COMMENT OPEN

Check for updates

Early-life microbiota dysbiosis as a link between Autism Spectrum Disorder and Parkinson's Disease

Ming-Ming Zhao[1], Kenji Hashimoto[1,2]✉ and Jian-Jun Yang[1,3]✉

Molecular Psychiatry; https://doi.org/10.1038/s41380-025-03281-w

Autism spectrum disorder (ASD) arises from a complex interplay of genetic and environmental factors that disrupt early brain development. Heritability exceeds 80%, with contributions from rare de novo mutations, common polygenic variants, and prenatal exposures (e.g., maternal infection, heavy metals, or herbicides) collectively altering synaptic connectivity and neural circuit formation [1, 2]. Clinically, ASD typically emerges before age two, manifesting as delays or atypicalities in social communication alongside restricted, repetitive behaviors or sensory sensitivities. Although core symptoms often persist, early intervention, comorbidities (such as intellectual disability or epilepsy), and tailored supports can significantly improve language, social skills, and adaptive functioning, whereas others may continue to require lifelong assistance. In this commentary, we propose a mechanistic link between early-life gut microbiota dysbiosis in ASD and long-term vulnerability to Parkinson's disease (PD), and outline key directions for future epidemiological and interventional studies.

To explore the possibility that ASD predisposes to neurodegenerative disorder PD in later life, we next examined epidemiological links with PD. Although ASD has traditionally been viewed as a purely neurodevelopmental disorder, reports of degenerative-like changes in the brains of individuals with ASD raises the possibility that early developmental disturbances may predispose individuals to later neurodegeneration [3]. A recent nationwide, population-based cohort study of 2278,565 individuals (33.9 million person-years) found that PD occurred in 0.05% of those with ASD versus 0.02% of those without, yielding a relative risk of 4.43 (95% CI, 2.92–6.72) that persisted after adjusting for sex, socioeconomic status, family history, and age at ASD diagnosis [4]. Preterm or early-term birth did not modify this risk, whereas depression and antidepressant use roughly doubled PD risk independently of ASD (RR 2.01; 95% CI, 1.40–2.88), and antipsychotic exposure partially attenuated but did not eliminate the association (RR 2.00; 95% CI, 1.27–3.14). These data point to a shared vulnerability spanning neurodevelopmental and neurodegenerative processes. However, a relative risk of 4.43 reflects an epidemiological association—not proof of causation. Yet this link underscores the need for targeted mechanistic studies—such as longitudinal gut–microbiome profiling, in vivo models of α-synuclein propagation, and integrated immune–metabolite analyses—to elucidate pathways along the gut–brain axis.

Emerging data implicate gut microbiota dysbiosis in both ASD and PD. In ASD, reduced microbial diversity, lower levels of beneficial taxa, and overrepresentation of potential pathogens may compromise intestinal barrier integrity, promote low-grade systemic inflammation, and alter the production of microbial metabolites—such as short-chain fatty acids (SCFAs) and lipopolysaccharide—that influence microglial activation and synaptic pruning in the developing brain [5, 6]. In animal models, maternal glyphosate exposure alters the gut microbiome, induces neuroinflammation, and produces ASD-like behaviors in offspring [7]. Likewise, fecal microbiota transplantation (FMT) from ASD donors transfers social deficits to germ-free mice, illustrating dysbiosis-driven neurodevelopmental changes rather than direct α-synuclein aggregation or PD-like motor symptoms [8]. A recent meta-analysis found that microbiota-based interventions—particularly FMT and prebiotic blends—are promising, well tolerated, and effective at improving behavioral symptoms in ASD [9]. Consequently, strategies ranging from antibiotics and antifungals to probiotics, prebiotics, synbiotics, and healthy-donor FMT are being explored to improve both gastrointestinal function and neurobehavioral outcomes in ASD [10].

While our focus has been on ASD as a model of early gastrointestinal dysfunction and neurodevelopmental risk, similar dysbiosis-driven immune and metabolic disturbances have been reported in other developmental disorders (e.g., ADHD, schizophrenia). These perturbations may converge on common pathways—such as altered synaptic pruning and α-synuclein misfolding. Future studies should therefore examine both disorder-specific developmental windows and shared microbiota signatures across neurodevelopmental and neurodegenerative conditions.

