

FAECAL MICROBIOTA TRANSPLANTATION FOR TREATMENT OF PARKINSON'S DISEASE

FILIP SCHEPERJANS

Department of Neurology, Helsinki University Hospital,
and NeuroBiome Ltd., Helsinki, Finland

INTRODUCTION

There is a rapidly growing field of microbiota-based interventions in Parkinson's disease (PD). Although PD is usually defined by bradykinesia, rigidity and tremor, many patients develop gastrointestinal symptoms years before the motor syndrome becomes evident. This temporal sequence, together with accumulating epidemiological, microbiological and experimental evidence, has raised the possibility that the gut is not merely affected secondarily in PD, but may participate in disease initiation and progression in at least a subgroup of patients (*Kalia and Lang, 2015; Schapira et al., 2017; Horsager et al., 2020*).

PD remains one of the most challenging chronic neurodegenerative

disorders in clinical neurology. It is the second most common neurodegenerative disease, leads to progressive disability and frequently cognitive decline, and still lacks a disease-modifying therapy (*Kalia and Lang, 2015*). The highly relevant question is whether the intestinal microbiota can be used not only to better understand the biology of PD, but if it also can be used as a therapeutic target. This review moves stepwise from the prodromal phase of PD and gut-based epidemiology to microbiota signatures, plausible biological mechanisms, preclinical intervention studies and finally to human clinical trials, with particular emphasis on faecal microbiota transplantation (FMT).

PARKINSON'S DISEASE AS A MULTISYSTEM DISORDER WITH A LONG PRODROMAL PHASE

One of the core messages is that PD should be viewed as a multisystem disease rather than as an isolated degeneration of nigrostriatal dopaminergic neurons. Many non-motor features, including constipation, rapid eye movement sleep behaviour disorder (RBD), hyposmia, depression, fatigue, pain and autonomic dysfunction, may occur years before the diagnosis is made (*Kalia and Lang, 2015; Schapira et al., 2017*). This long prodromal interval is clinically important because it indicates that the pathological process is already

active when the classical motor syndrome first emerges.

Figure 1 illustrates how constipation can precede diagnosis by decades, while other non-motor symptoms gradually accumulate before motor impairment and later complications become prominent. In practical terms, this means that the gastrointestinal tract is involved early in the disease course and deserves attention not only as a source of symptoms, but also as a potential window into pathogenesis.

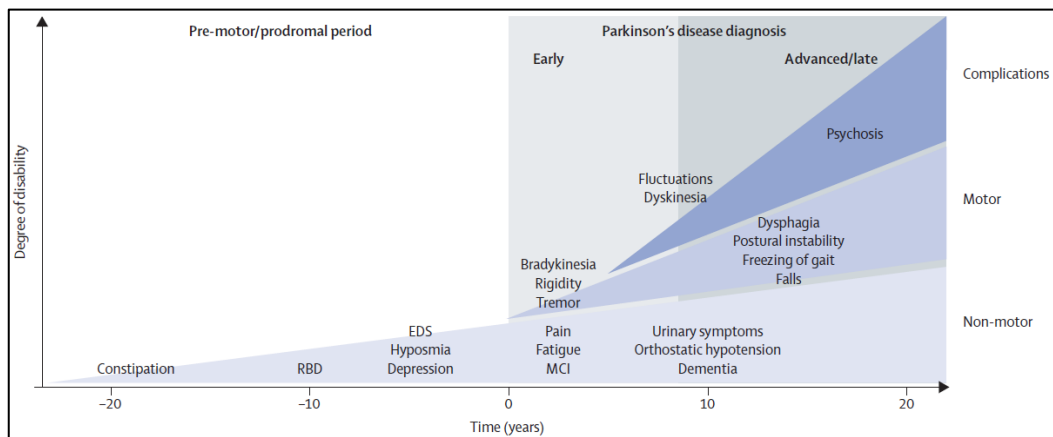


Figure 1: The prodromal phase of PD can extend for years and is dominated by non-motor symptoms such as constipation, RBD, hyposmia and depression before the classical motor syndrome becomes established. (Figure from *Kalia and Lang*, 2015).

