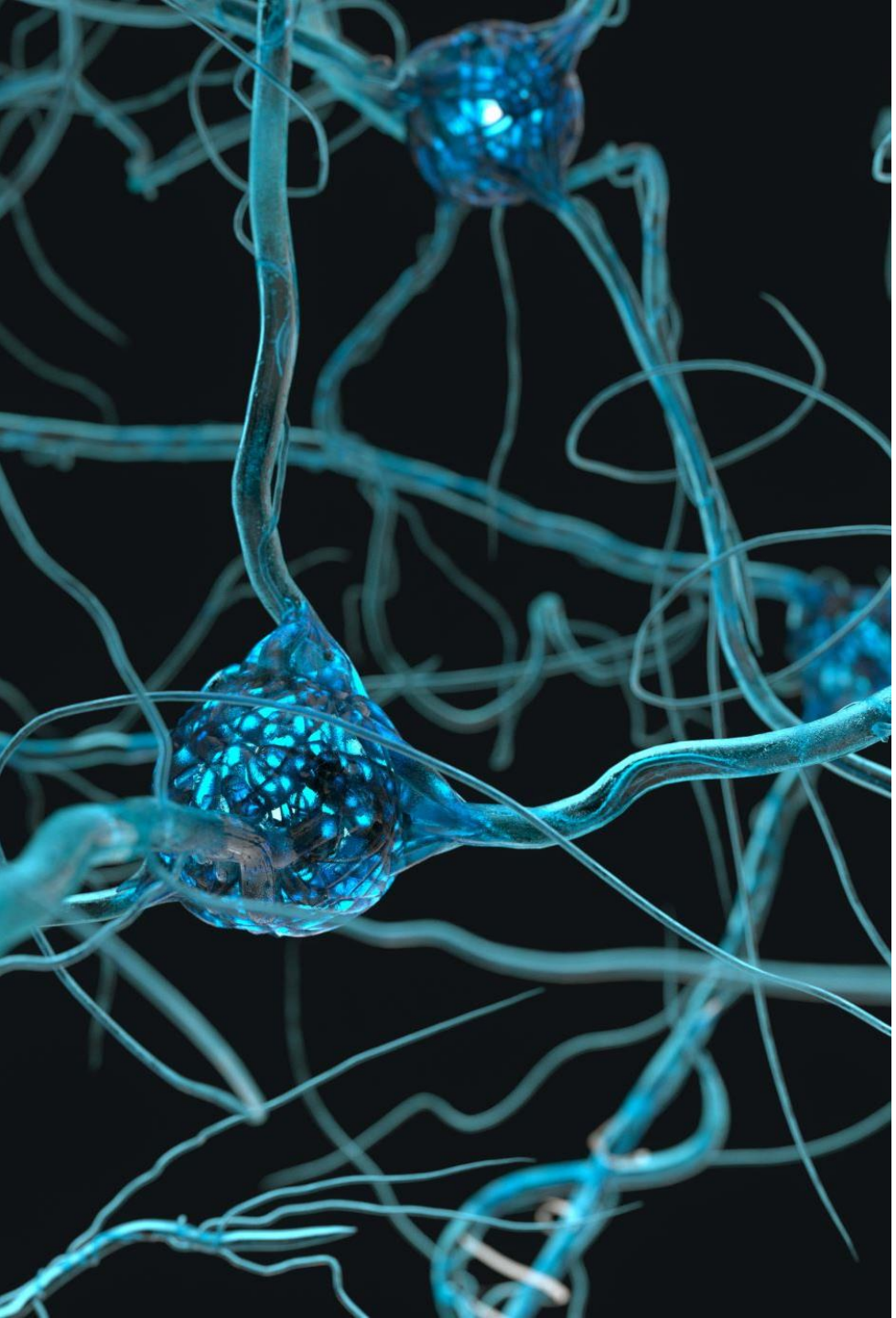


Neurodegeneration & Gut Microbiota

Trust your gut feeling!

KATERINA PALAIOLOGOU
Assist. Professor DMBG

DECEMBER 2023

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
ΜΕΤΑΦΡΑΣΤΙΚΗ ΕΡΕΥΝΑ ΣΤΗΝ ΒΙΟΙΑΤΡΙΚΗ
Μοριακή Διαγνωστική, Βιοδείκτες και Στοχευμένες Θεραπείες

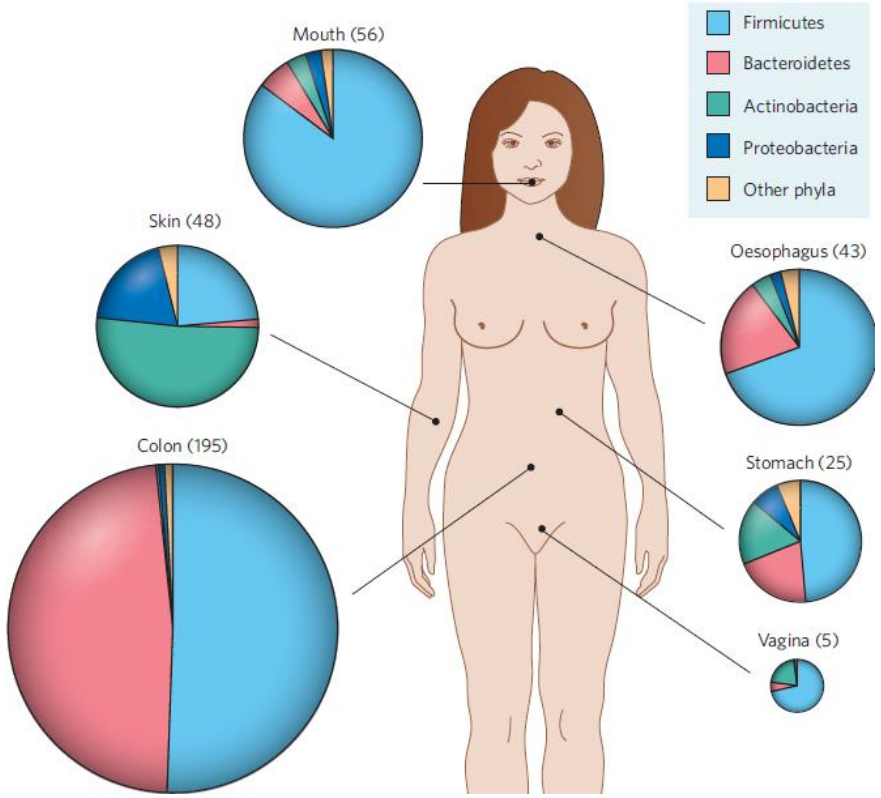
DEPARTMENT OF MOLECULAR BIOLOGY & GENETICS DUTH

Contents

- Gut Microbiota
- Background in Alzheimer's disease
  - Clinical symptoms
  - Histopathological hallmarks
    - Neurofibrillary tangles: tau (τ) protein
    - Senile plaques: β-amyloid (Aβ)
- Alzheimer's disease (AD) & Gut Microbiota
  - Can gut microbiota have an impact on AD pathology?
  - Gut microbiota alterations in AD
    - Clinical Studies
    - How gut microbiota promote AD?
  - Implications for AD diagnosis & treatment

The human gastrointestinal (GI) tract microbiota

- The largest reservoir of microbes in humans: ~10^{14} microorganisms from ~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	Ricketsia
		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
			Rumminococcaceae	Faecalibacterium Ruminococcus
	Bacilli	Bacillales	Staphylococcaceae Bacillaceae	Staphylococcus Bacillus
		Lactobacillales	Lactobacillaceae	Lactobacillus Pediococcus
			Enterococcaceae	Enterococcus
			Streptococcaceae	Streptococcus Lactococcus
Actinobacteria	Actinobacteria	Actinomycetales	Corynebacteriaceae	Campylobacter
			Mycobacteriaceae	Mycobacterium
			Micrococaceae	Microbacterium
		Bifidobacterales	Bifidobacteraceae	Bifidobacterium
Fusobacteria	Fusobacteriia	Fusobacteriales	Fusobacteriaceae	Fusobacterium
			Leptotrichiaceae	Streptobacillus
Bacteriodetes	Bacteroidia	Bacteroidales	Bacteriodaceae	Bacteroides
			Porphyromonadeceae	Porhyromonas
			Prevotellaceae	Prevotella
	Flavobacteriia	Flavobacteriales	Flavobacteriaceae	Flavobacterium
Verrucomicrobia	Verrucomicrobiae	Verrucomicrobiales	Verrucomicrobiaceae	Verrucomicrobium

Mentis *et al.* (2013) *ARCHIVES OF HELLENIC MEDICINE* **30:**272-288

The function of the nomral 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

Review by Jandhyala *et al.* (2015) *World J Gastroenterol* **21:** 8787-8803
DOI: 10.3748/wjg.v21.i29.8787

The gut-brain axis (GBA)

Also known as:

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

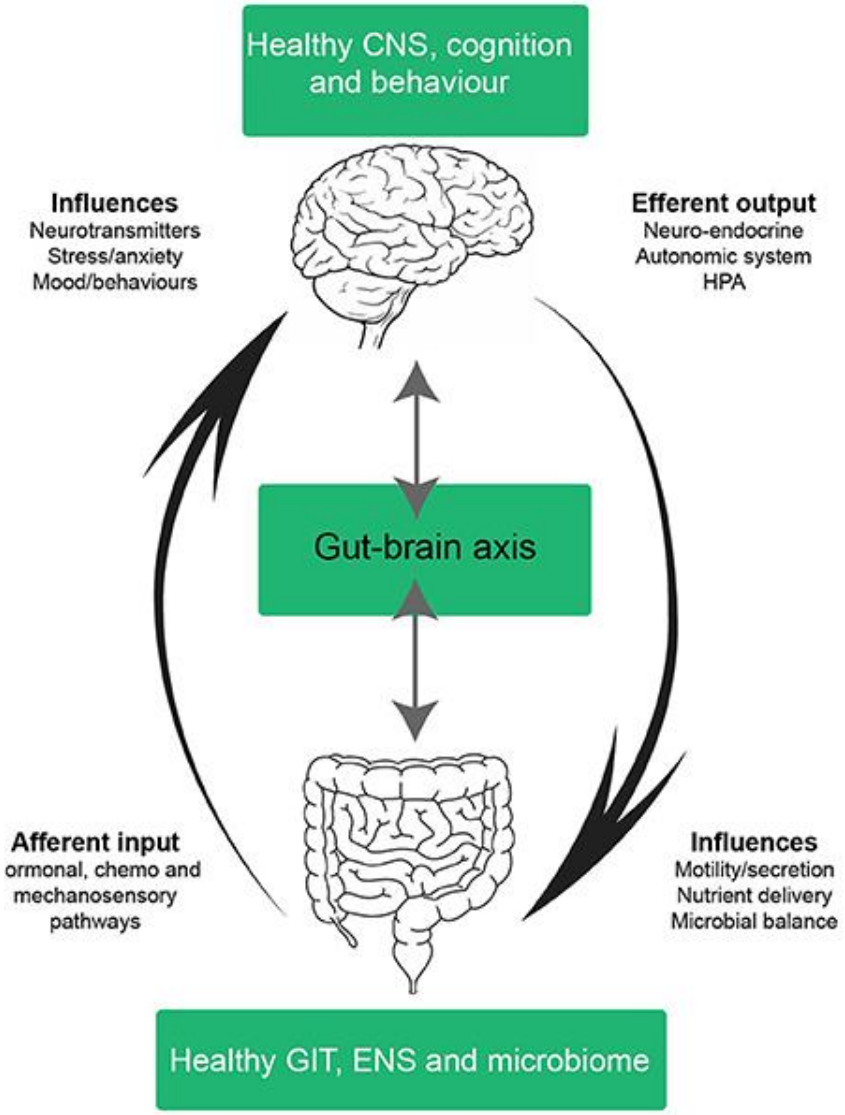
Bidirectional communication between the brain and the GI tract

The key components of GBA:

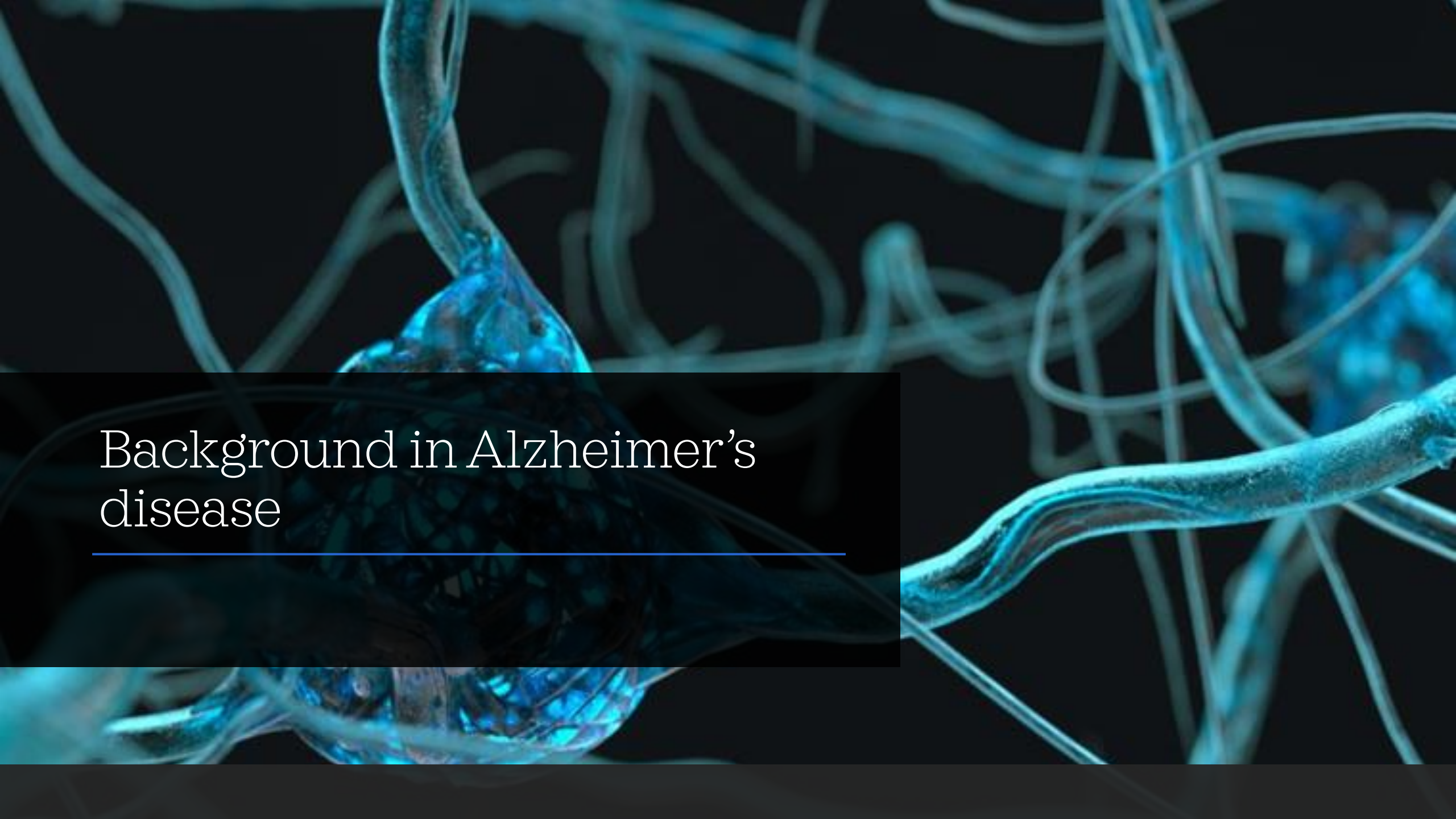
- CNS, ANS (vagus nerve and Enteric NS)
- Hypothalamic-pituitary-adrenal axis (HPA)
- Immune system (cytokines)

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*.)



