Unraveling gut microbiota in Parkinson's disease and atypical parkinsonism.

Il recente studio sul microbiota

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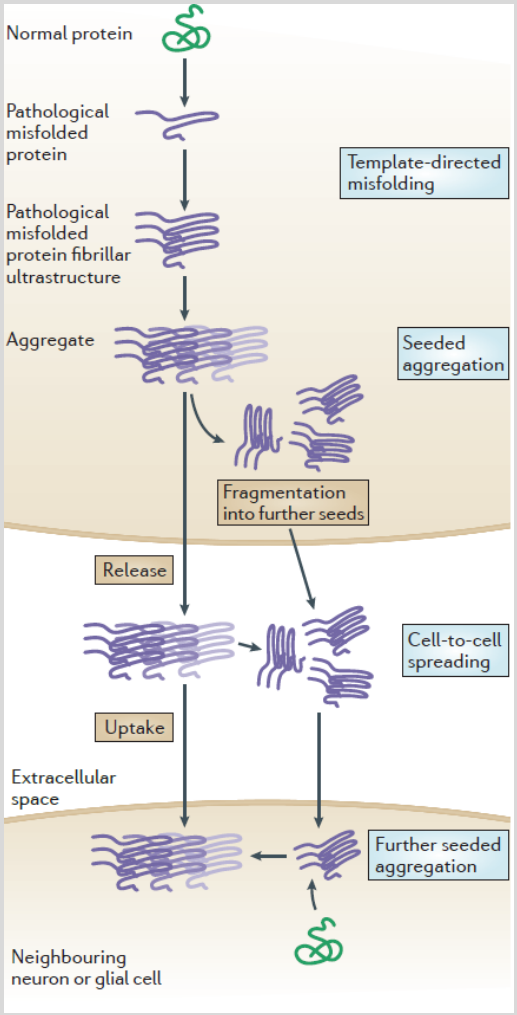
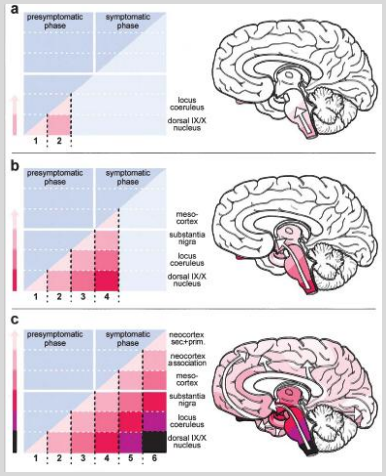
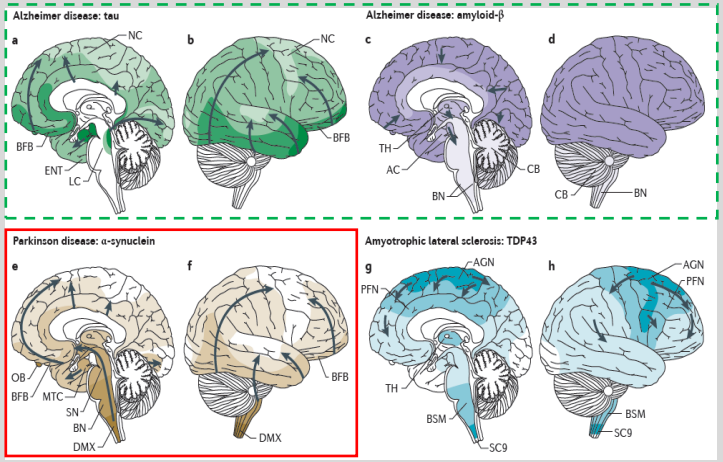
BRAIN AND MALNUTRITION
Chronic Diseases Association ONLUS

La propagazione da neurone a neurone per ‘misfolding su template’ della patologia nelle malattie Neurodegenerative







Evidences for a cell-to-cell (prion-like) propagation of pathology boosted research on the Braak hypothesis.

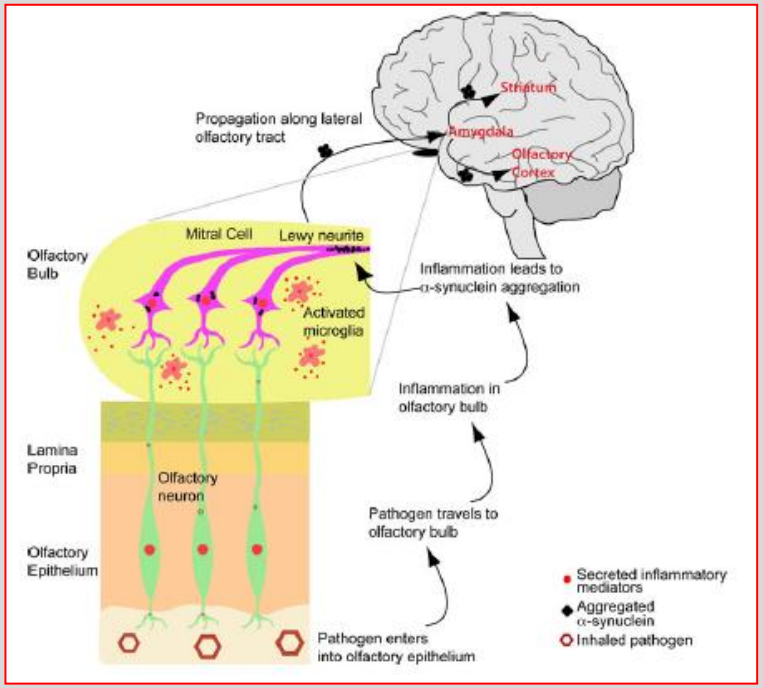
Similar mechanisms increasingly recognized in other degenerative disorders (eg AD, ALS)

Braak et al., 2003
Goedert, Science 2015
Brettschneider, Nat Rev Neurosci 2015

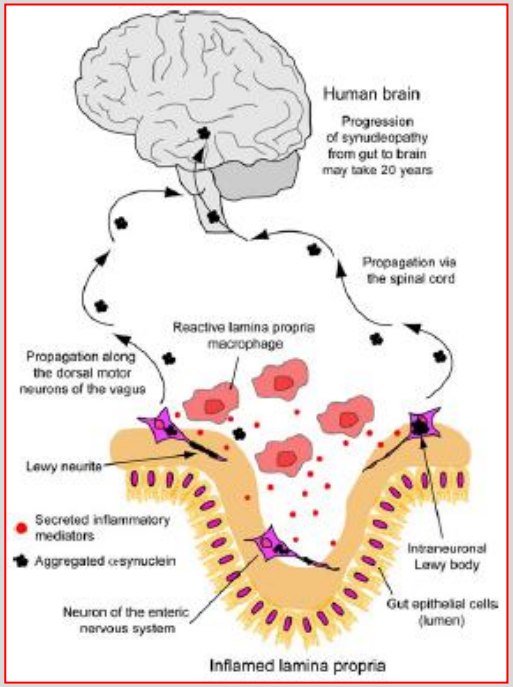
Qual’è il trigger iniziale del misfolding dell’ α-sinucleina?

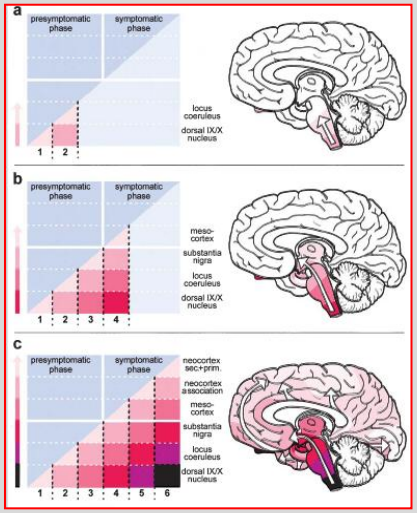
1. «Patogeni Esterni?»

Pathogen enters from the Olfactory Bulb



Pathogen enters from the Gut

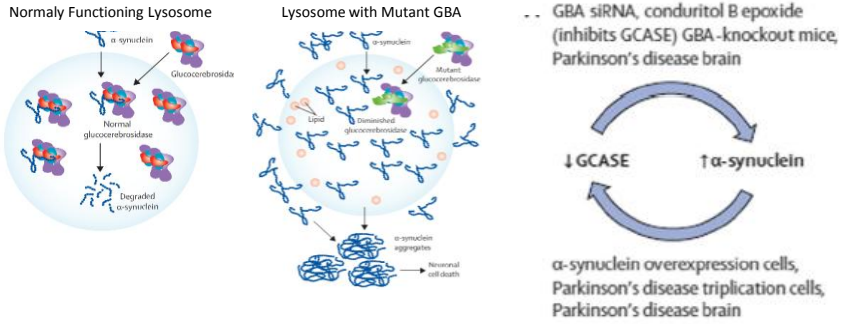




Braak et al, Neurobiol Aging 2003; Holmqvist et al, Acta Neuropathol 2014 Klingelhoefer & Reichmann, Nature Rev 2015; Pellegrini et al, Acta Neuropathologica 2018

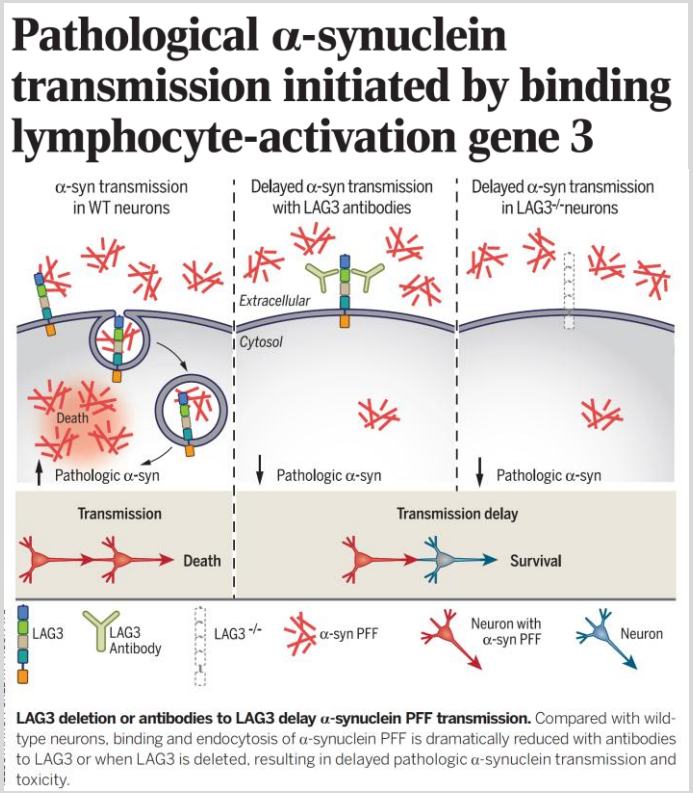
Qual'è il trigger iniziale del misfolding dell' α-sinucleina?

