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New challenges and future perspectives in parkinson's disease and age-related movement disorders

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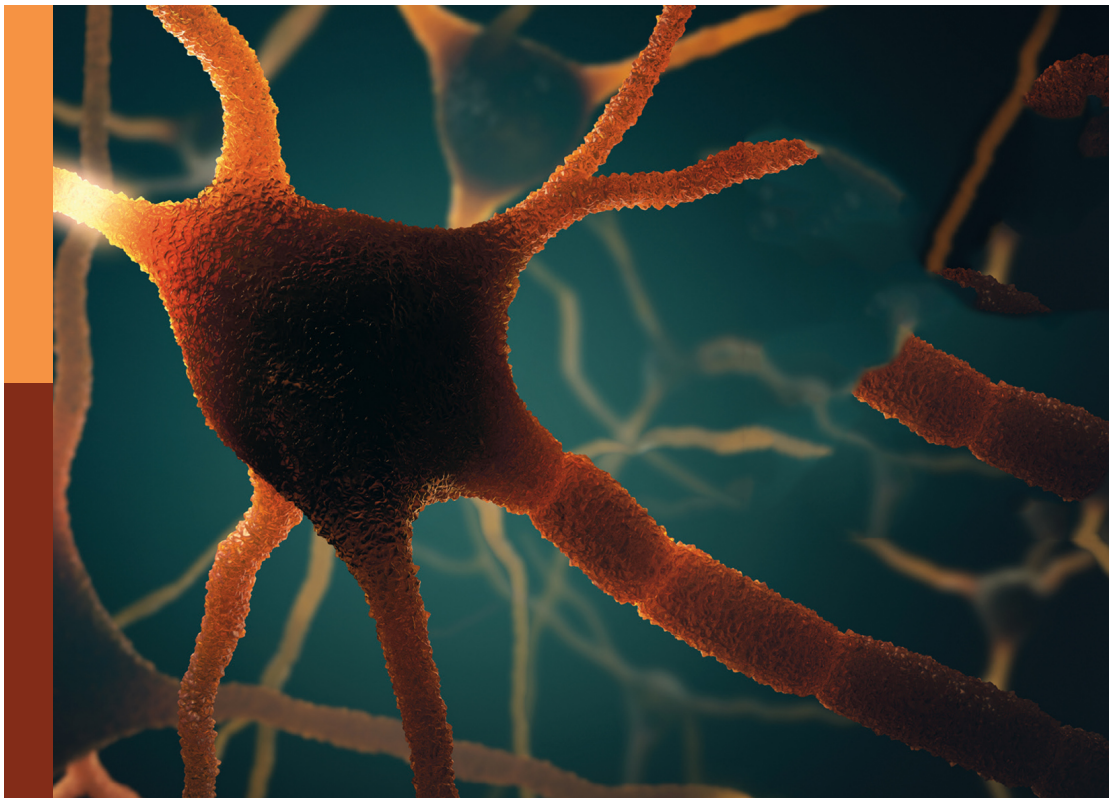

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New challenges and future perspectives in parkinson's disease and age-related movement disorders

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COMMUNITY CASE STUDY
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Transition and Sustainability of an Online Care Model for People With Parkinson's Disease in Response to the COVID-19 Pandemic

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Introduction: CoronaVirus Disease-2019 (COVID-19) led to social distancing and the need for alternative care models. Telehealth programs for people with Parkinson's (PWP) disease may ensure continuity of care. The goal of this observational survey study was to determine the practicability, satisfaction, and barriers to online programs, their relationship to perceived symptoms, mood, and quality of life, and program sustainability beyond the immediate pandemic.

Methods: In-person Parkinson's programs at New York Institute of Technology College of Osteopathic Medicine transitioned online at the start of the pandemic to include Rock Steady Boxing, Support Groups, and Rock Steady Buddies. A custom online survey sent to 150 participants investigated PD history, symptomatology, level of exercise before and during the pandemic, depression (PHQ-9), quality of life (PDQ-39), and practicability and perceived satisfaction related to these online programs. Descriptive statistics were reported.

Results: Of 69 respondents [mean age of 70.2y (SD 8.4 yrs)], >75% were satisfied with the transition to online programs. Consistent attendance and minimal barriers to programs indicated practicability, with increased adherence to exercise. Of 66 completed PHQ-9s, 22.7% had scores ≥9 (moderate to severe depression); of 61 completed PDQ-39s, scores averaged 21.4; better quality of life than national averages for PWP. Self-perceived physical and mental wellbeing were positively affected.

Conclusions: Results suggest the transition to online programs met the needs of the Parkinson's community in a practicable and sustainable manner during the pandemic. With COVID-19 still prevalent, the current model of blending synchronous online and in-person classes provides a more flexible, sustainable format compared to in-person alone. Institutions may consider including online components to existing programs to promote continuity of care for aging populations as part of best practices.

Keywords: Parkinson's disease, COVID-19, telehealth, telerehabilitation, Rock Steady Boxing

INTRODUCTION

During the spring of 2020, the onset of severe acute respiratory syndrome coronavirus-2 (SARS-COV-2; COVID-19) led to social distancing, shelter-in-place orders, and in some cases, quarantine (1). These measures, enacted to slow the rate of infection, resulted in negative consequences on health and well-being, particularly in older, vulnerable populations such as people with Parkinson's (PWP) disease (2, 3).

The Parkinson's community at New York Institute of Technology's College of Osteopathic Medicine (NYITCOM) and Health Care Center consists of patients, clients, caregivers, medical personnel, and student volunteers carefully and purposefully built over the past several years. The goal is to 'fight back against Parkinson's' through instilling bonds of support and friendship amongst people with a common vision (4). In addition to offering medical and rehabilitation services specific for PWP, other in-person programs include support groups (SG) and a Rock Steady Boxing (RSB) program.

With the onset of COVID-19, however, these in-person programs were no longer feasible. Therefore, an alternative model using an online platform for delivery of care was launched as virtual RSB (vRSB), virtual support groups (vSG), and a new online program developed specifically in response to the pandemic, called Rock Steady Buddies (*Buddies*). These online programs aimed to provide continuity of care with an emphasis on health maintenance, management of symptoms, maintaining community bonds, and reducing the effects of social isolation.

Parkinson's Disease and COVID-19

Parkinson's disease (PD) is a progressive neurodegenerative disorder caused by the loss of dopaminergic neurons in the brain, typically affecting adults aged 60 and older (5). This chronic disease presents with motor symptoms, such as tremor, rigidity, bradykinesia, and postural instability, non-motor symptoms, including anosmia, sleep disturbance, and cognitive deficits, and neuropsychiatric symptoms, notably depression and anxiety, that can adversely affect quality of life (QoL) (6). Older age and comorbid conditions are a leading risk factor of mortality in patients with COVID-19 (7). Although there are no formal reports suggesting PD increases the risk of contracting COVID-19, PWP are generally older and may have multiple comorbidities—including respiratory issues—thus, increasing their risk of serious illness and complications from COVID-19 (3, 7–10). Parkinson's disease is classically managed with an array of pharmacotherapy, and, adjunctively, exercise. In PWP, exercise has shown to improve clinical signs and symptoms and delay underlying disease processes through its neuroprotective and neuroplastic effects (11).

Exercise in Parkinson's Disease

Exercise is a subcategory of physical activity that is planned, structured, repetitive, purposeful, and intended to improve one or more components of physical fitness (12). Research shows that exercise benefits motor symptoms in PWP and may affect cognition (11). In older adults, exercise has shown to positively affect the acquisition and retention of memory, cognition, and depression (13–15). Despite evidence that exercise can reduce disability and improve QoL in PWP, many remain sedentary (11, 16). Common perceived barriers to exercise in PWP include low outcome expectation, lack of time, and fear of falling (16). These barriers can be addressed through communication with patients, exercise education, and behavioral change interventions targeting self-efficacy–including goal setting, social support, monitoring feedback and progress, and using a patient centered approach (17, 18). Exercise programs for PWP include a wide range of activities and formats, including walking, tai chi, and boxing (11). While exercise in general is beneficial for PWP, aerobic, goal-directed and group exercises may be most effective (19, 20).

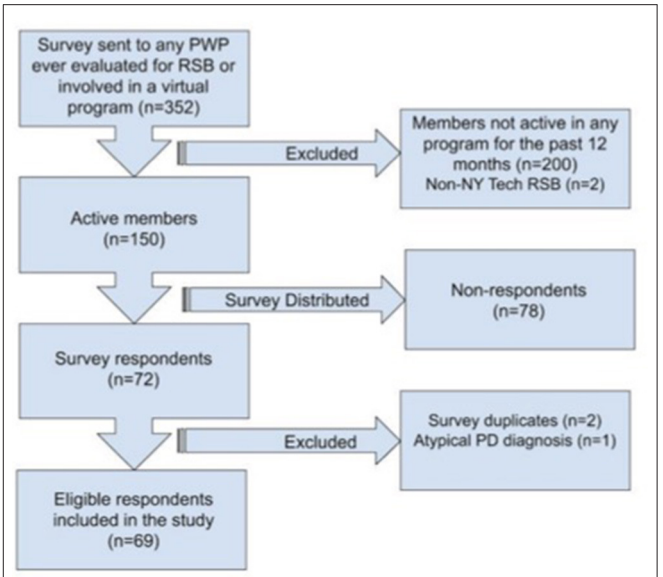

FIGURE 1 | Survey exclusion criteria flowchart.

Group exercise has been shown to enhance social support and peer bonding, increase enjoyment and compliance, and improve perceived health, more so than individual exercise (19, 20). The reciprocality, accessibility, and reliability of social support and connectedness are important in maintaining and/or initiating behavioral change, such as an exercise routine (21, 22). During the pandemic however, in-person group exercise classes were curtailed. Fortunately, video technology and tele-exercise programs have shown to be an effective mode of providing exercise in the home for people with movement disorders (23) including PD (23, 24).

Mental Health in Parkinson's Disease

While current interventions for PWP mitigate many of the physical symptoms (5, 25), non-physical symptoms, exacerbated by social isolation and stress from the COVID-19 pandemic, are more difficult to manage. Up to 40% of PWP present with anxiety (26) while 50% present with depression (27); combined with elevated stress levels, social distancing, and lack of usual support systems during the pandemic, feelings of helplessness and isolation may result (28).

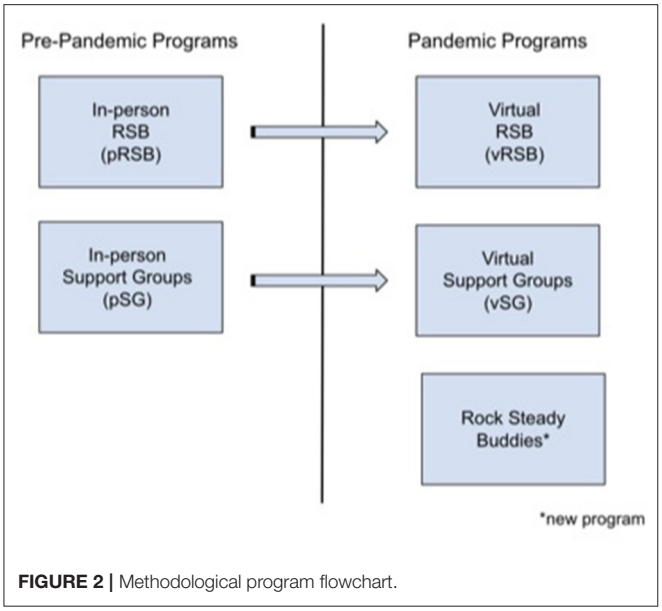

FIGURE 2 | Methodological program flowchart.

Social relationships with family, friends, and support groups—specifically, effective communication and acceptance—are necessary to maintain QoL in PWP (29, 30). Coping with the progression of PD presents challenges that may be relieved through support groups, thus improving QoL, depression, and anxiety in PWP (31). Although in-person support groups are common practice for managing the neuropsychiatric symptoms of PD (32), during the COVID-19 pandemic, barriers such as social distancing and shelter-in-place orders rendered in-person programs unavailable. Similar to tele-exercise, technological advances promote the use of online support groups as an alternative model to access care (32), and thus better serve populations with motor disability and disease.

Objectives

The purpose of this study was to investigate the practicability, perceived satisfaction, and barriers to participation of online programs developed in response to the COVID-19 pandemic, namely, vRSB, vSG, and *Buddies*. Sustainability of the programs, as the COVID-19 pandemic continues, was also considered. Online group exercise programs may be used to address the limited access to in-person programs resulting from the COVID-19 pandemic while preserving social interactions and providing emotional support. The authors hypothesized that the virtual programs were practicable, with low barriers to participation, and high perceived satisfaction. The current study also investigated self-reported symptomatology, mood and QoL of program participants, with expectations that this PD population had more manageable symptoms, less depression and better QoL in relationship to program participation.

METHODOLOGICAL ASPECTS

Study Design and Approval

This observational survey study was approved by the Institutional Review Board at New York Institute of Technology. Instructions for the survey included the agreement of informed consent upon completion and submission of the survey.

Participants

Participants in online Parkinson's programs were recruited from in-person programs for PWP and telemedicine/telerehabilitation visits at the institutions' Academic Health Care Center. The survey was intended for males and females of any age or PD stage who participated in pRSB classes prior to the pandemic and/or attended any of the three online programs during the pandemic. Participants who responded to the survey, but only attended pRSB before the pandemic, were used as a comparison to PWP who attended online programs during the pandemic for certain measures. People with PD who did not participate in pRSB within the past 12 months, did not participate in at least one online program, had a movement disorder diagnosis other than PD, or were involved in RSB at another institution were not included in the survey analysis (**Figure 1**). Participation in in-person and/or online programs were adjunctive to pharmacological treatment as determined by participants' neurologists on an individual basis.

Survey Measurement

A custom online observational survey was developed to gather quantitative and qualitative information regarding motivation, satisfaction, and barriers to online programs. An initial version of the survey was developed by medical and physical therapy students with knowledge of the pathophysiology of PD and experience working directly with boxers in the pRSB program. A movement disorder specialist (AL) and physical therapist with expertise in PD (RG) also contributed to question development. Questions were in closed ended format consisting of leading, matrix, multiple choice, drop down, Likert scale, dichotomous scale, and bipolar rating scale questions. Answer choices ranged from a 4-point Likert scale (strongly disagree, disagree, agree, strongly agree), to multiple choice and short answers. Questions regarding PD symptoms were adapted from the Unified Parkinson's Disease Rating Scale (UPDRS) parts I and II (33).

Five domains were addressed:

1. Demographics and PD history:
2. PD symptomatology since COVID-19: self- assessment of PD progression during the pandemic (*Due to social distancing and shelter-in-place orders, PD severity could not be objectively measured)
3. Exercise participation (pre- and post-pandemic)
4. Participation in pRSB: to determine participation in pRSB pre-COVID
5. Participation in online programs (vRSB, vSG, *Buddies*): to determine participation in online programs during COVID.

Collection of information in the aforementioned domains was used to determine practicability — defined by attendance and barriers to program participation — satisfaction, and barriers — defined as obstacles that prevented PWP from participating in the programs.

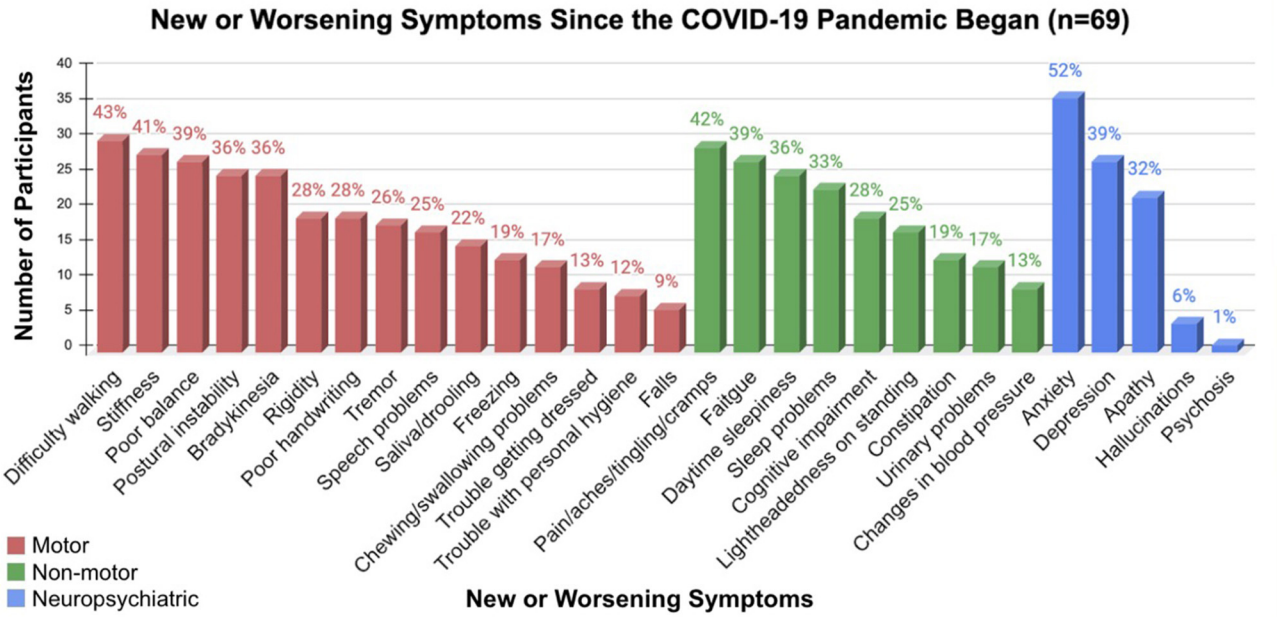

FIGURE 3 | Perceived new or worsening PD symptoms since the start of the COVID-19 pandemic.

Due to the high rates of depression in PWP (27) and its negative effect on QoL (6), two validated questionnaires were also used to better understand the mental health and QoL of the participants. The Patient Health Questionnaire-9 (PHQ-9), a screen for depression, consists of 9 DSM-IV criteria (34) scored from 0 (not at all) to 3 (nearly every day). Scores range from 0 (no depression) to 27 (severe depression) (34, 35). The Parkinson's Disease Questionnaire-39 (PDQ-39), is a commonly used health related QoL measure specific to PD. It consists of 39 items covering eight domains: mobility, activities of daily living, emotional well-being, social support, cognition, communication, and bodily discomfort (36). Each item is scored from 0 (best) to 4 (worst). Domain scores range from 0 (high QoL) to 100 (low QoL) (36).

A survey link was emailed 2–3 times a week (14 total) between July 3 and August 8, 2020, using REDCap (Research Electronic Data Capture), a secure, web-based application designed to support data collection and management. The survey was anonymous to reduce evaluator bias and ensure protection of participants' private health information. Approximate survey completion time was 20 min. The survey could be filled out by participants or caregivers if the participant did not have appropriate cognitive reserve to complete the survey independently. The data was analyzed in a descriptive manner.

Description of Programs

In-person Programs: Rock Steady Boxing and Support Groups

Rock Steady Boxing is a non-contact, group-based boxing program that addresses motor and nonmotor symptoms in PWP with the goal to improve coordination, mobility, dexterity, memory, and, ultimately, activities of daily living (11, 20, 37). Prior to the pandemic, the in-person RSB program at NYITCOM consisted of one-hour group exercise classes 3 days/week. Two of the classes were for higher functioning participants and one class for lower functioning participants. Class placement was determined by an evaluation with a physical therapist or movement disorder specialist and included the Unified Parkinson's Disease Rating Scale (UPDRS), the MiniBESTest, and the Montreal Cognitive Assessment (MOCA). Attendance tracked participation. Classes included a range of balance and agility exercises and boxing drills based on RSB principles (38).

The in-person support groups consisted of weekly meetings led by trained medical personnel, as well as a weekly peer-facilitated group of PWP. The initial 8 week program was sponsored by the American Parkinson's Disease Association's *Parkinson's Roadmap for Education and Support Services* (PRESS).

Virtual Programs: Rock Steady Boxing, Support Group, and Rock Steady Buddies

The pRSB and pSG were transitioned online at the start of the pandemic to become virtual RSB (vRSB) and virtual SG (vSG) respectively. An additional Rock Steady Buddies program was created to provide individual social support to the PD community (**Figure 2**). These virtual programs are described below.

Virtual Rock Steady Boxing (VRSB)

In-person RSB transitioned to vRSB in March 2020. Zoom video conferencing (San Jose CA, USA) was used for all RSB sessions. The Consensus on Exercising Reporting Template guidelines was

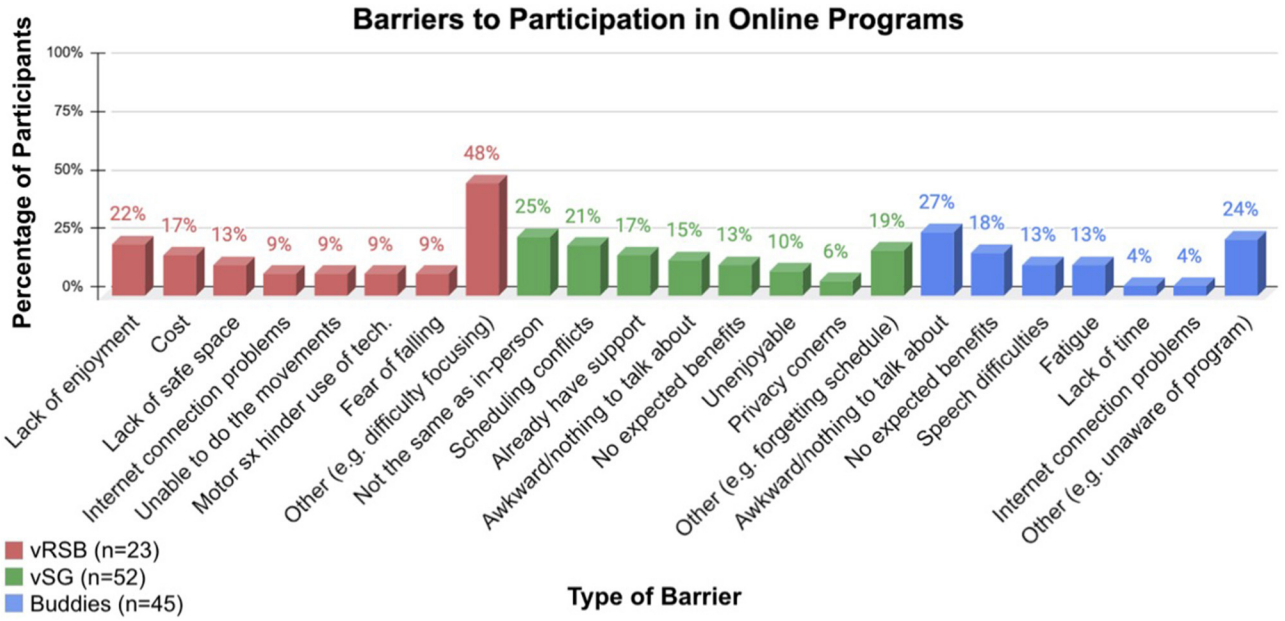

FIGURE 4 | Barriers preventing PWP from participating in our online programs.

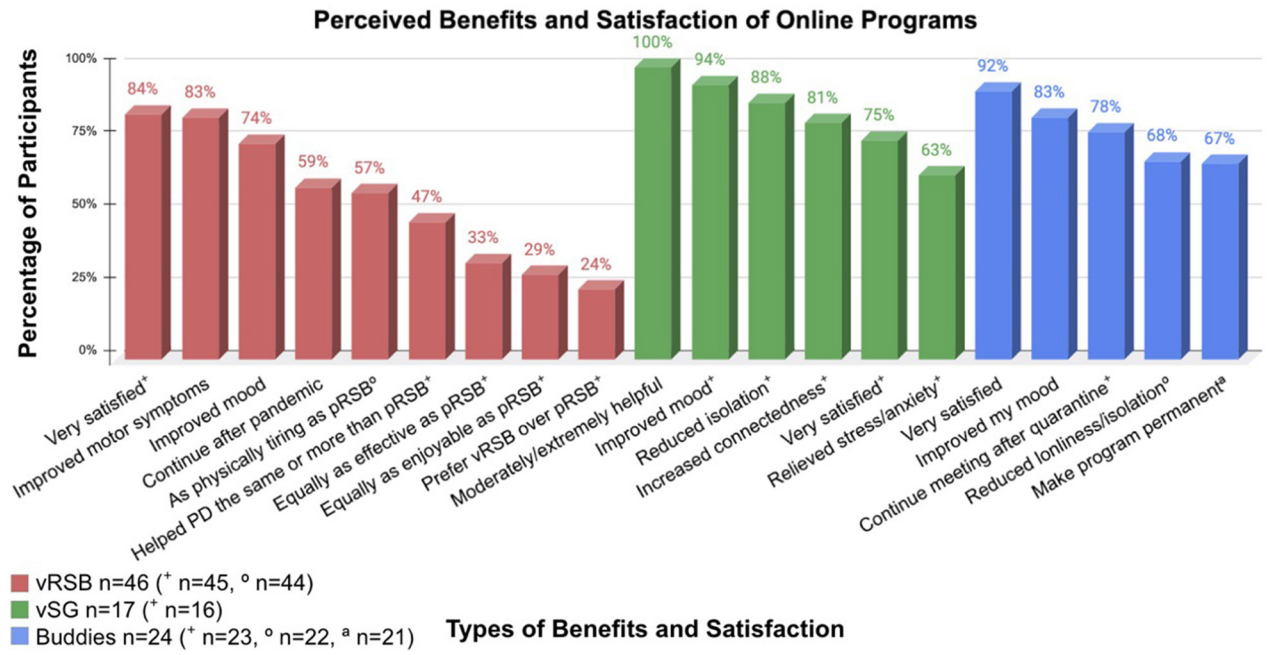

FIGURE 5 | Perceived benefits and satisfaction of the online programs.

used as a basis to describe this program (39). Online sessions followed the same format as in-person sessions with modification of activities depending on available equipment at home. Sessions open 15 min prior to class to allow participant interaction, thus encouraging social connections. Each class begins with a 20-min full-body warm-up including stretching, posture, and balance exercises. Next, boxing drills (35 min)—utilizing punching combinations and footwork—stress coordination and balance and challenge the cardiovascular system. A five-minute cool down completes the class. When applicable, modifications are demonstrated by the trained RSB coach (38). Equipment requirements include appropriate clothing, boxing gloves, and

a safe space to exercise. Potential adverse events include fatigue and falls; however, boxers are encouraged to sit when needed and many are accompanied by "cornermen" (spouses/caregivers) as a precaution. During the class, coaches instruct and monitor boxers to ensure appropriate form and class participation; volunteers are also present to ensure all boxers participate in the exercises and offer gentle reminders as needed. Although the boxers in this program were a highly motivated group, boxers could see the coach and other boxers, which may have further increased motivation. It has been shown that social connectedness while exercising may improve exercise adherence (19).

Virtual Support Groups (vSG)

In March 2020, NYITCOM also restructured its pSG to vSG with a goal to maintain social bonds and provide timely and accurate information about the pandemic — a practice that, along with continuity of care, may prevent acute clinical worsening and complications (40). Meetings, held one to two times a week *via* Zoom and led by a movement disorders specialist, covered topics such as staying fit and active, and how to safely navigate the community. Webinars and presentations from neurologists, neurosurgeons, physical therapists, and front-line COVID-19 physicians were offered.

Rock Steady Buddies (Buddies)

Buddies is a medical student-run program created in April 2020 with the aim of providing social connections and support systems for PWP. A secondary goal was to provide early patient exposure for medical students during the pandemic. Medical student volunteers were recruited and randomly matched with interested PWP, with preference for first year medical students to promote early patient exposure. Each pair of *Buddies* self-scheduled a minimum one hour per week to connect *via* phone or video conferencing. Students were provided with "ice-breakers" and conversation starters to use at their discretion such as, "What's something that made you laugh today", or "What are some of your hobbies"? Oftentimes, PWP would share personal information regarding their PD diagnosis or treatment, however, students were instructed to refrain from answering medical questions or sharing medical or confidential information.

RESULTS

Respondent Demographics

The survey was distributed to 150 PWP who participated in in-person and/or online programs from June 2019 to June 2020 (**Figure 1**). Results are expressed as percentages. Sixty nine respondents with an average age of 70.2 years (SD 8.4, range 47–88) yielded an overall response rate of 46%, which is considered adequate (41). Respondents were majority male (77%), Caucasian (94%) and college educated (74%). Eight percent identified as Hispanic or Latino. Of the 69 respondents, 62 attended pRSB pre-pandemic and 53 participated in at least one online program, 20 attended at least two online programs and seven participated in all three. Overall, 46 respondents attended vRSB, 17 attended vSG, and 24 participated in *Buddies*.

Depression and quality of life were also measured. Of 66 respondents who completed the PHQ-9, 22.7% of the scores were $\geq$9, which indicates moderate depression. This is below the norms reported in the literature for PWP (42). Of 61 completed PDQ-39's, scores averaged 21.4, which indicates better quality of life compared to normative data (43).

Self-Reported Symptomatology

Reported symptoms spanned motor, non-motor and neuropsychiatric categories. The most common symptoms were difficulty walking/gait impairment (43%), pain/aches/tingling/cramps (42%), and anxiety (52%) (**Figure 3**). Almost half reported faster perceived PD progression (41%) and worsening mood (43%). Feelings of loneliness/isolation were high (53%), despite most reporting having a good support system (87%). While 90% of respondents reported at least one new or worsening symptom since the start of the pandemic, participants attending online programs reported an average of 1.3 less new or worsening symptoms than those who only participated in pRSB pre-pandemic.

Practicability

Prior to the pandemic, an estimated 125 PWP regularly attended at least one pRSB per week. Attendance was not tracked for in person support groups for anonymity purposes. By the end of July 2020, an estimated 75 PWP were taking part in at least one virtual program. Virtual RSB averaged 34 participants for the high functioning class and 21 for the lower functioning class; vSG averaged 30 participants, and Buddies estimated 35 participants. This is in comparison to an estimated average of 20 people per pRSB class, where attendance was capped due to space limitations.

Barriers to participation in online programs were few and unique to each program with the most common barrier to vRSB being 'other' (ex: difficulty focusing) (48%), to vSG, 'not the same as in-person' (25%) and to Buddies, 'it would be awkward/I would have nothing to talk about' (27%) (**Figure 4**).

Satisfaction

Overall, perceived improvements in symptoms and mood, together with the majority of respondents reporting 'very satisfied' with each program, underscore satisfaction (**Figure 5**). Here results are presented according to program:

vRSB

The majority of vRSB respondents felt the program improved their motor symptoms (83%) and mood (74%), with many reporting they would continue with online classes post pandemic (59%). Satisfaction may also be measured by exercise compliance. Regarding weekly attendance, 62 people (89.9%) reported attending pRSB an average of 1.94 classes per week, whereas 45 people (65.2%) reported attending vRSB an average of 2.67 classes per week. Of the 44 people who reported weekly attendance to *both* pRSB and vRSB, the average increase in classes per week from pRSB to vRSB was 0.55; 59% (n=44) attended vRSB an average of 1.3 classes more per week than pRSB (an average of 1.3 classes).

vSG

The majority of vSG participants reported that the program improved mood (94%), reduced isolation (88%), and facilitated connections with friends and their community (81%). Information regarding COVID-19 relieved stress and anxiety in 63% of respondents.

Buddies

The majority of participants agreed that meeting with their buddy improved mood (83%) and reduced loneliness (68%). Over 75% reported they would continue meeting with their buddy post-pandemic. Qualitative feedback from respondents included, but was not limited to, the following:

> "*100% satisfied. He's a great kid and we learn from each other. Would love to continue.*"

> "*The support student I have now is really great. We discuss many topics and enjoy the depth of our conversations. Since my buddy is a first-year med, I hope to be connected with him for a long time.*"

> *"My buddies are wonderful, caring, empathetic young people. They have the right personal skills to be great doctors."*

DISCUSSION

In response to the COVID-19 pandemic, NYITCOM transitioned to an online platform for exercise (vRSB) and social support (vSG and *Buddies*) to maintain continuity of care for PWP. The results of a custom online observational survey found the online programs to be practicable, with minimal barriers to participation and high rates of satisfaction. Participants also reported perceived benefits relating to depression and QoL. This practicable and comprehensive online plan increases access to care and is currently ongoing in a hybrid format with the programs that have returned to in-person. The long-term plan is to sustain classes in a hybrid manner even after the pandemic has fully subsided.

Practicability & Barriers

A consistent number of participants and low number of barriers were found in the online classes, thus, attesting to their success and practicability. The literature supports these findings. Telemedicine platforms are a valid and practicable method for assessing PWP (3). When comparing a self-monitored home exercise program to a tele-coach assisted program in PWP, Lai et al. found participants in the tele-coach program had higher attendance (99%) compared to the self-monitored group (35%). More time exercising, especially at a higher intensity, was also found for the tele-coach participants (24), indicating the effectiveness of online exercise programs for PWP.

However, barriers to online programs exist. Older and less educated adults access the internet at a lower rate, 64 and 68% respectively, than younger adults (16). As a demographic, PWP are generally older and experience difficulties with technology that can be further impacted by motor and/or cognitive deficits (44). Despite this, internet access for the vRSB class was a barrier for only 9% of respondents, with little to no internet access problems for vSG or *Buddies*. This may be attributed to the participants in this study living in a suburban area with good internet access, high levels of education and having assistance from family members and/or caregivers. Transportation issues, distance, and weather have also been cited as barriers to exercise (16, 18, 45). Removing the need for travel may have contributed to the facilitation of attendance to online programs.

Satisfaction, Depression and Quality of Life

Benefits of online programs were underscored by high satisfaction, a perceived positive effect on PD symptoms, and exercise compliance. The findings agree with the literature. Online platforms for health have proven effective for remote diagnosis and treatment (46) including for PWP (3). When compared to in-person visits, telehealth has produced similar satisfaction, patient compliance and QoL (47, 48).

While PHQ-9 and PDQ-39 scores were not obtained prior to COVID-19 for which to compare, the number of PWP reporting depression and poor QoL is relatively low when compared to national averages. This may indicate that these programs and the tight-knit community adequately supported the PWP.

The Importance of Physical Activity: VRSB

Exercise is associated with slower progression of disease, and improved function, mobility, and improved QoL in PWP (49). However, quarantining during the pandemic may prevent PWP from an active lifestyle, which may already be impeded by pre-existing conditions (3). Group exercise, such as vRSB, using an online platform may be an alternative for managing motor and non-motor symptoms of PD, even post-pandemic. Through group exercise, social interactions and emotional support can be preserved in older adults, which is associated with improved self-efficacy, reduced risk of depression and all-cause mortality, and greater intrinsic motivation for moderate to vigorous physical activity (21, 48).

While RSB is a long-standing national program, to the authors' knowledge it has never before been employed online (38). The urgency of social distancing due to the COVID-19 pandemic resulted in lack of guidelines on how to deliver the classes in an online format, therefore, this may be one of the first studies to do so. Other institutions—such as the Michael J. Fox Foundation (50)—have begun to offer RSB instruction in an online format. This current study may provide valuable information to those institutions who seek to add an online RSB component to their programming.

The Psychological Importance of Social Connections: vSG and Buddies

Human connection is an innate and essential part of life. Diminished contact with others may be associated with lasting negative consequences on physical and mental health (51). High rates of comorbidity in PWP, including depression and anxiety (52), combined with elevated stress, social distancing, and lack of usual support systems during the pandemic created the potential for feelings of helplessness and isolation (28). Quarantining has been associated with negative psychological effects, especially in people with pre-existing poor mental health

(28). This may hold true for PWP due to depletion of dopamine. Dopamine in the mesolimbic circuit regulates the processing of emotion and motivation (53). Chronic stress may reduce dopaminergic neurons in the basal ganglia and worsen mental health, especially in PD, where dopamine is already deficient (54). The American Parkinson's Disease Association encourages PWP to manage stress and mental health by establishing and maintaining social connections (4, 55). Virtual support groups and *Buddies* programs addressed these issues.

The aims of vSG were to maintain social connections and to positively influence QoL (25, 31). Other aims included the provision of timely and accurate information about the pandemic (28, 40), thus providing a forum for participants to discuss concerns and fears regarding the pandemic and its potential impact on their health. The findings of the survey show that vSG helped decrease the effects of isolation, foster connections with others and improve mood; these findings reinforce existing literature (28).

NYITCOM's *Buddies* program was developed to provide companionship to offset the effects of isolation in PWP during the pandemic. The secondary aim was to provide osteopathic medical students with early patient exposure. The program was based on existing in-person Buddy programs that focused on student education and interactions with geriatric neurologic patients (56). These programs found benefits for students and patients alike. Participants reported a decreased sense of loneliness and improved mood through participation in the program. Anecdotally, as pairs became closer with one another, they discussed more personal issues regarding difficulties faced due to the COVID-19 pandemic. Some pairs added online games, such as chess, to their weekly conversations. Specific positive feedback from participants regarding their experience with *Buddies* may be interpreted as an indicator of success of the program.

Sustainability: Online-Programs Today

Once in-person programs resumed in the Spring of 2021, many participants expressed the desire to continue the online programs. With the return of in-person RSB classes, a new "blended" format was developed; an online component has been added to the in-person classes and are held synchronously for participants who find the online format more amenable to their needs. As high as 30% of boxers continue using the online format at this time. Both groups are able to see and interact with each other, thus keeping with the desire to encourage social bonding and support *via* group exercise. This same blended format is planned for our support groups once in-person meetings resume. Rock Steady Buddies has continued to be successful among students and PWP alike. Each semester PD participants are paired with a new Buddy with whom to build new relationships. The program has plans to continue and expand to include older adults from local nursing homes.

Implications for further research include investigating the sustainability of these programs beyond the pandemic. In addition, now that online programs have been found to be effective as well as convenient, together with advances in technology, the use of telehealth and telerehab platforms are likely to become a mainstay in healthcare. This program may serve as a model for other institutions to adopt not only for their population with PD, but other patient populations as well.

Limitations

Limitations and areas for improvement are addressed here. This was an observational study; therefore, no comparisons were made to pre-COVID-19 program conditions. The PHQ-9 and PDQ-39 are validated tools; however, the survey developed for this study, although based on the UPDRS Parts I and II, was not a validated survey, therefore, future studies may consider utilizing a validated tool. Since the survey was anonymous and completed online, objective measurements of PD severity and participant cognition were not included, therefore, reporting of symptomatology relied on respondents' self-reported scores. Potential response-bias — or more specifically, volunteer or self-selection bias — may have also been present; motivated individuals who enjoyed the programs may have responded to the survey at a higher rate than non-motivated individuals who did not enjoy the programs. Also, while a small subset of participants reported internet access as a barrier to participation, those who responded to the electronically distributed survey inevitably had adequate access to the internet while those with technology challenges may not have participated at all, thus potentially affecting the results. Lastly, results of this study cannot be generalized beyond the demographic group of educated, primarily male, Caucasian, PWP living in a suburban setting.

CONCLUSION

While the COVID-19 pandemic compromised standard interventions for PWP, it also created an opportunity to develop innovative approaches for alternative care models. The institution pivoted in-person programs to an online format tailored specifically to address the physical and mental wellbeing of PWP during a global pandemic. The practicability of vRSB, vSG, and *Buddies* programs are underscored by consistent attendance, limited number of barriers to participation, exercise compliance, and the high satisfaction, mood and QoL of participants. This suggests that these programs are beneficial for the physical and mental health of this PD community during the COVID-19 pandemic. Other healthcare and academic institutions may consider implementing similar programs to promote continuity of care for PWP and other aging populations during times of crises, and as part of best practices. Future directions include investigating the sustainability of online programs for PWP and for other patient populations beyond COVID-19.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board at New York Institute of Technology (BHS-1569). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, drafted the article or revised it critically for important intellectual content, gave final approval of the version of the article to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Retinal Nerve Fiber Layer Thickness and Associations With Cognitive Impairment in Parkinson's Disease

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Objective: This study intended to investigate whether retinal nerve fiber layer (RNFL) thickness could become a potential marker in patients with Parkinson's disease with cognitive impairment (PD-CI).

Methods: Fifty-seven PD patients and 45 age-matched healthy controls (HCs) were recruited in our cross-sectional study and completed optical coherence tomography (OCT) evaluations. PD with normal cognition (PD-NC) and cognitive impairment (PD-CI) patients were divided following the 2015 Movement Disorder Society criteria. RNFL thickness was quantified in subfields of the 3.0-mm circle surrounding the optic disk; while a battery of neuropsychiatric assessments was conducted to estimate the Parkinsonism severity. General linear models and one-way ANOVA were adopted to assess RNFL thickness between subgroups with different cognitive statuses; logistic regression analyses were applied to determine the relation between RNFL and PD-CI cases.

Results: Compared with HCs, more thinning of the RNFL was observed in the inferior and temporal sectors in PD patients, especially in the PD-CI group. Inferior RNFL thickness was reduced in PD-CI compared with PD-NC patients. Logistic regression analysis found that inferior RNFL thickness was independently associated with PD-CI cases (odds ratio = 0.923, $p = 0.014$). Receiver operating characteristic analysis showed that the RNFL-involved combined model provided a high accuracy in screening cognitive deficiency in PD cases (area under the curve = 0.85, $p < 0.001$).

Conclusion: Reduced RNFL thickness especially in the inferior sector is independently associated with PD-CI patients. Our study present new perspectives into verifying possible indicators for neuropathological processes or disease severity in Parkinsonians with cognitive dysfunction.

Keywords: Parkinson's disease, cognitive impairment, retinal nerve fiber layer, indicator, optical coherence tomography

INTRODUCTION

Parkinson's disease (PD) is a highly prevalent neurodegenerative disorder worldwide with characteristic motor dysfunctions including bradykinesia, stiffness and resting tremor (Tolosa et al., 2021). Ours and other studies have indicated that some indicators such as neuroinflammatory, neuroimaging mediators and serum neurofilament light chain are usually applied as markers in diagnosing and evaluating the progression and severity of PD and PD Syndromes (Wang et al., 2020, 2021; Yang et al., 2020; Zhu et al., 2020, 2021a; Bestwick et al., 2021; Liu et al., 2021; Quadalti et al., 2021). Identifying potential biomarkers for early diagnosis and assessment is one of the research hotspots in the field of PD (Avenali et al., 2020; Papuć and Rejdak, 2020; Ma et al., 2021). Interestingly, recent increasing evidence indicates that dopamine (DA), as a neurotransmitter, plays a critical role in the retina for visual processing (Archibald et al., 2009; Tsokolas et al., 2020), and previous studies found phosphorylated or misfolded alpha-synuclein accumulation in retinal cells and progressive retinal degeneration in PD patients. These findings imply that structural or functional deficiency of the retina may reflect pathological deterioration in the brain, and visual dysfunctions, especially retinal impairment, in PD might be associated with disease severity and reflected in neuropathogenesis. Whether retinal changes in PD could be used as a potential marker to evaluate severity remains unknown.

Previous studies have demonstrated that multiple disease-specifically structural changes have been verified in the retinas of patients with neurological diseases, for instance, Huntington's disease, Alzheimer's disease (AD) and PD. Optical coherence tomography (OCT), a well-developed imaging tool, offers unique high-definition transverse scanning and stereoscopic volume measures of the retina. Several lines of evidence have shown that retinal thickness assessment could provide multiple parameters in distinguishing healthy subjects from those with neurodegenerative diseases (Tsokolas et al., 2020). Previous studies also revealed that the retinal nerve fiber layer (RNFL), macula and fovea thickness in PD cases were markedly reduced compared with that of healthy participants (Chrysou et al., 2019; Tsokolas et al., 2020; Zhou et al., 2021). Other studies also described the connection between the RNFL loss and the disease progression (Garcia-Martin et al., 2014; Jimenez et al., 2014), further indicating the potential application of RNFL thickness as a marker in the clinical evaluation of PD.

However, to our knowledge, very few studies have evaluated OCT-based retinal changes in PD patients with cognitive impairment (CI), which is one of the non-motor symptoms in PD at the mid-late stage (Aarsland et al., 2017; Orgeta et al., 2020; Yuan et al., 2020). Exploring potential markers for CI in PD is critical to better comprehend its pathogenesis and monitor disease progression (Schrag et al., 2017; Reyes-Perez and Bandres-Ciga, 2021). Considering that the potential relation between RNFL degeneration and cognitive deterioration in PD remains undiscovered, it would be valuable and fascinating to investigate whether RNFL thickness could become a potential indicator for CI in PD.

In our study, we (1) conducted a well-ordered data collection from PD patients and healthy controls; (2) characterized their OCT examination and undertook cognitive performance; and (3) evaluated the associations between RNFL parameters and Parkinsonian severity. Last, we hypothesized that peripapillary RNFL thinning in a specific sector could be used as a potential indicator for decreased cognition in PD, and the RNFL-involved model might be effective in distinguishing PD cases with normal cognition from participants with poor cognition.

MATERIALS AND METHODS

Study Design and Participants

From July 2020 to May 2021, 57 PD patients and 45 age- and sex-matched healthy controls were prospectively recruited in our cross-sectional observational study from Zhujiang Hospital, Southern Medical University in Guangzhou, P. R. China. The PD patients diagnosed by experienced neurologists specialized in neurodegenerative disorders, met the 2015 Movement Disorder Society criteria (Postuma et al., 2015), and underwent extensive clinical examination. Healthy controls (HCs) lacking a history of neurological or ophthalmological disease were enrolled from the Medical Examination Center of our hospital. The exclusion criteria were listed as below: (1) presence of incapacity owing to neuropsychiatric comorbidities such as severe cerebral ischemia, psychosis, Alzheimer's disease (AD), multiple sclerosis or epilepsy; (2) presence of a history of eye trauma, ocular surgery, glaucoma, retinopathy, fundus disease, severe ocular media opacity that hampers the acquisition of high-quality OCT images, and other comorbid ophthalmic pathologies that might influence retinal thickness; (3) medical drugs or severe somatic diseases that may interfere with the neuropsychiatric assessment (e.g., malignancy, severe heart failure, end-stage renal disease, severe anemia); and (4) inability to cooperate with researchers and complete the whole study.

Parkinson's disease patients were categorized into two groups, comprising the PD with normal cognition (PD-NC) and PD with cognitive impairment (PD-CI), on the basis of MDS Task Force criteria for mild cognitive impairment (PD-MCI) and Parkinson's disease dementia (PDD) and previously published studies (Goldman et al., 2017). In brief, the patients who met clinically established PD diagnosis, presented cognitive decline reported by either the patient, informant or clinician, and impairment on a scale of global cognitive abilities (*i.e.*, the Montreal Cognitive Assessment [MoCA]) without impaired functional independence in daily life were classified as PD-MCI (Litvan et al., 2012); the patients who presented a dementia syndrome developing based on the established PD diagnosis, more than one cognitive domain impairment, functional deficits in daily life, typical cognitive features and behavioral symptoms were classified as PDD (Emre et al., 2007). PD patients who either fulfilled the MDS PD-MCI or PDD criteria were classified together as PD-CI in the current study; PD cases without meeting the MDS PD-MCI criteria and dementia were designated PD-NC.

Standard Protocol Approvals and Patient Consents

The Ethics Committee of Zhujiang Hospital, Southern Medical University authorized this study (NO: 2020-KY-004-02) and it was performed following the 1999 National Institutes of Health Human Subjects Policies and Guidance and the principles of the Declaration of Helsinki. Every participant was required to provide a written consent for this study to allow investigators to measure their clinical status.

Clinical Evaluation

All PD patients underwent comprehensive neurological evaluation. The Unified Parkinson's Disease Rating Scale (UPDRS) and the modified Hoehn & Yahr scale (H&Y) were applied to determine the Parkinsonism severity and progression (Hoehn and Yahr, 1967; Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, 2003). The Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) were applied to estimate the cognitive function of PD patients (Hoops et al., 2009; Dalrymple-Alford et al., 2010). All the above scales were administered in a blinded manner. Information on sex, age, education, levodopa equivalent daily dosage (LEDD), and disease duration was recorded. Specifically, PD cases were categorized into various subtypes in terms of their parkinsonian symptoms: tremor-dominant (TD) subtype, akinetic rigid/postural instability gait difficulty (AR/PIGD) subtype and mixed subtype according to previously published studies (Marras et al., 2020; Tang et al., 2021; von Coelln et al., 2021).

Optical Coherence Tomography

We used Spectralis OCT machines in the ophthalmology department of Zhujiang Hospital, Southern Medical University, to obtain the parameters of the peripapillary RNFL. An experienced technician was responsible for performing all the OCT scans and choosing the images of best quality. The diagrammatic map of the OCT examination of participants in the current study is present in **Figure 1**. The peripapillary region surrounding the optic disk was segmented into four parts, being, superior (S), inferior (I), temporal (T) and nasal (N) sectors. The global (G) RNFL thickness in **Figure 1C** represents the average thickness of these four sectors. The superior and inferior sectors were further divided into temporal-superior (TS), nasal-superior (NS), temporal-inferior (TI) and nasal-inferior (NI) subregions (**Figure 1C**). In our study, the RNFL thickness of both eyes in every participant was recorded; then the average of specific RNFL thickness from both eyes of one participant was used in the following analyses.

Statistical Analysis

Participants with missing necessary data were removed from our study before the final analyses. We conducted a chi-square (χ^2) test to evaluate differences in gender distribution and one-way analysis of variance (one-way ANOVA) to determine age differences across the three groups (HCs, PD-NC, and PD-CI). Student's *t* test or Wilcoxon rank-sum/Mann–Whitney *U* test was adopted to compare the differences or distributions of parameters between the PD-NC and PD-CI groups based on whether they met a normal distribution or were ranked data.

For OCT measurements, we performed one-way ANOVA and *post hoc* Bonferroni-corrected analysis to verify differences in RNFL thickness of different sectors among the three groups listed above. A general linear model was used for further identifying adjusted RNFL thickness between PD-NC and PD-CI patients. Logistic regression analyses were conducted to assess the relation between specific RNFL thickness and impaired cognition in PD. E-values were generated from sensitivity analysis to evaluate the confounding by potential uncontrolled or unmeasured confounders (VanderWeele and Ding, 2017). Receiver operating characteristic (ROC) analysis for RNFL and RNFL-related model was performed to further assess the efficacy of RNFL thickness in identifying cognitive deficiency in PD patients. Binary logistic regression analysis and step forward selection of independent variables were applied to produce the combined models, where the dependent variable was group (PD-CI/PD-NC) and the independent variables were potential influencing factors. The Hosmer–Lemeshow test was conducted to assess the model fitness. *P* less than 0.05 was accepted as statistically significant. Statistical Product and Service Solutions 23.0 was applied in all these statistical analyses.

RESULTS

Demographic and Clinical Characteristics

The demographic and clinical data are reported in **Table 1**. Compared with the PD-NC group, the PD-CI patients showed less educated years and more scores of UPDRS-III, MMSE and MoCA (**Table 1**).

Comparison of OCT Measurements Among PD-NC and PD-CI Patients and HCs

One-way ANOVA showed that the thickness of the global RNFL, inferior RNFL and temporal RNFL was markedly reduced in PD-CI cases compared with HCs (**Figures 2B,C** and **Table 2**). Only the inferior RNFL showed significant thinning in the PD-CI group compared with the PD-NC group (126.87 ± 12.53 *vs.* 139.33 ± 11.75, $p = 0.001$, **Figure 2B** and **Table 2**), indicating a potential specific association between inferior RNFL thickness and Parkinsonian cognitive impairment. Similar findings were identified in the temporal-inferior subregion but not in the nasal-inferior subregion (**Figures 2E,F** and **Table 2**).

To further investigate the RNFL thickness in PD patients with different cognitive statuses, we performed general linear model analysis. The thickness of the inferior RNFL and its subregion temporal-inferior RNFL was substantially thinner in PD-CI patients than that of PD-NC group (*e.g.*, inferior RNFL:

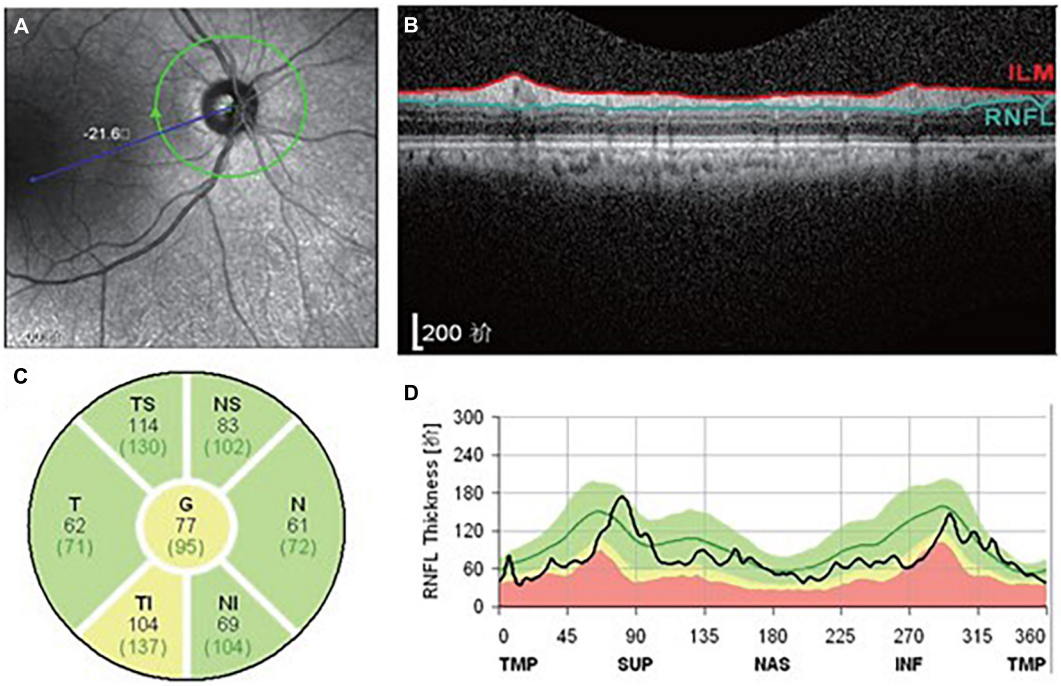

FIGURE 1 | Diagrammatic map revealing the OCT examination of participants in the present study. **(A)** The appearance of the optic nerve. **(B)** Transverse image of RNFL. **(C)** Segmentation of RNFL. **(D)** RNFL thickness map.

TABLE 1 | Demographic and clinical characteristics of the study subjects.

Variables †	Controls (*n* = 45)	PD			*p* ‡
		All (*n* = 57)	PD-NC (*n* = 23)	PD-CI (*n* = 34)	
Demographic					
Age, years	61.42 ± 9.75	63.67 ± 9.27	60.52 ± 8.68	65.79 ± 9.18	0.059
Male sex, No. (%)	21 (46.7%)	34 (59.6%)	12 (52.2%)	22 (64.7%)	0.276
Education, years	/	9 (6)	9 (3)	6 (4)	0.009**
Clinical					
H&Y staging	/	2.50 (0.5)	2.00 (0.5)	2.50 (1.0)	0.325
Disease duration, months	/	36 (54)	36 (36)	48 (75)	0.189
LEDD, mg	/	511.50 (242.75)	436.50 (461.50)	515.25 (177.00)	0.083
PD-subtype, No. (%)					0.857
AR/PIGD subtype		34 (59.6%)	14 (60.9%)	20 (58.8%)	/
TD subtype		7 (12.3%)	2 (8.7%)	5 (14.7%)	/
Mixed subtype		16 (28.1%)	7 (30.4%)	9 (26.5%)	/
UPDRS-total	/	46.0 (26.0)	37.0 (26.0)	49.5 (29.0)	0.016*
UPDRS-I	/	4.0 (3.0)	3.0 (3.0)	4.0 (3.0)	0.137
UPDRS-II	/	15.0 (9.0)	13.0 (8.0)	16.0 (9.0)	0.022*
UPDRS-III	/	25.0 (16.0)	22.0 (17.0)	26.5 (19.0)	0.037*
UPDRS-IV	/	3.0 (4.0)	3.0 (4.0)	3.50 (5.0)	0.094
MMSE	/	25.0 (4.0)	28.0 (2.0)	24.5 (3.0)	< 0.001***
MoCA	/	22.5 (8.0)	24.5 (2.0)	19.5 (7.0)	< 0.001***

‡*The continuous variables are presented as mean ± standard deviation or median with interquartile range according to normality test; the categorical variables are presented with percentages.* ‡*From Chi-square (χ^2) test for gender and one-way ANOVA for age differences across three groups (healthy controls, PD-NC and PD-CI); Wilcoxon rank-sum/Mann-Whitney U test for education, H&Y staging, disease duration, LEDD, UPDRS, MMSE and MoCA differences between PD-NC and PD-CI group; Chi-square (χ^2) test for PD-subtype difference between PD-NC and PD-CI group. PD, Parkinson's disease; PD-NC, PD with normal cognition; PD-CI, PD with cognitive impairment; LEDD, levodopa equivalent daily dosage; AR/PIGD, akinetic-rigid/postural instability gait difficulty; TD, tremor-dominant; UPDRS: Unified Parkinson's Disease Rating Scale; H&Y, modified Hoehn and Yahr staging scale; MMSE, mini-mental state examination; MoCA, Montreal Cognitive Assessment.*

TABLE 2 | Comparisons of retinal nerve fiber layer among different groups based on one-way ANOVA.

RNFL (μ m)	Controls	PD-NC	PD-CI	*P*	*p*	*p*
	Group A	Group B	Group C	A *vs*. B	A *vs*. C	B *vs*. C
Global	107.02 ± 6.55	104.48 ± 9.07	98.50 ± 9.95	0.719	< 0.001***	0.029*
Superior	134.82 ± 10.83	128.37 ± 16.81	129.57 ± 15.42	0.221	0.301	1.000
Inferior	138.98 ± 13.31	139.33 ± 11.75	126.87 ± 12.53	1.000	< 0.001***	0.001**
temporal	82.31 ± 12.65	76.83 ± 12.01	70.78 ± 16.09	0.369	0.001**	0.321
Nasal	73.29 ± 12.14	73.63 ± 13.53	67.79 ± 14.62	1.000	0.217	0.323
sub-region:						
temporal-superior	149.04 ± 17.13	142.07 ± 16.15	140.62 ± 20.64	0.412	0.132	1.000
nasal-superior	121.33 ± 16.33	114.52 ± 20.09	117.85 ± 19.49	0.449	1.000	1.000
temporal-inferior	158.22 ± 17.68	160.46 ± 14.94	140.79 ± 18.97	1.000	< 0.001***	< 0.001***
nasal-inferior	120.14 ± 16.22	117.98 ± 20.69	113.01 ± 19.58	1.000	0.276	0.963

** p < 0.05, ** p < 0.01, *** p < 0.001. RNFL: retinal nerve fiber layer; PD: Parkinson's disease; PD-NC: PD with normal cognition; PD-CI: PD with cognitive impairment.*

TABLE 3 | General linear model analysis in the RNFL levels in PD patients with different cognitive status.

RNFL	Global RNFL (μ m)		*p* †	Inferior RNFL (μ m)		*p* †
	PD-NC	PD-CI		PD-NC	PD-CI	
(A)						
Unadjusted	104.48 ± 9.07	98.50 ± 9.95*	0.025	139.33 ± 11.75	126.87 ± 12.53***	<0.001
Adjusted	103.16 ± 9.63	99.39 ± 9.48	0.166	138.03 ± 12.41	127.75 ± 12.22**	0.005
RNFL	**Temporal-inferior RNFL (μ m)**		***p*** †	**Nasal-inferior RNFL (μ m)**		***p*** †
	PD-NC	**PD-CI**		**PD-NC**	**PD-CI**	
(B)						
Unadjusted	160.46 ± 14.94	140.79 ± 18.97***	<0.001	117.98 ± 20.69	113.01 ± 19.58	0.363
Adjusted	159.64 ± 18.20	141.34 ± 17.92**	0.001	116.20 ± 21.29	114.22 ± 20.96	0.740

†*p values were produced from analysis of covariance, after adjusting for pairwise comparisons. The covariates comprised age, sex, H&Y staging, LEDD, disease duration and PD-subtype. *p < 0.05, **p < 0.01, ***p < 0.001, vs. PD-NC Group.*
Abbreviations: RNFL: retinal nerve fiber layer; PD: Parkinson's disease; PD-NC: PD with normal cognition; PD-CI: PD with cognitive impairment.

TABLE 4 | Logistic regression analysis for the relation between RNFL and the impaired cognition in PD patients.