Bajic *et al* (2018) *Front. Behav. Neurosci.* **12**:104

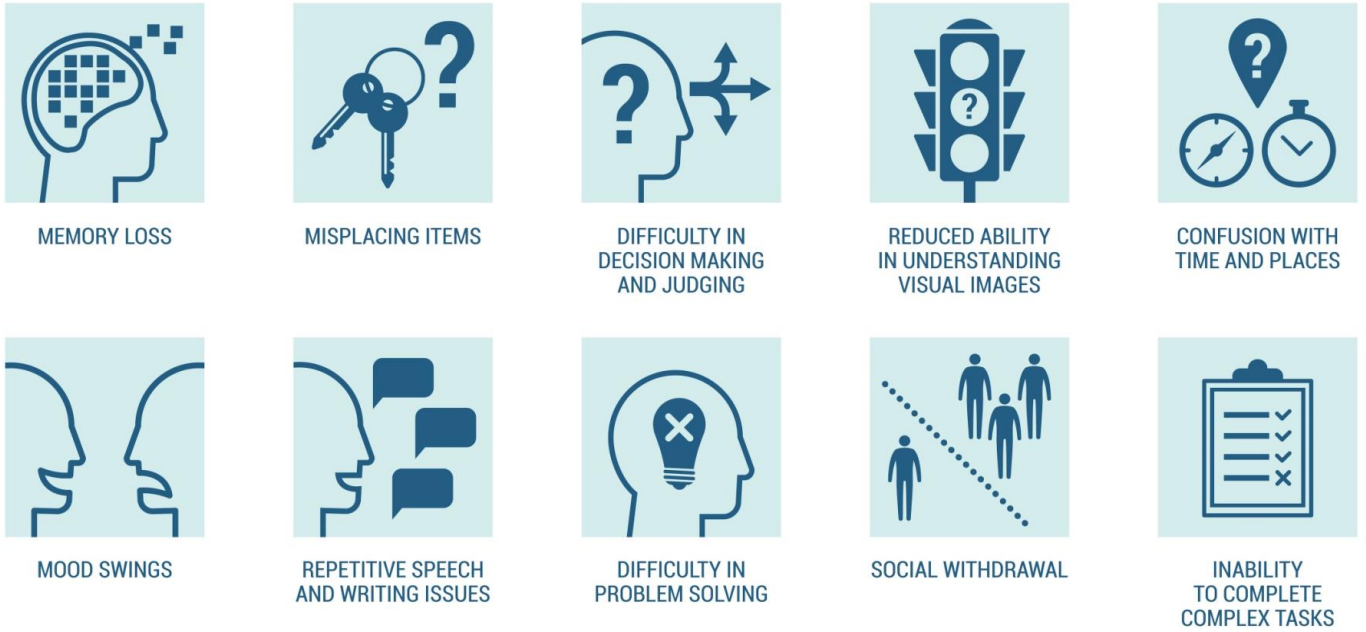


Background in Alzheimer's disease

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*



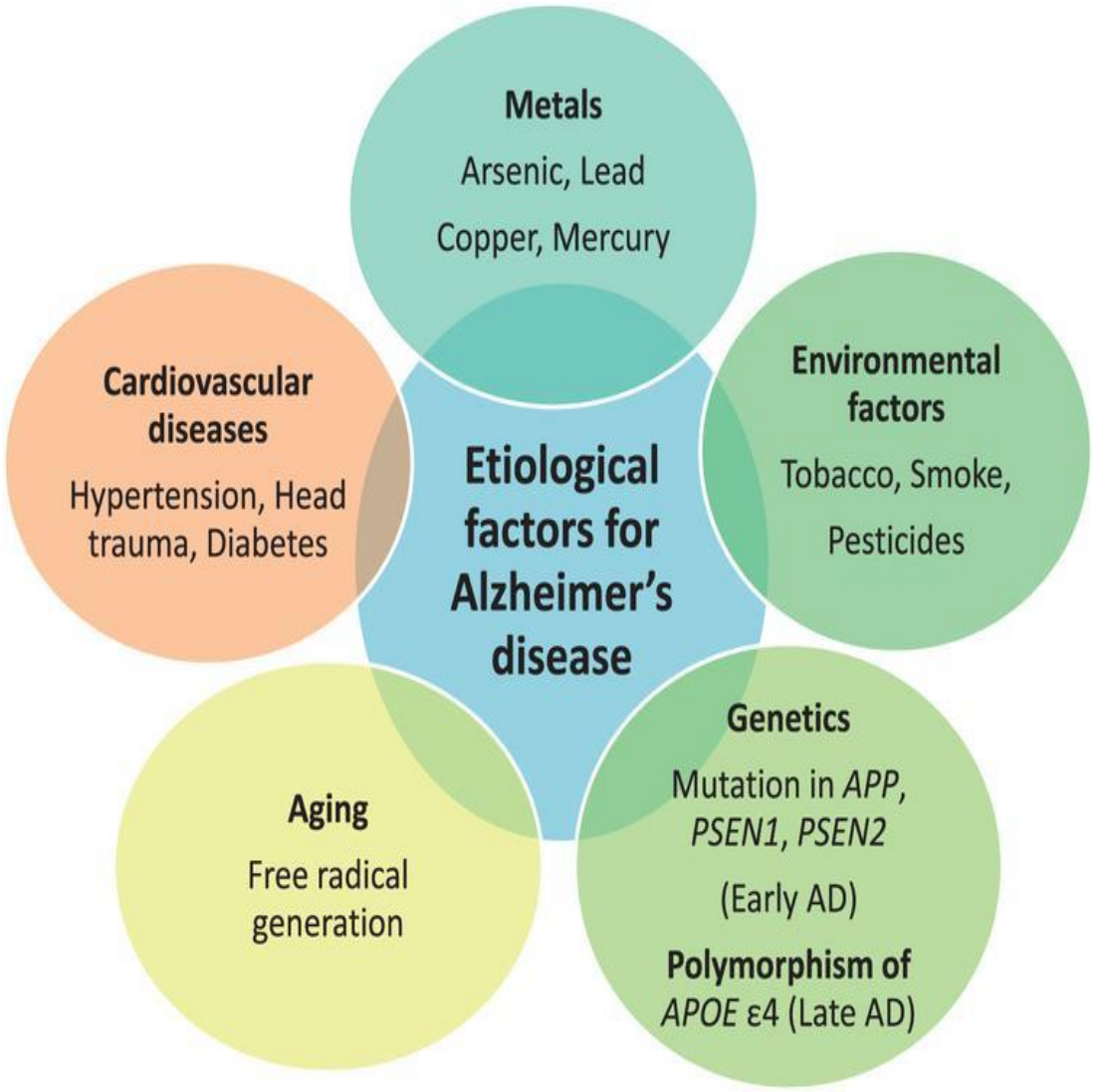
Memory and behavioral impairment

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.*

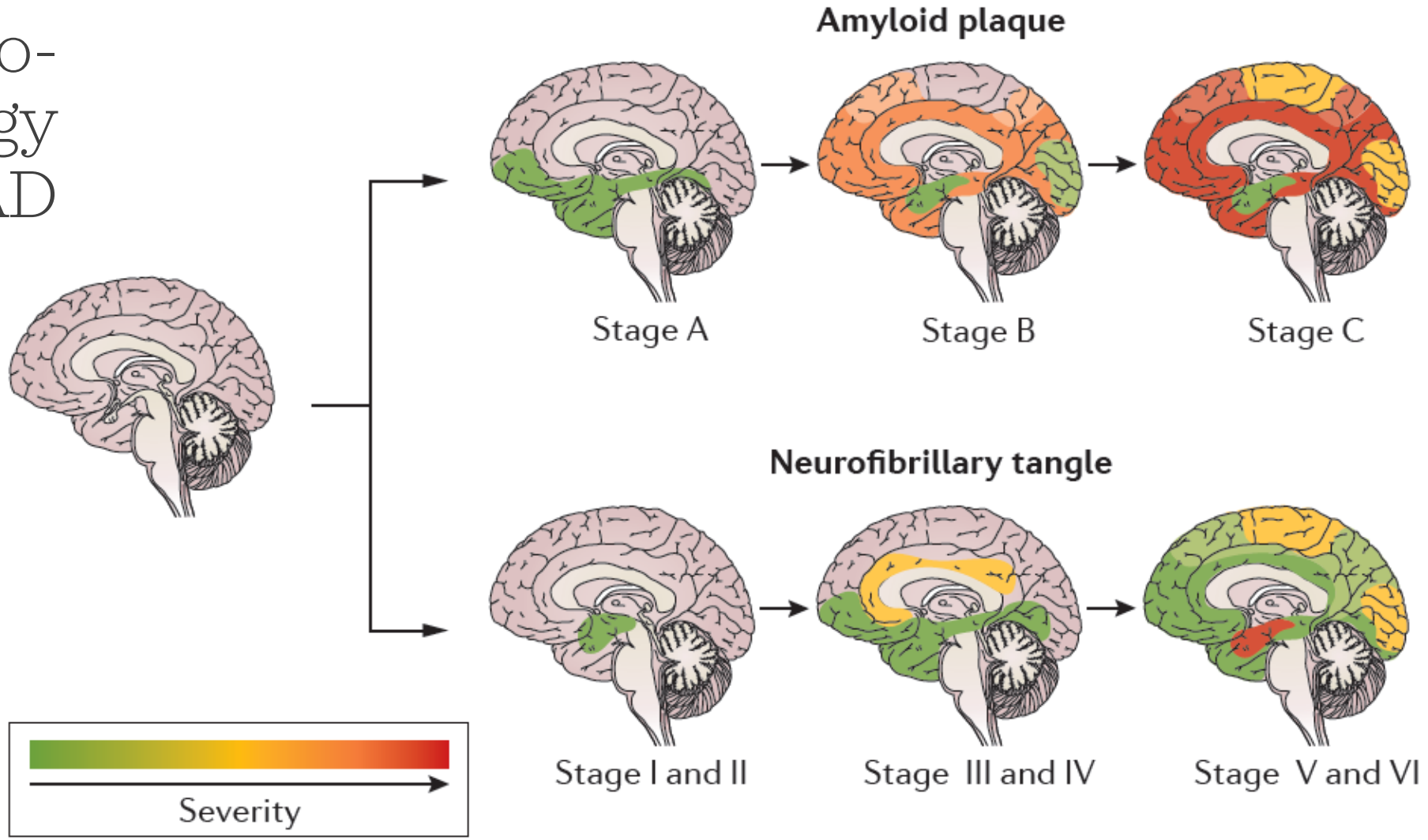


Duggal & Mehan (2019)/DOI 10.3233/ADR-190125

Aetiology of AD

Multifactorial

The neuro-pathology of AD



Masters *et al.* (2015) *Nature Reviwes* 1

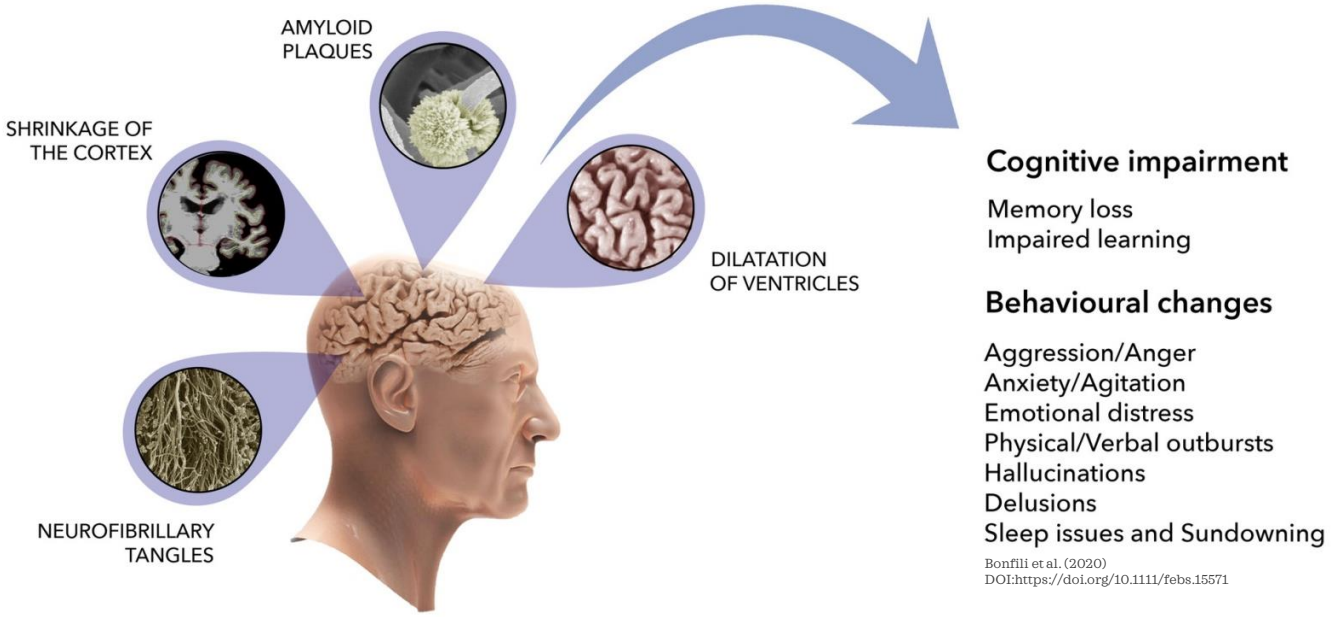
Cerebral modifications in AD

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 histopathologival hallmarks:

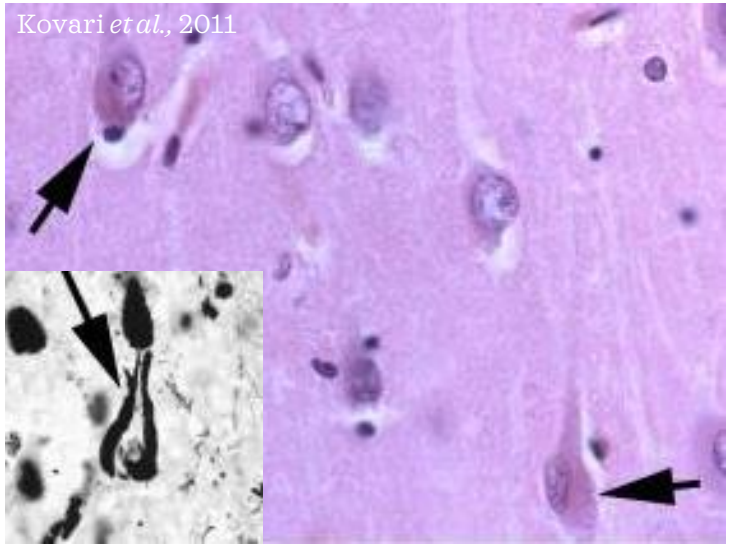
- intraneuronal neurofibrillary tangles
- extracellular amyloid beta plaques