BODY-FIRST AND BRAIN-FIRST PARKINSON'S DISEASE

An increasingly influential concept claims that PD may consist of at least two major biological routes of disease spread. In the body-first subtype, pathology may initially arise in the enteric or peripheral autonomic nervous system and ascend to the brainstem and higher structures. In the brain-first subtype, the earliest pathology is thought to begin within the central nervous system and only later involves the peripheral autonomic system and gut (Figure 2) (*Horsager et al.*, 2020). This framework helps to explain why some patients have a striking prodromal burden of gastrointestinal and autonomic symptoms, whereas others present more directly with central motor features.

For microbiota-oriented research, this distinction is crucial. If a subgroup of patients truly has a body-first form of synucleinopathy, then gut microbial changes may be more than an epiphenomenon. They could be mechanistically linked to early disease biology and therefore represent rational targets for intervention. The presentation emphasized that imaging and clinical work from the Borghammer group has provided a coherent conceptual basis for this subdivision, and that this framework is especially relevant when interpreting microbiome findings and treatment responses (*Horsager et al.*, 2020).

GASTROINTESTINAL EPIDEMIOLOGY AND MICROBIOTA-ASSOCIATED RISK SIGNALS

There are several epidemiological observations that support a gut-brain connection in PD. Constipation is one of the strongest and best replicated prodromal gastrointestinal features of PD, with

meta-analytic data suggesting a clearly increased later risk of diagnosis. Similar associations have been reported for irritable bowel syndrome (IBS) and inflammatory bowel disease. The key point is