2. «Fattori Genetici?»



GBA1 mutations (10-11% of PD) reduce neuronal ability to degrade α-syn. Risk for Dementia 3-fold higher than for PD -> diffuse α-syn pathology.

Murphy et al., Brain 2014



Mao et al., Science 2016

Qual'è il trigger iniziale del misfolding dell' α-sinucleina?

3. «Fattori Ambientali?»

Exposure to pesticides or solvents and risk of Parkinson disease

Gianni Pezzoli, MD
Emanuele Cereda, MD, PhD

Neurology® 2013;80:2035-2041

In a meta-analysis, high-quality case-control studies evidence that exposure to any-type pesticides, herbicides, and solvents, increase the risk for PD.
Exposure to Paraquat -> 2-fold increased risk.

Oral Exposure to Paraquat Triggers Earlier Expression of Phosphorylated α-Synuclein in the Enteric Nervous System of A53T Mutant Human α-Synuclein Transgenic Mice

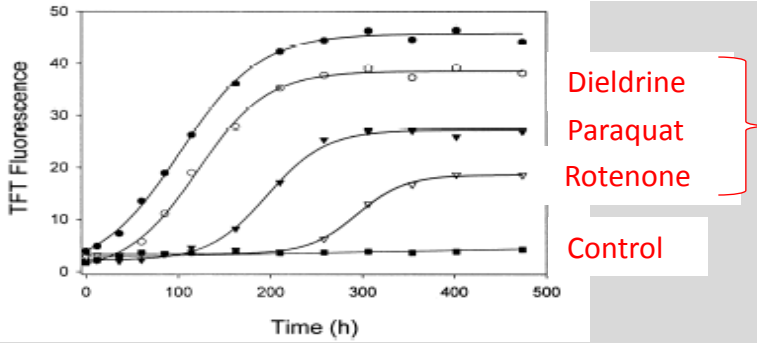
Nicolas Naudet, MSc, Emilie Antier, BS, Damien Gaillard, BS, Eric Morignat, MSc, Latifa Lakhdar, PhD, Thierry Baron, DVM, PhD, HDR, and Anna Bencsik, PhD, HDR

Pesticidi (Paraquat) are able to trigger α-syn aggregation in the gut and to accelerate the formation of toxic oligomers.

FEBS 25011 FEBS Letters 500 (2001) 105–108

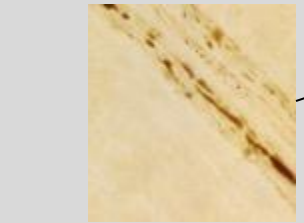
Pesticides directly accelerate the rate of α-synuclein fibril formation: a possible factor in Parkinson's disease

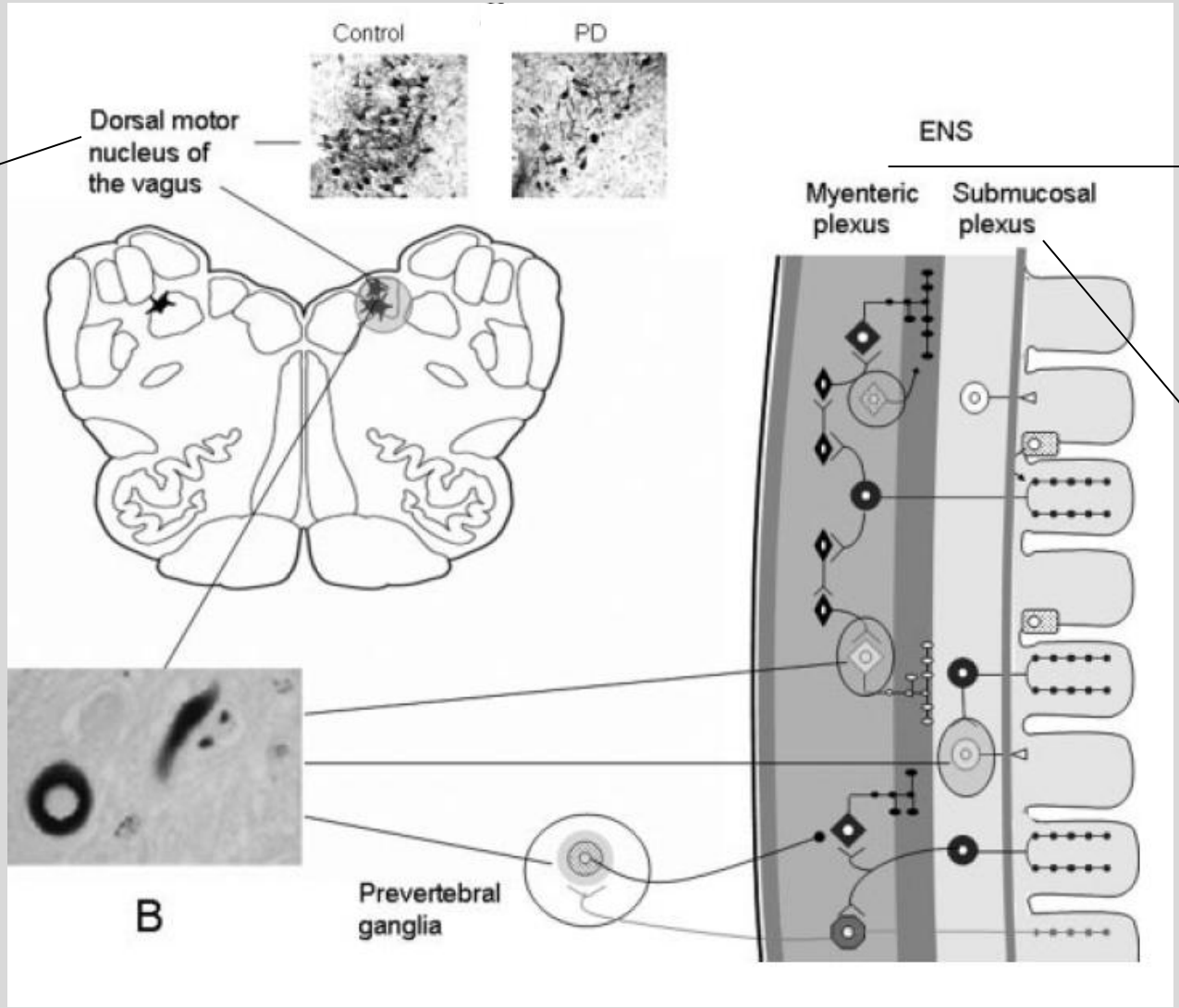
Vladimir N. Uversky, Jie Li, Anthony L. Fink*

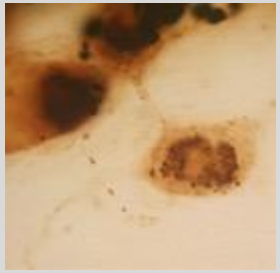


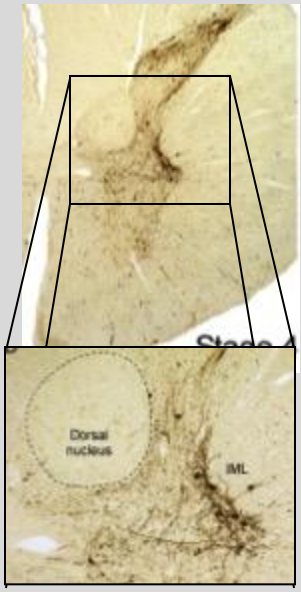
Uversky et al., FEBS Letters 2008; Cereda and Pezzoli, Neurology 2013; Naudet et al., J Neuropathol Exp Neurol 2017

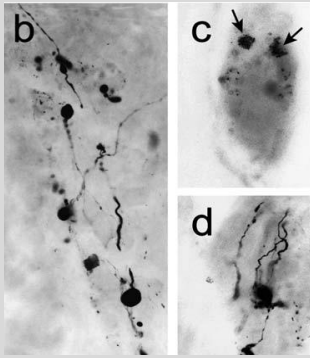
α-synuclein in DMV and GI of PD patients







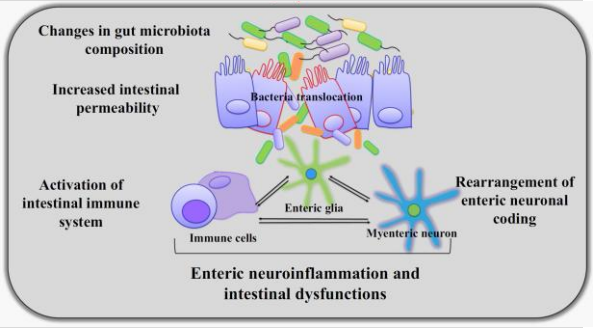




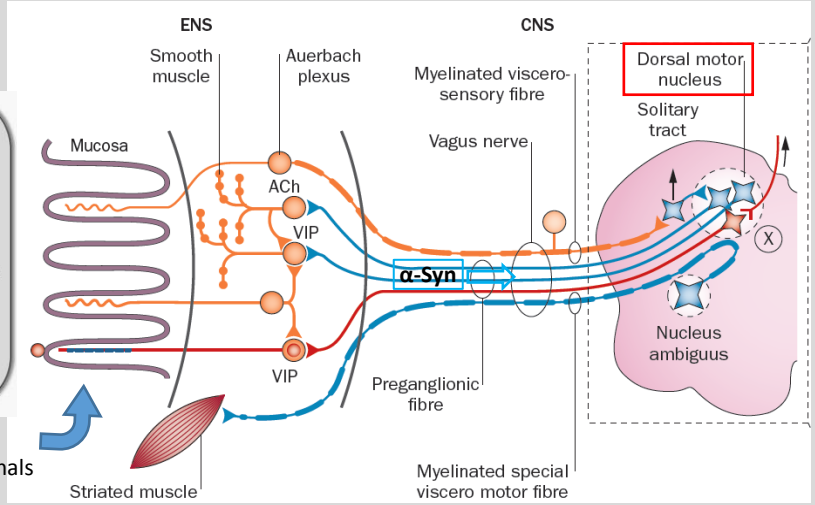
Braak et al., 2003; 2006; 2007;
Braak & Del Tredici, 2008;
Cersosimo et al., 2008

Braak's Hypothesis of gut-to-brain propagation of α-syn pathology

1) A **pathogen** passes the GI mucosal lining (increased epithelial permeability?)