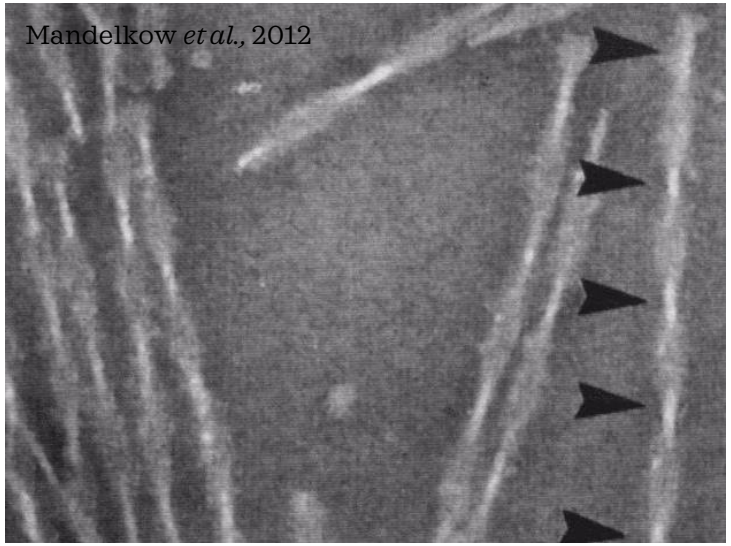
Bonfili et al. (2020)
DOI:https://doi.org/10.1111/febs.15571

