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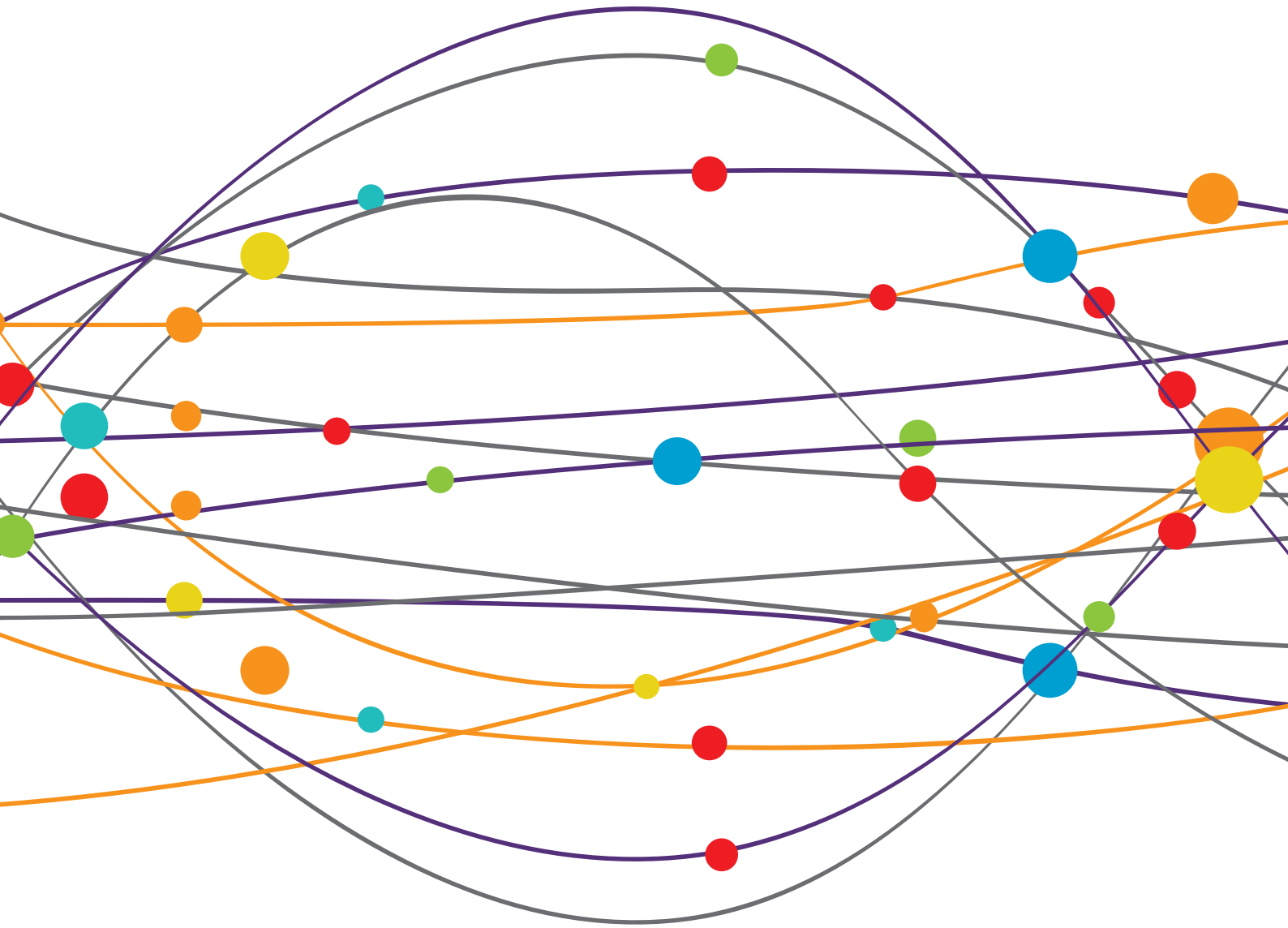

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MOVEMENT DISORDERS EDITOR'S PICK 2021

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CLINICAL TRIAL
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Repetitive Transcranial Magnetic Stimulation in Spinocerebellar Ataxia: A Pilot Randomized Controlled Trial

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Spinocerebellar ataxia (SCA) is a neurodegenerative disorder caused by dysfunction of the cerebellum and its connected neural networks. There is currently no cure for SCA and symptomatic treatment remains limited. We aimed here to examine the effects of a repetitive transcranial magnetic stimulation (rTMS) targeting the cerebellum on clinical impression, postural control and gait in patients with SCA. In this randomized, double-blinded and sham-controlled study, 20 individuals aged 18–75 years with SCA confirmed by genetic testing completed rTMS or sham intervention comprising 20 sessions of MRI-guided stimulation over the cerebellum. Baseline assessments included the Standard Ataxia Rating Assessment (SARA), the 9-hole peg test of manual dexterity, the Timed Up-and-Go (TUG) test, standing postural control with eyes-open and eyes-closed, and gait. Immediate (within 1-week) and 1-month follow-ups were completed. Intervention compliance was high (19 ± 2 of 20 sessions) and no rTMS-related adverse events were reported. rTMS, compared to sham, was associated with greater percent improvement in SARA total score from baseline to the 1-month follow-up ($p = 0.008$). Secondary analyses of individual SARA items revealed that rTMS improved performance within the "stance" sub-score only ($p = 0.002$). This functional change was accompanied by improvement to several objective metrics of postural sway during eyes-open and eyes-closed standing ($p < 0.008$). rTMS did not influence the 9-hole peg test, TUG, or gait kinematics. A 20-session rTMS intervention is safe and feasible for those with SCA. Additional research is warranted to confirm the observed longer-term benefits of this intervention on standing postural control.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier: NCT01975909

Keywords: rTMS, spinocerebellar ataxia, cerebellum, Standard Ataxia Rating Assessment, standing postural control

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INTRODUCTION

Autosomal dominant spinocerebellar ataxia (SCA) is associated with degeneration of the cerebellum and its efferent and/or afferent cerebello-thalamocortical tracts (1, 2). Patient with SCA often present with a host of motor symptoms, including deficits to the control of both standing posture and gait (3–5). Such deficits are progressive in nature and greatly increase one's risk of falling (6, 7) and losing functional independence (8). There is currently no cure for SCA and attempts to improve the clinical symptoms of ataxia have been largely unsuccessful and/or

short-lasting (9). There is thus an urgent need to develop novel therapeutic interventions for this vulnerable population.

Dysfunction in the cerebellar region and its connected neural networks is thought to be the proximal root cause of movement disorder in patients with SCA (1, 2, 10). Therapeutic strategies aimed at functional improvement of the cerebellum may thus lead to significant clinical benefit within this vulnerable population. Repetitive transcranial magnetic stimulation (rTMS) enables non-invasive modulation of cortical excitability (11). rTMS targeting cerebellar structures is capable of inducing long-lasting changes in the excitability of cerebello-thalamo-cortical pathways (12–14). Shiga et al. (15) reported that as compared to a sham intervention, 21 daily sessions of rTMS targeting the cerebellum improved performance in several short clinical tests of gait and posture, when tested immediately after the intervention was completed, in a cohort of patients with spinocerebellar degeneration. Still, the longer-term effects of rTMS on the clinical impression of symptom severity, as well as the biomechanical control of gait and standing posture, have not been established. We therefore conducted a small, yet well-controlled trial to assess the effects of a four-week, 20-session rTMS intervention targeting the cerebellum, as guided by individual brain anatomy using structural MRI, on the clinical severity of SCA and the control of standing posture and gait using quantitative kinematic assessments, in patients with SCA as confirmed by genetic testing.

METHODS

Trial Design

A parallel-group, randomized controlled trial was conducted (NCT01975909). Enrolled participants completed baseline assessments and a structural brain MRI. They were then assigned to receive the rTMS or sham intervention via permuted block randomization with stratification by sex. rTMS was administered by study personnel uninvolved in other study procedures. Participants and the study staff who assessed outcomes were blinded to intervention arm. Immediate (i.e., within 1 week of intervention completion) and 1-month follow-up assessments were completed.

Trial Registration

This study was registered prospectively at https://clinicaltrials.gov/ (NCT01975909).

Participants

Participants were recruited between 2013 and 2015 from the Neurogenetics Clinic and Movement Disorders Center at the Beth Israel Deaconess Medical Center (BIDMC), local ataxia support organizations, the National Ataxia Foundation and clinicaltrials.gov.

Inclusion criteria included SCA confirmed by genetic testing, age 18–75, the ability to ambulate without assistance from another person (canes/walkers allowed), a score >3 on the "gait" subsection of the Scale for the Assessment and Rating of Ataxia (SARA) (16), a negative pregnancy test and stable medications. Exclusion criteria were unstable neurological illness or concomitant medical condition (i.e., stroke, arthritis, etc.), clinically-significant abnormalities on screening (e.g., basic lab work or EKG abnormalities), concurrent participation in another clinical study, history of substance abuse, untreated depression, dementia, psychiatric illness, subjects who were wheelchair bound, Mini Mental Status Exam score <24, legal incapacity or limited legal capacity. TMS and MRI-specific exclusions included metal in the head, history of neurosurgical procedures, ferromagnetic bioimplants, metallic paint, history of seizure disorder, claustrophobia, current usage of buproprion or other medications that may increase risk of TMS-induced seizures.

We screened 110 individuals. Seventy-nine were ineligible and 11 were uninterested (**Figure 1**). The remaining 20 completed baseline testing. Ten were randomized to the rTMS intervention (women = 8; SCA type 3 = 8; mean ± SD age = 53 ± 9 years; height = 164 ± 10 cm; body mass = 71 ± 13 kg) and ten to sham (women = 8; SCA type 3 = 6; age = 49 ± 4 years; height = 161 ± 6 cm; body mass = 67 ± 13 kg). All 20 participants were naïve to TMS and completed the intervention and all study assessments.

Intervention

The rTMS intervention comprised 20 sessions over 4 consecutive weeks. A Magstim 200 (UK) and 14 cm circular coil delivered stimuli at 100% of maximal stimulator output intensity with the coil centered over three regions: the inion, 4 cm lateral to the left of the inion, 4 cm lateral to the right of the inion. Participants were asked to lay their head down on a pillow placed on a table in front of them, and the handle of the TMS coil was held facing upwards. Structural MRIs were used to locate and mark each region for rTMS and neuronavigation using Brainsight® (Rogue Resolutions, Cardiff, Wales) ensured that all stimuli for a given region within and across daily sessions targeted the same cerebellar regions. For each region, five pulses separated by 6 s were delivered counter-clockwise, followed by five pulses delivered clockwise, for a total of 10 pulses per region and session, and a total of 30 pulses per session (15). For sham intervention, the same parameters and procedures were used except the coil was angled 90 degrees from the scalp, inducing non-measurable changes of the excitability in cerebellum (17).

Ethics

This study was carried out in accordance with the recommendations of the BIDMC Institutional Review Board with written informed consent from all subjects. All participants gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the BIDMC Institutional Review Board.

Assessments

Assessments were conducted at the Harvard-Catalyst Clinical Research Center at the BIDMC at approximately the same time of day. Screening included health history, neurological exam, the Mini Mental State Examination and the SARA. A nurse recorded medications, resting EKG, vital signs, height and body mass. Hematology, pregnancy testing (if applicable), renal and liver panels were completed. A study physician reviewed screening

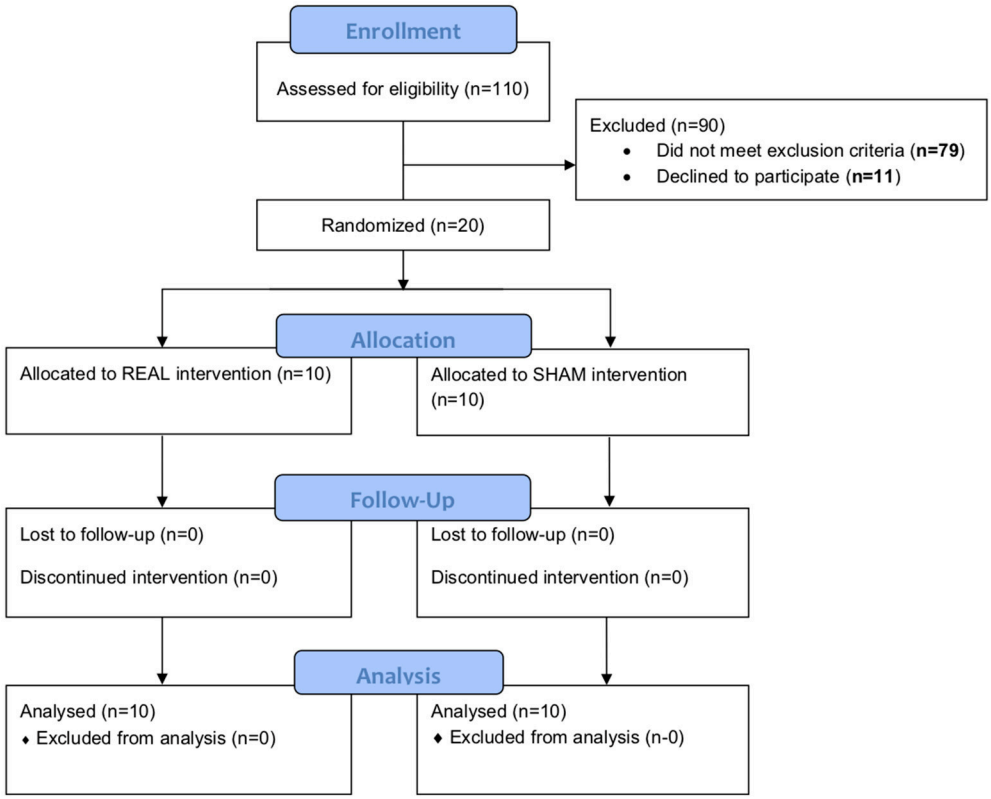

FIGURE 1 | Study CONSORT diagram. One hundred and ten individuals were screened. Seventy-nine were ineligible and 11 were uninterested. The remaining 20 completed baseline testing. Ten were randomized to the rTMS intervention and ten to sham. All of them completed the intervention and both follow-ups.

data to determine eligibility. The SARA, nine-hole peg test, Timed Up-and-Go (TUG) and biomechanical assessments of standing posture and gait were measured at baseline and at both follow-ups. Assistive devices were allowed on all tests except standing posture.

Scale for the Assessment and Rating of Ataxia (SARA)

The clinical severity of SCA was measured using the valid and reliable SARA scoring scale (16). This scale consists of eight items related to gait, stance, sitting, speech, finger-chase test, nose-finger test, fast alternating movements, and heel-shin test.

9-Hole Peg Test

The peg test was used to assess fine motor control hand and manual dexterity (18). Participants were asked to remove the pegs from the holes, one by one, and then replace them back into the container. The time to complete the test was recorded, with longer times reflecting worse performance.

Timed Up-and-Go Test (TUG)

The TUG test was used to assess functional mobility (19). The time taken to stand from a chair, walk forward three meters, turn around, walk back, and return to a seated position was recorded.

Assessment of Standing Posture and Gait

Standing postural control and gait were assessed using standard procedures. Postural control was assessed by measuring postural sway (i.e., center of pressure) fluctuations (240 Hz) during standing on a stationary force platform (AMTI, Watertown, MA). Participants were asked to stand barefoot on the platform and complete two 30-s trials under both eyes-open and eyes-closed conditions. Trial order was randomized. Tissue paper was placed on the force platform and foot placement of each participant was outlined prior to the first trial. This outline was then used throughout all future assessments and trials to ensure consistent foot placement over time. Participants were instructed to "stand as still as possible" prior to each trial. For eyes-open trials, participants were further instructed to visually focus on a target "X" placed on the wall approximately 3-m in front of them at eye-level.

Gait was assessed by measuring the kinematics of walking using the wireless Mobility Lab® system (APDM, Seattle WA) during a 90-s walk. Participants were instructed to walk at their normal, preferred paced. The use of assistive device (e.g.,

cane) was allowed and if it was used, the same device was used throughout the study.

Study Outcomes

The primary outcome of this study was the SARA total score. Secondary outcomes included performance within clinical functional tests (9-hole peg test, TUG) and metrics related to standing postural control and gait. Standing postural control metrics were chosen based upon their sensitivity to change in SCA severity (3) and included average sway speed (i.e., center-of-pressure path length divided by trial duration) and area (i.e., the area of a confidence ellipse enclosing 95% of the center-of-pressure trajectory) during both eyes-open and eyes-closed conditions. Gait metrics included average walking speed, stride time variability (i.e., the coefficient of variation about the mean between consecutive heel strikes of the right foot) and double support time (i.e., the average percentage of each stride time spent with both feet on ground), as each has been linked to SCA severity and related functional decline (4, 5).

Statistical Analysis

Analyses were performed using JMP Pro 12 (SAS Institute, Cary, NC). Descriptive statistics summarized group demographics and outcomes. Potential between-group differences in baseline characteristics were tested with Student's *t*-tests or chi-square tests. Primary analyses examined the effects of rTMS on primary and secondary outcomes using two-way repeated-measures ANOVAs. As groups differed in several measures of functional performance at baseline, dependent variables were *the percent change in each outcome from baseline to each follow-up visit*. Model effects included follow-up time (within-subject: one-week, one-month), group (between-subject: rTMS, sham), and their interaction. Models were completed with and without adjustments for age, sex, and intervention compliance. Two secondary analyses were complete based upon the observed effects of rTMS intervention on SARA performance. First, as a potential placebo effect was observed in SARA total score at the one-week follow-up, a one-way repeated-measures ANOVA was completed to determine the between-subject effect of group on the percent change in SARA total score *only* from baseline to the 1-month follow-up visit. Second, similar two-way models as described above were completed to examine the effects of intervention on each of the nine SARA items. Significance level for all statistical tests within this pilot study was set to $p < 0.05$. Effect sizes of significant models was measured using Cohen's d and the partial eta square metric (η^2).

Sample size considerations: To our knowledge, this was the first pilot study to systematically test the effects of MRI-guided cerebellar rTMS on the SARA and other functional and biomechanics outcomes over a 1-month follow-up period in patients with genetically-confirmed SCA. While the primary objective of this study was to provide the data needed to appropriately power more definitive trials in the future, we conducted a priori sample size calculations based upon Shiga et al. (15). That study reported the immediate after-effects of a non-MRI-guided, 21-day cerebellar rTMS intervention on 10-m walking speed in 74 patients with suspected SCA. The rTMS group decreased their 10-m walk time (from 14.3 ± 1.8 to 9.9 ± 0.7 s, mean ± SD) significantly more than those receiving the sham treatment (from 13.7 ± 1.2 to 13.6 ± 1.2 s). We estimated that a sample size of 20 would provide over 80% power to detect a similar effect size, after adjusting for three covariates.

RESULTS

The demographic, SCA and health characteristics of each participant are listed in **Table 1**. The groups receiving rTMS and sham intervention had similar age, height and body mass. At baseline, the rTMS group, as compared to the sham group, exhibited lower SARA scores ($p = 0.01$), faster 9-hole peg test time ($p = 0.03$) and faster postural sway speed during eyes-open standing ($p = 0.01$) (**Table 2**). No other between-group baseline differences were observed. Baseline functional outcomes did not differ by sex ($p > 0.56$) and were not significantly correlated with participant age ($p > 0.33$) or BMI ($p > 0.40$). Intervention compliance was high (19 ± 2 of 20 sessions) and similar between groups. The rTMS and sham interventions were well-tolerated and no unexpected side effects or adverse events were reported.

Primary and secondary outcomes are presented by intervention group in **Table 2**. A two-way, repeated-measures ANOVA revealed a trend toward a main effect of group for SARA total score ($F = 2.0$, $p = 0.16$, Cohen's d = 0.5, $\eta^2 = 0.06$). As can be observed in **Figure 2A**, both groups exhibited relatively large percent reductions (i.e., improvements) in this outcome from baseline to the immediate follow-up. Secondary analyses omitting the one-week follow-up assessment revealed that the rTMS intervention, as compared to sham, induced a greater percent decrease in SARA total scores from baseline to the 1-month follow-up ($F = 9.3$, $p = 0.008$, Cohen's d = 1.3, $\eta^2 = 0.38$) (**Figure 2A**). This effect was independent of age, sex, and intervention compliance. Spurred by this observation, the effects of intervention on the percent change from baseline to the 1-month follow-up in each of the nine SARA sub-scores were also examined. rTMS, compared to sham, improved performance within the "stance" sub-score ($F = 10.4$, $p = 0.002$, Cohen's d = 0.9; $\eta^2 = 0.24$) (**Figure 2B**). No other item-specific changes within the SARA exam were observed between groups.

The beneficial effect of rTMS on the clinical assessment of posture was corroborated by improvements within several objective kinematic metrics of standing postural sway. As compared to sham, those who completed the rTMS intervention exhibited a greater percent decrease in postural sway speed when standing with eyes open (group effect: $F = 9.5$, $p = 0.004$, Cohen's d = 1.0; $\eta^2 = 0.28$) and eyes closed (group effect: $F = 11.4$, $p = 0.002$, Cohen's d = 1.0, $\eta^2 = 0.26$) (**Figures 2C,D**). rTMS, as compared to sham, also reduced sway area during eyes-closed standing ($F = 8.5$, $p = 0.007$, Cohen's d = 0.9, $\eta^2 = 0.17$). Each of these observed group effects were independent of age, sex, and intervention compliance. No main effects of time, nor group by time interactions, were observed for any metric.

Participant-level results of intervention on postural sway speed are presented in **Figure 3**. Seven of ten participants who received rTMS exhibited slower sway speed (i.e., better standing

TABLE 1 | Demographics and baseline functional performance of each participant.

Participant ID	Age (years)	Sex	BMI	SCA-type	rTMS	SARA	9-hole peg test (s)	TUG time (s)
P001	61	Male	29.3	3	Real	22.5	78.0	65.0
P002	52	Female	21.7	3	Sham	13.5	39.5	22.1
P003	45	Female	25.8	3	Sham	24	45.8	68.8
P004	45	Female	21.9	3	Sham	15.5	51.7	49.7
P005	47	Male	27.1	1	Sham	13.5	41.8	20.4
P006	38	Male	19.8	3	Real	10	34.8	42.6
P007	47	Male	24.5	3	Sham	24.5	76.9	119.9
P008	52	Male	27.3	3	Real	14	37.2	24.4
P009	44	Female	28.3	3	Real	11	32.4	21.2
P010	54	Female	18.1	6	Sham	19.5	61.0	51.3
P011	65	Female	30.2	3	Real	14.5	40.5	39.3
P012	47	Female	29.3	2	Sham	19	55.2	33.5
P013	54	Female	28.7	3	Real	16.5	28.6	36.0
P014	56	Female	32.9	8	Sham	12	29.9	31.3
P015	46	Female	22.5	3	Sham	16	37.9	35.3
P016	49	Female	20.1	3	Real	15	30.4	24.9
P017	49	Female	32.3	14	Sham	13.5	18.3	20.6
P018	50	Male	25.6	6	Real	13	27.7	18.8
P019	47	Female	22.9	3	Real	11	21.1	14.3
P020	68	Female	25.6	6	Real	18.5	32.4	18.8

TABLE 2 | SCA severity, postural control and gait outcomes (mean ± SD) at baseline and follow-up.

	rTMS			Sham		
	Baseline	Follow up (immediate)	Follow-up (1 month)	Baseline	Follow up (immediate)	Follow-up (1 month)
SARA (total)	13.7 ± 2.8	10.7 ± 3.4	9.8 ± 2.6	17.1 ± 4.5	12.9 ± 4.9	14.7 ± 4.0
TUG	26.7 ± 10.1	22.5 ± 7.8	20.2 ± 5.6	32.0 ± 16.6	30.5 ± 11.6	31.5 ± 13.9
9-hole peg test (sec)	31.6 ± 5.7	30.6 ± 5.6	30.8 ± 5.4	42.3 ± 13.1	42.3 ± 14.3	41.0 ± 13.5
POSTURAL SWAY						
Eyes-open						
Speed (mm/s)	41.2 ± 15.9	27.0 ± 10.2	24.8 ± 10.7	21.5 ± 9.0	20.3 ± 8.9	22.9 ± 7.1
Area (mm^2)	639 ± 376	467 ± 228	436 ± 173	602 ± 636	479 ± 303	674 ± 249
Eyes-closed						
Speed (mm/s)	81.4 ± 46.5	51.0 ± 24.3	55.0 ± 30.0	61.0 ± 17.1	63.0 ± 40.4	68.4 ± 40.3
Area (mm^2)	1992 ± 1337	824 ± 404	1303 ± 839	868 ± 780	1156 ± 938	1517 ± 1382
GAIT						
Speed (m/s)	1.0 ± 0.3	1.0 ± 0.4	1.0 ± 0.4	0.9 ± 0.4	0.9 ± 0.4	0.9 ± 0.4
Variability (%)	7.0 ± 3.3	5.9 ± 2.3	5.6 ± 3.8	8.0 ± 5.8	7.8 ± 6.2	8.3 ± 5.9
Double support (%)	27.9 ± 6.9	25.2 ± 7.8	24.2 ± 11.3	27.6 ± 15.2	30.0 ± 14.2	31.2 ± 14.5

SCA, spinocerebellar ataxia; rTMS, repetitive transcranial direct current stimulation; SARA, scale for the assessment and rating of ataxia; TUG, Timed Up-and-Go.

postural control) during eyes-open standing at the 1-month follow-up assessment as compared to baseline. In contrast, only two sham participants demonstrated such improvements. Nine rTMS participants exhibited slower sway speed during eyes-closed standing 1 month following the intervention, as compared to only three sham participants.

rTMS did not have significant effects on performance within the 9-hole peg test, the TUG test of mobility, or on metrics of gait performance (i.e., walking speed, stride time variability, double support time).

DISCUSSION

This randomized sham-controlled pilot clinical trial provided preliminary evidence that cerebellar rTMS intervention is safe and feasible for patients with SCA who vary considerably in

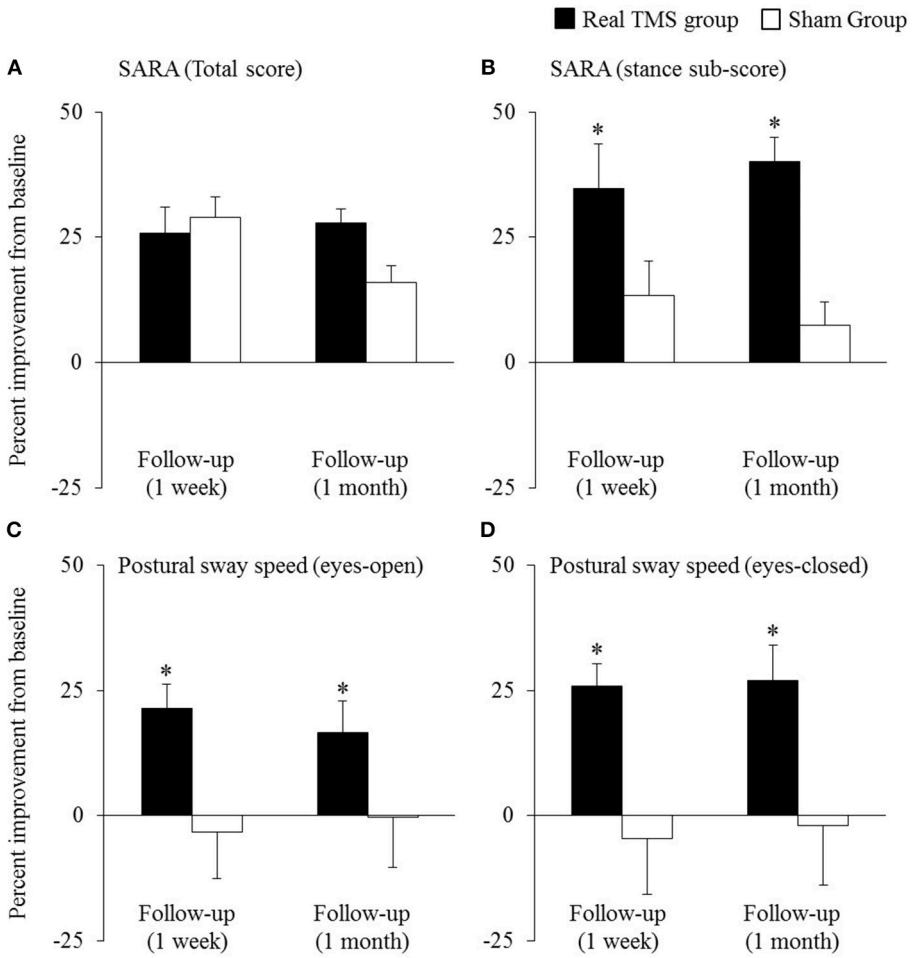

FIGURE 2 | The effects of cerebellar rTMS on the clinical assessment of ataxia and standing postural control (mean ± SE). Both groups exhibited relatively-large improvement (i.e., percent reduction) in SARA total score from baseline to the immediate follow-up **(A)**. The rTMS group, however, exhibited greater percent improvement in this outcome, as compared to the sham group, at the 1-month follow-up. Secondary analyses revealed that compared to sham, the rTMS group exhibited greater improvements specifically within the SARA "stance" sub-score **(B)**, yet no other SARA item (outcomes not pictured). Moreover, rTMS improved postural sway speed (i.e., sway speed decreased) during both eyes-open **(C)** and eyes-closed **(D)** standing. *Indicates significant main effects of group within two-way, repeated-measures ANCOVAs adjusted for age, sex, and intervention compliance.

age and disease progression. Participants who completed the 4-week rTMS intervention exhibited significant improvements to both clinical and kinematic outcomes of standing postural control, over a 1-month follow-up period, as compared to those who received the sham intervention. rTMS did not influence manual dexterity, functional mobility or gait kinematics during the follow-up period. Still, the potential benefits of rTMS on posture warrant larger, more definitive trials to establish the effects of MRI-guided cerebellar rTMS on postural control, as well as activities of daily living and quality of life in SCA.

rTMS intervention improved the clinical impression of standing posture (i.e., the SARA "stance" sub-score), along with multiple metrics of postural sway when standing with eyes open and closed. In each case, the value of Cohen's d was greater than 0.8, indicating a large effect size of intervention on this important functional domain. These results are supported by Shiga et al. (15), who reported that an rTMS intervention targeting the cerebellum improved the capacity to stand with different bases of support (i.e., foot placements), when tested soon after completion of the intervention. The current results further suggest that rTMS may enhance standing balance by improving the capacity to control (i.e., minimize) the speed and magnitude of postural sway, and that such improvements may persist for at least 1 month. Future large-scale studies are thus needed to confirm these results, and, to establish the mechanisms through which cerebellar stimulation may improve standing posture. The regulation of posture when standing relies upon a complex control system that utilizes and integrates multiple sources of sensory input within spinal and supra-spinal networks to generate both automatic and volitional corrective muscular actions (20–22). Neuroimaging studies indicate that the task of standing, as compared to sitting, activates a distributed

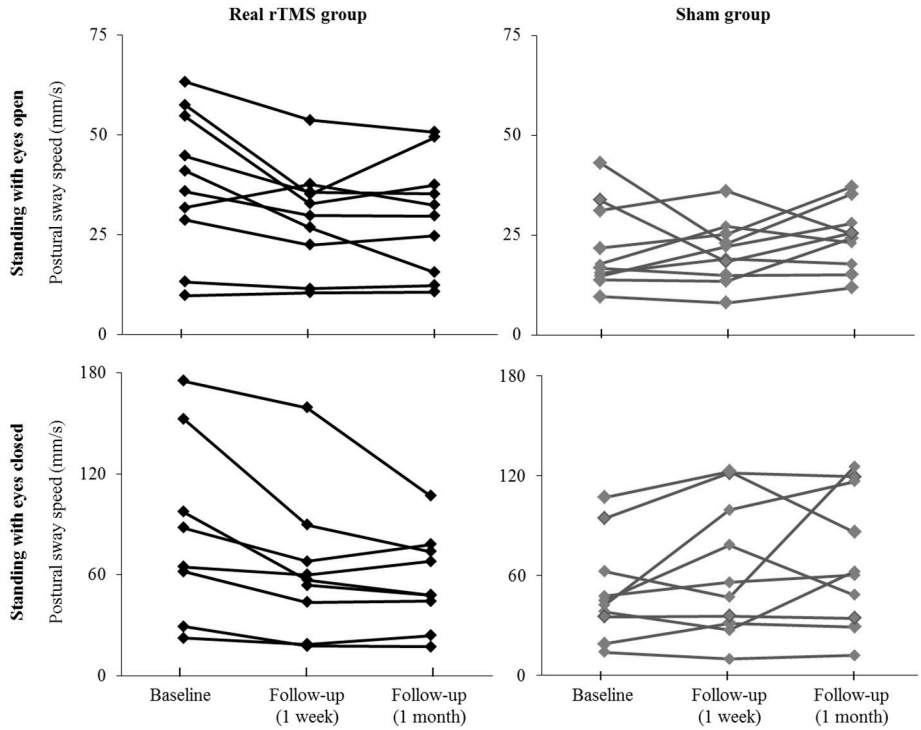

FIGURE 3 | Individual effects of cerebellar rTMS intervention on standing postural control. The average speed of standing postural sway fluctuations for each participant when standing with eyes open **(top)** and eyes closed **(bottom)** at baseline and at the immediate and 1-month follow-up assessments. Two participants with extremely high sway speed values at baseline (out of the mean ± 2XS.D.) were excluded from the figure for better visual effects.

network of brain regions including the cerebellum, primary motor cortex, and other regions involved in sensory integration and/or cognitive-motor control (22, 23). SCA causes postural disturbances, at least in part, by impairing functional activation of cerebellar Purkinje cells. This in turn inhibits cortical motor activation via a complex neural pathway involving the dentate nucleus (10). Several recent studies have demonstrated that cerebellar rTMS is capable of facilitating motor cortical activation via modulation of Purkinje cell excitability (24–26). Future studies employing paired-pulse TMS methodology are thus needed to examine the effects of cerebellar rTMS intervention on motor cortex excitability, and its links to postural control, in those individuals with SCA.

Both the rTMS and sham groups demonstrated improved performance in the SARA total score at the immediate follow-up assessment, as compared to baseline (**Figure 2A**). However, within the sham group, this initial improvement was attenuated at the 1-month follow-up assessment. This short-lasting positive effect of rTMS in the sham group was only present for the SARA total score, and may have reflected a placebo effect of the intervention. Such placebo effects have been reported in several other studies in those with cerebellar degeneration (27, 28). For example, in a multi-center study of patients with cerebellar ataxia, ondansetron and placebo interventions resulted in a similar improvement in performance on the International Cooperative Ataxia Rating Scale (ICARS) over the follow-up period (27). Additionally, in the current study, a proportion of participants within each intervention arm stayed within the hospital's Clinical Research Center for the duration of the study and thus received ongoing clinical research staff supervision that was likely greater than their normal care. The possibility that this increased attention confounded the initial effects of intervention, together with the potential for a significant placebo effect within this population, are thus important factors to consider when designing future trials of rTMS or other therapies in SCA.

While the effects of rTMS on outcomes related to postural control were independent of age, sex, and intervention compliance, the small sample size of this pilot study limited our capacity to statistically control for additional, important covariates such as SCA subtype. Considerable between-subject variance in symptom severity and functional status was present, and despite random assignment to intervention arm, the rTMS group exhibited better functional performance at baseline. Nevertheless, the observations that the rTMS intervention was well-attended and not associated with any unexpected side effects or adverse events, together with preliminary evidence of improved postural control, highlight the potential for this form of non-invasive brain stimulation to serve as a therapeutic rehabilitative strategy for SCA.

AUTHOR CONTRIBUTIONS

BM, PG, and AP-L designed the study. BM, PG, SW, and PD-P collected the data. BM, PD-P, and JZ analyzed the data and performed statistical analyses. BM, PG, PD-P, JZ, and AP-L drafted the manuscript. All authors contributed to and approved the final version.

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Conflict of Interest Statement: AP-L serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Neuroelectrics, Axilum Robotics, Magstim Inc., and Neosync; and is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation with electroencephalography and magnetic resonance imaging.

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REM-Sleep Behavior Disorder in Patients With Essential Tremor: What Is Its Clinical Significance?

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Objective: REM sleep behavior disorder (RBD) is an important risk factor for the dementia development and for the deterioration of autonomic functions in patients with Parkinson's Disease. RBD has also been reported in patients with Essential Tremor (ET). However, its clinical significance in ET remains still unknown. We aimed to investigate clinical, neuropsychological and cardiac autonomic scintigraphic differences between ET patients with and without RBD.

Methods: To assess RBD symptoms, RBD Single-Question has been administered in a cohort of 55 patients with a clinical diagnosis of ET. Patients with clinical RBD underwent polysomnography (PSG) confirmation. All patients completed a battery of neuropsychological assessment of memory, executive function, attention, language, and visuospatial function. Cardiac MIBG scintigraphy was performed in order to measure the cardiac autonomic innervation.

Results: Ten ET patients (18%) had a PSG-confirmed RBD (ET^{RBD+}). Compared to ET patients without RBD (ET^{RBD-}), significantly reduced scores on memory domain tests such as Rey auditory verbal learning test immediate recall ($p = 0.015$) and Rey auditory verbal learning test delayed recall ($p = 0.004$) and phonemic fluency test ($p = 0.028$) were present in ET^{RBD+}. By contrast, no other significant clinical difference has emerged from the comparison between two ET groups. Similarly, ET^{RBD+} patients have cardiac MIBG tracer uptake in the normal value range as occurred in those with ET^{RBD-}.

Conclusions: This study improves the knowledge on clinical significance of RBD symptoms in ET patients. Our preliminary findings demonstrate that presence of RBD in ET is associated with neurocognitive impairment, but not with cardiac autonomic dysfunction. Further longitudinal studies are needed to investigate whether ET patients with RBD will develop a frank dementia over the time.

