Efficacy of faecal microbiota transplantation in patients with progressive supranuclear palsy-Richardson's syndrome: a phase 2, single centre, randomised clinical trial

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Summary

Background Faecal microbiota transplantation (FMT) has demonstrated efficacy in treating gastrointestinal (GI) diseases, such as *Clostridium difficile* infection (CDI) and inflammatory bowel disease (IBD). GI dysfunction is a frequent and occasionally dominating symptom of progressive supranuclear palsy-Richardson's syndrome (PSP-RS). However, it is not known whether FMT has clinical efficacy for PSP-RS.

Methods This 36-week, randomised, placebo-controlled, parallel-group, phase 2 clinical trial was performed at a university tertiary referral hospital in China. From August 15 2021 to December 31 2021, a total of 68 newly diagnosed patients with PSP-RS (male 40 [59%], female 28 [41%]) who had never received any antiparkinsonian medications were enrolled and randomly assigned to receive either healthy donor FMT (n = 34, FMT group) or a mixture of 0.9% saline and food colouring (E150c) as sham transplantation (n = 34, placebo group) through transendoscopic enteral tubing (TET). Two days after oral antibiotics, participants received 1 week of transplantation. After an interval of 4 weeks, retransplantation was performed. Then, the last transplantation was given after another interval of 4 weeks, and the participants were followed up for 24 weeks (week 36). Clinicaltrials.gov identifier: ChiCTR-2100045397.

Findings Among 68 patients who were randomised (mean age, 67.2 (SD 5.1); 40 [59%] were male, 28 [41%] were female), 63 participants completed the trial. Efficacy analyses were performed on the intention-to-treat (ITT) analysis set. At week 16, the mean PSP Rating Scale (PSPRS) scores (the primary outcome) improved from 40.1 (SD 7.6) to 36.9 (SD 5.9) in the FMT group, whereas the scores changed from 40.1 (SD 6.9) to 41.7 (SD 6.2) in the placebo group, for a treatment benefit of 4.3 (95% CI, 3.2–5.4) ($P < 0.0001$). After 3-cycle intervention, symptoms of constipation, depression, and anxiety (the secondary outcome) improved significantly at week 16 in the FMT group compared with the placebo group, the majority of which were maintained at the 24-week follow-up (week 36).

Interpretation Our findings suggest that, compared with placebo, FMT treatment significantly improved motor and nonmotor symptoms in patients with PSP-RS, as well as reduced intestinal inflammation and enhanced the intestinal barrier by regulating the intestinal microbiota composition.

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Research in context

Evidence before this study

Faecal microbiota transplantation (FMT) has increasingly become an effective treatment for *Clostridium difficile* infection. Further research is encouraged to examine the therapeutic efficacy of FMT on the treatment of other diseases associated with gastrointestinal dysfunctions and intestinal microbiota disturbance. Remarkably, more than 80% of progressive supranuclear palsy (PSP) patients experience gastrointestinal symptoms. Furthermore, an altered gut microbiota composition has been reported in PSP patients. We searched PubMed for studies including clinical trials, randomised controlled trials, systematic reviews, and meta-analyses from the inception of the database to January 31, 2023 using the search terms "faecal microbiota transplantation", "fecal microbiota transplantation" or "FMT" in combination with "progressive supranuclear palsy". However, there are no clinical trials of FMT for PSP reported to date.

Added value of this study

This is the first randomised, placebo-controlled, parallel-group clinical trial that evaluated the efficacy and safety of FMT for newly diagnosed drug-naïve PSP-RS patients. This study provides strong evidence that a 3-cycle, 12-week intermittent FMT treatment was safe and effective in improving motor and nonmotor symptoms in patients with PSP-RS, accompanied with changed microbiota community characterised by reducing *Escherichia-Shigella* and increasing short-chain fatty acids (SCFAs) producing bacteria, reduced intestinal inflammation and improvement of the intestinal barrier.

Implications of all the available evidence

The conclusions of this study will encourage the clinical use of FMT as a safe and effective treatment for PSP-RS patients. Future studies may include validating the clinical value of FMT for PSP patients in a multicenter setting, evaluating its long-term safety and efficacy, and elucidating the mechanisms of FMT.

Introduction

Progressive supranuclear palsy (PSP) is a progressive and devastating neurodegenerative disease that is also the most common atypical parkinsonism, characterised by motor and nonmotor impairments.[1,2] The most recognised and common form of PSP, now referred to as PSP–Richardson's syndrome (PSP-RS), characteristically involves early and severe gait instability, frequent falls, slowing of vertical saccades, vertical gaze palsy, axial rigidity and neuropsychiatric abnormalities,[1,3,4] which pose a tremendous medical and socioeconomic burden to society. Currently, there are no effective medical or surgical treatments for PSP.[1,5] Levodopa is central to the symptomatic management of PSP and only transiently improves motor functions, but it cannot cure the disease.[1,5,6] Death occurs within a median of approximately 6.8–8.0 years after the onset of symptoms.[7,8]

Gastrointestinal (GI) dysfunction occurs frequently in neurodegenerative diseases, indicating that gut microbiota could be associated with neurodegenerative diseases via the microbiota–gut–brain axis.[9,10] An imbalance in the intestinal microbiota has been proven to be a factor that contributes to neurodegenerative disorders, such as Alzheimer's disease (AD)[11] and Parkinson's disease (PD).[10] Faecal microbiota transplantation (FMT) is currently considered the most efficient method to restore the normal intestinal microbiota composition and has been regarded as a promising strategy for neurodegenerative diseases in addition to GI diseases.[12,13] Unfortunately, there are still insufficient levels of experience and numbers of clinical trials in the area of neurodegenerative diseases. Remarkably, more than 80% of PSP patients experience GI symptoms, mainly constipation and dysphagia.[14–16] Moreover, an altered gut microbiota composition has been reported in PSP patients compared to healthy controls.[17] In addition, phosphorylated tau (ptau), the disease-causing protein in PSP, has been detected in the colon of patients with PSP.[18] However, it is not clear whether intestinal microbiota dysbiosis contributes to the pathogenesis of PSP. Moreover, we aimed to investigate whether restoring the normal intestinal microbiota composition could be effective in treating PSP. The objective of this study was to evaluate the efficacy and safety of FMT in patients with PSP-RS.

Methods

Study design, setting, and patients

A phase 2, single centre, randomised, double-blind clinical trial of FMT that included 68 patients with PSP-RS was conducted between August 15 2021 and September 10 2022 at the First Affiliated Hospital of Zhengzhou University (ZZU) in China. All participants were over the age of 18 and gave written informed consent. The protocol was approved by the Institutional Ethics Committees of the First Affiliated Hospital of ZZU (2021-KY-0385-002). Clinicaltrials.gov identifier: ChiCTR-2100045397. A schematic illustration of the study protocol is shown in Fig. 1.

