Universitätsklinikum Carl Gustav Carus
DIE DRESDNER.

Гипотеза энетрической нервной системы о болезни паркинсона

Уфа, 28 мая, 2020

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Прогрессирование болезни паркинсона

Universitätsklinikum Carl Gustav Carus
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Обонятельная потеря
RBD?, запор,
беспокойство,
депрессия

Брадикинезия, регидность,
Рест-тремор,
(+/- немоторные симптомы)

Моторные осложнения:
износ? / дискинезия,
проблемы с походкой и
равновесием, осевые
деформации,
дизартрия / дисфагия

Немоторные симптомы:
снижение когнитивных
функций /
деменция, психоз,
вегетативная дисфункция,
нарушение сна-
бодрствования

Генные мутации, уровни
альфа-синуклеина,
[illegible] визуализации

Болезнь паркинсона до первых клинических проявлений

Не моторная форма

Ранняя стадия болезни паркинсона

Умеренная БП (стабильный)

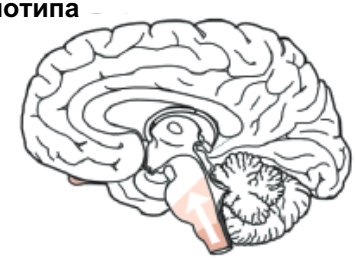
Расширенная болезнь паркинсона

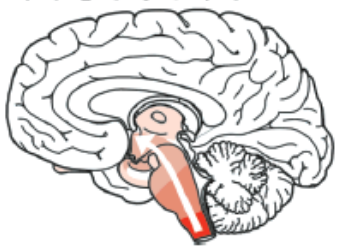
-10лет -6лет 0 2года 5лет 10лет 15лет

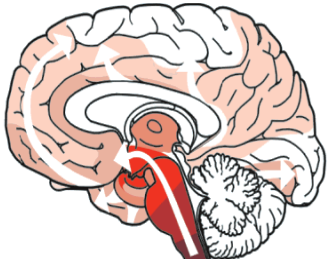
Начало клинического премоторного фенотипа

Начадл клинического Моторного фенотипа

Постановка диагноза







Желудочно- кишечный тракт: Окно или зона входа

Frequency of bowel movements and the future risk of Parkinson's disease

R.D. Abbott, PhD; H. Petrovitch, MD; L.R. White, MD; K.H. Masaki, MD; C.M. Tanner, MD, PhD; J.D. Curb, MD; A. Grandinetti, PhD; P.L. Blanchette, MD; J.S. Popper, MD; and G.W. Ross, MD

NEUROLOGY 2001;57:456–462

Частота дефекации у 6790 мужчин в период с 1971 по 1974 гг.

- **Следить за инцидентом PD в течение 24 лет**
- **69 ПД со средним временем начала 12 лет**

- **18,9/ 10.000 мужчин в год <1 ипорожнение кишечника/ день**
- **3,8 / 10.000 мужчин в год >2 испорожнение кишечника/ день**

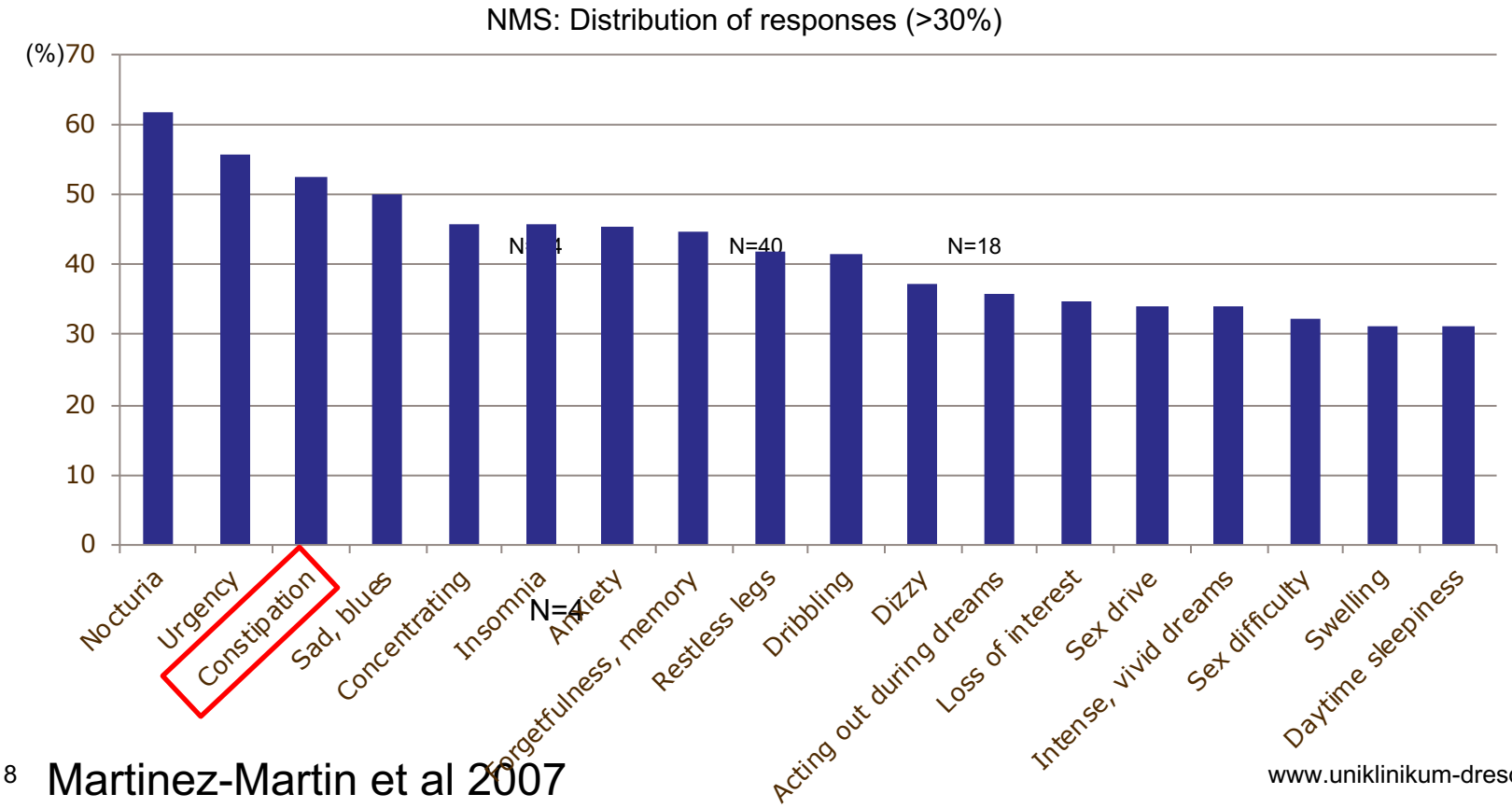
➢Запор как маркер раннего БП, восприимчивости или факторов окружающей среды, которые могут вызвать БП.

NMS при БП по сравнению с контрольной группой соответствующего возраста

- NMSQuest study: Немоторная анкета для пациентов с БП
  - 123 пациента с болезнью паркинсона (средний возраст 68 лет, продолжительность заболевания 6.4года, H&Y? 2.5)
  - Контрольная группа 96 пациентов средний возраст 65 лет

Chaudhuri & Odin 2010; Chaudhuri et al 2006

- Наблюдательное, многоцентровое, международное, перекрестное исследование
  - 545 пациентов с БП завершили пересмотренный NMSQuest
  - Средний возраст 68лет, продолжительность заболевания 7 лет, H&Y 2.5
  - Среднее количество NMS на пациента (NMSQ-T): 10.3



Martinez-Martin et al 2007

Проявления ЖКТ в предморторной фазе

J Neurol (2013) 260:1332–1338
DOI 10.1007/s00415-012-6801-2

ORIGINAL COMMUNICATION

Gastrointestinal manifestations in Parkinson's disease: prevalence and occurrence before motor symptoms

Maria G. Cersosimo · Gabriela B. Raina · Cristina Pecci · Alejandro Pellene · Cristian R. Calandra · Cristiam Gutiérrez · Federico E. Micheli · Eduardo E. Benarroch

Received: 5 August 2012 / Revised: 13 November 2012 / Accepted: 11 December 2012 / Published online: 21 December 2012

Предмоторные знаки

Table 3 Gastrointestinal manifestations with onset before motor symptoms in Parkinson's disease patients with a disease duration no longer than 5 years ($n = 72$)

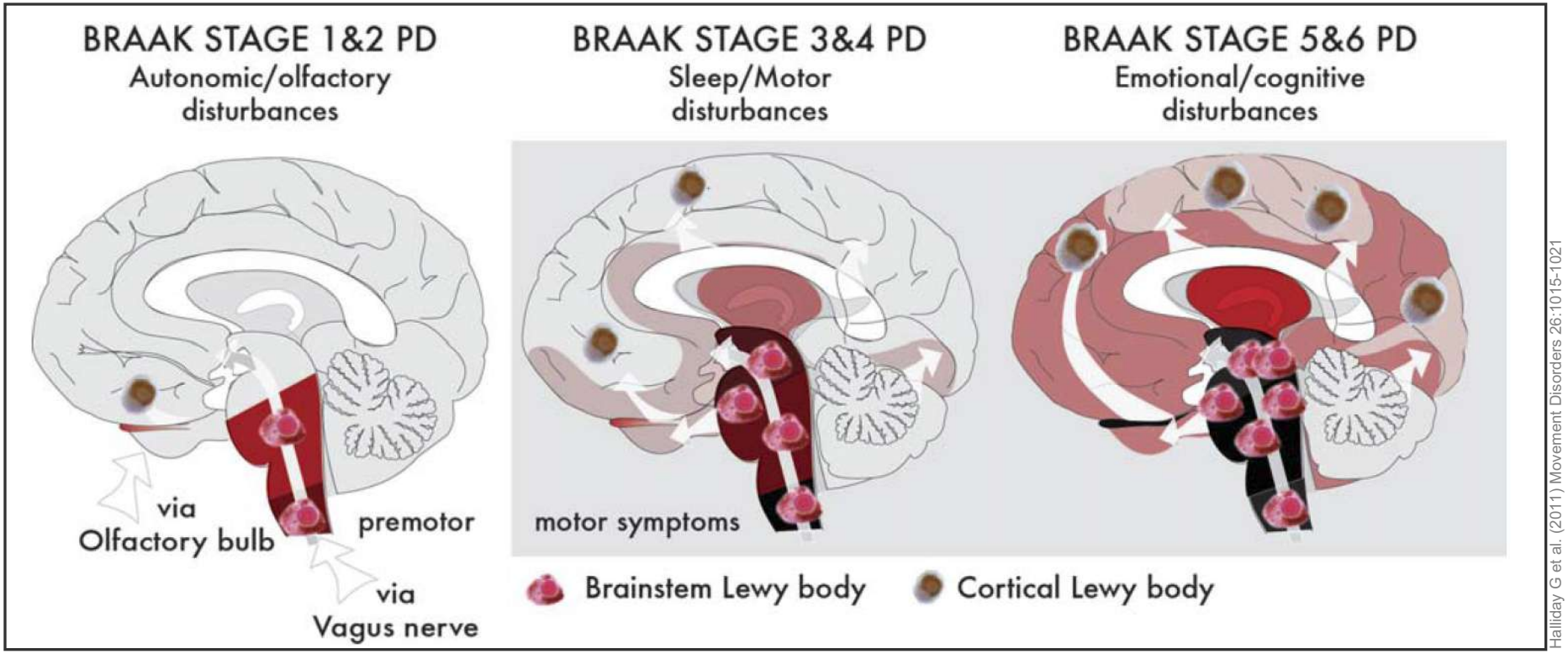
GIS (n)	Onset before motor symptoms			
	n (%)	Always present[a]	Not always present	
			n (%)	Years before the onset of MS (mean ± SD, range)
Dry mouth (39)	8 (20.5)	0	8	5.2 ± 4.5 (1–10)
Drooling (24)	0	–	–	–
Dysphagia (13)	0	–	–	–
Heartburn (25)	16 (64)	7 (43.7)	9 (56.2)	6.1 ± 6.2 (1–17)
Bloating and satiety (35)	23 (65.7)	16 (69.5)	7 (30.4)	11.5 ± 6.5 (3–18)
Nausea (10)	0	–	–	–
Constipation (31)	27 (87)	16 (59.2)	11 (40.7)	4 ± 4.6 (1–13)
Defecatory dysfunction (39)	23 (58.9)	17 (73.9)	6 (26)	3.7 ± 2.7 (1–7)

MS motor symptoms, *GIS* gastrointestinal symptoms

[a] Symptoms reported as lifelong problems

Cersosimo MG et al. (2013) J Neurol 260:1332-1338

Этапы Браака



Halliday G et al. (2011) Movement Disorders 26:1015-1021

FIG. 1. Stylized representation of the Braak staging for Parkinson's disease showing the initiation sites in the medulla oblongata and olfactory bulb through to the later infiltration of Lewy pathology into the cortical regions.

