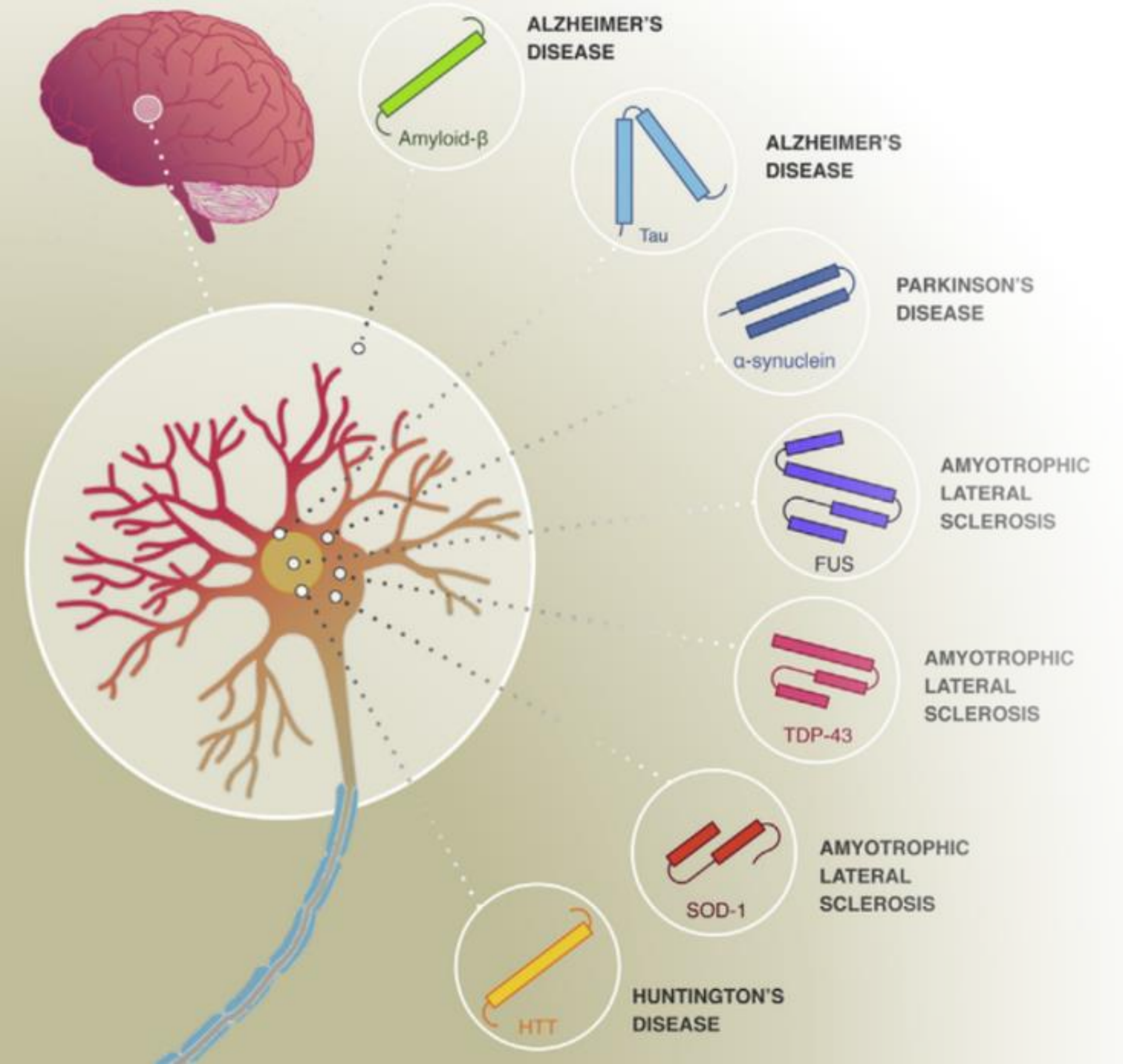
Het intestinaal microbioom en neurodegeneratie

