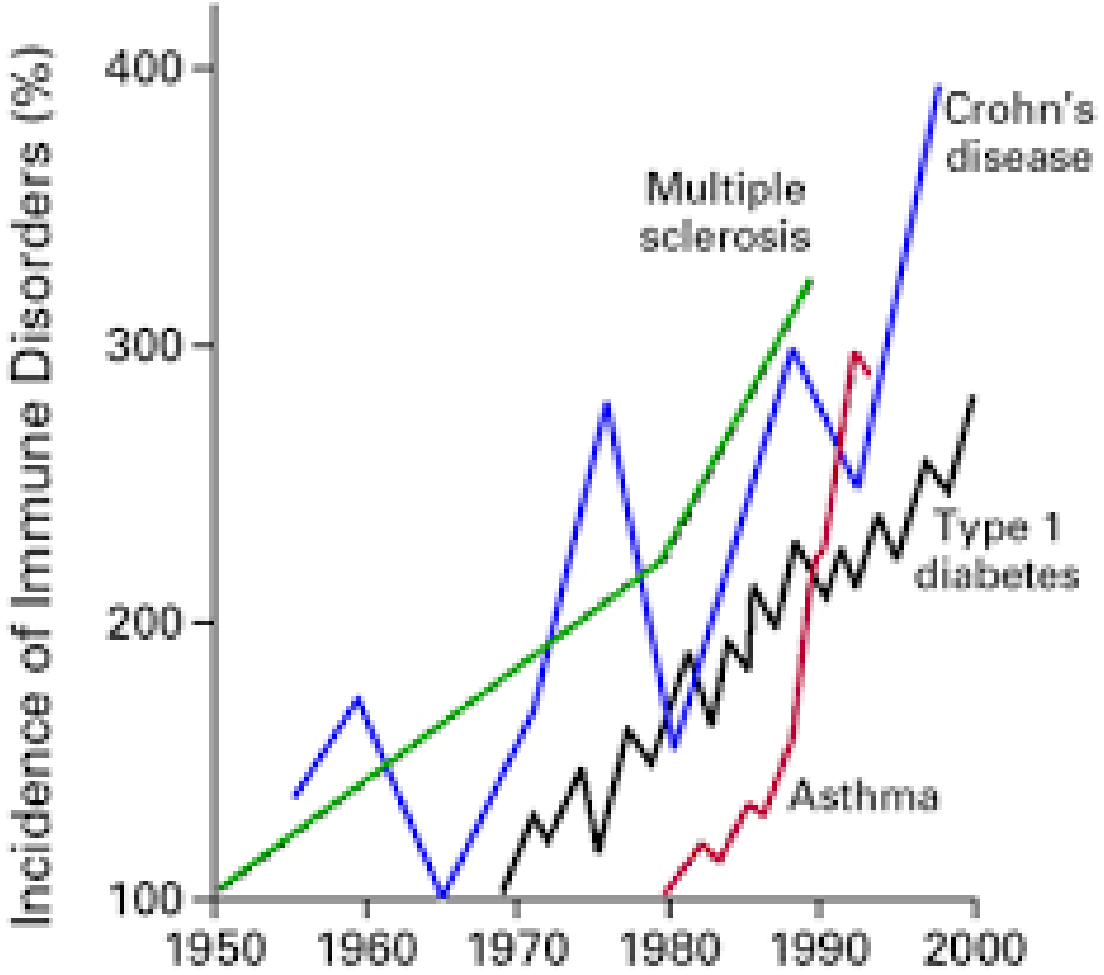
Tryptophan derivatives and secondary bile acids

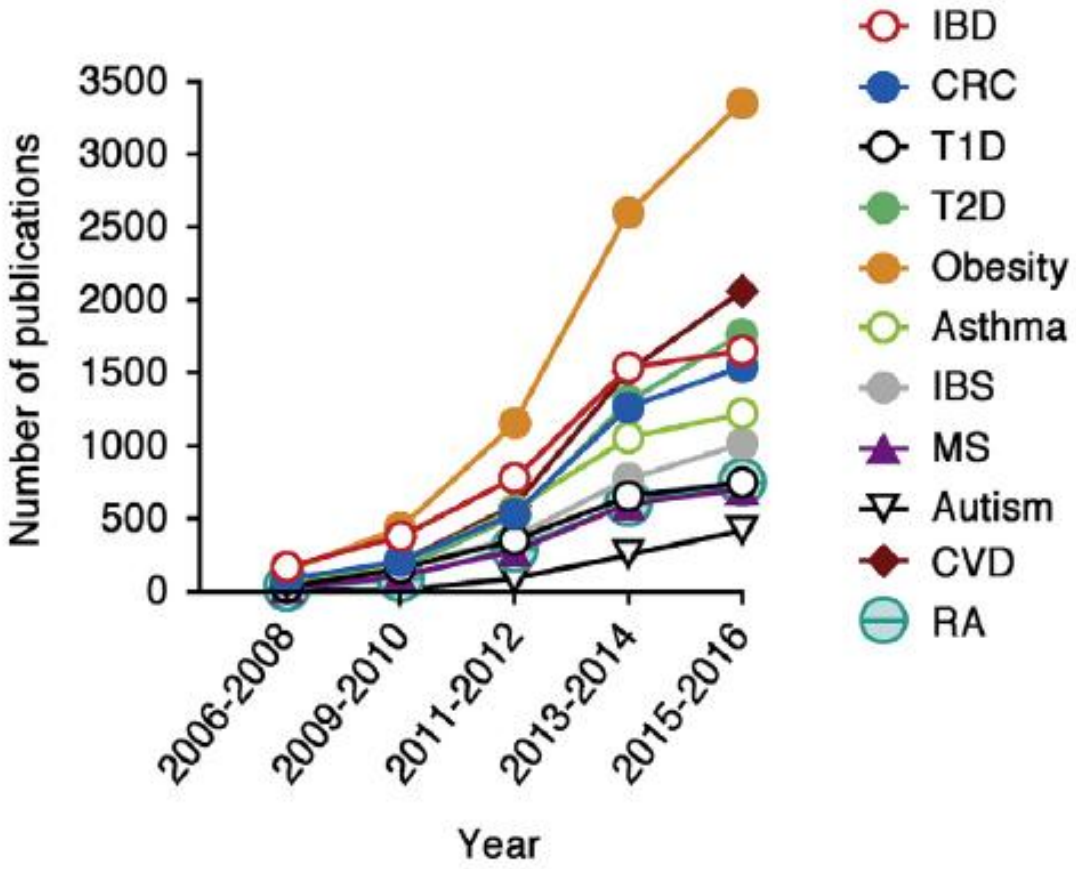
Promote anti-inflammation by activating host cell receptors.

Control of the vagal nerve.