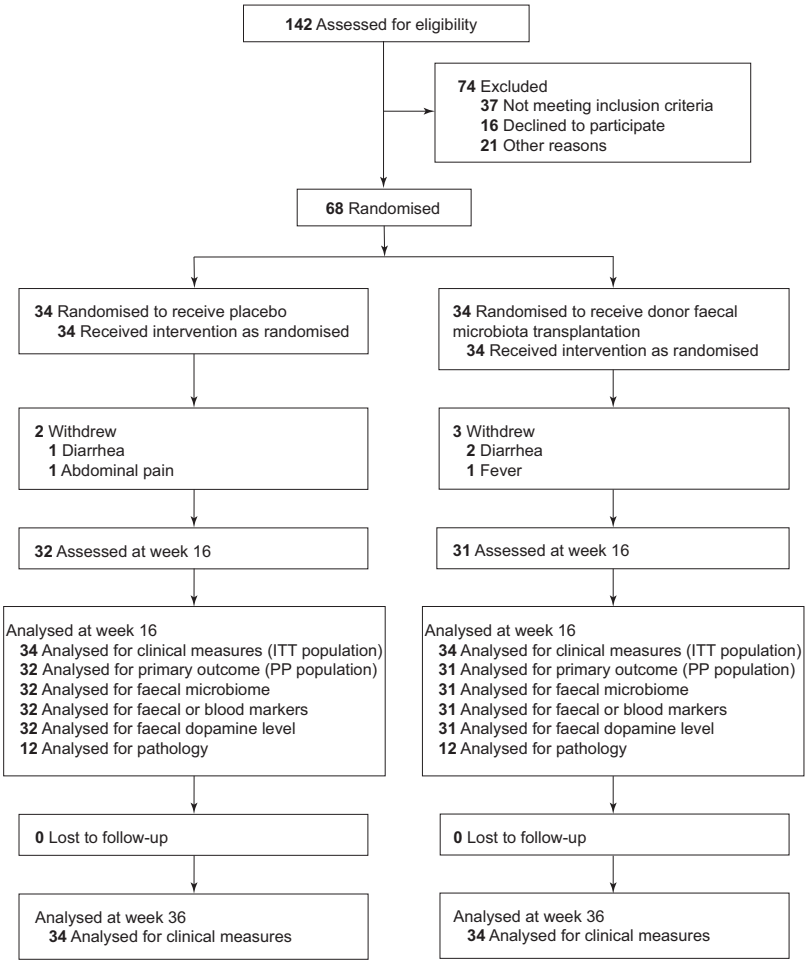

Fig. 1: **Profile of randomised controlled trial.**

Eligible patients had a diagnosis of probable or possible PSP-RS based on modified National Institute of Neurological Disorders and Stroke and the Society for Progressive Supranuclear Palsy (NINDS-SPSP) criteria,[1,19] namely, at least a 1-year history of postural instability or falls during the first 3 years of symptom presence; the presence of slow-velocity vertical saccades or vertical supranuclear gaze palsy; and an akinetic-rigid syndrome with prominent axial rigidity. At screening, the main eligibility criteria were as follows: Participants were aged 41–86 years of age with a score of at least 20 on the Mini-Mental State Examination (MMSE). Participants had to be able to take at least 5 steps with assistance. No consideration was given to other disorders, such as neurological and psychiatric disorders, including PD, AD, dementia with Lewy bodies, multiple system atrophy, or hydrocephalus. Participants had to be able to tolerate procedures such as positron emission tomography/magnetic resonance imaging, intravenous anaesthesia, and colonoscopies and to have a reliable caregiver present at all study visits. In addition, participants were excluded if they had received antiparkinsonian drugs before enrollment.

Donor selection and stool processing

Donors were recruited from students in ZZU. To minimise risks of disease transmission, strict criteria were used for screening potential donors as described previously.[20,21] Potential stool donors received a screening questionnaire, medical interview, and blood and stool tests in sequence. Sixty-four potential donors were screened, with 16 (25%) meeting all criteria for screening. The 16 faecal donors signed a commitment pledge to maintain their lifestyle, mainly including their dietary habits and regular sleep-wake rhythm, during the sample collection period. Each donor provided at least 18 fresh stool samples. Each selected stool sample could weigh not less than 200 g. Each batch of stool was mixture of 2 stool samples from a donor preparing for a cycle of intervention for a patient, weighing 350 g. Accordingly, we collected totally 144 batches of stool

from 16 donors. Each patient received 3 cycles of faecal transplants from a donor. We randomly selected 2 donors, each of them provided stool samples for 3 patients' transplants, while each of the remaining 14 donors provided stool samples for 2 patients' transplants. The faecal suspension (containing pooled stool (25%), normal saline (65%) and glycerol (10%) aliquoted into 7 containers and stored immediately at −80 °C. The placebo consisted of normal saline mixed with 3 drops of food coloring (E150c) and glycerol (10%).

Randomization and masking

Eligible participants were allocated (in a 1:1 ratio) using a computer-generated simple randomization algorithm (http://www.random.org) to receive either FMT or placebo. The randomisation and blinding procedures were conducted by nursing staff who did not participate in FMT or placebo administration. Participants were informed that the treatments would not be active. No other information was disclosed publicly to maintain the integrity of blinding. The study data, including the randomisation record, the patient record, and other study data, were kept in a separate document. The participants and clinicians who performed the procedures and assessed the primary and secondary outcomes were blinded to the treatment received.

Intervention and control

Before transplantation, all participants were treated with oral ciprofloxacin (500 mg, twice daily) (Jingxin Pharma, China) and oral metronidazole (500 mg, three times daily) (Shuanghe Pharma, China) for 5 consecutive days. Two days later, the participants underwent bowel preparation using 3 L of polyethylene glycol electrolyte solution and fasted overnight (≥8 h) before their scheduled colonoscopies. All screening colonoscopies were conducted by a board-certified attending gastroenterologist and assisted by a gastroenterology fellow under intravenous anaesthesia (propofol, 12.5 mg/kg/h). After examination of the entire colon, the transendoscopic enteral tubing (TET) tube was placed into the ileocecal junction of the colon, and the line circle on the TET tube was immobilised onto the inner intestinal wall using titanium clips under direct vision. Then, the colonoscope was withdrawn carefully and slowly, and the distal tube was fixed onto the skin of the buttocks with medical adhesive plaster. A valve was connected to the terminal TET tube. Every participant received a single injection of 200 mL faecal suspension or placebo at 5 mL/min via the TET tube for 7 consecutive days to ensure infusion and colonization of donor faecal microbiota in the colon. After injection, participants were required to maintain a prone position for 2 h. Retention of the faecal suspension for more than 1 h was regarded as successful delivery of the microbiota through the colonic TET tube. After an interval of 4 weeks, retransplantation was performed. The last transplantation was given after another interval of 4 weeks. Total of 3 transplantations were performed and each treatment for 7 days. Participants were followed up for 24 weeks (week 36) after the final transplantation (Supplementary Fig. S1).

16S rDNA amplicon sequencing

Bacterial DNA was extracted from faecal samples, and then the V3–V4 variable region of the bacterial 16S rRNA gene was amplified using 341-Forward and 806-Reverse primers from human faecal samples.[22] The NovaSeq platform was used to sequence purified DNA, and 250 bp paired-end reads were produced. Initial Amplicon Sequence Variants (ASVs) were obtained using DADA2 or the deblur module of the QIIME2 program (version QIIME2-202006).[23] The duplicated and low occurrence (n < 5 within all samples) sequences were eliminated, and the representative sequences (referred to as "features" in QIIME2 terminology) were created. A standard of sequence number matching to the sample with the fewest sequences was used to standardise the absolute abundance of ASVs. The 16S rDNA amplicon sequencing data from faecal samples were obtained from Beijing Novogene Biotechnology Co., Ltd, China.

Outcomes

Primary outcome

The primary outcome was the change in the PSPRS score from baseline to week 16 in participants treated with FMT relative to those treated with placebo. The PSSRS score ranges from 0 to 100 (0 = no disease and 100 = most severe disease).

Secondary outcome

There were several secondary outcomes, including the mean changes in the PSPRS score from baseline to weeks 2, 7, 12 and 36; mean changes in the scores on PSPRS parts V and VI (PSPRS-V+VI), a clinician-rated score of the severity of motor signs (range, 0 to 36, with higher scores indicating more severe motor symptoms) from baseline to weeks 2, 7, 12, 16 and 36; mean changes in the Unified Parkinson's Disease Rating Scale (UPDRS) part II score evaluating motor experiences of daily living (range, 0 to 52, with higher scores indicating worse quality of life) from baseline to weeks 2, 7, 12, 16 and 36; mean changes in the Constipation Scoring System score (CSS score; range, 0 to 30, with higher scores indicating more severe constipation) from baseline to weeks 2, 7, 12, 16 and 36; mean changes in the Patient Assessment of Constipation Quality of Life score (PAC-QoL; range, 28 to 140, with higher scores indicating a higher effect of constipation on quality of life) from baseline to weeks 2, 7, 12, 16 and 36; mean changes in the Gastrointestinal Symptom Rating Scale score (GSRS; range, 0 to 45, with higher scores indicating more severe GI symptoms) from baseline to weeks 2, 7, 12, 16 and 36; mean

changes in the Schwab and England Activities of Daily Living (SEADL) scale score (range, 0 to 100, with higher scores indicating a greater level of independence) from baseline to weeks 2, 7, 12, 16 and 36; mean changes in the MMSE score (range, 0 to 30, with higher scores indicating better performance) from baseline to weeks 2, 7, 12, 16 and 36; mean changes in the rapid eye movement sleep behavior disorder score (RBDQ-HK; range, 0 to 100, with higher scores indicating worse sleep impairment) from baseline to weeks 2, 7, 12, 16 and 36; mean changes in the Hamilton Depression Rating Scale score (HAMD, range, 0 to 81, with higher scores indicating more severe depression) from baseline to weeks 2, 7, 12, 16 and 36; and mean changes in the Hamilton Anxiety Rating Scale score (HAMA, range, 0 to 56, with higher scores indicating more severe anxiety) from baseline to weeks 2, 7, 12, 16 and 36. The other secondary outcomes included changes in intestinal microbiota, gut inflammation, and intestinal barrier at week 16, the alterations in dopamine, calprotectin (CALP), lactoferrin (LF), alpha-1-antitrypsin (α1-AT), and zonulin levels in the faeces, as well as altered zonulin level in serum from baseline at week 16, and the proportion of patients with ptau deposition in the colon at week 16. Secondary outcomes included adverse events. Outcomes were assessed by investigators who were unaware of the trial-group assignments.