Prof.Dr.P.Santens

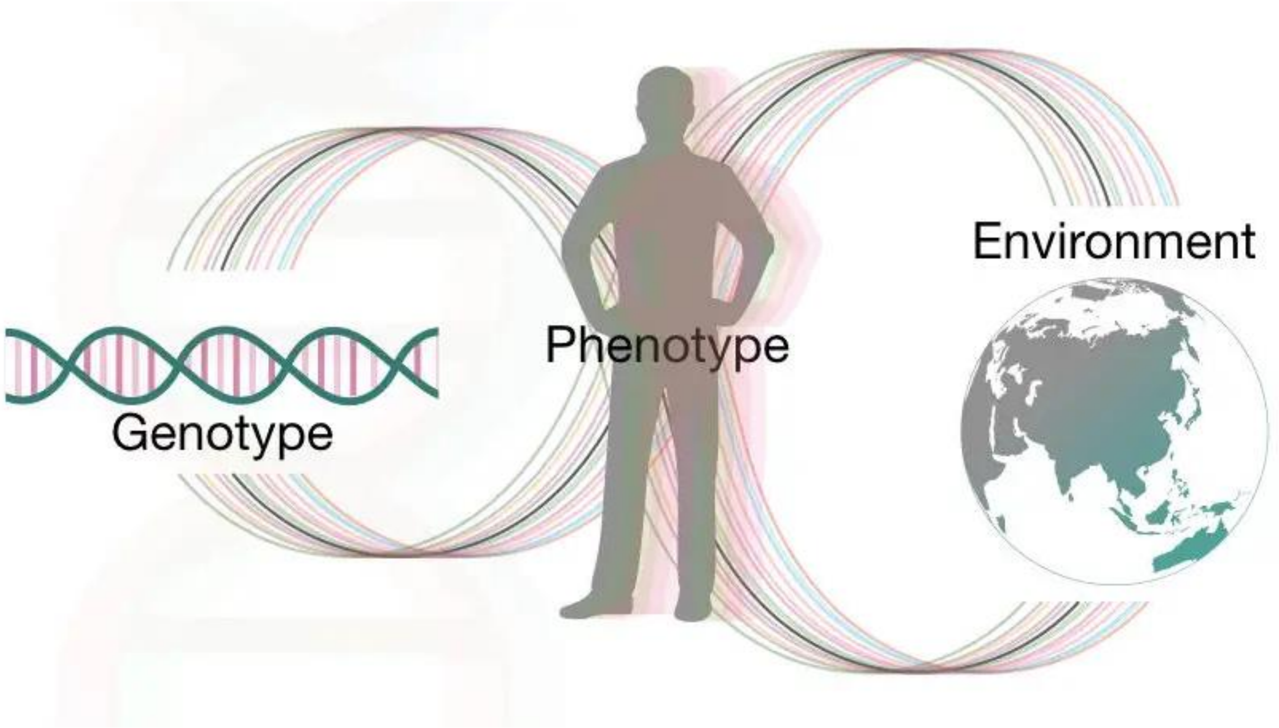
Neurologie UZ Gent



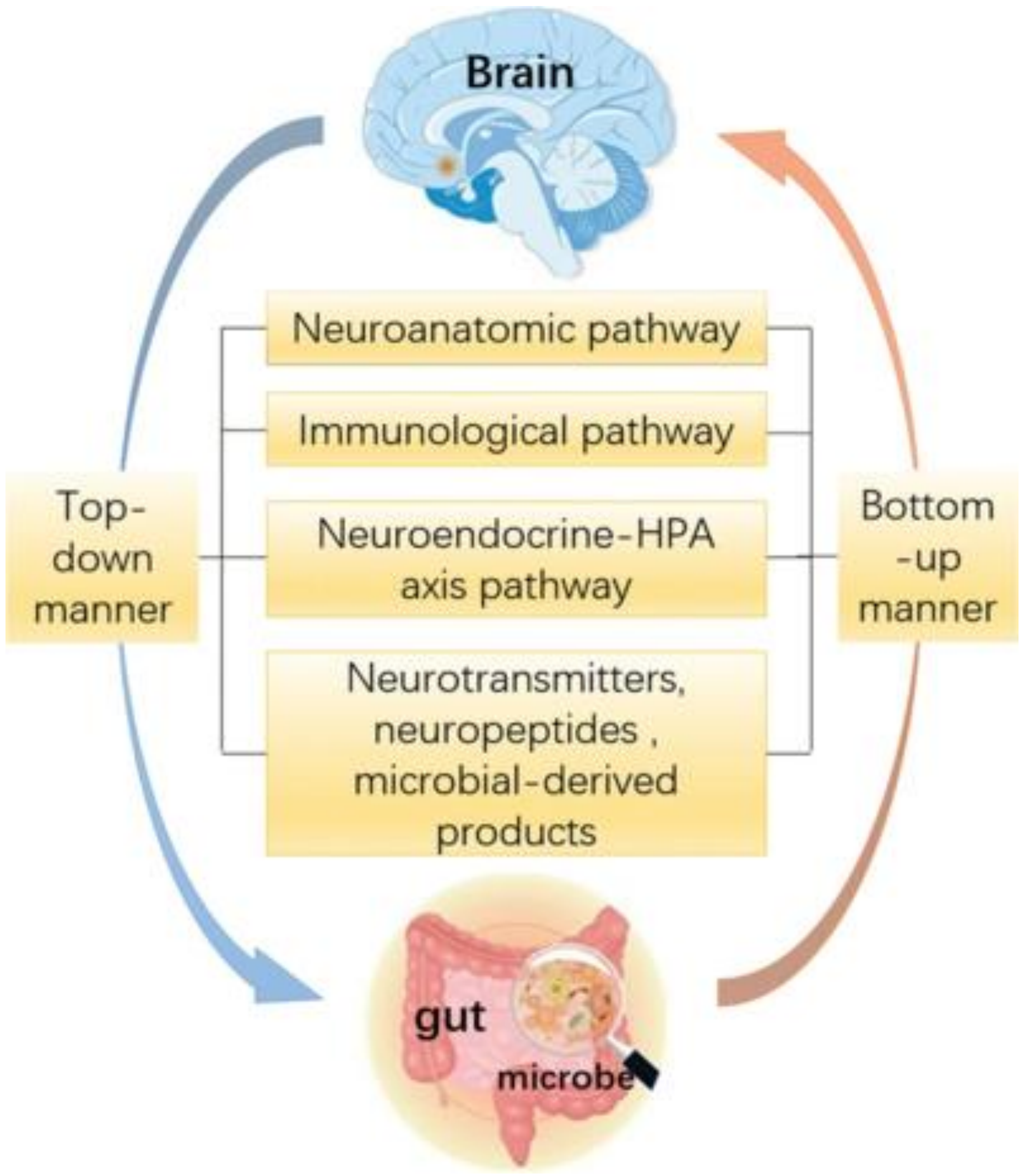
Neurodegeneratieve ziekten

Neurodegeneratie en pathofysiologie

- Proteinopathie
- Mitochondriale dysfunctie
- Inflammatie
- Vasculaire factoren

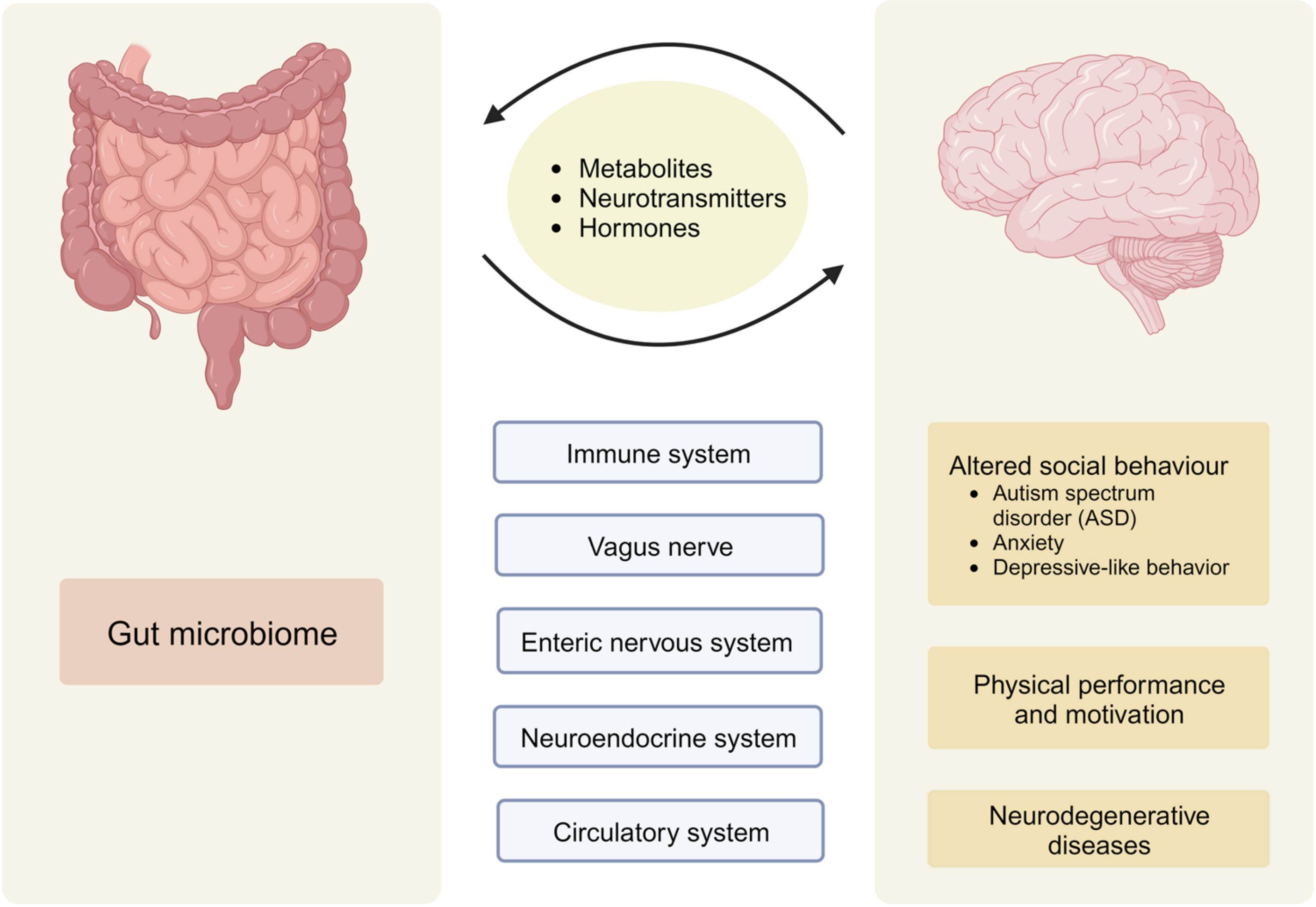


“Gut – brain axis”

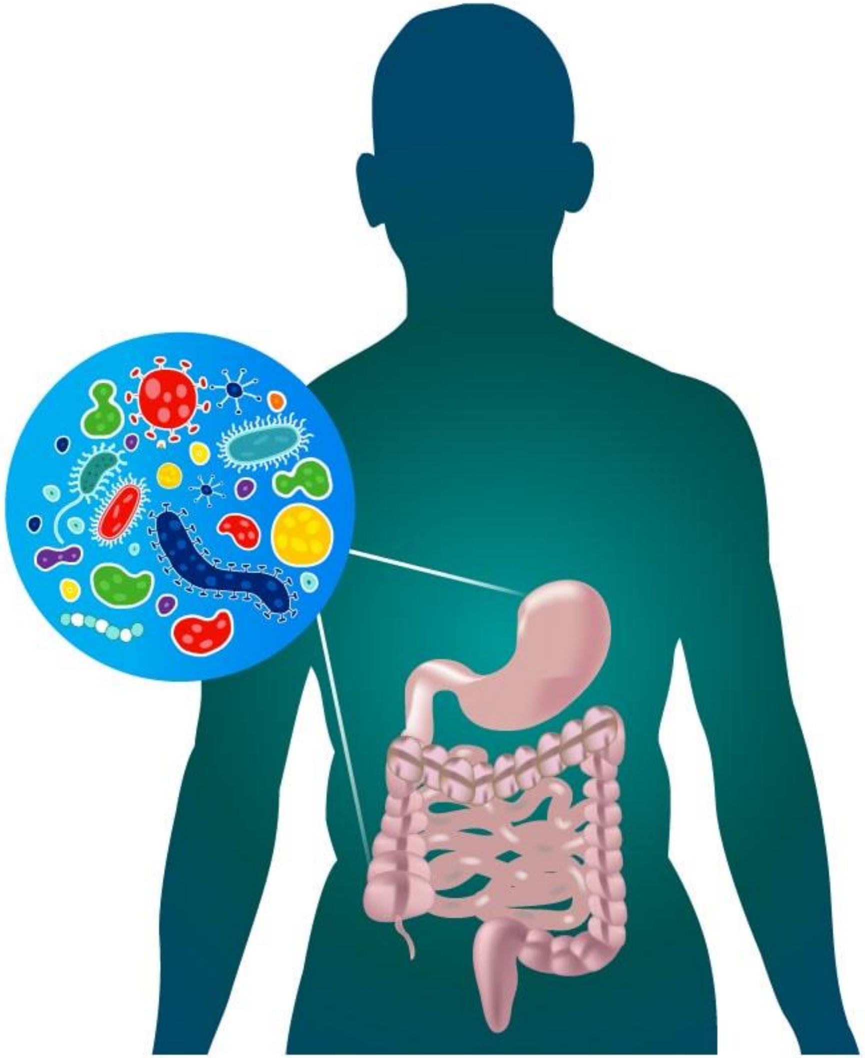


“Gut - brain axis”

Microbiota gut-brain axis



Het darmmicrobioom



- Bestaat uit bacteriën, virussen en eukaryoten
- Klassiek >1000 species, wat resulteert in een genenpoel die 25 maal rijker is dan typisch menselijk genoom (750000 vs 30000)
- Relatief stabiel vanaf de leeftijd van ongeveer 3 jaar
- Verschillend van persoon tot persoon
- Geografische variabiliteit

Nature. ; 486(7402): 222–227. doi:10.1038/nature11053.

Human gut microbiome viewed across age and geography

Tanya Yatsunenko[1], Federico E. Rey[1], Mark J. Manary[2], Indi Trehan[2], Maria Gloria Dominguez-Bello[4], Monica Contreras[5], Magda Magris[6], Glida Hidalgo[6], Robert N. Baldassano[7], Andrey P. Anokhin[3], Andrew C. Heath[3], Barbara Warner[2], Jens Reeder[8], Justin Kuczynski[8], J. Gregory Caporaso[8,*], Catherine A. Lozupone[8], Christian Lauber[8], Jose Carlos Clemente[8], Dan Knights[8], Rob Knight[8,9], and **Jeffrey I. Gordon[1]**

The gut microbiome

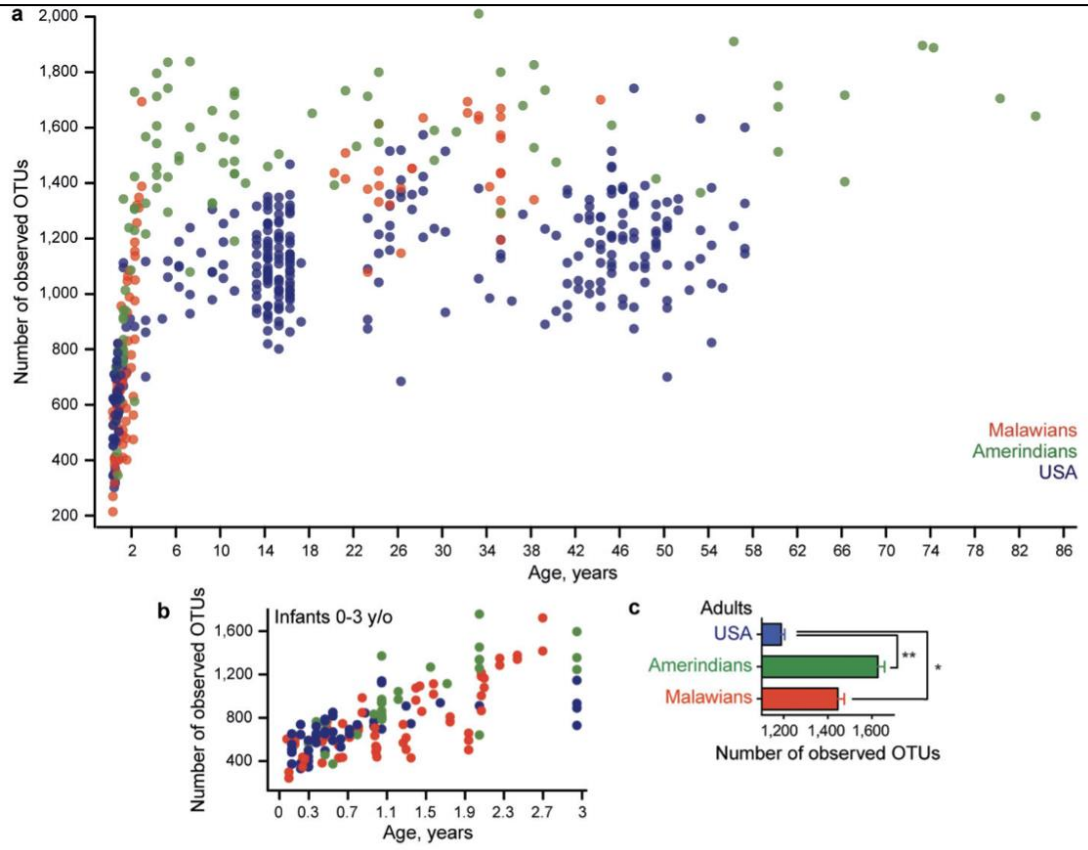
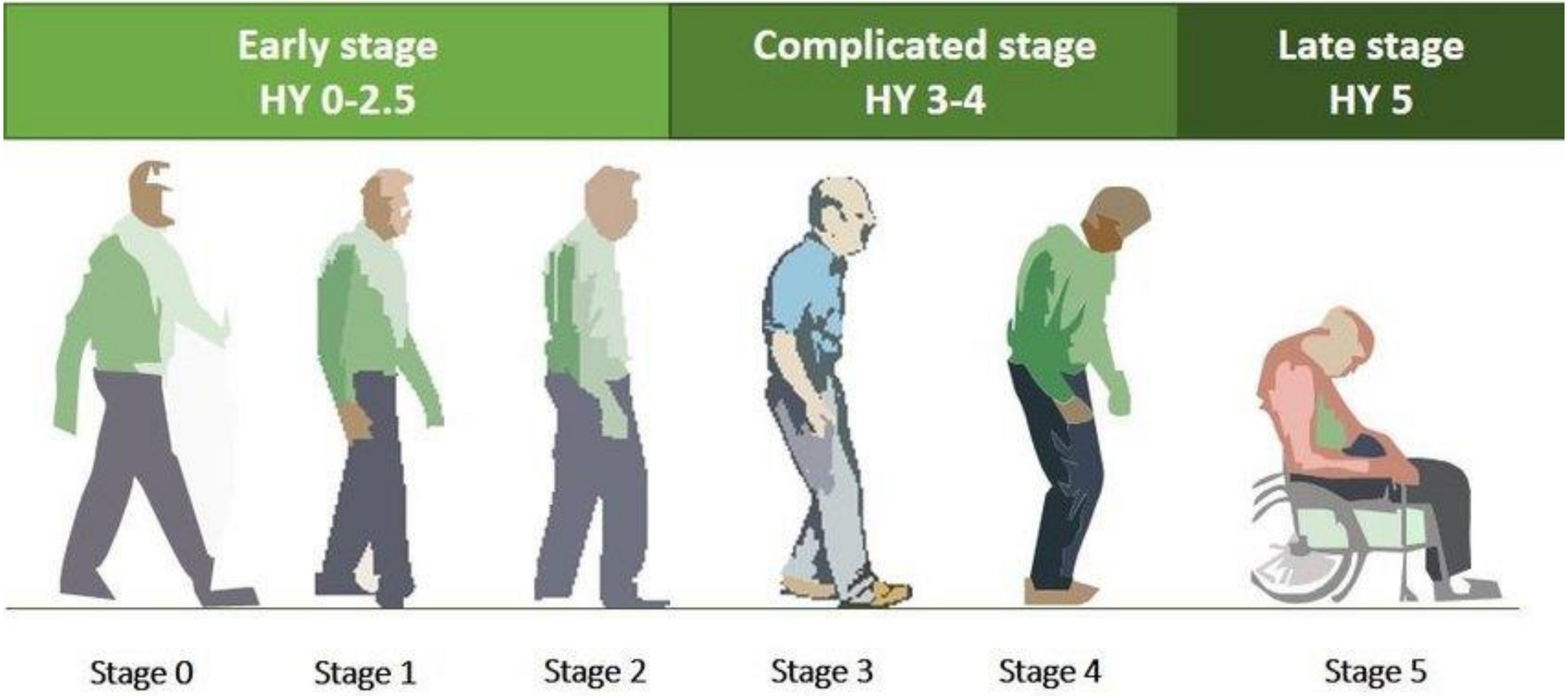