Halliday G. et al. (2011) Mov Disord 26:1015-1021

Доказательства Г.И. -Нарушения при БП

Regular papers

Parkinson's disease: the presence of Lewy bodies in Auerbach's and Meissner's plexuses

K. Wakabayashi, H. Takahashi, S. Takeda, E. Ohama, and F. Ikuta

Department of Pathology, Brain Research Institute, Niigata University, 1 Asahimachi, Niigata 951, Japan

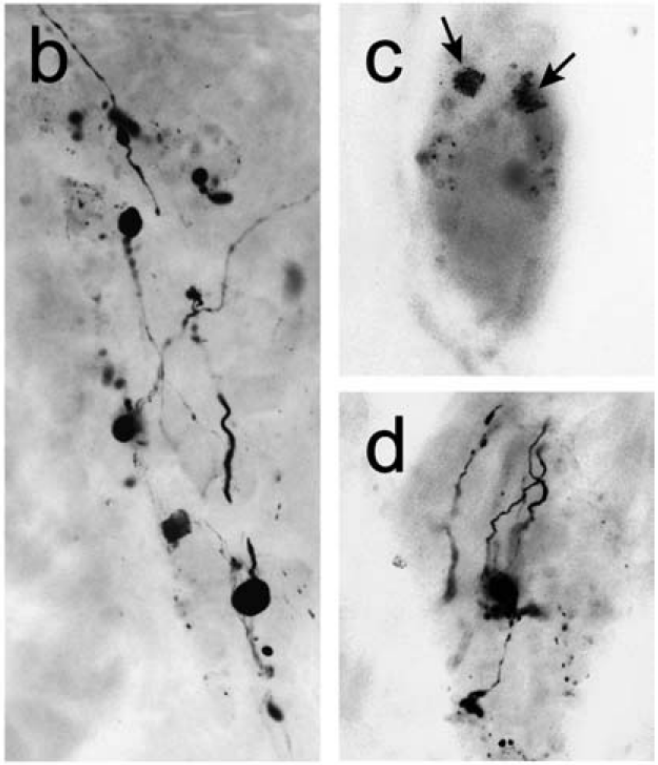
Table 1. Occurrence of Lewy bodies (LBs) in the enteric nervous system of the alimentary tract in Parkinson's disease

Case no.	Age, sex (duration in years)	Esophagus			Sto.	Small intestine			Colon			Rec.
		Upper	Middle	Lower		duo.	jej.	ile.	asc.	trans.	des.	
1	56, M (18)			●● ●● ●●●			○				○○	
2	56, F (<1)			●	●							○
3	59, M (16)	●	●	●● ●● ●●●								
4	61, M (7)	N.E.		N.E.		N.E.			○	N.E.	N.E.	N.E.
5	65, M (8)		●●● ●●● ●●●	●●●● ●●●● ●●●●★ ●●●●★	●							
6	65, M (3)		●	●● ●●		●● ●●						
7	75, F (27)			●●			●●		●			●●

Acta Neuropathol 1988; 76:217-221

- **Появление тельца Леви в сплетении Ауэрбаха и Мейснера**
- Пристрастие ЛБ в верхнем отделе желудочно-кишечного тракта

Включения α-Синуклеина в ENS



Gastric α-synuclein immunoreactive inclusions in Meissner's and Auerbach's plexuses in cases staged for Parkinson's disease-related brain pathology

Heiko Braak [a,*], Rob A.I. de Vos [b], Jürgen Bohl [c], Kelly Del Tredici [a]

[a] *Institute for Clinical Neuroanatomy, J.W. Goethe University Clinic, Theodor Stern Kai 7, 60590 Frankfurt/Main, Germany*
[b] *Laboratorium Pathologie Oost Nederland, Burg Edo Bergmalaan 1, AD 7512 Enschede, The Netherlands*
[c] *Department of Neuropathology, Johannes Gutenberg University, Langenbeckstrasse 1, Mainz, Germany*

Received 25 August 2005; received in revised form 23 October 2005; accepted 4 November 2005

Neuroscience Letters 396 (2006) 67–72

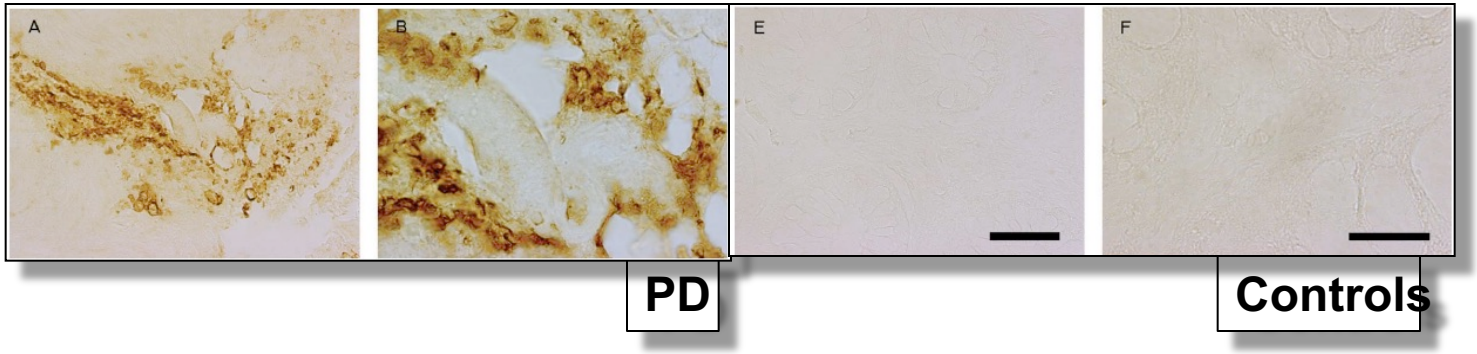
- Присутствие в желудке включений а-синуклеина может обеспечить первую связь в восприимчивых нейронах, которые простираются от кишечника до людей центральной нервной системы.

Биопсия толстой кишки при БП

RESEARCH ARTICLE

Alpha-Synuclein in Colonic Submucosa in Early Untreated Parkinson's Disease

Kathleen M. Shannon, MD,[1]* Ali Keshavarzian, MD,[2] Ece Mutlu, MD,[2] Hemraj B. Dodiya, MS,[3] Delia Daian,[2] Jean A. Jaglin, RN,[1] and Jeffrey H. Kordower, PhD[3]



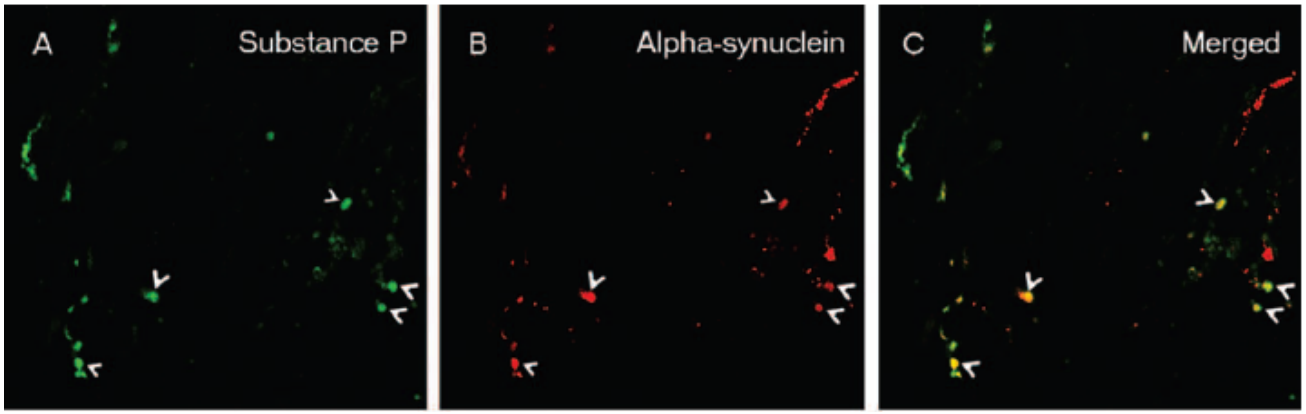
- 10 нелеченных пациентов с болезнью Паркинсона; все положительные на альфа-синуклеин
- Сигмоидоскопия и Вх: альфа-синуклеин и 3-нитро-тирозин (маркер митохондриального стресса)

Mov Disord 2012: 27:709-715

Премоторные проявления БП
И биопсия толстой кишки

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]



- Альфа-синуклеин-положительная иммуногистохимия в 3 биопсиях за 2-5 лет до начала

Mov Disord 2012: 27:716-719

Почему у нас противоречивые результаты по патологии альфа синуклеина в кишечнике?

TABLE 2. Issues hindering consensus on the optimal method for reliable and reproducible GI ASN detection

Source of heterogeneity	Suggested consensus approach
ASN-reactive antibody	• Use at least 2 antibodies reactive for different epitopes and/or variants of ASN (eg, P-ASN and T-ASN), on the same number of consecutive sections. • Consider antibodies reactive for oligomeric ASN.
Biopsy site	• For use as clinical biomarker, prioritize low discomfort for patient (ie, flexible sigmoidoscopy) and reproducibility. • For research into pathogenic mechanisms, prioritize vagal innervation (ie, esophagus and stomach).
Amount of stained tissue	• Apply software-based image analysis (SBIA) to adjust for variability in stained area between different biopsy samples.
Definition of pathological staining	• Increase sharing of images. • Apply reproducible SBIA algorithms. • Be aware of nonneuronal ASN staining patterns.
Neuronal marker	• Always use at least 1 reliable marker of nervous tissue. • Selection should take into account characteristics of available tissue (superficial versus whole wall).

Ruffmann C & Parkkinen L (2016) Movement Disord 31:193-202

Дрезденская модель болезни паркинсона.