Statistical analysis

Anticipating a dropout rate of approximately 10%, the sample size of 68 participants was determined to provide 80% power to detect a difference of 7 points in the change in the PSPRS total score from baseline to week 36 for FMT relative to placebo, using a two-sided, two-sample *t* test with an α level at 0.05 and assuming a standard deviation of 9.95.[24] The complete statistical analysis plan can be found in the Supplementary materials. Efficacy analyses were conducted according to the intention-to-treat (ITT) model, with all randomised participants who received at least one dose of blinded study treatment included and assigned to the treatment group to which they were randomised. Missing data for the continuous variables were imputed using the last observation carried forward method. The effectiveness endpoints including mean changes in total PSPRS, PSPRS-V+VI, UPDRS part II, CSS, PAC-QoL, GSRS, MMSE, RBDQ-HK, HAMA, and HAMD scores from baseline at weeks 2, 7, 12, 16, and 36 were assessed using a mixed-model for repeated-measures, with fixed effects of treatment group, time (categorical), treatment group by time interaction, baseline value, and baseline value by time interaction. The mean changes in dopamine, CALP, LF, α1-AT, and zonulin concentrations in faecal samples and serum zonulin level at week 16 were assessed using *t* test based on per-protocol (PP) population. Statistical analyses were performed using SPSS version 27.0, and R version 4.2.1. The lme4 and emmeans packages were used to conduct the analyses in R version 4.2.1. $P \leq 0.05$ was considered statistically significant.

Role of the funding source

The funder of the study had no role in the study design or the data collection, analysis, and interpretation, or in the writing of the report, and in the decision to publish the results. All the authors had full access to all the data in the study and had the final responsibility to submit the study for publication.

Results

Intestinal dysfunction and dysbiosis of the intestinal microbiota in patients with PSP-RS

We recruited 68 patients with PSP-RS and 50 spouses of the patients as healthy controls (HC) (Supplementary Fig. S2), the demographic and clinical characteristics of all individuals are summarised in Supplementary Table S1. GI symptoms were found in 58 [85%] of patients with PSP-RS, and the incidence was much higher than that in the HC group 12 [24%] (Supplementary Fig. S3a). Moreover, the severity of GI dysfunction in patients with PSP-RS evaluated by the GSRS and CSS was significantly higher in the PSP-RS group than in the HC group (Supplementary Fig. S3a).

We then assessed the diversity and composition of the intestinal microbiota in faecal samples (PSP-RS, n = 68; HC, n = 50) using 16S rDNA sequencing. α-Diversity showed that the microbial richness and evenness significantly increased in the PSP-RS group compared to the HC group (Supplementary Fig. S3b, Supplementary Table S2). Moreover, the β-diversity using principal coordinates analysis (PCoA) revealed significant clustering of patients with PSP-RS and HC, implying that the intestinal microbiota composition significantly differed between the two groups (Supplementary Fig. S3c). Next, linear discriminant analysis effect size (LEfSe) analysis combined with linear discriminant analysis (LDA) was performed to identify the bacterial community structure (Supplementary Fig. S3d). The findings revealed a higher relative abundance of *Proteobacteria* and a lower relative abundance of *Firmicutes* at the phylum level. In addition, patients with PSP-RS displayed a microbiota profile characterised by an increase in the relative abundance of *Escherichia-Shigella* and *Lactobacillus* and a reduction in the relative abundance of *Blautia* and *Faecalibacterium* at the genus level (LDA > 4.0) (Supplementary Fig. S3d). We next identified the top 20 most abundant genera based on the mean relative abundance across all faecal samples at the genus level (Supplementary Fig. S3e). There were significant changes in the relative abundance of 9 genera detected in patients with PSP-RS compared to HC, including a higher relative abundance of *Escherichia-Shigella*, *Lactobacillus*, *Klebsiella*, and *Eubacterium_coprostanoligenes_group*, and a lower relative abundance of *Faecalibacterium*, *Blautia*, *Agathobacter*,

Romboutsia, and *Roseburia* (Supplementary Fig. S3f and Supplementary Table S3). Notably, the relative abundance of *Escherichia-Shigella* was most increased in the PSP-RS group compared to the HC group (Supplementary Fig. S3f and Supplementary Table S3). We next examined the relationship between the relative abundance of the 9 genera mentioned above and the clinical parameters. Spearman correlation analysis demonstrated that the total PSPRS score was positively correlated with the relative abundance of *Escherichia-Shigella*, *Lactobacillus* and *Klebsiella*. The PSPRS-V+VI score was positively correlated with the relative abundance of *Escherichia-Shigella* and *Klebsiella*. Additionally, CSS and PAC-QoL scores showed a significantly positive correlation with the relative abundance of *Escherichia-Shigella*. In contrast, the MMSE score was negatively correlated with the relative abundance of *Eubacterium_coprostanoligenes_group* but positively correlated with the relative abundance of *Blautia*. The Montreal Cognitive Assessment (MoCA) score was negatively correlated with the relative abundance of *Klebsiella* but positively correlated with the relative abundance of *Romboutsia* (Supplementary Fig. S3g). Specifically, the prominently increased relative abundance of *Escherichia-Shigella* accompanied by the strongest correlations between symptom severity and *Escherichia-Shigella* in the PSP-RS group indicated the possibility that the expansion of *Escherichia-Shigella* plays an important role in the pathogenesis of PSP-RS.

Hematoxylin and eosin (HE) staining showed marked inflammatory cell infiltrations in patients with PSP-RS compared to HC (Supplementary Fig. S3h). Given that the integrity of the intestinal epithelial barrier serves as the first boundary of defence between blood circulation and the luminal environment, we then detected the expression of adherens junction (AJ) proteins, including E-cadherin and β-catenin, using immunofluorescence (IF). Moreover, we assessed the expression of tight junction (TJ) protein, including claudin-5 and occludin, using immunohistochemical staining (IHC) to further evaluate the integrity of the colonic mucosal barrier. The findings showed that the expression levels of E-cadherin, β-catenin, claudin-5 and occludin were markedly decreased in the PSP-RS group compared to the HC group (Supplementary Fig. S3i, l, and m), implying disrupted intestinal barrier integrity in the colon of PSP-RS. Furthermore, to further assess intestinal inflammation and permeability, we measured the levels of faecal CALP, LF, α1-AT and zonulin, and serum zonulin by enzyme-linked immunosorbent assay (ELISA). The results showed that elevated faecal concentrations of CALP, LF, α1-AT and zonulin, and serum zonulin were detected in patients with PSP-RS compared to HC (Supplementary Fig. S3j). Moreover, we detected ptau in the colon by IHC. Accumulation of ptau in the colon mucosa was found in 74% (n = 50) of patients with PSP-RS and in 8% (n = 1) of HC (Supplementary Fig. S3k). Collectively, these data demonstrated intestinal dysfunctions and microbiota dysbiosis in patients with PSP-RS.

Primary outcome of the clinical trial

Based on the finding of intestinal microbiota dysbiosis in patients with PSP-RS, we conducted a single-centre, randomised, double-blind clinical trial to assess the efficacy and safety of FMT in patients with PSP-RS. A total of 142 patients were assessed for eligibility, and 68 patients were randomised: 34 to FMT and 34 to placebo. Three participants withdrew from the FMT group, and 2 participants withdrew from the placebo group, leaving 63 participants who completed assessments at weeks 16 and 36. At week 2, all participants completed the assessment, 63 participants (FMT group, n = 31; Placebo group, n = 32) completed the assessment at weeks 7, 12, 16, and 36. Baseline disease characteristics, including patient demographics, clinical data, intestinal microbiota composition, and intestinal inflammation, were generally similar between the two groups (Table 1).

