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LETTER TO THE EDITOR

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Gut microbiota helps identify clinical subtypes of Parkinson's disease

Jing-Yi Wang[1†], Rui Xie[1†], Yun Feng[2†], Min-Na Zhang[1], Le He[1], Bo Yang[1], Hong-Gang Wang[1*] and Xiao-Zhong Yang[1*]

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Dear Editor,

The role of the microbiota-gut-brain axis in Parkinson's disease (PD) has garnered increasing attention [1]. Among the various empirical subtype systems of PD, motor subtype classification into tremor-dominant (TD) and postural instability and gait difficulty (PIGD) is the most commonly utilized [2]. However, the relationship between gut microbiota and clinical subtypes of PD remains unclear.

This study aimed to investigate the distinctions in gut microbiota between the two motor subtypes by obtaining fresh stool samples from patients with PD for metagenomic sequencing, along with assessing brain function using resting-state functional magnetic resonance imaging (rs-fMRI). Subsequently, differences in brain mean amplitude of low-frequency fluctuation (mALFF) values and their association with gut microbiota were analyzed.

A total of 24 patients with PD were included in the study, comprising 12 PIGD, 9 TD, and 3 indeterminate (IND) subtype patients (Additional file 1: Materials and methods). Following exclusion of the 3 IND subtype patients, no significant differences in age, sex, body mass index (BMI), Hoehn-Yahr score, Unified Parkinson's Disease Rating Scale part III (UPDRS-III) score, Hamilton Depression Scale (HAMD) score, Hamilton Anxiety Scale (HAMA) score, drug use, duration of disease, and medical history including hypertension, diabetes, heart disease, and cerebral infarction were observed between the TD and PIGD groups ($P > 0.05$, Additional file 1: Table S1). Alpha diversity of the gut microbiota was evaluated using Chao1, Shannon, and Simpson indices, while beta diversity was assessed through principal coordinates analysis (PCoA) and nonmetric multidimensional scaling (NMDS). However, the analysis revealed no significant variations in alpha and beta diversities between the two groups ($P > 0.05$, Additional file 1: Fig. S1).

The gut microbiota was further analyzed at various taxonomic levels using a cladogram and bar plot generated by Liner discriminant analysis effect size (LEfSe). The PIGD group exhibited enrichment in *Bacteroidetes*, *Bacteroidia*, and *Bacteroidales*, while the TD group showed predominant enrichment for *Firmicutes*, *Clostridiaceae*, and *Clostridium* (Fig. 1a). At the phylum level, the proportion of *Bacteroidetes* was significantly higher in PIGD group compared with TD group (45.57% vs. 23.64%, $P = 0.003$, Fig. 1b).

A binary logistic regression model was developed using the proportion of *Bacteroidetes* to predict the motor subtypes of patients with PD. The ROC curve analysis yielded an AUC of 0.8889 ($P = 0.0028$), with a cut-off value of 23.04%, sensitivity of 75.75%, and specificity of 66.67% (Fig. 1c). Additionally, at the genus level, PIGD group

†Jing-Yi Wang, Rui Xie and Yun Feng contributed equally to this work.

*Correspondence:
Hong-Gang Wang
jgzwhg@njmu.edu.cn
Xiao-Zhong Yang
hayyyxzh@njmu.edu.cn
[1] Department of Gastroenterology, the Affiliated Huai'an No.1 People's Hospital of Nanjing Medical University, Huai'an 223301, Jiangsu, China
[2] Department of Radiology, the Affiliated Huai'an No.1 People's Hospital of Nanjing Medical University, Huai'an 223301, Jiangsu, China