Histopathology: neurofibrillary tangles

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



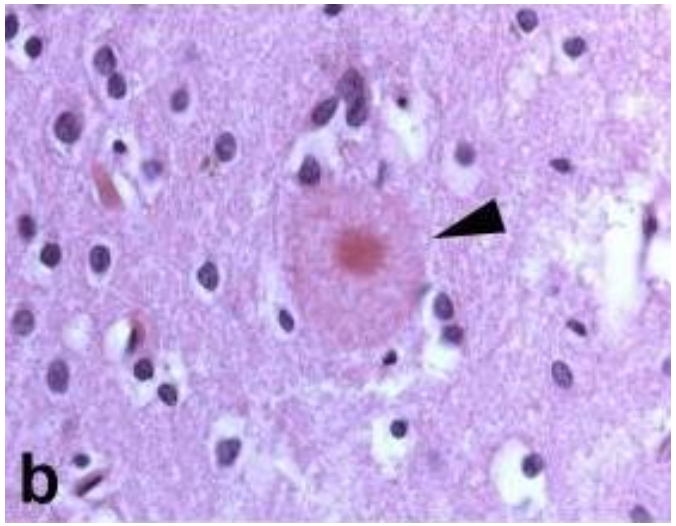
Haemotoxylin/Eosin staining



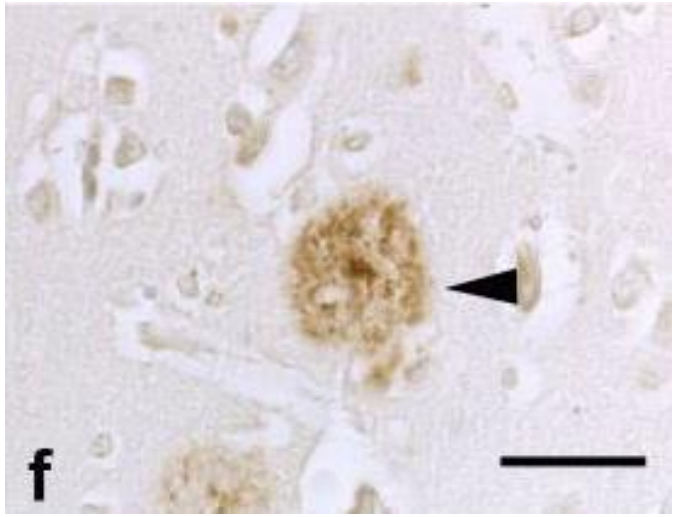
Pairs of helical filaments

Histopathology: senile plaques

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

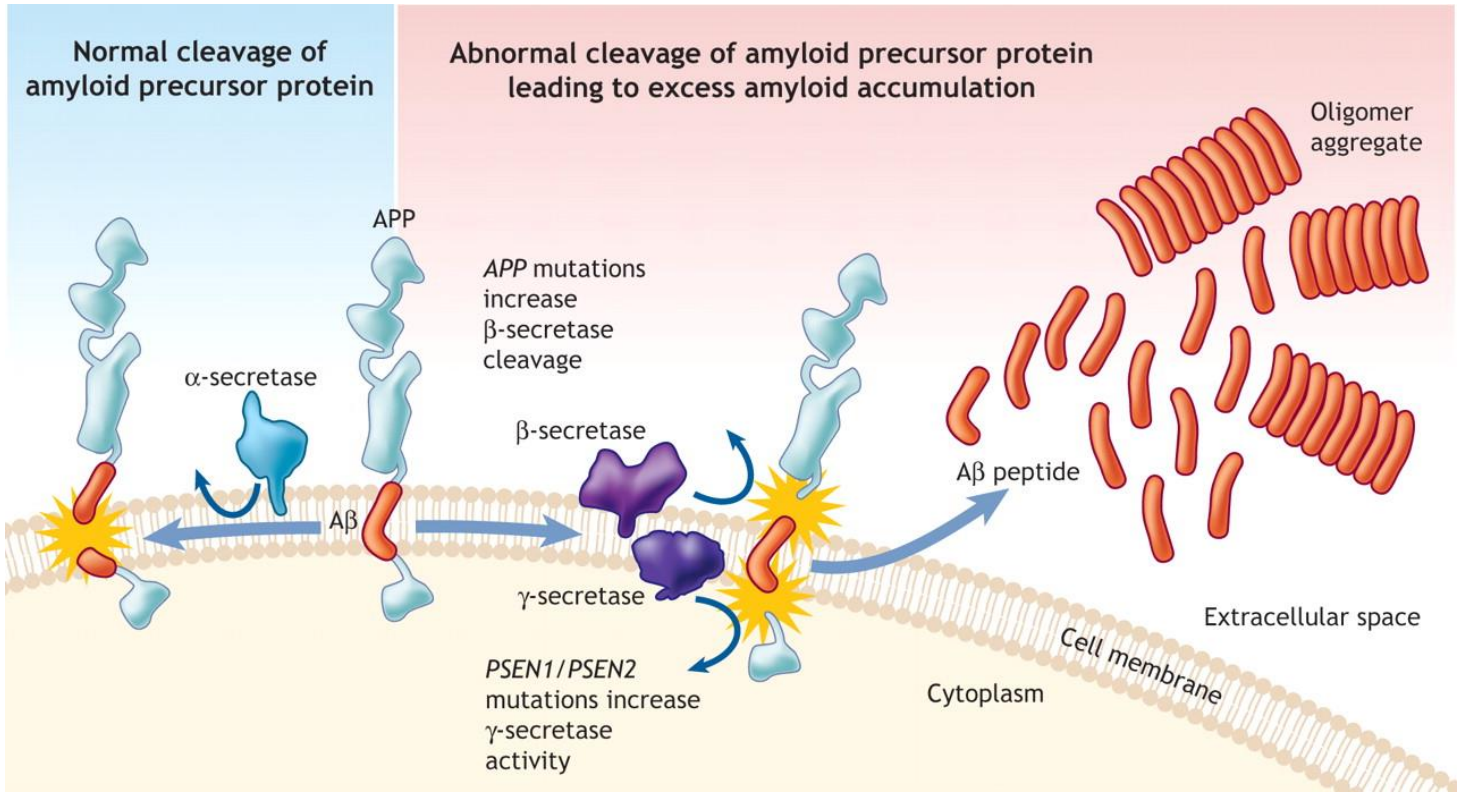


Haematoxylin/Eosin staining



Anti-**Aβ** immunostaining

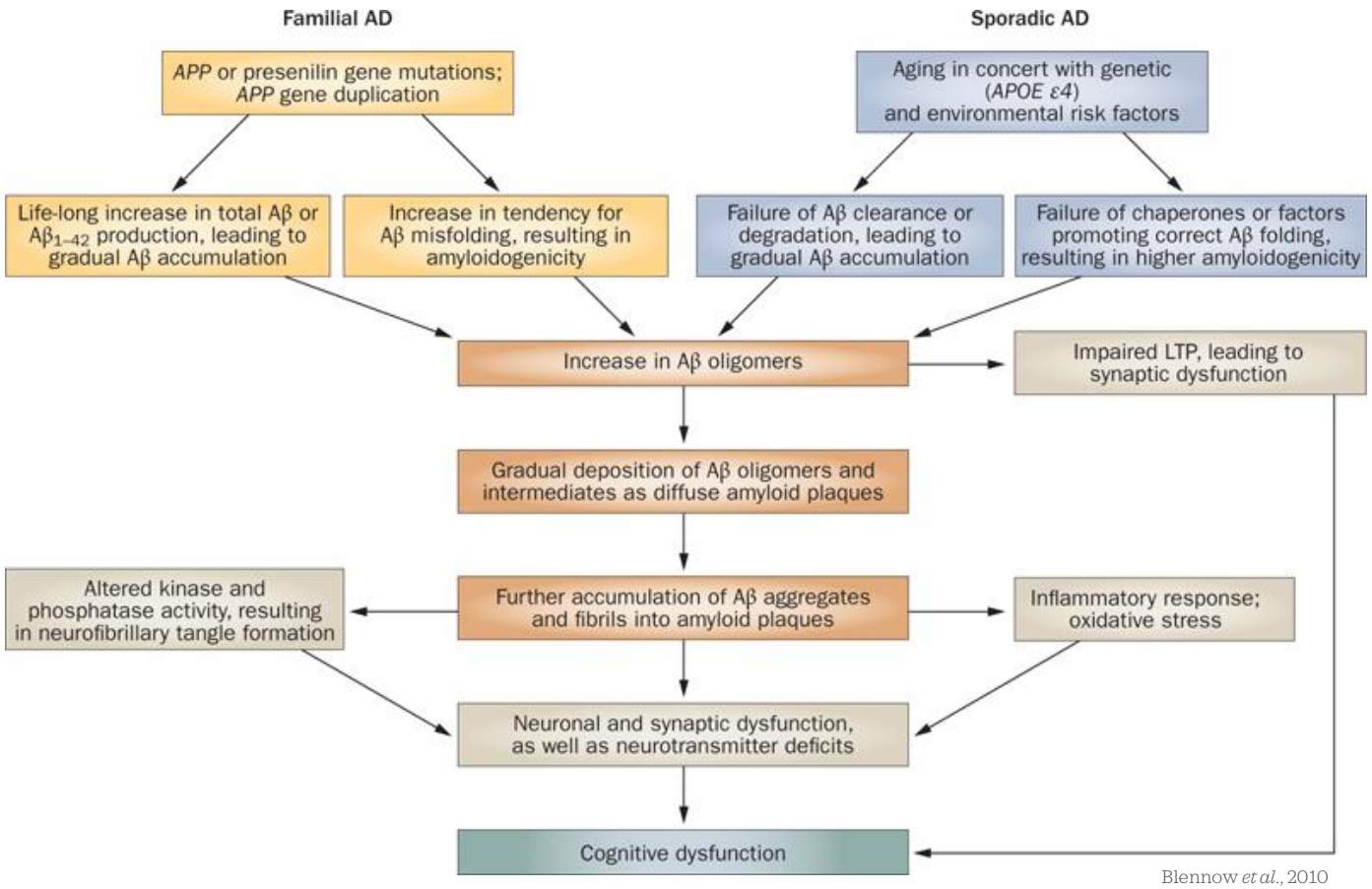
Kovari *et al.*, 2011



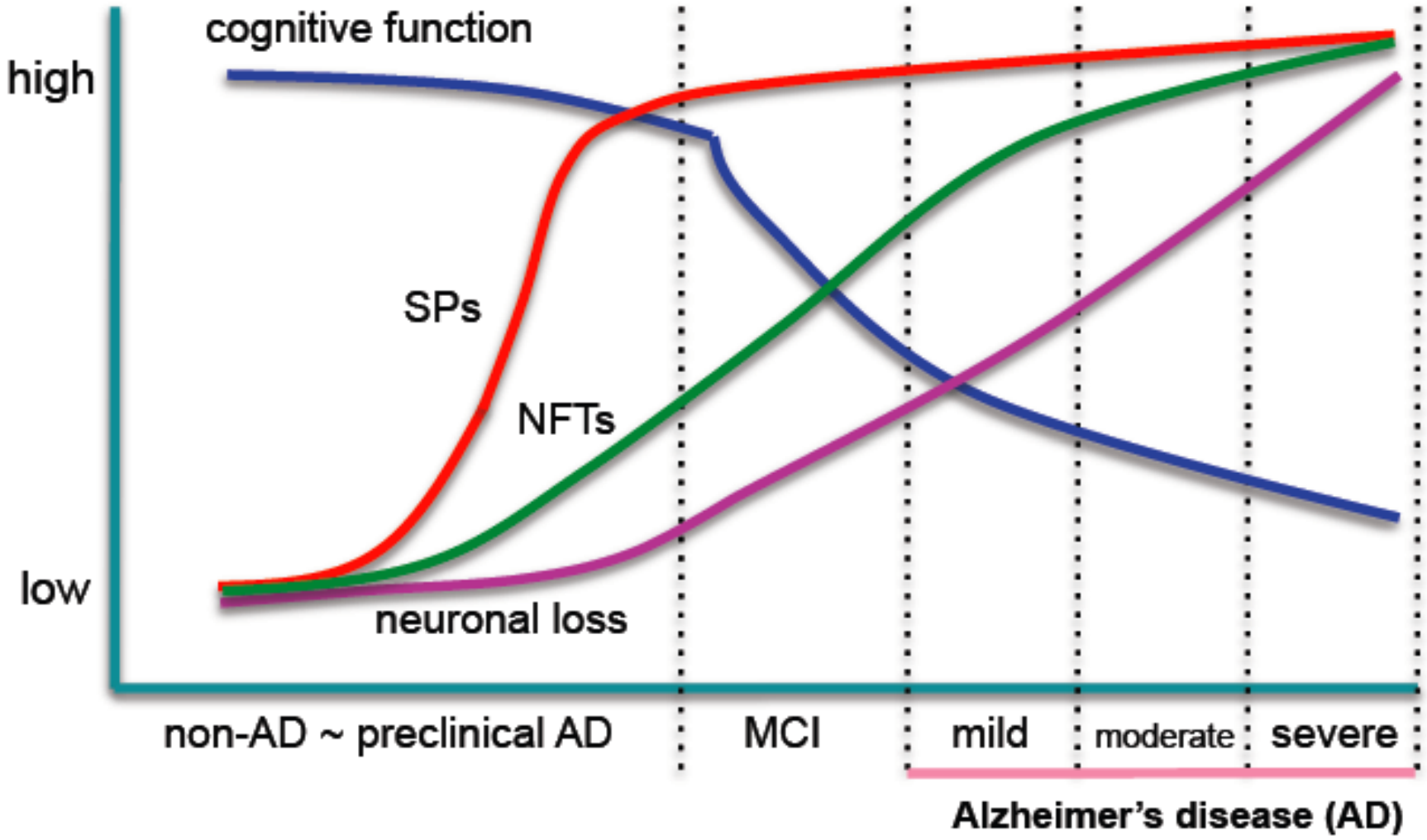
Patterson *et al.* (2008) *CMAJ* 178

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

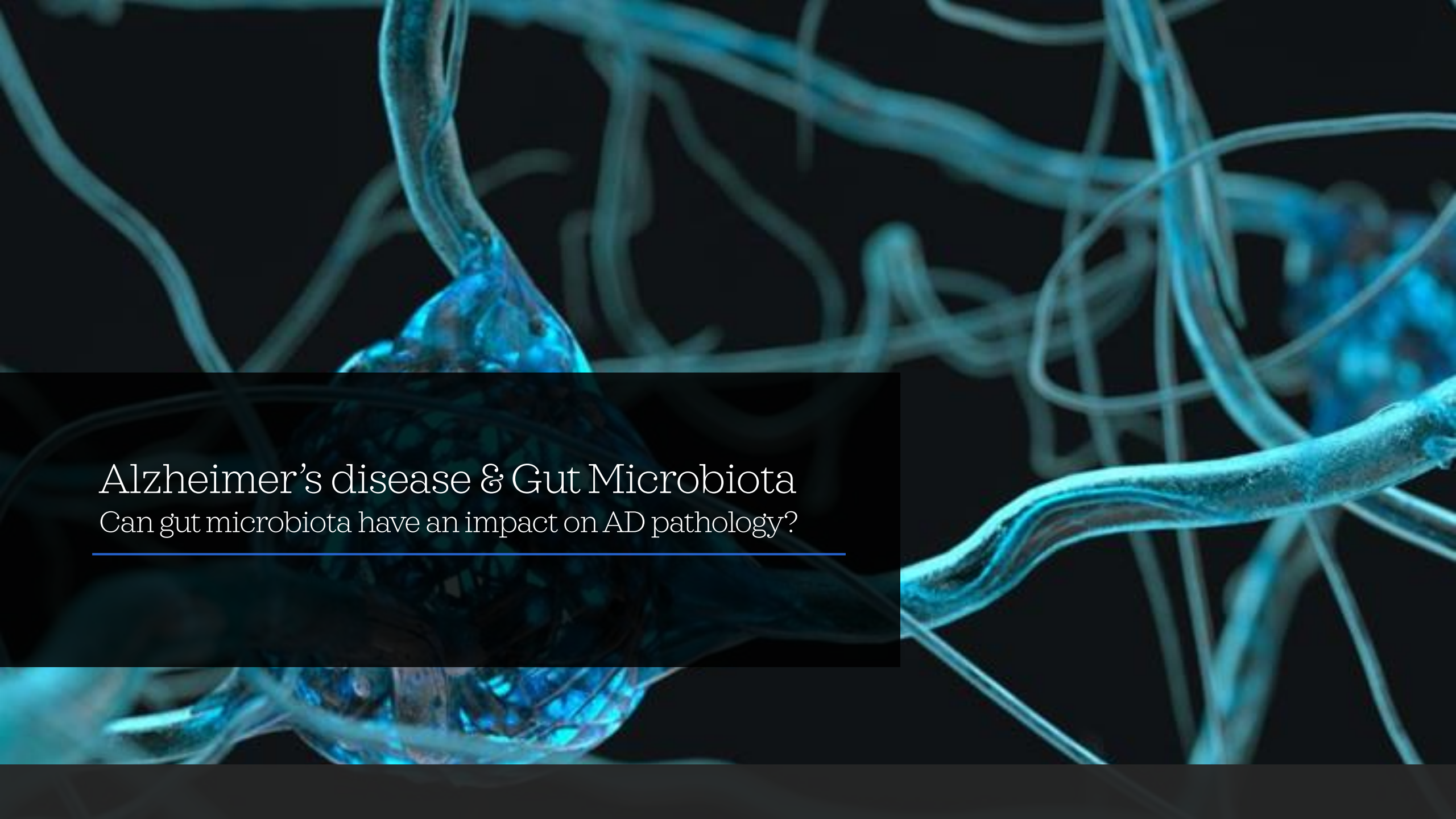
The Amyloid Cascade Hypothesis



Blennow *et al.*, 2010


cognitive function
high
low
SPs
NFTs
neuronal loss
non-AD ~ preclinical AD
MCI
mild
moderate
severe
Alzheimer's disease (AD)

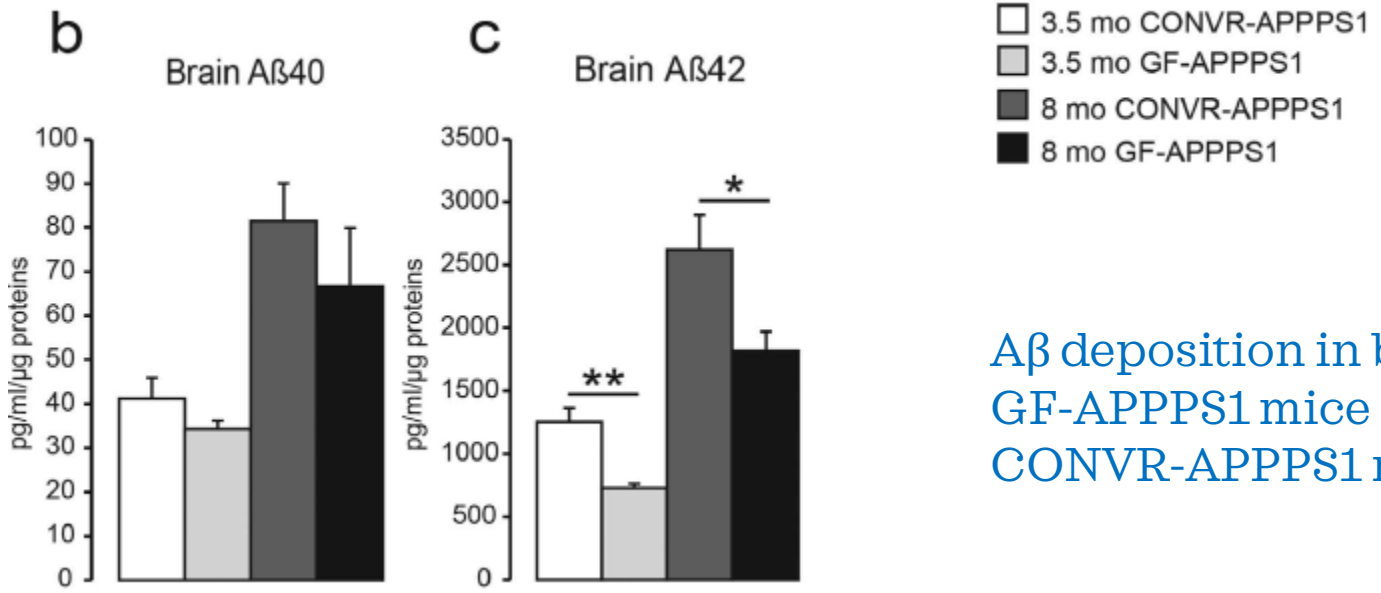
Chiba, 2013



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

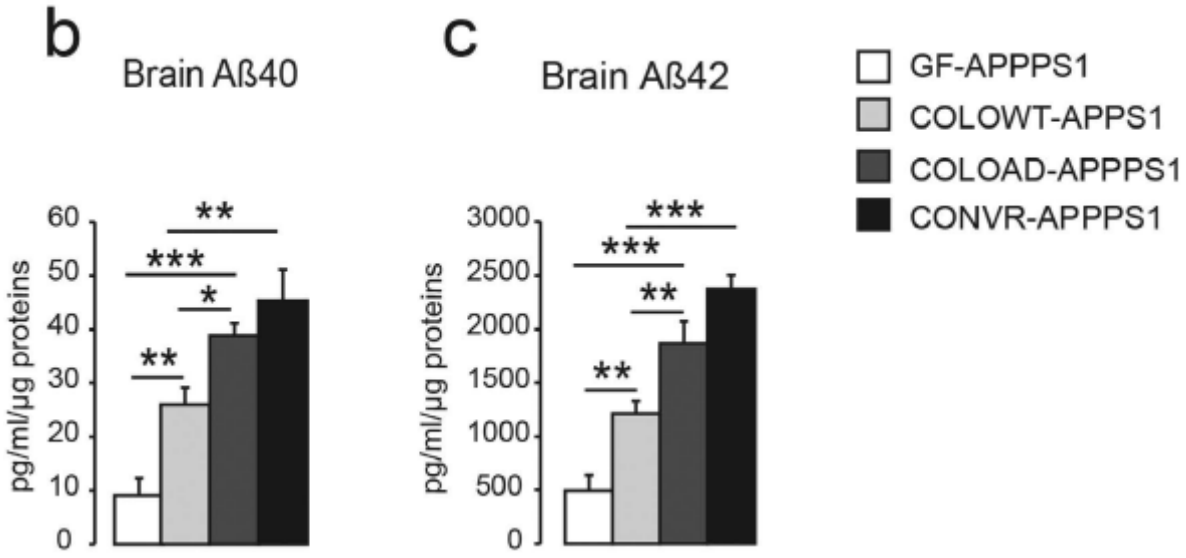


Aβ deposition in brain is reduced in GF-APPPS1 mice compared to CONVR-APPPS1 mice

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

Harach *et al.* (2017) *Scientific Reports* **7**, DOI: 10.1038/srep41802

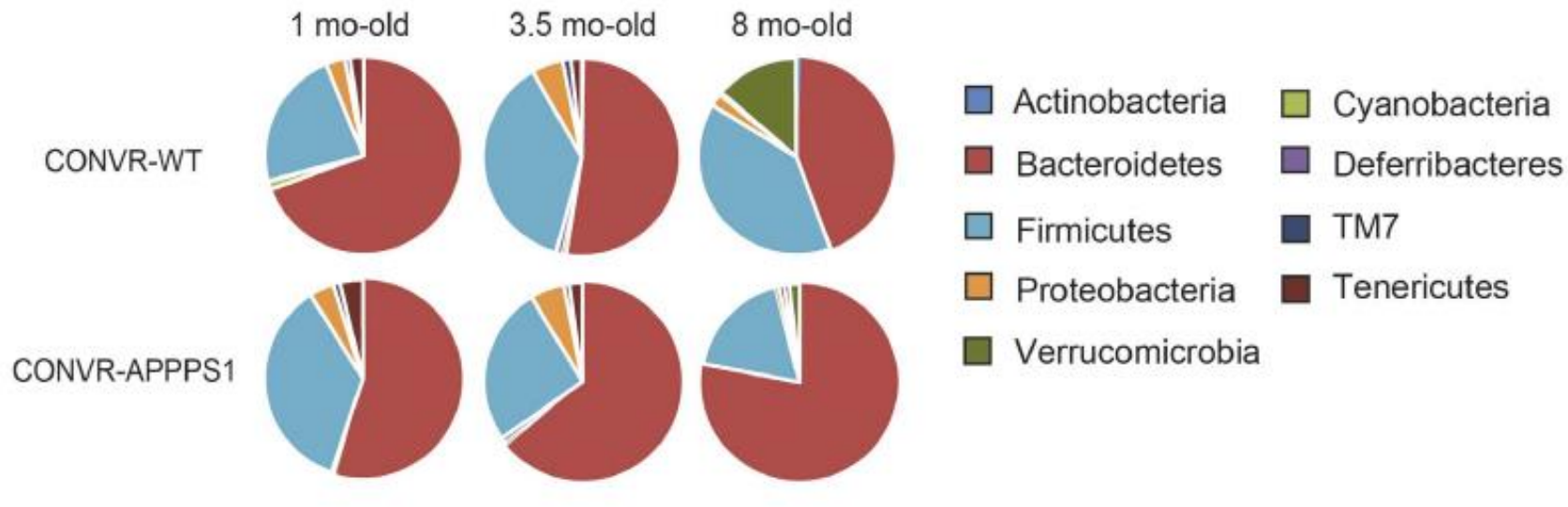
Can gut microbiota have an impact on AD pathology?
Feacal microbiota transplantation to GF



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)

Harach *et al.* (2017) *Scientific Reports* **7**, DOI: 10.1038/srep41802

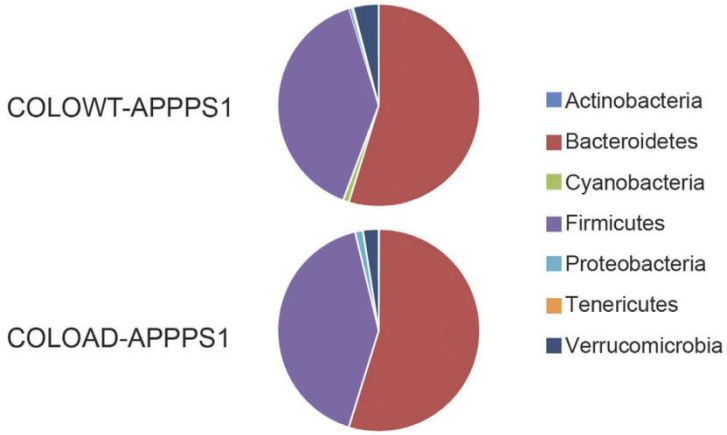
The composition of the gut microbiota of APP/PS1 mice differ substantially from the corresponding one of wt mice



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

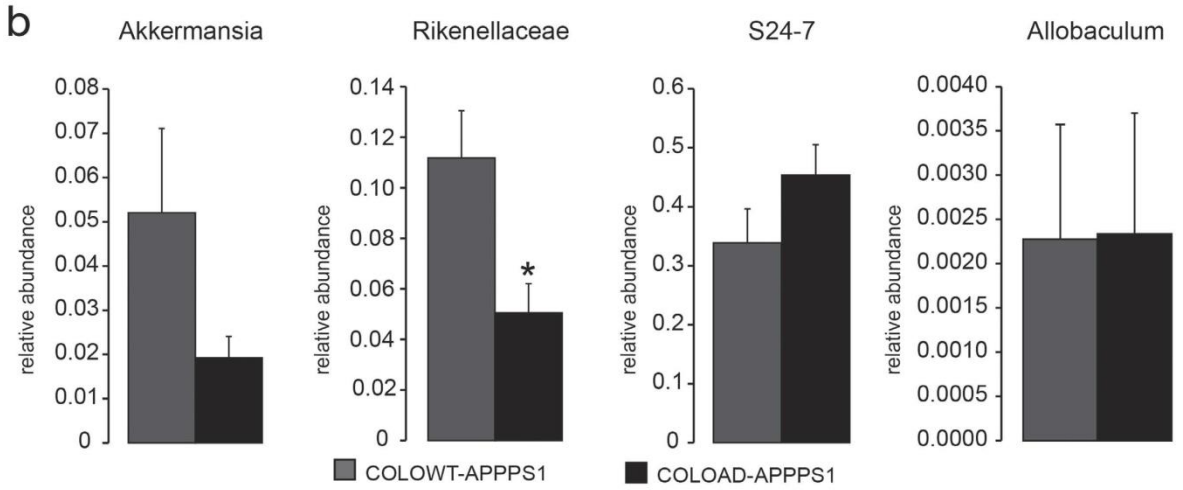
Harach *et al.* (2017) *Scientific Reports* **7**, DOI: 10.1038/srep41802

