

Erasmus MC

Universitair Medisch Centrum Rotterdam



CVS/ME en Neuroinflammatie

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Effects on the Body

Brain Tumor

headaches

seizures

changes in personality

memory loss

mood swings

loss of balance

fatigue

anxiety or depression

difficulty concentrating

confusion

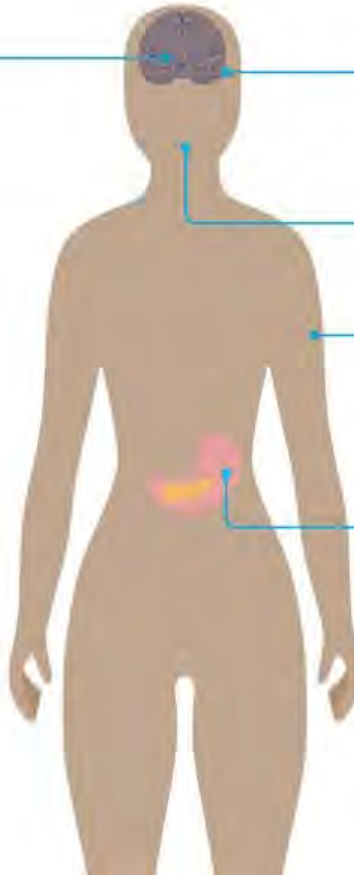
disorientation

vision problems

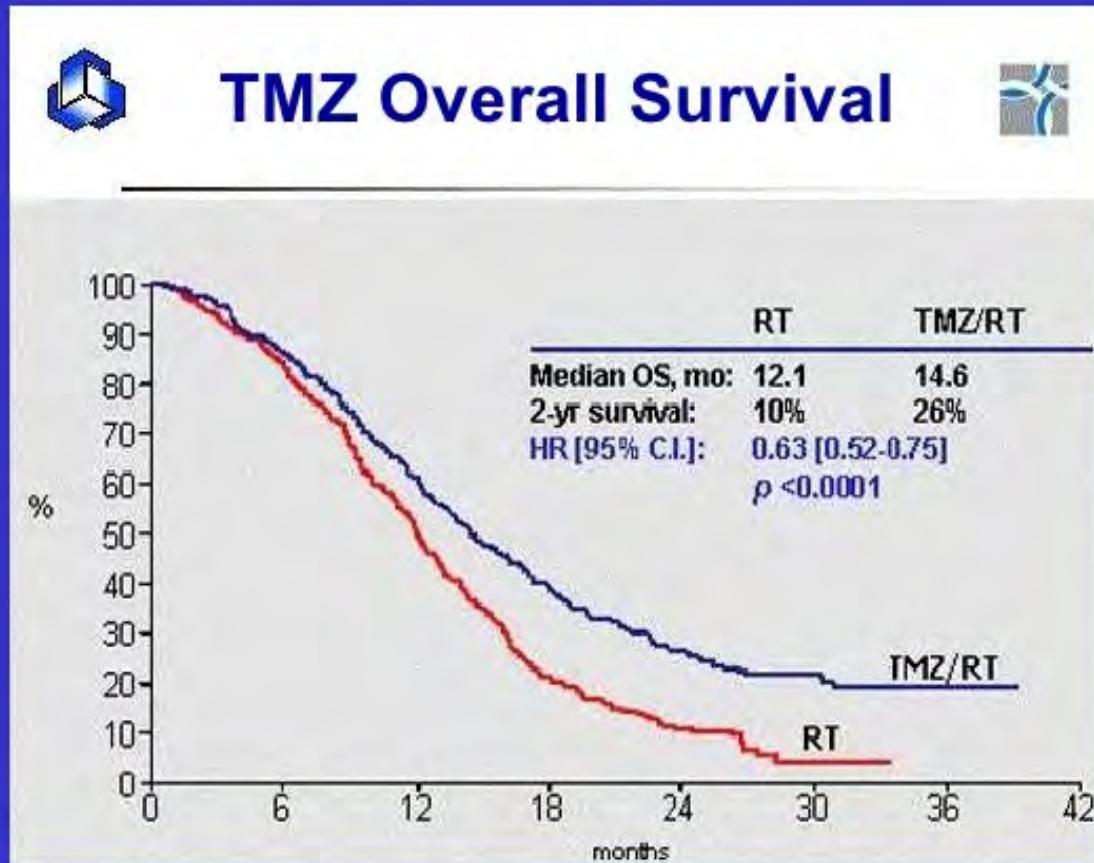
difficulty communicating

tingling or stiffness
on one side of the
body

nausea

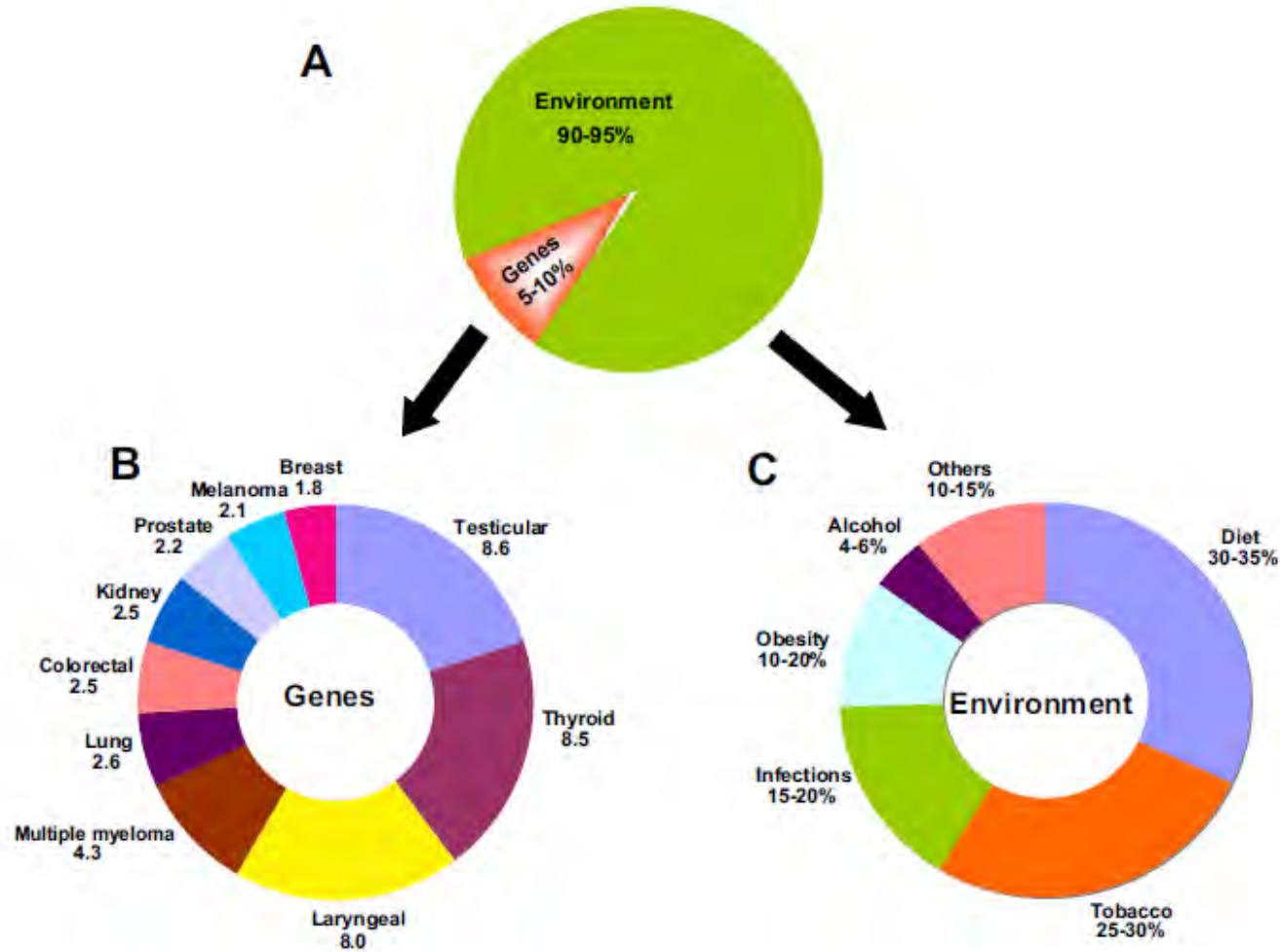


SURVIVAL IN GLIOBLASTOMA



Stupp, R. et al. N Engl J Med 2005;352:987-996