The change in the total PSPRS score for each participant is presented in Fig. 2a. ITT analysis showed that the mean total PSPRS score decreased in the FMT group at week 16 (–2.6 [SE 0.5]) but increased in the placebo group (1.7 [SE 0.3]), with an adjusted mean between-group difference of 4.3 (95% CI, 3.2–5.4; $P < 0.0001$) (Table 2, and Fig. 2b). The PP analysis showed that the mean total PSPRS score decreased in the FMT group at week 16 (–2.3 [SE 0.5]) but increased in the placebo group (0.9 [SE 0.3]), with an adjusted mean between-group difference of 3.2 (95% CI, 2.2–4.2; $P < 0.0001$) (Fig. 2b).

Secondary outcomes of the clinical trial

The mean decreases in the PSPRS total score from baseline at weeks 2, 7, 12, and 36 in the FMT group were always significantly greater than those in the placebo group (week 2: difference: 1.7, 95% CI: 0.6–2.8, $P = 0.0046$; week 7: difference: 2.8, 95% CI: 1.7–3.9, $P < 0.0001$; week 12: difference: 4.8, 95% CI: 3.7–5.9, $P < 0.0001$; week 36: difference: 3.8, 95% CI: 2.7–4.9, $P < 0.0001$, respectively) (Table 2). The mean changes of the scores on PSPRS-V+VI from baseline at all evaluation points in the FMT group were significantly different from those in the placebo group (Table 2). The mean changes in UPDRS part II scores gradually became greater in the FMT group than in the placebo group, with statistical significance being reached by week 7 ($P = 0.0026$), being maximal at week 12 (difference: 2.6, 95% CI: 1.7–3.5, $P < 0.0001$) and this benefit was largely maintained at week 36 (Table 2). The mean differences in the mean changes from baseline in the CSS score between placebo and FMT groups reached statistical significance by week 7 ($P = 0.011$), and the statistically significant difference was maintained at week 16 (Table 2). The mean changes in the PAC-QoL

Characteristics	FMT group (n = 34)	Placebo (n = 34)
Age, years	67.1 (5.1)	67.2 (5.1)
Male, n (%)	21 (62%)	19 (56%)
Female, n (%)	13 (38%)	15 (44%)
Height, cm	168.0 (7.4)	168.2 (6.6)
Weight, kg	66.0 (7.3)	66.6 (7.7)
BMI, kg/m^2	23.4 (2.3)	23.5 (2.0)
Time to onset, years	2.5 (1.1)	2.7 (1.1)
PSPRS total score	40.1 (7.6)	40.1 (6.9)
PSPRS-I	8.9 (2.0)	8.9 (2.3)
PSPRS-II	5.4 (2.0)	5.4 (1.8)
PSPRS-III	3.4 (1.1)	3.4 (1.1)
PSPRS-IV	6.9 (2.3)	7.0 (2.5)
PSPRS-V	5.9 (1.6)	5.9 (1.8)
PSPRS-VI	9.6 (3.3)	9.6 (3.5)
PSPRS-V+VI	15.5 (3.9)	15.5 (4.0)
UPDRS-II	28.1 (7.5)	28.0 (7.9)
CSS	14.1 (6.0)	13.6 (5.7)
PAC-QoL	70.0 (23.2)	69.4 (21.0)
GSRS	14.2 (6.7)	14.4 (6.5)
SCOPA-AUT	40.4 (13.0)	40.2 (12.8)
RBDQ-HK	19.9 (13.3)	20.2 (13.9)
MMSE	23.8 (2.6)	23.5 (2.6)
MOCA	18.1 (3.3)	18.6 (2.7)
HAMD	11.7 (7.3)	11.4 (5.3)
HAMA	10.7 (6.5)	11.1 (5.8)
NMSS	53.7 (23.6)	53.9 (23.2)
SEADL	66.5 (18.9)	66.5 (16.7)
Faecal CALP, ng/mL	798.1 (181.9)	806.8 (136.9)
Faecal LF, ng/mL	61.4 (22.0)	59.4 (23.5)
Faecal α1-AT, ng/mL	489.8 (216.0)	500.8 (224.4)
Faecal zonulin, ng/mL	2.2 (0.9)	2.1 (0.6)
Serum zonulin, ng/mL	21.7 (6.6)	20.6 (5.1)
Faecal dopamine, pg/mL	61.8 (24.0)	60.8 (24.8)

Note: Data are mean (SD) or n (%). BMI, Body-mass index; CSS, Constipation Scoring System; FMT, faecal microbiota transplantation; GSRS, Gastrointestinal Symptom Rating Scale; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; PAC-QoL, Patient Assessment of Constipation Quality of Life; PSP-RS, progressive supranuclear palsy–Richardson's syndrome; PSPRS, Progressive Supranuclear Palsy Rating Scale; RBDQ-HK, REM sleep behavior disorder questionnaire-Hong Kong; SCOPA-AUT, Scales for Outcomes in Parkinson's Disease-Autonomic Dysfunction. SEADL, Schwab and England Activities of Daily Living. SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale. Demographic factors and clinical characteristics were compared using chi-square test, Student's *t* test, or two-sided Mann-Whitney U-test.

Table 1: **Baseline demographics and characteristics of the patient population.**

scores from baseline at all evaluation points were significantly different between the FMT and placebo groups (Table 2). The mean changes from baseline in the scores on GSRS between two groups reached statistical significance at weeks 16 and 36 (week 16: difference: 2.9, 95% CI: 1.8–4.1, $P < 0.0001$; week 36: difference: 2.6, 95% CI: 1.4–3.7, $P = 0.0001$) (Table 2). The mean decreases in HAMA and HAMD scores from baseline at all evaluation points in the FMT group were significantly greater than those in the placebo group (Table 2). The mean changes from baseline in MMSE scores gradually became more favourable in the FMT group than in the placebo group, with statistical significance being reached by week 12 ($P = 0.024$), and being maximal at week 16 (difference: 1.0, 95% CI: 0.4–1.6, $P = 0.0007$). This benefit was largely maintained at week 36 ($P = 0.0040$) (Table 2). The mean changes in the RBD-HK scores from baseline were significantly different between the FMT and placebo groups only at week 36 ($P = 0.0051$) (Table 2). The mean change from baseline to week 36 in the SEADL score did not differ between the FMT and placebo groups (Table 2).

Microbial diversity and abundance

There were no differences in the α-diversity index between the two groups at week 16, suggesting no significant effect of FMT on the enrichment of intestinal microorganisms in patients with PSP-RS (Supplementary Table S4). PCoA analyses showed that the gut microbiota compositions clustered differently between the FMT and placebo groups at week 16 ($P = 0.0010$, Fig. 3a). The significant change in the β-diversity (composition) of the faecal microbiota in the FMT ($P = 0.0010$) but not placebo ($P = 0.25$) group was confirmed through the Adonis analysis at week 16 (Fig. 3b). LEfSe analysis indicated that the intestinal microbiota of patients with PSP-RS was more enriched with *Escherichia-Shigella* and *Bacteroides* before FMT but *Bifidobacterium* after FMT at week 16, whereas *Dialister* was more enriched in the placebo group at week 16 (Fig. 3c). Next, according to the mean relative abundance levels of genera in the intestinal microbiota of the 68 patients with PSP-RS at baseline, the top 10 genera were identified (Fig. 3d). Among the top 10 genera, 5 genera were found to be significantly changed after FMT, including markedly decreased *Escherichia-Shigella*, *Bacteroides* and *Klebsiella* and significantly increased *Bifidobacterium* and *Faecalibacterium* (Fig. 3e and Supplementary Table S5).

