

Neurodegeneration & Gut Microbiota

Trust your gut feeling!

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Assist. Professor DMBG

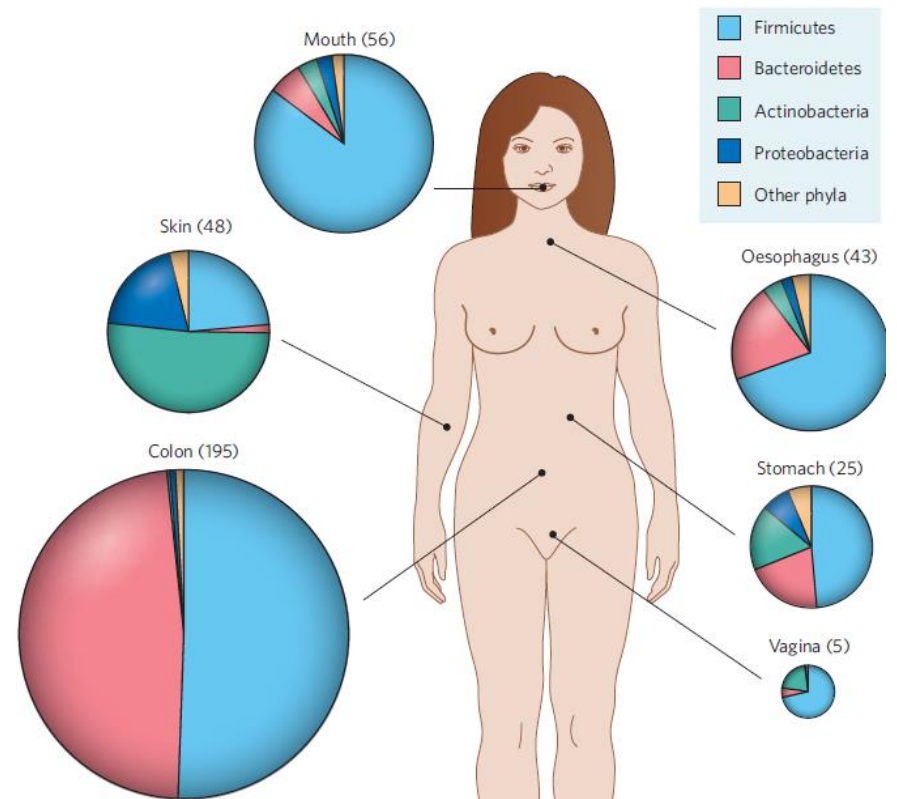
DECEMBER 2024

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- Background in Alzheimer's disease
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 - Senile plaques: β -amyloid ($A\beta$)
- Alzheimer's disease (AD) & Gut Microbiota
 - Can gut microbiota have an impact on AD pathology?
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 - How gut microbiota promote AD?
 - Implications for AD diagnosis & treatment

The human gastrointestinal (GI) tract microbiota

- The largest reservoir of microbes in humans: $\sim 10^{14}$ microorganisms from $\sim 35,000$ distinct microbial species/ outnumbers human host cells by about 100-fold
- The exact composition of the gut microbiota not fully known: 70% of these microbes cannot grow in the laboratory
- Main bacterial phyla in the GI tract: *Firmicutes* & *Bacteroidetes* (followed by *Proteobacteria*, *Actinobacteria* & *Verrucomicrobia*)
- Composition = highly dynamic influenced by many factors (diet, age, stress, antibiotics etc.)



Dethlefsen et al. (2007) *Nature* 449: 811-818

Site-specific distributions of bacterial phyla in healthy humans

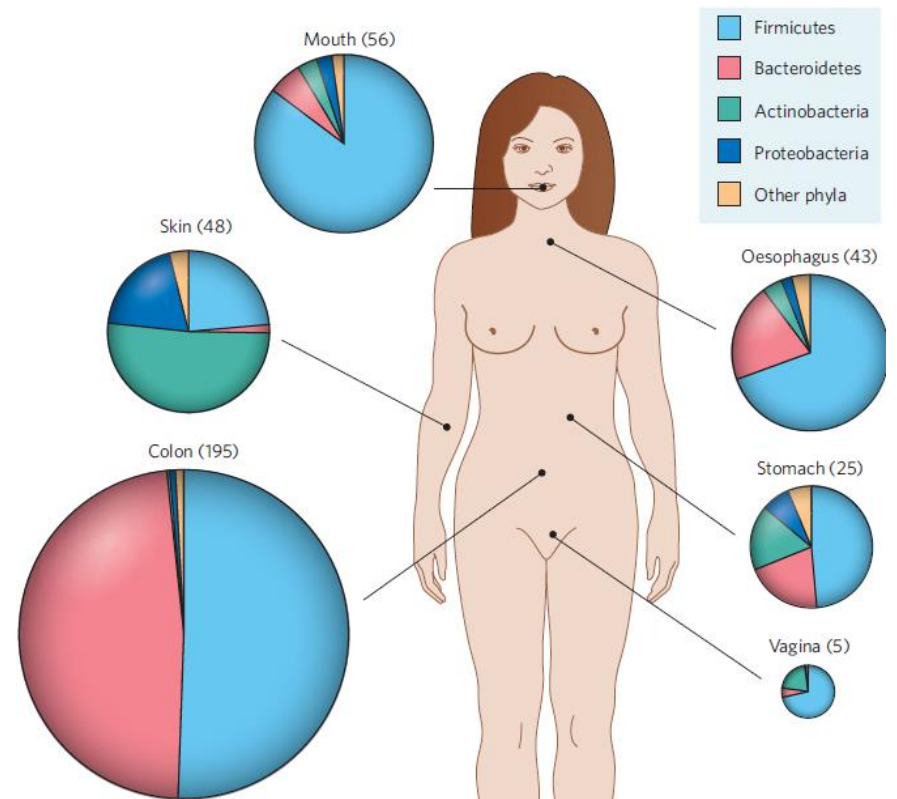
GI microbiota taxonomy

- Large numbers
- Small numbers

Phylum	Class	Order	Family	Genus
Proteobacteria	Alphaproteobacteria	Rickettsiales	Rickettsiaceae	Rickettsia
		Rhizobiales	Brucellaceae	Brucella
	Betaproteobacteria	Neisseriales	Neisseriaceae	Neisseria
		Burkholderiales	Alcaligenaceae	Bordetella
	Gammaproteobacteria	Legionellales	Coxiellaceae	Coxiella
			Legionellaceae	Legionella
		Pseudomonadales	Pseudomonadaceae	Pseudomonas
		Vibrionales	Vibrionaceae	Vibrio
		Aeromonadales	Aeromonaceae	Aeromonas
		Enterobacteriales	Enterobacteriaceae	Enterobacter,
				Escherichia
				Salmonella
		Pasteurellales	Pasteurellaceae	Aggregatibacterium Haemophilus Pasteurella
	Epsilonproteobacteria	Campylobacterales	Campylobacteraceae	Campylobacter
Firmicutes	Clostridia	Clostridiales	Clostridiaceae	Clostridium
			Lachnospiraceae	Lachnospira
			Ruminococcaceae	Faecalibacterium Ruminococcus
	Bacilli	Bacillales	Staphylococcaceae Bacillaceae	Staphylococcus Bacillus
				Lactobacillus
		Lactobacillales	Lactobacillaceae	Pediococcus
			Enterococcaceae	Enterococcus
			Streptococcaceae	Streptococcus
	Actinobacteria	Actinomycetales	Corynebacteriaceae	Campylobacter
			Mycobacteriaceae	Mycobacterium
			Micrococaceae	Microbacterium
		Bifidobacteriales	Bifidobacteraceae	Bifidobacterium
Fusobacteria	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	Fusobacterium
			Leptotrichiaceae	Streptobacillus
Bacterioidetes	Bacteroidia	Bacteroidales	Bacteriodaceae	Bacteroides
			Porphyromonadaceae	Porphyromonas
			Prevotellaceae	Prevotella
	Flavobacteriia	Flavobacteriales	Flavobacteriaceae	Flavobacterium
Verrucomicrobia	Verrucomicrobiae	Verrucomicrobiales	Verrucomicrobiaceae	Verrucomicrobium

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Site-specific distributions of bacterial phyla in healthy humans

The function of the normal gut microbiota

- Nutrient metabolism

synthesis of vitamin K, B12, folic acid, SCFA (short chain fatty acids, *e.g.* butyrate)

- Maintain the structure and function of the GI tract

e.g. *Bacteroides thetaiotaomicron* induce the expression of the sprr2A protein required for maintenance of desmosomes at the epithelial villi

- Antimicrobial protection

gut microbiota (via their structural components *e.g.* LPS, peptidoglycans) induce synthesis of antimicrobial proteins *e.g.* cathelicidins by the host enterocytes & Paneth cells

- Immunomodulation

- Xenobiotic and drug metabolism

The gut-brain axis (GBA)

Also known as:

- brain-gut axis
- gut-brain connection
- microbiota-gut-brain axis

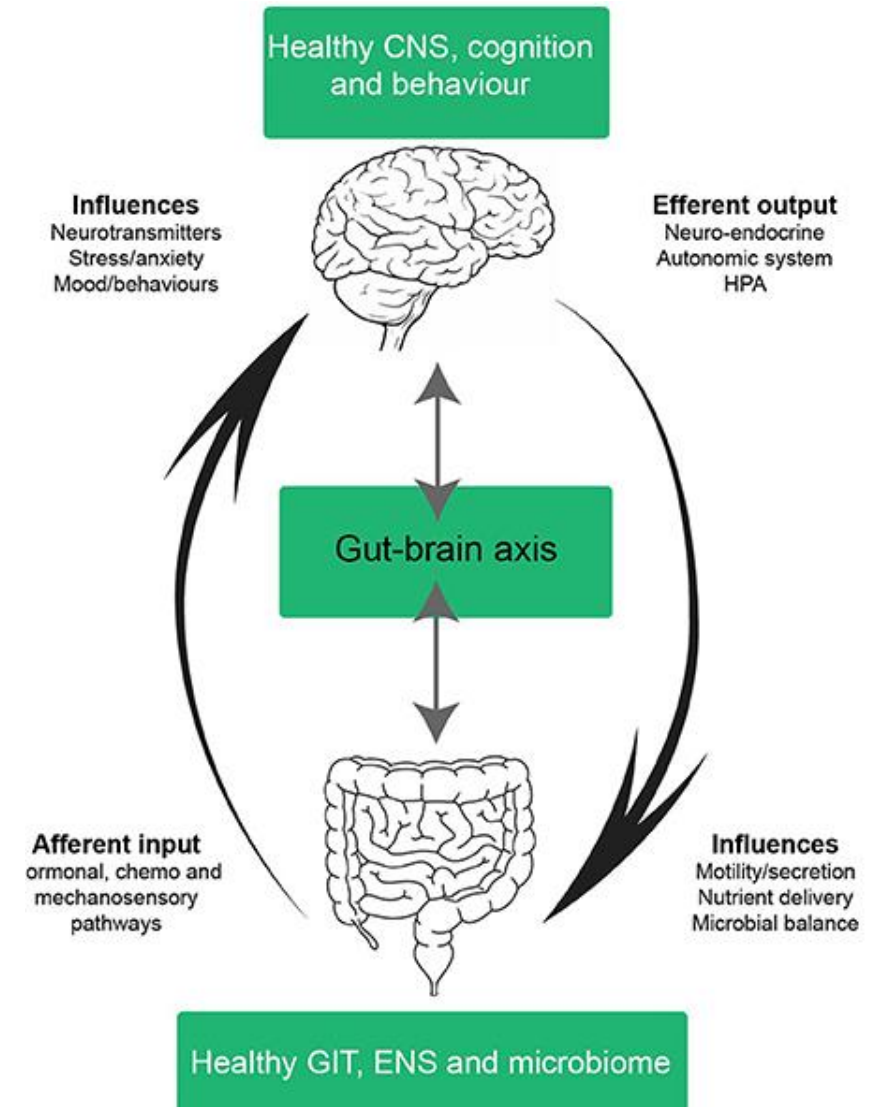
Bidirectional communication between the brain and the GI tract

The key components of GBA:

- CNS, ANS (vagus nerve and Enteric NS)
- Hypothalamic-pituitary-adrenal axis (HPA)
- Immune system (cytokines)

Gut microbiota influence the GI tract-brain interaction

Dysbiosis *i.e.* imbalance between good and opportunistic bacteria (harmful bacteria) in GI tract → various diseases including anxiety, depression and neurodegenerative diseases (*e.g.* Alzheimer's disease, Parkinson's disease *etc.*)



A microscopic image of neural tissue, likely from a brain, showing complex, intertwined structures. The tissue is stained with a blue dye, possibly DAPI, which highlights the nuclei of cells. There are also some red-stained areas, possibly indicating specific protein deposits or another type of staining. The overall appearance is that of a dense, fibrous network.

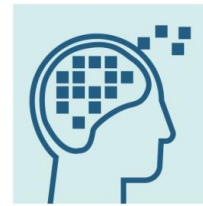
Background in Alzheimer's disease

Alzheimer's Disease (AD)

- First described by the German psychiatrist Alois Alzheimer in 1907
- The commonest form of dementia in the elderly
- Affects 7% of the population above the age of 65 years and possibly the 40% of the population above the age of 80 years

Background on Alzheimer's disease (AD)