Keywords: essential tremor, REM sleep behavior disorder, cognitive impairment, cardiac MIBG scintigraphy, DAT-SPECT imaging

INTRODUCTION

Essential tremor (ET) is one of the most common neurological disease among adults. Traditionally, it is defined by a core of clinical motor symptoms characterized by kinetic/postural tremor affecting hand, head, or other parts of the body without other clinical signs of parkinsonism (1). ET, however, is a phenotypically heterogeneous disease including both motor and non-motor symptoms (NMS). In recent years, a growing body of literature has been focused on the prevalence of some of the NMS in ET, such as cognitive impairment, depression, olfactory deficits and sleep disturbances as REM sleep behavior disorder (RBD) (2). Among the NMS, depression and RBD are reported to have higher prevalence in ET patients than in the general population (3).

Interestingly, the NMS especially RBD, found in patients with ET are known to be prodromal conversion symptoms of α-Synuclepathaties such as Parkinson's Disease (PD). However, the presence of RBD in PD patients identifies a specific clinical subtype of the disease. Indeed, in PD, RBD is associated with older age, longer disease duration (4), rigid-akinetic form of PD and more severe parkinsonian symptoms (5). These patients may also have increased autonomic dysfunction and higher risk to develop dementia and therefore worse prognosis (6). Moreover, in PD-RBD patients, cardiac Meta-iodobenzylguanidine (MIBG) uptake, a measure of cardiac autonomic innervation was lower compared to that observed in PD patients without RBD (7).

As occurs in PD, the presence of RBD in ET could identify a specific clinical phenotype. However, the literature regarding the clinical, neuropsychological and scintigraphic features in ET patients associated with RBD is poor or absent. Indeed, only a study (8) has assessed the difference regarding demographics tremor characteristics, and prevalence of autonomic symptoms between ET patients with and without RBD. These authors found that ET patients with RBD had higher scores on Scales for outcomes in Parkinson's Disease-Autonomic Questionnaire (SCOPA-AUT) than those without RBD suggesting that RBD in ET is associated with dysautonomic symptoms. Few reports have investigated cardiac MIBG uptake in patients with ET (9, 10) a no evidence has been reported in ET patients associated with RBD. Finally, no study has previously evaluated neurocognitive performance in ET patients associated RBD.

Thus, several questions regarding the clinical significance of RBD in ET patients are still answered.

Considering that RBD is an important risk factor for the dementia development and for the deterioration of autonomic functions, we aimed to investigate clinical, neuropsychological, and cardiac autonomic scintigraphic differences between ET patients with and without RBD.

METHODS

Study Population

This cross sectional study included 55 consecutive patients with a clinical diagnosis of ET made by a movement disorders specialist (MS) according to established criteria (11). Each patient underwent an accurate clinical history and a neurological evaluation. Fahn-Tolosa was used for clinical evaluation of ET patients. We assess the presence of clinical symptoms suggestive of REM-sleep behavior disorder (RBD) by using of RBD Single-Question (RBD1Q), a single "yes-no" question querying the classic dream-enactment behavior of RBD (12). According to RBD1Q results, we divided the ET patients into two groups, ET with RBD (ET^{RBD+}) and ET without RBD (ET^{RBD-}). ET^{RBD+} underwent polysomnographic (PSG) recording. Patients were diagnosed with RBD using polysomnography according to the International Classification of Sleep Disorders, version 3 (ICSD-3) criteria (13). The following cognitive functions were assessed in all enrolled ET patients: (i) global cognitive status (Mini Mental State Examination [MMSE](14); ii) executive functions (Frontal Assessment Battery [FAB] (15), Modified Card Sorting Test [MCST] (16); iii) attention (Digit Span Forward) (17); (iv) verbal short and long term memory, episodic memory (Rey Auditory-Verbal Learning Test Immediate [RAVLT-I] and Delayed [RAVLT-D] (18); v) visuo-spatial functions (Judgments of Line Orientation test form V [JLO-V])(19); (vi) phonemic verbal fluency (Controlled Oral Word Association Test [COWAT] (20); vii) language comprehension [Token Test] (21); (viii) anxiety and depression [Hamilton Rating Scale Anxiety [HRS-A] (22) and Beck Depression Inventory II [BDI-II] (23), respectively]. Before inclusion in the study, written informed consent was obtained from all participants and the study was approved by the institutional review board according to the Helsinki Declaration.

Imaging Protocol

Imaging protocol included brain MRI, DAT-SPECT, and cardiac MIBG scintigaphy. Participants underwent MRI on a 3T GE system (GE Healthcare, Rahway, NJ). The MRI protocol included: 3-dimensional T1-weighted volumetric spoiled gradient echo (GE), T2-weighted fast spin echo, and T2-weighted fluid attenuated inversion recovery sequences. In all ET patients (with and without RBD) we performed DAT-SPECT (24) to support the clinical diagnosis of ET and Cardiac MIBG scintigraphy to measure the cardiac autonomic innervation thus investigating cardiac autonomic function (24).

Cardiac MIBG Scintigraphy

Cardiac MIBG scintigraphy was performed at rest. A total of 111 MBq of I-MIBG (Amersham, Eindhoven, NL) was injected intravenously in 60 s. Data were collected using a dual-head gamma camera (Axis, Picker, Bedford, OH) at 10 min (early image) and 240 min (delayed image) after the isotope injection. Static planar imaging and regional MIBG uptake were obtained with 128 matrix. Only planar images in thoracic anterior view were used for quantitative evaluation. Regions of interest (ROI) were drawn around the whole heart and mediastinum of the anterior image, and tracer uptake was measured within each ROI to calculate the heart/mediastinum (H/M) ratio.

The H/M ratio from early and delayed images was evaluated in all subjects, and values were considered abnormal if they were more than three standard deviations (SDs) below the respective control mean. Regional MIBG uptake was assessed using single-photon emission tomography (SPECT) on the three

axes displayed (short axis, vertical long axis, and horizontal long axis). Images were evaluated by an investigator who was blinded to the patients' diagnosis (24).

Statistical Analysis

Differences in distribution of sex, familiarity, and clinical features between ET^{RBD+} and ET^{RBD-} groups were assessed by means of the Fisher's exact test. The Shapiro-Wilk test was used to check for normality before performing comparisons between continuous variables. When comparing ET^{RBD+} and ET^{RBD-} groups, the Mann–Whitney *U*-test was used to assess differences in age at evaluation, education, disease duration, age at ET onset, Fahn-Tolosa score, part A and part B of Fahn-Tolosa scale, MMSE, MCST, JLO-V, Digit Span scores, HRS-A and BDI-II, while DAT-SPECT, MIBG, Token test, RAVLT I.R., RAVLT D.R., FAB, and phonemic fluency test scores were compared by means of Student's *t*-test. In order to control for false discovery rate, Benjamini–Hochberg correction was applied to *p*-values when comparing neuropsychological variables. All tests were two-tailed and the α level was set at $p < 0.05$. Statistical analysis was performed with R Statistical Software (R for Unix/Linux, version 3.1.1, The R Foundation for Statistical Computing, 2014).

RESULTS

Demographics and Clinical Characteristics

According to RBD1Q results, 10 ET patients (18%) were positive (ET^{RBD+}) whereas 45 were negative (ET^{RBD-}). All ET^{RBD+} patients received a PSG-confirmation of clinical suspicion of RBD. Sleep and dream-related behaviors reported by the history and documented during video PSG were present in our ET^{RBD+} patients and included violent complex motor behaviors both disruptive (60%) to the bed partner (punching, kicking etc..) and injurious (40%) (biting an arm, leaping from the bed etc..). Indeed, ET^{RBD+} patients showed clear abnormal REM sleep behaviors during PSG recording. Interestingly, in three patients with ET^{RBD+}, RBD preceded the onset of motor symptoms by several years while in 1 patient was contemporary. Demographic and clinical characteristics of all participants are summarized in **Table 1**. Patients groups were not statistically different regarding sex, onset, family history, disease duration, and severity of disease. Patients with ET^{RBD+} had a slight higher prevalence of head tremor, kinetic tremor, and lower of asymmetrical postural tremor than those with ET^{RBD-}. NMS such as hyposmia and constipation did not show significant difference between two groups (**Table 1**).

Neurological Test Scores

The neurological test scores and results of analyses are presented in **Table 1**. Neuropsychological assessment revealed that ET^{RBD+} had significant lower scores concerning verbal short and long term memory tests such as RAVLT I.R. ($p = 0.015$) and RAVLT D.R. ($p = 0.004$) and phonemic verbal fluency as COWAT ($p = 0.028$) than ET^{RBD-}. Moreover, RAVLT D.R results resist multiple comparisons ($p = 0.038$) with a trend for RAVLT I.R. ($p = 0.068$) and COWAT ($p = 0.084$). Of note, although ET^{RBD+} patients had slightly higher MMSE scores than ET^{RBD-} patients, they showed overall cognitive performances lower for FAB, MCST, JLO-V, and Token Test compared to those of patients with ET^{RBD-}. Finally, concerning anxiety and depression, ET^{RBD+} patients did not significant differ from those with ET^{RBD-} (**Table 1**).

Imaging Results

MRI scan indicated no signal abnormalities in any ET patient. **Table 2** shows the comparisons among scintigraphic data of patients affected by ET^{RBD+} and ET^{RBD-}. No ET patient had a damage of nigrostriatal presynaptic dopaminergic system on DAT-SPECT imaging thus supporting the clinical diagnosis of ET in both groups. In addition, DAT-SPECT tracer uptake did not differ in qualitative and quantitative (Putamen/Occ ratio) analyses between two groups (**Table 2**). Similarly, cardiac MIBG uptake (Heart/Mediastinum ratio) both early and delayed images, showed no difference between the two groups (**Table 2**). Finally, DAT-SPECT and cardiac MIBG uptakes were both within the normal range values in the two groups of ET (**Table 2**). **Figure 1** shows the qualitative images of DAT-SPECT and cardiac MIBG tracers in a patient with ET^{RBD+} (**Figures 1A,B**) and in patient with ET^{RBD-}(**Figures 1C,D**).

DISCUSSION

Our goal was to investigate for the first time clinical, neuropsychological, and scintigraphic differences between ET patients with and without RBD. In particular, we found that neurocognitive function, including verbal short and delayed memory and phonemic verbal fluency, was worse in ET patients with RBD than in those without RBD. By contrast, no significant clinical and scintigraphic difference emerged between the two ET groups. Our preliminary findings suggest that ET patients with RBD could be a subgroup of ET at higher risk to develop a frank dementia over the time.

The presence of RBD in ET patients raises some clinical questions. First, RBD and dementia development. Accumulating evidence suggest that RBD is an important determinant of cognitive impairment in patients with α-Synucleinopathies as Parkinson's Disease (PD). Most studies have reported that the prevalence of MCI was significantly higher (until 70%) in PD with RBD than in those without RBD (25). A longitudinal study (26) also found that all PD-RBD with MCI on baseline (48%) developed a frank dementia on 4 years' follow-up evaluation thus suggesting that RBD may be a valid phenoconversion biomarker of dementia.

In our study we questioned whether in ET patients, as occurs in those with PD, RBD could be associated with neurocognitive dysfunctions. We found that all ET patients with PSG-confirmed RBD (18%) (ET^{RBD+}) had worse cognitive abilities than those of ET patients without RBD (ET^{RBD-}). In particular, although ET^{RBD+} patients had slightly higher MMSE scores, they showed overall executive and visuospatial functions, attention and language comprehension worse than those with ET^{RBD-}. Of note, compared to ET^{RBD-} significantly lower performances on RAVLT I.R. (Immediate) and RAVLT D.R. (Delayed) were present in ET^{RBD+}. The RAVLT is a powerful neuropsychological

TABLE 1 | Comparisons among demographic, clinical, and neuropsychological data of patients affected by ET, ET^{RBD+}, and ET^{RBD-}.

Variables	All ET group (*N* = 55)	ET^{RBD+} (*N* = 10)	ET^{RBD-} (*N* = 45)	*p*-value
DEMOGRAPHICS				
Sex: No. men/women	25/30	7/3	21/24	0.75[a]
Age, years (mean ± SD)	65.0 ± 10.1	62.9 ± 12.2	65.5 ± 9.6	0.52[b]
Education, years (mean ± SD)	9.4 ± 4.5	10.8 ± 2.5	9.1 ± 4.8	0.12[b]
FAMILY HISTORY				
Postural/kinetic tremor, n. (%)	30 (54.5)	5 (50)	25 (56.8)	0.74[a]
DISEASE FEATURES				
Disease duration, years (mean ± SD)	13.9 ± 14.3	10.1 ± 9.2	14.7 ± 15.7	1[b]
Age at onset of ET, years (mean ± SD)	51.5 ± 16.3	52.7 ± 13.3	51.3 ± 17.0	0.99[b]
Head tremor, n. (%)	27 (45.4)	6 (60)	19 (42.2)	0.48[a]
Kinetic tremor, n. (%)	41 (74.5)	9 (90)	32 (71.1)	0.1[a]
Asymmetric postural tremor, n. (%)	31 (53.5)	4 (40)	26 (57.8)	0.34[a]
Fahn-Tolosa score (mean ± SD)	22.3 ± 12.9	17.7 ± 7.1	23.8 ± 14.3	0.11[c]
Part A of Fahn-Tolosa scale (mean ± SD)	7.3 ± 3.1	6.7 ± 2.3	7.5 ± 3.4	0.72[b]
Postural tremor, n. (%)	55 (100)	10 (100)	45 (100)	1[a]
Part B of Fahn-Tolosa scale (mean ± SD)	9.4 ± 7.3	8.0 ± 5.2	10.0 ± 8.1	0.39[c]
Hyposmia/Anosmia, n. (%)	4 (7.2)	1 (10)	3 (6.6)	1[a]
Constipation, n. (%)	10 (18.1)	1 (10)	9 (22.5)	0.71[a]
NEUROPSYCHOLOGICAL BATTERY				
MMSE mean ± SD (range)	25.7 ± 3.7	26.3 ± 2.5	25.6 ± 3.9	0.78[b]
Token test mean ± SD (range)	30.1 ± 2.5	29.4 ± 2.2	30.2 ± 2.6	0.46[c]
RAVLT I.R. mean ± SD (range)	36.2 ± 10.4	29.0 ± 6.6	37.7 ± 10.5	0.015[c]
RAVLT D.R. mean ± SD (range)	6.9 ± 2.8	4.2 ± 2.0	7.4 ± 2.6	0.004[c]
MCST mean ± SD (range)	4.7 ± 2.2	4.7 ± 2.3	4.7 ± 2.3	0.93[b]
FAB (mean ± SD)	14.1 ± 1.8	13.7 ± 1.2	14.1 ± 1.9	0.55[c]
JLO-V (mean ± SD)	22.2 ± 5.5	21.5 ± 5.6	22.4 ± 5.6	0.76[b]
Digit Span (mean ± SD)	5.3 ± 3.2	4.6 ± 0.2	5.4 ± 3.4	0.50[b]
COWAT (mean ± SD)	24.0 ± 5.9	20.3 ± 3.8	24.7 ± 6.0	0.028[c]
HRS-A (mean ± SD)	10.8 ± 4.5	11.2 ± 4.8	10.6 ± 4.6	0.95[b]
BDI-II (mean ± SD)	11.9 ± 5.9	12.6 ± 6.0	11.6 ± 6.1	0.77[b]

ET^{RBD+} group, Essential tremor (ET) patients with Rem sleep behavior disorder (RBD); ET^{RBD-}, ET patients without RBD;
MMSE, Mini Mental State Evaluation (n.v. ≥ 24); Range, ET^{RBD+} group, (25–29); ET^{RBD-} group, (25–30);
Token test (n.v. ≥ 26.25); Range, ET^{RBD+} group, (27–31); ET^{RBD-} group, (27.75–34);
RAVLT R.I., Rey auditory verbal learning test immediate recall (n.v. ≥ 28.53); Range, ET^{RBD+} group, (21.8–33.2); ET^{RBD-} group, (29–67.3);
RAVLT R.D., Rey auditory verbal learning test delayed recall (n.v. ≥ 4.69); Range, ET^{RBD+} group, (1.6–6.9); ET^{RBD-} group, (5–11.8);
MCST, Modified card sorting test (n.v. ≥ 3); Range, ET^{RBD+} group, (3–6); ET^{RBD-} group, (3–6);
FAB, frontal assessment battery (n.v. ≥ 13.4); Range, ET^{RBD+} group, (12.2–14.4); ET^{RBD-} group, (12.9–18);
JLO-V, Judgment of Line Orientation-Form V (n.v. ≥ 20); Range, ET^{RBD+} group, (21–26); ET^{RBD-} group, (21–27);
Digit span (n.v. ≥ 3.5); Range, ET^{RBD+} group, (4.25–4.75); ET^{RBD-} group, (3.75–6.25);
COWAT, Controlled Oral Word Association Test (n.v: ≥ 17.35); Range, ET^{RBD+} group, (17.3–25.5); ET^{RBD-} group, (17.9–38.2);
HRS-A, Hamilton Rating Scale Anxiety (n.v. > 14); Range, ET^{RBD+} group, (8–14); ET^{RBD-} group, (9–18);
BDI-II, Beck Depression Inventory II (n.v: > 13); Range, ET^{RBD+} group, (8–18); ET^{RBD-} group, (8–19);
n.v., normal values in Italian Population.
[a]Fisher's exact test.
[b]Mann–Whitney U-test (Wilcoxon rank sum test).
[c]Two-sample t-test. P-values are calculated ET^{RBD+} group vs. ET^{RBD-} group.
Multiple comparison tests: RAVLT D.R p = 0.038; RAVLT R I.R., p = 0.068; COWAT, p = 0.084.

tool widely used for the cognitive assessment in dementia and pre-dementia conditions. It is sensitive to verbal memory deficits caused by several neurological diseases (27, 28). Different scores may be derived from RAVLT, but RAVLT Immediate and Delayed are the most used scores in the clinical setting since they highlight different aspects of episodic memory (learning and delayed memory, respectively). Thus, RAVLT is considered an effective marker for discriminating normally aging subjects from MCI and Alzheimer's disease (AD) patients (29). Decreased RAVLT performance found in our ET^{RBD+} could reflect a deficit verbal episodic memory. Of note, in our study RAVLT Delayed resisted multiple comparisons thus suggesting that our results are solid.

TABLE 2 | Comparisons among scintigraphic data of patients affected by ET, ET^{RBD+}, and ET^{RBD-}.

Variables	All ET group ($N = 55$)	ET^{RBD+} group ($N = 10$)	ET^{RBD-} group ($N = 45$)	*p*-value[a]
DAT-SPECT IMAGING*				
Putamen R/Occ ratio	4.41 ± 0.61	4.64 ± 0.45	4.36 ± 0.6	0.12[a]
Putamen L/Occ ratio	4.38 ± 0.62	4.62 ± 0.60	4.34 ± 0.61	0.20[a]
CARDIAC MIBG SCINTIGRAPHY**				
Heart/Mediastinum ratio early image	1.72 ± 0.25	1.81 ± 0.3	1.70 ± 0.24	0.28[a]
Heart/Mediastinum ratio delayed image	1.73 ± 0.28	1.84 ± 0.33	1.69 ± 0.25	0.21[a]

*ET^{RBD+} group, Essential tremor (ET) patients with Rem sleep behavior disorder (RBD); ET^{RBD-}, ET patients without RBD; DAT-SPECT, Dopamine transporter ligand (DAT)-Single photon emission computerized tomography (SPECT); Putamen/Occ ratio [Putamen specific (Left/Right) to non-specific (occipital) area]; MIBG, Cardiac I^{-123} Metaiodobenzylguanidine (MIBG) scintigraphy; *Normal values: Put/Cau right (mean ± SD, 4.29 ± 0.34) and Put/Cau left (mean ± SD, 4.19 ± 0.39). **Normal values: Heart/Mediastinum ratio: mean ± SD, 1.94 ± 0.18 early; 2.02 ± 0.19 delayed.*

[a]*Two-sample t-test. P-values are calculated ET^{RBD+} group vs. ET^{RBD-} group.*

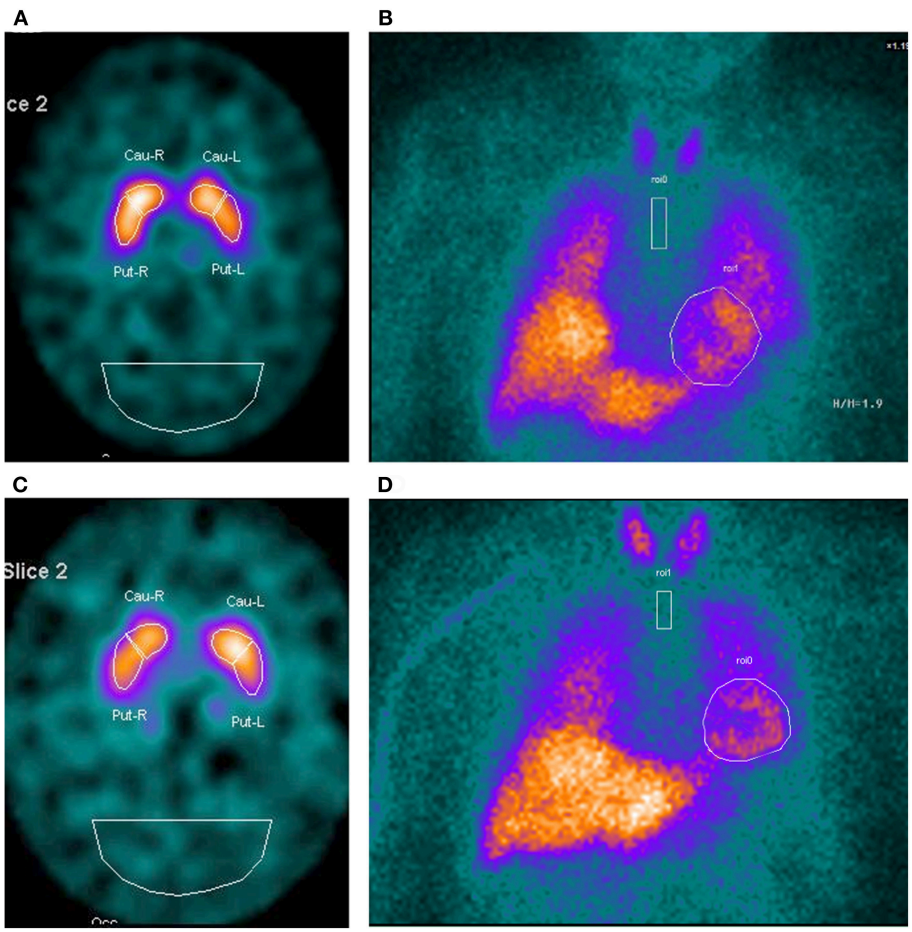

FIGURE 1 | DAT-SPECT imaging and cardiac MIBG scintigraphy in a patient with ET^{RBD+} **(A,B)** and in a patient with ET^{RBD-} **(C,D)**. The images show in both patients a normal uptake of the tracers.

Interestingly, we also found a significantly lower performance on COWAT in ET^{RBD+} compared to ET^{RBD-}. The COWAT allows to evaluate phonemic verbal fluency thus investigating both language and executive function domains. Recent evidence (30) has demonstrated that a decreased COWAT performance is a strong predictor of conversion from normal cognition to preclinical AD. Thus, the decreased score on COWAT found in our ET^{RBD+} could be suggestive of initial mild cognitive impairment. Moreover, we are in agreement with previous evidences (31) reporting that in RBD symptoms usually correlate with specific cognitive domains including verbal memory and executive functions. Supporting this hypothesis, some authors

(32) also found that PD-RBD patients performed worse than PD-nRBD in attention, executive functions, verbal learning and memory RAVLT I.R. and RAVLT D.R., thus suggesting that the presence of RBD in their PD patients was associated with increases the risk of a MCI diagnosis. Taken together our evidences, although preliminary, suggest that RBD in ET could be associated with cognitive impairment.

Cognitive impairment and dementia, however, are not surprising in ET. A series of neuropsychological investigations (33–36) have well-documented that ET may exhibit a clinical spectrum of mild cognitive deficits including attention, executive function, memory, and naming. Indeed, has been reported that ET patients have an increased risk for developing both amnestic and non-amnestic MCI (37). Neurocognitive deficits in ET, are usually deficits in specific aspects of neurocognitive functioning particularly those thought to rely on the integrity of the prefrontal cortex suggesting an involvement of fronto-cerebellar circuits (33, 34). Moreover, epidemiological evidences have demonstrated ET patients have greater risk of developing dementia and at a faster rate of progression than in normal elders thus suggesting that this could be not a simple age-related consequence (38–42). It remains still unknown, however, whether ET patients exhibiting cognitive impairment had or not RBD symptoms. In our study, only ET patients with RBD showed cognitive impairment with scores on Immediate, Delayed RAVLT and COWAT similar to those observed in ET patients with cognitive impairment (34). Thus, we can speculate that ET patients with cognitive impairment reported in the latter cited studies, could have clinical or subclinical RBD symptoms.

The second question regarding the presence of RBD in ET is the association with dysautonomic symptoms and the development of α-Synucleinopathies as PD. Some authors (8) reported that ET with RBD had higher prevalence of dysautonomic symptoms compared to those without RBD. As these symptoms are known to be PD prodromal symptoms, they suggest that ET-RBD may be a subgroup of ET at higher risk for PD progression (8). The biological support for this notion could consist in neuropathological investigations revealing the presence of Lewy bodies in some ET brains defining a "Lewy bodies ET subtype" (43). On the other hand, it is well-documented that in idiopathic RBD (iRBD) patients, the initial α-synuclein aggregation targets the nerve terminals of the peripheral autonomic nervous system (44). Thus, we investigated in all ET patients (with and without RBD) the integrity of cardiac autonomic system using cardiac MIBG scintigraphy, a tool able to measure the cardiac autonomic innervation. Indeed, cardiac MIBG scintigraphy has been recently proposed to be a useful predictor of RBD phenoconversion. When iRBD converts vs. Lewy bodies disease as PD, it is characterized by cardiac sympathetic denervation whereas it converts vs. multiple system atrophy, cardiac sympathetic innervation is preserved (44). Only two studies (9, 10) have previously investigated cardiac autonomic innervation in ET. Both studies, found that in ET cardiac sympathetic innervation was preserved unlike to occur in PD. We are in agreement with these evidences since in ET^{RBD+} cardiac MIBG uptake was in the normal value range as occurred in ET^{RBD-}. This finding is strongly indicative of preserved cardiac sympathetic innervation and suggest that in our ET cohort, the presence of RBD was not associated with cardiac sympathetic system damage. In addition, there was any clinical significant difference between ET patients with and without RBD concerning, demographics, tremor characteristics (kinetic, postural tremors etc.) and prevalence of other NMS such as constipation and hyposmia. Considering the lack of clinical and imaging differences between ET patients with and without RBD, we suggest that ET patients with RBD could be a subgroup belong to ET syndrome rather than a subgroup higher risk for PD progression. This assertion needs confirmation in future studies.

Our study has some limitations. The most significant is the lack of neuropathological investigation thus we cannot exclude that ET^{RBD+} have Lewy bodies in the brains. Cardiac MIBG scintigraphy, however, is considered a valid tool to investigate the cardiac sympathetic system, a system usually damaged in patients with Lewy bodies disease as PD. Second, the two subgroups of ET patients have different sample sizes, probably caused by the prevalence of RBD in ET. However, in our study we found statistical significant differences between two groups resisting multiple comparison (RAVLT D.R.) thus suggesting that discrepancy does not affect the obtained results. Third, we used RBD1Q to investigate clinical symptoms of RBD and to screen the subjects to send to PSG confirmation. This questionnaire is widely used in clinical setting having a sensitivity of 93.8% and a specificity of 87.2% for identifying subjects with RBD clinical suspicion. Finally, the lack of a follow up period of evaluation. Further longitudinal studies in a wider cohort of ET patients with RBD are needed to investigate whether these patients will develop a frank dementia over the time.

Despite to these limitations, our preliminary results are important to better characterize the clinical phenotype ET-RBD. Reduced performances on verbal short and delayed memory and phonemic verbal fluency test reported in patients with RBD, but not in those without RBD, suggest that ET patients with RBD may be subgroup at higher risk to developing dementia.

AUTHOR CONTRIBUTIONS

MaS contributed to the design of the study, drafting and revising the manuscript, analysis, acquisition, and interpretation of the data. GA, MM, RN, FN, and AG contributed to the analysis and the interpretation of the data. LM and AnQ contributed to the acquisition and analysis of the data. BV contributed to statistical analysis of the data. AlQ contributed in the study concept/design, critical supervision of the article, and approved the final version of the manuscript. CC contributed to the acquisition and analysis of the neuropsycological data. MiS contributed to the acquisition of the PSG data.

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Alteration of Tremor Dominant and Postural Instability Gait Difficulty Subtypes During the Progression of Parkinson's Disease: Analysis of the PPMI Cohort

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Background: Classifying PD into tremor dominant (TD) and postural instability gait difficulty (PIGD) subtypes may have several limitations, such as its diagnostic inconsistency and inability to reflect disease stage. In this study, we investigated the patterns of progression and dopaminergic denervation, by prospective evaluation at regular time intervals.

Methods: 325 PD dopamine replacement drug-naïve patients (age 61.2 ± 9.7, M:F = 215:110) were enrolled. Patients were grouped into TD, indeterminant, and PIGD subtypes. Clinical parameters and I-123 FP-CIT SPECT images of each groups were analyzed and compared at baseline, 1, 2, and 4 years of follow up periods.

Results: Baseline I-123 FP-CIT uptakes of the striatum were significantly higher in the TD group compared with the indeterminant group and PIGD group ($p < 0.01$). H & Y stage and MDS-UPDRS part III scores of the indeterminant group were significantly worse at baseline, compared with the TD and PIGD groups ($p < 0.001$ and $p < 0.01$, respectively), and MDS-UPDRS part II scores of the indeterminant group were significantly worse than the PIGD group ($p < 0.001$). There were no other significant differences of age, gender, weight, duration of PD, SCOPA-AUT, MOCA, usage of dopamine agonists, and levodopa equivalent daily doses at baseline. After 4 years of follow up, there were no differences of I-123 FP-CIT uptakes or clinical parameters, except for the MDS-UPDRS part II between the TD and indeterminant group ($p < 0.05$). The motor-subtypes were reevaluated at the 4 years period, and the proportion of patients grouped to the PIGD subtype increased. In the reevaluated PIGD group, MDS-UPDRS part II score ($p < 0.001$), SCOPA-AUT ($p < 0.001$), the proportion of patients who developed levodopa induced dyskinesia were higher than the reevaluated TD group, and the striatal I-123 FP-CIT uptakes were significantly lower ($p < 0.01$).

Conclusion: There are no significant differences of symptoms and dopaminergic innervation between the TD and PIGD group after a certain period of follow up. Significant portion of patients switched from the TD subtype to the PIGD subtype during disease progression, and had a worse clinical prognosis.

Keywords: Parkinson's disease, tremor dominant, postural instability gait difficulty, PPMI, I-123 FP-CIT SPECT

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder that is mainly known for the deterioration of one's motor functions. However, it is also accompanied by a broad spectrum of non-motor symptoms such as cognitive decline, mood disorder, sleep disorder, and autonomic dysfunction (1), and each PD patient presents with heterogenous symptoms and progression rates (2). Due to the various and complex manifestations of PD, the pathophysiology of each respective symptoms has been one of the major fields of investigation. For instance, the progression of gait disturbance is known to be associated with nigrostriatal dopaminergic denervation, while the progression of other non-motor symptoms such as autonomic dysfunction and cognitive deterioration is known to be associated with extrastriatal pathologies (3). Thus, identifying the homogenous groups of PD and categorizing into subtypes have been of interest for decades.

Previous studies have proposed that classifying PD into homogenous motor subtypes would be of value, by providing a better understanding of the pathology, prognosis, progression pattern, and the key to develop proper treatment strategies (4). Analysis of the motor symptoms came to define the subtypes of PD into the tremor dominant (TD) type and the postural instability gait difficulty (PIGD) type (5), and the clinical outcomes of the two subtypes have been investigated. However, there are some controversies on this topic, while some report the TD subtype to have a better prognosis and mild disease progression rate compared with the PIGD subtype, while others claim no differences of long term outcomes (6–15). Regarding to pathologies, several studies have depicted different patterns of striatal dopaminergic denervation between the two subtypes (16, 17), and some studies investigated the patterns of dopamine denervation in different motor subtypes of PD, via [I-123] N-ω-fluoropropyl- 2β-carbomethoxy- 3β-(4-iodophenyl) nortropane (I-123 FP-CIT) SPECT imaging. However, they have also have failed to show a consistent description. Some described higher striatal I-123 FP-CIT uptake in the TD subtype, while some described no significant differences between the TD and PIGD subtypes (18–21). Therefore, there still remains several unclarified issues on the progression and dopaminergic denervation of PD, in a subtype-based aspect.

The aim of our study was to compare the progressive pattern and dopaminergic denervation of PD between different subtypes, by evaluating the clinical symptoms, and I-123 FP-CIT SPECT images at regular time intervals. Loss of dopaminergic innervation and the severity of symptoms are known to worsen throughout the lifetime in a non-linear, exponential pattern (22, 23). Therefore, the functional decline and disease progression should be investigated in a prospective approach. In our study, patients were periodically evaluated in a prospective PD cohort, under the assumption that different subtypes may have different progression patterns and paces. Clinical parameters and I-123 FP-CIT SPECT image findings were evaluated and quantified upon a subgroup-based analysis, on a regular basis at baseline, 1, 2, and 4 years of follow up. Finally, the clinical subtypes of the whole group of patients were reevaluated after 4 years of follow up, to observe any changes of main motor phenotypes.

MATERIALS AND METHODS

Patients

Subject data were downloaded from the Parkinson's Progression Markers Initiative (PPMI) database (http://www.ppmi-info.org) in April, 2018. Three hundred and twenty-five PD patients (age 61.2 ± 9.7, M:F = 215:110) were enrolled. The inclusion criteria were as follows: a diagnosis of PD for 2 years or less at the time of screening, dopamine transporter (DAT) deficit on baseline I-123 FP-CIT SPECT images, age 30 years or more, Hoehn and Yahr (H & Y) stage I or II at baseline. Patients had at least two or more I-123 FP-CIT SPECT images acquired during follow up at 1, 2, and 4 years of time points. Movement Disorder Society-Unified Parkinson's disease rating scale (MDS-UPDRS) scores, H & Y stages, levodopa equivalent daily doses (LEDD), Scale for Outcomes in Parkinson's disease-Autonomic (SCOPA-AUT), and Montreal Cognitive Assessment (MOCA) were evaluated at baseline, 1, 2, and 4 years of follow up. Patients on any kinds of PD related medications on baseline were excluded. Patients were asked to withhold their PD related medication for 12 h before motor assessment. The patient group was subdivided into tremor dominant (TD), indeterminant, and postural instability/gait difficulty (PIGD) subtypes according to TD and PIGD scores based on UPDRS items. In short, the ratio of the mean tremor scores to the mean PIGD scores was used to define TD patients (ratio $\geq$1.5), PIGD patients (ratio $\leq$1), and indeterminate patients (ratios $>$1.0 and $<$1.5) (5). All methods were performed in accordance with the relevant guidelines and regulations. Written informed consent for all clinical data were obtained of all PPMI participants, and all subjects gave written informed consent in accordance with the 1964 Declaration of Helsinki and its later amendments. The study was approved in all participating sites, respectively, by each local Institutional review boards.

I-123 FP-CIT SPECT Analysis

I-123 FP-CIT SPECT scans were acquired 4 ± 0.5 h after I-123 FP-CIT injection (111–185 MBq). Images were reconstructed iteratively, without any filtering. In order to maintain a uniform dataset from multiple institutions, the core imaging lab of PPMI performs quality controls, such as phantom studies, validation of acquisition protocols, and standardization of image processing procedures. Respective institutions also received technical setup visits from the core imaging lab before study enrollment. Image analysis were done with the PMOD software (PMOD Technologies, Zurich, Switzerland). Specific binding ratios [SBRs, (target region/reference region)-1] of each caudate and putamen were acquired with the occipital cortex as a reference tissue. Minimum SBR values among the bilateral striatal regions were selected for analysis.

Statistical Analysis

Medcalc version 18.9.1 (MedCalc Software, Belgium) was used for analysis. Demographic factors and striatal SBRs between the groups were compared by one-way ANOVA or Kruskal-Wallis test.

RESULTS

Demographic Characteristics

Among our cohort of 325 patients, 221 patients were classified as TD (68.0%), 29 patients as indeterminant type (8.9%), and 75 patients as PIGD type (23.1%) at baseline. Baseline demographic and clinical characteristics are presented in **Table 1**. H & Y stage and MDS-UPDRS part III scores of the indeterminant group were significantly worse at baseline, compared with the TD and PIGD groups ($P < 0.001$ and $P < 0.01$, respectively), and MDS-UPDRS part II scores of the indeterminant group were significantly worse than the PIGD group ($P < 0.001$). The SBRs of the caudate and putamen were significantly lower in the indeterminant group and PIGD group compared with the TD group ($P < 0.01$ for both caudate and putamen). No significant differences were observed in age, gender, weight, duration of PD, SCOPA-AUT, MOCA, usage of dopamine agonists, and LEDD between any groups.

Serial Changes of SBRs During 4 Years of Follow Up

Caudate SBRs of the indeterminate and PIGD groups were significantly lower than that of the TD group until 1 year follow up ($P < 0.01$), and at 2 years of follow up the difference was significant in between the PIGD group and TD group only ($P < 0.01$). There were no significant differences between any groups at 4 years of follow up. Putaminal SBRs of the PIGD group were significantly lower than that of the TD group until 1 year follow-up ($P < 0.05$), and there was a significant difference between the PIGD group and TD group, at 2 years of follow up ($P < 0.05$). There were no significant differences between any groups at 4 years of follow up (**Table 2**).