Loss of microbiome diversity occur over time

Increasing risks of autoimmune disorders





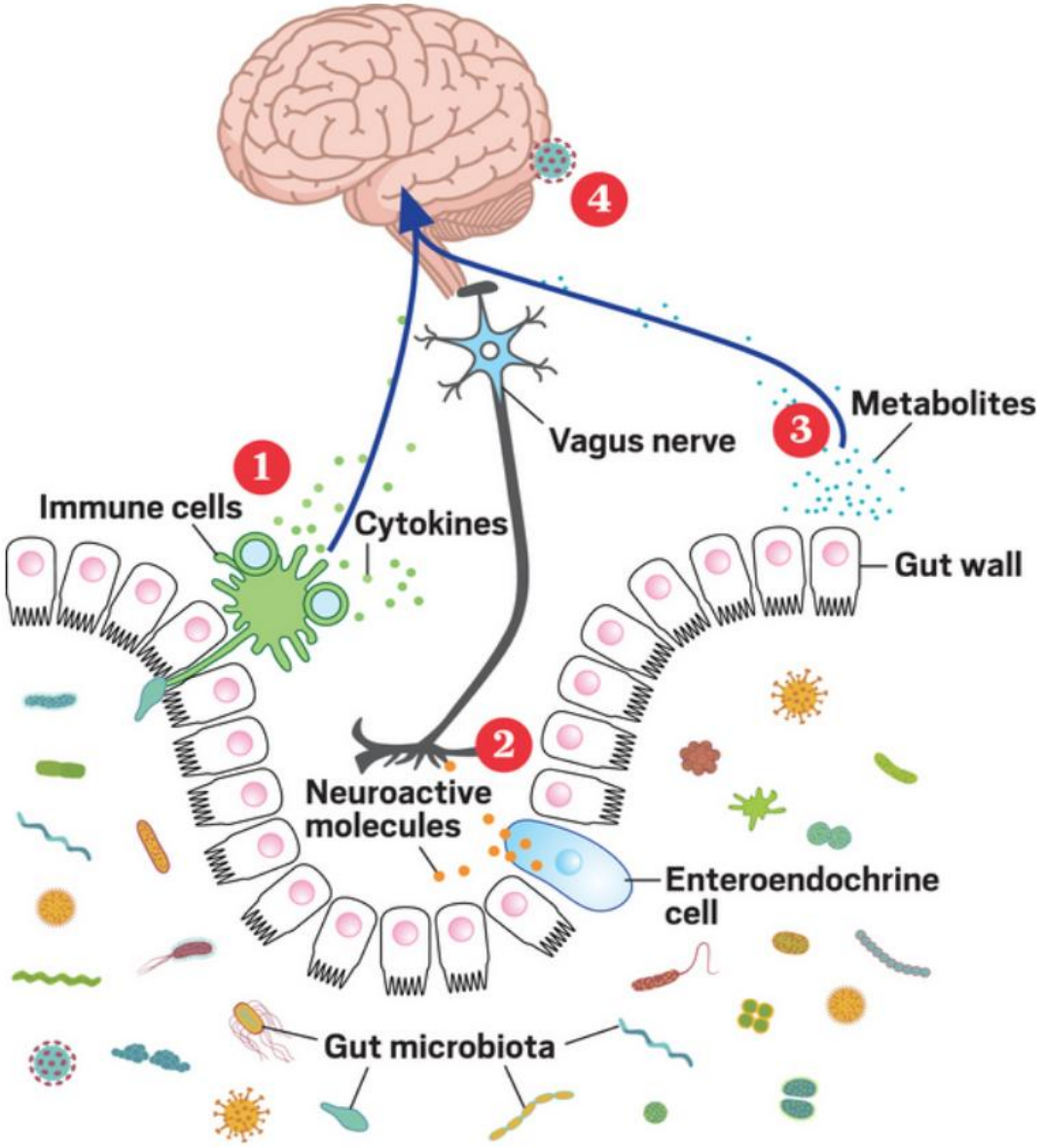
Our Hippocampal Inflammation and Gut Brain Axis Study

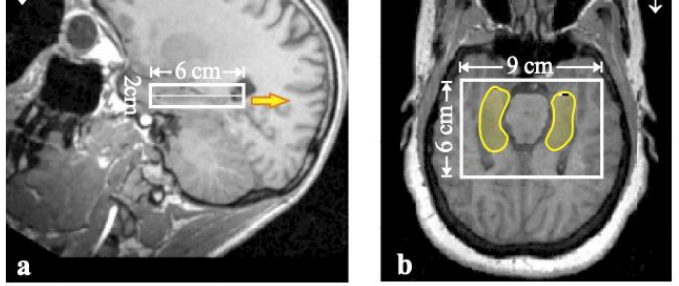
- Research Interview (DIGS, DIPAD, PANSS, Early Trauma)
- MATRICS Cognition *(Ruby et al, in review)*
- ANS Resting and Reflexes (vagal, sympathetic activity)
- MRS for Hippocampal inflammation (Gonen et al)
  (multivoxel, entire 3-dimensional structure)
- Microbiome Oral and Gut *(Lee et al, 2023)*
- Blood (DNA, metabolomics, cytokines etc)

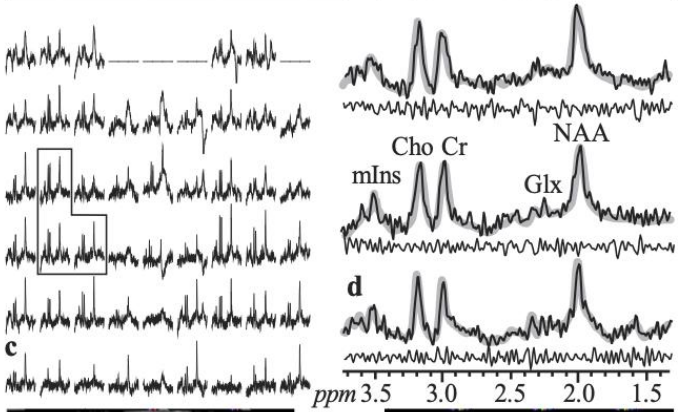
-Gut Brain Axis Questionairre *(Fendrich et al 2020).*
demographics, diet, mental & physical health,
exposures, lifestyle, birth mode, breast feeding, etc….
-Study groups: Psychotic, Nonpsychotic Mood, Controls
-Approach: DSM and RDoC transdiagnostic psychosis