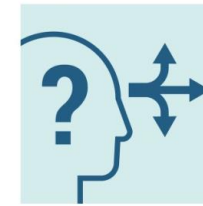
Clinical features



MEMORY LOSS



MISPLACING ITEMS



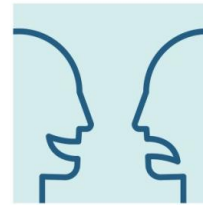
DIFFICULTY IN
DECISION MAKING
AND JUDGING



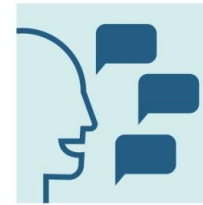
REDUCED ABILITY
IN UNDERSTANDING
VISUAL IMAGES



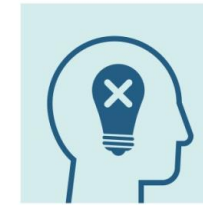
CONFUSION WITH
TIME AND PLACES



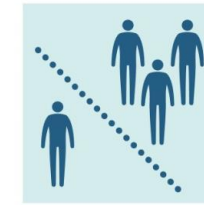
MOOD SWINGS



REPETITIVE SPEECH
AND WRITING ISSUES



DIFFICULTY IN
PROBLEM SOLVING



SOCIAL WITHDRAWAL



INABILITY
TO COMPLETE
COMPLEX TASKS

Memory and behavioral impairment

Psychotic symptoms such as hallucinations

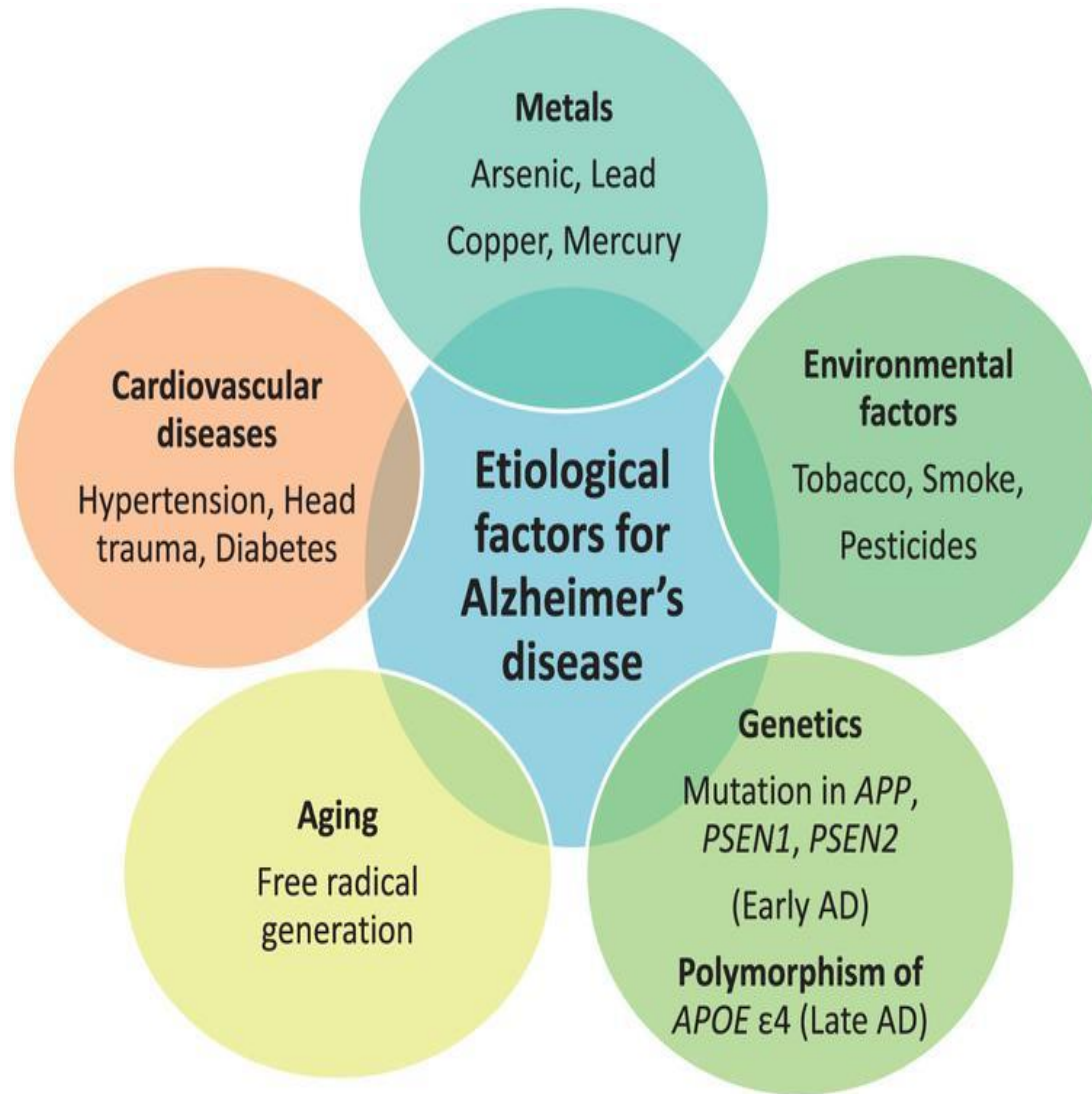
Progressive cognitive decline

Late stages (severe AD): the patients are bedridden and unable to speak

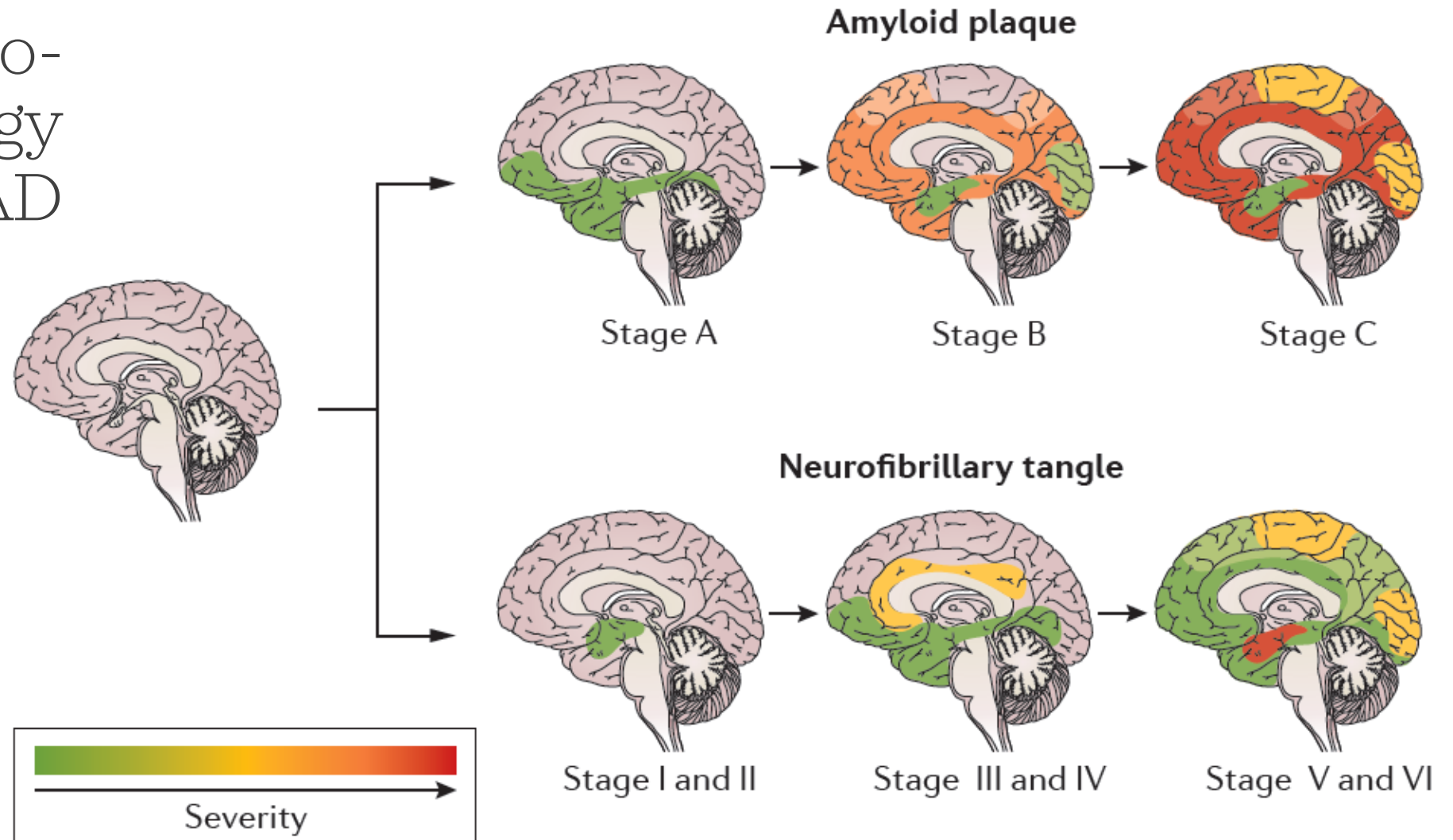
Death due to secondary medical conditions, *e.g.* infections, pneumonia *etc.*

Aetiology of AD

Multifactorial



The neuro-pathology of AD



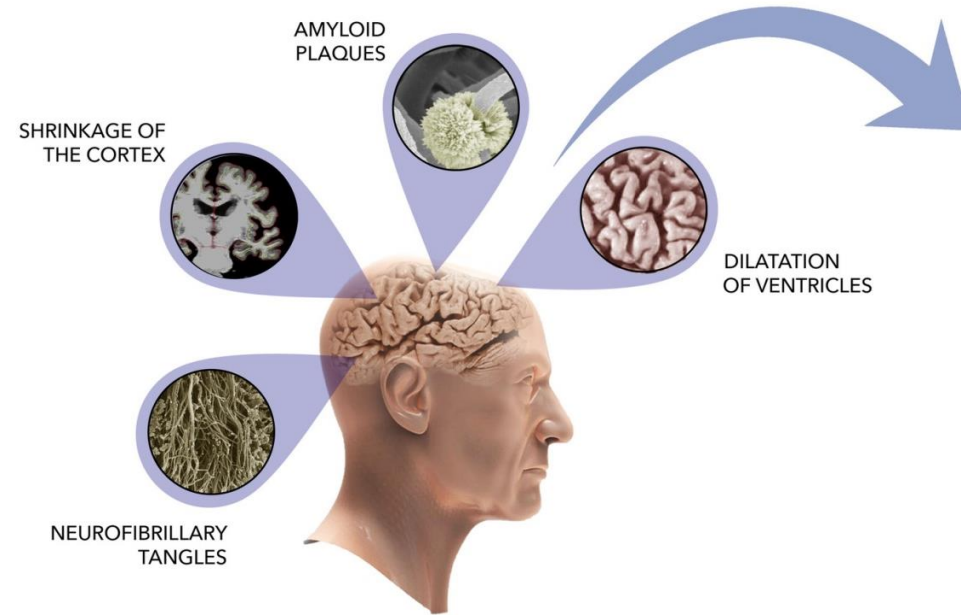
Cerebral modifications in AD

AD is characterized by

- loss of neurons in the hippocampus and cerebral cortex
- shrinkage of the cortex and enlargement of ventricles → progressive decline in cognitive function

Main histopathological hallmarks:

- intraneuronal neurofibrillary tangles
- extracellular amyloid beta plaques



Cognitive impairment

Memory loss
Impaired learning

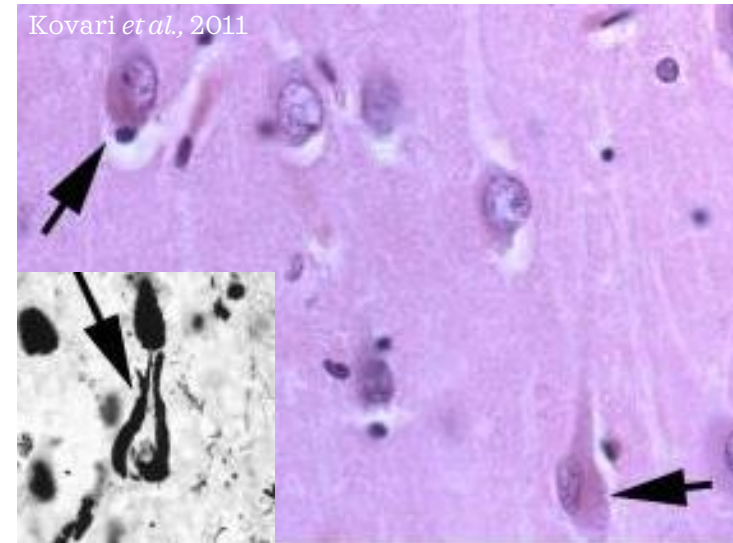
Behavioural changes

Aggression/Anger
Anxiety/Agitation
Emotional distress
Physical/Verbal outbursts
Hallucinations
Delusions
Sleep issues and Sundowning

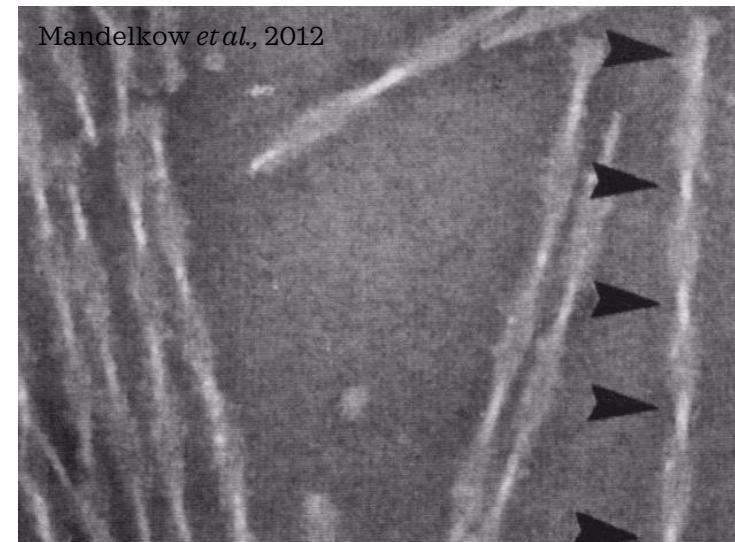
Bonfili et al. (2020)
DOI: <https://doi.org/10.1111/febs.15571>

Histopathology: neurofibrillary tangles

- Neurofibrillary tangles: flame-shaped brain lesions
- NFTs contain pairs of helical filaments composed of aggregates of hyperphosphorylated tau (τ) protein



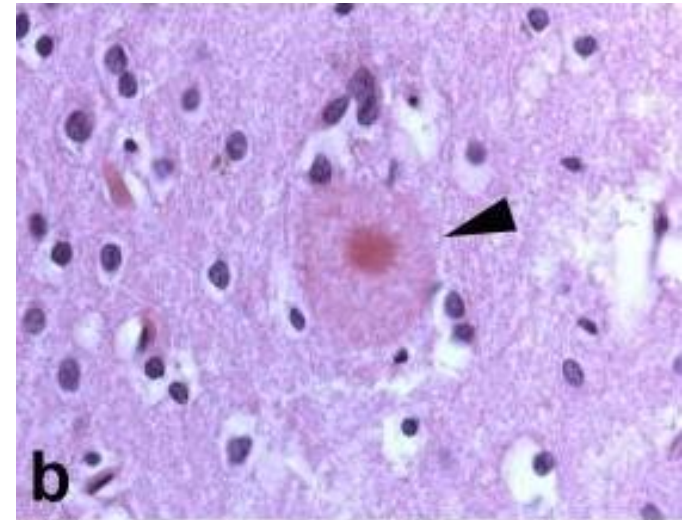
Haematoxylin/Eosin staining



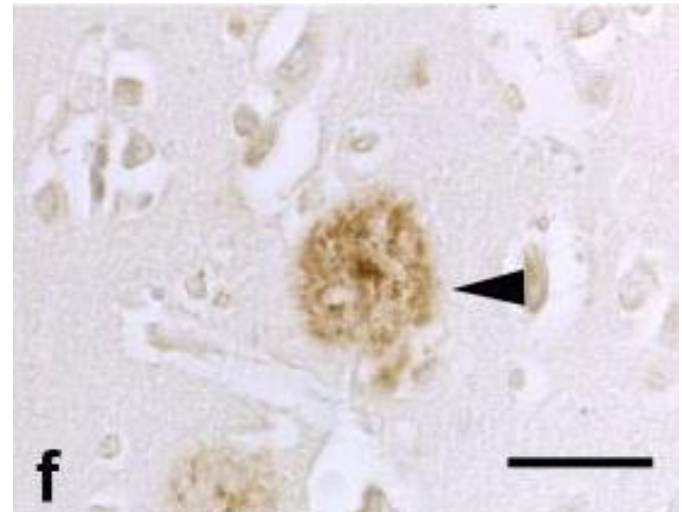
Pairs of helical filaments

Histopathology: senile plaques

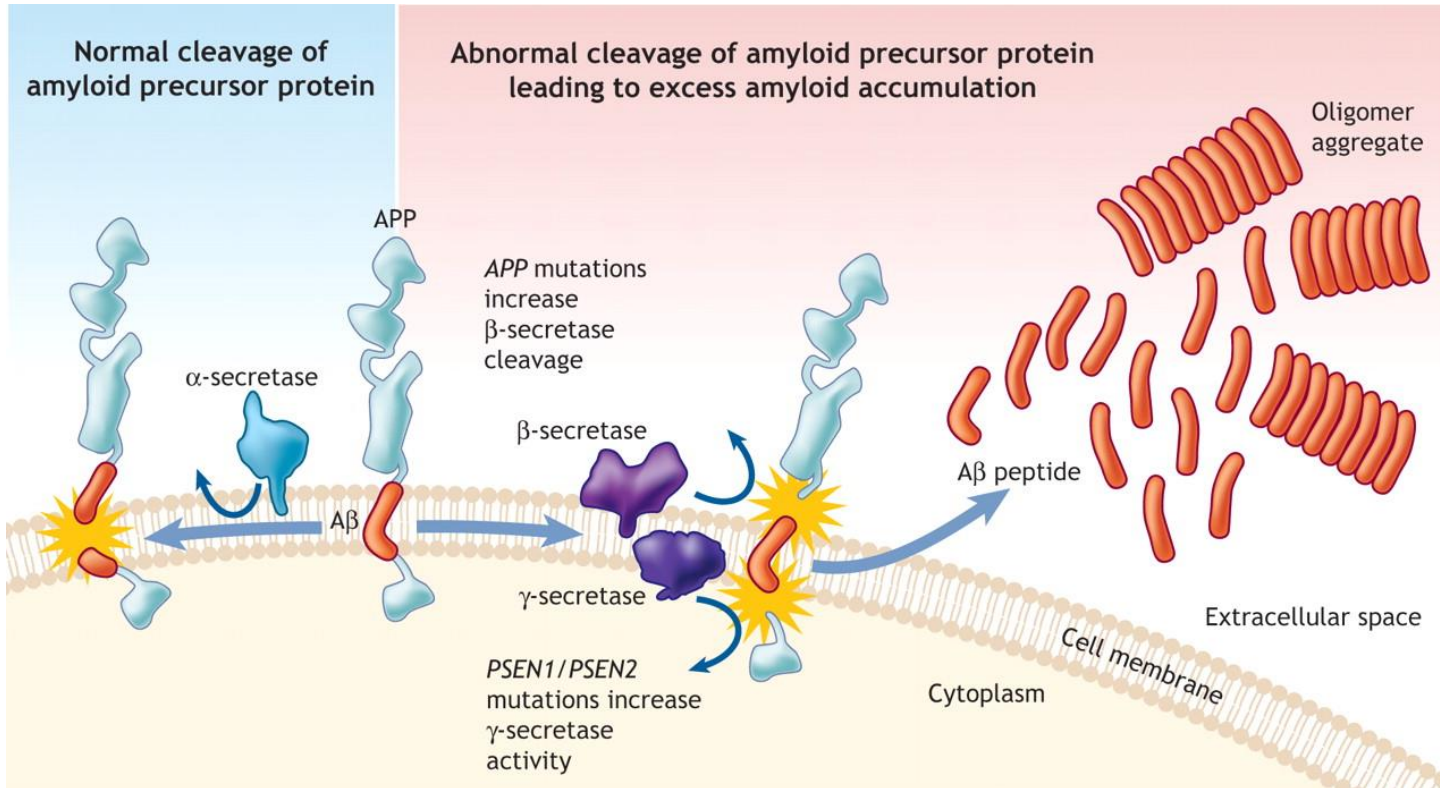
- Senile plaques (SPs) are deposits of fibrillar A β
- β -Amyloid (A β)
 - Derived by proteolytic processing of Amyloid Precursor Protein (APP)
 - 39-43 amino acid residues, MW=4,000
 - Major forms in the brain, CSF, plasma: A β_{40} and A β_{42} (5-10%)
 - A β_{42} : the major form of A β in senile plaques/more amyloidogenic than A β_{40}
 - Senile plaques are deposits of fibrillar A β