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



- Akkermansia (genus)(*Verrucomicrobia)*
- Rikenellaceae (genus) (*Bacteriodetes*)
- S24-7 (genus) (*Bacteriodetes*)
- Allobaculum (genus) (*Firmicutes*)

6wks after colonization

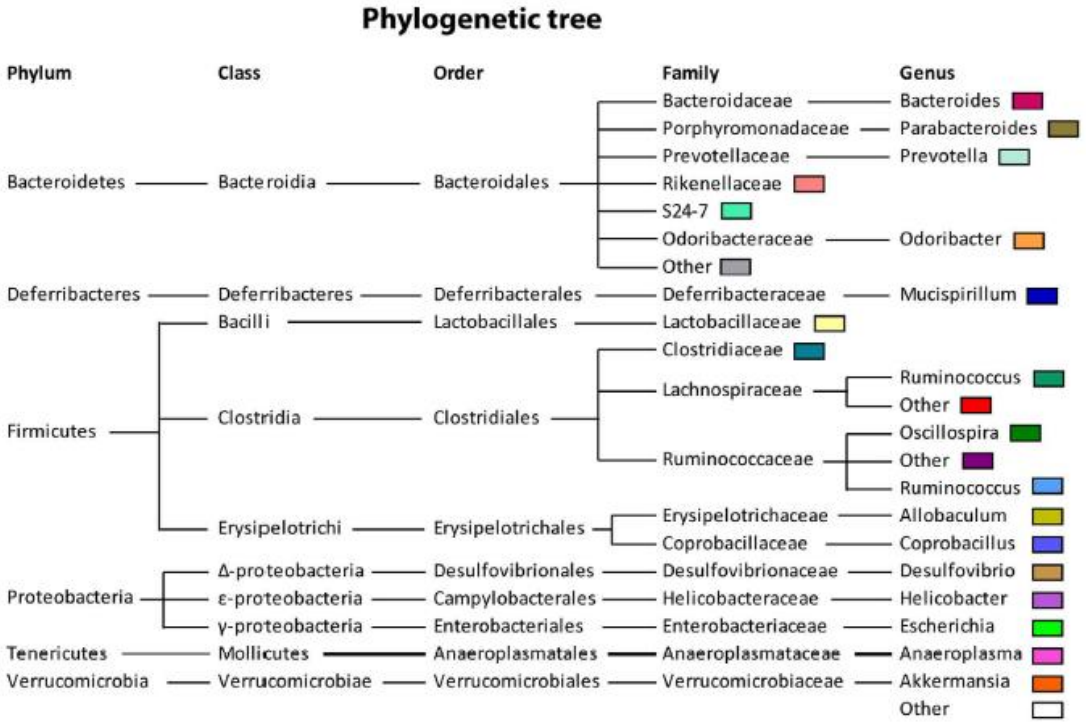


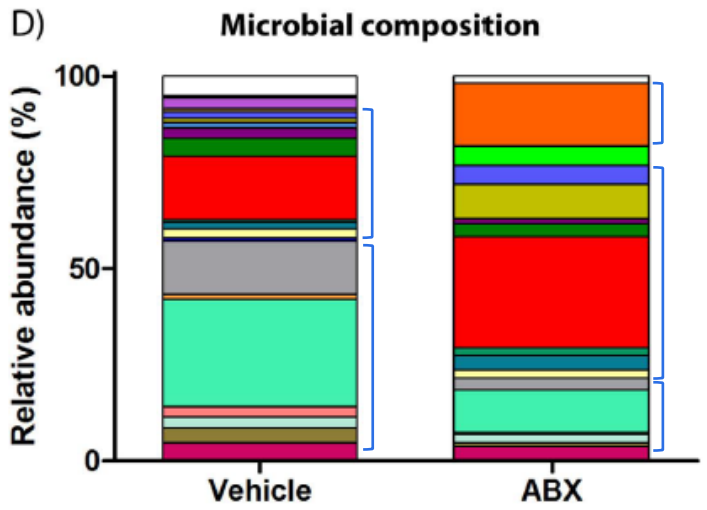
Harach *et al.* (2017) *Scientific Reports* 7, DOI: 10.1038/srep41802

Can gut microbiota have an impact on AD pathology?

Antibiotic-altered composition of gut microbiota (1)

- Animal model: $APP_{SWE}/PS1_{\Delta E9}$
- 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



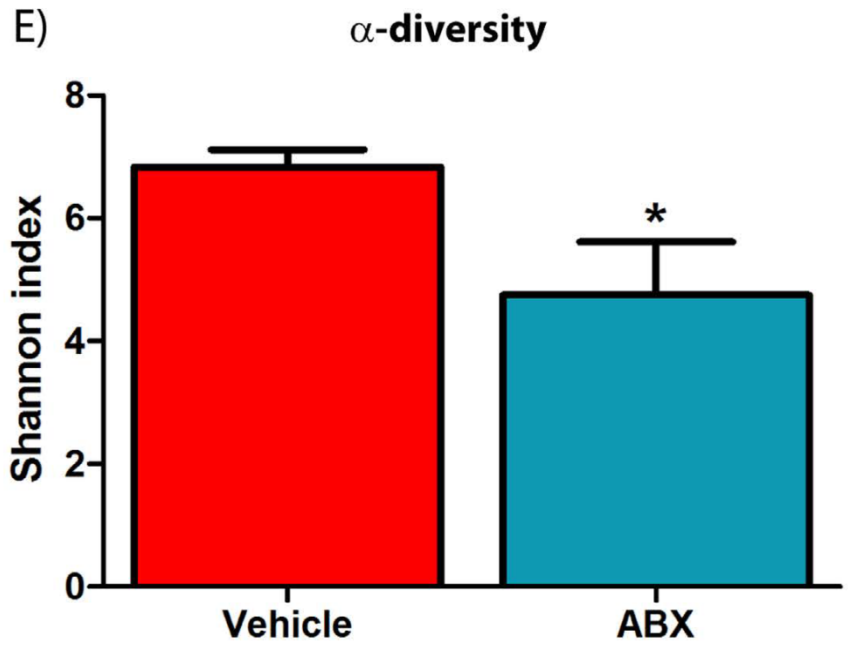


6 month old mice

Minter *et al.* (2016) *Scientific Reports* 6 DOI: 10.1038/srep30028

Can gut microbiota have an impact on AD pathology?

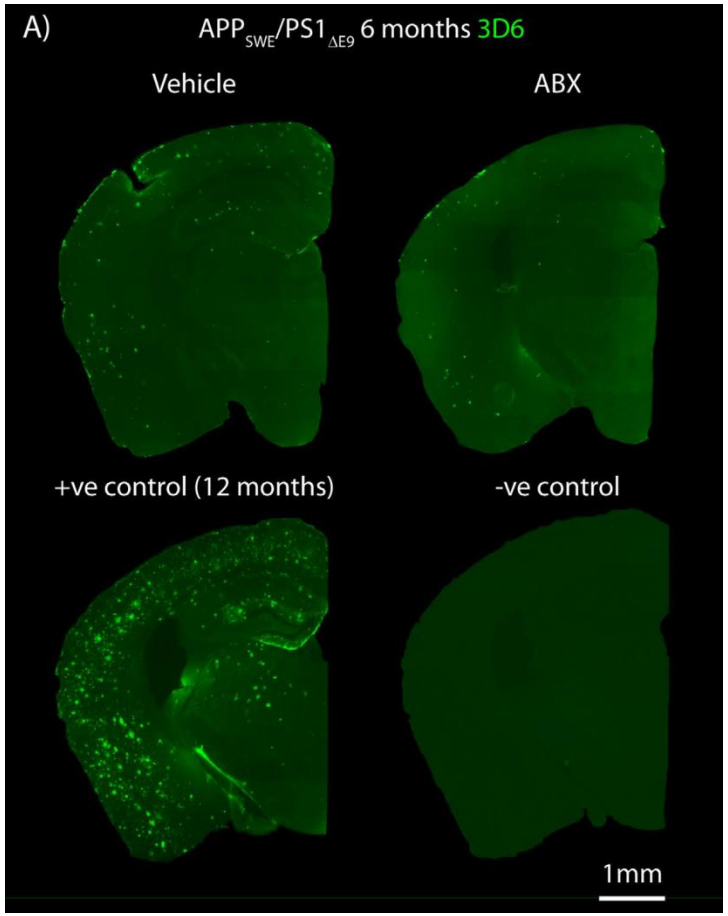
Antibiotic-altered composition of gut microbiota (2)

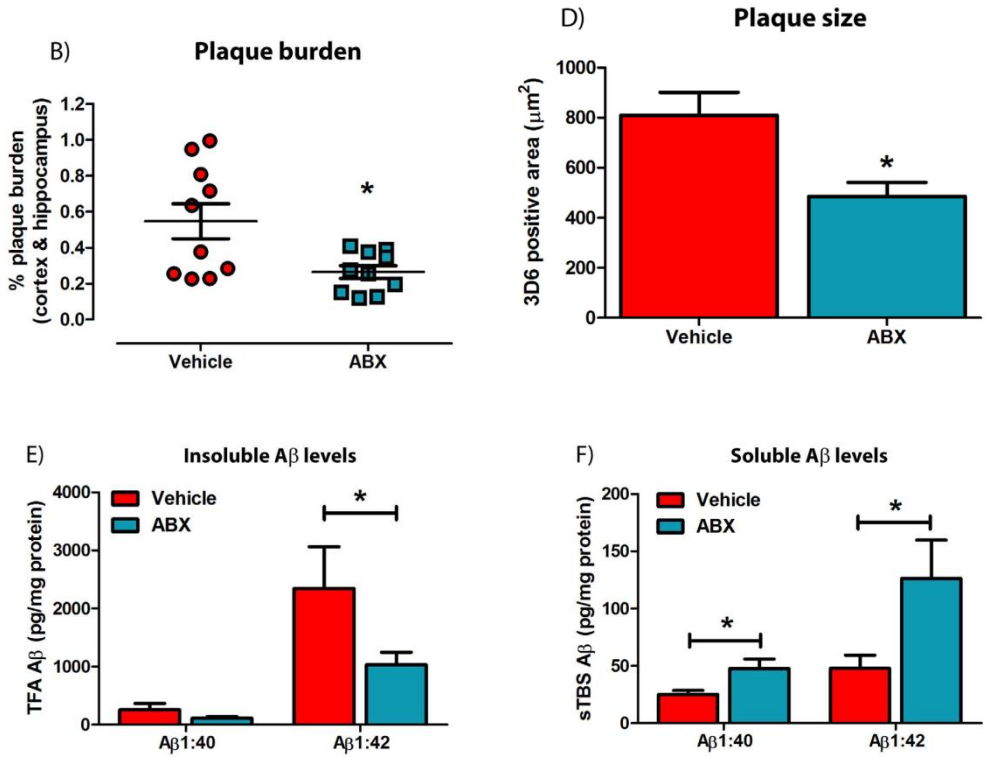


- Significant decrease in microbial diversification ABX-treated mice

Can gut microbiota have an impact on AD pathology?

Antibiotic-altered composition of gut microbiota (3)



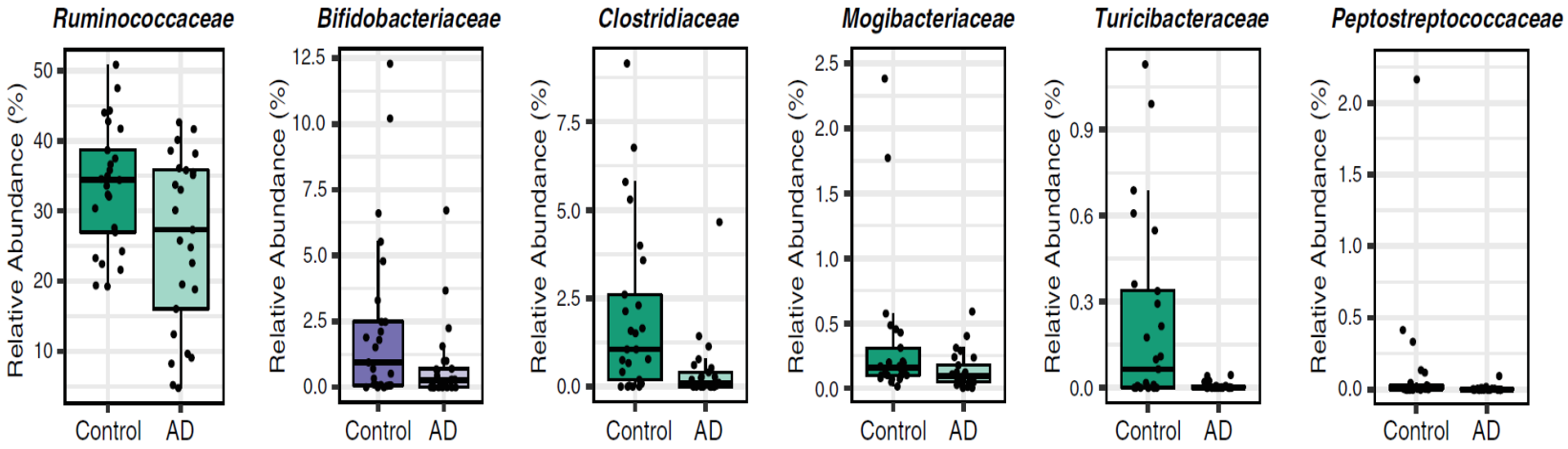


- Reduced amyloid deposition/reduced number of amyloid plaques in ABX-treated mice
- Increased levels of soluble Aβ in ABX-treated mice

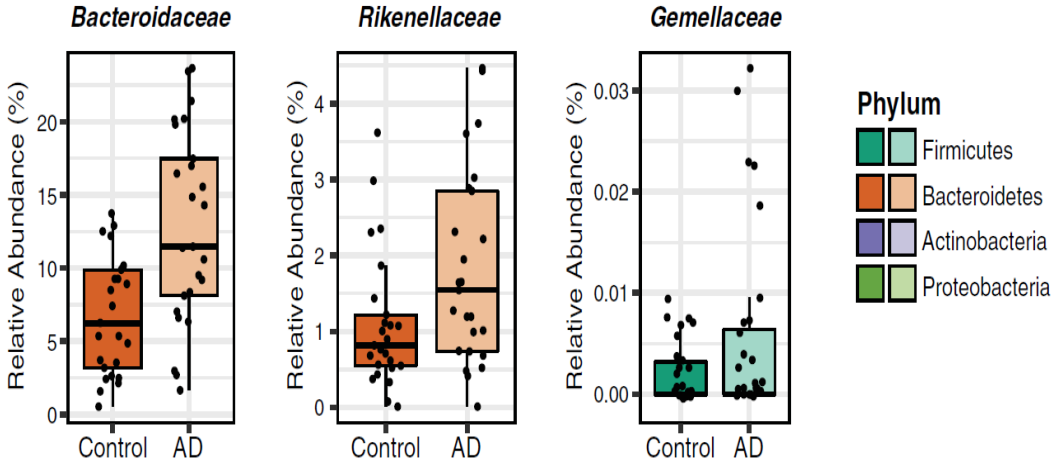
Altered gut microbiome in AD patients (1)