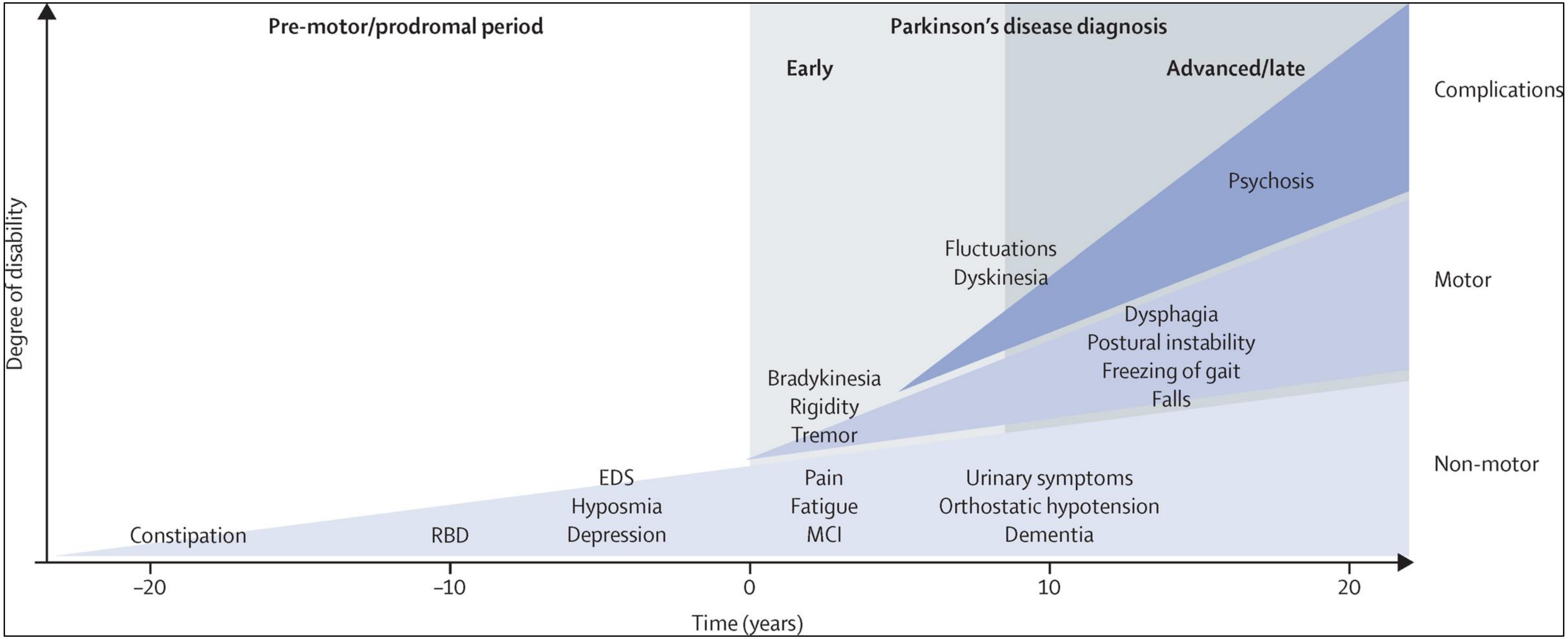
Fig. 2. Bacterial diversity increases with age in each population

Number of observed 97%ID OTUs plotted against age for **(a)** all subjects, **(b)** during the first 3 years of life, and **(c)** adults (in the latter panel, average values ± SEM are plotted). *p<0.05, **p<0.005 (ANOVA with Bonferroni post-hoc test).

1. De ziekte van Parkinson



De evolutie van de ziekte van Parkinson



Wat is er aan de hand met het microbioom bij de ziekte van Parkinson ?

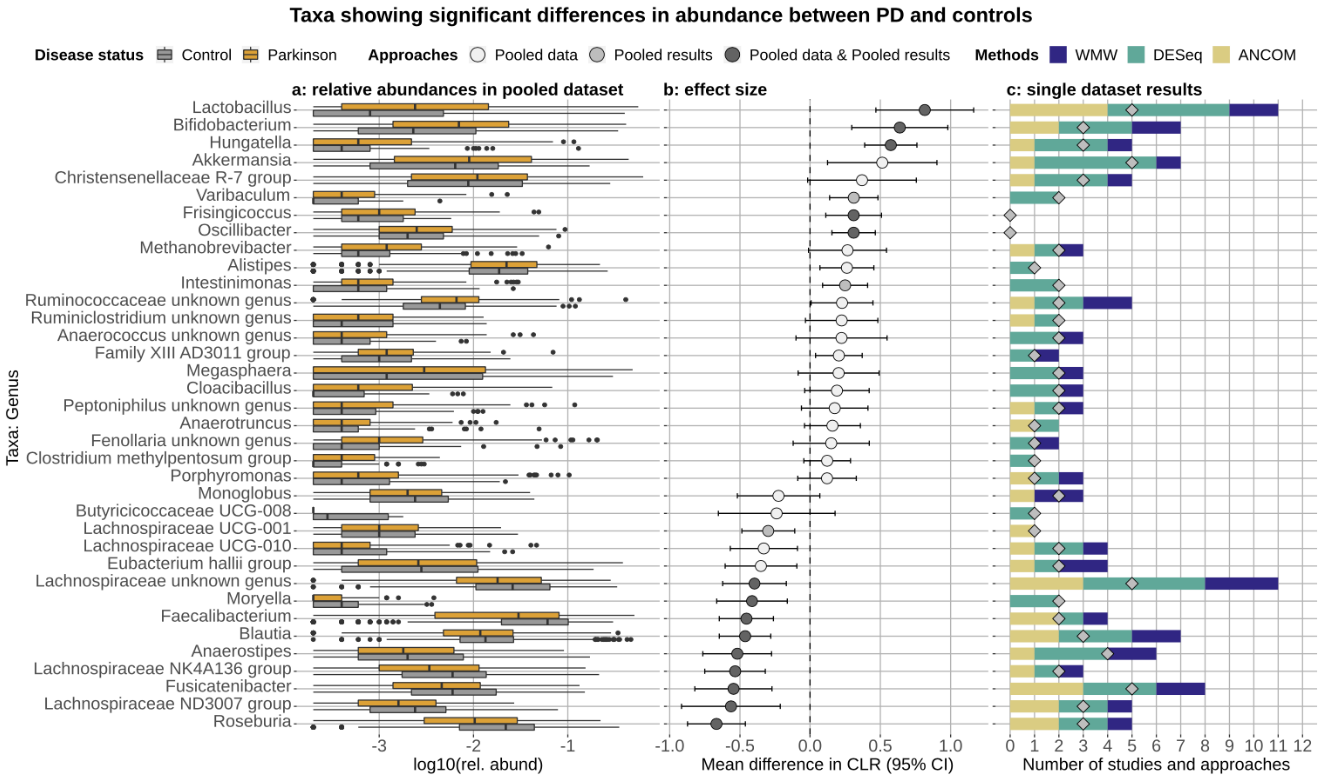


Fig. 5 Genera showing a significant difference in abundance between PD patients and controls. The relative abundances of the genera retrieved from the rarefied pooled data are reported in panel **a**. Effect sizes were estimated via the mean difference in CLR (panel **b**) using a random-effect meta-analysis approach (Pooled results approach). This was calculated for all taxa resulting differentially abundant in the Pooled results or Pooled data approaches. The color of the dots indicates which of the two above approaches detected the taxa differentially abundant. Taxa more abundant in controls have an effect size shifted to the left, whereas taxa more abundant in PD have an effect size shifted to the right. Panel **c** shows the number of times each genus was detected differentially abundant between PD patients and control samples across studies (diamonds) and approaches (bars). We used ten studies and three approaches, hence the maximum number of times a taxon can be detected differentially abundant is 30.

ARTICLE OPEN

Check for updates

Meta-analysis of the Parkinson's disease gut microbiome suggests alterations linked to intestinal inflammation

Stefano Romano[1]✉, George M. Savva[1], Janis R. Bedarf[1,2], Ian G. Charles[1,3], Falk Hildebrand[1,4]✉ and Arjan Narbad[1]

npj Parkinson's Disease (2021)7:27 ; https://doi.org/10.1038/s41531-021-00156-z

Samengevat: het darmmicrobioom bij de ziekte van Parkinson

- Toename van species die slijmlaag afbreken en doorgankelijkheid van de darmwand doen toenemen ("lekkende darm")
- Afname van bacteriën die vezels omzetten tot korte keten vetzuren (acetaat, propionaat, butyraat), wat aanleiding geeft tot een inflammatoire toestand in de darmwand
- Toename van inflammatoire mediatoren en afname van anti-inflammatoire
- Veranderingen in neurotransmitter concentraties
- Microbiële endotoxines (e.g. lipopolysacchariden) versterken inflammatoire status

Samengevat: het darmmicrobioom bij de ziekte van Parkinson

ANNALS OF MEDICINE
2021, VOL. 53, NO. 1, 611–625
https://doi.org/10.1080/07853890.2021.1890330

Taylor & Francis
Taylor & Francis Group

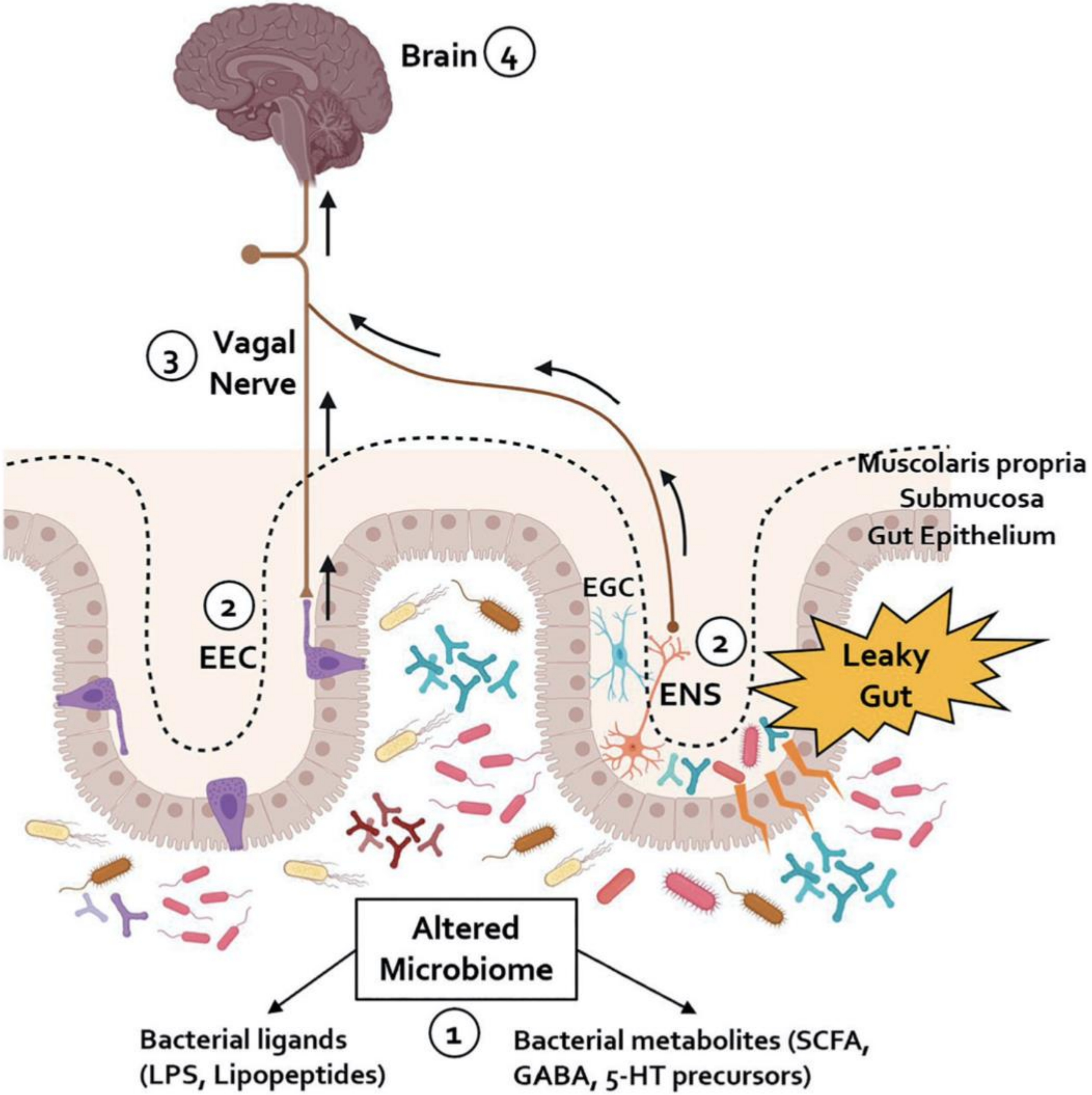
REVIEW ARTICLE

OPEN ACCESS Check for updates

The gut-brain axis and Parkinson disease: clinical and pathogenetic relevance

Elisa Menozzi[a], Jane Macnaughtan[b] and Anthony H. V. Schapira[a]