Global RNFL	Cognitive Impairment (CI)		*p* †	Inferior RNFL	Cognitive Impairment (CI)		*p* †
	OR	95% confidence intervals			OR	95% confidence intervals	
(A)							
Unadjusted	0.935*	0.897 – 0.994	0.032	Unadjusted	0.922**	0.877 – 0.970	0.002
Adjusted	0.962	0.893 – 1.037	0.314	Adjusted	0.923*‡	0.865 – 0.984	0.014
Temporal-inferior RNFL	**Cognitive Impairment (CI)**		***p*** †	**Nasal-inferior RNFL**	**Cognitive Impairment (CI)**		***p*** †
	OR	**95% confidence intervals**			**OR**	**95% confidence intervals**	
(B)							
Unadjusted	0.932**	0.894 – 0.973	0.001	Unadjusted	0.987	0.961 – 1.015	0.358
Adjusted	0.923**§	0.870 – 0.978	0.007	Adjusted	0.991	0.959 – 1.023	0.558

†*the covariates included age, sex, disease duration, H&Y staging, LEDD, PD-subtype, education level, and UPDRS score.* ‡*the E-value generated from sensitivity analysis for OR and upper limit of confidence interval is 1.25 and 1.14, respectively.* §*the E-value for OR and upper limit of confidence interval is 1.25 and 1.17, respectively. *p < 0.05, **p < 0.01. RNFL, retinal nerve fiber layer; PD, Parkinson's disease; CI, cognitive impairment; OR, odds ratio.*

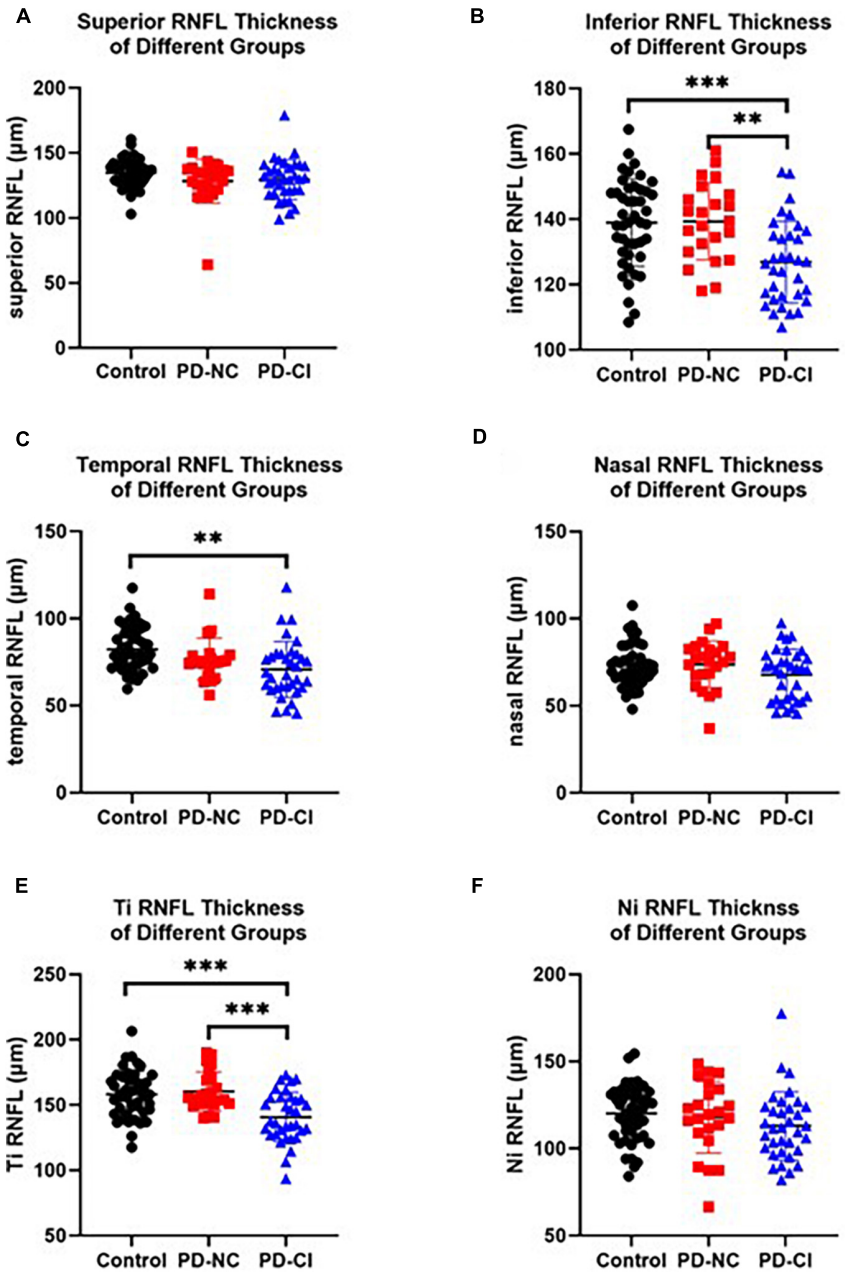

FIGURE 2 | RNFL thickness in PD patients with different cognitive conditions and healthy subjects. The scatter plots accompanied by the mean ± SD present the peripapillary RNFL thickness in healthy controls, PD-NC and PD-CI patients in inferior **(A)**, inferior **(B)**, temporal **(C)**, nasal **(D)**, Ti (temporal-inferior, **E**) and Ni (nasal-inferior, **F**) sectors. $^{**}p < 0.01$, $^{***}p < 0.001$.

127.75 ± 12.22 *vs.* 138.03 ± 12.41, $p = 0.005$, **Table 3**) after adjusting for other confounders.

Logistic Regression and Correlation Analyses Between RNFL Thickness and Cognitive Impairment

Logistic regression analyses were implemented to further estimate the relation between RNFL thinning and cognitive deficiency in participants with PD. By means of adjusting for possible confounders including sex, age, disease duration, H&Y staging, LEDD, PD subtype, education level, and UPDRS score, inferior RNFL was independently associated with decreased cognition in PD (odds ratio [OR] = 0.923 for every one-micrometer increase, 95% confidence interval 0.865–0.984, $p = 0.014$; **Table 4A**). Similar findings were confirmed in the logistic regression analysis of temporal-inferior RNFL thickness (**Table 4B**). In contrast, no such associations were identified

between superior, temporal and nasal RNFL thickness and cognitive impairment (**Supplementary Table 1**). Correlation analysis confirmed a positive correlation between inferior RNFL thickness and MMSE/MoCA scores (**Supplementary Table 2**).

Discriminative Efficacy of the RNFL-Involved Model in the Identification of Parkinsonian Cognitive Impairment

ROC analysis was applied to investigate whether RNFL thickness could offer reliable differentiation between PD cases with good cognition and the others with impaired cognition. We found that among the several sectors, only inferior and temporally inferior RNFL thickness exhibited a moderate accuracy in distinguishing PD-CI from PD-NC patients (*e.g.*, AUC of temporal-inferior RNFL thickness: 0.78, $p < 0.001$, **Figure 3A**; cutoff thickness: 138.8 μm, sensitivity: 52.94%, specificity: 100%).

Then, after stepwise forward selection of demographic, clinical and OCT variables, temporal-inferior RNFL thickness, education level and UPDRS-III were screened out in logistic regression analysis to compose the discriminative model (**Supplementary Table 3**). This combined model revealed higher accuracy for discrimination than RNFL thickness alone (AUC = 0.85, $p < 0.001$, **Figure 3B**; cutoff value: 0.56 in the algorithm of the model, sensitivity: 88.24%, specificity: 69.57%).

DISCUSSION

The present study showed an independent association between peripapillary RNFL thinning and CI in PD. Our findings presented several original observations. First, the RNFL thickness of specific inferior region was declined in PD-CI patients compared with PD-NC subjects by adjusting for confounders, including sex, age, H&Y staging, disease duration, LEDD and PD subtypes. Second, we identified that inferior RNFL thickness was closely associated with CI in PD with logistic regression analysis, independent of various other factors. Third, our study indicated that the RNFL-involved model might be useful to discriminate PD patients with normal cognition from those with impaired cognition. This study suggests that the inferior RNFL thickness may become a possible marker for parkinsonian cognitive impairment.

Recently increasing evidences show that neuroimaging or neuroinflammatory markers are closely related with the pathological neurodegeneration in PD (Lian et al., 2020; Yang et al., 2020; Anandhan et al., 2021; Li et al., 2021; Liu et al., 2021; Que et al., 2021; Wang et al., 2021; Zhu et al., 2021b). These humoral inflammatory or imaging biomarkers may provide valuable information for early identification, differential diagnosis, assessment of severity and even prognosis prediction for PD patients (Avenali et al., 2020; Beheshti et al., 2020). As a window to the brain, the retina may consistently suffer inflammation and degeneration, and provide potential neuroimaging, or, neuroinflammatory markers (Ramirez et al., 2017; Fernández et al., 2021). The uncovering of the disease-specific biomarker α-synuclein accompanied by the retinal progressive degeneration further emphasizes the potential role of the retina in the pathological process or pathogenesis of PD (Adam et al., 2013; Bodis-Wollner, 2013; Bodis-Wollner et al., 2014; Ortuno-Lizaran et al., 2018). One OCT study found thinner RNFL thickness of the inferior quadrant of PD cases than that of healthy subjects, with the inferotemporal area being the thinnest region (Inzelberg et al., 2004). Ahn and his colleague observed RNFL thinning in the inferior and temporal 2.22-mm sectors in drug-naive patients with PD (Ahn et al., 2018). Some meta-analyses further summarized a remarkable loss of the peripapillary RNFL in PD patients, with one article describing an exception for the nasal sector (Chrysou et al., 2019; Zhou et al., 2021). Consistent with previous studies, we found evident peripapillary RNFL thinning particularly in the inferior and temporal sectors in PD cases (**Table 2** and **Figures 2B,C**).

Strikingly, RNFL thinning in the current study was more significant in PD-CI cases than in PD-NC cases (**Table 2** and **Figure 2**), implying that patients with PD-CI may suffer more severe retinal degeneration. General linear model analysis further verified this hypothesis and showed a remarkable decline in the RNFL thickness of the inferior sector and its temporal-inferior subregion in PD-CI subjects compared with the PD-NC subjects (**Table 3**). Few studies, as we know, have explored OCT parameters especially in individuals suffering from Parkinsonian disease with cognitive impairment. Yıldız et al. described significant parallel association between MMSE-recall score and RNFL-right in PD in a cross-sectional study (Yıldız et al., 2019). Other compelling evidence about OCT investigations on cognitive dysfunction emerged mostly from studies in mild cognitive impairment or AD, demonstrating a reduction of the RNFL thickness surrounding the optic papilla, particularly in the superior and inferior quadrants (Doustar et al., 2017; Kashani et al., 2021). This current study observed a different changing pattern showing a thickness loss in specific inferior RNFL in PD-CI cases (**Tables 2**, **3** and **Figure 2B**), implying that the inferior RNFL, to some extent, is more likely to be injured than the other three peripapillary sectors in PD cases with CI. Consequently, the pathological mechanisms underlying the specificity of inferior RNFL thinning in PD patients with CI have become an interesting question.

Evidences from previous studies have indicated that the aggregation of phosphorylated α-synuclein and its subsequent DA loss within the retina may be the primary cause of visual dysfunctions including reduced visual acuity, hallucinations and abnormal spatial contrast sensitivity in individuals with PD (Jackson and Owsley, 2003; Hamedani and Willis, 2020; Mohana Devi et al., 2020). These retinal alterations suggest simultaneous changes in the brain (Kashani et al., 2021). Another study proposed that neurodegenerative pathology in the central nervous system (CNS) may cause retrograde degeneration toward the axon and related soma of retinal ganglion cells (Peng et al., 2020). These studies strongly implied that the specific thinning of the peripapillary RNFL may be triggered by local disease-specific protein inclusions. Similar studies showed that Aβ plaques with concurrent neuronal degeneration were substantial in the superior and inferior retinal quadrants in

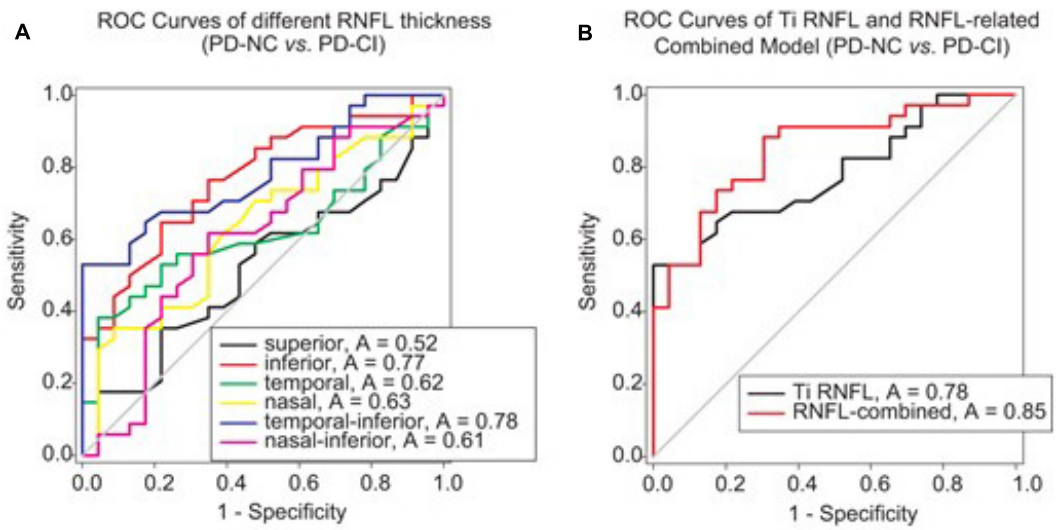

FIGURE 3 | ROC analysis to assess the validity of RNFL thickness or RNFL-involved models for differentiating PD patients with different cognitive conditions. **(A)** The ROC curves of RNFL thickness from different peripapillary sectors are shown. The AUCs of RNFL thickness in the inferior and temporal-inferior sectors were 0.77 ($p = 0.001$) and 0.78 ($p < 0.001$), respectively, for discriminating between PD-NC and PD-CI cases. **(B)** The RNFL-involved combined model for differentiating PD-CI from PD-NC patients comprised three variables, namely Ti (temporal-inferior) RNFL thickness, education level and UPDRS-III. The AUC was 0.85 for this model ($p < 0.001$). Note that the RNFL-involved combined model was generated from the logistic regression analysis in **Supplementary Table 3**.

cases with AD (Koronyo et al., 2017). Since there is a partial overlap of the pathological abnormalities among varieties of neurodegenerative disorders such as AD and PD (Aarsland et al., 2017; Kotagal et al., 2018; Ghadery et al., 2020), the vulnerability of inferior or temporal peripapillary RNFL in PD-CI (shown in **Tables 2**,**3**) may suggest more misfolded protein aggregation in these retinal segments, which should be addressed in future studies (Doustar et al., 2017).

Logistic regression analyses were implemented to further investigate the relation between RNFL thickness and cognitive impairment. It showed that inferior and temporal-inferior thickness was associated with decreased cognition in PD, independently of various risk factors for parkinsonian cognitive deterioration including age, sex, H&Y staging, levodopa usage, disease duration, akinetic-rigid/postural instability gait difficulty (AR/PIGD) phenotype, education level and UPDRS score (**Table 4**; Vasconcellos and Pereira, 2015; Aarsland et al., 2017; Baiano et al., 2020). Meanwhile, inferior RNFL thickness was positively correlated with MoCA and MMSE scores (**Supplementary Table 2**). Previous studies have implied that the retinal thinning correlated with disease duration or parkinsonian severity as measured by UPDRS or H&Y staging (Garcia-Martin et al., 2014; Jimenez et al., 2014). However, few studies declared the relationship between retinal thinning and parkinsonian cognitive deficiency. Thus, we provided an interesting finding to indicate inferior RNFL thickness as an independent marker in PD-CI patients.

Finally, the discriminative efficacy of retinal thinning for parkinsonian cognitive impairment was investigated. The RNFL thickness of the inferior sector, especially the temporal-inferior subregion, exhibited a moderate accuracy in differentiating PD-CI from PD-NC patients (**Figure 3A**); the RNFL-involved model revealed a higher accuracy in distinguishing PD-CI from PD-NC patients in comparison to temporal-inferior RNFL thickness alone (**Figure 3B**) when three variables (i.e., temporal-inferior RNFL thickness, education level and UPDRS-III) were screened out in this model. This implies that even though various demographic and clinical variables have been documented as hazard factors for cognitive deficiency in PD, inferior RNFL thickness could still become a possible indicator for cognitive impairment in PD (Vasconcellos and Pereira, 2015; Guo et al., 2019; Baiano et al., 2020).

The first limitation in our investigation arises from the relatively small sample size, though the statistical power is sufficient. Besides, due to this relatively small sample, we did not specifically divide PD-CI patients into PD-MCI and PDD groups. Thus, the disease-specific changing pattern of RNFL thinning in parkinsonian cognitive deterioration deserves further investigation. Given the trend of inferior RNFL thickness with increasing cognitive impairment in PD at a cross sectional level, longitudinal follow-up is needed to determine inferior RNFL thickness changes over time and to offer insight into predictors of cognitive deterioration in PD. A previous study found the inner retinal layers suffered more obvious thinning in PD patients with long disease duration (Garcia-Martin et al., 2014). Another study reported a regression equation that could predict the UPDRS score with using RNFL thickness as an independent variable (Jimenez et al., 2014). From the perspective of cognition, whether RNFL be used to predict cognitive impairment when a PD patient still has normal cognition at early stage remains an unsolved question. Thus, the advantage and significance of our study is that we first provide additional evidence to show the relation between RNFL thinning and cognitive impairment in PD cases, and further present new perspectives into verifying

possible predictors for parkinsonian cognitive deterioration in future longitudinal studies.

CONCLUSION

In brief, we confirmed that inferior RNFL thickness was specifically decreased in PD patients with cognitive impairment compared with those with normal cognition; RNFL thinning of the peripapillary inferior sector is a possible indicator of decreased cognition in PD. Our data further indicate the integral roles of retinal degeneration in the pathophysiological mechanisms underlying cognitive deficiency in PD. Large PD cohorts and longitudinal studies are needed to verify our results. Further studies are encouraged to reveal more precise features of peripapillary RNFL thinning in various PD subgroups (e.g., PD-MCI versus PDD; PD-MCI single-domain versus PD-MCI multiple-domain) and PD-plus.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Ethics Committee of Zhujiang Hospital, Southern Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZC, XW, SZ, and QW conceived and designed the study. ZC, FX, HL, LZ, and FY performed the study. XL and LS revised the article for intellectual content. XW and ZC performed data statistics and analysis. ZC, XW, and QW wrote the article. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.832768/full#supplementary-material

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REVIEW
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Monogenetic Forms of Parkinson's Disease – Bridging the Gap Between Genetics and Biomarkers

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The therapy of neurodegenerative diseases such as Parkinson's disease (PD) is still limited to the treatment of symptoms and primarily aimed at compensating for dopaminergic hypofunction. Numerous disease-modifying therapies currently in the pipeline attempt to modify the underlying pathomechanisms. In recent decades, the results of molecular genetics and biomarker research have raised hopes of earlier diagnosis and new neuroprotective therapeutic approaches. As the disease-causing processes in monogenetic forms of PD are better understood than in sporadic PD, these disease subsets are likely to benefit first from disease-modifying therapies. Recent studies have suggested that disease-relevant changes found in genetically linked forms of PD (i.e., PARK-LRRK2, PARK-GBA) can also be reproduced in patients in whom no genetic cause can be found, i.e., those with sporadic PD. It can, therefore, be assumed that as soon as the first causal therapy for genetic forms of PD is approved, more patients with PD will undergo genetic testing and counseling. Regarding future neuroprotective trials in neurodegenerative diseases and objective parameters such as biomarkers with high sensitivity and specificity for the diagnosis and course of the disease are needed. These biomarkers will also serve to monitor treatment success in clinical trials. Promising examples in PD, such as alpha-synuclein species, lysosomal enzymes, markers of amyloid and tau pathology, and neurofilament light chain, are under investigation in blood and CSF. This paper provides an overview of the opportunities and current limitations of monogenetic diagnostic and biomarker research in PD and aims to build a bridge between current knowledge and association with PD genetics and biomarkers.

Keywords: genetic, biomarkers, Parkinson's disease, alpha-synuclein, LRRK2

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INTRODUCTION

Parkinson's disease (PD) [sporadic (sPD) and (mono)genetic forms of PD (gPD)] represents a heterogeneous group of disorders with the pathophysiological shared end of a dopaminergic deficit. Therapy of PD is still limited to the treatment of symptoms and is primarily aimed at compensating for dopaminergic hypofunction. Accurate diagnosis of PD according to the underlying pathophysiology is important because of current and future treatment options. In recent years, many efforts have been made to identify specific and sensitive biomarkers (Parnetti et al., 2019;

Lawton et al., 2020). Because of its proximity to neuronal structures, cerebrospinal fluid (CSF) is, of course, the most promising liquid biomarker for neurodegenerative diseases. Nevertheless, blood, saliva, skin biopsies, and urine also appear to be good candidates as they are easily accessible and less invasive. Biomarkers from body fluids, skin biopsies, or imaging studies have the advantage of identifying the risk for future PD, diagnosing PD early, and monitoring disease progression, and can serve to monitor possible treatment success in clinical trials. Hence, biomarkers should also be able to distinguish between different entities of neurodegenerative diseases [e.g., sPD vs. gPD vs. atypical Parkinson's syndromes (aPD)] to decrease the number of false-positive diagnosed patients. An unmet need for future neuroprotective trials in neurodegenerative diseases is an objective parameter such as biomarkers with high specificity and sensibility for the diagnosis and course of the disease. Promising examples in PD, such as alpha-synuclein species, lysosomal enzymes, markers of amyloid and tau pathology, and neurofilament light chain, are under investigation in the blood and CSF (Parnetti et al., 2019). Unfortunately, it has not been possible to date to implement a robust biomarker in the early diagnosis or follow-up of PD. One reason is that biomarker profiles vary from patient to patient due to the great heterogeneity of the disease.

In contrast to sPD, in which the etiology remains elusive for most cases, gPD offer the possibility of better understanding the cause of the disease. Many autosomal dominant and recessive genes have been found since the first description of *SNCA* as a genetic cause of PD in 1997 (Polymeropoulos et al., 1997). The clinical symptoms between sPD and a monogenetic form are similar in most cases. However, since the course of PD can differ greatly from individual to individual, the question arises whether the etiological heterogeneity might have different causes. Examples include the tremor-dominant or akinetic rigid subtypes of sPD or the early cognitive involvement in some patients with PD. The results of molecular genetics and biomarker research have raised hopes of resolving these unanswered questions in PD and finding new neuroprotective therapeutic approaches. As the disease-causing processes in gPD are better understood than in sPD, patients with these subsets of the disease are likely to benefit first from disease-modifying therapies. A synergistic effect between research on monogenetic forms of the disease and sPD is also likely. Recent studies have suggested that disease-relevant changes found in genetically linked forms of PD (i.e., PARK-LRRK2, PARK-GBA) can also be reproduced in patients in whom no genetic cause can be found (Di Maio et al., 2018). Even if these patients with gPD currently represent only a small group (approximately 10%) (Cook et al., 2021), it is expected that availability of a causal therapy for genetic forms of PD will substantially increase demand for genetic testing and counseling. Therefore, we aim to provide an overview of the most common genetically linked forms of PD and the associated biomarker studies. **Table 1** summarizes the genetic causes of PD with regard to the corresponding biomarker.

TABLE 1 | An overview of the genetic causes of Parkinson's disease (PD), the corresponding biomarker, and the diagnostic and/or prognostic value.

Genetics	Source	Biomarker	Findings (diagnostic/ prognostic*)	Study
SNCA	Blood	Oligomeric aSyn	↑sPD vs. HC (sensitivity 75%; specificity 100%)	Williams et al., 2016
	CSF	Total aSyn	↓sPD vs. HC	Mollenhauer et al., 2008
			↑PARK-LRRK2/HC vs. sPD	Vilas et al., 2016
		Oligomeric aSyn	↑sPD vs. HC (sensitivity 71%; specificity 64%)	Eusebi et al., 2017
			↑sPD vs. HC (RT-QuIC) (sensitivity 95%; specificity 100%)	Fairfoul et al., 2016; Sano et al., 2018; Shahnawaz et al., 2020
		Phosphorylated aSyn	↑sPD vs. HC vs. PSP	Eusebi et al., 2017
GBA	CSF	GCase activity	↓sPD vs. HC	Parnetti et al., 2014a; Lerche et al., 2021
			↓PARK-GBA vs. HC	Xicoy et al., 2019
			↓PARK-LRRK2 vs. HC	
			↓PARK-PRKN vs. HC	
	Blood		Positive correlation with disease duration*	Kim et al., 2016
LRRK2	Blood	Total LRRK2	↑sPD vs. HC	Atashrazm et al., 2019
			sPD = PARK-LRRK2/HC	Padmanabhan et al., 2020
		pS935-LRRK2	↓PARK-LRRK2 vs. sPD/HC	Padmanabhan et al., 2020
			↑sPD vs. HC	Melachroinou et al., 2020
		pRab10	PARK-LRRK2 = sPD/HC	Atashrazm et al., 2019
	CSF	Total LRRK2	↑PARK-LRRK2 vs. sPD/HC	Mabrouk et al., 2020
		pS1292-LRRK2	PARK-LRRK2 = sPD/HC	Wang et al., 2017
		Aβ1-42, total-, phospho-Tau	PARK-LRRK2 = sPD/HC	Vilas et al., 2016
	Urine	pS1292/total LRRK2	↑PARK-LRRK2 vs. sPD/HC	Fraser et al., 2016
	Neuro-imaging	PET multitracer	↓LRRK2 vs. controls	Nandhagopal et al., 2008
		I-123 FP-CIT SPECT	LRRK2 PD conversion rate = 16%*	Sánchez-Rodríguez et al., 2021

(Continued)

TABLE 1 | (Continued)

Genetics	Source	Biomarker	Findings (diagnostic/ prognostic*)	Study
PRKN/ PINK1	Blood	pS65-Ub	↓PARK-PINK1 vs. HC	Watzlawik et al., 2020
		Ccf-mtDNA	↑PARK-PRKN/PINK1 vs. sPD/HC	Borsche et al., 2020
		IL6	↑sPD vs. HC	Qin et al., 2016
			Positive correlation with disease severity*	Green et al., 2019
			↑PARK-PRKN/PINK1 vs. sPD vs. HC	Borsche et al., 2020
	CSF	Ccf-mtDNA	↓sPD vs. HC	Pyle et al., 2015
	Neuro-imaging	PET 18F-BCPP-EF tracer	sPD = HC	Wilson et al., 2020
		31P-MR-spectroscopy	↑PARK-PINK1 vs. HC	Hilker et al., 2012
DJ-1	CSF	DJ1	Conflicting results in sPD	
	Saliva		Conflicting results in sPD	
	Urine	Oxidized DJ1	↑sPD vs. controls	Jang et al., 2018

*aSyn, alpha-synuclein; CSF, cerebrospinal fluid; GCase, activity of the lysosomal hydrolase ß-glucocerebrosidase; HC, healthy controls; IL6, interleukin 6; PET, Positron emission tomography; RT-QuIC, real-time quaking-induced conversion; sPD, sporadic Parkinson's disease; SPECT, single photon emission computed tomography; ↑, increased levels; ↓, decreased levels; *, prognostic.*

ALPHA-SYNUCLEIN

Alpha-synuclein (aSyn) is a rather small protein (14 kDa) that is widely expressed in the brain (Braak et al., 2003). It seems to play a role in the stability of neuronal membranes, influencing presynaptic signaling and membrane trafficking through vesicular transport (Henderson et al., 2019). Several papers show that aSyn can be released from neurons and taken up by surrounding neurons or other cell types (Henderson et al., 2019). Therefore, it is not surprising that aSyn, despite constituting an intracellular protein, can be found in CSF, blood, and plasma (Atik et al., 2016; Maass et al., 2019). aSyn aggregates represent the main component of Lewy bodies (LB) (Spillantini et al., 1997). Therefore, PD, together with dementia with Lewy bodies (DLB) and multiple system atrophy (MSA), is referred to as a-synucleinopathy. LB are found in various regions of the CNS, depending on the disease stage (for example, substantia nigra, the dorsal motor nucleus of the vagus, nucleus basalis of Meynert, the locus coeruleus, and diffusely in late stages of the disease) (Forno, 1996). However, LB are also found in the peripheral nervous system in early or prodromal stages of the disease (e.g., sympathetic ganglia, sympathetic cardiac nerves, cholinergic nerve endings of salivary glands, autonomic nerve fibers of the skin).

First described with point mutations, the gene for aSyn (*SNCA*) was the first gene to be associated with the development of PD with an autosomal-dominant transmission (Polymeropoulos et al., 1997). Over time, duplications and triplications of *SNCA* have also been shown to play a causal role in hereditary forms of PD. Regarding symptoms, *SNCA* point mutations are associated with an earlier age at the onset (Ibáñez et al., 2009). *SNCA* gene duplications are associated with a mean age of the onset and clinical phenotype that overlaps with sPD (Ibáñez et al., 2009). *SNCA* triplications are associated with the early age of the onset, more rapid progression, and memory impairment (Ibáñez et al., 2009). Nonetheless, mutations in *SNCA* as a disease cause in PD remain rare.

Total aSyn and isoforms of aSyn appear to play a major role in PD pathogenicity and, accordingly, are also available as a candidate biomarker. The concentration of total aSyn in CSF may discriminate between patients with PD and healthy controls (Wang et al., 2012), and has been found at a lower concentration in patients with PD (Mollenhauer et al., 2008). This was confirmed in early-diagnosed, treatment-naïve patients (Stewart et al., 2014).

However, no uniform picture emerges regarding total aSyn. In patients with *LRRK2* mutations, total aSyn CSF levels were increased in *LRRK2*-associated PD, non-manifesting carriers, and healthy controls compared to sPD (Vilas et al., 2016). In another study, lower but not statistically significant total aSyn CSF levels were recognized in *LRRK2*-associated PD, non-manifesting carriers, and sPD compared to healthy controls (Aasly et al., 2014). Follow-up data in patients with PD from the DATATOP study revealed an increase of total aSyn after 2 years (Majbour et al., 2016). An increase in total aSyn has also been reported over 2 years in another study with 63 patients with PD and 21 controls (Hall et al., 2016). In the latter study, higher total aSyn values were associated with longer disease duration (Hall et al., 2016). The authors hypothesized that total aSyn levels were bimodal, with a decrease in early disease stages followed by an increase with advanced neurodegeneration.

Unfortunately, unlike MSA or progressive supranuclear palsy (PSP), it is not possible to distinguish between sPD and aPD based on the aSyn concentration. Therefore, total aSyn is unable to distinguish between alpha-synucleinopathies (sPD, MSA) or between alpha-synucleinopathies and aPD such as PSP or corticobasal degeneration. Because of the cognitive impairment in *SNCA* triplication carriers, an association between total aSyn and patients with PD with dementia (PDD) could be considered. However, similar levels of total aSyn have been reported for patients with PD and PDD (Farotti et al., 2017).

The reason for the large heterogeneity of the results with respect to total aSyn is likely due to clinical heterogeneity, the number of included patients, and methodological differences that could compromise diagnostic accuracy. Another important confounding variable is hemolysis during the specimen collection, where contamination of blood or CSF leads to increased total aSyn levels (Barkovits et al., 2020).

Before aSyn aggregates into mature amyloid fibrils in LB, aSyn undergoes oligomerization. There is strong evidence that oligomeric aSyn is a key player in PD pathophysiology (Conway et al., 2000). It has been found at higher concentration in patients with PD compared to controls, but with poor diagnostic sensitivity and specificity (Parnetti et al., 2014b; Eusebi et al., 2017). However, there are conflicting results with respect to oligomeric aSyn reported over recent years. One example is the results in asymptomatic and symptomatic PARK-LRRK2 mutation carriers. Asymptomatic PARK-LRRK2 mutation carriers showed elevated oligomeric aSyn levels compared to healthy controls (Aasly et al., 2014); that oligomeric aSyn reflects a presymptomatic precursor of the disease cannot be concluded with certainty because symptomatic PARK-LRRK2 mutation carriers in the same study showed no difference to healthy controls (Aasly et al., 2014). Again, there is no evidence that oligomeric aSyn in the CSF might distinguish between sPD, gPD, and/or aPD. Among the isoforms of aSyn, phosphorylated 129 aSyn has been reported to enhance synuclein toxicity both *in vivo* and *in vitro* due to increasing formation of aSyn aggregates (Fujiwara et al., 2002; Smith et al., 2005), whereas a protective effect of phosphorylated 129 aSyn has also been described (Gorbatyuk et al., 2008; Da Azeredo Silveira et al., 2009). Another biomarker could be the 129 aSyn/total aSyn ratio, which seems to be elevated in PD (Wang et al., 2012). Regarding aSyn aggregates, *in vitro* conversion methods such as real-time quaking-induced conversion (RT-QuIC) have been developed as promising new methods for measuring aggregated aSyn in the CSF of patients with PD. RT-QuIC was originally developed for the detection of the abnormal form of prion protein, e.g., in Creutzfeldt-Jakob disease. In alpha-synucleinopathies, RT-QuIC has been reported with a high sensitivity and specificity of 95-100% for alpha-synucleinopathies (Fairfoul et al., 2016; Sano et al., 2018; Shahnawaz et al., 2020) and a positive predictive value of > 90% (van Rumund et al., 2019), but only 75% sensitivity in patients with an unclear diagnosis of parkinsonism (van Rumund et al., 2019). In addition, RT-QuIC does not appear to be suitable for monitoring the disease course (Nakagaki et al., 2021). The method has also been used to distinguish between alpha-synucleinopathies and other neurodegenerative diseases (Groveman et al., 2018). Due to an improved aSyn RT-QuIC test, a diagnostic sensitivity of 93% and 100% specificity has been achieved when comparing nine patients with synucleinopathy (12 PD; 17 DLB) and 31 non-synucleinopathy controls (including 16 patients with Alzheimer's diseases). A recent study has presumed that RT-QuIC of aSyn in the CSF could be a promising candidate for prodromal stages for PD and DLB. In patients with isolated REM sleep behavior disorder (RBD), a known risk factor in the development of PD and DLB, a sensitivity and specificity of 90% have been shown (Iranzo et al., 2021). In addition, these patients had a subsequent higher risk of developing PD or DLB. Nearly two-thirds of the patients with RBD were diagnosed with PD or DLB, a mean 3.4 years after the aSyn measurement, of whom 97% were aSyn positive at the baseline (Iranzo et al., 2021). This finding of aSyn in the CSF by RT-QuIC and its value in presymptomatic patients is important, but must be confirmed by further studies.

The different forms of aSyn (total aSyn, oligomeric aSyn, phosphorylated aSyn) also reveal different results in blood serum and plasma. For total aSyn, conflicting results of increased, decreased, or unchanged total aSyn levels have been reported (Parnetti et al., 2019). Oligomeric aSyn in blood serum or red blood cells seems valuable candidates, with a sensitivity of 75% and specificity of up to 100% (Williams et al., 2016). However, these results must be confirmed in larger studies.

ß-GLUCOCEREBROSIDASE

Lysosomes are one of the key players for protein degradation in human cells, including a-Syn (Webb et al., 2003). It is obvious that lysosome malfunction leads to an accumulation of dysfunctional proteins and cell organelles. This pathway is shared by several monogenetic forms of PD, including *SNCA*, *ATP13A2*, *VPS35*, *DNAJC6*, *SYNJ1*, *LRRK2*, *RAB39B9*) (Abeliovich and Gitler, 2016). An association between aSyn and lysosomes has long been hypothesized. It is assumed that a disturbed autophagy-lysosomal pathway is directly related to aSyn aggregates (Sardi et al., 2011; Bae et al., 2015; Suzuki et al., 2015).

Mutations in the corresponding gene for ß-glucocerebrosidase (*GBA*) are considered the most common genetic risk factor in PD, meaning that not every carrier of a *GBA* mutation will develop PD. Historically, the observation of an increased risk of PD in type I Gaucher disease (GD) and its families was first surmised from clinical findings (Neudorfer et al., 1996). GD type I represents an autosomal-recessive systemic disorder that can present with various degrees of systemic and neurological manifestations, usually manifesting in childhood. Since the first description, more than 300 different genetic alterations, such as point mutations, insertion, deletion, missense mutations, and splice junctions, have been described in the literature (Beutler et al., 2005; Hruska et al., 2008; Smith et al., 2017). Among GBA mutation carriers, an increasing penetrance of PD (PARK-GBA) with age has been reported (Anheim et al., 2012). Penetrance ranges from 7.6% at age 50 years to 30% at age 80 (Anheim et al., 2012). If patients have two homozygous mutations and thus affected with GD, the risk of PD is higher and the age at the onset (AAO) is earlier (Thaler et al., 2017). Depending on the origin of the patients, the frequency of *GBA* mutations varies. For example, *GBA* mutations can be found in 10–31% of patients with Ashkenazi background but only in 2.3% of Norwegian patients (Neumann et al., 2009). For the European non-Ashkenazi patients, the range is between 3 and 12% (Neumann et al., 2009).

Clinical differentiation between sPD and gPD caused by a heterozygous *GBA* mutation (PARK-GBA) is not possible. However, the AAO of PARK-GBA is 3–6 years earlier than in sPD (Riboldi and Di Fonzo, 2019). The progression of PARK-GBA is more often characterized by prominent cognitive impairment, hallucination, and RBD. Due to the phenotypic description, it is not surprising that *GBA* mutations have also been found in cases of DLB (Nalls et al., 2013). The frequency of patients with DLB with *GBA* mutations was up to 13% in pathologically proven patients with DLB (Gámez-Valero et al., 2016).

A few studies have focused on the activity of the lysosomal hydrolase ß-glucocerebrosidase (GCase) in alpha-synucleinopathies, with a significant decrease of GCase activity in the CSF of patients with PD compared to controls (Parnetti et al., 2014a; Lerche et al., 2021). As a biomarker decreased, GCase activity was consistently found in PARK-GBA (see below) but also in other gPD (PARK-LRRK2, PARK-SNCA, PARK-RKN) (Xicoy et al., 2019). The overall utility of GBA as biomarkers in peripheral biosamples of sPD is highly controversial because, as with the results in CSF, dried blood spots are conflicting (Balducci et al., 2007; Parnetti et al., 2017; Pchelina et al., 2017). In a very recently published work, the authors have hypothesized that low GCase activity was not responsible for the phenotype because low GCase activity has been found in patients with PARK-GBA and non-manifesting GBA carriers (Omer et al., 2022). However, patients with PARK-GBA were nearly 10 years older than non-manifesting GBA carriers (64.9 vs. 53.4 years, respectively). An additional role could be the respective GBA mutation, as there are indications that this causes different changes in GCase activity (Lerche et al., 2021). GCase activity could also be promising as a progression parameter in leukocytes, as a positive correlation between GCase levels in leukocytes and disease duration has been reported in sPD (Kim et al., 2016). Unfortunately, the treatments currently available for patients with GD do not reach the CNS. Hence, these treatment options do not play a role in PARK-GBA. However, there are several approaches to therapy development. One example is the capacity to increase GCase levels, currently being tested using the chaperone ambroxol in patients with PARK-GBA in an ongoing study (NCT02914366) (Mullin et al., 2020). The rationale behind this is that mutant *GBA* is unable to fold the endoplasmic reticulum correctly and thus promotes protein aggregation. Chaperone proteins able to facilitate the refolding of their substrates were tested. Another approach is gene replacement therapy *via* adeno-associated virus 9 to deliver a functional copy of the *GBA* gene to the CNS (Du et al., 2019; Abeliovich et al., 2021). In several animal models of PD or *GBA*-associated PD, direct application to the CNS was successful (Rocha et al., 2015; Jackson et al., 2019). Accordingly, a phase 1/2a study using these techniques has been recently started (NCT04127578).

LEUCINE-RICH REPEAT KINASE

Mutations in the leucine-rich repeat kinase (*LRRK2*) gene are the most common genetic cause of autosomal-dominant late-onset PD (Paisán-Ruíz et al., 2004; Zimprich et al., 2004). *LRRK2* variants are also considered significant risk factors in sPD cases (Kluss et al., 2019). G2019S is the most frequent variant, accounting for 4% of gPD and 1% of sPD, with variable distribution among different ethnic populations and incomplete, age-related penetrance (26–84%) (Healy et al., 2008; Lee et al., 2017). *LRRK2* encodes a multifunctional protein with a catalytic core of kinase and GTPase activity. Physiologically, LRRK2 is involved in various cellular processes, encompassing cytoskeletal maintenance, vesicular trafficking, mitochondrial function, autophagy, lysosomal degradation, and the inflammatory response (Jeong and Lee, 2020; Mancini et al., 2020). Most *LRRK2* mutations cause a toxic gain of function with increased kinase activity. In viral and transgenic rodent models, overexpression of *LRRK2* G2019S induced striatal neurodegeneration in a kinase-dependent manner (Lee et al., 2010; Tsika et al., 2015). There is also evidence that LRRK2 interacts with aSyn, mediating its aggregation and propagation (O'Hara et al., 2020).

The phenotype of PARK-LRRK2 resembles that of sPD in terms of cardinal motor features and good response to levodopa (Healy et al., 2008; Marras et al., 2011). PD symptoms manifest at a slightly younger age (57 years). Several studies have observed a more benign disease course in G2019S mutation carriers with a slower decline in motor scores, albeit a similar risk for motor complications (Healy et al., 2008; Marras et al., 2016; Ben Romdhan et al., 2018; Saunders-Pullman et al., 2018) that could not be confirmed by other studies that report no difference (Nabli et al., 2015) or even worse motor symptoms and a higher rate of dyskinesia (Nishioka et al., 2010; Shu et al., 2018). Various studies have indicated that PARK-LRRK2 is associated with less non-motor involvement. Hyposmia and RBD are less prevalent compared to sPD (Saunders-Pullman et al., 2015; Marras et al., 2016), and cognitive function seems to be more mildly impaired, even after many years of disease duration (Aasly et al., 2005; Alcalay et al., 2015).

Given the therapeutic advances of small molecule kinase inhibitors and antisense oligonucleotides to diminish LRRK2 activity, reliable and feasible biomarkers that reflect LRRK2-related pathways are mandatory. LRRK2 is highly expressed in peripheral tissues, such as lung, kidney, and blood cells (Fuji et al., 2015), and the latter serves as an easily accessible source [i.e., peripheral blood mononuclear cells (PBMCs)]. Indeed, by using flow cytometry, significantly elevated LRRK2 levels have been detected in B cells, T cells, CD16 + monocytes (Cook et al., 2017), and neutrophils of subjects with sPD compared to controls (Atashrazm et al., 2019), supporting the link to immune regulation. However, no difference in total LRRK2 levels could be detected in PBMCs among various sample groups, irrespective of PD or *LRRK2* mutation status (Melachroinou et al., 2020; Padmanabhan et al., 2020). Alterations of total LRRK2 levels in PBMCs could be obscured by cellular heterogeneity. Considering cell-specific expression patterns of LRRK2, it seems important to purify and analyze different subcellular types separately in future investigations. A prominent site for heterologous LRRK2 phosphorylation is at serine 935 (pS935) that has been shown to be significantly reduced in PBMCs of affected G2019S carriers, distinguishing them from sPD, healthy G2019S carriers, and controls (Padmanabhan et al., 2020). Another study reported significantly elevated *in vitro* kinase activity of LRRK2 in PBMCs from *LRRK2* G2019S mutation carriers in comparison to non-carriers, while the pS935-LRRK2 level was increased in sPD compared to controls (Melachroinou et al., 2020). The molecular mechanisms that alter the regulation of S935 phosphorylation are not fully understood and need further clarification. Moreover, LRRK2 is sensitized to dephosphorylation by LRRK2 kinase inhibitors, with reduced pS935-LRRK2 that could be used as a marker of pharmacological

LRRK2 inhibition (Dzamko et al., 2010). Whether the GTPase Rab10, the key substrate of LRRK2 that can be pharmacologically modified, could serve as a marker for target engagement is still inconclusive and needs further assessment (Steger et al., 2016; Thirstrup et al., 2017). At least, for discriminative purposes, Rab10 cannot be suggested since no difference could be found in blood cells between patients with PD and controls (Fan et al., 2018; Atashrazm et al., 2019). Although it has been challenging to directly measure LRRK2 in CSF, LRRK2 quantification in CSF could be obtained by an improved monoclonal antibody technique that has revealed significantly higher CSF LRRK2 levels in G2019S-PD compared to sPD, healthy controls, and non-manifesting G2019 carriers (Mabrouk et al., 2020). Auto-phosphorylation of LRRK2 at serine 1292 (pS1292) reflects kinase activity that is measurable in CSF, but possibly masked by saturation effects no changes in pS1292 levels could be detected in the CSF of G2019S carriers (Wang et al., 2017). As mentioned in the previous section, CSF protein analysis revealed the differential pha-synuclein profiles of individuals with LRRK2 mutation (Aasly et al., 2014; Vilas et al., 2016) that could result from the variable presence of LB pathology in PARK-LRRK2. No differences were found in terms of the AD-related proteins amyloid-β1-42, total-tau, or phospho-tau (Vilas et al., 2016). Fraser et al. (2013) demonstrated the presence of LRRK2 in urinary exosomes, small endosomal-derived vesicles released from cells to the periphery. Intriguingly, G2019S carriers with PD displayed higher pS1292 to the total LRRK2 ratio in urinary exosomes compared to non-carriers and even asymptomatic G2019S carriers, indicating the potential for risk prediction (Fraser et al., 2016). Further studies on LRRK2 exosomes will explore their biomarker potential in PD.

Regarding imaging biomarkers, positron emission tomography (*PET*) detected reduced tracer binding in presymptomatic LRRK2 mutation carriers compared to controls, with greater progression of dopaminergic dysfunction (Nandhagopal et al., 2008). In this PET study, multiple tracers were applied, including multitracer PET using 18F-6-fluoro-l-dopa, 11C-(±)-α-dihydrotetrabenazine and 11C-d-threo-methylphenidate. Dopamine transporter imaging with I-123 FP-CIT showed potential to monitor progression, although a certain degree of intraindividual variability limited its ability to predict phenoconversion (Sánchez-Rodríguez et al., 2021). Studies that investigate markers to discriminate LRRK2-PD from aPD are lacking.

PRKN/PINK1

Given the common biological pathways affecting mitochondrial function and biomarker studies, including both *PRKN* and *PINK1* mutations, these genes are discussed together.

The majority of early-onset parkinsonism with autosomal-recessive inheritance is linked to mutations of the *PRKN/PARK2* gene (Kitada et al., 1998; Lücking et al., 2000). More than 130 disease-causing mutations have been identified throughout all 12 exons, including point mutations, exon rearrangements, and small deletions (Kasten et al., 2018). Whereas biallelic *PRKN* mutation results in overt disease, the question whether heterozygous mutations predispose to disease risk still remains an issue of debate (Huttenlocher et al., 2015; Lubbe et al., 2021; Yu et al., 2021). The encoded Parkin protein is an E3-ubiquitin ligase that transfers ubiquitin to protein substrates, thus targeting them to proteasomal degradation (Shimura et al., 2000; Moore, 2006). Moreover, Parkin regulates mitochondrial quality control and clearance of damaged mitochondria through mitophagy in concert with the other PD-linked gene *PINK1* (Narendra et al., 2012). In the Drosophila model, mutant *PRKN* caused a *degenerative phenotype with* flight muscle defects, *mitochondrial alterations, and abnormalities of dopaminergic neurons (Greene et al., 2003; Pickrell and Youle, 2015).*

PARK-PRKN is characterized by a slowly progressive disease course at an early age of the onset (mean, 31 years) (Khan et al., 2003; Kasten et al., 2018). Beyond the typical clinical triad, hyperreflexia can be present, and dystonia, often affecting the lower limb, can be an initial sign (Khan et al., 2003; Grünewald et al., 2013). The marked and sustained response to levodopa is complicated by frequently associated levodopa-induced motor fluctuations and dyskinesias (Clarimon et al., 2005). With regard to non-motor aspects, olfactory function and cognition are mostly well preserved (Khan et al., 2004; Alcalay et al., 2015; Abeliovich and Gitler, 2016). However, a multicenter, case-control study reported an earlier occurrence and a higher frequency and severity of impulsive-compulsive behaviors in PARK-PRKN (Morgante et al., 2016).

Mutations in the *phosphatase and tensin homolog (PTEN)-induced putative kinase 1* (*PINK1*) gene represent the second most frequent cause of autosomal-recessive inherited early-onset parkinsonism (Valente et al., 2004). The frequency of *PINK1* mutations ranges between 1 and 9%, with variations across different ethnic populations (Schulte and Gasser, 2011; Klein and Westenberger, 2012). Mutations are highly diverse and include missense, non-sense, frameshift mutations, and deletions. As with *PRKN*, the role of heterozygous *PINK1* mutation as a risk factor in PD has not yet been clarified (Krohn et al., 2020). PINK1 encodes a serine/threonine kinase involved in the regulation of the mitophagy pathway by activating ubiquitin and Parkin through phosphorylation (Valente et al., 2004; Narendra et al., 2010; Kane et al., 2014). Drosophila-lacking *PINK1* exhibited mitochondrial abnormalities and muscle and neuronal degeneration that could be rescued by *PRKN* overexpression but not *vice versa*, suggesting that *PINK1* acts upstream of Parkin in the shared pathway (Clark et al., 2006; Park et al., 2006; Yang et al., 2006).

In general, PARK-PINK1 shares similar features as PARK-PRKN regarding early AAO (mean, 32 years), slow disease progression, and excellent levodopa response, although associated with motor fluctuations and dyskinesias (Bonifati et al., 2005; Ibáñez et al., 2006; Kasten et al., 2018). Dystonia at the onset and hyperreflexia are also described in patients with *PINK1* mutation. However, non-motor symptoms are more pronounced. Hyposmia is commonly reported (Ferraris et al., 2009). Neuropsychiatric features are multifaceted, including mostly depression and anxiety but also traits of the schizophrenic spectrum and obsessive-compulsive personality

disorder (Ephraty et al., 2007; Steinlechner et al., 2007; Ricciardi et al., 2014). Although cognitive function was thought to be less affected (Bonifati et al., 2005; Kasten et al., 2018), a recent study has observed a higher rate of cognitive dysfunction in *PINK1* mutations (Piredda et al., 2020).

Biomarkers for mitochondrial integrity are not only required to prove target engagement and drug-induced effects but also to identify patients who will most likely benefit from mitophagy-targeted treatments. PINK1 phosphorylates ubiquitin at a serine residue (pS65-Ub), which could reflect PINK1 activity. Autopsy studies have revealed elevated pS65-Ub levels in brain tissues of patients with sPD, DLB, and normal elderly controls, suggesting that pS65-Ub accumulates upon mitochondrial stress during disease or aging (Fiesel et al., 2015; Hou et al., 2018). In contrast, *PINK1/PRKN* mutants lacked pS65-Ub signals, consistent with their loss of function to label damaged mitochondria. More intriguingly, pS65-Ub signals detected by sensitive enzyme-linked immunosorbent assay were significantly reduced in blood plasma of patients with homozygous *PINK1*-mutation carriers compared to controls with heterozygous mutation and non-carriers (Watzlawik et al., 2020). Whether pS65-Ub levels can be used as a diagnostic or prognostic disease marker in blood needs to be confirmed in further investigations. Mitochondrial DNA (mtDNA) is closely related to mitochondrial function. Whereas reduced mtDNA copy numbers were reported in the substantia nigra of PD postmortem brains (Pyle et al., 2016), the findings in peripheral blood are inconclusive (Gui et al., 2015; Pyle et al., 2016; Davis et al., 2020). Circulating cell-free mtDNA (ccf-mtDNA) is a fragment of mtDNA released from cells in response to stress. Reduced ccf-mtDNA levels were reported in the CSF of patients with sPD (Pyle et al., 2015), showing an inverse correlation with treatment (Lowes et al., 2020). Notably, a recent study has observed higher ccf-mtDNA levels in the sera of *PRKN* and *PINK1* biallelic mutation carriers and affected heterozygotes compared to patients with sPD, possibly resulting from impaired mitophagy in PRKN/PINK1-associated PD (Borsche et al., 2020). As inflammation evidently contributes to PD pathogenesis and progression, peripheral inflammatory cytokines have been attributed biomarker potential. Among these, interleukin-6 (IL6) levels were elevated in blood samples from patients with PD (Qin et al., 2016), correlating with motor severity. A recent study has reported higher serum IL6 levels in patients with biallelic *PRKN/PINK1* mutations compared to healthy controls, whereas heterozygous *PRKN/PINK1* mutation carriers and sPD showed only a trend toward elevated IL6 levels, indicating a gene dosage effect (Borsche et al., 2020). Moreover, IL6 levels correlated only in affected *PRKN/PINK1* mutation carriers with disease duration. Mitochondrial dysfunction is also implied in the pathophysiology of a PD such as MSA and PSP (Nicoletti et al., 2021). Comparative studies exploring discriminative biomarkers of *PRKN/PINK1*-associated PD vs. aPD have not yet been conducted.

Imaging methods can be useful to monitor mitochondrial energy metabolism. Mitochondrial complex I activity can be assessed *in vivo* by the PET radiotracer ^{18}F-BCPP-EF, which is reduced in a non-human primate model for PD (Tsukada et al., 2016) but could not be translated to patients with PD (Wilson et al., 2020). Alternatively, phosphorus magnetic resonance spectroscopy (^{31}P-MRS) can visualize cerebral mitochondrial metabolism by measuring phosphorous-containing energy metabolites (Henchcliffe et al., 2008). Increased putaminal levels of high-energy phosphates distinguished homozygous *PINK1* mutation carriers from heterozygous mutation carriers and controls (Hilker et al., 2012). This finding was interpreted as compensatory mechanisms with respect to the impaired cellular stress resistance.

Two current trials testing vitamin K2 (Prasuhn et al., 2020) and coenzyme Q10 (Prasuhn et al., 2019) include *Parkin/PINK1* mutation carriers and use ^{31}P-MRS for patient stratification and as a secondary end point.

DJ1

DJ-1 is a widely expressed protein that participates in antioxidative stress mechanisms and mitochondrial regulation (Dolgacheva et al., 2019). Mutations in the corresponding gene *DJ-1* are responsible for an autosomal-recessive form of gPD (PARK-DJ-1). The phenotype of patients with PARK-DJ-1 consists of an early onset and slow progression of the disease and is, therefore, comparable with other autosomal-recessive forms like PARK-PRKN or PARK-PINK1. However, mutations in *DJ-1* are less frequent than PARK-PRKN or PARK-PINK1.

There are conflicting results regarding DJ-1 as a biomarker in the CSF and peripheral tissues, with increased and decreased DJ-1 levels in patients with sPD (Saito, 2014; Farotti et al., 2017). The same conflicting results were obtained when DJ-1 in the CSF was examined in the differential diagnosis of sPD vs. aPD (Farotti et al., 2017). A few studies with a low number of patients have investigated the concentration of DJ-1 in saliva in sPD with conflicting results. Therefore, DJ-1 in saliva does not play a role in daily routine (Farah et al., 2018). Another option is to determine the concentration of oxidized DJ-1 in blood or urine. Oxidized DJ-1 is induced by oxidative stress, which plays a major role in the pathophysiology of neurodegenerative diseases. Increased levels of oxidized DJ-1 have been described in patients with sPD compared to controls (Jang et al., 2018).

CONCLUSION

A biomarker with a high sensitivity and specificity that could be introduced into clinical routine is currently not available. Biomarker research for PD has made great progress in recent years. Nevertheless, there is still a lack of robust biomarkers with high sensitivity and specificity that would satisfy diagnostic requirements. This is also true for monitoring disease progression and differential diagnosis of sPD, gPD, and aPD. Even for the most common monogenetic forms described here, this has not yet been achieved. This is true for the different forms of PD, including sPD, gPD, and aPD. Further research activity will be necessary to improve or find new techniques (e.g., RT-QuIC) and find the most suitable liquid biomaterial. The key

to the diagnosis of PD, especially for future disease-modifying therapies, is likely to be a combination of different biomarkers with different modalities. In addition to peripheric biomarkers and CSF, imaging techniques (nuclear medicine, MRI, etc.) will play a crucial role.

AUTHOR CONTRIBUTIONS

LT and SK contributed to conception and design of the study. SK and EK wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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Complications After Deep Brain Stimulation: A 21-Year Experience in 426 Patients

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Background: Deep brain stimulation is an established treatment for movement disorders such as Parkinson's disease, essential tremor, and dystonia. However, various complications that occur after deep brain stimulation are a major concern for patients and neurosurgeons.

Objective: This study aimed to analyze various complications that occur after deep brain stimulation.

Methods: We reviewed the medical records of patients with a movement disorder who underwent bilateral deep brain stimulation between 2000 and 2020. Among them, patients requiring revision surgery were analyzed.

Results: A total of 426 patients underwent bilateral deep brain stimulation for a movement disorder. The primary disease was Parkinson's disease in 315 patients, followed by dystonia in 71 patients and essential tremor in 40 patients. Twenty-six (6.1%) patients had complications requiring revision surgery; the most common complication was infection (12 patients, 2.8%).

Conclusion: Various complications may occur after deep brain stimulation, and patient prognosis should be improved by reducing complications.

Keywords: deep brain stimulation, complication, Parkinson's disease, essential tremor, dystonia, movement disorder, postoperative infection, intracerebral hemorrhage

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INTRODUCTION

Deep brain stimulation (DBS) is non-destructive and reversible compared with ablative stereotactic neurosurgical procedures, such as thalamotomy and pallidotomy. Therefore, DBS is currently considered a conventional treatment for movement disorders, including Parkinson's disease, essential tremor, and dystonia (Limousin et al., 1998; Schuurman et al., 2000; Simuni et al., 2002; Umemura et al., 2003; Okun, 2012; Larson, 2014; Krack et al., 2019).

However, various complications occurring after DBS are a major concern for patients and neurosurgeons (Umemura et al., 2003; Voges et al., 2006; Larson, 2014). For example, due to intracranial electrode insertion, DBS can cause intracerebral hemorrhage (ICH). In addition, DBS may cause skin erosion and infection because of the subcutaneous placement of a bulky foreign body called an internal pulse generator (IPG) and a long extension. The complications

that require revision surgery after DBS exhaust patients physically, mentally, and economically (Chen et al., 2017).

Short-term studies with less than 4 years of mean follow-up on the complications occurring after DBS have been published, but no long-term follow-up studies have been conducted (Oh et al., 2002; Umemura et al., 2003; Lyons et al., 2004; Voges et al., 2006). Therefore, we aimed to conduct a large long-term study to review bilateral DBS performed by a single neurosurgeon at a single institution for 21 years. The complications that required revision surgery after DBS were analyzed, and our efforts to reduce the complication rate were described.

MATERIALS AND METHODS

Unilateral or bilateral DBS stimulation is performed for movement disorders (Parkinson's disease, essential tremor, and dystonia), psychiatric disorders (Tourette's syndrome and obsessive-compulsive disorder), and pain disorders. However, only patients with movement disorder who underwent bilateral DBS were included in this study to reduce bias due to various characteristics of the study subjects.

We selected the research subjects by reviewing medical records based on the following criteria: (1) patients who underwent bilateral DBS surgery (2) diagnosis of movement disorders such as Parkinson's disease, essential tremor, and dystonia (3) DBS performed during the period from January 2000 to August 2020 and (4) postoperative follow-up period of more than 1 year.

Six hundred and ten patients who underwent DBS surgery between 2000 and 2010 were identified. A total of 109 patients underwent unilateral DBS, and 501 underwent bilateral DBS. Among the 501 patients, 450 had bilateral DBS for movement disorders, such as Parkinson's disease, essential tremor, and dystonia. Twenty-four patients who were followed up for less than 1 year were excluded from the study. Four hundred and twenty-six patients who underwent bilateral DBS were finally enrolled and analyzed retrospectively.

Patients who underwent bilateral DBS surgery for movement disorders (Parkinson's disease, essential tremor, and dystonia) between January 2000 and August 2020 and who had a follow-up period of more than 1 year were included in the study. All surgeries were performed by the same neurosurgeon (JWC).

We defined complications requiring revision surgery as an additional surgical treatment performed due to complications after DBS. In addition, complications after DBS surgery were divided into hardware- and surgery-related complications. Hardware-related complications were caused by device problems such as extension fracture or disconnection. Surgery-related complications were defined as complications caused by the surgical technique and included postoperative infection and ICH.

We divided the 426 cases of bilateral DBS surgery performed in the 21-year period into four chronological groups based on the operation date. Group A included 106 cases (March 2000–June 2007), group B, 106 cases (June 2007–March 2011), group C, 107 cases (April 2011–February 2017), and group D, 107 cases (March 2017–September 2020). The operation time, complication rate, and infection rate for each group were compared. Comparing these four chronological groups, it was possible to identify changes in surgical outcomes according to our institution's surgical method and learning curve.

This study was conducted following the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of our institute (4-2021-1273). The requirement to obtain the patient's written consent was waived as this was a retrospective study.