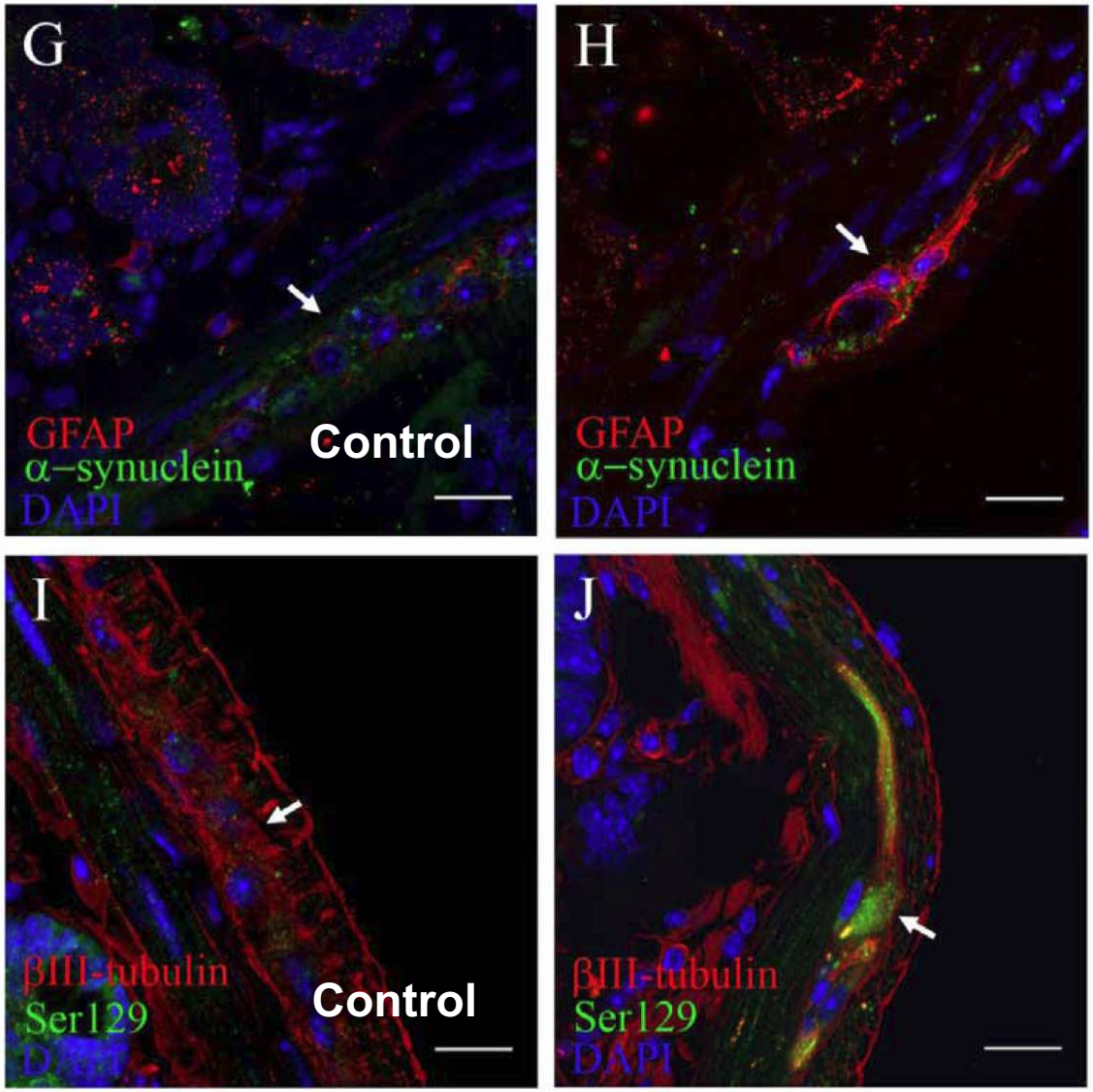
OPEN ACCESS Freely available online

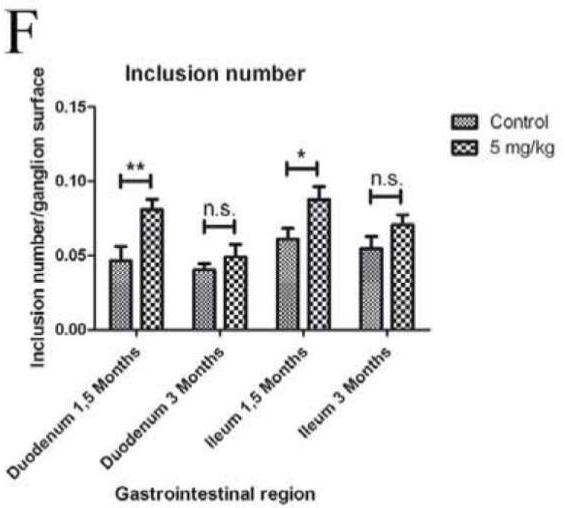
PLoS one

Progression of Parkinson's Disease Pathology Is Reproduced by Intragastric Administration of Rotenone in Mice

Francisco Pan-Montojo[1,2,6]*, Oleg Anichtchik[3], Yanina Dening[1], Lilla Knels[1], Stefan Pursche[4], Roland Jung[5], Sandra Jackson[2], Gabriele Gille[2], Maria Grazia Spillantini[3], Heinz Reichmann[2], Richard H. W. Funk[1]*

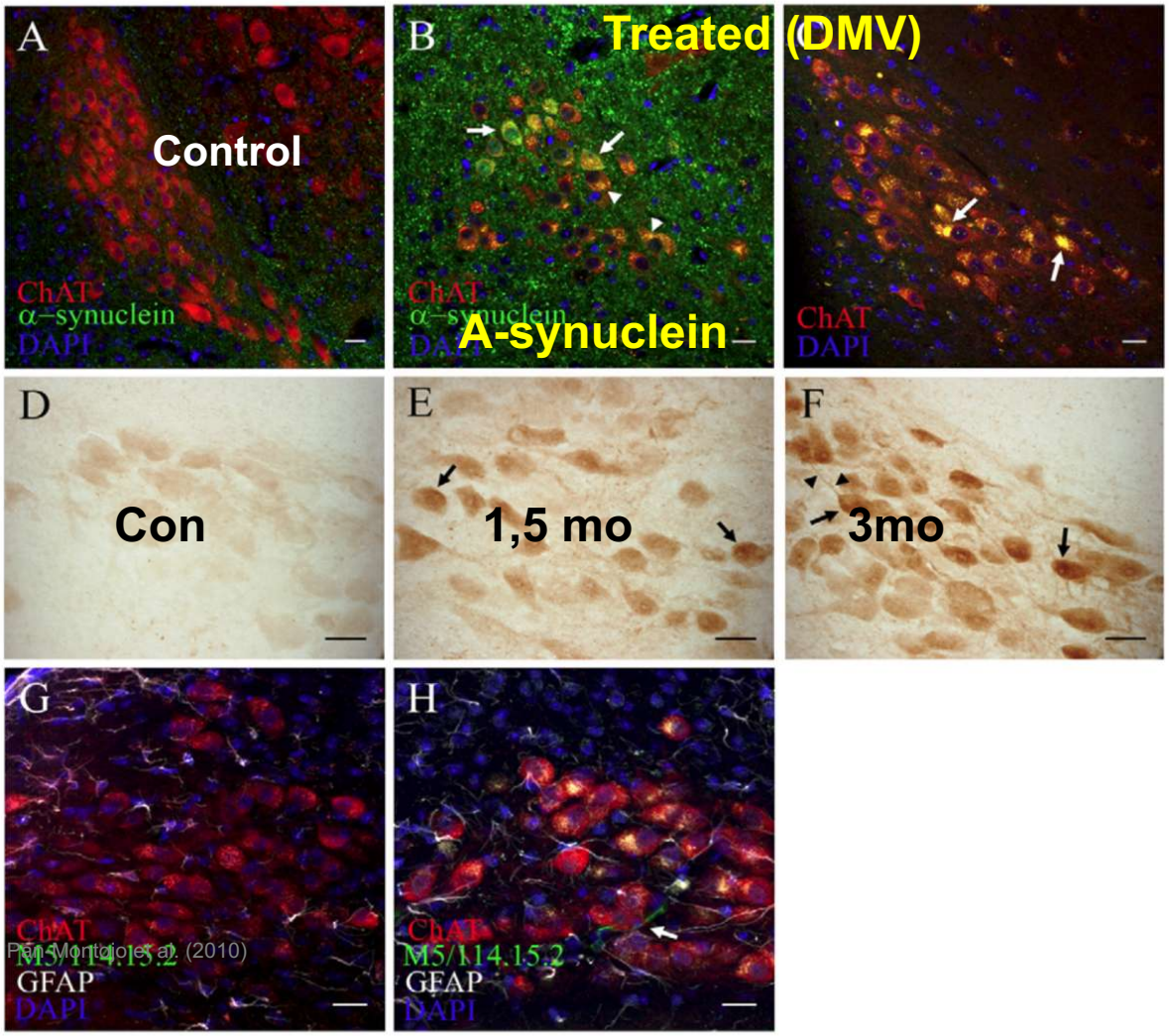
1 Institute of Anatomy, Medical Faculty Carl Gustav Carus, Dresden University of Technology, Dresden, Germany, **2** Department of Neurology, Medical Faculty Carl Gustav Carus, Dresden University of Technology, Dresden, Germany, **3** Center for Brain Repair, University of Cambridge, Cambridge, United Kingdom, **4** Department of Internal Medicine I, Medical Faculty Carl Gustav Carus, Dresden University of Technology, Dresden, Germany, **5** Experimental Center, Medical Faculty Carl Gustav Carus, Dresden University of Technology, Dresden, Germany, **6** International Max-Planck Research School, Max-Planck Institute for Cell Biology and Genetics, Dresden, Germany





Pan-Montojo et al. (2010)

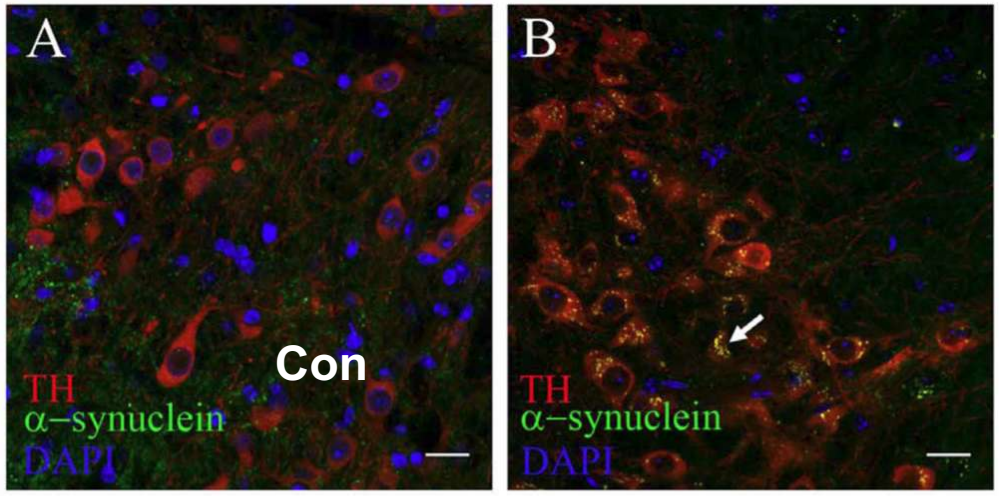
Рисунок 1 (продолжение). Местно вводимый ротенон индуцирует фосфорилирование, накопление и агрегацию альфа-синуклеина при глиозе в ганглиях ENS. (масштабные полосы 20 мкм). F, каждый столбец представляет общее количество включений альфа-синуклеина / поверхности ганглия. Все графики показывают среднее +/- с.м. G, H, max-проекция окрашивания против GFAP, альфа-синуклеина и DAPI на срезах двенадцатиперстной кишки у контрольных (G) и обработанных (H) мышей. I, J, макс-проекция анти-βIII-тубулина, антифосфо-альфа-синуклеина (Ser 129) и окрашивания DAPI на срезах двенадцатиперстной кишки у контрольных (I) и обработанных (J) животных.



