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ORIGINAL ARTICLE

Gait performance and non-motor symptoms burden during dual-task condition in Parkinson's disease

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Abstract

Introduction Impaired gait is observed in patients with Parkinson's disease (PD) in both single-task (ST) and dual-task (DT) conditions. Non-motor symptoms (NMSs), another vital symptom future experienced along the PD disease trajectory, contribute to gait performance in PD. However, whether DT gait performance is indicative of NMS burden (NMSB) remains unknown. This study investigated correlation between NMS and DT gait performance and whether NMSB is reflected in the DT effects (DTEs) of gait parameters in PD.

Methods Thirty-three idiopathic PD participants were enrolled in this study; the median H-Y staging was 2.5. NMSB was assessed by Non-motor Symptoms Scale (NMSS). Spatiotemporal gait parameters under ST and DT conditions were evaluated by wearable sensors. Gait parameters under ST and DT conditions and DTEs of gait parameters were compared across NMSB groups. The associations between NMS and DTEs of gait parameters were analyzed by correlation analysis and linear regression models.

Results Compared to PD patients with mild-moderate NMSB, the severe-very severe NMSB group showed slower gait speed and shorter stride length under both ST and DT conditions ($p < 0.05$). DT had significantly negative effect on gait parameters in PD patients, including gait speed, stride length, and gait cycle duration ($p < 0.05$). PD patients with mild-moderate NMSB showed larger DTEs of cadence and bilateral gait cycle duration ($p < 0.05$). DTEs of bilateral gait cycle duration and swing phase on the more affected (MA) side were significantly correlated with NMSS scores ($|rSp| \geq 0.3$, $p < 0.05$). Gait cycle duration on the less affected (LA) side explained 43% of the variance in NMSS scores, when accounting for demographic and clinical confounders ($\beta = -1.095$ 95% CI $-4.061 \sim -0.058$, $p = 0.044$; adjusted $R^2 = 0.434$).

Conclusion DT gait performance could reflect NMSB in PD patients at early stage, and gait cycle duration is a valuable gait parameter to further investigate and to provide more evidence for PD management.

Keywords Gait · Dual task · Non-motor symptoms · Parkinson's disease

Introduction

Parkinson's disease (PD) is characterized by a series of motor and non-motor symptoms that affect, to a greater or lesser extent, the activities of daily life of patients [1]. In particular, gait impairments are common, are considered the most disabling symptom among PD patients, and draw great attention from clinicians. Data from quantitative gait analyses have shown that PD patients have reduced gait velocity, reduced stride length and step width, reduced cadence and swing time, and increased variability [2–5]. Walking as a complex process requires motor and cognitive involvement, especially executive function and attention [6], while 20–70% of PD patients experience mild cognitive impairment, according to several prospective and cross-sectional

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studies [7], which further aggravates gait performance in patients with PD.

Dual-task (DT) walking is a situation in which a second task is added to walking. The second task can be a cognitive task, such as speaking or thinking of something else, or a motor task such as holding a glass or crossing obstacles as we walk in our daily lives. Dual-task effects (DTEs) refer to the quantitatively assessed influence of DT. Positive effects, called DT benefits, indicate better performance, and negative effects, called DT costs, indicate poorer performance. Studies have suggested that DT conditions can exacerbate gait performance in PD patients, such as gait velocity, cadence, stride length, swing time, and stride-to-stride variability [8, 9].

Non-motor symptoms (NMSs) are also experienced throughout patients' disease trajectory and cannot be ignored in PD clinical management; these symptoms include cognitive, mood, sleep, cardiovascular, gastrointestinal, urinary, and sensory symptoms. The Non-motor Symptoms Scale (NMSS), an objective and reliable tool, enables a comprehensive assessment of the NMS that occurs in PD, both for the identification of problems and measurement of intervention outcomes [10]. The NMSS covers 9 domains of NMS and was suggested to assess the frequency and severity of NMS in PD across all stages [10]. Non-motor symptoms burden (NMSB), assessed by the NMSS, could reflect the severity of NMS by grade [11]. To the best of our knowledge, no studies have described gait performance characteristics across degrees of NMSB.

Associations or interactions between cognition and gait in PD have been investigated extensively [12–14]. Correlations between other NMS and gait performance have also been investigated. Dragasevic-Miskovic et al. found that swing time variability was significantly higher in PD patients with depression, especially for those performing in DT condition [15]. PD patients with high anxiety also showed increased step length and step time variability and reductions in walking speed and step length in single-task (ST) and DT conditions [16]. However, correlation between NMS and quantitatively assessed DTEs remains unknown. In addition, previous studies have mostly focused on the effects of NMS on gait performance or the effects of DT conditions on gait performance in PD. However, it has not been precisely characterized whether NMS could be reflected in gait performance in DT condition.

Therefore, the aim of our study was to investigate correlations between NMS and DT gait performance and whether NMSB could be reflected in DTEs on spatiotemporal gait parameters in PD patients.