Serial Changes of Clinical Parameters During 4-Years of Follow Up

Serial changes of the clinical parameters of each group were analyzed at baseline, 1, 2, and 4 years of follow up (**Table 3**). H & Y stage of the indeterminant group was significantly higher than the TD and PIGD groups at 2 years of follow up ($P < 0.01$), but there were no significant differences at 4 years of follow up. MDS-UPDRS part II scores of the indeterminant group were significantly higher than the TD group until 4 years of follow up ($P < 0.05$), but there were no significant differences of the MDS-UPDRS part III scores between any groups at 4 years of follow up. The SCOPA-AUT of the indeterminant group was significantly higher than the TD group at 1 year follow up, but there were no significant differences of SCOPA-AUT between any groups at 2 and 4 years of follow up. There were no significant differences of MOCA scores between any groups at throughout the follow up. There was a significantly higher portion of LID development in the indeterminant group after 4 years of follow up, with a higher score of MDS-UPDRS part IV question 4.1 (time spent with dyskinesias) (**Table 4**).

Reevaluation of Clinical Subtypes After 4 Years of Follow Up

TD and PIGD scores were reevaluated after 4 years of follow up, and the patients were reevaluated into TD, indeterminant, and PIGD subtypes. The total proportion of TD group decreased from 68.0% at baseline to 44.6% at 4 years, and the proportion of PIGD group increased from 23.1% at baseline to 44.2% at 4 years. 77.8% of the indeterminant group altered to PIGD group (**Table 5**). Based on the reevaluated clinical subtypes, the clinical parameters at 4 years follow up were compared between each group (**Table 6**). MDS-UPDRS part II score, SCOPA-AUT were significantly higher in the PIGD group compared with the TD group ($P < 0.001$, both). Proportion of patients who developed levodopa induced dyskinesia was higher in the PIGD group than the TD group at 4 years of follow up, with a higher MDS-UPDRS 4.1 score ($P < 0.01$). SBRs of the caudate and putamen were significantly lower in the PIGD group than the TD group ($P < 0.01$, both).

DISCUSSION

There have been several previous studies that examined the prognoses and clinical courses of TD and PIGD subtypes. However, there are controversies on whether the clinical progression and severity of the PIGD group is worse or not, and also on whether there are any differences of the pace of dopaminergic denervation between the TD subtype and the PIGD subtype. This may be due to the relatively small number of patients, inconsistent periods of disease evaluation, and irregular timepoints of I-123 FP-CIT SPECT image acquisition. In our study, we demonstrated the sequential changes of clinical parameters and I-123 FP-CIT uptakes at baseline, and at regular periods of 1, 2, and 4 years of follow up. Additionally, we demonstrated that the clinical subtypes may also change in a large proportion, during the progression of PD. MDS-UPDRS

TABLE 1 | Baseline patient characteristics.

	TD subtype ($n = 221$)	Indeterminant subtype ($n = 29$)	PIGD subtype ($n = 75$)	*P*-value
Age at PD onset (years)	61.2 ± 9.6	62.2 ± 9.1	60.5 ± 10.1	0.71
Gender (Male: Female)	144: 78	23: 6	48: 17	0.15
Weight (kg)	82.2 ± 17.8	82.8 ± 12.7	79.5 ± 16.6	0.51
Duration of symptoms until study enroll (months)	24.7 ± 23.4	29.4 ± 21.6	18.7 ± 12.4	0.05
Caudate SBRs	1.9 ± 0.5[a]	1.6 ± 0.3[b]	1.7 ± 0.5[b]	<0.01
Putaminal SBRs	0.7 ± 0.2[a]	0.6 ± 0.1[b]	0.6 ± 0.2[b]	<0.01
H&Y staging	1.5 ± 0.5[a]	1.9 ± 0.4[b]	1.6 ± 0.5[a]	<0.001
MDS-UPDRS Part II score	5.9 ± 3.6[a]	9.4 ± 4.5[b]	8.0 ± 4.3[b]	<0.001
MDS-UPDRS Part III score	20.1 ± 8.6[a]	25.2 ± 8.9[b]	20.1 ± 8.0[a]	<0.01
SCOPA-AUT	8.4 ± 5.8	10.6 ± 5.0	9.4 ± 5.9	0.09
MOCA	27.2 ± 2.2	26.3 ± 2.7	27.2 ± 2.4	0.14
Use of dopamine agonist, %	56.5	51.7	61	0.63
Average LEDD at 48 months (g)	1264.0 ± 1288.8	1377.7 ± 1414.8	1264.2 ± 1191.6	0.90

For a particular variable, values with different superscripts indicate statistically significant difference.

TABLE 2 | SBRs of I-123 FP-CIT during follow up.

	TD subtype	Indeterminant subtype	PIGD subtype	*P*-value
CAUDATE				
Baseline	1.9 ± 0.5[a] (221)	1.6 ± 0.3[b] (29)	1.7 ± 0.5[b] (75)	<0.01
1 year	1.7 ± 0.5[a] (202)	1.4 ± 0.4[b] (25)	1.5 ± 0.5[b] (67)	<0.01
2 years	1.6 ± 0.5[a] (196)	1.3 ± 0.4 (28)	1.4 ± 0.5[b] (70)	<0.01
4 years	1.4 ± 0.5 (173)	1.1 ± 0.4 (22)	1.2 ± 0.5 (64)	<0.05
PUTAMEN				
Baseline	0.7 ± 0.2[a] (221)	0.6 ± 0.1[b] (29)	0.6 ± 0.2[b] (75)	<0.01
1 year	0.6 ± 0.2[a] (202)	0.5 ± 0.2 (25)	0.5 ± 0.2[b] (67)	<0.05
2 years	0.6 ± 0.2[a] (196)	0.5 ± 0.2[b] (28)	0.5 ± 0.2 (70)	<0.05
4 years	0.5 ± 0.2 (173)	0.4 ± 0.2 (22)	0.4 ± 0.2 (64)	<0.05

For a particular variable, values with different superscripts indicate statistically significant difference. The values in parentheses represent the number of patients.

part II scores and striatal SBRs were worse in the PIGD group than the TD group at baseline, but there were no significant differences of the H & Y staging, MDS-UPDRS part III scores, MOCA scores, MDS-UPDRS part IV question 4.1 (time spent with dyskinesias), and SCOPA-AUT at baseline between the TD group and the PIGD group. Moreover, there were no differences of any parameters between the two subtypes after 4 years of follow up. This finding corresponds to the fact that the tremor dominant feature is not related with a favorable long term prognosis (7, 13). In conclusion, our results showed no significant differences of any important clinical parameters between TD and PIGD groups after a certain period of time. This may be due to the regular periodic assessment during the follow of 4 years, but also because of the changes of motor subtypes during the progression of PD, which will be discussed in the next paragraph.

In our patient population, the proportion of PIGD patients increased after 4 years of follow up. It has been previously suggested that the subtype may change during the course of PD, and the transition of the TD subtype to the PIGD subtype suggests that motor subtypes are not different entities of PD, but are rather different stages of PD (24, 25). Our study adds evidence and several additional points of view to this stream. First of all, in regards to the progression rate, the loss of dopaminergic neurons in PD is known to progress in an exponential pattern (22, 23), which implicates a more rapid progression in the early stage of PD than the later stage. In our study, the TD subtype had higher striatal SBRs than the PIGD subtype at baseline, but the differences disappeared during the 4 years of follow up. Therefore, we also suggest that not only TD and PIGD subtypes are sequential stages of PD, but that the TD subtype has a more rapid rate of dopaminergic denervation than the PIGD subtype. Secondly, patients grouped to the TD subtype at baseline did not have a favorable prognosis. Instead, we could say that the patients who changed from the TD subtype to the PIGD subtype has a worse and faster prognosis, considering that there were no differences of symptom duration between the TD and PIGD groups prior to enrollment. Among numerous risk factors for PD, conversion of subtype may have its strength as an indicator of disease progression. Recently, it has been suggested that the conventional motor-phenotype based subtyping has several shortcomings for clinical application. As mentioned above, it is still questionable whether the subtyping is valid in predicting prognosis. Also, there may be potential confounding factors such as age, disease stage, and genetic factors that affect the reliability of subtype diagnosis at baseline (26). To overcome the limitations of TD/PIGD subtyping, recent studies performed cluster analysis with other biomarkers, and non-motor phenotypes (27, 28). According to these cluster analyses, patients grouped to the diffuse malignant subtype had a faster prognosis, but only one-third of this subtype was PIGD dominant at baseline (28). Similarly, in our study, among patients who were grouped to the PIGD subtype at 4 years, only 42% of patients were subtyped to

TABLE 3 | Clinical parameters during follow up.

	TD subtype	Indeterminant subtype	PIGD subtype	*P*-value
H &Y STAGE				
Baseline (325)	1.5 ± 0.5^a	1.9 ± 0.4^b	1.6 ± 1.5^a	0.001
1 year (325)	1.7 ± 0.5	1.9 ± 0.3	1.7 ± 0.6	0.09
2 years (325)	1.7 ± 0.5^a	2.0 ± 0.5^b	1.8 ± 0.6^a	<0.01
4 years (325)	1.8 ± 0.5	2.0 ± 0.5	2.0 ± 0.8	0.06
MDS- UPDRS II				
Baseline	5.9 ± 3.6^a (221)	9.4 ± 4.5^b (29)	8.0 ± 4.3^b (75)	<0.001
1 year	7.5 ± 4.6^a (203)	11.0 ± 4.8^b (26)	9.0 ± 4.5 (70)	<0.001
2 years	8.1 ± 4.7^a (206)	11.9 ± 5.3^b (28)	9.4 ± 5.6 (71)	<0.001
4 years	10.3 ± 6.0^a (204)	13.9 ± 6.2^b (26)	11.5 ± 7.8 (73)	<0.05
MDS- UPDRS III				
Baseline	20.1 ± 8.6^a (221)	25.2 ± 8.9^b (29)	20.1 ± 8.0^a (75)	<0.001
1 year	22.8 ± 10.1 (203)	27.8 ± 9.3 (26)	23.0 ± 10.8 (70)	0.07
2 years	24.3 ± 11.2^a (206)	30.0 ± 11.8^b (28)	26.6 ± 12.0 (71)	<0.05
4 years	29.8 ± 11.2 (182)	32.5 ± 12.4 (22)	30.9 ± 14.2 (69)	0.57
SCOPA-AUT				
Baseline	8.4 ± 5.8 (221)	10.6 ± 5.0 (29)	9.4 ± 5.9 (75)	0.09
1 year	9.3 ± 7.0^a (221)	12.6 ± 7.6^b (29)	11.0 ± 6.7 (75)	<0.05
2 years	12.1 ± 7.0 (206)	14.1 ± 6.1 (28)	13.1 ± 7.9 (71)	0.30
4 years	12.3 ± 7.3 (203)	16.0 ± 7.4 (26)	13.4 ± 8.5 (72)	0.05
MOCA				
Baseline	27.2 ± 2.2 (221)	26.3 ± 2.7 (29)	27.2 ± 2.4 (75)	0.14
1 year	26.5 ± 2.7 (220)	26.2 ± 2.8 (29)	26.5 ± 2.6 (75)	0.84
2 years	26.7 ± 2.7 (203)	25.6 ± 3.7 (28)	26.3 ± 2.6 (71)	0.13
4 years	26.8 ± 3.1 (208)	26.0 ± 4.2 (27)	26.5 ± 3.7 (73)	0.54

For a particular variable, values with different superscripts indicate statistically significant difference. The values in parentheses represent the number of patients.

TABLE 4 | Ratio of patients affected with levodopa induced dyskinesia during follow up.

	TD subtype	Indeterminant subtype	PIGD subtype	*P*-value
1 year	2% (115: 2)	6% (17: 1)	2% (48: 1)	0.39
2 years	5% (161: 9)	7% (26: 2)	7% (63: 5)	0.67
4 years	8% (177: 16)	29% (17: 7)	18% (59: 13)	<0.01
MDS-UPDRS 4.1 at 4 year	0.1 ± 0.5^a	0.6 ± 1.2^b	0.2 ± 0.5^a	<0.001

For a particular variable, values with different superscripts indicate statistically significant difference. The values in parentheses represent the number of patients without: and with levodopa induced dyskinesia.

TABLE 5 | Changes of subtypes, reevaluated after 4 years of follow up.

	TD at 4 years	Indeterminant at 4 years	PIGD at 4 years	Total
TD at baseline	82 (58.3%)	18 (12.8%)	41 (29.1%)	141
Indeterminant at baseline	4 (22.2%)	0 (0%)	14 (77.8%)	18
PIGD at baseline	10 (17.8%)	6 (10.7%)	40 (71.4%)	56
Total	96	24	95	

the PIGD group at baseline. In conclusion, our findings support the suggestion that TD and PIGD are not different subtypes of PD, but are rather different clinical stages with different disease progression features. The indeterminant group may be the transitional stage from the TD group to the PIGD group, considering that the baseline striatal SBRs, H&Y stage, and MDS-UPDRS scores of the indeterminant group were worse than the TD group. Though most of the baseline indeterminant group

TABLE 6 | Comparison of clinical parameters based on the reevaluated subtypes after 4 years of follow up.

	TD subtype ($n = 96$)	Indeterminant subtype ($n = 24$)	PIGD subtype ($n = 95$)	*P*-value
MDS-UPDRS Part II score	8.7 ± 5.2^a	9.9 ± 5.1	12.5 ± 6.9^b	<0.001
MDS-UPDRS Part III score	29.2 ± 10.5	31.0 ± 9.4	31.4 ± 13.7	0.49
SCOPA-AUT	11.2 ± 5.9^a	12.7 ± 8.0	14.5 ± 8.5^b	<0.001
MOCA	26.6 ± 3.1	26.7 ± 2.9	26.9 ± 3.4	0.76
No. of patients with LID (% of total)	6 (6.3%)	4 (16.7%)	19 (20.0%)	<0.05
MDS-UPDRS 4.1	0.1 ± 0.2^a	0.2 ± 0.5	0.3 ± 0.8^b	<0.01
Caudate SBRs	1.5 ± 0.5^a	1.2 ± 0.4^b	1.2 ± 0.3^b	<0.01
Putaminal SBRs	0.5 ± 0.2^a	0.4 ± 0.1	0.4 ± 0.2^b	<0.01

For a particular variable, values with different superscripts indicate statistically significant difference.

patients (77.8%) converted to the PIGD group after 4 years, baseline H & Y staging and baseline MDS-UPDRS part III scores were worse in the indeterminant group compared with the PIGD group. This may be because of the limitation of H & Y staging, that stage II does not necessarily have a severe motor disability than stage I (29). And also, the MDS-UPDRS part III is composed of more tremor related items than posture/gait related items (5).

Unlike bradykinesia and rigidity, the severity of tremor does not correlate with striatal dopaminergic denervation (30), and has been suggested to be due to abnormal neural firing of the basal ganglia (31). Assuming from our results, tremor related pathologic changes of the basal ganglia seems to precede in the early stage of PD, followed by dopaminergic denervation of the striatum in the later stage, resulting in the conversion of dominant motor features. We have utilized the SBR values from I-123 FP-CIT SPECT images as a clinical indicator of PD progression. The degree of PD pathology is usually referred to the Braak staging, which describes the spread of Lewy bodies starting from the brain stem to the neocortex. However, the I-123 FP-CIT SPECT images do not wholly reflect the pathophysiology of PD, but show dopaminergic denervation of the striatum. We have adopted the striatal SBRs as an indirect biomarker for clinical progression, since I-123 FP-CIT SPECT image findings are known to correlate with the disease severity and duration while Braak staging does not (32–34). Though it is hard to know one's Braak stage during follow up, future studies may focus on the pathophysiology contributing to the conversion of one's phenotypes during disease progression.

There are some limitations in our study. First, the I-123 FP-CIT SPECT images could have variations since the PPMI data were collected from multiple institutions. To maintain a reliable dataset, quality control was done by the core imaging lab of PPMI, as described in the operations manual (www.ppmi-info.org). Second, our study does not include the dataset of healthy controls. The PPMI only provides the baseline clinical information of the healthy control group. By comparing the deterioration of dopaminergic innervation in normal controls, we would be able to investigate the contribution of normal aging process in the progression of PD. Finally, though we have concluded that the patient groups tended to shift to the PIGD subtype, there were still some portion of patients that were inconsistent with the tendency. 22.2 and 17.8% of the baseline indeterminant group and baseline PIGD group were reevaluated as the TD group after 4 years of follow up, respectively. The pathophysiology of PD is complex and there are many factors that can affect the subtyping. Future studies may focus on the risk factors and pathologic factors that contribute to the conversion of the subtypes, with a more sophisticated analysis of the indeterminant group.

Our study revealed that there were no significant differences of motor, autonomic dysfunction, and cognition related parameters between the TD and PIGD group after 4 years of follow up. However, this was due to the conversion of motor subtypes, resulting in a transition to a higher proportion of the PIGD subtype after 4 years. Most clinical parameters were significantly worsened in the reevaluated PIGD subtype. Therefore, instead of approaching PD as predefined TD and PIGD subtypes before treatment, it would be more reasonable to consider the conversion to the PIGD subtype as a clinical indicator for poor prognosis. Additionally, our study may give a guidance to modifying treatment strategies during the progression of PD. Some drugs such as MAO-B inhibitors have been suggested to have neuroprotective effects, but has several remaining issues to be solved, such as when it becomes effective (35, 36). Our study may contribute to future studies in applying therapeutic adjustments taking consideration into initial subtypes and subtype conversion, in order to delay disease progression.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and/or the supplementary files.

ETHICS STATEMENT

The PPMI study was approved by the local Institutional Review Boards of all participating sites, and written informed consent for clinical and SPECT data were obtained from each participant at enrollment. All subjects gave written informed consent in accordance with the Declaration of Helsinki and its later amendments. All methods were

performed in accordance with the relevant guidelines and regulations.

AUTHOR CONTRIBUTIONS

JL participated in analysis of data, drafting the text, and preparing the tables. YS participated in conception and design of the study, analysis of data, drafting the text, and preparing the tables. HK participated in study concept, data analysis. BK participated in study concept, data analysis. WL participated in study concept, drafting the text.

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Pre-frontal Cortical Activity During Walking and Turning Is Reliable and Differentiates Across Young, Older Adults and People With Parkinson's Disease

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Introduction: Mobility declines with age and further with neurodegenerative disorders, such as Parkinson's disease (PD). Walking and turning ability, in particular, are vital aspects of mobility that deteriorate with age and are further impaired in PD. Such deficits have been linked with reduction in automatic control of movement and the need for compensatory cognitive cortical control via the pre-frontal cortex (PFC), however the underlying neural mechanisms remain unclear. Establishing and using a robust methodology to examine PFC activity during continuous walking and turning via mobile functional near infra-red spectroscopy (fNIRS) may aid in the understanding of mobility deficits and help with development of appropriate therapeutics.
This study aimed to: (1) examine test re-test reliability of PFC activity during continuous turning and walking via fNIRS measurement; and (2) compare PFC activity during continuous turning and walking in young, old and Parkinson's subjects.

Methods: Twenty-five young (32.3 ± 7.5 years), nineteen older (65.4 ± 7.0 years), and twenty-four PD (69.3 ± 4.1 years) participants performed continuous walking and 360° turning-in-place tasks, each lasting 2 min. Young participants repeated the tasks a second time to allow fNIRS measurement reliability assessment. The primary outcome was PFC activity, assessed via measuring changes in oxygenated hemoglobin (HbO_2) concentrations.

Results: PFC activity during continuous walking and turning was moderately reproducible (Intra-class correlation coefficient = 0.67). The PD group had higher PFC activation than young and older adults during walking and turning, with significant group differences for bilateral PFC activation ($p = 0.025$), left PFC activation ($p = 0.012$), and the early period (first 40 s) of walking ($p = 0.007$), with greater activation required in PD. Interestingly, older adults had similar PFC activation to young adults across conditions, however older adults required greater activation than young adults during continuous turning, specifically the early period of the turning task (Cohens $d = 0.86$).

Conclusions: PFC activity can be measured during continuous walking and turning tasks with acceptable reliability, and can differentiate young, older and PD groups. PFC activation was significantly greater in PD compared to young and older adults during walking, particularly when beginning to walk.

Keywords: Parkinson's disease, fNIRS, turning, walking, pre-frontal cortex

INTRODUCTION

Decline in mobility occurs with age (1–3), and gait and turning impairments, which are central to reduction in independence, with links to increased falls risk (4–6), occur early in Parkinson's disease (PD) (7–9). Previous studies have shown that gait and turning are slower in PD, with shorter steps during walking and a greater number of steps required during turns (10–12). Turns during walking have been found to be impaired in PD (13, 14), and continuous 360° turning-in-place is particularly complex for people with PD and elicits intermittent mobility issues (15), such as freezing of gait (11, 16). While the motor contributions of mobility decline in older adults and people with PD have been well-studied through static imaging assessments (1), considerable evidence is building for non-motor contributions, such as the role of cognition (17, 18). Deficits in cognition can occur with age and are common in PD, with early impairment of executive function, visuo-spatial ability, working memory, and attention (19). Executive-attention may be an important contributor to gait and turning control in older adults and more so in PD, with associative and dual-task studies highlighting a strong association between them (20–25). Executive-attentional projections stem from the pre-frontal cortex (PFC), and may become over-active during gait or turning in PD compared to healthy controls (26, 27) to compensate for the impaired basal ganglia output that affects the automaticity of movement (28).

Technological advancement has recently allowed monitoring of PFC activity during mobility tasks, using methods such as mobile functional near infrared spectroscopy (fNIRS) (29) or electroencephalography (EEG) head caps. These devices are a valid means to measure cortical activity in humans (30, 31) and can be used in a variety of different motor tasks, from static seated tasks to more dynamic mobility tasks, such as walking in different conditions (32–41). The majority of previous studies that have used mobile fNIRS or EEG during walking have examined healthy young or older adults (33), with few investigating changes in PD (32, 36–40). Measurement of PFC activity via fNIRS in individuals with PD may be particularly useful, as it is relatively quick and easy to set-up and use compared to EEG (42). The previous studies that have examined PFC response using fNIRS in PD during dynamic mobility tasks have generally shown increased PFC activity in people with PD, generally tested ON dopaminergic medication, compared to older adults (32, 33, 37–41, 43). However, the majority of these previous studies have used different protocols and two recent reviews of this research area have highlighted methodological issues with previous studies that may prevent the generalization of results (32, 33). In fact, the majority of the studies have examined relatively small cohorts ($N < 15$), and have lacked short-separation reference channels (emitter-detector distances <1.5 cm apart) that are used remove peripheral hemodynamic response (i.e., increased skin or superficial blood flow due to physical activity rather than cortical activity) from regular channels (3 cm apart) (44), which limits or possibly inflates interpretation of results. Similarly, previous studies have provided no information on the reliability of findings, with little information on how reliable findings are in different populations, such as differences with age or neurological disease. Therefore, using a mobile fNIRS system with short-separation reference channels, this study aimed to: (1) examine test re-test reliability of PFC activity during turning and walking tasks in young adults; and (2) compare PFC activity during turning and walking tasks in young, old and people with PD.

METHODS

Participants

A total of 68 participants participated in this study; twenty-five young adults (YA), nineteen older adults (OA) and twenty-four people with PD. Young and older adult participants were recruited via local advertisement (i.e., posters within campus notice boards and e-mails circulated to students and staff members). People with PD were recruited from local Neurology clinics via referrals from movement disorder specialist neurologists. All study procedures were approved by the Oregon Health and Science University Institutional Review Board, with written informed consent obtained before participation.

Participants were included if they were aged 20–40 (young adults) or 50–90 (older adults or PD) years, able to stand or walk for 2 min without assistance. People with PD were included if they had a diagnosis of PD as defined by the UK Brain Bank criteria, Hoehn and Yahr score II-IV and were taking anti-Parkinsonian medication. Exclusion criteria were; musculoskeletal, vestibular, visual, or other medical condition that affected gait or balance.

Experimental Design and Equipment

Participant characteristics of age, sex, height, and weight were recorded. Global cognition was measured with the Montreal Cognitive Assessment (MoCA) (45). All testing in people with PD was performed in the OFF medication state, ∼12 h after taking last medication dosage. Disease severity was measured using the Movement Disorders Society (MDS-revised) unified Parkinson's disease rating scale (MDS-UPDRS) (46), freezing-status was measured using the new Freezing of Gait Questionnaire (nFOGQ) (47), and levodopa equivalent daily dosage (LEDD) was calculated (48). Specifically, out of twenty-four participants

with PD, twelve had freezing of gait, as reported by the nFOGQ (nFOGQ>1).

The participants completed two different motor tasks at self-selected pace; (1) a 2-min 360° turning-in-place task, alternating 360° turning to the left and 360° turning to the right; and (2) a 2-min walking task. Each condition included a baseline of 20 s of standing at the start and end of the task (with 80 s of performing the turning or walking task in between). The walking condition was conducted over-ground with participants walking back and forth over a 9 m straight path, with a 180° degree turn at each end. Condition order was randomized for the participants, with breaks between tasks if needed. A research assistant walked with the participants and stood by the participants during turning to ensure their safety.

Test re-test reliability of the fNIRS measurement of PFC activity during the continuous turning and walking trials was conducted within the young adult subjects. The young adult group performed the same walking and turning tasks for a second time after having the fNIRS device removed and replaced following a short break (∼5–10 min).

A mobile fNIRS system (Oxymon, Artinis, Netherlands) was used to record changes in oxygenated hemoglobin (HbO_2) and deoxygenated hemoglobin (HHb) within the PFC at a sampling rate of 50 Hz. Distance from transmitter to detector was 3.5 cm (38) and data was collected and processed in line with previous studies (32, 33). Additionally, two short-separation reference channels at a distance of 1.5 cm (one left and one right hemisphere) were used to allow for removal of peripheral interference (i.e., from blood flow changes in the extra-cerebral layers of the head) in the long source-detector separation channels (44).

Data Processing and Analysis

All processing of fNIRS signals followed current recommendations where possible. A digitizer (PATRIOT, Polhemus, VT, USA) was used to provide 3-dimensional morphological locations for cortical regions of interest relative to scalp position and the fNIRS optode measure. Data from the digitizer was entered into the software package NIRS-statistical package metric mapping (NIRS-SPM, http://www.nitrc.org/projects/nirs_spm) (49), which was implemented within MATLAB 2017a (Mathworks, MA, USA). NIRS-SPM allows registration of fNIRS channel data onto the Montreal Neurological Institute (MNI) standard brain space (50). NIRS-SPM used probabilistic registration of the fNIRS co-ordinate data to determine channels that related to ROIs at the group level [described in detail elsewhere (51)]. HbO_2 changes were recorded bilaterally (left and right) within the pre-frontal cortex (PFC). The Brodmann areas (BA) that corresponded to the PFC consisted of BA9 and BA10 for all of the participants.

The fNIRS data were processed within custom-made MATLAB algorithms, which consisted of several steps:

1. **Data filtering**: After zeroing data to the initial time-point, a low-pass filter with a cut-off frequency of 0.14 Hz, based on canonical hemodynamic response function, removed high-frequency noise (52).
2. **Baseline correction:** Removing the median of the initial 20 s of baseline standing fNIRS signal from the entire trial (i.e., subtracting the baseline period from the rest of the signal).
3. **Reference channel correction:** This step corrected signal distortions due to artifact caused by breathing, cardiac cycle, vasomotor or other error related to movement (53, 54). First, a scaling factor was determined by detecting the peaks (positive and negative) of the heart rate within the long and short-separation channel signals, then dividing them to produce the scaling factor. This was then used to remove the noise detected within the short-separation reference channels within the long-separation channels. The following formula describe the reference channel correction:

$$\begin{aligned} Scaling\ factor &= \frac{Peak\ to\ peak\ difference\ in\ heart\ rate\ in\ long\ seperation\ channel}{Peak\ to\ peak\ difference\ in\ heart\ rate\ in\ short\ separation\ channel} \\ fNIRS\ signal &= long\ separation\ channel\ signal \\ &- (short\ separation\ channel\ signal \times Scaling\ factor) \end{aligned}$$

4. **Visual signal inspection:** All of the fNIRS signals were visually examined to ensure divergence between the HbO_2 and HHb traces. This step allowed exclusion of trials that had poor fNIRS signal collection from participants, as a lack of divergence in HbO_2 and HHb indicates noise interference.
5. **Averaging across fNIRS channels:** In line with previous research (32), bilateral signals from fNIRS optodes over the PFC were median averaged for further analysis. We also median averaged the left and right sided fNIRS optodes separately for further analysis.

Primary Outcome

The primary outcome for this study was change in oxygenated hemoglobin (HbO_2) from baseline standing to walking or turning, which is a proxy for cortical activation. The fNIRS system used emitter-detector pairs to emit light into the skull that diffused through brain tissues resulting in scattering of multiple photons (55). These photons were then detected by the fNIRS detector channels when exiting the skull after passing through the cortical brain layers (typically ∼1–2 cm deep, with an emitter-detector optode distance of 3.5 cm). Importantly, HbO_2, and HHb have different absorption rates for different wavelengths of near-infrared light, which can be analyzed with Beer-Lamberts law equations (56) within the fNIRS software to calculate the relationship between an exciting photon intensity and incident photon intensity to derive changes in HbO_2 and HHb (57). Therefore, the fNIRS system measured optical density of the raw signal and converted this to HbO_2 and HHb using Beer-Lamberts law (57). HbO_2 rather than HHb was reported as our primary outcome due to its sensitivity to walking and cognitive tasks (58, 59). Additionally, changes in HbO_2 concentration within local brain capillary networks are caused by neuron firings with brain activity, which is commonly referred to as neurovascular coupling (60). Relative changes from baseline standing (initial 20 s) in HbO_2 concentration was reported in an attempt to account for between individual physiological variations (33); see below calculations.

Walking and turning periods;

1. Early = Median HbO_2 first 40 s of task—Median HbO_2 initial standing period (20 s)
2. Late = Median HbO_2 second 40 s of task—Median HbO_2 initial standing period (20 s)

Statistical Analysis

Statistical analysis was conducted in SPSS (v.24, IBM, Armonk, NY, USA) and Shapiro-Wilks tests determined data normality with parametric analysis used throughout. Mean differences with paired-sample *t*-tests, intra-class correlation coefficients (Absolute Agreement: $ICC_{2,1}$) and Bland-Altman plots with 95% limits of agreement (LoA 95%) were used to determine the test re-test reliability of PFC activity measurement via fNIRS between the first and second data captures in young adults. Acceptance ratings for ICCs were set at excellent (>0.75), moderate (0.40–0.75), and poor (<0.40) agreement (61).

TABLE 1 | Participant demographic characteristics.

	YA ($n = 25$) Mean (SD)	OA ($n = 19$) Mean (SD)	PD ($n = 24$) Mean (*SD*)	Group *p*
DEMOGRAPHICS				
Age (years)	32.3 ± 7.5	65.38 (6.95)	69.29 (4.05)	**<0.001***
Gender	F (15)/M (10)	F (10)/M (9)	F (8)/M (16)	0.160
Height (cm)	1.70 (0.11)	1.67 (0.10)	1.62 (0.13)	**0.035***
Weight (kg)	70.86 (13.95)	73.51 (15.42)	77.47 (14.56)	0.287
MoCA	28.67 (1.24)	27.47 (3.91)	27.69 (3.29)	0.227
CLINICAL				
Disease duration (years)	–	–	9.88 (6.37)	–
MDS-UPDRS III	–	–	36.54 (11.90)	–
FOGQ	–	–	6.54 (8.18)	–
LEDD	–	–	861.34 (499.07)	–
H&Y	–	–	I (0)/II (21)/III (3)	–

*UPDRS III, unified Parkinson's disease rating scale—motor subsection, FOGQ, freezing of gait questionnaire, LEDD, levodopa equivalent daily dosage, H&Y, Hoehn and Yahr scale. *Significance $p < 0.05$ should be in bold.*

PFC HbO_2 activation during turning and walking in young, older and PD groups was reported via mean and standard deviation. Separate linear mixed-effect models compared groups (YA, OA, PD), Periods (Early vs. Late) and PFC regions (Left vs. Right), with a random intercept for each subject within the models. *Post-hoc* independent *t*-tests explored significant differences between specific groups (YA vs. OA, YA vs. PD, OA vs. PD). We also compared between groups differences using Cohen's *d* effect sizes based on mean (SD) scores. Effect sizes were interpreted as small (0.2), medium (0.5), and large (0.8) (61). Due to the exploratory nature of the analysis, statistical significance was set at $p < 0.05$.

RESULTS

Participants

Demographic characteristics of the participants are shown in **Table 1**. Groups were significantly different for age ($p < 0.001$), but age was not significantly different between older adults and PD groups ($p = 0.166$). Similarly, young adults tended to be taller than the older adults and PD subjects, but the older adults and PD groups did not significantly differ for height ($p = 0.146$). The groups were well-matched for gender ($p = 0.160$), weight ($p = 0.287$), and cognitive ability ($p = 0.227$).

Test Re-test Reliability of fNIRS Measurement During Turning and Walking

Following removal of fNIRS data that had poor signal quality, data from 19 young adult subjects were analyzed for walking ($n = 6$ young adult walking trials were excluded following visual signal inspection: 4 first trial and 2 second trial errors) and 25 subjects were analyzed for turning to determine test re-test reliability of fNIRS measurement.

On average, there was moderate ($ICC_{2,1} = 0.67$) reliability of PFC activity measured via mobile fNIRS during turning and walking in young adults (**Table 2**). There were no significant differences between any of the outcomes over the two sessions, with very low average difference between testing sessions (Mean Difference = 0.03 μm, **Figures 1**, **2**). Reliability across the

TABLE 2 | Reliability of fNIRS recording of PFC activity in young adults.

Task	Time	PFC region	Trial 1 Mean (SD)	Trial 2 Mean (SD)	Mean Difference[a]	*p*	$ICC_{2,1}$ (95% CI)	LoA 95%
Turning ($n = 25$)	Overall	B/L	−0.02 (0.25)	−0.01 (0.33)	0.02	0.859	0.673 (0.245 to 0.857)	0.819
		L	−0.02 (0.19)	0.03 (0.55)	0.12	0.297	0.512 (−0.093 to 0.784)	1.162
		R	0.03 (0.28)	0.01 (0.27)	−0.01	0.745	0.658 (0.213 to 0.850)	0.823
	Early	B/L	−0.02 (0.19)	−0.02 (0.27)	0.02	0.863	0.793 (0.517 to 0.911)	0.616
	Late	B/L	0.01 (0.33)	0.01 (0.43)	0.00	0.959	0.709 (0.316 to 0.875)	0.919
Walking ($n = 19$)	Overall	B/L	−0.19 (0.24)	−0.18 (0.41)	0.04	0.940	0.714 (0.239 to 0.891)	0.925
		L	−0.23 (0.33)	−0.19 (0.64)	0.09	0.786	0.685 (0.164 to 0.880)	1.355
		R	−0.15 (0.32)	0.18 (0.36)	−0.03	0.682	0.709 (0.231 to 0.889)	0.938
	Early	B/L	−0.16 (0.26)	−0.17 (0.34)	−0.04	0.897	0.520 (−0.511 to 0.846)	0.831
	Late	B/L	−0.17 (0.34)	−0.17 (0.51)	0.07	0.977	0.707 (0.220 to 0.888)	1.224
Average	Overall	B/L	–	–	0.03	–	0.668 (0.154 to 0.867)	0.961

[a] *Trial 2 minus Trial 1, PFC, pre-frontal cortex; ICC, Intra-class correlation coefficient; CI, confidence interval; LoA, limits of agreement; B/L, bilateral; L, left; R, right. * $p < 0.05$.*

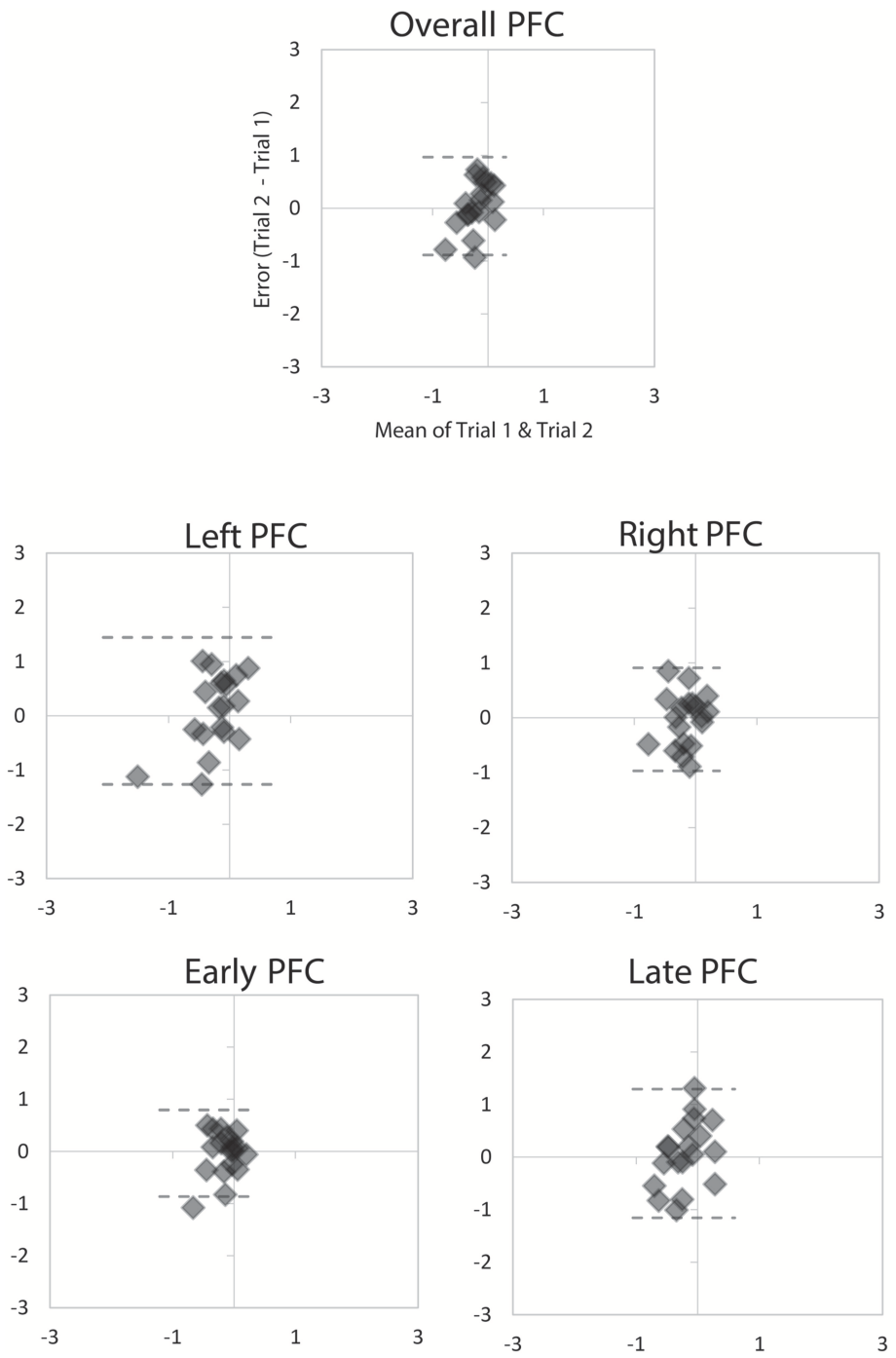

FIGURE 1 | Bland Altman plots demonstrating agreement between the two 2-min trials of walking for overall PFC activity, Left and Right PFC activity, and Early and Late PFC activity. Dashed lines represent LoA.

different time periods (early vs. late) and regions of interest (Left, Right or combined) within the PFC ranged from moderate ($ICC_{2,1}$ = 0.52) to excellent ($ICC_{2,1}$ = 0.79). Importantly, the primary outcome over the duration of the motor tasks (combined left and right PFC regions) had moderate reliability (turning; $ICC_{2,1}$ =0.67, walking; $ICC_{2,1}$ 0.71) (**Table 2**).