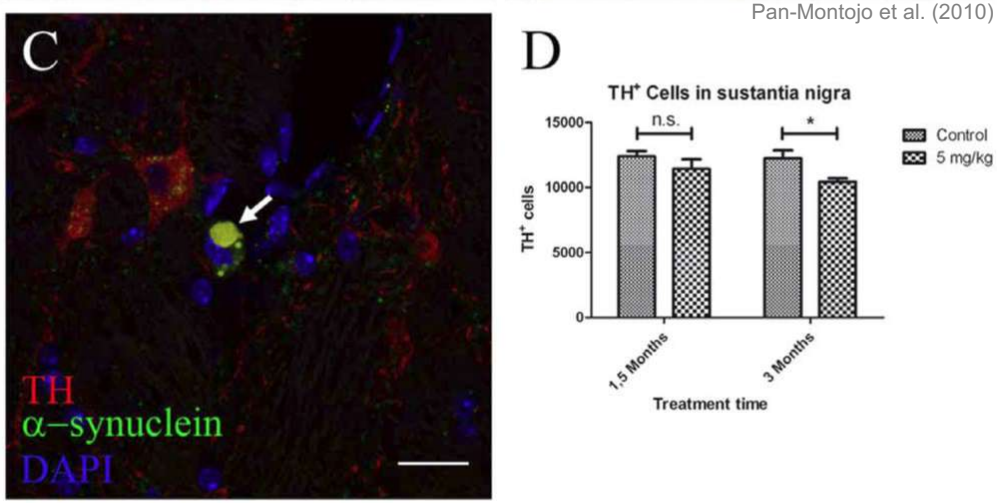
Perez-Montoiola et al. (2010)

Рисунок 3. Внутрижелудочно введенный ротенон вызывает накопление альфа-синуклеина, окислительный стресс и воспаление в блуждающем дорсальном двигательном ядре. (масштабные полосы 20 мкм). A, B, двойное иммунофлуоресцентное окрашивание против альфа-синуклеина и ChAT на срезах DMV от мышей контрольной (A) 1,5 месяцев и обработанных (B) 1,5 месяцев мышей. Стрелки B, повышенный внутриклеточный альфа-синуклеин в нейронах ДМВ уже через 1,5 месяца. Стрелки B, автофлуоресцентный пунктирный паттерн включения внутри ChAT + нейронов. C, срезы DMV, окрашенные ChAT и DAPI, последовательно возбуждали с длинами волн лазера 488 и 561. Стрелки в C, крупные внутриклеточные аутофлуоресцентные включения внутри ChAT + нейроны DMV (стрелки). D, E, F, Изображения световой микроскопии окрашивания альфа-синуклеина у мышей, которым вводили 1,5 месяца контрольной (D), 1,5 месяца (E) и 3 месяца (F). Стрелки E и F, повышенная интенсивность окрашивания внутри нейрональной сомы DMV у обработанных мышей. Стрелки в F, повышенное окрашивание альфа-синуклеином внутри нейрональных отростков G, H, средняя проекция окрашивания тройной иммунофлуоресценции против ChAT, GFAP, MHC II (клон M5 / 114.15.2) и DAPI на срезах из контроля (G) и обработанных (H) мыши после 3 месяцев лечения. Стрелка в H, активированная микроглиальная клетка в DMV.

Субстанция Нигра Парс Компакта



Pan-Montojo et al. (2010)



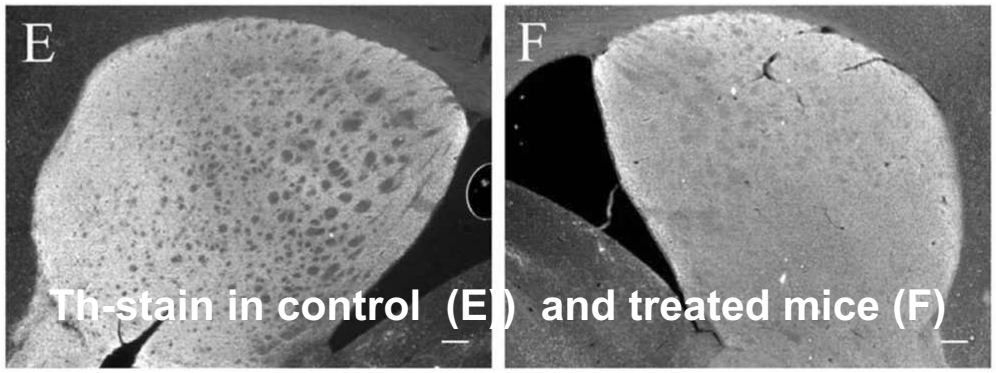


Рис. 4. Накопление альфа-синуклеина и потеря нейронов в SNc через 3, а не через 1,5 месяца внутрижелудочного лечения ротеноном. (A – C, масштабные полосы 20 мкм; E – F, масштабные полосы 200 мкм). A, B, C, иммуноокрашивание против TH, альфа-синуклеина и DAPI на срезах SNc у мышей, получавших 1,5 месяца контрольной (A) и 3 месяцев (B – C). Стрелка в B, небольшие включения альфа-синуклеина внутри TH + нейронов. Стрелка в C, большое включение альфа-синуклеина (|> 8,14 мкм) внутри дофаминеров нейрона в SN. D - стереологическое количественное определение (n = 3) TH + нейронов в SN у контрольных и обработанных мышей. Звездочка, P <0,05. Количество нейронов определяли по принципу оптического фракционатора с использованием программного обеспечения StereoInvestigator (MicroBrightField Inc., Williston, США). Каждый столбец представляет общее количество TH + нейронов в SN у 1,5 и 3 месяцев контрольных и обработанных мышей. График показывает среднее +/- с.м. E, F, TH иммуноокрашивание на полосатом теле через 1,5 месяца у контрольных (E) и 3 месяцев у обработанных (F) мышей.

The vagus nerve

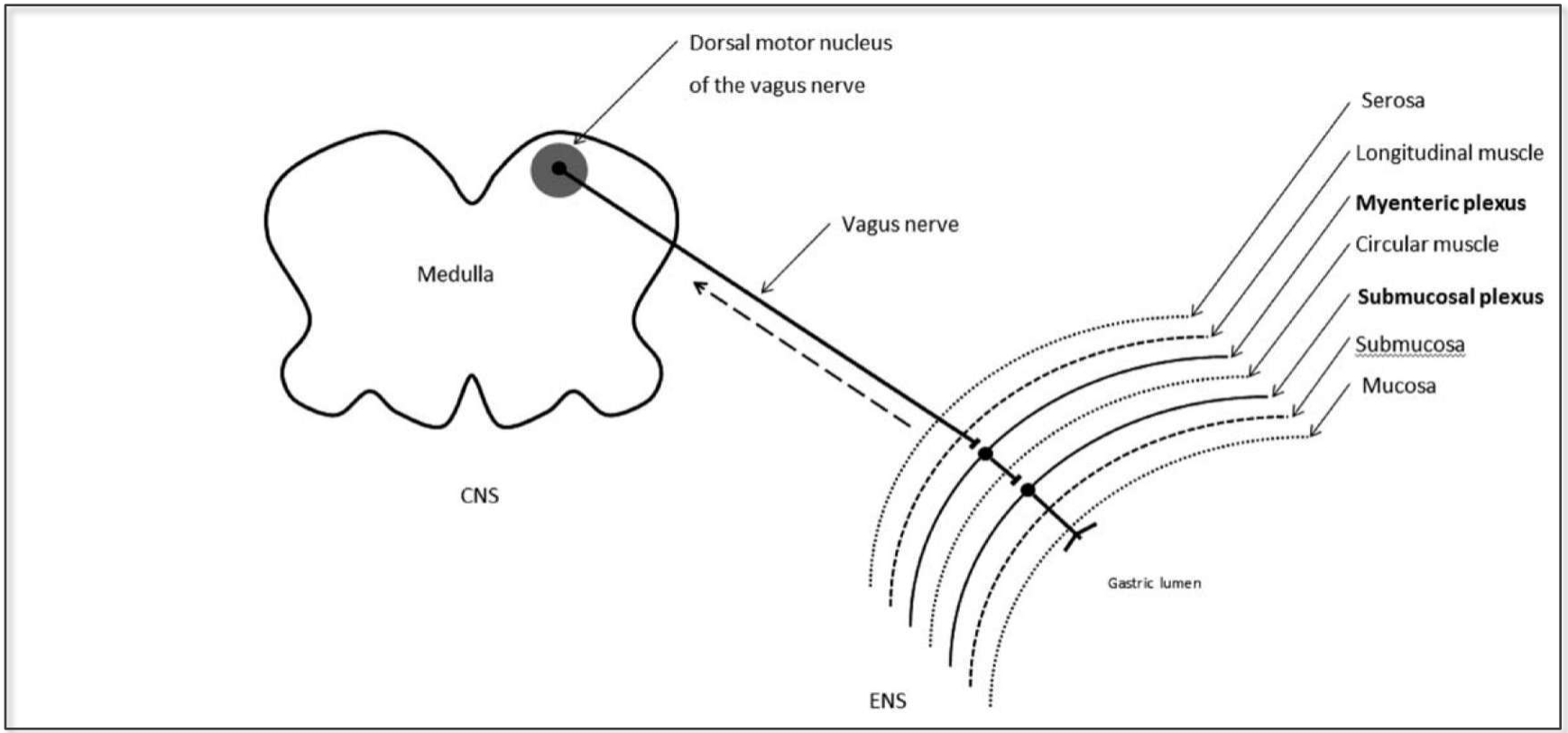


FIG. 1. Interaction of the central nervous system with the enteric nervous system via the vagus nerve

Marrinan S et al. (2014) Movement Disorders 26:23-32

Дальнейшие доказательства

Hemivagotomy and partial sympathectomy delay Parkinson's disease progression in mice

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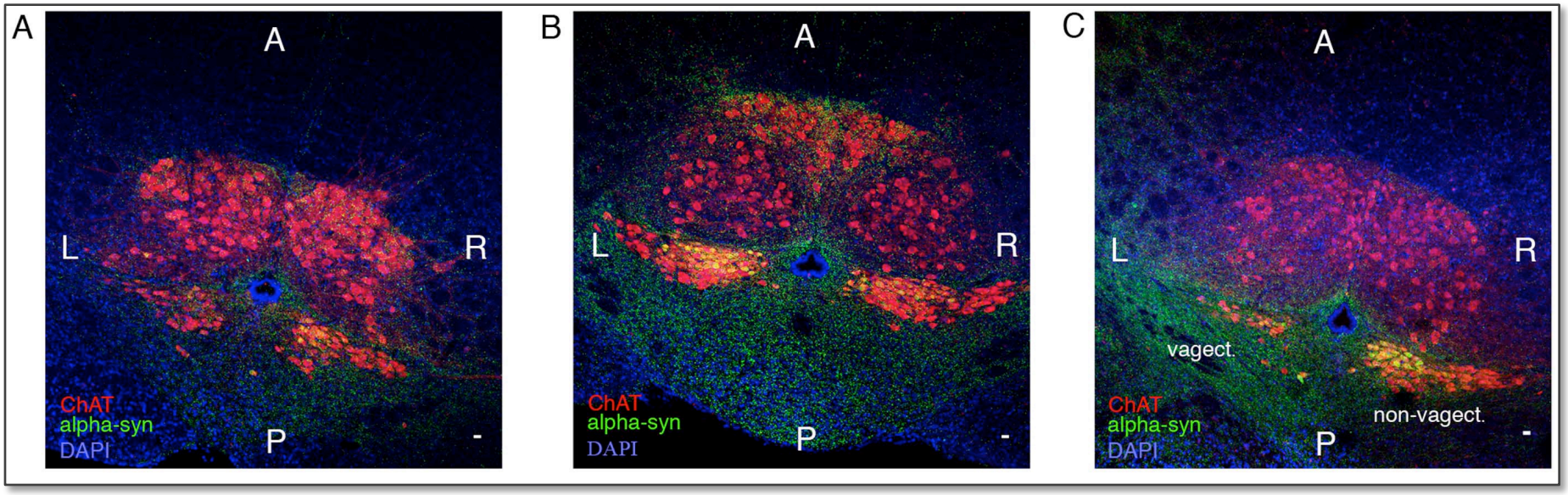
Abstract

Pathological studies on Parkinson's disease (PD) patients suggest that PD pathology starts at the olfactory bulb (OB) and the enteric nervous system (ENS) progressing into the central nervous system (CNS). In our previous study, we showed that the local effect of rotenone on the ENS reproduces this pathological progression in mice affecting only synaptically connected structures, suggesting transsynaptic and retrograde axonal transport as underlying mechanisms of this progression. Here, we tested this hypothesis by performing a hemivagotomy or a partial sympathectomy prior to rotenone oral treatment on mice and using primary enteric and sympathetic neuron co-cultures. For the first time, our results show that the appearance of motor dysfunctions is delayed in hemi-vagotomized and sympathectomized treated mice when compared to non-operated treated mice. Moreover, we only observed accumulation of alpha-synuclein in those structures still connected to the ENS. Interestingly, enteric neurons secrete alpha-synuclein only upon exposure to rotenone and secreted alpha-synuclein can be up-taken by non-neuronal cells or presynaptic sympathetic neurons. Altogether, these results suggest that pesticide-dependent alterations in the ENS can induce idiopathic PD pathology and trigger its progression. Moreover, it seems that this progression is based on the transsynaptic and retrograde axonal transport of alpha-synuclein, playing here the role of a prionic protein.