Causes of Cancer



Life style risk factors

High fat diet

Tobacco

Env. Pollution

Stress

Radiation

Infections

Turmeric
Red chilli
Ginger
Black pepper
Cardamum
Cumin

**NF- κ B
Activation**

Curcumin
Capsaicin
Gingerol
Piperine
Cardamonin
Thymoquinone

Major Pro-inflammatory biomarkers

IL-1

IL-6

IL-8

IL-17

TNF- α

COX2

5LOX

CRP

PSA

STAT3 Activation

Major Chronic diseases

Cancer

Diabetes

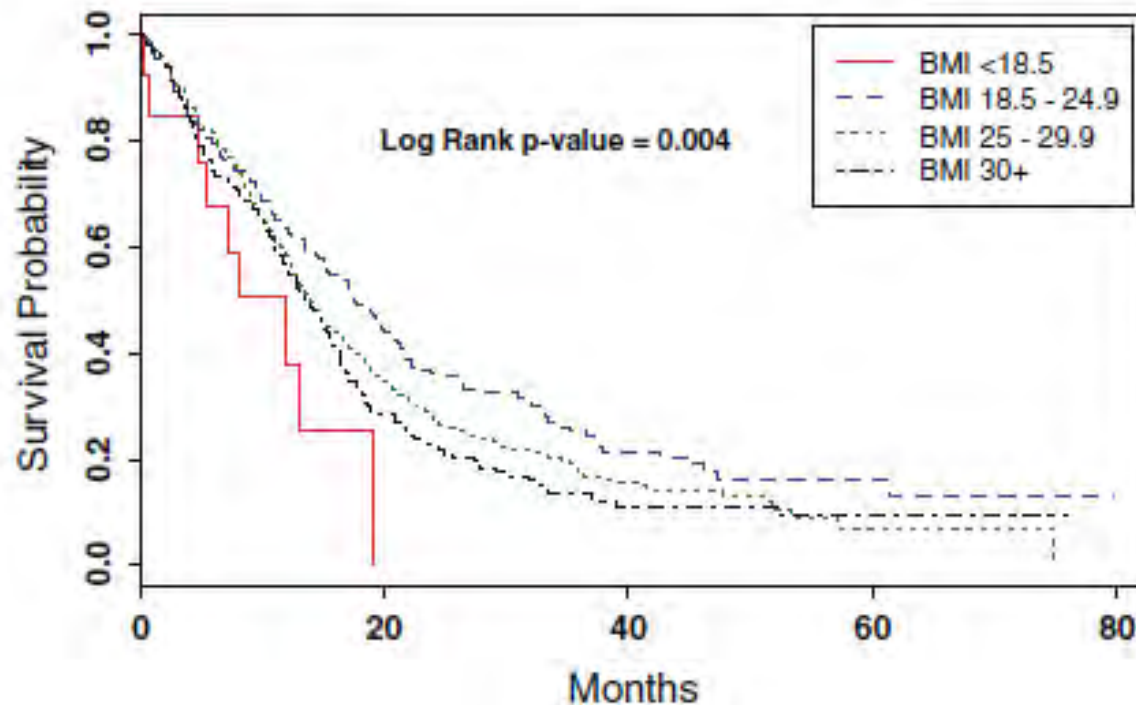
Obesity

Cardiovascular
diseases

Pulmonary
diseases

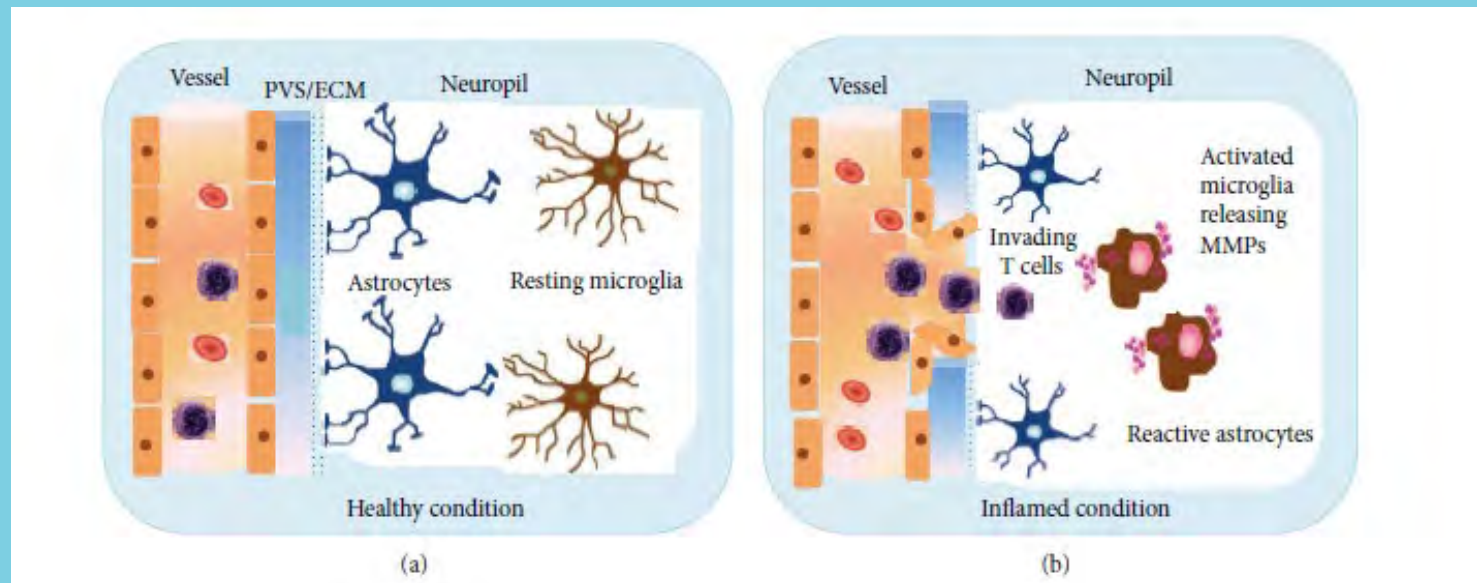
Neurological
diseases

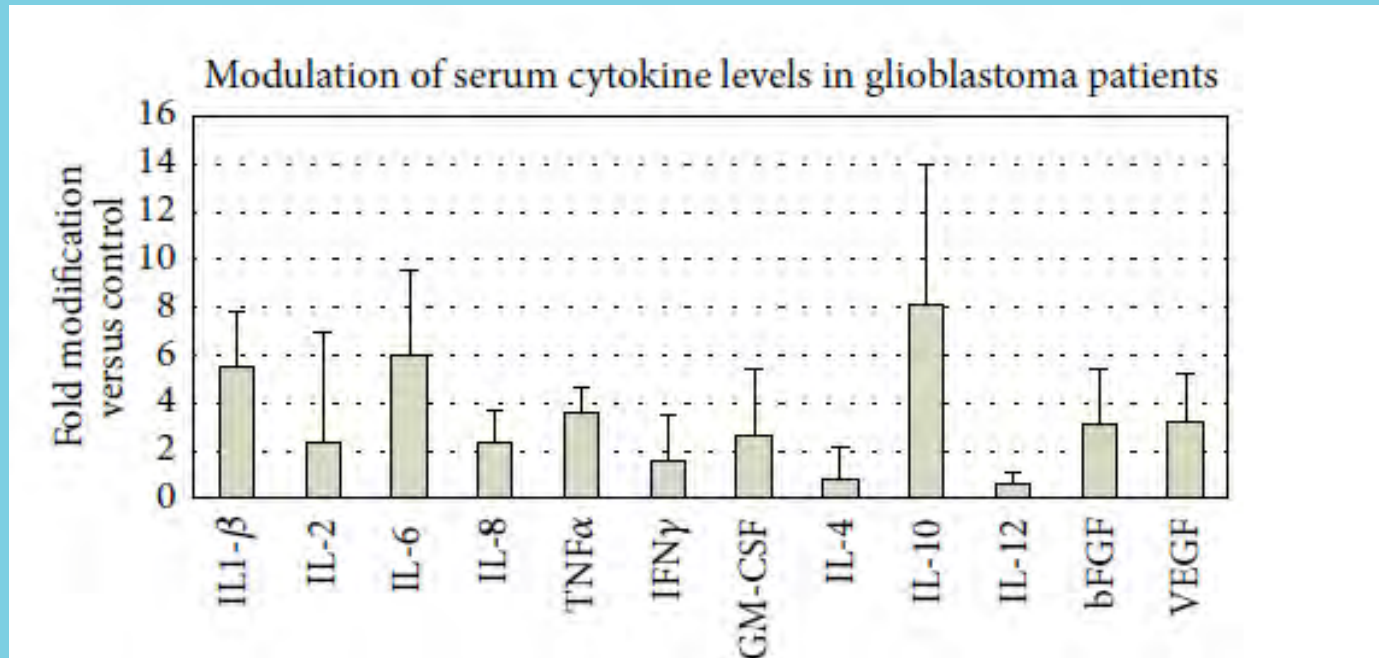