Intestinal pathology

The CALP, LF, α1-AT and zonulin levels in faecal samples decreased significantly after FMT treatment. The mean changes in the CALP, LF, α1-AT and zonulin levels in faecal samples from baseline to week 16 in the FMT group were greater than those in the placebo group (CALP: difference: 106.1, 95% CI: 51.2–161.1, $P = 0.0003$; LF: difference: 21.5, 95% CI: 15.0–27.9, $P < 0.0001$; α1-AT: difference: 160.5, 95% CI: 81.6–239.4, $P = 0.0001$; faecal zonulin: difference: 0.8, 95% CI: 0.5–1.2, $P < 0.0001$) (Supplementary Table S6). The mean changes in the zonulin levels in serum samples from baseline to week 16 in the FMT group were greater than those in the placebo group, but not statistically significant ($P = 0.061$) (Supplementary Table S6). Furthermore, the participants in the FMT

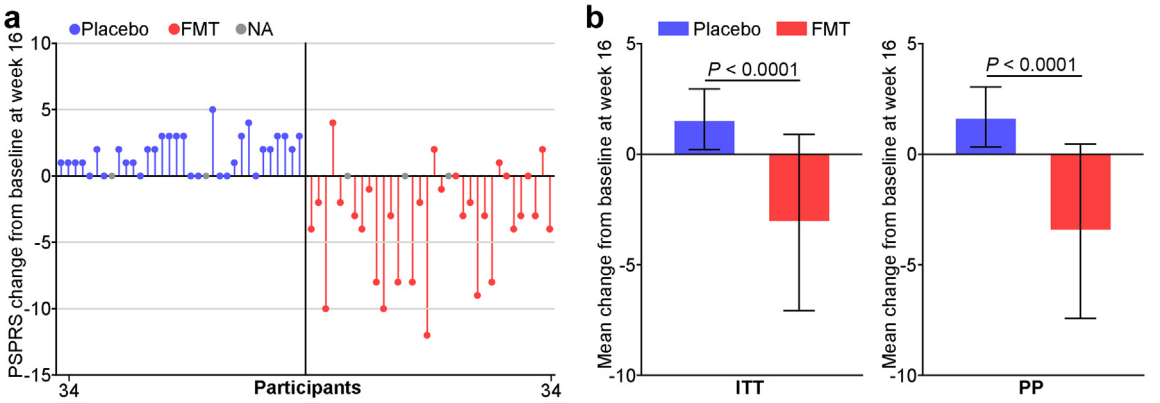

Fig. 2: **Change in PSPRS score from baseline at week 16.** (a) Change in PSPRS score for individual patients (FMT group, n = 34; Placebo group, n = 34) from baseline at week 16. (b) Mean change in PSPRS score from baseline at week 16 for ITT analysis (FMT group, n = 34; Placebo group, n = 34) and PP analysis (FMT group, n = 31; Placebo group, n = 32). The primary outcomes at week 16 between treatment groups were assessed using a mixed-model, repeated-measures analysis with fixed effects of treatment group, time (categorical), treatment group by time interaction, baseline value, and baseline value by time interaction. Two observations in placebo group and 3 observations in FMT group were missing due to participant withdrawal from the study.

group showed increased expressions of occludin and claudin-5 using IHC at week 16, while no significant changes were detected in the participants in the placebo group (Supplementary Fig. S3l and n). The mean change in the faecal dopamine level from baseline at week 16 was significantly different between the FMT and placebo groups (P = 0.021) (Supplementary Table S6). The proportion of participants with ptau accumulation in the colon detected by IHC was basically equal between the two groups (P > 0.99).

Safety outcome

A total of 5 adverse events (7%) occurred in this study, most were GI upsets, with 3 occurring in the FMT group and 2 occurring in the placebo group. Two participants in the FMT group experienced moderate diarrhea during the first treatment cycle, and the other developed fever during the second treatment cycle. One participant in the placebo group experienced mild diarrhea during the first treatment cycle, and the other developed abdominal pain during the second treatment cycle. Although all participants healed completely after receiving symptomatic treatment, they still dropped out of the study. No serious adverse events occurred in this study.

Discussion

Bidirectional communication between the gut microbiota and CNS, referred to as the microbiota–gut–brain axis, has been demonstrated to be involved in multiple neurological diseases.[25,26] The close crosstalk between them suggests that a disease process affecting the CNS could also involve its enteric counterpart, and vice versa. It is therefore not surprising that many patients with neurodegenerative diseases also experience GI symptoms, such as PSP.[15,27] In this study, our data showed that 85% of patients with PSP-RS displayed different severities of GI symptoms, which was in line with the study by Radicati FG et al.[14] Our findings demonstrated that the present gut dysbiosis in patients with PSP-RS was characterised by a remarkable increase in the genus *Escherichia-Shigella* in the gut microbiota. Noticeably, in addition to a significant increase in the pathogenic bacteria (*Escherichia-Shigella*), most of the producers of short-chain fatty acids (SCFAs), including the genera *Faecalibacterium*, *Blautia* and *Roseburia*,[28,29] were significantly lower in the patients with PSP-RS than those in the HC. SCFAs exert a protective effect on host health by reducing colonic pH and inflammation,[30] and increasing intestinal epithelial cell metabolism and proliferation.[31,32] We suspected that gut dysfunction might be associated with the change of the microbiota, the producers of SCFAs. In addition, the intestinal mucosal barrier was disrupted, reflected by increased serum and stool zonulin levels, and decreased expression of AJ and TJ proteins in patients with PSP-RS. Both stool and serum zonulin levels have been used previously as biomarkers for intestinal barrier integrity.[33,34] The same trends of changes in the two biomarkers were observed, and were consistent with the results of AJ and TJ proteins expression. Moreover, dopamine produced in the gut is responsible for protecting the intestinal mucosa and controlling GI motility, primarily in the colon.[35] We speculate that the reduced dopamine level in the gut could be one of the potential mechanisms of constipation in patients with PSP-RS. More studies are required to further clarify the above hypothesis.