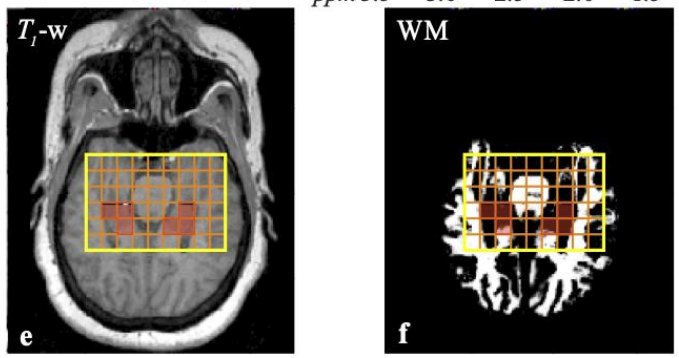
NIMH R01MH110418 Malaspina & Clemente

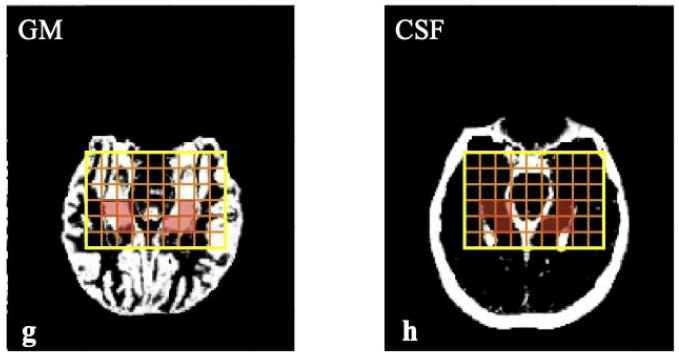
Collaboration: Psychiatry, Neurology, Radiology, Genetics. Ophthalmology, Cell Biology, Neuroscience











Gut & oral microbiome modulate molecular and clinical markers of schizophrenia-related symptoms

Imaging hippocampal metabolites for cellular pathologies

3-Dimensional whole Hippocampal H^1MRSI and MRI

Comprehensive Assessment: Autonomic Nervous System

Clinical Measures:

Symptoms, Illness course, Diagnoses, Exposures, Cognition…

Oral and Stool Microbiome

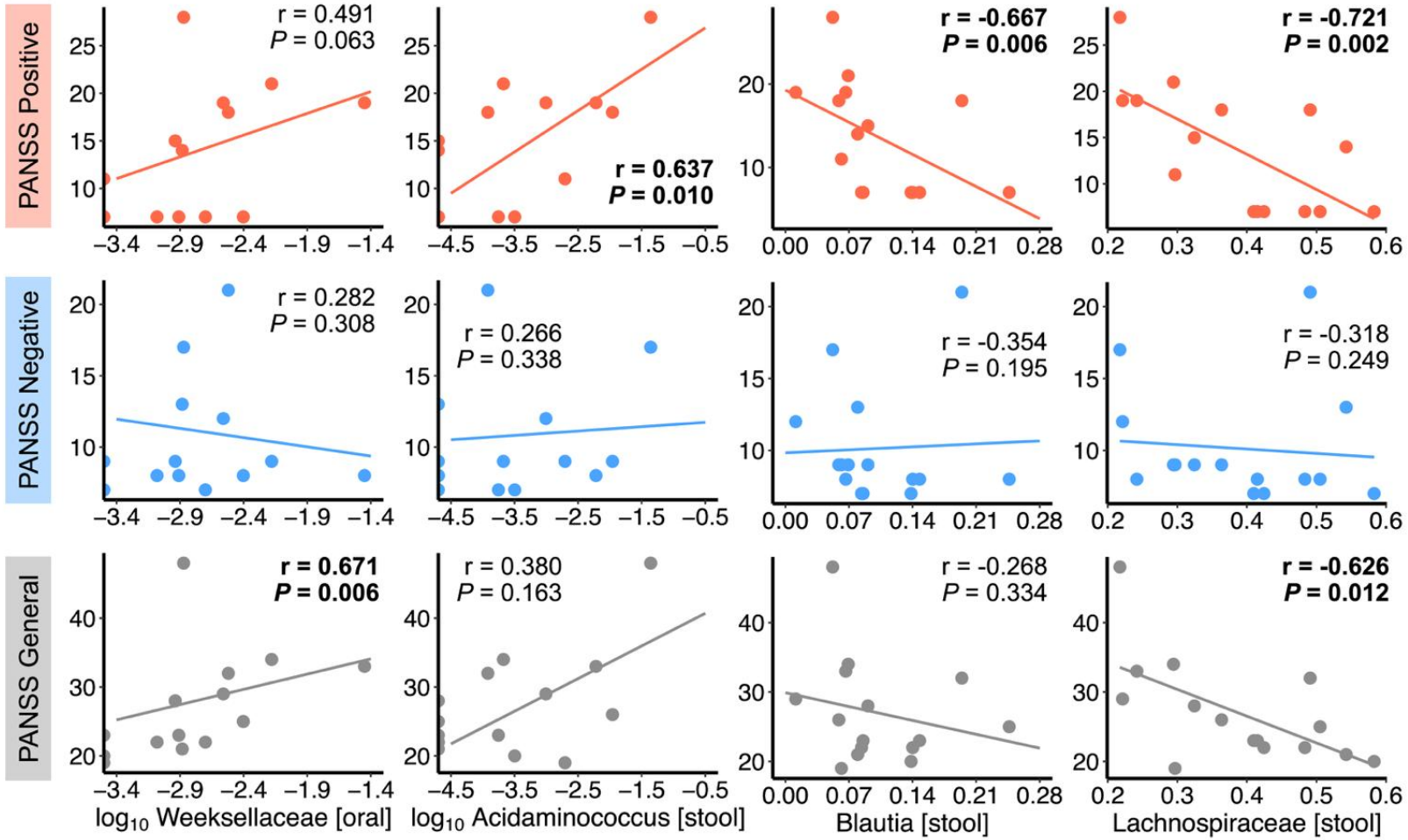
Assess alpha diversity (# of unique microbes in each sample) beta diversity (distance between samples for microbiome composition)

Conducted differential correlation analysis, predictive modeling, and correlation analysis, to assess case and control differences and identify potential biomarkers associated with psychiatric features.

Peter Joe et al, 2021; Lee et al; Psychiatry Research, 2023-08-01,

At our half-way analysis microbiota were associated wiith PANSS Scales

Correlations in cases of the scores with the relative abundances of *Oral Weeksellaceae* and gut *Acidaminococcus, Blautia* and *Lachnospiraceae:*



Lee J, Piras E, Tamburini S, Bu K, Wallach D, Remsen B, Cantor A, Kong J, Goetz D, Hoffman K, Bonner M, Joe P, Mueller BR, Robinson-Papp J, Lotan E, Gonen O, Malaspina D, Clemente JC. Gut and oral microbiome modulate molecular and clinical markers of schizophrenia-related symptoms: A transdiagnostic, multilevel pilot study. Psychiatry Res. 2023 : PMC10595250.