Constipation is a well-recognized prodromal feature of PD, often predating motor signs by decades and reflecting early α-synuclein accumulation in the enteric nervous system and slowed colonic transit [11–13]. Concurrently, PD patients exhibit gut dysbiosis characterized by decreased SCFA–producing bacteria and increased mucin-degrading or opportunistic species, which can weaken the intestinal barrier, trigger local inflammation, and promote α-synuclein aggregation and vagal transmission to the brain. Experimental truncal vagotomy or α-synuclein deficiency prevents this propagation, supporting a gut-to-brain mechanism in idiopathic PD [14, 15].

Given these parallels, we propose that early-life microbiota disturbances in ASD may not only drive neurodevelopmental deficits but also increase long-term vulnerability to

[1]Department of Anesthesiology, Pain and Perioperative Medicine, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, China. [2]Chiba University Center for Forensic Mental Health, Chiba 260-8670, Japan. [3]Department of Anesthesiology, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China.
✉email: hashimoto@faculty.chiba-u.jp; yjyangjj@126.com

Received: 17 June 2025 Revised: 4 September 2025 Accepted: 18 September 2025
Published online: 09 October 2025

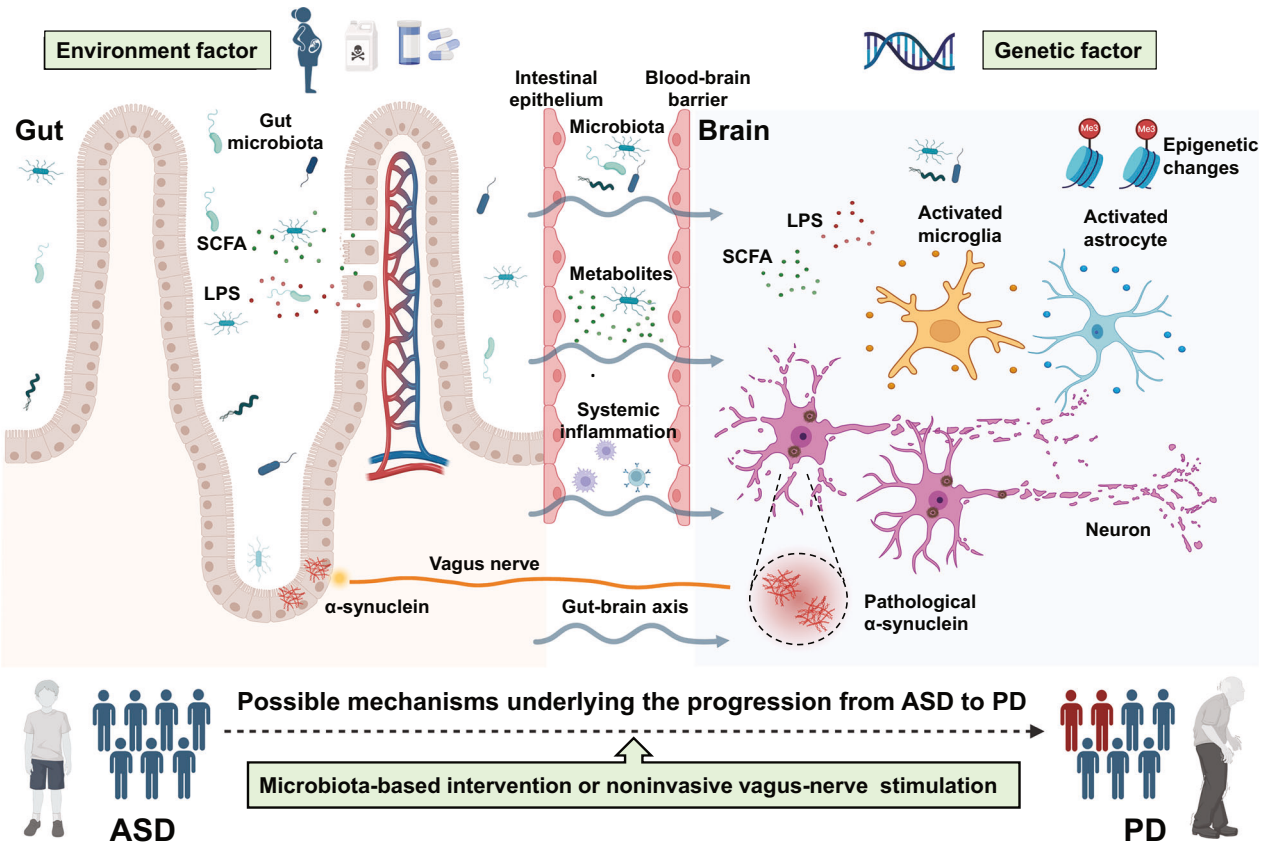

Fig. 1 Vagus nerve-mediated gut-brain axis by which early-life microbiota dysbiosis in ASD may increase PD risk. Children with ASD frequently develop gut microbiota imbalances, leading to chronic immune activation and altered microbial metabolites—most notably reduced short-chain fatty acids (SCFAs) and increased lipopolysaccharide (LPS). These changes drive systemic inflammation and facilitate misfolding and aggregation of α-synuclein within enteric neurons. Pathogenic α-synuclein can then ascend via vagal afferents to central nervous system (CNS) targets, seeding Lewy-type pathology that contributes to PD development later in life. Host genetic or epigenetic susceptibilities, as well as environmental exposures, may modulate this gut–brain axis at multiple points or operate via independent mechanisms. Together, these insights suggest that early interventions—such as microbiota-correcting therapies or noninvasive vagus nerve stimulation—could mitigate long-term PD risk in individuals with ASD. This illustration was created using BioRender.com.