Surgical Procedure

The process of mounting the stereotactic frame and the magnetic resonance imaging (MRI) for planning has been described in our previous report (Park et al., 2011; Kim et al., 2020; Jung et al., 2021). All patients were mounted on the Leksell stereotactic frame G (Elekta Instruments AB, Stockholm, Sweden) under local anesthesia on the day of the surgery. After the stereotactic frame was fixed to the head, the patients underwent an MRI evaluation (1.5 Tesla Philips Achieva). The MRI sequences for the stereotactic biopsy included gadolinium-enhanced T1-weighted images with a slice thickness of 1.5 mm and T2-weighted images with a slice thickness of 2.5 mm. The DBS surgery consists of two stages. The first stage is the insertion of an intracranial electrode, and the second stage is the insertion of an IPG. The first stage was usually performed with local anesthesia, but if the patient could not tolerate the intracranial procedure with local anesthesia, the procedure was performed under general anesthesia. After creating a burr hole, a 2–3-mm dura incision was made. The microTargeting Single Insertion Electrode (FHC, Inc., Bowdoin, ME, United States) was inserted as planned using the microTargeting Drive System (FHC, Inc.). An intracranial lead was inserted when the final electrode target was determined through a microelectrode recording. In patients with Parkinson's disease, the target of the DBS electrode was the subthalamic nucleus or globus pallidus internus. In patients with essential tremor, the target was the ventralis intermedius nucleus, and in patients with dystonia, the target was the globus pallidus internus. When the first stage (i.e., insertion of the intracranial electrode) was completed, brain computed tomography (CT) was used to verify the accuracy of the DBS electrode placement and detect hemorrhage. The second stage was performed under general anesthesia, and an IPG was inserted into the anterior chest wall pocket above the pectoralis major muscle. After surgery, the condition of the device was checked using a cranial and chest X-ray.

Statistical Analysis

Patients visited the outpatient clinic regularly to get an IPG check and medication adjustment. We identified the complications requiring revision operation during the follow-up period. The complications were divided into hardware- and surgery-related complications. The IBM SPSS Statistics software (version 25.0; IBM, Armonk, NY, United States) was used for the statistical analyses. The categorical variables were evaluated using the chi-square and Fisher's exact tests. The continuous variables were evaluated using Student's *T*-test, and the equality of variance

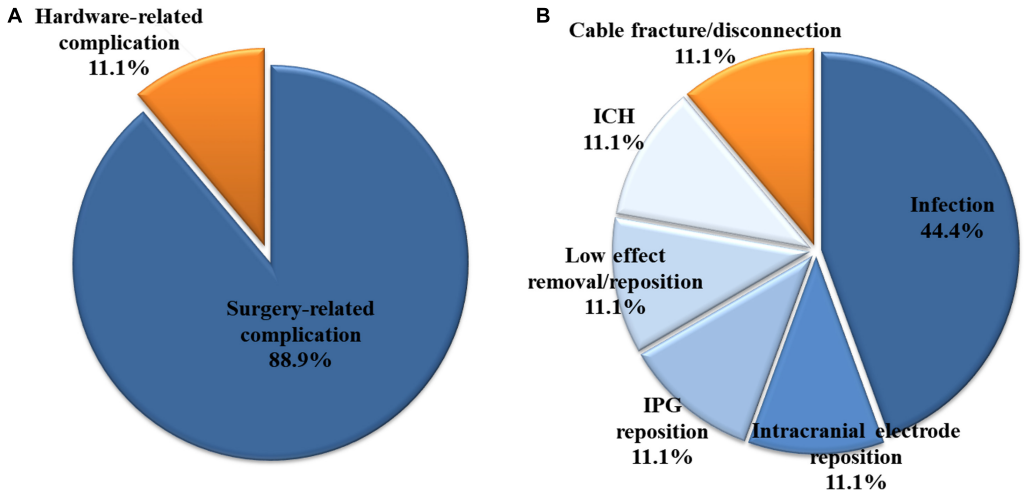

FIGURE 1 | Among the 426 patients who underwent bilateral deep brain stimulation, 27 had complications requiring revision surgery. **(A)** Three (11.1%) and 24 (88.9%) of the 27 patients had hardware- and surgery-related complications, respectively. **(B)** All three hardware-related complications were impedance problems due to extension fracture or disconnection. Among the surgery-related complications, infection was the most common, accounting for 44.4% (12/27 patients) of all complications. ICH, intracerebral hemorrhage; IPG, internal pulse generator.

was considered using Levene's test. A *p*-value less than 0.05 was considered statistically significant.

RESULTS

Four hundred and twenty-six patients who underwent bilateral DBS were finally included and analyzed retrospectively. The analyzed patients comprised 227 (53.3%) women and 199 (46.7%) men. The mean age of the patients at the time of surgery was 57.5 years (range 8–77, standard deviation [SD] 11.9). The mean follow-up was 79.4 months (range 0–239, SD 54.6). The primary disease was Parkinson's disease in 315 (73.9%) patients, followed by dystonia in 71 (16.7%) patients and essential tremor in 40 (9.4%) patients. The mean operation time was 287.2 min (range 135–581, SD 74.9), the mean blood loss was 19.8 mL (range 5–540, SD 49.3), and the mean patients' body mass index (BMI) was 22.8 (range 12.6–41.4, SD 3.3).

The mortality rate was 0.5% (2/426). One patient died from aspiration pneumonia during the management of ICH and intraventricular hemorrhage (IVH) caused by intracranial electrode insertion. The other died from ventricular tachycardia during general anesthesia regardless of the surgical procedure. The morbidity rate was 1.4% (six patients; one intracranial abscess, two minor intracranial hemorrhages, and three major intracranial hemorrhages).

Among the 426 patients, 27 (6.3%) had complications requiring revision surgery. Three of the 27 patients had hardware-related complications, and 24 patients had surgery-related complications (**Figure 1**). All three hardware-related complications were impedance problems due to extension fracture or disconnection (**Figures 1B**, **2**). The problems were solved by replacing the extensions. They occurred a minimum of 3 years after surgery (39.7 months, 48.7 months, and 116.3 months).

Among the surgery-related complications, infection was the most common, accounting for 44.4% (12/27 patients) of all complications. Most cases (11 patients) involved extracranial infections, but one case described a brain abscess located at the intracranial electrode. Of the 12 cases, infection occurred after the primary DBS operation and after battery change operation in eight and four cases, respectively. After the last operation, infection occurred after an average of 23.7 months (range 5.2–47.1, SD 14.7). Two of the 12 cases had infection after skin laceration due to trauma, and four cases had the wire exposed due to skin erosion. The characteristics of the 12 patients who developed infection are detailed in **Table 1**, and their characteristics were compared with those of the 414 patients who did not develop infection (**Table 2**). Sex, age, primary disease, operation time, blood loss, BMI, hypertension, and diabetes mellitus were not significantly different between the two groups. However, the BMI of patients who had infection tended to be lower than that of patients who had no infection ($p = 0.080$).

In surgery-related complications, DBS removal or intracranial electrode reinsertion was performed in six patients due to lower DBS effects than expected. IPG repositioning was also performed in three patients because of a problem in the interrogation and charging of the IPG. In one patient, the IPG was firmly fixed by revision surgery due to Twiddler's syndrome (**Figure 3**). This syndrome is the conscious or subconscious manipulation of an IPG within its subcutaneous pocket, leading to twisting of extension wires and, ultimately, wire fracture.

Asymptomatic minor ICH that did not require surgical management occurred in four patients, and symptomatic minor ICH that did not require surgical management occurred in three patients. Major ICH requiring surgical treatment was observed in three patients. In one patient, no abnormalities were observed

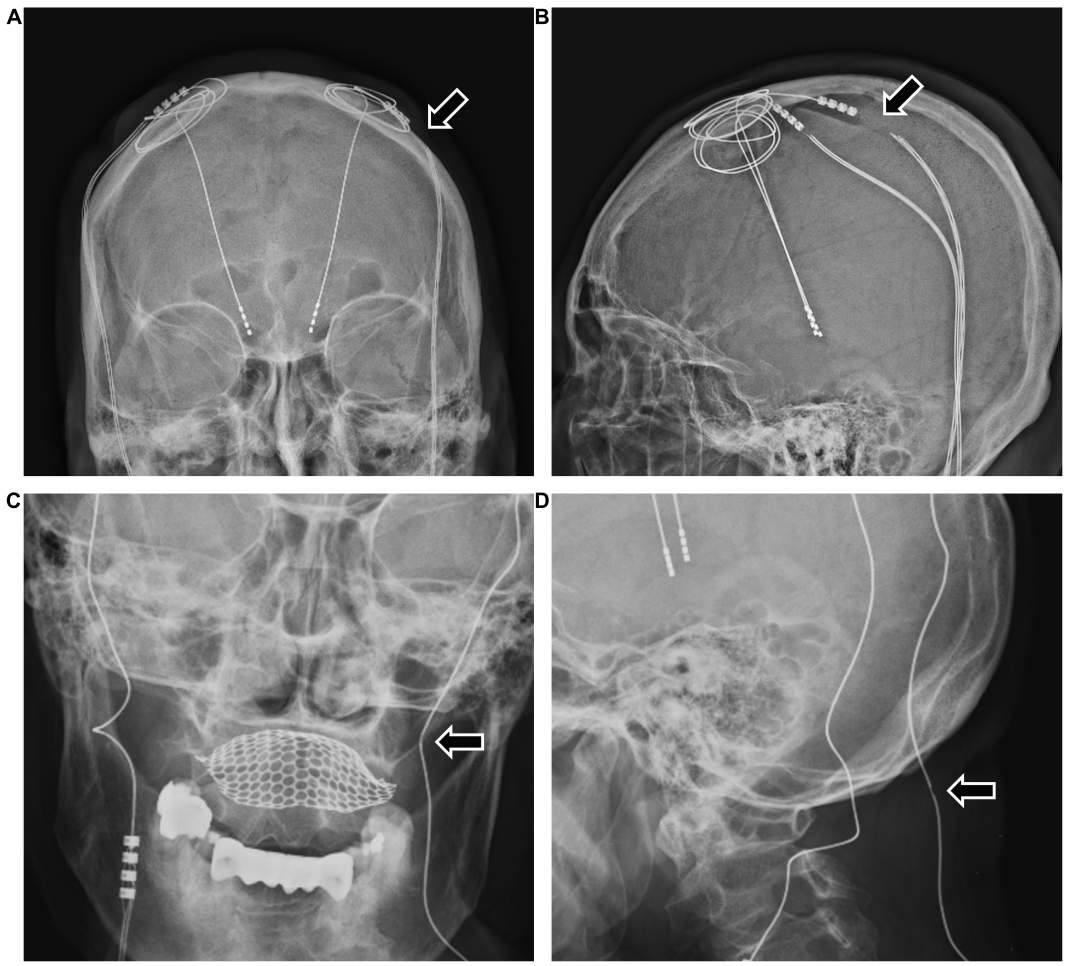

FIGURE 2 | The two patients with bilateral DBS with high impedance due to extension wire fracture or disconnection. **(A,B)** A 63-year-old woman with Parkinson's disease experienced sudden worsening of symptoms 3 years after bilateral DBS. The examination revealed high impedance of the patient's left DBS system due to extension fracture (**A,B** arrows). After the revision operation to replace the extension wire, the patient's DBS system was restored to normal function. **(C,D)** A 48-year-old woman with Parkinson's disease experienced worsening symptoms 4 years after bilateral DBS. The examination revealed high impedance of the patient's left DBS system and an extension wire abnormality (**C,D** arrows). After the revision operation to replace the electrode and the extension wire, the patient's DBS system was restored to normal function. DBS, deep brain stimulation.

on brain CT immediately after surgery, but an ICH developed in the right frontal lobe with seizures 8 h after surgery. The patient underwent craniotomy and hematoma evacuation due to the large ICH, increased edema, and a midline shift. The patient was transferred for rehabilitation (**Figures 4A–C**). In another patient, right thalamic ICH and IVH were observed on the brain CT after intracranial electrode insertion, and a hematoma catheter insertion was performed immediately. After 1 month, the ICH was resolved, and the patient was transferred for rehabilitation (**Figures 4D–F**). Finally, in one patient, no abnormalities were observed on the brain CT immediately after surgery, but right thalamic ICH and IVH were observed on brain CT 16 h after the operation, and a hematoma catheter insertion was performed. The hematoma was resolved, but the patient died from aspiration pneumonia on postoperative day 30 (**Figures 4G–I**).

The characteristics of the 10 patients who developed ICH were compared with those of 416 patients who did not develop ICH (**Table 3**). Sex, age, primary disease, operation time, blood loss, BMI, hypertension, and diabetes mellitus were not significantly different between the two groups.

We divided the 426 cases of bilateral DBS surgery performed for 21 years into four groups based on the operation date. Group A included 106 cases operated between March 2000 and June 2007; group B, 106 cases operated between June 2007 and March 2011; group C, 107 cases operated between April 2011 and February 2017; and group D, 107 cases operated between March 2017 and September 2020. The operation time, complication rate, and infection rate for each group are described in **Figure 5**. The average operation time initially exceeded 300 min, but recently, with the accumulated experience, the average operation time had been reduced to $<$ 200 min. In addition, the recent complications and infections rates were also lower than those in the early days of DBS surgery.

TABLE 1 | Twelve cases of infection after deep brain stimulation.

Patient No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Sex	M	M	M	M	F	M	M	F	M	F	F	F
Age at diagnosis	58	44	68	49	57	72	41	60	54	12	52	57
Last operation	DBS insertion	IPG change	DBS insertion	DBS insertion	DBS insertion	IPG change	DBS insertion	DBS insertion	DBS insertion	IPG change	IPG change	DBS insertion
Estimated blood loss (cc)	<10	<10	<10	<10	<10	<10	<10	<10	100	<10	<10	<10
Infection period (months)	13.2	40.9	36.3	47.1	34.1	26.0	9.5	13.3	37.0	12.6	9.8	5.2
Scalp laceration due to trauma					✓							✓
Skin erosion	✓	✓					✓	✓				
Microbiology culture	No growth	*Staphylococcus aureus*	*Pseudomonas aeruginosa*	No growth	*Staphylococcus aureus*	*Staphylococcus epidermidis*	*Staphylococcus aureus*	No growth	*Staphylococcus epidermidis*	*Staphylococcus epidermidis*	Staphylococcus, coagulase negative	*Staphylococcus aureus*
Device removal	Only debridement	Only debridement	Bilateral intracranial & IPG removal	Lt intracranial & IPG removal	Lt intracranial & IPG removal	Lt intracranial & IPG removal	Lt intracranial & IPG removal	Rt intracranial & IPG removal	Bilateral intracranial & IPG removal	Lt intracranial & IPG removal	Bilateral intracranial & IPG removal	Bilateral intracranial & IPG removal
BMI	18.4	24.7	21.1	19.3	18.2	23.9	25.3	21.9	24.7	12.6	18.9	24.7

DBS, deep brain stimulation; IPG, internal pulse generator.

TABLE 2 | Characteristics of patients who developed infection after deep brain stimulation surgery.

Characteristics	Normal cases (*N* = 414)	Cases with infection (*N* = 12)	*p*
Sex			0.600
Female	222 (53.6%)	5 (41.7%)	
Male	192 (46.4%)	7 (58.3%)	
Age (y)	57.7 ± 11.7	52.0 ± 15.4	0.102
Primary disease			0.156
Parkinson's disease	309 (74.6%)	6 (50.0%)	
Dystonia	67 (16.2%)	4 (33.3%)	
Essential tremor	38 (9.2%)	2 (16.7%)	
Operation time (min)	287.3 ± 74.6	285.9 ± 85.8	0.952
Blood loss (mL)	20.0 ± 49.8	12.9 ± 27.4	0.406
BMI	22.8 ± 3.3	21.1 ± 3.8	0.080
Hypertension	88 (21.3%)	4 (33.3%)	0.518
Diabetes mellitus	38 (9.2%)	1 (8.3%)	1.000

BMI, body mass index.

DISCUSSION

Complications that can occur after DBS surgery are diverse, and these severely affect doctors and patients. Among the 426 patients with movement disorders who underwent bilateral DBS insertion, 27 (6.3%) patients had complications requiring revision operation. Infection was the cause of the complication in 12 patients. The infection rate was 2.8%, lower than the 2.95–6.2% reported in previous studies (Umemura et al., 2003; Lyons et al., 2004; Voges et al., 2006; Pepper et al., 2013; Tolleson et al., 2014; Chen et al., 2017; Doshi et al., 2021). Infection after DBS surgery is the most frustrating complication because, in many cases, all devices inserted during the primary operation must be removed (Voges et al., 2006; Chen et al., 2017; Kim et al., 2020). The DBS system is physically connected from the intracranial electrode to the IPG by an extension wire. Once an infection occurs, the bacteria spread readily along the wire. Therefore, infection after DBS surgery cannot be resolved with only local debridement without device removal. Among the 12 cases with infection, only two were resolved with simple debridement and antibiotics without device removal. In six of the remaining 10 cases, the extension wire, IPG, and an intracranial electrode on the side of the infection were all removed. In the remaining four cases, the infection was resolved after removing the infected side and the opposite site device.

Short-term follow-up studies with less than 4 years of mean follow-up of complications occurring after DBS have been published (Oh et al., 2002; Umemura et al., 2003; Lyons et al., 2004; Voges et al., 2006), but no long-term follow-up studies have been conducted. Our study had a mean follow-up period of 79.4 months (6.6 years). Therefore, we consider that our study has an adequate power due to its larger size and follow-up duration than previous studies. In addition, the postoperative infection of the 12 patients developed at an average of 23.8 months (5.2–47.1 months) after the DBS surgery. It is noteworthy that no infection was identified after 4 years post-surgery. Hence, our investigation has a longer follow-up period than the previous ones, but the complication rate is not higher.

In six of the 12 cases, infection occurred after external environment connection, e.g., scalp laceration and skin erosion. Defects of the skin barrier are a common finding in patients with infection after DBS surgery because they provide an entrance for causative bacteria (Oh et al., 2002; Kenney et al., 2007; Sillay et al., 2008; Fily et al., 2011). Therefore, patients with DBS should avoid trauma-related laceration, and neurosurgeons

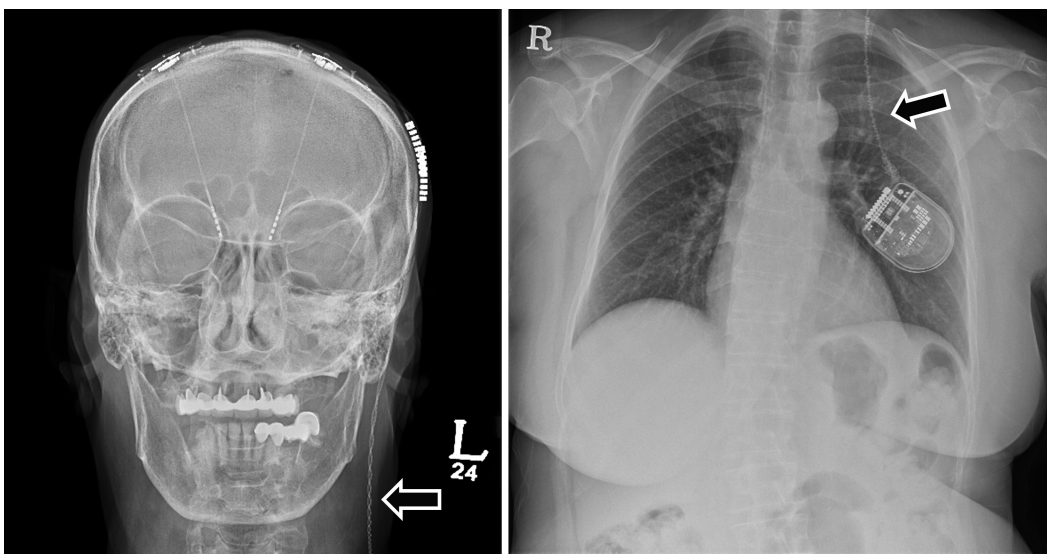

FIGURE 3 | A 70-year-old woman with Parkinson's disease had a broken extension wire due to Twiddler's syndrome 3 months after primary DBS surgery. The skull and chest X-rays demonstrate twisted and broken extension wires due to Twiddler's syndrome (arrows). The patient underwent revision surgery to replace the extension wire and perform multiple firm internal pulse generator anchor sutures. DBS, deep brain stimulation.

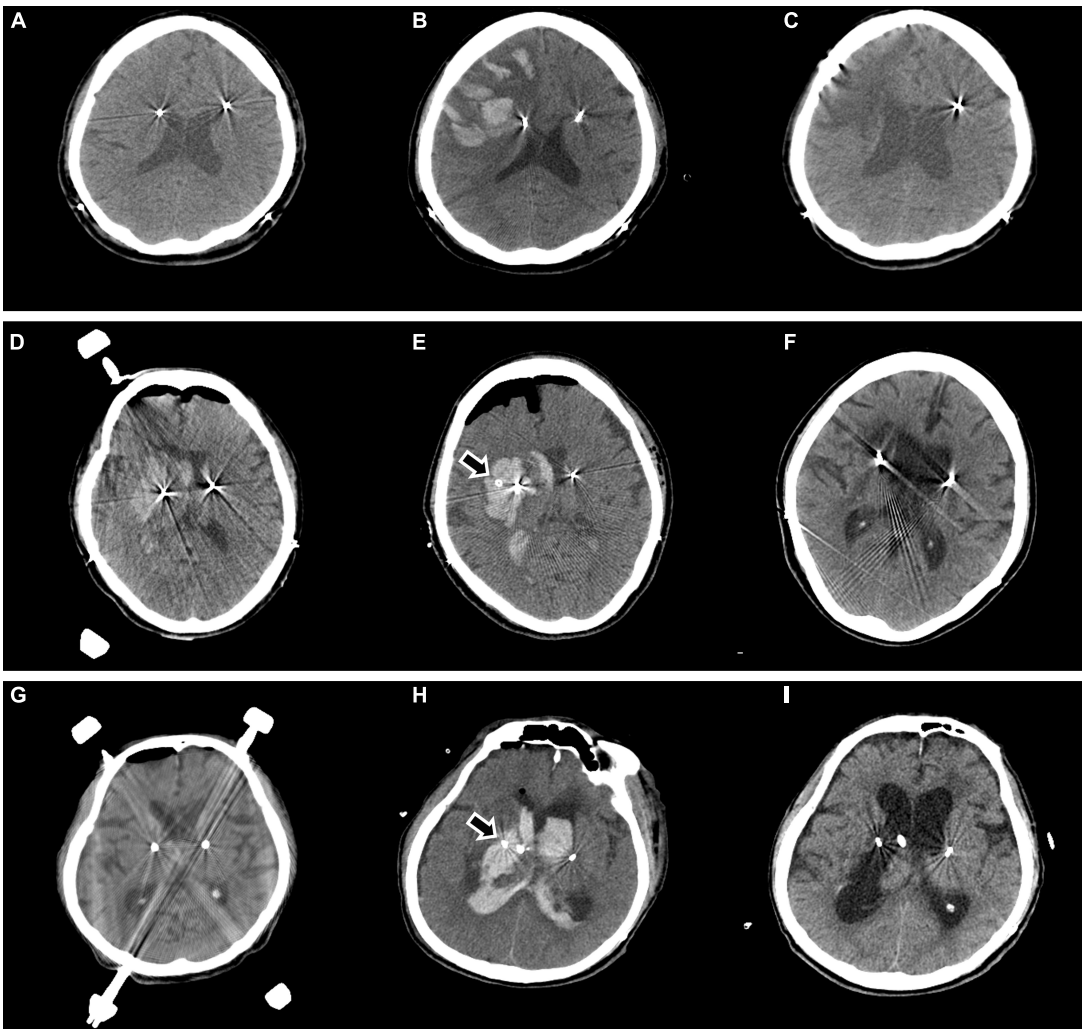

FIGURE 4 | Major ICH requiring surgical treatment is observed in three cases. In one patient, no abnormalities are observed on brain CT immediately after surgery **(A)**, but ICH developed in the right frontal lobe with seizures 8 h after surgery **(B)**. The patient underwent craniotomy and hematoma evacuation due to a large ICH, increased edema, and a midline shift. Two months later, the patient was transferred for rehabilitation **(C)**. In another patient, right thalamic ICH and IVH are observed on brain CT after intracranial electrode insertion **(D)**, and hematoma catheter insertion was performed immediately (**E** arrow). After 1 month, the ICH was resolved, and the patient was transferred for rehabilitation **(F)**. In another patient, no abnormalities are observed on brain CT immediately after surgery **(G)**, but right thalamic ICH and IVH are observed on brain CT 16 h after the surgery, and hematoma catheter insertion was performed (**H** arrow). The hematoma is resolved **(I)**, but the patient died from aspiration pneumonia on postoperative day 30. ICH, intracerebral hemorrhage; CT, computed tomography; IVH, intraventricular hemorrhage.

should perform subcutaneous tunneling of extension wires at an appropriate depth during surgery. Skin erosion may occur later if the tunneling at a subcutaneous level is too shallow and close to the skin. We predicted that people with low BMI have a thin subcutaneous fat layer, so the extension passes close to the skin, increasing the occurrence of skin erosion and infection. However, our prediction did not achieve statistical significance in this study but only a statistical tendency. In patients with a thin subcutaneous fat layer, additional small skin incisions in the retro auricular or peri clavicle areas could help in subcutaneous tunneling at the appropriate depth.

Although statistical significance was not reached in the present study, many studies had reported that operation time and blood loss affect postoperative infection in DBS surgery (Ogihara et al., 2009; Wong et al., 2012; Tolleson et al., 2014). Therefore, we attempted to minimize operation time and blood loss in DBS surgery. The average operation time at our institution was 326.7 min in the beginning, but recently, it has been greatly reduced to 215.5 min. The primary reason for the shortened surgery time is the application of a single subcutaneous tunneling and a single battery insertion by using one double-channel battery instead of two single-channel batteries in bilateral DBS surgery since 2017. The second reason is using intraoperative CT, performed in our institution since 2018. Previously, after the first stage of intracranial electrode insertion, the patient had to leave the operating room and move to the CT room to verify electrode location. After the introduction of intraoperative CT, performing CT scans in the operating room allowed shortening

TABLE 3 | Characteristics of patients who developed intracerebral hemorrhage after deep brain stimulation surgery.

Characteristics	Normal case (*N* = 416)	Case with ICH (*N* = 10)	*p*
Sex			0.756
Female	221 (53.1%)	6 (60.0%)	
Male	195 (46.9%)	4 (40.0%)	
Age (y)	57.5 ± 11.9	60.1 ± 9.1	0.488
Primary disease			0.644
Parkinson's disease	306 (73.6%)	9 (90.0%)	
Dystonia	70 (16.8%)	1 (10.0%)	
Essential tremor	40 (9.6%)	0 (0.0%)	
Operation time (min)	288.2 ± 74.7	245.5 ± 74.5	0.075
Blood loss (mL)	19.3 ± 47.8	41.0 ± 95.0	0.490
BMI	22.8 ± 3.3	23.0 ± 3.2	0.827
Hypertension	88 (21.2%)	4 (40.0%)	0.233
Diabetes mellitus	37 (8.9%)	2 (20.0%)	0.231

ICH, intracerebral hemorrhage; BMI: body mass index.

of the operation time. The last reason is the accumulation of experience. This includes advances in the skills of the neurosurgeon, such as skin incision, drilling, and suture, and the rapid assessment of microelectrode recording when inserting intracranial electrodes. In addition, fast and accurate reading of the microelectrode recording is important for the proper placement of the intracranial electrode (Kocabicak et al., 2019; Soares et al., 2019; Reddy et al., 2020). We consider that the accumulation of experience and the technological advances in DBS surgery could shorten the operation time and reduce the complications and infections rates.

Intracerebral hemorrhage caused by intracranial electrode insertion is the most fatal among the complications after the DBS surgery; it is the most common cause of mortality and morbidity in DBS surgery. In this study, asymptomatic minor ICH that did not require surgical management occurred in four patients, symptomatic minor ICH that did not require surgical management occurred in three patients, and major ICH that required surgical management occurred in three patients. After the DBS surgery, the incidence of all ICH is 2.3%, and the incidence of a major ICH is 0.7%. In previous investigations, the incidence of an ICH after DBS surgery was 2.5–5.1% (Schuurman et al., 2000; Oh et al., 2002; Fenoy and SimpsonJr., 2014; Falowski et al., 2015; Park et al., 2017). Since the target location is fixed in DBS surgery, neurosurgery can modify the intracranial electrode trajectory by moving the entry point. Therefore, the neurosurgeon should carefully analyze the preoperative MRI to establish a trajectory to avoid arteries and veins. Although hypertension was not significantly higher in patients who developed ICH after DBS surgery in this study, previous investigations reported hypertension as a risk factor for ICH after DBS surgery. Voges et al. (2007) found that arterial hypertension and coagulopathy are risk factors for ICH after DBS surgery in patients aged ≥ 60 years. Yang et al. (2020) reported that male sex and hypertension are risk factors for ICH after

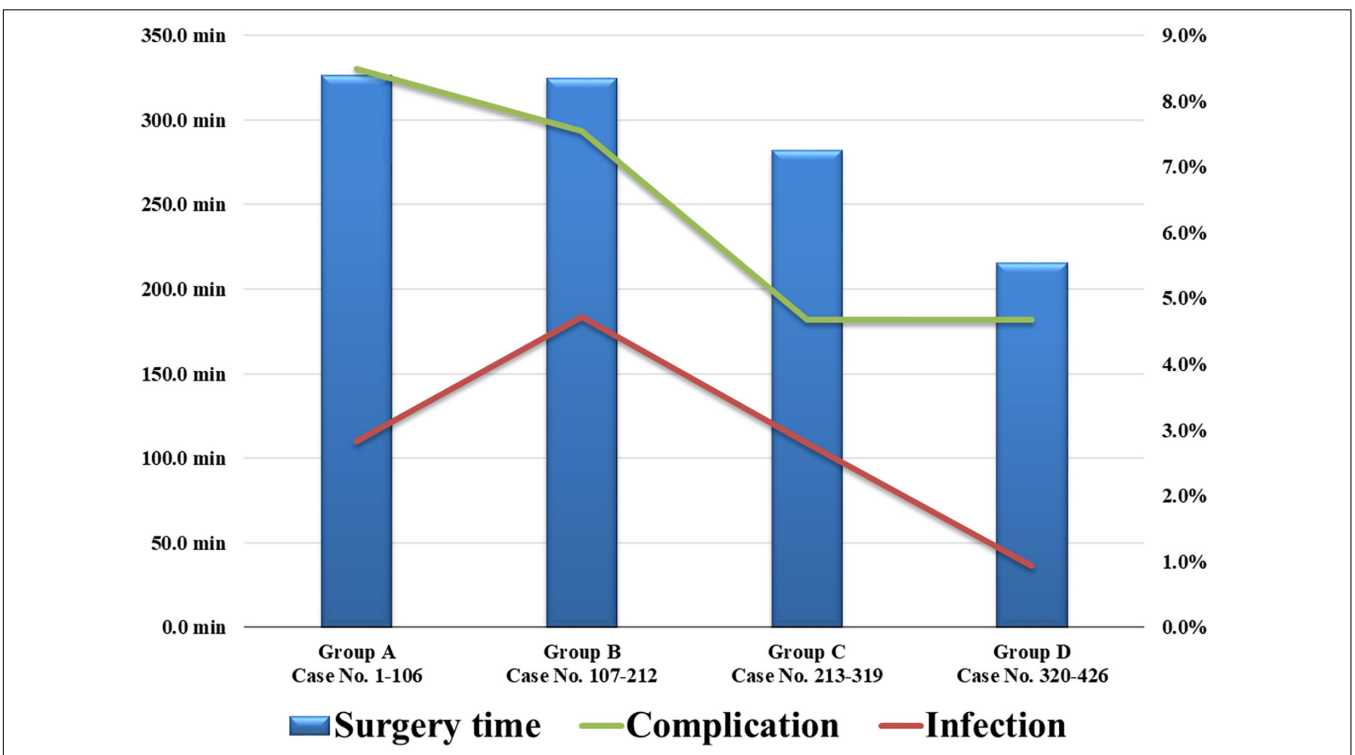

FIGURE 5 | The 426 cases of bilateral DBS surgery were divided into four chronological groups based on their operation date. The recent average operation time and complications and infections rates were reduced. DBS, deep brain stimulation.

DBS in Parkinson's disease. Two of the three patients with major ICH had no specific findings on immediate postoperative CT, but an ICH was observed on follow-up CT within 16 h of surgery. Therefore, we recommend careful blood pressure control during DBS surgery and up to 1 day after surgery.

Apart from infection and ICH, surgery-related complications include IPG repositioning, removal due to low therapeutic effect, and intracranial electrode repositioning.

Internal pulse generator repositioning was performed in three cases due to interrogation or recharging problems. This problem was not due to a defective device but due to an improper fixation of the IPG. Therefore, we classified these three cases of IPG repositioning as surgery-related complications and not hardware-related complications. IPG repositioning causes discomfort to the patient and may cause the IPG to overturn, thus interfering with the interrogation and recharging of the IPG. In addition, the continuation of IPG movement is the cause of the Twiddler's syndrome mentioned earlier. The Twiddler's syndrome was first described in patients with pacemakers and has been occasionally reported in patients with DBS (Burdick et al., 2010; Gelabert-Gonzalez et al., 2010; Penn et al., 2012; Franzini et al., 2018; Jackowiak et al., 2019; Adams and Shivkumar, 2020). This syndrome occurs because of the manipulation of the IPG within its subcutaneous pocket by the patient, leading to twisting of the extension wires and eventually an extension wire fracture. In previous studies, loose subcutaneous tissue, obesity, old age, obsessive-compulsive behavior, large subcutaneous pockets, and inappropriate IPG fixation were reported as predisposing factors for Twiddler's syndrome (Machado et al., 2005; Geissinger and Neal, 2007; Israel and Spivak, 2008; Burdick et al., 2010; Gelabert-Gonzalez et al., 2010; Astradsson et al., 2011; Silva et al., 2014; Sobstyl et al., 2015, 2017). Neurosurgeons cannot change patient characteristics such as subcutaneous tissue, age, and behavior. However, the IPG repositioning revision surgery incidence can be reduced by creating an appropriately sized subcutaneous pocket and performing firm multiple suture anchors.

Low therapeutic effect removal was performed in three cases. The device was removed or repositioned when the patient's symptoms did not improve despite the precise placement of the intracranial electrode in the planned location. The incidence of these complications requiring revision surgery may be reduced through a more careful patient selection and better preoperative target planning.

There were three cases where intracranial electrode repositioning was performed due to displacement of the intracranial electrode from our planned location. These complications can be reduced if the neurosurgeon fixes the electrode firmly and prevents the electrode from moving during skin and subcutaneous sutures.

Hardware-related complications occurred in three patients, including fracture or disconnection of extension wires. Normal DBS function was restored in all three patients by replacing the defective extension wire. Hardware-related complications accounted for a small proportion of the complications requiring revision surgery after DBS (3/27, 11.1%). We expect that advances in technology and improvement of DBS devices will further lower the hardware-related complication rate. All hardware-related complications occurred before 2010, and none occurred after 2010.

Our study is limited by its retrospective study design. In addition, since the number of infection cases (12 cases) and ICH cases (10 cases) was small, there may be a bias in statistical analyses identifying their characteristics. Therefore, caution should be exercised in the interpretation of the statistical analyses.

In conclusion, various complications can occur after DBS surgery. Twenty-six (6.1%) patients had complications requiring revision surgery, with the most common complication being infection (12 patients, 2.8%). These complications worsen the patient's prognosis. We attempted through this study to share our experience in the management of DBS complications and our efforts to reduce them. We believe that our experience is potentially helpful for neurosurgeons performing DBS surgery.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of Severance Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

I-HJ: original draft, data curation, formal analysis, and methodology. KC and SP: data curation and formal analysis. WC and HJ: review and editing. JC: supervision, resources, review, and editing. All authors contributed to the article and approved the submitted version.

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Application of Neurotoxin-Induced Animal Models in the Study of Parkinson's Disease-Related Depression: Profile and Proposal

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Depression can be a non-motor symptom, a risk factor, and even a co-morbidity of Parkinson's disease (PD). In either case, depression seriously affects the quality of life of PD patients. Unfortunately, at present, a large number of clinical and basic studies focused on the pathophysiological mechanism of PD and the prevention and treatment of motor symptoms. Although there has been increasing attention to PD-related depression, it is difficult to achieve early detection and early intervention, because the clinical guidelines mostly refer to depression developed after or accompanied by motor impairments. Why is there such a dilemma? This is because there has been no suitable preclinical animal model for studying the relationship between depression and PD, and the assessment of depressive behavior in PD preclinical models is as well a very challenging task since it is not free from the confounding from the motor impairment. As a common method to simulate PD symptoms, neurotoxin-induced PD models have been widely used. Studies have found that neurotoxin-induced PD model animals could exhibit depression-like behaviors, which sometimes manifested earlier than motor impairments. Therefore, there have been attempts to establish the PD-related depression model by neurotoxin induction. However, due to a lack of unified protocol, the reported results were diverse. For the purpose of further promoting the improvement and optimization of the animal models and the study of PD-related depression, we reviewed the establishment and evaluation strategies of the current animal models of PD-related depression based on both the existing literature and our own research experience, and discussed the possible mechanism and interventions, in order to provide a reference for future research in this area.

Keywords: Parkinson's disease, non-motor symptoms, depression, animal model, neurotoxin

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INTRODUCTION

Parkinson's disease (PD) is the most common degenerative dyskinesia disease at present. Motor retardation is the core diagnostic symptom of PD (Postuma et al., 2015). Pathologically, the progressive loss of dopaminergic neurons in substantia nigra and the formation of Lewy bodies are its main features (Ross and Bu, 2018). It has been more than 200 years since our recognition of PD (Zeng et al., 2018b), but its real etiology and pathogenesis are still unclear. The mainstream hypothesis is that PD is triggered by multiple factors including environmental, genetic, and aging factors (Fleming, 2017). Under the predicament that overemphasis on the diagnosis and treatment of motor symptoms still fails to stop the progression of the disease, people gradually realize that the non-motor symptoms (such as depression and olfactory disorder) that may manifest before the motor symptoms are potential indicators for early detection and early intervention of PD (Hasegawa, 2012). Depression, as one of the indicators, is receiving more and more attention. Similar to the effects of depression on other neurological diseases, it can cause many adverse consequences in PD patients (Menon et al., 2015) such as increasing the difficulty in the diagnosis and treatment of PD, inducing or aggravating PD symptoms, reducing patient compliance to treatment and rehabilitation, significantly increasing the rates of functional disability, recurrence, and mortality, severely reducing the quality of life of patients, and significantly increasing the economic burden on society. Although physicians and neuroscientists have been trying to solve the problem of PD-related depression, unfortunately, the relationship between depression and PD is still unclear. In the past, it was believed that depression is only a psychological stress reaction to the diagnosis of PD, just like people's pessimistic reaction to other chronic diseases such as diabetes. However, depression actually more commonly affects PD patients than people with other chronic diseases, it shows that the rate of severe depression is twice that seen in other equivalently disabled patients (Remy et al., 2005). Especially, there is a high risk of depression in the first year after the initial diagnosis of PD (Galts et al., 2019). Therefore, it is definitely not as simple as a psychological stress reaction after the diagnosis of the disease. Of course, it is also not likely that depression occurs solely as a secondary reaction to motor deficits in PD because the natural history of depression in PD does not parallel the progression of physical symptoms (Lemke et al., 2004).

With the progress of the study, people also found that depression may be a non-motor symptom in the whole course of PD, which can occur before (in the prodromal phase), synchronous to, and after the manifestation of motor symptoms (Storch et al., 2008). A recent-year study showed that the incidence of PD is higher in people with depression than in those without depression (Schuurman et al., 2002), which suggested that depression may also be a pathogenic factor of PD (Gustafsson et al., 2015). Based on these, we can see that the relationship between depression and PD is very complex. This also explains why there are big differences in the incidence (between 4% and 75%) and prevalence (between 2.7% and 90%) of PD-related depression based on epidemiological surveys (Reijnders et al., 2008). Whether depression is a premonitory non-motor symptom (Lemke et al., 2004), a risk factor (Ishihara and Brayne, 2006), or a co-morbidity of PD (Yapici Eser et al., 2017) is still unanswered at present. However, in either case, depression will lead to catastrophic consequences, as it increases the risk of developing PD and aggravates the conditions of PD patients. Therefore, early detection, diagnosis, and treatment of PD-related depression are particularly important. Especially if depression acts as a risk factor or non-motor symptom in the prodromal period of PD, we could stretch its potential as a biological marker to assist diagnosis, guide intervention, and predict prognosis before the occurrence of motor impairment, in order to maintain the health of patients.

Unfortunately, the reality is not optimistic. At present, a large number of clinical and basic studies are focused on how to better prevent and treat depression secondary to or combined with PD. Therefore, it is difficult to really achieve the early detection, diagnosis, and treatment. Why is there such a dilemma? The lack of systematic and standardized establishment and application of the animal model of PD-related depression may be an important reason. As we all know, the utilization of PD animal models has been very mature, especially the neurotoxin-induced model (Schober, 2004; Zeng et al., 2018a), and more and more studies have found that many non-motor symptoms similar to clinical patients, including depression-like behavior, can be seen in neurotoxin-induced PD animal models (Faivre et al., 2019). Therefore, it is worth thinking whether the neurotoxin-induced PD model can be used directly or after modification in the study of PD-related depression. This article comprehensively reviewed the general depression-like phenotype of PD animal models induced by different neurotoxins, and summarized the possible mechanisms and effective intervention measures, in order to provide new ideas for the study of PD-related depression.

1-METHYL-4-PHENYL-1,2,3,6-TETRAHYDROPYRIDINE (MPTP) AND PD-RELATED DEPRESSION

The induction of Parkinsonian-like symptoms by MPTP was discovered in the 1980s from the misuse of defective chemosynthetic drugs by drug users (Schintu et al., 2012). Since then, with the in-depth study of the role of environmental toxins in the development of PD, MPTP has received widespread attention as an experimental tool to simulate PD, especially in the establishment of PD animal models. Non-human primates and mice are common MPTP-induced PD model animals, and other models using rats, guinea pigs, and miniature pigs have also been reported. However, it is worth noting that rats are not sensitive to MPTP due to the limited ability of transforming MPTP to its active form 1-methyl-4-phenylpyridium (MPP^+). Therefore, rats should be induced directly with $MPP^+$for the modeling of PD. In general, MPTP is mostly administered by intraperitoneal injection (Airavaara et al., 2020), and of course, there are other routes including subcutaneous injection, intramuscular injection, intravascular injection, tube feeding,

nasal dripping, and brain stereotactic injection. According to the dose and frequency of intraperitoneal injection of MPTP, the MPTP-induced PD models can be divided into three types: acute, subacute, and chronic (Jackson-Lewis and Przedborski, 2007). In the acute model, MPTP was administered at 15–20 mg/kg every 2 h for four times. In the subacute model, the animals were treated with 25 mg/kg MPTP per day for five consecutive days. In the chronic model, also called the "progressive model", MPTP was given at 25 mg/kg every 3.5 days for 5 weeks, with the addition of Probenecid before each injection to increase the abundance of MPTP in the brain. Each type has its own pros and cons, and the phenotypes varied with the type and age of animals. In either type, most animal studies simulated the motor impairment symptoms of PD, but non-motor symptoms, especially depression-like behavior, were still inconclusive. With the continuous attempts at modification of the MPTP induction method, some studies have developed potential MPTP-induced animal models that could be used for the study of PD-related depression.

General State of PD-Related Depression Model Induced by MPTP

As summarized in **Table 1**, the administration route of MPTP in PD-related depression models included intraperitoneal injection (Krupina et al., 2000, 2002, 2006, 2010; Pankova et al., 2004; Khlebnikova et al., 2009a,b, 2013; Chung et al., 2015; Zhang et al., 2015, 2016; Li et al., 2018; Sampaio et al., 2018; Kiselev et al., 2019; Okano et al., 2019; Tang et al., 2020; Yan et al., 2020), intranasal injection (Castro et al., 2013; Schamne et al., 2018), and stereotactic injection (Santiago et al., 2010; Barbiero et al., 2014; Moretti et al., 2015; Cunha et al., 2017), of which intraperitoneal injection was the main route. However, there were differences in the dose and time of MPTP administration. Notably, the neurotoxic effects of MPTP seem to be mediated by its active oxidative product MPP^+. In addition, it was also reported that MPP^+ was directly used to induce PD-related depression (Moretti et al., 2015; Cunha et al., 2017). It is worth noting that in the MPTP-induced model of PD-related depression, some only showed depression behavior without causing motor damage (Castro et al., 2013; Moretti et al., 2015; Cunha et al., 2017), which well simulated PD-related depression that occurs as a premonitory symptom to motor symptoms. Depression-like behaviors in MPTP-induced PD models were mostly evaluated by a set of classical animal behavior tests, such as the learned helplessness paradigm (Winter et al., 2007), including the forced swimming test (FWT), and tail suspension test (TST), which mainly manifested a helpless state of animals. Additionally, the splash test (ST) and the sucrose preference test (SPT), which were performed as an indicator of anhedonia (Matheus et al., 2016) also can be considered using. The brain regions studied were mainly the hippocampus, frontal cortex, and striatum. In particular, some studies reported the incidence of depression in the MPTP-induced PD model. For example, Tang et al. injected MPTP (30 mg/kg/day for 7 days) into 6–8-week old male C57BL/6 mice, and found about 60% of mice showed depression-like behavior (Tang et al., 2020), while Zhang et al. (2015) reported depression behavior in 66.7% of 22–26 g C57BL/6 mice after injection of MPTP (20 mg/kg/day for 7 days). Dissimilarly, some studies performed on MPTP models show no depressive symptoms in the SPT (Vucković et al., 2008; Gorton et al., 2010), FST (Santiago et al., 2010), and TST (Gorton et al., 2010). Another issue is that most MPTP-induced PD-related depression models used male rodents, whereas Schamne et al. induced PD model by intranasal administration of MPTP (1 mg/nostril) to female C57BL/6 mice of different ages (some underwent ovariectomy) to investigate the effects of gender and age (which actually reflect different hormone levels) on PD-related depression. It was found that adult female mice treated with MPTP were more likely to develop PD-related depression, and the manifestations were more diverse (such as easy to despair, anhedonia, and apathy; Schamne et al., 2018). Interestingly, anxiety-like behavior and cognitive memory impairment could also be seen in the MPTP-induced PD-related depression model (Cunha et al., 2017; Li et al., 2018). And PD models with the coexistence of pain and depression were also reported (Krupina et al., 2002, 2010).

Possible Mechanism of PD-Related Depression Induced by MPTP

Current research hotspot of the mechanism of PD-related depression in the MPTP-induced PD model lies in whether depressive behavior is accompanied by changes in neurotransmitters, neurotrophic factors, neuroinflammatory factors, oxidative stress, nerve regeneration, and synaptic plasticity. However, there have been few reports of altered signaling pathways, one of which is the PKA-CREB pathway (Zhang et al., 2016). The involvement of the mTOR-regulated VTA-mPFC (Ventral tegmental area-medial prefrontal cortex) neural loop on PD-related depression in the MPTP-induced mouse model has been reported (Tang et al., 2020), which for the first time verified the neural loop hypothesis in PD-related depression using PD animal model. Another research team explored the electrophysiological mechanism of MPTP-induced PD-related depression (Pankova et al., 2004). In addition, abnormal peripheral blood granulocyte count (suggesting changes in anti-inflammation and immune status) might play an important role in the development of PD-related depression (Krupina et al., 2000). Some studies also revealed that the changes in prolyl endopeptidase and dipeptidyl peptidase IV activities were also important influencing factors of PD-related depression (Bastías-Candia et al., 2019; Khlebnikova et al., 2009a).

Possible Interventions in PD-Related Depression Induced by MPTP

At present, therapeutic intervention against depression in MPTP-induced PD models mainly includes transmitter supplementation, anti-inflammation, anti-oxidation, promoting nerve regeneration, etc., and most of the drugs used are "traditional" drugs. Among them, the use of lipid-lowering agents has been mentioned by several studies. A nasal drip of Atorvastatin could improve the MPTP-induced depression behavior by increasing the levels of nerve growth factors in the striatum and hippocampus (Castro et al., 2013). Simvastatin

TABLE 1 | Summary of animal models of PD-related depression induced by MPTP.

Number	Reference	Model animal	Gender	Route	Dosage of MPTP/MPP+	Assessment of depression behavior
1	Zhang et al. (2016)	8-week 24–26 g C57BL/6 mice	Male	i.p.	MPTP (25 mg/kg) once a day for five consecutive days	FST↑, TST↑
2	Chung et al. (2015)	8–9-week 18–25 g C57BL/6 and ICR mice	Male	i.p.	MPTP (20 mg/kg) every 2 h for three times in one day	TST↑
3	Okano et al. (2019)	8–10-week 20–27 g C57BL/6J mice	Male	i.p.	MPTP (16, 17.5, 19, 20 mg/kg) every 2 h for four times in one day	TST↑
4	Sampaio et al. (2018)	90-day 22–30 g C57BL/6 mice	Male	i.p.	MPTP (20 mg/kg) every 2 h for four times in one day	FST↑
5	Yan et al. (2020)	C57BL-6 mice	Male	i.p.	MPTP (30 mg/kg) once a day for five consecutive days	TST↑, ST↓
6	Tang et al. (2020)	6–8-week C57BL/6 mice	Male	i.p.	MPTP (30 mg/kg) once a day for seven consecutive days	TST↑, FST↑, SPT↓
7	Zhang et al. (2015)	22–26 g C57BL/6 mice	Male	i.p.	MPTP (25 mg/kg) once a day for seven consecutive days	SPT↓, FST↑, TST↑
8	Krupina et al. (2000)	320–380 g albino Wistar rats	Male	i.p.	MPTP (20 mg/kg) once a day for 14 consecutive days	SPT↓, FST↑
9	Pankova et al. (2004)	380–430 g Wistar rats	Male	i.p.	MPTP (20 mg/kg) once a day for 13 consecutive days	/
10	Krupina et al. (2006)	320–450 g Wistar rats	Male	i.p.	MPTP (20 mg/kg) once a day for 14 consecutive days	SPT↓, FST↑
11	Khlebnikova et al. (2009a)	400–450 g Wistar rats	Male	i.p.	MPTP (20 mg/kg) once a day for 14 consecutive days	SPT↓, FST↑
12	Khlebnikova et al. (2013)	340–400 g Wistar rats	Male	i.p.	MPTP (20 mg/kg) once a day for 14 consecutive days	SPT↓, FST↑
13	Khlebnikova et al. (2009b)	320–450 g Wistar rats	Male	i.p.	MPTP (20 mg/kg) once a day for 14 consecutive days	SPT↓, FST↑
14	Kiselev et al. (2019)	20–22 g outbred mice, 24–26 g inbred C57BL/6 mice, 250–280 g outbred albino rats	Male	i.p.	MPTP (30 mg/kg)	FST↑
15	Li et al. (2018)	8-week C57BL/6 mice	Male	i.p.	MPTP (25 mg/kg) once a day for five consecutive days	SPT↓, FST↑, TST↑
16	Krupina et al. (2010)	350–450 g Wistar rats	Male	i.p.	MPTP (20 mg/kg) once a day for 2 weeks	SPT↓, FST↑

(Continued)

TABLE 1 | Continued

Number	Reference	Model animal	Gender	Route	Dosage of MPTP/MPP+	Assessment of depression behavior
17	Krupina et al. (2002)	350–450 g albino Wistar rats	Male	i.p.	MPTP (20 mg/kg) once a day for 16 consecutive days	SPT↓, FST↑
18	Schamne et al. (2018)	3-month 20–25 g C57BL/6 mice (some were ovariectomized at 2 months old) and 20-month 25–30 g female C57BL/6 mice	Male Female	bilateral nasal drip	MPTP (1 mg/nostril)	SPT↓, ST↓, TST↑, FST↑
19	Castro et al. (2013)	4-month 300–350 g Wistar rats, 25–30 day Wistar rats	Male	bilateral nasal drip	MPTP (1 mg/nostril)	FST↑, SPT↓
20	Barbiero et al. (2014)	3-month 280–320 g Wistar rats	Male	stereotactic injection (bilateral SN)	MPTP (100 μg/site)	FST↑
21	Santiago et al. (2010)	280–320 g Wistar rats	Male	stereotactic injection (bilateral SN)	MPTP (100 μg/site)	ModifiedFST↑, SPT↓
22	Moretti et al. (2015)	3-month 30–35 g C57BL/6 mice	Male	stereotactic injection (bilateral SN)	MPP+ (8 μg/site)	TST↑, ST↓
23	Cunha et al. (2017)	60–75-day 25–35 g C57BL/6 mice	Male	stereotactic injection (bilateral SN)	MPP+ (1.8 μg/mouse and 18 μg/mouse)	FST↑, TST↑, ST↓

i.p., intraperitoneal injection; SN, substantia nigra; FST, forced swimming test; TST, tail suspension test; SPT, sucrose preference test; ST, spatter test. ↑, The increased immobility time;↓, The presence of anhedonia.

treatment alleviated hippocampal nerve inflammation and to some extent reversed the depression symptoms of PD mice (Yan et al., 2020). In addition to statins, Fenofibrate, a fibrate type of lipid-lowering drug, has been found to have antidepressant effects in MPTP-induced PD Wistar rats (Barbiero et al., 2014). At present, among the widely used antidepressants, only Fluoxetine has been used in the treatment of MPTP-induced PD-related depression (Zhang et al., 2015), and its antidepressant effect was not achieved through the classical pathway, but by affecting the expression of the 5-HT2B receptor on astrocytes. The role of Praxol, an antidepressant drug recommended in the clinical guidelines, on MPTP-induced PD-related depression was only mentioned when compared to the antidepressant effect of Selegiline, a monoamine oxidase B (MAOB) inhibitor (Okano et al., 2019). In addition, it was found that 1-[2-(4-Benzyloxyphenoxy) Ethyl] Imidazole could also improve the motor and depression symptoms of MPTP-induced mice by inhibiting MAOB (Chung et al., 2015). Other drugs, such as Crocin (Tang et al., 2020), dopamine D1 receptor agonist (Zhang et al., 2016), Pioglitazone (Barbiero et al., 2014), 7-Fluoro-1, 3-diphenylisoquinoline (Sampaio et al., 2018), Agmatine (Moretti et al., 2015), N-(5-Hydroxynicotinoyl)-L-glutamic acid (Khlebnikova et al., 2009a; Kiselev et al., 2019), benzyloxycarbonyl-methionyl-2(S)-cyanopyrrolidine (Khlebnikova et al., 2009b, 2013), and serum albumin (Pankova et al., 2004) also showed different degrees of anti-depressant effects in MPTP-induced PD models.

6-HYDROXYDOPAMINE (6-OHDA) AND PD-RELATED DEPRESSION

6-OHDA is a neurotoxin formed by the reaction of dopamine quinone (a substance produced by the redox reaction of dopamine during oxidation) in the presence of iron. It was found in the 1960s that 6-OHDA could lead to the degeneration of the substantia nigra-striatum system. In the 1970s, 6-OHDA was successfully used to establish the first animal model of PD with substantia nigra-striatum lesions (Airavaara et al., 2020). After that, there were more studies on 6-OHDA-induced PD models *in vivo*, and all of them have achieved good results. The animals used were mainly rodents (rats, mice, and guinea pigs), cats, and primates, and the most popular method was the injection of 6-OHDA into the medial forebrain bundle (MFB), substantia nigra, and striatum. As more and more studies have confirmed that there is a window between 6-OHDA-induced substantia nigra degeneration and the appearance of dyskinesia, which emphasizes its value in the preclinical study of PD (Branchi et al., 2008).

General State of PD-Related Depression Induced by 6-OHDA

As shown in **Table 2**, the administration route of 6-OHDA-induced PD-related depression models was only stereotactic cerebral injection. Besides the three common injection sites MFB, substantia nigra, and striatum, injection in the locus ceruleus (Szot et al., 2016; Sampaio et al., 2019), lateral ventricle (Chenu et al., 2007), and ventral tegmental area of the midbrain (Furlanetti et al., 2016) have also been reported. Injections can be bilateral or unilateral, and the MFB is the most common site for unilateral injection, whereas the striatum is the most common site for bilateral injections. One study compared bilateral striatum injection and unilateral substantia nigra injection (Chen et al., 2014). In terms of the choice of animals, rats were most commonly used and mice accounted for only 8 out of 45 studies. The dosage of 6-OHDA is not uniform at present. The depression phenotypes were evaluated by behavioral tests such as SPT, FST, TST, and ST, but it is worth noting that more than half of the studies (28/45) used only one test to evaluate depression-like behavioral changes, which was mostly FST (16/28). PD-related depression is more common in 6-OHDA-induced animals with motor impairment and is sometimes combined with other non-motor manifestations such as anxiety, cognitive memory impairment, olfactory disorder, and rhythm disorder. Meanwhile, it is encouraging that the study of depression as a prodrome of motor impairment is increasing (Branchi et al., 2008; Matheus et al., 2016; Szot et al., 2016; Marques et al., 2019; Sampaio et al., 2019), in which a small dose injection of 6-OHDA in locus ceruleus is worthy of attention. In addition, it is worth further investigation that some 6-OHDA-induced models developed transient hypokinesia that spontaneously remitted, but with a persistent depressant phenotype. The exploration of the influence of gender on PD-related depression has also been reported in the 6-OHDA-induced model (Sullivan et al., 2014). Interestingly, this study not only looked into the gender factor but also compared the correlations between each cerebral hemisphere and PD-related depression. Other studies on 6-OHDA induction combined life stress (Furlanetti et al., 2015; Dallé et al., 2020) suggested that stress+neurotoxin might be a better composite model for the study of PD-related depression.

Possible Mechanism of PD-Related Depression Induced by 6-OHDA

The exploration of the mechanism of PD-related depression using the 6-OHDA induction model is currently focused on the changes in nerve regeneration, neurotransmitter, oxidative stress, nerve inflammation, neuronutrition, etc. The hotspot brain area of study included the striatum, hippocampus, nucleus accumbens, lateral habenular nucleus, and ventral tegmental area, but there were still few studies on signaling pathways, including the BDNF-TrkB (brain-derived neurotrophic factor-tyrosine kinase receptor B; Tuon et al., 2014; Sun et al., 2016) and Wnt/β-catenin signaling pathways (Singh et al., 2017; Mishra et al., 2019). In the studies of 6-OHDA-induced PD-related depression, there was no report on the involvement of the neural loop. But some studies, suggested that the ipsilateral and contralateral connections between the midbrain dopamine system and the medial prefrontal cortex might play an important role (Petri et al., 2015).

TABLE 2 | Summary of animal models of PD-related depression induced by 6-OHDA.