Outcome	Estimates and standard errors		Adjusted mean difference (95% CI)	*P* value
	Placebo group (n = 34)	FMT group (n = 34)		
Primary outcome				
Mean change from baseline to week 16				
PSPRS total score	1.7 (0.3)	−2.6 (0.5)	4.3 (3.2, 5.4)	<0.0001
Secondary outcomes				
Mean change from baseline to week 2				
PSPRS total score	0.2 (0.3)	−1.5 (0.5)	1.7 (0.6, 2.8)	0.0046
PSPRS-V+VI	0.0 (0.1)	−0.6 (0.2)	0.6 (0.2, 1.1)	0.0079
GSRS	−1.2 (0.4)	−1.3 (0.4)	0.1 (−1.1, 1.2)	0.89
CSS	−1.0 (0.4)	−2.5 (0.7)	1.5 (0.0, 3.1)	0.067
UPDRS II	−0.1 (0.3)	−0.5 (0.4)	0.4 (−0.5, 1.3)	0.37
PAC-QoL	−3.5 (2.2)	−12.9 (2.5)	9.4 (4.3, 14.4)	0.0005
RBDQ-HK	−0.1 (0.2)	0.1 (0.2)	−0.1 (−0.7, 0.5)	0.67
MMSE	0.0 (0.2)	0.0 (0.2)	0.0 (−0.5, 0.6)	0.96
HAMD	0.3 (0.7)	−1.9 (0.7)	2.3 (0.6, 3.9)	0.0083
HAMA	−0.5 (0.8)	−2.5 (0.8)	2.0 (0.1, 3.9)	0.045
SEADL	0.0 (0.4)	0.0 (0.6)	0.0 (−1.4, 1.4)	1.0
Mean change from baseline to week 7				
PSPRS total score	0.3 (0.3)	−2.5 (0.5)	2.8 (1.7, 3.9)	<0.0001
PSPRS-V+VI	0.1 (0.1)	−1.4 (0.2)	1.5 (1.0, 1.9)	<0.0001
GSRS	−1.5 (0.4)	−2.4 (0.4)	0.9 (−0.3, 2.0)	0.15
CSS	−1.3 (0.4)	−3.4 (0.7)	2.2 (0.6, 3.8)	0.011
UPDRS II	0.0 (0.3)	−1.4 (0.4)	1.4 (0.5, 2.3)	0.0026
PAC-QoL	−4.5 (2.3)	−15.3 (2.6)	10.9 (5.8, 16.0)	0.0001
RBDQ-HK	−0.2 (0.2)	0.1 (0.2)	−0.2 (−0.8, 0.3)	0.42
MMSE	0.0 (0.2)	−0.1 (0.2)	0.2 (−0.4, 0.7)	0.58
HAMD	1.1 (0.6)	−2.3 (0.7)	3.4 (1.7, 5.1)	0.0001
HAMA	−0.4 (0.8)	−3.2 (0.8)	2.8 (0.9, 4.8)	0.0051
SEADL	0.0 (0.4)	0.0 (0.6)	0.0 (−1.4, 1.4)	1.0
Mean change from baseline to week 12				
PSPRS total score	0.6 (0.3)	−4.2 (0.5)	4.8 (3.7, 5.9)	<0.0001
PSPRS-V+VI	0.2 (0.1)	−2.4 (0.2)	2.6 (2.2, 3.1)	<0.0001
GSRS	−2.0 (0.4)	−2.8 (0.4)	0.8 (−0.3, 2.0)	0.16
CSS	−2.0 (0.4)	−4.6 (0.7)	2.6 (1.0, 4.1)	0.0033
UPDRS II	0.1 (0.3)	−2.5 (0.4)	2.6 (1.7, 3.5)	<0.0001
PAC-QoL	−4.5 (2.6)	−18.7 (2.9)	14.1 (9.0, 19.2)	<0.0001
RBDQ-HK	−0.2 (0.2)	0.1 (0.2)	−0.3 (−0.9, 0.3)	0.31
MMSE	0.0 (0.2)	−0.7 (0.2)	0.6 (0.1, 1.2)	0.024
HAMD	1.0 (0.7)	−2.4 (0.7)	3.5 (1.8, 5.1)	0.0001
HAMA	−0.2 (0.9)	−3.3 (0.9)	3.1 (0.9, 4.8)	0.0022
SEADL	0.0 (0.4)	1.2 (0.6)	−2.1 (−2.5, 0.2)	0.095
Mean change from baseline to week 16				
PSPRS-V+VI	0.6 (0.1)	−1.6 (0.2)	2.3 (1.8, 2.7)	<0.0001
GSRS	0.1 (0.4)	−2.8 (0.4)	2.9 (1.8, 4.1)	<0.0001
CSS	−0.3 (0.4)	−2.7 (0.7)	2.5 (0.9, 4.0)	0.0049
UPDRS II	1.5 (0.3)	−2.2 (0.4)	3.7 (2.8, 4.6)	<0.0001
PAC-QoL	−0.8 (2.4)	−13.1 (2.7)	12.4 (7.3, 17.5)	<0.0001
RBDQ-HK	0.4 (0.2)	0.7 (0.2)	−0.3 (−0.9, 0.3)	0.32
MMSE	−0.7 (0.2)	−1.6 (0.2)	1.0 (0.4, 1.6)	0.0007
HAMD	3.1 (0.7)	−0.8 (0.7)	3.9 (2.2, 5.6)	<0.0001
HAMA	2.1 (0.9)	−1.6 (0.9)	3.7 (1.7, 5.7)	0.0003
SEADL	0.6 (0.4)	1.8 (0.6)	−1.2 (−2.5, 0.2)	0.095

(Table 2 continues on next page)

Outcome	Estimates and standard errors		Adjusted mean difference (95% CI)	*P* value
	Placebo group (n = 34)	FMT group (n = 34)		
(Continued from previous page)				
Mean change from baseline to week 36				
PSPRS total score	5.4 (0.3)	1.5 (0.5)	3.8 (2.7, 4.9)	<0.0001
PSPRS-V+VI	2.7 (0.1)	0.8 (0.2)	1.9 (1.4, 2.3)	<0.0001
GSRS	2.3 (0.4)	−0.3 (0.4)	2.6 (1.4, 3.7)	0.0001
CSS	0.9 (0.4)	−0.2 (0.6)	1.0 (−0.5, 2.6)	0.20
UPDRS II	−4.2 (0.3)	1.0 (0.4)	3.2 (2.4, 4.1)	<0.0001
PAC-QoL	4.3 (2.6)	−4.1 (2.9)	8.5 (3.3, 13.6)	0.0016
RBDQ-HK	2.3 (0.2)	1.5 (0.2)	0.8 (0.3, 1.4)	0.0051
MMSE	−1.6 (0.2)	−2.4 (0.2)	0.8 (0.3, 1.4)	0.0040
HAMD	4.3 (0.7)	0.6 (0.7)	3.7 (2.0, 5.4)	<0.0001
HAMA	3.9 (0.8)	0.2 (0.8)	3.7 (1.8, 5.7)	0.0003
SEADL	−0.3 (0.4)	−1.1 (0.6)	0.9 (−0.5, 2.2)	0.21

Note: α1-AT, alpha-1-antitrypsin; BMI, Body-mass index; CALP, calprotectin; CI, confidence interval; CSS, Constipation Scoring System; FMT, faecal microbiota transplantation; GSRS, Gastrointestinal Symptom Rating Scale; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; LF, lactoferrin; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; PAC-QoL, Patient Assessment of Constipation Quality of Life; PSP-RS, progressive supranuclear palsy–Richardson's syndrome; PSPRS, Progressive Supranuclear Palsy Rating Scale; RBDQ-HK, REM sleep behavior disorder questionnaire-Hong Kong; SEADL, Schwab and England Activities of Daily Living; UPDRS, Unified Parkinson's Disease Rating Scale. The primary and secondary outcomes between treatment groups were assessed on an intention-to-treat basis using a mixed-model, repeated-measures analysis with fixed effects of treatment group, time (categorical), treatment group by time interaction, baseline value, and baseline value by time interaction.

Table 2: **Outcome measures comparing FMT with placebo.**

FMT has been proposed as a therapeutic option for CDIs and ulcerative colitis, which are closely related to gut dysbiosis.[13,36–38] Beyond this application, the potential of this new treatment method has been examined for the treatment of neurodegenerative diseases such as PD and AD, while most studies are limited to animal experiments.[39–42] We performed a single-centre, randomised, double-blind, placebo-controlled trial involving 68 patients with PSP-RS. We excluded patients who received antiparkinsonian medication to preclude the confounding effect of medication, given that the gut microbiome composition can be influenced by drugs, including nonantibiotic medications.[43,44] The main finding of the study was that a 3-cycle, 12-week intermittent FMT produced significant improvements in both motor and nonmotor symptoms in patients with PSP-RS. Analyses of secondary outcomes indicated an effect of FMT on activities of daily living and constipation, as well as psychological health in patients with PSP-RS. Recent clinical trials have failed to show a benefit for the treatment of PSP, mainly determined by no statistically significant differences for change of the PSPRS score.[45,46] Our study showed a decrease in PSPRS scores, which suggests that FMT therapy is clinically meaningful for patients with PSP-RS, and can even slow the progress of PSP-RS to certain extent. The low dropout rate (7%) implies that FMT is generally acceptable to patients with PSP-RS. Furthermore, our results indicated that sex had no effect on the clinical outcomes of FMT treatment (Supplementary Table S7).

Moreover, we found that FMT altered the intestinal microbiota composition of patients with PSP-RS. In particular, the relative abundance of *Escherichia-Shigella* was markedly decreased, and the levels of SCFAs producing bacteria including *Faecalibacterium* and *Bifidobacterium*[47] were significantly increased in the FMT group compared to the placebo group. These changes may contribute to the reduced gut inflammation and improved intestinal barrier function. Additionally, it appears that the effect of FMT on gut inflammation is greater than intestinal barrier function. Previous studies demonstrated that the restoration of intestinal barrier function was complex, achieved by regulating the expression of epithelial proteins,[48,49] promoting the synthesis of mucins,[50] and so on. Further metabolomics investigations of microbiome-associated metabolites may help to explore the underlying mechanisms. In addition, FMT restored the levels of dopamine in the gut, which might explain why FMT significantly alleviated constipation.

This study has several limitations. First, the analysis of 16S rDNA rather than shotgun metagenomic sequencing limited our analysis to the genus level but had an impact on the identification of the microbiome at the species level. Second, the control group received water-based placebo stool rather than autologous stool, whereas the latter might have been a more effective control for this investigation. Third, the study was not powered to assess safety, and therefore, further larger studies are required to draw the relevant conclusions. Fourth, the duration of follow-up was relatively short and longer-term follow-up is needed. Finally, this single-centre study limited the clinical value of FMT for patients with PSP-RS, and future studies are needed to perform in a multicentre setting.