Pan-Montojo et al. (2012)
Science Rep 2:898 f



Pan-Montojo et al. (2012) Science Rep 2:898 f

RESEARCH ARTICLE

Vagotomy and Subsequent Risk of Parkinson's Disease

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Reimar W. Thomsen, PhD,[1] Jens Christian Djurhuus, DMSc,[2] Lars Pedersen, PhD,[1]
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Objective: Parkinson's disease (PD) may be caused by an enteric neurotropic pathogen entering the brain through the vagal nerve, a process that may take over 20 years. We investigated the risk of PD in patients who underwent vagotomy and hypothesized that truncal vagotomy is associated with a protective effect, whereas superselective vagotomy has a minor effect.
Methods: We constructed cohorts of all patients in Denmark who underwent vagotomy during 1977–1995 and a matched general population cohort by linking Danish registries. We used Cox regression to compute hazard ratios (HRs) for PD and corresponding 95% confidence intervals (CIs), adjusting for potential confounders.
Results: Risk of PD was decreased in patients who underwent truncal (HR = 0.85; 95% CI = 0.56–1.27; follow-up of >20 years: HR = 0.58; 95% CI: 0.28–1.20) compared to superselective vagotomy. Risk of PD was also decreased after truncal vagotomy when compared to the general population cohort (overall adjusted HR = 0.85; 95% CI: 0.63–1.14; follow-up >20 years, adjusted HR = 0.53; 95% CI: 0.28–0.99). In patients who underwent superselective vagotomy, risk of PD was similar to the general population (HR = 1.09; 95% CI: 0.84–1.43; follow-up of >20 years: HR = 1.16; 95% CI: 0.80–1.70). Statistical precision of risk estimates was limited. Results were consistent after external adjustment for unmeasured confounding by smoking.
Interpretation: Full truncal vagotomy is associated with a decreased risk for subsequent PD, suggesting that the vagal nerve may be critically involved in the pathogenesis of PD.

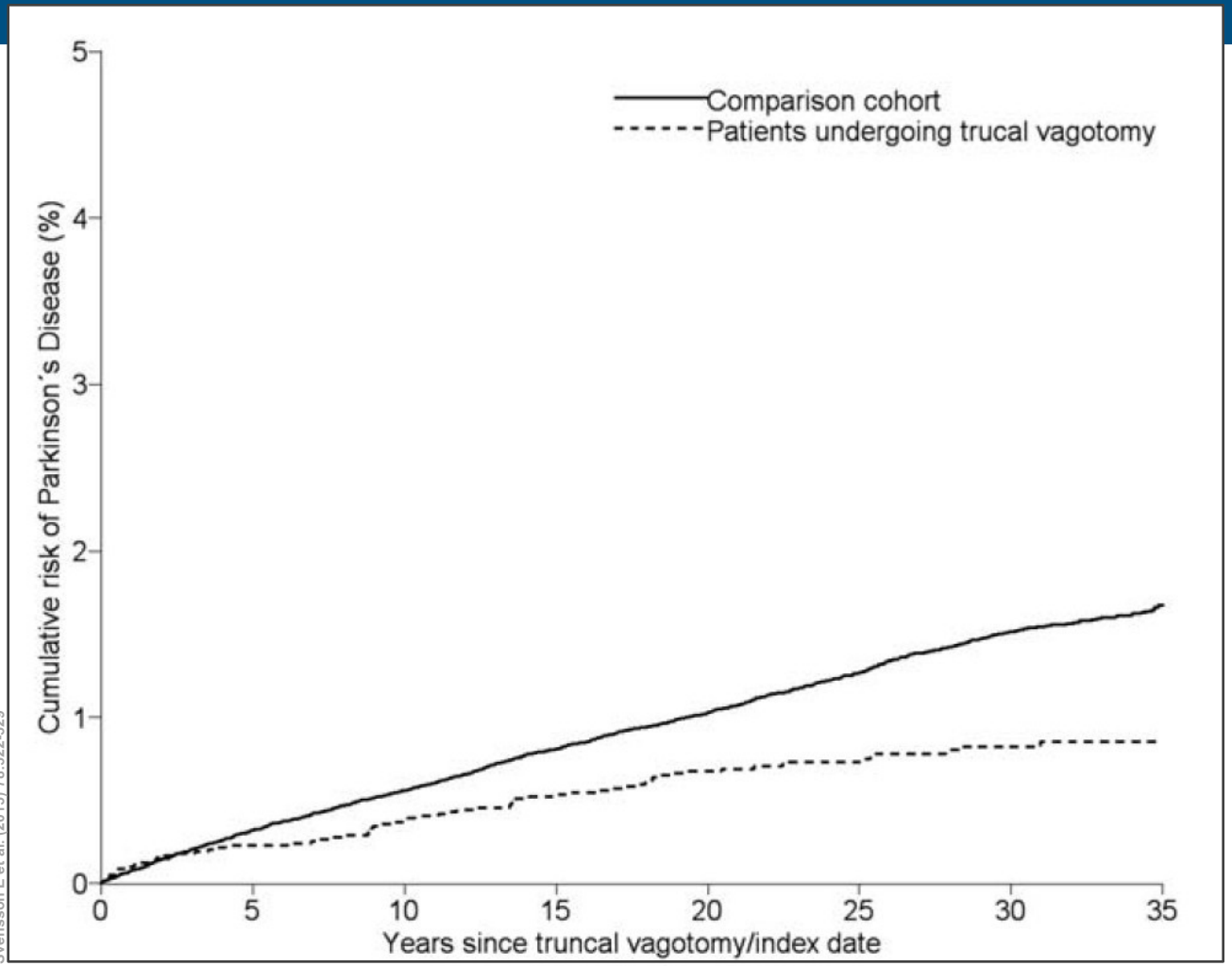
ANN NEUROL 2015;78:522–529

TABLE 1. Epidemiological studies investigating vagotomy and subsequent PD risk

		Vagotomy				No vagotomy	
Author	Country	Number	Classification	Age at surgery, mean	Year of vagotomy	Number	Key findings
Liu et al., 2017[24]	Sweden	9,430	Truncal vs selective (including both selective and highly selective)	54.3 years	1970-2010	377,200	When cases restricted to >5 years after the date of surgery, truncal (but not selective) vagotomy had lower PD risk
Svensson et al., 2015[26]	Denmark	11,209[a]	Truncal (including both truncal and selective) vs highly selective[b]	56 years (truncal), 47 years (highly selective)	1977-1995	127,211	Truncal vagotomy had statistically non-significant reduction in PD risk >5 years after surgery, but stronger effect when restricted >20 years
Tysnes et al., 2015[27]	Denmark	15,079	Truncal vs selective[b]	NR	1977-2011	NR[c]	No significant risk reduction found

All studies were nationwide cohort studies with data linkage. NR, not reported.
[a]Although 14,883 vagotomy patients were identified, only 11,209 had more than 5 years of postsurgical follow-up.
[b]Different operative coding classification applied to the same data source.
[c]The number of cases without vagotomy was not reported, but this data was available to calculate relative risk reduction for the development of PD in patients undergoing different vagotomy procedures.

Breen DP et al. (2019) Movement Disord 34:307-316



Svensson E et al. (2015) 78:522-529

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

Заболеваемость БП среди пациентов с воспалительными заболеваниями кишечника

Killinger et al. Sci. Trans. Med. (2018)

- В двух независимых исследованиях, в которых участвовало более 1,6 млн. человек и более 91 млн. человеко-лет, обнаружено , что удаление аппендикса за десятилетия до начала БП было связано с более низким риском развития БП и задержкой начала заболевания.

- Аппендикс здорового человека содержал интранейрональные агрегаты альфа-синуклеина и множество продуктов усечения альфа-синуклеина, связанных с патогенезом БП, которые, как известно, накапливаются в тельцах Леви.

- Предполагается, что нормальный человеческий аппендикс содержит патогенные формы альфа-синуклеина, которые влияют на риск развития БП.

Заболеваемость БП среди пациентов с воспалительными заболеваниями кишечника

Peter et al. JAMA Neurology (2018) 75:939-946

- Peter et al. JAMA Neurology (2018) 75:939-946
- Сравнить частоту БП среди людей с воспалительными заболеваниями кишечника (ВЗК) или без таковой и оценить, изменяется ли риск БП среди пациентов с ВЗК терапией анти-ФНО.
- 144,018 человек с ВЗК. Частота возникновения БП среди пациентов с ВЗК была на 28% выше, чем среди не подвергавшихся воздействию контрольных групп.
- Снижение частоты случаев БП на 78% было выявлено среди пациентов с ВЗК, которые подвергались терапии анти-ФНО.

Mov Disord. 2018 Sep;33(9):1492-1496

BRIEF REPORTS

Appendectomy and Risk of Parkinson's Disease in Two Large Prospective Cohorts of Men and Women

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who did not was 1.08 (95% confidence interval, 0.94-1.23). In women, appendectomy for appendicitis, but not incidental appendectomy, was associated with a modestly elevated risk of Parkinson's disease (hazard ratio, 1.23 [95% confidence interval, 1.00-1.50]).
Conclusions: Overall, this study suggests limited to no association between appendectomy and Parkinson's disease risk. © 2018 International Parkinson and Movement Disorder Society

Key Words: appendectomy; Parkinson's; epidemiology; gut-brain axis

Parkinson's disease (PD) is increasingly recognized as a systemic disease, with well-known effects on the peripheral nervous system, particularly the gut. Recently, it has been proposed that the initial misfolding of α-synuclein, a protein key to PD pathology, may occur in the gut and then spread to the brain via retrograde axonal transport.[1–4] A reduced risk of PD was observed after truncal vagotomy in the Danish[5] and, to

tomy and PD has produced mixed results. In this study we examined whether history of self-reported appendectomy was related to risk of incident Parkinson's disease in the Nurses' Health Study and the Health Professionals Follow-up Study.
Methods: We used the Cox proportional hazards model to estimate the hazard ratio of Parkinson's disease associated with self-report of appendectomy in men and women. Among women, we estimated the hazard ratio of Parkinson's disease associated with appendectomy for appendicitis and incidental appendectomy.
Results: In pooled analyses, self-report of any appendectomy was not related to Parkinson's disease risk: the hazard ratio of Parkinson's disease comparing participants who reported any appendectomy with those

microbiome.

In a recent report,[17] the appendix was found to be particularly rich in α-synuclein relative to other areas of the gastrointestinal system, suggesting this organ as a potential point of initiation of PD pathology. Several studies to date have examined the association between appendectomy and PD with mixed results. In an analysis of the Danish National Registry, with 34 years of follow-up, appendectomy was associated with a modest 15% increase (95% CI, 3%-27%) in PD risk.[18] In contrast, no association between appendectomy and PD risk was found in a registry-based study in Ontario, Canada, comparing 42,999 participants with appendectomy with those with cholecystectomy or no procedures.[19]

In this study, we sought to examine the association between self-reported appendectomy and incidence of PD in 2 large prospective cohort studies, the Nurses' Health Study and the Health Professionals Follow-up Study.

Methods

Study Population

We investigated the association between self-reported appendectomy and risk of PD in 2 large prospective epidemiological cohorts: the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study

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Relevant conflicts of interest/financial disclosures: The authors have no conflicts of interest to disclose.