Number	Reference	Model animal	Gender	Location of stereotactic cerebral injection	Dosage of 6-OHDA	Assessment of depression behavior
1	Santiago et al. (2010)	280–320 g Wistar rat	Male	bilateral SN	6 μg/side	Modified FST↑, SPT↓
2	Matheus et al. (2016)	12–16-week Wistar rats	Male	bilateral dorsal striatum	10 μg/side	SPT↓, ST↓, FST↑
3	Kamińska et al. (2017)	290–320 g Wistar Han rats	Male	unilateral MFB	8, 12, 16 μg	SPT↓
4	Alzoubi et al. (2018)	150–200 g adult Wistar rats	/	unilateral MFB	4 μg	TST↑
5	Souza et al. (2018)	75-day 280–320 g Wistar rats	Male	bilateral SN	6 μg/side	SPT↓
6	Beppe et al. (2015)	350 g Wistar rats	Male	unilateral SN	12.5 μg	FST↑
7	Feng et al. (2020)	350–400 g Wistar rats	Male	unilateral MFB	8 μg	FST↑
8	Santiago et al. (2015)	280–320 g Wistar rat	Male	bilateral SN	6 μg/side	Modified FST, ↑ SPT↓
9	Santiago et al. (2014)	280–320 g Wistar rat	Male	bilateral SN	6 μg/side	Modified FST↑, SPT↓
10	Kumari et al. (2018)	250–270 g adult Wistar albino rats	/	unilateral MFB	10 μg	FST↑
11	Casas et al. (2011)	60–120-day 280–340 g Sprague-Dawley rats	Male	unilateral striatum	2 μg	FST↑
12	Prakash et al. (2013)	180–250 g adult Wistar rats	Male	unilateral SN	12 μg	FST↑
13	Antunes et al. (2014)	18-month 25–35 g C57BL/6 mice	Female	unilateral striatum	5 μg	TST↑
14	Yan et al. (2019)	8-week 20–25 g C57BL/6 mice	Male	unilateral MFB	4 μg	SPT↓
15	Sampaio et al. (2019)	3-month 180–220 g Wistar rats	Male	bilateral locus ceruleus	5, 10, 20 μg/side	FST↑, SPT↓
16	Szot et al. (2016)	3-month 25 g adult C57BL/6 mice	Male	bilateral locus ceruleus	5, 10, 14 μg/side	FST↑, SPT↓
17	Kuter et al. (2011)	300–360 g Wistar rats	Male	bilateral ventrolateral region of caudate nucleus	3.75 μg/side	FST↑
18	Bonato et al. (2018)	280–320 g Wistar rats	Male	bilateral SN	6 μg/side	FST↑
19	Chenu et al. (2007)	4-week 18–20 g Swiss mice	Male	bilateral lateral ventricle	10, 20, 30 μg	FST↑
20	Guo et al. (2021)	adult 220–250 g Sprague-Dawley rats	Male	unilateral SN	12 μg	FST↑, SPT↓
21	Tuon et al. (2014)	25–30 g adult C57BL mice	Male	bilateral striatum	4 μg /side	FST↑
22	Ilkiw et al. (2019)	280–320 g Wistar rat	Male	bilateral SN	3 μg /side	Modified FST↑, SPT↓
23	Hsueh et al. (2018)	8–12-week-old 200 g–300 g Sprague-Dawley rats	Female	unilateral MFB	8 μg	FST↑
24	Marques et al. (2019)	3-month 300–350 g Wistar rats	Male	bilateral dorsal striatum	10 μg/side	SPT↓, ST↓, FST↑

(Continued)

TABLE 2 | Continued

Number	Reference	Model animal	Gender	Location of stereotactic cerebral injection	Dosage of 6-OHDA	Assessment of depression behavior
25	Vecchia et al. (2018)	270–300 g Wistar rats	Male	bilateral SN	6 μg/side	SPT↓
26	Silva et al. (2016)	3-month 270–300 g Wistar rats	Male	bilateral dorsal striatum	12 μg/side	SPT↓
27	Campos et al. (2013)	300–350 g young adult Wistar rats	Male	bilateral SN	8 or 6 μg/side	FST↑, SPT↓
28	Goes et al. (2014)	90-day 20–30 g C57BL/6J mice	Male	unilateral striatum	5 μg	TST↑
29	Chiu et al. (2015)	12-week C57BL/6 mice	Male	bilateral SN	4 μg/side	FST↑
30	Tadaiesky et al. (2008)	250 g-370 g Wistar rats	Male	bilateral dorsal striatum	12 μg/side	SPT↓, FST↑
31	Furlanetti et al. (2016)	250 g adult Sprague-Dawley rats	Female	bilateral ventral tegmental area of midbrain	3.6 μg/side	FST↑, SPT↓
32	Furlanetti et al. (2015)	250 g adult Sprague-Dawley rats	Female	unilateral MFB	19.8 μg	FST↑, SPT↓
33	Sun et al. (2016)	200–220 g adult Sprague-Dawley rats	/	unilateral MFB	8 μg	FST↑, SPT↓
34	Yu et al. (2020)	adult Sprague-Dawley rats	Male	unilateral striatum	20 μg	FST↑, TST↑
35	Bonito-Oliva et al. (2014)	25–30 g C57BL/6J mice	Male	bilateral dorsal striation	4 μg/side	TST↑, FST↑
36	Sinen et al. (2021)	3-month 250–300 g Wistar rats	Male	unilateral MFB	12 μg	SPT↓
37	Masini et al. (2018)	3-month 25–30 g C57BL/6J mice	Male	bilateral dorsal striatum	4 μg/side	FST↑
38	Petri et al. (2015)	220–280 g adult Wistar rats	Male	unilateral MFB	12.48 μg	FST↑
39	Branchi et al. (2008)	4-month Wistar rats	/	bilateral dorsal striatum	10.5 μg/side	FST↑, SPT↓
40	Chen et al. (2014)	280–300 g Wistar rats	Male	bilateral striatum, unilateral SN	12 μg/side of striatum; 8 μg per SN	SPT↓
41	Foyet et al. (2011)	230 ± 50 g Wistar rats	Male	unilateral SN	8 μg	FST↑
42	Dallé et al. (2020)	PND60-day 300 g Sprague-Dawley rats	Male	unilateral MFB	5 μg	SPT↓
43	Singh et al. (2017)	200–250 g Sprague-Dawley rats	Male	unilateral MFB	16 μg	FST↑
44	Sullivan et al. (2014)	250–275 g, Sprague-Dawley rats	Male, Female	left, right hemispheres (not bilateral)	4 μg	SPT↓
45	Mishra et al. (2019)	200–250 g adult Sprague Dawley rats	Male	unilateral MFB	16 μg	FST↑

PND, postnatal Day; SN, substantia nigra; MFB, medial forebrain bundle; FST, forced swimming test; SPT, sucrose preference test; ST, spatter test; TST, tail suspension test; ↑, The increased immobility time; ↓, The presence of anhedonia.

Possible Interventions in PD-Related Depression Induced by 6-OHDA

Among the many studies that discussed the prevention and treatment of PD-related depression in the 6-OHDA-induced models, a drug intervention is the most common method. Dixipramine (Kamińska et al., 2017), Piroxicam (Santiago et al., 2014), 5-HT4R agonists (Guo et al., 2021), Reboxetine (Bonito-Oliva et al., 2014), and Fluvoxamine (Dallé et al., 2020) could improve the depression symptoms in the 6-OHDA-induced models by increasing the level of relevant neurotransmitters. Etazolate (Alzoubi et al., 2018), aqueous extract of albizia leaves (Beppe et al., 2015), 1-(7-imino-3-propyl-2, 3-dihydrothiazolo [4, 5-d] pyrimidin-6(7H)-yl)urea (IDPU; Kumari et al., 2018), hesperidin (Antunes et al., 2014) and methanol extract of cottonrose hibiscus leaves (Foyet et al., 2011) could antagonize 6-OHDA-induced PD-related depression through the antioxidant stress response. Schisanhenol A (Yan et al., 2019) has been reported to improve depression symptoms in the 6-OHDA-induced PD model through the anti-inflammatory pathway. Although the antidepressant effect of Praxol has been verified in the 6-OHDA-induced PD model, its mechanism might involve changes in hippocampal regeneration (Chiu et al., 2015). In addition, MK-801 (Diazolizepine; Singh et al., 2017) and D1 receptor agonist (Mishra et al., 2019) were also suggested to improve depression behavior in 6-OHDA-induced PD model by promoting hippocampal nerve regeneration. Other drugs that could improve depression behaviors in 6-OHDA-induced PD models included Agametine (Souza et al., 2018), progesterone (Casas et al., 2011), granulocyte colony stimulating factor (G-CSF; Prakash et al., 2013), β3-adrenergic receptor agonist (Sampaio et al., 2019), Pioglitazone (Bonato et al., 2018), guanosine (Marques et al., 2019), Ketamine (Vecchia et al., 2018), imipramine (Vecchia et al., 2018), neuropeptide-S (Szot et al., 2016), Rapamycin (Masini et al., 2018) and Apamin (a selective blocker of small conductance calcium-activated potassium channels; Chen et al., 2014). It is alarming that Agomelatine has the risk of aggravating rhythm disorder besides its antidepressant effect (Souza et al., 2018). Excitingly, transcranial direct current stimulation (Feng et al., 2020), deep brain stimulation (Furlanetti et al., 2015, 2016), electroacupuncture (Sun et al., 2016; Yu et al., 2020), and exercise therapy (Goes et al., 2014; Tuon et al., 2014; Hsueh et al., 2018) also demonstrated certain effects on the improvement of depression in 6-OHDA-induced PD models, and most of them had multiple targets.

ROTENONE AND PD-RELATED DEPRESSION

With the in-depth epidemiological investigation of PD, more and more attention has been attracted to the relationship between environmental toxins, especially pesticides used in agriculture, and the development of PD, and Rotenone is one of them. Rotenone is an insecticidal flavonoid found in many legumes and has been used as fish poison in Peru. It was later found to have high lipophilicity and therefore easy to pass through the blood-brain barrier. Like MPTP, Rotenone leads to PD-like symptoms by inhibiting mitochondrial complex I and causing oxidative stress (Heinz et al., 2017). Also, it mediates the degeneration of dopaminergic neurons in the substantia nigra striatum caused by the accumulation of α-synuclein. Notably, rotenone leads to non-specific toxicity and motor impairment unrelated to nigral cell damage as well (Fleming et al., 2004; Klein et al., 2011). At present, Rotenone is often used to induce PD models in zebrafish and rodents, and the latter is mainly achieved by systemic injection or direct stereotactic injection. High-dose Rotenone effectively induces motor dysfunction but produces a significant lethal effect. Based on this, people have tried to modify its application to achieve a proper balance between efficacy and lethality. It is under this background that Rotenone-induced non-motor phenotypes of PD have also attracted much attention (Fontoura et al., 2017), among which the depression phenotype is one of the research hot spots.

General State of PD-Related Depression Induced by Rotenone

As shown in **Table 3** (Santiago et al., 2010; Morais et al., 2012; Noseda et al., 2014; Zaminelli et al., 2014; Shin et al., 2017; Wang et al., 2017; Madiha and Haider, 2019), there are less than 10 reports on Rotenone-induced PD-related depression by now, with most reports using rats as the model animal (6/8), and one report each with mouse and zebrafish. The number of reports of each administration route of Rotenone were: brain stereotactic injection (3/8), intraperitoneal injection (2/8), subcutaneous injection (2/8), and addition in water (similar to environmental exposure; 1/8). And the dosage of Rotenone was different in each report, even with the same administration route. As predicted, the brain areas affected were mostly the hippocampus and striatum, and in one article the dorsal raphe nucleus was affected (Shin et al., 2017). In terms of behavioral evaluation, due to the restriction in the living environment of zebrafish, the depression-like behavioral changes could only be evaluated by limited methods, which was the dark box test in this study (Wang et al., 2017). For the behavioral evaluation of rats and mice induced by rotenone, only SPT and FST, but no TST or ST were reported. In addition, the depression-like behavioral changes mostly occurred after the manifestation of dyskinesia, of course, occasionally accompanied by anxiety, olfactory disorders, and other non-motor symptoms. In addition, some studies have used a compound model of rotenone combined with rapid eye movement sleep deprivation (Noseda et al., 2014).

Possible Mechanism of PD-Related Depression Induced by Rotenone

Like the small number of total reports, there were few literatures on the mechanism of PD-related depression induced by Rotenone, which generally involved oxidative stress or neurotransmitter changes, whereas no specific signaling pathways or neural loops were involved.

Possible Interventions in PD-Related Depression Induced by Rotenone

In the limited number of reports, curcumin (Madiha and Haider, 2019), ibuprofen (Zaminelli et al., 2014), the melatonin

TABLE 3 | Summary of animal models of PD-related depression induced by Rotenone.

Number	Reference	Model animal	Gender	Administration route	Dosage of Rotenone	Assessment of depression behavior
1	Santiago et al. (2010)	280–320 g Wistar rats	Male	stereotactic injection (bilateral SN)	12 μg/side	ModifiedFST↑, SPT↓
2	Madiha and Haider (2019)	15–200 g Albino-Wistar rats	/	s.c.	1.5 mg/kg/day for eight consecutive days	FST↑, SPT↓
3	Morais et al. (2012)	200–230 g Wistar rats	Male	i.p.	2.5 or 5 mg/kg/day for 10 consecutive days	Modified FST↑, SPT↓
4	Zaminelli et al. (2014)	12-week 290–330 g Wistar rats	Male	i.p.	2.5 mg/kg/day for 10 consecutive days	Modified FST↑
5	Wang et al. (2017)	5–7 month wild-type Danio rerio	Male	in water	2 μg/L for 4 weeks	Dark box test
6	Noseda et al. (2014)	28–320 g Wistar rats	Male	stereotactic injection (bilateral SN)	12 μg/side	Modified FST↑
7	Chen et al. (2017)	8-week ICR mice	Male	stereotactic injection (unilateral lateral cerebroventricle)	0.2 μmol/kg, 5 μl	SPT↓, FST↑
8	Shin et al. (2017)	9-week Sprague-Dawley rats	Male	s.c.	3.0 mg/kg/day for 10 consecutive days	FST↑

SN, substantia nigra; i.p., intraperitoneal injection; s.c., subcutaneous injection; FST, forced swimming test; SPT, sucrose preference test.↑, The increased immobility time;↓, The presence of anhedonia.

MT2 receptor-selective antagonist 4-P-PDOT (Noseda et al., 2014), and exercise therapy (Shin et al., 2017) were found to improve the depression symptoms in the Rotenone-induced PD model.

LIPOPOLYSACCHARIDE (LPS) AND PD-RELATED DEPRESSION

LPS is an endotoxin released from the destroyed outer cell wall of Gram-negative bacteria. LPS can activate epithelial cells, mononuclear macrophages, and endothelial cells to synthesize and release many inflammatory mediators and cytokines through a variety of signaling pathways, thus triggering a series of reactions in the body (Morris and Li, 2012). In general, a high concentration of LPS causes an extensive and strong inflammatory response, while an appropriate concentration can initiate a moderate immune response to enhance immune function. With the increasing attention on the role of neuroinflammation in the development of PD (Vivekanantham et al., 2015), the successful establishment of animal PD models induced by LPS (Joers et al., 2017), and the in-depth exploration of the function of LPS in depression, the reports of LPS in the study of PD-related depression are also gradually increasing.

General Status of PD-Related Depression Induced by LPS

As shown in **Table 4**, there were fewer reports of PD-related depression induced by LPS. In the six studies we retrieved, the PD models were mainly induced by intraperitoneal injection of LPS in mice (4/6), with variance in sex and dose. The remaining two articles reported LPS-induced depression in PD rats, one by intraperitoneal injection and the other by brain stereotactic injection. Interestingly, despite the limited number of articles, several studies attempted low-dose LPS induction that caused only depression but no motor damage. In addition, FST was used in all six studies, either alone or in combination with SPT, SP, or TST. The only other non-motor symptom manifested was anxiety-like behavioral changes in these models.

Possible Mechanism of PD-Related Depression Induced by LPS

As LPS induces a strong inflammatory response, the mechanism of PD-related depression induced by LPS is generally considered to be related to neuroinflammation and neuroimmunity. As a matter of fact, neuronutrition and oxidative stress may also play important roles, especially the changes in the BDNF signaling pathway.

Possible Interventions in PD-Related Depression Induced by LPS

Based on the pro-inflammatory role of LPS, in theory, anti-inflammatory therapy should be the first choice of intervention for LPS-induced PD-related depression. However, among the interventional studies, there was only one literature that suggested improved depression symptoms in the LPS-induced PD model "simply" through anti-inflammatory

TABLE 4 | Summary of animal models of PD-related depression induced by lipopolysaccharide (LPS).

Number	Reference	Model animal	Gender	Administration route	Dosage of LPS	Assessment of depression behavior
1	Chen et al. (2017)	8-week ICR mice	Male	i.p.	0.8 mg/kg	FST↑, SPT↓
2	Hritcu and Gorgan (2014)	3-month 200 ± 50 g Wistar rats	Male	stereotactic injection (unilateral SN)	3 μg/kg, 10μg/kg	FST↑
3	Ventorp et al. (2017)	200 g Wistar rats	Male	i.p.	1 mg/kg	FST↑
4	Lieberknecht et al. (2017)	60–120-day 40–55 g Swiss mice	Female	i.p.	0.1 mg/kg	FST↑, ST↓
5	Yuan et al. (2020)	20–25 g C57BL/6 mice	Male	i.p.	0.83 mg/kg	FST↑, TST↑
6	Yang et al. (2016)	12-week adult mice	/	i.p.	330 μg/kg	FST↑, TST↑
7	Santiago et al. (2010)	Male Wistar rats	Male	stereotactic injection	2 μg/side	SPT↓, Modified FST↑

i.p., intraperitoneal injection; SN, substantia nigra; FST, forced swimming test; SPT, sucrose preference test; ST, splatter test; TST, tail suspension test.↑, The increased immobility time; ↓, The presence of anhedonia.

therapy using not conventional drugs but dopamine receptor agonist Praxol (Lieberknecht et al., 2017). In addition, BCG vaccination could improve LPS-induced PD-related depression through immune regulation, which was a far-fetched evidence of the interventional efficacy of anti-inflammation on PD-related depression (Yang et al., 2016). Although Besarotene was reported to play certain roles against LPS-induced PD-related depression through anti-inflammation, this effect might be mainly related to the restoration of dysregulated CREB/BDNF/ERK signaling pathway (Yuan et al., 2020). More surprisingly, the anti-depressant effect of Exendin-4, a glucagon-like peptide 1 (GLP-1) receptor peptide agonist, does not involve anti-inflammation, but to a large extent related to its effect on the synthesis or metabolism of dopamine (Ventorp et al., 2017). As previously mentioned, oxidative stress is one of the mechanisms of LPS-induced PD-related depression, Resveratrol might effectively intervene the depression symptoms in the LPS-induced PD model through blockade of oxidative stress (Chen et al., 2017).

OTHERS: PARAQUAT AND LACTOCIN AND PD-RELATED DEPRESSION

In addition to the above neurotoxins, paraquat, and lactocin were also reported to induce depression in PD animal models. Since there were only two reports of depression induced by paraquat and one report by lactocin, they are discussed together here.

Paraquat and PD-Related Depression

Paraquat (N,N'-dimethyl-4,4'-bipyridine) is an herbal compound with a similar structure to MPP^+, and is used as a herbicide in agriculture. It is specifically toxic to many organs of the human body. It crosses the blood-brain barrier into brain dopaminergic neurons unreliable on DAT but may be transported by neutral amino acid transporters in an age-dependent manner. The mechanism of paraquat-induced cell death is also different from that of MPP^+ and rotenone, because it cannot effectively block mitochondrial complex I, but involves the mitochondrial endogenous pathway (Fei et al., 2008). As paraquat can induce the accumulation of α-synuclein and the degeneration of dopamine neurons in substantia nigra, it was also used to establish PD animal models (Bastías-Candia et al., 2019). However, the phenotypes of models constructed by different studies were not consistent, and even contradictive in some cases, which more or less restricted its application. With the accumulating evidences that combined the use of paraquat with other compounds (such as manganic manganese) could cause more severe motor damage, its application in the establishment of PD models has regained new attention. Of course, its effects on PD-related depression and other non-motor disorders are also worthy of study.

Between the two studies of paraquat-induced PD models, one of them successfully induced PD-related depression by combined use of paraquat with mancozeb (Hou et al., 2019). Three-month-old male C57BL/6J mice received intraperitoneal

injection of paraquat (10 mg/kg) + mancozeb (30 mg/kg) twice a week for 4 weeks. Depression-like behavior was verified by FST. At the same time, this model also displayed non-motor functional changes such as constipation, learning difficulty, and memory impairment. In addition, this study inversely proved through pharmacological approaches that depression symptoms in the PD model might not be related to locus coeruleus and norepinephrine. In another report, a miniature osmotic pump was implanted in the subscapular area to introduce paraquat at a rate of 0.7 mg/day for 28 days, which successfully induced motor disorders as well as depression and anxiety (Campos et al., 2013).

Lactocin and PD-Related Depression

Lactocin, a proteasome inhibitor, is derived from the metabolites of Streptomyces in soil and widely exists in the environment (Kisselev and Goldberg, 2001). When susceptible people ingest Lactocin through daily contact and diet, it can cause functional deficiency of the ubiquitin-proteasome system by inhibiting the 20S/26S proteasome function, leading to the accumulation of abnormal proteins, and inducing a variety of diseases including PD. This is mainly because it can cause synuclein accumulation similar to the effect of paraquat, selectively kill dopaminergic neurons in the substantia nigra-striatum system, and decrease the level of striatal dopamine, resulting in motor dysfunction (Niu et al., 2009).

Some researchers have successfully constructed PD animal models using Lactocin, which showed typical PD symptoms that progressively aggravated (Harrison et al., 2019). There was no toxin accumulation in the animals and did not cause animal death or paralysis. However, some researchers believed that this model has poor repeatability which might be due to the poor absorption of Lactocin by the brain tissue due to the low solubility of Lactocin before administration or due to the formation of precipitation after injection, which could easily lead to the failure of the experiment. But it is still a method worth exploring if this problem can be solved. Recent studies have optimized the dose of Lactocin or used it in combination with other drugs such as LPS and observed a more significant phenotype of PD (Deneyer et al., 2019). However, the research on non-motor symptoms such as depression in Lactocin-induced models is still rarely reported. Only one study detected signs of depression for the first time in a preclinical experimental model of PD rat induced by intranasal administration of Lactocin (Ekimova et al., 2018).

REFLECTION AND CONCLUSION

The negative influences of depression in PD patients are more and more recognized. However, because of the complex relationship between depression and PD, the definition and classification of "PD-related depression" are not uniform at present. Accumulating clinical evidences show that depression is not only a risk factor for PD, but also a non-motor symptom, or even a co-morbidity of PD. When regarded as a non-motor symptom of PD, depression can appear synchronous with, before or after the motor impairment. Based on previous reports and our own clinical experience, we summarized the above issues in **Figure 1**, and put forward some thoughts on PD-related depression. Firstly, all the clinical cases of "depression" and "PD" encountered at present can be collectively referred to as "depression related to PD". When depression is "as a risk factor" of PD, it can be called "PD associated with depression", when "as a non-motor symptom" can be called "depression in PD", and when "as a co-morbidity" can be called "PD with depression." Secondly, it is unfortunate for individual patients no matter which of the above situations, therefore proper identification and treatment are most important. But from the aspect of community prevention and control, the situations shown in "1" and "2a" in **Figure 1** are the key nodes to achieve early detection and early intervention to avoid or delay subsequent dopaminergic neuronal damage, and to achieve proper neuroprotection. Thirdly, in the current clinical prevention and treatment guidelines for PD, treatment of depression is mostly based on the treatment of motor impairments. This is inevitable because as required by the current evidence-based medical principles, a patient with depression but without motor symptoms cannot be treated as PD-related depression in the first place even if the patient later developed PD symptoms. To resolve this dilemma, on one hand, it is necessary to launch large-scale prospective cohort studies in the target population, for example, the "Taicang cohort study" led by Professor Chun-feng Liu of our research team, which is currently carried out in Taicang, China. On the other hand, it is necessary to establish a suitable preclinical animal model for basic research. This is because when the neurobiological nature of PD-related depression is not yet fully understood, the use of animal models is still of great significance to improve our understanding of the etiology, pathophysiology, and molecular mechanism of PD. Besides, the research time for constructing animal models is relatively short. It will undoubtedly accelerate the research of PD-related depression if we can establish a suitable animal model.

At present, many animal models of PD have been recognized and widely used, which can be divided into two categories (Blesa et al., 2012): one is by damaging dopaminergic neurons using natural (e.g., Rotenone, LPS, Lactocin) or synthetic neurotoxins (e.g., MPTP, 6-OHDA, paraquat), and the other is by using transgenic animals containing PD-related gene variants. At present, the transgenic PD model is actually limited to transgenic mice with synaptic dopamine depletion, and the behavioral phenotype is usually not obvious. In addition, although there are several gene variants associated with the development of non-motor symptoms in PD patients (e.g., LRRK2, SNCA, Parkin, and VPS35), only a few studies have explored their effects on depression-like behavior in mice (Fontoura et al., 2017). It is worth noting that some studies have constructed a depression-PD co-morbidity animal model using Pitx3 (a risk gene of PD) deficient mice (Kim et al., 2014) or mice treated intraperitoneally with reserpine (Skalisz et al., 2002). Another study found Reserpine could be used to establish the depression-PD association animal model. An ideal PD-related depression animal model has four characteristics: (1) with significant and detectable depress

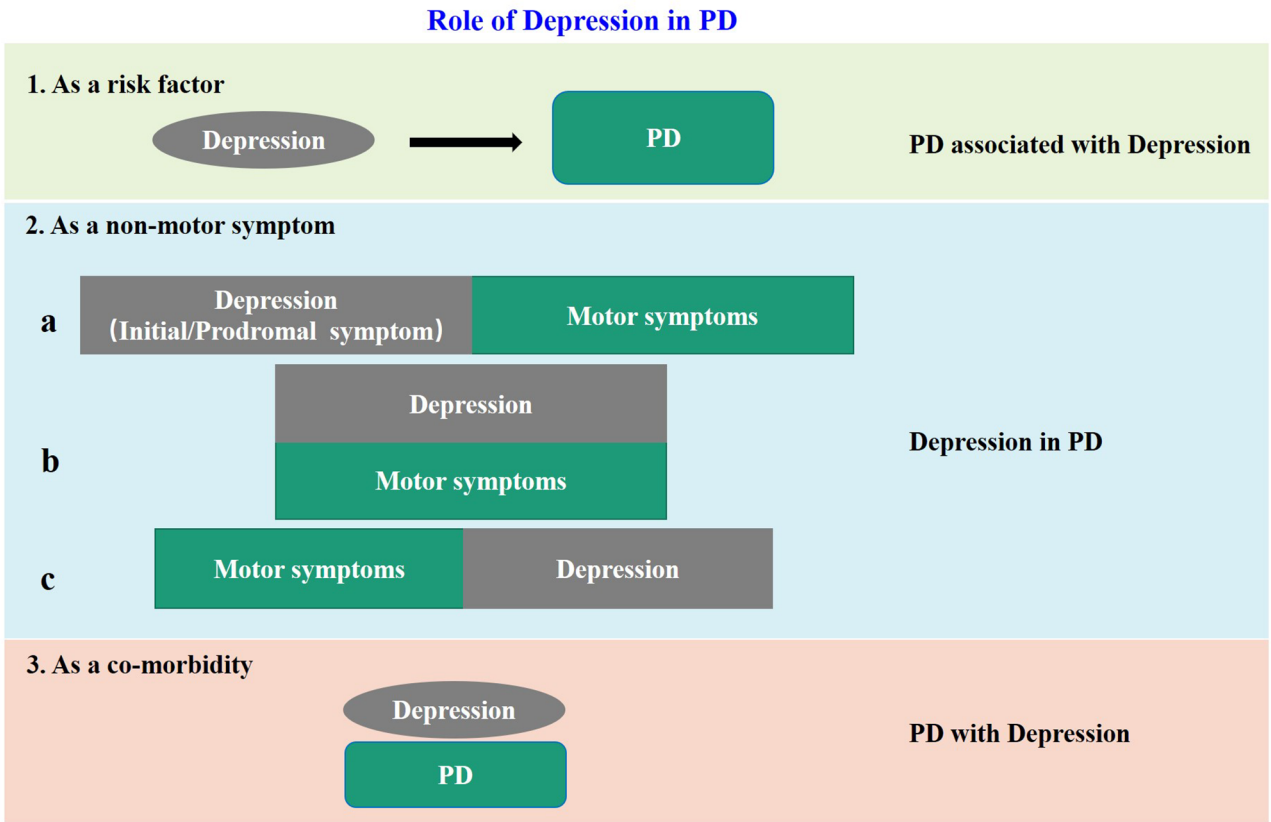

FIGURE 1 | The model diagram of the relationship between depression and PD. In case 1, depression is a risk factor for PD; in case 2, depression is a non-motor symptom of PD, and there are three sub cases, that is, it appears before motor symptoms as a prodromal symptom: (a) occurs simultaneously with motor symptoms; (b) and appears after motor symptoms; and (c) in case 3, it appears as an independent disease and comorbidity of PD.

phenotype; (2) with typical and detectable PD-specific motor impairment that aggravates progressively with aging; (3) simulates the clinical pathophysiological evolution of patients with PD-related depression; and (4) reproduces the progressive changes of neurotransmitters in different brain regions of patients with PD-related depression. Regardless of whether the above co-morbidity models meet these characteristics, they still fail the "early detection and early intervention" requirement in situations "1" and "2a" (**Figure 1**). Although situation "1" has been achieved through initial induction of PD by stress, followed by induction of motor impairment by neurotoxin (Hemmerle et al., 2012), this protocol might actually complicate the situation, because more and more studies found that the PD model induced by neurotoxin alone exhibited depression-like behavior. And as we have previously concluded, after administration of neurotoxin, depression changes can occur before motor damage, which simulates the "2a" situation, and may even partially represent the "1" situation. In summary, under the current condition of lacking spontaneous PD-related depression models, the PD models induced by neurotoxins may be used at this stage or even for a long time in the future. Due to the differences in the phenotype of PD-related depression induced by different neurotoxins, it is a difficult problem for the majority of researchers at present to select the appropriate neurotoxin, method, and dose in the construction of PD-related depression models. Facing this predicament, researchers compared the effects of different neurotoxins on PD-relation depression models. For example, a study used rats matched with age, body weight, and sex and induced by stereotactic injection of MPTP, 6-OHDA, Rotenone, and LPS in bilateral substantia nigra (Santiago et al., 2010). All but LPS induced depression-like behavior, and 6-OHDA had the best phenotype. Another study compared the non-motor symptoms of three PD models (Campos et al., 2013): 6-OHDA (8 or 6 μg, stereotactic injection of bilateral substantia nigra pars compacta), paraquat (micro-osmotic pump implanted in the subscapular area at the rate of 0.7 mg/day for 28 days) and α-synuclein overexpression transgenic model, and found that 6-OHDA and paraquat-induced depression-like behavioral changes in model animals. From the above two comparative studies, it is not difficult to find that the 6-OHDA might have the best effect in inducing PD-related depression. From **Tables 1–4** we can also find that there were the largest number of reports of 6-OHDA-induced PD-related depression, and unilateral MFB brain stereotactic injection was the first choice of administration route. However, the specific dosage of 6-OHDA should be determined according to the actual conditions of

animals, as there is no unified standard at present, which inevitably leads to a variety of study results. What we can do is to carefully analyze and identify the genuinely useful information.

In addition to the usage of different types of neurotoxins and their dosage, the success rate of model construction also needs to be considered. At present, the incidence of PD–related depression induced by neurotoxins has only been reported in MPTP-induced models. Of course, the conditions of animals such as species, sex, age, bodyweight, etc., also need to be concerned, especially the sex factor itself has an impact on depression and PD in humans (both occur more in women than in men), which have been particularly emphasized in some studies (Sullivan et al., 2014; Schamne et al., 2018). Another factor that requires comprehensive analysis is the behavioral evaluation of model animals. As we have summarized in **Tables 1–4**, a single behavioral test was used in many neurotoxin-induced PD-related depression models, which would affect the extrapolation of the results to certain extents. For example, FST, TST, and ST all involve "movement", therefore, it is necessary to rule out the interference of motor impairment. On the other hand, as the SPT test involves the taste function as well as the motor function of the animal, the interference of both factors should be excluded for proper evaluation of depression behaviors. At the same time, different behavioral testing operations are different (specific operations are not described here due to limited space and specific literature can be searched), and their sensitivities are also different. Therefore, we suggest that multiple behavioral tests should be used for cross-validation, and even introduce a rescue experiment for forward and backward validation. Of course, if the model modulates situations "1" and "2a", the interference of motor factor is neglectable, but it is important to truly rule out motor dysfunction through movement experiments. Further, there is also an important challenge that the results of these depressive behavior tests have not been convincingly coupled to neuropathological changes (Nestler et al., 2002).

Last but not least, the purpose of establishing a PD-related depression animal model is to facilitate the study of the pathogenesis and prevention and treatment strategies of PD-related depression. At present, the research on the mechanism of PD-related depression in neurotoxin-induced animal models is mostly originated from the hypothetical factors of the development of PD-related depression, such as the neurotransmitters, neuronutrition, nerve regeneration, nerve inflammation, and oxidative stress. However, there are very few studies on the involvement of the nerve loop, which is the focus of clinical study, in the PD-related depression model induced by neurotoxin. Moreover, the intrinsic differences of toxins in generic models may also play a role in the mechanisms underlying the depression phenotype. It is worth mentioning that their effects on the neurotransmitter system are different. For example, both MPTP and 6-OHDA can act on the mitochondrial complex in the cell and produce cytotoxicity, resulting in the disorder of neurotransmitters in the dopamine system, but it seems that 6-OHDA can also cause other neurotransmitter changes, such as 5-HT (Zhang et al., 2010). More interestingly, rotenone increased the level of 4-hydroxy-3-methoxyphenylacetic, a norepinephrine metabolite, in the striatum (Thiffault et al., 2000). These tips NA-5HT-DA cross-link in the neurotoxin PD models may be an important breakthrough to explore the mechanism of PD depression. As is known to all, structures define functions, so the structural alterations of depression-related brain areas (Remy et al., 2005), for example, the amygdala and hippocampus, in the neurotoxin PD model should also be concerned. With the continuous improvement of optogenetics and single-cell analysis technology, we believed that there will be a more and more precise exploration in this field in the future. In the meantime, it is encouraging that in the exploration of effective prevention and treatment of PD-related depression using neurotoxin-induced models, deep brain stimulation, electrostimulation, and exercise therapy have emerged besides pharmacological interventions. However, there has been no report using the noninvasive transcranial magnetic stimulation (TMS) that may be effective in the clinical treatment of PD-related depression patients. We look forward to future research that uses TMS in animal models of PD-related depression induced by neurotoxin.

In conclusion, in order to better reveal the relevant changes in the development of PD-related depression and its possible mechanism, and to develop targeted prevention and treatment strategies, it is the key point in current studies to establish a preclinical animal model that is generally in line with the three validity criteria [predictive validity (the ability of the model to predict certain clinical events), face validity (phenomenological similarities between models and clinical conditions), and construct validity (similarities between potential mechanisms of animal behavior and psychological or neurobiological mechanisms under clinical conditions)] (Skalisz et al., 2002) and infinitely close to the four characteristics of ideal PD-related depression models. Neurotoxin-induced PD-related depression models are worthy of further improvement and optimization.

AUTHOR CONTRIBUTIONS

S-ZW: conception and design. CR and Y-QJ: administrative support. X-YS, J-HW, and Y-QJ: provision of study materials. X-YY, L-NG, and Y-KM: collection and assembly of data. CR and S-ZW: data analysis and interpretation. All authors: manuscript writing and final approval of manuscript. All authors contributed to the article and approved the submitted version.

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Associations of Sleep Disorders With Depressive Symptoms in Early and Prodromal Parkinson's Disease

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Background: Non-motor symptoms, including sleep disorders and depression, are common in Parkinson's disease (PD). The purpose of our study is to explore the effect of sleep disorders, including the probable rapid eye movement (REM) sleep behavior disorder (pRBD) and the daytime sleepiness, on depressive symptoms in patients with early and prodromal PD.

Methods: A total of 683 participants who obtained from the Parkinson Progression Markers Initiative (PPMI) were included, consisting of 423 individuals with early PD, 64 individuals with prodromal PD, and 196 healthy controls (HCs), who were followed up to 5 years from baseline. Multiple linear regression models and linear mixed-effects models were conducted to explore the relationship between sleep disorders and depression at baseline and longitudinally, respectively. Multiple linear regression models were used to further investigate the association between the change rates of daytime sleepiness score and depression-related score. Mediation analyses were also performed.

Results: At baseline analysis, individuals with early and prodromal PD, who had higher RBD screening questionnaire (RBDSQ) score, or who were considered as pRBD, or who manifested specific behaviors of RBD (things falling down when sleep or disturbance of sleep), showed significantly the higher score of depression-related questionnaires. Our 5-year follow-up study showed that sleep disorders, including pRBD and daytime sleepiness, were associated with the increased depressive-related score in individuals with early and prodromal PD. Interestingly, we also found that the increased possibilities of daytime sleepiness were associated with depressive-related score. Finally, mediation analysis demonstrated that the relationship between RBD and depressive symptoms was partially mediated by autonomic symptoms, such as postural hypertension, salivation, dysphagia, and constipation.

Conclusion: Our study shows that sleep disorders, including pRBD and daytime sleepiness, are associated with depression at baseline and longitudinally, which is partially mediated by the autonomic dysfunction in early and prodromal PD, with an implication that sleep management is of great value for disease surveillance.

Keywords: Parkinson's disease, sleep disorders, depression, rapid-eye-movement sleep behavior disorder, daytime sleepiness, autonomic dysfunction

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INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disease characterized by bradykinesia, tremor at rest, rigidity, and postural instability. However, various non-motor symptoms, including depression, sleep disorders, constipation, and hyposmia, often predate the motor symptoms, with the most common being depression (Postuma et al., 2015b; Schapira et al., 2017). In total, 90.3% of patients with PD had prodromal non-motor symptoms before the clinical diagnosis of PD (Durcan et al., 2019). Most notably rapid eye movement (REM), sleep behavior disorder (RBD), and olfactory, autonomic, neuropsychiatric, and cognitive dysfunctions, are relatively frequent in patients who progress into PD in the future (Moscovich et al., 2020).

Sleep disorders are considered one of the potential risks and progression factors of PD and a significant source of disability (Dauvilliers et al., 2018; Bohnen and Hu, 2019). Insomnia, RBD, excessive daytime sleepiness (EDS), and restless legs are common sleep disorders in PD. RBD, which is considered as parasomnia, is characterized by loss of normal muscle atonia, accompanied by violent motor manifestations of undesirable dreams during REM sleep (Dauvilliers et al., 2018). RBD is a promising risk marker of synucleinopathies such as PD. Approximately 50% patients with PD have RBD (Barone and Henchcliffe, 2018). Prodromal RBD is related to more rapid motor progression and non-motor PD subtypes, especially depressive disorders and cognitive decline (Ferini-Strambi et al., 2014; Barone and Henchcliffe, 2018; Bohnen and Hu, 2019). Comorbidity of idiopathic RBD and depression accelerates the neurodegenerative process (Ghazi Sherbaf et al., 2018). EDS is characterized by the inability to maintain wakefulness during the daytime, with sleep occurring unintentionally or at inappropriate times (Hustad and Aasly, 2020). EDS, as one of the earliest and most common non-motor symptoms of PD, substantially impacts the quality of life (Yousaf et al., 2018; Xiang et al., 2019). Patients who are tended by night shift nurses have a higher risk of PD, indicating that circadian rhythm disorder is related to the progression of PD (Zverev and Misiri, 2009; Hustad and Aasly, 2020). One of the pathologic features of PD is the aggregation of α-synuclein (α-syn) into proteinaceous inclusions (Lewy bodies, LBs). The spread of α-syn in the brain leads to the decline of the total cerebrospinal fluid (CSF) α-syn levels (Dolatshahi et al., 2018). Both pRBD and daytime sleepiness were significantly related to lower and decreased levels of CSF α-syn, suggesting a higher risk of PD progression (Wang et al., 2021).

The most common psychiatric symptom in PD is anxiety and depression (Grover et al., 2015). Compared with motor symptoms, sleep disorders, constipation, and other non-motor symptoms, depression has not been paid high attention. Meta-analyses have confirmed the incidence of depression in patients with PD is around 23% (Goodarzi et al., 2016), which is higher than in the ordinary elderly or in patients suffering from other chronic and disabling diseases (Chwastiak et al., 2002; Nilsson et al., 2002). The occurrence of depression is closely related to the course of PD. As the duration of PD progresses, the incidence of depression will increase exponentially (Cooney and Stacy, 2016). However, depression often overlaps with other symptoms of PD. Patients with PD and their caregivers are rarely aware of the manifestation of depression, which results in the delay in diagnosis and earlier treatment, and finally leads to the poor living quality of patients with PD. Many factors can predict the prognosis of PD, including age, depression, and gait disorder (Louis et al., 1999; Soh et al., 2011; Postuma and Berg, 2019; Sklerov et al., 2020). With the progress of the disease, depression will eventually affect the daily life activities in patients with PD (Ravina et al., 2007; Lawrence et al., 2014). Previous studies revealed that sleep disorders were independently associated with depressed mood and autonomic symptoms (Chung et al., 2013). PD and sleep disorders comorbidities indicate more non-motor symptoms, including depressive symptoms, lower quality of life, and poor cognition, and fatigue (Neikrug et al., 2013). Therefore, the early identification of high-risk patients for depressive symptoms is of great significance for improving the prognosis and the quality of life of patients with PD.

However, the associations of RBD and daytime sleepiness with depressive symptoms have not yet been clarified. Therefore, we examined the associations of sleep disorders with depressive symptoms in patients from the Parkinson's Progression Markers Initiative (PPMI) database, by using cross-sectional and longitudinal analyses. In addition, mediating effect analyses were also performed for this study.

MATERIALS AND METHODS

Participants From Parkinson Progression Markers Initiative

Data used in this study were obtained from the PPMI database, a comprehensive observational, international, multicenter study aimed at identifying PD progression biomarkers. The detailed information is available online,[1] including inclusion/exclusion criteria, sites, complete lists of evaluations, and procedures. Our cohort was made up of healthy controls (HCs), prodromal PD (refers to the stage in which the condition has not yet progressed sufficiently to be defined as clinical PD, but several non-motor symptoms or signs of neurodegeneration are detectible), and early PD (refers to the stage where individuals were diagnosed with PD within 2 years but had not been treated with anti-parkinsonian therapy) (Postuma and Berg, 2019). In the PPMI database, hyposmia and RBD are used as the criteria for prodromal PD enrollment. Each individual participating in the cross-sectional analysis has completed the RBD screening questionnaire (RBDSQ) and Epworth sleep scale (ESS), and depression-related assessments (Geriatric Depression Scale [GDS]-short form and the Movement Disorder Society Unified Parkinson's Disease Rating Scale [MDS-UPDRS] Part I Depressed Mood) at baseline. The clinical parameters included in our study were age, gender, years of education, blinded site, ethnicity, race, and Montreal Cognitive

[1]https://www.ppmi-info.org

Assessment (MoCA) score. We did not find any participants with severe neurological disorders that may affect the results. All research procedures included in PPMI were approved by the local Institutional Review Boards of the participating centers. Written informed consent was obtained from all participants before study enrollment (Parkinson Progression, and Marker, 2011).

Sleep Characterization in Parkinson Progression Markers Initiative

Sleep-related characteristics of participants were evaluated by RBDSQ and ESS, which were both patient self-assess questionnaires. RBDSQ consists of 10 items covering the clinical symptoms of RBD and dichotomic responses (Yes = 1 or No = 0) (Stiasny-Kolster et al., 2007). Items 1–4 enquire about the frequencies and contents of dreams and the relationship between dreams and actions. Item 5 enquires about self-injury and others' injuries. Item 6 is divided into 4 subitems to assess specific conditions of abnormal movements, such as speaking in sleep, sudden limb movements, and complex movements. Items 7 and 8 enquire about the awakening at night, and item 9 enquires about the overall sleep. Item 10 concerning central nervous system diseases is excluded from our study. The total score of RBDSQ is 13 points. The best threshold for diagnosing RBD in the general population is 5 points. Probable RBD (pRBD) is screened using RBDSQ with a cutoff of 6 in patients with PD (Stiasny-Kolster et al., 2007; Miyamoto et al., 2009; Nomura et al., 2011). ESS is a handy questionnaire for patients to self-evaluate the degree of daytime sleepiness, which simulates eight scenarios to assess the possibility of drowsiness (never = 0, slight = 1, moderate = 2, and high = 3). The highest score of ESS is 24 points, and EDS is diagnosed with ESS $\geq$ 10 (Simuni et al., 2015; Wang et al., 2021).

Depression Characterization in Parkinson Progression Markers Initiative

Depression-related characteristics of participants were evaluated by GDS (short form) and MDS-UPDRS Part I Depressed Mood. GDS comprises 15 items to evaluate the following symptoms of people over 56 years old: depression, decreased activity, irritability, withdrawal, and negative evaluation of the past and present. A higher score of GDS indicates a higher burden of depression. A score of 5 or more suggests depression. MDS-UPDRS is divided into five items. Item 1 concerning mentation, behavior, and mood includes the assessment of the degree of depressive symptoms (normal = 0, slight = 1, mild = 2, moderate = 3, and severe = 4). The higher the score, the more serious the depression is.

Autonomic Dysfunction Assessments in Parkinson Progression Markers Initiative

Autonomic dysfunction has been confirmed to be related to depression and affects daily function in PD. The overall morbidity of autonomic dysfunction varies from 2% for urinary incontinence to 72% for constipation in patients with PD. To some extent, they were associated with disease duration, severity, or use of antiparkinsonian drugs (Visser et al., 2004). Autonomic dysfunctions were assessed by the Scales for Outcomes in Parkinson's Disease-Autonomic (SCOPA-AUT), which consists of 25 items evaluating the six regions: gastrointestinal (GI, 7 subitems), urinary (6 subitems), cardiovascular (3 subitems), thermoregulatory (4 subitems), pupillomotor (1 subitem), and sexual (2 subitems for men and 2 subitems for women) dysfunction (never = 1, sometimes = 2, regularly = 4, and often = 4). A higher score of SCOPA-AUT indicates a higher burden of autonomic dysfunction (Sklerov et al., 2020).

Data Analysis

Descriptive statistics were used to summarize the basic characteristics of participants. Age, gender, years of education, MoCA score, ethnicity, and race were considered as covariates. The differences between the three groups were compared by the Kruskal–Wallis test.

In the cross-sectional analyses, multiple linear regression models were used separately for combinations of every sleep subitems with the depression-related questionnaires, using the score of GDS or MDS-UPDRS Part I Depressed Mood as the dependent variable and sleep subitem as the independent variable after controlling possible covariates.

In the longitudinal analyses, the impacts of baseline sleep behaviors on the longitudinal depression-related questionnaires were investigated by the fitted linear mixed-effects model. The interaction between time and baseline score of RBDSQ or ESS was used as a predictor. We additionally calculated change rates of the possibility of daytime sleepiness and the score of GDS or MDS-UPDRS Part I Depressed Mood during the follow-up by the sim function in the "arm" package with 1,000 replicates *via* linear mixed-effects models. Then multiple linear regression models were used to investigate the associations between the change rates of ESS subitems and depression-related questionnaires. Due to fewer patients with prodromal PD included, we combined patients with early PD with patients with prodromal PD into a group, collectively referred to as the PD group. All the above analyses were carried out in PD and HC participants separately. **Figure 1** shows the flowchart of this study.

Mediation analyses were performed to investigate whether autonomic dysfunction, as measured by the SCOPA-AUT, might mediate the association between sleep disorders, as measured by the RBDSQ and ESS, with depressive symptoms, as measured by the GDS and MDS-UPDRS Part I Depressed Mood. The detection of the mediation effect is carried out by bootstrapping using the "mediation" package in R language.

Statistical significance was determined at a two-tailed p-value < 0.05. All statistical analyses and figure design were carried out in R version 4.1.2.

RESULTS

Characterization of Participants at Baseline

The demographic characteristics of participants is shown in **Table 1**. A total of 683 individuals were included, consisting of

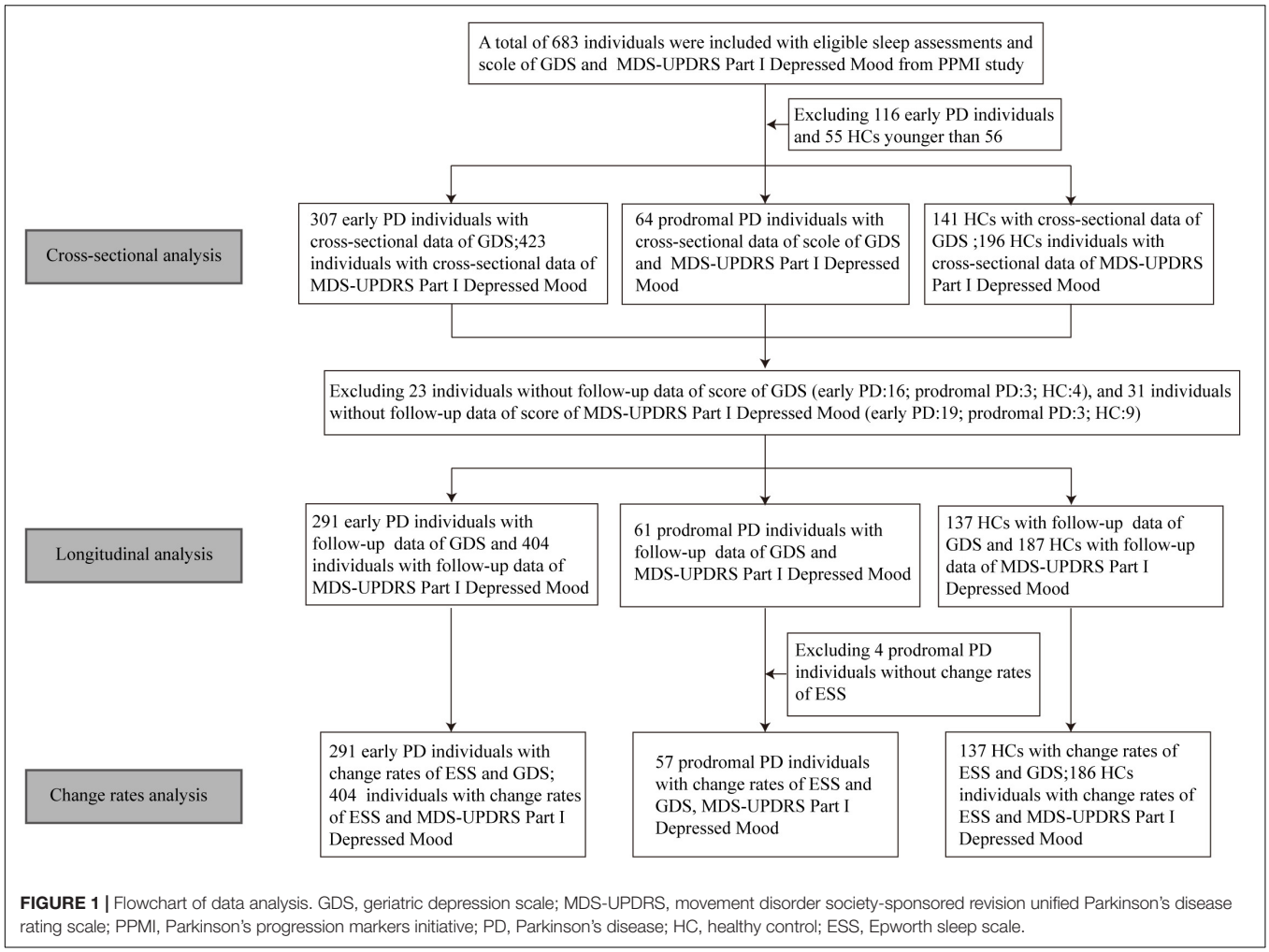

FIGURE 1 | Flowchart of data analysis. GDS, geriatric depression scale; MDS-UPDRS, movement disorder society-sponsored revision unified Parkinson's disease rating scale; PPMI, Parkinson's progression markers initiative; PD, Parkinson's disease; HC, healthy control; ESS, Epworth sleep scale.

423 individuals with early PD, 64 individuals with prodromal PD, and 196 HCs. Individuals with prodromal PD had a mean age of 68.93 (SD: 5.788) years, which was more significant than those of early PD and HC groups. There were no statistically significant differences in the sex ratio of the samples among the three groups. The mean education years of different groups were all 15 years roughly. The participants were all cognitively well with the mean MoCA scores above 25. Total score of RBDSQ and ESS of prodromal PD group were higher than those of early PD and HC groups. The total score of MDS-UPDRS Part I Depressed Mood was lower in the HC group than early PD and prodromal groups. After excluding the population younger than 56 years old (including 116 individuals with early PD and 55 HCs), a total of 512 individuals were included in the statistics of GDS, consisting of 307 individuals with early PD, 64 individuals with prodromal PD, and 141 HCs. The total score of GDS was lower in the HC group than those of the other two groups. The proportion of participants with depression (assessed by GDS or MDS-UPDRS) and pRBD, and EDS in each group is shown in **Table 1**. In addition, there was no significant difference in the proportion of depression between prodromal and early PD groups, assessed by either GDS (p = 0.841) or MDS-UPDRS (p = 0.6079). In term of the abnormalities of sleep pattern, the pRBD (p = 1.338e−11), but not EDS (p = 0.2335) was significantly different between these two groups.

The Associations of Sleep Disorders With Depressive Symptoms in Cross–Sectional Analyses

The associations between sleep disorders and depressive symptoms were revealed at baseline (**Figure 2**). Individuals with PD who had a higher RBDSQ score (β = 0.128939; p = 0.00121) or who were considered as pRBD (β = 0.771984; p = 0.00421) had a higher score of GDS. Moreover, individuals with PD who manifested specific behaviors of RBD, such as aggressive or action-packed dreams (β = 0.5929138; p = 0.0280), moving arms/legs during sleep (β = 0.656553; p = 0.0110), sudden limb movements (β = 0.739566; p = 0.00484), complex movements (β =−1.088929; p = 0.0012), things falling down when sleep (β =−1.189109; p = 0.00297), being awakened by one's own movements (β = 0.636220; p = 0.0215), and disturbance of sleep (β = 1.002893; p = 0.000175) showed significantly

TABLE 1 | Baseline characteristics of participants of three groups.

Variables	Early PD	Prodromal PD	HC	*p*-values
	n = 423	*n* = 64	*n* = 196	
Age				
Mean ± SD	61.66 ± 9.706	68.93 ± 5.788	60.82 ± 11.23	**2.53E−08**
(min, max)	(33.50, 84.88)	(58.91, 82.53)	(30.62, 83.68)	
Sex (n, %)				0.1064
male	277 (65.48%)	50 (78.12%)	126 (64.29%)	
female	146 (34.52%)	14 (21.88%)	70 (35.71%)	
Educate years				0.1387
Mean ± SD	15.56 ± 2.968	14.67 ± 4.511	16.04 ± 2.891	
(min, max)	(5.00, 26.00)	(0.00, 23.00)	(8.00, 24.00)	
MOCA				
Mean ± SD	27.13 ± 2.318	26.22 ± 3.494	28.23 ± 1.106	**7.03E−09**
(min, max)	(17, 30)	(11, 30)	(26, 30)	
RBDSQ total scores				**<2.2e−16**
Mean ± SD	4.121 ± 2.690	7.297 ± 3.736	2.827 ± 2.258	
(min, max)	(0, 12)	(1, 13)	(0, 11)	
ESS total scores				**0.03226**
Mean ± SD	5.801 ± 3.460	7.094 ± 4.245	5.621 ± 3.425	
(min, max)	(0, 20)	(0, 20)	(0, 19)	
GDS				**9.42E−07**
Mean ± SD	2.251 ± 2.348	2.250 ± 2.323	1.418 ± 2.306	
(min, max)	(0, 14)	(0, 10)	(0, 15)	
MDS-UPDRS Part I Depressed Mood				**0.004643**
Mean ± SD	0.2766 ± 0.5435	0.2500 ± 0.5909	0.1487 ± 0.4580	
(min, max)	(0, 4)	(0, 3)	(0, 4)	
Depression (n, %)				
Assessed by GDS	41 (13.44%)	8 (14.29%)	11 (7.69%)	
Assessed by MDS-UPDRS	100 (23.64%)	12 (18.75%)	24 (12.31%)	
pRBD (n, %)	43 (67.19%)	108 (25.53%)	25 (12.76%)	
EDS (n, %)	14 (21.88%)	66 (15.60%)	24 (12.24%)	

PD, Parkinson's disease; HC, healthy control; SD, standard deviation; MoCA, Montreal Cognitive Assessment; RBDSQ, rapid eye movement sleep behavior disorder screening questionnaire; ESS Epworth sleepiness scale, GDS, Geriatric Depression Scale, MDS-UPDRS, Movement Disorder Society-Sponsored Revision Unified Parkinson's disease rating scale, pRBD, probable RBD, EDS, excessive daytime sleepiness.

The bold font of P-values means P value < 0.05.

a higher total score of GDS (**Figure 3** and **Supplementary Table 1**). In addition, individuals with PD who had a higher RBDSQ score (β = 0.021491; p = 0.011292) or who were considered as pRBD (β = 0.143605; p = 0.009413) had a higher score of MDS-UPDRS Part I Depressed Mood. Moreover, individuals with PD who manifested specific behaviors of RBD, such as hurting bed partner (β = 0.139480; p = 0.035867), speaking in sleep (β = 0.114828; p = 0.03070), sudden limb movements (β = 0.106329; p = 0.048694), things falling down when sleep (β = 0.263490; p = 0.00185), and disturbance of sleep (β = 0.121387; p = 0.02337) showed significantly a higher total score of MDS-UPDRS Part I Depressed Mood (**Supplementary Figure 1** and **Supplementary Table 2**). However, there was no significant association between daytime sleepiness and GDS or MDS-UPDRS Part I Depressed Mood in individuals with PD (**Supplementary Tables 3**, **4**).

Furthermore, we found HCs who had specific behaviors of RBD, such as moving arms/legs during sleep (β = 0.90715; p = 0.0355) and disturbance of sleep (β = 0.89649; p = 0.0450) showed a higher total score of GDS, and who had disturbance of sleep (β = 0.1939777; p = 0.0179) showed a higher total score of MDS-UPDRS Part I Depressed Mood (**Supplementary Tables 1**, **2**). There was no significant association between daytime sleepiness and GDS in HCs *via* cross-sectional analyses. And HCs with higher possibilities of daytime sleepiness when lying down to rest in the afternoon (β =−0.0689633; p = 0.0404) showed a significantly a higher total score of MDS-UPDRS Part I Depressed Mood (**Supplementary Tables 3**, **4**).

The Effects of Sleep Disorders at Baseline on Depressive Symptoms in Longitudinal Analyses

Excluding 23 individuals without follow-up data of GDS (early PD: n = 16; prodromal PD: n = 3; HC: n = 4) and 31 individuals without follow-up data of MDS-UPDRS Part I Depressed Mood (early PD: n = 19; prodromal PD: n = 3; HC: n = 9) during the 5-year follow-up (baseline, 1st, 2nd, 3rd, 4th, and 5th annual follow-up): Associations of sleep disorders with depression during the follow-up are shown in **Figure 4**. As for individuals with PD with only disturbance of sleep (a specific behavior of RBD) were significantly associated with an increased total score of GDS (β = 0.1549074; p = 0.0429) during the follow-up (**Supplementary Table 5**). Individuals with PD who had a higher RBDSQ score (β = 2.872e−02; p = 0.00707), who were considered as pRBD (β = 2.201e−01; p = 0.001114), or had things falling down when sleep (β = 3.089e−01; p = 0.00367), showed an increasing trend of MDS-UPDRS Part I Depressed Mood (**Supplementary Table 6**). The PD participants with higher possibilities of daytime sleepiness when sitting inactive in public places (β = 9.717e−02; p = 0.03279) or stopped in traffic in a car (β = 1.830e−01; p = 0.04692) showed an increasing total score of MDS-UPDRS Part I Depressed Mood (**Figure 5** and **Supplementary Tables 7**, **8**).

In HCs, we did not identify any associations between daytime sleepiness and changes of depressive-related assessments. However, HCs who were considered as pRBD (β =−0.3860169; p = 0.0353) or had vivid dreams (β =−0.2347880; p = 0.0484) and moving arms/legs during sleep (β = 0.3253684; p = 0.0090) were found with an increased trend of GDS. Among the behaviors

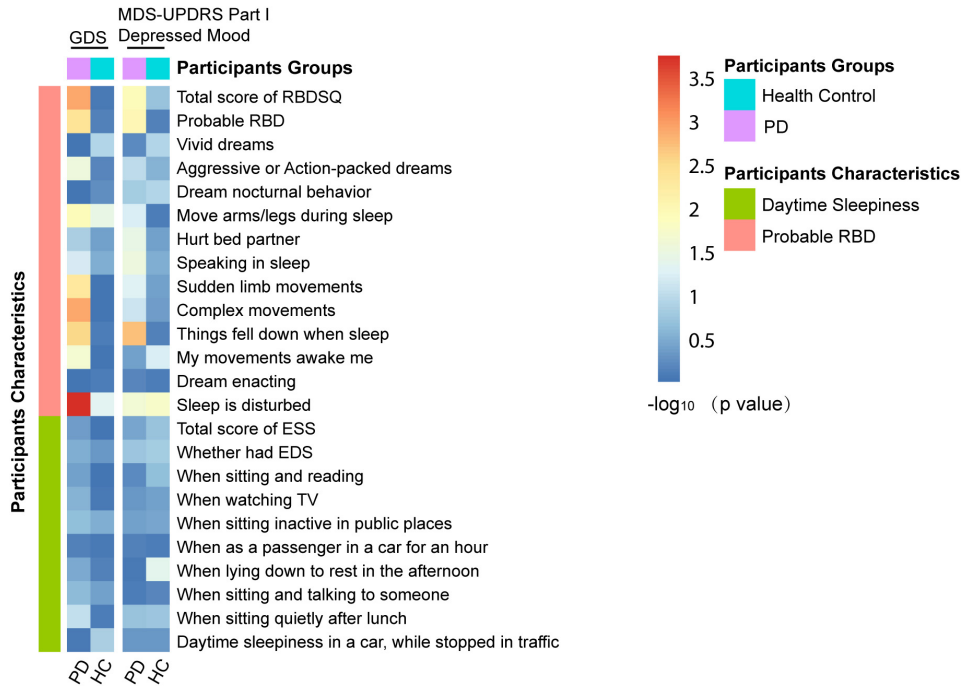

FIGURE 2 | Associations of sleep disorders with depression in cross-sectional analyses.

of RBD, only moving arms/legs during sleep (β = 0.228169; p = 0.035525) and complex movements (β = 0.472286; p = 0.036917) showed a significant development in MDS-UPDRS Part I Depressed Mood.

Associations Between Longitudinal Changes in Scores of Epworth Sleep Scale and Change Rates of Geriatric Depression Scale or Movement Disorder Society Unified Parkinson's Disease Rating Scale Part I Depressed Mood

Excluding 4 prodromal individuals without change rates of ESS: Associations between longitudinal change rates of daytime sleepiness and GDS or MDS-UPDRS Part I Depressed Mood in individuals with PD and HCs are shown in **Supplementary Figure 2**. As for individuals with PD, increased total score of ESS (β = 0.0937800; p = 0.001248) and increased possibilities of daytime sleepiness on four occasions (sitting and reading [β = 0.420573; p = 0.040591], sitting inactive in public places [β = 0.5232037; p = 0.003995], sitting quietly after lunch [β = 1.0065711; p = 4.95e−06], and stopped in traffic in a car [β = 0.3770992; p = 0.038161]) showed significant associations with a greater incline in GDS (**Supplementary Table 9**). While a greater increase in total score of ESS (β = 1.236e−02; p = 0.000279) and possibilities of daytime sleepiness on six occasions (sitting and reading [β = 5.877e−02; p = 0.0155], sitting inactive in public places [β = 6.492e−02; p = 0.00448], staying in a car as a passenger for an hour without a break [β = 7.551e−02; p = 0.00477], sitting and talking to someone [β = 6.852e−02; p = 0.00436], sitting quietly after lunch [β = 9.400e−02; p = 0.000386], and stopped in traffic in a car [β = 9.500e−02; p = 1.05e−05]) were significantly associated with a greater increase of MDS-UPDRS Part I Depressed Mood (**Supplementary Figure 3** and **Supplementary Table 10**).