Haematoxylin/Eosin staining



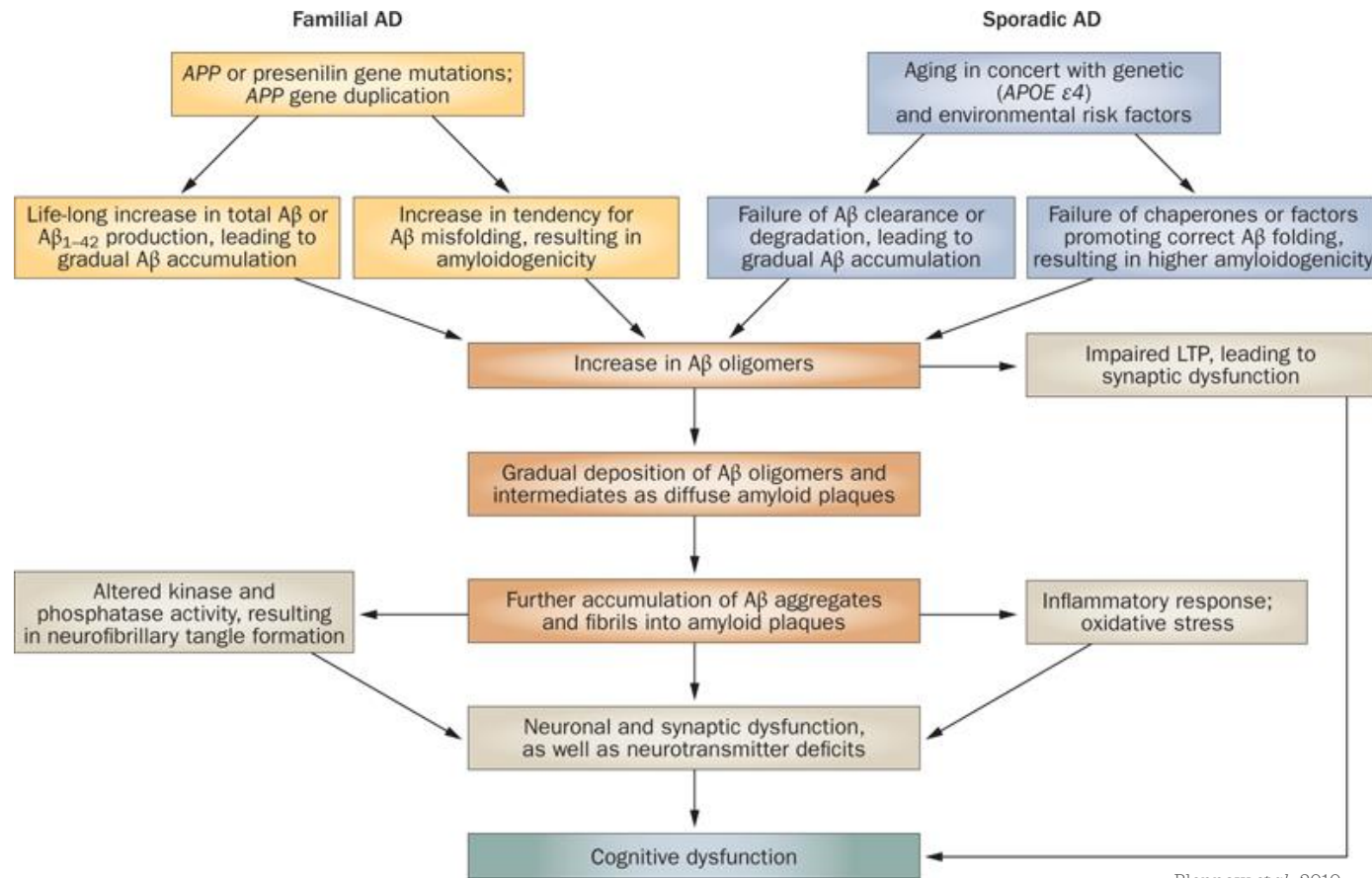
Anti-A β immunostaining



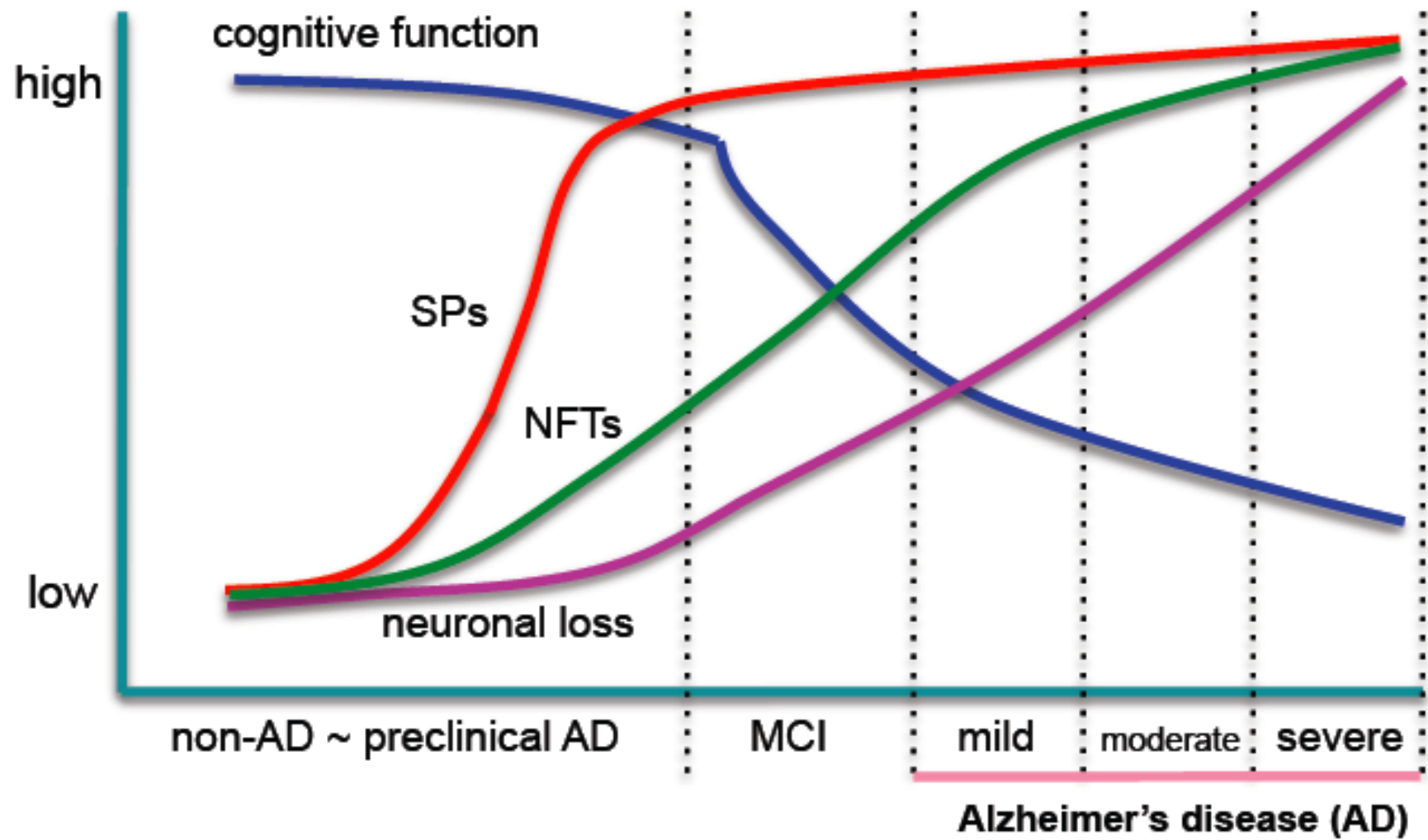
Patterson *et al.* (2008) *CMAJ* 178

A β is produced by the proteolytic processing of Amyloid Precursor Protein (APP)

The Amyloid Cascade Hypothesis



Blennow *et al.*, 2010



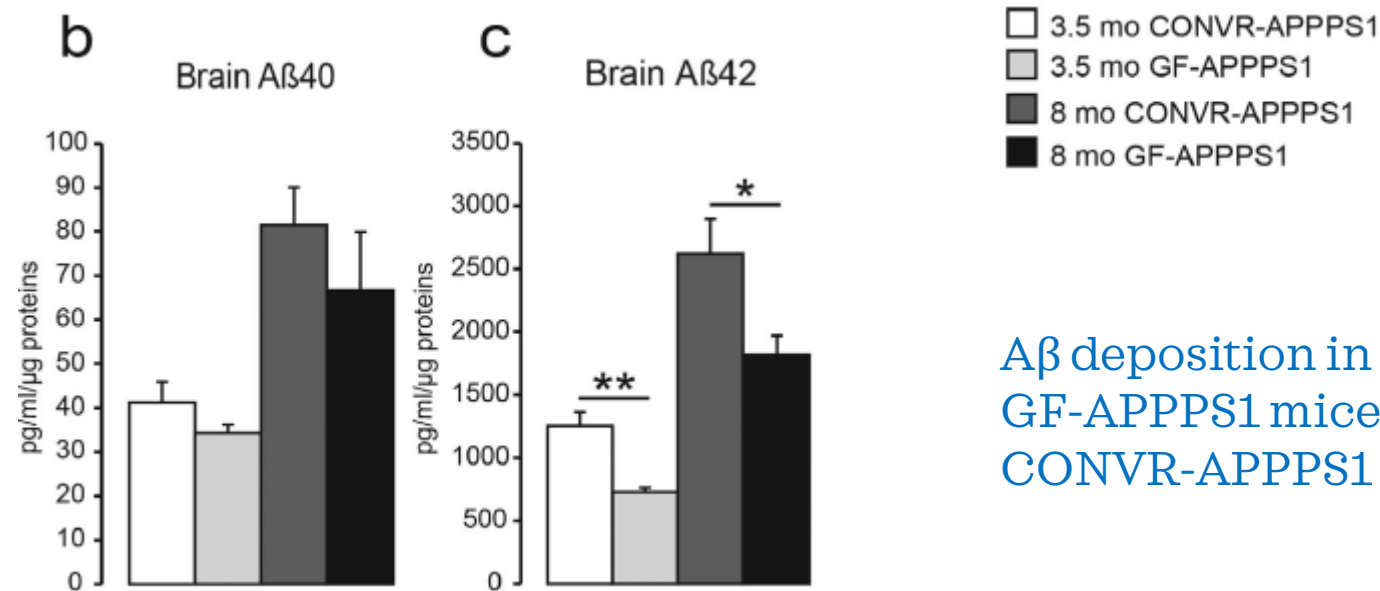
A microscopic image of neural tissue, possibly a brain section, stained with a blue fluorescent dye. The image shows a complex network of fibers and structures, with some areas appearing more densely stained than others. The overall tone is dark blue and black, with the fluorescence providing a bright contrast.

Alzheimer's disease & Gut Microbiota

Can gut microbiota have an impact on AD pathology?

Can gut microbiota have an impact on AD pathology?

Germ free mice

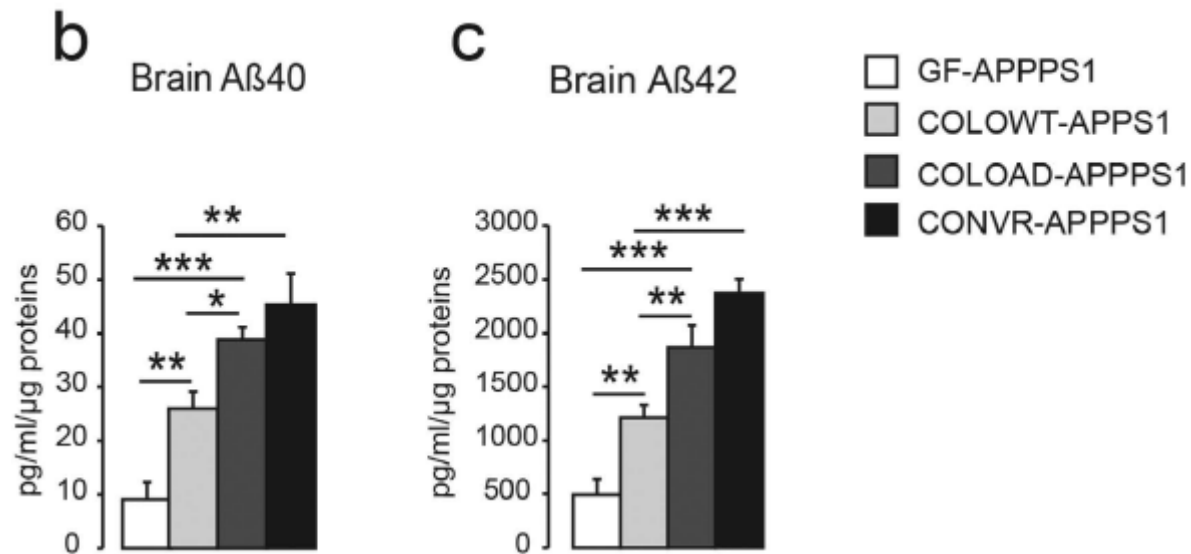


Aβ deposition in brain is reduced in GF-APPPS1 mice compared to CONVR-APPPS1 mice

- Mouse model for AD: APP/PS1
- GF-APPPS1 **vs** conventionally-raised transgenic APPPS1 mice (CONVR-APP/PS1) at various ages (months)

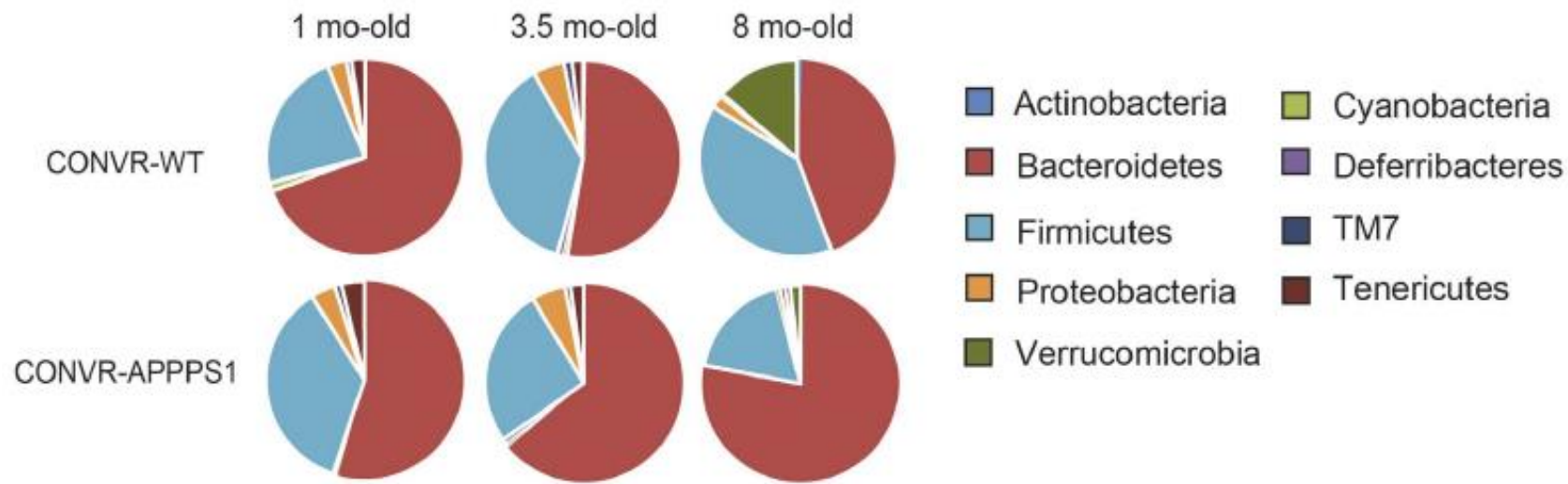
Can gut microbiota have an impact on AD pathology?