Lifestyle and cancer: BMI and glioma



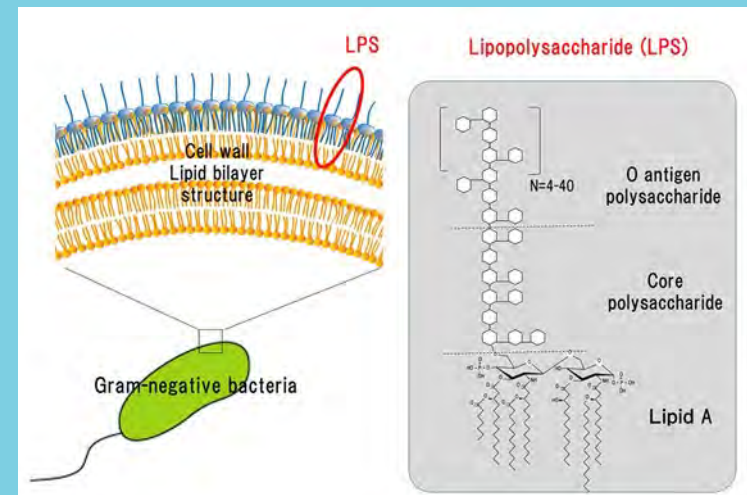
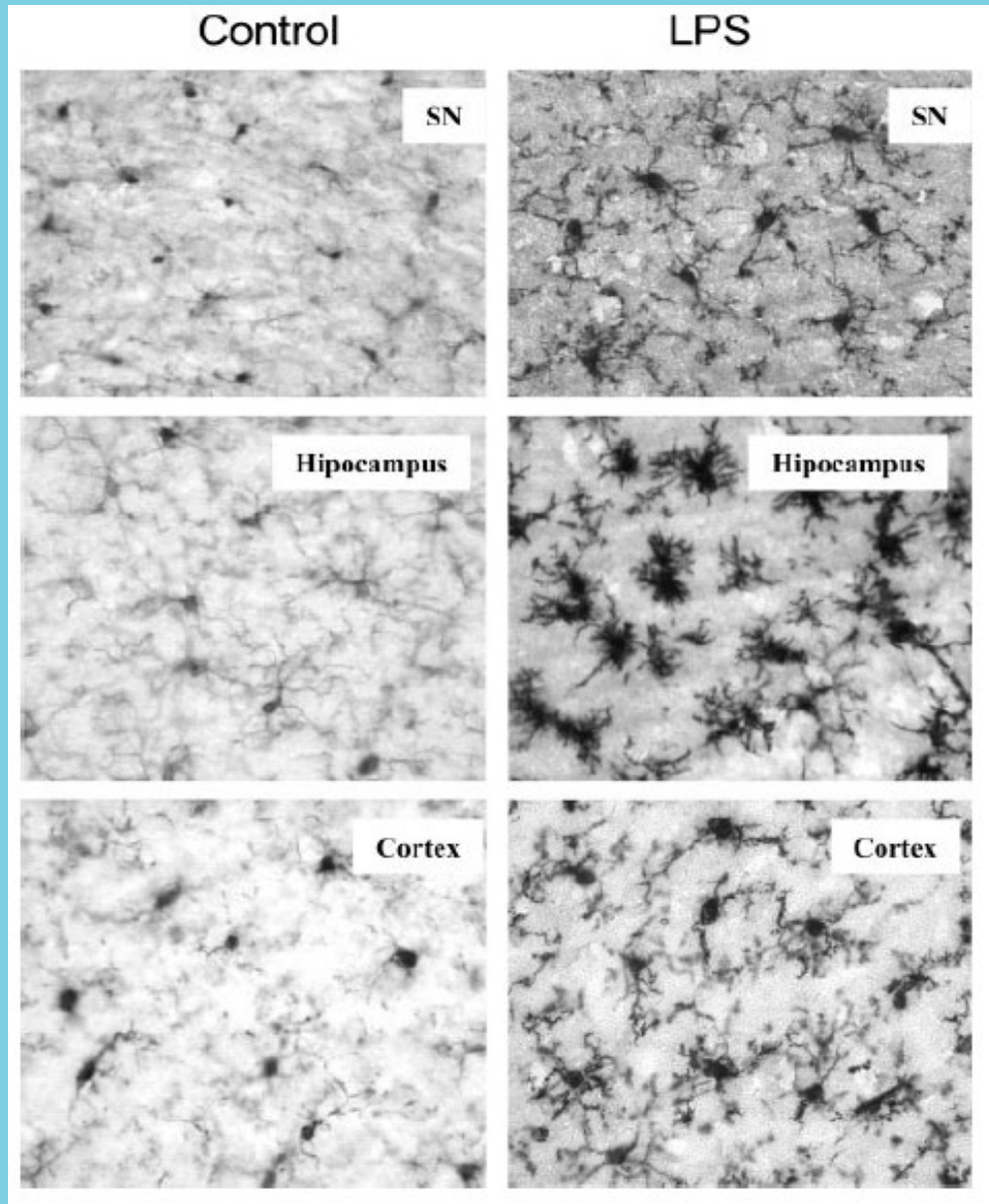
Review Article

The Role of Microglia and Matrix Metalloproteinases Involvement in Neuroinflammation and Gliomas



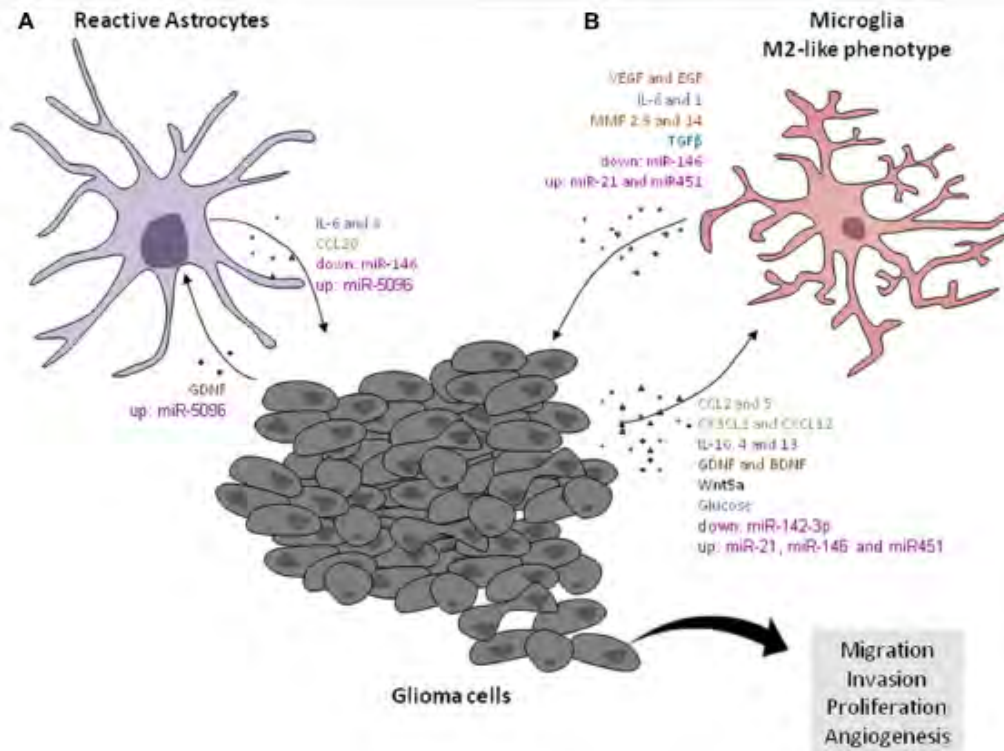


Systemic LPS Causes Chronic Neuroinflammation and Progressive Neurodegeneration

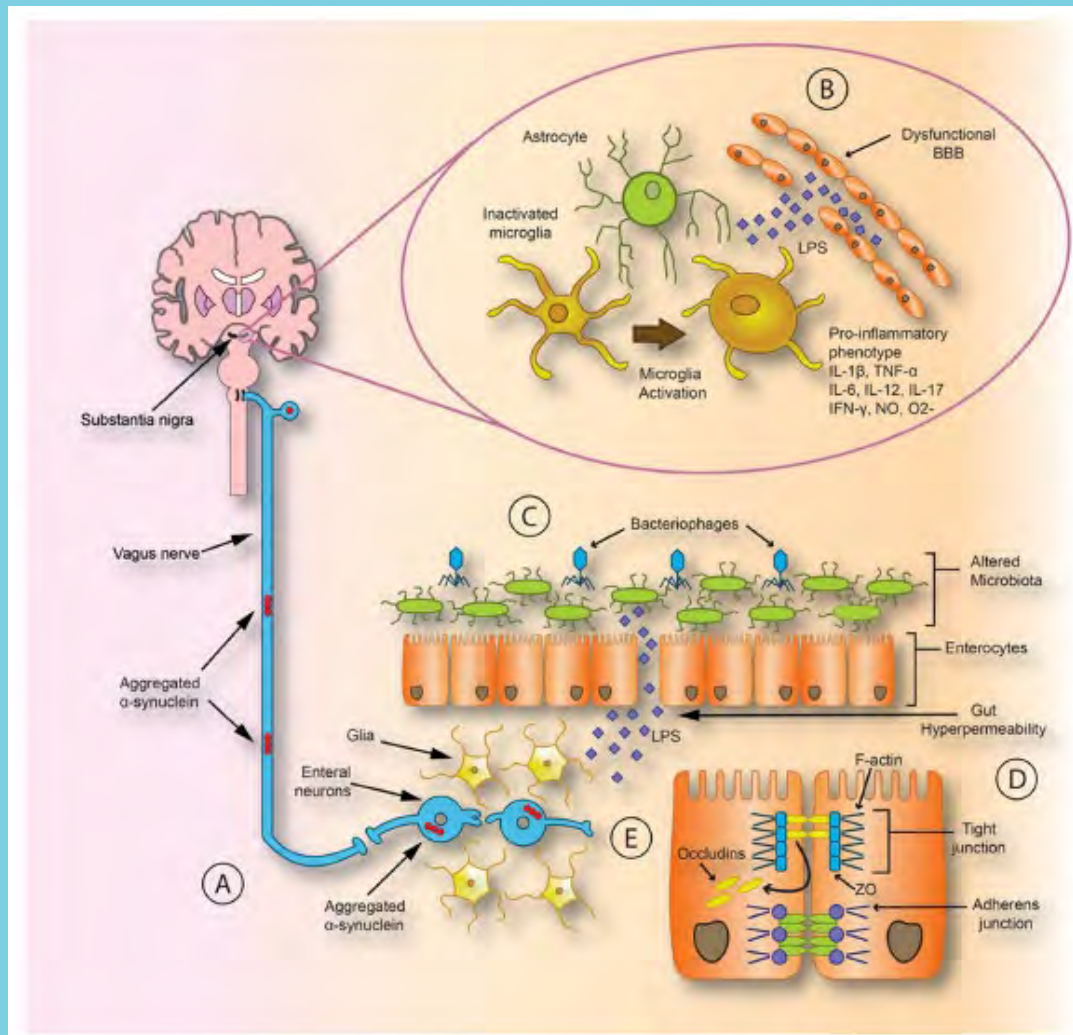


GLIA 55:453-462 (2007)

Microglia/Astrocytes–Glioblastoma Crosstalk: Crucial Molecular Mechanisms and Microenvironmental Factors



The Link between Gut Dysbiosis and Neuroinflammation in Parkinson's Disease



Leaky gut?