PFC Activity During Continuous Turning and Walking in Young, Old, and Parkinson's

Table 3 shows the relative change in HbO_2 during continuous turning and walking in the groups. Overall, the PD group had higher average levels of PFC activation during turning and walking than young or older adults across the majority of the

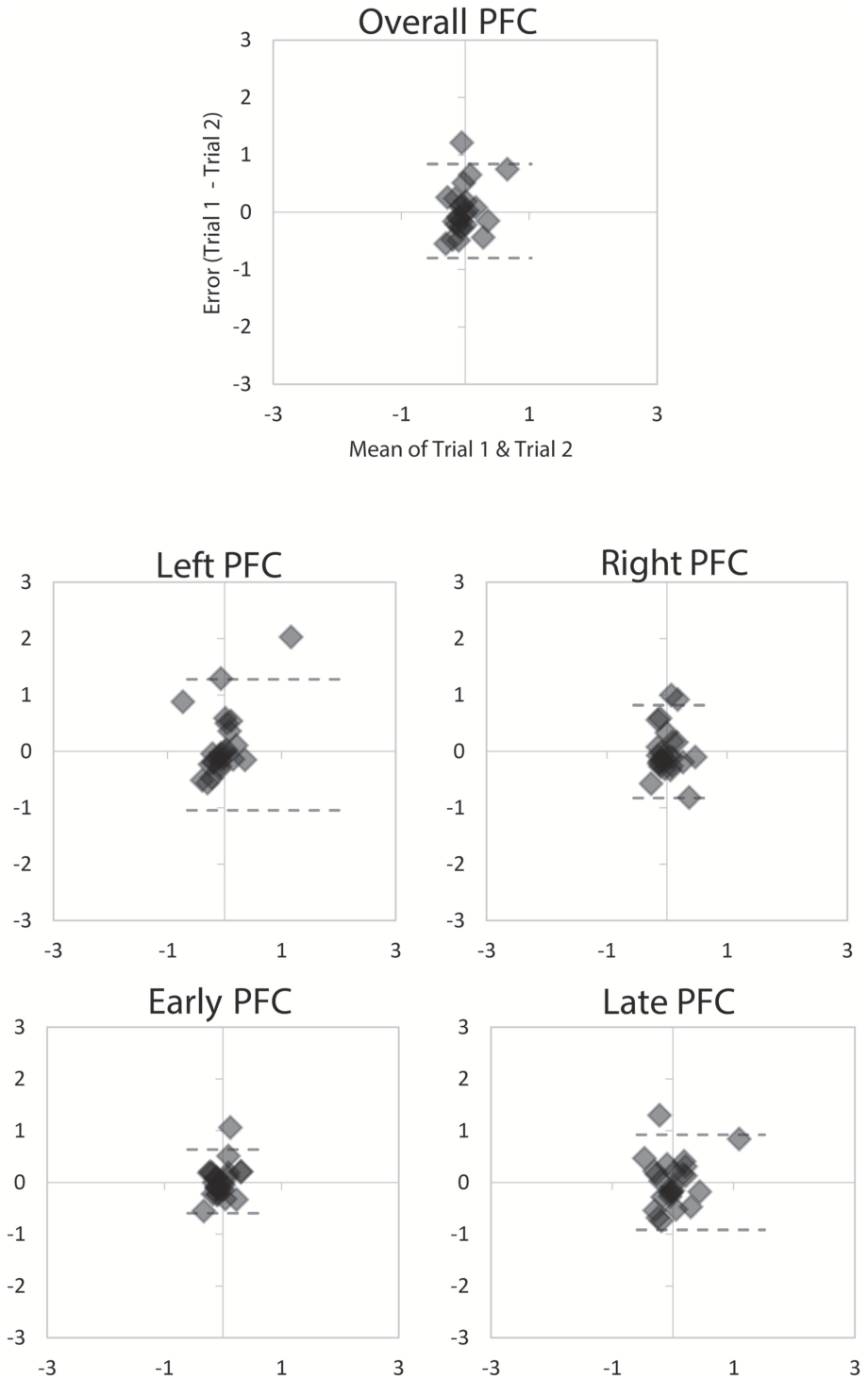

FIGURE 2 | Bland Altman plots demonstrating agreement between the two 2-min trials of turning for overall PFC activity, Left and Right PFC activity, and Early and Late PFC activity. Dashed lines represent LoA.

time-points and PFC regions. Older adults also had higher average PFC activation during turning and walking compared to young adults.

During walking the groups were significantly different for overall PFC activation ($p = 0.025$), left PFC activation ($p = 0.012$) and for the early period (first 40 s) of walking ($p = 0.007$)

TABLE 3 | Relative change in HbO_2 during turning and walking in young, old and Parkinson's participants.

Task	Time	PFC region	YA Mean (SD)	OA Mean (SD)	PD Mean (SD)	Group *p*	Period (early vs. late) *p*	Hemisphere (L vs. R) *p*	*Post-hoc*
Turning	Overall	B/L	−0.01 (0.25)	0.01 (0.30)	0.06 (0.35)	0.464	0.647	0.059	–
		L	−0.06 (0.34)	0.03 (0.30)	0.05 (0.28)	0.198			–
		R	0.03 (0.28)	0.08 (0.33)	0.09 (0.41)	0.573			–
	Early	B/L	−0.17 (0.19)	0.04 (0.31)	0.10 (0.26)	0.114			–
	Late	B/L	−0.01 (0.31)	0.02 (0.41)	0.05 (0.46)	0.646			–
Walking	Overall	B/L	−0.26 (0.28)	−0.25 (0.36)	−0.03 (0.37)	**0.025***	**0.012***	0.185	**0.025* (YA < PD)**
		L	−0.29 (0.32)	−0.21 (0.33)	−0.03 (0.37)	**0.012***			**0.017* (YA < PD)**
		R	−0.21 (0.36)	−0.18 (0.40)	0.02 (0.49)	0.065			–
	Early	B/L	−0.18 (0.30)	−0.14 (0.32)	0.07 (0.29)	**0.007***			**0.008* (YA < PD)** **0.037*(OA < PD)**
	Late	B/L	−0.29 (0.37)	−0.25 (0.43)	−0.10 (0.44)	0.136			–

**Significance p < 0.05 should be in bold. PFC, pre-frontal cortex; YA, young adults; OA, older adults; PD, Parkinson's disease; B/L, bilateral; L, left; R, right.*

(**Table 3**). There was also a significant difference in PFC activation between early and late periods of walking across the groups ($p = 0.012$), with higher PFC activity in the early period. *Post-hoc* testing indicated that the PD group had significantly higher PFC activation during the early period of walking compared to the young ($p = 0.008$) and older adults ($p = 0.037$). The PD group also had significantly higher overall ($p = 0.025$) and left side ($p = 0.017$) PFC activation than the young adults. However, the older adult group did not have significantly different PFC activation compared to the young adults, with small effect size differences between groups (**Table 4**). Overall, the PD group had moderate to large differences (Cohen's *d* 0.52 to 0.86) in PFC activation during walking compared to young and older adults (**Table 4**), particularly for the early period and left PFC region.

Tables 3, **4** demonstrate that the effect of turning on PFC activation was similar across groups, as during continuous 360° turning there were no significant group differences for any outcome. However, there was a trending difference between PFC regions during turning (left vs. right, $p = 0.059$), with higher right PFC activity compared to left (**Table 3**). Despite the lack of a significant difference, effect sizes showed that the early period of turning differentiated the young group from the older adult and PD groups (**Table 4**; Cohens *d* of 0.86 and 1.21, respectively), with young adults having the lowest activation of the three groups (**Table 3**).

TABLE 4 | Effect sizes (Cohens d) for differences in HbO_2 during turning and walking between groups.

Task	Time	PFC region	YA vs. OA	YA vs. PD	OA vs. PD
Turning	Overall	B/L	0.08	0.24	0.16
		L	0.28	0.36	0.07
		R	0.17	0.18	0.03
	Early	B/L	**0.86**	**1.21**	0.22
	Late	B/L	0.09	0.16	0.07
Walking	Overall	B/L	0.03	**0.72**	**0.62**
		L	0.25	**0.77**	**0.52**
		R	0.08	**0.55**	0.45
	Early	B/L	0.13	**0.86**	**0.71**
	Late	B/L	0.10	0.48	0.35

Bold indicates effect size > 0.50 (medium effect). PFC, pre-frontal cortex; YA, young adults; OA, older adults; PD, Parkinson's disease; B/L, bilateral; L, left; R, right.

DISCUSSION

To the best of our knowledge, this is the first study to examine the test re-test reliability of PFC activity measurement via fNIRS during continuous walking and turning tasks. Findings demonstrate that the measurement of PFC activity during continuous (2 min) turning or walking has acceptable reliability, as there was little difference in HbO_2 measurement between separate re-test trials. With a growing interest in understanding brain activity during motor tasks, our results contribute to the development of robust protocols to examine PFC activity using fNIRS during continuous walking or turning tasks.

This study also reports differences in PFC activation during continuous (2 min) 360° turning and walking in young adults, older adults and people with PD. Specifically, people with PD had significantly higher PFC activation during walking compared to young and older adults; however, older adults were not significantly different compared to young adults. Increased PFC activation may indicate greater cognitive demand during walking in PD due to impaired movement automaticity.

Reliability of fNIRS Monitoring of PFC Activation During Turning and Walking

The mobile fNIRS device used in this study is a commercial device that allows access to the raw data that registers HbO_2 concentration and subsequent implementation of our custom-made algorithms for data analysis. Re-test reliability of HbO_2 signal recorded with the mobile fNIRS device was conducted within our young adult group with some variations across the

conditions (walking or turning), as well as when the HbO_2 signal was broken into different PFC hemispheres (left or right) or trial times (early or late). When using our fNIRS system with short-separation reference channels and fixed data analysis pipeline we found moderate reliability ($ICC_{2,1}$ 0.67) of the PFC HbO_2 signal during the continuous walking and turning tasks. These results, together with small LoA between trials, indicated that we could be confident that this signal is reliable, as reported in **Figures 1**, **2**. However, there were changes in reliability when breaking the fNIRS signal down into individual hemispheres or times of the signal (early vs. late), which is similar to previous static fNIRS findings (62). On the basis of our results, it can be stated that HbO_2 outcomes measured using a mobile fNIRS device during continuous (2 min) walking or turning are relatively stable. However, when breaking the signal into specific features, such as hemispheres or time-periods, the stability of the HbO_2 signal can be altered.

Impact of Aging and PD on PFC Activation During Turning and Walking

This study confirms that PFC activity, measured through mobile fNIRS, can show differences in PFC activation during continuous walking and turning between young, older and subjects with PD. Specifically, we found that people with PD, OFF their medication, had significantly higher PFC activation during walking than young and older adults, in line with previous studies where PD subjects were ON medication (32, 33, 37–40). Higher levels of PFC activation during continuous walking, particularly the early period of walking, in PD compared to the other groups likely reflects the need to use executive-attentional resources even during relatively simple tasks (i.e., usual walking) (21, 26). The use of cognitive resources to compensate for PD related deficits is similar to previously reported theories of PD walking, which hypothesized that to compensate for movement automaticity deficits people with PD increased cognitive control (63), particularly executive control (26). However, executive-attentional deficits are common in PD (64) and these impact the ability to effectively compensate for underlying deficits. Therefore, when tasks become more challenging (such as dual-tasks, obstacles etc.) people with PD may not be able to effectively respond (24), which impacts gait and mobility, with implications for falls risk. Future studies may uncover further age or PD-related deficits with the use of more complex tasks that provide additional cognitive burden to participants.

Interestingly, although older adults had slightly greater PFC activation levels than young adults during walking, our findings were not significantly different which is in agreement to another previous fNIRS study (32). This demonstrated that healthy young and older adults may use their executive-attentional resources in a similar manner when walking, with little need to activate the PFC due to intact lower-level neural structures and activity compared to people with PD. Similarly, there were limited group differences found during the continuous 360° turning-in-place task, which may indicate that this complex task requires cognitive resources regardless of age or disease. Indeed, average PFC activation was higher in young adults, older adults and PD during continuous turning compared to walking, with PD participants having the highest HbO_2 concentrations across groups. Interestingly, although there were no significant group differences, there were large between group effects for PFC activation during the early period of the turning task. This highlighted that young adults had much lower PFC activation during the early period of continuous turning than older adults or people with PD. Aging and PD may therefore lead to greater cognitive control being required to begin complex continuous motor tasks, however less cognitive control is required once the task underway.

Clinical Interpretation

PFC activation appears to increase with walking in PD, but not with age. This may represent cortical compensation for sub-cortical dysfunction with PD. Findings suggest that targeting cortical activation, particularly executive-attentional activity within the PFC, with interventions such as pharmaceuticals, cueing strategies (visual, auditory or proprioceptive) or transcranial magnetic or direct current stimulation may help to alleviate the cortical burden of walking in PD. However, future studies are needed to establish findings and examine response to such interventions. Specifically, future studies should assess whether the observed increase in PFC activation is related to PD itself or to freezing of gait. In fact, as freezing of gait could represent a disruption of gait automaticity, people experiencing freezing of gait, even without PD, may show an increased cortical control of gait.

Study Strengths and Limitations

A key strength of this study was the use of short-separation reference channels (1.5 cm apart) to account for the peripheral hemodynamic response that is associated with physical activity (44). Short-separation channels have only been used in one other mobile fNIRS study (65), but they should be used within future work to reduce noise and ensure repeatable findings. Another strength is that we have provided detailed data analysis steps from our fNIRS signal processing, whereas other previous studies often use 'black-box' data analysis tools such as NIRS-SPM (66) or Homer2 (67).

A limitation of this study was that, despite being the first to asses test re-test reliability of fNIRS HbO_2 measurement during walking and turning, test re-test analysis was only conducted in young adults. Reliability could possibly change in older adults or PD, as previous studies have shown this in patients with TBI (68). However, we may expect that reliability would even be higher in older adults and further in PD as, unlike young adults, they require more cognitive control of movement due to a loss of motor automaticity (1, 28), therefore findings in these groups may be more consistent. However, this is mainly speculative at this point, future studies could examine re-test reliability in older adult and PD using the same protocol developed here. Additionally, we did not examine the influence of disease stage, duration or other clinical factors (e.g., freezing of gait) in PD, which future studies should examine to provide greater understanding of cortical activation during walking and turning in PD.

CONCLUSIONS

This study has demonstrated that the measurement of PFC activation during continuous turning and walking using a mobile fNIRS system with short-separation reference channels is repeatable. PFC activation during continuous turning and walking differs between young adults, older adults and PD, with greater activation required in PD compared to control groups for these motor tasks. Using the robust method developed in this study, future work could establish these findings within larger cohorts and examine the impact of more complex tasks on PFC activation.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Oregon Health & Science University IRB Committee with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the OHSU IRB.

AUTHOR CONTRIBUTIONS

SS and MM conceptualized the question and hypothesis. MM designed the study from which the data originates. SS, VB, and MM contributed to data collection and analysis. SS, VB, JQ, and MM contributed to the interpretation, writing and editing of the manuscript. SS wrote the first draft.

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International Guidelines for the Treatment of Huntington's Disease

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The European Huntington's Disease Network (EHDN) commissioned an international task force to provide global evidence-based recommendations for everyday clinical practice for treatment of Huntington's disease (HD). The objectives of such guidelines are to standardize pharmacological, surgical and non-pharmacological treatment regimen and improve care and quality of life of patients. A formalized consensus method, adapted from the French Health Authority recommendations was used. First, national committees (French and English Experts) reviewed all studies published between 1965 and 2015 included dealing with HD symptoms classified in motor, cognitive, psychiatric, and somatic categories. Quality grades were attributed to these studies based on levels of scientific evidence. Provisional recommendations were formulated based on the strength and the accumulation of scientific evidence available. When evidence was not available, recommendations were framed based on professional agreement. A European Steering committee supervised the writing of the final recommendations through a consensus process involving two rounds of online questionnaire completion with international multidisciplinary HD health professionals. Patients' associations were invited to review the guidelines including the HD symptoms. Two hundred and nineteen statements were retained in the final guidelines. We suggest to use this adapted method associating evidence base–medicine and expert consensus to other rare diseases.

Keywords: Huntington's disease, guidelines, treatment, care, clinical practice

INTRODUCTION

HD is a rare neurodegenerative disorder of the central nervous system, with a genetic autosomal-dominant inheritance, that first involves basal ganglia (caudate nucleus and putamen) and results from expansion of a CAG trinucleotide repeat in the HTT (huntingtin) gene: alleles with 40 or more repeats are fully penetrant. The disease is characterized by motor, cognitive and psychiatric disorders, and a range of somatic symptoms. Progressive worsening leads to a bedridden state with cognitive deterioration. Death occurs about 20 years after the onset of symptoms.

More than a century after the first description of Huntington's disease (HD), there is still no curative treatment of the disease; however, symptomatic treatments are thought to be efficacious in controlling some of its troublesome symptoms. Yet, symptomatic management of HD remains inadequately documented (1–4), which may lead to variations in care mainly based on clinical experience and not on scientific evidence (5–7).

This document provides scientifically supported and consensual pharmacological, surgical and non-pharmacological recommendations for the treatment of HD.

MATERIALS AND METHODS

Methodology

The EHDN guidelines task force developed guidelines between 2015 and 2018 based on a formalized consensus method, adapted from the 2015 French Health Authority recommendations (HAS) (https://www.has-sante.fr/portail/jcms/c_272505/recommandations-par-consensus-formalize-rcf). This method combines exhaustive review of the literature, experts' proposals, and external scoring of the proposals until agreement (**Figure 1**). This is particularly suitable when at least two of the following conditions are met (1) absence or insufficiency of high-level evidence specifically addressing the questions asked; (2) possibility of declining the theme in easily identifiable clinical situations; (3) controversy, with the need to identify by an independent group situation in which a practice is deemed appropriate. Its main advantages are (1) its ability to identify the degree of agreement or indecision among experts (2) the strict independence between the steering group, which formulates the proposals to be put to the vote, and the rating group which judges the appropriateness.

Search Strategy

First, we conducted a search of scientific evidence published between 01/01/1965 and 01/08/2015 in the following databases: Cochrane Library, Embase, MEDLINE, PASCAL, BMJ Clinical Evidence, Current Contents, Infobanque AMC, National Guidelines Clearinghouse, PEDro, and BDSP (Public Health Database) as well as in the following websites: CEBAM, EBM sources, OMS Réseau de bases factuelles en santé, CBEM Oxford, Center for Evidence based child health, Center for health evidence, Center for reviews and Dissemination, Evidence based neurology, National institute for health and clinical excellence, Orphanet, ClinicalTrials.gov, OpenSIGLE (System for Information on Gray Literature in Europe). We also hand searched abstracts of international congresses of the Movement Disorders Society. Search terms were chosen based on a list of symptoms to focus on determined following discussions within the guidelines committee and working groups (neuroprotective, rehabilitation, and cognitive) of the European Huntington's Disease Network. Search terms were: "Huntington disease," "drug therapy," and symptoms (Huntington chorea, drug therapy, Chorea, Dystonia, Falls, Chokes, Bradykinesia, Rigidity, Depression, Apathy, Irritability, aggression, Obsessions, perseverations, Anxiety, Agitation, Hallucinations, delusions, paranoia, Impatience, Impulsivity, Suicidal Ideation, Memory, Loss of fluency, speech, Dysarthria, Attention disorders, Social cognition impairments, Disorientation, Bradyphrenia, Indecision, Weight loss, Incontinence, Sleep disorders, Diarrhea, Sweating, Constipation, Vomiting, Swallowing, Pain, Dental decay, and Surgery).

Drug manufacturers and authors were also contacted in order to obtain additional information on unpublished trials. In total 637 publications were collected.

Data Extraction and Analysis

The Task Force committees reviewed the 637 collected publications with the French and UK committees focusing on pharmacological/surgical and non-pharmacological interventions, respectively. First, two members of each national committee conducted independently a screening of the collected publications and retained results from clinical trials, observational studies, meta-analysis, systematic reviews, case studies, previous recommendations, or conference and congress summaries. Studies including patients with HD clinical features and a confirmatory genetic diagnosis or a compatible family history (mostly for studies published before gene discovery in 1993) were also included 288 and 88 papers on pharmacological/surgical and non-pharmacological interventions, respectively, were retained for further analysis. The remaining members of the Task force validated the list of excluded publications. Second, a pair of members from each national committee summarized the key elements of the retained studies by filling a table with the following columns: authors, date of publication, type of intervention, daily dose (both of the active drug and the placebo), genetic characteristics of the patients (genetically diagnosed), study design, number of participants, duration of the study, primary and secondary endpoints, outcome, scales used, conclusion of the reviewers, and level of proof. Then they analyzed independently each study by assessing the methods (quality of the study) and results (the contents of the study) and assigned a level of scientific evidence according to the HAS classification (see below).

Quality Appraisal and Data Synthesis

Following the HAS recommendations, a quality grade was attributed to each study according to the level of scientific proof they provided (**Table 1**) (**Appendix 1**).

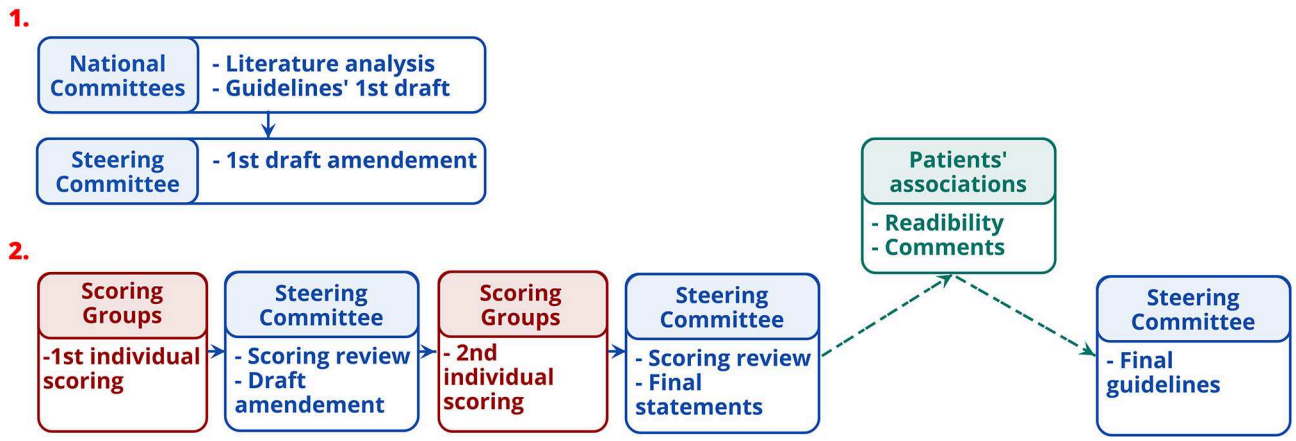

FIGURE 1 | Guidelines' developing stages.

TABLE 1 | Level of scientific evidence and gradation of studies.

Level of scientific proof provided by the study	Quality grade
Level 1 • Meta-analyses of randomized controlled trials • Randomized controlled trials of high power	**A** Established scientific proof
Level 2 • Randomized controlled trials of low power • Properly conducted non-randomized controlled trials • Cohort studies	**B** Scientific presumption
Level 3 Case-control studies	**C** Low-level of scientific proof
Level 4 • Comparative studies with major bias • Case series	

Method for Reaching a Consensus

The subsequent steps for developing the guidelines are displayed in **Figure 1**. First, the experts of the national committees formulated provisional recommendations for each HD symptom, classified in four categories of disorders (motor, psychiatric, cognitive, and "others"). Recommendations were based on the synthesis of information from the studies, i.e., quality grade, accumulation of scientific evidence, and professional expertise. Recommendations were rated according to the quality grades of the studies on which they are based, with the highest quality grade determining the score. When scientific evidence was lacking, best clinical practice (professional agreement) was formulated, based on the experience of the National committees. The International Steering Committee reviewed the initial recommendations before initiating process to reach a consensus with the International Multidisciplinary HD Health Professionals group (**Table 2**). This involved two rounds of online questionnaire completion. After the first round, only appropriate recommendations with strong consensus were retained (**Table 3**). Those without strong consensus were reviewed and modified by the International Steering Committee prior to the second round of ranking (**Table 3**). After the second round, all recommendations were deemed appropriate, and agreed as such, except two of the motor chapter and two of the psychiatric chapter. Two hundred and nineteen statements were retained in the final guidelines. The steering committee added a rider considered important by the multidisciplinary group to the four recommendations that did not reach a consensus. Whereas, the literature basis scored through survey monkey ends in 2015, experts' and knowledge input were provided through the survey scoring and comments as well as the last face-to-face meeting until October 2018.

Patients' Associations Involvement

European, Chinese and French HD associations as well as the Italian League for Research on Huntington and related diseases Foundation were invited to review the guidelines.

RESULTS

A condensed version of HD symptoms and recommendations is provided in the main text. A full version is available in **Appendix 2**. Publications justifying the grades of the recommendations are cited in the text. Recommendations provided without specific grading are underpinned by professional agreements.

Given that any HD symptoms may be worsened by stress, fatigue, and intercurrent disorders (e.g., anxiety, digestive disorders, infectious or painful conditions, etc.), these aspects must be assessed and should be treated with appropriate measures alongside managing the Huntington's symptoms.

Motor Disorders

The wide spectrum of motor manifestations are the best known and the most visible symptoms in HD. Among them, involuntary movements (i.e., chorea) are the most obvious. However, while the diagnosis of manifest HD is based on the presence of motor symptoms, these are frequently preceded by cognitive

TABLE 2 | Composition of the international multidisciplinary HD health professionals.

		Motor disorders		Cognitive disorders		Psychiatric disorders		Other disorders	
		1st survey	2nd survey	1st survey	2nd survey	1st survey	2nd survey	1st survey	2nd survey
Number of participants		67	38	63	36	60	32	56	30
Expertises	Dentists	1	1	0	0	0	0	0	0
	Geneticists	4	3	3	2	2	0	3	1
	Neurologists	39	24	35	20	34	20	33	22
	(Neuro)psychologists	8	2	11	6	10	4	7	2
	Nurses	3	3	2	2	2	2	3	2
	Physiotherapists	5	1	4	2	4	1	3	1
	Psychiatrists	7	4	8	4	8	5	7	2
	Countries	Australia Belgium Brazil Chile Cyprus Czech R. Denmark Estonia France Germany Hungary Italy Netherlands Peru Poland Portugal Romania Russia South Korea Spain Sweden Switzerland UK USA	Australia Brazil Chile Cyprus Czech R. Denmark Estonia France Germany Hungary Italy Netherlands Poland Portugal Russia Spain Switzerland UK USA	Australia Belgium Brazil Chile Cyprus Czech R. Denmark Estonia France Germany Italy Netherlands Poland Portugal Romania Russia Spain Switzerland UK USA	Australia Belgium Brazil Chile Cyprus Czech R. Denmark Estonia France Germany Italy Netherlands Poland Portugal Romania Russia Spain Switzerland UK USA	Australia Belgium Brazil Chile Cyprus Czech R. Denmark Estonia France Germany Italy Netherlands Peru Poland Portugal Romania Russia Spain Switzerland UK USA	Australia Brazil Chile Cyprus Czech R. Denmark Estonia France Italy Netherlands Peru Poland Portugal Romania Russia Spain Switzerland UK USA	Australia Belgium Brazil Chile Cyprus Czech R. Denmark Estonia France Germany Italy N. Zealand Netherlands Peru Poland Portugal Romania Russia Spain Switzerland UK USA	Australia Brazil Chile Czech R. Denmark Estonia France Italy Netherlands Peru Poland Portugal Romania Russia Switzerland UK USA

and behavioral symptoms (8). While motor symptoms are easily detected, and might be the source of anxiety and ostracism, they are often well-tolerated by the patients and their proxies in contrast to cognitive and behavioral symptoms that often lead to family and social/professional's issues.

Chorea

Chorea is characterized by abnormal, involuntary, spontaneous, uncontrollable, irregular, intermittent, non-rhythmic and aimless movements affecting the trunk, the face, and the limbs.

Drug treatment should be considered if chorea causes the patient distress or discomfort.

Tetrabenazine is one of the first-line treatments for this symptom (Grade A) (9) unless the patient suffers from not well-managed depression or suicidal thoughts. Second generation neuroleptics (Grade B) (10, 11) are first-line treatments for this symptom in particular when the patients have associated personality and/or behavioral or psychotic disorders. Monotherapy to treat chorea is preferred because combination therapy increases the risk of adverse effects and may complicate the management of non-motor symptoms. In the presence of disturbing chorea, appropriate protective measures (especially during meal times and during the performance of instrumental activities of daily living) should be put in place to avoid traumatic injury or chokes. Rehabilitation specialists can help identify appropriate assistive technology devices and positioning techniques.

Dystonia

Dystonia is characterized by abnormal postures that may affect all body segments and is frequently associated with rigidity (12). Dystonia intensity varies from a slight intermittent abnormal posture to severe twitch of muscles with major impact on movements and functions of daily living.

Both active and passive physiotherapy approaches are recommended as a preventive measure to maintain the range of joint motion, limit postural and musculoskeletal deformities and, prevent the development of contractures. Injection of botulinum toxin in the case of focal dystonia or to prevent secondary deformities should be performed by a trained professional. Customized chairs can provide a comfortable environment in view of the dystonia-related deformities.

Rigidity

Rigidity is an increase in muscle tone leading to a resistance to passive movement that can induce joint stiffness and

TABLE 3 | Rules to determine the strength of the consensus of the multidisciplinary experts.

Recommendations deemed as		1st round			2nd round	
		Median value	Responses' distribution	Submitted to the 2nd round	Median value	Responses' distribution
Appropriate	Strong agreement	≥7	All between (7-9)	No	≥7	All between (7-9); two values missing or <7 tolerated
	Relative agreement	≥7	All between (5-9)	Yes	≥7	All between (5-9); two values missing and/or <5 tolerated
Inappropriate	Strong disagreement	≤3	All between (1-3)	No	≤3	All between (1-3); two values missing or >3 tolerated
	Relative disagreement	≤3.5	All between (1-5)	Yes	≤3.5	All between (1-5); two values missing or >5 tolerated
Indeterminate	Indecision	Between [4–6.5]	Whatever the distribution	Yes	Between [4–6.5]	Whatever the distribution
	No consensus	≥7	At least one <5 or missing	Yes	≥7	At least three <5 or missing
		≤3.5	At least one >5 or missing	Yes	≤3.5	At least three >5 or missing

limited range of motion, which might be distressing for patients.

Rigidity may be increased or induced by the use of neuroleptics or tetrabenazine. If this impacts the functional capacity of the patient, a reduction in dosage or the withdrawal of neuroleptics and/or tetrabenazine should be considered considering overall benefit on chorea and/or behavioral symptoms vs. severity of rigidity.

Levodopa may provide partial and temporary relief of the akinetic–rigid symptoms of HD, especially in juvenile forms (Grade C) (13–18). Treatment with levodopa should be started gradually and the total daily dose is usually lower than in Parkinson's disease.

Physiotherapy is recommended to improve or maintain mobility and prevent the development of contractures and joint deformity (Grade C) (19).

Akathisia

Akathisia is a syndrome characterized by unpleasant sensations of "inner" restlessness that manifests as an inability to sit still.

An iatrogenic cause of akathisia should be investigated as the priority.

Tetrabenazine (Grade C) (20, 21), neuroleptics and Selective serotonin reuptake inhibitors (SSRI) may cause akathisia in HD and reducing the dose or changing the treatment may be helpful.

Swallowing Disorders

Swallowing disorders can occur in patients at the early stages of the disease and become a major problem in later stages by inducing repeated choking and leading to secondary bronchopulmonary infections or even cardiac arrest.

Regular assessment of swallowing disorders should be provided throughout the progression of the disease (Grade C) (22) and referral to a Speech and Language Therapist is recommended as soon as the disorders appear (Grade C) (22–24).

Ancillary assessments that may help in managing swallowing disorders include: generalized motor skills, respiratory status, dental health, mood, behavior and emotional status, cognition, nutrition, and hydration status. Provision of information and advice on safe swallowing procedures, on posture and positional changes can help to avoid aspirations and leads to improvement of swallowing disorders. Oral-facial exercise with swallow sequence individualization and cough post swallow may also improve swallowing difficulties. In some cases, treating chorea might help in improving swallowing problems. However, side effects of treatments for chorea (e.g., sedation, attention, and parkinsonism) might also negatively impact swallowing capacities.

The education of carers is important as they are often managing the eating, drinking, and swallowing regime.

For severe swallowing disorders impacting nutrition and quality of life of the patient, the use of a gastrostomy device Percutanous Endoscopic Gastrostomy (PEG) may be considered and should be discussed on a case-by-case basis with the patient and the caregivers. PEG should be anticipated and discussed with relatives and patients still able to understand the benefits and burdens of the methods. Before advanced stages of the disease, patients should be educated to make an informed choice concerning the PEG methods even if they can change their decision at any time.

Myoclonus

Myoclonus refers to sudden muscle contractions, brief and involuntary, axial, in extremities or generalized, similar to spams and jerks in epileptic seizures but not related epilepsy. In HD, myoclonus can be observed in a predominant akineto-rigid phenotype and can be associated with an at rest or action tremor, especially in the juvenile forms but also in later-onset forms. In juvenile forms, non-epileptic myoclonus can coexist with epilepsy.

In case of myoclonus impacting the functional capacity of the patients, treatment with sodium valproate or clonazepam, used alone or in combination, and in escalating doses, is recommended (Grade C) (25–32). Levetiracetam is a therapeutic alternative for the same indication. In case of myoclonus of cortical origin that is not associated with epileptic seizures, piracetam has a marketing authorization (Grade C) (29). Benzodiazepines, in particular clonazepam, may be used to manage myoclonus whilst remaining vigilant with regard to adverse effects such as somnolence and increasing falls, and the risk of drug-dependence.

Gait and Balance Disorders

Gait and balance disorders impairments include disruption of cadence regulation, increased variability of step width and length, disturbed initiation and increased postural sway (33). These develop as a result of the progressive complex movement disorder seen in HD adding to the overall burden of motor morbidity with falls and loss of independence in HD (34).

Generally, interventions for gait and balance should start as early as possible and be continued and adapted throughout the progression of the disease (Grade C) (33, 35–38). Physiotherapy interventions (Grade B) (39–42) and the introduction of falls prevention programs, gait, core stability, and balance interventions (Grade C) (35, 43–45) as well as attentional training are recommended.

Pharmaceutical management of chorea may improve walking and balance as they can be affected by chorea (Grade C) (46–49). However, they should always be used cautiously and regularly reassessed as their adverse effects may also aggravate walking disorders.

Maintaining physical activity and low impact exercises is recommended.

The use of assistive devices such as four-wheeled walker (Grade B) (50) as recommended by Physiotherapist or Occupational Therapist should be considered to improve stability and reduce fall risk.

Bruxism

Bruxism is an involuntary clenching with excessive contraction of the jaw muscles. It typically causes lateral movements (or front to back) responsible for gnashing and can lead to tooth damage.

Injecting botulin toxin A into the masseter muscles is proposed as the first-line treatment of bruxism (Grade C) (51). Customized protective mouth guards may be used to reduce the complications of bruxism on a case-by-case basis, mostly in early stage patients.

Bruxism may occur as a side effect of neuroleptics (Grade C) (51, 52) and serotonin reuptake inhibitors, thus reducing their dose should be considered.

Manual Dexterity

Manual dexterity can be impaired secondary to chorea/dystonia/akinesia/rigidity but also occur in their absence—due to abnormal motor planning and sequencing.

Neuroleptics and tetrabenazine may possibly have a beneficial effect on dexterity as a result of reducing chorea (Grade C) (46, 47, 53) but may also have a detrimental effect on dexterity by aggravating other symptoms such as bradykinesia.

Management with physiotherapy and occupational therapy may be useful to reduce the functional impact of fine motor skill deterioration (Grade B) (41). Adaptive aids may help to compensate for the deterioration of manual dexterity.

Global Motor Capacities

Early referral to a physiotherapist is recommended in order to facilitate the development of a therapeutic relationship, promote sustainable exercise behaviors and ensure long-term functional independence.

Physiotherapy and/or personalized exercise programs (Grade B) (40) are beneficial for the overall functional ability, motor function, and independence in HD, in combination with pharmacological treatments (Grade B) (39, 40, 42).