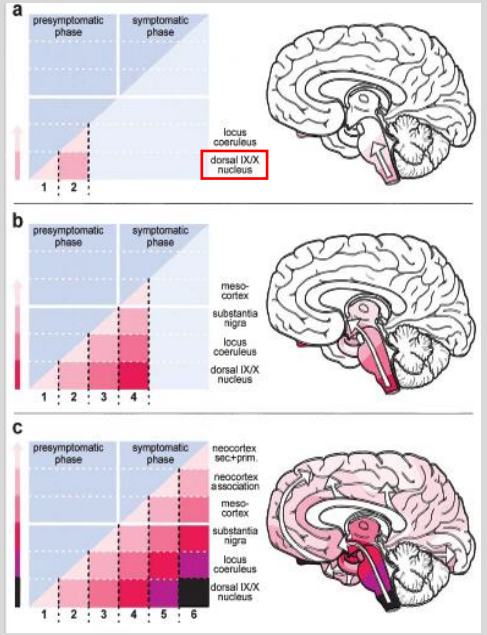
2) Triggers **α-Syn misfolding** in post-ganglionic ENS terminals



3) α-Syn aggregates in GI walls
(LBs in GI biopsies)

4) α-Syn retrogradely propagates along the vagus nerve

5) α-Syn reaches the DMV

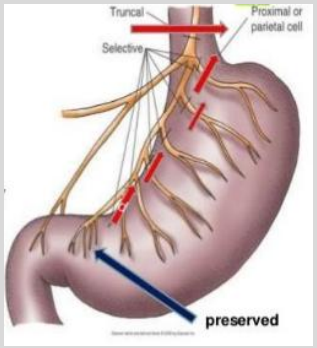


6) α-Syn spreads and aggregates in LBs throughout the CNS
(LBs in the LC and SNc)

7) LBs induce neuronal death and PD symptoms/signs

Braak et al., Neurobiol Aging 2003; Klingelhoefer & Reichmann, Nature Review 2015; Pellegrini et al., Acta Neuropathologica 2018

Vagotomia Tronculare e rischio di PD



Vagotomy and Subsequent Risk of Parkinson's Disease

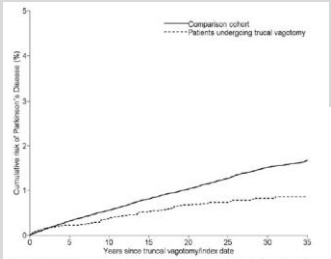


FIGURE 1: Cumulative incidence curves of Parkinson's disease for patients who underwent truncal vagotomy compared to a matched general population cohort.

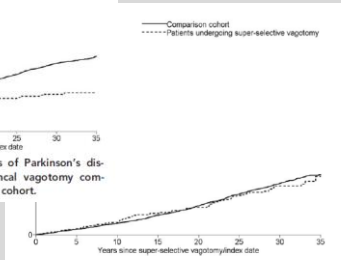


FIGURE 2: Cumulative incidence curves of Parkinson's disease for patients undergoing superselective vagotomy compared to a matched general population cohort.

Danish registry. Follow-up 1977-1995
Nonsignificant lower PD risk at 5 years F-up
(adjusted HR 0.85; 95% CI: 0.56–1.27)
Marginal significance only >20-y F-up (HR 0.53, 95% CI 0.53–0.99)
«limited statistical precision, wide associated CIs»

Does Vagotomy Reduce the Risk of Parkinson's Disease?

Ole-Bjørn Tysnes, MD, PhD,[1,6] Line Kenborg, MSc, PhD,[2] Karen Herlofson, MD, PhD,[3] Marianne Steding-Jessen, MSc,[2] Arild Horn, MD, PhD,[4] Jørgen H. Olsen, DMSc,[2] Heinz Reichmann, MD, PhD[5]

Same Danish population with extended Follow-up 1977–2011
Truncal vagotomy -> nonsignificantly lower PD risk (HR 0.88, 95% CI 0.55–1.21)
Nonsignificantly elevated PD risk >20 years after the surgery (HR 1.14, 95% CI 0.23–2.05)

Vagotomy and Parkinson disease

A Swedish register–based matched-cohort study

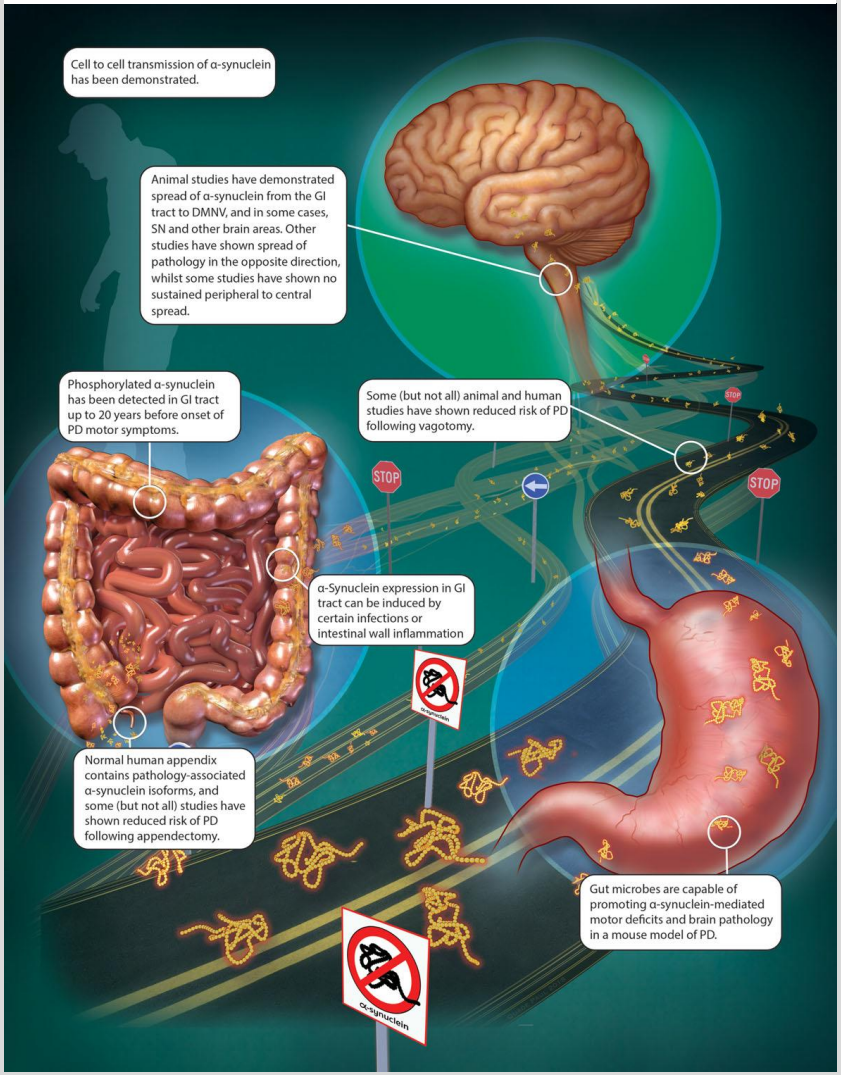
9,430 vagotomized patients (3,445 truncal and 5,978 selective) Follow-up 1970-2010
N = 4,930 incident PD during 7.3 million person-years of follow-up.
Truncal vagotomy -> nonsignificantly lower PD risk (HR 0.78, 95% CI 0.55–1.09)

TAKE HOME MESSAGE:
- Nonsignificant Risk Reduction (CIs > 1.0)
- Conflicting Data at 20-y F-up

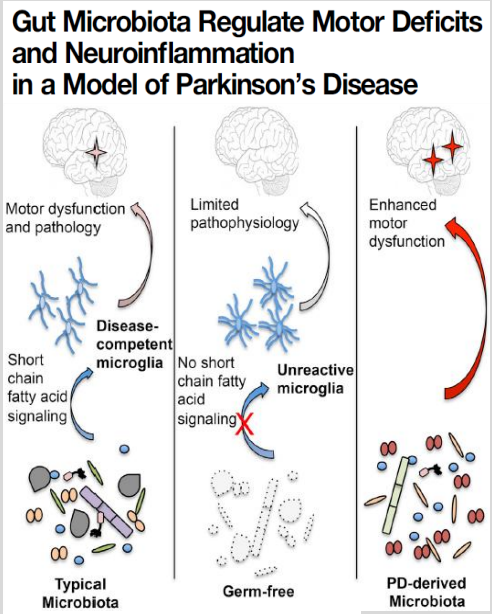
Svensson et al., Ann Neurol 2015; Tysnes et al., Ann Neurol 2015; Liu et al., Neurology 2017

Gut–Brain Axis and the Spread of α-Synuclein Pathology: Vagal Highway or Dead End?