Human beings have **THE SAME NUMBER**
of cells as bacteria



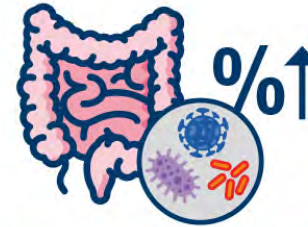
Our microbiota
WEIGHS APPROXIMATELY 1KG



Each individual's
microbiome **IS UNIQUE**



WE COULD NOT LIVE
WITHOUT our microbiome



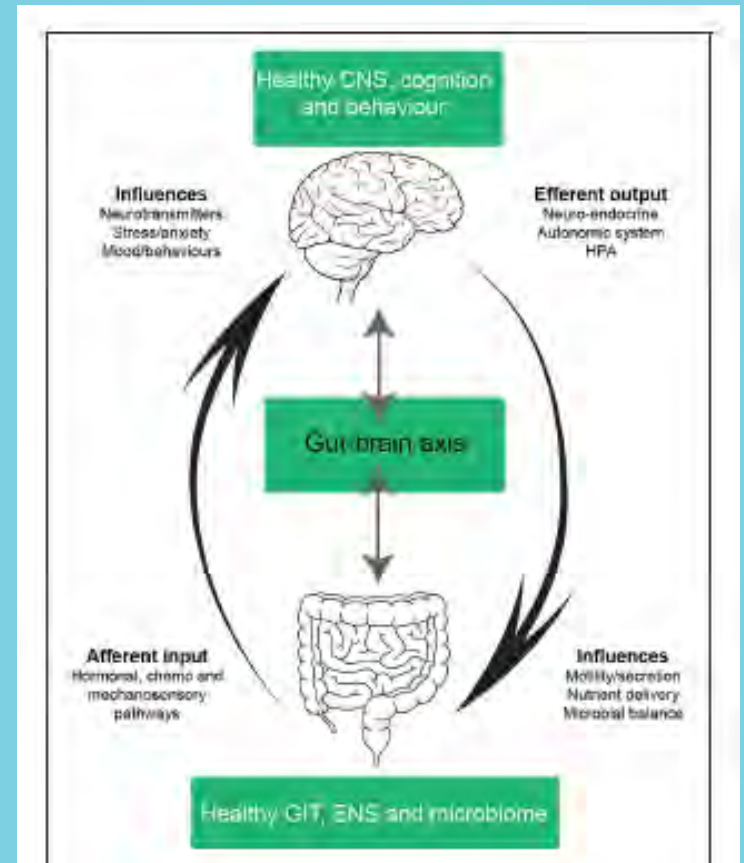
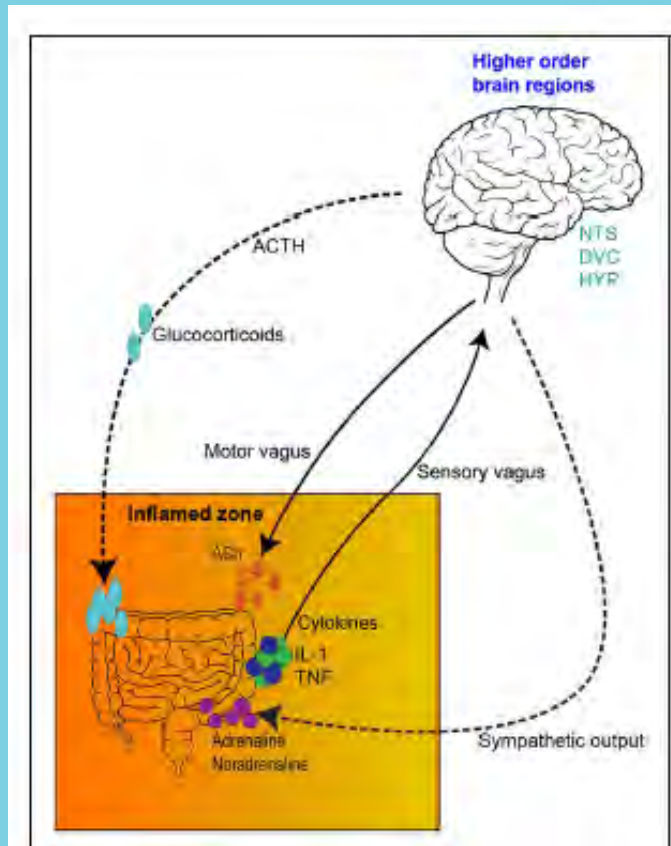
Most of our microbiome
IS FOUND IN THE GUT

www.barcelonamaculafound.org

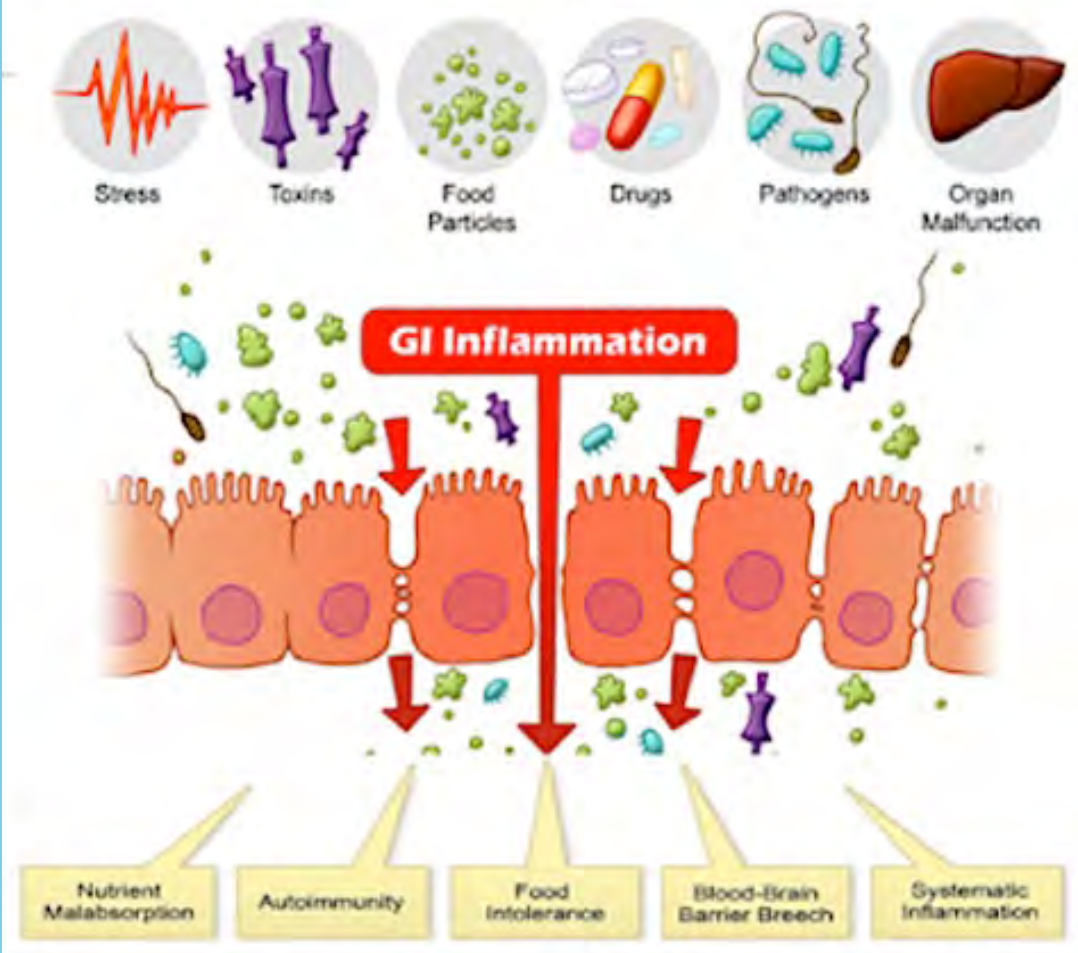




Gut-Brain interaxis



Leaky Gut



- Chronic diarrhea, constipation, gas or **bloating**.
- Nutritional deficiencies
- Poor immune system.
- Headaches, brain fog, memory loss.**
- Excessive fatigue.**
- Skin rashes and problems such as acne, eczema or rosacea.
- Cravings for sugar or carbs.
- Arthritis or joint pain.