Activation (hostility) Factor Overlaps With Reported Immune Conditions

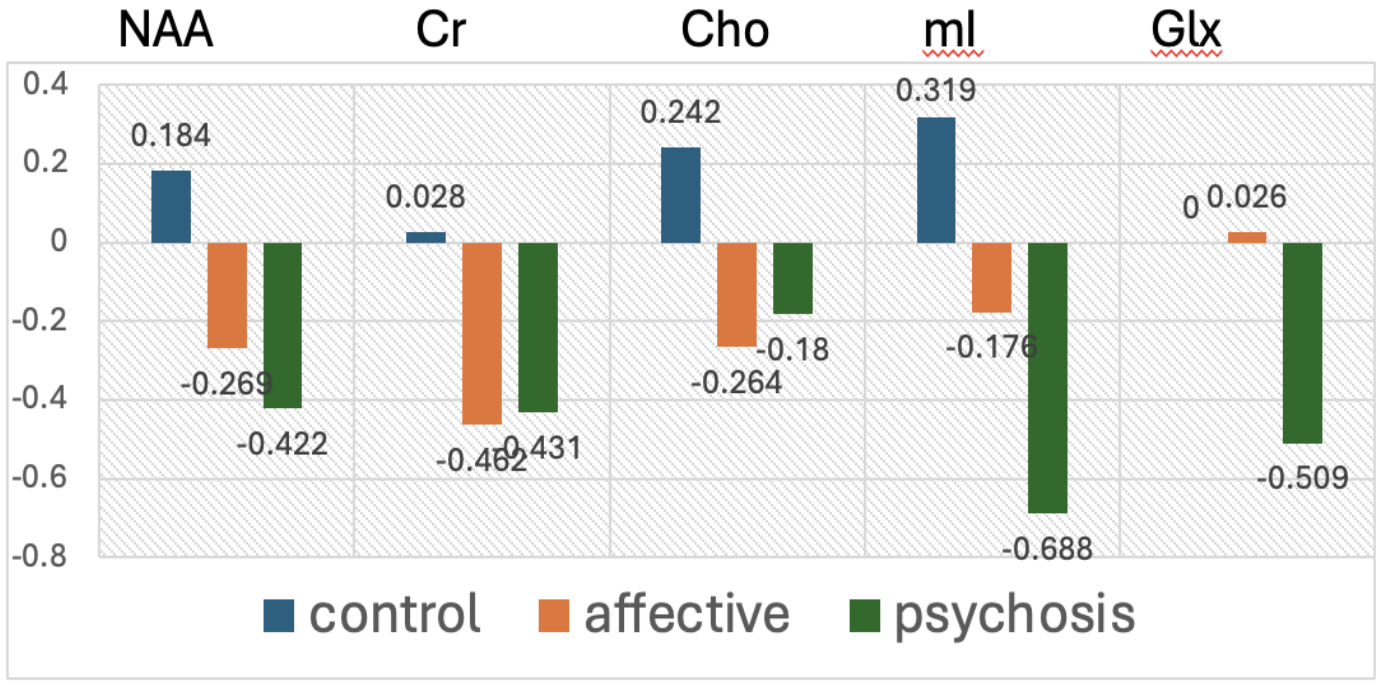
- A distinct domain of symptoms derived from the 30 item PANSS symptom scale \
  - (AKA the Resistance, Excitement, Activity, or hostility factor)
- Items for Hostility (attitudes and behaviors); Poor impulse control (impulsivity);Excitement (motor and emotional excitement);uncooperativeness (resistance to intervention).
- For persons with uncooperative and aggressive behavior with agitation or lack of behavioral control, the best antipsychotic is for activation is clozapine, next is lurasidone. *(Citrome L et al. Psych Serv. 2001; 2005)*

	Activation		Autistic Preoccupation		Dysphoria	
	(95% C.I.)	p-value	(95% C.I.)	p-value	(95% C.I.)	p-value
BMI	0.12 (0.04 - 0.20)	0.003**	0.05 (-0.07 - 0.16)	0.396	0.15 (-0.01 - 0.30)	0.061
GI GERD	1.91 (0.40 - 3.42)	0.014*	1.91 (-0.24 - 3.92)	0.082	1.91 (-1.72 - 4.07)	0.004
Skin Condition	3.18 (1.66 - 4.69)	0.000**	3.18 (-2.15 - 2.49)	0.885	3.18 (-0.06 - 6.11)	0.054
Lactose Intolerance	1.48 (0.00 - 2.96)	0.050*	1.48 (-2.95 - 1.11)	0.368	1.48 (-1.45 - 4.12)	0.341
# Med Comorbiid	0.82 (0.30 - 1.34)	0.003**	0.82 (-0.62 - 0.90)	0.720	0.82 (0.00 - 2.00)	0.050*
# Psych Comorbid	1.14 (0.30 - 1.98)	0.009**	1.14 (-1.48 - 0.90)	0.624	1.14 (0.23 - 3.36)	0.025*

Fendrich SJ, Koralnik LR, Bonner M, Goetz D, Joe P, Lee J, Mueller B, Robinson-Papp J, Gonen O, Clemente JC, Malaspina D. Patient-reported exposures and outcomes link the gut-brain axis and inflammatory pathways to specific symptoms of severe mental illness. Psychiatry Res. 2022 PMID: 35462090.

Controls	NAA	Neuronal integrity	.184[be]
	Cr	energy	.028
	Cho	membranes	.242[e]
	ml	glia	.319[be]
	Glx	excitation	.000
Affective	NAA	Neuron Integ	-.269[e]
	Cr	energy	-.462*
	Cho	membranes	-.264
	ml	glia	-.176[e]
	Glx	excitation	.026
Psychosis	NAA	Neuron Integ	-.422
	Cr	energy	-.431
	Cho	membranes	-.180
	ml	glia	-.688
	Glx	excitation	-.509