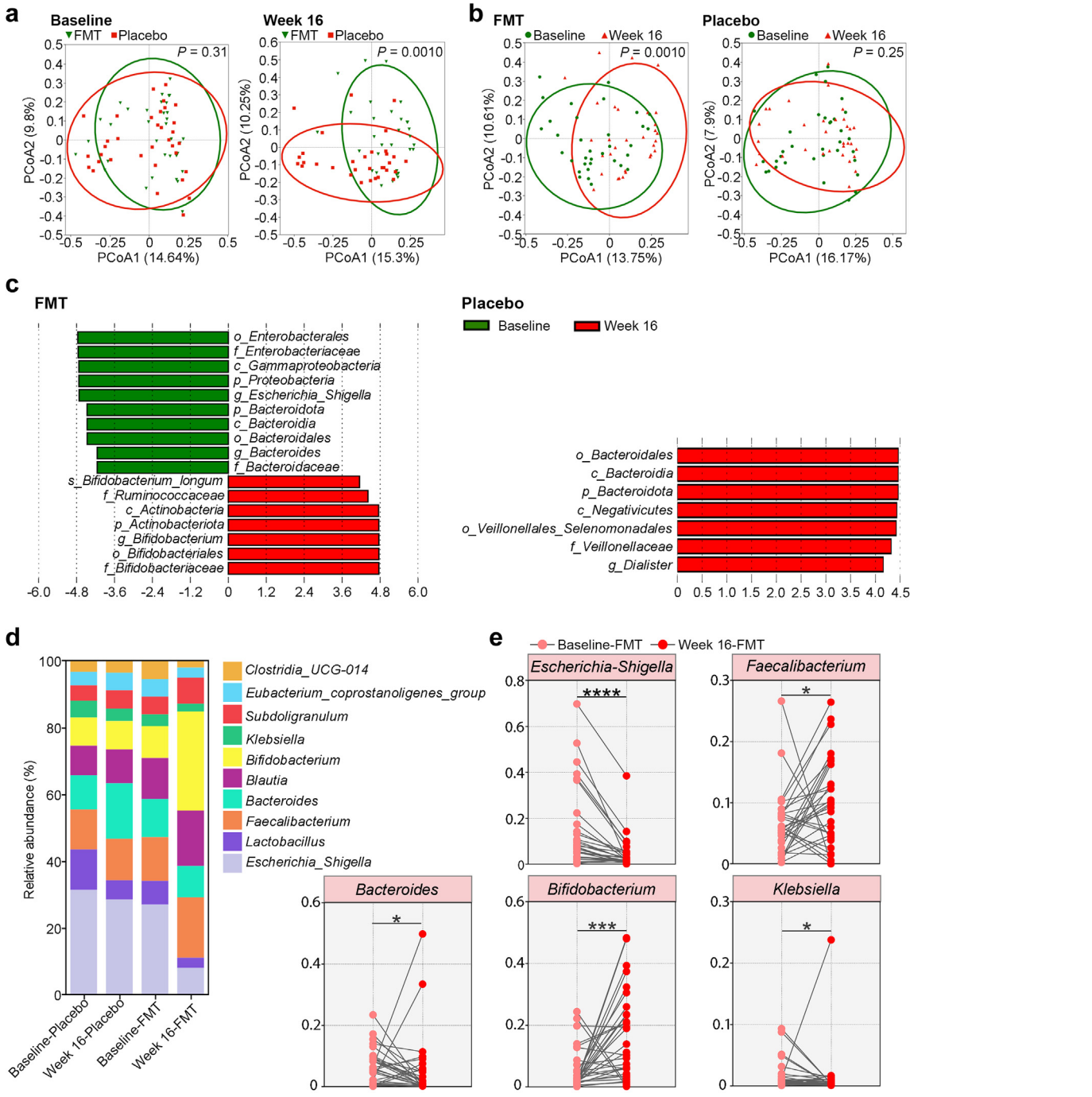

***Fig. 3:* Change in the intestinal microbiota composition from baseline at week 16.** (a) PCoA plot based on Bray–Curtis dissimilarities of the faecal microbiota at genus level in terms of 16S rDNA sequencing between FMT (n = 31) and placebo (n = 32) groups, at baseline (left) and Week 16 (right), respectively. (b) PCoA plot based on Bray–Curtis dissimilarities of the faecal microbiota at genus level in terms of 16S rDNA sequencing between baseline (FMT group, n = 34; Placebo group, n = 34) and Week 16 (FMT group, n = 31; Placebo group, n = 32). (c) Bar charts of the LDA scores for differentially abundant bacterial taxa between baseline (FMT group, n = 34; Placebo group, n = 34) and Week 16 (FMT group, n = 31; Placebo group, n = 32). (LDA score threshold: >4.0). (d) Bar charts of the genus level in faecal samples based on 16S rDNA sequencing among Baseline-FMT (n = 34), Week 16-FMT (n = 31), Baseline-Placebo (n = 34), Week 16-Placebo (n = 32) groups. (e) Comparison of the relative abundance distributions of faecal microbiota genera between Baseline-FMT (n = 31) and Week 16-FMT (n = 31) groups (Wilcoxon matched-pairs signed rank test).

In conclusion, our findings showed that the gut dysbiosis, accompanied with impaired intestinal mucosal integrity and gut inflammation existed in patients with PSP-RS. Importantly, a 3-cycle, 12-week intermittent FMT treatment was effective in improving motor and nonmotor symptoms in patients with PSP-RS. Further research is needed to assess longer-term efficacy and safety.

Contributors

XJW, XBD and JFT conceived and designed the study; HYT, RZ, DXL, QYZ and YPZ acquired the data; JQW, LM and RYF analysed and interpreted the data; HL, YKC and YF accessed and were responsible for the raw data associated with the study; HYT, CQ, XY and JQW performed the statistical analysis; LJJ guided statistical analysis; HYT, JQW and XJW drafted the manuscript; XBD and JFT critically revised the important intellectual content of the manuscript; XJW, XBD, and JFT have verified the data.

All authors red, revised and approved the final version of the manuscript. All the authors had full access to all the data in the study and the corresponding authors had the final responsibility to submit the study for publication.

Data sharing statement

The data collected in this study, including de-identified participant data and the data dictionary are available to researchers through corresponding author Xuejing Wang upon reasonable request. These data will be available for 3 years after publication. Data requests require a methodologically sound proposal as well as a data access agreement and approval by the local ethics committee.

Declaration of interests

All the authors disclose no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101888.