In HCs, change rates of the total score of ESS (β = 0.105651; p = 0.0191) and the possibility of daytime sleepiness only in a situation when sitting quietly after lunch (β = 1.015139; p = 0.000901) showed significant associations with change rates of GDS. Given that, an increasing daytime sleepiness score contributed to the greater incline in depressive-related scales, which was mainly found in individuals with PD.

Analysis of Mediating Effect Between Sleep Disorders and Depressive Symptoms

To date, there is no significant association found between daytime sleepiness and depression at baseline, so a mediation analysis was performed to investigate whether the association between RBD and depression is mediated by autonomic symptoms. The results showed a significant indirect effect of RBD on GDS through the SCOPA-AUT total score (β = 0.0698, 95% CI: 0.0354–0.11, p < 2e−16), cardiovascular subscore (β = 0.0558, 95% CI: 0.0288–0.09, p < 2e−16), GI subscore (β = 0.0509, 95% CI: 0.0218–0.09, p < 2e−16), thermoregulatory subscore (β = 0.03872, 95% CI: 0.01415–0.07, p < 2e−16), and urinary subscore (β = 0.02231, 95% CI: 0.00352–0.05, p < 2e−16) at baseline, indicating that autonomic dysfunction, especially cardiovascular, GI, and thermoregulatory dysfunction acted as full mediators

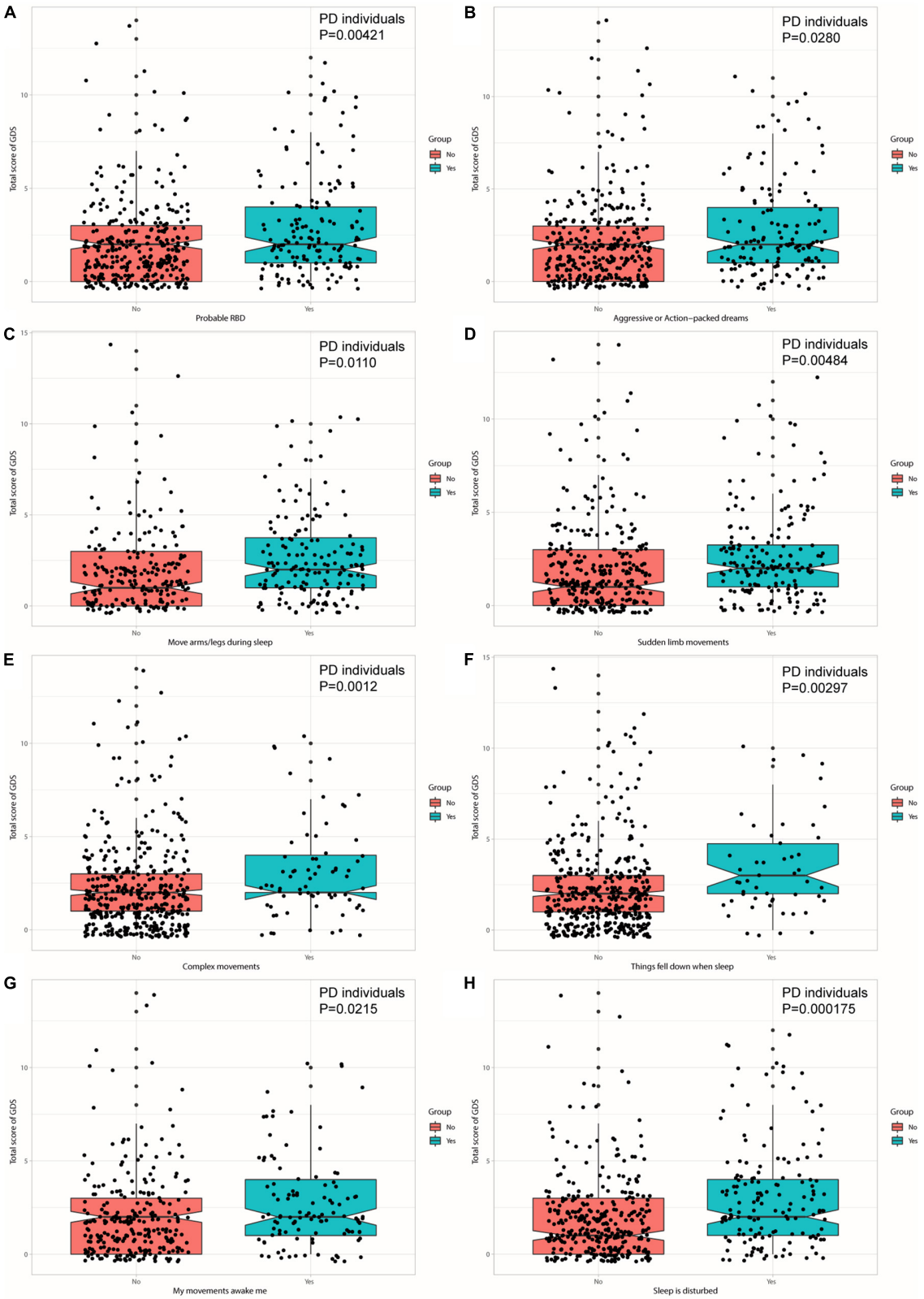

FIGURE 3 | Individuals with PD with pRBD **(A)** and specific behaviors—aggressive or action-packed dreams **(B)**, moving arms/legs during sleep **(C)**, sudden limb movements **(D)**, complex movements **(E)**, things falling down when sleep **(F)**, being awakened by one's own movements **(G)**, and disturbance of sleep **(H)** contribute to a higher score of GDS.

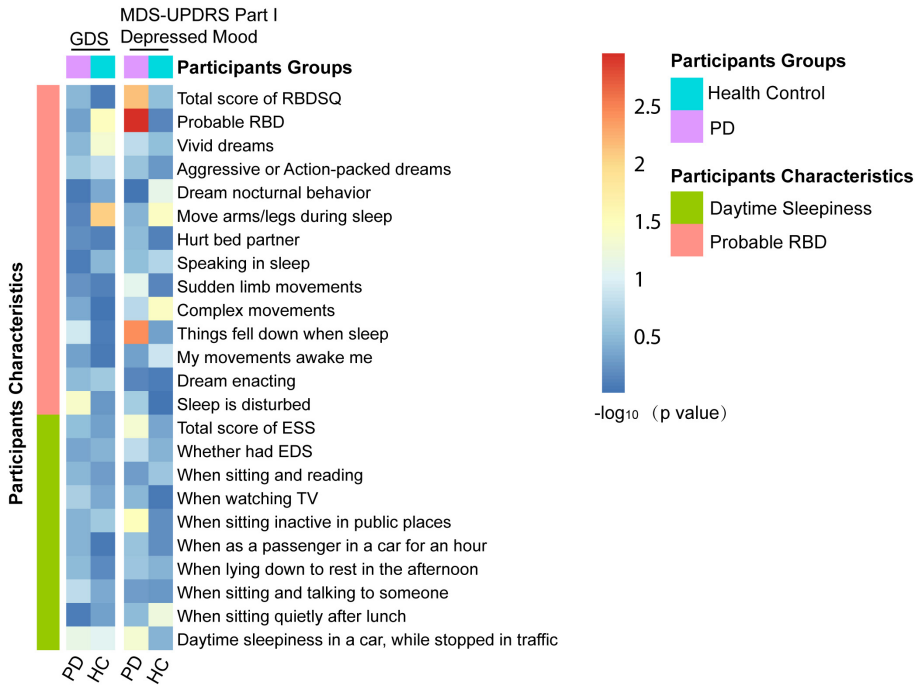

FIGURE 4 | Associations of sleep disorders with depression in longitudinal analyses.

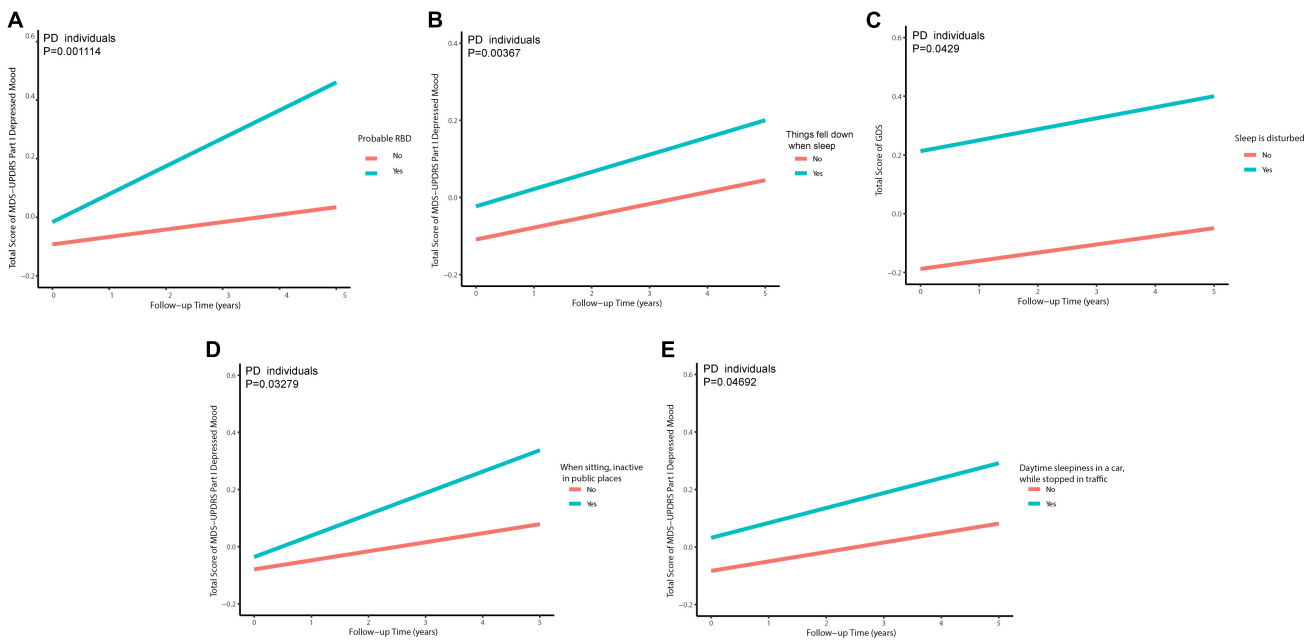

FIGURE 5 | Individuals with PD with pRBD **(A)**, things falling down when sleep **(B)**, disturbance of sleep **(C)**, daytime sleepiness when sitting inactive in public places **(D)**, and daytime sleepiness in a car, while stopped in traffic **(E)** contribute to a higher score of depression-related scales in PD in longitudinal analyses.

between RBD and GDS, and also urinary dysfunction as a part mediator (**Figure 6** and **Supplementary Tables 11**, **12**). Similarly, the indirect effect of the total score of SCOPA-AUT (β = 0.01206, 95% CI: 0.00605–0.02, $p < 2e{-}16$), cardiovascular subscore (β = 0.005397, 95% CI: 0.000956–0.01, $p < 2e{-}16$), GI subscore (β = 0.00840, 95% CI: 0.00324–0.02, $p < 2e{-}16$), pupillomotor subscore (β = 0.00243, 95% CI: 0.000134–0.01, $p = 0.04$), thermoregulatory subscore (β = 0.005054, 95% CI:

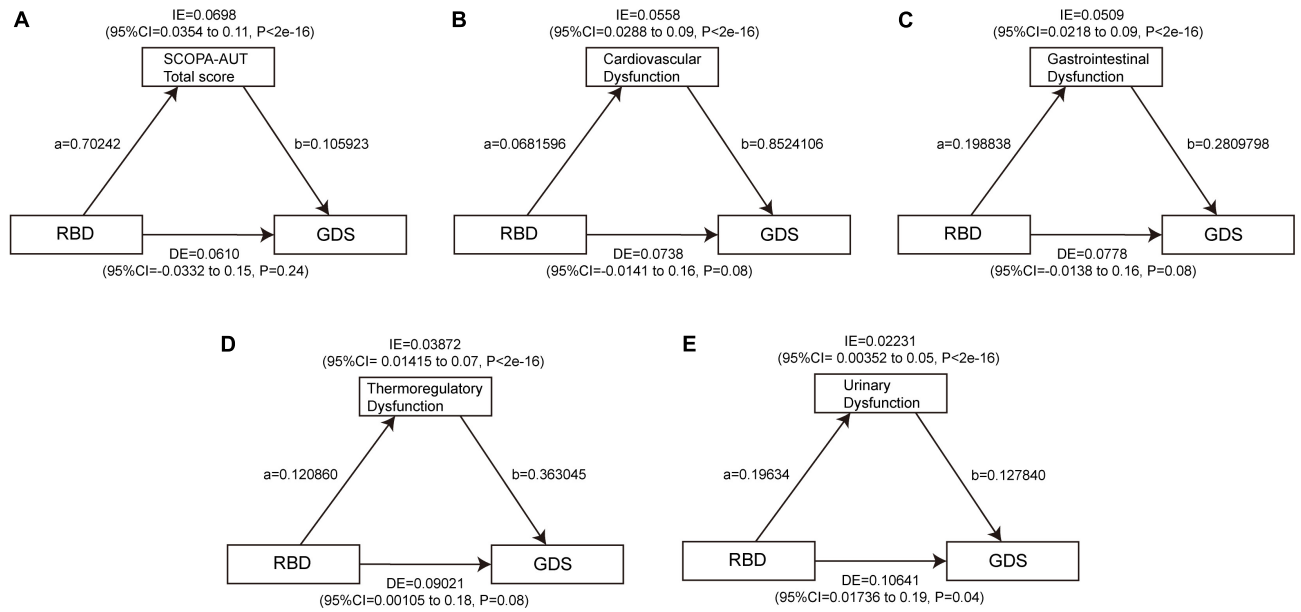

FIGURE 6 | Autonomic dysfunctions mediate the effects of RBD on GDS. The significant mediating effect of RBD on GDS through the SCOPA-AUT total score **(A)**, cardiovascular dysfunction **(B)**, gastrointestinal dysfunction **(C)**, thermoregulatory dysfunction **(D)**, and urinary dysfunction **(E)** at baseline. Path a indicates the direct effect of RBD on autonomic symptoms. Path b indicates the direct effect of autonomic symptoms on depression. GDS, Geriatric Depression Scale; RBD, rapid eye movement sleep behavior disorder; SCOPA-AUT, Scales for Outcomes in Parkinson's Disease-Autonomic.

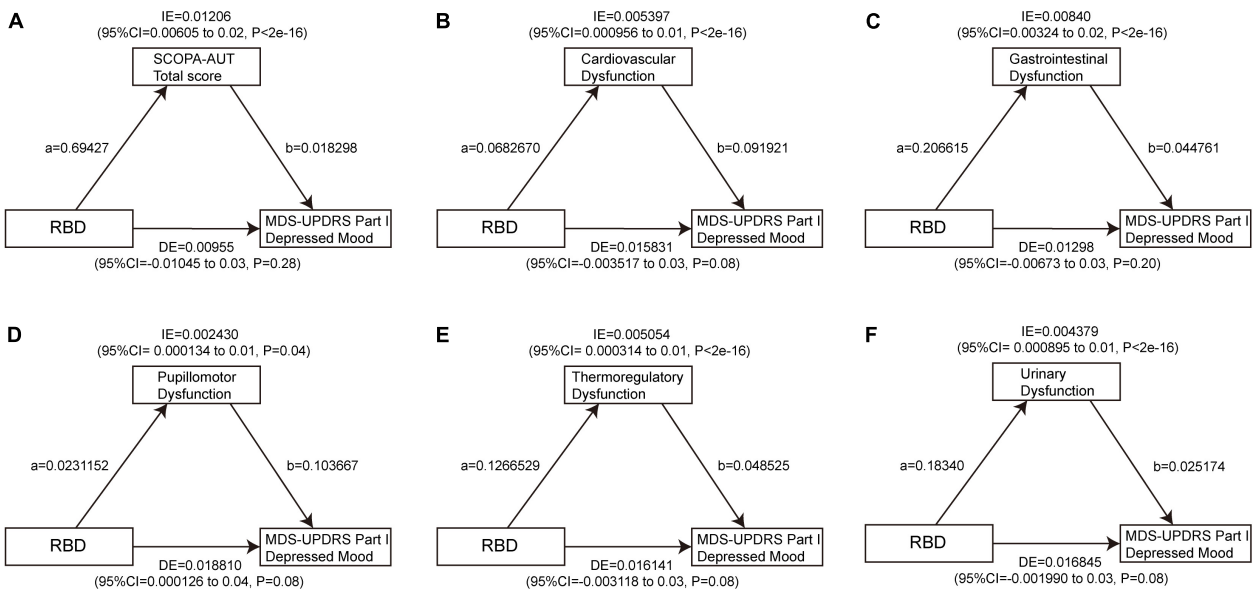

FIGURE 7 | Autonomic dysfunctions mediate the impacts of RBD on MDS-UPDRS Part I Depressed Mood. The significant mediating effect of RBD on MDS-UPDRS Part I Depressed Mood through the SCOPA-AUT total score **(A)**, cardiovascular dysfunction **(B)**, gastrointestinal dysfunction **(C)**, pupillomotor dysfunction **(D)**, thermoregulatory dysfunction **(E)**, and urinary dysfunction **(F)** at baseline. Path a indicates the direct effect of RBD on autonomic symptoms. Path b indicates the direct effect of autonomic symptoms on depression. RBD, rapid eye movement sleep behavior disorder; MDS-UPDRS, movement disorder society unified Parkinson's disease rating scale.

0.000314–0.01, $p < 2e{-}16$), and urinary subscore (β = 0.004379, 95% CI: 0.000895–0.01, $p < 2e{-}16$) were strong predictors of increase in MDS-UPDRS Part I Depressed Mood at baseline (**Figure 7** and **Supplementary Tables 13**, **14**).

We further tested whether autonomic dysfunctions mediate the relationship between RBD and depression in HCs. The total score of SCOPA-AUT (β = 0.00976, 95% CI: 0.00102–0.02, $p = 0.04$) was a strong harbinger of the

association between RBD and GDS. This analysis also revealed a significant indirect effect of RBD on MDS-UPDRS Part I Depressed Mood score through the SCOPA-AUT total score (β = 0.00976, 95% CI: 0.00102–0.02, p = 0.04), GI subscore (β = 0.0143, 95% CI: 0.0043–0.03, $p < 2e{-}16$), and sexual subscore (β = 0.00849, 95% CI: 0.00113–0.02, p = 0.04) at baseline.

Taken together, autonomic dysfunctions, especially cardiovascular, GI, thermoregulatory, and urinary dysfunction, are mediating effects between RBD and depressive symptoms in PD.

DISCUSSION

Non-motor symptoms in the early/prodromal stages of PD act as useful biomarkers for predicting the onset of motor symptoms and diagnosing PD, and identifying patients at risk of developing other complications (Bang et al., 2021).

Our findings suggested at baseline, a higher RBDSQ score was associated with a higher depression-related score in the PD group compared with HCs. In individuals with PD, patients with pRBD are significantly tend to concomitant with depression than patients with non-pRBD. In this regard, we further analyzed the correlation between each subitem of the RBDSQ and depression. For patients with geriatric PD over 56 years old, several specific behaviors of RBD, including subitem 2 (aggressive or action-packed dreams), subitem 4 (moving arms/legs during sleep), and subitems 6.2–6.4 (sudden limb movements, complex movements, and things falling down when sleep), and subitem 9 (disturbance of sleep), were significantly related to depressive symptoms, as measured by GDS. For patients with PD of all ages, subitem 5 (hurting bed partner), subitems 6.1, 6.2, and 6.4 (speaking in sleep, sudden limb movements, and things falling down when sleep), and subitem 9 (disturbance of sleep) showed significant positive correlations with depression, as measured by MDS-UPDRS Part I Depressed Mood. Accordingly, it has been reported that there is a close relationship between poor sleep quality in PD with depression (Rana et al., 2018). However, the causal relationship in the between remains to be further investigated.

In longitudinal analyses, for patients with geriatric PD over 56 years old, only subitem 9 (disturbance of sleep) of RBDSQ was a significant harbinger of depression, as measured by GDS. Individuals with PD with a higher RBDSQ score, pRBD or subitem 6.4 (things falling down when sleep) is of high possibility for depression incidence, basing on the scoring with MDS-UPDRS Part I Depressed Mood. For longitudinal analyses of daytime sleepiness with depression, we used the linear mixed-effects models and multiple linear regression models of change rates, respectively. Interestingly, we found that either the increased total score of ESS or the increased possibilities of daytime sleepiness on four occasions (sitting and reading, sitting inactive in public places, sitting quietly after lunch, and stopped in traffic in a car) are positively related with GDS scoring. Meantime, by using MDS-UPDRS Part I Depressed Mood, we observed that there is a significant correlation between the depression score with the high score of ESS, or the possibilities of daytime sleepiness on six occasions (sitting and reading, sitting inactive in public places, staying in a car as a passenger for an hour without a break, sitting and talking to someone, sitting quietly after lunch, and stopped in traffic in a car). Together, we argue that patients with PD with pRBD and daytime sleepiness are more prone to depression, based on the evaluation results with GDS or MDS-UPDRS. In consistent with the finding it has been found that there is a high frequency of sleep disorders during PD progression (Xu et al., 2021). Here, our work provides a detailed and longitudinal relationship of RBD and daytime sleepiness with depression, which might be used for the depression prediction in patients with the early stage and prodromal PD.

A multivariate analysis showed that older age, longer disease duration, and worse quality of sleep were independently associated with a higher SCOPA-AUT scale score (Arnao et al., 2015). It has been reported that the autonomic dysfunction is related to the development of depression of PD (Sagna et al., 2014). Idiopathic RBD is also significantly related to the mild-to-moderate autonomic dysfunction (Lee et al., 2015). We herein seek to investigate whether the autonomic dysfunction is involved depression development associated with the sleep disorders. By using the baseline mediating effect analyses, we found that RBD affected depression partially through autonomic dysfunction, especially the dysfunction of cardiovascular, GI, thermoregulatory, or urinary systems.

Postmortem autopsy of patients with PD with depression found a decrease in dopamine neurons and in the density of serotonin neurons in the dorsal and ventral tegmental areas of the raphe nuclei (Maillet et al., 2016; Rutten et al., 2017; Park et al., 2020). The biochemical basis of depression in PD may be related to extensive serotonin and reduced dopaminergic changes (Maillet et al., 2016; Patterson et al., 2019). We further analyze possible mechanisms at the anatomical and molecular levels. Increased α-syn oligomer in CSF and serum, and greater pathological density and range of synuclein could be observed in patients with PD with pRBD (Hu et al., 2015; Postuma et al., 2015a; Dušek et al., 2019). Areas involved in RBD are not only limited to the brainstem regions regulating REM sleep, but also may extend to other areas such as the olfactory system, the nigrostriatal system, and the autonomic system (Barone and Henchcliffe, 2018). Circadian rhythms affect the CSF production by regulating the accumulation and clearance of α-syn (Kudo et al., 2011; Benveniste et al., 2017; Sundaram et al., 2019). As a common symptom of circadian rhythm disruption, EDS manifests prior to Lewy pathology affects the topographic transmission of α-syn (Abbott et al., 2005, 2019). Therefore, α-syn is initially enriched in the lower brain stem, leading to sleep disturbances and autonomic dysfunction. In the later stage, the limbic system and neocortex are involved, followed by neuropsychiatric symptoms, such as depression (Braak et al., 2003, 2006; Beach et al., 2009; Park et al., 2020). It has been confirmed that RBD is associated with hyposmia, autonomic dysfunction, depression, cognitive impairment, and mild motor symptoms, which indicate diffuse α-syn pathology (Dušek et al., 2019). The direct effect of sleep disorders is fatigue (Chung et al., 2013; Stocchi et al., 2014), which is related

to decreased serotonergic function in the basal ganglia and limbic structures (Remy et al., 2005; Pavese et al., 2010; Politis and Niccolini, 2015; Zuo et al., 2016). Depression in PD is attributable to serotonergic and noradrenergic lesions in the limbic system (Stocchi et al., 2014; Thobois et al., 2017; Jones et al., 2019). In addition, raphe serotonergic system is associated with sleep disorders and depression (Boileau et al., 2008; Politis et al., 2010; Xiao-Ling et al., 2020). Accumulation of phosphorylated α-syn depositing in the raphe nuclei contributes to depression (Xiao-Ling et al., 2020). Similarly, norepinephrine denervation is also involved in autonomic dysfunction in patients with PD, indicating that depression and autonomic dysfunction share a common neurochemical substrate (Sharabi and Goldstein, 2011). Damaged noradrenergic function in PD was also associated with RBD (Sommerauer et al., 2018; Pilotto et al., 2019). Taken together, depression in PD may be attributed to the disruption of neurotransmitter systems, such as dopamine (SN), serotonin (raphe nuclei), and noradrenaline (locus coeruleus) (Maillet et al., 2016; Jin et al., 2017; Hustad and Aasly, 2020; Park et al., 2020; Bang et al., 2021).

The above analyses prove that monitoring RBD and daytime sleepiness contributes to predicting and identifying depressive symptoms in patients with early PD and prodromal PD at baseline and within 5 years. Few previous studies have investigated this association, in particular the various subitems of RBD and daytime sleepiness. Previous studies reported that both depression and sleep disorders trigger a negative spiral in patients with PD, where one enhances the other. Sleep disturbances and depression severity share a bidirectional association (Kay et al., 2018; Sklerov et al., 2020). Therefore, independent clinical attention should be paid to these symptoms in patients with PD (Rutten et al., 2017; Kay et al., 2018).

However, our research still has some shortcomings. First of all, RBDSQ and ESS are both self-report questionnaires, which lack objective measures such as the polysomnography system for sleep monitoring. Second, the sample size is not large enough, with some participants losing follow-up, which may affect the reliability of results to a certain extent. The results require to be further verified by expanding of sample size and strengthening the follow-up.

CONCLUSION

Sleep disorders were significantly associated with the higher and increased score of questionnaires assessing depression, suggesting a higher risk of progression to PD. Sleep disorders are identified as potential risk factors in predicting the depression and monitoring the progression of PD.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/ **Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Local Institutional Review Boards of the participating centers. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AX and ZY: conception and design of the study. JM, KD, and RL: acquisition and analysis of the data. JM, KD, and YL: drafting of the manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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New Understanding on the Pathophysiology and Treatment of Constipation in Parkinson's Disease

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Constipation, one of the most common prodromal non-motor symptoms of Parkinson's disease (PD), usually occurs several years earlier than the onset of motor symptoms. Previous studies have shown that constipation occurrence increases as the disease progresses. However, the mechanism underlying this pathologic disorder is not clear yet. Moreover, chronic constipation causes slowness in gastric emptying and, therefore, may lead to a delay in the absorption of medications for PD, including levodopa and dopamine agonists. Accordingly, it is necessary to understand how the pathophysiological factors contribute to constipation during PD as well as pursue precise and effective treatment strategies. In this review, we encapsulate the molecular mechanism of constipation underlying PD and update the progress in the treatments of PD-associated constipation.

Keywords: Parkinson's disease, constipation, molecular mechanism, non-pharmacological treatments, medication

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INTRODUCTION

Parkinson's disease (PD) is a complex chronic neurodegenerative disease highly prevalent with aging (Collaborators, 2019). Most PD cases are sporadic and less than 10% of them are familial. The prominent pathological feature of PD is the dopaminergic (DAergic) neuronal loss in the substantia nigra of the midbrain, leading to the significant reduction of DA content in the striatum and impairing the nigrostriatal projections (Carmichael et al., 2021). There are many contributing factors associated with the development of PD, including genetic and environmental factors (Samii et al., 2004; Simon-Sanchez et al., 2009). Currently, the diagnosis of PD mainly relies on its motor symptoms, such as resting tremor, bradykinesia, rigidity, and postural/gait abnormalities, based on the 2015 MDS clinical diagnostic criteria for PD (Postuma et al., 2015). However, these classical clinical features always occur at the advanced stage of disease progression. Recently, the non-motor symptoms of PD attract a special interest due to their early onset compared to motor symptoms and provide a promising perspective for early diagnosis and treatments of PD (Martinez-Martin et al., 2011; Bloem et al., 2021), including olfactory dysfunction, gastrointestinal (GI) dysfunction, mood symptoms, sleep disorders, autonomic dysfunction, and fatigue (Chaudhuri et al., 2006; Liu and Le, 2020). Constipation, a GI disturbance, is one of the most frequent non-motor symptoms and affects more than 80% of PD patients. Importantly, constipation may precede the motor symptoms of PD by at least 10 years (Fasano et al., 2015). Also, the colonic transit time is significantly prolonged in PD patients (Sakakibara et al., 2003; Knudsen et al., 2017; Zhang et al., 2021).

The dysfunction of bowel movements undergoing PD may be contributed by many factors, such as neuro-humoral factors, intestinal microorganisms, intestinal inflammation, drugs, and lifestyle (Barichella et al., 2019). Currently, most of the therapeutic strategies for constipation applied in the general population are also effective for PD patients (Travagli et al., 2020). However, a better understanding of the pathophysiological mechanism underlying PD may promote the development of specialized treatments for constipation in PD patients. For example, deep brain stimulation (DBS) and vagal nerve stimulation (VNS), these two common surgical treatments for PD have been proven to mitigate constipation in PD patients as well, by facilitating intestinal emptying (Jost, 1997; Payne et al., 2019). In this review, we seek to encapsulate the molecular mechanisms discovered underlying constipation of PD, as well as update the progress of recent pharmacological and clinical findings.

PATHOPHYSIOLOGY OF CONSTIPATION IN PD

Constipation in PD may occur due to the improper functioning of the autonomic nervous system, i.e., the intestinal tract may operate slowly and trigger constipation (Metta et al., 2022). Pathophysiology of constipation in PD is to discover the intrinsic and extrinsic factors contributing to PD-associated constipation (Warnecke et al., 2022). Generally, the normal function of the colon depends on the orderly and controllable unidirectional movement of its contents under the impetus of intestinal motility. Many factors have been known to affect colonic movements and intestinal contents, including neuro-humoral factors, gut microbiota imbalance, intestinal inflammation, drugs, and lifestyle. Once they are dysregulated, the transportability of intestinal contents is altered, resulting in constipation ultimately (as shown in **Figure 1**).

Neuro-Humoral Factors

The innervation of the digestive tract determines its movement pattern, regulates the fluid movement of the intestinal cavity, and releases intestinal hormones (Furness et al., 2014). Different from other peripheral organs, the movement of the intestine is controlled by two distinct types of nerves. One is the extrinsic nervous system, which is composed of sympathetic and parasympathetic nerves. Sympathetic postganglionic fibers release norepinephrine, which can inhibit the excitation of neurons and further repress their forward conduction activities; the parasympathetic nerve, especially the vagus nerve, has a role in facilitating digestion-related enzyme, hormone secretion, and smooth muscle peristalsis. The other type of intestinal nerve system is the extensive intrinsic nervous system, the enteric nervous system (ENS). ENS consists of the intestinal wall intermuscular plexus and the submucosal nerve plexus, where a large number of sensory and motor neurons are located (Furness et al., 2014; Walsh and Zemper, 2019). The function of ENS is mainly in charge of contractile activity, local blood flow, and transmucosal movement of fluids (Furness, 2012). In PD, GI dysfunction is largely caused by the abnormalities of ENS and the vagus nerve (Quigley, 1996).

Aggregated α-Synuclein (α-Syn) is the major constituent of Lewy bodies, which are a pathogenic hallmark of PD (Li and Le, 2020). The vagus nerve is considered to be the main route of transmission of α-Syn. There is a degree of vagus nerve atrophy in the process of PD (Del Tredici and Braak, 2016), inhibiting gastric emptying and intestinal transport (Grijalva and Novin, 1990). Moreover, aggregate dα-Syn has also been found in the peripheral nerves including the ENS (Casini et al., 2021). The number of Lewy neurites in ENS is negatively correlated with neuron counts and positively correlated with constipation (Lebouvier et al., 2010). Therefore, aberrant accumulations of α-Synmay trigger vagus neurodegeneration, slow down intestinal peristalsis, and promote constipation (Liddle, 2018).

The dysfunction of the intestinal nervous system may bring out the imbalance of secretion, and dysregulation of intestinal neurotransmitters, further aggravating the disorder of intestinal motility. Vasoactive intestinal peptide (VIP), innervating the mucosa throughout the small and large intestines, plays a major role in the digestive system to relax intestinal smooth muscle and promote the secretion of intestinal fluid (Schwartz et al., 1974; Larsson et al., 1976). The studies from Giancola et al. (2017) showed that the impaired colonic motor and rectal sensory in most PD patients were associated with a decreased VIP expression in submucosal neurons. Such reduction of intestinal VIP potentially leads to intestinal diastolic disorder and loss of normal intestinal peristalsis mode, further limiting colonic transport and reducing intestinal fluid secretion. Secretory abnormalities may thereby affect the composition of the fecal water content, leading to hard stools and delayed colonic transit time (Lam et al., 2016).

Nitric oxide (NO), an inhibitory neurotransmitter secreted by NOS (nitric oxide synthase)—positive neurons in ENS, regulates the relaxation of smooth muscle, to maintain normal colon motility, colonic reflexes, and defecation (Stark et al., 1993). NOS is the key rate-limiting enzyme for NO production. In normal physiological conditions, NOS causes tissues to slowly release NO and maintains the body's physiological requirements. When the body is in a pathological state, deficient NO production will affect intestinal transport (Shah et al., 2004). Studies with the animal models of PD confirmed that loss of NOS impairs the expression of the antioxidant gene, which deregulates NO synthesis and increases abnormal aggregation of α-Syn in ENS, thereby contributing to the development of GI dysmotility and constipation (Sampath et al., 2019). Additionally, NO appears to be important to maintain DA synthesis in the colon. The signals from NOS–NO may influence DA neurotransmission, and loss of NOS–NO signaling in the GI system may induce DAergic neuronal degeneration *via* oxidative stress, aggravating the degree of dyskinesia and constipation (Sampath et al., 2019).

Cholinergic neurons are the most abundant neurons in the ENS. The cells of cholinergic excitatory nerves are scattered under the intestinal mucosa and in the myenteric plexus. Acetylcholine, the neurotransmitter released by cholinergic neurons, stimulates the muscarinic receptors on smooth muscles and nicotinic receptors on ganglion cells, affects GI

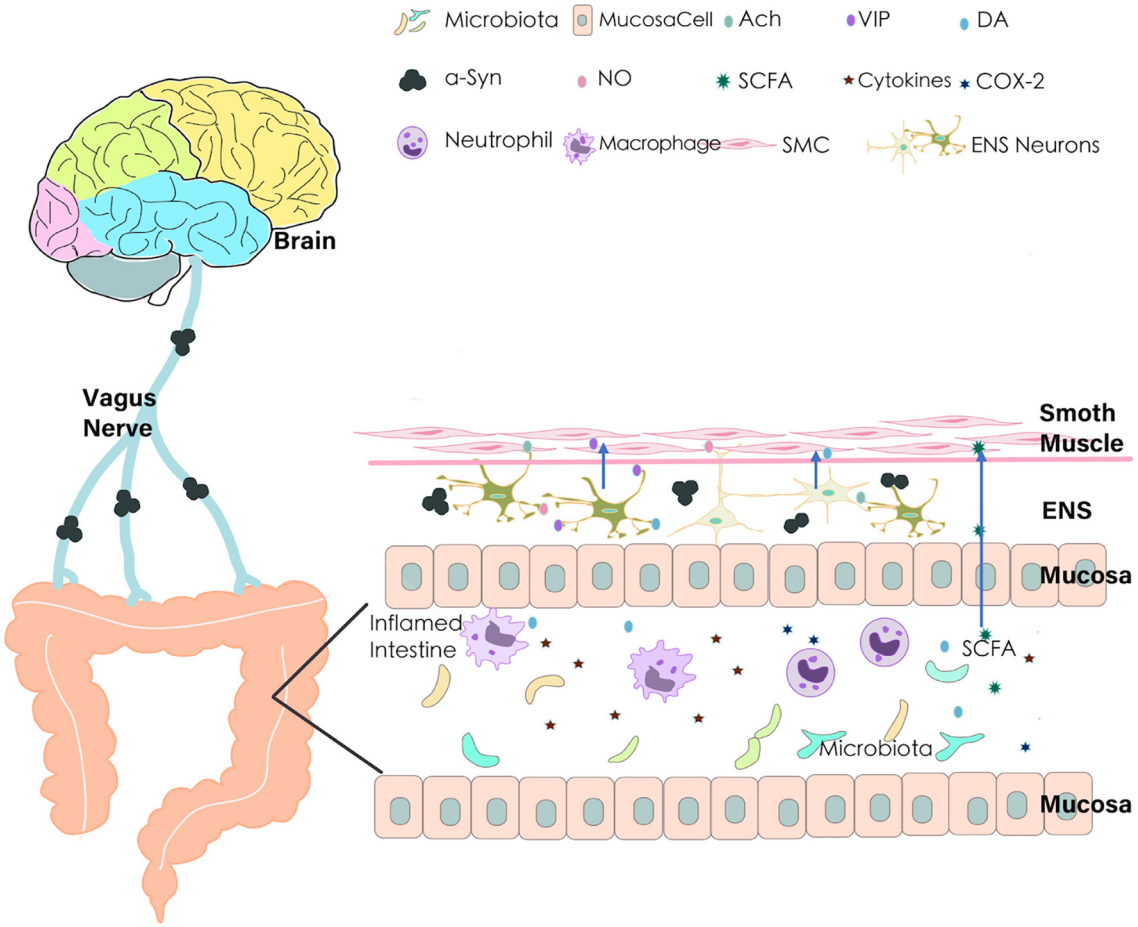

FIGURE 1 | Pathophysiology of constipation in Parkinson's disease (PD). Many factors may contribute to the alterations of colon transport and consequently lead to constipation in PD. Aberrant aggregation of α-Synuclein leads to the vagus nerve and ENS degeneration; dysfunction of the intestinal nervous system brings out the imbalance of secretion and regulation of neurotransmitters (NO, VIP, DA, Ach); gut microbiota imbalance and product of bacterial fermentation (such SCFAs) affect intestinal dysfunction; pro-inflammatory cytokines and COX-2 in the inflamed intestine leads to decrease of The gastrointestinal (GI) transport. ENS, Enteric Nervous System; VIP, Vasoactive Intestinal Peptide; NO, Nitric Oxide; Ach, Acetylcholine; DA, Dopamine; SCFA, Short-Chain Fatty Acids; COX-2, Cyclooxygenase-2; SMC, Smooth Muscle Cell; α-Syn, α-Synuclein.

muscle excitatory and participates in intestinal peristalsis reflex (Picciotto et al., 2012). Therefore, alterations in excitatory cholinergic neurotransmitters have a significant impact on the movements of the distal colon. In PD, the loss of myenteric neuronal choline acetyltransferase and decreased acetylcholine release, likely contribute to the reduction of colonic transit rate by affecting the formation of excitatory electrical activity in the colon (Fornai et al., 2016), resulting in the impairment of fecal output and leading to constipation (Fidalgo et al., 2018).

DA is a key neurotransmitter for colon movements and is widely distributed to the intestine regions, including the colon muscle layer, intermuscular plexus, and mucosal epithelial cells. Therefore, dysfunction of DA receptors (DR) can affect GI transport (Li et al., 2006). It was reported that the rats with PD-related constipation show a significant reduction in D2R expression in the colon (Levandis et al., 2015). DA dysfunction is also closely related to DA transporter (DAT). DAT, a membrane protein, removes DA from the synaptic space, deposits it into surrounding cells, and terminates the signal of neurotransmitters. The neuroimaging data from PD patients showed that constipation is most closely associated with caudate-DAT reductions (Hinkle et al., 2018). Additionally, DA itself regulates GI transport as well. DA dysfunction weakens its inhibitory effect on gut motility and leads to spasms and hyper-contractility of colonic smooth muscles, which slows down intestinal transport (Anderson et al., 2007). In such a situation, an enteric DA deficit induces constipation in PD patients.

Gut Microbiota Imbalance

The intestinal microbiota is a complex system composed of parasites, viruses, yeast, and bacteria (Gasbarrini et al., 2007; Jandhyala et al., 2015). The composition of the microbiota and the diverse metabolites they produce are widely related to the health of the host. Studies on gut microbiota have shown

that PD patients are prone to show intestinal flora imbalance. A lower proportion of the bacterial phylum *Bacteroidetes* and the bacterial family *Prevotellaceae* were both identified in fecal samples from PD, where *Enterobacteriaceae* were more abundant instead (Unger et al., 2016). Such microbiota imbalance has been associated with motor dysfunction, GI injury, and colon transport time increase *via* affecting neurotransmitters and microbial metabolites (Scheperjans et al., 2015; Vandeputte et al., 2016; Cirstea et al., 2020; Shao et al., 2021). Short-chain fatty acids (SCFAs) are the main product of bacterial fermentation of dietary fiber or glycosylated host proteins such as mucins in the colon (Cummings et al., 1987; Park et al., 2019). SCFAs play an important role in acting as an energy source for colonocytes (Kaiko et al., 2016), regulating the gut barrier (Kelly et al., 2015), influencing inflammatory responses (Inan et al., 2000), enhancing neuronal survival, and promoting enteric neurogenesis (Vicentini et al., 2021). Thus it is essential to maintain SCFA homeostasis in the gut microbiota (Yang and Chiu, 2017; Cirstea et al., 2020). Moreover, the SCFA concentrations were significantly reduced in fecal samples of PD patients, potentially contributing to GI dysmotility (Unger et al., 2016).

Intestinal Inflammation

Intestinal inflammation has been proposed to mediate gut-to-brain PD progression (Sharma et al., 2019). It was reported that the expression levels of pro-inflammatory cytokines and the markers of glial cells were significantly increased in the colon of PD patients (Devos et al., 2013), suggesting that GI inflammation is associated with PD. Furthermore, patients with PD-related constipation have shown the decreased content of SCFAs, the increased intestinal permeability, and the down-regulated regulatory T cells, all of which accelerate the neuronal inflammation in ENS (Hirayama and Ohno, 2021). Meanwhile, the induced inflammatory mediators promote the infiltration of neutrophils and macrophages into the smooth muscle layer and the production of NO, leading to the reduction of contractility of smooth muscle cells (Turler et al., 2006). Importantly, in the inflamed intestine, the increased expression of cyclooxygenase (COX)-2 resulted in a significant augment of prostaglandins within the circulation and peritoneal cavity, which aggravates the contractility dysfunction of GI smooth muscles and leads to constipation (Schwarz et al., 2001).

Adverse Drug Reactions and Lifestyle

Constipation can be a side effect of PD drugs. A population-based study investigated that constipation was slightly increased after 1 year of DA treatments in PD patients, most of whom were using Levodopa (Pagano et al., 2015). Thus, Levodopa may exacerbate delayed gastric emptying and constipation by affecting DR to slow down intestinal movements (Bestetti et al., 2017). Moreover, ropinirole, bromocriptine, and piribedil can promote a high incidence rate of constipation, accompanied by nausea, dyskinesia, hallucination, dizziness, and somnolence symptoms (Li et al., 2017). On the other hand, at the advanced stage of disease progression, PD patients move slowly with limited activity, and even stay in bed for a long time, which may lead to slow GI peristalsis and constipation. Dysphagia is commonly seen in older adults with PD, who usually experience dehydration (Thiyagalingam et al., 2021). Such dehydration may induce the release of antidiuretic hormone and aldosterone to increase the salt and water absorption in the colon, resulting in constipation in PD (Read et al., 1995).

TREATMENTS

Currently, the treatments for idiopathic chronic constipation are equally effective in treating PD-associated constipation, including lifestyle alteration, diet control, and medication (Black and Ford, 2018; as shown in **Figure 2**). In recent years, DBS as an effective surgical procedure for PD, not only improves motor dysfunction but also alleviates constipation symptoms in PD patients (Hogg et al., 2017; Kahan et al., 2019). Thus, the development of drug and therapeutic strategies for PD will greatly benefit the treatments of constipation in PD patients.

Non-pharmacological Treatments

Diet and Lifestyle

Diet and lifestyle interventions play an important role in managing constipation (Fathallah et al., 2017). A large-scale lifestyle study found that PD patients consumed more energy and protein, compared to controls. It was known that protein can stimulate insulin and incretin hormone secretion as well as slow gastric emptying (Ma et al., 2009). Thus, the increased protein intake may reduce oral levodopa absorption and aggravate constipation symptoms (Fasano et al., 2015; Barichella et al., 2017). Additionally, another diet survey demonstrated that the sugar intake of PD patients increased significantly, accompanied by aggravated severity of constipation and a greater need for levodopa (Palavra et al., 2021). Thus, the management of protein and sugar intake should be considered an integral part of the care of PD patients. Furthermore, after providing a vegetarian diet and bowel cleansing for PD patients, UPDRS III (Unified Parkinson Disease Ratings Scale III) can be significantly improved, and levodopa usage was decreased (Hegelmaier et al., 2020). UPDRS III is an internationally well-established rating scale for assessing the motor symptoms of PD patients. Additionally, the Mediterranean diet is considered a combination of healthy foods and has been proved to be negatively correlated with multiple prodromal features of PD, including constipation. The studies indicated that the higher score for adherence to the Mediterranean diet, the more obvious probability of constipation relief. Thus, a healthy diet pattern can improve the constipation symptom of PD patients at the early stage (Maraki et al., 2019; Molsberry et al., 2020). Together, these findings suggest that dietary management may help to maintain nutritional status, optimize levodopa treatment, and minimize its related motor complications.

Surgical Treatment

The GI tract has substantial two-way neural interactions with the central nervous system through the vagus nerve (Powell et al., 2017). Thus, the vagus nerve, the channel of information exchange, is an attractive target of neurostimulation therapy for

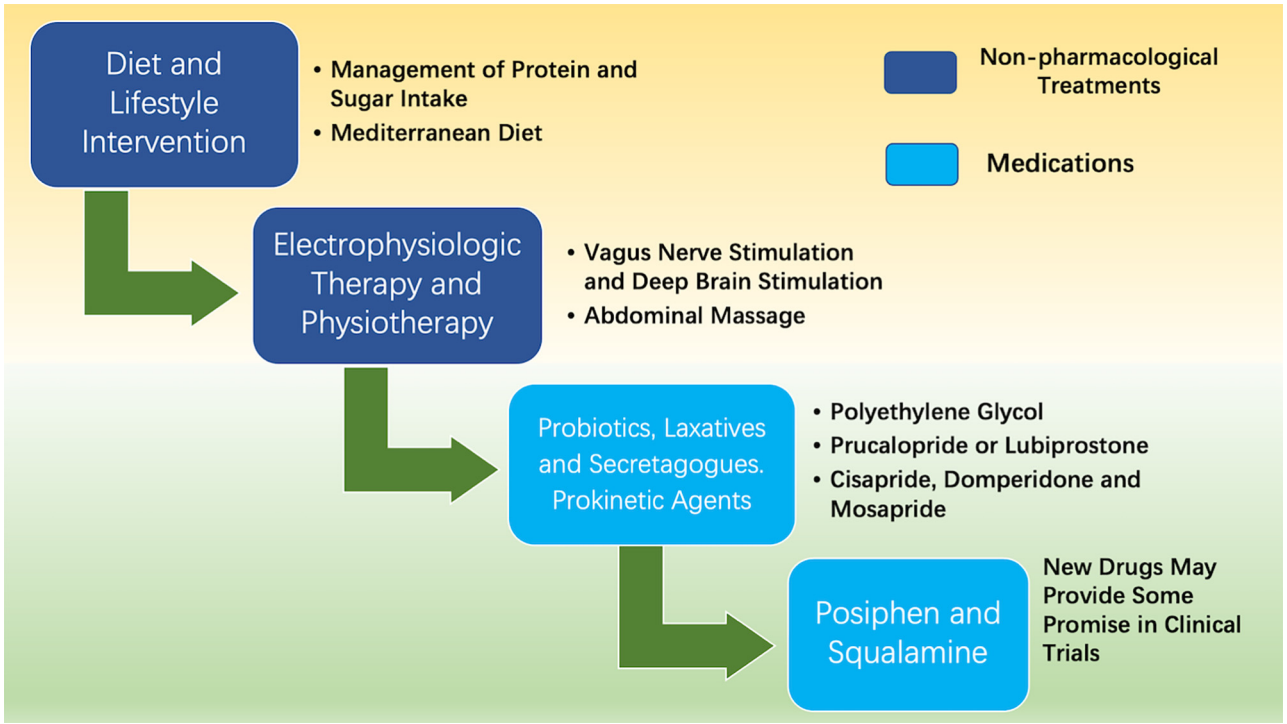

FIGURE 2 | Treatments of constipation in PD. The treatments for PD patients with complicated constipation include diet control, electrophysiologic therapy, physiotherapy, and medications.

the treatment of GI disorders (Breit et al., 2018). Utilization of bioelectronic therapy has been applied to the vagus nerve, called VNS. VNS activated the dorsal motor nucleus (DMV), reduced intestinal pro-inflammation cytokine expression, decreased leukocyte recruitment to the manipulated intestine segment, and eventually improved GI transit (Hong et al., 2019). Importantly, VNS is well tolerated with fewer relevant side effects (such as abdominal pain, flatulence, and bloating), and thereby is considered to be a promising non-invasive therapy to improve gastroenteric symptoms in PD (Kaut et al., 2019).

DBS is a surgical technique in which one or more electrodes are attached to leads and implanted in specific regions of the brain (Malek, 2019). Two specific sites in the brain have been the most common targets for DBS in PD: the subthalamic nucleus and the internal segment of the globus pallidus (Morishita et al., 2013). A follow-up evaluation found that DBS effectively ameliorated motor symptoms, and greatly adapted non-motor symptoms, including constipation (Zibetti et al., 2007). After DBS, the severity of constipation was significantly improved and the number of complete spontaneous bowel movements remarkably increased (Kola et al., 2021). Animal experiments also indicated that DBS in rats could accelerate colonic transit and increase colonic motor activity through the central DAergic pathway (Derrey et al., 2011).

Additionally, abdominal massage is perceived to be beneficial in relieving symptoms of constipation for PD patients (McClurg et al., 2016b). It can stimulate peristalsis, reduce colonic transit time, increase the frequency of bowel movements in constipated patients, and also alleviate the feelings of discomfort and pain that accompany constipation (Sinclair, 2011). Some experts believe that abdominal massage, an adjunct to the management of constipation, offers an acceptable and potentially beneficial intervention for PD patients (McClurg et al., 2016a).

Medications

Chronic constipation is the most frequent symptom of autonomic system involvement in PD, which becomes severe as the disease progress and greatly impairs the life quality of patients (Stocchi and Torti, 2017). Considering the efficacy and cost, management of constipation should begin with diet or laxatives. Laxatives are commonly used to treat constipation. Although initial observations suggested that long-term use of laxatives could induce ENS damage, more evidence and guidelines indicate that stimulant laxatives, such as polyethylene glycol, are safe and effective for chronic constipation (Siegel and Di Palma, 2005; Pare and Fedorak, 2014).

If patients are not responding to traditional laxatives, intestinal secretagogues or prokinetic agents can also be accounted for in the constipation treatment, such as prucalopride or lubiprostone (Black and Ford, 2018; Bharucha and Lacy, 2020). Prucalopride is a selective agonist of serotonin 5-HT_4 receptors. With a favorable safety profile, prucalopride is effective in many forms of constipation, such as opioid-

induced constipation usually appearing at the early stages of PD (Omer and Quigley, 2017). Lubiprostone, working by increasing fluid and electrolyte flux into the intestinal lumen, seemed to be well tolerated and effective for the short-term treatment of constipation in PD (Ondo et al., 2012). Cisapride, a prokinetic agent, can enhance the physiological release of acetylcholine from postganglionic nerve endings of the myenteric plexus and stimulate bowel movement (Neira et al., 1995). In addition, domperidone and mosapride can also stimulate digestive gastrointestinal tract motility, thereby ameliorating constipation in PD patients (Soykan et al., 1997; Liu et al., 2005).

Recently, several new drugs have been developed and are considered to be potential for the treatment of constipation in PD. Posiphen, an α-Syn protein translation inhibitor, was confirmed to normalize the colonic motility in mouse models with GI dysfunction (Kuo et al., 2019). Further study in humans showed that posiphen is well tolerated and significantly lowers inflammatory markers (Maccecchini et al., 2012). Squalamine, a zwitterionic amphipathic amino sterol, originally isolated from the liver of the dogfish shark, dramatically affects α-Syn aggregation *in vitro* and *in vivo* (Perni et al., 2017). After taking squalamine in the PD mouse model, the excitability of intrinsic primary afferent neurons of ENS can be rapidly restored (West et al., 2020). A double-blind, placebo-controlled study also confirmed that oral tablets of squalamine are safe and significantly improve bowel function in PD-related constipation (Hauser et al., 2019). Together, these drugs may provide some promise in clinical trials but need to be evaluated further.

Besides chemicals, multi-strain probiotics are also considered an effective strategy for alleviating constipation, by restoring the balance of gut microbiota, increasing the intestinal opening frequency, and improving the whole intestinal transmission time (Westfall et al., 2017; Tan et al., 2021). The consumption of fermented milk containing multiple probiotic strains and prebiotic fiber was superior to placebo in improving constipation in patients with PD (Barichella et al., 2016). Such treatments can greatly improve the quality of life in PD patients with constipation (Ibrahim et al., 2020; Tan et al., 2021).

Summary and Prospects

Since the relationship between the pathogenesis of constipation and disease progression in PD patients is still unclear, no completely effective radical therapeutic method is identified yet. Currently, the clinical treatments of constipation in PD patients are similar to the treatments in the general population. Although these managements have limited effects in the short term, the long-term efficacy is still poor. Thus, more efforts in the studies of PD pathogenesis may be needed to expand the scope of research, provide new strategies, and improve the life quality of patients.

AUTHOR CONTRIBUTIONS

LW conceptualized the manuscript. JX and WL drafted the manuscript. LW and XC revised and supervised the manuscript. All authors contributed to the article and approved the submitted version.

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Altered Prefrontal Blood Flow Related With Mild Cognitive Impairment in Parkinson's Disease: A Longitudinal Study

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Cognitive impairment is a common non-motor symptom in Parkinson's disease (PD), with executive dysfunction being an initial manifestation. We aimed to investigate whether and how longitudinal changes in the prefrontal perfusion correlate with mild cognitive impairment (MCI) in patients with PD. We recruited 49 patients with PD with normal cognition and 37 matched healthy control subjects (HCs). Patients with PD completed arterial spin labeling MRI (ASL–MRI) scans and a comprehensive battery of neuropsychological assessments at baseline (V0) and 2-year follow-up (V1). HCs completed similar ASL–MRI scans and neuropsychological assessments at baseline. At V1, 10 patients with PD progressed to MCI (converters) and 39 patients remained cognitively normal (non-converters). We examined differences in the cerebral blood flow (CBF) derived from ASL–MRI and neuropsychological measures (a) between patients with PD and HCs at V0 (effect of the disease), (b) between V1 and V0 in patients with PD (effect of the disease progression), and (c) between converters and non-converters (effect of the MCI progression) using *t*-tests or ANOVAs with false discovery rate correction. We further analyzed the relationship between longitudinal CBF and neuropsychological changes using multivariate regression models with false discovery rate correction, focusing on executive functions. At V0, no group difference was found in prefrontal CBF between patients with PD and HCs, although patients with PD showed worse performances on executive function. At V1, patients with PD showed significantly reduced CBF in multiple prefrontal regions, including the bilateral lateral orbitofrontal, medial orbitofrontal, middle frontal, inferior frontal, superior frontal, caudal anterior cingulate, and rostral anterior cingulate. More importantly, converters showed a more significant CBF reduction in the left lateral orbitofrontal cortex than non-converters. From V0 to V1, the prolonged completion time of Trail Making Test-B (TMT-B) negatively correlated with longitudinal CBF reduction in the right caudal anterior cingulate cortex. The decreased accuracy of the Stroop Color-Word Test positively correlated with longitudinal CBF reduction in the left medial orbitofrontal cortex. In addition, at V1, the completion time of TMT-B negatively

correlated with CBF in the left caudal anterior cingulate cortex. Our findings suggest that longitudinal CBF reduction in the prefrontal cortex might impact cognitive functions (especially executive functions) at the early stages of PD.

Keywords: Parkinson's disease, mild cognitive impairment, arterial spin labeling, longitudinal, prefrontal cortex

INTRODUCTION

Cognitive impairment occurs at the early stages of Parkinson's disease (PD) and impacts the quality of life (Aarsland et al., 2017). The spectrum of cognitive impairment in PD encompasses subjective cognitive decline, mild cognitive impairment (PD–MCI), and dementia (PDD) (Aarsland et al., 2021). Approximately one-third of the newly diagnosed patients with PD exhibit PD–MCI (Broeders et al., 2013). About 38% of patients with PD with normal cognition convert to PD–MCI or PDD over 3 years (Nicoletti et al., 2019). Executive dysfunction is an initial manifestation of PD–MCI, including deficits in cognitive flexibility and inhibitory control (Svenningsson et al., 2012). The prefrontal cortex encompasses the lateral prefrontal cortex, medial prefrontal cortex, and orbitofrontal cortex, which play a key role in executive cognitive functions (Jones and Graff-Radford, 2021). Dopaminergically mediated fronto-striatal executive impairment is to be considered partly accountable for cognitive deficit in PD (Kehagia et al., 2013). In this study, we aimed to investigate whether and how longitudinal changes in the prefrontal perfusion correlate with the progression of PD–MCI and executive dysfunction.

Cognitive impairment in PD is associated with cortical hypoperfusion, in addition to other cortical structure and function changes (Melzer et al., 2012; Al-Bachari et al., 2014; Wang et al., 2018). Cortical perfusion is often measured as cerebral blood flow (CBF) derived from the arterial spin labeling (ASL) MRI (Williams et al., 1992). CBF is thought to reflect neural activity and brain glucose metabolism at the capillary level (Musiek et al., 2012). Widespread CBF reduction in the prefrontal cortex, hippocampus, parietal cortex, and precuneus has been linked to global cognitive decline in PD (Fernandez-Seara et al., 2012; Al-Bachari et al., 2014). The frontal lobe has been reported to be associated with executive functions (Fuster, 2000). Patients with PDD showed reduced left inferior frontal CBF, compared with patients with PD with MCI or normal cognition (Azamat et al., 2021). CBF reductions in the right superior frontal gyrus, right middle frontal gyrus, and right anterior and medial orbitofrontal cortex are associated with global cognitive impairment in patients with PD (Liu et al., 2021). Moreover, CBF reduction in the left middle frontal gyrus is associated with executive dysfunction (Suo et al., 2019). Although many cross-sectional studies have demonstrated that lower CBF in patients with PD (relative to healthy adults) is associated with cognitive impairment, longitudinal studies allow us to look at cognitive decline over time in patients with PD. Confounding factors such as age, education, and socioeconomic status can be better controlled in longitudinal studies. In addition, frontal CBF predicts cognitive decline in a healthy aging cohort with 4-year follow-up (De Vis et al., 2018). Hence, the changes in frontal CBF associated with cognitive status alternations in patients with PD is worth verifying.

Therefore, in the longitudinal study herein, we aimed to investigate whether and how prefrontal CBF changes correlate with mild cognitive decline in patients with PD over 2 years. Patients with PD with normal cognition completed ASL–MRI scans and a comprehensive battery of neuropsychological assessments (executive functions, attention/working memory, visuospatial functions, memory, and language) at baseline (V0) and 2-year follow-up (V1). Matched healthy control subjects (HCs) were assessed once at baseline. First, we wanted to detect group differences in prefrontal CBF and neuropsychological measures between patients with PD and HCs at V0 (effect of the disease). Second, we wanted to examine whether prefrontal CBF decreased between V1 and V0 (effect of the disease progression). Third, we separated patients with PD who were converted to MCI (converters) and those who stayed cognitively normal at V1 (non-converters). We aimed to examine whether prefrontal CBF decreased more in converters than non-converters (effect of the MCI progression). Finally, we sought to identify relationships between prefrontal CBF reduction and executive dysfunction. In particular, we asked whether prefrontal CBF changes correlated with changes in the neuropsychological measures of cognitive flexibility or inhibitory control.

METHODS AND MATERIALS

This study was approved by the ethics committee of the Fudan University Zhongshan Hospital, according to the Declaration of Helsinki. Before participating in this study, each participant signed a written informed consent.

Study Design

It is a longitudinal study. In total, 49 patients with PD with normal cognition were recruited and measured at baseline (V0). All the patients completed ASL–MRI scans and a comprehensive battery of neuropsychological assessments. After 2 years (V1), 10 patients with PD converted to MCI (converters), and 39 patients stayed cognitively normal (non-converters). In total, 37 HCs completed similar ASL–MRI scans and neuropsychological assessments at V0.