[a]Department of Clinical and Movement Neurosciences, UCL Queen Square Institute of Neurology, London, UK; [b]Institute for Liver and Digestive Health, University College London, Royal Free Campus, London, UK



FEATURED ARTICLE

Is Alpha-Synuclein in the Colon a Biomarker for Premotor Parkinson's Disease? Evidence from 3 Cases

Kathleen M. Shannon, MD,[1*] Ali Keshavarzian, MD,[2] Hemraj B. Dodiya, MS,[3] Shriram Jakate, MD,[4] and Jeffrey H. Kordower, PhD[3]

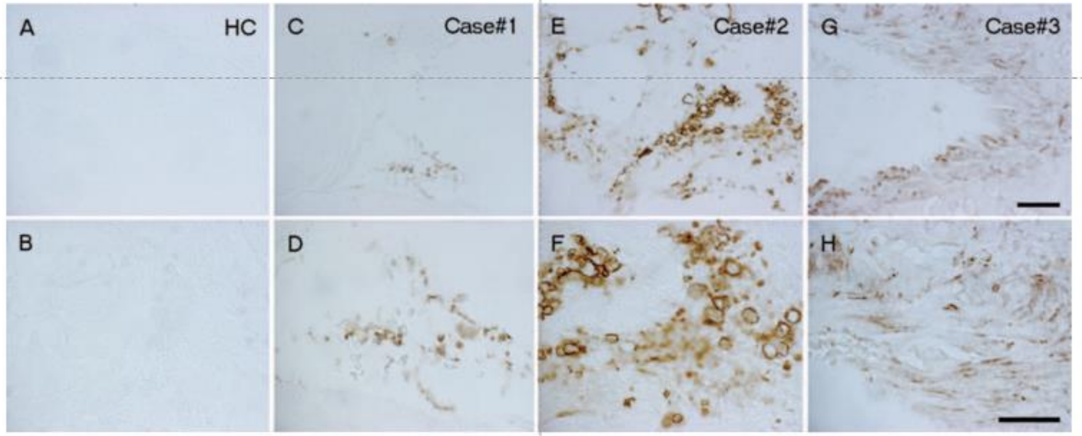


FIG. 1. Low- (A, C, E, and G) and high-power (B, D, F, and H) photomicrographs showing α-SYN histology through the colon from a healthy control (A and B), case 1 (2 years pre-PD diagnosis) (C and D), case 2 (2 years pre-PD diagnosis) (E and F), and case 3 (5 years pre-PD diagnosis) (G and H). Scale bar in (A, C, E, and G) represents 50 um and in (B, D, F, and H) represents 30 um.

Mov Disord. 2012 May;27(6):716-9.

Enteric nervous system α-synuclein immunoreactivity in idiopathic REM sleep behavior disorder

OPEN

ABSTRACT

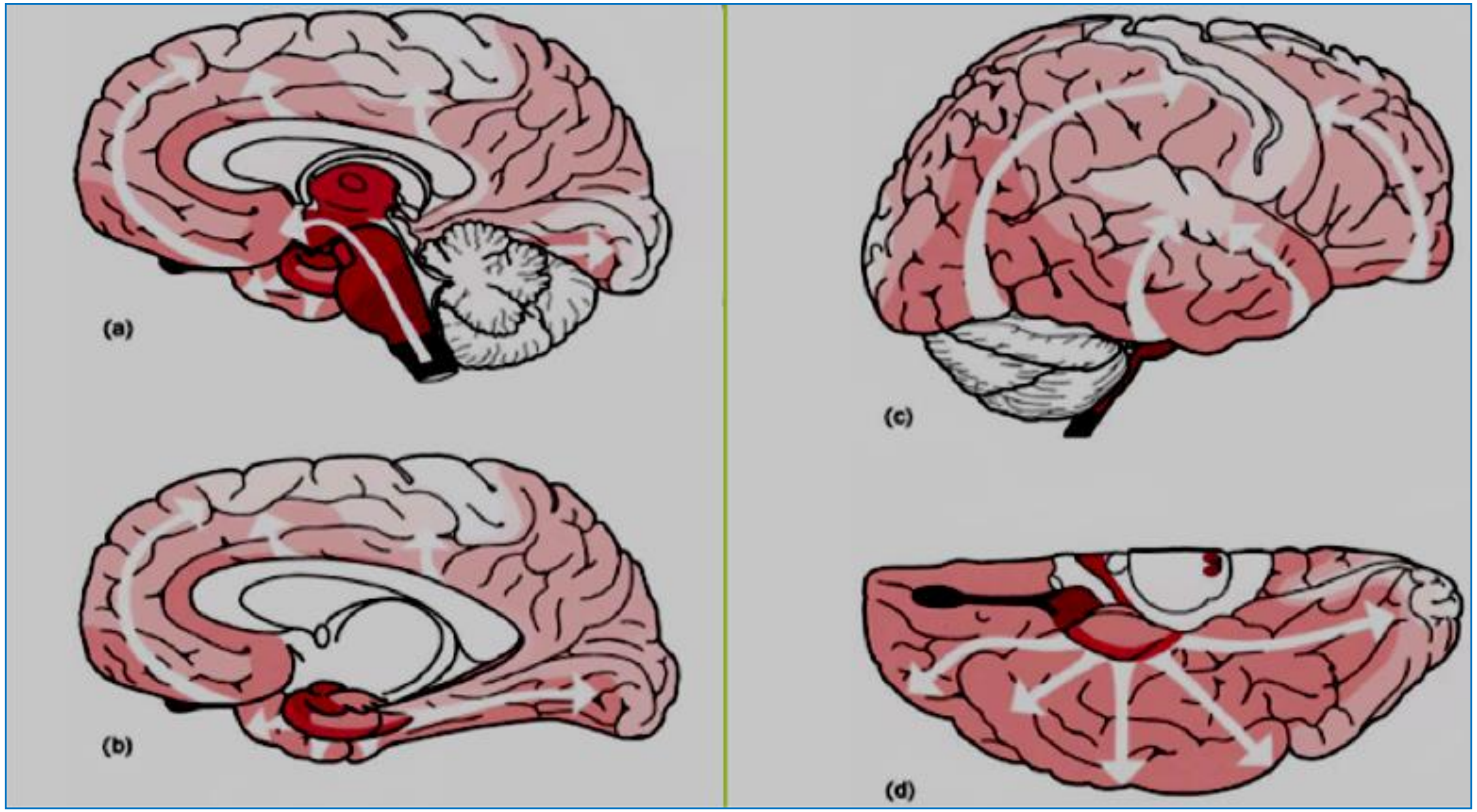
Objective: To investigate the expression of α-synuclein in colonic biopsies of patients with idiopathic REM sleep behavior disorder (iRBD) and address if α-synuclein immunostaining of tissue obtained via colonic biopsies holds promise as a diagnostic biomarker for prodromal Parkinson disease (PD).

Methods: Patients with iRBD, patients with PD, and healthy controls were prospectively recruited to undergo colonic biopsies for comparison of α-synuclein immunoreactivity patterns between the groups by using 2 different antibodies.

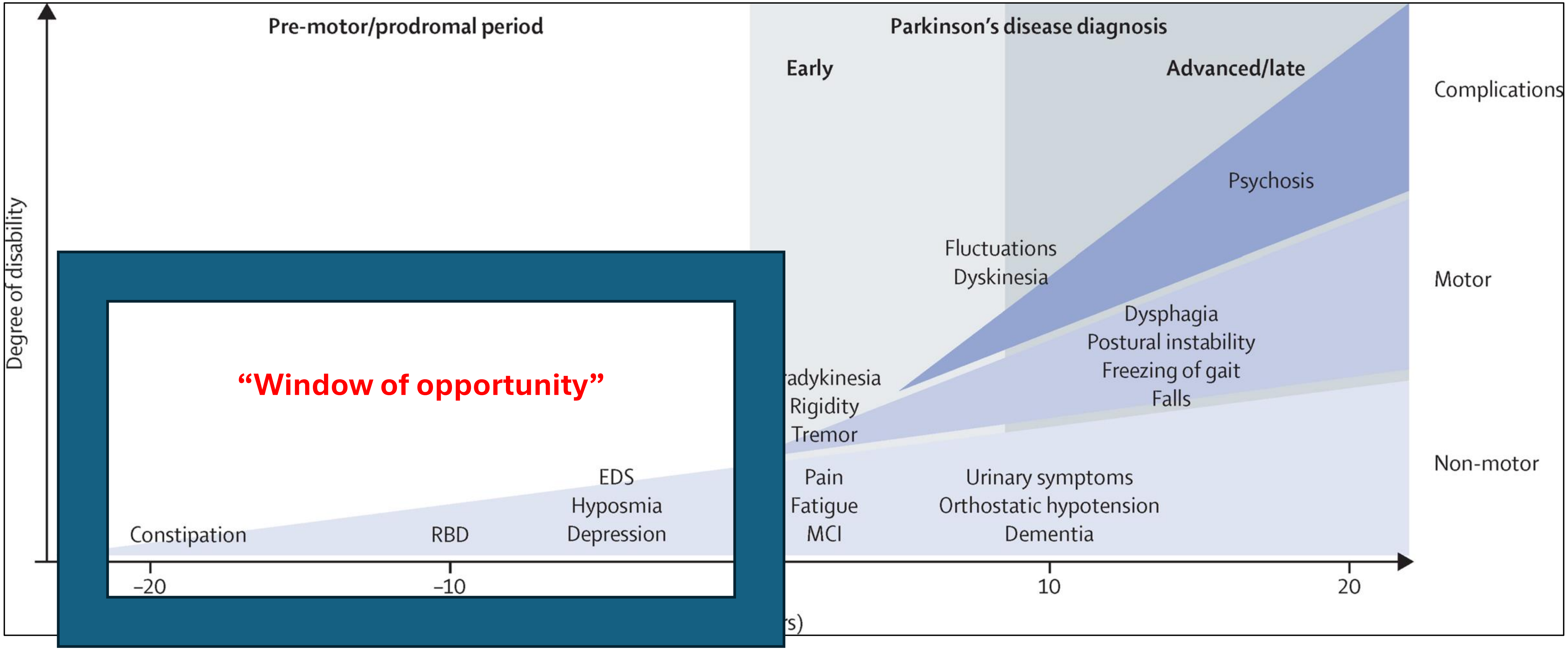
Results: There was no difference in colonic mucosal and submucosal immunostaining between groups using the 15G7 α-synuclein antibody, which was found in almost all participants enrolled in this study. By contrast, immunostaining for serine 129-phosphorylated α-synuclein (pSyn) in submucosal nerve fibers or ganglia was found in none of 14 controls but was observed in 4 of 17 participants with iRBD and 1 out of 19 patients with PD.