Methods

Participants

Patients who were diagnosed with idiopathic PD from November 2021 to April 2022 in the Department of Neurology of Beijing Tiantan Hospital, Capital Medical University, were invited to participate in the study. The inclusion criteria comprised the following: (1) clinically definite PD according to 2015 Movement Disorder Society (MDS) Clinical Diagnosis Criteria [17]; (2) stable anti-Parkinsonism medication for the past 3 months; (3) able to walk 30 m without assistance; and (4) Mini-Mental State Examination score ≥ 24. The exclusion criteria included patients with (1) non-PD-related gait impairments, such as spasticity, cerebrovascular diseases, multiple sclerosis, and osteoarticular diseases; (2) deep brain stimulation; (3) visual or auditory disorders; and (4) severe mood disorder that prevented completion of the assessment. This study was approved by the Ethics Committee of the Beijing Tiantan Hospital and was performed in accordance with the Declaration of Helsinki. Informed consent was obtained either from the participants or their closest relatives.

Assessments

All assessments were carried out in a medication "ON" state, which was defined as 1.5 h after receiving levodopa.

Clinical assessment

Demographic information, including age, sex, body mass index (BMI), years of education, age at onset, and disease duration, was collected. Disease severity was rated by Hoehn and Yahr (H-Y) staging and Movement Disorder Society Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS III) scores. The levodopa equivalent daily dosage (LEDD) was calculated as levodopa dose + levodopa dose × 1/3 if on entacapone + piribedil (mg) + pramipexole (mg) × 100 + selegiline (mg) × 10 + amantadine (mg) + controlled-release levodopa (mg) × 0.75[18]. Global cognition was assessed using the Montreal Cognitive Assessment (MoCA). The 39-item Parkinson's Disease Questionnaire (PDQ-39) was used to assess quality of life of the PD patients.

Non-motor symptom assessment

The NMSS, a 30-item questionnaire, covers 9 domains of NMS: cardiovascular and falls, sleep/fatigue, mood/apathy, perceptual problems/hallucinations, attention/

memory, gastrointestinal symptoms, urinary function, sexual function, and miscellaneous (consisting of pain, smell, weight change and hyperhidrosis) [10]. The scale was quantified by multiplying severity (score 0–3) and frequency (score 1–4) for each question, and the range for the total score is 0–360. NMSB was assessed by the NMSS. According to a study of 935 PD patients, the NMSS total score of 0 was defined as "no," 1–20 as "mild," 21–40 as "moderate," 41–70 as "severe," and ≥ 71 as "very severe" NMSB [11].

Gait assessment

Equipment

We used the BTS G-Walk to assess spatiotemporal gait parameters. It is a portable, wireless, inertial system with wearable sensors, weighs 37 g, and has dimensions of 70 × 40 × 18 mm. This device comprises a triaxial accelerometer (16 bit/axes) with multiple levels of sensitivity (± 2, ± 4, ± 8, ± 16 g), a triaxial gyroscope (16 bit/axes) with multiple levels of sensitivity (± 250, ± 500, ± 1000, ± 2000°/s), and a triaxial magnetometer (13 bit, ± 1200 μT). The device was attached with a semi-elastic belt to the S1 spinal segment of the examined subjects while walking, and acceleration was recorded. All acceleration data were sampled at a 100 Hz frequency, transmitted by Bluetooth to a laptop, and processed using the special software program BTS G-Studio (BTS Bioengineering S.p.A., Italy). A previous study indicated that G-Walk had high levels of agreement with GAITRite and could be used for evaluating the gait characteristics of healthy individuals and PD patients [19], as GAITRite was considered the gold standard in gait parameter measurement and gait analysis [20].

Procedure

Gait assessment was performed over a predefined 2 × 10-m walking distance that included a turn (180°) after the first 10 m (walking during turn was not calculated by the system). The PD participants were instructed to walk at a self-selected usual and comfortable speed along the walkway in ST and DT conditions, separately.

ST condition: walk at a self-selected usual and comfortable speed along the walkway.

DT condition: walk at a self-selected usual and comfortable speed along the walkway while performing a serial-7 subtraction task randomly selected from the Arabic numbers 300–500[8].

Rest breaks were given between ST and DT conditions when requested by the participant.

Gait parameters

The spatiotemporal parameters evaluated using G-Walk were as follows: gait speed (m/s), cadence (steps/min), stride length (m), gait cycle duration (s), step length (% stride length), swing phase (% gait cycle), and double support phase (% gait cycle). The stride length, gait cycle duration, step length, swing phase, and double support phase were bilaterally measured, separately. The more affected (MA) and less affected (LA) sides were determined by summing the right and left scores in the MDS-UPDRS III (subitems 3.3–3.8 and 3.15–3.17), with the higher score determining the MA side.