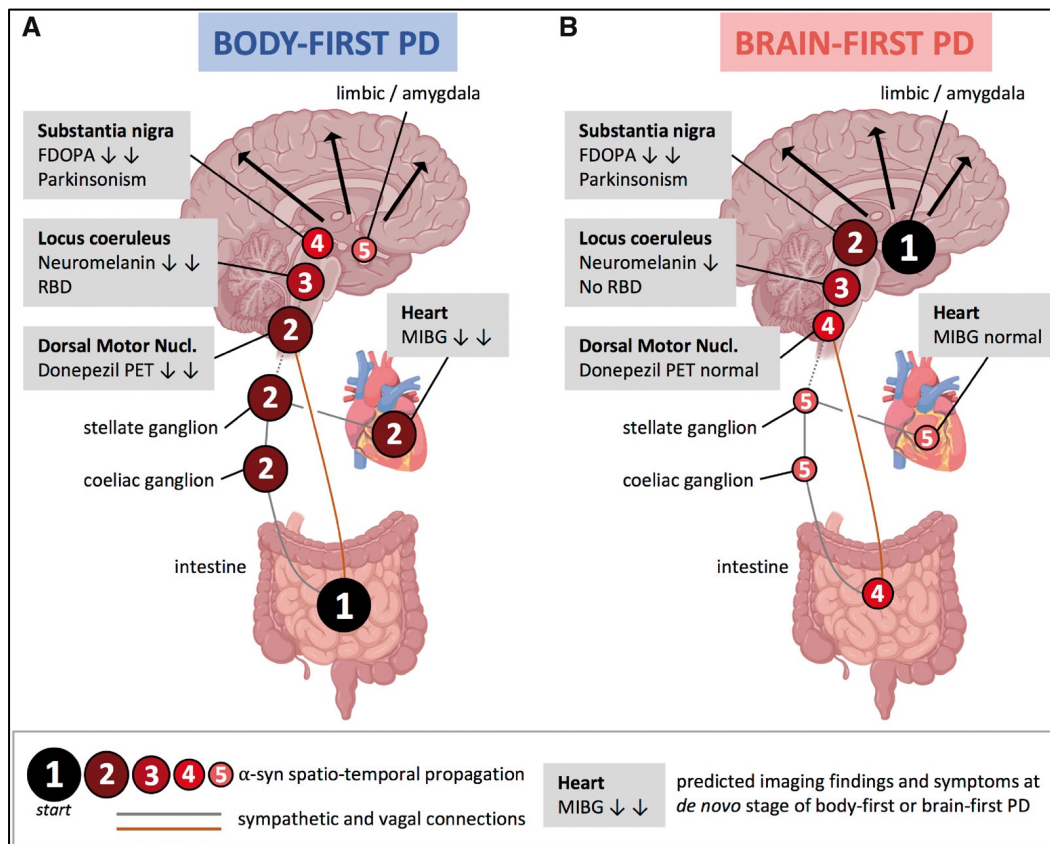


Figure 2: Schematic distinction between body-first and brain-first PD. In the body-first subtype, pathology is hypothesized to start in the enteric/autonomic nervous system and ascend centrally; in the brain-first subtype, the earliest pathology is thought to arise within the brain. (Figure from Horsager et al., 2020).

that these disorders are not direct causes of PD, but that they consistently point toward early gastrointestinal involvement and toward inflammatory or microbial factors that may modify susceptibility (Lai et al., 2014; Adams-Carr et al., 2016; Zhu et al., 2019).

Of especially interest is antibiotic exposure. In a large Finnish nationwide case-control study, exposure to certain oral antibiotics was associated with an

elevated later risk of PD, with the timing of exposure fitting the idea of a long pre-diagnostic interval. Such findings are important because antibiotics are among the strongest routine modifiers of the intestinal microbiome. Although antibiotic use itself cannot be equated with causation, these data again support the idea that perturbation of gut microbial ecology may be linked to PD risk over the long term (Mertsalmi et al., 2020).

GUT MICROBIOTA SIGNATURES AND LINKS TO SYMPTOMS AND PROGRESSION

Extensive literature describes alterations in the gut microbiota of patients with PD. Alpha-diversity measures such

as richness, evenness and Shannon index are not consistently changed, and loss of overall diversity is not a

consistent feature of PD. What appears more reproducible are specific compositional shifts. Across studies, differences in taxa related to short-chain fatty acid (SCFA) production, *Prevotella*, *Akkermansia*, *Lactobacillus*, *Bifidobacterium* and several other genera have repeatedly been reported (Plassais et al., 2021; Romano et al., 2021).

Important are longitudinal as well as symptom-linked findings. In the work from Aho and colleagues (Aho et al., 2019), microbiota differences remained relatively stable over time, and certain

microbial patterns appeared to relate to disease progression. Other studies linked reduced butyrate-producing bacteria or lower faecal butyrate to depressive symptoms, while additional datasets associated specific microbial profiles with constipation, IBS symptoms, cognitive measures and motor subdomains. Taken together, these observations suggest that the microbiome may help explain part of the well-known clinical heterogeneity of PD (Aho et al., 2019; Xie et al., 2022).

POTENTIAL MECHANISMS LINKING THE GUT MICROBIOTA TO PARKINSON'S DISEASE BIOLOGY

The mechanistic section of this review integrates microbiology, immunology and alpha-synuclein biology into a coherent pathophysiological model. Dysbiosis may reduce the production of beneficial SCFAs, alter bile acid metabolism and weaken the intestinal barrier. This can increase local immune activation, facilitate exposure to bacterial products such as lipopolysaccharide and affect enteroendocrine signalling, enteric glial function and vagal pathways. In parallel, bacterial amyloids and inflammatory mediators may influence alpha-synuclein expression and aggregation, while systemic immune activation may further amplify neuroinflammation (Tan et al., 2022).

The review by Tan and colleagues (Tan et al., 2022) summarized these interacting pathways elegantly: altered fibre fermentation and metabolite production, barrier dysfunction, innate immune activation, cytokine signalling,

blood-borne mediators and neural propagation are all plausible contributors (Figure 3). The important point is that the microbiota does not need to 'cause' PD in a simplistic one-microbe-one-disease manner. Rather, it may shape the intestinal and immune environment in a way that promotes or protects against pathogenic processes relevant to PD.