Hippocampal Cellular Pathology for "Activation" Differs by Diagnostic Category

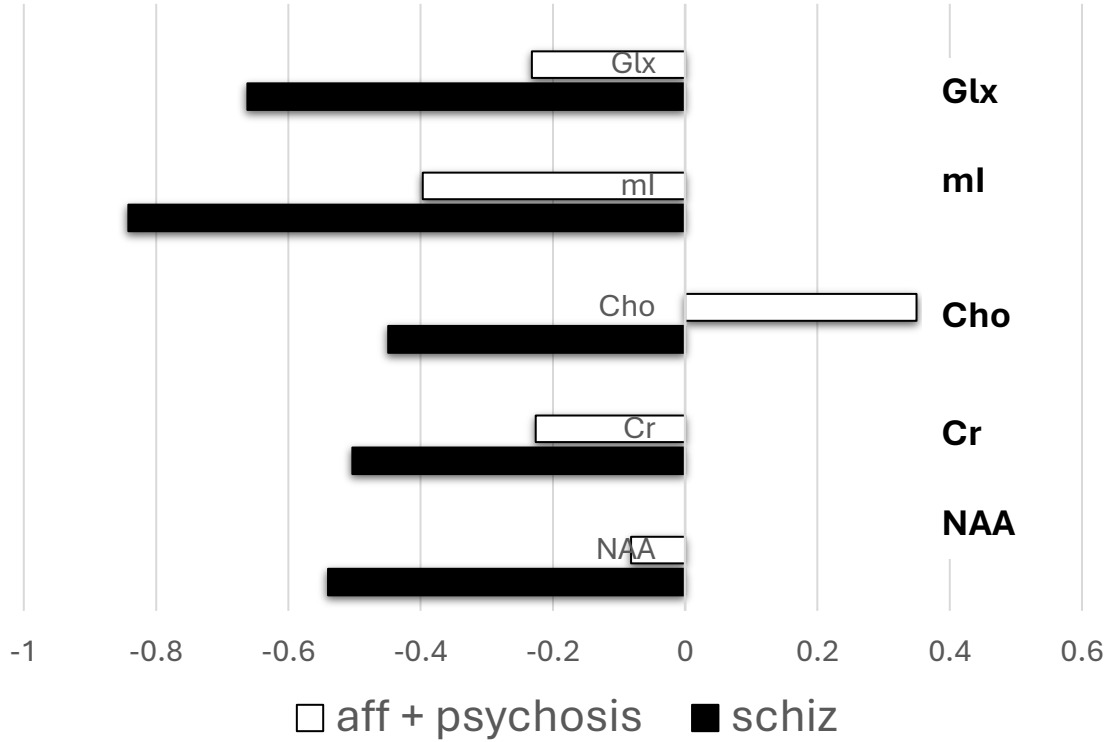


In controls, more neuronal density, more myelin and glia
In mood cases: less neuronal integrity, less energy, less myelin
In all psychosis: all reduced, predominantly reduced myelin and glutamate accounted for the severity of hostility

Gene Ruby PhD dissertation, Preliminary Data

Hippocampal Cellular Pathology for "Activation" Also Differs Across Affective Psychosis and Schizophrenia

Schiz	NAA	Neuron Integ	-.540*[ac]
	Cr	energy	-.503*
	Cho	membranes	-.449*[cd]
	mI	glia	-.842*[ac]
	Glx	excitation	-.662*
Aff +Psych	NAA	Neuron Integ	-.082
	Cr	energy	-.226
	Cho	membranes	.352[e]
	mI	glia	-.397
	Glx	excitation	-.232



Gene Ruby PhD dissertation
Preliminary Data

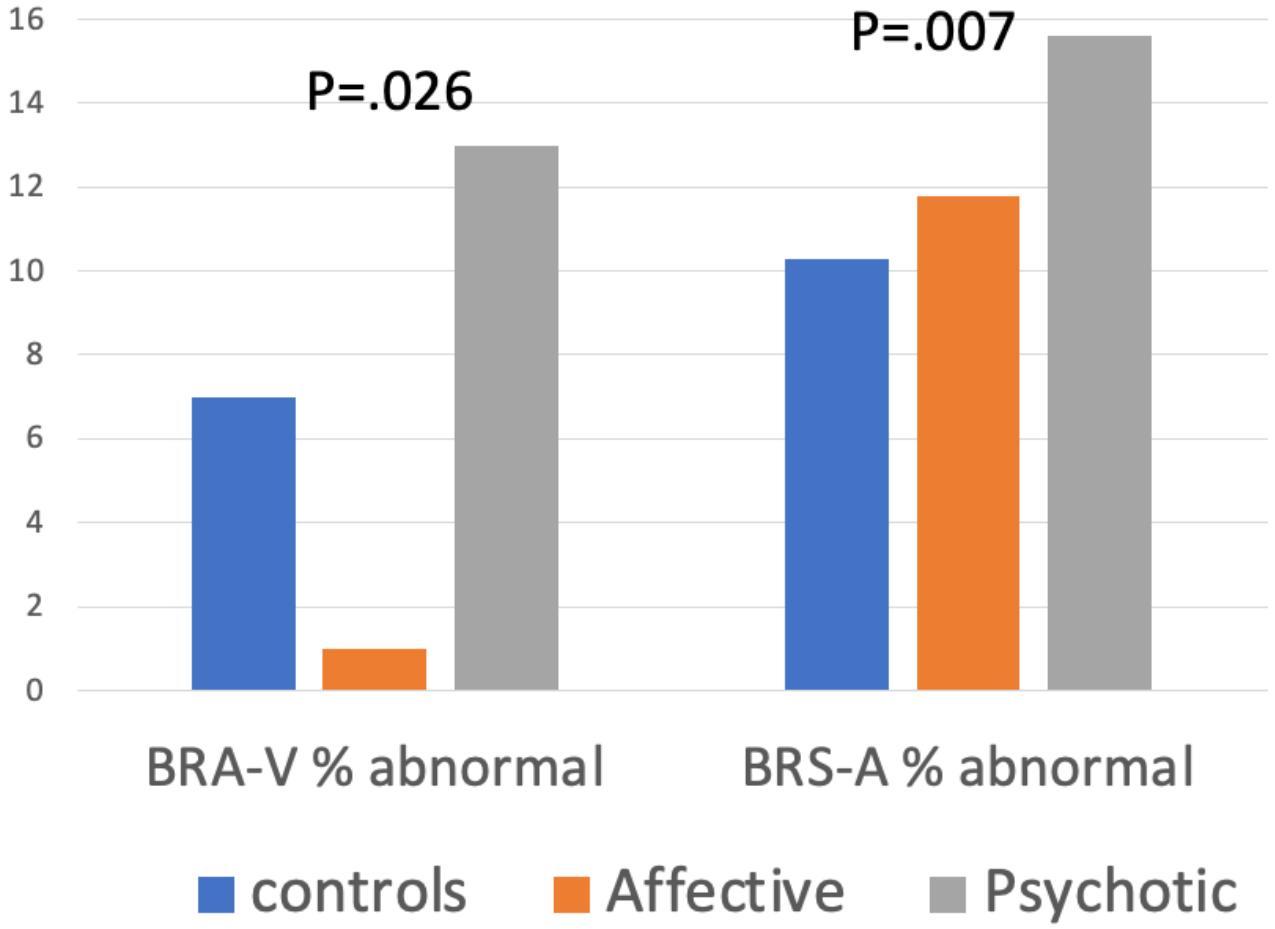
In Affective Psychosis "activation" is associated with increased myelin turnover, usually inflammatory etiology

In Schizophrenia, "activation" is predicted by reduced myelin, and reductions in all metabolites correlated with reduced excitation

Peripheral Neuropathy was highly prevalent in psychotic cases

- Baroreceptor reflex sensitivity (BRS) controls regional blood flow.
- Can be inefficient from increased sympathetic activity (that drives down vagal (parasympathetic) or from decreased vagal tone.