Faecal microbiota transplantation to GF



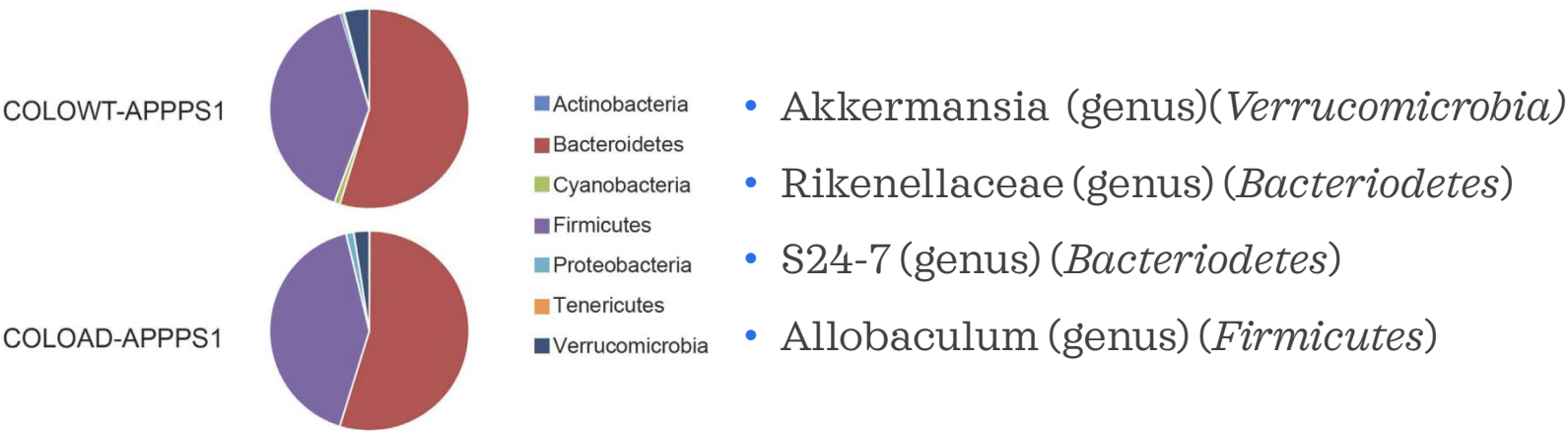
4-month-old GF-APP/PS1 mice colonized from gut microbiota from aged (12-month-old) CONVR-WT or CONVR-APP/PS1 mice by oral gavage: COLOWT-APP/PS1 and COLOAD-APP/PS1 mice)

The composition of the gut microbiota of APP/PS1 mice differ substantially from the corresponding one of wt mice

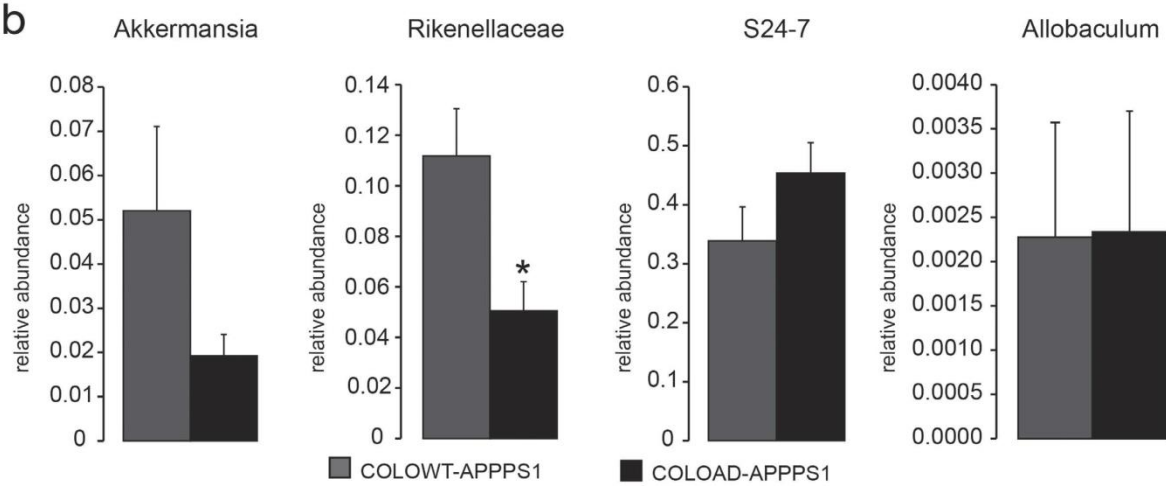


- Distinct microbial compositions may influence the A β deposition in the brain
- Specific microbes may be involved in progression of cerebral A β amyloidosis

Gut microbiota composition in COLOWT-APP/PS1 & COLOAD-APP/PS1 mice



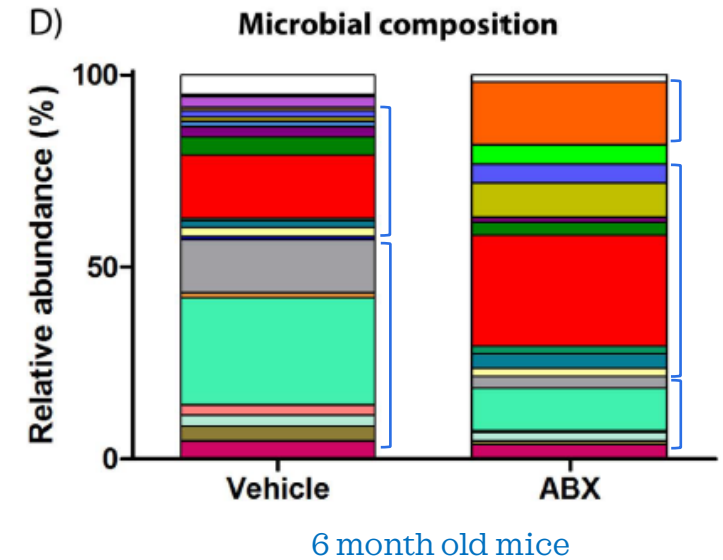
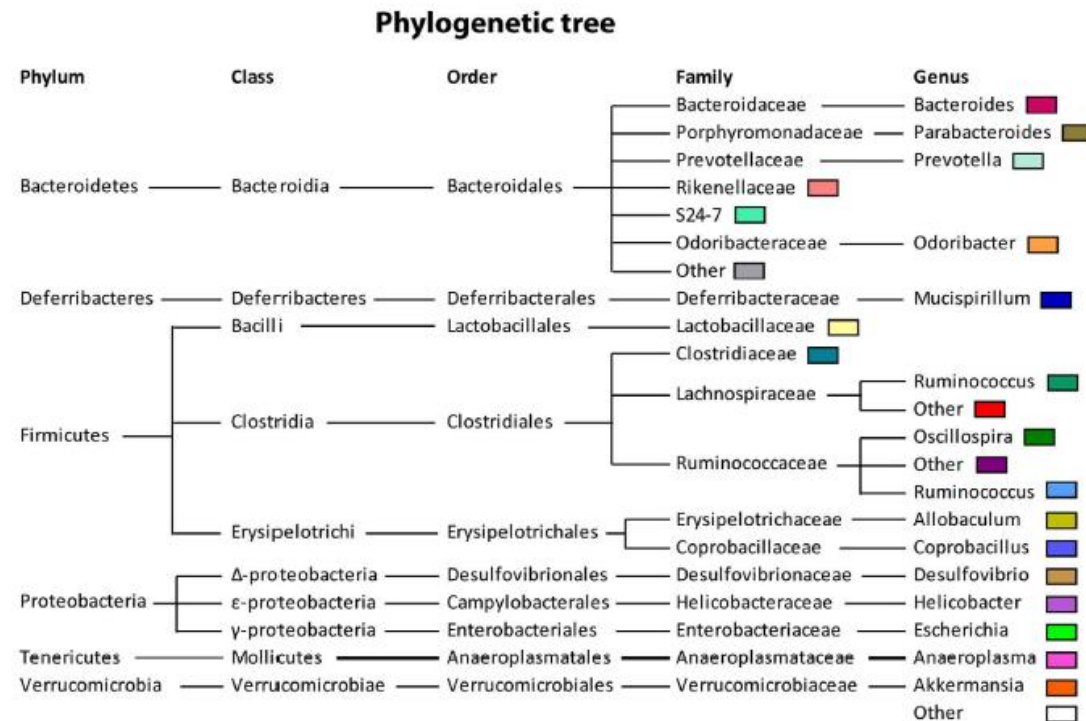
6wks after colonization



Can gut microbiota have an impact on AD pathology?

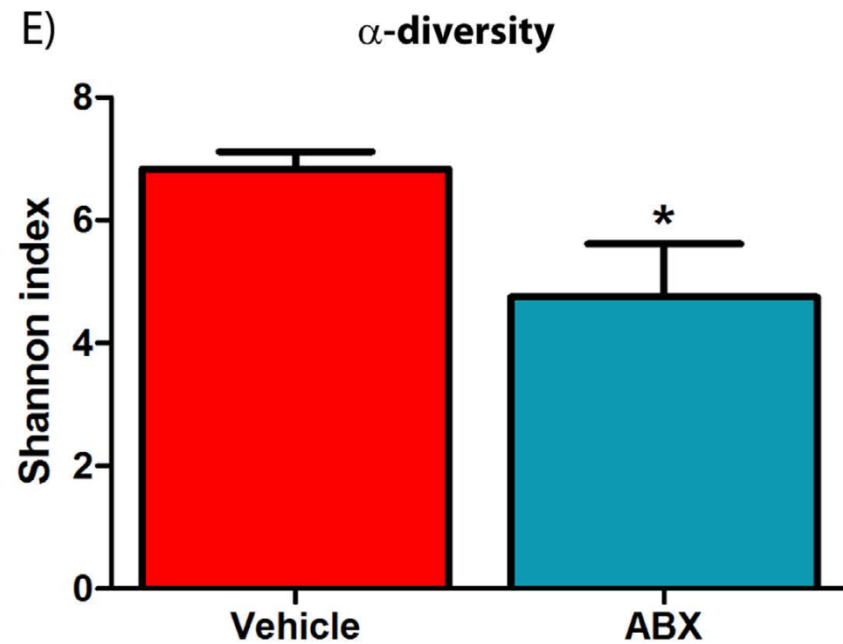
Antibiotic-altered composition of gut microbiota (1)

- Animal model:
APP_{SWE}/PS1_{ΔE9}
- ABX: combinatorial antibiotics (gentamicin, vancomycin, metronidazole, neomycin, ampicillin, kanamycin, colistin, cefaperazone)
- Control: autoclaved water
- Treatment regime: PN day 14-21, then supplemented with ABX-containing drinking water (1/50th of gavage concentration) for the duration of lifespan



Can gut microbiota have an impact on AD pathology?

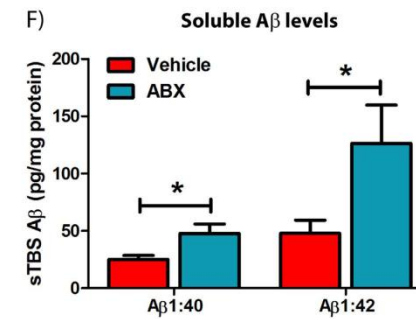
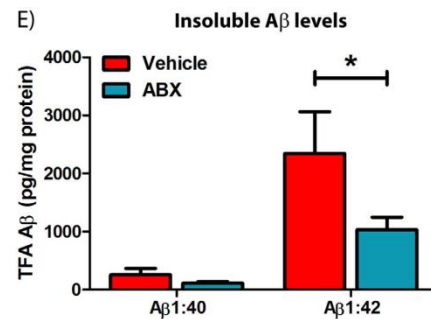
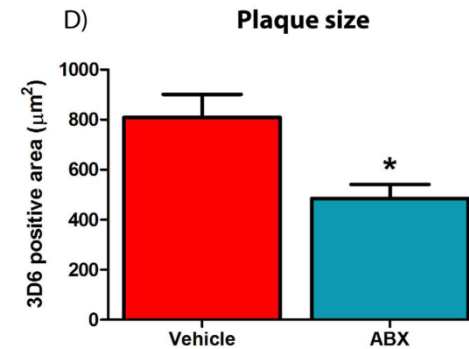
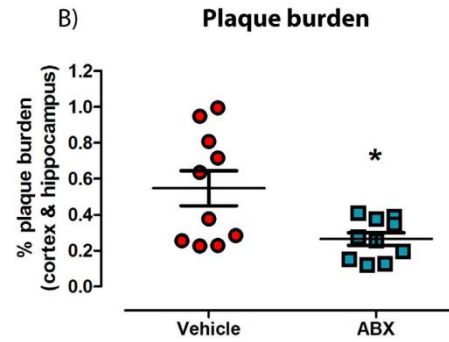
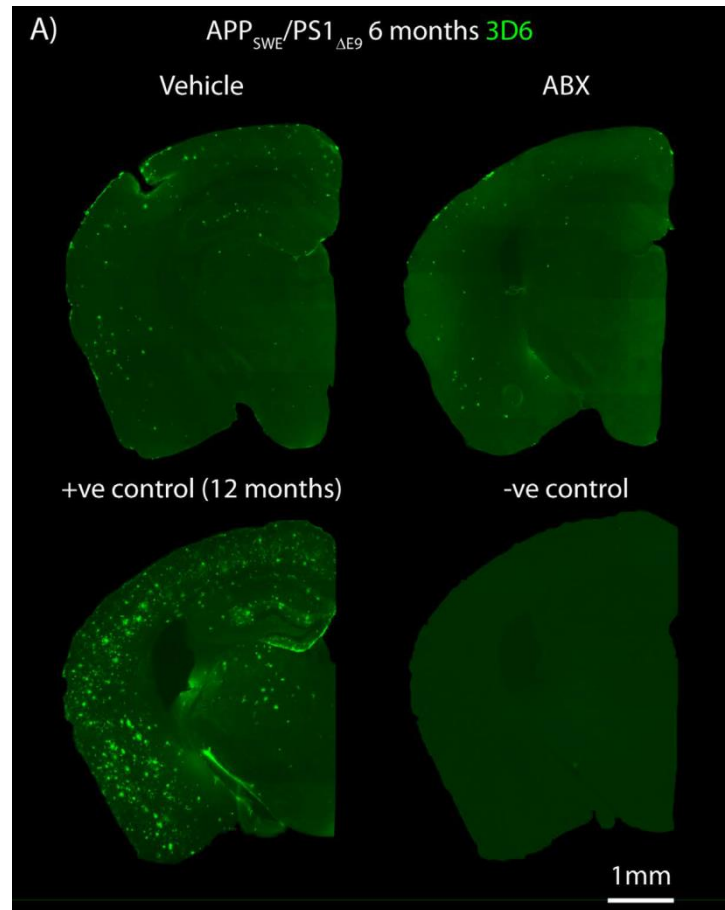
Antibiotic-altered composition of gut microbiota (2)



- Significant decrease in microbial diversification ABX-treated mice

Can gut microbiota have an impact on AD pathology?