Increase in pro-inflammtory microbes

Families less abundant in AD



Families more abundant in AD

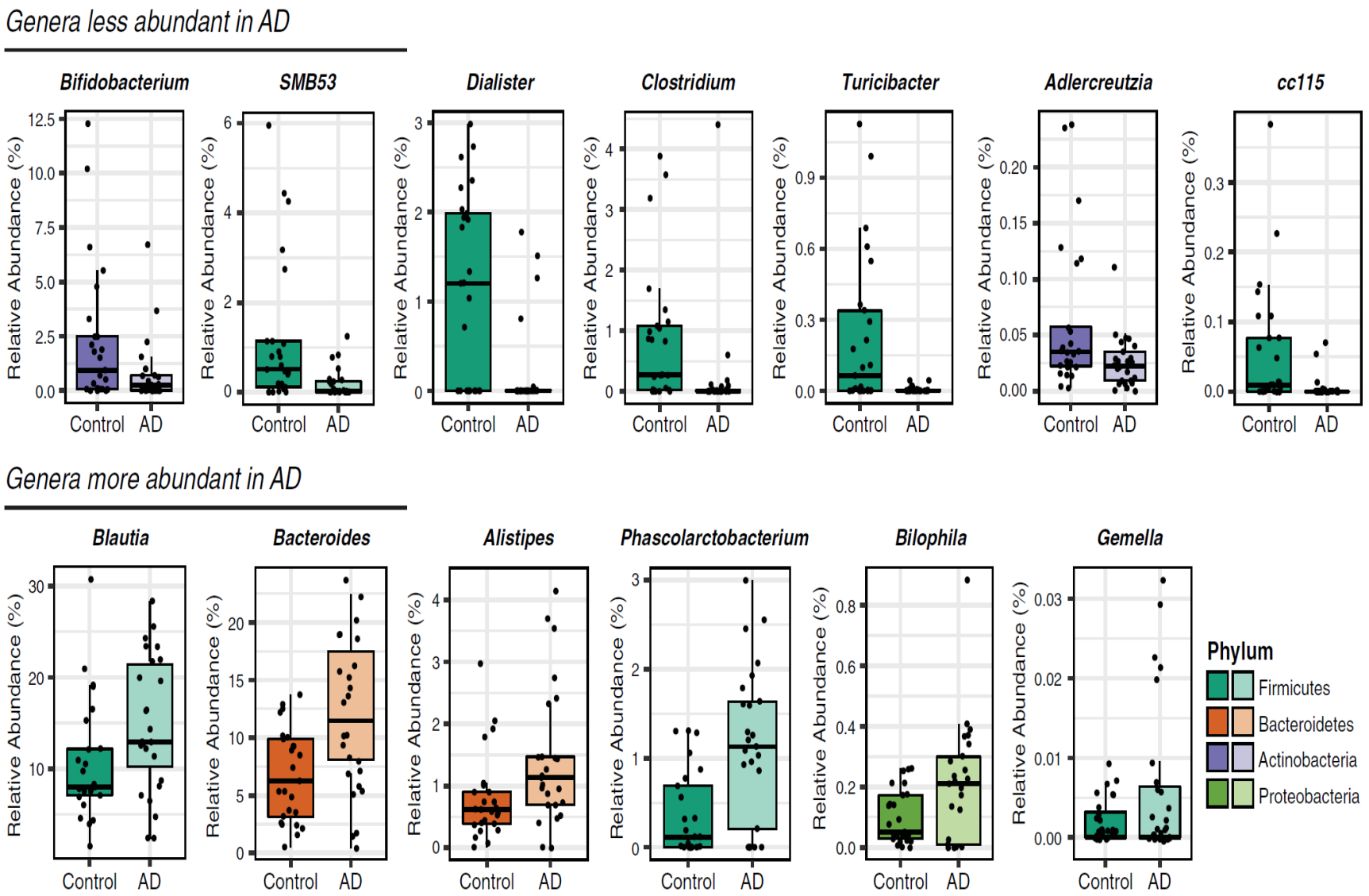


	Control	AD
n	25	25
Age (yrs, mean ± SD)	69.3 ± 7.5	71.3 ± 7.3
Sex (% Female)	72% (18/25)	68% (17/25)
Clinical dementia rating (CDR) score		
0–normal	100% (25/25)	0
0.5–very mild dementia		40% (10/25)
1–mild dementia		36% (9/25)
2–moderate dementia		24% (6/25)
APOE ε4 genotype	20% (5/25)	72% (18/25)
Ethnicity (% 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]

Vogt *et al.* (2017) *Scientific Reports* **7** DOI:10.1038/s41598-017-13601-y

Altered gut microbiome in AD patients (2)

Increase in pro-inflammtory microbes



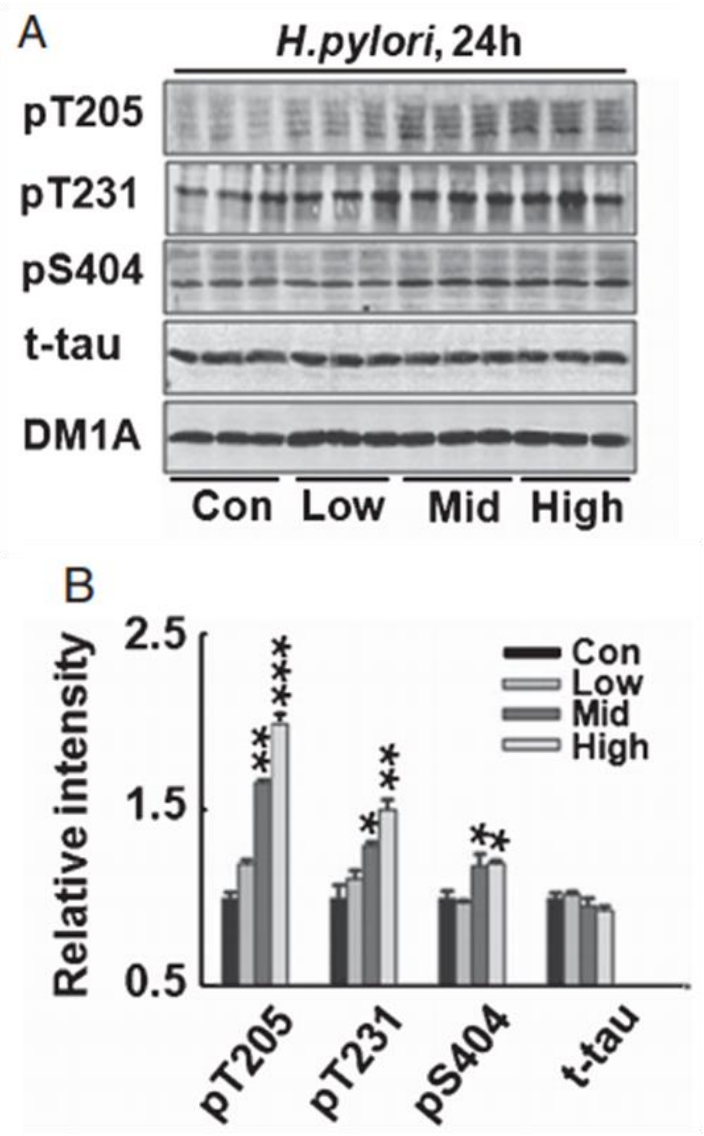
Vogt *et al.* (2017) *Scientific Reports* **7** DOI:10.1038/s41598-017-13601-y

Clinical studies in AD patients' microbiota

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



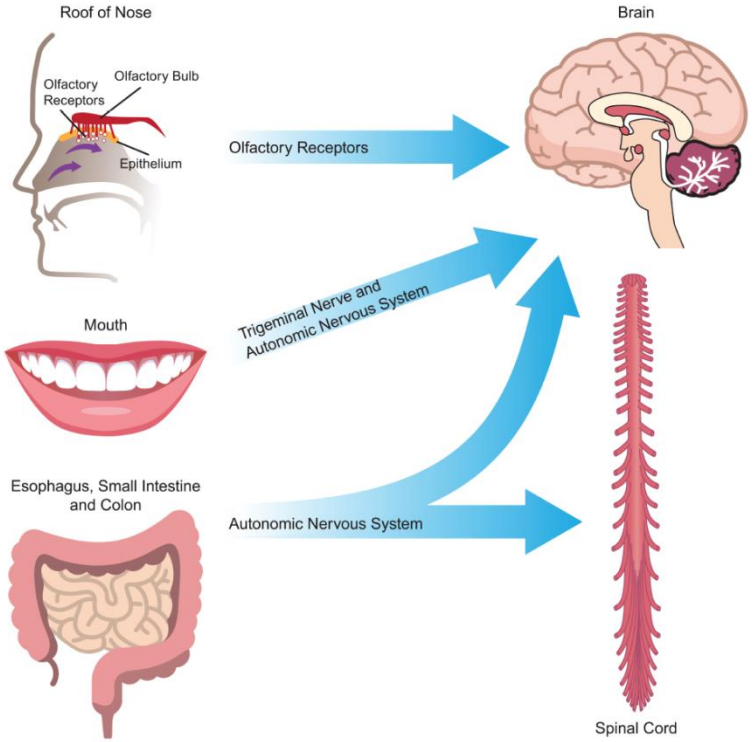
Wang et al. (2015) *J Alzheimer's Dis* **43:** 153–165

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 (Aβ, α-synuclein, tau)



Friedland & Chapman (2017) *PLoS Pathog* **13:** e1006654. https://doi.org/10.1371/journal.ppat.1006654

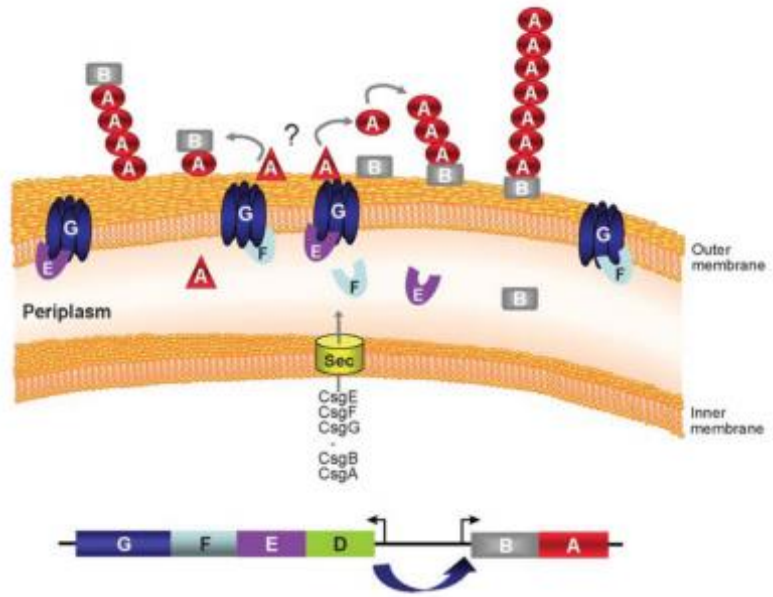
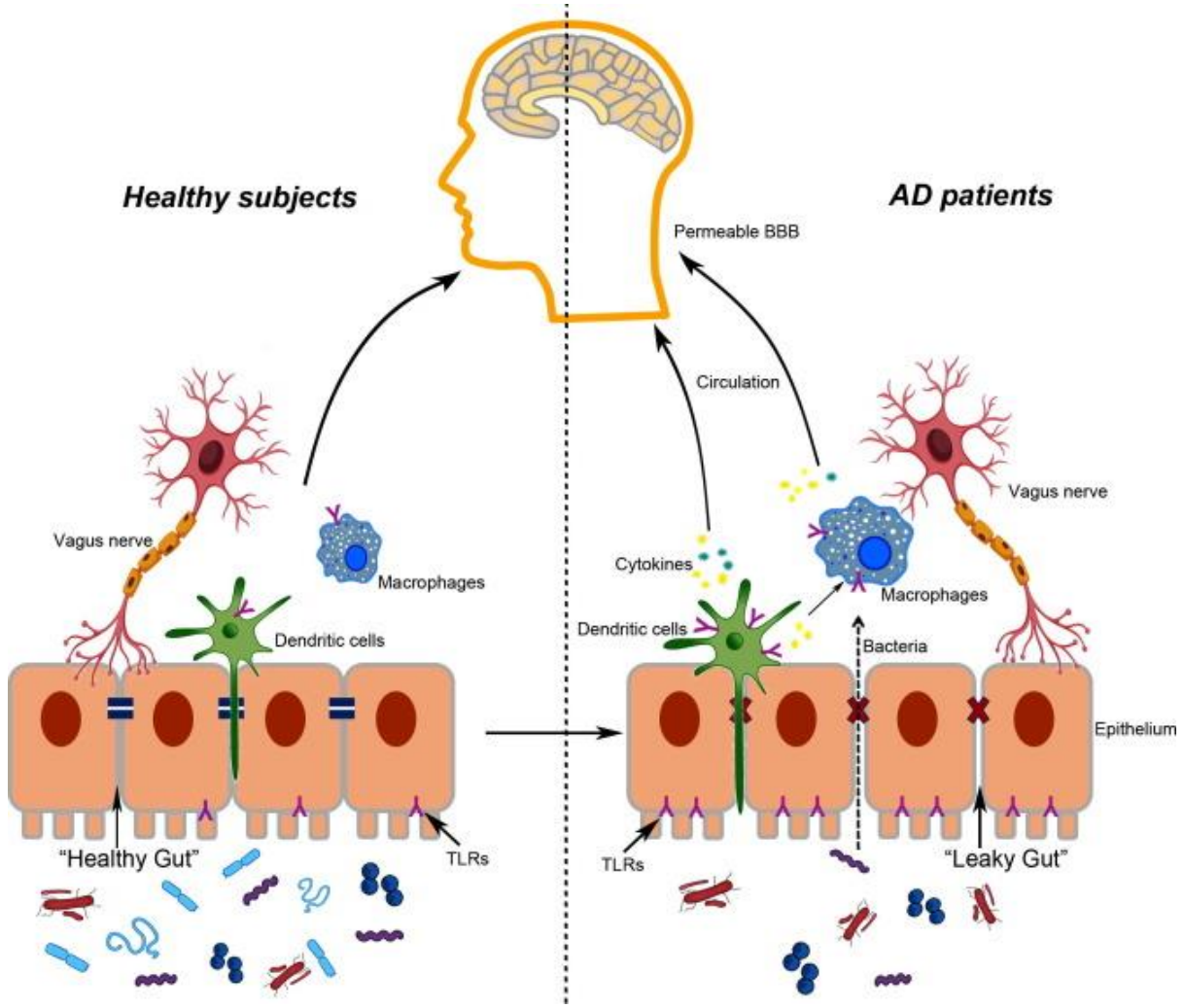


Figure 1. Model of curli assembly

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.