David P. Breen, MBChB, PhD,[1,2,3*] Glenda M. Halliday, PhD[4,5,6] and Anthony E. Lang, MD[7,8]



Does Gut Microbiota influence PD risk via the vagus nerve or systemic inflammation?



Sampson et al, Cell 2016

In α-syn overexpressing mouse model of PD:

- **Typical Microbiota** promote α-synuclein pathology
- Depletion of gut bacteria (**Germ-Free**) reduces microglia activation and α-syn pathology
- **Human gut microbiota from PD cases** (but not HC) enhances motor dysfunction

HOWEVER:

Change in Microbiota alone is not sufficient to trigger α-syn pathology in the ENS

a) Microbiota **-> SCFAs signaling -> Microglia activation** -> α-syn pathology

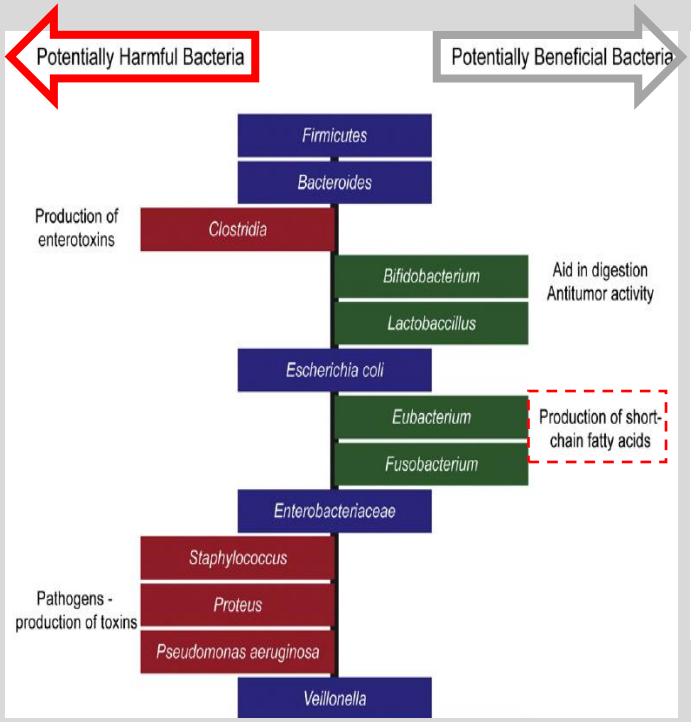
b) Oral feeding by SCFAs induces α-syn pathology *without* microbiota colonization

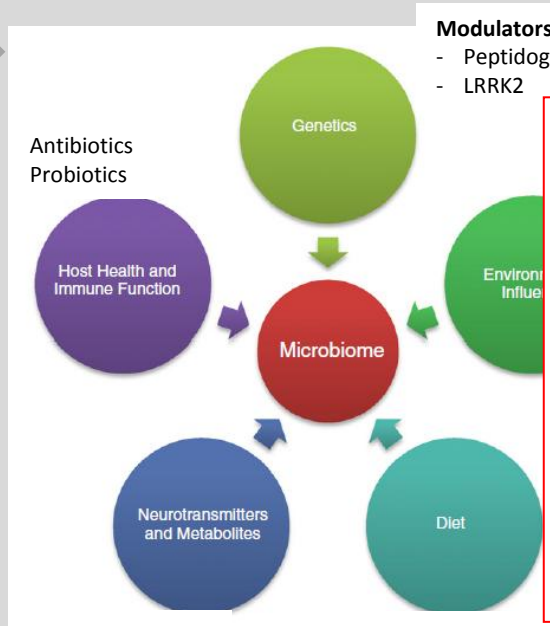
QUESTIONS:

- *What is the role of SCFAs? (..protective for gut epithelium and anti-inflammatory..)*
- *Is systemic route associated to Microbiota-induced changes (instead vagal nerve)?*

Microbiota: Potential Effects and Modulators

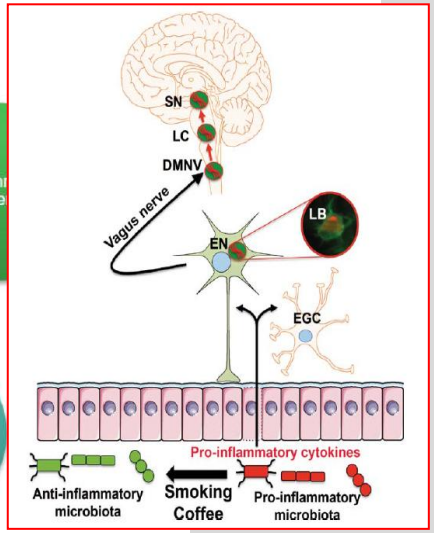
Harmful (Pro-Inflammatory) vs. Beneficial (Anti-Inflammatory)





Modulators of immune response

- Peptidoglycan Recognition Proteins genes
- LRRK2



Stressors
(input from CNS)

Dietary habits

- Plant-based (Bacteroides, Firmictues)
- Animal-based (Bacteroides)
- Fiber-based (Prevotella)

Wu et al., Science 2011; Goldman et al., Mov Disord 2014; Visanji, Mov Disord 2014; Ghaisas et al., Pharmacology & Therapeutics 2016

Microbiota in PD/PKS: the (conflicting) results

	Scheperjans 2015	Keshavarzian 2015	Hasegawa 2015	Hill-Burns 2017	Unger 2016	Hopfner 2017	Heintz-Buschart 2017	Engen 2017
Study area	Finland	U.S.A.	Japan	U.S.A.	Germany	Germany	Luxemburg/ Germany	U.S.A.
Diagnosis	PD	PD	PD	PD	PD	PD	PD	MSA
N° of Cases/CNTR	72/72	38/36	52/36	197/130	34/34	29/29	76/78 (21 iRBD)	6/11
Samples	Fecal	Fecal and Mucosal	Fecal	Fecal	Fecal	Fecal	Fecal & Nasal	Fecal and Mucosal
Antibiotics-free / Nutrition Diaries	>1month / No	>3months / No	Not reported / No	Not reported / No (diet assessed)	Not reported / No	Not reported / No	Not reported / No	Not reported / No
Main Outcome	↓ Prevotellaceae PD phenotype -> Enterobacteriaceae	Anti-inflamm in HC Pro-inflamm in PD ↓ SCFAs ↑ LPS synthesis	↓ hydrogen-producing bacteria in PD ↑ LPS (↓ serum LPS-binding protein)	Diet fruits/vegetables ↑Xenobiotics degradation ↓ SCFAs PD duration -> Ruminococcaceae	↓ SCFAs	↑ Lactobacillaceae	80% microbiota differences PD vs HC similar in iRBD	Intestinal barrier dysfunction ↑ LPS synthesis
Decreased (fecal)	Prevotellaceae	Firmicutes, Lachnospiraceae, Coprobacillaceae, Roseburia, (No change in Prevotellaceae)	Clostridium c/Clostridium I Bacteroides f.	Lachnospiraceae, (No change in Prevotellaceae)	Firmicutes (Prevotellaceae, n.s.) Lactobacillaceae Bacteroidetes	None	None	Firmicutes
Increased (fecal)	Lactobacillaceae, *Verrucomicrobiaceae*, Clostridiales i.s. IV, Ruminococcaceae	Bacteroidetes, Proteobacteria, *Verrucomicrobia*, Clostridiaceae,	Lactobacillaceae	Lactobacillaceae, *Verrucomicrobiaceae* Bifidobasteriaceae Christensenellaceae	Enterobacteriaceae *Verrucomicrobia*,	Lactobacillaceae Bifidobacterium Barnesiellaceae Enterococcacea	*Verrucomicrobia*,	Bacteroidetes Proteobacteria
Clinical Features	UPDRS III Non-tremor phenotype iCOMT -> Lactob,, Enterob	*Disease Duration* Treated ≠ Untreated	*Disease Duration* (No association between microbiota & medications)	iCOMT Anticholinergics Levodopa/Carbidopa	Not reported	No effect of iCOMT	Correlat with NMS (Bacteroides)	Not reported

Microbiota in PD/PKS: the (conflicting) results

Sources of Variability

	Scheperjans 2015	Keshavarzian 2015	Hasegawa 2015	Hill-Burns 2017	Unger 2016	Hopfner 2017	Heintz-Buschart 2017	Engen 2017
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Diagnosis	PD	PD	PD	PD	PD	PD	PD	MSA
N° of Cases/CNTR	72/72	38/36	52/36	197/130	34/34	29/29	76/78 (21 iRBD)	6/11
Samples	Fecal	Fecal and Mucosal	Fecal	Fecal	Fecal	Fecal	Fecal & Nasal	Fecal and Mucosal
Antibiotics-free / Nutrition Diaries	>1month / No	>3months / No	Not reported / No	Not reported / No (diet assessed)	Not reported / No	Not reported / No	Not reported / No	Not reported / No
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Decreased (fecal)	Prevotellaceae	Firmicutes, Lachnospiraceae, Coprobacillaceae, Roseburia, (No Prevotellaceae)	Clostridium c/Clostridium I Bacteroides f.	Lachnospiraceae, (No Prevotellaceae)	Firmicutes Lactobacillaceae (No Prevotellaceae) Bacteroidetes	None	None	Firmicutes
Increased (fecal)	Lactobacillaceae, Verrucomicrobiaceae, Clostridiales i.s. IV, Ruminococcaceae	Bacteroidetes, Proteobacteria, Verrucomicrobia, Clostridiaceae,	Lactobacillaceae	Lactobacillaceae, Verrucomicrobiaceae Bifidobasteriaceae Christensenellaceae	Verrucomicrobia, Enterobacteriaceae	Lactobacillaceae Bifidobacterium Barnesiellaceae Enterococcacea	Verrucomicrobia,	Bacteroidetes Proteobacteria
Clinical Features	UPDRS III Non-tremor phenotype iCOMT -> Lactob., Enterob	*Disease Duration* Treated ≠ Untreated	*Disease Duration* (No association between microbiota & medications)	iCOMT Anticholinergics Levodopa/Carbidopa	Not reported	No effect of iCOMT	Correlated with NMS (Bacteroides)	Not reported

Consistency: ↑Verrucomicrobiaceae (Akkermansia); ↑Lactobacillaceae; ↓Lachnospiraceae; ↓Firmicutes
Conflicting: Bacteroidetes; Clostridiaceae; (↓) Prevotella

Microbiota Intestinale e PD: Più Domande che Risposte?