Patients and Clinical Assessments

In total 49 patients with PD were recruited from the movement disorders clinically at the Zhongshan Hospital from September 2016 to October 2018. Inclusion criteria included the following: (1) PD diagnosis, according to the Movement Disorder Society clinical diagnostic criteria for PD (Postuma et al., 2015); (2) cognitively normal at V0, not meeting the diagnostic criteria of PDD (Emre et al., 2007) or level 2 criteria of PD–MCI (i.e., 1.5

SDs below the normative score) (Litvan et al., 2012); (3) Hoehn and Yahr stages 1–2; (4) age 40–80 years; and (5) education >6 years. Exclusion criteria included the following: (1) a history of other neurologic or psychiatric diseases; (2) alcohol or drug abuse; or (3) contraindication to MRI. Six additional patients were excluded from data analysis because of excessive head motion during scanning ($n = 1$), MRI artifacts ($n = 3$), or poor MRI co-registration ($n = 2$).

Healthy Control Subjects

In total, 37 HCs were recruited from the local community. Inclusion criteria included the following: (1) age 40–80 years and (2) education >6 years. Exclusion criteria included the following: (1) a history of significant neurologic or psychiatric disorders; (2) a family history of PD, essential tremor, or other movement disorders; or (3) contraindication to MRI. In total, three additional HCs were excluded from data analysis due to MRI artifacts.

Neuropsychological Assessments

Neuropsychological tests measured executive functions (Stroop Color and Word Test, Trail Making Test-B), attention/working memory (Symbol Digit Modalities Test, Trail Making Test-A), visuospatial functions (Rey-Osterrieth Complex Figure Test, Clock-Drawing Test), memory (Auditory Verbal Learning Test, delayed recall of the Rey-Osterrieth Complex Figure Test), and language (Animal Fluency Test, Boston Naming Test).

First, we detected group differences between patients with PD and HCs at V0 using two-sample *t*-tests or the Mann–Whitney *U* tests, if the data were not normally distributed ($p < 0.05$ false-discovery-rate-corrected, FDR-corrected). Second, we detected differences between V0 and V1 in patients with PD using paired *t*-tests or the Wilcoxon signed-rank tests, if the data were not normally distributed ($p < 0.05$ FDR-corrected). Third, we detected subgroup differences between converters and non-converters using two-sample *t*-tests or the Mann–Whitney *U* tests, if the data were not normally distributed ($p < 0.05$, FDR-corrected).

Acquisition of T1-MRI and ASL–MRI Data

Brain imaging data were acquired on a GE Discovery MR750 3T MR scanner. High-resolution T1-weighted images used a 3D brain volume imaging (BRAVO) sequence (136 axial slices; time of repetition, 8.2 ms; time of echo, 3.2 ms; inversion time, 450 ms; field-of-view, 240 × 240 mm; slice thickness, 1.0 mm; no intersection gap; matrix, 256 × 256; number of excitations, 1; flip angle, 12°; bandwidth, 31.25 kHz).

Arterial spin labeling images used a three-dimensional pseudo-continuous ASL (3D pCASL) technique (Ding et al., 2014) with background suppression and outward-direction spiral readout (time of repetition, 4,830 ms; time of echo, 10.5 ms; labeling duration, 1,500 ms; post labeling delay, 2,025 ms; field-of-view, 240 × 240 mm; slice thickness, 4 mm; matrix, 128 × 128; number of excitations, 3; flip angle, 155°; eight spiral arms with 512 points in each arm; bandwidth, 62.5 kHz; the resolution, 1.9 × 1.9 mm). An additional proton density-weighted image of absolute CBF quantification used the same acquisition parameters. Then, ASL images were transferred to the Advantage Workstation for Diagnostic Imaging 4.6 (GE Medical Systems, Milwaukee, WI, USA), and the quantitative CBF maps, in units of ml/100 g/min, were calculated using vender provided toolbox. There were no user-modifiable parameters for generating CBF maps in the toolbox for ASL images.

Preprocessing and Analysis of MRI Data

MRI data were preprocessed and analyzed using Freesurfer v7.1.0 (Dale et al., 1999; Fischl et al., 2002; Reuter et al., 2012) and FMRIB Software Library v6.0 (Parker Jones et al., 2018) with a standard pipeline. T1 images were corrected for head motion, normalized to reduce signal intensity, non-uniformity, and fluctuation, and transformed into the Talairach space. Non-brain tissues (e.g., skull and neck) were removed. White matter and deep grey matter nuclei were segmented using an automated algorithm. Regions of interest were parcellated according to the Desikan–Killiany atlas, and their tissue volumes were computed. We monitored the potential effects of tissue volume. First, we examined whether patients with PD showed smaller prefrontal volumes than HCs at V0 and whether converters showed smaller prefrontal volumes than non-converters at V1 using two-sample

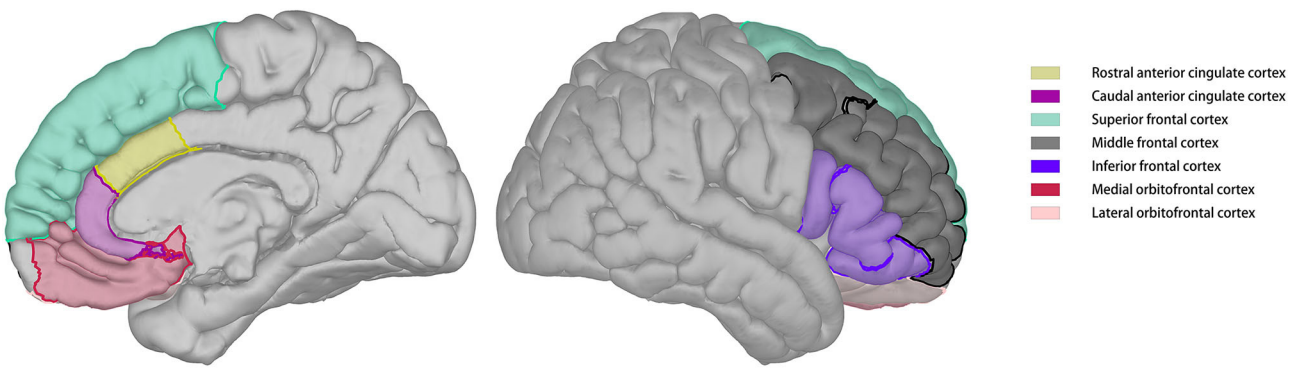

FIGURE 1 | ROIs distribution on brain model.

t-tests (FDR-corrected). Second, we examined whether patients with PD showed smaller prefrontal volumes at V1 than V0 using paired *t*-tests (FDR-corrected). Third, we examined whether longitudinal changes in the prefrontal volume correlated with those in the prefrontal CBF (FDR-corrected).

Analysis of Cortical CBF and Statistical Analyses

Cerebral blood flow images were skull-stripped and automatically co-registered with reconstructed T1 images. Co-registration results were visually inspected and manually adjusted to ensure quality. Regional CBF was calculated according to the parcellation of T1 images. The regions of interest for this study included the lateral orbitofrontal cortex, medial orbitofrontal cortex, superior frontal cortex, middle frontal cortex, inferior frontal cortex, caudal anterior cingulate cortex, and rostral anterior cingulate cortex of both the hemispheres (**Figure 1**).

First, we examined whether patients with PD showed lower prefrontal CBF than HCs at V0 using two-sample *t*-tests or the Mann–Whitney *U* tests, if the data were not normally distributed ($p < 0.05$, FDR-corrected). Second, we examined whether patients with PD showed lower prefrontal CBF at V1 than V0 using paired *t*-tests or the Wilcoxon signed-rank tests if the data were not normally distributed ($p < 0.05$, FDR-corrected). Third, we explored whether converters showed a more significant prefrontal CBF reduction than non-converters using repeated-measures ANOVAs ($p < 0.05$) with two factors, subgroups (converters and non-converters) and visit (V0 and V1). Forth, we identified the relationship between prefrontal CBF and neuropsychological measures of executive functions using stepwise linear regressions ($p < 0.05$, FDR-corrected). In particular, we asked whether longitudinal changes in the completion time of TMT-B or accuracy of Stroop Test between V1 and V0 correlated with prefrontal CBF changes, prefrontal volume changes, UPDRS motor score changes, depression score changes, cortical volume changes, age changes, or education. In addition, we asked whether the completion time of TMT-B or accuracy of Stroop Test at V0 or V1 correlated with prefrontal CBF, when prefrontal volume, UPDRS motor scores, depression scores, age, and education were controlled.

TABLE 1 | Demographic, clinical, and neuropsychological data of PD patients and HCs (means, SDs, and statistic differences).

Features/Measures	HC ($n = 37$)	PD ($n = 49$)		Statistic differences (p values)	
		V0	V1	PD at V0 vs. HC	PD at V1 vs. V0
Male/Female	15/22	26/23	26/23	0.157	–
Age (years)	62.2 (6.9)	63.8 (9.0)	65.8 (9.0)	0.373	–
Education (years)	12.2 (2.6)	12.0 (3.3)	12.0 (3.3)	0.430	–
Disease duration (months)		42.7 (69.0)	66.9 (68.4)	–	–
Motor symptoms					
Hoehn and Yahr stage		1.3 (0.5)	1.6 (0.6)	–	0.005*
UPDRS III		16.7 (7.5)	18.7 (8.4)	–	0.011*
Non-motor symptoms					
REM Sleep Behavior Disorder Screening Questionnaire score		3.6 (3.4)	4.6 (3.0)	–	0.028
Geriatric Depression Scale score (30-items)		7.8 (6.4)	10.9 (5.4)	–	0.002*
Executive functions					
Stroop (completion time)	66.7 (17.2)	76.7 (19.0)	77.6 (22.0)	0.013*	0.604
Stroop (number of correct answers)	48.0 (2.3)	47.2 (3.1)	46.5 (3.4)	0.297	0.114
TMT-B (completion time)	111.3 (39.9)	138.8 (37.9)	144.1 (41.9)	0.002*	0.309
Attention/working memory					
Symbol Digit Modalities Test score	47.7 (10.3)	40.5 (10.3)	38.3 (10.2)	0.002*	0.040
TMT-A (completion time)	52.2 (20.2)	60.4 (17.1)	58.9 (19.5)	0.043	0.379
Visuospatial functions					
Rey-Osterrieth Complex Figure Test score	32.9 (2.3)	32.4 (2.5)	31.9 (3.0)	0.441	0.126
Clock Drawing Test score	9.3 (0.7)	9.4 (0.8)	9.1 (1.5)	0.644	0.292
Memory					
Auditory Verbal Learning Test total score	32.4 (7.9)	31.2 (9.5)	32.5 (12.3)	0.540	0.283
Rey-Osterrieth Complex Figure Test delayed recall score	16.8 (6.5)	16.7 (7.0)	15.6 (6.9)	0.901	0.094
Language					
Animal Fluency Test score	18.6 (4.9)	19.9 (5.3)	18.8 (5.7)	0.267	0.150
Boston Naming Test score (30-items)	25.7 (2.9)	25.8 (2.4)	25.6 (2.8)	0.965	0.564

Statistic differences, p values of two-sample t-tests, paired-sample t-tests, Mann-Whitney U tests or Wilcoxon signed-rank tests as appropriate; asterisks, p < 0.05 false-discovery-rate-corrected.
UPDRS, Unified Parkinson's Disease Rating Scale; TMT, Trail Making Test.

RESULTS

Group Differences and Longitudinal Changes in Neuropsychological Measures

Table 1 shows neuropsychological data of patients with PD and HCs. At V0, patients with PD performed worse than HCs on executive functions and working memory. However, no significant longitudinal changes were found between V0 and V1. **Table 2** illustrates neuropsychological data of converters and non-converters. Converters performed worse than non-converters on executive functions, visuospatial functions, and language at V1 but not V0. Converters performed worse than non-converters on working memory and memory at both visits.

Prefrontal CBF Difference Between Patients With PD at V0 and V1

No significant difference was found between PD and HC at V0 ($p > 0.36$ for all the ROIs). **Figure 2A**, **Table 3** show decreased prefrontal CBF in patients with PD at V1. Patients with PD showed significantly lower CBF at V1 than V0 in multiple ROIs ($p < 0.05$).

Prefrontal CBF Differences Between Converters and Non-converters

In patients with PD, converters showed a more significant CBF reduction (25.8%) than non-converters at V1(7.8%) in the left lateral orbitofrontal cortex (**Figure 2B**). A marginal subgroup difference was found in the left lateral orbitofrontal cortex, an interaction between subgroup and visit was found [$F(1,96) = 4.66$, $p = 0.036$, partial $\eta^2 = 0.90$] in addition to an effect of visit [$F(1) = 16.0$, $p < 0.001$, partial $\eta^2 = 0.254$]. No main effect of the subgroup was found ($p = 0.256$). No effect of the subgroup was found in any other prefrontal ROIs ($ps > 0.145$).

Relationships Between Longitudinal CBF Reduction and Cognitive Decline

Figures 2C,D shows relationships between longitudinal CBF reduction and executive dysfunction. The stepwise regression model for cognitive flexibility (i.e., TMT-B

TABLE 2 | Demographic, clinical, and neuropsychological data of converters and non-converters (means, SDs, and statistic differences).

Features/Measures	V0 ($n = 49$)		V1 ($n = 49$)		Subgroup differences (p values)	
	Non-converters	Converters	Non-converters	Converters	V0	V1
Male/Female	21/18	5/5	21/18	5/5	0.157	0.157
Age (years)	63.1 (9.6)	66.4 (5.8)	65.1 (9.6)	68.5 (5.8)	0.301	0.301
Education (years)	12.6 (3.2)	9.3 (1.9)	12.6 (3.2)	9.3 (1.9)	0.005*	0.005*
Disease duration (months)	45.3 (75.2)	32.5 (36.4)	69.8 (75.4)	58.0 (35.5)	0.634	0.634
Motor symptoms						
Hoehn and Yahr stage	1.3 (0.4)	1.6 (0.5)	1.5 (0.6)	1.8 (0.6)	0.039	0.163
UPDRS III	15.4 (6.1)	21.5 (10.5)	17.9 (7.6)	21.8 (11.0)	0.117	0.194
Non-motor symptoms						
REM Sleep Behavior Disorder Screening Questionnaire score	3.6 (3.5)	3.8 (3.0)	4.5 (3.1)	4.8 (3.1)	0.862	0.792
Geriatric Depression Scale score (30-items)	7.2 (5.9)	10.1 (7.9)	10.3 (5.1)	13.1 (6.4)	0.197	0.144
Executive functions						
Stroop (completion time)	74.3 (19.1)	86.2 (15.8)	74.0 (20.5)	98.9 (21.5)	0.076	0.001*
Stroop (number of correct answers)	47.2 (3.3)	47.3 (2.4)	47.3 (2.6)	42.6 (4.2)	0.914	<0.001*
TMT-B (completion time)	133.7 (37.7)	158.9 (35.1)	133.2 (35.6)	186.0 (37.9)	0.060	<0.001*
Attention/working memory						
Symbol Digit Modalities Test score	42.6 (10.0)	32.1 (6.2)	40.5 (9.8)	29.9 (6.9)	0.003*	0.003*
TMT-A (completion time)	59.4 (17.8)	64.3 (14.1)	54.1 (15.9)	77.7 (21.5)	0.427	<0.001*
Visuospatial functions						
Complex Figure Test score	32.8 (2.1)	30.7 (3.2)	17.4 (6.2)	28.8 (3.7)	0.018	0.002*
Clock Drawing Test score	9.5 (0.6)	8.9 (1.2)	9.2 (1.4)	8.7 (1.8)	0.041	0.308
Memory						
Auditory Verbal Learning Test total score	32.4 (10.0)	26.2 (4.9)	35.1 (11.5)	22.1 (9.9)	0.039	0.002*
Rey-Osterrieth Complex Figure Test delayed recall score	18.5 (6.1)	9.6 (5.2)	17.4 (6.2)	8.2 (3.8)	<0.001*	<0.001*
Language						
Animal Fluency Test score	16.7 (3.5)	20.8 (5.4)	20.3 (5.1)	13.1 (4.2)	0.030	<0.001*
Boston Naming Test score (30-items)	26.0 (2.4)	24.7 (2.2)	26.3 (2.4)	23.0 (2.8)	0.114	<0.001*

Subgroup differences, p values of two-sample t-tests, paired-sample t-tests, Mann-Whitney U tests or Wilcoxon signed-rank tests as appropriate; asterisks, p < 0.05 false-discovery-rate-corrected.

UPDRS, Unified Parkinson's Disease Rating Scale; TMT, Trail Making Test.

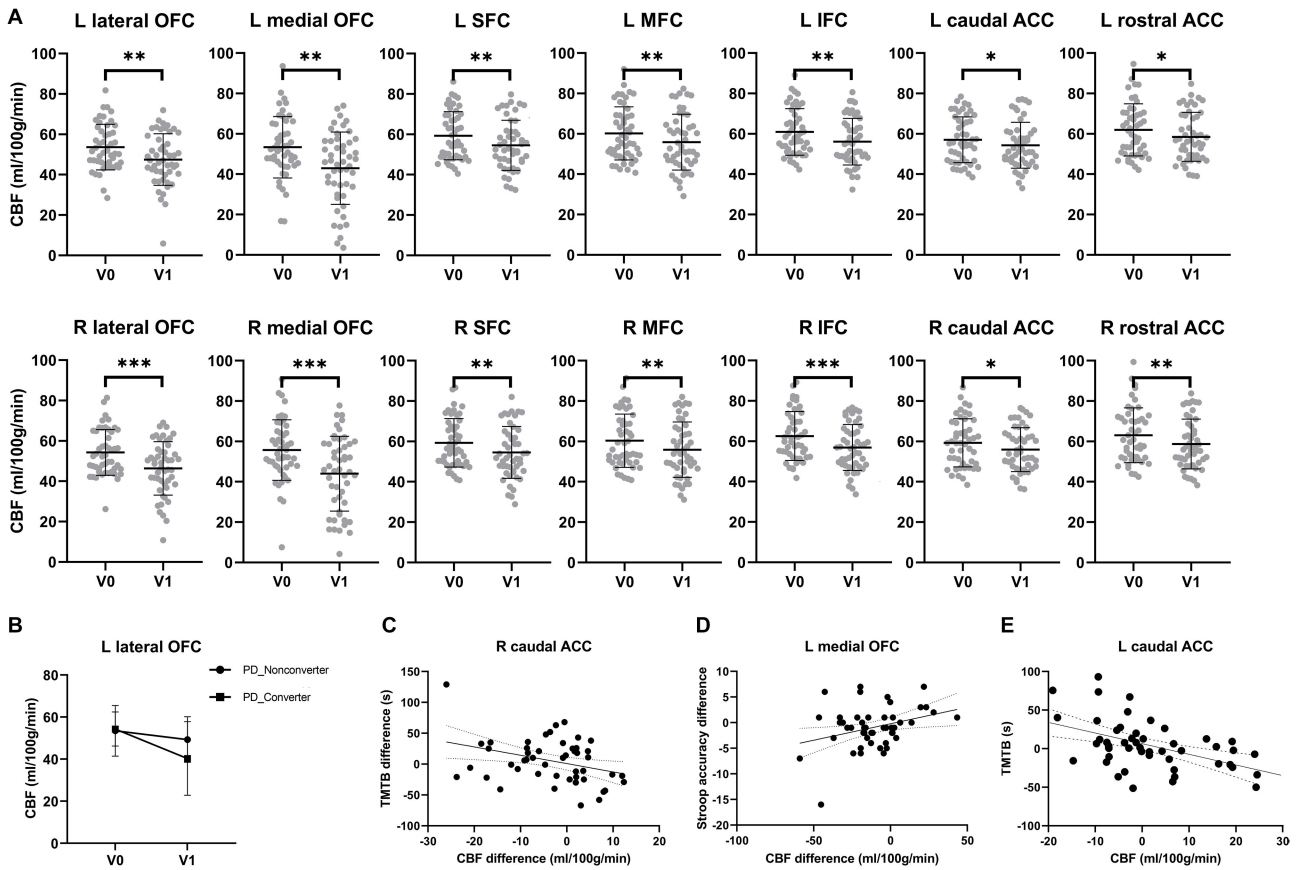

FIGURE 2 | Reduced prefrontal cerebral blood flow and executive dysfunction over time in PD patients. **(A)** Significant CBF reduction in the lateral orbitofrontal cortex, medial orbitofrontal cortex, middle frontal cortex, inferior frontal cortex, superior frontal cortex, caudal anterior cingulate cortex and rostral anterior cingulate cortex of both hemispheres over 2 years. Asterisks indicate significant group difference (*: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$). **(B)** Converters showed a more significant perfusion reduction in the left lateral orbitofrontal cortex than non-converters over 2 years. **(C)** The prolonged completion time of Trail Making Test-B (TMT-B) was negatively correlated with longitudinal CBF reduction in the right caudal anterior cingulate cortex. **(D)** Longitudinal CBF reduction in right caudal anterior cingulate cortex was significantly related to the progressive worse accuracy of Stroop test over time. **(E)** At V1, completion time of TMT-B had a significantly negative correlation with the CBF in left caudal anterior cingulate cortex.

completion time difference between V1 and V0) was significant [$F(1,47) = 6.27$, $R^2 = 0.118$, $p = 0.016$]. The model included longitudinal CBF changes in the right caudal anterior cingulate cortex ($t = -2.50$, $p = 0.016$) but no other factors ($ps > 0.875$). The stepwise regression model for inhibitory control (i.e., Stroop accuracy difference between V1 and V0) was also significant [$F(1,47) = 5.52$, $R^2 = 0.105$, $p = 0.023$]. The model included longitudinal CBF changes in the left medial orbitofrontal cortex ($t = 2.35$, $p = 0.023$) but no other factors ($ps > 0.737$). No such correlation was obtained for the TMT-A completion time difference ($p = 0.569$).

Figure 2E shows relationships between prefrontal CBF and cognitive flexibility at V1. The stepwise regression model for the TMT-B completion time was significant [$F(4,44) = 17.3$, $R^2 = 0.536$, $p < 0.001$]. The model included CBF in the left caudal anterior cingulate cortex ($t = -3.71$, $p = 0.001$), education ($t = -3.07$, $p = 0.004$), and age ($t = 4.23$, $p < 0.001$) but no other factors ($ps > 0.052$). No such correlation was obtained for the TMT-A completion time. No significant correlation was found for either the TMT-A or TMT-B completion time at V0.

Effects of Tissue Volume

Finally, we excluded potential effects of tissue volume. Patients with PD were similar as HCs at V0 in the total intracranial volume ($p = 0.856$), total cortical grey matter volume ($p = 0.885$), the volume of prefrontal ROIs ($ps > 0.173$). Converters were similar to non-converters at V1 in the total intracranial volume ($p = 0.452$), total cortical grey matter volume ($p = 0.737$), and the volume of prefrontal ROIs ($ps > 0.150$). However, from V0 to V1, subjects with PD showed a significantly cortical atrophy in the bilateral lateral orbitofrontal cortex (left: $t(48) = 2.91$, $p = 0.005$; right: $t(48) = 2.98$, $p = 0.005$), left medial orbitofrontal cortex ($t(48) = 2.65$, $p = 0.011$), left superior frontal cortex ($t(48) = 2.97$, $p = 0.005$), bilateral middle frontal cortex (left: $t(48) = 2.98$, $p = 0.005$; right: $t(48) = 3.19$, $p = 0.002$), bilateral inferior frontal cortex (left: $t(48) = 2.48$, $p = 0.017$; right: $t(48) = 3.62$, $p < 0.001$), and bilateral rostral anterior cingulate cortex (left: $t(48)$

TABLE 3 | The prefrontal perfusion significantly different between V0 and V1 in PD patients.

Region	*t*-value	*p*-value
Left lateral orbitofrontal cortex	3.52	$p = 0.002$
Right lateral orbitofrontal cortex	4.52	$p < 0.001$
Left medial orbitofrontal cortex	3.57	$p = 0.001$
Right medial orbitofrontal cortex	3.88	$p < 0.001$
Left middle frontal cortex	2.85	$p = 0.006$
Right middle frontal cortex	3.01	$p = 0.004$
Left inferior frontal cortex	3.72	$p = 0.001$
Right inferior frontal cortex	4.55	$p < 0.001$
Left superior frontal cortex	3.16	$p = 0.003$
Right superior frontal cortex	3.11	$p = 0.003$
Left caudal anterior cingulate cortex	2.22	$p = 0.031$
Right caudal anterior cingulate cortex	2.53	$p = 0.015$
Left rostral anterior cingulate cortex	2.53	$p = 0.015$
Right rostral anterior cingulate cortex	3.32	$p = 0.002$

$= 2.63$, $p = 0.011$; right: $t(48) = 2.82$, $p = 0.007$). Importantly, longitudinal changes in the prefrontal CBF did not correlate with those in the prefrontal volume ($ps > 0.369$).

DISCUSSION

Mild cognitive impairment is a common non-motor symptom in PD. Approximately 28% of patients with PD converted to PD–MCI and 6% converted to PDD over 1–16 years (Saredakis et al., 2019). However, biological mechanisms underlying the progression of cognitive impairment are still unclear. This longitudinal study investigated whether and how prefrontal perfusion changes correlate with mild cognitive decline in patients with PD using ASL–MRI. Patients with PD with normal cognition showed normal prefrontal perfusion at baseline but worse performance on executive functions than healthy controls. As the disease progressed, patients with PD showed decreased perfusion in multiple prefrontal regions over 2 years (effect of the disease progression). More importantly, patients with PD who converted to MCI showed a more significant perfusion reduction in the left lateral orbitofrontal cortex than those who stayed cognitively normal at 2-year follow-up (effect of the MCI progression). In particular, the impairment of cognitive flexibility (reflected as the prolonged completion time of TMT-B) correlated with perfusion reduction in the right caudal anterior cingulate cortex, and the impairment of inhibitory control (reflected as the fewer correct responses of the Stroop Test) correlated with perfusion reduction in the left medial orbitofrontal cortex. Although patients with PD showed additional cortical atrophy in the prefrontal cortex, prefrontal volumetric reduction did not significantly contribute to the progression of MCI or executive dysfunction. These findings suggest that longitudinal prefrontal perfusion reduction may be underlying the progression of cognitive impairment at the early stages of PD.

Parkinson's disease is a neurodegenerative and progressive disorder. However, autopsy studies are not sufficient to discover the underlying causes of the progression of PD-related pathology, especially in the early stages. Neuroimaging studies provide an alternative way that might help to reveal the pathophysiology of disease progression. In the present study, at baseline, no group difference was found in prefrontal CBF between patients with PD and HCs, while reduced CBF was shown in the bilateral lateral and medial orbitofrontal cortex, bilateral inferior, middle, and superior cortex and caudal, rostral anterior cingulate cortex over 2 years in patients with PD *via* ASL–MRI. A primary novel finding is that the converters showed progressive hypoperfusion in the left lateral orbitofrontal gyrus, compared with the non-converters between V0 and V1. In addition, there were subtle differences between converters and non-converters at V0 in attention/working memory and memory. Our result was also consistent with Wilsen et al., which showed severer motor symptoms and poor performance on cognitive tests were associated with cognitive decline at the early stages of PD (Wilson et al., 2020). Overall, our results indicated the serial reduction of frontal perfusion along with disease progression and partly contribute to cognitive decline in the early stage of PD. The mechanisms/pathophysiology of cognitive decline in PD is not fully clear, and it is generally considered that multiple degenerations of neurotransmitter systems were associated with cognitive impairment (Aarsland et al., 2021). In addition to the fundamental pathological changes associated with cognitive impairment, some previous studies report cerebral perfusion deficiencies in PD (Fernandez-Seara et al., 2012; Al-Bachari et al., 2014), including our study. It is not known how CBF influences cognitive function. Several reviews summarize that hypoperfusion leads to cognitive impairment partly because of the neurovascular unit dysfunction, disrupted neurotransmitter circuits, and mitochondrial energy deficiency (Iadecola, 2017; de la Torre et al., 2020). One review demonstrated cerebral hypoperfusion, and glucose hypometabolism trigger neuroinflammation and oxidative stress that in turn decrease nitric oxide, upregulating amyloid, and tau in AD (Daulatzai, 2017). Brain perfusion was correlated with cerebrospinal fluid Aβ42 levels which reflected neurodegeneration in patients with amnestic MCI (Quattrini et al., 2021). Moreover, chronic cerebral hypoperfusion *via* stenosis of the bilateral common carotid arteries may exacerbate cognitive impairment in a mouse model of PD (Tang et al., 2017). To some extent, the current study might aid our understanding of the pathophysiology of cognitive conversion in PD.

In addition, neuroimaging features that can track changes in brain structure and functions and associate with neurobiological processes might be applied as longitudinal progression markers in clinical use in PD. Using dopamine transporter imaging, Kaasinen et al. reported progressive striatal dopamine loss (Kaasinen and Vahlberg, 2017). However, the cost, availability, and ceiling effect of dopaminergic deficit limited the use of dopamine transporter imaging in the follow-up study. In total, two recent longitudinal studies demonstrated serial neuromelanin signal loss in substantia nigra (SN), and associated

were with changes in motor severity in patients with PD (Gaurav et al., 2021; Xing et al., 2022). Even so, SN neuronal loss might not play a key role in the pathophysiology of non-motor symptoms in PD. To date, several studies using voxel-based morphometry analyses have reported alternation of gray volume and thickness with follow-up period, but inconsistent results indicated that this biomarker was not sensitive to reflect small changes in the disease progression (Yang et al., 2018). Our longitudinal data suggested prefrontal CBF reduction over time and related to cognitive decline in PD, which might be a potential imaging marker associated with cognitive impairment. Along with the neuroimaging biomarker, we note that some neuropsychological tests were reported to be a predictor of developing PDD in the longitudinal cohort (Kim et al., 2019; Lawson et al., 2021). Byeon H also reported a random forest model including MMSE total score, MoCA total score, UPDRS motor score, and Clinical Dementia Rating (CDR) sum of boxes that can predict PD–MCI with an overall accuracy of 65.6% (Byeon, 2020). Since ASL–MRI is relatively low-cost neuroimaging and can be repeated many times for its non-invasion to quantify CBF objectively and quickly, we thought neuropsychological tests, together with an imaging marker or blood/ CSF-based marker might be more sensitive and accurate to predict PD–MCI and PDD in the future study. On the contrary, our results inferred that patients with PD should avoid cerebral hypoperfusion which might in turn cause disease progression in the clinical practice.

Executive dysfunction occurs at a relatively higher frequency in PD–MCI (Zalonis et al., 2008; Baiano et al., 2020). Our longitudinal analyses revealed that over 2 years, reduction of prefrontal CBF in the medial orbitofrontal cortex and caudal anterior cingulate cortex have a significant correlation with poorer performance on inhibitory control and cognitive flexibility, bypassing the potential confounding effects of tissue volume. This could suggest that the prefrontal hypoperfusion might partly be involved in executive dysfunction. High-level cognitive abilities involve cortical regions. TMT-B tests provide a measure of cognitive function associated with the working memory, sequencing, and set-shifting (Sánchez-Cubillo et al., 2009), while Stroop measures executive inhibition of irrelevant responses (Treisman and Fearnley, 1969). Consistently, Brück et al. revealed performance in the Stroop test negatively correlated with the Fdopa uptake in the medial frontal cortex of early PD using positron emission tomography scanning (Brück et al., 2005). Moreover, in an animal study, impaired cognitive flexibility may be partly because of the disruption of the anterior cingulate cortex and its neuromodulation with thalamic nuclei (Bubb et al., 2021). Further studies would be required to detect the role of the prefrontal cortex in large-scale networks or neural circuits.

A previous report by Zhou et al. showed progressive bilateral superior frontal lobe atrophy was found in the converters (Zhou et al., 2020). In the present study, significant prefrontal cortical atrophy was not found compared with the HCs at baseline, and significantly decreased between V1 and V0 in some prefrontal regions. However, we also found significant CBF reduction in the right medial orbitofrontal, right superior frontal, and bilateral caudal anterior cingulate cortex, while no cortical atrophy was observed. Furthermore, there were no correlations between the changes in cortical CBF and volume. Some cross-sectional studies report that the patients with PD showed hypoperfusion in the parietal lobule or occipital lobe with the absence of gray matter volume loss (Pelizzari et al., 2020). Combining our results and the abovementioned studies, it might suggest that functional changes may potentially be involved in neurodegeneration, independent of gray matter atrophy. Notably, there is evidence that insufficient CBF made a chronic and cumulative effect on brain atrophy (de la Torre, 2012). It would be interesting to test in future studies whether CBF reduction contributes to brain atrophy or synchronize with volume loss in the early stage of PD.

Moreover, our data suggested that CBF was not significantly different between HCs and early-stage PD at baseline. This result is consistent with Al-Bachari et al. (2014), but differs from the majority of studies (Derejko et al., 2006; Arslan et al., 2020; Liu et al., 2021), which showed decreased cortical perfusion in the early-stage PD cohort, compared with the healthy controls. This discrepancy may be partly due to the subjects recruited in the studies, as only patients with PD with the normal condition were recruited in our study. In addition, differences in the scanning sequence and measurement methods might be the reasons for inconsistent results.

Several limitations should be recognized in our study. First, the small patient pool subsequently led to fewer patients in the converter subgroup, thus, probably resulting in bias. The intrinsic difference of converter in both CBF and cognitive function may be revealed with a larger sample group, and the data from the PD–MCI cohort may also help to explain the differences. In addition, there seems to be a reasonable chance of types 1 and 2 errors in a small sample size. However, since this is a pilot longitudinal exploration studying the association between changes in CBF and cognition decline, we focused on sample quality rather than the sample size. Future studies, ideally from multiple centers and with more patients recruited, might help to confirm the results of our study and generalize to individuals. Second, a time-match follow-up data acquisition was not performed in HCs, which may provide information on the CBF and cognitive function changes under the effect of aging. Further study should recruit healthy controls, along with the data on patients with PD.

In conclusion, this study demonstrated that longitudinal changes in the prefrontal perfusion underlay the progression of cognitive impairment at the early stages of PD. Patients with PD with normal cognition did not show prefrontal hypoperfusion at baseline, but significant perfusion reductions as the disease progressed over 2 years. More importantly, patients with PD who were converted to MCI showed a more significant perfusion reduction in the left lateral orbitofrontal cortex than those who stayed cognitively normal over 2 years. In particular, declines in cognitive flexibility and inhibitory control were associated with perfusion reductions in the

right caudal anterior cortex and the left medial orbitofrontal cortex, respectively.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Fudan University Zhongshan Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

LJ: conceptualized and designed the study. JW, YZ, JJ, YL, KL, and LJ: collected data. WZ and LJ: analyzed the data. WZ, ZY, and LJ: wrote the original draft of the manuscript. JW, YZ, JJ, YL, and KL: edited and reviewed the manuscript. All authors approved the submitted version.

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Association of Plasma and Electroencephalography Markers With Motor Subtypes of Parkinson's Disease

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Objective: The aim of this study was to investigate the correlations of plasma neurodegenerative proteins and electroencephalography (EEG) dynamic functional network (DFN) parameters with disease progression in early Parkinson's disease (PD) with different motor subtypes, including tremor-dominant (TD) and postural instability and gait disorder (PIGD).

Methods: In our study, 33 patients with PD (21 TD and 12 PIGD) and 33 healthy controls (HCs) were enrolled. Plasma neurofilament light chain (NfL), α-synuclein (α-syn), total-tau (t-tau), β-amyloid 42 (Aβ42), and β-amyloid 40 (Aβ40) levels were measured using an ultrasensitive single-molecule array (Simoa) immunoassay. All the patients with PD underwent EEG quantified by DFN analysis. The motor and non-motor performances were evaluated by a series of clinical assessments. Subsequently, a correlation analysis of plasma biomarkers and EEG measures with clinical scales was conducted.

Results: In the TD group, plasma NfL exhibited a significant association with MDS-UPDRS III and Montreal Cognitive Assessment (MoCA). A higher Aβ42/40 level was significantly related to a decrease in Hamilton Depression Rating Scale (HAMD) and Hamilton Anxiety Rating Scale (HAMA) in the PIGD group. In terms of the correlation between EEG characteristic parameters and clinical outcomes, trapping time (*TT*) delta was positively correlated with MDS-UPDRS III and MoCA scores in the TD group, especially in the prefrontal and frontal regions. For other non-motor symptoms, there were significant direct associations of k_{PLI} theta with HAMD and HAMA, especially in the prefrontal region, and k_{PLI} gamma was particularly correlated with Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire (RBDSQ) scores in the prefrontal, frontal, and parietal regions in the TD group. Furthermore, there was a significant positive correlation between plasma t-tau and k_{PLI}, and pairwise correlations were found among plasma NfL, theta *TT*, and MoCA scores in the TD group.

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Conclusion: These results provide evidence that plasma neurodegenerative proteins and EEG measures have great potential in predicting the disease progression of PD subtypes, especially for the TD subtype. A combination of these two kinds of markers may have a superposition effect on monitoring and estimating the prognosis of PD subtypes and deserves further research in larger, follow-up PD cohorts.

Keywords: Parkinson's disease, motor subtype, TD, PIGD, EEG, biomarker, plasma

INTRODUCTION

Parkinson's disease (PD) is a common chronic progressive neurodegenerative disease with a series of etiologies and clinical manifestations, and it eventually has an adverse impact on quality of life, with a range of physical, emotional, and economic consequences. The prevalence of PD is gradually increasing with age and tends toward the younger population, affecting approximately 1% of the population aged over 60 (Tysnes and Storstein, 2017). It is acknowledged that patients with PD are classified into three subtypes: tremor-dominant (TD), postural instability and gait disorder (PIGD), or indeterminate, derived from the defined and universally recognized algorithms utilizing the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (Stebbins et al., 2013). It is of vital importance to identify and verify reliable biomarkers that could mirror the preclinical and early stages of different PD motor subtypes, providing a reference for their correct and timely therapeutic management.

Parkinson's disease comprises a clinically heterogeneous group of motor subtypes with diverse progression patterns, characterized by different motor symptoms and non-motor symptoms (NMSs). NMSs precede motor dysfunction sometimes by several years, including hyposmia, sleep disorders, depression, bladder dysfunction, constipation, and even fatigue (Lee et al., 2013; Pfeiffer, 2016), which virtually are more crushing and crippling than motor symptoms. The utility of accessible and objective blood-based biomarkers, particularly correlated with motor or non-motor trajectories of PD phenotypes, could achieve an appropriate and credible correspondence with clinical consequences. Currently, several biomarkers associated with neurodegeneration, such as neurofilament light chain (NfL), α-synuclein (α-syn), total-tau (t-tau), and β-amyloid 42 (Aβ42) and β-amyloid 40 (Aβ40), have been investigated as potential predictors of disease progression. There is reliable evidence that higher NfL was associated with significantly worse global cognition and MDS-UPDRS motor scores in the PIGD group (Ng et al., 2020), and the plasma concentration of Aβ42 was significantly associated with the severity of PIGD score (Ding et al., 2017). Accordingly, plasma biomarkers may be reliable tools for predicting disease severity and progression in PD subtypes.

It is acknowledged that brain activity and network vary in different patients with PD with personalized motor symptoms and NMSs. Complexity and dynamic functional connectivity (dFC) within and between cerebral regions could mirror motor and cognition organization and functional changes to some extent (Chu et al., 2020; Yi et al., 2022). Accordingly, resting-state electroencephalography (EEG) recording at the scalp composed of electric potential discrepancy not only has particular attractions compared to MRI or PET imaging, such as non-invasiveness, low cost, and wide acceptability, but also directly reflects cortical rhythms and imperceptible network changes (Gratwicke et al., 2015). Previous studies implied that different PD motor subtypes have different degeneration of subcortical/cortical pathways and structures and influence the activity of multiple cortical functional regions, such as motor, cognition, emotions, and sleep (Jiang et al., 2016; Vervoort et al., 2016b). Changes in active brain regions linked to motor/sensorimotor areas have been exhibited in different PD motor subtypes (Orcioli-Silva et al., 2021). Vervoort et al. (2016a) have shown differential connectivity alterations in neural networks and between motor and cognitive control loops that correlated with the behavioral heterogeneity in patients with TD and PIGD. Similar to plasma biomarkers mentioned above, utility resting-state EEG for brain activity feature extraction is also a reliable and easily achievable method. Hence, a combination of blood-based and EEG measurements may have a synergistic effect to explore the predictors of disease progression in early PD with different motor subtypes.

The aim of this study was to investigate the association of plasma neurodegenerative proteins (NfL, α-syn, t-tau, Aβ42, and Aβ40) and EEG signature with disease progression in early PD with different motor subtypes. In this study, we used an ultrasensitive single-molecule array (Simoa) immunoassay for plasma biomarker measurement and a novel electroencephalographic analysis technique-dynamic functional network (DFN) analysis for electroencephalographic feature extraction.

MATERIALS AND METHODS

Study Participants

A total of 36 patients with PD were recruited from the movement disorders outpatient clinics of the General Hospital of Tianjin Medical University. All of the patients with PD fulfilled the United Kingdom Parkinson's Disease Society Brain Bank (UKPDSBB) criteria (Hughes et al., 1992). Based on the MDS-UPDRS classification method, the ratio of the mean UPDRS tremor scores (11 items) to the mean UPDRS-PIGD scores (5 items) was used to define patients with TD (ratio $\geq$1.15), patients with PIGD (ratio $\leq$0.9), and "indeterminate" patients (ratios $>$0.9 and $<$1.15) (Stebbins et al., 2013). Patients defined as "indeterminate" were excluded from our study. Eventually, 33 patients with PD (21 TD and 12 PIGD) were enrolled in our analysis. Simultaneously, 33 age-matched healthy controls (HCs) who showed no sign of neuropsychiatric and systemic

disorder were recruited from the local community during the same period. The research protocols were approved by the Ethics Committee of the General Hospital of Tianjin Medical University. All subjects provided informed written consent before entering the study.

Clinical Evaluation

The motor symptoms of patients with PD were evaluated using the MDS-UPDRS (Goetz et al., 2008) and Hoehn and Yahr (H&Y) staging scale (Hoehn and Yahr, 1967) as measurements of clinical parkinsonian severity, which were performed during off medication, more than 12 h after the last dose of dopaminergic therapy. NMSs were examined with a series of neuropsychological assessments, including the Montreal Cognitive Assessment (MoCA), Hamilton Depression Rating Scale (HAMD), Hamilton Anxiety Rating Scale (HAMA), Non-motor Symptoms Questionnaire (NMSQ), Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire (RBDSQ), and Parkinson's Disease Sleep Scale-2 (PDSS-2).

Measurement of Plasma Biomarkers

A total of 10 ml of venous blood from all the participants was collected in tubes containing ethylenediaminetetraacetic acid (EDTA) and centrifuged (2,500 × *g* for 15 min) within 1 h after collection according to the recommendation by the manufacturer and previous reports. Plasma was stored in polypropylene tubes at −80°C until analysis. The Simoa NfL Advantage kits (Quanterix, Lexington, MA, United States), Neurology 3-Plex A Advantage Kit (Lot 502473), and α-syn discovery kit (Lot 502566) were used for measurement of plasma NfL, t-tau, Aβ42, Aβ40, and α-syn concentrations assayed by researchers who were blinded to the diagnosis based on manufacturer's introductions and standard procedures.

Electroencephalography Recording and Preprocessing

Electroencephalography was recorded for all patients with PD during off medication in an isolated low-light room at the General Hospital of Tianjin Medical University. Patients were requested to sit in a comfortable chair with their eyes closed but not fall asleep. According to the international standard 10/20 system, 19 Ag/AgCl electrodes were placed on the scalp, including channels Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, and Pz. Meanwhile, electrooculogram (EOG), electromyogram (EMG), and electrocardiogram (ECG) signals were recorded through another four channels.

All of the EEG preprocessing was performed using the EEGLab toolbox in MATLAB software (MathWorks Inc., Natick, MA, United States). First, EEG signals were processed by a 1–45 Hz band-pass zero-phase shift filter for filtering out the 50 Hz power frequency interference to ensure that the phase information of the original signal remained unchanged. To eliminate artifacts, fast independent component analysis (FastICA) (Hyvärinen, 1999) was then conducted. The FastICA algorithm decomposed 19-channel EEG signals into ICs that are statistically independent of each other through a hybrid matrix. Subsequently, the correlation between the extracted ICs and the EOG, EMG, and ECG signals was analyzed. The IC whose absolute value of the correlation coefficient exceeds 0.5 was considered as the component that has a strong correlation with a certain artifact signal. We then zeroed out these ICs and multiplied them by the resulting mixture matrix to obtain the EEG signals with the artifacts removed. The manual screen was applied to remove noise interference signals. Finally, a band-pass finite impulse response (FIR) filter was used to filter the signals into five frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (30–45 Hz).

Construction of Dynamic Functional Networks

The empirical mode decomposition (EMD) method could well describe the local transient characteristics of time-varying nonlinear signals. EMD could divide different windows according to the signal characteristics of different patients, facilitating the finding of information with significant differences in time-varying signals (Chen et al., 2010). The sliding window method based on EMD could determine the dynamic window length by the frequency of EEG signals of patients at different times. A previous study reported that this adaptive window method could obtain better dynamic information about cognitive function and behavior (Zhuang et al., 2020). Hence, in this study, we utilized the adaptive sliding window based on EMD to seek out the local information on dynamic brain activity in patients with PD.

Based on the data after dividing windows by the above method, we used the phase lag index (PLI) to characterize DFNs. The PLI method, proposed by Stam et al. (2007), could estimate the phase synchronization between signals. We used PLI to calculate the phase coupling degree by calculating the instantaneous phase and the asymmetry of the phase difference distribution between two time signals, and the calculation formula is as follows:

$$PLI = \left|\left\langle \text{sign}\left[\Delta\phi\left(t_k\right)\right]\right\rangle\right|, \quad k = 1, 2, \ldots, N,$$

where $\Delta\phi(t_k)$ represents phase differences calculated at different times. *PLI* ranges from 0 to 1. The larger the *PLI*, the stronger the coupling strength between signals.

Fluctuation Analysis of Dynamic Functional Connectivity

The noise of EEG signals could also produce random fluctuations of network connection, such that the existence of dFC could not be proved only by the FC fluctuations of EEG signals collected from patients. We used alternative data to observe if the fluctuations in FC were representative of the real dFC. We represented stationary processes by using suitable alternative data to verify the authenticity of fluctuations and used the amplitude-adjusted Fourier transform (AAFT) to construct alternative data (Kugiumtzis, 2002). The AAFT method was used to generate 20 groups of alternative data corresponding to real data, and then we used the window of real data selection to partition

and constructed the dFN of alternative data. By calculating the time-series standard deviations of each edge in DFN's dynamic process of real data and alternative data, we obtained the dynamic fluctuation characteristics of brain connectivity for both. We calculated the average fluctuation of 20 sets of alternative data and the k_{PLI}, which was the ratio of standard deviation between fluctuations in real data and fluctuations in alternative data. The formula is given as follows:

$$k_{PLI}(v, w) = \frac{\sigma(D_{ture}(v, w))}{1/M \sum_{i=1}^{M} \sigma(D_{rand}(v, w))},$$

where D represents the DFNs of real data and alternative data, v and w are EEG channels, and M is the group number of alternative data. As the ratio of fluctuation of real data to the fluctuation of substitute data, if k_{PLI} was greater than 1, then there was a real fluctuation in dynamic brain FC, and k_{PLI} could represent the magnitude of fluctuation.

Network State Transition Analysis

Time-by-Time Graph

We used the form of the weighted DFNs to define time in constructing the time-by-time graph (Medaglia et al., 2015). Each node represented a different time window of DFNs, and the different edges indicated the correlations between the corresponding time windows of DFNs. We utilized the Frobenius norm for distance measurement to calculate the similarity between networks (Kurmukov et al., 2016), and the distance measure was inversely proportional to similarity. The calculation formula is as follows:

$$d_F(P(t_1), P(t_2)) = \| P(t_1) - P(t_2) \|_F,$$
$$= \sqrt{\sum_{i=1}^{N} \sum_{j=1}^{N} (p_{ij}(t_1) - p_{ij}(t_2))^2}$$

where P represents DFNs of different patients, p represents the edge of DFNs, i and j are the EEG channels, and N represents the total number of EEG channels. The time-by-time graph T of each patient was obtained, through which we could get the necessary information on the same brain state during the evolution of dynamic brain functional networks (Chen et al., 2017).

Recurrence Plot

Based on the time-by-time graph obtained from the patient, we determined a threshold to define the upper limit of the distance between similar networks. When the calculated distance was less than a, we concluded that the two brain functional networks were in the same state and set the edge of the time-by-time graph T_{ij} to 1. On the contrary, we set it to 0. We could get the recurrence plot (RP) using this method, and the recurrence matrix R of DFNs is as follows:

$$R_{ij} = \begin{cases} 1, & T_{ij} < a \\ 0, & T_{ij} > a \end{cases},$$

where i and j are the different times of the brain's functional network, and T_{ij} is the distance measure of the functional network at two moments.

Recurrence Quantification Analysis

We used the recurrence quantification analysis (RQA) parameters, which were recurrence rate (RR) and trapping time (TT), to evaluate the degree of network state transition of DFNs (Marwan et al., 2007). RR indicated the number of times that a network in the same state occurred in DFNs. The RR is defined as follows:

$$RR = \frac{1}{N^2} \sum_{i,j=1}^{N} R_{ij},$$

where N represents the total number of brain functional networks at different time windows. TT represents the average duration of the same network state in DFNs. The larger the TT, the longer the same state lasts on the network. The TT is defined as follows:

$$TT = \frac{\sum_{h=h_{\min}}^{h_{\max}} hP(h)}{\sum_{h=h_{\min}}^{h_{\max}} P(h)},$$

where h was the length of the vertical line in RP, and $P(h)$ is the number of vertical lines whose length is h in RP. The $P(h)$ is calculated as follows:

$$P(h) = \sum_{i,j=1}^{N} (1 - R_{i,j-1})(1 - R_{i,j+h}) \prod_{k=0}^{h-1} R_{i,j+k}$$

Statistical Analysis

All data were analyzed using SPSS 22.0 (IBM, Inc., Armonk, NK, United States) and GraphPad Prism 9 (La Jolla, CA, United States). The Shapiro–Wilk test was used to examine the Gaussian distribution of our data ($p > 0.05$). The demographic and clinical characteristics were displayed as mean ± SD. Comparisons of continuous variables among different diagnostic groups were assessed using one-way analysis of variance (ANOVA) and the Mann–Whitney U test. A Chi-square test was used to compare categorical variables. Group comparisons of clinical assessments and marker measures were made using multiple linear regression analyses with sex, age, and disease duration at testing as covariates. The correlation among plasma neurodegenerative proteins, EEG characteristic parameters, and clinical outcomes was accessed using Spearman's rank correlation analysis. Statistical significance was set at $p < 0.05$.

RESULTS

Demographic and Clinical Characteristics

A total of 66 participants consisting of 33 patients with PD and 33 age- and sex-matched normal control subjects were enrolled in this study. The demographic and clinical characteristics of study participants are presented in **Table 1**. There were no significant differences in gender and age between patients with PD and HC. Similarly, in terms of disease duration, H&Y stage, MDS-UPDRS II and III scores, global cognition status-MoCA, and other non-motor scales, no statistical differences were found between the

TABLE 1 | Demographic and clinical characteristics of study participants.

Characteristics	TD ($n = 21$)	PIGD ($n = 12$)	HC ($n = 33$)	*P*-value
Male, %	47.62	50.00	51.52	0.96
Age, years	65.48 ± 6.83	63.92 ± 5.78	66.15 ± 4.75	0.74
Disease duration, years	5.38 ± 2.52	5.00 ± 1.81	NA	0.99
Hoehn and Yahr stage	1.24 ± 0.44	1.67 ± 0.49	NA	0.03
MDS-UPDRS I	2.00 ± 2.03	4.45 ± 2.70	NA	<0.01**
MDS-UPDRS II	4.21 ± 3.99	5.09 ± 5.20	NA	0.87
MDS-UPDRS III	19.71 ± 11.71	18.58 ± 11.12	NA	0.90
MoCA	26.32 ± 2.96	25.73 ± 3.74	NA	0.93
NMSQ	5.62 ± 3.79	8.42 ± 4.33	NA	0.06
RBDSQ	2.79 ± 3.61	3.27 ± 3.80	NA	0.54
HAMD	2.58 ± 3.49	5.09 ± 4.04	NA	0.06
HAMA	1.47 ± 2.17	4.91 ± 7.35	NA	0.10
PDSS-2	4.84 ± 4.51	11.91 ± 8.87	NA	0.02

PD, Parkinson's disease; TD, tremor-dominant; PIGD, postural instability and gait disorder; HCs, healthy controls; MoCA, Montreal Cognitive Assessment; NfL, neurofilament light chain; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; NMSQ, Non-motor Symptoms Questionnaire; RBDSQ, Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire; PDSS-2, Parkinson's Disease Sleep Scale-2; NA, not available.
Data are presented as mean ± SD. The p-values were obtained from comparisons of variables between TD and PIGD using the Mann–Whitney U test. The Chi-square test was used to compare categorical variables.
***$p < 0.01$.*

two motor phenotypes. In the PIGD group, the score of MDS-UPDRS I was significantly higher than the TD group ($p < 0.01$).

Plasma Biomarker Levels and Electroencephalography Characteristic Parameters in Different Groups

Plasma biomarkers and EEG characteristic parameters are summarized in **Table 2**. The levels of plasma Aβ42, Aβ40, Aβ42/40, and α-syn were significantly increased in patients with PD when compared to controls (Aβ42: TD vs. HC: $p < 0.0001$, PIGD vs. HC: $p < 0.0001$; Aβ40: TD vs. HC: $p < 0.0001$, PIGD vs. HC: $p < 0.001$; Aβ42/40: TD vs. HC: $p < 0.05$, PIGD vs. HC: $p < 0.01$; α-syn: TD vs. HC: $p < 0.0001$, PIGD vs. HC: $p < 0.001$), while there was no significant difference between the TD and PIGD groups, after adjustment for age, sex, and disease duration. No differences were found in the concentrations of plasma NfL and t-tau among the TD, PIGD, and control groups (NfL, $p = 0.65$; t-tau, $p = 0.39$). Similarly, there was no difference in EEG characteristic parameters (k_{PLI}, *TT*, *RR*) between the TD and PIGD groups (k_{PLI}, $p = 0.49$; *TT*, $p = 0.51$; *RR*, $p = 0.59$, **Table 2**).

Plasma Biomarker Correlations With Clinical Outcomes

For clarifying whether there was any relationship between plasma biomarkers and clinical features, we conducted the following correlation analysis. In the TD group, plasma NfL exhibited significant association with MDS-UPDRS III ($r = 0.443$, $p < 0.05$, **Figure 1A**) and MoCA ($r = -0.555$, $p < 0.01$, **Figure 1B**). Higher Aβ42/40 level significantly related to a decrease in HAMD ($r = -0.590$, $p < 0.05$, **Figure 1C**) and HAMA ($r = -0.635$, $p < 0.05$, **Figure 1D**) in the PIGD group. No relationship was found between any plasma biomarkers and NMSQ, RBDSQ, and PDSS-2 scores.

TABLE 2 | The levels of plasma biomarkers and EEG characteristic parameters in patients with PD and HCs.

	TD ($n = 21$)	PIGD ($n = 12$)	HC ($n = 33$)	*P*-Value
Plasma biomarker				
NfL (pg/ml)	18.01 ± 10.16	25.32 ± 22.10	15.99 ± 5.18	0.65
T-tau (pg/ml)	1.05 ± 0.57	0.87 ± 0.23	0.93 ± 0.63	0.39
Aβ42 (pg/ml)	9.93 ± 2.58	10.48 ± 2.58	5.26 ± 2.01	<0.01[a,b]
Aβ40 (pg/ml)	165.43 ± 48.40	162.37 ± 40.92	103.90 ± 31.00	<0.01[a,b]
Aβ42/40	0.06 ± 0.01	0.07 ± 0.01	0.05 ± 0.01	<0.01[a,b]
α-Syn (pg/ml)	49.27 ± 41.06	41.39 ± 24.37	10.36 ± 6.51	<0.01[a,b]
EEG parameter				
K_{PLI}	1.91 ± 0.07	1.20 ± 0.10	NA	0.49
TT	16.85 ± 18.70	17.88 ± 23.77	NA	0.51
RR	0.34 ± 0.25	0.38 ± 0.30	NA	0.59

PD, Parkinson's disease; TD, tremor-dominant; PIGD, postural instability and gait disorder; HCs, healthy controls; NfL, neurofilament light chain; t-tau, total tau; Aβ42, β-amyloid 42; Aβ40, β-amyloid 40; α-syn, α-synuclein; NA, not available.
[a]Differences were found between TD vs. control.
[b]Differences were found between PIGD vs. control.

Electroencephalography Correlations With Clinical Outcomes

Correlations Between Electroencephalography Signature and Motor Severity

We performed exploratory correlation analysis for the EEG signature as a marker for clinical features and disease progression. Meanwhile, EEG parameters were further refined into brain regions to explore the brain regions with specific changes in different motor subtypes of patients with PD with different clinical manifestations. The results suggested that *TT* delta was positively correlated with MDS-UPDRS III scores in the TD group ($r = 0.585$, $p < 0.05$, **Figure 2A**), especially in prefrontal ($r = 0.638$, $p < 0.01$, **Figure 2B**) and frontal ($r = 0.685$, $p < 0.01$) regions. No such association was found between EEG parameters and the H&Y stage.

Correlations Between Electroencephalography Signature and Cognition

We next investigated the relevance between EEG parameters and global cognitive status (MoCA). There were significant direct associations between k_{PLI} alpha ($r = -0.466$, $p < 0.05$, **Figure 3A**) and *TT* theta ($r = 0.571$, $p < 0.01$, **Figure 3B**) with MoCA scores, particularly in the prefrontal and frontal regions (**Figures 3C,D**).

Correlations Between Electroencephalography Signature and Other Non-motor Symptoms

In the TD group, both k_{PLI} delta ($r = 0.539$, $p < 0.05$, **Figure 4A**) and theta ($r = 0.616$, $p < 0.01$, **Figure 4B**)

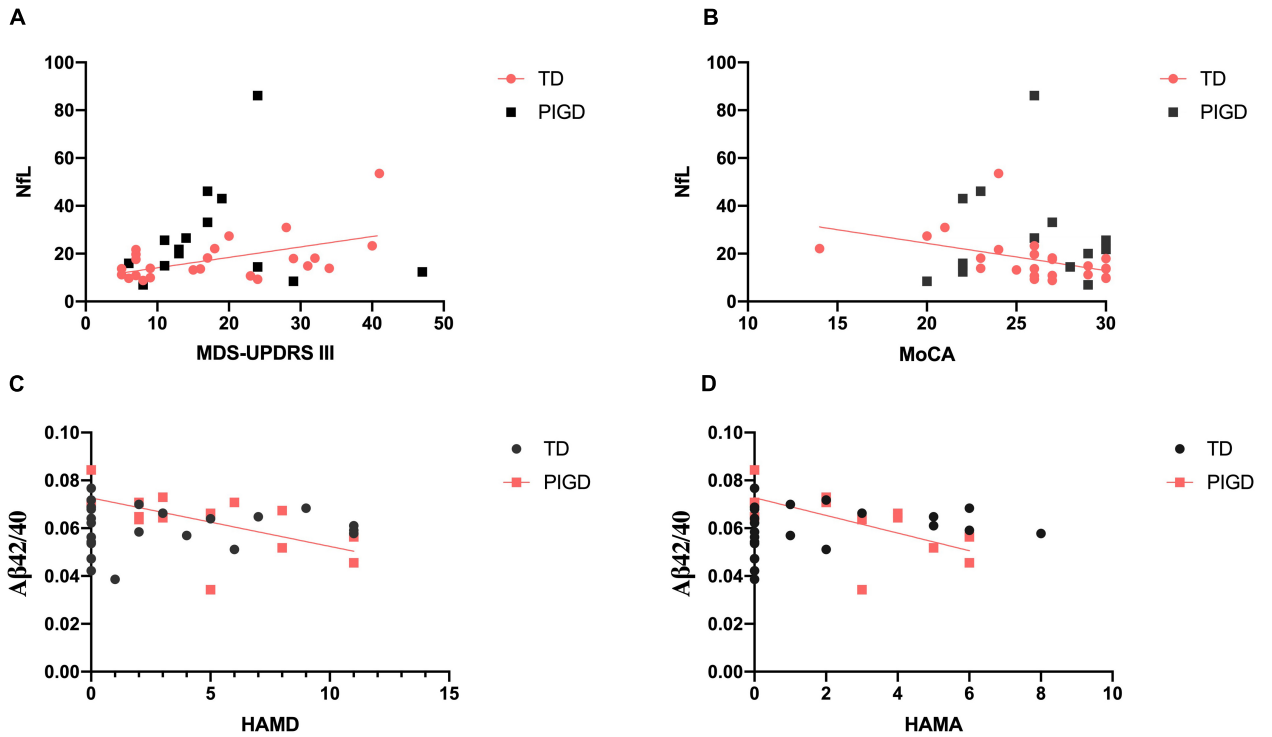

FIGURE 1 | Correlations between plasma biomarkers and clinical features in patients with PD. There were significant relationships between plasma NfL and MDS-UPDRS III **(A)** and MoCA **(B)** in the TD group. Plasma Aβ42/40 level was negatively correlated with HAMD **(C)** and HAMA **(D)** in PIGD. Significant correlation ($p < 0.05$) is marked in solid red line.