Bacterial amyloids (2)

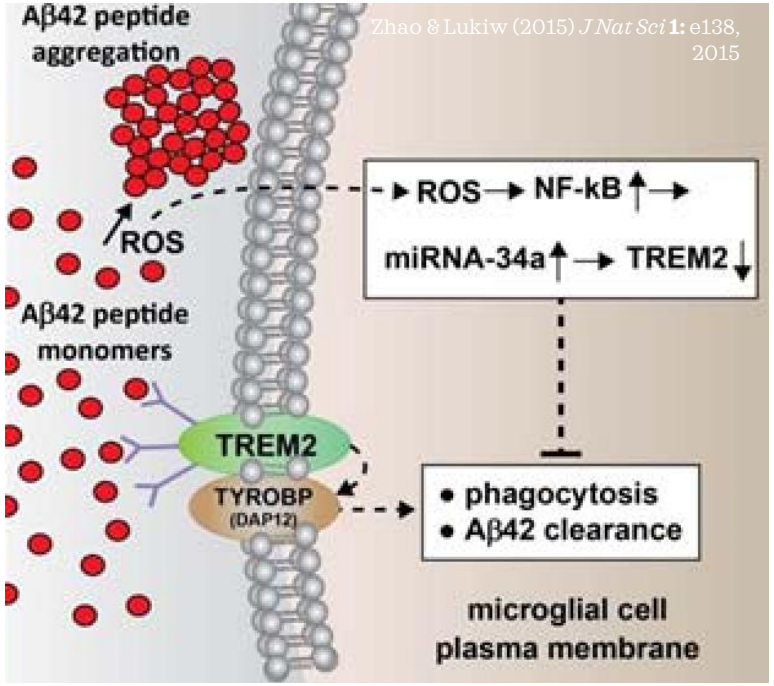
- Bacterial amyloids recognized as PAMPs (pathogen associated molecular patterns), *e.g.* the Curli subunit (CsgA) contains a PAMP that is recognized by human TLR2
- Activation of Toll-like receptor 2 (TLR2)
- TLR2 signaling
- Pro-inflammatory cytokine production (IL-17, IL22)



Lin *et al.* (2017) *Comput Struct Biotech J* **17:** 1309–1317 https://doi.org/10.1016/j.csbj.2019.09.008

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



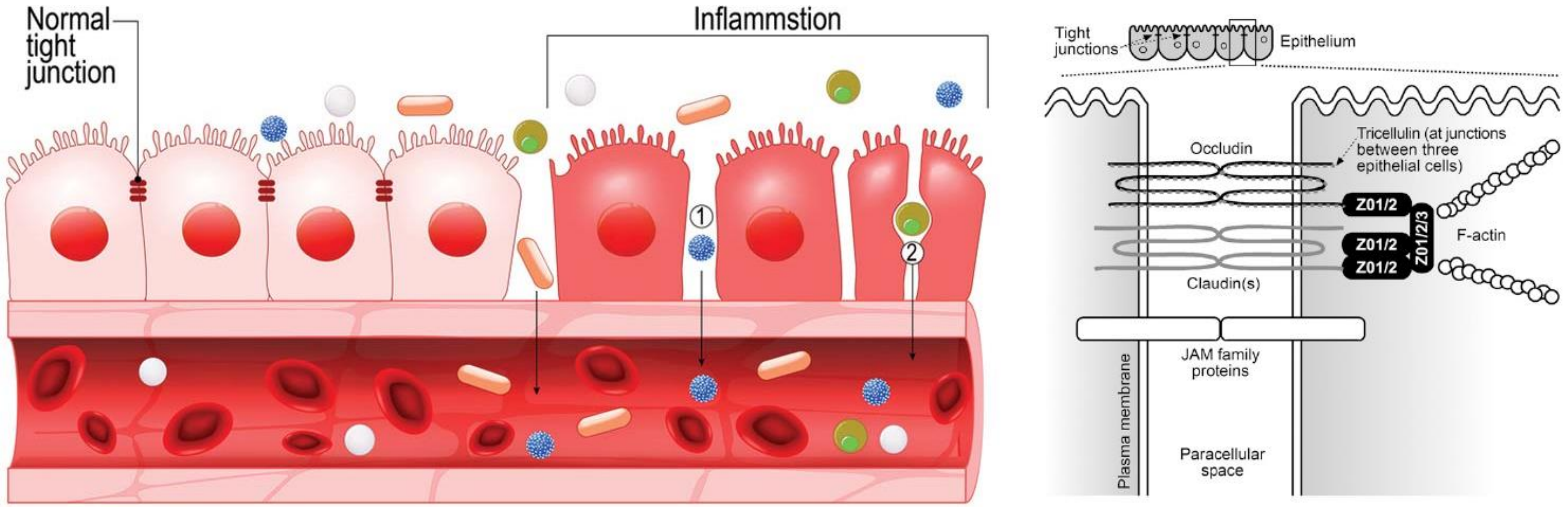
Zhao & Lukiw (2015) *J Nat Sci* **1:** e138, 2015

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 Aβ 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 Aβ in hippocampus region resulting in cognitive defects
- LPS been detected in the hippocampus and cortex brain lysates from AD patients
- LPS co-localizes with Aβ40/42 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

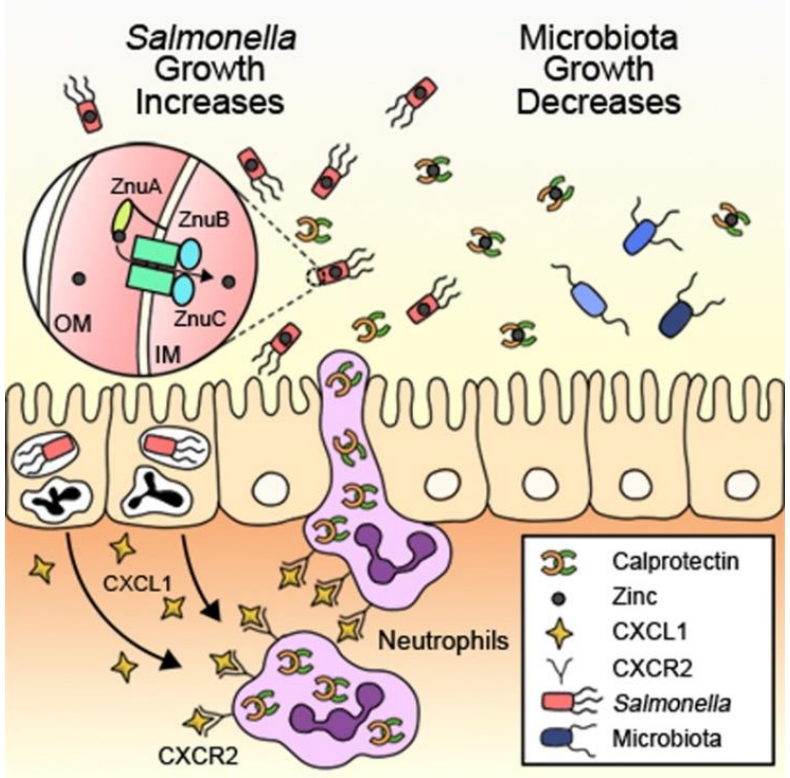
  e.g. Zonula Occludens-1 (ZO-1), Claudin-1, Occludin: keep epithelian cells together

- 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)

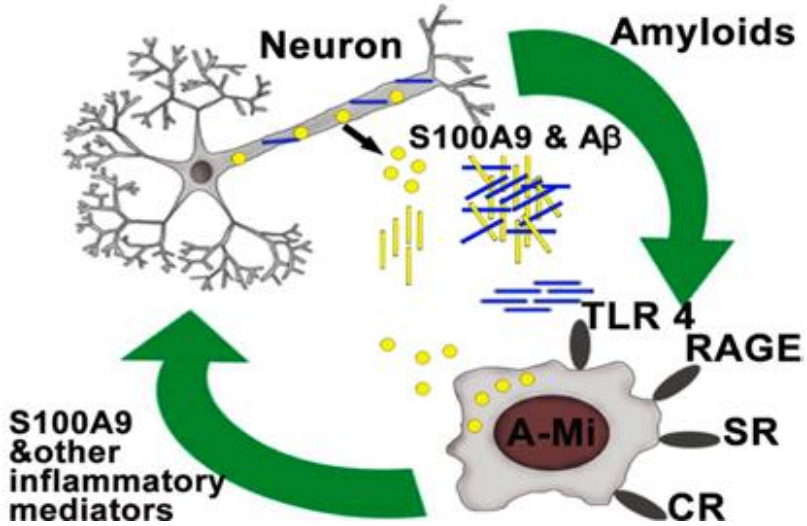
- Intestinal inflammation can be indirectly measured by assessing stool calprotectin concentration
  - small Ca-binding protein
  - a heterodimer: S100A8 (93 a.a.) & S100A9 (113 a.a)
  - S100A8 and S100A9 comprise ~ 60% of the cytosolic proteins in neutrophils
  - possesses antimicrobial properties (bacterial & 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 Aβ 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 Aβ
- Calprotectin levels are significantly increased in the cerebrospinal fluid and the brain of AD patients, which promotes its amyloid aggregation and co-aggregation with Aβ
- Elevated fecal calprotectin levels found in ~ 70% of AD patients/ hypothesized that it could translocate into circulation (via leaky gut) and contribute to neuroinflammation



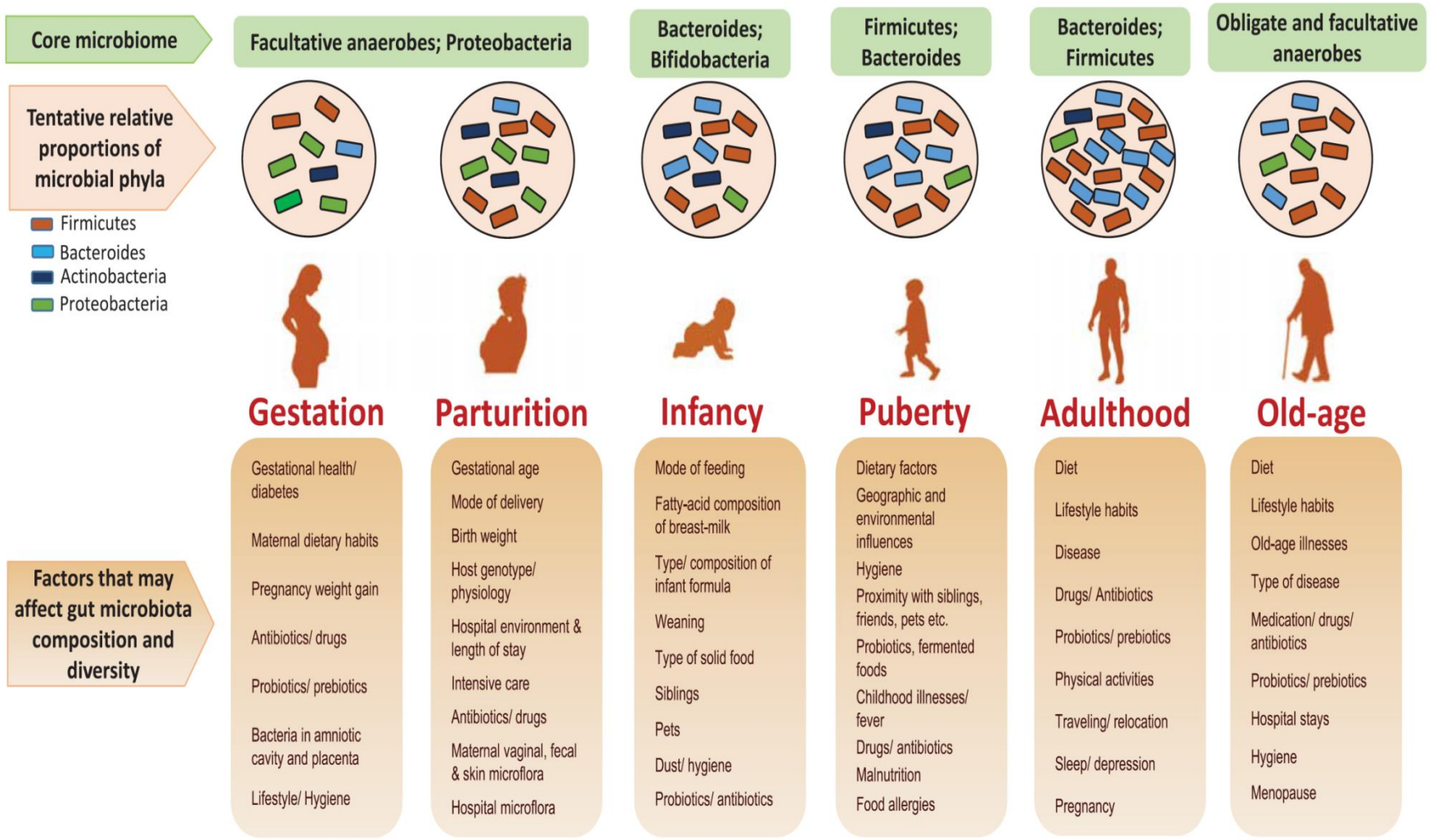
Wang et al. (2014) Acta Neuropathol 127:507–522
DOI 10.1007/s00401-013-1208-4

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



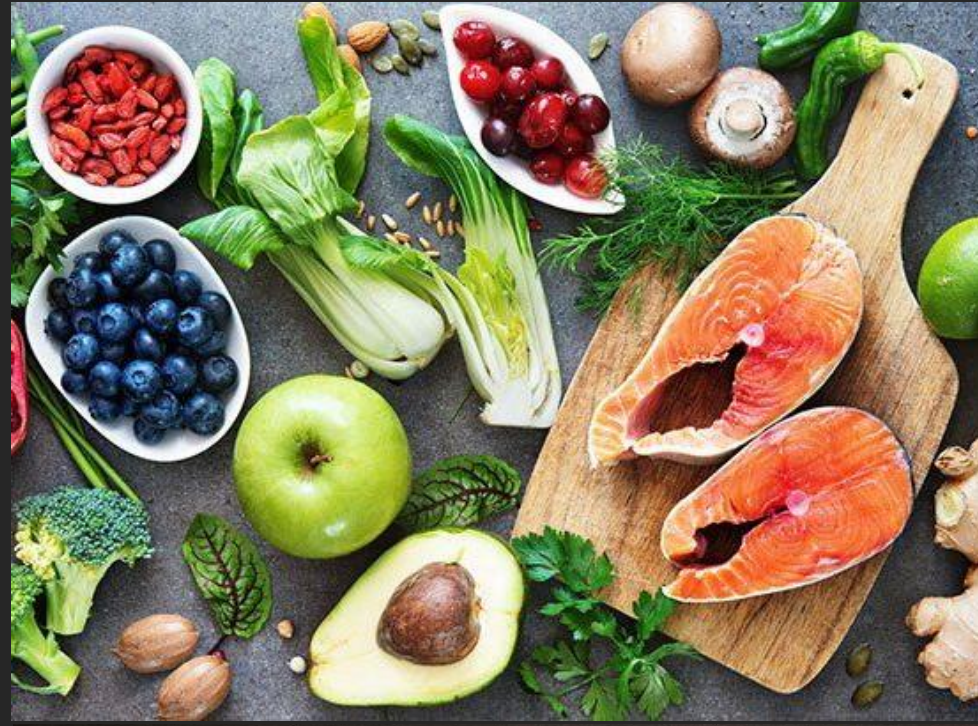
Adapted from Nagpal *et al.* (2018) *Nutr Healthy Aging* **4**:267–285
doi: 10.3233/NHA-170030