- Markers serum: **Zonuline, Actine, LPS**

DEGREES OF DEVELOPMENT OF DYSBIOSIS



Normal



1

REDUCTION IN THE
AMOUNT OF NORMAL
ANAEROBIC MICROFLORA



2

AN EVEN GREATER DECREASE
IN THE AMOUNT OF NORMAL
ANAEROBIC MICROFLORA
COLONIZATION OF THE
PATHOGEN MICROFLORA



3

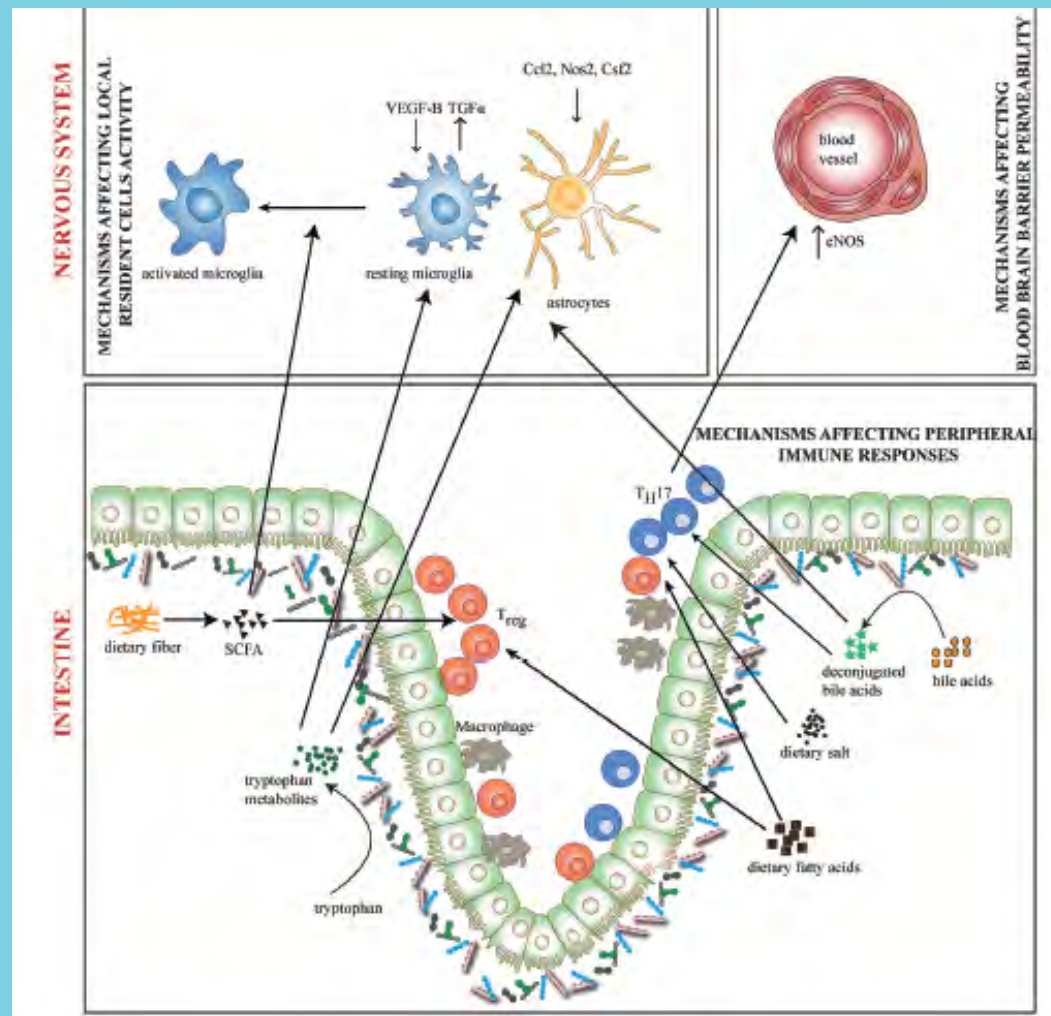
SIGNIFICANT DECREASE IN
THE AMOUNT OF ANAEROBES
ACTIVE REPRODUCTION
OF AEROBES AND FUNGAL
MICROFLORA



4

BIFIDOBACTERIA AND
LACTIC ACID BACTERIA
DECREASED DRAMATICALLY
ACTIVE REPRODUCTION
OF AEROBES AND FUNGAL
MICROFLORA

Emerging Role of Diet and Microbiota Interactions in Neuroinflammation



Unhealthy gut, unhealthy brain: The role of the intestinal microbiota in neurodegenerative diseases

- Alzheimer**
- Parkinson**
- Amyotrofische lateraal sclerose (ALS)**
- MS**
- Depressie**
- Autisme**
- Glioom?**
- Chemotherapie bij kanker**
- CFE/ME?**

Neurologische aandoeningen en inflammatie in de hersenen

Disease	fatigue	cognition decrease	inflammation serum	neuroinflammation	dysbiosis	association with BMI	complement activated
ALZHEIMER	+	+	+	+	+	-	+
PARKINSON	+	+	+	+	+	-	+
AMYOTROFIC LATERAL SCLEROSIS	+	+	+	+	+	+	+
MULTIPLE SCLEROSIS	+	+	+	+	+	-	+
DEPRESSION	+	+	+	+	+	+	+
SCHIZOFRENIA	+	+	+	+	+	+	+
GLIOMA	+	+	+	+	+	-	+
CVS /ME	?	?	?	?	?	?	?



CFS /ME: Definitie Centre for Disease control : (Fukuda)

Chronic fatigue syndrome (CFS), also referred to as myalgic encephalomyelitis (ME), is a complex, **fatiguing**, long-term medical condition that causes worsening symptoms after physical or mental activity, a greatly lowered functional ability to complete routine daily activities compared to prior onset of the disease, and unrefreshing sleep. Difficulty sitting and standing upright or **cognitive dysfunction** are also present. Other common symptoms may involve numerous body systems in those affected.

Signs and symptoms: *The United States Centers for Disease Control and Prevention (CDC) recommends the following criteria for diagnosis:*

- Greatly lowered ability to do activities that were usual before the illness. This drop in activity level occurs along with fatigue and must last six months or longer.*
- Worsening of symptoms after physical or mental activity that would not have caused a problem before illness. This is known as post-exertional malaise (PEM).*
- Sleep problems*

Additionally, one of the following symptoms must be present:

- Problems with thinking and memory (cognitive dysfunction, sometimes described as "brain fog")*
- While standing or sitting upright; lightheadedness, dizziness, weakness, fainting or vision changes may occur (orthostatic intolerance)*

Other common symptoms *Many, but not all people with ME/CFS report:*

- Muscle pain, joint pain without swelling or redness, and headache*
- Tender lymph nodes in the neck or armpits*
- Sore throat*
- Irritable bowel syndrome*
- Chills and night sweats*
- Allergies and sensitivities to foods, odors, chemicals, lights, or noise*
- Shortness of breath*
- Irregular heartbeat*

MOGELIJKE OORZAKEN

- onbekend, genetische psychologische factoren spelen een rol
- post infectieus? Soms na griepachtige verschijnselen

Chlamydomphila pneumoniae, human herpesvirus, and Lyme disease, **Epstein-Barr** geassocieerd met CVS/ME

--→ Niet iedereen heeft een infectie gehad!

RISICO FACTOREN:

- African-Americans, Hispanics
- Vrouwen?
- Stress, trauma in jeugd, perfectionistische persoonlijkheid, slechte conditie, psychologische aandoening, depressie, hoge verwachtingen van ouders

PATHOFYSIOLOGIE

Neurologisch:

- Lager metabolisme hersenstam
- Verminderde doorbloeding
- Neuroinflammatie (PET scan)
- Autonome CZS dysfunctie
- wisselende resultaten!!

Immunologisch:

- verminderde NK activiteit (waarschijnlijk door uitputting)
- verhoogd: complement factoren, oxidatieve stress, interleukines, TLR4, IFN, NF-kB
- chronische inflammatie!

Endocrien:

- gestoorde HPA-as: lage cortisol, lage variatie over de dag, verminderde HPA respons



Pathofysiologie CVS/ME

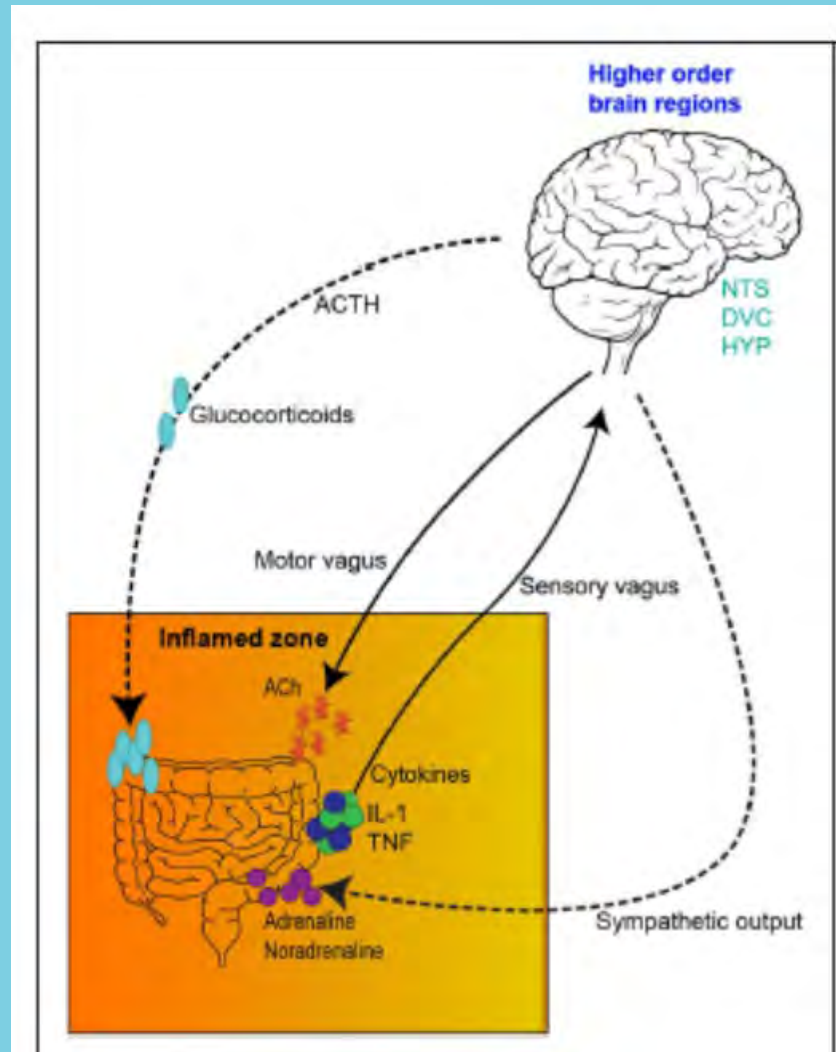
Neurologisch

Immunologisch

Endocrien



Verhoogde darm permeabiliteit ?