Cognitive Disorders

Cognitive deficits appear frequently before motor symptoms (8). They are, in addition to behavioral symptoms, the major cause of family disruption and social withdrawal (54). Cognitive symptoms cause intense psychological discomfort and a sense of powerlessness that can lead to behavioral symptoms.

Based on present knowledge, no pharmacological treatment is recommended for the treatment of cognitive symptoms.

Multiple rehabilitation strategies (speech therapy, occupational therapy, cognitive and psychomotricity) might improve or stabilize transitorily cognitive functions at some point of time in the course of the disease (Grade B) (55).

Executive Functions

Executive functions refer to the functions that allow the realization of complex task in daily living. They consist in a set of functions mostly dedicated to cognitive and behavior control and adaptation, which may be impaired in HD, even at the premanifest stages and thus impose adaptation from the environment, organization support including proactivity in planning appointments, behavior or daily life activities like cooking.

For the patients to maintain their independence for as long as possible, it is better to help the patients organize themselves and initiate activities rather than substitute for them, as long as they do not endanger themselves.

Treatment for anxiety and depression may help to improve executive function and cognitive stimulation through rehabilitation may improve planning and initiation more specifically (Grade C) (56). Sedative drugs and neuroleptics should be closely monitored as they impair executive functions and attention.

Bradyphrenia

Bradyphrenia is defined by slowing of cognitive information processing and a prolongation of reaction time depending on the complexity of the cognitive task (57). It becomes more apparent with HD disease progression.

Management is based on giving the patient enough time to process information and perform a task and avoiding time-pressured situations. Cognitive stimulation as part of rehabilitation may be beneficial.

Language and Communication Disorders

Language and communication disorders can be divided in speech and language disorders *per se*. Speech disorders consist of slurred and slowed speech causing dysarthria, inappropriate pauses or bursts of speech, and progressive reduction in verbal fluency (58). Language (e.g., syntax) impairments appears early in the disease course, with progressive difficulties in understanding and producing complex sentences. Reduction of lexical capacities appears later. This often goes unnoticed and may cause misunderstanding and impaired communication.

The changing communication needs of the person with HD should be reassessed throughout the course of the disease to plan effective management strategies (Grade C) (59). As communication disorder in HD is variable, its monitoring requires comprehensive assessment of language and of other factors such as mood, motivation, and behavior.

Early referral to Speech and Language Therapists is recommended (Grade C) (59) as they can play a major role in assessing and managing communication problems in HD at all stages of the disease. Communication strategies and techniques may include: management options (e.g., voice therapy techniques), advice on facilitation of communication (e.g., allowing time for communication, reduction of environmental distractions and noise) and the use of simple technics (e.g., gestures and rephrasing) or tools (e.g., pen and phones).

Family members and other communication partners should be educated to support patients to attempt verbal communication as long as possible. Augmentative and alternative communication (talking mats) can compensate for communication difficulties and increase the individual's chance of participation in daily life. These strategies need to be implemented whilst there is still motivation and a capacity to learn (Grade C) (60).

Social Cognition Impairments

Social cognition impairments refer to a set of symptoms that affect relationships and social behavior. The most studied are the inability to recognize emotion others (61) but also to express emotions, both through facial expression or through the voice. Executive function impairments can make difficult for the patients to express their feelings. The capacity to infer other thoughts or feeling, are also reported to be impaired in patients (61). Furthermore, motor impairments can create a "facial mask," often misunderstood as indifference.

Improvement of behavioral disorders may help with social and family integration. However, impact of SSRI or neuroleptics on social interaction *per se* has not yet been properly assessed to allow any recommendation specific to this domain.

Explaining the patients' disorders to their family, health care professionals or to their colleagues may facilitate the patient's social relationships. Moreover, third party intervention (e.g., caregiver, nurse, and social worker) may stimulate patients' social interaction.

Memory Disorders

Memory disorders are frequently reported in HD and may be confounded with or exacerbated by attention disorders. They are mostly characterized by difficulties in learning new information and retrieving information acquired (62).

Strategies such as establishing and keeping a regular daily routine may compensate memory loss. Rehabilitative approaches (speech therapy or neuropsychology) may help memory as part of an overall intervention plan. Specifically, domain-specific transcoding (verbal and visual) may help in recalling items.

Sedative drugs, neuroleptics and tetrabenazine may impact negatively on memory.

Disorientation

Disorientation, both in time and space, appear during the progression of HD but temporal orientation is altered earlier (63–66).

Investigations should be carried out to detect any potential intercurrent cause for a confusional state. Establishing a regular routine, in tune with the patient's environment as much as possible, and milestones enables the patient to manage their time better.

Visuospatial and Visual Perceptual Disorders

Visuospatial and visual perceptual disorders appear late in the course of the disease through interference with the integration and understanding of visual information (66).

It may be useful to make the patient's environment safe (padding furniture) to minimize falls and shocks linked to visual spatial difficulties and aggravated by motor disorders.

Psychiatric Disorders

Behavioral symptoms may appear before the motor diagnosis of the disease. They are, in addition to and in conjunction with cognitive symptoms, the major cause of family disruption, social isolation, and withdrawal.

Their management should be based on the identification of the underlying triggers causing changes in mood or behavior. Patients should be given the opportunity to express their worries and frustrations.

Using methods to calm and reassure patients is a major component of care of psychiatric disorders. Based on data from other neurodegenerative conditions, mindfulness-based cognitive therapy and Acceptance and Commitment Therapy may be useful in HD.

Depression

Depression is one of the most common psychiatric symptoms seen in HD (67, 68) with a significant negative impact on quality of life. It may affect patients at any stage of the disease, even before motor manifestation (69). Thus, vigilance to detect and treat depression is required at all stages of the disease.

Psychotherapy and cognitive behavioral therapy may enable early detection of mood changes. An antidepressant may be suggested if depression occurs in HD (Grade B) (70). It is recommended to use a selective SSRI or a serotonin noradrenaline reuptake inhibitor (SNRI), or alternatively Mianserin or Mirtazapine, in case of sleep disruption. In case of recurrent depression, long-term mood-stabilizer treatment may be introduced in complement to the treatment of the current episode to prevent relapses. If depression is thought to be an

adverse effect of other medication, the dosage of the responsible drug should be reduced gradually. In the case of resistant depression, or depression associated with psychotic symptoms, a psychiatrist should be consulted. In case of severe depression and resistant to oral medications, electroconvulsive therapy (ECT) may be suggested under the guidance of a psychiatrist (Grade C) (71–73).

Suicidal Ideation or Attempts

Suicidal ideation or attempts are common in HD (74) and correlate with family history of suicide, a history of previous suicide attempts and the presence of depression, especially in prodromal stages (75).

Suicide risk should be assessed in HD irrespective of the stage, being particularly vigilant at the time of diagnosis and when the disease starts to impact on day-to-day life. Prevention of suicide includes treating risk factors such as underlying depression, social isolation and impulsivity.

Irritability

Irritability is a very common symptom in HD (67, 68, 76). This disorder is of fluctuating nature, characterized by impatience and a tendency to become angry in response to minimal provocation. Overflow and loss of control are favored by impulsivity, and can lead to aggressive behavior toward self or others, and rarely, to criminal behavior. This symptom can be caused by the frustrations felt by the patient because of the great loss of his capacities, and by troubles in expressing himself, as well as by neurological/psychological fatigue brought by the latter.

Before initiating pharmacological treatment, possible environmental causes for the patient's frustration and irritability should be explored. In order to reduce irritability, behavioral strategies should be considered. A structured plan with a regular routine in a calming environment is desirable. In addition, psycho-education for the patient's family regarding diversion strategies should be attempted to avoid confrontation as much as possible.

Whilst SSRIs are first lines for irritability (Grade C) (77, 78), it may be necessary to use them at or near the maximum recommended dose in order to be effective. Irritable patients who do not benefit from an SSRI alone may benefit from combination therapy with Mianserine or Mirtazapine, especially when sleep disorders are present. In patients with aggressive behavior, the recommended first-line treatment is a neuroleptic (Grade C) (79–81). In case of overt aggression associated with depression, neuroleptic treatment should be associated with sedative antidepressants. If irritability does not respond to antidepressant therapies and/or neuroleptics, a mood stabilizer (Grade C) (82, 83) can be added.

Apathy

Apathy has been defined by Levy and Czernecki (84) as "a quantifiable reduction in goal-directed behavior," manifesting clinically as a reduction in interest, spontaneity, motivation, and drive. In patients with HD it is compounded by emotional blunting, resulting in social withdrawal, and lack of concern for others. It is the most frequent psychological and behavioral symptom in HD, especially in the middle and later stages, causing a severe reduction in the activities of daily living and often being a source of conflict in the family. With regard to cognitive and psychological symptoms, apathy and irritability are the two faces of the same coin (85). A patient can be apathic the morning and irritable the afternoon, depending on the situation. As for irritability, apathy can be caused by environmental and psychological issues. Apathy may also be an adaptive response when the patient feels overwhelmed by too much stimulation (HD patients are more sensitive to noise and environmental interferences), or with the feeling that his/her disease is progressing.

It is important to explain the various aspects and causes of the apathy to the family circle.

Personalized cognitive stimulation, establishing routines and a structured programme of activities is recommended when possible. A professional intervention at home can improve compliance and reduce the patient's opposition and irritability.

Depression may increase apathy. If depression is suspected, an SSRI should be tried.

Sedative medication may increase apathy, thus avoiding unnecessary prescription or reduce dosage is recommended.

Anxiety

Anxiety as defined by the uncomfortable feeling of nervousness or worry about something that is happening or might happen in the future, is common in HD. Anxiety is linked to the other symptoms (motor and cognitive), as the patient is anxious because of the loss of essential functions, and correlated to family, social and economic issues, and to the burden of his pathology (and the one of his proxies). However, anxiety does not increase with disease progression. It is associated with depression, suicide, irritability, quality of life, pain, illness beliefs, and coping.

SSRI or SNRI are first line treatments of anxiety, especially when associated with depression. On-demand prescription of an anxiolytic might be beneficial, but caution is required because of the associated risk of worsening or causing falls. Neuroleptics (Grade C) (86, 87) are valuable therapeutic alternatives in the treatment of anxiety when other treatments fail.

Obsessions

Obsessions are defined by recurrent and persistent thoughts, ideas or images that do not let the mind rest, causing anxiety. True obsessions, according to this definition, are not very common in patients with HD, but perseveration is very common, particularly in the middle and later stages (76). Perseveration may be defined as the repetition of a thought, behavior or emotion beyond the psychological context in which it arose, and in patients with HD these repetitive thoughts and behaviors can persist for hours, months, or even years after the original trigger. Patients have little or no insight into the problem (in contrast to obsessional thoughts, which are distressing and recognized as abnormal); however, it has been shown that perseveration is the one behavioral symptom in HD which has a significant negative impact on the quality of life of family members and caregivers (88).

Over the course of HD, symptoms may change and repetitive thoughts may replace obsessive–compulsive disorder. The distinction between obsessive–compulsive phenomena and perseverations is important for the care strategy, both requiring differential approaches.

If pharmacological treatment is necessary for perseverative symptoms, an SSRI could be prescribed (Grade C) (89), in particular when symptoms are associated with anxiety. Olanzapine and risperidone (Grade C) (81, 86) are two valuable therapeutics for ideational perseverations, in particular when they are associated with irritability.

True obsessive–compulsive phenomena are sensitive to psychological intervention, such as Cognitive Behavioral Therapy, in non-cognitively impaired patients. If pharmacological treatment is necessary for obsessive-compulsive phenomena, a SSRI should be prescribed as first-line treatment (Grade C) (89).

Impulsivity

Impulsivity consists of acting without prior planning, which can lead to unpredictable behavior. When impulsivity is associated with depression or irritability, there is a significant increased risk of self-harm or suicide or aggressiveness. Impulsivity may be the result of cognitive impairments, which lead to an intense frustration toward patience, the patient being in the incapacity to wait or to deal cognitively with planning. Impulsivity may then be an adaptive response to language difficulties of patients who cannot explain what stresses them.

When impulsivity is associated with depression or personality disorders, there is a risk of auto- or hetero-aggressiveness, which justifies the prescription of a neuroleptic in combination with a SSRI. Long-term mood-stabilizer treatment may be introduced in the case of mood lability and impulsivity.

Sexual Disorders

Sexual disorders are very common in HD. Decreased libido is the most common symptom while hypersexuality or disinhibited behavior are rarer, but can cause significant problems in relationships. Repetitive hypersexual behaviors are often a result of perseveration.

Identifying the existence of sexual disorders and determining their triggers and their impact on relationships is important. Psychological support and/or referral to a specialist in psychosexual disorders might be useful. In the case of decreased libido, an iatrogenic cause should be investigated (e.g., the use of an SSRI) and reducing the dose or substituting the treatment responsible may be suggested. In the case of erectile dysfunction, treatment for impotence may be suggested and seeking the opinion of an endocrinologist and/or a specialist in psycho-sexual disorders may be useful. In case of impotence, prescription of phophoesterase 5 inhibitors should be considered in the clinic when asked for by the patient and his sexual partner. A behavioral and psychological approach is useful in the case of hypersexuality, by re-establishing appropriate standards of behavior in the patient's social setting. If hypersexuality involves social discomfort or violence, the proposed first-line treatment is a neuroleptic (Grade C) (90) and/or a SSRI. If the treatment for hypersexuality with neuroleptics and/or SSRI is not successful, the addition of or substitution for an anti-androgen may be proposed (Grade C) (91–93) under the guidance of a specialist in sexual disorders or an endocrinologist. Where hypersexuality poses a risk to others, specific measures should immediately be put in place (e.g., referral to a psychiatrist).

Hallucinations

Hallucinations are defined as a perception without an object, at which the subject adheres to and reacts as if the perception came from outside. Delusions are false beliefs based on incorrect inferences about external reality, the cultural and social context to which the patient belongs.

The use by the patient of psychotropic agents should be searched for and interrupted in case of hallucinations and delusions. Second generation neuroleptics are the first line treatment for hallucinations and delusions (Grade C) (80, 81, 86, 94–106). Clozapine should be proposed as the first-line treatment in the case of akinetic forms of HD with debilitating Parkinsonian symptoms. Perseverative ideation can sometimes mimic psychotic symptoms, and in such circumstances the patient may benefit from treatment with serotoninergic antidepressants in combination with an atypical neuroleptic. Psychiatric intervention and support are particularly useful in the case of psychotic disorders occurring in HD, for treatment adjustments. If pharmacological treatments fail, the option of ECT can be discussed with psychiatrists (Grade C) (71, 73, 107).

In case of agitation, priority should be given to identifying environmental or somatic triggers (bladder distension, fecal impaction, pain, etc.) in order to treat the underlying cause, especially in the advanced stages of the disease when communication difficulties exist. When agitation is associated with an anxiety disorder, a benzodiazepine should be prescribed as needed to reduce the risk of dependence and falls (Professional agreement). Some benzodiazepines (e.g., midazolam) may be useful in emergency situations. Long-term treatment with benzodiazepines should be avoided as much as possible but remains necessary in some patients. In the case of extreme agitation, and if there are associated behavioral and personality disorders, it is advised to prescribe a neuroleptic (Grade C) (82, 90, 91, 102, 108, 109).

Other Disorders

Other symptoms than motor, cognitive and psychiatric disorders are often present. Among those, weight loss, dysphagia, and sleep disturbance are not unfrequently the most prominent symptoms. As they may cause discomfort, they should be looked for in order to limit them when present.

Sleep Disorders

Sleep disorders are common in HD. Around two-thirds of HD patients suffer from sleep disorders, with diverse causes such as depression, anxiety, intrinsic alteration in the circadian sleep-wake rhythm, and involuntary movements during sleep inducing awakenings (110, 111). They may present as difficulties in falling asleep and/or early awakenings in the middle of the

night followed by insomnia. They may be associated with aimless wandering, and lead to difficulties in coping by the proxies. However, disturbances of diurnal rhythm (day-night reversal, etc.) are probably more common than simple insomnia in HD patients.

Potential underlying cause of sleep-related difficulties (e.g., depressive syndrome, anxiety, and severe involuntary movements) should be investigated. Simple lifestyle and dietary strategies (e.g., avoiding long nap, having no stimulants after 4 pm) are the first-line treatment of insomnia. When lifestyle strategies are ineffective to treat insomnia, prescribing a hypnotic may be suggested for a short duration to avoid the risk of drug dependence. Some agents may be proposed in place of a hypnotic and for a long duration (e.g., mianserin, mirtazapine, and antihistaminic drugs) as they have a reduced tendency for causing dependency. Melatonin may be suggested in case of sleep phase inversion. A neuroleptic should be prescribed in the evening when sleep disorders are associated with behavioral disorders or chorea.

Urinary Incontinence

Urinary incontinence may either be multifunctional or linked to a deterioration of the frontal lobe control centers, causing an overactive bladder with urge incontinence and/or unannounced urination (112).

Where there is urinary incontinence, a precipitating factor should always be investigated (urinary infection, prostate disease). It is useful to investigate the presence of diurnal unexpected complete urination (complete and sudden bladder emptying, without urge) for which carbamazepine may be of benefit (Grade C) (112). In the case of an overactive bladder with leakage and urge incontinence, therapy with selective antimuscarinic may be tried, whilst watching out for the appearance of potential side effects, in particular confusional state. If, after few weeks, the incontinence therapy has not been effective, it should be stopped. If simple therapeutic measures have failed, it is advised to undergo urodynamic testing to help guide the choice of drug therapy and to consult a urologist if necessary.

In all cases, it is recommended to implement simple lifestyle strategies: urination before every outing and at regular times.

Pain

Pain assessment is sometimes difficult because of communication disorders. Moreover, because of communication's disorders and a tendency for these patients not to complain, pain is often related to non-verbal language and behavioral disorders such as irritability and restfulness.

Behavioral change or worsening of involuntary movements should trigger the search for an underlying source of discomfort, and in particular pain.

Dental Pain

Patients suffer from poor oral health for a variety of reasons, including impaired motor ability (e.g., difficulties brushing teeth) or reduced motivation to maintain oral health, the use of drugs affecting salivary secretion and frequent dental trauma due to falls and injuries, bruxism.

Multidisciplinary teamwork, especially with dietitians to avoid highly cariogenic foods, is recommended (Grade C) (113, 114). Verbal and written instructions on how to provide good oral hygiene at home should be given to patients and carers (Grade C) (114, 115). Dental care including descaling by a dentist or dental hygienist should be carried out at least once a year but should be more frequent in the later stages of the disease.

At later stages of the disease, treatment options should be discussed carefully and in advance. Treatment intervention, especially in late stage disease may require conscious sedation (midazolam, Diazepam) or general anesthesia in a hospital setting (Grade C) (115–117).

In view of the frequency of digestive disorders in HD (e.g., constipation, diarrhea, and vomiting) and their impact on the quality of life of patients, routine assessment for these symptoms is recommended in order to ensure their management.

Their diagnostic workup should be conducted by the relevant specialists (general and digestive examination, biological and radiological tests, scan, fibroscopy, colonoscopy, etc.). Fecal impaction should be routinely investigated where there is constipation/ diarrhea ("false" diarrhea) and/or vomiting. Vomiting is sometimes intractable. If no specific etiology is identified, the following should be considered: staggering meals, reviewing the patients' posture during and after the meal, and possibly reducing antichoreic agents, in particular neuroleptics.

Excessive Perspiration

Excessive perspiration can occur at all stages of HD. It can be associated with other autonomic disorders and reflects discomfort or emotional burst when sudden.

In the case of excessive perspiration, care must be taken to ensure patients are well-hydrated, monitored and that their fluid and electrolyte balance is adjusted. Thyroid function and the possibility of infection should be assessed in case of excessive perspiration.

Weight Loss

Weight loss is often present in HD, sometimes prior to the appearance of other symptoms. It might occur despite normal, or even high calorie intake, due to a significant energy expenditure in HD patients. It can also be caused by swallowing disorders, depressive syndrome with reduced appetite or gastrointestinal disturbance and gut abnormalities due to enteric neuron dysfunction (118).

Good nutritional care is a fundamental element of the management of HD (Grade C) (119, 120). Early assessment by a dietitian or nutritionist, and regular timely reviews of nutritional needs are recommended. Factors such as swallowing ability, cognitive changes, behavior, mood, and general functional ability should be considered to determine possible other causes of weight loss (Grade C) (23, 120–123). A multi-disciplinary approach is recommended and may include a Speech Language Therapist and an Occupational Therapist to assist with swallowing, positioning and feeding aids. Screening tools

for malnutrition [e.g., malnutrition Universal Screening Tool (MUST)] are recommended.

A high Body Mass Index (BMI) within normal values should be maintained if possible and medical and/or social intervention is recommended when unintended weight loss is higher than 10% within last 3–6 months or when BMI is <20 kg/m^2 and unintentional weight loss of 5% is observed within last 3–6 months. When weight loss is observed, high-calorie and high-protein food supplements should be prescribed under instruction and monitored by a dietician/nutritionist (Grade C) (124, 125).

A Mediterranean diet may improve Quality of Life and nutritional composition (Grade C) (126).

In case of the initiation of antidepressant and/or neuroleptic treatments, treatments inducing weight gain should be preferred in patients with significant weight loss, whilst treatments inducing weight loss should be avoided (these effects can vary from one patient to another) (Grade C) (127).

Advanced care planning is essential and alternative feeding methods (PEG, see swallowing disorders) should be anticipated and discussed with relatives and patients still able to understand the benefits and risks of the intervention.

Hypersalivation

Hypersalivation can be troublesome in HD patients when associated with a salivary incontinence (caused by poor oral occlusion and or fault swallowing).

In the absence of a specific treatment for HD, drugs used in other chronic diseases may be considered to reduce salivary secretion: scopolamine given percutaneously, atropine given orally or other drugs that have an anticholinergic effect (amitriptyline), whilst watching out for iatrogenic risks, in particular confusional state, constipation, ocular hypertension and urinary retention. Injections of botulinum toxin into the salivary glands may be considered in a specialized setting if oral or oral mucosa treatment options have not induced benefit or were not well-tolerated.

Reduced Lung Function and Respiratory Muscle Strength

Reduced lung function and respiratory muscle strength are not only associated with end stage disease but occur much earlier, with evidence of some upper airway changes in pre-symptomatic individuals and reduction of cough effectiveness, reduced lung volume, and impaired respiratory strength by mid-disease. Along with changes in posture reduced exercise capacity, these impairments negatively impact respiratory function, leaving patients vulnerable to respiratory infections.

Home-based respiratory muscle training program appeared to improve pulmonary function in manifest HD patients but had only a small effect on swallowing function, dyspnea, and exercise capacity (Grade B) (128).

CONCLUSION

The EHDN guidelines task force provides here scientific and consensual guidelines from experts from 15 European experts from the national and steering committees and 73 worldwide additional experts from 25 countries. Whereas, the literature extraction and scoring extent from 1965 to 2015, experts' input extended until October 2018. To ensure the validity of the guidelines in the light of the latest scientific results, two authors reviewed the literature from 2015 to 2019. They extracted 573 abstracts and selected the 17 relevant studies to HD management, which were then added to the grids. Two authors analyzed them separately and assigned each of them a level of scientific evidence. Because these recent relevant studies were not used to formulate recommendations reviewed by the International Multidisciplinary HD Health Professionals group, they are mentioned in the conclusion. Except for deutetrabenazine (Grade A) (129, 130), none of the studies justified to modify the recommendations. Deutetrabenazine may indeed be proposed as an alternative to tetrabenazine for the treatment of chorea in countries where the marketing authorization is already obtained, like in the USA. In addition, a number Grade B and C studies were in agreement with the current recommendations and reinforce the interest of rehabilitation (131–135). Therefore, as they stand, with this precision, these guidelines are likely to serve as international for care in HD. They are likely to support both general practitioners and specialists' decisions. Patients associations and patients themselves may use them and also disseminate them to inform their doctors.

It becomes increasingly clear that the cost of health is one of the major issues of public policy. In countries where there is a medical insurance system, the question of the choice of therapeutic care or medication and rehabilitation in the insured basket constitutes a central issue. The difficulty is even greater in rare diseases such as HD because the number of patients is too small to carry out double-blind placebo-controlled studies on large cohorts (Grade A) as required for the selection of health policies according to evidence-based medicine. In this work, based on therapeutic trials conducted between 1965 and 2015, only one grade A study was found among 376 studies analyzed, which is insufficient to eliminate or recommend enough products to meet the patients' needs. In parallel, thanks to specific international networks dedicated to HD (EHDN, HSG, and ERN) experts' know-how has increased with a knowledge-learning culture over time. In this context, the French Ministry of Health has labeled Rare Diseases Reference Centers in 2004, imposing on them various duties, one of which is producing National Protocols for Diagnostics and Care (NPDC). These protocols are designed as a combination of comprehensive literature reviews and expert consensus combining the work of an expert panel, and then its validation by outside experts to compensate for the information that is lacking. The recommendations from these NPDCs made it possible to provide decision-makers with comprehensive information based on an adapted version of evidence-based medicine to rare diseases. In addition, they allowed the health professional to refer to a document to answer their questions of day-to-day care. EHDN, with more than 2,000 members in 50 countries, is concerned by the relevance of prescriptions, medical procedures, hospital stays, care pathways, and care arrangements. It thus commissioned an international adaptation of the French NPDC. To give it an international value, we replaced face-to-face meetings with

electronic votes and added international committees and patient associations to national committees. Thus, beyond offering international guidelines to practitioners for the management of HD, this document proposes a method that is likely usable in all rare diseases.

AUTHOR CONTRIBUTIONS

A-CB-L supervised the elaboration of the guidelines. OA, KY, CS-G, and RM selected the studies to be analyzed. A-CB-L, KY, CP, CS-G, and DR analyzed each study and assigned a level of scientific evidence. Members of the National Committees (A-CB-L, CV, KY, CP, CS-G, OA, DR, and DC) formulated initial recommendations for each HD symptom. Members of the Steering Committee (A-CB-L, JF, KY, AR, MB, DC, RR, GD, DR, FS, KS, and J-MB) reviewed the initial recommendations and supervised the writing of the final recommendations. RM supervised the online surveys, analyzed the results, and assisted the Steering Committee in the writing of the recommendations. Members of the Steering Committee and RM wrote the manuscript (original draft preparation, review, and editing).

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00710/full#supplementary-material

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Conflict of Interest Statement: J-MB was chair of the European Huntington's Disease Network (EHDN) during the completion of the work, and received honoraria for the duties involved in this position. AR received reimbursements as Co-Chair and Chair of the EHDN. RR is the owner of the George-Huntington-Institut GmbH and the QuantisMedis GmbH. He is a member of the EHDN Executive Committee and of the Huntington Study Group Executive Committee.

The remaining 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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Plasma and Serum Alpha-Synuclein as a Biomarker of Diagnosis in Patients With Parkinson's Disease

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Background: Parkinson's disease (PD) is the second most common neurodegenerative disease, and α-synuclein plays a critical role in the pathogenesis of PD. Studies have revealed controversial results regarding the correlation between motor severity and α-synuclein levels in peripheral blood from patients with PD.

Objective: We examined α-synuclein levels in plasma or serum in patients with PD and investigated the relationship between plasma or serum α-synuclein level and motor symptom severity.

Methods: We recruited 88 participants (48 patients with PD and 40 healthy controls). Clinical information was collected, and venous blood was drawn from each participant to be processed to obtain plasma or serum. The plasma or serum α-synuclein level was detected using monoclonal antibodies with magnetic nanoparticles, and was measured through immunomagnetic reduction. Plasma or serum α-synuclein levels were quantitatively detected.

Results: In patients with PD, the means of plasma and serum α-synuclein level were 3.60 ± 2.53 and 0.03 ± 0.04 pg/mL, respectively. The areas under the receiver operating characteristic curve of plasma and serum α-synuclein for distinguishing patients with PD from healthy controls were 0.992 and 0.917, respectively. The serum α-synuclein level also showed a significant correlation with patients in H-Y stages 1–3 ($r = 0.40$, $p = 0.025$), implying that the serum α-synuclein level may be a potential marker of motor symptom severity in patients with early PD.

Conclusions: Our data suggest that the α-synuclein level in serum or plasma can differentiate between healthy controls and patients with PD. Serum α-synuclein levels moderately correlate with motor severity in patients with early PD.

Keywords: Parkinson disease, α-synuclein, biomarker, modified Hoehn and Yahr scale, immunomagnetic reduction

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INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease, affecting more than 1% of the global population over the age of 65 years (1). The severity of motor symptoms in patients with PD is commonly evaluated with unified Parkinson's disease rating scale (2) or modified Hoehn and Yahr scale (modified H-Y scale) (3). Because those scales are subjective, there are many objective biomarkers to be developed to diagnose PD or predict disease progression currently. Depending on pathogenesis, many published studies focused on α-synuclein, which is a major constituent of Lewy bodies (4). The majority of researches on levels of different subtype α-synuclein including total (5–7), oligomeric (8, 9), and phosphorylated (9, 10) form in body fluids have been conducted for the cerebrospinal fluid (CSF) (8–14); however, only a few studies have investigated α-synuclein levels in peripheral blood (5–7, 15, 16), and two studies have been done in serum (16, 17). The results of those body fluids between patients with PD and normal control has been controversial (18, 19); additionally, the correlation between the severity of motor symptoms and the levels of α-synuclein in CSF or peripheral blood is still under investigation (7, 9). Therefore, we investigated whether the plasma or serum α-synuclein levels of patients with PD are correlated with motor symptom severity by using a newly developed commercial antibody.

MATERIALS AND METHODS

Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (CGMH) in Taiwan (IRB No. 104-7443B) and all examinations were performed after obtaining written informed consents.

Patient Recruitment

The appropriate number was predicted by G-power, which was a software developed by Universitat Dusseldorf (20). Under preset alpha error (0.05), statistical power (0.9), and medium effect size (0.5), the predicted sample number was 86. On the other hand, Online web-tool, easyROC (http://www.biosoft.hacettepe.edu.tr/easyROC/), was used to predict adequate sample size in ROC curve. Based on alpha error (0.05), statistical power (0.9), area under the ROC curve (0.75), and allocation ratio (1), the predicted minimal sample size (control and case) was 20 and 20, respectively. Thus, we recruited 88 participants, including 48 patients with PD (hereinafter referred to as PDs) and 40 healthy controls (hereinafter referred to as HCs). PD was diagnosed by an experienced neurologist according to the Movement Disorder Society Clinical Diagnostic Criteria for PD (21). We collected clinical information including initial presentation, sex, age, disease duration, cognitive function, and modified H-Y scale scores. According to the modified H-Y scale, patients scoring between 1 and 3 were classified as having early PD, whereas those scoring between 4 and 5 were classified as having advanced PD.

Plasma and Serum Samples

Venous blood (10 mL) was drawn and blood samples were processed to obtain plasma or serum from each participant within 1 h of collection. Plasma was prepared after collection of the whole blood in Ethylenediaminetetraacetic acid-treated tube, while serum was prepared by leaving blood samples undisturbed at room temperature for 15–30 min. Those processed samples were treated by centrifugation for 15 min at 1,500 g in refrigerated condition, and the resulting supernatant was designated plasma or serum. Following centrifugation, the serum or plasma was immediately transferred into a clean and low residue polypropylene tube using a pipette with low-residue tip. Plasma and serum were stored at −80°C for <3 months before examination. Samples which are hemolyzed, icteric or lipemic were not used.

Detection and Measurement of Plasma and Serum α-Synuclein in Human Samples

The level of α-synuclein in peripheral blood was examined using the immunomagnetic reduction (IMR) assay. The reagent (MF-ASC-0060, MagQu, Taiwan) used in the assay contained magnetic Fe3O4 nanoparticles (MF-DEX-0060, MagQu, Taiwan) biofunctionalized with monoclonal antibodies which recognizes amino acid residues 121–125 of human α-synuclein (SC-12767, Santa Cruz Biotech, Texas, USA), which was used in a previously study for total α-synuclein measurement (22). The antibody-functionalized magnetic nanoparticles were well-dispersed in phosphate-buffered saline (pH of 7.2). Then, 80 μL of the reagent was mixed with 40 μL of plasma or serum for α-synuclein level measurement by using an alternative current magnetosusceptometer (XacProS, MagQu, Taiwan). The alternative-current magnetic susceptibility of the mixture approximates the association between magnetic nanoparticles and α-synuclein molecules in the plasma or serum. Based on the reduction in the alternative-current magnetic signal of the mixture that was recorded using the analyzer, the α-synuclein level in the plasma or serum could be quantified. Detailed methodologies to immobilize antibodies onto magnetic Fe3O4 nanoparticles, to measure the magnetic concentration of the immunocomplex and to establish a standard curve using liquid form of recombinant human α-synuclein protein (ab51189, Abcam, UK) spiked in phosphate buffered saline between α-synuclein level with and reduction in the alternative-current

TABLE 1 | Clinical characteristics of the patients with PD and healthy controls.

	Control (n = 40)	PD (n = 48)	P-value
Age (years)	64.7 ± 6.8	67.2 ± 9.8	0.17
Gender (male, %)	52.5	50.0	0.83
Duration(years)	N.A.	9.1 ± 6.5	N.A
MMSE	N.A.	23.9 ± 5.8	N.A
Hoehn-and-Yahr stage	N.A.	2.8 ± 1.4	N.A

Numbers are expressed as mean ± standard deviation. P-values were determined by a parametric t-test and non-parametric chi-square and fisher exact tests.
MMSE, Mini-Mental Status Examination; N.A., not available; PD, Parkinson's disease.

magnetic signal have been published previously (23). The measurement of the α-synuclein level in plasma or serum was duplicated to improve accuracy.

Statistical Methods and Data Analysis

Numerical variables were expressed as the mean ± standard deviation. Because of small sample size, the Mann-Whitney U test was used for the comparisons of disease activity between HCs and PDs. A receiver operating characteristic (ROC) curve was applied for distinguishing between the PDs and HCs via the levels of serum or plasma α-synuclein if difference between two groups existed. Additionally, correlation between serum and plasma α-synuclein level, and the relationship between the levels of serum or plasma α-synuclein and disease activity were analyzed using linear regression, and correlation coefficient (*r*) was presented. We performed all analyses using SPSS software, version 24 (IBM, Armonk, NY, USA). A *P*-value of <0.05 was considered significant.

RESULTS

Among the recruited patients, the ratio of the men in the HCs (21/40) was similar to that in the PDs (24/48) ($P = 0.83$). The average age of the HCs and PDs was 64.7 and 67.2 years, respectively ($P = 0.17$; **Table 1**). PDs had mild cognitive impairment (minimal mental status examination: 23.9 ± 5.8), and various degrees of constipation. Levodopa equivalent dose was 869.3 ± 501.2 among PDs.

The level of plasma α-synuclein in HCs and PDs were 0.157 ± 0.285 pg/mL (coefficient of variance (CV): 11.4%) and 3.598 ± 2.531 pg/mL (CV: 13.7%), respectively (**Figure 1A**); in contrast, the level of serum α-synuclein in HCs and PDs were 0.0038 ± 0.0020 (CV: 10.9%) and 0.031 ± 0.042 (CV: 13.1%), respectively (**Figure 1B**). Compared with the HCs, both plasma and serum α-synuclein levels were significantly higher in the PDs ($P < 0.001$ and $P < 0.001$, respectively). The areas under the ROC

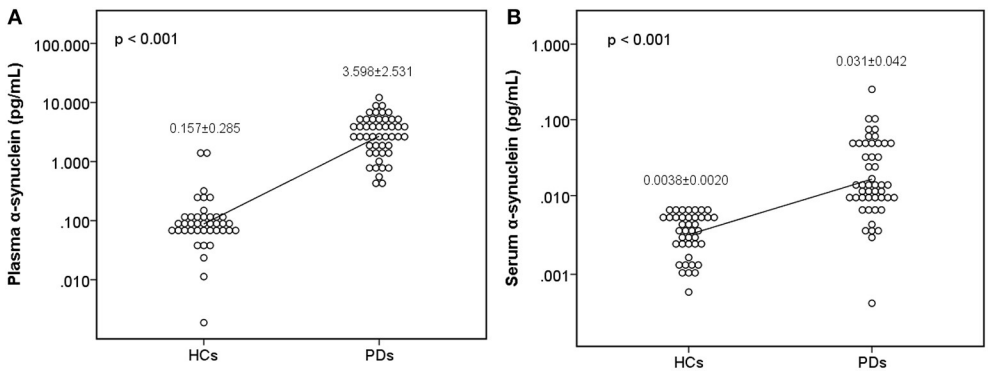

FIGURE 1 | Scatter diagram of plasma α-synuclein levels and serum α-synuclein levels on a logarithmic scale between the healthy control group and the Parkinson's disease group. Significant differences in α-synuclein levels were detected between the two groups in both plasma samples **(A)** and serum samples **(B)**. PD, Parkinson's disease.

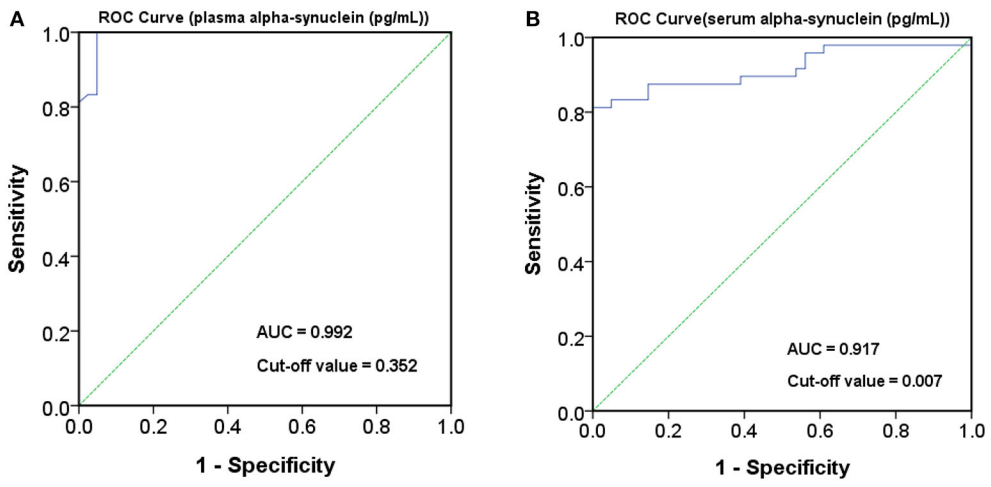

FIGURE 2 | Receiver operating characteristic (ROC) curve for plasma and serum α-synuclein levels to detect Parkinson's disease (PD). ROC curves of plasma **(A)** and serum **(B)** α-synuclein levels for distinguishing PD patients from healthy controls (HCs). AUC, area under the ROC curve.