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 lederly, improves cognitive function
  - increases in microbiota diversity after 1 year (higher ratio of Firmicutes/Bacteroidetes)

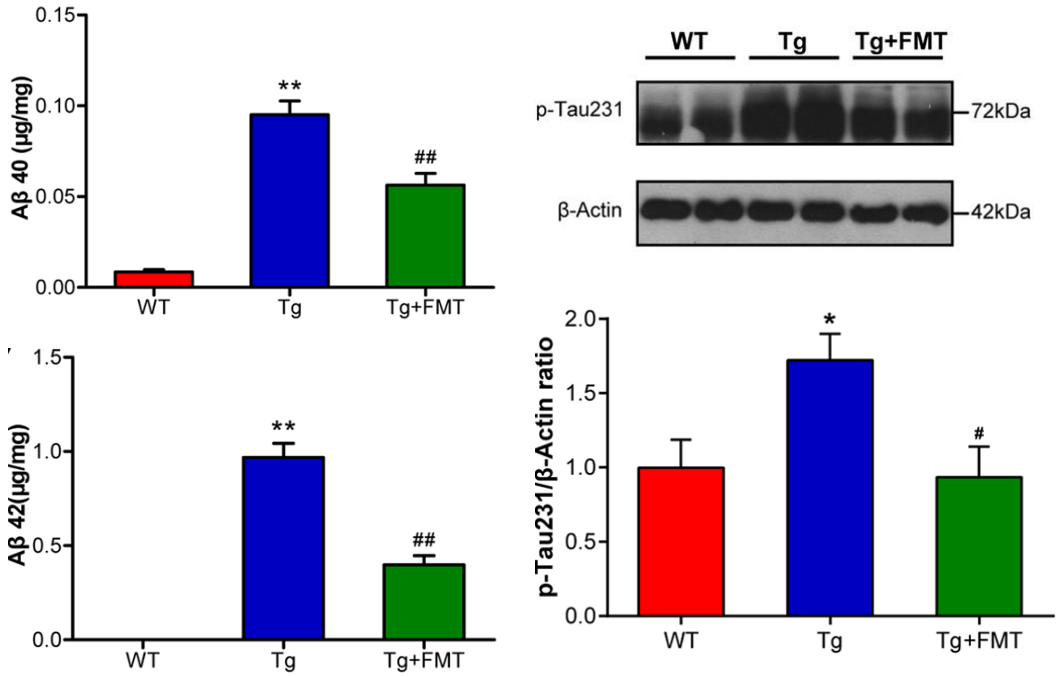
- **Ketogenic (keto) diet**, *i.e.* low carbohydrate, high fat intake, enough protein
  - (in young healthy mice) can modify gut microbiota composition (↑Firmicutes & Actinobacteria, ↓Proteobacteria)
  - preserves cognition in mild cases of AD
  - (followed at an early stage) ↓ risk of AD & ↑ beneficial gut microbiota



Can gut microbiota modulation alleviate AD?

Feacal Microbiota Transplantation (FMT) (1)

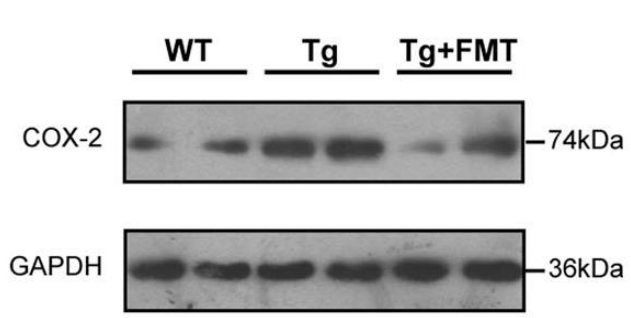
- FMT: transplantation of GI microbiota from a healthy donor to replace/replenish the gut microbiota of an unhealthy individual
- Animal model: $APP_{SWE}/PS1_{\Delta E9}$ (6wks old)
- + FMT group: intragastrically administered with 0.2 ml fresh fecal solution of WT mice once daily for 4 wks
- Control: same dose of physiological saline
- Amelioration of Aβ deposition, τ phosphorylation and cognitive decline

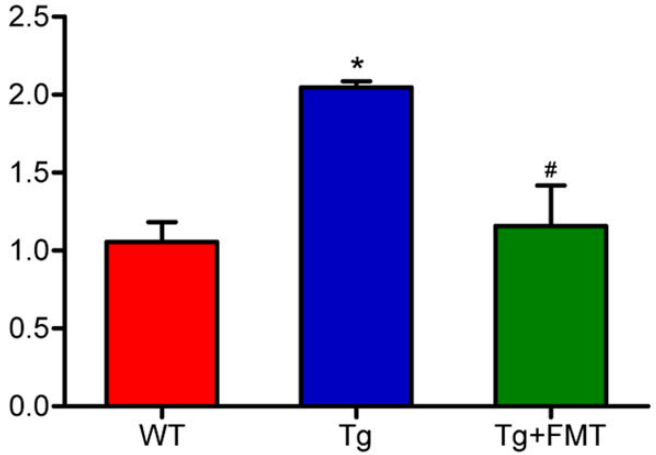


Sun et al. (2019) *Translational Psychiatry* 9:189 DOI:https://doi.org/10.1038/s41398-019-0525-3

Can gut microbiota modulation alleviate AD?

Feacal Microbiota Transplantation (FMT) (2)





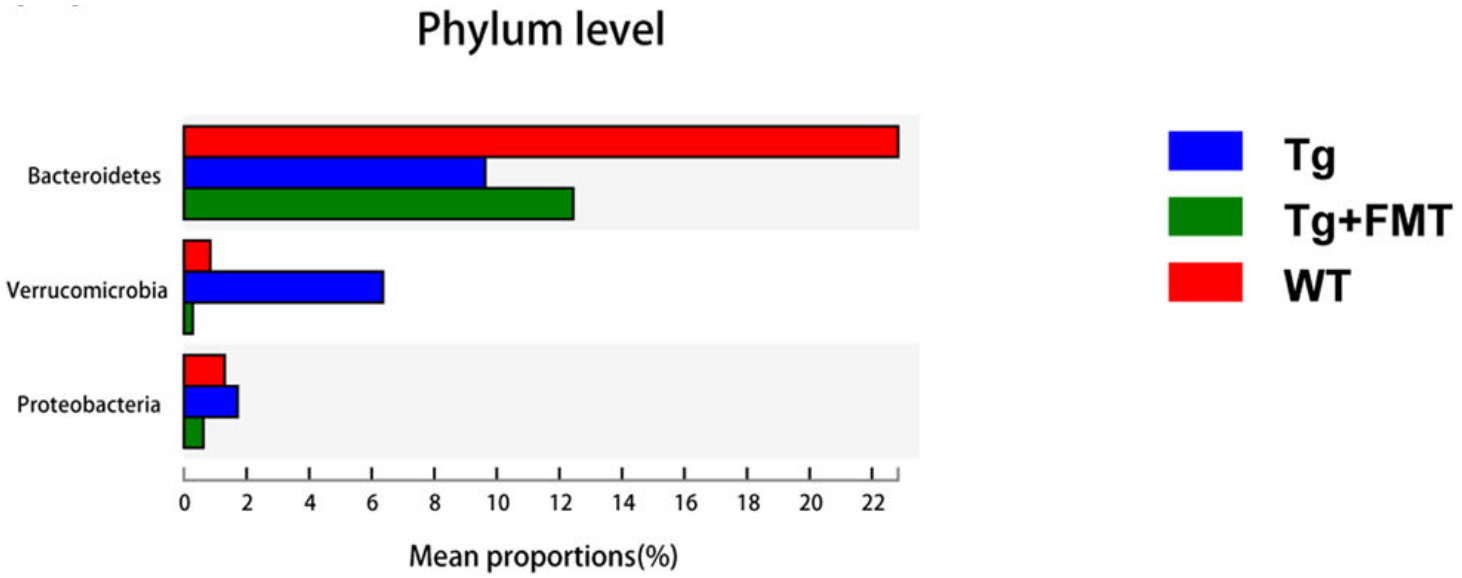
COX-2 is decreased in FMT animals

Attenuation of inflammation

Sun et al. (2019) *Translational Psychiatry* **9**:189 DOI:https://doi.org/10.1038/s41398-019-0525-3

Can gut microbiota modulation alleviate AD?

Feacal Microbiota Transplantation (FMT) (3)



Sun et al. (2019) *Translational Psychiatry* **9**:189 DOI:https://doi.org/10.1038/s41398-019-0525-3

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, ↓$A\beta_{42}$ 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

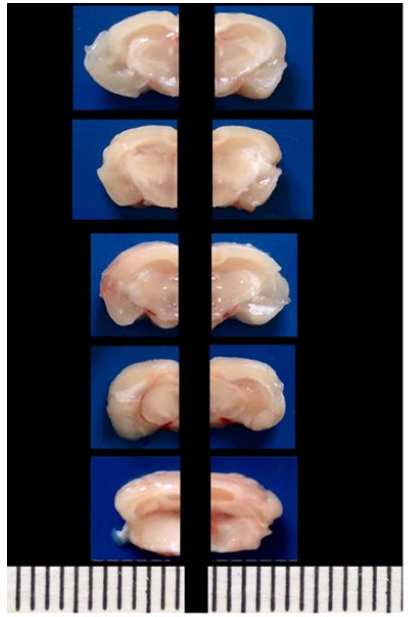
Can gut microbiota modulation alleviate AD? *Probiotics (1)*

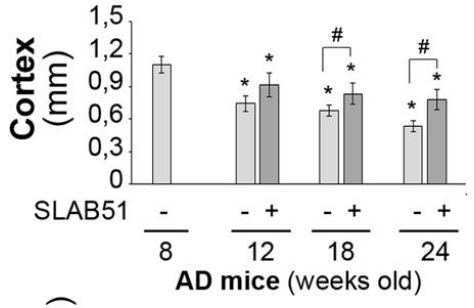
- Probiotics: live microorganisms that, when administered in adequate amounts, confer health benefits to the host
- Psychobiotics: mental health benefits

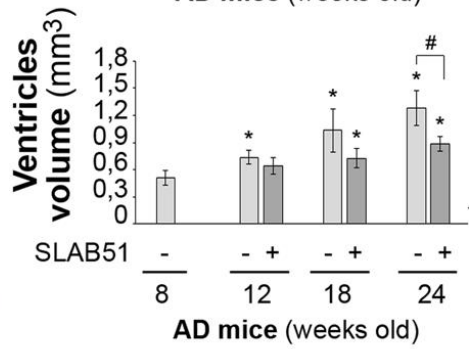
Can gut microbiota modulation alleviate AD?
Probiotics (2)

- 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 (IL1α, IL1β, IL2, IL12, IFNɣ, TNFα)
  - ↓ in Aβ42 deposition in mice brain
  - ↓ in accumulation of ubiquitinated proteins, and pro-apoptotic proteins (p53) /restored proteosomal activity



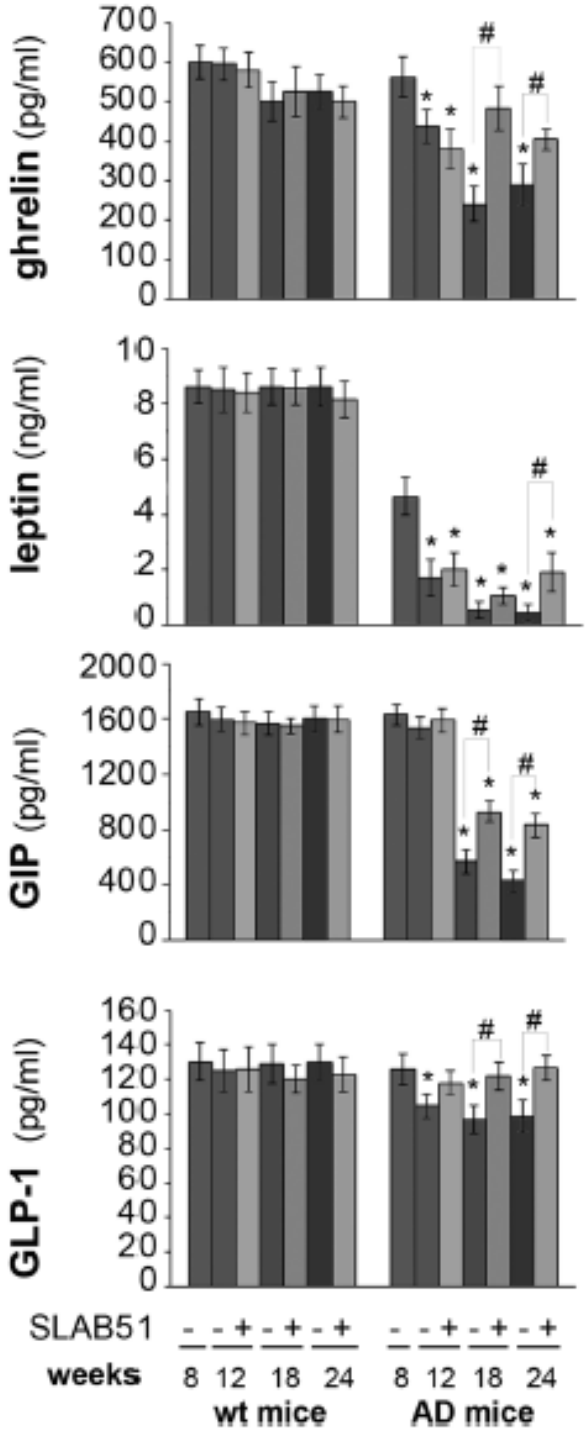




Bonfili *et al.* (2017) *Scientific Reports* 7 DOI:10.1038/s41598-017-02587-2

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 Aβ toxicity induced
- Plasma leptin concentration is negatively correlated to Aβ levels in the brain due to its direct regulatory effect on γ-secretase (↓ mRNA of PS1 , nicastrin, PEN2, APH1)
- AD animal models treated with leptin showed a reduction in Aβ and phosphorylated τ levels
- GLP-1 protects cultured neurons form oxidative damage and reduces the levels of Aβ
- GIP and its analogs were shown to improve memory, cognitive decline, reduce number of Aβ plaques
- Increase in GI tract hormones in SLAB51 treated mice



Bonfili *et al.* (2017) *Scientific Reports* **7** DOI:10.1038/s41598-017-02587-2

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

Zheng Y, Bonfili L, Wei T, Eleuteri AM. (2023) Understanding the Gut-Brain Axis and Its Therapeutic Implications for Neurodegenerative Disorders. Nutrients. **15:**4631. doi: 10.3390/nu15214631.