Antibiotic-altered composition of gut microbiota (3)

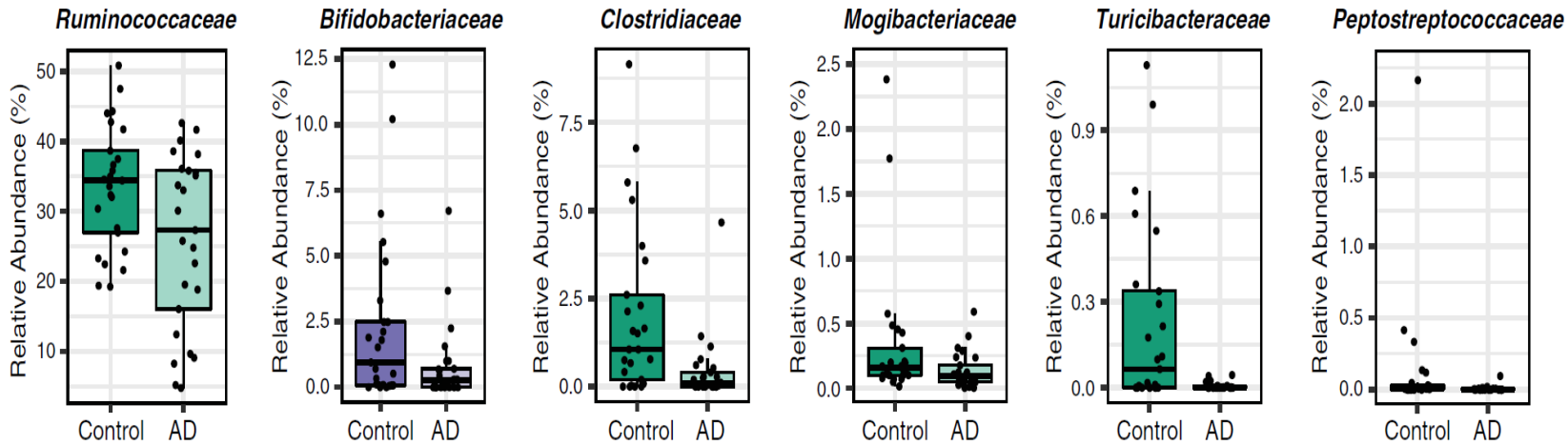


- Reduced amyloid deposition/reduced number of amyloid plaques in ABX-treated mice
- Increased levels of soluble A β in ABX-treated mice

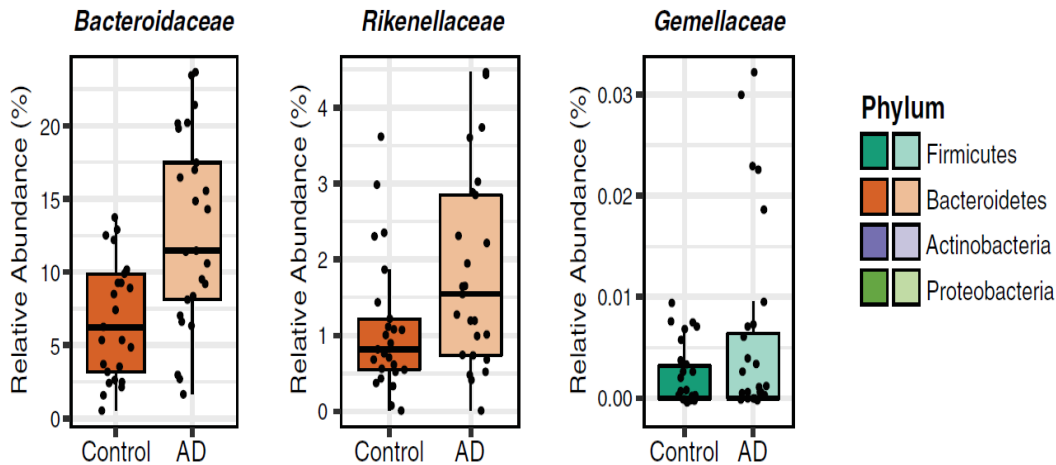
Altered gut microbiome in AD patients (1)

Increase in pro-inflammatory microbes

Families less abundant in AD



Families more abundant in AD

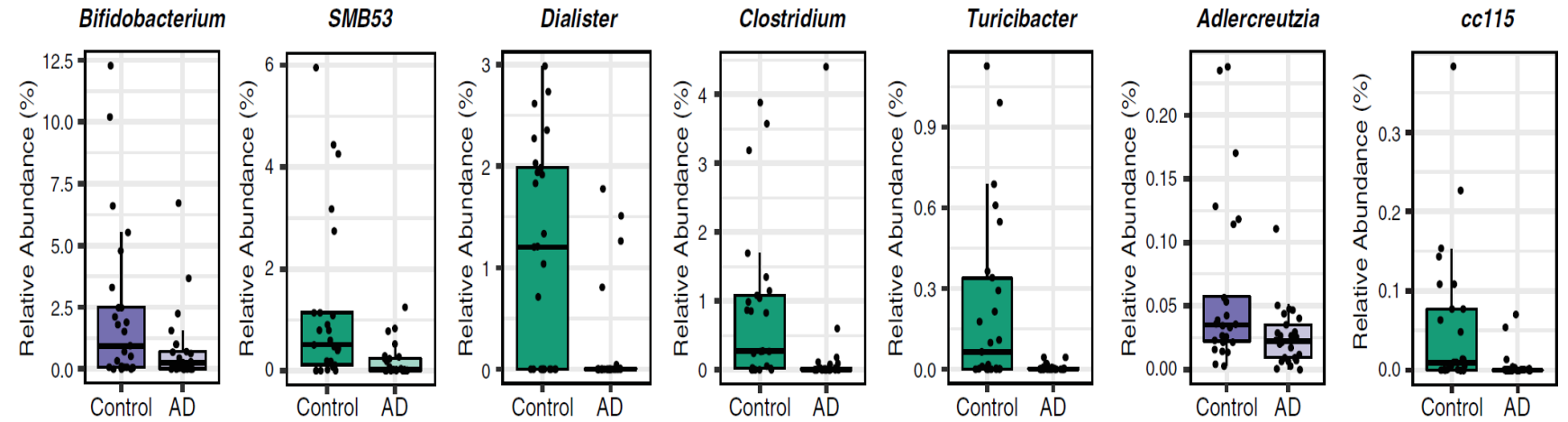


	Control	AD
n	25	25
Age (yrs, mean \pm SD)	69.3 \pm 7.5	71.3 \pm 7.3
Sex (% Female)	72% (18/25)	68% (17/25)
Clinical dementia rating (CDR) score		
0-normal	100% (25/25)	0
0.5-very mild dementia		40% (10/25)
1-mild dementia		36% (9/25)
2-moderate dementia		24% (6/25)
APOE ϵ 4 genotype	20% (5/25)	72% (18/25)
Ethnicity (% Caucasian)	96% (24/25)	92% (23/25)
BMI (kg/m ² , median [IQR])	26.1 [24.3-33.2]	26.0 [22.9-29.1]

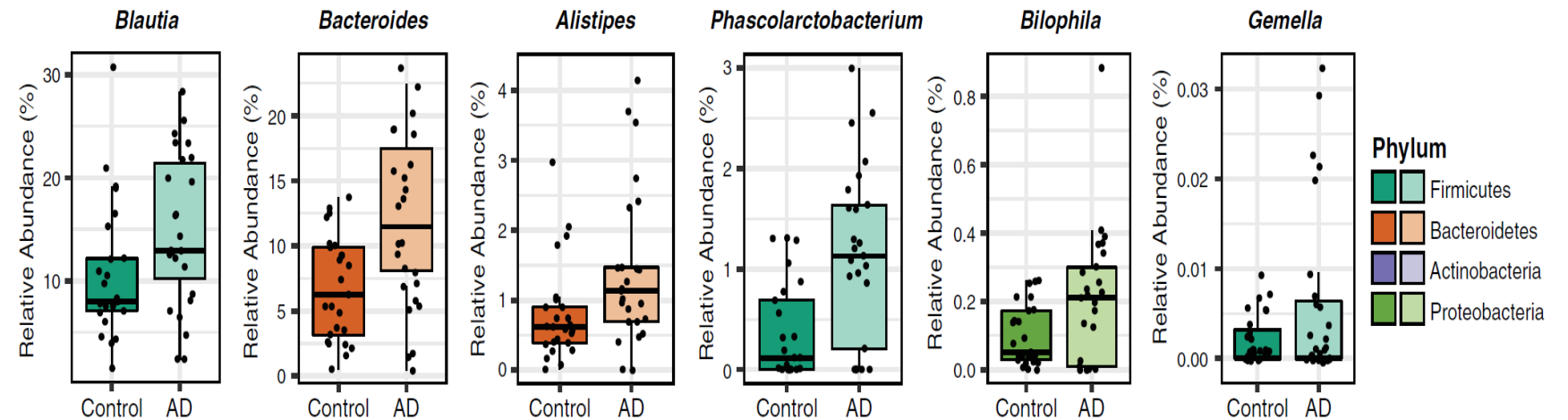
Altered gut microbiome in AD patients (2)

Increase in pro-inflammatory microbes

Genera less abundant in AD



Genera more abundant in AD

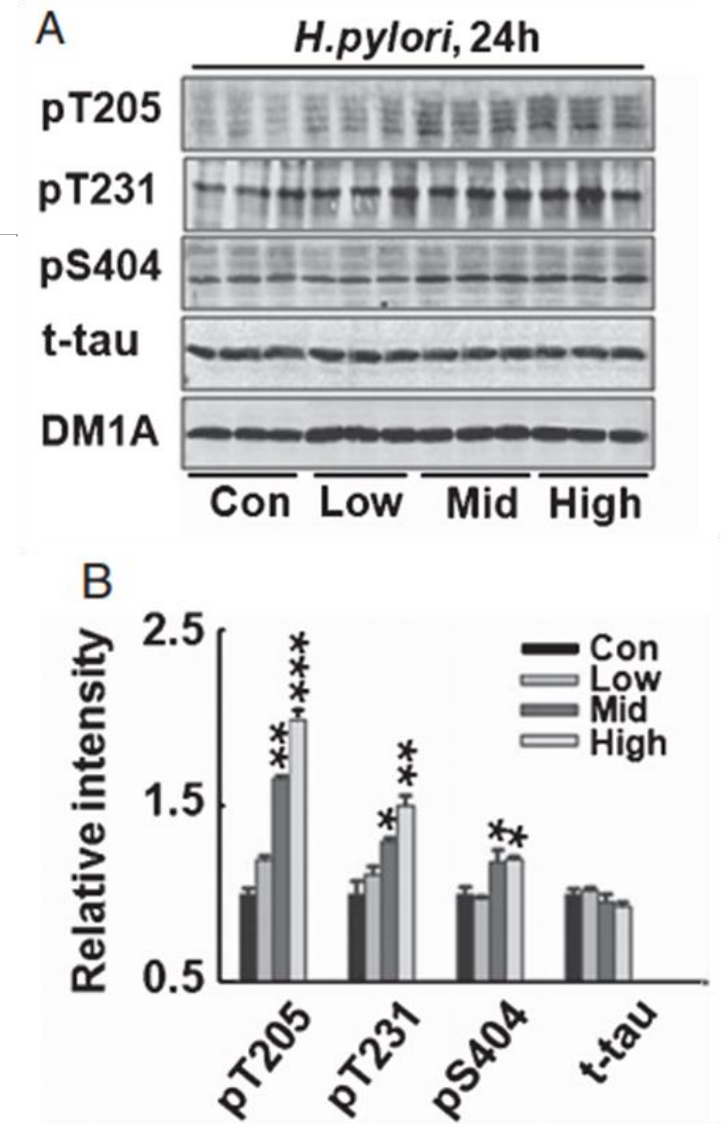



Clinical studies in AD patients' microbiota

Study	Sample	Sequencing	Findings
Zhuang et al. (2018)	43 AD 43 controls	16S rRNA V3-V4 regions, fecal samples	Alternation in all levels (phylum to genus) e.g. Genus level: <i>Bacteroides</i> ↑, <i>Ruminococcus</i> ↑, <i>Subdoligranulum</i> ↑, <i>Lachnoclostridium</i> ↓
Li et al. (2019)	30 AD 30 MCI 30 controls	16S rRNA V3-V4 regions, fecal & blood samples	↓Bacterial diveristy in feces and blood in AD & MCI <u>AD fecal microbiota</u> : ↑ in <i>Dorea</i> , <i>Lactobacillus</i> , <i>Streptococcus</i> , <i>Bifidobacterium</i> , <i>Blautia</i> , <i>Escherichia</i> / ↓ in <i>Alistipes</i> , <i>Bacteroides</i> , <i>Parabacteroides</i> , <i>Sutterella</i> , <i>Paraprevotella</i> <u>AD Blood microbiota</u> : ↑ in <i>Propionibacterium</i> , <i>Pseudomonas</i> , <i>Glutamicibacter</i> , <i>Escherichia</i> , <i>Acidovora</i> / ↓ in <i>Acinetobacter</i> , <i>Aliihoeflea</i> , <i>Halomonas</i> , <i>Leucobacter</i> , <i>Pannonibacter</i> , <i>Ochrobactrum</i>
Liu et al. (2019)	33 AD 32 aMCI 32 controls	16S rRNA V3-V4 regions, fecal samples	↓Bacterial diverity in AD <u>AD</u> : Firmicutes↓, Proteobacteria↑ <u>Controls</u> : More Gammaproteobacteria, Enterobacteriales, Enterobacteriaceae
Ling et al. (2021)	100 AD 71 controls	16S rRNA V3-V4 regions, fecal samples	↓Bacterial diversity in AD <u>AD</u> : ↓ in <i>Faecalibacterium</i> & Butyrate-producing genera ↑ in <i>Bifidobacterium</i> & Lactate-producing genera

Helicobacter pylori & AD patients

- Chronic *H. pylori* (*Proteobacteria*) infection in AD patients is associated with higher cognitive impairment compared to non-infected patients
- The levels of $A\beta_{40}$ & $A\beta_{42}$ in the serum are higher in AD patients infected by *H. pylori*
- Exposure of neuroblastoma cells (N2a) to *H. pylori* filtrate induced τ hyperphosphorylation mainly at Thr205 & Thr231 in a dose-dependent manner
- Eradication of *H. pylori* improved AD patients cognitive state and everyday functionality (2 year follow up study)



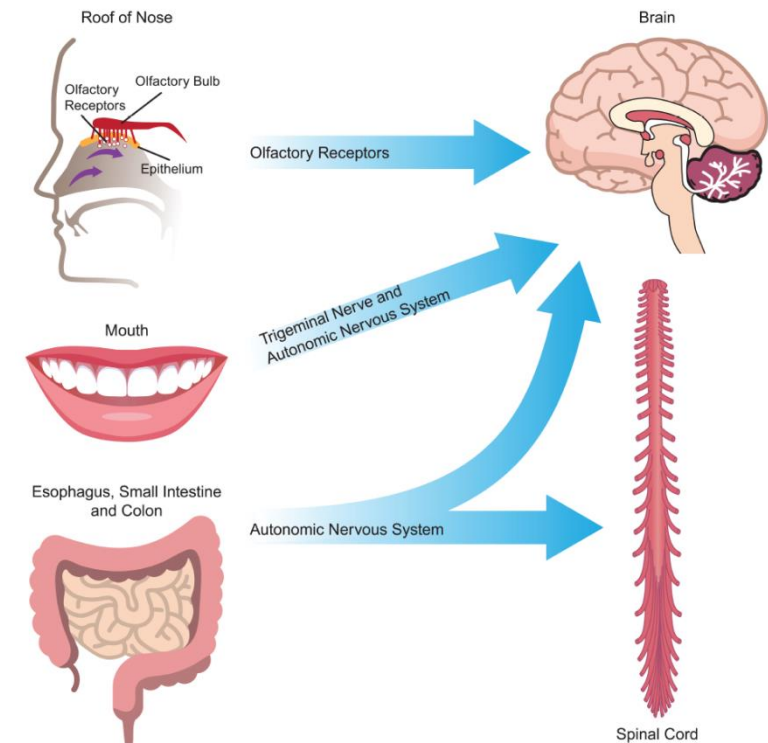
A microscopic image of neural tissue, possibly a brain section, stained with a blue fluorescent dye. The image shows a complex network of fibers and structures, with some areas appearing more densely stained than others. The overall tone is dark blue and black, with the fluorescence providing a bright contrast.

Alzheimer's disease & Gut Microbiota

How microbiota promote AD?