Conclusions: The present findings of pSyn immunostaining of colonic biopsies in a substantial proportion of iRBD participants raise the possibility that this tissue marker may be a suitable candidate to study further as a prodromal PD marker in at-risk cohorts. *Neurology®* 2015;85:1761–1768

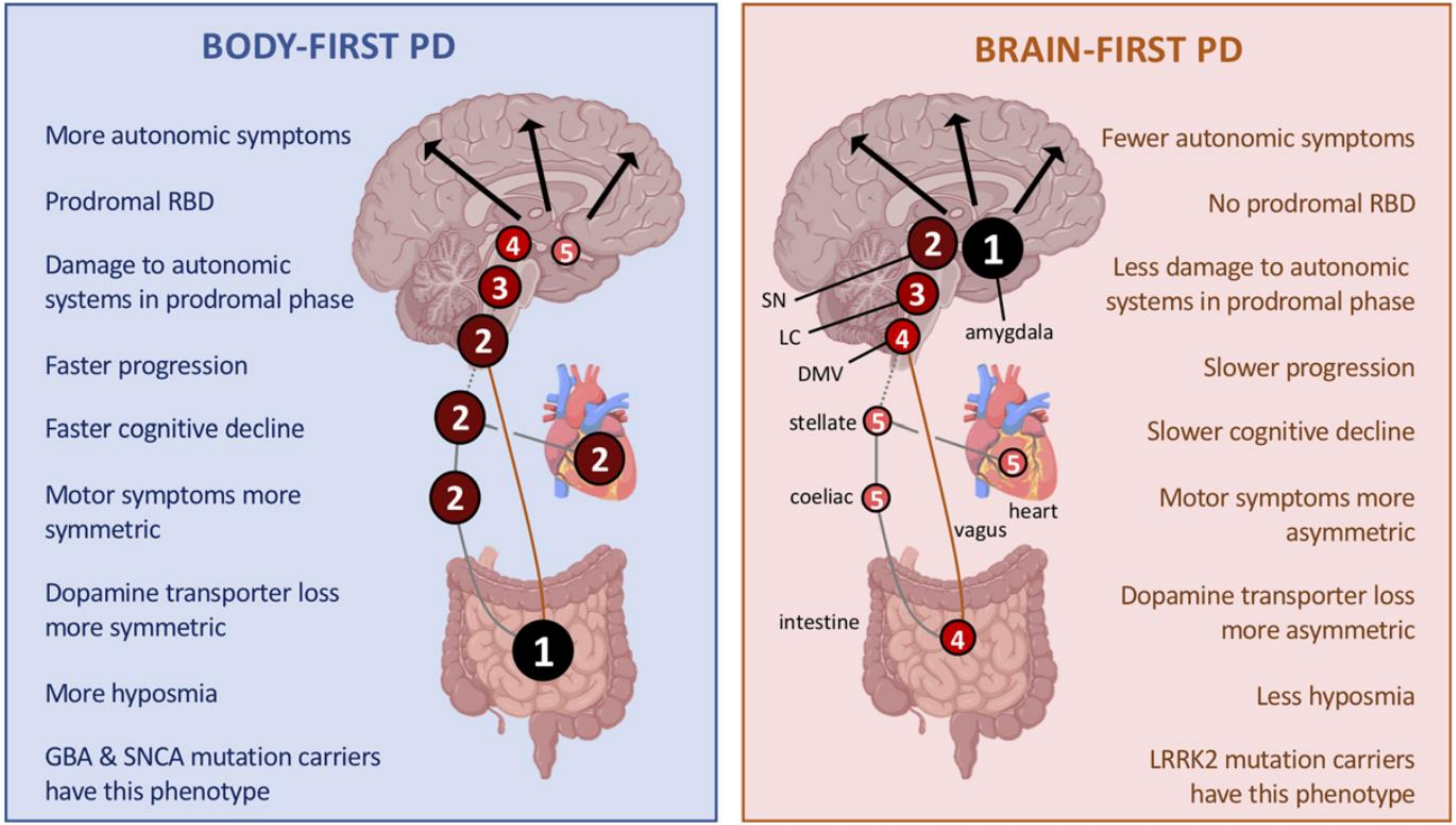
Progressie synucleine depositie



Klinische correlaten?



Subtypes in PD?



FMT in animal models of PD

Zhao *et al. Microbiome* (2021) 9:226
https://doi.org/10.1186/s40168-021-01107-9

Microbiome

RESEARCH **Open Access**

Check for updates

Fecal microbiota transplantation protects rotenone-induced Parkinson's disease mice via suppressing inflammation mediated by the lipopolysaccharide-TLR4 signaling pathway through the microbiota-gut-brain axis

Zhe Zhao, Jingwen Ning, Xiu-qi Bao, Meiyu Shang, Jingwei Ma, Gen Li and Dan Zhang*

ELSEVIER

Brain, Behavior, and Immunity
Volume 70, May 2018, Pages 48-60

Neuroprotective effects of fecal microbiota transplantation on MPTP-induced Parkinson's disease mice: Gut microbiota, glial reaction and TLR4/TNF-α signaling pathway

Meng-Fei Sun [1], Ying-Li Zhu [1], Zhi-Lan Zhou, Xue-Bing Jia, Yi-Da Xu, Qin Yang, Chun Cui, Yan-Qin Shen

Open-label FMT trials in human PD patients

RESEARCH ARTICLE: OBSERVATIONAL STUDY

Xue et al. Medicine (2020) 99:35

Fecal microbiota transplantation therapy for Parkinson's disease

A preliminary study

N=15
Three months

Xue, Liu-Jun MD[a]; Yang, Xiao-Zhong MD, PhD[b]; Tong, Qiang MD[a]; Shen, Peng MD[b]; Ma, Shi-Jie MD[b]; Wu, Shang-Nong MD[b]; Zheng, Jin-Long MD, PhD[a,*]; Wang, Hong-Gang MD[b,*]

RESEARCH Open Access

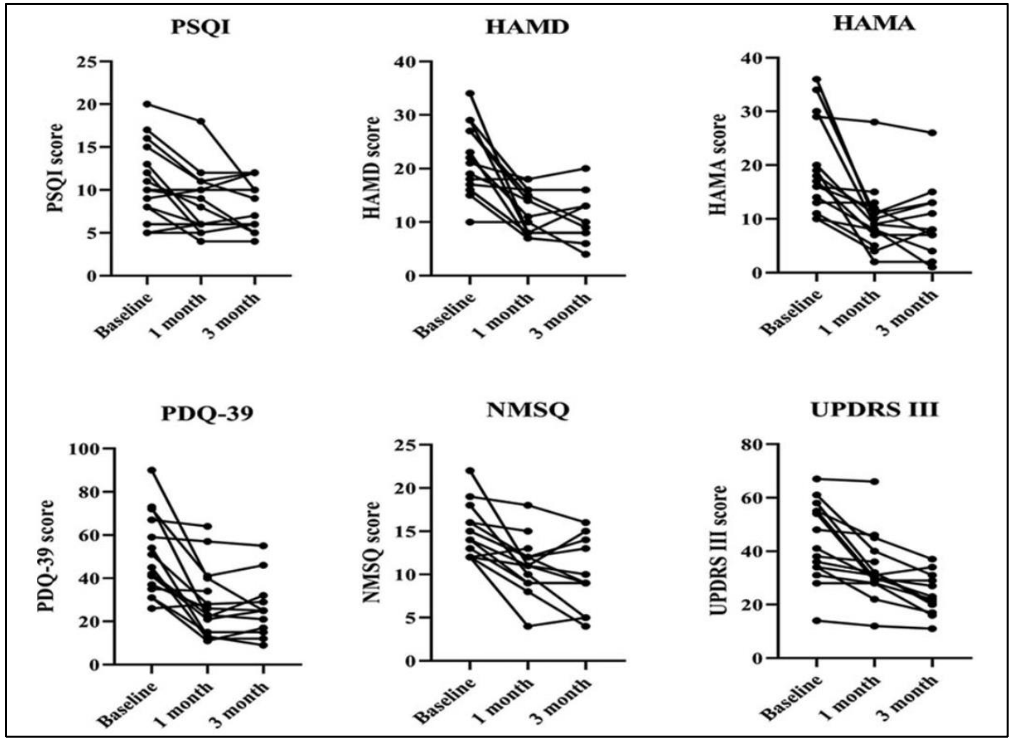
N=11
Three months

Check for updates

Evaluation of fecal microbiota transplantation in Parkinson's disease patients with constipation

Xiao-yi Kuai[1†], Xiao-han Yao[2†], Li-juan Xu[1], Yu-qing Zhou[1], Li-ping Zhang[1], Yi Liu[2*], Shao-fang Pei[2*] and Chun-li Zhou[1*]

Kuai et al. Microb Cell Fact (2021) 20:98
https://doi.org/10.1186/s12934-021-01589-0



Double-blind placebo-controlled FMT trial in human PD patients

N=49

One year FU

- The Ghent University Trial in PD with Fecal Microbiota Transplantation (GUT-PARFECT)

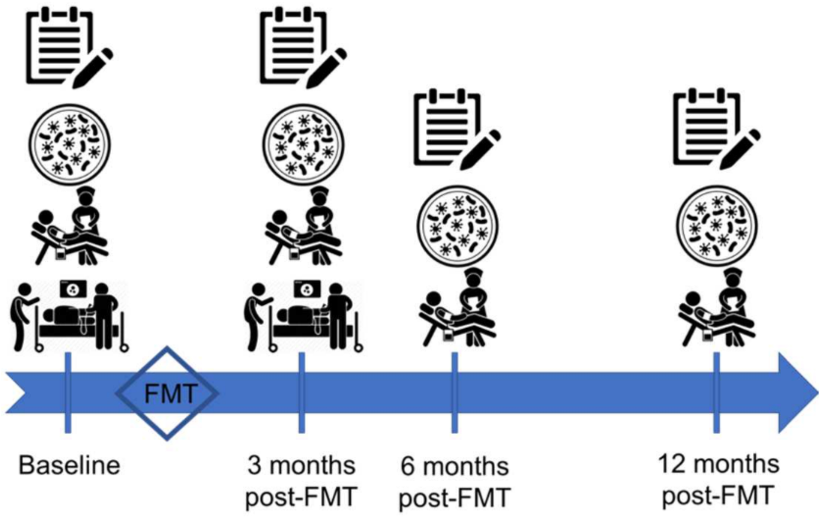


Figure 1. Overview timing of the fecal microbiota transplantation (FMT) trial. At baseline and 3, 6 and 12 months following the FMT a neurologist will score the clinical motor symptoms, clinical characteristics will be assessed via validated questionnaires, and stool and blood samples will be collected. At baseline and 3 months after the FMT, a colonoscopy will be performed to collect mucosal fecal samples (proximal colon) and gastrointestinal tissue biopsies (proximal and distal colon). Additionally, on the first five days following the FMT, candidates will collect fecal samples at home using the DiviMat system.