References

1 Boxer AL, Yu JT, Golbe LI, Litvan I, Lang AE, Hoglinger GU. Advances in progressive supranuclear palsy: new diagnostic criteria, biomarkers, and therapeutic approaches. *Lancet Neurol*. 2017;16(7):552–563.
2 Coyle-Gilchrist IT, Dick KM, Patterson K, et al. Prevalence, characteristics, and survival of frontotemporal lobar degeneration syndromes. *Neurology*. 2016;86(18):1736–1743.
3 Hoglinger GU, Respondek G, Stamelou M, et al. Clinical diagnosis of progressive supranuclear palsy: the movement disorder society criteria. *Mov Disord*. 2017;32(6):853–864.
4 Williams DR, Lees AJ. Progressive supranuclear palsy: clinicopathological concepts and diagnostic challenges. *Lancet Neurol*. 2009;8(3):270–279.
5 Ling H. Clinical approach to progressive supranuclear palsy. *J Mov Disord*. 2016;9(1):3–13.
6 Levin J, Kurz A, Arzberger T, Giese A, Hoglinger GU. The differential diagnosis and treatment of atypical parkinsonism. *Dtsch Arztebl Int*. 2016;113(5):61–69.
7 Golbe LI, Ohman-Strickland PA. A clinical rating scale for progressive supranuclear palsy. *Brain*. 2007;130(Pt 6):1552–1565.
8 O'Sullivan SS, Massey LA, Williams DR, et al. Clinical outcomes of progressive supranuclear palsy and multiple system atrophy. *Brain*. 2008;131(Pt 5):1362–1372.
9 Doifode T, Giridharan VV, Generoso JS, et al. The impact of the microbiota-gut-brain axis on Alzheimer's disease pathophysiology. *Pharmacol Res*. 2021;164:105314.
10 Sun MF, Shen YQ. Dysbiosis of gut microbiota and microbial metabolites in Parkinson's Disease. *Ageing Res Rev*. 2018;45:53–61.
11 Hu X, Wang T, Jin F. Alzheimer's disease and gut microbiota. *Sci China Life Sci*. 2016;59(10):1006–1023.
12 Costello SP, Hughes PA, Waters O, et al. Effect of fecal microbiota transplantation on 8-week remission in patients with ulcerative colitis: a randomized clinical trial. *JAMA*. 2019;321(2):156–164.
13 Juul FE, Garborg K, Bretthauer M, et al. Fecal microbiota transplantation for primary Clostridium difficile infection. *N Engl J Med*. 2018;378(26):2535–2536.
14 Radicati FG, Martinez Martin P, Fossati C, et al. Non motor symptoms in progressive supranuclear palsy: prevalence and severity. *NPJ Parkinsons Dis*. 2017;3:35.
15 Ou R, Song W, Wei Q, et al. Characteristics of nonmotor symptoms in progressive supranuclear palsy. *Parkinsons Dis*. 2016;2016:9730319.
16 Schmidt C, Herting B, Prieur S, et al. Autonomic dysfunction in patients with progressive supranuclear palsy. *Mov Disord*. 2008;23(14):2083–2089.
17 Barichella M, Severgnini M, Cilia R, et al. Unraveling gut microbiota in Parkinson's disease and atypical parkinsonism. *Mov Disord*. 2019;34(3):396–405.
18 Dugger BN, Hoffman BR, Scroggins A, et al. Tau immunoreactivity in peripheral tissues of human aging and select tauopathies. *Neurosci Lett*. 2019;696:132–139.
19 Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. *Neurology*. 1996;47(1):1–9.
20 Costello SP, Tucker EC, La Brooy J, Schoeman MN, Andrews JM. Establishing a fecal microbiota transplant service for the treatment of Clostridium difficile infection. *Clin Infect Dis*. 2016;62(7):908–914.
21 Cammarota G, Ianiro G, Tilg H, et al. European consensus conference on faecal microbiota transplantation in clinical practice. *Gut*. 2017;66(4):569–580.
22 Liu H, Chen X, Hu X, et al. Alterations in the gut microbiome and metabolism with coronary artery disease severity. *Microbiome*. 2019;7(1):68.
23 Caporaso JG, Kuczynski J, Stombaugh J, et al. QIIME allows analysis of high-throughput community sequencing data. *Nat Methods*. 2010;7(5):335–336.
24 Stamelou M, Schope J, Wagenpfeil S, et al. Power calculations and placebo effect for future clinical trials in progressive supranuclear palsy. *Mov Disord*. 2016;31(5):742–747.
25 Bermudez-Martin P, Becker JAJ, Caramello N, et al. The microbial metabolite p-Cresol induces autistic-like behaviors in mice by remodeling the gut microbiota. *Microbiome*. 2021;9(1):157.
26 Ma Q, Xing C, Long W, Wang HY, Liu Q, Wang RF. Impact of microbiota on central nervous system and neurological diseases: the gut-brain axis. *J Neuroinflammation*. 2019;16(1):53.
27 Chaithra SP, Prasad S, Holla VV, et al. The non-motor symptom profile of progressive supranuclear palsy. *J Mov Disord*. 2020;13(2):118–126.
28 Yang K, Deng X, Jian S, et al. Gallic acid alleviates gut dysfunction and boosts immune and antioxidant activities in puppies under environmental stress based on microbiome-metabolomics analysis. *Front Immunol*. 2021;12:813890.
29 Nishiwaki H, Ito M, Hamaguchi T, et al. Short chain fatty acids-producing and mucin-degrading intestinal bacteria predict the progression of early Parkinson's disease. *NPJ Parkinsons Dis*. 2022;8(1):65.
30 Sivaprakasam S, Prasad PD, Singh N. Benefits of short-chain fatty acids and their receptors in inflammation and carcinogenesis. *Pharmacol Ther*. 2016;164:144–151.
31 Chen SJ, Chen CC, Liao HY, et al. Association of fecal and plasma levels of short-chain fatty acids with gut microbiota and clinical severity in patients with Parkinson disease. *Neurology*. 2022;98(8):e848–e858.
32 Rupp SK, Stengel A. Bi-directionality of the microbiota-gut-brain Axis in patients with functional dyspepsia: relevance of psychotherapy and probiotics. *Front Neurosci*. 2022;16:844564.

33 Bona MD, Torres CHM, Lima S, Lima AAM, Maciel BLL. Intestinal barrier function in obesity with or without metabolic syndrome: a systematic review protocol. *BMJ Open*. 2021;11(5):e043959.
34 Balmus IM, Ilie OD, Ciobica A, et al. Irritable bowel syndrome between molecular approach and clinical expertise-searching for gap fillers in the oxidative stress way of thinking. *Medicina (Kaunas)*. 2020;56(1).
35 Mittal R, Debs LH, Patel AP, et al. Neurotransmitters: the critical modulators regulating gut-brain Axis. *J Cell Physiol*. 2017;232(9):2359–2372.
36 Paramsothy S, Nielsen S, Kamm MA, et al. Specific bacteria and metabolites associated with response to fecal microbiota transplantation in patients with ulcerative colitis. *Gastroenterology*. 2019;156(5):1440–14454 e2.
37 Moayyedi P, Surette MG, Kim PT, et al. Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. *Gastroenterology*. 2015;149(1):102–109 e6.
38 El-Salhy M, Hatlebakk JG, Gilja OH, Brathen Kristoffersen A, Hausken T. Efficacy of faecal microbiota transplantation for patients with irritable bowel syndrome in a randomised, double-blind, placebo-controlled study. *Gut*. 2020;69(5):859–867.
39 Sun MF, Zhu YL, Zhou ZL, et al. 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*. 2018;70:48–60.
40 Zhao Z, Ning J, Bao XQ, et al. Fecal microbiota transplantation protects rotenone-induced Parkinson's disease mice via suppressing inflammation mediated by the lipopolysaccharide-TLR4 signaling pathway through the microbiota-gut-brain axis. *Microbiome*. 2021;9(1):226.
41 Kim MS, Kim Y, Choi H, et al. Transfer of a healthy microbiota reduces amyloid and tau pathology in an Alzheimer's disease animal model. *Gut*. 2020;69(2):283–294.
42 Kim N, Jeon SH, Ju IG, et al. Transplantation of gut microbiota derived from Alzheimer's disease mouse model impairs memory function and neurogenesis in C57BL/6 mice. *Brain Behav Immun*. 2021;98:357–365.
43 Maier L, Pruteanu M, Kuhn M, et al. Extensive impact of non-antibiotic drugs on human gut bacteria. *Nature*. 2018;555(7698):623–628.
44 Weersma RK, Zhernakova A, Fu J. Interaction between drugs and the gut microbiome. *Gut*. 2020;69(8):1510–1519.
45 Dam T, Boxer AL, Golbe LI, et al. Safety and efficacy of anti-tau monoclonal antibody gosuranemab in progressive supranuclear palsy: a phase 2, randomized, placebo-controlled trial. *Nat Med*. 2021;27(8):1451–1457.
46 Hoglinger GU, Litvan I, Mendonca N, et al. Safety and efficacy of tilavonemab in progressive supranuclear palsy: a phase 2, randomised, placebo-controlled trial. *Lancet Neurol*. 2021;20(3):182–192.
47 Alkasir R, Li J, Li X, Jin M, Zhu B. Human gut microbiota: the links with dementia development. *Protein Cell*. 2017;8(2):90–102.
48 Li HY, Zhou DD, Gan RY, et al. Effects and mechanisms of probiotics, prebiotics, synbiotics, and postbiotics on metabolic diseases targeting gut microbiota: a narrative review. *Nutrients*. 2021;13(9).
49 Robinson K, Deng Z, Hou Y, Zhang G. Regulation of the intestinal barrier function by host defense peptides. *Front Vet Sci*. 2015;2:57.
50 Visser JT, Lammers K, Hoogendijk A, et al. Restoration of impaired intestinal barrier function by the hydrolysed casein diet contributes to the prevention of type 1 diabetes in the diabetes-prone Bio-Breeding rat. *Diabetologia*. 2010;53(12):2621–2628.