Bacterial amyloids (1)

- GI microbiota are a source of amyloids (“functional” amyloids)
 - The production of amyloid proteins assists bacteria in structural support, surface adherence, dissemination of virulence factors, propagation, biofilm formation, resisting destruction by physical or immune factors
- *E.coli* amyloid: curli/major subunit CsgA
- Similarly to CNS amyloids, curli are β -sheet rich fibers resistant to protease
- Cross-seed amyloid formation by CNS amyloids ($A\beta$, α -synuclein, tau)



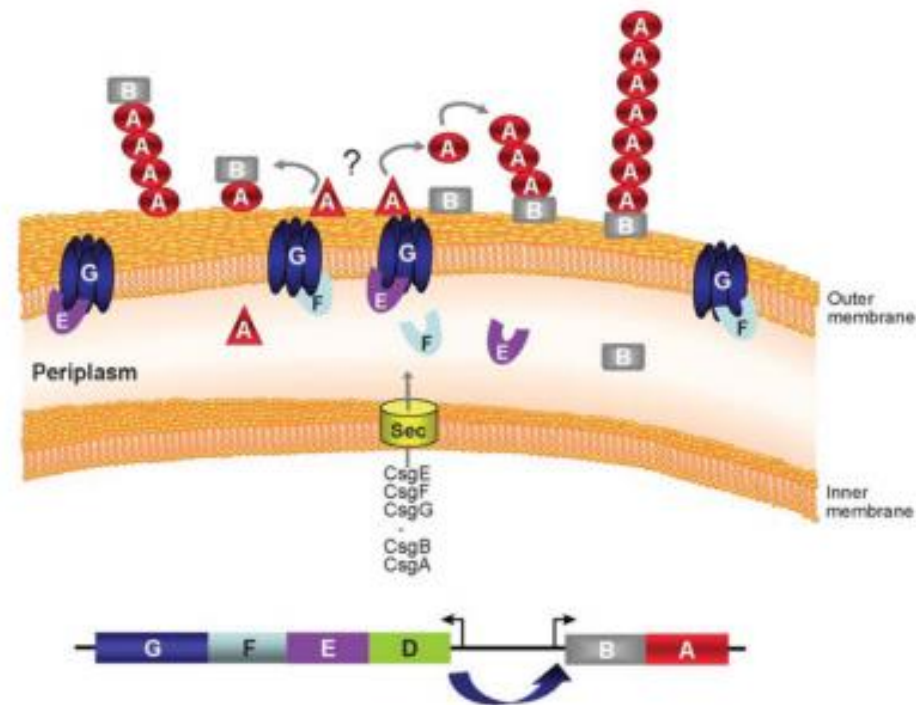
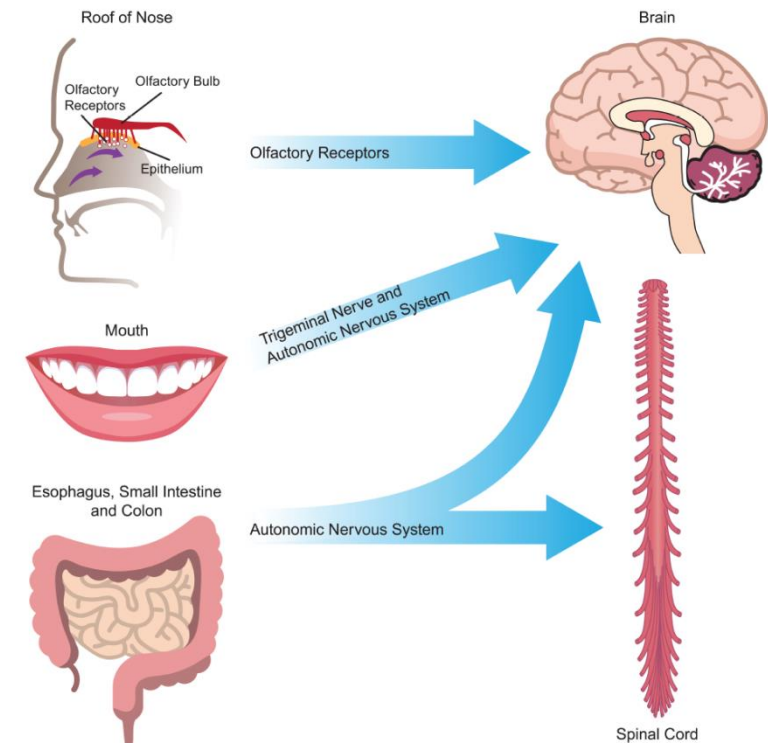


Figure 1. Model of curli assembly

A schematic diagram of the two curli gene operons is shown (*bottom*). CsgD is a positive transcriptional regulator of the *csgBA* operon. All the proteins encoded by the *csg* operons, except for CsgD, contain *sec* signal sequences for translocation into the periplasm. CsgG is an outer membrane protein required for the secretion of the two curli structural subunits CsgA and CsgB. CsgA is secreted outside of the cell where CsgB nucleates it into a fiber. CsgE and CsgF both interact with CsgG and are required for efficient curli assembly.

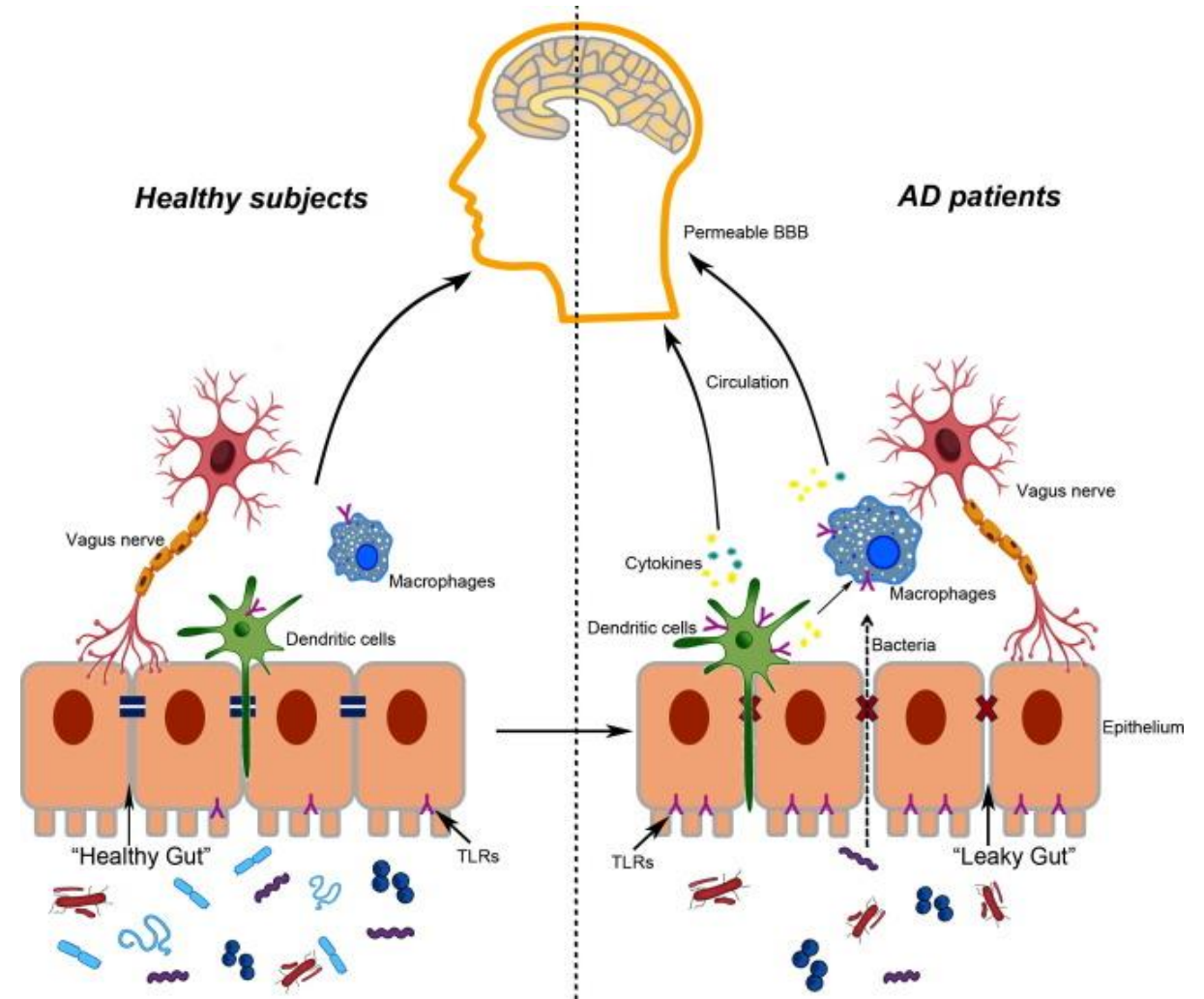
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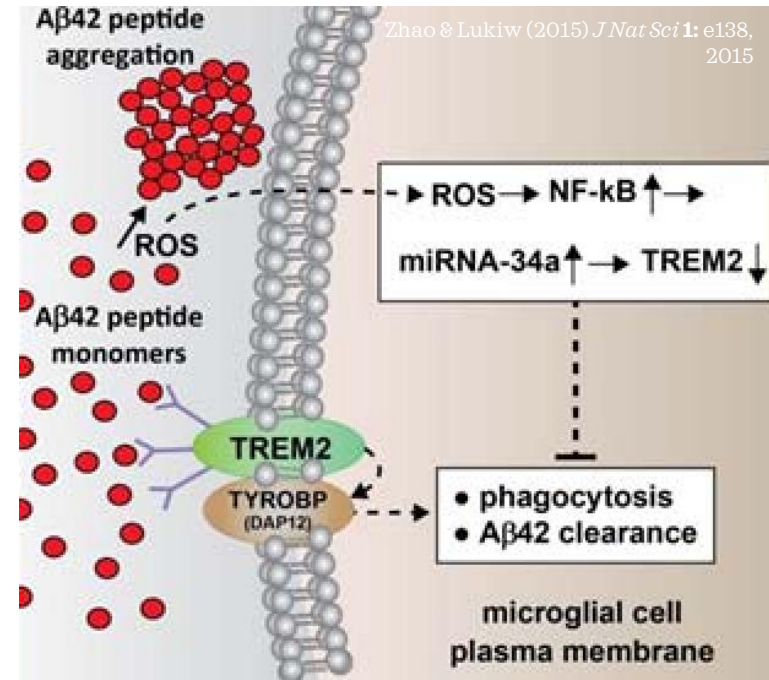
Bacterial amyloids (2)

- Bacterial amyloids recognized as PAMPs (pathogen associated molecular patterns), *e.g.* the Curli subunit (CsgA) contains a PAMP that is recognized by human TLR2
- Activation of Toll-like receptor 2 (TLR2)
- TLR2 signaling
- Pro-inflammatory cytokine production (IL-17, IL22)



Bacterial amyloids (3)

- Bacterial amyloids might activate the NFkB signaling, which induces upregulation of the pro-inflammatory miRNA-34a
- miRNA-34a down-regulates TREM2 (triggering receptor expressed on microglia), which may impair the ability of the microglia to phagocytose and facilitate the accumulation of A42 peptide

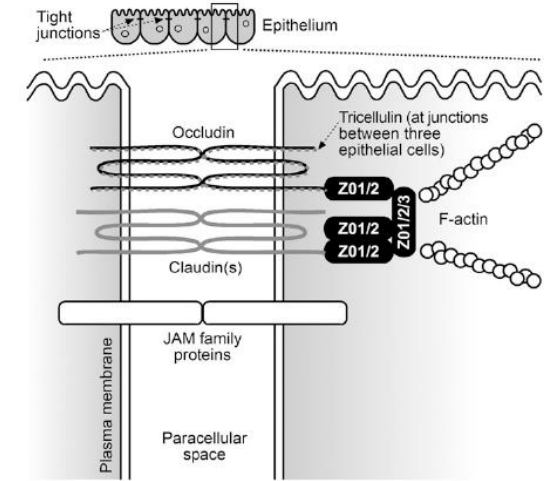
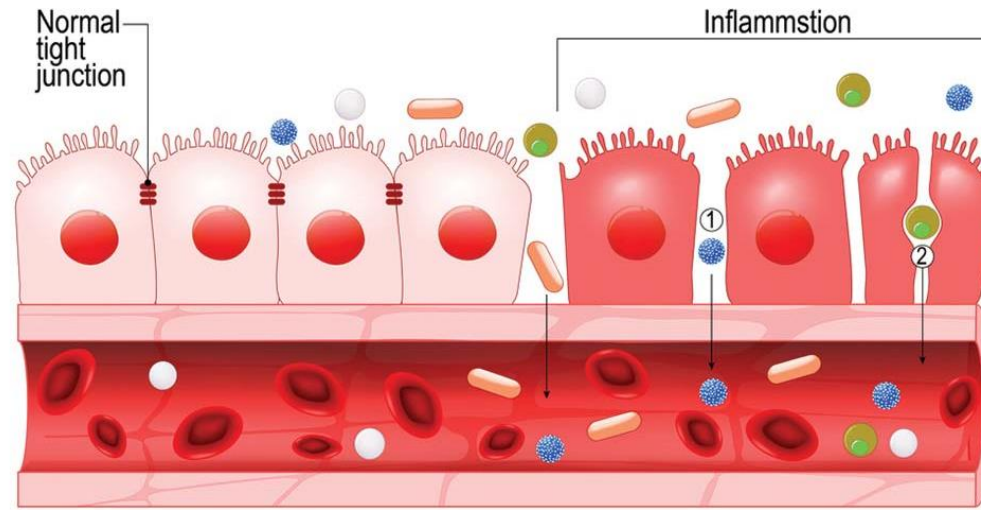


Reviewed by Jiang *et al.* (2017)

Lipopolysaccharides (LPSs) & AD

- A.k.a. endotoxin/ components of the outer surface of the outer membrane of Gram-negative bacteria
- LPS promotes A β aggregation *in vitro*
- Injection of bacterial LPS into the fourth ventricle of rat brains reproduces many of the inflammatory and memory impairments seen in AD
- Injection of LPS into the peritoneal cavity of mice → prolonged elevation of A β in hippocampus region resulting in cognitive defects
- LPS been detected in the hippocampus and cortex brain lysates from AD patients
- LPS co-localizes with A β 40/42 in senile plaques and around blood vessels
- The plasma concentration of LPS in AD patients is also significantly higher than in healthy people
- LPS activates the TLR2 & TLR4

Increased gut permeability: “Leaky gut” (1)

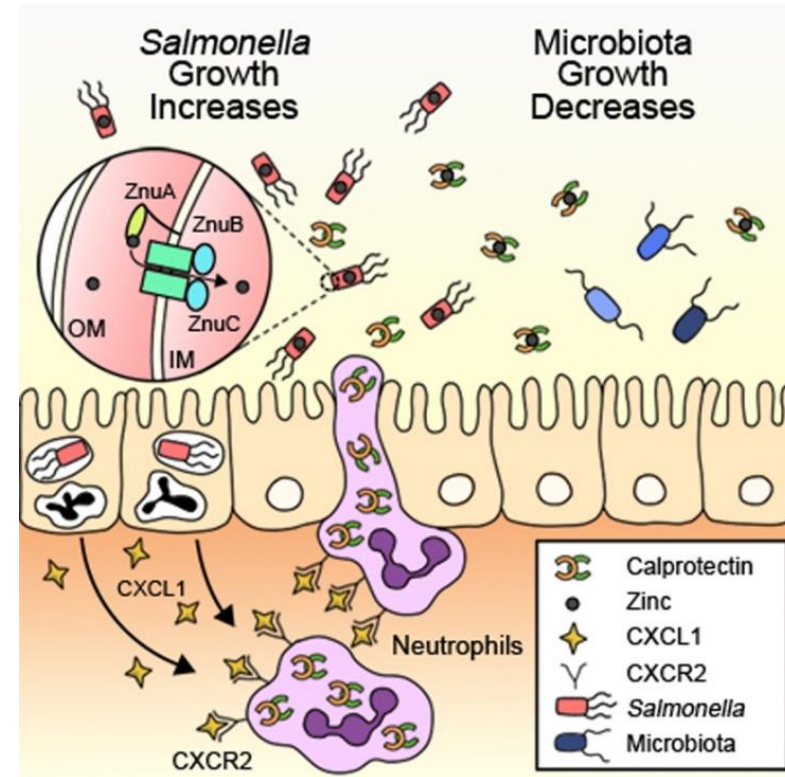


Ulluwishewa *et al.* (2011) *J. Nutr.* **141**:769–776 doi:10.3945/jn.110.135657

- *E.coli* metabolites and curli promote intestinal inflammation and decrease the expression level of the epithelial cell tight junction proteins
 - e.g.* Zonula Occludens-1 (ZO-1), Claudin-1, Occludin: keep epithelial cells together
- Leaky gut allows bacterial amyloids & LPS to translocate into the bloodstream and aggravate inflammation