This mechanistic plausibility is strengthened by experimental data. Germ-free or microbiota-depleted alpha-synuclein-overexpressing mice show reduced motor deficits, less microglial activation and improved gut motility compared with conventionally colonized animals (Sampson et al., 2016). Such results do not automatically translate into treatment effects in humans, but they provide strong proof of principle that microbial manipulation can modify PD-relevant phenotypes *in vivo*.

FROM MECHANISM TO INTERVENTION: PRECLINICAL AND EARLY CLINICAL MODULATION STUDIES

Several preclinical studies suggest that transferring a healthier microbial community or administering microbiota-associated products can attenuate

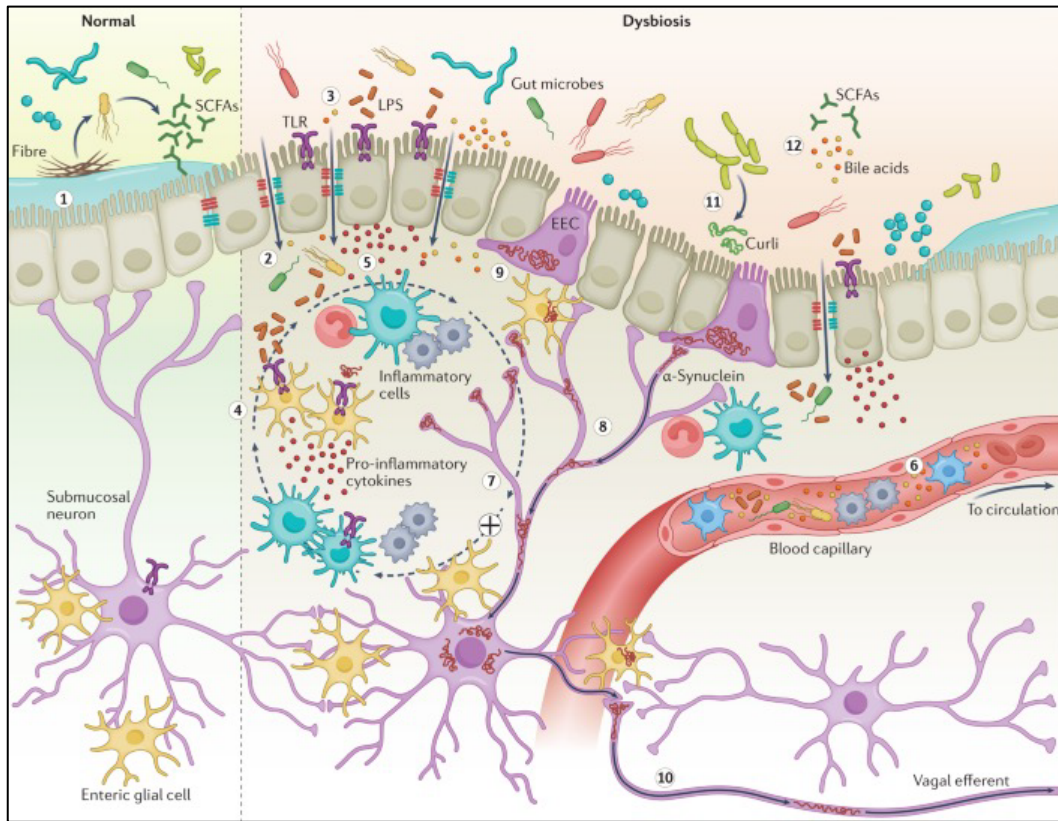


Figure 3: Proposed mechanisms by which gut dysbiosis may contribute to PD pathophysiology, including altered microbial metabolites, impaired epithelial barrier function, innate and adaptive immune activation, inflammatory signalling, effects on enteroendocrine and enteric nervous system neurons, and possible propagation of alpha-synuclein-related pathology through neural and systemic routes. (Figure from *Tan et al., 2022*).