neurodegeneration (Fig. 1). We speculate that chronic gastrointestinal dysfunction in ASD could sustain immune activation or metabolite imbalances, thereby promoting α-synuclein misfolding and propagation. At the same time, shared genetic or epigenetic risk factors, chronic inflammation, and environmental exposures could independently heighten susceptibility to both ASD and PD. Untangling these complex interactions will require integrative approaches—combining genomic and exposomic profiling with longitudinal microbiome analyses. Future studies should link repeated microbiome and inflammatory-marker assessments with gut–brain imaging in ASD cohorts, and evaluate whether microbiota-targeted therapies or noninvasive vagus-nerve stimulation (VNS) can reduce subsequent PD risk.

In conclusion, disturbances in the gut–brain axis—particularly early-life microbiota dysbiosis, chronic gastrointestinal dysfunction, and systemic inflammation—may underlie both the core neurodevelopmental features of ASD and an elevated risk of PD later in life. To test this hypothesis, we call for longitudinal ASD cohort studies that integrate serial microbiome profiling, peripheral inflammatory-marker assessments, and gut–brain imaging. In parallel, interventional trials should evaluate whether microbiota-based therapies (e.g., probiotics, prebiotics, healthy-donor FMT) or noninvasive VNS can reduce long-term neurodegenerative vulnerability. Because these strategies remain untested in this context, rigorous preclinical studies—assessing safety, target engagement, and impacts on α-synuclein pathology—must inform any move to clinical trials. Finally, disentangling microbiota-driven effects from other etiological factors will require the integration of polygenic risk scores, comprehensive inflammatory-marker panels, and detailed exposomic histories.