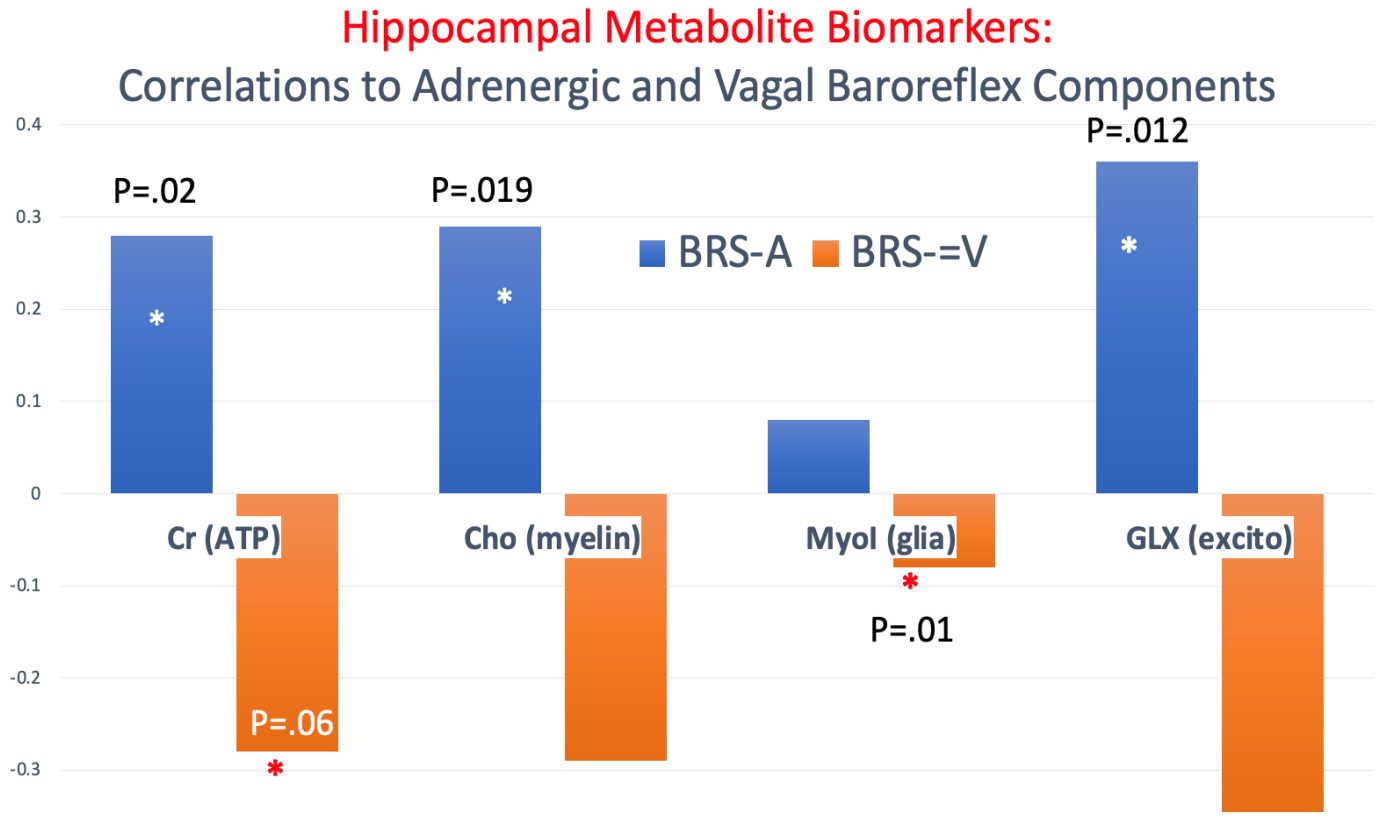
\



Mueller B, Robinson-Papp J, Suprun M, Suarez-Farinas M, Lotan E, Gonen O, Malaspina D. Baroreflex sensitivity is associated with markers of hippocampal gliosis and dysmyelination in patients with psychosis. Clin Auton Res. 2023 Apr;33(2):101-110. doi: 10.1007/s10286-023-00929-x. Epub 2023 Mar 6. PMID: 36877302.

Baroreflex sensitivity and hippocampal abnormalities in psychosis

Only in psychotic cases was the baroreceptor reflex related to brain imaging indicating inflammation



- <u>Increased sympathetic</u> Greater energy-use (Cr) & dysmyelination & excitotoxicity→ (Psych + Aff ?)
- <u>Decreased vagal</u>: Loss of glia (ml), myelin & excitatory drive → (Sz ???)

*Mueller, B., Robinson-Pappet al. Baroreflex gliosis and dysmyelination in psychosis. Clin Auton Res **33**,:101–110 (2023).*