Intestinal inflammation (1)

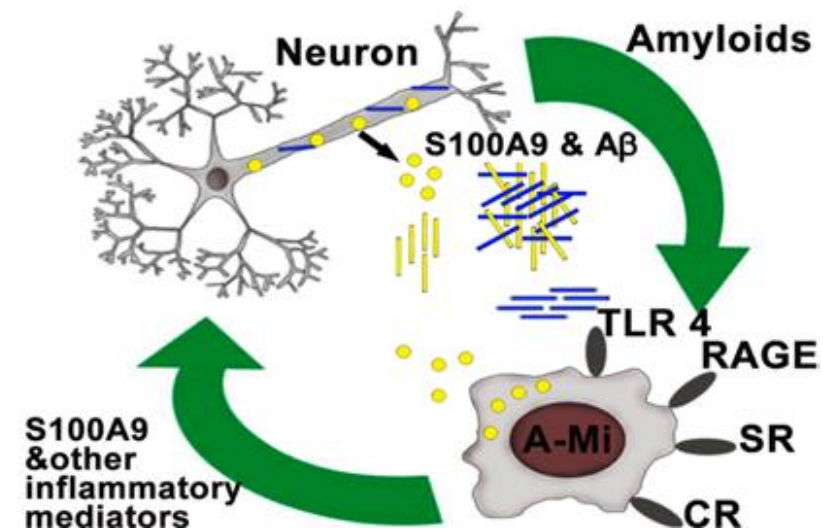
- Intestinal inflammation causes migration of neutrophils to the gut mucosa or even further to the gut lumen (leaky gut)
- Intestinal inflammation can be indirectly measured by assessing stool calprotectin concentration
 - small Ca-binding protein
 - a heterodimer: S100A8 (93 a.a.) & S100A9 (113 a.a)
 - S100A8 and S100A9 comprise ~ 60% of the cytosolic proteins in neutrophils
 - possesses antimicrobial properties (bacterial & fungal)



Li u et al. (2012) *Cell Host & Microbe* 11:227-239 <https://doi.org/10.1016/j.chom.2012.01.017>

Intestinal inflammation (2)

- S100A8 & S100A9 have intrinsically disordered sequences and can form oligomers and fibrils, which resemble bacterial amyloids/activation of TLR2/4 signaling
- Monomeric & dimeric S100A9 induces A β fibrillization *in vitro*
- Calprotectin levels are significantly increased in the cerebrospinal fluid and the brain of AD patients, which promotes its amyloid aggregation and co-aggregation with A β
- Calprotectin levels are significantly increased in the cerebrospinal fluid and the brain of AD patients, which promotes its amyloid aggregation and co-aggregation with A β
- Elevated fecal calprotectin levels found in ~ 70% of AD patients/ hypothesized that it could translocate into circulation (via leaky gut) and contribute to neuroinflammation



Wang et al. (2014) Acta Neuropathol 127:507-522
DOI 10.1007/s00401-013-1208-4

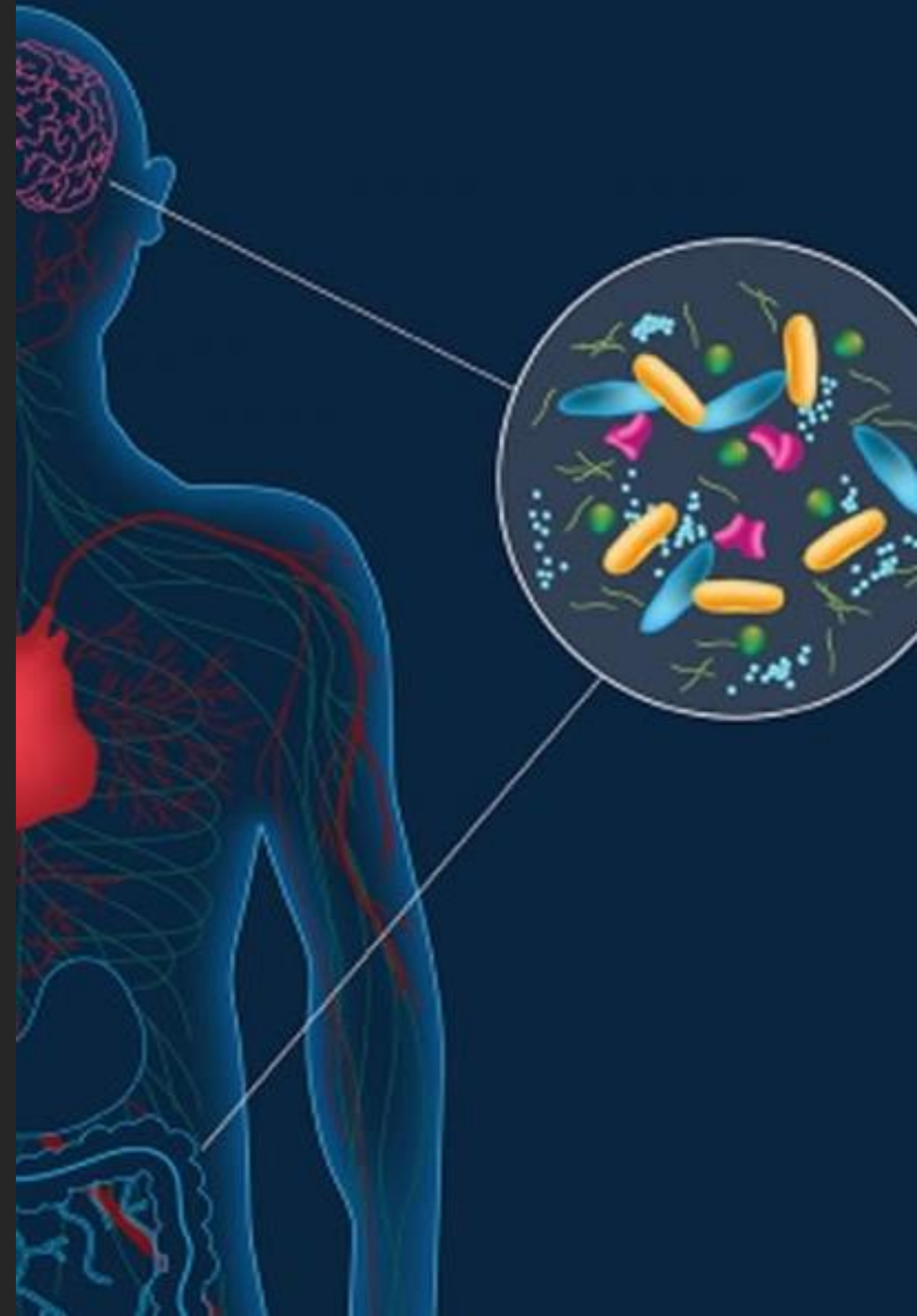
A microscopic image of neural or gut tissue, showing a complex network of fibers and structures. A prominent, thick, and somewhat bulbous structure is visible on the left side, with a blue glow emanating from it. The background is dark, and the overall image has a blue tint.

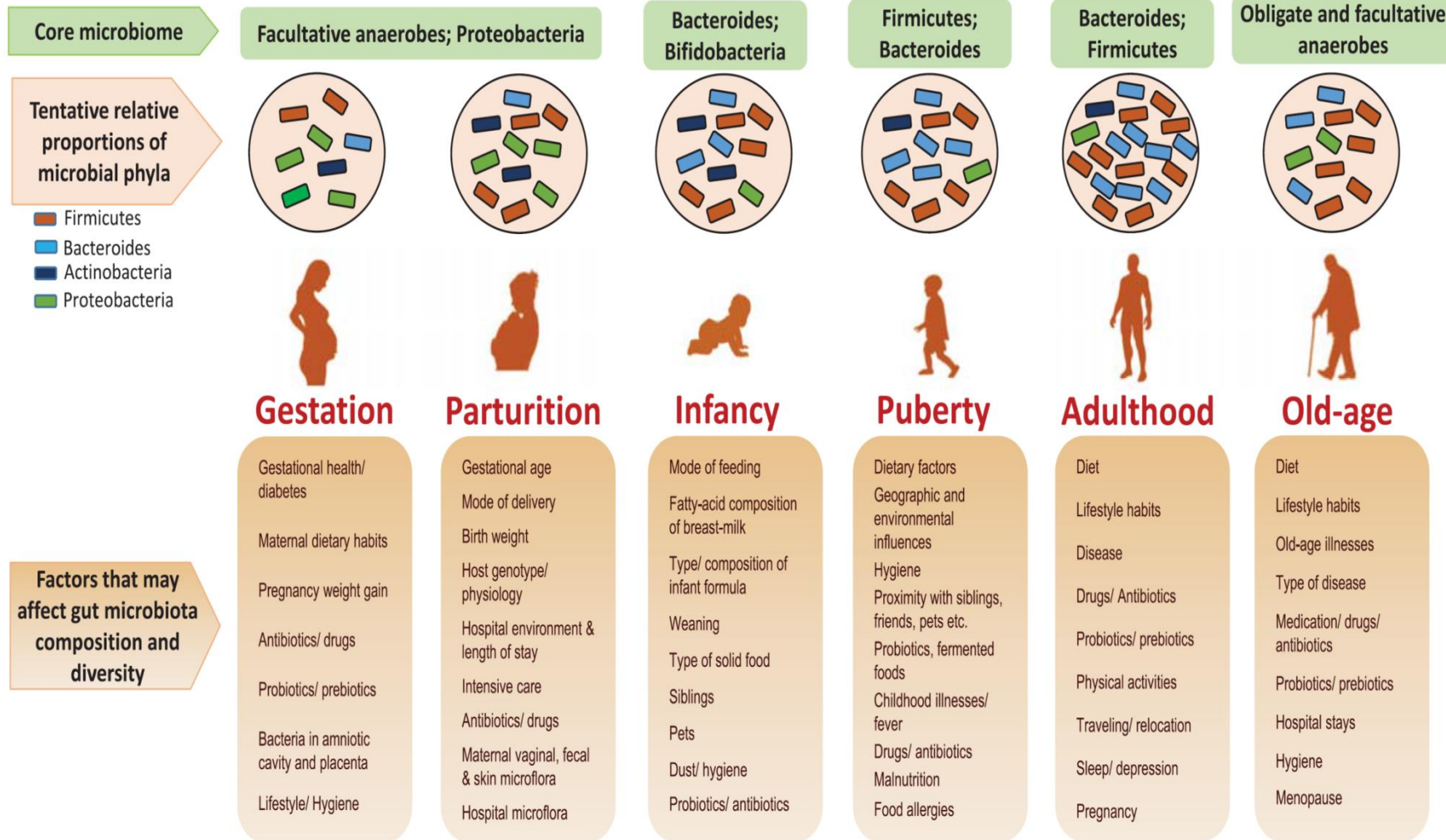
Alzheimer's disease & Gut Microbiota

Implications for AD diagnosis & treatment

Can gut microbiota alterations be used as a marker for AD?

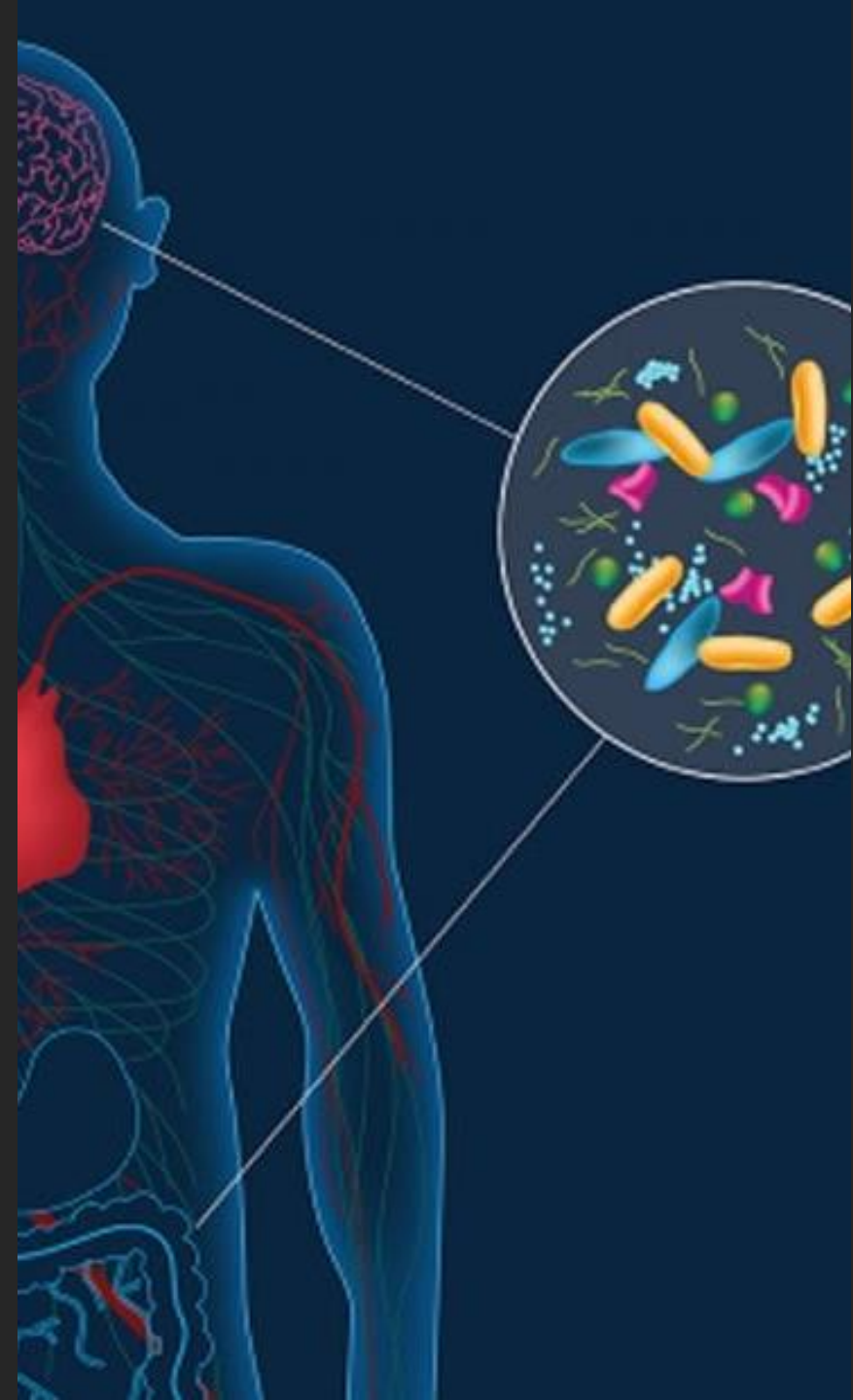
- What is the composition of the healthy microbiome?
- What is the composition of microbiome in disease?
- Findings so far are based on cross-sectional studies /longitudinal studies are needed





Adapted from Nagpal *et al.* (2018) *Nutr Healthy Aging* 4:267–285
doi: 10.3233/NHA-170030

Gut microbiota
alterations in AD:
modulation of gut
microbiota as a
treatment for AD



Can gut microbiota modulation alleviate AD?