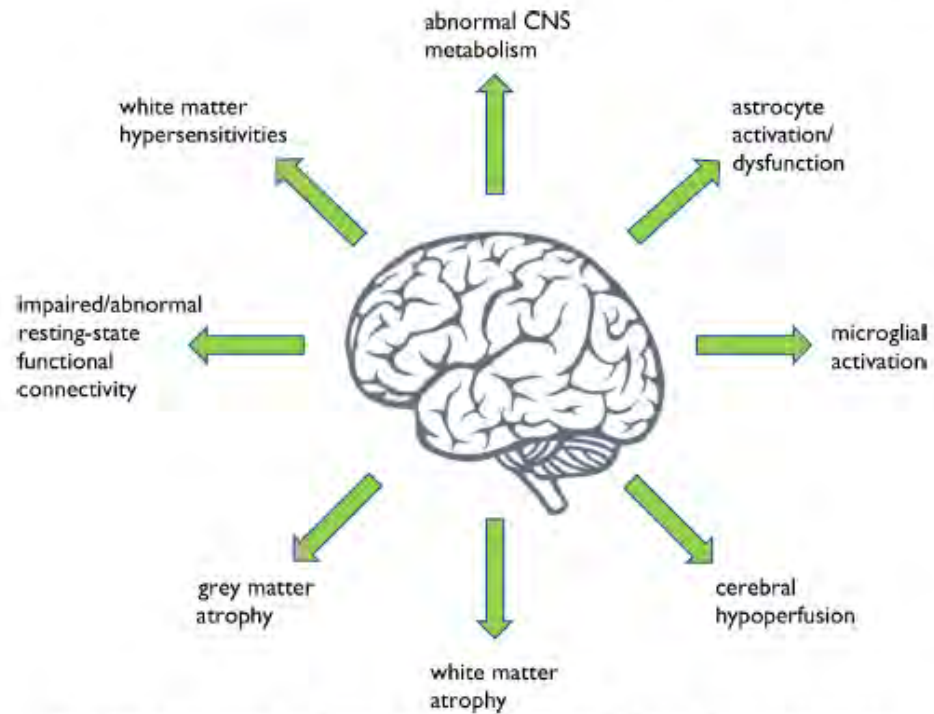
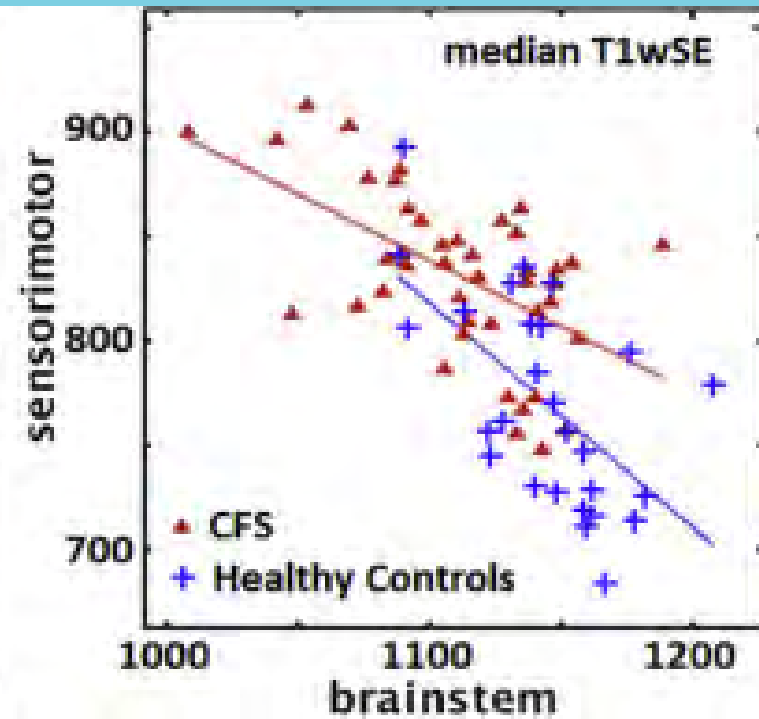
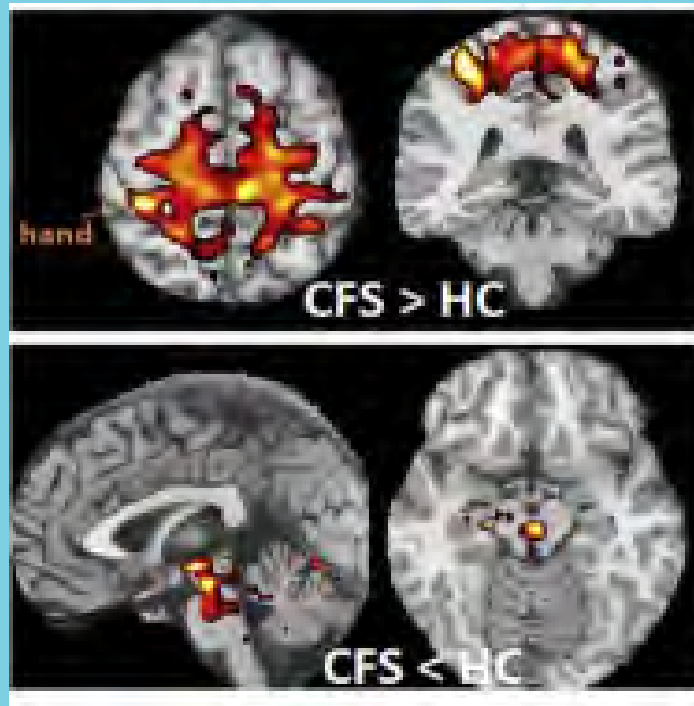
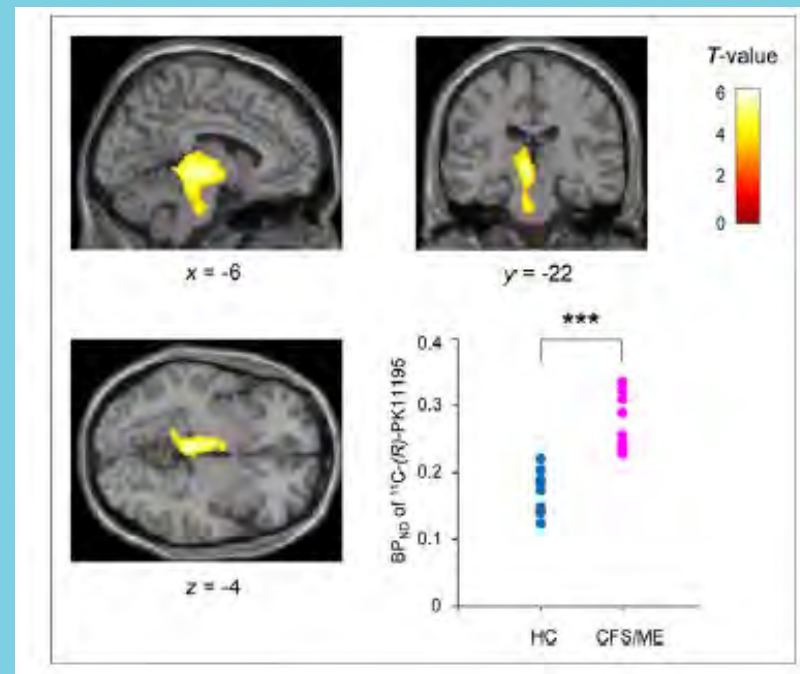