PD-like pathology in toxin-based animal models. Reported mechanisms include reduced microglial activation, suppression of TLR4-related inflammatory signalling, improved intestinal function and restoration of microbial metabolites such as butyrate. These studies remain model-dependent and should be interpreted cautiously, but together they suggest that PD-related mechanisms are not fixed and may be manipulable through the microbiota (*Sun et al., 2018*).

The human intervention literature remains less mature but is growing steadily. Probiotic trials and the RESISTA-PD resistant-starch study

suggest that gastrointestinal outcomes are presently the most consistent target, with improvements reported for constipation-related measures and, in some studies, quality of life. By contrast, benefits on global motor scores have been smaller or less reproducible. This imbalance is not surprising. Gut-targeted therapies are most likely to show their earliest clinical effects on bowel symptoms, whereas robust effects on established central motor manifestations may require either longer treatment periods, more targeted patient selection or disease stages in which gut-driven biology is still especially relevant (*Jin et al., 2024; Becker et al., 2024*).

FAECAL MICROBIOTA TRANSPLANTATION AS A THERAPEUTIC CONCEPT

FMT represents the most direct available strategy for altering the intestinal microbial ecosystem. Instead of supplying one or a few strains, it transfers an entire microbial community from a carefully screened donor to the recipient. In established gastroenterological practice, FMT is best known as a highly effective treatment for recurrent *Clostridioides difficile* infection. For PD, however, it remains an experimental intervention. The translational challenge is fundamentally different: the goal is not to eradicate a single pathogen, but to remodel a complex host-

microbiota interaction that may contribute to symptoms and possibly to progression.

This distinction has several consequences. In PD, the relevant donor profile is uncertain, the optimal route of administration is not established, the durability of engraftment is unknown, and clinically meaningful endpoints are broader than simple microbiological change. FMT in PD should therefore be interpreted as a platform for biological discovery as much as a treatment in itself.

CLINICAL FAECAL MICROBIOTA TRANSPLANTATION TRIALS IN PARKINSON'S DISEASE

Two randomized trials reported on the use of FMT in PD patients. The first was the Belgian GUT-PARFECT trial, a double-blind phase 2 study in early-stage PD that compared one-time nasojejunal application of healthy donor stool with autologous transplantation. The trial showed that FMT is feasible in PD and that adverse effects were mainly mild transient gastrointestinal symptoms such as abdominal cramps and nausea. The donor-FMT group showed encouraging small improvements in motor symptoms as compared to the control group (Bruggeman et al., 2024).

The second dataset was the Finnish randomized placebo-controlled double-blind trial led by Scheperjans and colleagues (Scheperjans et al., 2024). In this study, patients with PD were screened for dysbiosis, randomized to one-time intracaecal infusion of healthy donor stool or placebo carrier solution, and eventually underwent bowel preparation and colonoscopy. The design is noteworthy because it treated the micro-

biota phenotype as a clinically relevant variable and because it allowed careful follow-up of both symptoms and microbial dynamics. A proportion of patients shifted from a dysbiotic to a non-dysbiotic state shortly after donor FMT, yet this effect diminished over time. In contrast, the placebo group showed a slower but more sustained improvement in dysbiosis status. On the clinical side, signals were seen in bowel-related outcomes and in selected motor subdomains, while the overall pattern suggested that efficacy may depend on the dynamics of dysbiosis recovery rather than on the label of donor versus placebo alone (Scheperjans et al., 2024). This leads to one of the most original conclusions. Because all participants underwent bowel cleansing before the intervention, bowel cleansing itself may have contributed substantially to the observed benefit. In other words, the trial may have revealed not only information about donor microbiota transfer, but also an effect of resetting the intesti-

nal environment. This possibility is clinically attractive because bowel cleansing is simpler, cheaper and easier to standardize than FMT. These hypo-

theses now require direct testing in specifically designed trials (*Scheperjans et al., 2024*).