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Аппендэктомия не вызывает снижения риска развития БП

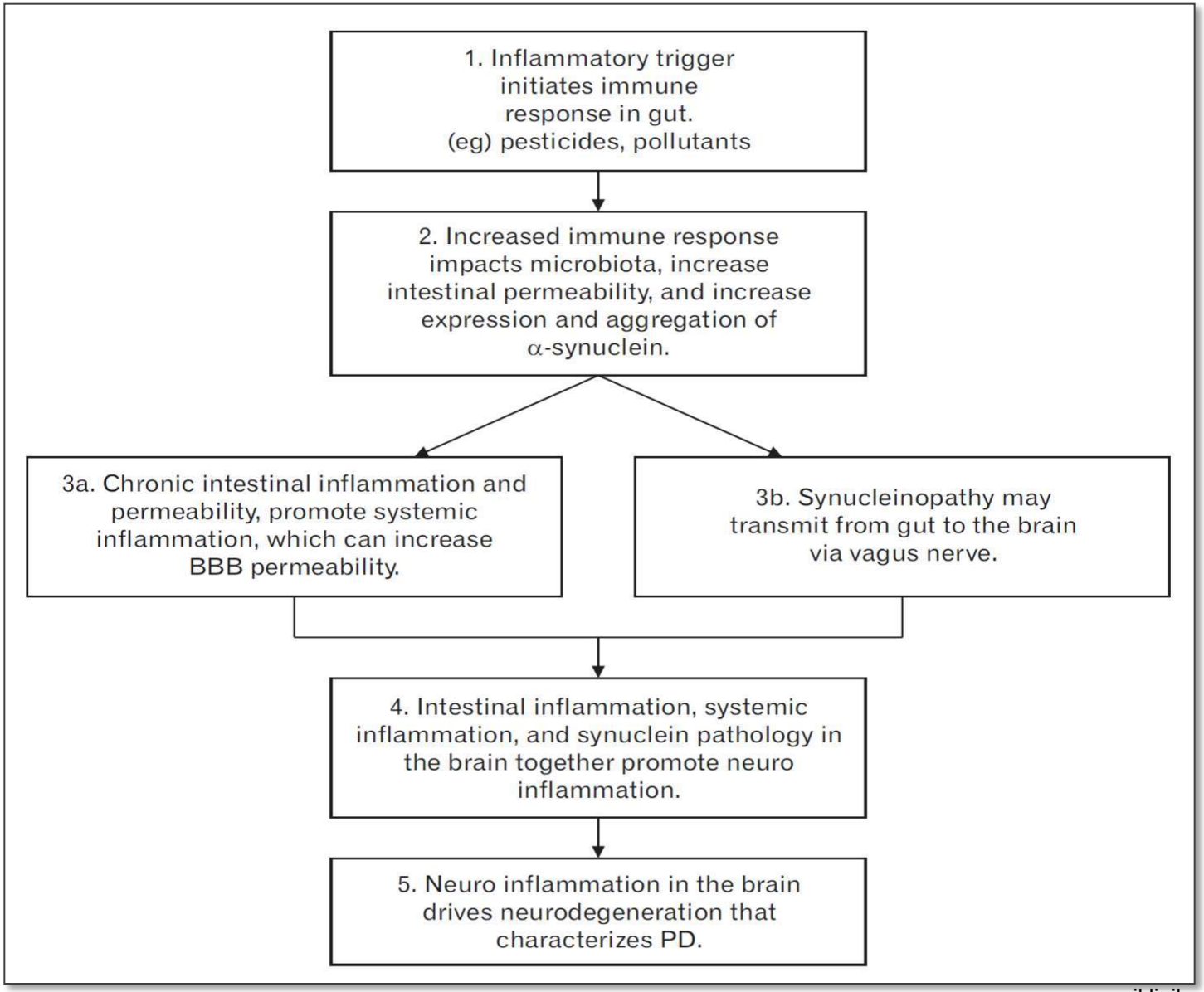
TABLE 1. Any appendectomy and risk of Parkinson's disease in women (NHS) and men (HPFS)

		Women				Men				Pooled		
		PY[1]	Cases	HR	95% CI	PY	Cases	HR	95% CI	HR	95% CI	p-Heterogeneity (sex)
No appendectomy		1,249,191	406	Ref		842,764	460	Ref				
Any appendectomy	Model 1	442,700	177	1.09	(0.92-1.31)	167,509	109	1.02	(0.83-1.26)	1.06	(0.93-1.22)	0.62
	Model 2			1.08	(0.91-1.30)			1.04	(0.84-1.29)	1.08	(0.94-1.23)	0.72

Model 1 adjusted for age in months at baseline.
Model 2 adjusted for age in months, smoking (never, past, current), pack-years smoking, PMH use (in NHS only: never, past, current) at baseline.
[1] Person-years of follow-up

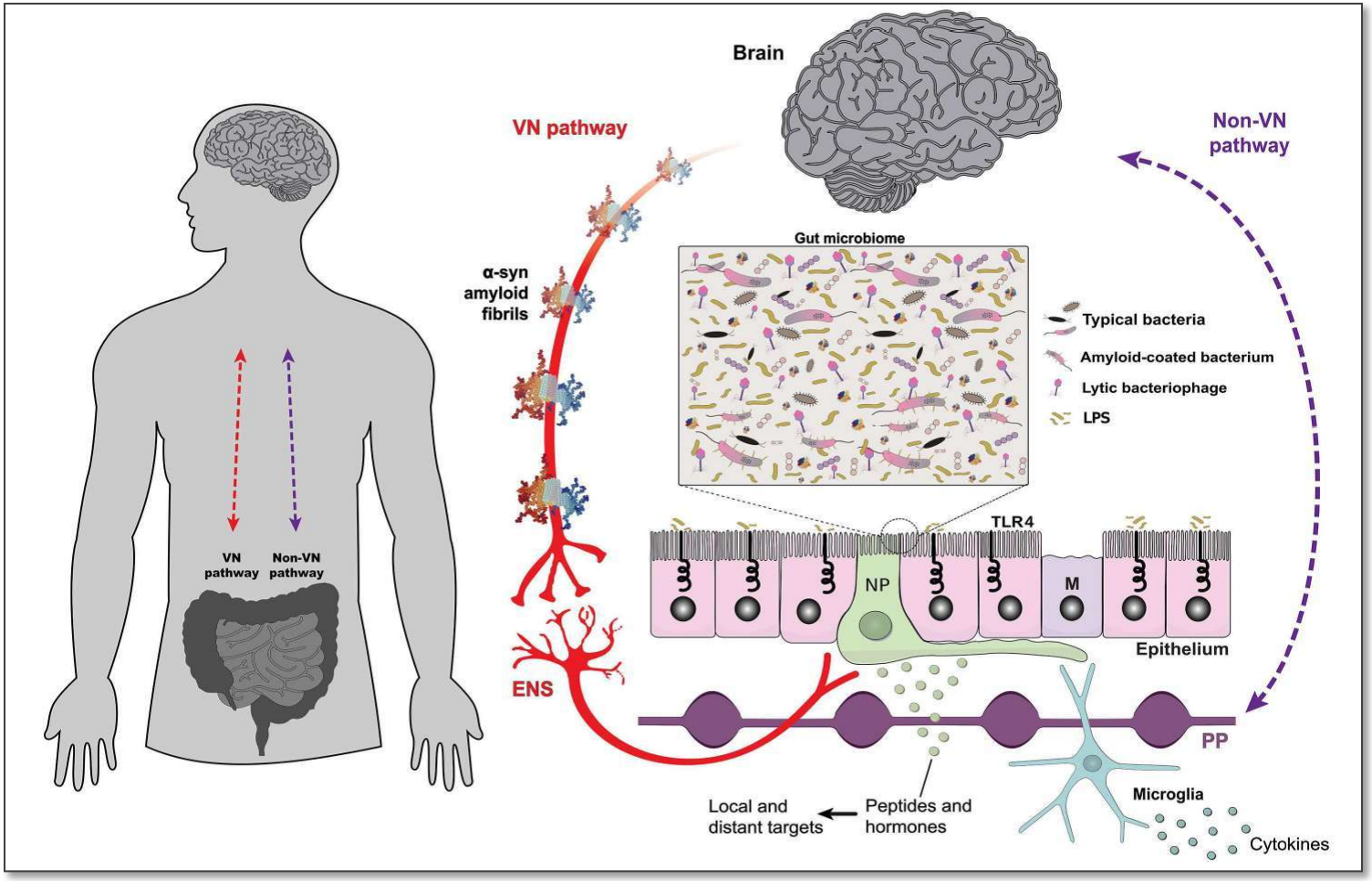
Palacios N et al. (2018) Movement Disord 33(9):1492-1496.

Взаимодействие кижечника и ГМ



Nair AT et al. (2018) J Neurogastroenterol Motil 24:30-42

Кишечник и БП – дорога в двух нарпавлениях



Fonesca Santos S et al. (2019) Front Neurol: 10.3389/fneur.2019.00574

Сообщение кишечника и мозга: норма и патология

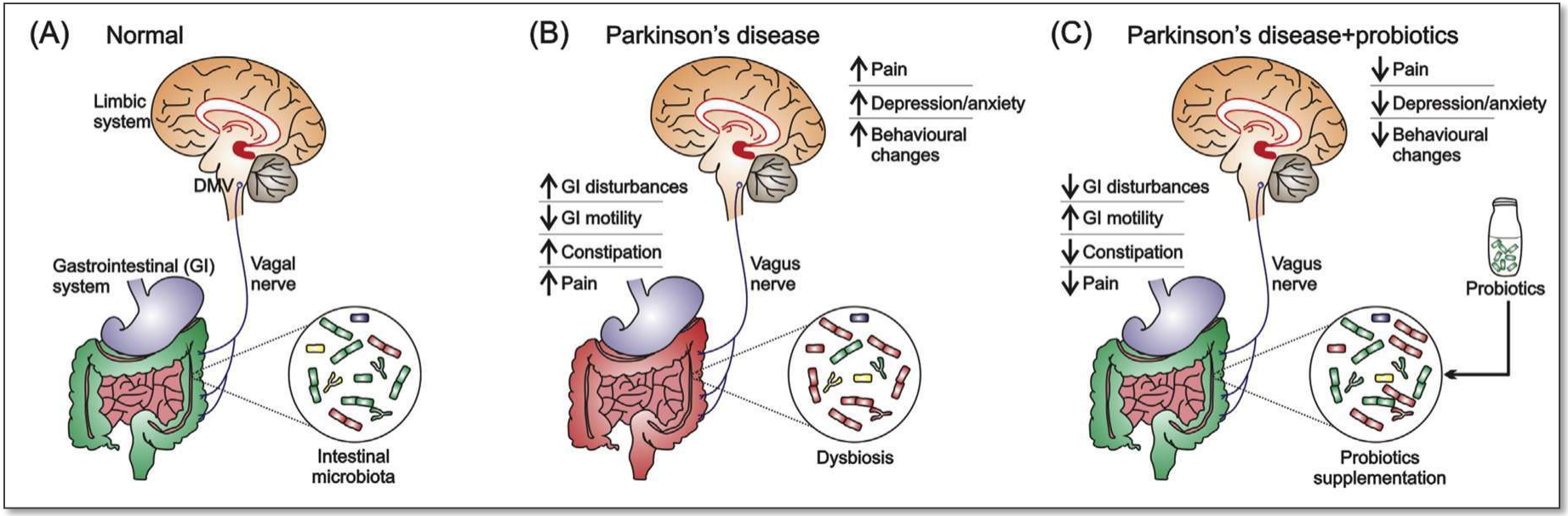


Fig. 1. The brain-gut axis in health and disease, with relevance to Parkinson's disease. (A) The healthy bi-directional communication between the brain and the gut, high-lighting the involvement of the vagus nerve. (B) The brain-gut axis and non-motor symptoms of Parkinson's disease including both central and GI dysfunction. (C) The manipulation of the gut microbiota through the use of probiotics and potential alleviation of non-motor symptoms of Parkinson's disease. SN: substantia nigra; DMV: dorsal motor nucleus of the vagus.

Felice VD et al. (2016) Parkinsonism Rel Disord 27:1-8

О функции пробиотиков при БП

Journal of Microbiology (2018) Vol. 56, No. 3, pp. 172–182
DOI 10.1007/s12275-018-8032-4
eISSN 1976-3794
pISSN 1225-8873

REVIEW

Mind-altering with the gut: Modulation of the gut-brain axis with probiotics

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(Received Jan 21, 2018 / Revised Feb 7, 2018 / Accepted Feb 12, 2018)

It is increasingly evident that bidirectional interactions exist among the gastrointestinal tract, the enteric nervous system, and the central nervous system. Recent preclinical and clinical trials have shown that gut microbiota plays an important role in these gut-brain interactions. Furthermore, alterations in gut microbiota composition may be associated with pathogenesis of various neurological disorders, including stress, autism, depression, Parkinson's disease, and Alzheimer's disease. Therefore, the concepts of the microbiota-gut-brain axis is emerging. Here, we review the role of gut microbiota in bidirectional interactions between the gut and the brain, including neural, immune-mediated, and metabolic mechanisms. We highlight recent advances in the understanding of probiotic modulation of neurological and neuropsychiatric disorders via the gut-brain axis.