FOOD AS MEDICINE

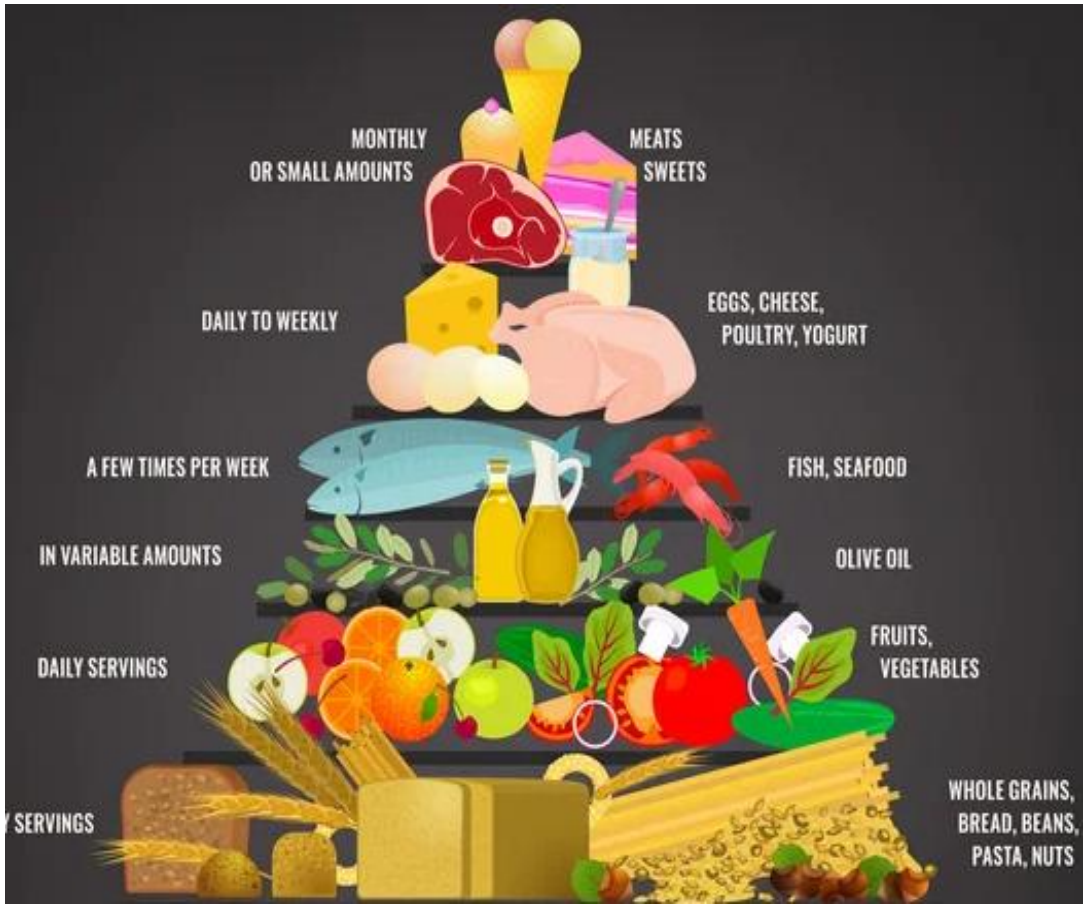
Prior Dietary Guide

Distinctly new & controversial diet advice is presented in a recently revised Food Pyramid

Emphasizes Red Meat, Full-fat dairy. One goal is to support American farmers, ranchers, & companies growing & producing al food."

Limit or Avoid Processed Foods

Mediterranean Diet



Daily Exercise; Unlimited Olive Oil
Fermented Foods, Supplements

Akerele C, Koralnik L, Lafont E, Gilman C, Walsh-Messinger J, Malaspina D. Nutrition and brain health: Implications of Mediterranean diet elements for psychiatric disorders. Schiz Res. 2025. PMID: 40315757.

The Mediterranean Diet supports a diverse & balanced gut microbiota

Improved diversity of the gut microbiota reduces inflammation

- Mediterranean Diet rich in polyphenols, fiber, and unsaturated fatty acids
- Emphasizes fresh fruits and vegetables, whole grains, legumes, nuts, seeds, and healthy fats such as olive oil.
- Limit red and processed meats, refined sugars, and eliminate ultra-processed foods.

In contrast, The Western diet is high in saturated fats, refined sugars, and low in fiber. It is linked to dysbiosis and increased inflammation.

Plant-based fibers needed for the bacteria producing short-chain fatty acids (SCFAs) SCFA have anti-inflammatory properties and support gut health.

Fermented foods increase gut diversity & reduce inflammation. Yogurt, kefir, kimchi, sauerkraut contain live microorganisms and bioactive compounds for the gut microbiome.

Summary, a diet rich in fruits, vegetables, whole grains, legumes, nuts, seeds, healthy fats (olive oil) recommended for maintaining a healthy gut microbiota.

Our Study of Mediterranean Diet vs. Standard American Diet

- Standard American Diet (SAD): rich in saturated fat, processed carbohydrates, and poor in fruits and vegetables vs the Mediterranean Diet (MD).
- SAD Causes inflammation and insulin resistance
- MD improves multiple sclerosis (RR=0.91), Sjögren's syndrome (OR=0.81) and RA.

We assessed diet in our participants with our comprehensive questionnaire (GBAQ)
The psychosis group more likely to consume the SAD than controls ($p = 0.007$)
MD adherence in psychosis predicted <u>better working memory</u> ($r = 0.461$, $p < 0.001$).
MD adherence in mood disorders predicted:

→ <u>faster processing speed</u> ($r = 0.376$, $p = 0.049$)
→ <u>Lower General Psychopathology scores</u> ($r = -0.449$, $p = 0.013$)
→ <u>Low Activation/hostility</u> ($r = -0.362$, $p = 0.049$) and <u>Dysphoric Mood</u> scores ($r = -0.403$, $p = 0.027$).

Our first-of-its kind study identified poor dietary choices in psychosis, showed MD diet predicted lower symptoms and better cognition.
→ Supports dietary interventions research for prevention and treatment of psychiatric conditions.

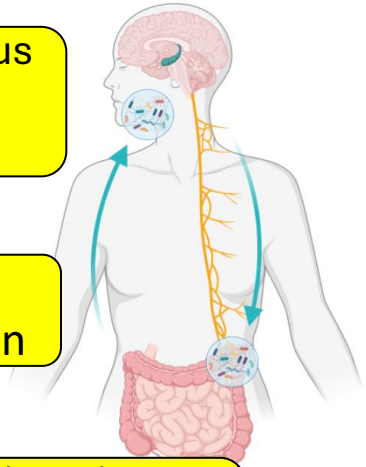
Lauren R. Koralnik, Ezequiel Lafont, Christa Akerele, Mharisi Bonner, … Dolores Malaspina. Mediterranean and standard American diet consumption in psychosis and non-psychosis affective disorders groups: Symptoms and cognition. Schiz Research. 2025

Gut & Oral microbiome differed in psychosis vs healthy and mood cases

Schizophrenia best predicted by oral microbiome

Hippocampus
Symptoms
Cognition

Peripheral inflammation



Microbiome perturbations in oral and gut

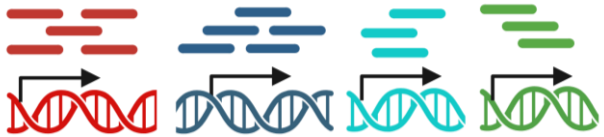
All cases predicted by:
GUT (Firmicutes, Bacteroidetes)
ORAL (Firmicutes, Proteobacteria)

All psychotic cases predicted by gut microbes
Cases (Lactobacillus and Coprobacillus)
Controls (Alistipes, Peptostreptococcaceae, Ruminococcaceae)

And by oral microbes
Cases (Veillonella, Prevotella, Actinomyces)
Controls (Actinobacillus, Haemophilus, unID Pasteurellaceae)

Community-Level Proteins/Functions

Read protein-coding genes



Read bacterial genomes/markers

Shotgun sequencing of microbiome sample

Lee JJ, Piras E, Tamburini S, Bu K, Wallach DS, Remsen B, Cantor A, Kong J, Goetz D, Hoffman KW, Bonner M, Joe P, Mueller BR, Robinson-Papp J, Lotan E, Gonen O, Malaspina D, Clemente JC. Gut and oral microbiome modulate molecular and clinical markers of schizophrenia-related symptoms: A transdiagnostic, multilevel pilot study. Psychiatry Res. 2023 PMC10595250.