1) Conflicting results due to methodological difficulties/issues

Question: Shall we focus on biopsies (more stable flora) rather than fecal samples?

2) Microbiota is influenced by several confounders

Question: *adjusting the analyses by nutrient intake, type of delivery and feeding, habits?*

3) Microbiota may be modifyied by PD medications and progression

Question: Are microbiota abnormalities a cause of PD or compensatory changes?
(Need of Longitudinal studies on de novo PD and at-risk populations)

4) Microbiota may promote α-syn aggregation and trigger cell-to-cell propagation

Question: Does gut microbiota influence Tau pathology as well?

5) Beyond the gut, Beyond bacteria

Question: What about nasal microbiota (olfactory bulb as first site of seeding)?
Question: What about virome?

RESEARCH ARTICLE

Unraveling Gut Microbiota in Parkinson's Disease and Atypical Parkinsonism

Michela Barichella, MD,[1] Marco Severgnini, MSc,[2] Roberto Cilia, MD,[1] Erica Cassani, MD,[1] Carlotta Bolliri, ScD,[1] Serena Caronni, ScD,[1] Valentina Ferri, MD,[1] Raffaella Cancello, PhD,[3] Camilla Ceccarani, PhD,[2,4] Samanta Faierman, ScD,[1] Giovanna Pinelli, MD, PhD,[1,5] Gianluca De Bellis, MSc,[2] Luigi Zecca, MSc,[2,6] Emanuele Cereda, MD, PhD,[7*] Clarissa Consolandi, PhD,[2] and Gianni Pezzoli, MD[1]

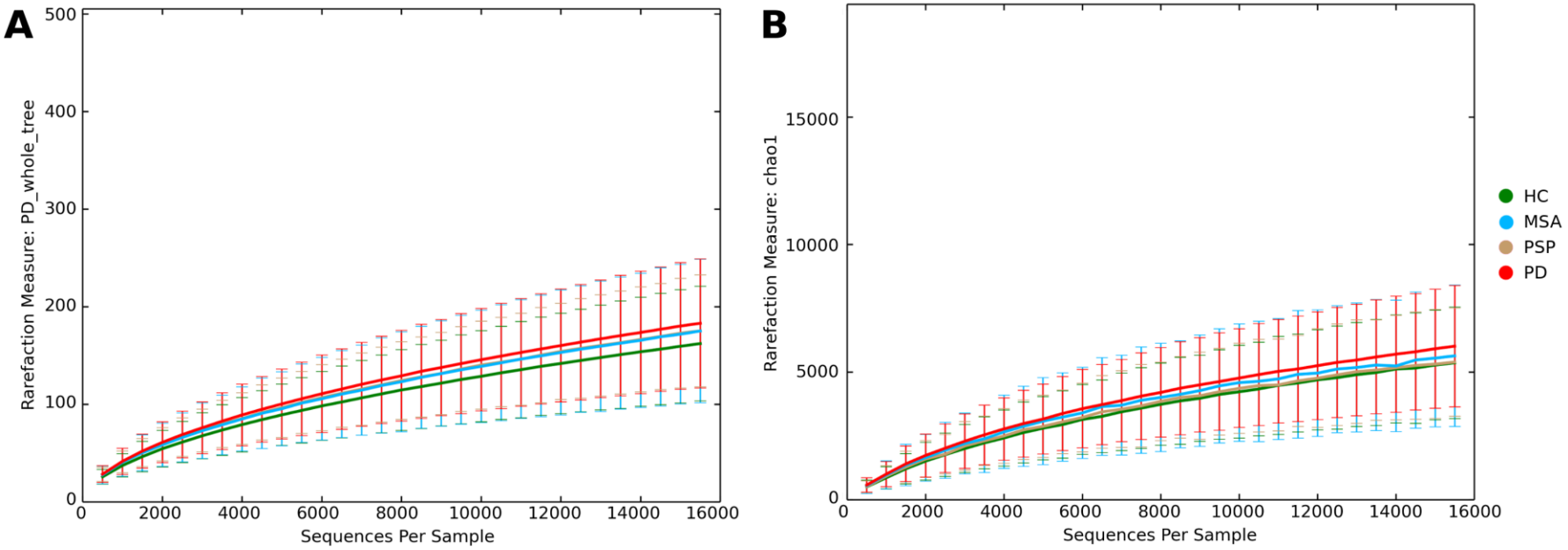
Movement Disorders, 2018

- Studio osservazionale prospettico caso-controllo (07/2014 -> 02/2017)
- N=350 soggetti
  - PD n=193 (De Novo n=39)
  - PSP n=22
  - MSA n=22
  - HC n=113
- Scale cliniche (UPDRS, H&Y, MMSE, NMSQ) e terapia farmacologica.
- Valutazione Nutrizionale: diario alimentare 10 giorni e 24-h recall (WinFood software)
- Studio microbiota con metodica di amplificazione 16S ribosomiale RNA

TABLE 1. General characteristics of the study population and related subgroups

Variable	Healthy controls, n = 113	PD patients					MSA patients, n = 22	PSP patients, n = 22
		All cases, n = 193	De novo, n = 39	Early stage, n = 57[*,a]	Mid stage, n = 53[*,§]	Advanced stage, n = 44[*,#]		
Male gender, n (%)	47 (41.6)	115 (59.6)	27 (69.2)	36 (63.1)	31 (58.5)	21 (47.7)	8 (36.4)	13 (59.1)
Age, y, mean (SD)	65.9 (9.9)	67.6 (9.7)	67.0 (8.5)	66.1 (10.9)	68.6 (9.0)	68.8 (9.9)	67.0 (7.0)	71.0 (7.9)
Cesarean delivery, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Formula fed, n (%)	11 (9.7)	18 (9.3)	1 (2.6)	7 (12.3)	6 (11.3)	4 (9.1)	0 (0)	0 (0)
Current smoking, n (%)	15 (13.3)	18 (9.3)	3 (7.7)	7 (12.3)	5 (9.4)	3 (6.8)	1 (4.5)	1 (4.5)
Body weight, kg, mean (SD)	69.1 (14.0)	69.4 (14.6)	67.3 (11.8)	72.4 (12.4)	71.2 (15.9)	64.7 (16.3)	60.1 (11.4)	71.1 (17.2)
Body mass index, kg/m^2, mean (SD)	25.3 (4.6)	25.2 (4.6)	24.0 (3.3)	26.3 (4.9)	25.6 (4.5)	24.3 (5.0)	24.7 (3.8)	26.0 (4.6)
Constipation, n (%)	21 (18.6)	99 (51.3)	19 (48.7)	24 (42.1)	31 (58.5)	25 (56.8)	16 (72.7)	14 (63.6)
Disease duration, y, mean (SD)	–	7.7 (7.3)	1.6 (1.4)	3.2 (1.5)	8.0 (1.4)	18.4 (7.4)	5.8 (4.1)	6.7 (4.4)
Hoehn-Yahr stage, mean (SD)	–	2.0 (0.8)	1.6 (0.5)	1.7 (0.6)	2.2 (0.7)	2.6 (0.9)	3.1 (1.0)	3.2 (0.8)
UPDRS-part I score, mean (SD)	–	2.0 (1.9)	1.1 (1.1)	1.6 (1.6)	3.0 (2.1)	2.3 (2.3)	2.2 (1.7)	3.6 (1.8)
UPDRS-part II score, mean (SD)	–	9.4 (5.9)	5.5 (3.1)	6.9 (3.5)	10.9 (5.1)	14.9 (6.7)	18.5 (8.3)	22.1 (6.8)
UPDRS-part III score, mean (SD)	–	17.2 (11.4)	15.7 (9.2)	13.9 (9.2)	18.8 (13.0)	20.8 (12.6)	39.0 (19.5)	33.8 (17.5)
UPDRS-part IV score, mean (SD)	–	1.9 (2.6)	0.2 (0.4)	0.9 (1.8)	2.6 (2.7)	4.3 (2.8)	1.2 (0.9)	0.7 (1.5)
MMSE score, mean (SD)	27.9 (2.1)	27.5 (3.5)	28.4 (1.3)	27.8 (4.0)	27.2 (3.2)	26.6 (4.4)	26.6 (4.3)	25.4 (4.4)
NMSQuest total score, mean (SD)	–	11.4 (5.5)	7.4 (4.0)	10.2 (5.2)	12.8 (4.9)	13.3 (5.8)	13.5 (4.0)	13.3 (4.9)
Diabetes, n (%)	8 (7.1)	11 (5.7)	3 (7.7)	3 (5.3)	4 (7.5)	1 (2.3)	3 (13.6)	2 (9.1)
Hypertension, n (%)	39 (34.5)	65 (33.7)	16 (41.0)	22 (38.6)	18 (34.0)	9 (20.5)	7 (31.8)	10 (45.5)
Levodopa, n (%)	–	147 (76.2)	–	53 (93.0)	53 (100)	44 (100)	18 (81.8)	15 (68.2)
Levodopa dose,[b] mg/day, mean (SD)	–	393 (334)	–	347 (180)	573 (326)	586 (326)	414 (306)	269 (270)
Concomitant DA, n (%)	–	80 (41.5)	–	23 (40.4)	31 (58.5)	26 (59.1)	6 (27.3)	5 (22.7)
Concomitant COMT, N (%)	–	29 (15.0)	–	5 (8.8)	13 (24.5)	11 (25.0)	0 (0)	0 (0)
Concomitant MAO-B, n (%)	–	27 (14.0)	–	10 (17.5)	11 (20.8)	6 (13.6)	1 (4.5)	4 (18.2)
Total LEDD, mg/day, mean (SD)	–	525 (440)	–	429 (219)	694 (379)	727 (366)	463 (351)	326 (265)
Anticholinergics, n (%)	–	1 (0.5)	0 (0)	0 (0)	0 (0)	1 (2.3)	1 (4.5)	1 (4.5)
Antipsychotics, n (%)	–	9 (4.7)	0 (0)	2 (3.5)	3 (5.7)	4 (9.1)	0 (0)	0 (0)
Dementia medications, n (%)	–	3 (1.6)	0 (0)	0 (0)	1 (1.9)	2 (4.5)	0 (0)	0 (0)
Proton pump inhibitors, n (%)	7 (6.2)	22 (11.4)	3 (7.7)	7 (12.3)	6 (11.3[/])	6 (13.6)	3 (13.6)	3 (13.6)
Calorie intake, kcal/kg/day, mean (SD)	27.5 (8.1)	27.0 (8.2)	27.8 (6.5)	25.8 (6.8)	26.0 (7.7)	29.2 (10.9)	26.9 (7.9)	24.5 (7.1)
Protein intake, g/kg/day, mean (SD)	1.05 (0.34)	1.00 (0.32)	1.07 (0.28)	0.94 (0.27)	1.00 (0.35)	1.03 (0.37)	1.07 (0.42)	0.98 (0.30)
Animal-vegetal ratio, g/day, mean (SD)	2.0 (1.3)	1.6 (1.1)	1.80 (0.87)	1.60 (1.69)	1.63 (0.87)	1.56 (0.61)	1.08 (0.9)	2.3 (1.4)
Alcohol intake, g/day, mean (SD)	10.5 (14.2)	7.0 (11.1)	7.8 (10.2)	8.6 (13.9)	7.0 (10.8)	4.2 (7.0)	5.1 (9.3)	5.3 (8.7)
Water intake, mL/kg/day, mean (SD)	27.6 (11.7)	26.2 (9.0)	26.2 (9.9)	25.6 (7.5)	26.2 (8.4)	26.9 (10.7)	28.4 (12.3)	23.9 (9.1)
Coffee intake, cup/week, mean (SD)	9.4 (6.1)	7.4 (6.7)	8.4 (7.9)	8.1 (6.6)	7.0 (6.6)	6.3 (5.6)	6.6 (5.2)	5.6 (4.1)
Fibers intake, g/day, mean (SD)	17.6 (6.0)	18.3 (6.7)	18.2 (6.4)	18.9 (7.2)	18.3 (7.3)	17.6 (5.9)	15.9 (5.1)	15.9 (5.0)
Insoluble-soluble ratio, mean (SD)	2.3 (0.6)	2.4 (0.7)	2.5 (0.7)	2.3 (0.6)	2.5 (0.8)	2.3 (0.5)	2.4 (0.7)	2.1 (0.4)