Keywords: probiotics, gut microbiota, nervous system, gut-brain axis, gut dysbiosis, neurological disorders

al., 2011). The scaffolding of the gut-brain axis includes the gastrointestinal tract, central nervous system (CNS), autonomic nervous system (ANS), enteric nervous system (ENS), neuroendocrine system, and immune system (Grenham *et al.*, 2011). Recent studies have shown that the gut microbiota is involved in the neurodevelopment and diverse brain functions through regulating the gut-brain axis (Carabotti *et al.*, 2015; Erny *et al.*, 2015). Gastrointestinal symptoms, such as constipation, diarrhea, and abdominal pain, are common comorbidities in many neurological diseases (Westfall *et al.*, 2017). Moreover, recent advances in metagenomic sequencing have revealed that dysregulation in the composition of gut microbiota (gut dysbiosis) is present in a variety of neurological diseases. Consequently, the importance of maintaining a healthy microbiota community (gut symbiosis) in the regulation of the gut-brain axis cannot be overly emphasized. The term microbiota-gut-brain (MGB) axis was introduced to highlight the role of the microbiota in the gut-brain axis.

Probiotics are defined as living microorganisms that, when ingested in adequate quantities, confer a health benefit on the host; these microorganisms have been reported to exert a wide range of effects (Hill *et al.*, 2014). Although their mechanisms in modulating host physiology are not yet fully elucidated, probiotics might be able to modulate host immune system (Bermudez-Brito *et al.*, 2012). For example, *Weissella cibaria* WIKIM28 isolated from kimchi ameliorates atopic

Table 1. List of neuroactive compounds detected within various bacteria

Gut microbiota	Neurochemical	References
Lactobacillus, *Bifidobacterium* spp.	GABA	Barrett *et al.* (2012)
Bifidobacterium infantis, *Streptococcus*, *Escherichia*, *Enterococcus*, *Lactococcus*, *Lactobacillus*, *Candida*,	Serotonin (5-HT)	Özogul (2011), Holzer and Farzi (2014)
Clostridium sporogenes, *Ruminococcus gnavus*	Tryptamine	Williams *et al.* (2014)
Escherichia, *Bacillus*, *Saccharomyces*	Norepinephrine	Holzer and Farzi (2014)
Escherichia, *Bacillus*, *Lactococcus*, *Lactobacillus*, *Serratia*	Dopamine	Özogul (2011), Holzer and Farzi (2014)
Lactobacillus, *Bacillus*	Acetylcholine	Kawashima *et al.* (2007)
Lactococcus, *Lactobacillus*, *Streptococcus*, *Enterococcus*	Histamine	Landete *et al.* (2008), Thomas *et al.* (2012), Hemarajata *et al.* (2013)
Bacillus sp. JPJ	L-dopa	Surwase and Jadhav (2011)

Kim Net al. (2018) J Microbiol 56(3):172-182

Table 2. Links between altered gut microbiota composition and a variety of neurological and psychiatric disorders

Disease	Altered gut microbiota	References
Stress	Porphyromonadaceae ↓	Bailey *et al.* (2010)
	Clostridium ↑, *Bacteroides* ↓	Bailey *et al.* (2011)
	Oscillibacter ↑, *Anaerotruncus* ↑, *Peptococcus* ↑, *Lactobacillus* ↓	Golubeva *et al.* (2015)
Depression	*Bifidobacterium* ↓, *Lactobacillus* ↓	Aizawa *et al.* (2016)
	Bacteroidetes ↑, Proteobacteria ↑, Actinobacteria ↑, Firmicutes ↓	Jiang *et al.* (2015)
Autism	*Clostridium* ↑	Song *et al.* (2004), Parracho *et al.* (2005)
	Sutterella spp. ↑, *Ruminococcus torques* ↑, *Akkermansia muciniphila* ↓	Wang *et al.* (2011, 2013)
	Clostridium ↑, Sutterellaceae ↑, Enterobacteriaceae ↑, *Bifidobacterium* ↓	De Angelis *et al.* (2013)
	Collinsella ↑, *Corynebacterium* ↑, *Dorea* ↑, *Lactobacillus* ↑, *Alistipes* ↓, *Bilophila* ↓, *Dialister* ↓, *Parabacteroides* ↓, *Veillonella* ↓	Strati *et al.* (2017)
	Desulfovibrio ↑, *Bacteroides vulgatus* ↑, *Ruminococcus* ↑, *Bifidobacterium* ↓	Finegold *et al.* (2010)
Alzheimer's disease	Association with bacterial and viral infection	Bu *et al.* (2015)
	Bacteroidetes ↑, Tenericutes ↑, Firmicutes ↓, Verrucomicrobia ↓, Proteobacteria ↓ Actinobacteria ↓, *Allobaculum* ↓, *Akkermansia* ↓	Harach *et al.* (2017)
	Bacteroidetes ↑, Firmicutes ↓, *Bifidobacterium* ↓	Vogt *et al.* (2017)
Parkinson's disease	*Ralstonia* ↑, *Blautia* ↓, *Coprococcus* ↓, *Roseburia* ↓, *Faecalibacterium* ↓	Keshavarzian *et al.* (2015)
	Enterobacteriaceae ↑, Prevotellaceae ↓	Scheperjans *et al.* (2015)

Kim Net al. (2018) J Microbiol 56(3):172-182

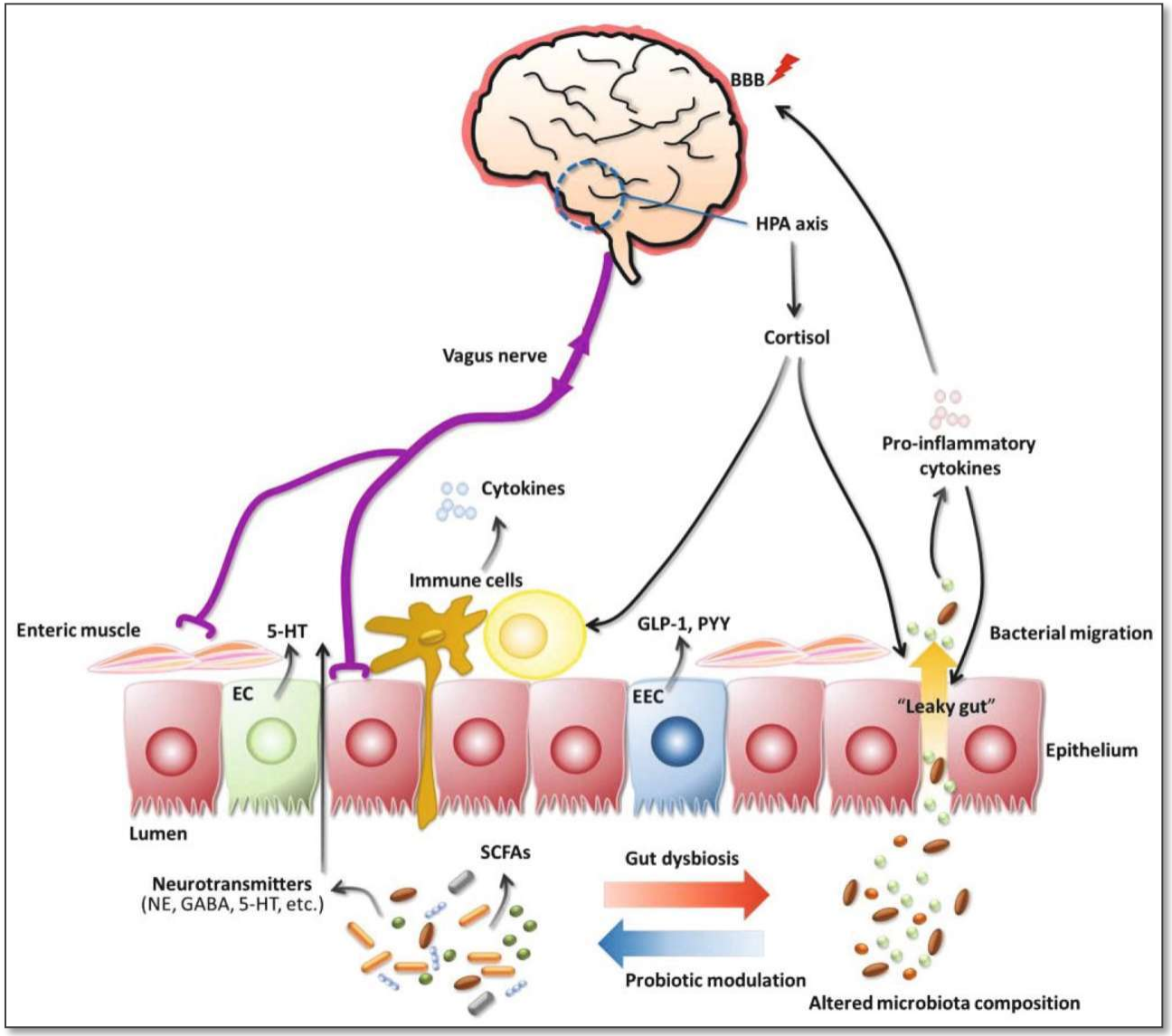

Fig. 1. Modulation of the gut-brain axis by probiotics. The routes of communication between the gut and the brain include neuronal, immune-mediated, and metabolite-mediated pathways. Gut dysbiosis leads to increased inflammation, as well as, activation of the HPA axis, and altered levels of neurotransmitters and bacterial metabolites; these may contribute to abnormal signaling through the vagus nerve. Reduced integrity of the gastrointestinal barrier triggers bacterial migration ("leaky gut") and inflammation. Inflammatory cytokines induce the disruption of blood-brain barrier integrity. Probiotics have the potential to normalize such processes (Abbreviations: HPA axis, hypothalamus-pituitary gland-adrenal gland axis; NE, norepinephrine; GABA, γ-aminobutyric acid; BBB, blood brain barrier; EEC, enteroendocrine cell; EC, enterochromaffin cell); GLP-1, glucagon-like peptide-1; PYY, peptide tyrosine tyrosine; 5-HT, 5-hydroxytryptamine; SCFAs, short-chain fatty acids.

Kim Net al. (2018) J Microbiol 56(3):172-182

976 *Movement* Disorders, Vol. 29, No. 8, 2014

VIEWPOINT

Gut Feelings About Smoking and Coffee in Parkinson's Disease

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ABSTRACT: Strong epidemiologic evidence suggests that smokers and coffee drinkers have a lower risk of Parkinson's disease (PD). The explanation for this finding is still unknown, and the discussion has focused on two main hypotheses. The first suggests that PD patients have premorbid personality traits associated with dislike for coffee-drinking and smoking. The second posits that caffeine and nicotine are neuroprotective. We propose an alternative third hypothesis, in which both cigarette and coffee consumption change the composition of the microbiota in the gut in a way that mitigates intestinal inflammation. This, in turn, would lead to less misfolding of the protein alpha-synuclein in enteric nerves, reducing the risk of PD by minimizing propagation of the protein aggregates to the central nervous system, where they otherwise can induce neurodegeneration.