Poor oral microbiota predicted schizophrenia

Also linked to increased risk for oral diseases and multiple systemic conditions
cardiovascular disease, diabetes, respiratory infections, rheumatoid arthritis, chronic kidney disease, various cancers and neurodegenerative disorders

Metabolic diseases, particularly T 2 diabetes mellitus, associated with periodontitis

Oral dysbiosis / periodontitis linked to atherosclerotic cardiovascular disease.

Respiratory conditions oral microflora enter the respiratory system and through dysbiosis-induced immune reactions. COPD, pneumonia, aspiration pneumonia.

Neurodegenerative condition linked to oral microbiome dysbiosis.
Alzheimer's, Parkinson's disease, major depression, multiple sclerosis and schizophrenia.

Mechanism: Subgingival microorganisms from periodontitis may enter the bloodstream and distribute throughout the body, reaching distant tissues and organs, or directly stimulate inflammation and immune activation.

Take Away Messages….

- A large portion of serious mental illness has an inflammatory basis
- Early stress or infection-triggered immune activation→ lifelong immune reactivity.
- Poor gut health further increases inflammation, including vagal disruption
- Dietary health is a key factor in prevention and improvement of SMI
- The gut and oral microbiome are disrupted in psychosis
- Oral microbiome dysbiosis is more specific to schizophrenia

- A clinical history should include prenatal and life course exposures and diet
- Diet influences the microbiome and plays a major role for maintaining mental health
- Dietary interventions may prevent or moderate severe mental illness
- Certain anti-inflammatories can be developed for specific patient groups

Ambitious: My astonishing mother and her mentor

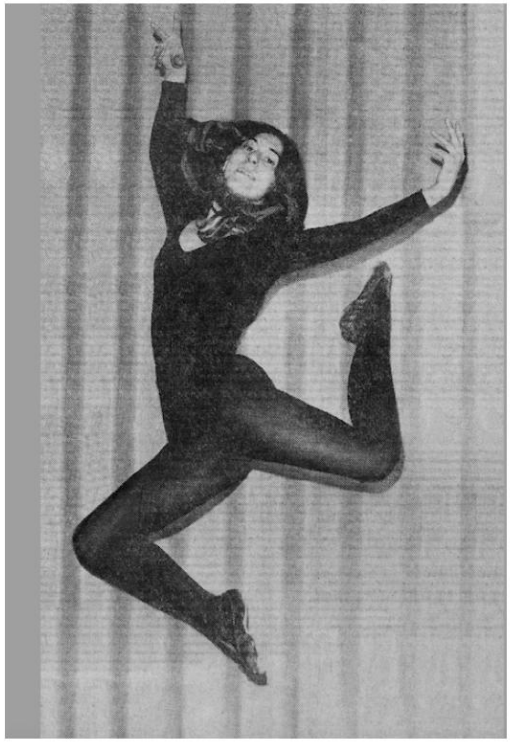
Edna Dorothy Tett
Malaspina
1927-2009

Theodore H Elsasser
1899-1985
Physician-scientist: NYU ‘1924

Published:
Elsasser TH; Wallace GB
Science; 1939. 17;89(2307)

Harvey Society Member
Full time Medical Practice
Mouse studies in his basement

My Muse: Eileen Malaspina



Eileen Marie Malaspina
1954-2021

"Some facts are wrong in the 'seeds of psychosis' article". My sister wrote:...

"Eileen Malaspina dreamed of becoming a physician," but she did more than dream in her life. She entered Rutgers New Brunswick immediately after high school graduation and did not go into a psychiatric hospital as advised.

She received a Pell grant and scholarship- moved into her dorm room and became a thriving member of college life in the mid 1970's. She had friends and lovers and difficult courses. She traveled to Europe and studied at the University of Vienna after her freshman year. She married her college sweetheart, with whom she had danced for three straight days in an American Cancer Society Marathon fund raiser. She belonged to the Cook County Soil Conservation Society, went on ski trips and had friends on all three campuses of RU.

I know all of this is the truth because I am Eileen Malaspina. My diagnosis is bipolar disorder and anxiety disorder and not schizophrenia.

I can see that my past is not so different than other creature people. I am an accomplished poetess and patient elder caretaker. Bipolar's are mentally ill – so I have accepted that I have a mental illness. But it is not, as the article seems to state by using the phrase "a devastating mix of mania, psychosis and depression, all- consuming of the self".

The mentally ill are part of the general public; not exceptions or freaks. (Mental health professionals have spoken of my life as a circus.')

By Eileen Malaspina

Mentored by Lynn Margulis, PhD. “Symbiosis Theory of Evolution”

My mentor got “Environmental Biology”, an independent major ahead of its time

1938 -2011

an iconoclastic evolutionary theorist, Her paper *“On the Origin of Mitosing Cells (*1967)”was first rejected by 15 journals.

Proposed eukaryotic cells are symbiotic unions of primitive prokaryotic cells.

Her idea was a great achievements of twentieth-century evolutionary biology.

She showed courage & stamina in sticking to her theory and carrying it through from unorthodoxy to an accepted truth.
I belatedly applied this to psychiatry.

E. O. Wilson called her “the most successful synthetic thinker of modern biology.”

NIMH R01 Hippocampal Inflammation and The Gut Brain Axis

NIH K 07. SZ Academic Award
NIMH K 24 TMH01699 ,Training the next generation of translational researchers
Mentee K01; K23 Grants

BBRF (formerly NARSAD) 4 Grants

NIMH P20MH50727 CRC in Schizophrenia

G. Harold and Leila Y. Mathers Foundation

NIMH R01 Jerusalem Cohort
NIMH R01 Olfaction Social Function
NIH RC1 ARRA Challenge Grant
NIMH R01 Hormonal Drivers of Perimenopausal Inflammation and Mood Symptoms

NIMH Psychiatric Genetics Initiative
NIMH Genomic Psychiatry Cohort

<u>Gut Brain</u>: Oded Gonen, Jose Clememte, Jakleen Lee: Microbiology; Jessica Papp Robinson, Bridget Mueller: Neurology; Gene Ruby, Hippocampal Cellular Pathologies

<u>Epidemiology</u> Susan Harlap, Mary Perrin….
<u>Clinical</u> R Raymond Goetz, Cheryl Corcoran, David Kimhy, *Mary Perrin*, Julie Walsh Messinger; Debbie Goetz, Jill Harkavy Friedman…

<u>Genetics</u>: Moses Chao; Thorsten Kranz PhD Carlos and Michele Pato, Tim Bignelli, Mark Rappoport; Peter Buckley; Doug Lehrer Psychiatric Genomics Cohort Team

<u>Trainees who are still in training:</u>
Gene Ruby; Jackleen Lee, Lauren Koralnik, Crista Akerle, Ezeqiel LaFont; Emily Aledorph