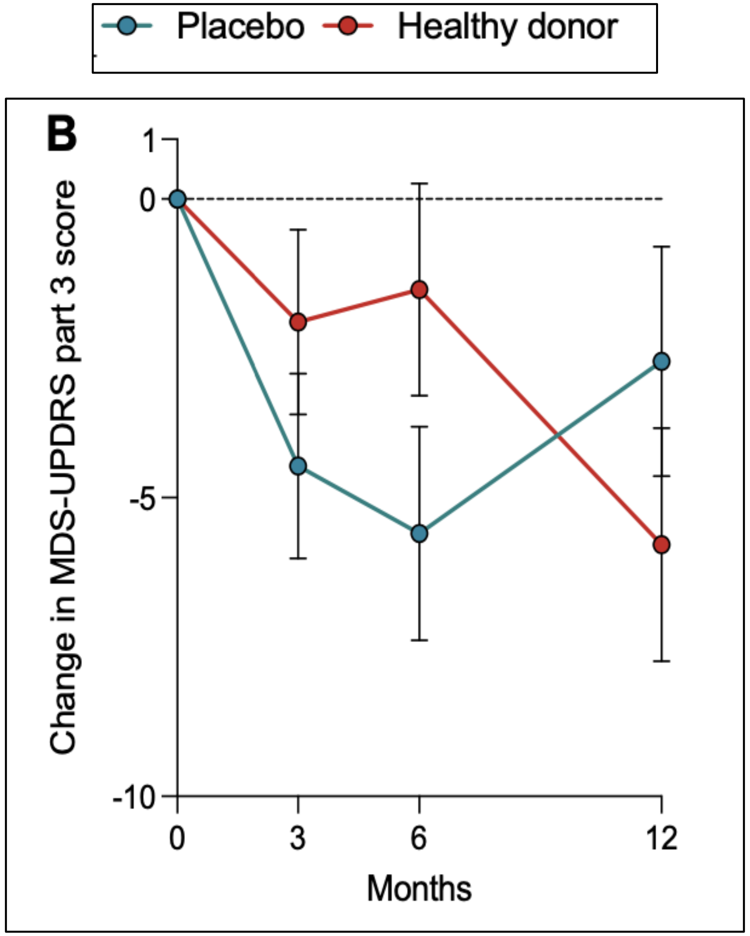
Targeting the gut microbiome: FMT

Safety and efficacy of faecal microbiota transplantation in patients with mild to moderate Parkinson's disease (GUT-PARFECT): a double-blind, placebo-controlled, randomised, phase 2 trial

Arnout Bruggeman,[a,b,c,d] Charysse Vandendriessche,[c,d] Hannelore Hamerlinck,[b,e] Danny De Looze,[b,f] David J. Tate,[b,f] Marnik Vuylsteke,[c,g] Lindsey De Commer,[h,i] Lindsay Devolder,[h,i] Jeroen Raes,[h,i] Bruno Verhasselt,[b,e] Debby Laukens,[b,j] Roosmarijn E. Vandenbroucke,[c,d,j] and Patrick Santens[a,b,j,]*

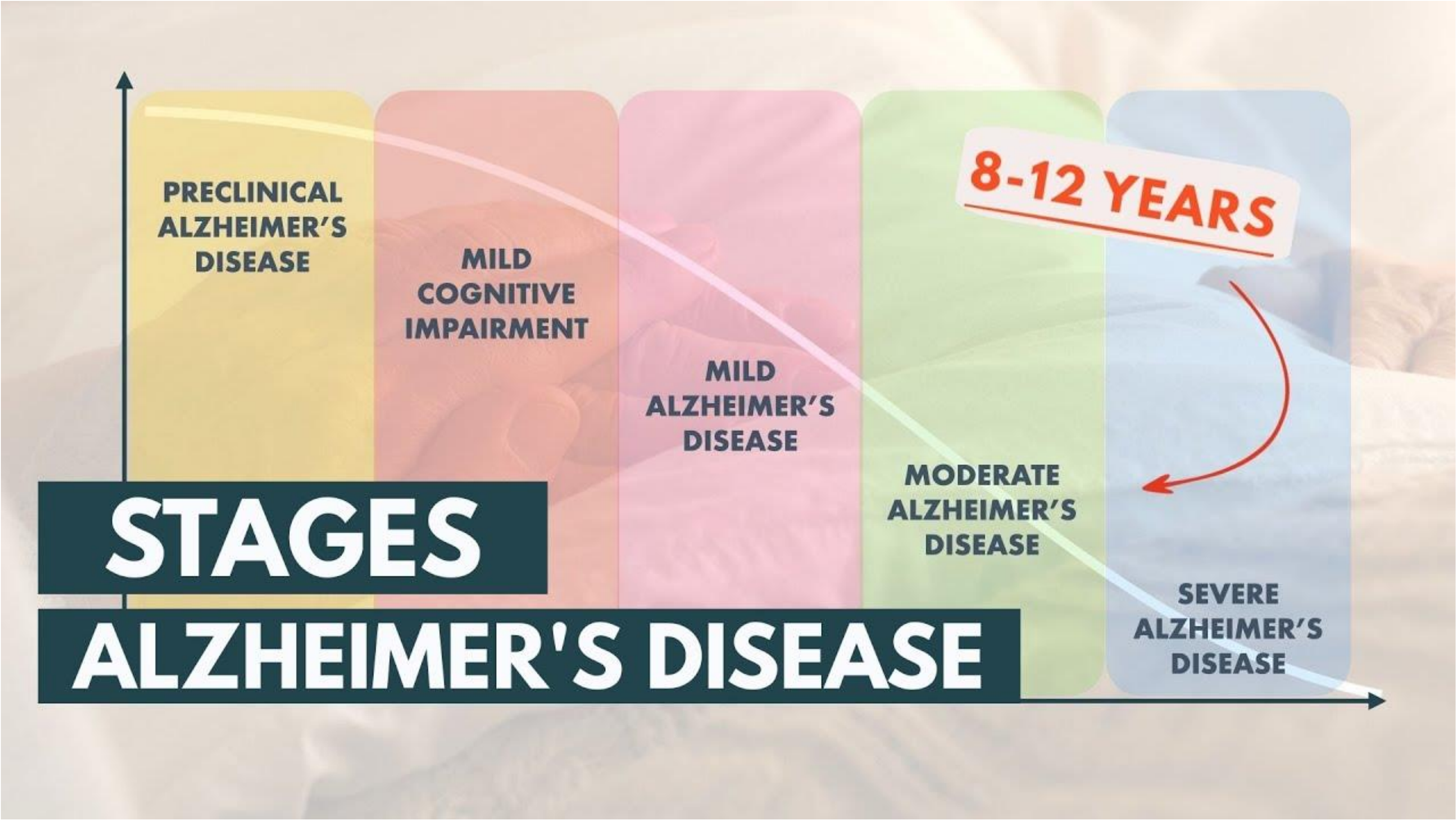
eClinicalMedicine
2024;71: 102563

Published Online xxx
https://doi.org/10.1016/j.eclinm.2024.102563

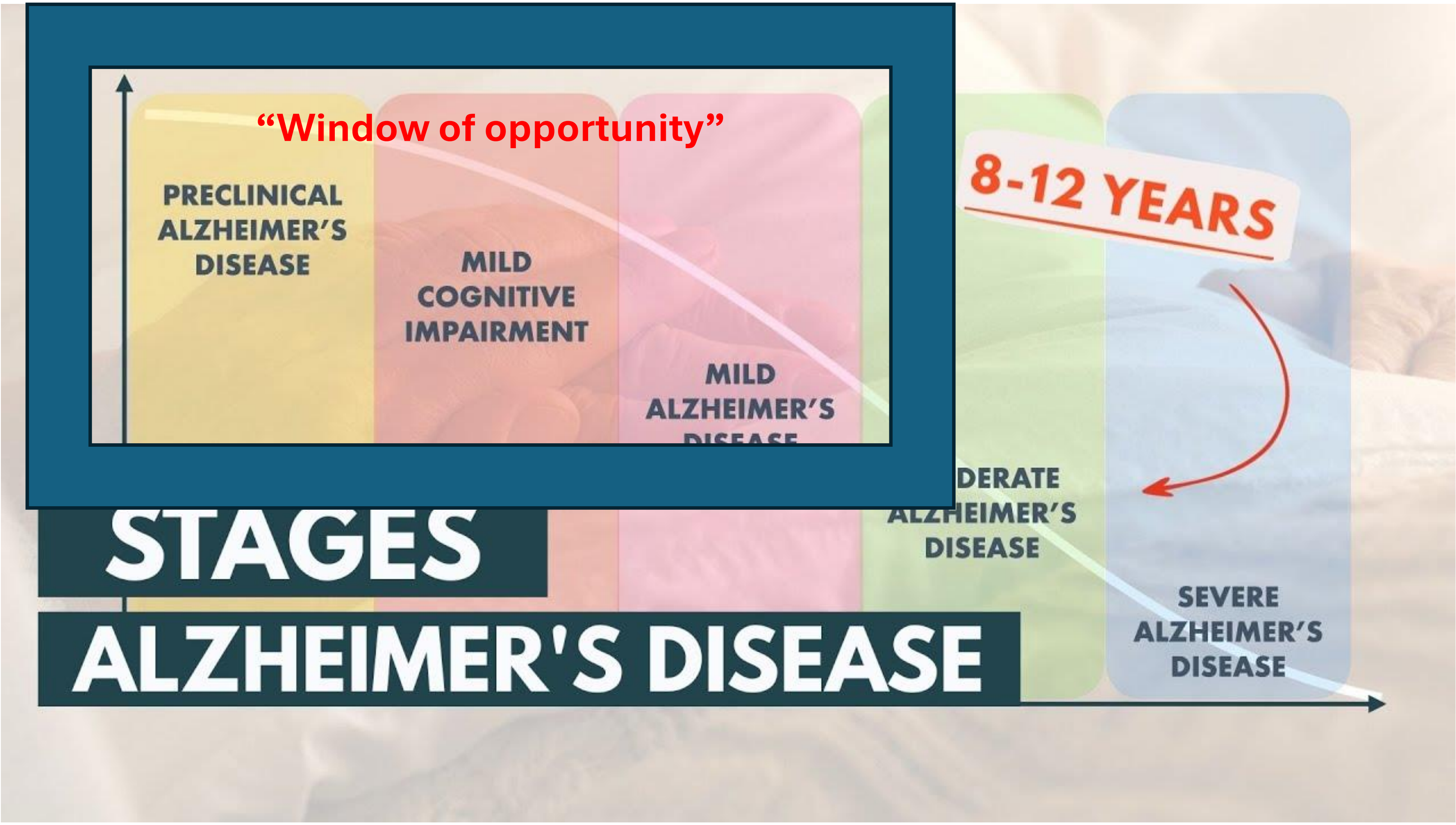


Interpretation Our findings suggested a single FMT induced mild, but long-lasting beneficial effects on motor symptoms in patients with early-stage PD. These findings highlight the potential of modulating the gut microbiome as a therapeutic approach and warrant a further exploration of FMT in larger cohorts of patients with PD in various disease stages.

2. De ziekte van Alzheimer



2. De ziekte van Alzheimer



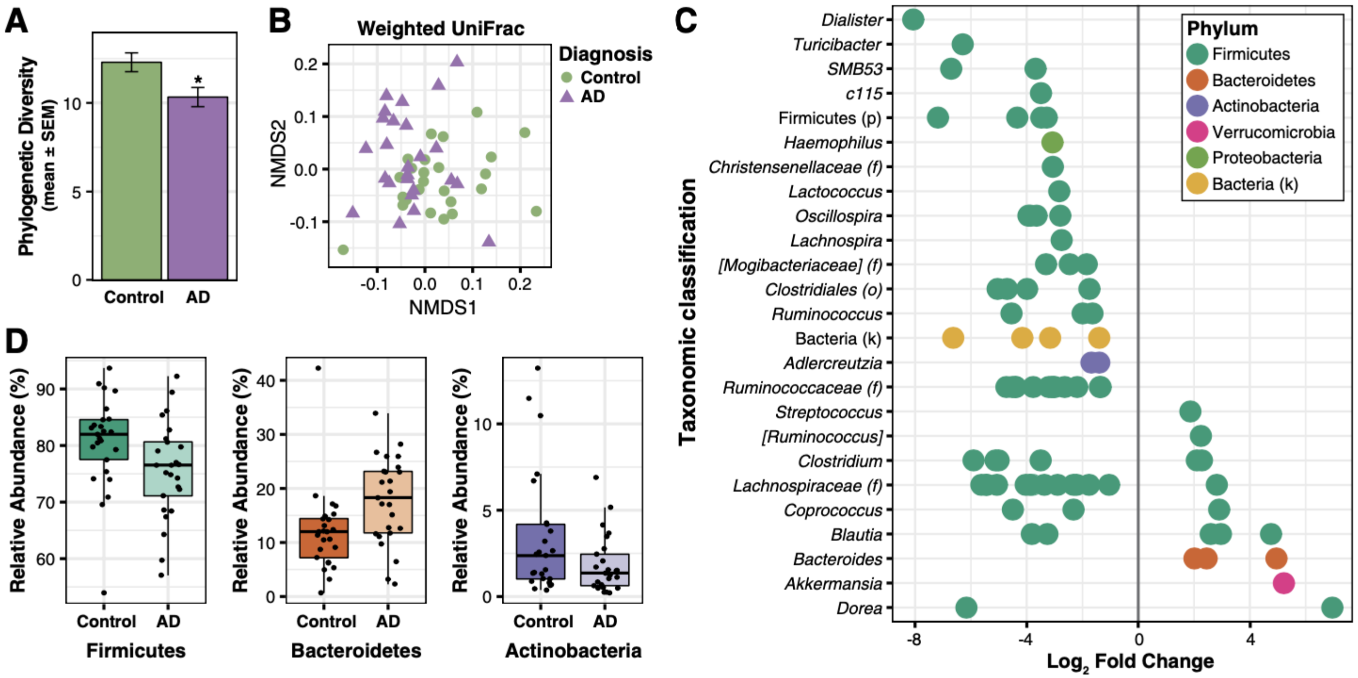
Het darmmicrobioom in AD

SCIENTIFIC REPORTS

OPEN

Gut microbiome alterations in Alzheimer's disease

Nicholas M. Vogt[1], Robert L. Kerby[2], Kimberly A. Dill-McFarland[2], Sandra J. Harding[1], Andrew P. Merluzzi[1], Sterling C. Johnson[3,1,4], Cynthia M. Carlsson[3,1,4], Sanjay Asthana[3,1], Henrik Zetterberg[5,6,7,8], Kaj Blennow[5,6], Barbara B. Bendlin[1,4] & Federico E. Rey[2]