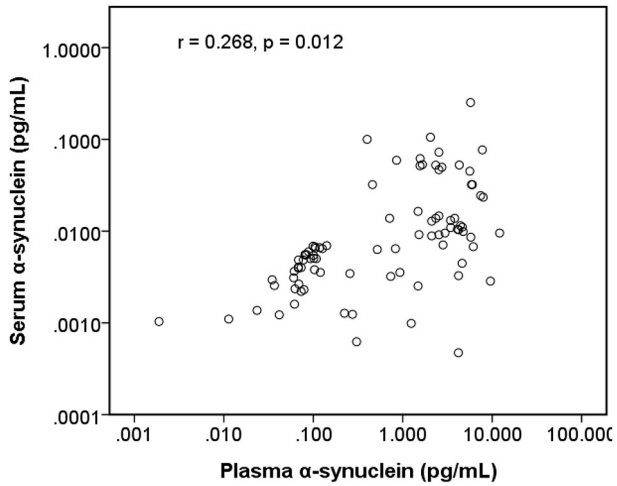

FIGURE 3 | Scatter diagram between plasma α-synuclein levels and serum α-synuclein levels on a logarithmic scale.

curve (AUCs) of plasma (**Figure 2A**) and serum (**Figure 2B**) α-synuclein levels to distinguish PDs from HCs were 0.992 (cutoff value = 0.352 pg/mL) and 0.917 (cutoff value = 0.007 pg/mL), respectively. A weak correlation was observed between plasma and serum α-synuclein levels, and the correlation coefficient of the linear regression was 0.268 ($P = 0.012$; **Figure 3**).

Among early PDs (modified H-Y stage = 1–3; **Figure 4**), the level of serum α-synuclein was correlated with modified H-Y stage ($r = 0.402$, $P = 0.025$), whereas plasma α-synuclein was not ($r = 0.044$, $P = 0.815$). Neither plasma ($r = 0.081$, $P = 0.585$) nor serum α-synuclein ($r = 0.134$, $P = 0.366$) correlated with modified H-Y stage in all PDs (**Figure 5**).

DISCUSSION

Currently, no reliable biofluid biomarker for distinguishing PDs from HCs has been found. In our study, we demonstrated that not only plasma but also serum α-synuclein levels were higher in the patients with PD than in the HCs through IMR. For the first time, we demonstrated a positive correlation between the serum levels of α-synuclein and the degree of motor symptoms among the patients with early stages of PD. Our observations indicate the potential of serum α-synuclein to be used as an objective biomarker for PD for accurate diagnosis or disease progression monitoring.

α-synuclein, a principal constituent of Lewy bodies, plays a crucial role in the pathogenesis of PD. Because α-synuclein is widely expressed by central and peripheral tissue (24, 25), many studies have targeted different forms of α-synuclein in different samples, such as CSF or blood. Total, oligomeric or phosphorylated α-synuclein levels in CSF could distinguish PDs from HCs (26), and only oligomeric α-synuclein levels in CSF correlated negatively with the severity of motor symptoms (9). By contrast, significant increases in plasma α-synuclein levels have been found in PD patients in previously published studies (5–7, 15, 19). For example, Lee et al. used a commercially available enzyme-linked immunosorbent assay (ELISA) kit to measure the plasma α-synuclein level in subjects with PD. According to the manufacturer's protocol (RPN 5902, Amersham Biosciences, UK), the monoclonal antibody was specific for human synuclein peptide 117–131. The level of α-synuclein was 79.9 ± 4.0 pg/ml in patients with PD (5). Ding et al. used a Chinese sourced commercial ELISA showing higher plasma level of α-synuclein (319.56 ± 64.22 vs. 274.31 ± 70.71, $p = 0.004$) than controls (6). Foulds et al. reported vastly different results using same monoclonal antibody in individual subjects (15), which might be due to their recombinant standard was highly impure. According to the published papers, the commonly used technologies for assaying plasma α-synuclein included bead-based multi-analyte profiling technology (Luminex), sandwiched ELISA or IMR (19). However, these reports showed highly inconsistent results in levels of plasma α-synuclein. Mata et al. and Shi et al. used Luminex assays to evaluate plasma α-synuclein in PD; and the levels were 46.9 ± 32.6 and 36.8 ± 23.9 ng/mL, respectively (27, 28). The antibodies used in both studies were biotinylated anti-human α-synuclein antibody (R&D systems, Minneapolis, MN, USA). It is unclear, however, whether these α-synuclein species were oligomers or monomers conjugated with other macromolecules.

Moreover, Wang et al. used the same kit to measure plasma α-synuclein and found sub-ng/ml levels in PD and HC (29). The principal origin of α-synuclein are red blood cells (RBCs) (>99% of its blood levels), with the residue in plasma. Hemolysis and platelet contamination confound the results. The inconsistence in levels of plasma α-synuclein among groups using the same assay kits might be possibly caused by plasma preparation and storage period of plasma samples. Groups using ELISA technologies reported several tens of pg/ml, or thousands of ng/ml for plasma α-synuclein in PD and HC (5, 15). The levels of plasma α-synuclein using ELISA are different from that using Luminex. This difference could be due to antibodies, signal sensing technologies and sample preparation. Therefore, we could also expect that high heterogeneity across studies could be attributed to the co-existence of several components such as assays, disease duration, disease staging, and study setting.

Thus, the levels of α-synuclein in plasma measured by IMR could be different from those using Luminex or ELISA. In this study, the levels of α-synuclein in plasma are pg/ml, which is consistence with previous work using IMR (7). Moreover, the discrimination between PD and HC using the levels of plasma α-synuclein is clear in this and previous works (5, 23). These results reveal the high reliability of detected levels of plasma α-synuclein using IMR, although the levels using IMR are much lower than that using Luminex or ELISA.

The potential mechanism underlying increased plasma and serum levels of α-synuclein in patients is still unclear. α-synuclein is a product of *SCNA* gene in neurons, erythrocytes, lymphocytes, and enteroendocrine cells (25). The protein is released from neurons through exocytosis and membrane leakage such as apoptosis, necrosis, or other damage (30). According to gut-brain axis of PD, misfolded or toxic α-synuclein is originated from the peripheral enteric plexus. Therefore, the increase in plasma and

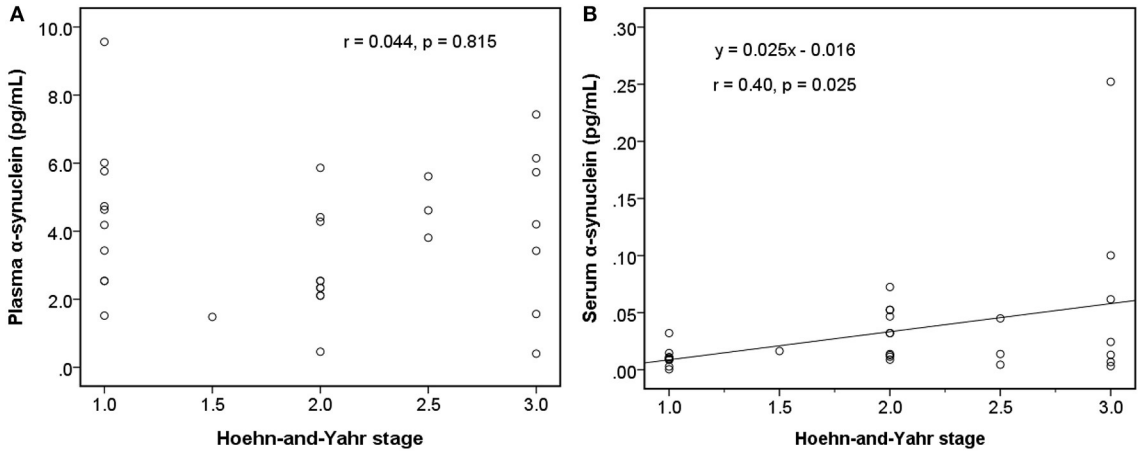

FIGURE 4 | Relationship between α-synuclein levels in plasma or serum samples and clinical severities [modified Hoehn and Yahr stage (H-Y stage)] among patients with early Parkinson's disease (modified H-Y stage from 1 to 3). **(A)** No correlation was detected between α-synuclein levels in plasma samples and modified H-Y stage. **(B)** α-synuclein levels in serum samples and modified H-Y stage were correlated.

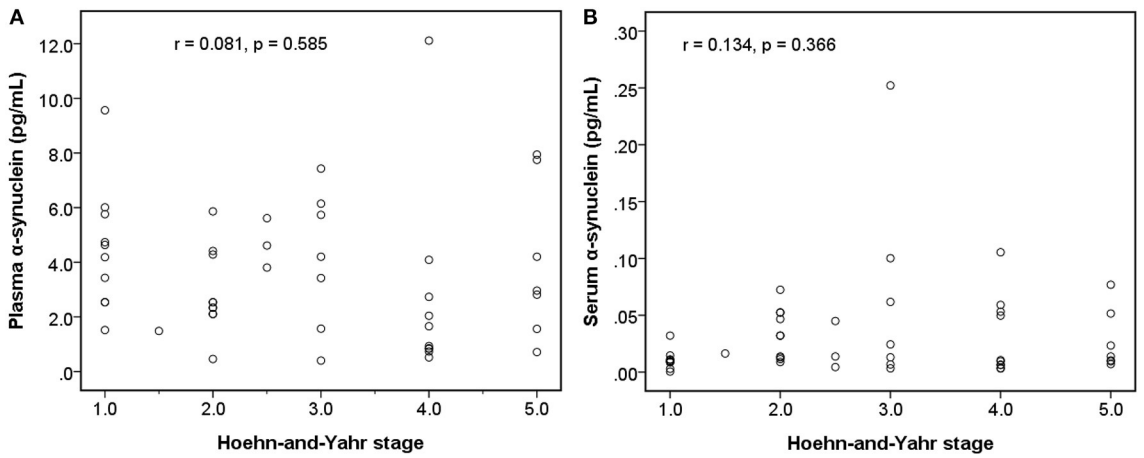

FIGURE 5 | Relationship between α-synuclein levels in plasma or serum samples and clinical severities [modified Hoehn and Yahr stage (H-Y stage)] among patients with Parkinson's disease. **(A)** No correlation was detected between α-synuclein levels in plasma samples and modified H-Y stage. **(B)** No correlation was detected between α-synuclein levels in serum samples and modified H-Y stage.

serum α-synuclein levels may be attributed to peripheral origin including enteric plexus or erythrocyte in early stage PD (31, 32). Along with disease progression, abnormal erythrocyte-derived and peripheral neuron-derived α-synuclein migrates to the brain, and then deposits (33). The α-synuclein can be removed from the brain through exocytosis with exosomes, and the exosomes containing α-synuclein and specific surface markers derived from the brain can be found in peripheral blood (34). Excess α-synuclein in the brain may trigger efflux of the protein from the CSF to blood; thus, the α-synuclein level increased in plasma and serum but decreased in the CSF (35, 36). The α-synuclein level is higher in blood than in the CSF; therefore, its transport from the CSF to blood may be energy dependent for concentration gradient (37). Because of the limited number of pump and energy for efflux of excess α-synuclein, serum, and plasma α-synuclein level may become steady in the late stage of PD and excess α-synuclein deposited in brain parenchyma. This possible can explain why serum and plasma α-synuclein levels could distinguish patients with PD from HCs, whereas they could not correlate with motor symptom severity in the late stages of PD.

Another critical finding in our study was that serum α-synuclein levels showed a positive correlation with motor symptom severity in patients in the early stages of PD, whereas plasma α-synuclein level did not. The plasma α-synuclein level was significantly higher than the α-synuclein level in serum. Higher plasma α-synuclein level may be attributed to cell lysis of free erythrocyte and platelets (38), and to more α-synuclein-containing exosomes from free erythrocytes (33), whereas serum might contain fewer exosomes because of erythrocytes that are

trapped in the fibrin complex. Furthermore, proteases such as plasmin in platelet activation cleaved free α-synuclein from cell lysis in serum (39) during clot formation; by contrast, materials in exosome may be protected (40). As a result, serum contained less erythrocyte-derived α-synuclein in the free form or in the exosome. The correlation between the levels of plasma and serum α-synuclein became week, and serum α-synuclein, which contained more CNS-derived α-synuclein in exosome, may reflect the α-synuclein burden in the CNS more accurately.

This study has several limitations. First, this is a cross-sectional study, so a longitudinal study is needed to keep track of the plasma or serum α-synuclein levels in one subject to disclose the change of α-synuclein level in plasma or serum over the time during the disease progression. Second, the sample size of the study is still relatively small; therefore, a larger and multi-center study discovering the relationship between α-synuclein in peripheral blood and disease activity is necessary to validate the practicality of using plasma and serum α-synuclein as a reliable biomarker for PD. Third, because the selected antibody in our study only identify very short amino acid sequence 121–125 of α-synuclein, alpha-synuclein with epitope modified by polymerization, methylation, phosphorylation, or other chemical reaction could be not detected in the study. Moreover, measuring sub-picograms of protein may be influenced significantly by measurement bias and cross-reactivity of a selected antibody. Further studies using another commercial antibody through the same assay is necessary to validate this new technique and to reduce the influence of cross-reactivity.

In conclusion, our data suggests that α-synuclein levels in serum or plasma can differentiate between HCs and patients with PD. Serum α-synuclein levels moderately correlated with motor symptom severity in patients with early PD. A larger, multicenter study is necessary to investigate the mechanism underlying α-synuclein aggregation and the relationship between α-synuclein and disease progression.

ETHICS STATEMENT

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (CGMH) in Taiwan (IRB No.104-7443B) and all examinations were performed after obtaining written informed consents.

AUTHOR CONTRIBUTIONS

Y-RW conceived and designed the study. S-YY, C-CY, and C-WenC conducted the experiments. C-WeiC and Y-RW analyzed the data and wrote the paper. All authors read and approved the final manuscript.

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Conflict of Interest: S-YY is an employee at MagQu Co., Ltd. and holds stock shares of MagQu. C-CY has been an employee at MagQu Co., Ltd., and is resigned now.

The remaining 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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Gut Microbiota Altered in Mild Cognitive Impairment Compared With Normal Cognition in Sporadic Parkinson's Disease

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Background and Aim: Gut bacteria play an important role in the pathogenesis of Parkinson's disease (PD). However, the alteration of fecal microbiota in PD with cognitive impairment remains unexplored. This study aimed to explore whether the gut microbiota of patients with PD having mild cognitive impairment (PD-MCI) were different from those with PD having normal cognition (PD-NC) and from healthy controls (HC). Also, the study probed the association between altered gut microbiota and cognitive ability in patients with PD.

Methods: The fecal bacteria composition and short-chain fatty acids of 13 patients with PD-MCI, 14 patients with PD-NC, and 13 healthy spouses were analyzed using 16S ribosomal RNA sequencing and gas chromatography–mass spectrometry.

Results: Compared with HC, the fecal microbial diversities increased in patients with PD-MCI and PD-NC. After adjusting the influence of age, sex, body mass index, education, and constipation using the statistical method, the relative abundances of two families (Rikenellaceae and Ruminococcaceae) and four genera (*Alistipes*, *Barnesiella*, *Butyricimonas,* and *Odoribacter*) were found to be higher in the feces of the PD-MCI group compared with the other two groups. Moreover, the abundance of genus *Blautia* and *Ruminococcus* decreased obviously in the PD-MCI group compared with the PD-NC group. Further, the abundance of genera *Butyricimonas, Barnesiella, Alistipes, Odoribacter*, and *Ruminococcus* negatively correlated with cognition ability.

Conclusion: Compared with HC and patients with PD-NC, the gut microbiota of patients with PD-MCI was significantly altered, particularly manifesting in enriched genera from Porphyromonadaceae family and decreased the abundance of genera *Blautia* and *Ruminococcus*.

Keywords: Parkinson's disease, cognition impairment, gut micro biome, short fatty acids, high throughput sequencing

INTRODUCTION

Parkinson's disease (PD) is the most prevalent neurodegenerative motor disease. Cognitive impairment is a frequent complication of the non-motor symptoms in PD, commonly described as PD with mild cognitive impairment (PD-MCI) and PD dementia (PDD), and is recognized to worsen the outcomes. Early studies indicated dementia prevalence of 15–20% after 5 years and 46% after 10 years (1, 2). The Movement Disorder Society (MDS) Task Force concluded that PD-MCI was common in non-demented patients (mean prevalence, 27%; range, 19–38%) and associated with the subsequent development of PDD (3).

Recently, converging lines of evidence supported the hypothesis that gut microbiota were associated with the pathogenesis of PD (4, 5). Many of these studies focused on the composition of gut microbiota (6, 7) and the bacterial metabolites, short-chain fatty acids (SCFAs) (8). According to Braak's hypothesis (9), the accumulation of aberrant alpha-synuclein (α-Syn) is initiated in the gut and propagated via the vagus nerve to the brain. Recent animal studies also confirmed that gut bacteria regulated movement disorders by impacting neuroinflammation and aggregation of α-Syn, supporting Braak's hypothesis in the etiology of PD (10). Nonetheless, no previous study investigated the composition of fecal microbiota in PD-MCI. This study hypothesized that fecal microbiota of patients with PD-MCI differed from those of matched healthy controls (HC) and patients with PD having normal cognition (PD-NC).

METHODS

Recruitment

Ethics approval and written informed consent were obtained from the hospital and the patients, respectively. The patients with PD were recruited and assessed in the Department of Neurology at the Guangdong Provincial People's Hospital, Guangdong Province, China (from June 2018 to January 2019). All patients eligible for this study were diagnosed for PD according to the UK Brain Bank criteria (11). Of these patients, 14 were clinically diagnosed with PD-NC and 13 with PD-MCI based on the MDS Task Force Guidelines (12). Moreover, 13 age-matched healthy spouses of the recruited patients were enrolled as controls (**Figure S1**).

Clinical Assessment

Clinical data were collected through face-to-face interviews with movement disorder specialists. Each participant's weight and height were measured, and the body mass index (BMI) was calculated. PD clinical characteristics included disease duration, education, motor and non-motor symptoms, and medication. The part III scores of MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and Hoehn and Yahr stage (H-Y stage) were analyzed during the "on" state. The PD-related non-motor symptoms were evaluated using the Parkinson's Disease Questionnaire (PDQ-39) and activities of daily living (ADL). Constipation was assessed using the Wexner constipation score. Cognition abilities were estimated using the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA), and the scores were obtained from two other neuropsychological tests in each of the five cognitive domains. On the day of the stool sample collection, all the participants completed a questionnaire assessing their dietary habits in the last month, including the consumption of caffeine and alcohol.

16S rRNA Amplicons and SCFAs Analysis

Each study participant was given a fecal collection container to collect a fecal sample. The containers were stored at −80°C until DNA extraction. The DNA was extracted using a QIAamp DNA Stool Mini Kit (Qiagen, Hilden, Germany). Polymerase chain reaction (PCR) amplification of *16S rRNA* genes was performed with general bacterial primers (515F 5′-GTGCCAGCMGCCGCGGTAA-3′and 926R 5′-CCGTCAATTCMTTTGAGTTT-3′). Prior to library pooling, the barcoded PCR products were purified using a DNA gel extraction kit (Axygen, China) and quantified using the FTC-3000 real-time PCR. The *16S rRNA* amplicon (V3–V4 regions) sequencing analysis was performed using an Illumina MiSeq 2 × 300bp (MiSeq v3 Reagent Kit, CA, USA). The 16S sequences were analyzed using a combination of mothur (version 1.33.3), UPARSE (usearch version v8.1.1756), and R software (version 3.2.3). The demultiplexed reads were clustered at 97% sequence identity into operational taxonomic units (OTUs) using the UPARSE pipeline. The OTU representative sequences were selected and their taxonomies were assigned against the Silva 128 database with a confidence score ≥0.6 using the classify.seqs command in mothur. The OTU taxonomies (from phylum to genera) were determined based on National Center for Biotechnology Information. The measurement of SCFAs was carried out using the Gas Chromatography and Mass Spectrometry (GC-MS) analysis and a single quadrupole mass spectrometer equipped with 6890N GC (Agilent Technologies, CA, USA). Seven SCFA standards were obtained from Sigma–Aldrich (MO, USA) and Sinopharm Chemical Reagent Co., Ltd (Shanghai, China) at a minimum purity of 98%. The GC was fitted with a capillary column Agilent HP-INNOWAX (30 m × 0.25 mm) (Agilent Technologies).

Bioinformatic and Statistical Analysis

The SPSS (version 20.0, SPSS Inc., IL, USA) and R software (version 3.2.3, the R Project for Statistical Computing) were used for the statistical analysis of data. The normality test was conducted using the Shapiro–Wilk test. The three groups were compared using the one-way analysis of variance and Pearson's chi–square test for quantitative and categorical variables, respectively. Subsequently, the *post hoc* Bonferroni adjustments were applied to account for multiple comparisons, with alpha set at 0.0167. The differences between PD-NC and PD-MCI groups were compared using the Student *t*-test and Pearson's chi-square test for quantitative and categorical variables, respectively, with alpha set at 0.05. Both alpha-diversity (Chao, Shannon, Simpson, sobs indexes, and so on) and beta-diversity metrics (unweighted UniFrac ANOSIM indexes, weighted UniFrac ANOSIM indexes, and PERMANOVA analysis) were calculated using Quantitative

Insights into Microbial Ecology (13, 14). Alpha-and beta-diversity analyses were performed using mothur and visualized using principal coordinate analysis. Differences in abundance (at multiple taxonomic levels) among three groups were detected using a Kruskal–Wallis test. The linear discriminant analysis (LDA) effect size method was used to characterize the taxa with statistical significance and biological relevance (13, 15). Differences in significant bacterial communities among the three groups and between the clinical parameters were evaluated using a generalized linear model (GLM) (16). An OTU normalized by DESeq table was used to infer microbiota metabolic functions using the Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUSt). The OTU tables were normalized by copy number, and functions were predicted using the Kyoto Encyclopedia of Genes and Genomes (KEGG) orthologs (5). Significant KEGG pathways at level 2 and 3 for the fecal microbiome of the three groups identified by STAMP software. In STAMP, differences in abundances among the PD-MCI, PD–NC and healthy groups were compared using the Kruskal–Wallis test. The Kruskal–Wallis test was also used for testing the difference in SCFAs between the three groups. Correlations between clinical parameters as well as significant bacterial communities and SCFAs for 40 participants were calculated using Spearman's rank-correlation analysis.

RESULTS

Demographics

A total of 40 Cantonese people were recruited for the study. Both the patients and the controls reported to be omnivores with a conventional diverse diet and without any dietary restrictions. No significant differences in age, BMI, education, and ADL scores were found among the three groups. Moreover, no significant discrepancy in PD disease duration, MDS-UPDRS-III score, H-Y stage, anti-Parkinson medicine intake, and PDQ-39 scores was found between the PD-NC and PD-MCI groups. Significant differences in the MMSE and MoCA scores were found among the three groups ($P = 0.014$; $P < 0.001$). Moreover, obvious differences in MoCA scores were found between the PD-MCI and HC groups ($P < 0.001$, $P_{corr} < 0.001$) as well as between the PD-MCI and PD-NC groups ($P < 0.001$, $P_{corr} < 0.001$), while no difference was found between the PD-NC and HC groups ($P > 1.000$, $P = 0.391$). The sex difference reflected higher prevalence of PD in men and greater participation of women as volunteers. Further, a higher proportion of patients reported constipation in the PD-NC and PD-MCI groups compared with the HC group. However, the influence of sex and constipation were corrected after GLM analysis (**Table 1**).

Alpha and Beta-Diversity

On average, about 33,259 (±3809; median 29,694) read pairs were sequenced per sample. In total, 561 different OTUs were identified across the 40 samples. The full dataset included bacteria from 108 genera, 42 families, 24 orders, 19 classes, and 11 phyla. The phylum Bacteroidetes was typically the dominant phylum in the gut microbiome (**Figure S2**). As for fecal microbiota, the mean community alpha-diversity indexes were significantly higher in the PD-NC and PD-MCI groups than in the HC group (Chao, Simpson, ACE, and Shannon indexes). Moreover, the PD_whole tree index was obviously higher in the PD-MCI group than in the HC group. However, no significant difference in alpha-diversity index was found between the PD-NC and PD-MCI groups. An obvious discrepancy was also found in beta-diversity based on the unweighted UniFrac ANOSIM metric (qualitative, ANOSIM $R = 0.183$, $P = 0.002$), but not the weighted UniFrac ANOSIM metric (quantitative, ANOSIM $R = 0.053$, $P = 0.082$) among the PD-MCI, PD-NC, and HC groups. Furthermore, based on the UniFrac index (PERMANOVA analysis on weighted UniFrac—HC vs. PD-NC: $R^2 = 0.118$, $P = 0.004$; HC vs. PD-MCI: $R^2 = 0.086$, $P = 0.059$; and PD-MCI vs. PD-NC: $R^2 = 0.037$, $P = 0.438$; unweighted UniFrac—HC vs. PD-NC: $R^2 = 0.119$, $P = 0.001$; HC vs. PD-MCI: $R^2 = 0.074$, $P = 0.065$; and PD-MCI vs. PD-NC: $R^2 = 0.078$, $P = 0.039$), the structures of fecal microbiota were found to be significantly different between PD-MCI and PD-NC groups (**Figure 1**).

Alteration of Fecal Microbiota

The results suggested a remarkable difference in fecal microbiota among the PD-MCI, PD-NC, and healthy groups based on the LDA LEfSe analysis. The LDA analysis is often used to identify the presence and effect size of region-specific OTUs among different groups. After the LDA method, a higher relative abundance of the genus *Veillonella* and was detected in the HC group compared with the PD-NC and PD-MCI groups, whereas the abundance of the genera *Blautia* and *Ruminococcus* was higher in the PD-NC group compared with the remaining two groups. Additionally, the relative abundance of genera *Alistipes*, *Barnesiella*, *Butyricimonas*, *Odoribacter*, and *Anaerotruncus* was higher in the PD-MCI group compared with the other two groups (**Figure S3**).

Generalized Linear Model

The GLM was used to model the microbiota that were significantly different at multiple taxonomic levels among the three groups after controlling for possible confounding factors (age, gender, BMI, education, and constipation). At the phylum level, the abundance of Bacteroidetes was obviously higher in the HC group than in the other two groups, while Actinobacteria was more abundant in the PD-MCI group. Particularly, the main differences between feces from the PD-MCI, PD-NC, and HC groups were associated with the genera *Alistipes*, *Barnesiella*, *Butyricimonas*, and *Odoribacter* ($P < 0.05$), suggesting that these microbiota were associated with PD-MCI. Additionally, the alteration in the abundance of genus *Blautia* (class Clostridia) and *Ruminococcus* obviously increased in the PD-NC group compared with the PD-MCI group ($P < 0.05$) (**Table 2**).

Predictive Function Analysis

PICRUSt based on closed-reference OTU was used to predict the abundances of functional categories in the KEGG ortholog (KO). In this study, 664 KOs having significantly different abundances were identified between PD and HC fecal samples. A plot of top 20 KOs identified with significantly different

TABLE 1 | Selected demographic and clinical parameters of HC group, PD-NC group and PD-MCI group.

		HC ($n = 13$)	PD-NC ($n = 14$)	PD-MCI ($n = 13$)	*P-value*	*Pcorr (Bonferroni corrected)*		
						PD-NC VS.PD-MCI	PD-NC VS. HC	PD-MCI VS. HC
Age [a]		63.00 (8.76)	60.00 (9.20)	65.23 (10.96)	0.379	0.506	>1.000	>1.000
Sex[b]	F	10	4	4	0.019 (7.943)	−0.901 (0.016)[1]	−0.012 (6.312)[2]	−0.018 (5.571)[3]
	M	3	10	9				
BMI[a]		22.67 (2.06)	22.63 (2.52)	22.74 (2.62)	0.993	>1.000	>1.000	>1.000
Education[a]		10.46 (3.53)	13.93 (2.62)	9.08 (4.46)	0.046	0.048	>1.000	0.242
ADL[a]		14.00 (0.00)	16.36 (4.24)	19.77 (10.86)	0.099	0.577	>1.000	0.101
MMSE[a]		28.54 (1.56)	28.00 (1.67)	26.38 (2.40)	0.014	0.087	>1.000	0.016
MoCA[a]		27.23 (1.53)	26.07 (1.77)	20.08 (2.43)	<0.001	<0.001	0.391	<0.001
Wexner score[a]		3.92 (2.99)	8.92 (2.02)	8.46 (1.98)	<0.001	>1.000	<0.001	<0.001
Duration[c]		–	5.64 (3.34)	7.00 (8.07)	0.568 (0.579)			
H-Y stage[c]		–	1.89 (0.49)	1.80 (0.43)	0.637 (−0.478)			
MDS-UPDRS III[c]		–	30.07 (14.01)	30.08 (14.40)	0.999 (0.001)			
PDQ-39[c]		–	27.29 (19.44)	32.46 (19.16)	0.493 (0.696)			
Anti-Parkinson medicine[b]	Y	–	10	10	0.745 (0.106)			
	N	–	4	3				
COMT- inhibitors[b]	Y	–	3	2	0.686 (0.163)			
	N	–	11	11				
Alcohol[b]	Y	2	1	0	0.329 (2.222)			
	N	11	13	13				
Coffeine[b]	Y	6	4	2	0.229 (2.951)			
	N	7	10	11				

Data are shown as mean (SD).

[a]Means with One-way ANOVA. Pcorr denotes values corrected for multiple comparisons using the Bonferroni method. Alpha was set at 0.0167.

[b]Means with Pearson's Chi-square test. 1, 2, and 3 mean difference of sex between PD-MCI and PD-NC group, PD-NC and HC group as well as PD-MCI and HC group, respectively. Alpha was set at 0.05.

[c]Means with student's t-test. Alpha was set at 0.05.

abundances in the fecal microbiota among the three groups (FDR, $P < 0.05$) was made. Most reference pathways had more genes in HC compared with patients with PD, particularly pathways involved with energy metabolism, metabolism of cofactors and vitamins, glycan biosynthesis and metabolism, and metabolism of other amino acids in the level 2 KEGG pathway. The microbial gene functions related to membrane transport, including transporters, ATP-binding cassette (ABC) transporters, transcription factors, and benzoate degeneration, in the level 3 KEGG pathway were higher in the fecal microbiome of the PD-MCI group. Additionally, the microbial gene functions related to glycerophospholipid metabolism, base excision repair, and signal transduction mechanism in the level 3 KEGG pathway were higher in the fecal microbiome of the PD-NC group (**Figures S4A–C**).

Association Between Altered Microbiota and Cognitive Ability

Mostly, the abundance of altered fecal microbiota showed a negative association with cognitive performance. The genera *Ruminococcus, Bilophila, Desulfovibrio, Barnesiella, Butyricimonas, Acidaminococcus, Pyramidobacter*, and *Oxalobacter* were negatively associated with the MMSE scores. In addition, the genera *Alistipes*, *Sutterella, Odoribacter, Butyricimonas, Hungatella, Helicobacter, Solobacterium, Oscillospira*, and *Hydrogenoanaerobacterium* were negatively associated with the MoCA scores (**Figure S5**). No significant difference in the SCFA level was found among the three groups (**Table S1**). However, the isovaleric and isobutyric levels negatively correlated with the MMSE scores (**Figure S6**).

DISCUSSION

The differences in gut microbiota composition among Chinese patients with PD-MCI and PD-NC were not explored by previous studies. This study was novel in showing that the composition of gut microbiota changed in the PD-MCI group compared with the PD-NC and HC groups in the Chinese population. Both alpha-diversity and beta-diversity indexes in this study provided powerful evidence that the gut microbiota in patients with PD were different from those in HC, which was consistent with the results of previous studies (6, 13, 17, 18). Additionally, although no statistically significant differences were found with respect to commonly used alpha-diversity indices in the PD-MCI and PD-NC groups, this study confirmed the significant differences in beta-diversity indexes, particularly at the genus level, between

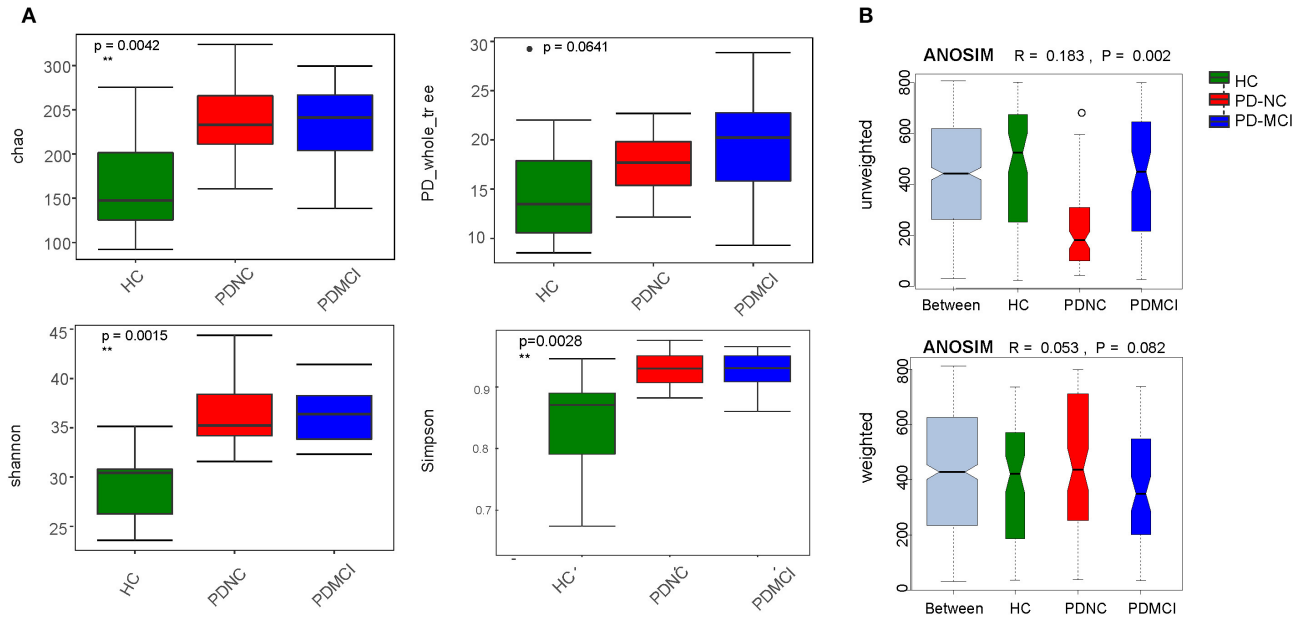

FIGURE 1 | The alpha-diversity and beta-diversity indices of the fecal microbiome in the PD-MCI, PD-NC, and health group. **(A)** Box plots depict differences in the fecal microbiome diversity indices among three groups according to the Chao 1 index, PD whole tree index, Shannon index and Simpson index based on the OTU counts. Each box plot represents the median, interquartile range, minimum, and maximum values. **(B)** Unweighted and weighted ANOSIMs Unifrac analysis based on the distance matrix of UniFrac dissimilarity of the fecal microbial communities in the three groups. Respective ANOSIM R values show the community variation between three groups and significant P values are indicated. The axes represent the two dimensions explaining the greatest proportion proportion of variance in the communities. OTU, operational taxonomic unit, ANOSIM, analyses of similarities.

the PD-MCI and PD-NC groups. Taken together, this study provided powerful evidence that the gut microbiota in PD-MCI were different from those of PD-NC and HC.

Bajaj and coworkers claimed that the Porphyromonadaceae family was associated with a poor cognitive performance (19). Recently, an increased abundance of *Porphyromonas gingivalis* was found in the feces of patients with Alzheimer's disease (20). According to the report of Lee and Trojanowski (21), PD shared similar pathological changes with AD, such as neurofibrillary tangles, amyloid-beta plaques, and tau propagation, which might accelerate the process of cognitive decline in PD. Then, consistent with former studies on gut microbiota in patients with PD (7, 8, 13, 18), a significant higher abundance of several genera of the Porphyromonadaceae family, including *Barnesiella*, *Butyricimonas*, and *Odoribacter* as well as *Alistipes* from the Rikenellaceae family was found in the PD-MCI group after GLM analysis in this study. Furthermore, this study found that the genus *Butyricimonas* negatively correlated with the MMSE and MoCA scores, in line with the results of a previous study in China (13). Also, the genus *Barnesiella* negatively correlated with the MMSE scores. Further, genera *Alistipes* and *Odoribacter* negatively correlated with the MoCA scores.

Consistent with the recent studies reporting a decrease in the abundance of the Lachnospiraceae family and genus *Blautia* in the feces of patients with PD (6, 7), this study found a significantly lower abundance of genus *Blautia* in the feces of the PD-MCI group compared with that in the PD-NC group. Although the correlation between genus *Blautia* and cognition performance was not observed in this study, it was reported that decreased abundance of the Lachnospiraceae family was associated with cognitive decline (7, 14). Nevertheless, the abundance of genus *Blautia* in the feces was higher in the patients with PD-NC compared with that in HC. As genus *Blautia* is the main force of SCFA-producing bacteria, it may prevent PD and reverse the disease as a compensatory mechanism in patients with PD-NC who are in the earlier stage of PD. To conclude, a further study on patients with different PD duration is needed to clarify the presence of genus *Blautia*.