INTERPRETATION AND FUTURE DIRECTIONS

Gastrointestinal and microbiota disturbances are real, clinically relevant and mechanistically plausible features of PD, especially in patients with a body-first biology or marked bowel dysfunction. Microbiota modulation therefore deserves serious clinical investigation, but future studies must define which patients to treat, which biological endpoints to monitor and which interventions are most rational at different disease stages (*Horsager et al., 2020; Tan et al., 2022; Scheperjans et al., 2024*).

In this perspective, microbiota-based phenotyping may become as important

as the intervention itself. If only a subset of patients has microbiota-driven symptom generation or progression, then broad unselected trials will underestimate true treatment effects. Repeated microbiological sampling, metabolite measurements and deeper analysis of donor-recipient dynamics may help identify responders and reveal new live biotherapeutic or metabolite-based treatment candidates that are easier to standardize than whole-stool transplantation (*Aho et al., 2019; Scheperjans et al., 2024*).

CONCLUSIONS

The evidence reviewed supports several linked conclusions on why the gut deserves serious attention in PD:

- Gastrointestinal symptoms and microbiota disturbances are integral features of PD and may precede motor diagnosis by many years.
- The body-first versus brain-first framework offers an important biological context for interpreting microbiome findings.
- Gut microbial composition is linked not only to case-control status but also to symptom profiles and disease

progression.

- Experimental work shows that microbiota manipulation can influence PD-relevant biology, supporting therapeutic exploration.
- First-generation clinical trials of FMT and other microbiota-modifying approaches have produced encouraging but complex results, suggesting that treatment effects may depend on route of administration, patient selection, dysbiosis recovery and possibly bowel cleansing itself.

LITERATURE

Adams-Carr, K.L., Bestwick, J.P., Shribman, S., Lees, A., Schrag, A., and Noyce, A.J.: Constipation preceding Parkinson's disease: a systematic review and meta-analysis. *J. Neurol. Neurosurg. Psychiatry* 87: 710-716

(2016).

Aho, V.T.E., Pereira, P.A.B., Voutilainen, S., Paulin, L., Pekkonen, E., Auvinen, P., and Scheperjans, F: Gut microbiota in Parkinson's disease: temporal stability and