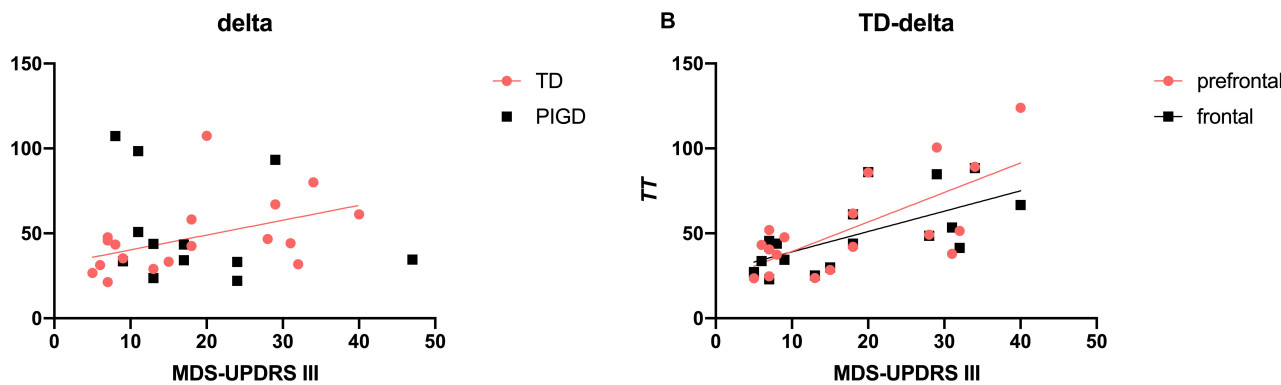

FIGURE 2 | Correlation between *TT* delta and MDS-UPDRS III scores in patients with PD. *TT* delta was positively associated with MDS-UPDRS III scores **(A)**, especially in the prefrontal and frontal regions **(B)**. A significant correlation ($p < 0.05$) is marked in solid red and black lines.

were positively correlated with increases in HAMD, especially in the prefrontal region (k_{PLI} delta: $r = 0.540$, $p < 0.05$, **Figure 4E**; k_{PLI} theta: $r = 0.476$, $p < 0.05$, **Figure 4F**). Similarly, a relationship was found between k_{PLI} theta and HAMA in the prefrontal region ($r = 0.620$, $p < 0.01$, **Figures 4C,G**). We further analyzed the correlation between EEG and sleep quality (RBDSQ and PDSS-2). K_{PLI} gamma was particularly associated with RBDSQ scores in the prefrontal ($r = 0.625$, $p < 0.01$), frontal ($r = 0.609$, $p < 0.01$), and parietal ($r = 0.542$, $p < 0.05$, **Figures 4D,H**) regions in the TD group. No relationship was found between any of the EEG variables with PDSS-2.

Correlations Between Electroencephalography Characteristic Parameters and Plasma Biomarkers

The relationship between plasma biomarkers and k_{PLI}, *TT*, and *RR* is presented in **Tables 3–5**, respectively. The level of NfL was negatively correlated with *TT* in the theta band in the TD group

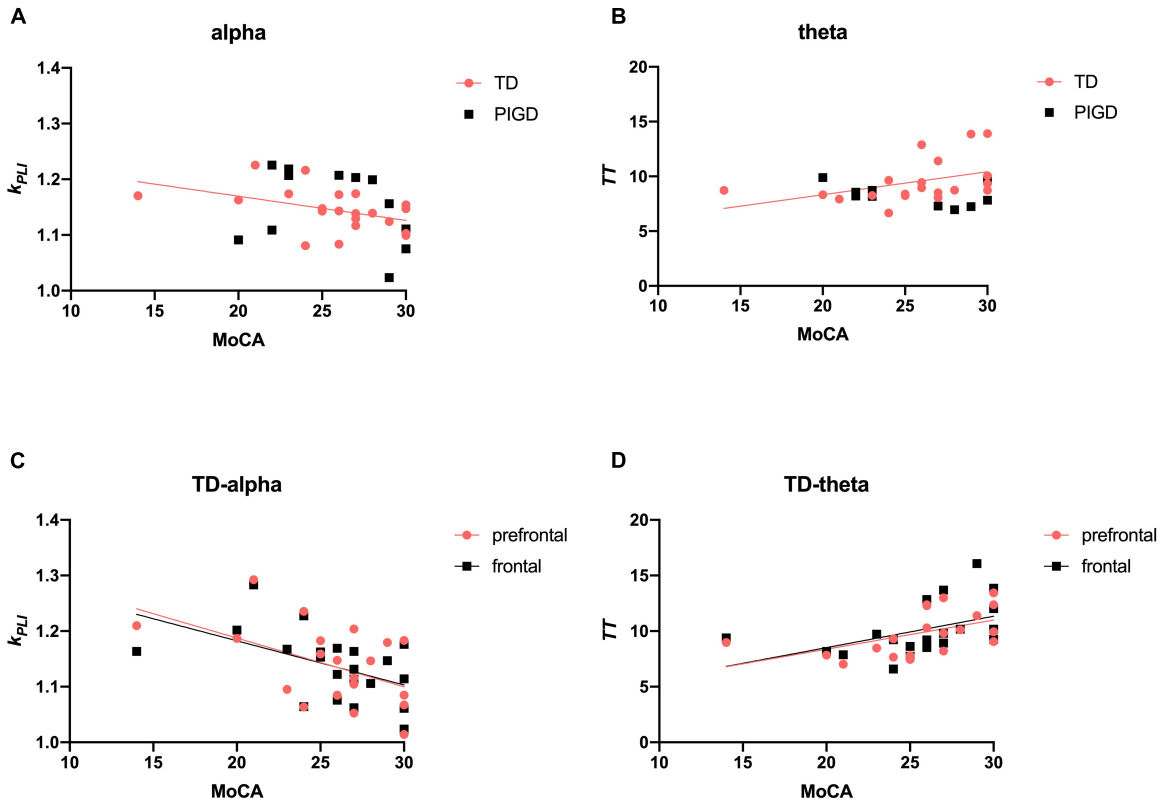

FIGURE 3 | Scatter plot illustrating the correlation between EEG signature and cognition in patients with PD. Upper row: correlations of EEG frequency bands with cognitive data **(A,B)**. Lower row: correlations of EEG characteristic brain regions with cognitive data **(C,D)**. A significant correlation ($p < 0.05$) is marked in solid red and black lines.

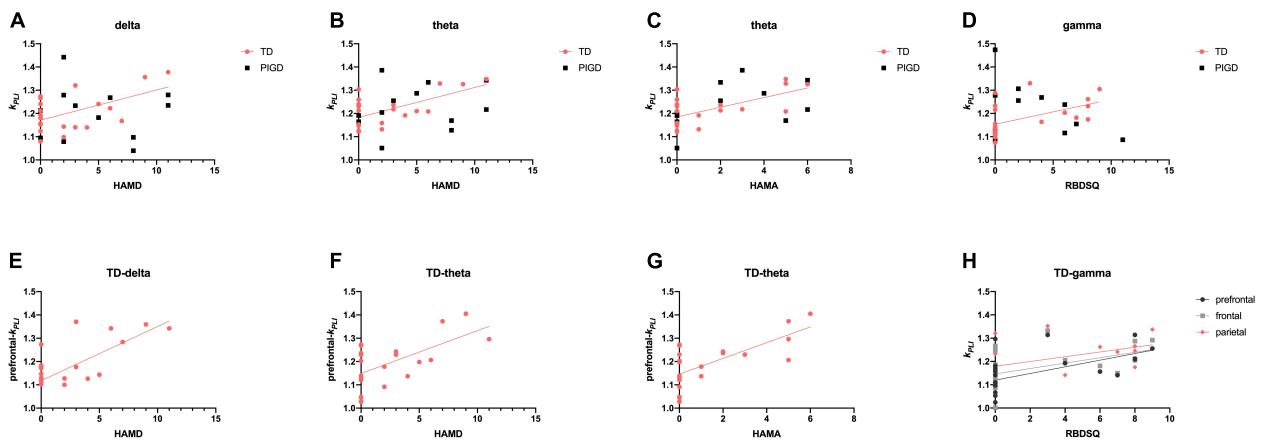

FIGURE 4 | Scatter plot illustrating the correlation between EEG signature and other non-motor symptoms in patients with PD. Upper row: correlations of EEG frequency bands HAMD **(A,B)**, HAMA **(C)**, and RBDSQ **(D)**. Lower row: correlations of EEG characteristic brain regions with HAMD **(E,F)**, HAMA **(G)**, and RBDSQ **(H)**. A significant correlation ($p < 0.05$) is marked in solid red, black, and gray lines.

($r = -0.490$, $p < 0.05$, **Table 4**) and with *RR* in the gamma band in the PIGD group ($r = -0.727$, $p < 0.01$, **Table 5**). In terms of plasma t-tau, there was a significant positive correlation with k_{PLI} in the delta ($r = 0.571$, $p < 0.01$), theta ($r = 0.697$, $p < 0.001$), beta ($r = 0.483$, $p < 0.05$), and gamma ($r = 0.442$, $p < 0.05$) frequency bands (**Table 3**), and a negative correlation with *TT* in the delta band ($r = -0.552$, $p < 0.05$, **Table 4**) in the TD group. Aβ42 showed an inverse association with *RR* delta in the TD group ($r = -0.491$, $p < 0.05$, **Table 5**). A close relationship of plasma α-syn with *TT* in the beta frequency band ($r = 0.983$,

TABLE 3 | Correlation between plasma biomarkers and k_{PLI}.

Plasma biomarker	Frequency band	TD	PIGD
NfL	Delta	0.207	0.245
	Theta	0.347	0.132
	Alpha	0.333	0.287
	Beta	0.318	0.573
	Gamma	0.187	0.552
T-tau	Delta	0.571[b]	0.098
	Theta	0.697[c]	−0.210
	Alpha	0.100	0.308
	Beta	0.483[a]	0.175
	Gamma	0.442[a]	−0.203
Aβ42	Delta	−0.097	−0.147
	Theta	0.063	−0.275
	Alpha	−0.179	0.119
	Beta	0.201	0.121
	Gamma	−0.167	0.115
Aβ40	Delta	−0.222	−0.089
	Theta	0.008	−0.241
	Alpha	−0.035	−0.101
	Beta	0.218	0.049
	Gamma	0.231	−0.252
Aβ42/40	Delta	−0.227	0.298
	Theta	−0.024	0.475
	Alpha	0.217	0.060
	Beta	−0.301	0.040
	Gamma	−0.253	0.313
α-Syn	Delta	0.093	−0.115
	Theta	0.096	−0.031
	Alpha	0.353	−0.127
	Beta	−0.002	−0.094
	Gamma	−0.062	0.305

TD, tremor-dominant; PIGD, postural instability and gait disorder; NfL, neurofilament light chain; t-tau, total tau; Aβ42, β-amyloid 42; Aβ40, β-amyloid 40; α-syn, α-synuclein; r, Spearman's rho.
[a]$p < 0.05$.
[b]$p < 0.01$.
[c]$p < 0.001$.

TABLE 4 | Correlation between plasma biomarkers and *TT*.

Plasma biomarker	Frequency band	TD	PIGD
NfL	Delta	0.435	−0.350
	Theta	−0.490[a]	−0.442
	Alpha	0.250	−0.190
	Beta	−0.120	−0.305
	Gamma	−0.183	−0.097
T-tau	Delta	−0.552[a]	−0.168
	Theta	−0.138	−0.277
	Alpha	−0.223	−0.433
	Beta	−0.078	−0.189
	Gamma	0.081	−0.145
Aβ42	Delta	−0.168	−0.147
	Theta	0.050	0.006
	Alpha	−0.134	−0.005
	Beta	−0.044	−0.612
	Gamma	−0.131	−0.146
Aβ40	Delta	−0.018	−0.237
	Theta	0.048	−0.223
	Alpha	−0.161	−0.029
	Beta	−0.007	−0.302
	Gamma	−0.069	0.036
Aβ42/40	Delta	−0.160	0.219
	Theta	−0.147	0.462
	Alpha	0.203	0.084
	Beta	−0.169	−0.325
	Gamma	−0.076	0.026
α-Syn	Delta	0.095	0.013
	Theta	0.059	0.013
	Alpha	0.380	−0.127
	Beta	−0.254	0.983[b]
	Gamma	0.004	0.456

TD, tremor-dominant; PIGD, postural instability and gait disorder; NfL, neurofilament light chain; t-tau, total tau; Aβ42, β-amyloid 42; Aβ40, β-amyloid 40; α-syn, α-synuclein; r, Spearman's rho.
[a]$p < 0.05$.
[b]$p < 0.001$.

$p < 0.001$) was found in the PIGD group (**Table 4**). No statistically significant correlation was found between Aβ42/40 level and EEG measures in patients with PD.

DISCUSSION

In this study, we aimed to demonstrate the possible association of plasma neurodegenerative proteins and EEG signature with disease progression in early PD with different motor subtypes and explore whether there was a link between plasma biomarkers and EEG DFN signature. For this purpose, we measured several plasma proteins (e.g., NfL, α-syn, t-tau, Aβ42, and Aβ40) quantified by high-sensitivity immunoassays and conducted characteristic DFN analysis for electroencephalographic feature extraction. We performed a correlation analysis between these two kinds of potential markers and a comprehensive clinical assessment battery. Our results suggested that plasma biomarkers and EEG parameters were found to be related to motor severity, cognition, and some NMS symptoms in patients with TD and PIGD. Furthermore, we investigated the correlation between plasma biomarkers and EEG characteristic parameters. Our findings indicated that there was a significant positive correlation between plasma t-tau and k_{PLI} and pairwise correlations were found among plasma NfL, theta *TT*, and MoCA scores in the TD group. Therefore, plasma biomarkers and EEG measures are considered to be potential tools to predict the disease progression of PD subtypes.

Plasma Biomarkers and Disease Severity Correlations

As the neural-specific cytoskeletal component and structural component of axon and synapse, NfL plays an essential role in neural electrical signal transmission and posttranslational modification. It is highly expressed in large-caliber myelinated

TABLE 5 | Correlation between plasma biomarkers and *RR*.

Plasma biomarker	Frequency band	TD	PIGD
NfL	Delta	0.091	−0.399
	Theta	−0.251	−0.259
	Alpha	−0.013	−0.546
	Beta	0.048	0.228
	Gamma	0.281	−0.727[b]
T-tau	Delta	0.023	−0.064
	Theta	−0.279	0.280
	Alpha	−0.248	0.227
	Beta	0.079	0.362
	Gamma	−0.012	−0.130
Aβ42	Delta	−0.491[a]	−0.021
	Theta	0.099	0.031
	Alpha	0.037	−0.048
	Beta	0.191	0.127
	Gamma	−0.100	−0.390
Aβ40	Delta	−0.222	−0.089
	Theta	0.008	−0.241
	Alpha	−0.035	−0.101
	Beta	0.218	0.049
	Gamma	0.231	−0.252
Aβ42/40	Delta	−0.255	0.328
	Theta	−0.024	0.475
	Alpha	0.217	0.060
	Beta	−0.301	0.040
	Gamma	−0.253	0.313
α-Syn	Delta	0.093	−0.115
	Theta	0.096	−0.031
	Alpha	0.353	−0.127
	Beta	−0.002	−0.094
	Gamma	−0.062	0.305

TD, tremor-dominant; PIGD, postural instability and gait disorder; NfL, neurofilament light chain; t-tau, total tau; Aβ42, β-amyloid 42; Aβ40, β-amyloid 40; α-syn, α-synuclein; r, Spearman's rho.
[a]$p < 0.05$.
[b]$p < 0.01$.

axons and is the main byproduct of neurodegeneration (Yuan et al., 2017). There was a tendency that NfL levels increased as the H&Y stage increased in our PD cohort. No differences were found in the concentrations of NfL between the TD and PIGD groups in our results, consistent with a previous study at baseline (Ng et al., 2020), which suggested that NfL levels were significantly increased in the PIGD group compared with the TD group after a 2-year follow-up, however. Previous studies have reported that NfL levels were significantly elevated in patients with PIGD with worse cognition outcomes and were modestly correlated with MDS-UPDRS III scores, indicating that there was a relationship between NfL and disease severity and progression in PIGD-PD (Ng et al., 2020; Ye et al., 2021). Nevertheless, our results only showed that there was an association between plasma NfL and MDS-UPDRS III, as well as MoCA scores in the TD group, and the correlation was absent in the PIGD cohort. We speculate these conflicting results might be due to the limited number of early-stage patients with PD we enrolled and the lack of follow-up.

It is considered that plasma and cerebrospinal fluid (CSF) amyloid β are reflections of brain amyloidosis (Nakamura et al., 2018; Schindler et al., 2019). Aβ peptides play a crucial role in neuronal information processing and are key components of amyloid plaques deposited in the brains of patients with neurodegenerative diseases, especially common in Alzheimer's disease and PD dementia (Gomperts et al., 2013). In our cohort, we found the levels of Aβ (Aβ42, Aβ40, and Aβ42/40) were higher in patients with PD than HC, while there was no significant difference between the two motor subtypes, in accordance with another Chinese PD cohort (Ding et al., 2017). Moreover, we are pleasantly surprised that a higher Aβ42/40 level was significantly related to a decrease in HAMD and HAMA in the PIGD group, that is, the lower the Aβ42/40 level is, the greater the possibility of depression and anxiety the patients with PIGD have. Previous studies have confirmed that the plasma Aβ42/40 level was lower in older individuals with depression than in HCs, and Aβ was more inclined to aggregation and polymerization in depression and anxiety patients (Sun et al., 2007; Baba et al., 2012; Nascimento et al., 2015; Johansson et al., 2020). Whether Aβ42/40 level is associated with anxiety and depression emotions in PD subtypes deserves further research.

Electroencephalographic Features and Disease Severity Correlations

The real relationship between electroencephalographic features and disease severity in patients with PD is not yet definite. To define and quantify brain dynamics and functional connectivity, we conducted a DFN analysis. We extracted three EEG characteristic parameters: *TT*, *RR*, and k_{PLI}. As a symbol of the average duration of the same network state in DFNs, the more the *TT* increased, the longer the same state lasted on the network. *RR* represented the number of times that a network in the same state occurred in DFNs. Both *TT* and *RR* were used to evaluate the degree of network state transition of DFNs (Marwan et al., 2007). In contrast, the k_{PLI}, which was the ratio of standard deviation between fluctuations in real data and fluctuations in alternative data, indicated the magnitude of dynamic fluctuation of brain connectivity. According to our findings, EEG characteristic parameters are proven to have correlations with motor, cognition, and emotions in patients with TD.

Based on our results, *TT* in the delta band was positively correlated with MDS-UPDRS III scores in the TD group, especially in the prefrontal and frontal regions. That means the longer the same state lasts on the network, the worse motor performance the patients with TD have. A possible explanation is that as the motor severity deteriorates, the maintenance of the network state gets longer; that is, the slower the brain network switches. Definitely, the supplementary motor area (SMA), the dorsolateral prefrontal cortex (DLPFC), and the primary motor cortex (M1) are the prime cortical motor regions in the frontal lobe that have been extensively studied. Cortical motor region dysfunction may interpret the pathogenesis of bradykinesia and postural instability and gait disorder, which are the core motor

manifestations of PD (Lefaucheur, 2005; Casarotto et al., 2019). This phenomenon is consistent with our findings that delta *TT* in the prefrontal and frontal areas were particularly relevant to motor severity in patients with TD. However, the reason why this correlation disappeared in the PIGD group may be the different mechanisms of altered brain network state in patients with PIGD.

Generally, patients with PD have a slowing tendency of global EEG activity observed to be significantly relevant to cognitive processes, including attention and working memory, executive function, emotion, and so on (Handojoseno et al., 2013). It has already been confirmed that as the cognitive status deteriorates, patients with PD have less stability and functional connectivity of the brain neuronal network, possibly resulting from pathological oscillations and dysregulation in the cortico-basal ganglia-thalamic-cortical pathways and synaptic degeneration (Aarsland et al., 2017; Wang et al., 2020). The frontal and prefrontal cortex assist us to make better decisions. Recent research on clarifying the definite role of neuronal oscillations in the frontal cortex as measured by EEG indicated that frontal theta was an essential integral mechanism in cognitive processes, especially in cognitive control (Cavanagh and Frank, 2014). Similarly, our study showed that *TT* in the theta band was positively correlated with MoCA score in the TD group, particularly in the prefrontal and frontal regions. In addition, alpha k_{PLI} in the prefrontal and frontal regions were significantly associated with global cognitive function. It could be speculated that the faster the network state switches and the greater the magnitude of dynamic fluctuation of brain connectivity in the frontal cortex is, the worse cognitive function the patients with TD have.

It is widely believed that dopamine (DA) system dysfunction in the substantia nigra pars compacta (SNc) is a trigger for the classical signs and symptoms in patients with PD (Wichmann, 2019). Recently, burgeoning data have connected dopamine system dysfunction to the pathophysiology and pathogenesis of depression and anxiety (Grace, 2016; Calipari, 2020), hence it could be assumed that patients with PD have a greater likelihood of suffering from mood disturbances. A neuroimaging meta-analysis implied increased neural activity and structural changes in the prefrontal regions in depressed and anxious patients with PD (Wen et al., 2016). EEG studies suggested spatiotemporal patterns of cortical activity and functional connectivity altered in patients with PD with affective symptoms (Iyer et al., 2020). Consistent with the above studies, our results suggested a positive correlation between the Hamilton emotion scale with k_{PLI} in the theta band (especially in the prefrontal region) in patients with TD, further confirming that patients with TD who develop mood disturbances have a greater magnitude of dynamic fluctuation of brain connectivity.

Idiopathic RBD (iRBD) is supposed to be a prodromal stage of PD. Research on resting-state EEG functional connectivity to examine the cerebral network subtle variations in patients with iRBD pointed out that functional networks in iRBD were altered at the early stage of the disease (Sunwoo et al., 2017). K_{PLI} gamma was particularly associated with RBDSQ scores in the prefrontal, frontal, and parietal regions in the TD group, which have been proved to be decreased regional cerebral blood flow in iRBD in a single-photon emission computerized tomography (SPECT) cerebral blood flow study (Vendette et al., 2011). Accordingly, EEG characteristic parameters show promise to become potential markers for disease progression in patients with TD.

Correlations Between Electroencephalography Characteristic Parameters and Plasma Biomarkers

In this study, it is the first time to explore the association between EEG features and plasma neurodegenerative proteins in different motor phenotypes of PD. One of the most crucial findings was the relationship of increased k_{PLI} (higher global dynamic fluctuation magnitude of brain connectivity) with higher t-tau levels in the TD group, which could be speculated that as tau pathology accumulates, so does the discordance of the dynamic brain network. In addition, plasma t-tau and Aβ42 were negatively associated with *TT* and *RR* in the delta band, respectively, which was especially involved in the slow-frequency band, speculating that the more the tau and amyloid pathology deposits in patients with TD, the faster the brain network state switches and the larger fluctuation the brain network has. Similar network alternations associated with biofluid markers have been put forward. For example, increased CSF p- and t-tau levels were correlated with EEG slowing and decreasing synchronization in patients with cognitive impairment (Smailovic et al., 2018; Tanabe et al., 2020); the combined p-tau/Aβ42 ratio exhibited a stronger correlation with the slow-frequency band in elderly individuals (Stomrud et al., 2010). Beyond plasma t-tau, we also found some specific correlations between other plasma biomarkers (NfL and α-syn) and EEG parameters in individual band power. Until now, there is no clear evidence for the link between NfL and EEG variables in PD, and our study first proposed and explored the relationship between them. It is acknowledged that NfL is a byproduct of neurodegeneration, and with the increase in NfL, the severity of neuronal damage aggravates. Our study showed that plasma NfL was negatively correlated with *TT* theta in patients with TD and *RR* gamma in patients with PIGD, speculating that as the plasma NfL increases and the neurodegenerative changes exacerbate, the fluctuation of DFNs becomes wilder. Particularly, pairwise correlations were found among plasma NfL, theta *TT*, and MoCA scores in the TD group, suggesting that an integrated measurement of plasma NfL and theta *TT* may be a powerful predictor of cognitive impairment in patients with TD. Furthermore, it is widely accepted that α-syn accumulation leads to abnormal communication with neuronal, synaptic, and/or dendritic membranes, resulting in pathophysiological changes, which may explain its correlation with network state abnormalities (Caviness et al., 2016). Concurrently, we found α-syn correlated strongly with *TT* beta in patients with PIGD, implying the anomalous network state switching in PIGD. Numerous studies support the hypothesis that positive correlation between blood α-syn and motor severity in patients with PD (Chang et al., 2020; Fan et al., 2020) and our finding that the *TT* in the delta band was positively correlated with MDS-UPDRS III scores and plasma α-syn in the TD group strengthened the hypothesis, implying that motor function impairment might lead to the abnormal slowing of

brain state transition. A seemingly contradictory finding was that *TT* was positively correlated with motor impairment and α-syn level while negatively correlated with the levels of NfL and tau. We speculate the probable cause is that the nerve damage characteristics represented by NfL and tau are different from syn since the NFL level mainly reflexes CNS axonal damage severity and tau itself may also have specific CNS damage pathology; that is, the damage of brain functional areas reflected by the accumulation of NfL and tau is different from that of α-syn. Above all, our results support the close relationship between plasma biomarkers and EEG measures. However, the definite correlation between the two kinds of markers and whether quantitative EEG could become an economic and alternative method for the diagnosis and prognosis of PD subtypes require further research and confirmation.

Limitations

This study has some limitations worth mentioning. First, due to the relatively restricted number of patients and short of EEG conducted among HCs, we cannot infer the definite correlation of EEG characteristic parameters and plasma biomarkers with disease severity in different motor subtypes and compare the discrepancy of EEG variables between PD and controls. Second, it is essential to track the dynamic changes in EEG and plasma protein profiles within individuals and over time to probe whether these could be potential instruments to monitor disease progression. Therefore, much more longitudinal research is badly needed. Finally, the detection of biomarkers in CSF has been extensively studied, which seems to better reflect the function of the central nervous system. In this study, we selected a more convenient blood-based detection means instead of CSF.

CONCLUSION

Our study highlighted the reliable relationship of EEG characteristic parameters and plasma biomarkers with disease severity in different motor subtypes of PD and simultaneously explored the potential association between EEG characteristic parameters and plasma biomarkers. Results confirmed that an integrated measurement of plasma NfL and theta *TT* is a powerful predictor of cognitive impairment in patients with TD. As a consequence, these two promising detection methods are expected to become potential markers to predict disease progression of PD subtypes, especially for patients with TD. A combination of these markers for monitoring and prognosis of PD progression deserves further research in larger, follow-up PD cohorts.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the General Hospital of Tianjin Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XY and ZeL drafted the manuscript for content, including medical writing for content, the acquisition of data, study concept or design, and analysis and interpretation of data, with contributions from LB, XS, FW, XH, RZ, ZuL, JZ, MD, YW, TC, and SZ. XZ, CL, and CC were responsible for the supervision, project administration, and funding acquisition. All authors read and approved the final version of the manuscript.

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Mild cognitive impairment in patients with Parkinson's disease: An updated mini-review and future outlook

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Mild cognitive impairment (MCI) is one of the common non-motor symptoms in patients with Parkinson's disease (PD). MCI is the transition stage between normal aging and full-blown dementia and is also a powerful predictor of dementia. Although the concept of MCI has been used to describe some of the PD symptoms for many years, there is a lack of consistent diagnostic criteria. Moreover, because of the diverse patterns of the cognitive functions, each cognitive impairment will have a different progression. In this review, we overviewed the diagnostic criteria for PD-MCI, primarily focused on the heterogeneity of PD-MCI patients' cognitive function, including various types of cognitive functions and their progression rates. A review of this topic is expected to be beneficial for clinical diagnosis, early intervention, and treatment. In addition, we also discussed the unmet needs and future vision in this field.

KEYWORDS

Parkinson's disease, dementia, mild cognitive impairment, heterogeneity, cognitive function

Introduction

Parkinson's disease (PD) is one of the common neurodegenerative diseases. Some critical clinical features include motor symptoms, such as tremors, bradykinesia, and rigidity (Obeso et al., 2017). Evidence showed that there were 6.1 million PD patients worldwide in 2016, and the prevalence continues to rise each year (Dorsey et al., 2018). PD is more common in males, and there is a slightly higher incidence and prevalence rate of PD in the West compared to the East (Abbas et al., 2018). The clinical diagnostic criteria of PD have been updated continuously (Gibbs and Lees, 1988; Gelb, 1999; Postuma et al., 2015; Marsili et al., 2018). New aspects are introduced in the updated diagnostic guidelines, such as the use of non-motor symptoms (NMSs) and

the application of the prodromal concept, which is essential for the early detection and treatment of the disease (Marsili et al., 2018).

In addition to motor symptoms, NMSs are common in patients with PD across cultures and countries (Yu et al., 2017). The NMSs may precede the development of motor features and have a more significant impact on a patient's quality of life (Liu et al., 2015; Pfeiffer, 2016). It may also serve as a predictor of mortality (Bugalho et al., 2019). PD's common NMSs include dementia, neuropsychiatric symptoms, autonomic failure, and sensory impairments (Gupta and Shukla, 2021). Among the NMSs, dementia has the most detrimental effect on patients' quality of life (Fan et al., 2020), caregivers' burden (Pantula and Vijay Harbishettar, 2012), and increases the need for hospitalization and mortality (Bugalho et al., 2019).

The clinical diagnostic criteria for PD patients with Dementia (PDD) were first published by the movement disorder society (MDS) task force (Emre et al., 2007), and then another practical guideline for diagnosing PDD using two-level criteria was proposed (Dubois et al., 2007). A review by Aarsland and Kurz (2010) showed that the point prevalence of dementia in the PD population is about 30%, and the incidence rate of dementia was 24.3/1,000 per year (95% confidence interval is 7.7–58.5) in a hospital-based PD cohort (Nicoletti et al., 2019). PD patients are 5∼6 times more likely to develop dementia than healthy aging populations (Hobson and Meara, 2004). Moreover, the longitudinal studies showed that 15–20% of PD patients develop dementia after 5 years (Williams-Gray et al., 2009) and 46% after 10 years (Williams-Gray et al., 2013). Although dementia does not necessarily occur in PD, the 12-year (Buter et al., 2008) and 20-year follow-up studies (Hely et al., 2008) revealed that about eighty percent of PD patients are eventually diagnosed with dementia. Mild cognitive impairment (MCI) is believed to be one of the best indicators for early detection of PDD (Galtier et al., 2016; Hoogland et al., 2017; Nicoletti et al., 2019). Therefore, the number of studies investigating PD patients with MCI (PD-MCI) has been significantly growing for the past 20 years.

Mild cognitive impairment in patients with Parkinson's disease

The evolution of the concept and the diagnostic criteria of Parkinson's disease patients with mild cognitive impairment

The concept of MCI comes from Alzheimer's disease research, and it is believed to be the transition stage between normal aging and dementia (Petersen et al., 1999; Petersen, 2004). The concept of MCI is also incorporated into the last version (fifth edition) of the Diagnostic and Statistical Manual (DSM) system of the mental disorder (Regier et al., 2013), in which neurocognitive disorders (NCD) are divided into major NCD and mild NCD according to whether the patient's independent living function is affected. Suppose the patient's social or occupational function is intact, but there is a deficit in cognitive function. In that case, the patient will be diagnosed with mild NCD, which is a synonym for MCI.

After the concept of MCI was introduced into PD research, many scholars and research teams began to explore the neurocognitive function profile of PD patients and its progression with the course of the disease through different definitions or diagnostic criteria of MCI. Most studies (Janvin et al., 2006; Monastero et al., 2012; Yu et al., 2012b) followed the diagnostic criteria from the original MCI criteria from Petersen (2004). In 2011, the Movement Disorder Society commissioned a Task Force to systematically review the literature and determine the PD-MCI patient's clinical characteristics (Litvan et al., 2011). After Litvan et al. (2012) proposed the standardized diagnostic criteria for PD-MCI, in the next 10 years, most of the PD-MCI related studies deployed this diagnostic criterion, and validation was conducted (Geurtsen et al., 2014). There is a two-level scheme (i.e., level I and II) in this standardized diagnostic criteria for PD-MCI (Litvan et al., 2012). In level I, the abbreviated testing tools are used to judge the patient's cognitive performance. Level II uses various cognitive domains (e.g., memory, executive, visuospatial function, etc.) to determine the patient's cognitive function; each cognitive domain contains at least two cognitive tests. Level II can be used to classify patients with PD-MCI to explore the heterogeneity of PD-MCI further. The classification methods include using the number of cognitive domain deficits as a classification, such as single-domain or multiple-domain subtypes. Another classification method is to use cognitive impairment content as a classification method, such as amnestic or non-amnestic subtypes. The Level I is often recommended for clinical practice, while Level II using comprehensive neuropsychological tests is recommended for research use. Recently, Goldman et al. (2018a) revisited the concept of MCI and the international Parkinson and MDS PD-MCI diagnostic criteria. They pointed out that using different diagnostic criteria (e.g., Level I or Level II) will lead to the different prevalence of PD-MCI. Which cognitive test is used and how the defect is defined (e.g., using 1 or 2 SD) can affect the diagnostic classification of PD-MCI. Most studies indicate that the use of −2SD will have the best sensitivity, and the proportion of PD-MCI with multiple domains was the most common. Delineation of PD-MCI cognitive subtypes is crucial for predicting cognitive decline and responding to associated pathological changes. Cognitive tests and other functional assessments play an essential role in the diagnosis, and Goldman et al. (2015) suggest related clinical and psychometric properties of scales should be considered in the diagnostic criteria.

Prevalence, progression, and subtype of Parkinson's disease patients with mild cognitive impairment

Litvan et al. (2011) conducted a critical systematic review and disclosed that about 26.7% (18.9–38.2%) of non-demented PD patients have MCI. Yarnall et al. (2014) applied different cut-off criteria of cognitive tests and found various PD-MCI prevalence; their results showed that under 1, 1.5, and 2 standard deviations, the prevalence of PD-MCI was 65.8, 42.5, and 22.4%, respectively (Yarnall et al., 2014). Recently, Baiano et al. (2020) conducted a meta-analysis study to elucidate the prevalence of MCI in PD. The authors recruited forty-one studies (7,053 PD patients) and found that the prevalence of MCI in PD was around 40% (95% confidence interval is 36–44). Moreover, this meta-analysis study revealed that the multiple-domain subtype was the most common phenotype of PD-MCI (about 31%) (Baiano et al., 2020). Nicoletti et al. (2019) enrolled a hospital-based cohort and showed the incidence rate of MCI among PD patients was 184.0/1,000 per year (95% confidence interval is 124.7–262.3).

Janvin et al. (2006) first used a small sample (72 non-demented PD patients) to explore this topic and found that sixty-two percent of PD-MCI patients developed PDD over 4 years (Janvin et al., 2006). Although it is difficult to compare all these studies due to the various research designs or methodologies, an updated review and meta-analysis article was done by Saredakis et al. (2019) to elucidate the conversion rate of PD-MCI to PDD. They included 39 articles (4,011 PD patients) in this study. They found that about 25% of PD patients converted to PD-MCI and 2% to dementia among the patients with intact cognitive function. Besides, 20% of PD-MCI converted to dementia, while 28% reverted to normal cognitive function. Here we summarized the primary longitudinal studies that elucidated the trajectory of cognitive function in patients with PD in **Table 1** (Broeders et al., 2013; Pedersen et al., 2013, 2017; Hobson and Meara, 2015; Pigott et al., 2015; Santangelo et al., 2015; Galtier et al., 2016).

The heterogeneity of the PD-MCI patients has long been noted (Kehagia et al., 2010). The original MCI concept proposed the amnestic and non-amnestic or the single or multiple domains impaired (Petersen, 2004). The MDS PD-MCI diagnostic criteria proposed a two-level diagnostic method. Level I is suggested for clinical practice, and level II is for research. The most commonly used tests for level I are the Mini-mental state examination or Montreal Cognitive Assessment. The conversion equation between the two tests was recently proposed (Yu et al., 2020). Level II is a more comprehensive evaluation that examines various cognitive domains and can be applied to classify different subtypes of PD-MCI (Litvan et al., 2012). Although various studies investigated the neuropsychological profile in PD-MCI patients (Sollinger et al., 2010; Goldman et al., 2012; Yu et al., 2012b; Galtier et al., 2016; Kalbe et al., 2016; Lawrence et al., 2016; Monastero et al., 2018); the results were inconclusive. Some studies showed that single domain PD-MCI is the most frequent subtype (Sollinger et al., 2010), especially the non-amnestic type, and the executive and visuospatial functions were the most vulnerable (Goldman et al., 2012; Yu et al., 2012b; Kalbe et al., 2016). On the other hand, other studies demonstrated that multiple domain impairment was the most common subtype (Galtier et al., 2016; Lawrence et al., 2016; Monastero et al., 2018). Recently, a updated meta-analysis study conducted by Baiano revealed that the multiple domain subtype was the most common phenotype of PD-MCI (about 31%) (Baiano et al., 2020). Janvin et al. (2006) found that non-amnestic PD-MCI was associated with the later development of dementia, whereas amnestic PD-MCI was not (Janvin et al., 2006). However, this finding was not supported by other studies. Chung et al. (2019) found that amnestic PD-MCI patients exhibited a more rapid cognitive deterioration in executive function than non-amnestic PD-MCI patients. Moreover, the amnestic PD-MCI group had a higher risk of converting to dementia than the non-amnestic PD-MCI group (Chung et al., 2019). In addition, Vasconcellos et al. (2019) showed that the amnestic PD-MCI patients have the worst quality of daily life.

The unmet need and future outlook

Different PD-MCI diagnostic criteria will generate different prevalence rates. The estimated prevalence of PD-MCI using MDS criteria is approximately 40% (Baiano et al., 2020). The prevalence may be overestimated (Monastero et al., 2012; Yu et al., 2012b) or underestimated (Muslimović et al., 2005; Aarsland et al., 2010) depending on the diagnostic criteria used. In recent years, most studies have used the diagnostic criteria which were proposed by the MDS Taskforce (Litvan et al., 2012); however, these criteria are still under modification. The PD-MCI diagnostic criteria can be revised and refined by considering other biomarkers and possible factors (e.g., gender or effective measurement) to increase the accuracy. For example, the Catechol-O-methyltransferase genotype was found to be related to executive-attention function (Foltynie et al., 2004; Williams-Gray et al., 2009; Fang et al., 2019), and the apolipoprotein E genotype is related to cognitive decline (Tropea et al., 2018), especially the posterior cortical dysfunction (Williams-Gray et al., 2009), in the PD population. Martinez-Horta and Kulisevsky first proposed two subtypes (i.e., frontostriatal and posterior-cortical cognitive defects) in patients with PD. They suggested that one subtype is frontostriatal cognitive dysfunction and the frontostriatal dopaminergic deficits leading to the dysexecutive syndrome and that this deficit may be a benign and non-progressive subtype. Furthermore, the other subtype is tissue damage due to the spread of Lewy bodies,

while damage to specific functions (e.g., visuospatial and language functions) is dependent on posterior cortical areas and represents a malignant and progressive subtype (Martínez-Horta and Kulisevsky, 2011). That is, the posterior cortical dysfunction is related to the progression of dementia; however, this is not the case with the frontal-related dysfunction. Later, Kehagia et al. (2013) proposed the "dual syndrome hypothesis" to describe the heterogeneity of neurocognitive function in patients with PD. In addition, certain race-specific genes (e.g., Aldehyde Dehydrogenase) (Yu et al., 2016, 2021) and other genes (e.g., β-glucocerebrosidase) (Szwedo et al., 2022) are associated with cognitive function should also be considered and further investigate.

Moreover, brain imaging is another potential biomarker. Evidence showed that PD-MCI patients' brain atrophy mainly occurs in the frontal, temporal and parietal regions and the basal forebrain (Delgado-Alvarado et al., 2016). Through whole-brain analysis (e.g., Voxel-based meta-analysis or coordinate-based meta-analysis), the cross-sectional studies revealed that PD-MCI patients have more atrophy in the left brain areas, including superior frontal gyrus, superior temporal lobe, and insula (Xu et al., 2016), left anterior insula extending to the inferior frontal gyrus, and orbital region (Zheng et al., 2019), angular gyrus, and right supramarginal gyrus, bilateral dorsolateral prefrontal cortex, and midcingulate cortex (Mihaescu et al., 2019). The longitudinal research showed that baseline volume of global white matter, global hippocampus, hippocampal sub-regions, thalamus, and accumbens nucleus are predictors of the PD patients with normal cognition (PDNC) conversion to PD-MCI (Atluri et al., 2013; Kandiah et al., 2014; Wen et al., 2015). While the baseline global gray matter volume cannot significantly predict the conversion rate to PD-MCI, one side to bilateral loss of gray matter volume is a predictor of progression from PD-MCI to PDD (Xu et al., 2016). The functional MRI studies showed that the functional connectivity between the medial prefrontal and posterior cingulate cortex within the default mode network at baseline predicts PD patients' conversion to PD-MCI (Zarifkar et al., 2021). PD-MCI patients have reduced connectivity in specific brain regions that are part of the default mode network (Wolters et al., 2019), and the functional connectivity changes involving the parieto-temporal regions may predict the evolution of dementia in PD-MCI patients (Dubbelink et al., 2014). In addition, cerebral blood flow abnormality is a detection marker for PD-MCI patients. Nobili et al. (2009) used single-photon emission computed tomography to evaluate the perfusion in patients with PD and found that PD-MCI patients have the hypo-perfusion pattern in the posterior brain area (e.g., bilateral posterior parietal lobe and right occipital lobe) compared with healthy individuals. The parietal cerebral blood flow was found to be a potential early biomarker for PD-MCI (Pelizzari et al., 2020). Recently, Arslan et al. (2020) found a "posterior hypo-perfusion" pattern *via* arterial spin labeling imaging (ASL-MRI), and this pattern can be differentiated PD-MCI from healthy individuals with an accuracy of 92.6%. Moreover, PD patients with microtubule-associated protein tau (MAPT) H1/H1 haplotype had decreased perfusion than the ones with H1/H2 haplotype in the posterior brain regions. They suggested that "posterior hypo-perfusion" in ASL-MRI could potentially be a biomarker for detecting cognitive dysfunction in the PD population (Arslan et al., 2020). Azamat et al. (2021) also found that the abnormities of cerebral blood flow are very different between PDD and non-demented PD patients (i.e., PDNC and PD-MCI). They found PDD patients especially have hypoperfusion in dopaminergically-mediated fronto-parietal and non-dopaminergically-mediated visual networks (Azamat et al., 2021). Those imaging studies suggest a dual characteristics of cognitive impairment (i.e., the dopaminergic fronto-striatal pathway and the parieto-temporal

TABLE 1 The longitudinal studies explore the trajectory of cognitive function in patients with PD.

References	Country	Center	Dropout rate	Follow-up year	PDCN→PD-MCI	PD-MCI→PDD
Broeders et al. (2013)	Holland	Single	21.1%	3	36.5	17.6
			40.7%	5	–	–
Pedersen et al. (2013)	Norway	Multi	8.2%	3	–	27%
Pigott et al. (2015)	United States	Single	19.1%	4	36.1%	78.7%
Santangelo et al. (2015)	Italy	Single	18.4%	2	29.2%	0%
			27.6%	4	33.3%	15.3%
Hobson and Meara (2015)	United Kingdom	Single	37.3%	4	40.5%	85.7%
			45.2%	6	62.5%	53%
Galtier et al. (2016)	Spain	Single	9.3%	7	–	42.3%
Pedersen et al. (2017)	Norway	Multi	1.69%	1	10.1%	0%
			8.43%	3	21.5%	34.5%
			15.73%	5	14.3%	38.5%

PD, Parkinson's disease; PDCN, PD patients without dementia; PD-MCI, PD patients with mild cognitive impairment; PDD, PD patients with dementia.

pathway (Kehagia et al., 2010, 2013). Future studies could target the combination of multiple biomarkers (e.g., imaging and genetics) to detect the occurrence of PD-MCI and predict the subsequent development of PD-MCI.

The impact of gender on a patient's cognitive function should not be underestimated. Male sex is a significant predictor of early cognitive decline, and females have slower progression to cognitive impairment (Cholerton et al., 2018). Evidence showed that gender was a significant determinant of specific cognitive domains, with a differential pattern of decline in male and female PD patients. Moreover, how to efficiently measure the functional deficit is another crucial issue. One is that functional deficits other than cognitive function have yet to be developed, and the other is the method in which function is assessed. The former refers to the fact that, in addition to cognitive function, PD patients have many functional impairments in life, such as instrumental activities of daily living (Pirogovsky et al., 2014) or interpersonal/social function (Perepezko et al., 2019; Su et al., 2020; Chuang et al., 2021). A few studies have explored this topic; however, research in these areas still requires more relevant studies and the accumulation of empirical data.

Regarding the way to measurement, common assessment methods include self-report, performance-based measurement, or informant-based measurement. Self-report and family reports rely on the reporter's observation. Evidence showed that not all PD patients could be precisely aware of their dysfunction due to the brain basis of the disease (Yu et al., 2010). The informant-based measurement may have more uncontrollable factors, including family members not living together (patients live alone) or family members' poor observation. In addition, the biggest challenge for performance-based measurement is the ecological validity of the test (Lea et al., 2021). Ecological validity refers to the degree to which the test content can reflect the actual living environment of the patient. Good ecological validity can improve the usability of assessment for diagnosis or treatment. The ecological validity of performance-based measurement is a key that needs to be studied in depth.

Past diagnostic criteria have focused on the contents of cognitive tests (Hoogland et al., 2018) or the optimal cut-off score of the cognitive tests (Goldman et al., 2013, 2015), but how would cognitive impairments reflect difficulties in PD patients' life? This question needs to be explored urgently. The ecological validity of cognitive tests needs to be noted, and it is also essential to develop tools that can assess the distress experienced by patients in their life. For example, the social function deficits would escalate a person's risk of dementia (Fankhauser et al., 2015) and expedite the dementia process (Bennett et al., 2006). This issue has gradually been noticed in the PD group (Bettencourt and Sheldon, 2001; Perepezko et al., 2019). The tools for measuring PD patients' social functioning were developed (Su et al., 2020). Developing such measurement and in-depth knowledge of related fields will help tailor rehabilitation programs for PD patients. It is particularly worth noting that during the COVID-19 pandemic, PD patients may be at particular risk for developing new cognitive symptoms or worsening existing cognitive symptoms, even if the patients are not infected with COVID-19 (Brown et al., 2020). Brown et al. (2020) revealed that PD patients may experience worsening or new symptoms of cognitive function after being canceled or postponed exercise or social activities or being asked to self-isolate/quarantine during the COVID-19 pandemic. In the past 2∼3 years, human-to-human contact has been limited. Under such conditions, the deterioration rate of the social function of PD patients may increase. Moreover, PD patients' social function performance in the post-epidemic period is also worth further study.

Since the brain pathology of each PD-MCI subtype may be different, the clinical characteristics of the PD-MCI subtype may be different too. PD patients have specific motor characteristics, and the correlation between these motor characteristics and PD-MCI subtypes needs to be explored. For example, a recent study demonstrated that multiple-domain PD-MCI and amnestic PD-MCI are related to gait disturbance, especially in the dual-task (Amboni et al., 2022). Our study also revealed that the PD-specific motor characteristic (e.g., hypomimia) might influence social cognition (i.e., facial emotion recognition) (Chuang et al., 2021). Based on the embodied simulation theory, the mechanism for understanding the thoughts and emotions of others is simulation through the mirror mechanism (Gallese et al., 2004). People can trigger sensorimotor neurons by simulating other people's facial expressions, followed by a series of responses to complete emotion recognition (e.g., triggering proprioceptive feedback, generating corresponding emotional states, recognizing emotions). Our findings revealed that PD patients with hypomimia had worse recognition of disgust than healthy aging, and hypomimia's severity was predictive of the recognition of disgust.

Different from other cognitive functions (e.g., memory, executive function, etc.), social cognition (e.g., facial emotion recognition, reading the mind in the eye, theory of mind, etc.) is an emerging research field (Regier et al., 2013) and has drawn more attention in neurodegenerative disease (Elamin et al., 2012), especially in the PD population (Lewis and Ricciardi, 2021). Social cognition refers to people's understanding and prediction of themselves and others by processing and using the information in social interaction and then forming the interactive behavior between people and themselves, including the cognitive and affective components. These components differentially served in distinct neural circuits (Shamay-Tsoory and Aharon-Peretz, 2007). Activity in the dorsolateral prefrontal cortex, posterior cingulate cortex, and the temporoparietal junction is responsible for the cognitive part of social cognition, while the affective domain relies on ventromedial, orbitofrontal cortices, and the mesolimbic circuit (Schurz et al., 2014). The Diagnostic and Statistical Manual of Mental Disorders

first juxtaposes social cognition with other cognitive functions (Regier et al., 2013). One main research directions in this field are the theory of mind (ToM) (Yu et al., 2012a, 2018; Yu and Wu, 2013a,b; Argaud et al., 2018; Adenzato et al., 2019; Foley et al., 2019; Romosan et al., 2019; Coundouris et al., 2020). ToM refers to individuals' ability to know what others think (cognitive ToM) and how they feel (affective ToM). Evidence showed that young-onset PD patients had preserved ToM (Yu et al., 2018); however, the idiopathic PD patients have impaired cognitive ToM, and the affective ToM will be affected in the advanced stages of the disease (Poletti et al., 2011; Bora et al., 2015).

Moreover, the deficits in affective ToM may make more significant in female than male PD patients (Yu et al., 2018). Recently, Coundouris et al. (2020) conducted a meta-analysis of 38 studies and revealed that cognitive or affective ToM only evident for performance-based tests. Moreover, Affect ToM in PD patients was less affected than cognitive ToM, but since there has been less research on this topic, the authors believe this finding still needs to be validated in future studies. Only a few studies were conducted to investigate the PD-MCI patient' theory of mind to the best of our knowledge. Adenzato et al. (2019) compared the ToM performance in twenty patients with PD-MCI and healthy controls. They found that PD-MCI patients' ToM performance was worse than that in the healthy controls. They also found that transcranial direct over the medial frontal cortex enhances ToM in PD-MCI patients; however, no effect on accuracy was observed. The limitation of the small sample size and methodology (e.g., classified PD-MCI on a global scale) may limit the application of results (Adenzato et al., 2019). The relationship between cognitive function and social cognition is still unclear. Some studies suggested that cognitive function and social cognition are two separate concepts that do not affect each other (Roca et al., 2010); however, other evidence showed that impairment in ToM might be explained by cognitive function (e.g., executive function and attention and visuospatial function) (Yu et al., 2012a; Bora et al., 2015; Foley et al., 2019; Romosan et al., 2019). If social cognition is inseparable from cognitive function, then it is conceivable that PD-MCI patients may have impaired social cognition. In the process of social cognition, cognitive function plays a key role is important. If expressing appropriate responses in social situations may require assistance with cognitive functions (e.g., inhibition or monitoring abilities), training these cognitive functions will help patients maintain good social cognition. Considering the heterogeneity of PD-MCI, it is also considered that preserved social cognition helps patients adhere to physician orders, maintain relationships with caregivers, and maintain quality of life during the disease course. Further research is needed to explore the relationship between cognitive function and social cognition.

Regarding the treatment of cognitive impairment in patients with PD, most of the treatment trials for dementia in patients with PD have focused on the development of drugs which was developed for the treatment of cognitive symptoms in Alzheimer's disease, including cholinesterase inhibitors and the N-methyl-D-aspartate receptor antagonist, memantine (Goldman and Weintraub, 2015). The cholinesterase inhibitors were evidence-based for the symptomatic treatment for PDD; however, less evidence is available for memantine (Seppi et al., 2011; Dubois et al., 2012). A recent meta-analysis was conducted to examine the efficacy of cholinesterase inhibitors and memantine for PDD and Lewy body dementia. A total of fifteen trials were recruited, and the results showed that cholinesterase inhibitors had effects on some cognitive functions (e.g., attention, processing speed, executive function, memory, and language); however, there was no significant effect on improving visuospatial perception. Memantine also significantly affected attention, processing speed, and executive functions (Meng et al., 2019). However, the authors suggested further clinical trials are required to verify their conclusions due to the few studies included in this study. Given the side effect of the medication and the lack of pharmacological treatments for MCI in PD, non-pharmacological treatments have attracted great interest in recent years (Goldman et al., 2018b). We searched and screened the literature from 2012 to 2022 in the PubMed database through the keywords "Parkinson's disease "&" Cogni* training," and excluded review articles, meta-analysis articles, articles that did not investigate cognitive training, and did not evaluate the changes of cognitive function. We found 1,679 articles in total, and the number of articles is increasing yearly (**Figure 1**).

The cognitive training methods can be divided into traditional cognitive training (or paper-pencil tasks training) and computerized cognitive training (Pupíková and Rektorová, 2020; Svaerke et al., 2020). Researchers began using computers from 2013 to 2014 to aid cognitive training. However, few studies were conducted on patients with PD-MCI (Costa et al., 2014; Angelucci et al., 2015). Three randomized controlled trials were conducted to evaluate the effect of cognitive training in the PD-MCI population. The research team of Costa et al. (2014) and Angelucci et al. (2015) recruited 15 and 17 PD-MCI patients, respectively, through the level II of the PD-MCI diagnostic criteria for paper-pencil cognitive training. The executive function (e.g., mental shifting) is the common focus of the two studies, while the study by Costa et al. (2014) additionally trained attention and working memory ability. After 4 weeks (12 sessions) of training, the patients' performance in the zoo map test, the trial-making test, and prospective memory were improved. In 2014, Cerasa et al. (2014) recruited 15 PD-MCI patients according to the level I of PD-MCI criteria; they used a computerized training program to train patients' attention ability. They found that after 6 weeks (12 sessions) of training, the patients' attention (e.g., digit span and the symbol digit modalities test) were improved. Although these studies revealed that cognitive training might help PD-MCI patients to improve their cognitive function; however, the evidence level of these articles was classified as "possibly effective or ineffective" (Pupíková and Rektorová, 2020). The limited

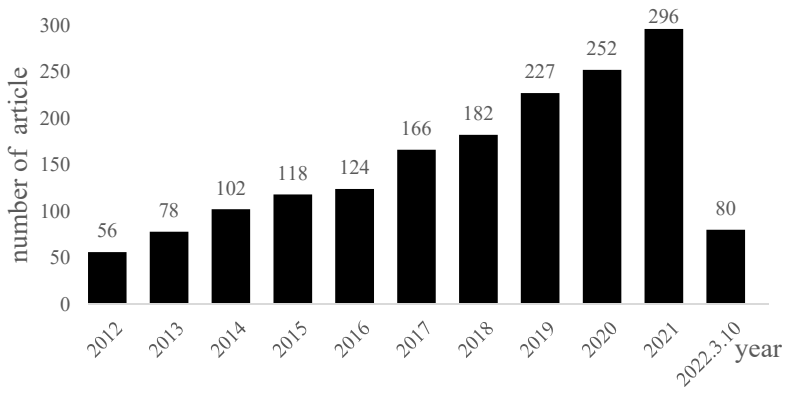

FIGURE 1
Yearly articles related to cognitive training for Parkinson's disease on PubMed.

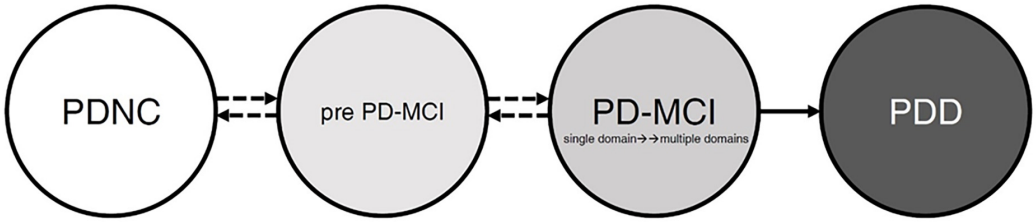

FIGURE 2
The possible patterns and evolution of cognitive function in patients with Parkinson's disease. Before full-blown dementia, the PD patients' cognitive patterns may be in the "PDNC," "pre PD-MCI," or "PD-MCI." The pathway from PD-MCI to PDD is relatively stable; however, the three cognitive states may transition before entering into PDD. PDNC, PD patients with normal cognition; pre PD-MCI, PD patients do not achieve PD-MCI diagnosis but have cognitive impairment; PD-MCI, PD patients achieve PD-MCI diagnosis; PDD, PD patients with dementia.

number of randomized controlled trials for PD-MCI patients' cognitive training makes it difficult to draw further conclusions. More studies on cognitive training were warranted, especially developing the cognitive training for other vulnerable cognitive domains (e.g., visuospatial function). Tailed training program to use a preserved cognitive function to assist impaired one. For example, we found impaired gist memory in advanced-stage but not early stage PD patients. The techniques used to take advantage of the preserved gist memory in early stage patients with PD and the preserved item-specific memory in patients with PD of all stages could be helpful for the memory training program (Yu et al., 2015).

Moreover, develop cognitive training programs through other equipment as a medium. For example, some researchers applied virtual reality technology (Pelosin et al., 2021) to enhance the sense of reality and used mobile applications (Yu et al., 2022) to improve the accessibility of cognitive training. Last, the prospective and longitudinal designed studies were also urgent to evaluate the long-term effects of cognitive training.

Last but not least, the cognitive state transitions during PD are noteworthy. We proposed possible transition states for cognitive functions (see **Figure 2**). The state includes the "PD patients with normal cognition," "pre PD-MCI," "PD-MCI," and "PDD." Many studies have confirmed the pathway for the conversion of PD-MCI to PDD (Galtier et al., 2016; Hoogland et al., 2017; Nicoletti et al., 2019), and once a patient is diagnosed with PDD, it means that the course of the disease will not be reversed back to PD-MCI. However, before developing PDD, we assume that there is a possibility of mutual conversion between these stages. For example, "PD-MCI" state converts back to "pre PD-MCI" or "pre PD-MCI" reverse to "PDNC." According to the diagnostic criteria of PD-MCI in MDS (Litvan et al., 2012), there may also be a "pre PD-MCI" group of PD patients. The "pre PD-MCI" is a less mentioned group, this group of patients has not yet met the diagnostic criteria of PD-MCI, but they have cognitive deficits (with one test score falling within the deficit range) (Goldman et al., 2018a). To our knowledge, no study was conducted to elucidate this group's characteristics and conversion or reversion rate. Future research will be encouraged to explore the characteristics of different states and the transition of each state as a basis for brain pathology research, and the findings can also provide a reference for rehabilitation planning.

Author contributions

R-MW and R-LY formed the concept and structure of the manuscript together. R-LY wrote the first draft of the manuscript. R-MW supervised, commented, revised, and critiqued this manuscript. Both authors approved the final version of the manuscript and agreed to be responsible for all aspects of the work.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Prevalence of lower urinary tract symptoms, urinary incontinence and retention in Parkinson's disease: A systematic review and meta-analysis

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Background: Lower urinary tract symptoms (LUTS) are common non-motor symptoms but are often overlooked in Parkinson's disease (PD). The prevalence of LUTS in PD is inconsistent among different studies.

Objective: To estimate the prevalence of LUTS, urinary incontinence, and urinary retention in PD patients, then, investigate potential sources of inconsistency in prevalence estimation.

Methods: We searched PubMed, EMBASE, and Web of Science databases from inception to May 2022. Studies reporting the prevalence of LUTS or LUTS subtypes in PD were included. Pooled prevalence of LUTS, LUTS subtypes, urinary incontinence, and urinary retention was calculated *via* random-effects models. Meta-regression and subgroup analyses were performed.

Results: Of 7,358 studies after duplicate removal, a total of 73 studies comprising 14,937 PD patients were included. The pooled prevalence of LUTS was 61% (95% CI 53–69; 27 studies; $n = 5,179$), while the pooled prevalence of storage symptoms and voiding symptoms was 59% (44–73; 9 studies; $n = 798$) and 24% (14–33; 11 studies; $n = 886$), respectively. The pooled prevalence of urinary incontinence, retention and post-void residual (PVR) volume $\geq$ 100 ml were 30% (95% CI 22–39; 21 studies; $n = 6,054$), 27% (17–37; 14 studies; $n = 1,991$), and 4% (1–7; 5 studies; $n = 439$), respectively. The prevalence of LUTS, urinary incontinence, or urinary retention was significantly associated with diagnostic methods.

Conclusion: LUTS and its subtypes present in a significant proportion of PD patients. It is necessary to use standardized and validated methods to detect and screen LUTS and its subtypes.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022311233, Identifier: CRD42022311233.