Moreover, the functional interpretation of the intestinal microbiome demonstrated that the progressive enrichment of the modules for membrane transport in patients with PD-MCI suggested a potentially active communication between the microbiota and the host. Membrane transport pathways, such as those involving transporters and ABC transporters, are essential to cell viability and growth (22). Moreover, the ABC efflux transporters have two contradictory effects on the development and progression of neurological diseases. On the one hand, they protect the central nervous system (CNS) by promoting detoxification, but also constitute an obstacle to brain penetration, diffusion, and bioavailability of CNS therapeutics (23). The enriched modules for membrane transport were also found in patients with AD (14). The ABC transporter A1 (ABCA1) provides transcriptional and translational evidence that the expression of ABCA1, a key modulator of cholesterol

TABLE 2 | GLMs for fecal at multiple taxons based on differences between the PD-MCI, PD-NC, and healthy groups.

Group	Names	HC		PD-NC		PD-MCI		*b*-value	95% CI	*P*-value
		Mean	SD	Mean	SD	Mean	SD			
HC	p__Bacteroidetes	0.564046999	0.113589923	0.402128905	0.147438829	0.48026331	0.121810186	0	−998.033260567641 to 998.033260567641	1.137e-06
	o__Bacteroidales	0.564042053	0.113597935	0.401756967	0.147520749	0.47924935	0.122609195	0	−998.033260567641 to 998.033260567641	1.137e-06
PD-MCI	f__Rikenellaceae	0.006425124	0.011347647	0.020687389	0.026993264	0.02967223	0.026466718	−39.8473849333268	−10941342.7946813 to 10941263.0999115	1.3025e-06
	g__Alistipes	0.006425124	0.011347647	0.020687389	0.026993264	0.02967223	0.026466718	−39.8473849333268	−10941342.7946813 to 10941263.0999115	1.3025e-06
	g__Odoribacter	0.000900909	0.001422584	0.002948696	0.002723746	0.00412749	0.003971608	−52.6246355204889	−1050.65789608813 to 945.408625047152	1.137e-06
	g__Barnesiella	3.0488E-05	0.000102306	0.004597766	0.00878484	0.0105767	0.020618392	−431.814685623343	−32925434976288792 to 32925434976287928	8.0939e-06
	g__Butyricimonas	0.001504989	0.002013678	0.007188302	0.008751651	0.00760577	0.006425853	−28.0999953907513	−302470.142449766 to 302413.942458985	1.2346e-06
PD-NC	p__Actinobacteria	0.004058595	0.004839057	0.015536206	0.018817958	0.01553621	0.018817958	18.0978142678544	−979.935446299786 to 1016.1310748355	1.137e-06
	c__Clostridia	0.209882136	0.15364877	0.362103725	0.153287927	0.32155621	0.1598763	0	−32925434976288360 to 32925434976288360	8.0939e-06
	o__Clostridiales	0.209882136	0.15364877	0.362103725	0.153287927	0.32155621	0.1598763	0	−998.033260567641 to 998.033260567641	1.137e-06
	f__Ruminococcaceae	0.087099771	0.079416241	0.214225472	0.112880227	0.19383011	0.141379614	1.06927265837216e-22	−998.033260567641 to 998.033260567641	1.137e-06
	g__Ruminococcus	0.013865641	0.029772867	0.042217669	0.051187442	0.02865663	0.031597992	−212.234360350757	−229.783877868329 to −194.684842833186	1.1406e-06
	g__Blautia	0.012762124	0.010803305	0.026715962	0.021761436	0.00752145	0.012040004	−2.99712948530676	−394854347.322569 to 394854341.32831	1.3046e-06

Result of the GLMs for significant phylum, class, order, family and genera (sequence counts) based on the group factors and possible confounding factors (age, gender, BMI education and constipation) of 40 individuals.
The b-value (positive number) indicated the taxa were associated with PD-MCI and PD-NC patients.
GLM, general linear model; CI, confidence interval; BMI, body mass index.

transport across the plasma membrane, is dysregulated in the brain of patients with AD and this dysregulation is associated with increased severity of AD, whether measured functionally as dementia severity or neuropathologically as increased neuritic plaque and neurofibrillary tangle density (24). Nevertheless, the association between cognition decline in patients with PD and membrane transporters should be further studied because the functional prediction analysis in this study was based on OUT in partial 16s RNA and not very reliable compared with metagenomics.

SCFAs were found to be the main factors inducing microglial activation and acceleration, indicating the role of acceleration of SCFA deficiency in the pathogenesis of PD (4, 25). SCFAs are made by bacteria in the gut, notably those belonging to the family Lachnospiraceae. Although no significant difference in SCFA concentration was found among the three groups in this study, genus *Blautia*, which belongs to the Lachnospiraceae family, was reported to be depleted in the PD-MCI group compared with the HC group. To some extent, a shortage of SCFA may be a common consequence of illness rather than a specific cause or even a biomarker of PD (6). This is because the depletion of SCFA and SCFA-producing organisms has been observed in diverse disorders. On the contrary, this study revealed alterations in at least six genera of bacteria and numerous metabolic pathways among the three groups, indicating that there was more to the microbiome dysbiosis in PD with cognition decline than SCFA discrepancy.

A strength of this study was the recruitment of healthy spouses as controls who shared the same direct environment and diet; also, the individuals enrolled were all Cantonese people with a balanced diet. Moreover, the influence of anti-Parkinson's medicines was taken into consideration in this study. According to Scheperjans and colleagues, Catechol-O-methyltransferase inhibitors were the only anti-parkinsonian drug significantly associated with the abundance of Enterobacteriaceae, which did not show a difference among the three groups in this study either (18). Elucidating the differences in the fecal microbiota composition of the patients with PD-MCI may improve the understanding of the pathogenesis of PD with cognitive impairment, provide a foundation to predict the development of PDD, and help find a novel treatment for cognition decline in patients with PD. Nevertheless, apart from the limited sample size, a bias might be caused by the higher prevalence of healthy spouses in women in this study. Therefore, additional gender-balanced large-scale studies on participants with cognitive impairment in different domains are needed to validate the findings of this study. The relationships between constipation, dietary habits, distinct microbiota in patients with PD, and SCFA concentrations were not detected in this study, which need further exploration.

DATA AVAILABILITY STATEMENT

The datasets generated for this study can be found in the National Center for Biotechnology Information (NCBI) BioProject database with project number PRJNA561023.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Guangdong Provincial People's Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Conception: KN, LW, and TR. Organization: KN and TR. Execution: TR, JZ, QZ, and SJ. Statistical analysis and design: TR and YQ. Execution: TR and JC. Review and critique: YZ, YG, LW, and KN. Manuscript preparation and writing of the first draft: TR and SJ.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00137/full#supplementary-material

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BRIEF RESEARCH REPORT
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Orthostatic Hypotension Is Associated With Cognitive Decline in Parkinson Disease

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Introduction: Cognitive impairment and orthostatic hypotension (OH) are common, disabling Parkinson disease (PD) symptoms that are strongly correlated. Whether the relationship is causative or associative remains unknown. OH may occur without classic orthostatic symptoms of cerebral hypoperfusion (i.e., lightheadedness or dizziness). Whether longitudinal differences in cognition occur between symptomatic and asymptomatic OH patients has not been explored.

Objectives: We characterized the prevalence of OH, orthostatic symptoms, and cognitive impairment among PD patients and compared cognition between patients with and without OH, and between patients with symptomatic and asymptomatic OH.

Methods: Our cross-sectional, retrospective, observational study included 226 clinically diagnosed PD patients who underwent repeated standardized evaluations. Among these, 62 had longitudinal follow-up of > 3.5 years. We compared longitudinal Montreal Cognitive Assessment (MoCA) scores between patients remaining OH-free ($n = 14$) and those without baseline OH that developed OH ($n = 28$), matched for age, sex, education, and PD duration. We also compared MoCA scores between groups with asymptomatic OH ($n = 13$) and symptomatic OH ($n = 13$) matched for the same factors.

Results: In the cross-sectional analysis, OH patients had worse cognition. In the longitudinal analysis (mean follow-up = 5.3 years), OH patients had worse cognitive decline ($p = 0.027$). Cognitive impairment was similar between asymptomatic and symptomatic OH patients in the cross-sectional and longitudinal analyses.

Conclusions: OH is associated with cognitive impairment in PD. Further studies are needed in larger cohorts to expand our findings and to determine whether treating OH can prevent or delay cognitive dysfunction.

Keywords: orthostatic hypotension, Parkinson disease, cognition, dysautonomia, movement disorders

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INTRODUCTION

While the manifestations of Parkinson disease (PD) affecting movement are well-recognized, PD also causes myriad non-motor symptoms, including cognitive and autonomic disorders, which can be as disabling as motor symptoms (1). Approximately 25% of PD patients have cognitive dysfunction at any given time (2). The likelihood of developing cognitive impairment increases with disease duration—up to 50% of cognitively normal individuals develop mild cognitive impairment within 6 years of PD onset, and over 80% develop dementia within 20 years (3, 4).

Autonomic nervous system dysfunction causing neurogenic orthostatic hypotension (OH) affects up to half of PD patients (5). OH is defined as a drop in systolic BP (SBP) of at least 20 mmHg or diastolic BP (DBP) of at least 10 mmHg within 3 min of standing (6). OH may manifest with temporary symptoms caused by hypoperfusion to the brain and other organs when upright, including lightheadedness, fatigue, dizziness, syncope, and visual, gait, and cognitive disturbances. Orthostatic symptoms increase functional disability and fall risk and negatively affect quality of life (7, 8). Cognitive impairment and OH are strongly correlated in PD, although the underlying pathophysiology remains unclear (9, 10). Potential contributing factors include neurodegeneration, repeated episodes of cerebral hypoperfusion, and/or noradrenergic deficits (9–11).

Therapeutic strategies for OH aim to raise blood pressure (BP) to reduce problematic orthostatic symptoms related to hypoperfusion (i.e., feeling lightheaded, dizzy, or faint when standing, or syncope). Treatment options include non-pharmacologic measures such as increasing hydration, consuming extra sodium, and using an abdominal binder use, as well as adding pharmacological agents including droxidopa, midodrine, fludrocortisone, and/or pyridostigmine (6). However, OH treatment is complex; orthostatic symptoms are often vague and non-specific, and may be difficult to distinguish clinically from other levodopa-related fluctuating symptoms in parkinsonian patients. In patients with neurogenic OH, autonomic dysfunction frequently causes concomitant supine hypertension (SH), which further complicates treatment given the potential risks of acute cardiovascular problems related to hypertension (12). Among PD patients, SH is also associated with worse cognition (13). However, whether long-term hypotension or hypertension is worse for cognition in PD remains to be explored. Generally, the urgency of increasing BP to prevent injuries associated with syncope and falls related to OH outweighs the risk of exacerbating SH (14).

Although the decision whether to treat OH is typically based on whether orthostatic symptoms are present (e.g., lightheadedness, dizziness), OH can occur without symptoms. The clinical relevance of asymptomatic OH (aOH) is unknown (15). Orthostatic symptoms may not correlate with absolute BP or the magnitude of BP drop (16). Additionally, basing the decision to treat OH solely on patient-reported symptoms when standing may miss individuals with unrecognized orthostatic cognitive fluctuations, which can occur without overt symptoms (17, 18). Currently, no therapeutic guidelines exist regarding whether to treat only OH patients suffering from symptoms when upright, or to treat a hemodynamic target. Although limited research exists comparing aOH and symptomatic OH (sOH) in PD, studies suggest similar ambulatory and functional capacity, falls, and health care utilization across both groups (15, 19). Thus, allowing repeated asymptomatic cerebral hypoperfusion to go untreated might cause worsening cognition over time. Alternatively, OH and cognitive impairment may be associated for other reasons. Whether aOH and sOH patients have longitudinal cognitive differences remains unknown. Several studies evaluating the relationship between OH and cognition longitudinally among PD patients found that OH is associated with cognitive decline (20, 21), but did not distinguish between aOH and sOH. A better understanding of the relationship between OH and cognitive impairment, and of the clinical significance of OH symptoms is essential to guide therapeutic decision-making.

This retrospective observational study aimed to investigate the relationship between OH, orthostatic symptoms, and cognition among patients with clinically defined PD seen at the University of California San Diego (UCSD) Movement Disorders Center. We aimed to (1) characterize the prevalence of OH, orthostatic symptoms, SH, and cognitive impairment in our cohort using cross-sectional data; and (2) compare change in Montreal Cognitive Assessment (MoCA) (22) scores over time between PD patients with OH (OH+) and without OH (OH–), and between those with aOH and sOH using longitudinal data. Based on existing literature and clinical experience, we hypothesized that OH would be associated with cognitive decline and that cognitive impairment would be similar between aOH and sOH patients.

Abbreviations: PD, Parkinson disease; OH, Orthostatic hypotension; OH–, Without orthostatic hypotension; OH+, With orthostatic hypotension; aOH, Asymptomatic orthostatic hypotension; sOH, Symptomatic orthostatic hypotension; SH, Supine hypertension; MoCA, Montreal Cognitive Assessment; MDS, Movement Disorders Society; MDS-UPDRS, Movement Disorders Society Unified Parkinson Disease Rating Scale; BP, Blood pressure; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; H&Y, Hoehn and Yahr; MCI, Mild cognitive impairment.

METHODS AND MATERIALS

Participants

Data were collected from patients seen by one movement disorders specialist (Dr. IL) at University of California San Diego Parkinson and Other Movement Disorders Center outpatient clinic between December 2011 and March 2020 under an Institutional Review Board-approved clinical research database. All patients provided written informed consent. Only patients with a clinical diagnosis of PD based on Movement Disorders Society (MDS) Clinical Diagnostic Criteria (23) were included. Exclusion criteria were as follows: (1) clinical findings consistent with atypical parkinsonism (including cognitive impairment within 1 year of motor symptom onset suggestive of dementia with Lewy bodies, severe and early autonomic failure suggestive of multiple system atrophy, etc.), (2) unclear diagnosis due to confounding medical conditions and/or an imprecise timeline, and (3) secondary parkinsonism, including normal pressure hydrocephalus, vascular parkinsonism, drug-induced parkinsonism, and fragile-X associated tremor/ataxia syndrome.

For the cross-sectional analysis ($n = 226$), the first clinic visit with complete data was selected. In most patients, this was the first visit, but if baseline visit data were incomplete (e.g., only one set of vital signs, missing MoCA, etc.), the subsequent chronologic visit with complete data was chosen. Patients returned for follow-up visits at clinically indicated intervals typically ranging between 6 and 12 months, and were evaluated by the same movement disorders specialist.

For the longitudinal analysis, we included only PD patients with at least 3.5 years of follow-up; patients with incomplete

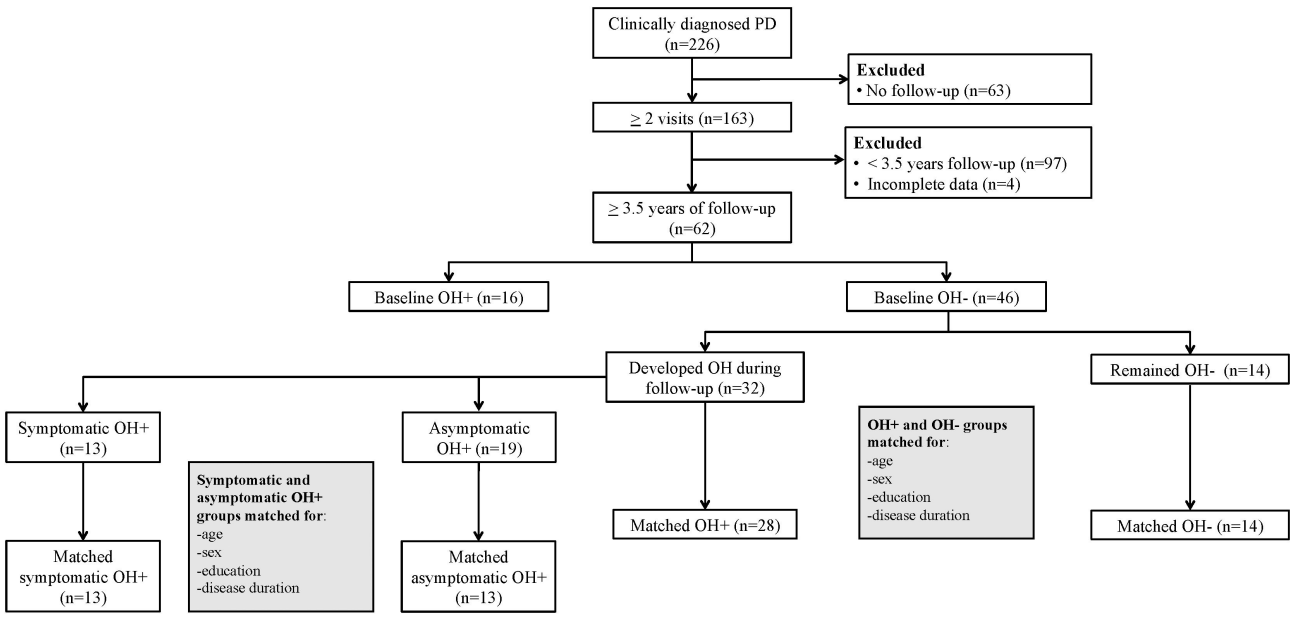

FIGURE 1 | Flow diagram of Parkinson disease (PD) patients with orthostatic hypotension (OH+) and without OH (OH–) included in the longitudinal comparisons.

data were excluded. This interval was selected based on prior research in PD patients that showed medium to large effect sizes for cognitive changes with follow-up testing at 4 years (24), and no significant MoCA score change after 3 years (25), supporting a longer study duration. Additionally, among a community-based sample of older adults, repeated MoCA was able to detect cognitive changes over a 3.5-year period (26). Among the 62 patients with a minimum 3.5-year follow-up interval, 16 had OH during the initial visit, 32 developed OH during follow-up, and 14 remained OH– (**Figure 1**). To evaluate OH group differences for MoCA change over time, the group that remained OH– ($n = 14$) was matched with the OH+ group (including only the patients without OH at the initial visit that developed OH during follow-up) for baseline age, sex, education, and disease duration ($n = 28$). Among the 32 patients that developed OH, 13 reported orthostatic symptoms at the initial visit that OH was diagnosed (sOH), while 19 did not (aOH). To evaluate sOH and aOH group differences for MoCA change over time, the sOH group ($n = 13$) was matched with the aOH group ($n = 13$) for baseline age, sex, education, and disease duration.

Clinical Evaluations

BP Measurements

Medical staff routinely measured orthostatic vital signs during each clinic visit using an electronic inflatable brachial sphygmomanometer after several minutes supine, 1 min after standing, and 3 min after standing. OH was defined as at least 20 mmHg drop in SBP and/or at least 10 mmHg drop in DBP within 3 min of standing (6). SH was defined as SBP at least 140 mmHg or DBP at least 90 mmHg while supine (12).

Rating Scales

At each clinic visit, patients were evaluated using the MoCA (22), the MDS-Unified Parkinson Disease Rating Scale (MDS-UPDRS) (27), and the Hoehn and Yahr (H&Y) Scale (28). The MoCA, a brief multi-domain cognitive screening test (maximum score is 30, higher is better), was administered using different test versions at subsequent visits to minimize learning effects. Mild cognitive impairment (MCI) was defined by a total MoCA score cutoff < 26, which has 90% sensitivity and 75% specificity for PD-MCI (29), and at least 21. PD-dementia was defined as a total MoCA score < 21, which has 81% sensitivity and 95% specificity (29).

The patient and/or caregiver completed the MDS-UPDRS Part 1 and 2 questionnaires. The same movement disorders specialist reviewed the questionnaire responses and performed the MDS-UPDRS Part 3 and H&Y scale at each visit. MDS-UPDRS Part 1 Item 12 (1.12, Lightheadedness on Standing: "Over the past week, have you felt faint, dizzy, or foggy when you stand up after sitting or lying down?") was used to categorize OH+ patients as aOH and sOH. We defined aOH as presence of OH with an Item 1.12 score of 0, and defined sOH as presence of OH with Item 1.12 score > 0. The movement disorders specialist verbally confirmed with all patients that the response to this item referred to the sensation of fainting when upright rather than postural instability in order to reduce the likelihood of false positives.

Statistics

Statistical analyses were performed using IBM SPSS v27 (IBM Corp., Armonk, N.Y., USA). For cross-sectional analyses, Fisher's exact, independent *t*, and Mann–Whitney *U* tests were used. MoCA between groups were compared using general linear model including age and disease duration, which differed for

TABLE 1 | Cross-sectional comparison of clinical characteristics, demographics, and cognition between Parkinson disease patients with and without orthostatic hypotension (OH) and between patients with symptomatic OH and asymptomatic OH.

	OH– (n = 157)	OH+ (n = 69)	p-value for OH– vs. OH+	aOH[a] (n = 45)	sOH[a] (n = 24)
Age, years	64.8 (10.8)	71.0 (9.3)	**<0.001***	71.3 (9.7)	69.2 (9.1)
Sex, female (%)	50 (31.8)	27 (39.1)	1.00	16 (35.6)	11 (45.8)
Education, years[b]	16.3 (2.8)	16.3 (3.3)	1.00	16.9 (3.4)	15.6 (3.1)
Disease duration, years	4.5 (4.0)	6.9 (4.9)	**0.002***	7.0 (4.9)	6.7 (4.9)
Levodopa use (%)	74 (47.1)	48 (69.5)	**0.029***	32 (71.1)	16 (66.7)
Supine hypertension (%)	29 (18.5)	40 (58.0)	**<0.001***	24 (53.3)	16 (66.7)
SBP change from supine to standing at 3 min, mmHg	0.0 (9.6)	−23.6 (14.0)	**<0.001***	−24.6 (13.5)	−21.7 (15.3)
DBP change from supine to standing at 3 min, mmHg	+4.8 (6.8)	−4.5 (9.3)	**<0.001***	−4.7 (9.6)	−4.3 (8.7)
Hoehn & Yahr scale	2.1 (0.7)	2.4 (0.8)	**0.024***	2.4 (0.9)	2.5 (0.8)
MDS-UPDRS Part 3	25.6 (12.9)	30.6 (16.0)	0.18	29.8 (15.0)	31.9 (17.9)
MoCA score	25.5 (3.3)	23.7 (5.0)	**0.016***	24.0 (4.9)	23.0 (5.2)
MCI (%)	50 (31.8)	23 (33.3)	1.00	13 (28.9)	10 (41.7)
Dementia (%)	12 (7.6)	15 (21.7)	0.081	10 (22.0)	5 (20.8)

*Continuous variables are reported as mean (standard deviation); categorical variables are reported as number (percentage). Statistical significance marked with *. The results reported in this table are the results of Fisher's exact test and independent t-test, with Bonferroni-adjusted p-values.*

[a] *All Bonferroni-adjusted p-values are 1.00 for aOH vs. sOH comparisons.*

[b] *Data missing for 55 patients.*

OH, orthostatic hypotension; OH–, without OH; OH+, with OH; aOH, asymptomatic OH; sOH, symptomatic OH; SBP, systolic blood pressure; DBP, diastolic blood pressure; MDS-UPDRS, Movement Disorders Society Unified Parkinson Disease Rating Scale; MoCA, Montreal Cognitive Assessment; MCI, mild cognitive impairment.

Statistically significant values are in bold.

OH+ and OH– groups, as covariates. Bonferroni correction was used for multiple comparisons. Longitudinal analyses were conducted using individual linear mixed models with autoregressive order 1 covariance structure. Models included main effect of groups (either OH+ vs. OH– or sOH vs. aOH), interaction of groups with time (interval between baseline MoCA and each longitudinal MoCA score), and baseline MoCA as a covariate. The same analyses were also performed for MDS-UPDRS Part 3 scores for the groups, with baseline MDS-UPDRS Part 3 as a covariate. Cohen's f^2 was estimated for effect sizes in the models (30); a value of 0.02 indicates a small effect, 0.15 indicates a medium effect and 0.35 indicates a large effect (31). $p < 0.05$ was considered statistically significant.

RESULTS

Cross-Sectional Analyses

Among our 226 PD patients (34.1% women), 69 (30.5%) had OH. Among these 69 OH+ patients, 45 (65.2%) were asymptomatic. About one-third ($n = 73$) of all patients had PD-MCI, and 11.9% ($n = 27$) had PD-dementia. Compared to OH– patients, OH+ patients were older and had longer disease duration, worse motor symptom severity, more levodopa use, and lower MoCA scores (**Table 1**). In the model adjusted for age and disease duration, MoCA was lower in OH+ compared to the OH– group, although this difference remained at a trend level [OH– mean (standard error, SE) = 25.3 (0.3) vs. OH+ mean (SE) = 24.2 (0.5); $F_{(1, 222)} = 3.53$, $p = 0.062$, $\eta_p^2 = 0.016$]. There were no differences in demographics, clinical features, mean BP change, or MoCA scores between aOH and sOH patients. Clinical and demographic characteristics were also similar between OH+ patients with and without SH (**Supplementary Table 1**).

Longitudinal Analyses

Among the 226 patients assessed, 164 were excluded from the longitudinal analysis due to < 3.5 years follow-up or missing data (**Figure 1**). Those excluded were older, with longer disease duration, and worse motor symptom severity (**Supplementary Table 2**). In the 62 subjects with minimum 3.5 years of follow-up, the mean follow-up interval was 5.3 (±1.3) years.

Demographics and clinical characteristics of groups included in the longitudinal analyses are summarized in **Table 2**. For the longitudinal model including the OH– ($n = 14$) and the OH+ groups ($n = 28$), OH did not have a main effect on MoCA [$F_{(1, 228)} = 3.31$, $p = 0.070$, $f^2 = 0.015$] or MDS-UPDRS Part 3 [$F_{(1, 228)} = 0.14$, $p = 0.71$, $f^2 = 0.0006$]. MoCA score declined more for the OH+ group over time [$F_{(2, 228)} = 3.67$, $p = 0.027$, $f^2 = 0.032$] (**Figure 2**). MDS-UPDRS Part 3 score increased more for the OH– group over time [$F_{(2, 228)} = 4.62$, $p = 0.011$, $f^2 = 0.041$].

For the longitudinal model including aOH ($n = 13$) and sOH groups ($n = 13$), orthostatic symptom presence did not have a main effect on MoCA [$F_{(1, 147)} = 0.039$, $p = 0.85$, $f^2 = 0.0003$] or MDS-UPDRS Part 3 [$F_{(1, 144)} = 0.047$, $p = 0.83$, $f^2 = 0.0003$]. There were also no orthostatic symptom presence and time interaction for MoCA or MDS-UPDRS Part 3 [$F_{(2, 147)} = 1.38$, $p = 0.25$, $f^2 = 0.019$; $F_{(2, 144)} = 1.85$, $p = 0.16$, $f^2 = 0.026$]. Baseline MoCA/MDS-UPDRS Part 3 scores were associated with longitudinal MoCA/MDS-UPDRS Part 3 scores for all models (p

TABLE 2 | Comparison of demographic and clinical characteristics between Parkinson disease patients that remained without OH during the follow-up period (OH–) and patients without OH at baseline that developed OH during the follow-up period; and asymptomatic and symptomatic OH patients within the OH+ group based on initial visit with OH.

	OH– patients (n = 14)	OH+ patients (n = 28)	p-value for OH– vs. OH+	aOH patients (n = 13)	sOH patients (n = 13)	p-value for aOH vs. sOH
Baseline age, years	58.3 (11.0)	62.7 (11.0)	0.22	64.1 (14.0)	63.2 (7.4)	0.72
Sex, female (%)	4 (28.6)	9 (32.1)	1.00	5 (38.5)	4 (30.8)	1.00
Education, years	15.1 (3.3)	15.8 (3.2)	0.41	16.0 (2.4)	15.2 (3.7)	0.73
Baseline disease duration, years	2.4 (1.9)	3.2 (2.4)	0.39	3.1 (1.8)	4.5 (2.7)	0.20
Follow-up interval, years	5.0 (1.1)	5.5 (1.3)	0.26	5.7 (1.0)	5.3 (1.5)	0.28
Baseline Hoehn & Yahr scale	1.6 (0.6)	1.8 (0.5)	0.45	1.8 (0.6)	2.0 (0.4)	0.40
Follow-up Hoehn & Yahr scale	2.1 (0.7)	2.3 (0.6)	0.55	2.2 (0.6)	2.4 (0.7)	0.43
Baseline MDS-UPDRS Part 3	21.1 (15.4)	21.0 (9.4)	0.61	23.2 (10.5)	22.6 (8.6)	0.82
Follow-up MDS-UPDRS Part 3	25.1 (15.5)	21.8 (12.7)	0.59	19.9 (11.1)	22.5 (12.6)	0.49
Baseline MoCA	25.8 (3.1)	26.1 (2.4)	0.97	25.8 (2.1)	25.1 (2.6)	0.66
Follow-up MoCA	25.6 (4.1)	25.0 (4.7)	0.74	26.9 (3.0)	25.1 (3.9)	0.22

All variables are reported as mean (standard deviation) or percentage. Follow-up visits indicate last visits during follow-up interval. The results reported in this table are the results of Fisher's exact test and Mann–Whitney U-test.
OH, orthostatic hypotension; OH–, without OH; OH+, with OH; aOH, asymptomatic OH; sOH, symptomatic OH; MDS-UPDRS, Movement Disorders Society Unified Parkinson Disease Rating Scale; MoCA, Montreal Cognitive Assessment.

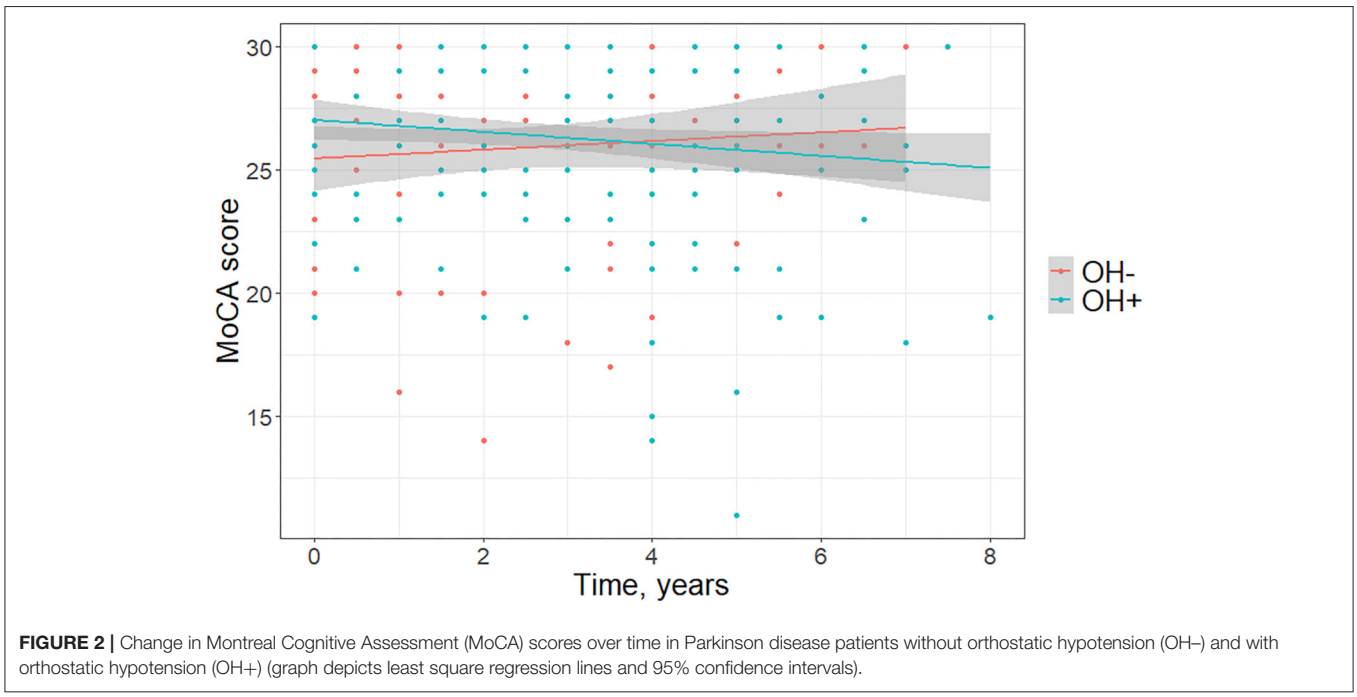

FIGURE 2 | Change in Montreal Cognitive Assessment (MoCA) scores over time in Parkinson disease patients without orthostatic hypotension (OH–) and with orthostatic hypotension (OH+) (graph depicts least square regression lines and 95% confidence intervals).

< 0.001 for all, $f^2 > 0.45$ for MoCA, $f^2 > 0.21$ for MDS-UPDRS Part 3 models).

DISCUSSION

The cross-sectional analysis of 226 patients showed that OH+ patients had worse total MoCA scores. After adjusting for age and disease duration, this difference remained at a trend level. Our longitudinal analysis comparing MoCA performance in 42 PD patients with and without OH matched for age, education, sex, and disease duration found worse cognitive decline among OH+ patients.

We found no cross-sectional or longitudinal differences in cognition between PD patients with aOH and sOH, although the group sizes in the longitudinal comparisons were small. These findings warrant further research regarding whether cognitive decline varies between OH patients with and without orthostatic symptoms. To date, only one cross-sectional study has explored cognitive differences between PD patients with aOH and sOH (15). This research found no difference in MoCA scores between

aOH and sOH or between OH– and OH+, substantiating the need for longitudinal cognitive assessment to better understand OH's role in cognitive decline. Our results reinforce the limited studies showing that patients with aOH and sOH have similar clinical features (15, 19), which supports the importance of OH screening in PD irrespective of whether patients report classic orthostatic symptoms (i.e., lightheadedness, dizziness, or fogginess on standing), especially since two-thirds of our cohort were asymptomatic. Therefore, in clinical practice, we advocate routinely measuring orthostatic vital signs while supine, 1 min after standing, and 3 min after standing for all PD patients (6). We also recommend implementing this approach to address OH in large prospective PD research studies.

Given the retrospective design, our study cannot determine whether OH directly contributed to cognitive deterioration or whether it is simply associated. Additional research is needed to clarify whether a causal relationship exists between OH and chronic cognitive impairment. Several studies have correlated acute hypotensive episodes with temporary cognitive worsening in PD, even in individuals with normal baseline cognition (17, 18, 32). Episodic OH likely transiently affects cognition by changing regional cerebral blood flow patterns (33). However, the mechanism of how OH affects the brain over time in PD is uncertain. OH may negatively affect cognition through hypoperfusion that directly and reversibly induces cortical dysfunction, or may cause cumulative brain damage from either oxidative stress, accelerated neurodegeneration, or microvascular insult (34, 35). Alternatively, OH may be a marker for a PD subtype that progresses more rapidly or causes cognitive decline for other reasons. Concurrent SH related to dysautonomia may also contribute to cognitive impairment in PD (13), although we did not find cross-sectional differences in cognition between OH+ patients with and without SH in our population.

Currently, no prevention exists for cognitive deterioration in PD (36). If OH represents a potential modifiable risk factor for cognitive impairment, then diagnosing and treating OH early would be an important strategy to reduce the risk of imminent cognitive decline. Several studies have examined whether anti-hypotensive medications benefit cognition in OH+ patients. Among 10 OH+ spinal cord injury patients, treating hypotension with midodrine improved verbal fluency compared to age- and sex-matched controls (33). After initiating midodrine, a PD-dementia patient with severe OH had sustained improvement in cognition and hypotensive episodes (37). A cohort of 40 OH+ parkinsonian patients showed better Cognitive Functional Independence Measures following treatment with midodrine and/or fludrocortisone (38). Although these results are suggestive, prospective studies with greater sample sizes are needed to establish whether treating OH can delay or prevent cognitive decline in PD.

Despite being retrospective, a strength of this study is the prospective standardized evaluation that included orthostatic BP measurements, MoCA repeated every 6 months, and longitudinal MDS-UPDRS evaluations performed by the same rater. Our study has several limitations. The main limitation is the small sample size due to the retrospective methodology. Due to the retrospective and observational nature of the study, all participants had follow-up visits at different time points, leading to missing data for some time points. While we only included those with over 3.5 years of follow-up in our longitudinal analyses, the non-significant group differences and small effect sizes suggest that this sample did not have pronounced differences in terms of cognitive decline. A more systematic assessment of cognitive decline in this population is necessary to draw reliable conclusions.

Another limitation is the use of MoCA as an outcome for cognition. Although relatively rapid, easy to administer in the office setting, and sensitive for diagnosing cognitive impairment in PD (29), MoCA was impractical to track cognitive decline in PD over 3 years (25), and does not allow detailed examination of individual cognitive domains. In our study, the mean MoCA score changed minimally in PD patients over the mean 5.3-year follow-up. Despite rotating different MoCA test versions at follow-up visits, there may have been learning effects. More extensive neuropsychological testing would be more sensitive to evaluate cognitive changes over time, and provide more reliable information on individual cognitive domains.

Although we evaluated for OH at each visit, in-office orthostatic BP measurements may not reflect the severity of OH occurring throughout the day in up to two-thirds of patients with chronic autonomic failure and may miss patients with delayed OH (39). Future studies to detect the impact of OH on cognition should use ambulatory BP testing, which is a more sensitive measure. Additionally, MDS-UPDRS Item 1.12 has not been validated for sOH. Since specific autonomic testing was not performed (e.g., beat-by-beat BP monitoring with Valsalva maneuver or plasma norepinephrine levels), we cannot be certain that all OH+ patients had neurogenic OH. Thus, some patients with secondary OH may have been included. However, the etiology of OH would unlikely impact our findings. Furthermore, our sample consisted of only PD patients that consented to participate in clinical research, so our findings may not be generalizable to all persons with PD. There were clinical differences between the population included in the longitudinal analysis and those excluded due to < 3.5 years of follow-up: patients included were younger, had shorter disease duration, and milder motor symptoms. These differences may be due to the fact that the older, sicker patients had difficulty attending appointments or they deceased during the study period.

To conclude, our findings support prior research demonstrating a strong relationship between OH and cognitive impairment in PD (9, 10), and add to the limited literature investigating clinical differences between patients with aOH and sOH, corroborating the similarities between these groups. While additional research with a greater sample size is needed to expound our findings, if OH contributes to cognitive impairment rather than merely being associated, it would be pertinent to identify and treat OH early as a modifiable risk factor for cognitive impairment in PD. Larger prospective longitudinal studies with comprehensive cognitive testing are warranted to determine whether treating OH in PD can prevent or delay cognitive decline, given the important implications for clinical practice.