PD con maggior alfa-diversità rispetto ai sani



Microbiota in PD/PKS al netto dei confounders

Population	Healthy controls (N=113)	PD patients					MSA patients (N=22)	PSP patients (N=22)
		All cases (N=193)	De-novo (N=39)	Early-stage (N=57)[a]*	Mid-stage (N=53)[a]§	Advanced-stage (N=44)[a]#		

	DeNovo	PD
HC	Lachnospiraceae *	~~Ruminococcaceae **~~ Lachnospiraceae *** Verrucomicrobiaceae *** ~~Enterobacteriaceae ***~~ ~~Porphyromonadaceae **~~ ~~Bifidobacteriaceae **~~ Christensenellaceae *** ~~Coriobacteriaceae *~~
DeNovo	--	Verrucomicrobiaceae *

	PSP	MSA	PD
HC	Lachnospiraceae * Verrucomicrobiaceae ** ~~Enterobacteriaceae *~~ Christensenellaceae ***	Verrucomicrobiaceae ** ~~Bifidobacteriaceae *~~ Christensenellaceae * ~~Streptococcaceae *~~ ~~Coriobacteriaceae *~~	~~Ruminococcaceae **~~ Lachnospiraceae *** Verrucomicrobiaceae *** ~~Enterobacteriaceae ***~~ ~~Porphyromonadaceae **~~ ~~Bifidobacteriaceae **~~ Christensenellaceae **
PSP	--	~~Bifidobacteriaceae *~~ ~~Streptococcaceae **~~	~~Prevotellaceae *~~ Christensenellaceae ** ~~Streptococcaceae *~~
MSA		--	~~Streptococcaceae *~~

<u>Numerosi fattori di 'confondimento' dei risultati sul microbiota:</u>

- GENERAL: **<u>age</u>**, <u>gender</u>; <u>breast-feeding</u>; <u>constipation</u>; <u>proton-pump inhibitors</u>; BMI; recessive gene mutations (Parkin/DJ1/Pink1)
- DIET: calorie intake, protein intake, animal-vegetal protein ratio, <u>fiber intake</u>, insoluble-soluble fiber ratio, smoking/coffee/alcohol/water intake
- DRUGS: use of catechol-O-methyltransferase inhibitors (<u>iCOMT</u>)

Microbiota influenced by <u>disease duration</u> and <u>severity</u> of PD clinical features (motor and nonmotor)

-> **more severe phenotype with ↑Lactobacillaceae ↓ Lachnospiraceae**

No major differences between Synucleinopathies (PD vs. MSA) vs. Tauopathies (PSP)

How many of these changes are primary? How many are compensatory?

Barichella*, Severgnini*, Cilia*, et al. Mov Disord 2018

Taxonomic Level [b]			Healthy controls (N=113)	De-novo PD (N=39)	Early PD (N=57)[a]*	Mid-stage PD (N=53) [a]§	Advanced PD (N=44) [a]#	P-value for trend [e]
Phylum	*Family*	*Genus*	*Mean (SD) [c] abundance*	*Mean (SD) [c] [P-value] [d]*	*Mean (SD) [c] [P-value] [d]*	*Mean (SD) [c] [P-value] [d]*	*Mean (SD) [c] [P-value] [d]*	
Actinobacteria			2.49 (3.29)	3.23 (4.43) [0.51]	2.98 (4.63) [0.89]	3.27 (3.30) [0.52]	5.19 (1.48)*** [0.24]	0.099
	Bifidobacteriaceae		1.50 (2.64)	2.24 (3.23) [0.87]	1.77 (3.78) [0.64]	2.27 (2.78)* [0.098]	3.69 (4.19)*** [0.26]	0.14
		Bifidobacterium	1.49 (2.63)	2.23 (3.23) [0.87]	1.76 (3.78) [0.62]	2.23 (2.73)* [0.11]	3.67 (4.18)*** [0.26]	0.14
	Coriobacteriaceae		0.95 (1.26)	0.97 (1.31) [0.82]	1.18 (1.43) [0.49]	0.94 (1.10) [0.58]	1.47 (1.48)** [0.11]	0.18
Bacteroidetes			--	--	--	--	--	
	Porphyromonadaceae		1.56 (2.18)	2.38 (2.84) [0.13]	2.15 (4.08) [0.27]	2.18 (2.59)* [0.15]	2.65 (2.95)** [0.19]	0.93
		Parabacteroides	1.55 (2.17)	2.34 (2.84) [0.17]	2.11 (4.07) [0.28]	2.16 (2.59)* [0.14]	2.63 (2.94)** [0.20]	0.97
Firmicutes			64.60 (26.46)	59.38 (25.15) [0.29]	60.01 (23.29)* [0.28]	55.19 (23.51)*** [0.49]	53.08 (22.07)*** [**0.049**]	0.74
	Christensenellaceae		0.56 (1.35)	0.96 (1.90) [0.090]	1.45 (2.84)*** [**0.034**]	1.37 (2.58)* [**0.048**]	1.15 (2.19)* [0.092]	0.57
		Unclassified	0.54 (1.35)	0.93 (1.90) [0.091]	1.41 (2.84) [**0.028**]	1.34 (2.57) [**0.037**]	1.11 (2.17) [0.13]	0.50
	Lachnospiraceae		19.39 (12.98)	14.43 (8.71)* [**0.049**]	16.38 (11.42)** [0.08]	13.22 (8.94)** [**0.038**]	12.66 (8.61)** [**0.034**]	**0.050**
		Roseburia	5.20 (6.16)	2.85 (3.60) [**0.049**]	3.04 (5.70)*** [**0.043**]	1.79 (2.50)*** [**0.030**]	2.26 (3.98)*** [**0.044**]	0.64
		Unclassified	4.45 (3.80)	3.28 (2.76) [**0.050**]	3.42 (3.22)** [0.50]	2.85 (2.60)*** [**0.044**]	2.50 (2.56)** [**0.045**]	0.46
	Lactobacillaceae		0.12 (0.40)	0.10 (0.36) [0.30]	0.90 (3.43) [0.065]	1.10 (2.58) [**<0.001**]	2.46 (4.75) [**<0.001**]	**<0.001**
		Lactobacillus	0.12 (0.39)	0.10 (0.36) [0.39]	0.87 (3.34) [0.055]	1.07 (2.49) [**<0.001**]	2.39 (4.68) [**<0.001**]	**<0.001**
	Ruminococcaceae		29.55 (16.75)	28.74 (16.30) [0.71]	27.16 (14.94) [0.92]	23.37 (15.10)** [0.39]	22.43 (13.13)** [0.79]	0.69
		Faecalibacterium	14.00 (10.98)	12.14 (12.43) [0.53]	10.36 (8.61)** [0.33]	8.18 (7.17)*** [0.26]	9.39 (10.36)** [0.82]	0.89
		Oscillospira	3.60 (3.53)	4.57 (3.91) [0.37]	4.93 (5.01)** [0.17]	4.31 (4.09) [0.96]	3.37 (2.47) [0.83]	0.41
	Streptococcaceae		1.07 (2.37)	0.67 (1.11) [0.12]	0.82 (1.76) [0.38]	1.65 (2.67) [0.29]	1.75 (3.09)* [0.80]	0.19
		Streptococcus	1.05 (2.37)	0.65 (1.11) [0.12]	0.81 (1.76) [0.39]	1.64 (2.65) [0.27]	1.71 (3.04) [0.84]	0.20
	Veillonellaceae		--	--	--	--	--	
		Acidaminococcus	0.25 (0.83)	0.10 (0.27) [0.17]	0.11 (0.24) [0.30]	0.60 (1.96) [0.080]	1.15 (2.94) [0.67]	0.26
		Megasphaera	0.32 (1.82)	0.16 (0.45) [0.72]	0.83 (3.53) [0.61]	1.11 (3.94) [0.063]	0.63 (2.00) [0.29]	0.29
Proteobacteria			3.46 (7.34)	5.75 (9.43) [0.15]	4.35 (5.37)** [0.062]	6.12 (7.90)*** [**0.011**]	5.71 (5.28)*** [**0.006**]	0.20
	Enterobacteriaceae		2.41 (6.86)	4.79 (9.44) [0.35]	3.08 (5.32)** [**0.040**]	4.61 (7.04)*** [**0.008**]	4.10 (5.04)*** [**0.022**]	0.21
		Escherichia	2.09 (6.35)	4.10 (8.33) [0.27]	1.91 (4.22) [0.39]	2.27 (2.78)*** [0.082]	2.39 (3.33)** [0.089]	0.56
Verrucomicrobia			1.62 (3.65)	2.67 (4.30) [0.30]	4.26 (6.46)*** [**0.021**]	4.47 (7.74)*** [**0.005**]	6.27 (9.75)** [**0.020**]	**0.037**
	Verrucomicrobiaceae		1.59 (3.64)	2.66 (4.29) [0.31]	4.19 (6.48)*** [**0.021**]	4.42 (7.69)*** [**0.008**]	6.23 (9.74)** [**0.019**]	**0.043**
		Akkermansia	1.58 (3.63)	2.66 (4.28) [0.30]	4.17 (6.46)*** [**0.019**]	4.40 (7.67)*** [**0.008**]	6.20 (9.72)** [**0.019**]	**0.048**