KEYWORDS

Parkinson's disease, urinary incontinence, urinary retention, meta-analysis, review, prevalence, lower urinary tract symptoms (LUTS)

Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease characterized by both motor and non-motor symptoms. Lower urinary tract symptoms (LUTS) are common non-motor symptoms of PD. However, they are frequently neglected (Chaudhuri et al., 2006). LUTS are group of symptoms related to the lower urinary tract. Typical LUTS include storage symptoms (including urinary incontinence) and voiding symptoms (including urinary retention), which often emerge 5–6 years after the onset of motor symptoms in PD (Bonnet et al., 1997). The mechanism of LUTS may be related to PD neuropathology, especially the disruption of the dopamine D_1-GABAergic direct and bypass pathway (Sakakibara et al., 2016). α-synuclein, the pathological hallmark of PD, has been found in the pontine, sacral spinal cord, pelvic plexus, and genitourinary tract of PD patients (Wakabayashi and Takahashi, 1997; Beach et al., 2010). The structures responsible for normal bladder control, including pre-ganglionic, post-ganglionic sympathetic neurons, sacral parasympathetic nuclei, and frontal cortex were even proven to have PD neuropathology (Oyanagi et al., 1990; Braak et al., 2007; Tkaczynska et al., 2017).

LUTS exert immense impact on patients' life. The quality of life was physically and psychologically limited for PD patients with LUTS. The main effects were decline in self-esteem and social communication, in addition to depression, anxiety, deterioration of sexual life, and a decrease in physical activity (Farage et al., 2008). PD patients with LUTS showed elevated all-cause mortality and were more likely to develop severe complications including falls, disabling motor symptoms, cognitive dysfunction, and other non-motor dysfunction (Vaughan et al., 2013; Rana et al., 2015; Zhang and Zhang, 2015; Sakushima et al., 2016; Lee et al., 2018). Moreover, LUTS were correlated with increasing health-related costs. These can lead to serious burdens for PD patients, caregivers, and society (Mohammed and Ragab, 2010). This urges the need for an up-to-date estimation of the prevalence of LUTS. Establishing the prevalence of LUTS may not only raise awareness of early interventions but also help refine diagnostic criteria and differential diagnosis of PD and other parkinsonian syndromes. This may also guide effective planning of medical services.

However, there was considerable heterogeneity in the prevalence of LUTS in PD, ranging from 27 to 85% as shown in previous reports (Winge et al., 2006; Sakakibara et al., 2008; Jain, 2011; Martinez-Ramirez et al., 2020). Previous studies reporting the prevalence of LUTS were predominantly cross-sectional, with limited focus on the nature of LUTS. Furthermore, methods of determining the presence of LUTS are diverse, potentially leading to different reported rates. Urinary incontinence and retention are crucial symptoms of LUTS. PD patients were generally considered less likely to develop those two symptoms, and the presence of unexplained voiding difficulties with elevated post-void residual (PVR) volume $\geq$ 100 ml or unexplained urinary urge incontinence was often considered to support the diagnosis of multiple system atrophy (MSA) (Yamamoto et al., 2016; Wenning et al., 2022). However, urinary incontinence and retention are not rare, even PVR volume $\geq$ 100 ml can also occur in PD (Irene, 2019; Tateno et al., 2021). For example, one study with large sample size found that the prevalence of urinary incontinence was 43% in PD (Wüllner et al., 2007). Utilizing the Danish Prostate Symptom Score (Dan-PSS), the prevalence of urge incontinence in PD was up to 65.8% (Akkoç et al., 2017). Another study found the prevalence of incomplete bladder emptying was 75.5% in PD (Irene, 2019). Until now, no meta-analysis has been carried out to estimate the overall prevalence of LUTS, urinary incontinence, and retention in PD.

We aimed to conduct a systematic review and meta-analysis to determine the prevalence of the overall LUTS and its subtypes including urinary incontinence and retention in PD patients, as well as to explore potential sources of heterogeneity across prevalence estimates.

Materials and methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Barendregt et al., 2013) (Supplementary Table 1). The protocol has been registered on PROSPERP (registration number: CRD42022311233).

Date source and strategy

We screened PubMed, EMBASE, and Web of Science databases to identify relevant research from the outset until May 2022 using the following MeSH (Medical Subject Heading) terms and keyword variations: ("urination disorders" OR "urinary bladder, neurogenic" OR "urinary retention" OR "overactive bladder symptom" OR "nocturia" OR "urinary bladder, overactive" OR "urinary incontinence" OR "lower urinary tract symptoms" OR "urinary dysfunction" OR "dysuria") AND ("Parkinson's disease" OR "Parkinsonism" OR "Parkinsonian" OR "Parkinson's disease"). Afterwards, endnote was utilized to integrate the citations from each database and additional eligible publications.

Eligibility criteria and study selection

Studies were eligible if they met the following criteria: (1) published in peer-reviewed English journals; (2) participants were diagnosed according to UK Parkinson's Disease Society

Brain Bank Diagnostic Criteria (Hughes et al., 1992) or MDS clinical diagnostic criteria for Parkinson's disease (Postuma et al., 2015); (3) reporting the prevalence of LUTS or LUTS subtypes; (4) LUTS or LUTS subtypes assessed by validated scales administered by experienced clinicians, self-report questionnaire, or published criteria from classification codes/definition; (5) prospective cohort study or cross-sectional study.

The studies were excluded if they: (1) did not provide full text; (2) included insufficient or unclear fragmented data for analysis; (3) enrolled patients who have been diagnosed with prostate carcinoma, uncontrolled diabetes, as well as any other diseases that cause urinary problems, or taken drugs such as diuretics; (4) with small sample size ($n < 20$). (5) duplicated publications; (6) systematic reviews, meta-analyses, letters, protocols. When results on the same dataset were reported in several publications, only the most complete publication was included in the analysis. Two independent observers (FFL, YSC) evaluated the results and resolved any disagreement by discussion or with recourse to a third arbitrator (TF).

Quality assessment

Two authors (FFL, YSC) independently assessed study quality and risk of bias using the Newcastle-Ottawa Scale (NOS) (Stang, 2010) for cohort study and the Agency for Healthcare Research and Quality (AHRQ) (Williams et al., 2010) for cross-sectional study in Table 1. The highest score was 9 points for the cohort and case-control studies: low quality = 0–4 points; moderate quality = 5–7 points; high quality = 8–9 points. The highest score was 11 points for cross-sectional studies: low quality = 0–3 points; moderate quality = 4–7 points; high quality = 8–11 points. Higher score indicates better quality.

Data extraction

Data extraction was performed independently by two authors (FFL, YSC), using a standardized data collection spreadsheet in EXCEL. The following items were extracted: study characteristics (first author, publication year, country/region, study design, source), participant characteristics (age, disease duration, sample size, number of patients with LUTS or LUTS subtypes, gender of participants and H&Y stage), and methods used to evaluate LUTS or its subtypes (definitions, urinary dysfunction questionnaires or clinical scales).

LUTS subtypes include urinary storage symptoms [urgency, Overactive bladder (OAB) syndrome, pollakiuria, frequency, nocturia, incontinence], urinary voiding symptoms (dysuria, hesitancy, prolongation, intermittency, weak stream, retention, straining to void), and post-voiding symptoms according to the International Continence Society (ICS) report (D'Ancona et al., 2019). The clinical scales contain the overactive bladder symptom score (OAB-SS) (Homma et al., 2006), the International Prostate Symptom Score (IPSS) (Araki and Kuno, 2000), the Non-Motor Symptom Scale (NMSS) (Koh et al., 2012), Scale for Outcomes in Parkinson's Disease for Autonomic Symptoms (SCOPA-AUT) (Kim et al., 2017), the Danish Prostate Symptom Score (Dan-PSS) (Akkoç et al., 2017), and the American Urological Association Symptom Index (AUA-SI) (Barry et al., 1992). If disagreements could not be resolved through careful discussion by two investigators (FFL, YSC), a consensus was achieved by the involvement of a third investigator (TF) when necessary.

Statistical analysis

The meta-analysis was performed with Rx64 4.1.0 and RStudio using the "Matrix", "Meta," and "metaphor" packages to analyze pooled prevalence of LUTS or its subtypes with 95% confidence intervals (CIs). Heterogeneity for the pooled estimate of prevalence were quantified using the I^2 statistic, and its significance was measured using the Q test p-value. The random-effects model was adopted if significant heterogeneity were detected ($I^2 > 50\%$ or $p > 0.1$). Otherwise, the fixed-effects model was used. Meta-regression was performed to assess the effects of following variables: age, disease duration, regions of the participant, quality of studies and diagnostic method. We conducted subgroup analyses using diagnosis criteria (Scales, questionnaire, and definition), gender (proportion of female), H&Y stage (<3 and ≥ 3), study site (single-center, multicenter, and community-based), study design (cross-sectional and cohort), mean age (<65 and ≥ 65) of participants, region (North American, European, and the other) and quality of studies (Low, moderate and high). Sensitivity analyses were performed to evaluated the robust of the synthesis results by leave-one-out method. Publication bias was checked by funnel plot and Egger's test. The trim-and-fill computation was used to estimate the effect of publication bias on the interpretation of the results. Statistical significance was set at two-tailed $p < 0.05$.

Results

Characteristics of the included studies

After duplicating removal, we identified 7,358 articles through the database searching. Screening titles and abstracts led to the elimination of 7,237 irrelevant articles, full-text versions of the remaining 121 potentially eligible articles were assessed. Of those, 79 articles were included in the qualitative synthesis. Overall, 73 studies comprising 14,937 PD patients were identified eligible for the meta-analysis

TABLE 1 Characteristics of studies included in the meta.

First author and year	Country	Region	Study design	Study site	LUTS diagnosis standard	Sample size	Male/female	Mean age (years)	Disease duration (years)	Quality assessment
Hattori (1992)	Japan	The other	Cross-sectional	Single-center	Definition	110	43/67	58.8	4.3	Low
Singe (1992)	USA	North American	Cross-sectional	Single-center	Questionnaire	48	48/0	65.9 (1.46)	7.76 (0.91)	Low
Araki (2000)	Japan	The other	Cross-sectional	Single-center	IPSS	208	82/121	66.6	9.2	Moderate
Sakakibara (2001)	Japan	The other	Cross-sectional	Single-center	Questionnaire	115	52/63	59	6	Low
Campos (2003)	Brazil	The other	Cross-sectional	Single-center	AUA-SI	61	31/30	59.6	4.9	Low
Hobson (2003)	UK	European	Cross-sectional	Community-based	Questionnaire	123	78/45	75.1 (9.3)	7.8 (8.01)	Low
Hahn (2005)	Germany	European	Cross-sectional	Single-center	Questionnaire	20	8/12	64.3 (6.7)	6.3 (4.2)	Low
Winge (2006)	Denmark	European	Cohort	Single-center	Dan-PSS/IPSS	107	64/43	62.8	8	High
Wüllner (2007)	Germany	European	Cross-sectional	Multicenter	Questionnaire	3,414	2,076/1,338	66.07	9.02 (6.36)	Moderate
Verbaan (2007)	Netherlands	European	Cohort	Single-center	SCOPA-AUT	420	269/151	61.6 (11.5)	10.5 (6.5)	Moderate
Cheon (2008)	Korea	The Other	Cross-sectional	Single-center	NMSS	74	28/46	64.9 (8.6)	6.4 (6.1)	Low
Coelho (2010)	Spain	European	Cross-sectional	Multicenter	Questionnaire	50	23/27	74.1 (7.0)	17.94 (6.3)	Moderate
Mohammed (2010)	Egypt	The other	Cross-sectional	Single-center	IPSS	49	31/18	63.73 (7.21)	7.81 (3.27)	Low
Swaminath (2010)	India	The other	Cross-sectional	Single-center	Questionnaire	150	111/39	57.4 (12)	1.9 (1.63)	Low
Muller (2011)	Norway	European	Cohort	Single-center	Questionnaire	207	122/85	67.9 (42.3–88.1)	2.3 (1.8)	Low
Ragab (2011)	Ghana	The other	Cross-sectional	Single-center	IPSS	49	31/18	63.73 (7.21)	7.81 (3.27)	Low

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TABLE 1 (Continued)

First author and year	Country	Region	Study design	Study site	LUTS diagnosis standard	Sample size	Male/female	Mean age (years)	Disease duration (years)	Quality assessment
Soliman (2011)	Egypt	The other	Cross-sectional	Single-center	IPSS	25	43/67	60.8 (8.3)	4.5 (2.7)	Moderate
Uchiyama (2011)	Japan	The other	Cross-sectional	Single-center	questionnaire	30	30/0	66.7 (8.4)	1.97 (1.93)	Low
Yamamoto (2011)	Japan	The other	Cross-sectional	Single-center	questionnaire	61	38/23	67	3.2	Low
Crosiers (2012)	Belgium	European	Cross-sectional	Community-based	NMSS	215	83/132	67.1 (10.4)	7.3 (6.3)	Low
Bostantjopoulou (2013)	Greece	European	Cross-sectional	Single-center	NMSS/questionnaire	166	109/55	59.5 (9.3)	7.09 (5.31)	Moderate
Guo (2013)	China	The other	Cross-sectional	Single-center	NMSS	616	347/269	61.54 (10.98)	4.76 (4.18)	Low
Khoo (2013)	UK	European	Cohort	Single-center	NMSS	159	347/269	66.6 (10.3)	0.36	Moderate
Špica (2013)	Serbia	The other	Cross-sectional	Single-center	NMSS	208	140/58	60.7 (11.4)	9.04 (6.02)	Low
Vaughan (2013)	USA	North American	Cross-sectional	Single-center	IPSS/definition	60	39/21	63.4 (8.99)	–	Moderate
Weerkamp (2013)	Netherlands	European	Cross-sectional	Multicenter	NMSS	73	33/40	78.8	10.1	Moderate
Zhou (2013)	China	The other	Cross-sectional	Single-center	NMSS	230	136/94	67.7	4.7	Moderate
Tsujimura (2014)	Japan	The other	Cross-sectional	Single-center	OABSS	161	161/0	71.4 (8.2)	8.9 (5.1)	Low
Vongvaivanich (2014)	Thailand	The other	Cross-sectional	Single-center	NMSS	165	60/55	68.77 (11.59)	4.64 (3.85)	Low

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TABLE 1 (Continued)

First author and year	Country	Region	Study design	Study site	LUTS diagnosis standard	Sample size	Male/female	Mean age (years)	Disease duration (years)	Quality assessment
de Souza (2015)	India	The other	Cross-sectional	Single-center	definition	171	102/69	67.1	4.69	Moderate
M. Liu (2015)	Taiwan	The other	Cohort	Single-center	NMSS	210	101/70	66.1 (9.86)	6.11 (4.13)	Low
Z.Liu (2015)	China	The other	Cross-sectional	Single-center	Questionnaire	58	35/23	66.8 (48–80)	5.4 (1–12)	Low
Raven (2015)	India	The other	Cross-sectional	Single-center	NMSS	81	50/31	62.93 (10.93)	–	Moderate
Rana (2015)	Canada	European	Cross-sectional	Community-based	Definition	314	177/137	75 (10.58)	–	Moderate
Telarovic (2015)	Croatia	European	Cross-sectional	Single-center	Questionnaire	110	54/56	58 (11.49)	6 (4.72)	Low
Vale (2015)	Brazil	The other	Cross-sectional	Single-center	Questionnaire	30	17/13	67.3 (7.5)	–	High
M. Zhang (2015)	China	The other	Cross-sectional	Single-center	Definition	91	17/13	68.3	12.2	Low
Zis (2015)	UK	European	Cross-sectional	Multicenter	NMSS	234	149/85	67.74 (11.23)	3.21 (1.43)	Low
Benli (2016)	Turkey	European	Cross-sectional	Single-center	IPSS/OABSS	39	20/19	69.7 (7.4)	5.36 (3.5)	Low
Mekawichai (2016)	USA	North American	Cross-sectional	Single-center	NMSS	136	73/63	63.1 (10.2)	4.99	Moderate
Mito (2016)	Japan	The other	Cross-sectional	Single-center	OABSS	31	12/19	72 (6.7)	1.9 (1.8)	Low
Ou (2016)	China	The other	Cohort	Single-center	NMSS	117	68/49	60.1 (11.8)	3.9 (3.6)	High
Sakushima (2016)	Japan	The other	Cohort	Single-center	OABSS	97	40/57	71.5 (7.3)	7.63 (5.3)	Moderate

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TABLE 1 (Continued)

First author and year	Country	Region	Study design	Study site	LUTS diagnosis standard	Sample size	Male/female	Mean age (years)	Disease duration (years)	Quality assessment
Smith (2016)	UK	European	Cross-sectional	Single-center	Questionnaire	23	17/6	68.5 (50–85)	10.1	Low
Yamamoto (2016)	Japan	The other	Cross-sectional	Single-center	Questionnaire	218	134/84	66.2 (0.46)	3.2	Low
S. Zhang (2016)	China	The other	Cross-sectional	Single-center	NMSS	454	260/194	61.54 (10.98)	4.76 (4.18)	Moderate
Akkoç (2017)	Turkey	European	Cross-sectional	Multicenter	Dan-PSS	73	49/24	68 (35–87)	4 (1–19)	Moderate
Tkaczynska (2017)	Germany	European	Cross-sectional	Single-center	Questionnaire	94	60/34	71 (56–89)	6.4 (1.2–24.4)	Low
Radicati (2017)	Italy	European	Cross-sectional	Single-center	NMSS	100	60/40	69.19 (8.27)	3.83 (2.25)	Low
Yamamoto (2017)	Japan	The other	Cross-sectional	Single-center	Questionnaire	91	41/50	67.03 (0.76)	7.16 (0.54)	Low
Kim (2018)	Korea	The other	Cross-sectional	Single-center	IPSS	79	36/43	72.4 (8.0)	6.8 (4.4)	Moderate
Lee (2018)	Korea	The other	Cross-sectional	Single-center	SCOPA-AUT	163	93/70	68.9 (9.9)	1.0 (1.6)	Low
Mito (2018)	Japan	The other	Cross-sectional	Single-center	OABSS	31	12/19	71.2 (6.7)	2.4 (2.6)	Low
Mukhtar (2018)	Pakistan	The other	Cross-sectional	Single-center	NMSS	85	70/15	57.61 (10.64)	–	Moderate
Serra (2018)	Europe and Australia	Europe and Australia	Cross-sectional	Multicenter	SCOPA-AUT	423	275/148	61 (9.7)	–	Low
Valentino (2018)	Italy	European	Cross-sectional	Single-center	SCOPA-AUT	48	28/20	62.7 (10.6)	6.2 (4.2)	Moderate
Valldeoriola (2018)	Spain	European	Cohort	Multicenter	NMSS	378	215/163	70.2 (9.9)	6.1 (4.8)	Moderate
Aldaz (2019)	France	European	Cross-sectional	Single-center	NMSS	45	22/23	66.13 (9.95)	10.11 (6.7)	Low

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TABLE 1 (Continued)

First author and year	Country	Region	Study design	Study site	LUTS diagnosis standard	Sample size	Male/female	Mean age (years)	Disease duration (years)	Quality assessment
Fanciulli (2019)	Italy	European	Cross-sectional	Single-center	Questionnaire	70	–	–	–	Low
Irene (2019)	Romania	European	Cross-sectional	Multicenter	SCOPA-AUT	86	48/38	70.6	6.33	Low
Sanchez (2019)	Spain	European	Cross-sectional	Single-center	NMSS	120	88/32	63.33 (8.6)	8 (5–13)	Moderate
Shin (2019)	Korea	The other	Cross-sectional	Single-center	Questionnaire	112	55/57	68	7.6 (4.6)	Moderate
Stanković (2019)	Serbia	The other	Cross-sectional	Single-center	SCOPA-AUT	107	59/48	61.5 (9.6)	2.2	Moderate
Xu (2019)	China	The other	Cross-sectional	Single-center	OABSS	100	55/45	65.97 (8.247)	4 (2.7)	Moderate
Zong (2019)	China	The other	Cross-sectional	Single-center	AUA-SI/OABSS	416	307/109	61.2 (5.9)	7.7 (4.1)	Moderate
Martinez (2020)	Mexico	North American	Cross-sectional	Multicenter	SCOPA-AUT	414	274/140	61.1 (9.7)	0.56 (0.55)	Moderate
Nakahara (2020)	Japan	The other	Cross-sectional	Single-center	Definition	91	34/57	75 (67–80)	9 (5–13)	Low
Schrag (2020)	Europe	European	Cross-sectional	Multicenter	NMSS	692	373/319	76.1 (8.4)	15.4 (7.7)	Moderate
Tkaczynska (2020)	Germany	European	Cross-sectional	Single-center	Questionnaire	189	93/96	64.7 (7.9)	5.1 (3.8)	Low
Ayele (2021)	Ethiopia	The other	Cross-sectional	Multicenter	NMSS	123	89/34	62.9 (10.4)	4 (2–6)	Low
Lichter (2021)	USA	North American	Cross-sectional	Multicenter	NMSS	164	112/52	72.05 (9.91)	8.9 (5.98)	Moderate
Ojo (2021)	Nigeria	The other	Cross-sectional	Multicenter	NMSS	825	604/221	63.7 (10.1)	3	High
Tateno et al. (2021)	Japan	The other	Cross-sectional	Single-center	OABSS/IPSS/questionnaires	30	18/12	69.5	1.29	Low

IPSS, the International Prostate Symptom Score; AUA-SI, the American Urological Association Symptom Index; OABSS, the overactive bladder symptom score; NMSS, the Non-Motor Symptom Scale; SCOPA-AUT, Scale for Outcomes in Parkinson's Disease for Autonomic Symptoms; DAN-PSS, the Danish Prostate Symptom Score.

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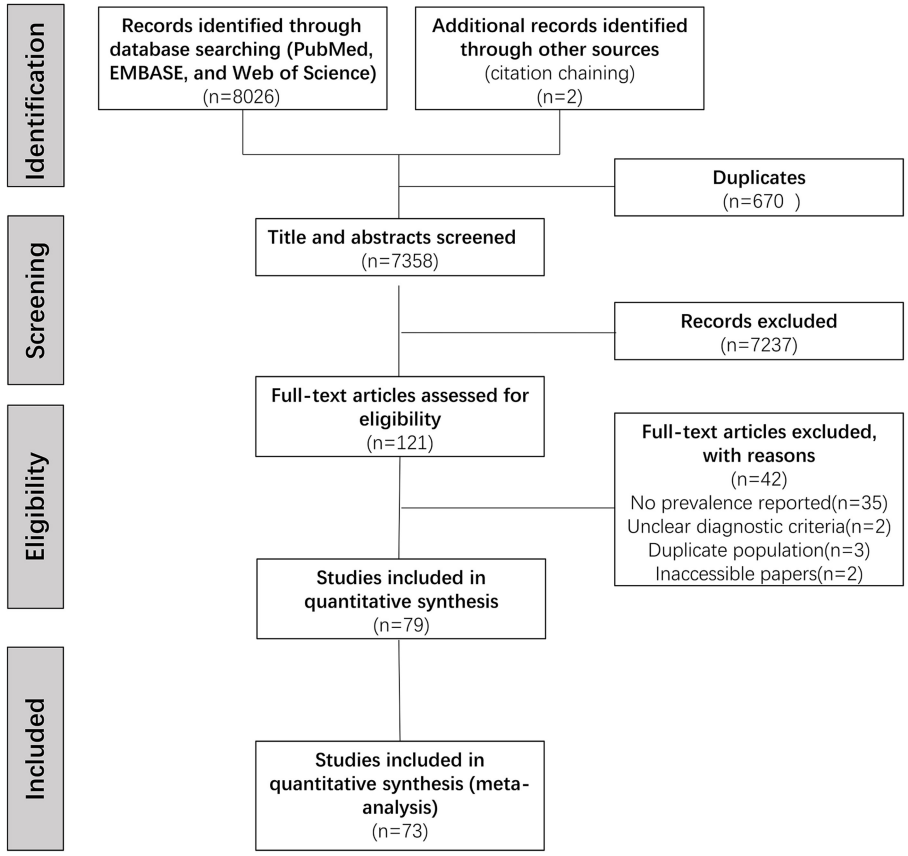

FIGURE 1
Study selection flowchart, performed according to the PRISMA 2020 guidelines.

(Supplementary Table 2). The procedure was shown flow chart in Figure 1.

Sample size ranged from 20 to 3,414. Average age of participants ranged from 57.4 to 76.1 years. The average disease duration of PD ranged from 0.36 to 17.94 years. Forty-seven studies used the scales, 19 used questionnaire, 4 used definitions, and 3 applied mixed methods. We classified 4 studies as high quality, 29 studies as moderate, and 40 studies as low. The results indicated that the overall quality of the included articles was relatively low. There were 65 cross-sectional studies and 8 cohort studies in the included research. The studies were conducted in 29 countries, 27 performed in Europe, 5 in North American, while others were undertaken in the other regions (n = 40). Table 1 shows the characteristics of included study.

Prevalence of LUTS in PD

The pooled prevalence of LUTS was 61% (95% CI 53–69; I^2 = 99%; 27 studies; n = 5,179; Figures 2A, 3).

For subgroup analyses, we found that H&Y stage, gender, and different diagnostic tools may be cause of heterogeneity related to the prevalence of LUTS (Table 2). The pooled prevalence of LUTS was 59% (95% CI 48–71; $I^2 = 68\%$; 3 studies; $n = 277$) in PD with H&Y stage < 3, whereas 70% (95% CI 52–88; $I^2 = 92\%$; 4 studies; $n = 194$) in PD with H&Y stage ≥ 3. The pooled prevalence of LUTS was 62% (95% CI 47–77; $I^2 = 96\%$; 6 studies; $n = 839$) in male PD patients, whereas 54% (95% CI 41–67; $I^2 = 78\%$; 5 studies; $n = 352$) in female PD patients.

Different diagnostic tools also influenced prevalence of LUTS. The pooled prevalence of LUTS based on definitions was 58% (95% CI 51–65; 2 studies; n = 201) with considerable heterogeneity (I^2 = 0%; p = 0.47). Using NMSS, the pooled prevalence of LUTS was 60% (95% CI 48–72; 10 studies; n = 2,172), also with considerable heterogeneity (I^2 = 98%; p < 0.01). Using IPSS, the pooled prevalence of LUTS was 39% (95% CI 11–67) in 1,331 PD patients reported by 3 studies, with considerable heterogeneity (I^2 = 94%; p < 0.01). Using SCOPA-AUT, the pooled prevalence of LUTS was 79% (95% CI 50– 100) estimated from 569 PD patients, with considerable heterogeneity of these 3 studies ($I^2 = 98\%$; $p < 0.01$). Using other questionnaires of LUTS diagnostic tools, the pooled prevalence

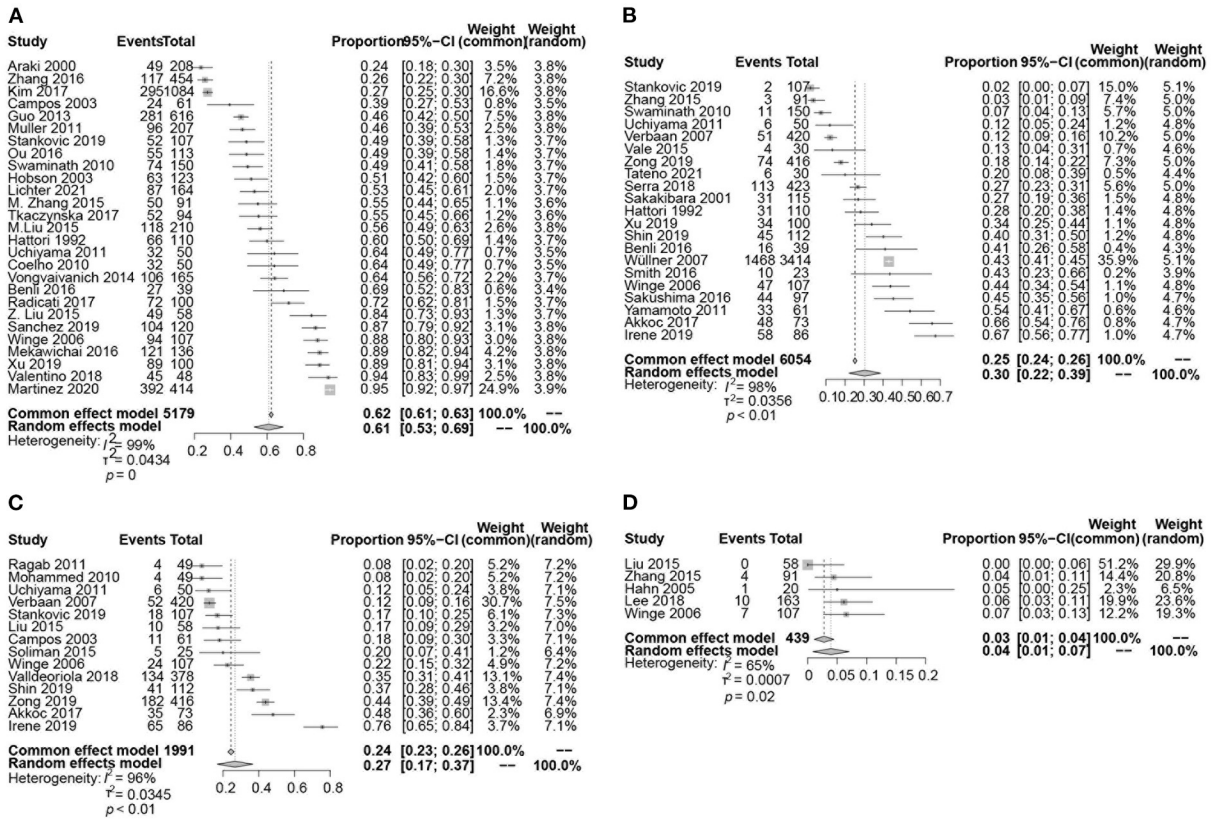

FIGURE 2
Forest plot showing the prevalence of LUTS **(A)**, urinary incontinence **(B)**, urinary retention **(C)**, and post-void residual (PVR) volume ≥ 100 ml **(D)** in PD patients.

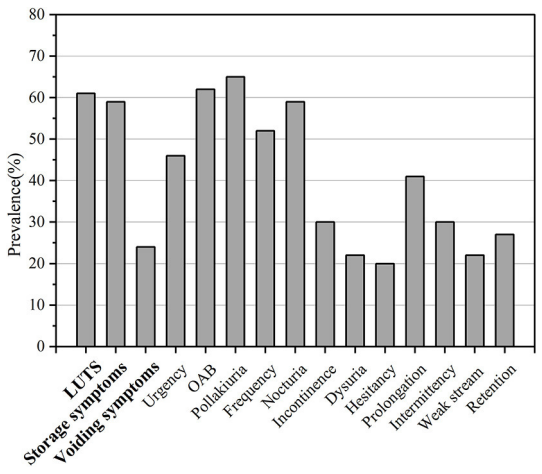

FIGURE 3
Frequency of LUTS or its subtypes in PD patients. The x-axis shows different kinds of LUTS while the y-axis shows the percentage.

of LUTS was 60% (95% CI 48–71) of 638 PD reported by 6 studies, with considerable heterogeneity (I^2 = 90%; p < 0.01).

The prevalence of LUTS was 89% using OABSS (n = 100), 39% using AUA-SI (n = 61), and 88% using Dan-PSS (n = 107), respectively, all from one study (Supplementary Figure S1; Supplementary Table 3).

By meta-regression analyses, region (p = 0.016) and number of PD patients (p = 0.031) were causes of heterogeneity related to the prevalence of LUTS, while the study site, quality assessment, age, and disease duration were not.

No significant publication bias was found by Begg's funnel plot (p = 0.695).

Prevalence of LUTS subtypes in PD

Storage symptoms

The pooled prevalence of storage symptoms was 59% (95% CI 44–73; 9 studies; 798 PD; I^2 = 98%; p < 0.01; Table 3; Figure 3; Supplementary Figure S2).

Incontinence

The pooled prevalence of urinary incontinence was 30% (95% CI 22–39; I^2 = 98%; p < 0.01; 21 studies; n = 6,054;

TABLE 2 Prevalence of LUTS or subtypes: results of the subgroup analysis.

	Subgroup prevalence, % (95% CI), *n* studies, *N* number, I^2											
	LUTS				Incontinence				Retention			
	Prevalence, % (95% CI)	*n*	*N*	I^2 (%)	Prevalence, % (95% CI)	*n*	*N*	I^2 (%)	Prevalence, % (95% CI)	*n*	*N*	I^2 (%)
Region												
North American	79 (54–100)	3	714	98	–	–	–	–	–	–	–	–
European	68 (57–79)	10	995	95	32 (18–46)	9	4,649	99	35 (16–54)	6	1,171	98
The other	52 (42–63)	14	3,470	98	29 (18–40)	12	1,405	96	21 (11–30)	8	820	94
	$p = 0.05$				$p = 0.75$				$p = 0.19$			
Methods												
Scales	62 (51–72)	19	4,340	99	34 (21–46)	11	1,898	98	28 (16–40)	11	1,771	97
Questionnaire	60 (48–71)	6	638	90	28 (14–42)	7	3,848	98	22 (7–37)	1	50	–
Definition	58 (51–65)	2	201	0	28 (20–38)	1	110	–	–	–	–	–
Urodynamic tests	–	–	–	–	21 (0–58)	2	203	98	27 (8–46)	2	170	88
	$p = 0.84$				$p = 0.86$				$p = 0.08$			
Disease severity												
H&Y stage < 3	59 (48–71)	3	277	68	20 (15–25)	3	256	0	16 (3–29)	2	240	76
H&Y stage ≥ 3	70 (52–88)	4	194	92	48 (24–71)	3	266	84	41 (7–75)	2	256	97
	$p = 0.33$				**$p = 0.03$**				$p = 0.19$			
Age(mean)												
<65	64 (50–78)	12	2,436	99	20 (11–29)	8	1,848	96	19 (10–27)	8	1,234	95
≥65	58 (49–67)	15	2,743	98	37 (26–48)	13	4,206	98	37 (19–56)	6	757	96
	$p = 0.47$				**$p = 0.02$**				$p = 0.07$			
Gender												
Male	62 (47–77)	6	839	96	31 (20–41)	7	2,579	87	21 (1–41)	4	414	95
Female	54 (41–67)	5	352	78	43 (25–62)	6	1,555	94	25 (3–47)	3	87	81
	$p = 0.44$				$p = 0.25$				$p = 0.78$			
Study site												
Single-center	60 (51–68)	24	4,592	98	29 (20–37)	19	5,545	98	22 (14–30)	12	1,527	94
Multicenter	80 (50–100)	2	464	95	47 (7–87)	2	509	98	55 (16–95)	2	464	98
Community-based	51 (42–60)	1	123	–	–	–	–	–	–	–	–	–
	$p = 0.12$				$p = 0.38$				$p = 0.10$			
Quality assessment												
High-moderate	58 (43–73)	12	3,175	100	27 (10–43)	7	1,243	97	28 (18–39)	7	1,526	96
Low	63 (55–71)	15	2,022	95	32 (23–42)	14	4,811	98	25 (7–43)	7	465	97
	$p = 0.55$				$p = 0.58$				$p = 0.76$			

Statistically significant values are reported in bold.

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TABLE 3 Prevalence of LUTS subtypes in PD.

	n studies	*N* number	Range	Prevalence (%), 95% CI	I^2 (p)	Egger's funnel plot for Publication bias	Trim and Fill
Storage symptoms	9	798	32–95	59 (44–73)	98 (<0.01)	–	–
Urgency	42	7,292	11–77	46 (41–51)	97 (<0.01)	$p = 0.097$	0
OAB	7	388	35–100	62 (44–80)	96 (<0.01)	–	–
Pollakiuria	2	177	47–83	65 (30–100)	96 (<0.01)	–	–
Frequency	27	4,591	21–87	52 (44–60)	97 (<0.01)	$p = 0.076$	0
Daytime-frequency	12	1,044	5–80	41 (29–53)	96 (<0.01)	$p < 0.001$	6
Nighttime-frequency	9	806	19–87	53 (37–70)	98 (<0.01)	–	–
Nocturia	40	7,784	21–95	59 (54–65)	97 (<0.01)	$p = 0.835$	0
Incontinence	21	6,054	2–67	30 (22–39)	98 (<0.01)	$p = 0.861$	0
Urge incontinence	13	1,422	7–66	32 (23–41)	94 (<0.01)	$p = 0.007$	6
Voiding symptoms	11	886	7–59	24 (14–33)	93 (<0.01)	$p = 0.027$	5
Dysuria	4	671	11–36	22 (11–34)	94 (<0.01)	–	–
Hesitancy	6	724	2–40	20 (7–32)	96 (<0.01)	–	–
Prolongation	3	184	12–72	41 (7–75)	97 (<0.01)	–	–
Intermittency	8	563	6–87	30 (9–51)	97 (<0.01)	–	–
Weak stream	8	494	2–83	22 (4–39)	95 (<0.01)	–	–
Retention	14	1,991	8–76	27 (17–37)	96 (<0.01)	$p = 0.492$	0
PVR > 100 ml	5	439	0–7	4 (1–7)	65 (0.02)	–	–

OAB, overactive bladder; PVR, post-void residual.

Figure 2B). The pooled prevalence of urge incontinence was 32% (95% CI 23–41; $I^2 = 94\%$; $p < 0.01$; 13 studies; $n = 1{,}422$).

Using urodynamic tests, the pooled prevalence of urinary incontinence was 21% (95% CI 0–58; 2 studies; $n = 203$), with significant heterogeneity ($I^2 = 98\%$; $p < 0.01$). Using clinical scales, the pooled prevalence of urinary incontinence was 34% (95% CI 21–46; 11 studies; $n = 1{,}898$), with significant heterogeneity ($I^2 = 98\%$; p <0.01); The pooled prevalence of urinary incontinence was 28% (95% CI 14–42; $I^2 = 98\%$; $p <$ 0.01; 7 studies; $n = 3{,}843$) using questionnaires and 28% using definition in one study.

The pooled prevalence of urinary incontinence was 20% (95% CI 15–25; $I^2 = 0\%$; 3 studies; $n = 256$) in PD with H&Y stage < 3, whereas 48% (95% CI 24–71; $I^2 = 84\%$; 3 studies; $n = 266$) in PD with H&Y stage ≥ 3. The pooled prevalence of urinary incontinence was 20% (95% CI 11–29; $I^2 = 96\%$; 8 studies; $n = 1{,}848$) in PD with age < 65 years, whereas 37% (95% CI 26–48; $I^2 = 98\%$; 13 studies; $n = 4{,}206$) in PD with age ≥ 65 years (Table 2).

By meta-regression analyses, age ($p = 0.017$) was a source of heterogeneity related to the prevalence of urinary incontinence, while the study site, quality assessment, region, number of PD patients, and disease duration were not.

OAB The pooled prevalence of OAB was 62% (95% CI 44–80; $I^2 = 96\%$; $p < 0.01$; 7 studies; $n = 388$) (Supplementary Figure S3).

Urinary urgency

The pooled prevalence of urgency was 46% (95% CI 41–51; $I^2 = 97\%$; $p < 0.01$; 46 studies; $n = 7{,}292$) (Supplementary Figure S4).

By subgroup analysis, we found that H&Y stage, sex, and different diagnostic tools may be factors affecting the prevalence of urgency. By meta-regression analyses, region ($p = 0.046$) was a source of heterogeneity, while the study site, quality assessment, age, number of PD patients, and disease duration were not.

Urinary frequency

The pooled prevalence of frequency was 52% (95% CI 44–60; $I^2 = 97\%$; $p < 0.01$; 27 studies; $n = 4{,}591$). The pooled prevalence of daytime frequency was 41% (95% CI 29–53; $I^2 = 96\%$; $p < 0.01$; 12 studies; $n = 1{,}044$). The pooled prevalence of nighttime frequency was 53% (95% CI 37–70; $I^2 = 98\%$; $p <$ 0.01; 9 studies; $n = 806$) (Supplementary Figure S5).

By meta-regression analyses, age ($p = 0.028$) was a cause of heterogeneity related to the prevalence of frequency, while study site, quality assessment, region, number of PD patients, and disease duration were not.

Nocturia

The pooled prevalence of nocturia was 59% (95% CI 54–65; $I^2 = 97\%$; $p < 0.01$; 40 studies; $n = 7{,}784$) (Supplementary Figure S6).

By subgroup analysis, we found that H&Y stage and different diagnostic tools may be factors affecting the prevalence of nocturia.

By meta-regression analyses, age ($p = 0.026$) was a cause of heterogeneity related to the prevalence of nocturia, while the study site, quality assessment, region, number of PD patients, and disease duration were not.

Pollakiuria

The pooled prevalence of pollakiuria was 65% (95% CI 30–100; $I^2 = 96\%$; $p < 0.01$; 2 studies; $n = 177$) (Supplementary Figure S7).

Voiding symptoms

The pooled prevalence of voiding symptoms was 24% (95% CI 14–33; 11 studies; $n = 886$; Figure 3). There was significant heterogeneity across these studies ($I^2 = 93\%$; $p < 0.01$) (Supplementary Figure S8). We did not find the factors such as study site, region, quality assessment, age, disease duration, number had effect on the heterogeneity of the prevalence of voiding symptoms by meta-regression.

Retention

A total of 14 studies investigated the prevalence of retention in 1,991 patients with PD ranging from 8 to 76% and yielding a pooled prevalence of 27% (95% CI 17–37; $I^2 = 96\%$; $p < 0.01$; Figure 2C). The pooled prevalence of PVR volume $\geq$ 100 ml was 4% (95% CI 1–7; $I^2 = 65\%$; $p = 0.02$; 5 studies; $n = 439$; Figure 2D).

Using the subgroup analysis, the pooled prevalence of urinary retention was 16% (95% CI 3–29; $I^2 = 76\%$; 2 studies; $n = 240$) in PD with H&Y stage < 3, whereas 41% (95% CI 7–75; $I^2 = 97\%$; 2 studies; $n = 256$) in PD with H&Y stage $\geq$ 3. The pooled prevalence of urinary retention was 19% (95% CI 10–27; $I^2 = 95\%$; 8 studies; $n = 1{,}234$) in PD with age < 65 years, whereas 37% (95% CI 19–56; $I^2 = 96\%$; 6 studies; $n = 757$) in PD with age $\geq$ 65 years (Table 2).

Using urodynamic tests, the pooled prevalence of retention was 27% (95% CI 8–46) estimated from 170 PD patients, 2 studies, with considerable heterogeneity ($I^2 = 88\%$; $p < 0.01$). Using clinical scales, the pooled prevalence of urinary incontinence was 28% (95% CI 16–40) estimated from 1,771 PD patients, 11 studies, with significant heterogeneity ($I^2 = 97\%$; $p < 0.01$); The pooled prevalence of urinary retention was 12% (95% CI 5–24; 1 study; $n = 50$) using questionnaires.

Further subgroup analysis showed that using urodynamic tests, the pooled prevalence of retention was 27% (95% CI 8–46) estimated from 170 PD patients, 2 studies, with considerable heterogeneity ($I^2 = 88\%$; $p < 0.01$). I prevalence of retention in PD was 12% (95% CI 5–24) using questionnaire and 35% (95% CI 31–41) using NMSS, respectively, all from one study. Utilizing IPSS, the estimated pooled prevalence of urinary retention was 21% (95% CI 7–35), the heterogeneity across these 5 studies in 303 PD patients was considerable ($I^2 = 90\%$; $p < 0.01$). Using SCOPA-AUT, the pooled prevalence of urinary retention was 35% (95% CI 0–75; $I^2 = 99\%$; $p < 0.01$; 3 studies; $n = 613$). Using AUA, the pooled prevalence of retention was 31% (95% CI 6–56) estimated from 477 PD patients, 2 studies, with considerable heterogeneity ($I^2 = 95\%$; $p < 0.01$) (Supplementary Figure S9; Supplementary Table 3).

Age was a source of heterogeneity related to the prevalence of retention ($p = 0.024$) by meta-regression.

Dysuria

The pooled prevalence of dysuria was 22% in PD (95% CI 11–34; $I^2 = 94\%$; $p < 0.01$; 4 studies; $n = 671$) (Supplementary Figure S10).

Hesitancy

The pooled prevalence of hesitancy was 20% in PD (95% CI 7–32; $I^2 = 96\%$; $p < 0.01$; 6 studies; $n = 724$) (Supplementary Figure S11).

Slow urinary stream/prolongation

The pooled prevalence of slow urinary stream was 41% in PD (95% CI 7–75; $I^2 = 97\%$; $p < 0.01$; 3 studies; $n = 184$) (Supplementary Figure S12).

Intermittency

The pooled prevalence of intermittency was 30% in PD (95% CI 9–51; $I^2 = 97\%$; $p < 0.01$; 8 studies; $n = 563$) (Supplementary Figure S13).

Spraying of urinary stream/weak stream of urine

The pooled prevalence of weak stream of urine was 22% in PD (95% CI 4–39; $I^2 = 95\%$; $p < 0.01$; 8 studies; $n = 494$) (Supplementary Figure S14).

Sensitivity analysis

This analysis validated the result's stability.

Discussion

This meta-analysis study indicates that LUTS and its subtypes present in a significant proportion of PD patients,

occurring at rates much higher than those found in the general population. The pooled prevalence was 61% (95% CI 53–69) for LUTS, 59% (44–73) for storage symptoms, and 24% (14–33) for voiding symptoms. We found that urinary incontinence and retention have higher prevalence in PD than previously assumed. The pooled prevalence was 30% (95% CI 22–39) for urinary incontinence, 27% (17–37) for retention and 4% (1–7) for post-void residual (PVR) volume $\geq$100 ml, respectively. Overall, we found considerable heterogeneity among studies. The wide variety of methods were used to assess LUTS and its subtypes. The prevalence of LUTS, urinary incontinence, and urinary retention was significantly associated with diagnostic methods.

LUTS in PD

LUTS were found in more than half of PD patients in this meta-analysis. Previous studies showed that LUTS was age-associated (Lee et al., 1998; Takahashi et al., 2022). However, it was found that patients with PD experienced significantly more LUTS than age-matched controls (10.8%) (Campos-Sousa et al., 2003). The prevalence of urinary incontinence (5.5%) in community-based elder people was lower than PD of the same age (Takahashi et al., 2022). Moreover, the prevalence of urinary retention (20.6%) in community-based men were also lower than PD in our meta-analysis (Lee et al., 1998).

However, the estimated prevalence rate of LUTS in PD was much lower than other neurodegenerative diseases, such as MSA (96%) (Sakakibara et al., 2000), progressive supranuclear palsy (PSP) (80%) (Xie et al., 2015), and dementia with Lewy bodies (91%) (Tateno et al., 2015). Previous study showed PD patients with LUTS demonstrated significantly lower dopamine transporter uptake in the striatum than patients without LUTS, according to single-photon emission computerized tomography (SPECT) imaging. LUTS were demonstrated to be correlated with putamen/caudate ratio and the degeneration of nigrostriatal dopaminergic neurons in PD patients with severe LUTS, suggesting that LUTS was associated with the degeneration of the caudate nucleus in patients with severe bladder dysfunction (Winge et al., 2005). Besides, there were potential associations between frontal executive dysfunction and LUTS or its subtypes in PD (Tkaczynska et al., 2017, 2020; Xu et al., 2019). PD dementia (PDD) and dementia with Lewy bodies were diseases with high prevalence of LUTS and characterized by cognitive impairment. Cortical alpha synuclein deposition and dysfunction of frontal cortex-basal ganglia dopaminergic circuit were hallmarks for those diseases. This further illustrated the role of frontal cortex in cognitive impairment and LUTS (Sakakibara et al., 2014). Unlike motor symptoms, LUTS were levodopa refractory symptoms, which suggest complex pathophysiological mechanisms beyond the dopaminergic system.

There were significant variations among the 27 studies evaluating LUTS prevalence in this meta-analysis. The pooled prevalence of LUTS was 59% in PD patients with mild H&Y score, whereas result for patients with severe H&Y score was 70% in this meta-analysis. This was in line with previous studies. However, the prevalence of LUTS did not differ significantly by gender, age, study site, and quality assessment of articles by subgroup analyses.

This discrepancy could be attributed to the following reasons. Firstly, the inclusion criteria of LUTS were variable among prevalence studies. LUTS can be divided into three categories including urinary storage symptoms, urinary voiding symptoms and post-voiding symptoms according to the international continence society (ICS) report (D'Ancona et al., 2019). Some studies assessing prevalence of LUTS included both storage and voiding symptoms, whereas others did not. Second, considerable heterogeneity mainly originated from the diagnostic methodological difference of LUTS. Studies assessed the prevalence of LUTS by definitions, urinary dysfunction questionnaires, clinical scales and urodynamic tests. The current meta revealed those validated ways, particularly those based on Dan-PSS and SCOPA-AUT, had higher prevalence estimates than non-validated methods, suggesting that such an approach had advantages of LUTS screening. Prevalence of LUTS assessed by IPSS scale was relatively low, suggesting that the prevalence of LUTS may be underestimated. However, some of clinical scales such as OAB-SS and AUA-SI were not validated in PD domain. OAB-SS only evaluated storage symptoms, such as urgency, frequency, nocturia and urge incontinence. NMSS only assessed urgency, frequency and nocturia, suggesting inaccuracy in diagnosing LUTS. It is quite necessary to unify the research methods. Thirdly, the heterogeneity may equally have arisen from confounders within gender, age, and disease severity. Sex and H&Y stage has been shown to be potential modifiers in our study, while age, study site and quality assessment were not.

Storage symptoms in PD

The pooled prevalence of storage symptoms was 59%. Polyuria was the most prevalent type of LUTS in the patients with PD (65%) followed by OAB (62%), nocturia (59%), frequency (52%), urgency (46%), and incontinence (30%). The results were almost the same with those reported previously (Sakakibara et al., 2001; Tateno et al., 2021). OAB was the second most prevalent storage symptom. It was urinary urgency, usually accompanied by increased daytime frequency and/or nocturia, with urinary incontinence or without according to the International Continence Society (ICS) report (D'Ancona et al., 2019).

Storage symptoms were frequent in PD because degeneration of dopaminergic neurons might lead to urination irritative symptoms in PD (Mito et al., 2018). Striatum

functionally controlled the urine storage. Disruption of D1-GABAergic direct striatal output pathway may cause bladder hyperactivity in PD which had been validated in SPECT and animal studies (Sakakibara et al., 2002; Yamamoto et al., 2005; Tateno et al., 2021). Besides, objective assessment with urodynamics showed that detrusor overactivity (DO) occur in 45–93% of PD patients, which was the most prevalent cause to OAB in PD (Sakakibara et al., 2001).

This meta-analysis revealed that the pooled prevalence of urinary incontinence was 30% in PD. Severe urinary incontinence in the first 5 year of disease is a red flag according to the MDS clinical diagnostic criteria for PD. However, a postmortem study identifying 11 cases confirmed the prevalence of urinary incontinence in PD was 82%, similar to that of MSA (87%) (Wenning et al., 1999). Although the sample size was relatively small in this study, the high prevalence rate challenged the prevailing view that urinary incontinence tended to be an exclusion criteria for PD diagnosis. However, the mean disease duration of collected cases was 16.58 years, much longer than the "5 year" indicated in the MDS diagnostic criteria. The finding suggested the possibility that disease duration might influence prevalence rate of urinary incontinence. Indeed, converging evidence pointed that urinary incontinence mainly occurs in the advanced stage of PD, ∼12–15.5 years after the onset of motor symptoms (Wenning et al., 1999; Uchiyama et al., 2011; Khoo et al., 2013), because urethral sphincter function was preserved in the early stages of PD (Stocchi et al., 1997). With the increasing age and disease duration, frontal lobe damage worsened accompanied with increase of alpha synuclein deposition, leading to cognitive dysfunction and LUTS (Tkaczynska et al., 2017). Among all the studies reporting urinary incontinence, the mean disease duration ranged from 1.29 to 12.2 years. One study showed that the frequency of urinary incontinence increased in the 1st (4.1%), 2nd (12%) and 3rd (15.1%) year of follow-up with mean 2.2 years of disease duration (Stanković et al., 2019). Another study showed that the prevalence of incontinence was 8.3, 30, 43.8, and 50% in PD patients with disease duration <2 years, 2–5 years, 5–10 years, and >10 years, respectively (Liu et al., 2015). The study with the largest sample size in this meta reported that incontinence prevalence was 43% in 3,414 PD patients with mean disease duration for 9 years (Wüllner et al., 2007). All of these suggested PD patients with longer disease duration may experience more urinary incontinence. H&Y score serves as a proxy for disease severity, which was closely correlated with disease duration. The pooled prevalence of urinary incontinence was 20% in PD patients with mild H&Y score, whereas 48% in patients with severe H&Y score in this meta-analysis. The consistent results indicate the severity of the disease should also be considered as a factor affecting prevalence in addition to the course of the disease.

Although severe urinary incontinence in the first 5 years of disease is a red flag of PD diagnosis, long-standing or small amount stress incontinence in women should be excluded. Unexplained urge incontinence was a supportive diagnostic criterion of MSA according to the newest MSA diagnostic (Wenning et al., 2022). These criteria suggest simply functional incontinence alone is not enough to distinguish Parkinson's disease from multisystem atrophy. Of the 21 included studies, there were 13 studies involving urge incontinence. The pooled prevalence of urge incontinence was 32% in PD patients in this meta-analysis. Few studies reported the types of urinary incontinence in PD. Therefore, we should pay attention to the types of urinary incontinence in the analysis of urinary incontinence.

The current study also demonstrated age and gender difference in prevalence of urinary in continence. The pooled prevalence of urinary incontinence was 20% in PD patients with age < 65 years, whereas 37% in PD with age ≥ 65 years in this meta-analysis. We found that the mean age was the source of heterogeneity related to the prevalence of urinary incontinence by meta-regression. The average age of 6,054 PD patients in the 21 studies varied from 57.4 to 75 years. In the study with youngest mean age, the prevalence of urinary incontinence was only 7% (Swaminath et al., 2010). These results suggested that age of PD patients contributed to the prevalence variance of urinary incontinence.

We found that the prevalence of urinary incontinence was 31% in the male PD patients, whereas 43% in female patients with PD. These results suggest that both age and gender influence the outcome of estimated prevalence.

The heterogeneity was equally possible to generate from other confounders. In the study of urinary incontinence, the diagnostic methods were not uniform, and the objective indicators are seldom applied. Using urodynamic tests, the pooled prevalence of urinary incontinence was 21%, which was less than that using scales, questionnaires, and definition. It implied that application of scales, questionnaires, and definition may have overestimated the prevalence of urinary incontinence. However, there are only two studies combining urodynamic tests. No studies in this meta-analysis reporting the urinary incontinence of pathological confirmed PD which indicated the scarcity of research in this meta. No significant publication bias of urinary incontinence was found.

The majority of studies were rated as low quality because of small sample sizes and other reason, although the results were robust in sensitivity analysis. Accounting for aforementioned factors, the prevalence results of urinary incontinence should be interpreted with caution.

Voiding symptoms in PD

The pooled prevalence of voiding symptoms was 24%. Prolongation was the most prevalent type of voiding symptoms in PD (41%) followed by the intermittency (30%), urinary

retention (27%), dysuria (22%), weak stream (22%), and hesitancy (20%). Some studies found that subclinical detrusor weakness during voiding may also occur in PD (Terayama et al., 2012; Sakakibara et al., 2016; Ogawa et al., 2017). These findings revealed that PD patients had both subclinical and clinical voiding symptoms. There was substantial heterogeneity in prevalence of voiding symptoms and its subtypes (intermittency, dysuria, weak stream, and hesitancy) among studies. The source of heterogeneity could be the limited number of articles, diverse diagnostic tools and different characteristic of participants.

Urinary retention is the most disabling voiding symptoms and often used to differentiate Parkinson's disease from multisystem atrophy. Previous studies have shown that the prevalence of urinary retention and large PVR was 43 and 14% in MSA (Ito et al., 2006; Lee et al., 2018) and PVR volume $\geq$ 100 ml might be an effective indicator to differentiate PD from MSA (Yamamoto et al., 2017; Lee et al., 2018; Wenning et al., 2022). Unexplained voiding difficulties with PVR volume $\geq$ 100 ml was one of the core clinical features to identify the clinically established MSA (Wenning et al., 2022). Furthermore, severe urinary retention in the first 5 year of disease is a red flag according to MDS clinical diagnostic criteria for PD.

Our study showed that the prevalence of retention was not low (27%) and the prevalence of large PVR ($\geq$100 ml) was even higher than 4% in PD. Using urodynamic tests, the pooled prevalence of retention was 27% (95% CI 8–46%). Of the overall 14 studies involved urinary retention, the mean disease duration ranged from 1.97 to 12.2 years. One study revealed that the duration of disease in patients without residual urine was lower than PD patients with residual urine (4.6 vs. 7.1 years) (Zhang and Zhang, 2015). Another finding of our study was that the pooled prevalence of urinary retention was 16% in PD with H&Y stage $<$ 3, whereas 41% in PD with H&Y stage $\geq$ 3. The pooled prevalence of urinary retention was 19% in PD patients with age $<$ 65 years, whereas 37% in PD by age $\geq$ 65 years. Furthermore, we found that age was the source of heterogeneity related to the prevalence of urinary retention by meta-regression. Of 1,991 PD in the 14 studies, the median age of participants varied from 59.6 to 70.6 years. One study revealed that the patients without residual urine were younger than patients with residual urine (67.5 vs. 70.1 years) (Zhang and Zhang, 2015). A higher weighted prevalence was calculated in older people than younger people (76 vs. 18%) (Campos-Sousa et al., 2003; Irene, 2019), suggesting PD patients with older age might be more likely to experience urinary retention. Overall, when distinguishing PD from MSA with urinary retention symptoms, we should be more cautious and consider relevant factors such as age, disease duration, and disease severity.

Diagnostic tools influenced prevalence results. The prevalence of urinary retention diagnosed using questionnaire was lower than that using clinical scales and urodynamic tests., There was difference in the prevalence identified by different scales. The pooled prevalence of urinary retention was 21% (using IPSS), 31% (using AUA) and 35% (using SCOPA-AUT), which was similar to 27% (using urodynamic tests).

No significant publication bias of urinary retention was found. The majority of articles evaluated with low-moderate quality were included due to the small number of research, but there was no significant difference between high-moderate and low quality of articles. Therefore, urinary retention requires attention and investigation in PD patients. Further research on mechanisms of urinary retention is also necessary.

Limitations

There were some limitations of the current study constituting an overall weaker level of evidence. First, present meta-analysis might be misleading given the variations in diagnostic tools of LUTS and its subtypes between studies. The heterogeneity of diagnostic tools limited the generalizability of the results. Second, only a small number of studies investigating urinary incontinence or retention were enrolled, which also indicated the scarcity of research on this area. Third, given the effect of geographical location, risk of bias, and population, high heterogeneity was found among the included studies. LUTS is associated with cognitive impairment. However, many articles did not distinguish subjects according to cognitive function. We could not conclude the definitive prevalence of LUTS and its subtypes in patients with PD. Fourth, the variables associate with LUTS, such as the UPDRS scores, laboratory indicators and related treatment methods were not included in most studies. Fifth, there was no studies reporting the prevalence of LUTS in pathological confirmed PD patients. Finally, the majority of studies were rated as low quality, although the results were robust in sensitivity analysis.

Conclusion

This meta-analysis showed that urinary incontinence and retention are not uncommon in PD. The high prevalence of LUTS confirmed the importance of LUTS as a notable non-motor characteristic of PD. LUTS were found in more than one-half of PD patients. It was evident that patients with PD experience significantly more urinary symptoms than age-matched controls. Overall, when distinguishing PD from MSA with urinary incontinence or retention, we should be more cautious and consider relevant factors such as age, disease duration, cognitive function and disease severity. The heterogeneity of diagnostic tools of LUTS and its subtypes limited the generalizability of the results. Therefore, future studies are warranted to address this issue by developing standardized diagnostic tools of LUTS,

and the utility of which needs to be validated in larger prospective trials.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author/s.

Author contributions

TF conceived and designed the study. F-FL performed the meta analysis and wrote the manuscript. F-FL and Y-SC prepared the draft and figures. All authors have read, revised, and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.977572/full#supplementary-material

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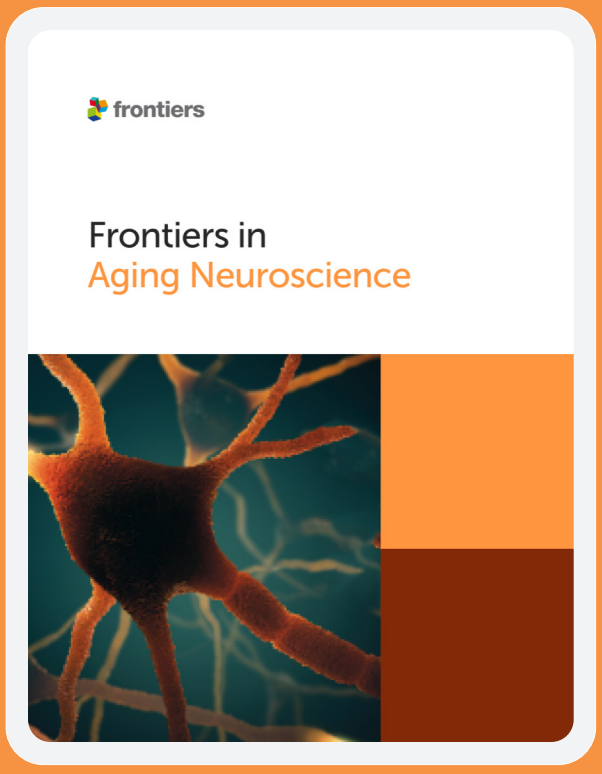

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