Dietary interventions

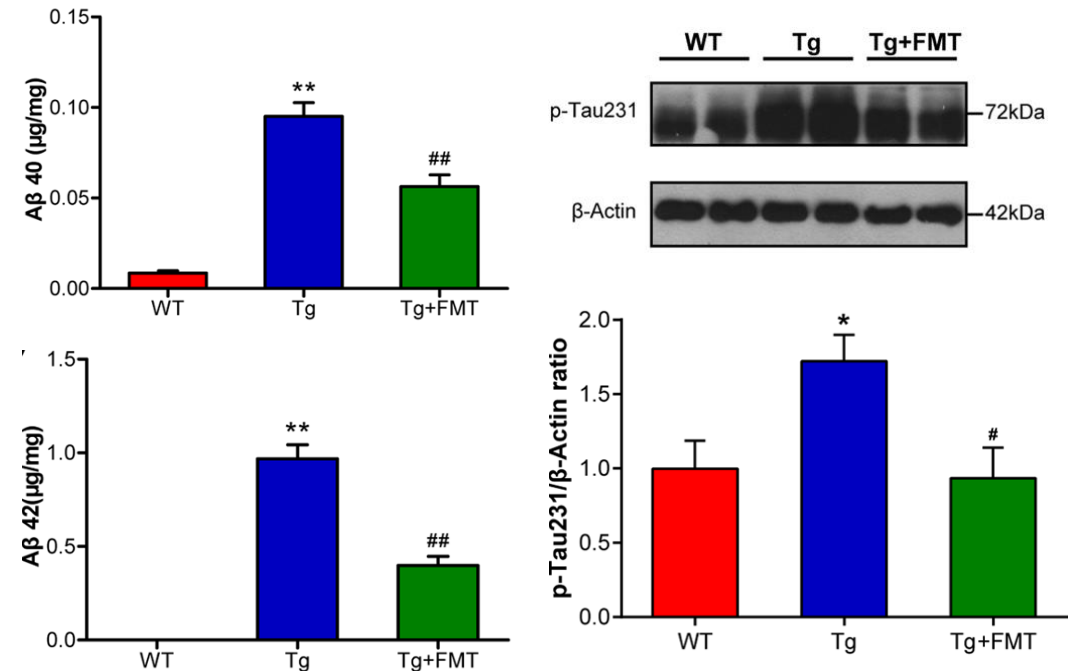
- **Mediterranean diet**, *i.e.* high intake of fruit, vegetables, cereals, legumes/low intake of meat, high-fat dairy, sweets
 - lowers risk for AD, preserves cognitive ability in the elderly, improves cognitive function
 - increases in microbiota diversity after 1 year (higher ratio of Firmicutes/Bacteroidetes)
- **Ketogenic (keto) diet**, *i.e.* low carbohydrate, high fat intake, enough protein
 - (in young healthy mice) can modify gut microbiota composition (↑Firmicutes & Actinobacteria, ↓Proteobacteria)
 - preserves cognition in mild cases of AD
 - (followed at an early stage) ↓ risk of AD & ↑ beneficial gut microbiota



Can gut microbiota modulation alleviate AD?

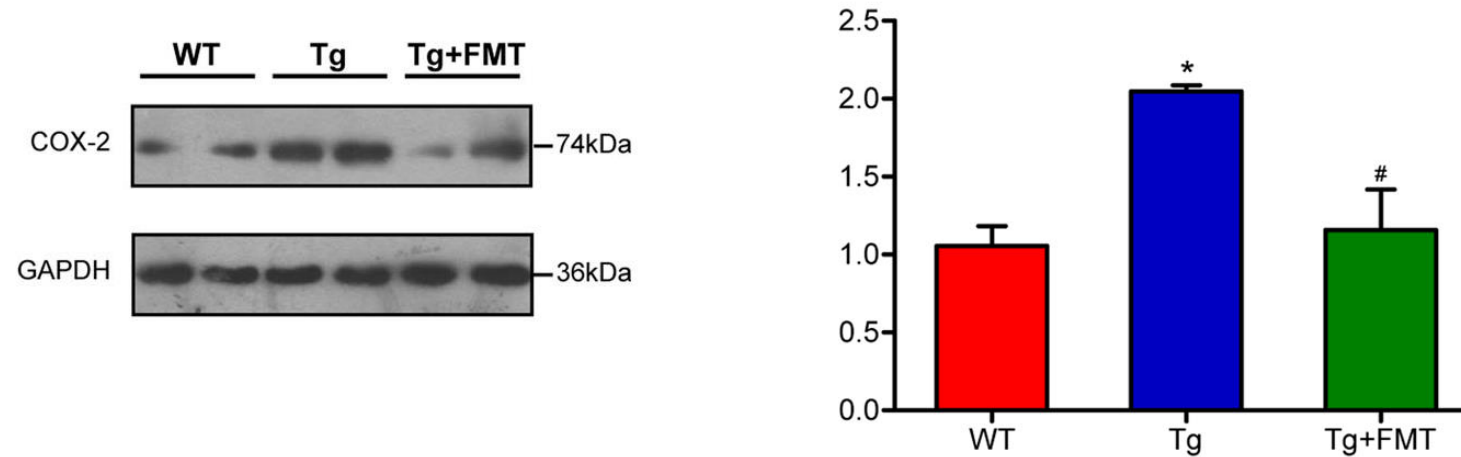
Faecal Microbiota Transplantation (FMT) (1)

- FMT: transplantation of GI microbiota from a healthy donor to replace/replenish the gut microbiota of an unhealthy individual
- Animal model: APP_{SWE}/PS1_{ΔE9} (6wks old)
- + FMT group: intragastrically administered with 0.2 ml fresh fecal solution of WT mice once daily for 4 wks
- Control: same dose of physiological saline
- Amelioration of A β deposition, τ phosphorylation and cognitive decline



Can gut microbiota modulation alleviate AD?

Faecal Microbiota Transplantation (FMT) (2)

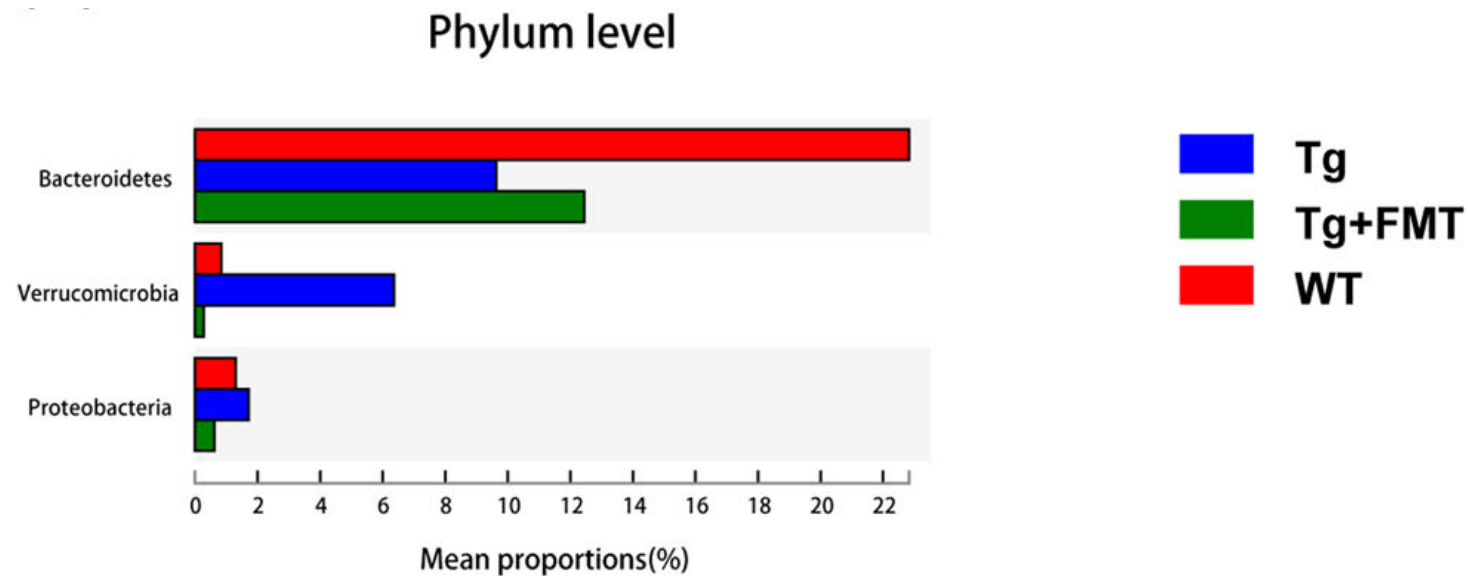


COX-2 is decreased in FMT animals

Attenuation of inflammation

Can gut microbiota modulation alleviate AD?

Faecal Microbiota Transplantation (FMT) (3)



Can gut microbiota modulation alleviate AD?

Faecal Microbiota Transplantation (FMT) (4)

Some animal model studies suggesting that cognitive impairment can be alleviated by FMT

- FMT from healthy to AD model mice → ↓SPs & NFTs, ↓A β ₄₂ brain deposition, cognitive impairment amelioration (Kim et al., 202)
- FMT from AD model mice to healthy mice → memory decline, increased inflammation (Kim et al., 2021)

One clinical study (Hazan, 2020):

- 82-year-old man suffering from recurrent *Clostridium difficile* infection following hospitalization
- Suffered from dementia symptoms, *e.g.* memory loss, confusion, depression
- Mini-Mental State Examination (MMSE) before FMT= 20
- FMT: stool donor – patient's 85-year-old wife
- 2 months after FMT: MMSE = 26/ 6 months after FMT: MMSE = 29
- Improved memory & mental acuity, increased interaction

Can gut microbiota modulation alleviate AD?

Probiotics (1)

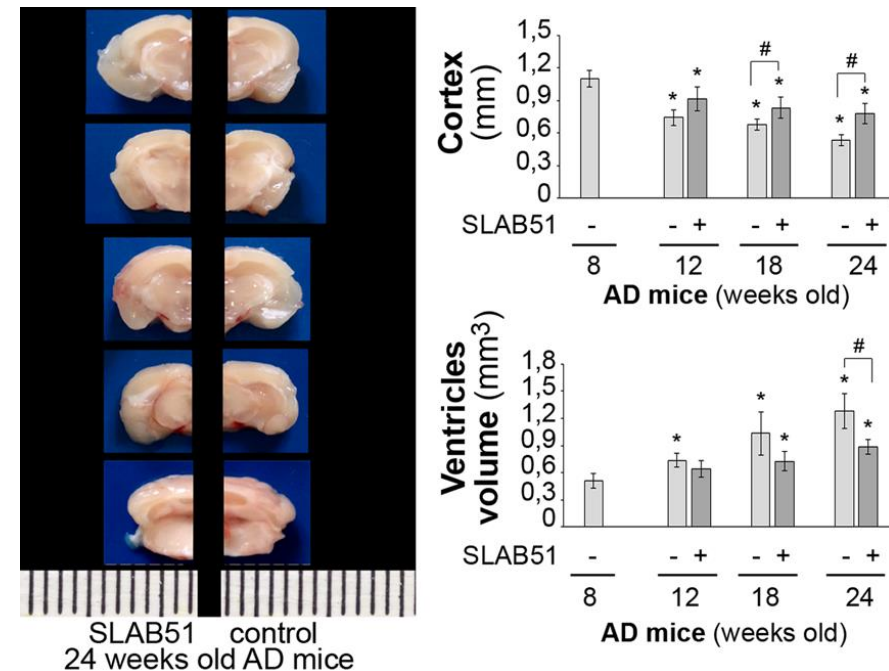
- Probiotics: live microorganisms that, when administered in adequate amounts, confer health benefits to the host
- Psychobiotics: mental health benefits



Can gut microbiota modulation alleviate AD?

Probiotics (2)

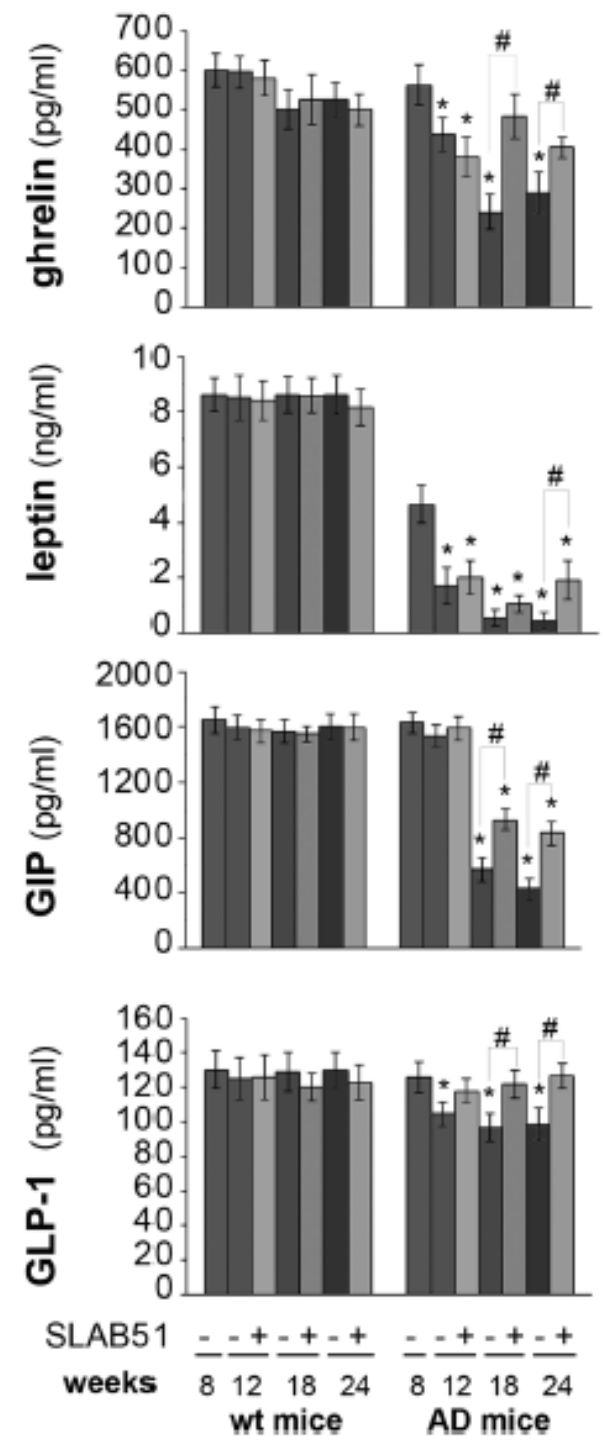
- Probiotic = SLAB51: 9 live bacterial strains [*Streptococcus thermophilus*, *bifidobacteria* (*B. longum*, *B. breve*, *B. infantis*), *lactobacilli* (*L. acidophilus*, *L. plantarum*, *L. paracasei*, *L. delbrueckii subsp. bulgaricus*, *L. brevis*)]
- Mouse model for AD: 3xTg-AD (8wk old)
- Treated mice: 4-month oral administration of SLAB51 in water
- Controls: water administration
- Results:
 - attenuation of cognitive impairment and brain damage
 - ↓ in pro-inflammatory cytokines (IL1 α , IL1 β , IL2, IL12, IFN γ , TNF α)
 - ↓ in A β 42 deposition in mice brain
 - ↓ in accumulation of ubiquitinated proteins, and pro-apoptotic proteins (p53) /restored proteosomal activity



Can gut microbiota modulation alleviate AD?

Probiotics (3)

- GI tract hormones such as ghrelin, leptin, glucagon-like peptide 1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP) are responsible among others for food intake regulation
- Ghrelin involved in higher brain functions *e.g.* learning & memory
- Ghrelin and leptin act as neurotrophic factors: protect cells against oligomeric A β toxicity induced
- Plasma leptin concentration is negatively correlated to A β levels in the brain due to its direct regulatory effect on γ -secretase (\downarrow mRNA of PS1, nicastrin, PEN2, APH1)
- AD animal models treated with leptin showed a reduction in A β and phosphorylated τ levels
- GLP-1 protects cultured neurons from oxidative damage and reduces the levels of A β
- GIP and its analogs were shown to improve memory, cognitive decline, reduce number of A β plaques
- Increase in GI tract hormones in SLAB51 treated mice



Can gut microbiota modulation alleviate AD?

Probiotics (4)

- Probiotics used in clinical studies: Lactobacillus (e.g. *L. acidophilus*), Bifidobacterium (*B. bifidum*)
- Supplementation period: 12 weeks
- Controversial results: some studies showed improvement of cognitive function/ some studies showed no beneficial effect on cognitive function

Suggested reading

Angelucci F, Cechova K, Amlerova J & Hort J. (2019) Antibiotics, gut microbiota, and Alzheimer's disease. *J Neuroinflammation* **16**:108. doi: 10.1186/s12974-019-1494-4

Jiang C, Li G, Huang P, Liu Z & Zhao B. (2017) The Gut Microbiota and Alzheimer's Disease. *J Alzheimers Dis*. **58**:1-15 . doi: 10.3233/JAD-161141

Kowalski K & Mulak A. (2019) Brain-Gut-Microbiota Axis in Alzheimer's Disease. *J Neurogastroenterol Motil*. **25**:48-60. doi: 10.5056/jnm18087

Ticinesi A, Tana C, Nouvenne A, Prati B, Lauretani F & Meschi T. (2018) Gut microbiota, cognitive frailty and dementia in older individuals: a systematic review. *Clin Interv Aging*. **13**:1497-1511. doi: 10.2147/CIA.S139163

Wu S, Liu X, Jiang R, Yan X, Ling Z. (2021) Roles and Mechanisms of Gut Microbiota in patients with Alzheimer's Disease. *Front Aging Neurosci*. **13**:650047. doi: 10.3389/fnagi.2021.650047