(= Prevotella)

↓ PD (Roseburia)

↑ PD

↑ PD (spt Akkermansia mucinifera)

Rapprto tra Microbiota e Fenotipo clinico: Possibile disease-modifier?

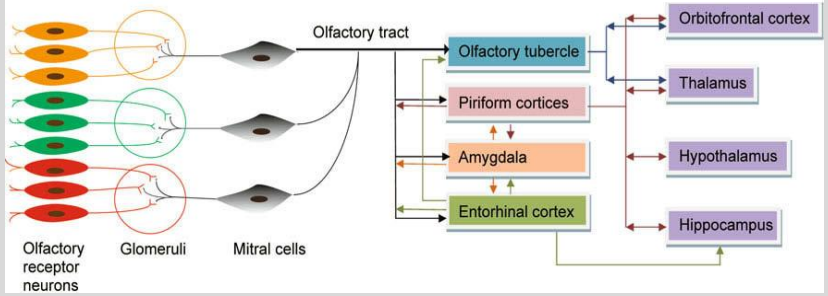
TABLE 2. Significant associations between clinical features and relative taxa abundance in PD patients

Feature	Taxonomic level: Phylum	Family	Genus	Effect[a]: Adj. diff. (SE)	OR [95% CI]	*P* value
NMSQuest total score, mean (SD)						
		↓ Christensenellaceae		0.80 (0.37)	–	.032
			Unclass. Christensenellaceae	0.75 (0.36)	–	.042
Intellectual impairment, n (%)						
		↑ Lactobacillaceae		–	1.66 [1.04-2.64]	.033
			Lactobacillus	–	1.63 [1.04-2.56]	.032
UPDRS part III total score, mean (SD)						
		↑ Lactobacillaceae		1.87 (0.88)	–	.036
			Lactobacillus	2.18 (0.87)	–	.013
UPDRS part III nondopaminergic score, mean (SD)						
			Unclass. Lachnospiraceae	−0.47 (0.22)	–	.033
		↑ Lactobacillaceae		0.47 (0.23)	–	.042
			Lactobacillus	0.52 (0.23)	–	.028
Gait disturbances, n (%)						
		↓ Lachnospiraceae		–	0.54 [0.35-0.82]	.004
			Unclass. Lachnospiraceae	–	0.68 [0.45-1.00]	.048
Postural instability, n (%)						
			Unclass. Lachnospiraceae	–	0.40 [0.22-0.73]	.003
		↑ Lactobacillaceae		–	1.65 [1.03-2.93]	.039
			Lactobacillus	–	1.62 [1.02-2.81]	.046

Microbiota Nasale-Orale & Neurodegenerazione:
Stessi trigger di misfolding proteico?

Hyposmia: a possible biomarker of Parkinson's disease

Qian Xiao[1], Sheng Chen[1], Weidong Le[1,2] Neurosci Bull February 1, 2014, 30(1): 134–140.



The Nasal and Gut Microbiome in Parkinson's Disease and Idiopathic Rapid Eye Movement Sleep Behavior Disorder

Anna Heintz-Buschart, PhD,[1] Urvashi Pandey, MS,[1] Tamara Wicke,[2,3] Friederike Sixel-Döring, MD,[2,3] Annette Janzen, MD,[3] Elisabeth Sittig-Wiegand, SN,[3] Claudia Trenkwalder, MD,[2,4] Wolfgang H. Oertel, MD,[3] Brit Mollenhauer, MD,[2,5]* and Paul Wilmes PhD[1]* *Movement* Disorders, Vol. 00, No. 00, 2017

Oral and nasal microbiota in Parkinson's disease

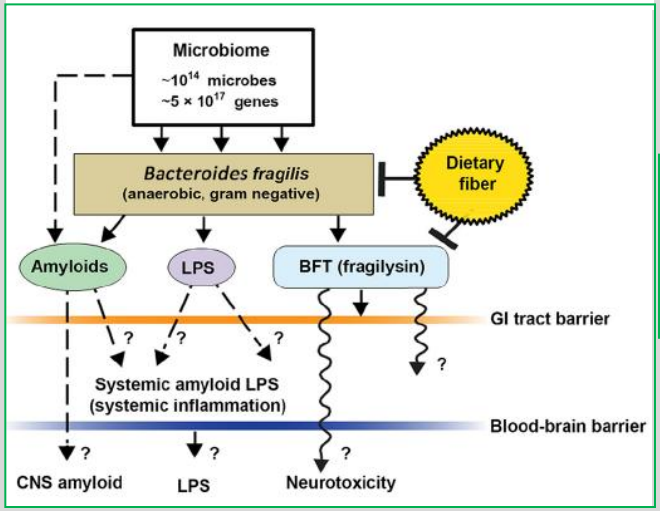
Pedro A.B. Pereira, MSc [a,1], Velma T.E. Aho, MSc, BA [a,1], Lars Paulin, MSc [a], Eero Pekkonen, MD, PhD [b], Petri Auvinen, PhD [a], Filip Scheperjans, MD, PhD [b,*]

Parkinsonism and Related Disorders xxx (2017) 1–7

Journal of Alzheimer's Disease 51 (2016) 979–984
DOI 10.3233/JAD-160152
IOS Press

Editorial

Microbes and Alzheimer's Disease



Parodontitis (Oral dysbiosis) increase the risk of Dementia

- Irregular tooth brushing (prospective study in US, N=4,883)
- Tooth loss (Sweedish twin study & Longitudinal US cohort)
- Periodontopathy associated with higher brain amyloid in elderly

Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly

Kamer et al., Neurobiol Aging 2015
Tamler et al., Anna Neurol 2017
Cattaneo et al, Neurobiol Aging 2017

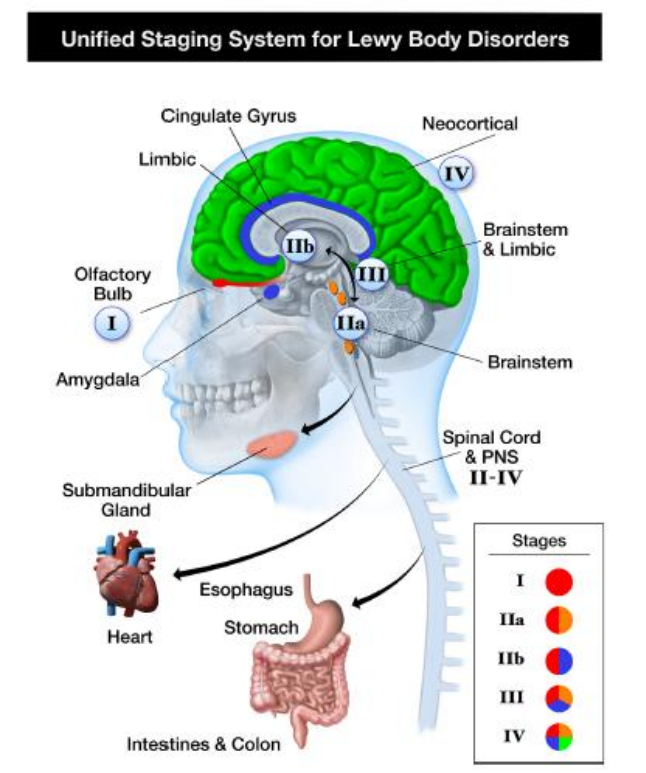
Dove inizia la malattia di Parkinson?