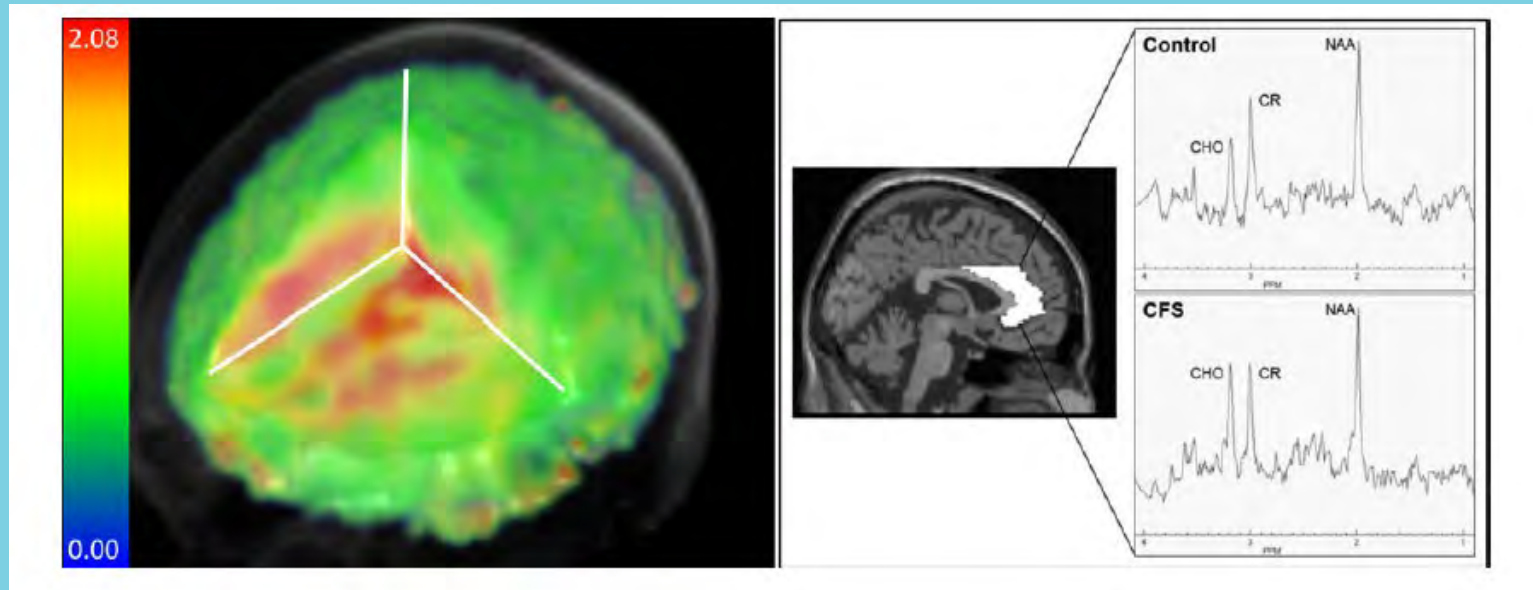
Fig. 3. Diagram summarising CNS abnormalities in patients diagnosed with ME/CFS (per the Fukuda criteria).



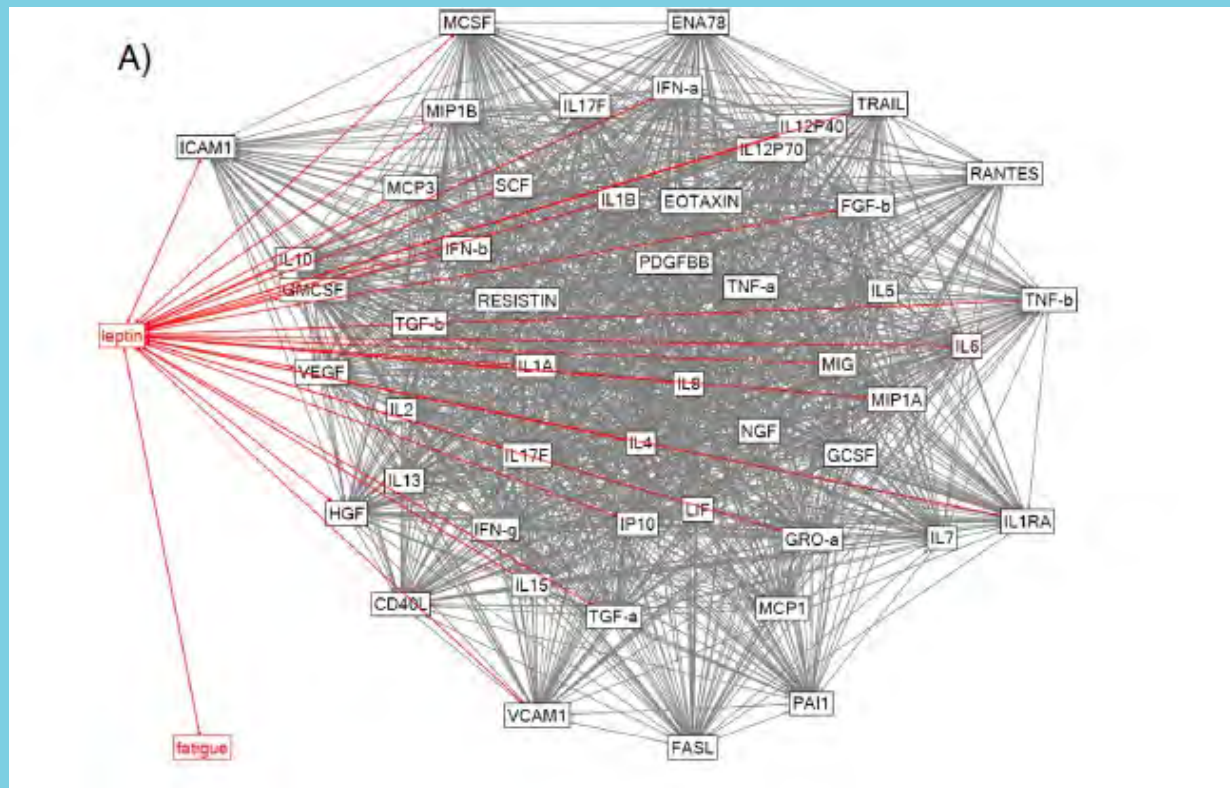
Neuroinflammation in Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: An ^{11}C -(R)-PK11195 PET Study



Evidence of widespread metabolite abnormalities in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Assessment with whole-brain Magnetic Resonance Spectroscopy.



Daily cytokine fluctuations, driven by leptin, are associated with fatigue severity in chronic fatigue syndrome: evidence of inflammatory pathology



Speelt het microbioom een rol bij CVS/ME?

Clinical Science (2018) **132** 523–542
<https://doi.org/10.1042/CS20171330>

Table 2 ME/CFS microbiome articles selected following literature review

Number	Year	Author	Title	Area of study
1	2017	Armstrong [93]	The association of faecal microbiota and faecal, blood, serum and urine metabolites in ME/CFS	Microbiome and metabolites
2	2017	Nagy-Szakai [90]	Faecal metagenomic profiles in subgroups of patients with ME/CFS	Microbiome
3	2016	Giloteaux [91]	Reduced diversity and altered composition of the gut microbiota in individuals with ME/CFS	Microbiome
4	2016	Giloteaux [107]	A pair of identical twins discordant for ME/CFS differ in physiological parameters and gut microbiome composition	Microbiome and virome
5	2013	Fremont [92]	High-throughput 16S rRNA gene sequencing reveals alterations of intestinal microbiota in ME/CFS patients	Microbiome
6	2009	Sheedy [94]	Increased d-lactic acid intestinal bacteria in patients with CFS	Microbiome and metabolites
7	2009	Fremont [109]	Detection of herpes virus and parvovirus B19 in gastric and intestinal mucosa of CFS patients	Virome
8	2008	Chia [108]	CFS is associated with chronic enterovirus infection of the stomach	Virome
9	2007	Evengård [176]	Patients with CFS have higher numbers of anaerobic bacteria in the intestine compared with healthy subjects	Microbiome
10	2001	Butt [177]	Bacterial colonisation in patients with persistent fatigue	Microbiome
11	1998	Butt [98]	Faecal microbial growth inhibition in chronic fatigue/pain patients	Microbiome and metabolites

Abbreviations: CFS, chronic fatigue syndrome; ME, myalgic encephalomyelitis

Brief report

Increased serum IgA and IgM against LPS of enterobacteria in chronic fatigue syndrome (CFS): Indication for the involvement of gram-negative enterobacteria in the etiology of CFS and for the presence of an increased gut–intestinal permeability

Michael Maes ^{a,b,*}, Ivana Mihaylova ^a, Jean-Claude Leunis ^c

ANTICANCER RESEARCH 29: 4717-4726 (2009)

Review

Immunological Similarities between Cancer and Chronic Fatigue Syndrome: The Common Link to Fatigue?