- relations to disease progression. *EBioMedicine* 44: 691-707 (2019).
- Becker, A., Schmartz, G.P., Groeger, L., Grammes, N., Galata, V., Philippeit, H., Weiland, J., Ludwig, N., Meese, E., Tierling, S., Walter, J., Schwirtz, A., Spiegel, J., Wagenpfeil, G., Faßbender, K., Keller, A., and Unger, M.M.: Effects of resistant starch on symptoms, fecal markers, and gut microbiota in Parkinson's disease - the RESISTA-PD trial. *Genomics Proteomics Bioinformatics* 22: 274-287 (2024).
- Bruggeman, A., Vandendriessche, C., Hamerlinck, H., De Looze, D., Tate, D.J., Vuylsteke, M., De Commer, L., Devolder, L., Raes, J., Verhasselt, B., Laukens, D., Vandenbroucke, R.E., and Santens, P.: 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. *EClinicalMedicine* 71: 102563 (2024).
- Horsager, J., Andersen, K.B., Knudsen, K., Skjærbæk, C., Fedorova, T.D., Okkels, N., Schaeffer, E., Bonkat, S.K., Geday, J., Otto, M., Sommerauer, M., Danielsen, E.H., Bech, E., Kraft, J., Munk, O.L., Hansen, S.D., Pavese, N., Göder, R., Brooks, D.J., Berg, D., and Borghammer, P.: Brain-first versus body-first Parkinson's disease: a multimodal imaging case-control study. *Brain* 143: 3077-3088 (2020).
- Jin, X., Dong, W., Chang, K., Yan, Y., and Liu, X.: Efficacy of probiotic supplements on Parkinson's disease: a systematic review and meta-analysis. *Complement. Ther. Med.* 82: 103045 (2024).
- Kalia, L.V. and Lang, A.E.: Parkinson's disease. *Lancet* 386: 896-912 (2015).
- Lai, S.W., Liao, K.F., Lin, C.L., and Sung, F.C.: Irritable bowel syndrome correlates with increased risk of Parkinson's disease in Taiwan. *Eur. J. Epidemiol.* 29: 57-62 (2014).
- Mertsalmi, T.H., Pekkonen, E., and Scheperjans, F.: Antibiotic exposure and risk of Parkinson's disease in Finland: a nationwide case-control study. *Mov. Disord.* 35: 431-442 (2020).
- Plassais, J., Gbikpi-Benissan, G., Figarol, M., Scheperjans, F., Gorochoy, G., Derkinderen, P., and Cervino, A.C.L.: Gut microbiome alpha-diversity is not a marker of Parkinson's disease and multiple sclerosis. *Brain Commun.* 3: fcab113 (2021).
- Romano, S., Savva, G.M., Bedarf, J.R., Charles, I.G., Hildebrand, F., and Narbad, A.: Meta-analysis of the Parkinson's disease gut microbiome suggests alterations linked to intestinal inflammation. *NPJ Parkinsons Dis.* 7: 27 (2021).
- Sampson, T.R., Debelius, J.W., Thron, T., Janssen, S., Shastri, G.G., Ilhan, Z.E., Challis, C., Schretter, C.E., Rocha, S., Gradinaru, V., Chesselet, M.F., Keshavarzian, A., Shannon, K.M., Krajmalnik-Brown, R., Wittung-Stafshede, P., Knight, R., and Mazmanian, S.K.: Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. *Cell* 167: 1469-1480.e12 (2016).
- Schapira, A.H.V., Chaudhuri, K.R., and Jenner, P.: Non-motor features of Parkinson disease. *Nat. Rev. Neurosci.* 18: 435-450 (2017).
- Scheperjans, F., Levo, R., Bosch, B., Lääperi, M., Pereira, P.A.B., Smolander, O.P., Aho, V.T.E., Vetkas, N., Toivio, L., Kainulainen, V., Fedorova, T.D., Lahtinen, P., Ortiz, R., Kaasinen, V., Satokari, R., and Arkkila, P.: Fecal Microbiota Transplantation for Treatment of Parkinson Disease: A Randomized Clinical Trial. *JAMA Neurol.* 81: 925-938 (2024).
- Sun, M.F., Zhu, Y.L., Zhou, Z.L., Jia, X.B., Xu, Y.D., Yang, Q., Cui, C., and Shen, Y.Q.: Neuroprotective effects of fecal microbiota transplantation on MPTP-induced Parkinson's disease mice: gut microbiota, glial reaction and TLR4/TNF-alpha signaling pathway. *Brain Behav. Immun.* 70: 48-60 (2018).
- Tan, A.H., Lim, S.Y., and Lang, A.E.: The microbiome-gut-brain axis in Parkinson disease — from basic research to the clinic. *Nat. Rev. Neurol.* 18: 476-495 (2022).
- Xie, A., Ensink, E., Li, P., Gordevičius, J., Marshall, L.L., George, S., Pospisilik, J.A., Aho, V.T.E., Houser, M.C., Pereira, P.A.B., Rudi,

K., Paulin, L., Tansey, M.G., Auvinen, P., Brundin, P., Brundin, L., Labrie, V., and Scheperjans, F.: Bacterial Butyrate in Parkinson's Disease Is Linked to Epigenetic Changes and Depressive Symptoms. *Mov. Disord.* 37: 1644-1653 (2022).

Zhu, F., Li, C., Gong, J., Zhu, W., Gu, L., and Li, N.: The risk of Parkinson's disease in inflammatory bowel disease: a systematic review and meta-analysis. *Dig. Liver Dis.* 51: 38-42 (2019).