«Braak's hypothesis: involvement of DMV is mandatory»

whole-body autopsies of 417 healthy elderly
55/417 with ILBD **-> Only 9% (5/55) involved dorsal medulla**
(**52 with the olfactory bulb as the only site involved**)

- The DMV is *NOT* necessarily involved
- Incidental LBD mainly involves the Olfactory Bulb

Unified Staging System for LB Disorders (proposed):
Stage I: Olfactory Bulb
Stage IIa: Brainstem



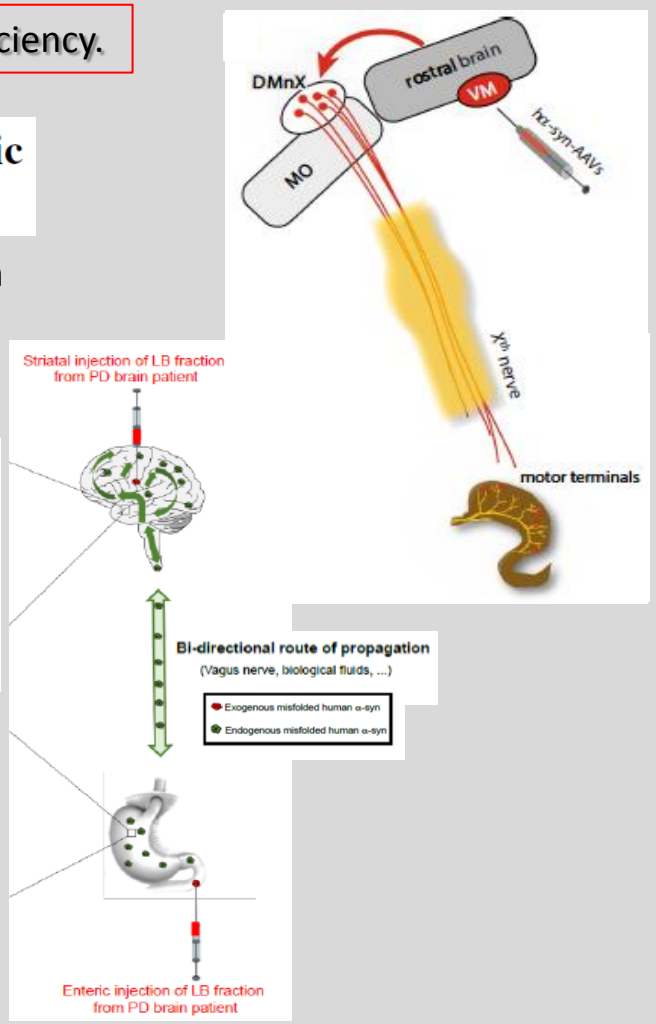
Beach et al., Acta Neuropathol 2009 and 2010; Kalaitzakis et al., Neuropathol Appl Neurobiol 2008; Adler & Beach, Mov Disord 2016

'Brain-to-Gut' come alternativa a 'Gut-to-Brain' ?
(seeding nel bulbo olfattorio, genetici, etc.)

α-SYN can transported anterogradely and retrogradely with similar efficiency.

Brain-to-stomach transfer of α-synuclein via vagal preganglionic projections

Overexpressed human *α-syn* can travel from the ventral mesencephalon into the DMV. Then, via vagal motor fibers, *α-syn* reaches preganglionic vagal terminals into the gastric wall.



Bidirectional gut-to-brain and brain-to-gut propagation of α-synuclein pathology in non-human primates

Marie-Laure Arotcarena[1,2,14], Sandra Dovero[1,2,14], Alice Prigent[3,14], Mathieu Bourdenx[1,2,14], Sandrine Camus[1,2], Gregory Porras[1,2], Marie-Laure Thiolat[1,2], Maddalena Tasselli[3], Philippe Aubert[3], Niels Kruse[4], Brit Mollenhauer[4], Inés Trigo Damas[5,6], Cristina Estrada[7,8], Nuria Garcia-Carrillo[9], Nishant N. Vaikath[10], Omar M. A. El-Agnaf[10] Maria Trinidad Herrero[7,8], Miquel Vila[6,11,12,13], Jose. A. Obeso[5,6], Pascal Derkinderen[3], Benjamin Dehay[1,2*#] and Erwan Bezard[1,2*#]

[1] Univ. de Bordeaux, Institut des Maladies Neurodégénératives, UMR 5293, F-33000 Bordeaux, France; [2] CNRS, Institut des Maladies Neurodégénératives, UMR 5293, F-33000 Bordeaux, France; [3] Inserm, U913, Nantes F-44035, France; Nantes University, Nantes

This may be allowed by a **direct SNpc -> DMV** pathway

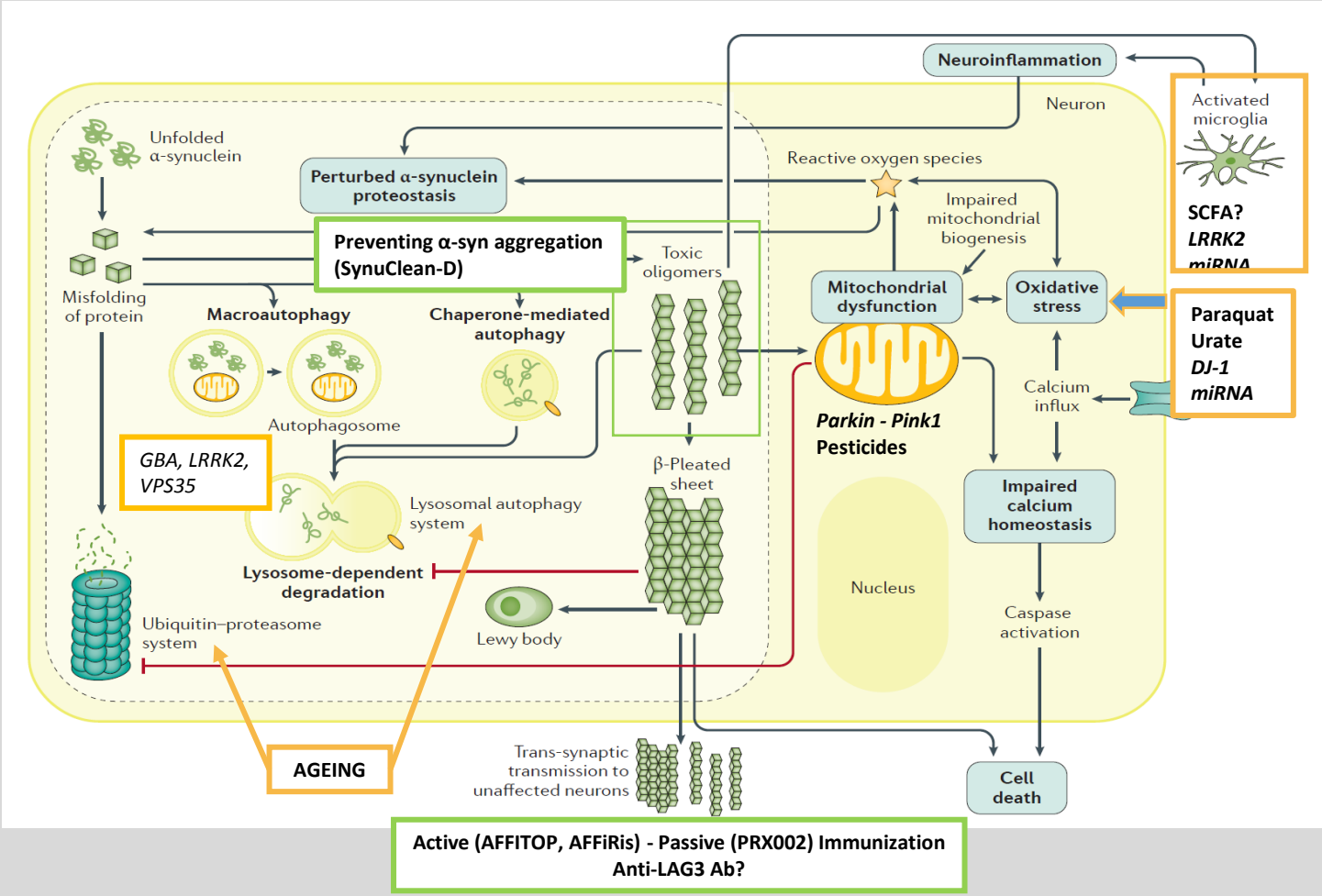
A Nigro—Vagal Pathway Controls Gastric Motility and Is Affected in a Rat Model of Parkinsonism

Ulusoy, Acta Neuropathol 2016; Anselmi, Gastroenterol 2017; Surmeier and Brundin, J Neurosci 2017; Arotcarena et al., MDS 2019 Poster N. 1663

TAKE-HOME MESSAGE

« Una malattia, meccanismi diversi? »

La MdP nasce dalla convergenza di diversi meccanismi da siti differenti



Lo sviluppo della malattia di Parkinson richiede il simultaneo fallimento di diversi meccanismi di difesa cellulare.

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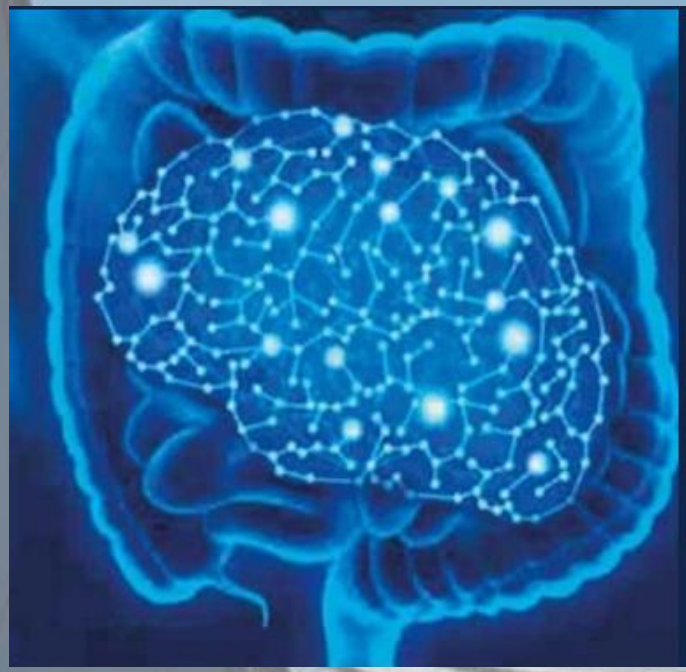

"All diseases begins in the gut"
Hippocrates 400 B.C.

GRAZIE PER L'ATTENZIONE!