Alzheimer's & Dementia 15 (2019) 1357-1366

Theoretical Article

Mild cognitive impairment has similar alterations as Alzheimer's disease in gut microbiota

Binyin Li[1], Yixi He[1], Jianfang Ma, Pei Huang, Juanjuan Du, Li Cao, Yan Wang, Qin Xiao, Huidong Tang**, Shengdi Chen*

Department of Neurology & Collaborative Innovation Center for Brain Science, Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, P.R. China

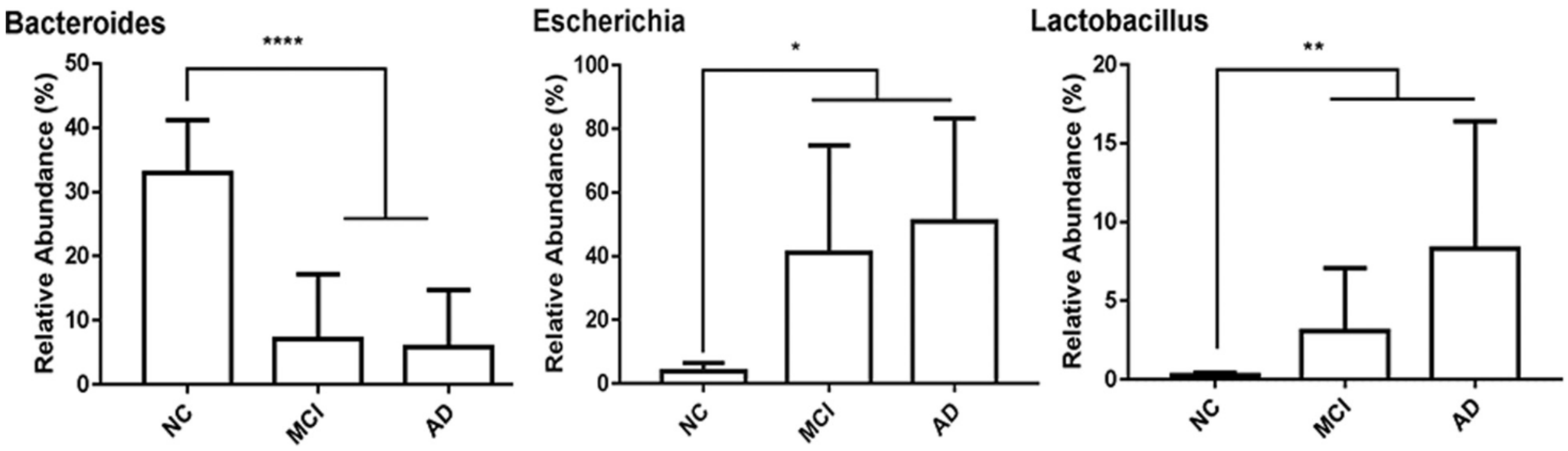


Fig. 3. The relative abundance of *Bacteroides, Escherichia,* and *Lactobacillus* measured by qPCR (ratio between the genera and 16S rRNA gene) were compared between three groups by the Kruskal-Wallis test. Post hoc comparison was performed by Dunn's test. No significant difference was found between AD and MCI. ****$P < .0001$; **$P < .01$; *$P < .05$. Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; NC, normal controls; qPCR, quantitative polymerase chain reaction.

Modificatie van het microbioom?

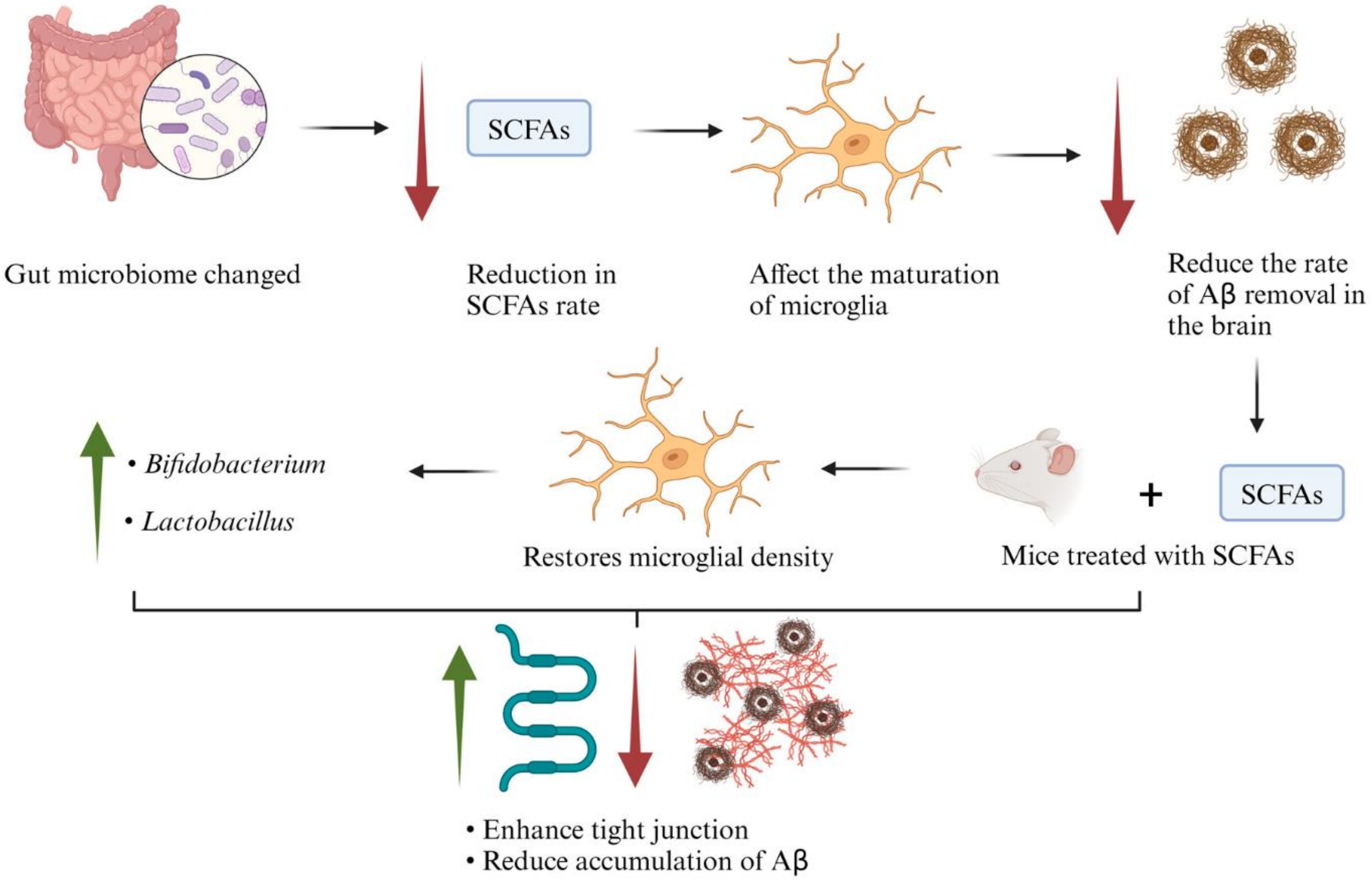
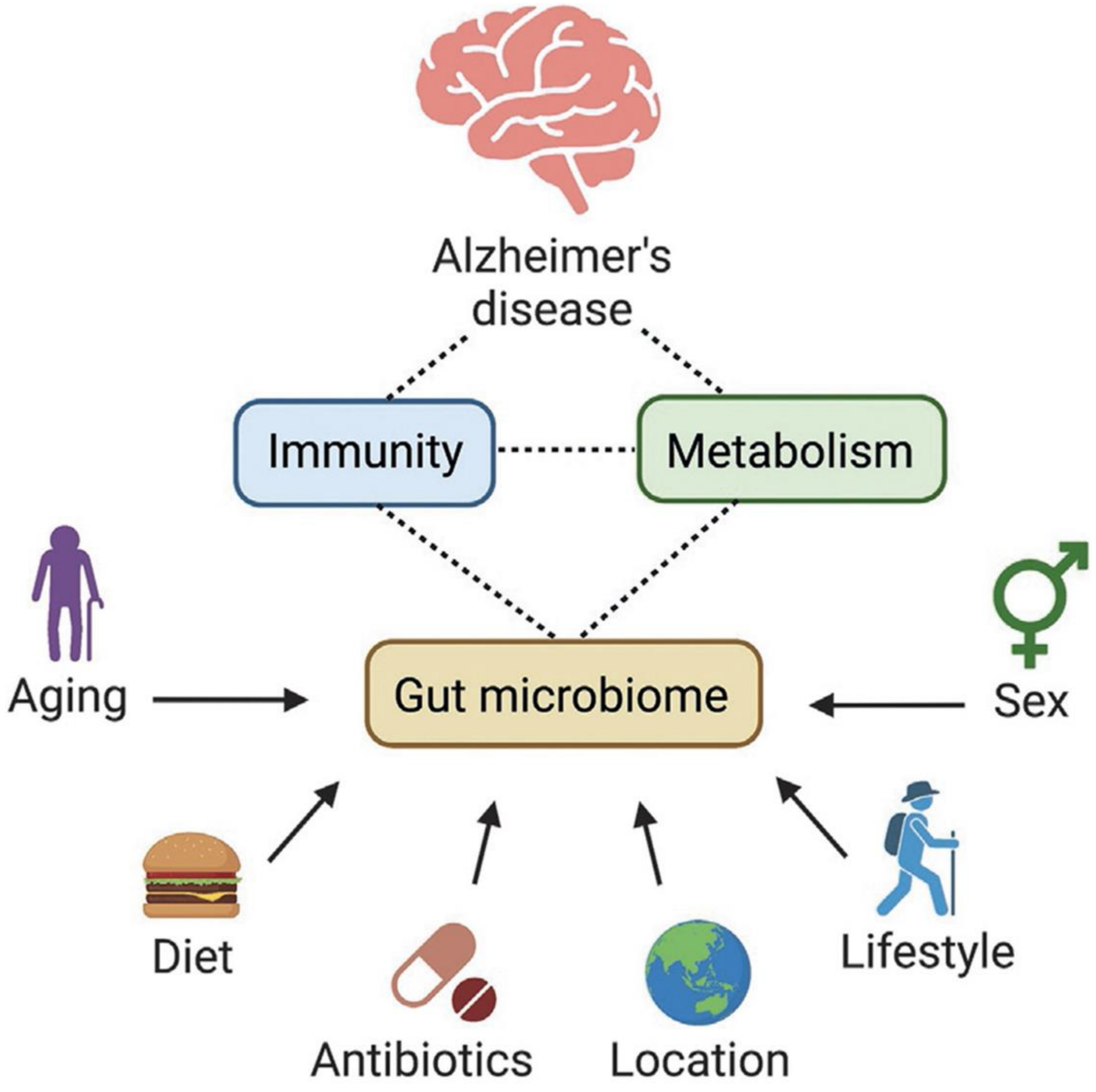


Figure 2. SCFAs in mice enhanced the tight junction and reduced the accumulation of Aβ.