Key Words: Parkinson's disease; enteric nervous system; nicrobiota

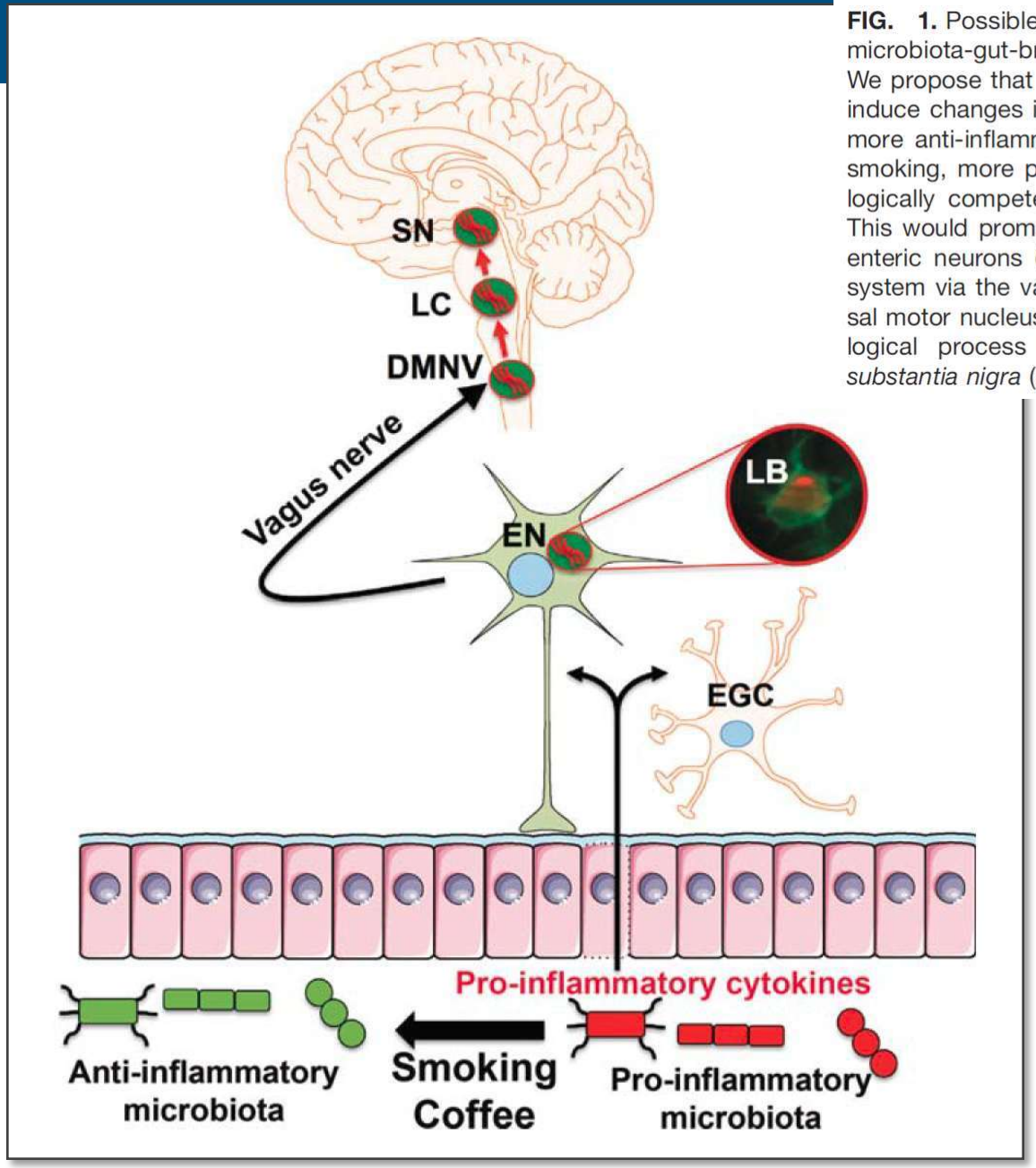
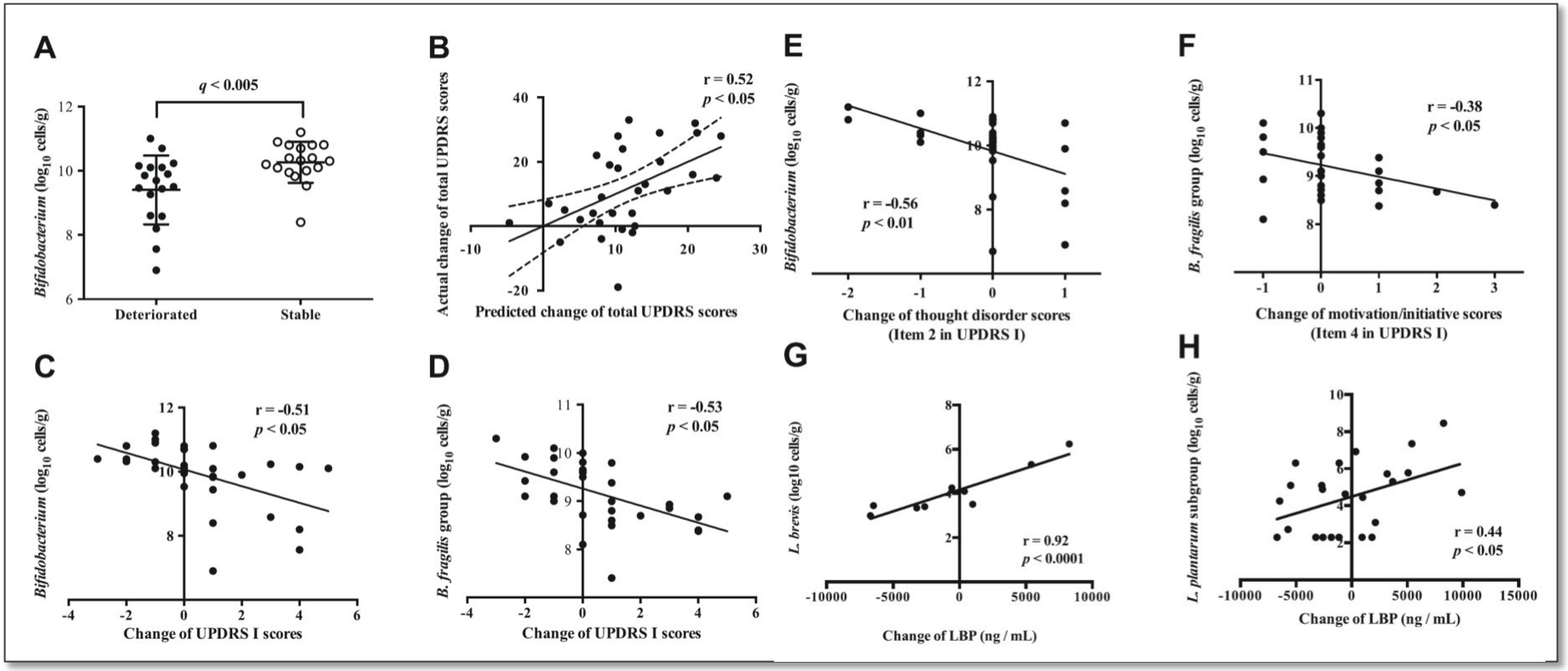


FIG. 1. Possible role of smoking and coffee consumption on microbiota-gut-brain-axis and the development of Parkinson's disease. We propose that both cigarette smoking and coffee consumption may induce changes in the composition of microbiota with a shift toward a more anti-inflammatory state. In the absence of coffee and cigarette smoking, more pro-inflammatory cytokines are produced by immunologically competent cells and by enteric glial cells (EGC) in the gut. This would promote a-synuclein aggregation (Lewy bodies, LB) within enteric neurons (EN) that may spread further to the central nervous system via the vagal preganglionic innervation of the gut and the dorsal motor nucleus of the vagus (DMNV). After several years, the pathological process would reach the *locus coeruleus* (LC) and the *substantia nigra* (SN).

Derkinderen P et al. (2014) Mov Disord 29:967

Микробиота кишечника при БП



Lin et al. (2018) PRD53:82-88: Significant increases in the abundance of 4 bacterial families and decreases in seventeen bacterial families in China.

Резюме

Болезнь Паркинсона, по-видимому, следует клинической картине с предмоторной фазой, за которой следует типичное нарушение моторики.

Ранние признаки присутствуют у большинства пациентов и включают потерю обоняния и запор.

Это хорошо согласуется с утверждением, что стадия Браака 1 характеризуется альфа-синуклеином в дорсальной части блуждающего нерва и обонятельной луковици.

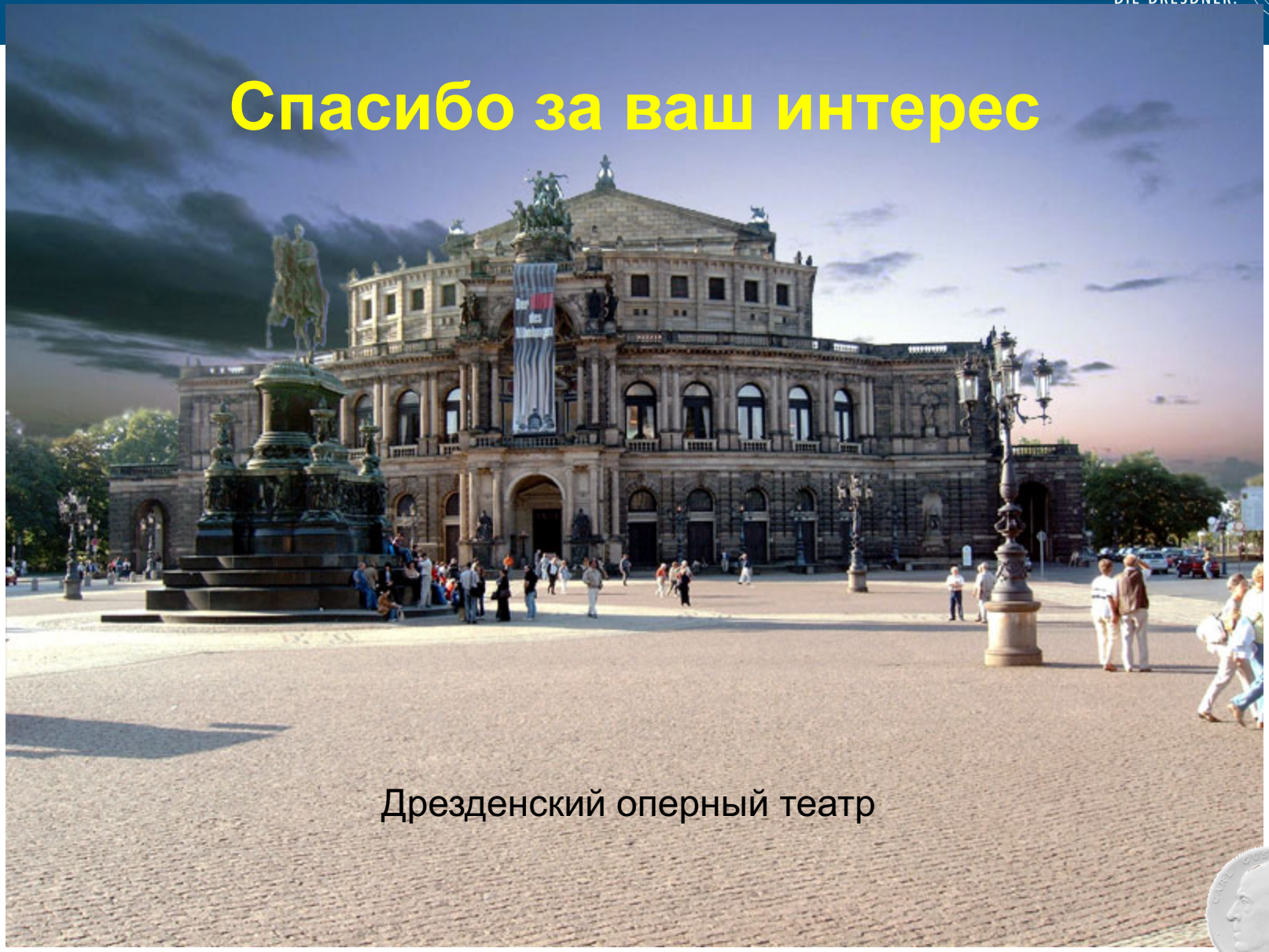
Более поздняя нейропатологическая работа показала, что есть также нарушение КНС и нервной системы подчелюстной железы.

Все эти места открыты для окружающей среды, поэтому интересно предположить, что вещество извне вызывает БП.

По этой причине мы разработали модель на животных и могли продемонстрировать, что эта модель полностью соответствует постановке Браака.

Микрофлора кишечника может играть важную роль в развитии БП, и необходима дальнейшая работа, чтобы проверить, полезно ли использование пробиотиков.

Спасибо за ваш интерес



Дрезденский оперный театр