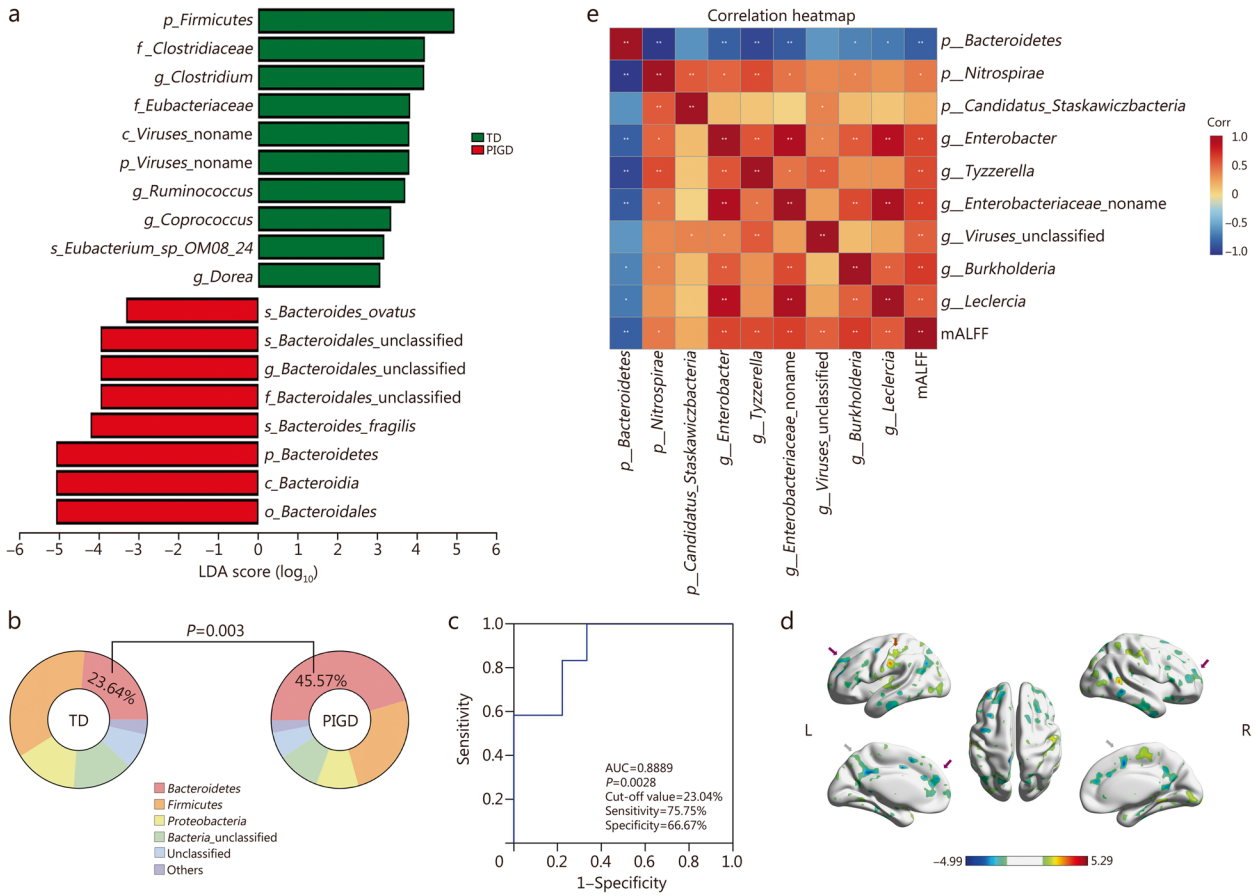

Fig. 1 Microbiota-gut-brain axis in PD. **a** Liner discriminant analysis effect size (LEfSe) analysis and Cladogram generated by LEfSe analysis. **b** Different proportion of phylum and statistical difference between the TD and PIGD subtypes ($P = 0.003$). **c** ROC curve. **d** Significant brain changes between the TD and PIGD subtypes (gray arrows: bilateral median cingulate and paracingulate gyri; purple arrows: precuneus; brown arrow: parietal lobes). **e** Spearman analysis was performed for correlation analysis. PD Parkinson's disease, TD tremor-dominant, PIGD postural instability and gait difficulty, mALFF mean amplitude of low-frequency fluctuation, Corr correlation coefficient

exhibited significantly lower abundance of *Clostridium*, *Ruminococcus*, *Coprococcus*, *Dorea*, *Enterobacter*, *Anaerotignum*, *Tyzzerella*, *Bacillus*, and *Evtepia* compared with TD group ($P < 0.05$, Additional file 1: Fig. S2).

Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis was conducted to explore differences in gene abundance between TD and PIGD patients, revealing significant enrichment in various categories including environmental information processing, human diseases, cellular processes, genetic information processing, and metabolism. Notably, the metabolic pathway emerged as the most significantly enriched pathway in KEGG pathway classification (Additional file 1: Fig. S3).

Functional brain MRI data from these patients with PD were utilized for brain mALFF analysis in this study. In comparison with TD group, individuals in PIGD group exhibited reduced mALFF signals in the bilateral median cingulate and paracingulate gyri, precuneus, and parietal lobes (Fig. 1d). The right median cingulate and paracingulate gyri were identified as the key brain regions, and the local mALFF values were collected from each participant. Subsequently, Spearman's correlation analysis was conducted between the extracted mALFF values and various significantly distinct gut microbiotas (Fig. 1e). The findings revealed a positive correlation between the abundance of *Enterobacter*, *Tyzzerella*, *Burkholderia*, and *Leclercia* and the mALFF values ($P < 0.05$). Conversely, the abundance of *Bacteroidetes* showed a negative correlation with the mALFF values ($P < 0.05$).

Our research contributes valuable insights into the microbiota-gut-brain axis and underscores the potential relationship between gut microbiota and motor

subtypes in PD. These findings lay the groundwork for future investigations into the pathogenesis of distinct motor subtypes. Despite being a small-scale study, we have innovatively established a connection between gut microbiota and brain function MRI, offering potential for future regulation of gut-directed therapies in PD.

Abbreviations

AUC	Area under the receiver operating characteristic curve
HAMD	Hamilton Depression Scale
HAMA	Hamilton Anxiety Scale
IND	Indeterminate
KEGG	Kyoto Encyclopedia of Genes and Genomes
LEfSe	Liner discriminant analysis effect size
mALFF	Mean amplitude of low-frequency fluctuation
NMDS	Nonmetric multidimensional scaling
PD	Parkinson's disease
PIGD	Postural instability and gait difficulty
PCoA	Principal coordinates analysis
rs-fMRI	Resting-state functional magnetic resonance imaging
TD	Tremor-dominant
UPDRS	Unified Parkinson's Disease Rating Scale

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40779-024-00545-4.

Additional file 1: Materials and Methods. Table S1 Characteristics of different motor subtypes (TD and PIGD) in PD patients. **Fig. S1** Alpha diversity and beta diversity of the gut microbiota. **Fig. S2** Relative abundance of discriminative gut microbiota at the genus level ($P < 0.05$). **Fig. S3** Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis.

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Authors' contributions
JYW and HGW designed the experiments; JYW and XZY performed the overall data analysis; MNZ and LH collected the samples; BY and YF contributed to figure generation; JYW, RX and HGW wrote the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The data presented in this study are available upon reasonable request from the corresponding author.

Declarations

Ethics approval and consent to participate
This study was approved by the Medical Ethics Committee of Affiliated Huai'an No.1 People's Hospital of Nanjing Medical University (KY-2022–004-01).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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