Het microbioom en AD



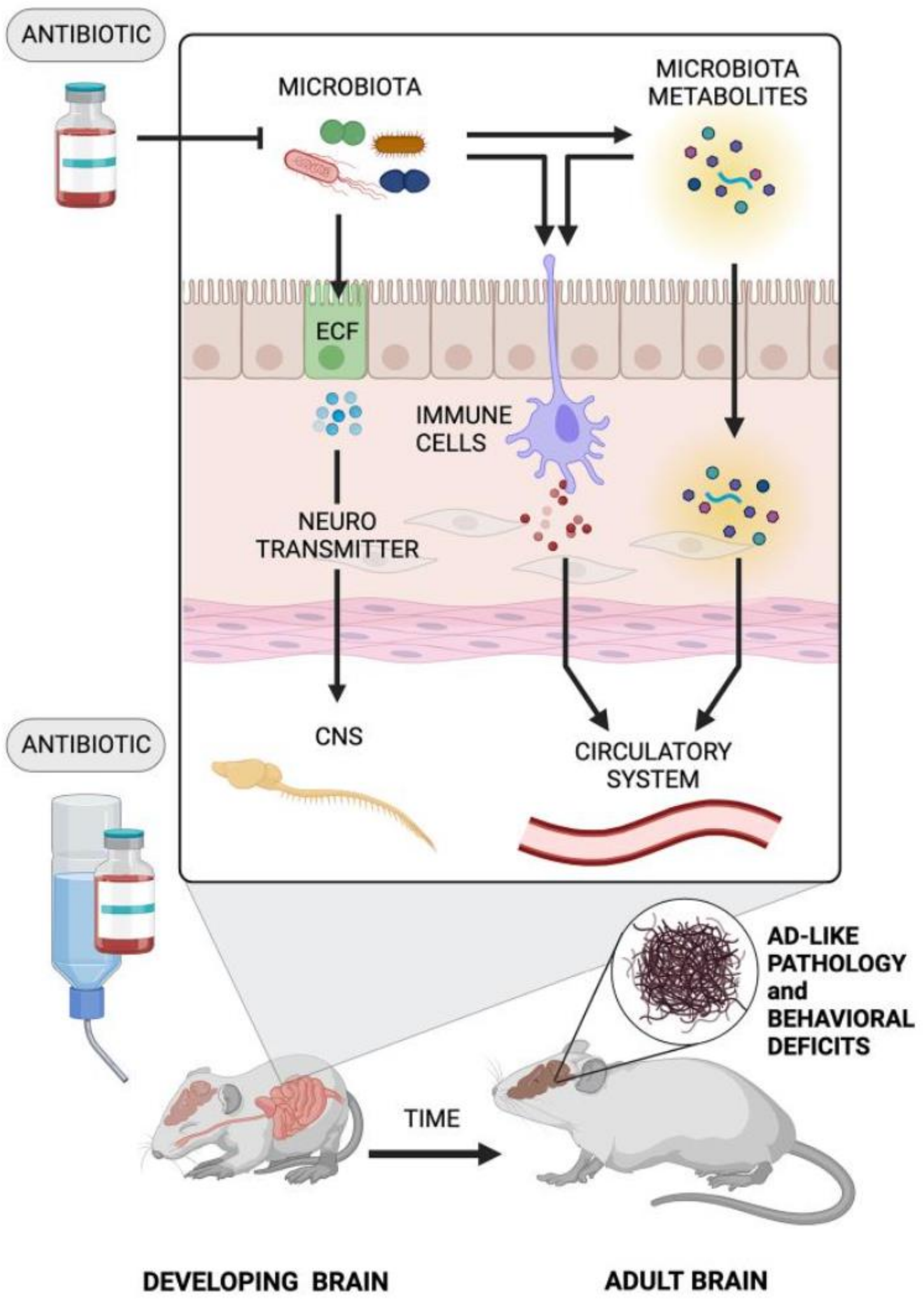
Uitdagingen voor de toekomst

- Herevaluatie van bestaande pathofysiologische modellen
- Heterogeniteit van causale en risicofactoren
- Vroegdetectie van inzettende pathologie
- Biomerkers voor vroegtijdige detectie/diagnose/follow-up
- Definitie van de impact van microbiomen
- Herevaluatie van early-life determinanten van ziekte via het microbioom
- Modificatie van het microbioom als preventie/therapie

The Journal of Infectious Diseases
SUPPLEMENT ARTICLE

Alzheimer's Disease Has Its Origins in Early Life via a Perturbed Microbiome

Stephen D. Ginsberg[1,2,3,4] and Martin J. Blaser[5,6]

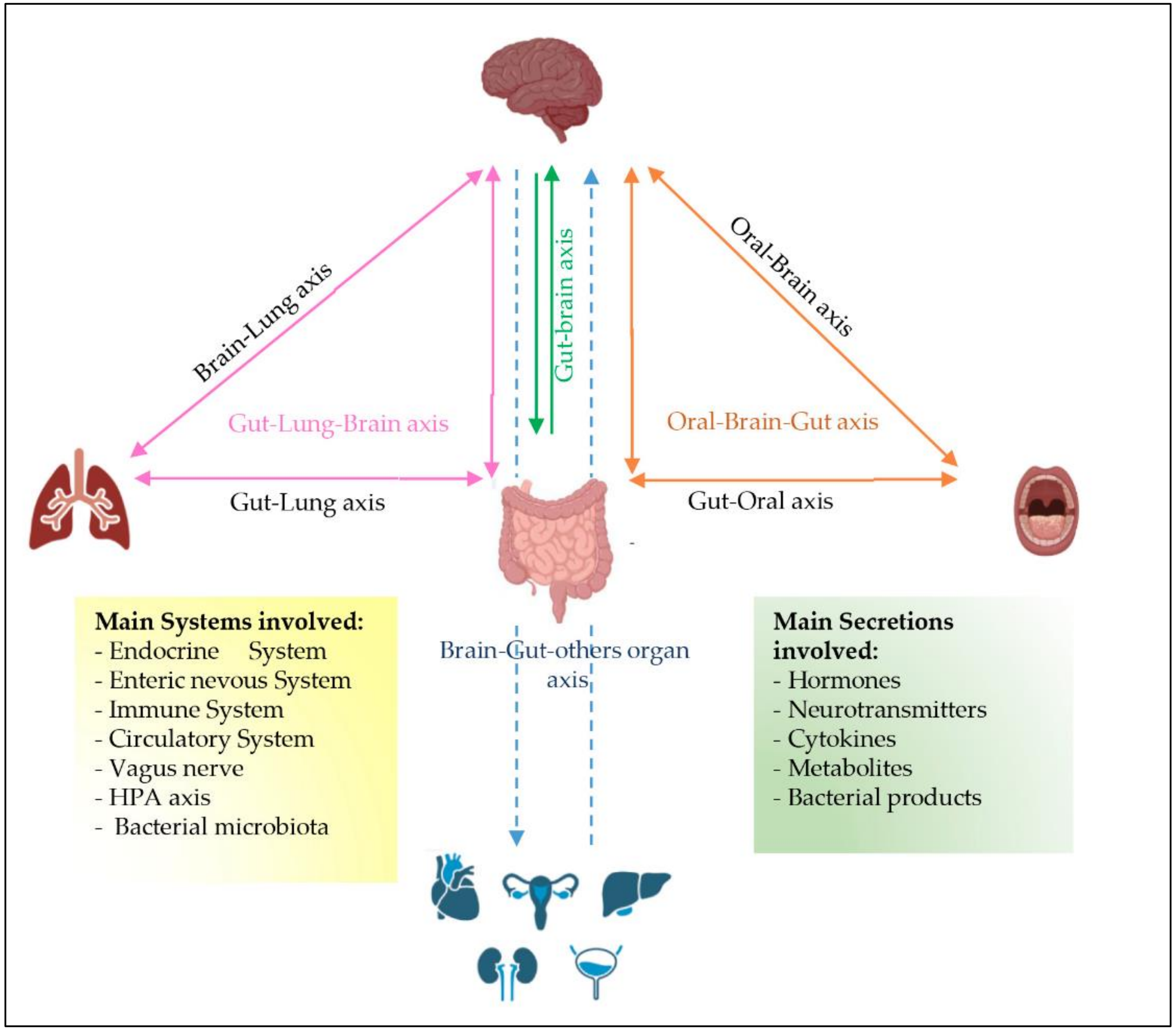


“Microbiomen”

International Journal of
Molecular Sciences
MDPI

Review
Microbiota-Derived Extracellular Vesicle as Emerging Actors in Host Interactions

Paola Margutti *, Antonella D’Ambrosio and Silvia Zamboni



Biomarkers: extracellulaire bacteriële vesikels?

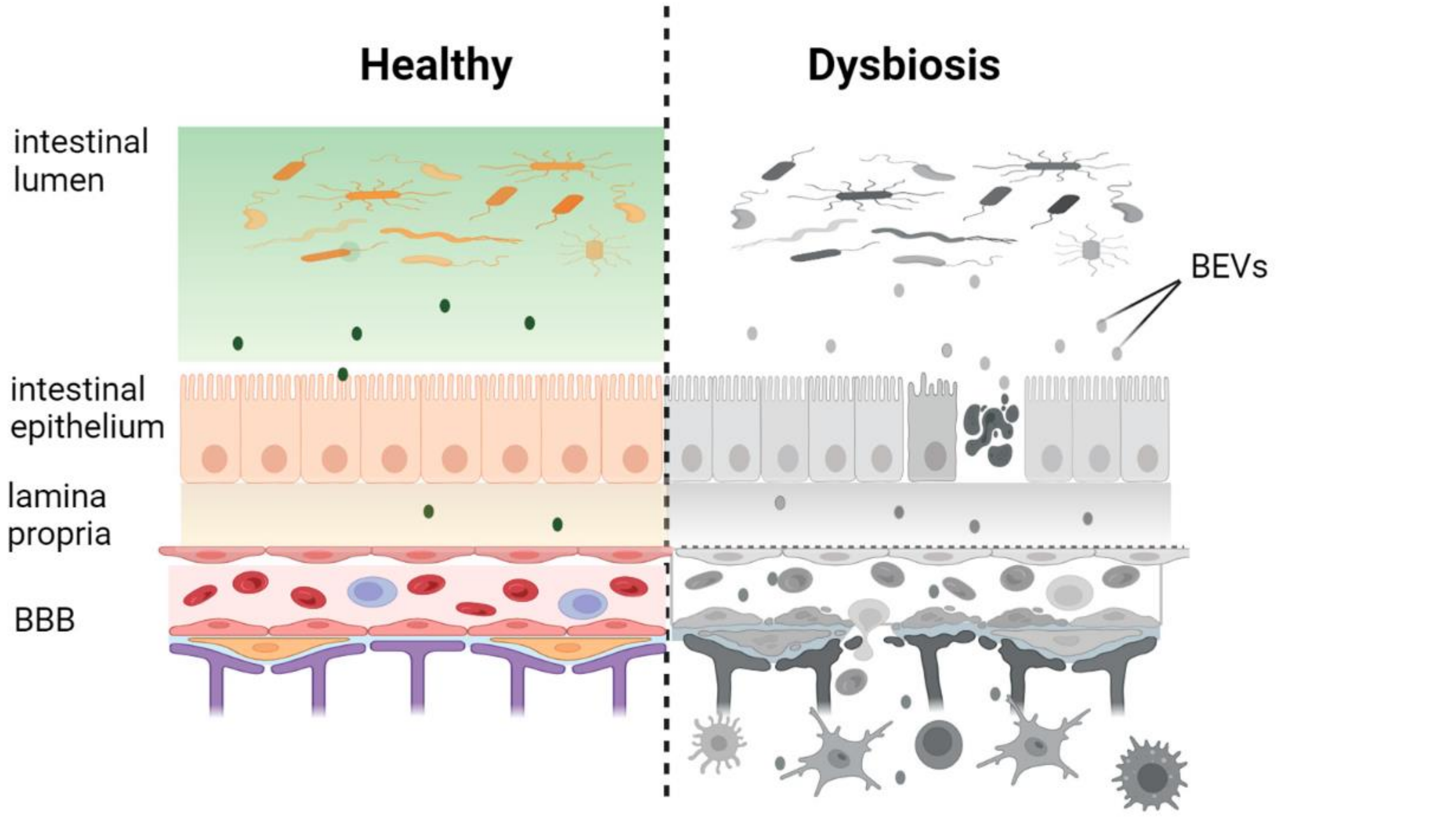


Figure 4. Schematic interaction between BEVs and cellular barriers in health and disease (created with BioRender.com).

The era of the microbiome