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 University of California San Diego Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KL: collected and organized the data, drafted the manuscript, and contributed to statistical analysis. EB: contributed to statistical analysis and critically reviewed the manuscript. IL: conceptualized the study and critically reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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PERSPECTIVE
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Do We Belittle Essential Tremor by Calling It a Syndrome Rather Than a Disease? No

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A task force of the International Parkinson and Movement Disorder Society (MDS) recently published a tremor classification scheme that is based on the nosologic principle of two primary axes for classifying an illness: clinical manifestations (Axis 1) and etiology (Axis 2). An Axis 1 clinical syndrome is a recurring group of clinical symptoms, signs (physical findings), and possibly laboratory results that suggests the presence of at least one underlying Axis 2 etiology. Syndromes must be defined and used consistently to be of value in finding specific etiologies and effective treatments. The MDS task force concluded that essential tremor is a common neurological syndrome that has never been defined consistently by clinicians and researchers. The MDS task force defined essential tremor as a syndrome of bilateral upper limb action tremor of at least 3 years duration, with or without tremor in other locations (e.g., head, voice, or lower limbs), in the absence of other neurological signs (e.g., dystonia, parkinsonism, myoclonus, ataxia, peripheral neuropathy, and cognitive impairment). Deviations from this definition should not be labeled as essential tremor. Patients with additional questionably-abnormal signs or with signs of uncertain relevance to tremor are classified as essential tremor plus. The MDS classification scheme encourages a thorough unbiased phenotyping of patients with tremor, with no assumptions of etiology, pathology, pathophysiology, or relationship to other neurological disorders. The etiologies, pathology, and clinical course of essential tremor are too heterogeneous for this syndrome to be viewed as a disease or a family of diseases.

Keywords: essential tremor, classification, diagnostic axes, tremor, syndrome

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INTRODUCTION

An international task force on tremor was convened by the International Parkinson and Movement Disorder Society (MDS) in 2011 to review the 1998 MDS consensus statement on tremor, which was devoted to the classification of pathologic tremors (1). The Task Force found that the 1998 consensus did not use a consistent approach to tremor classification. Tremor classifications were variably based on presumed anatomical origin (e.g., cerebellar tremor), presumed etiology (e.g., neuropathic tremor), and clinical phenomenology (e.g., primary writing tremor, isolated voice

tremor). The Task Force was concerned that essential tremor (ET) was often viewed as a specific disease, rather than a clinical syndrome, and that ET was not defined and diagnosed consistently in the clinic or in research. A revised classification scheme (2) emerged from a comprehensive review of the literature and 5 years of intense discussion that included four 1-h meetings, a 2-day conference, several teleconferences, and numerous e-mail exchanges and document drafts. The revised classification scheme is based on the nosologic principle of two primary axes for classifying an illness: clinical manifestations (Axis 1) and etiology (Axis 2) (3). The clinical manifestations in Axis 1 include symptoms, signs, and laboratory results that characterize the tremor disorder.

ESSENTIAL TREMOR IS A SYNDROME

A syndrome is a recurring group of Axis 1 clinical symptoms, signs (physical findings), and possibly laboratory results that suggests the presence of at least one underlying etiology (4). The Task Force acknowledged the existence of many useful Axis 1 tremor syndromes and broadly defined two groups of tremor syndromes: those in which tremor is the only abnormal sign (isolated tremor syndromes) and those in which tremor occurs in combination with one or more additional signs such as dystonia or ataxia (combined tremor syndromes). ET was originally viewed as "a tremor diathesis that was often familial and occurred in isolation of other neurologic signs" (5). The Task Force concluded that this view of ET is still valid and formally defined ET as an isolated tremor syndrome of bilateral upper limb action tremor of at least 3 years duration, with or without tremor in other locations (e.g., head, voice, or lower limbs). This definition of ET differs from the widely-used TRIG criteria (Tremor Investigation Group) only in the required 3-year history of tremor, instead of 5 years (1). The MDS definition of ET characterizes the vast majority of people with ET, most of whom have not seen a physician for their tremor (6, 7). These people have a long-standing, relatively-mild ET syndrome (8, 9) with strong heritability (10).

THE VALUE OF CLINICAL SYNDROMES

Syndromes are useful only to the extent that they facilitate the discovery of useful treatments and specific etiologies, and by this standard, the syndrome of ET has been disappointing. The Task Force debated extensively whether ET should be defined more broadly or more narrowly, but ultimately, no conclusion was possible because the syndrome of ET has never been defined and used consistently (11). ET has been used loosely to include tremor syndromes ranging from enhanced physiologic tremor to action tremor in patients with neurological diseases such as Parkinson disease (12). Louis (13) has referred to ET as a "family of diseases" with an "evolving definition" (13) and "premotor stage" (14). The validity of these concepts is questionable. The pathologic and etiologic heterogeneities of ET are so great that the concept of "family" has no validity. An "evolving definition" of ET is precisely what the MDS Task Force wanted to avoid. The Task Force encouraged the definition of additional tremor syndromes within Axis 1 if these syndromes are believed to be useful in defining cohorts of patients that lead to the identification of specific Axis 2 etiologies. However, a clinical syndrome must be defined and used consistently to be of value in the discovery of useful treatments and specific etiologies. Inconsistent "evolving" definitions of ET make published studies difficult or impossible to reconcile. Misdiagnosis is understandably common (15–17), even among movement disorder specialists (18).

ET is defined as an isolated tremor syndrome in which tremor is the only permissible neurologic sign. A major problem has been that specialists differ in their thresholds for identifying dystonia, Parkinsonism, ataxia, and other neurological signs. Mild neurological abnormalities are commonly missed or dismissed in the evaluation of patients with possible ET. Questionable signs of dystonia such as a mild head tilt, spooning posture of the extended hands (19), and index finger extension (20) occur too commonly in normal people to be used confidently in clinical diagnosis. Jerkiness and asymmetry are features of dystonic tremor (21), but these characteristics have never been operationally defined. Impaired tandem gait in ET patients is often interpreted as a cerebellar sign, but this common test has never been properly validated, making interpretation difficult, particularly in the elderly (22). The Task Force concluded that questionably abnormal clinical manifestations should be consistently documented and that ET plus should be the classification of patients who fulfill the criteria for ET but have one or more of these "soft" signs of uncertain significance (2). The classification ET plus encourages clinicians to document all deviations from the ET syndrome that are of questionable significance (e.g., spooning of the hands, unsteady tandem gait) or questionable relevance to tremor (e.g., mild cognitive impairment).

Retrospective reviews of outpatient clinical cohorts have shown that 40% or more of patients previously diagnosed as ET are reclassified as ET plus or a combined tremor syndrome when the new MDS classification scheme is applied (23–25). For example, 20 of the last 34 patients undergoing DBS surgery for ET at our center were reclassified as ET plus due to the following Axis 1 features: rest tremor or questionable rest tremor ($n = 9$), questionable dystonic posturing ($n = 14$), jerky tremor ($n = 7$), asymmetry in upper limb tremor exceeding 1 point on the Essential Tremor Rating Assessment Scale ($n = 8$) (26), rapid progression ($n = 6$), strained voice ($n = 3$), and impaired tandem gait ($n = 7$). These changes in diagnosis cannot be attributed to a drastic change in the definition of ET because the new definition of ET differs from the old TRIG definition only in the required duration of tremor (3 vs. 5 years) and differs from the old MDS consensus criteria only in the exclusion of isolated head tremor and the required 3-year history of tremor. Instead, the changes in diagnosis are primarily due to the new classification ET plus, which places great emphasis on documenting additional signs of uncertain abnormality and relevance to tremor. Previously, these additional signs were frequently overlooked, not documented, or wrapped into the diagnosis ET.

There is already evidence that the deeper phenotyping inherent in ET plus is worthwhile. Merchant et al. (27) found that patients with signs of ataxia were more likely to develop rapid tolerance to thalamic deep brain stimulation, and Picillo et al. (28) found that patients with ET plus were more likely to develop dystonia from thalamic neurosurgery. Geneticists are also beginning to embrace this approach to tremor classification (29).

THE LIMITATIONS OF CLINICAL SYNDROMES

The classifications ET and ET plus are purely clinical, and it is recognized that experts will disagree on the Axis 1 classification of patients, particularly those patients who are older and have greater tremor severity (18, 30). The presence of one questionably-abnormal sign, such as three missteps in a 10-step tandem walk, may not be deemed sufficient to exclude an older person from a therapeutic trial of ET but will likely reach the threshold for ET plus in a 20-year old with no other medical problems. A patient that is completely unable to tandem walk and is also unsteady when walking should be classified as having a combined tremor-ataxia syndrome, not ET or ET plus. Similarly, spooning hand posturing alone could be a normal variant, but spooning in combination with jerky asymmetric upper limb tremor [≥1 point on the Essential Tremor Rating Assessment Scale (26)] may be regarded as too suggestive of dystonic tremor to be classified as ET or ET plus. True rest tremor occurs in <15% of clinic patients (31) and in <5% of people in the general population who otherwise fulfill criteria for ET (32). Therefore, the MDS Task Force concluded that patients meeting the criteria for ET except for the presence of rest tremor should be classified as ET plus. These uncertainties illustrate that many aspects of the neurological exam are still in need of validation and standardization. Clinical constructs such as jerkiness, unsteadiness, and asymmetry need to be operationally defined and quantified, possibly with the aid of quantitative motion analysis and clinical electrophysiology (21).

One criticism of the new MDS classification scheme is that ET and ET plus are diagnostic placeholders, not final diagnoses or specific diseases (33). However, this is true of all medical conditions that are defined solely in terms of clinical manifestations (Axis 1) and not etiology (Axis 2). Clinical syndromes (e.g., acquired immunodeficiency syndrome, AIDS) are useful only to the extent that they facilitate the discovery of specific etiologies (human immunodeficiency virus, HIV) and effective treatments (antiretroviral drugs). A disease is not discovered until the underlying etiology is identified. Furthermore, a patient's syndrome or condition may change as the disease progresses. Thus, ET and ET plus may evolve into a more complex (combined) tremor syndrome before an Axis 2 etiology is discovered. Such patients are then classified with their Axis 2 etiology and current Axis 1 tremor syndrome and are said to have antecedent ET or ET plus (**Figure 1**).

ET can be a stable syndrome throughout a person's life, given the presence of this syndrome in many patients with a decades-long history of tremor. The stipulated 3-year history of tremor is an attempt, admittedly arbitrary, to increase the likelihood of a stable clinical syndrome. It is widely acknowledged that longitudinal studies are needed to determine the degree to which the ET syndrome is stable (34) and to determine the significance of a stable ET syndrome in terms of underlying etiology and pathophysiology.

ETIOLOGIES OF THE ESSENTIAL TREMOR SYNDROME

ET has an additive heritability of at least 75%, so environmental factors probably play a small and still undefined role (35). Large families with apparent Mendelian dominant inheritance are common, but after more than 25 years of extensive searching, only four genes with rare causative mutations have been discovered: fused in sarcoma gene (*FUS*) (36), GGC repeat expansion in the Notch 2 N-terminal like C gene (*NOTCH2NLC*) (37), HtrA Serine Peptidase 2 gene (*HTRA2*) (38), and teneurin transmembrane protein 4 gene (*TENM4*) (39). There is little doubt that others will be discovered. However, these rare causative mutations are not found in most ET patients. Moreover, studies of families with these mutations illustrate the important fact that ET is frequently not a stable phenotype. ET can be the initial phenotype of neuronal intranuclear inclusion disease (GGC repeat expansion in the *NOTCH2NLC* gene) (40) but may evolve into a more complex syndrome with dementia, parkinsonism, ataxia, convulsions, neuropathy, or autonomic dysfunction (41) (**Figure 1**). ET may exist for years before a patient with the *HTRA2 p.G399S* allele develops Parkinsonism (38). ET is also an early but temporary phenotype of hereditary dystonia (e.g., *ANO3*) (42), hereditary ataxia (e.g., SCA12) (43), and PARK-*parkin* disease (44). Progression of these diseases ultimately produces complex combined tremor syndromes. In summary, ET is a syndrome or phenotype with many genetic etiologies. Monogenic inheritance appears to be rare, and polygenic or epigenetic inheritance may be a factor, even in families with rare causative gene mutations (39). The genetic heterogeneity of ET seems inconsistent with the notion that ET is "a family of diseases."

Purkinje cell pathology is found in some but not all ET patients (45–47). However, comparable Purkinje cell loss is also found in diseases that do not cause tremor, such as Huntington disease (48) and Alzheimer disease (49). It is unclear whether distinctive cerebellar pathology is associated with ET (50), and it is also unclear whether the reported Purkinje cell pathology is tremorogenic. The notion that ET is a "Purkinjopathy" belies the etiologic, pathologic, and pathophysiologic complexity of ET (51). Purkinje cell pathology is no justification for regarding ET as "a family of diseases."

PATHOPHYSIOLOGY OF ESSENTIAL TREMOR SYNDROME

ET is produced by abnormal oscillation and neuronal entrainment in the cerebellothalamocortical pathway. However,

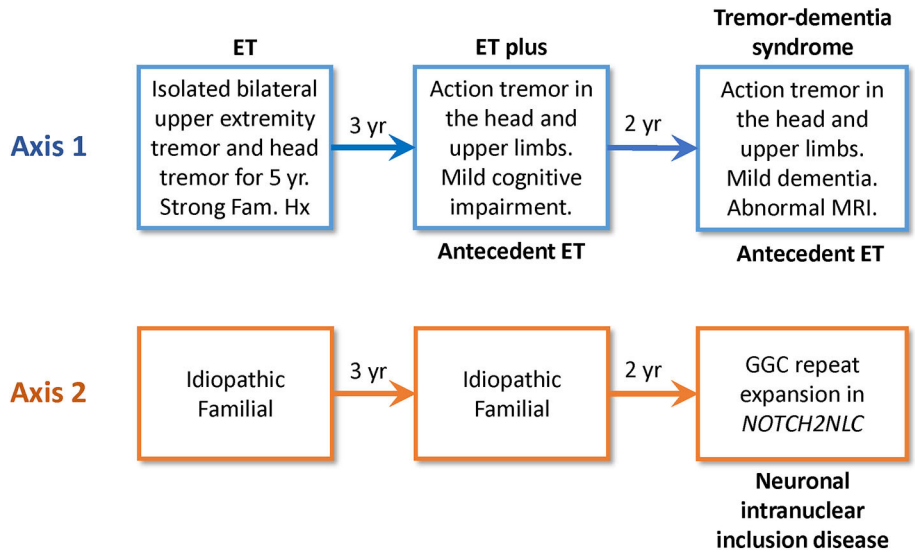

FIGURE 1 | This flow diagram illustrates how Axis 1 and 2 classifications may change over time. This clinical scenario is based on the work of Chen et al. (40). A 54-year-old Chinese man presented with a 5-year history of tremor in the head and upper limbs. His family history was consistent with autosomal dominant inheritance. His initial Axis 1 classification was ET, and his Axis 2 classification was idiopathic familial. Over time, his Axis 1 classification changed from ET to ET plus mild cognitive impairment, and his Axis 1 classification ultimately changed to a combined tremor-dementia syndrome with antecedent ET. His MRI brain revealed diffusion-weighted abnormality in the subcortical U-fibers of both frontal lobes, and genetic testing revealed a GGC repeat expansion in *NOTCH2NLC*. Thus, his Axis 2 diagnosis was ultimately neuronal intranuclear inclusion disease that presented initially as ET.

this is true for all forms of pathologic tremor (52). The cerebellum and thalamocortical loop have direct or indirect connections with virtually all motor pathways of the nervous system. Therefore, the source of oscillation in a patient with ET need not be the cerebellum or the thalamocortical loop, and the source may vary among etiologies of ET. Cerebellar Purkinje cells and neurons in the thalamocortical loop have intrinsic membrane properties that are conducive to oscillation (53, 54), and the cerebellum and thalamocortical loop have network properties that could amplify oscillation and promote neuronal entrainment of oscillation originating nearly anywhere in the nervous system (54–56). Oscillation in the cerebellothalamocortical pathway will produce tremor if there is sufficient neuronal entrainment. It is likely that virtually all etiologies of ET produce oscillation in the cerebellothalamocortical pathway. Therefore, the etiologic heterogeneity of ET and syndromic classification of ET should not deter us from conducting therapeutic trials that target the mechanisms of oscillation in the cerebellothalamocortical pathway.

SUBTYPES OF THE ESSENTIAL TREMOR SYNDROME

It is possible that the current definition of ET is too broad to identify etiologies and effective treatments. Researchers and clinicians are free to define subtypes of ET, such as late-onset ET (e.g., onset after age 65), familial (e.g., one or more first-degree relatives with ET), sporadic, and tremor predominantly (not exclusively) in the head or voice. However, data from one subtype may not be applicable to all patients with ET. The reasons are obvious. Elderly patients with late-onset action tremor are far more likely to have undiagnosed subclinical neurological comorbidities than young healthy adults (57), and they are more likely to have comorbid systemic illnesses that cause enhanced physiologic tremor, which is easily mistaken for mild ET (6). Familial and sporadic cases are likely to differ in their likelihood of harboring risk genes. Patients with predominant head or voice tremor may be more likely to have a form of dystonia.

It is also possible that the current definition of ET is too narrow to identify etiologies and effective treatments. The MDS classification scheme permits the definition of additional Axis 1 tremor syndromes in which the criteria for ET are met except for the existence of one or more additional Axis 1 features (e.g., gait ataxia). To avoid confusion, these combined tremor syndromes should not be referred to as subtypes or variants of ET.

DISCUSSION

Syndromes must be defined and used consistently to be of value in clinical care and research. The ET syndrome has never been defined and used consistently. This has made the sizeable literature on ET difficult to interpret because readers must carefully examine each paper for differences in definition that can affect outcome.

The new ET and ET plus classifications do not invalidate earlier studies that carefully defined the axis 1 clinical characteristics of their patient populations, but the results of

older studies may need some reinterpretation in the context of the new MDS classification scheme. The main problem with many older studies is that clinicians and researchers commonly used *ad hoc* definitions of ET, and neurological signs of uncertain significance (abnormality) and uncertain relevance to tremor (e.g., mild cognitive impairment in an elderly patient with ET) were often not documented or simply wrapped in a diagnosis of ET. Even patently abnormal signs other than tremor were deemed as permissible within some definitions of ET (58, 59). Furthermore, some studies included isolated head tremor, isolated voice tremor and tremor of <1 year duration (60).

ET plus is a new classification, not a specific syndrome. Clinicians are encouraged to carefully document the additional Axis 1 manifestations beyond tremor when using the classification ET plus. ET plus may include a variety of neurologic signs that are questionably abnormal or questionably relevant to the patient's tremor disorder. Specific ET plus syndromes are permissible within the new classification scheme, as long as the syndromes are defined and used consistently.

A syndrome should not be expanded or changed unless there is good reason to believe that the newly defined syndrome will be a better tool for the discovery of underlying etiology or effective treatment. Changing the definition of a syndrome like ET creates confusion in the comparison of new and old clinical studies. The new MDS definition of the ET syndrome does not differ significantly from the old and widely-used TRIG criteria (1) and is completely compatible with the original concept of ET (5). The new classification ET plus provides us with a tremor classification in which new syndromes can be defined, without disturbing the definition of ET. Subtypes of ET are permissible with the caveat that data from this subtype may not apply to the broad ET patient population.

People with ET and ET plus may be included in the same study cohort if this is believed to facilitate the study objectives. The new MDS definitions of ET and ET plus make no assumptions about underlying etiology or response to treatment. Patients with ET and ET plus may or may not have the same underlying etiology. Furthermore, it is clear that cerebellothalamocortical oscillation is a cornerstone of all forms of tremor, so the notion of ET being a syndrome should not deter one from pursuing new treatments. Careful phenotyping and classification under the new classification scheme will permit *post hoc* exploratory data analyses, and the results can be confirmed or refuted in subsequent studies.

In conclusion, the MDS classification scheme provides much-needed rigor to the classification of ET and puts ET in the proper perspective of being a clinical syndrome, not a specific disease. The classification ET plus facilitates a deeper phenotyping of patients without assumptions of etiology or causality. This should facilitate gene discovery, given the likely polygenic inheritance of ET in most patients. These views do not belittle ET, rather they properly acknowledge the importance of thorough Axis 1 phenotyping, unencumbered by any assumptions of etiology, pathology, or pathophysiology.

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

The author is solely responsible for the writing and content of this manuscript.

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Do We Belittle Essential Tremor by Calling It a Syndrome Rather Than a Disease? Yes

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Essential tremor (ET) is among the most prevalent neurological diseases. Appreciation in recent years of a richer tremor phenomenology, additional motor and non-motor features, variability in the natural course of tremor, associations with a host of other neurological conditions, and etiological and pathophysiological heterogeneity have resulted in general awareness of the clinical richness of ET. Along with this evolving view of ET have surfaced several conundrums regarding nomenclature. One of these is whether ET should be labeled a "syndrome" or "disease." Here, we revisit the classical definitions of "syndrome" and "disease" and discuss ET in this context. Considering the characteristics of "disease" and "syndrome" and evaluating the characteristics of ET, it seems to fit more into the "disease" construct. There are several reasons: There is considerable knowledge of the underlying etiologies and pathophysiology of ET, in numerous studies ET has been linked with other neurological conditions, the condition is progressive and deteriorative, and therapeutic approaches are grounded in an understanding of disease mechanisms and its associated neuroanatomy. Moreover, the etiological–pathological–clinical heterogeneity suggests that ET should be regarded as a "family of diseases" more appropriately termed "the essential tremors." This nomenclatural issue is not a mere matter of words; public health implications are numerous. A condition with the label "syndrome" may not be recognized as a serious problem, may be plagued by diminished public awareness, and may not garner funds for research that a condition with the label "disease" or "diseases" would. ET should be regarded as a family of diseases.

Keywords: essential tremor (ET), disease, syndrome, tremor, movement disorder

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INTRODUCTION

Essential tremor (ET) is one of the common neurological diseases. Our knowledge of its clinical phenomenology, natural course, and pathogenesis has expanded considerably during the past several decades (1). ET was considered a monosymptomatic illness, characterized only by tremor. Subsequent identification of a richer tremor phenomenology, additional motor features, a repertoire of non-motor features, variability in rates of progression, associations with a host of other neurological diseases, and etiological and pathophysiological heterogeneity have resulted in a greater general awareness of the clinical richness of ET (1). Along with this evolving view of ET have surfaced several conundrums regarding nomenclature (2–4). One of these is whether ET should be

labeled a "syndrome" or "disease." More specifically, although it is becoming increasingly clear to most experts that "ET" is a phenotypically heterogeneous condition or set of conditions, there is a debate as to whether to conceptualize ET as a "syndrome" or a "disease." Some experts are of the opinion that ET is a "syndrome" (5, 6), whereas others are of the opinion that ET is a "disease" or "family of diseases" or "group of diseases." (7–9). Interestingly, a similar conundrum may be found with respect to epilepsy (10), where the nomenclatural issues and their repercussions have been discussed in detail, and the public health implications have been well articulated—a condition with the label "disorder" or "syndrome" may not be recognized as a serious problem, may remain in the shadows, may be plagued by diminished public awareness, and may not garner funds for research that a condition with the label "disease" would (10).

In this review, we revisit the classical definitions of these terms, "syndrome" and "disease," and discuss ET in this context.

DEFINITIONS OF "SYNDROME" AND "DISEASE"

Syndrome

Although several definitions have been put forth for "syndrome" and "disease," there are no universally accepted definitions and no formally derived inclusion or exclusion criteria. Moreover, definitions have changed over time (11). This makes the current debate challenging.

The term "syndrome" is derived from Greek ("*syn*" together and "*dromus*" a course), and it means "a running together or concurrence." A syndrome is a recognizable complex of symptoms and physical findings that indicate a specific condition for which a direct cause is not necessarily understood (12). In other words, syndromes describe a specific collection of symptoms and signs which recurrently co-occur. Although classically, the word "syndrome" has been applied to conditions with no immediately recognizable etiopathogenesis (e.g., Angelman syndrome, West syndrome), there are conditions that have been labeled "syndromes" despite considerable development in our understanding of their pathogenesis (e.g., Guillain-Barré syndrome). However, in general, once medical science identifies the causative agents (i.e., etiology) and pathogenesis of a particular condition, the term "syndrome" tends to be replaced by "disease" (12–17). For example, with advances in knowledge, mucocutaneous lymph node syndrome (Kawasaki syndrome) is no longer viewed as a syndrome but as a proper disease (Kawasaki disease) (12).

Disease

Occasional views have been put forth that the concept "disease" is unnecessary for clinical thinking or clinical decision making (18); however, such views are not mainstream, and for the most part, the value of the concept "disease" is indisputable to patients, healthcare providers, and society. "Disease" is a fluid concept influenced by sociocultural attitudes and political motivations, which are prone to change with time and in response to new medical and scientific discoveries (19). What counts or does not count as a disease fluctuates over time, partly as a result of increasing expectations of health, partly due to changes in diagnostic ability, and also for social and economic reasons (20). For example, osteoporosis, which was considered a symptom/sign of aging, was, by the mid-1990s, regarded as a disease. This nomenclatural issue has consequences for sufferers' sense of whether they are "normally old" or "ill" and, more concretely, for their ability to have treatment reimbursed by health service providers (20). The other example is homosexuality, which was once regarded as a disease secondary to endocrine abnormalities or as an organic mental disorder. It was officially "de-pathologized" by the American Psychiatric Association, in 1974, as homosexual behavior is a widely prevalent aspect of human sexuality and not a pathologic entity (20, 21).

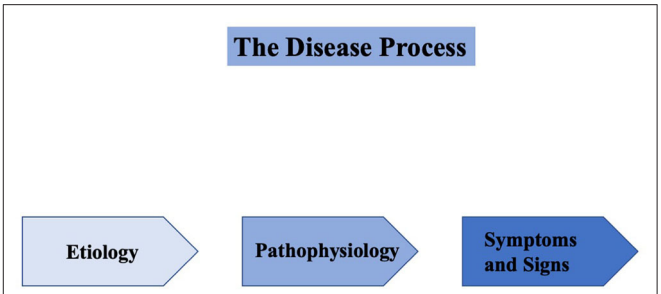

FIGURE 1 | Diseases are entities that have identifiable causes (etiologies), underlying pathophysiologies (sometimes with associated organ-based changes), and associated symptoms and signs.

However, the discussion of what constitutes a disease is not merely an abstract or sociological one. Although it is clear that "syndrome" and "disease" overlap in terms of the requirement of recurring symptoms and signs, the term "syndrome" refers to recurrent co-occurrence of a set of signs and symptoms in the absence of a robust understanding of the pathogenesis and etiology, whereas the term "disease" has additional characteristics in terms of information on etiology and pathogenesis (12–17). In other words, diseases are entities that have identifiable causes and underlying pathophysiologies (sometimes with associated organ-based changes) and are more than a loose arrangement of symptoms and signs (**Figure 1**). Additionally, there are three other general features of disease that should be highlighted. First, disease is a state that places individuals at increased risk of adverse consequences (i.e., additional morbidity and mortality). Second, the term disease usually connotes a progressive disorder or one in which deterioration and decline occur (16). Third, based on the fact that the etiology and pathogenesis of a disease are better elucidated compared to that of a syndrome, for diseases, therapies are more often biologically based and specifically targeted toward pathogenic mechanisms.

ET: SYNDROME vs. DISEASE

Having discussed the basic concepts and definitions of "syndrome" and "disease," we now consider whether ET better fits the "syndrome" or "disease" designation (**Figure 2**).

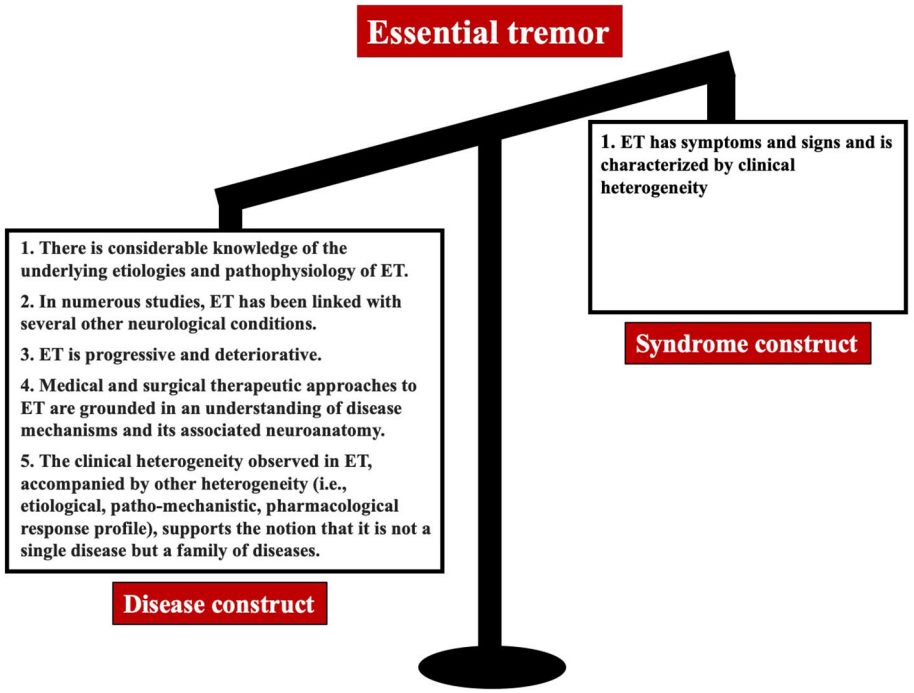

FIGURE 2 | The bulk of evidence favors the view that ET is a disease or family of diseases rather than a syndrome.

Etiology and Pathogenesis of ET

With ET, we are dealing with more than a mere collection of symptoms and signs. This collection of symptoms and signs is linked to and grounded in etiological and pathophysiological processes, suggesting that it is a proper "disease" rather than a mere "syndrome."

We start with a discussion of etiology. ET is not merely a collection of symptoms and signs without an apparent cause or set of causes. Both genetic and environmental factors (i.e., toxins) are identified as possible contributors to the etiology of ET. That genetic factors contribute to ET is clear. A large familial aggregation study reveals that first-degree relatives of ET patients were five times more likely to develop ET than were first-degree relatives of controls (22). Twin studies similarly demonstrate a considerable increase in disease concordance in monozygotic than dizygotic twins (22, 23). Although no major gene has been identified as of yet, several ET-linked genes are identified in ET families, and this growing collection of genes points to a clearer heterogeneity of genetic etiologies (24, 25). There is also accumulating evidence that non-genetic etiologies likely play a role in disease etiology. Several environmental toxins, which include β-carboline alkaloids (e.g., the dietary toxin harmane) and lead have been investigated, and there is growing support for the notion that these could be etiological agents (26, 27). Thus, as with Parkinson's disease (PD), in ET, both genetic and environmental factors serve as disease triggers. That is, both genetic and environmental factors are thought to launch the disease process or processes, and this, in turn, manifests clinically as symptoms and signs. Temporally, in between the prime mover (i.e., etiological factor or factors) and the symptoms and signs, is the pathophysiology (i.e., biological changes that occur once the disease process has been set in motion). A discussion of pathophysiology now follows.

Over the past several decades, advances in neuroimaging and neuropathology have provided valuable insights into the pathophysiology of ET. There is growing evidence that the underlying disease process, in all likelihood neurodegenerative, centrally involves the cerebellum. Numerous neuroimaging studies observe significant structural, functional, and metabolic alterations in the cerebellum and the cerebello–thalamo–cortical tracts in ET (28). The studies use a variety of methods, from magnetic resonance spectroscopy to volumetrics, and they suggest an underlying neuronal degeneration in the ET cerebellum (29). Postmortem studies reveal significant abnormalities in ET brains compared to matched control brains, indicating that these changes are disease-linked. The abnormalities in ET brains lie predominantly in the Purkinje cell population and include changes in the Purkinje cell dendrites (increase in dendritic swellings, pruning of dendritic architecture, loss of dendritic spines), Purkinje cell body (increase in Purkinje cell heterotopias), and Purkinje cell axon (increase in numbers of torpedoes, axonal recurrent collaterals, branching, terminal axonal sprouting, and arciform axons) (30). Changes to neighboring neuronal populations are also observed (i.e., climbing fibers and basket cells), and in properly designed studies, a reduction in the Purkinje cell population is seen (30). Along with this is the concept that there is an aberrant

reduction in gamma amino butyric acid (GABA)-ergic tone in ET (31).

The above-referenced studies highlight that there are identifiable underlying causes and identifiable tissue-based processes that are disease-linked in ET. In ET, we deal with more than a mere collection of symptoms and signs. We are dealing with a collection that is linked to and grounded in specific and observable etiological and pathophysiological processes.

Adverse Consequences of ET (i.e., Additional Morbidity and Mortality)

Disease is viewed as a state that places individuals at increased risk of adverse consequences (i.e., additional morbidity and mortality) (19). Although sometimes still debated, the overwhelming bulk of published clinical and epidemiological data support an association between ET and PD (32), and a population-based longitudinal study in Spain quantifies that patients with ET are four times more likely than controls to develop incident PD (33). Similarly, a growing number of epidemiological studies support the association between ET and mild cognitive impairment and between ET and both prevalent and incident dementia (34). Finally, although there has only been one prospective longitudinal study of mortality in ET vs. controls, that study reveals a slight but significant increased risk of mortality in ET (35). In summary, ET is a disease state that places individuals at increased risk of adverse consequences (i.e., both additional morbidities as well as increased risk of mortality).

Progressive Disorder

"Disease" usually connotes a progressive disorder or one in which deterioration and decline occur; this is certainly the case in ET, which is slowly yet relentlessly progressive in all cases (36).

Biologically Based Therapeutics of ET

As pathogenesis of a disease is better elucidated compared to that of a syndrome, therapies for diseases are more often biologically based and specifically targeted toward pathogenic mechanisms. The treatments for ET are increasingly biologically based and specifically targeted toward pathogenic mechanisms and/or neuroanatomic pathways. Thus, along with the older agent primidone, many of the more recently considered medications are based on the notion that GABA-ergic tone is reduced in ET, possibly as a result of changes in the Purkinje cell population although other specific molecular mechanisms are also implicated (37) and are the basis for pharmacotherapeutics. Newer generation agents, currently in testing, are similarly based on clear underlying biological considerations. Furthermore, deep brain stimulation surgery of the ventral intermediate nucleus of the thalamus and magnetic resonance image–guided focused ultrasound of the thalamus are based on the understanding that the disease is grounded in a specific neuroanatomical neuronal loop. In summary, for ET and other diseases, therapies are often biologically based and specifically targeted toward pathogenic mechanisms.

ET: "DISEASE" OR "FAMILY OF DISEASES''?

Having reviewed the data above and highlighted the abundant support for the notion that ET is a "disease" rather than a "syndrome," we must go one step further to discuss whether ET is a single disease or a family of diseases. In doing so, we revisit the marked heterogeneity of ET: etiological, pathological, and clinical. The etiological heterogeneity is apparent from the fact that different genes and, in some cases, no genes are associated with the emergence of ET. The heterogeneity from the pathological standpoint stems from the observation that, in contrast to changes in the Purkinje cells in the cerebellum, some ET brains were found to have an abundance of Lewy bodies that is above and beyond that normally seen in control brains (38), and some others have had neuronal inclusions (39). There is considerable evidence to highlight heterogeneity in the clinical features of ET. Heterogeneity is reported in the age at onset of tremor (e.g., bimodal pattern), distribution of tremor [e.g., higher prevalence of head tremor in female patients; (40)], presence of a family history of tremor, and response to treatment (9). Based on the presence of such multidimensional heterogeneity, involving etiology, pathogenesis, clinical features, and pharmacological response profile, it seems probable that ET is a "family of diseases" and that the term "the essential tremors" is now the appropriate one (9). It is important to note that a "family of diseases" is not the same as a "syndrome" as a family of diseases is comprised of individual diseases that each are characterized by each of the features of disease that we outline in this paper whereas a syndrome has the features, dissimilar to disease, that we also outline in this paper.

Why Might ET Be Referred to as a "Syndrome''?

Although we point out considerable evidence in favor of ET as a "disease" construct, several experts voice opinions that it is a "syndrome" (5, 6). It is the clinical heterogeneity of ET that underlies this view. However, such heterogeneity could easily be explained by a number of factors. First, the clinical features evolve with time as patients move through different disease stages; hence, different snapshots of the disease are apparent over time (41). Second, the observed clinical heterogeneity likely is a marker that one is not dealing with only one disease but that one is dealing with a family of diseases (i.e., a constellation of clinically similar etiological–pathological–clinical entities). The members of this family likely differ with respect to environmental and genetic determinants, pathophysiological, and tissue-based changes, responses to therapies, and clinical profiles.

CONCLUSION

Considering the characteristics of both "disease" and "syndrome," it seems that ET fits more into the "disease" construct than the "syndrome" construct. We review the features of diseases,

and ET fulfills each. Thus, there is considerable knowledge of the etiologies and pathogenesis of ET; in numerous studies, ET is linked with additional morbidities and/or mortality; ET is progressive and deteriorative; and therapeutic approaches, both medical and surgical, are grounded in an understanding of disease mechanisms and anatomy. Moreover, the etiological–pathological–clinical heterogeneity of ET suggests that ET should be regarded as a "family of diseases" better termed "the essential tremors." As noted above, the issue is not merely nomenclatural; public health implications are numerous. There is no doubt that conflicts and controversies regarding the nomenclature will persist as long as we do not have absolutely clear definitions of "syndrome" and "disease." However, considering the significant negative psychosocial and financial repercussions of ET, it seems the label "family of diseases" is apt for the time being.

AUTHOR CONTRIBUTIONS

AL designed and conceptualization of the work and prepared the first draft of the manuscript. EL designed and conceptualization of the work, critical review, and editing of the manuscript. All authors contributed to the article and approved the submitted version.

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