REFERENCES

1. Lord C, Elsabbagh M, Baird G, Veenstra-Vanderweele J. Autism spectrum disorder. Lancet. 2018;392:508–20. https://doi.org/10.1016/S0140-6736(18)31129-2
2. Tan S, Zhang Q, Zhan R, Luo S, Han Y, Yu B, et al. Monoallelic loss-of-function variants in GSK3B lead to autism and developmental delay. Mol Psychiatry. 2025;30:1952–65. https://doi.org/10.1038/s41380-024-02806-z
3. Kern JK, Geier DA, Sykes LK, Geier MR. Evidence of neurodegeneration in autism spectrum disorder. Transl Neurodegener. 2013;2:17 https://doi.org/10.1186/2047-9158-2-17
4. Yin W, Reichenberg A, Schnaider Beeri M, Levine SZ, Ludvigsson JF, Figee M, et al. Risk of Parkinson disease in individuals with autism spectrum disorder. JAMA Neurol. 2025;82:687–95. https://doi.org/10.1001/jamaneurol.2025.1284
5. Liu F, Li J, Wu F, Zheng H, Peng Q, Zhou H. Altered composition and function of intestinal microbiota in autism spectrum disorders: a systematic review. Transl Psychiatry. 2019;9:43. https://doi.org/10.1038/s41398-019-0389-6
6. Tao X, Li Z, Wang D, Pu J, Liu Y, Gui S, et al. Perturbations in gut microbiota in autism spectrum disorder: a systematic review. Front Neurosci. 2025;19:1448478. https://doi.org/10.3389/fnins.2025.1448478
7. Pu Y, Yang J, Chang L, Qu Y, Wang S, Zhang K, et al. Maternal glyphosate exposure causes autism-like behaviors in offspring through increased expression of soluble epoxide hydrolase. Proc Natl Acad Sci USA. 2020;117:11753–9. https://doi.org/10.1073/pnas.1922287117
8. Sharon G, Cruz NJ, Kang DW, Gandal MJ, Wang B, Kim YM, et al. Human gut microbiota from autism spectrum disorder promote behavioral symptoms in mice. Cell. 2019;177:1600–18.e17. https://doi.org/10.1016/j.cell.2019.05.004

9. Hassib L, Kanashiro A, Pedrazzi JFC, Vercesi BF, Higa S, Arruda Í, et al. Microbiota-based therapies as novel targets for autism spectrum disorder: a systematic review and meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2025;139:111385. https://doi.org/10.1016/j.pnpbp.2025.111385
10. Takyi E, Nirmalkar K, Adams J, Krajmalnik-Brown R. Interventions targeting the gut microbiota and their possible effect on gastrointestinal and neurobehavioral symptoms in autism spectrum disorder. Gut Microbes. 2025;17:2499580. https://doi.org/10.1080/19490976.2025.2499580
11. Yuan XY, Chen YS, Liu Z. Relationship among Parkinson's disease, constipation, microbes, and microbiological therapy. World J Gastroenterol. 2024;30:225–37. https://doi.org/10.3748/wjg.v30.i3.225
12. Hashimoto K. Emerging role of the host microbiome in neuropsychiatric disorders: overview and future directions. Mo Psychiatry. 2023;28:3625–37. https://doi.org/10.1038/s41380-023-02287-6
13. Ma L, Wang HB, Hashimoto K. The vagus nerve: an old but new player in brain-body communication. Brain Beha Immun. 2025;124:28–39. https://doi.org/10.1016/j.bbi.2024.11.023
14. Kim S, Kwon SH, Kam TI, Panicker N, Karuppagounder SS, Lee S, et al. Transneuronal propagation of pathologic α-synuclein from the gut to the brain models Parkinson's disease. Neuron. 2019;103:627–41.e7. https://doi.org/10.1016/j.neuron.2019.05.035
15. Xiang J, Tang J, Kang F, Ye J, Cui Y, Zhang Z, et al. Gut-induced alpha-Synuclein and Tau propagation initiate Parkinson's and Alzheimer's disease co-pathology and behavior impairments. Neuron. 2024;112:3585–601.e5. https://doi.org/10.1016/j.neuron.2024.08.003

ACKNOWLEDGEMENTS

This work received support by the Natural Science Foundation of China (to JJY: Grant numbers U23A20421 and 82171189). We used AI assisted tool ChatGPT to improve the readability of this manuscript.

AUTHOR CONTRIBUTIONS

MMZ, KH and JJY conceived, drafted and approved the final version of this work.

COMPETING INTERESTS

Dr. Hashimoto is one of the editorial board members of this journal. The authors declare no conflict of interest related to this study.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Kenji Hashimoto or Jian-Jun Yang.