MIRA MEEUS^{1,2}, WILHELM MISTIAEN¹, LUC LAMBRECHT^{3,4} and JO NIJS^{1,2}

Cancer and the gut microbiota: An unexpected link

Sci Transl Med. 2015 January 21; 7(271)

From the Bottom-Up: Chemotherapy and Gut-Brain Axis Dysregulation

Frontiers in Behavioral Neuroscience | 1 May 2018 | Volume 12 | Article 104

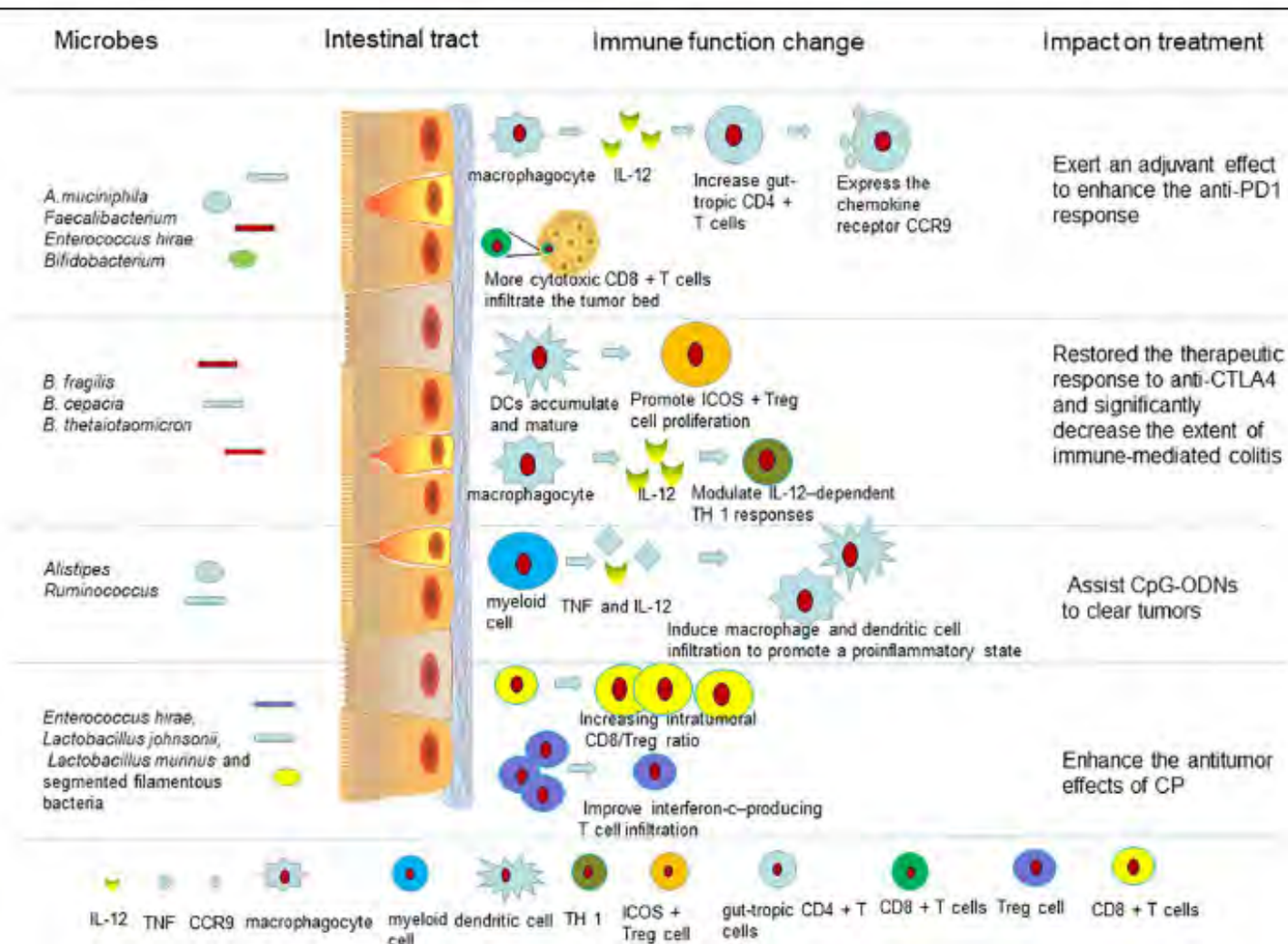
The chemo-gut study: investigating the long-term effects of chemotherapy on gut microbiota, metabolic, immune, psychological and cognitive parameters in young adult Cancer survivors; study protocol

BMC Cancer (2019) 19:1243

Chemotherapy-induced neuroinflammation is associated with disrupted colonic and bacterial homeostasis in female mice

Scientific Reports; Nature | (2019) 9:16490

Gut Microbiota Shapes the Efficiency of Cancer Therapy

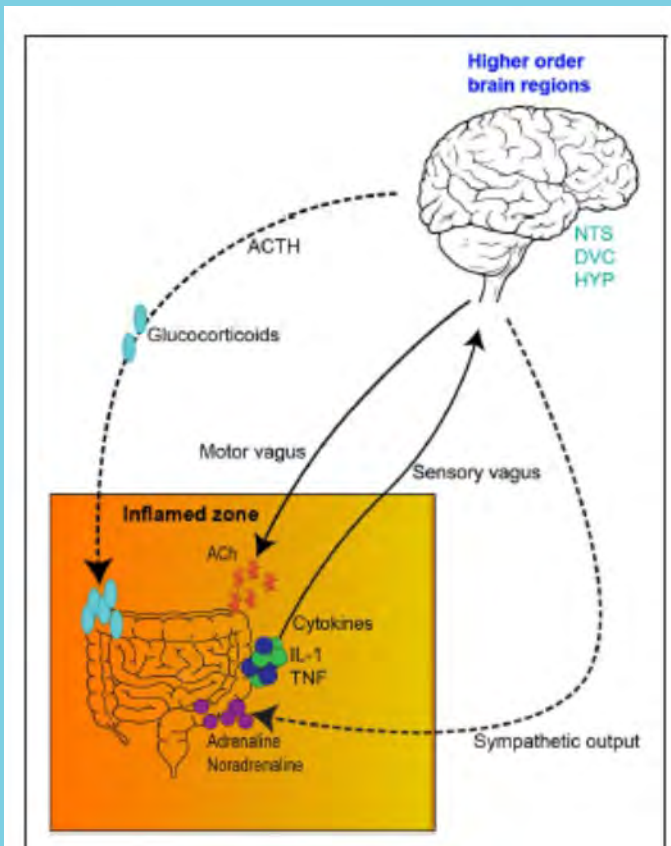


Disease	fatigue	cognition decrease	inflammation serum	neuroinflammation	dysbiosis	association with BMI	complement activated
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DEPRESSION	+	+	+	+	+	+	+
SCHIZOPRENIA	+	+	+	+	+	+	+
GLIOMA	+	+	+	+	+	-	+
CVS /ME	+	+	+	+	+	-	+

Conclusion:

CFS/ME is an neuroinflammatory disease.

The “unhealthy gut” is an important factor in the pathophysiology and should be further investigated.



Mogelijke nieuwe behandelingen CVE/ME?

-Faeces transplantatie herstellen darmflora

-LPS binding proteins

-Zonuline: darmpermeabiliteit

-Vagus stimulatie

Toekomstvisie onderzoek CVS/ME

-bacterieel DNA bloedonderzoek

-reproducieren beelvorming neuroinflammatie hersenen: biomarker?

-beïnvloeden darm-microbioom

-vagus activiteit metingen

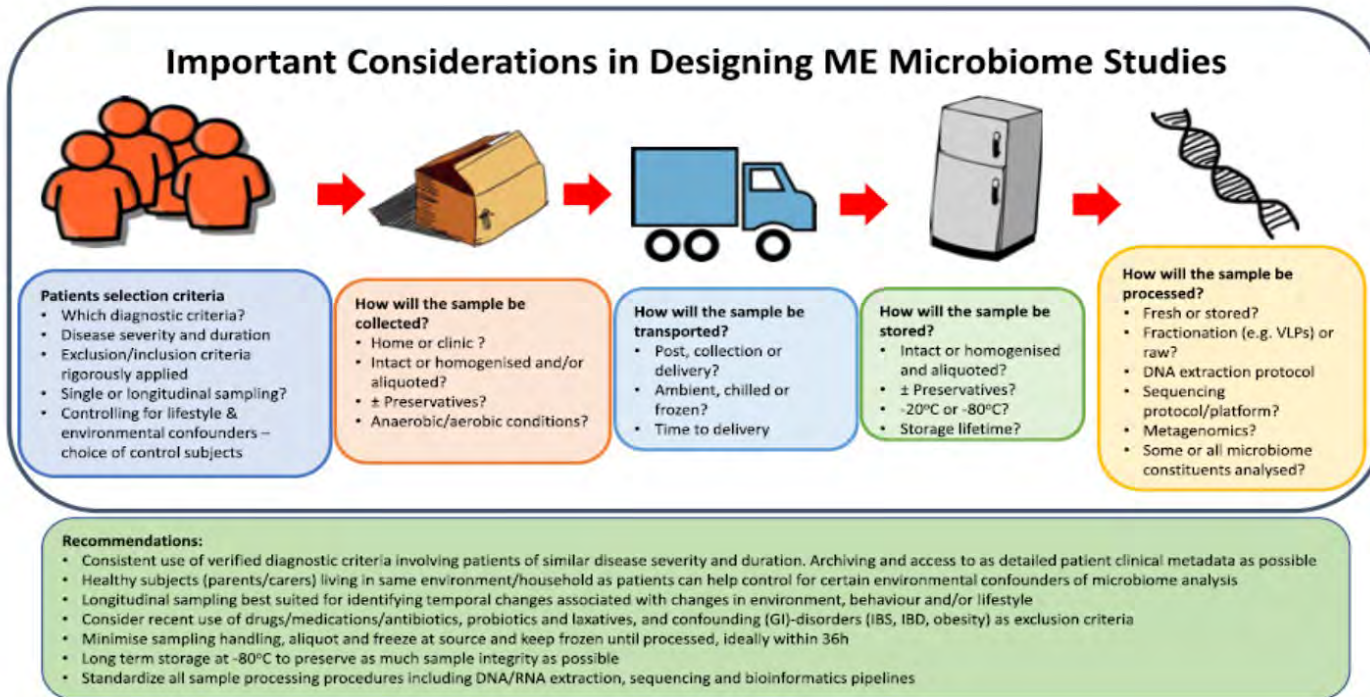


Figure 3. Important considerations in designing ME microbiome studies

Recommendations for designing a microbiome study and important questions to consider