The DTEs of gait parameters were calculated to determine the effects of the secondary task on the primary task according to the formula described by Kelly and colleagues [21]. The equation was as follows:

$$\mathrm{DTE}(\%) = \frac{\mathrm{Dualtask} - \mathrm{Singletask}}{\mathrm{Singletask}} \times 100\%$$

Statistical analysis

All statistical analysis were performed in SPSS 25.0. The Shapiro–Wilk test was used to check the normality of the data. Continuous variables were expressed as means and standard deviation (SD) or median and interquartile range (IQR) according to the normality of the data, and categorical variables were reported as numbers and percentages. Gait parameters were described as means and SD. Student's *t* test and the Mann–Whitney *U* test were used for comparison of normally and non-normally distributed data between groups created based on degree of NMSB. The paired-sample *t* test and Wilcoxon signed-rank test were used for comparison of gait parameters under ST and DT conditions. Correlation analysis between NMSB and DTEs of gait parameters was performed by Pearson's correlation (r) or Spearman's rank correlation (r_{Sp}) according to the normality of the variables. DTEs of gait parameters that showed correlation coefficients ($|r|$or $|r_{Sp}| \geq 0.3$) were included in the linear regression analysis. Standardized coefficients (β) and their 95% confidence intervals were calculated. The level of significance was $p < 0.05$ (two-sided).

Results

A total of 33 PD participants (19 females, 14 males) completed the study, with a mean age of 64.27 ± 8.53 years. The demographic and clinical characteristics of the participants are presented in Table 1. The median disease duration was

Table 1 Demographic and clinical characteristics of included PD participants

	Total ($n=33$)	Mild-moderate NMSB ($n=16$)	Severe-very severe NMSB ($n=17$)	p value
Sex, female, n (%)	19 (57.58%)	10 (62.50%)	9 (52.94%)	0.728
Age(years), mean ± SD	64.27 ± 8.53	59.81 ± 7.71	68.47 ± 7.14	**0.020**
BMI, mean ± SD	25.26 ± 3.85	24.79 ± 4.08	25.70 ± 3.68	0.503
Education (years), median (IQR)	12.00 (9.00,12.00)	10.50 (9.00,12.00)	12.00 (9.00,13.50)	0.510
Age at onset(years), median (IQR)	57.00 (51.00,64.50)	54.50 (46.00, 57.75)	64.00 (55.50,71.00)	**0.004**
Disease duration(years), median (IQR)	5.00 (2.75,7.50)	5.50 (2.25,10.75)	4.00 (2.75,6.25)	0.736
LEDD (mg/day), mean ± SD	647.28 ± 349.98	659.62 ± 346.06	645.68 ± 363.88	0.848
H-Y staging, median (IQR)	2.50 (2.00, 3.00)	2.75 (2.00, 3.00)	2.50 (2.00, 3.00)	0.873
MDS UPDRS III, mean ± SD	37.73 ± 16.10	35.63 ± 17.23	39.71 ± 15.21	0.475
MoCA scores, mean ± SD	24.15 ± 3.84	24.69 ± 3.00	23.65 ± 4.53	0.446
PDQ 39 scores, median (IQR)	20.00 (13.00, 34.50)	14.00 (6.25, 23.75)	31.00 (17.50, 43.50)	**0.003**
NMSS total scores, median (IQR)	44.00 (22.00, 49.50)	22.00 (12.75, 31.00)	48.00 (45.00, 61.00)	**< 0.001**
Cardiovascular including falls, median (IQR)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	1.00 (0.00, 4.00)	0.204
Sleep/fatigue, mean ± SD	9.64 ± 7.21	4.69 ± 3.61	14.29 ± 6.64	**< 0.001**
Mood/apathy, median (IQR)	4.00 (0.00, 6.50)	1.50 (0.00, 5.00)	5.50 (1.50, 11.00)	**0.041**
Perceptual problems/hallucinations, median (IQR)	0.00 (0.00, 1.00)	(0.00, 0.00)	0.00(0.00, 1.50)	0.191
Attention/memory, median (IQR)	2.00 (1.00, 5.00)	1.00 (1.00, 2.00)	3.00 (2.50, 5.00)	**0.005**
Gastrointestinal, median (IQR)	3.00 (1.00, 7.00)	1.00 (0.00, 7.75)	4.00 (2.00, 8.50)	**0.028**
Urinary, median (IQR)	9.00 (2.50, 12.00)	3.00 (0.00, 9.00)	12.00 (7.50, 17.00)	**0.003**
Sexual, median (IQR)	3.00 (2.00, 4.00)	2.00 (1.25, 3.75)	4.00 (2.50, 6.50)	**0.005**
Miscellaneous, median (IQR)	1.00 (0.00, 5.50)	0.00 (0.00, 2.00)	5.00 (1.00, 7.50)	**0.003**

Normally and non-normally distributed continuous variables are expressed as mean ± SD and median (IQR), respectively; categorical variables are expressed as number (percentage %). Statistically significant results are shown in bold

BMI body mass index, *LEDD* levodopa equivalent daily dosage, *H-Y staging* Hoehn–Yahr staging, *MDS-UPDRS III* Movement Disorder Society-Unified Parkinson's Disease Rating Scale part III, *MoCA* Montreal Cognitive Assessment, *PDQ-39*, 39-item Parkinson's disease Questionnaire, *NMSS* Non-motor Symptoms Scale, *NMSB* non-motor symptoms burden, *SD* standard deviation, IQR interquartile range

5.00 years, and the media H-Y staging was 2.5 of our study population. According to the level of NMSB, we classified the NMSB into two groups: mild-moderate and severe-very severe. Comparisons of demographic and clinical characteristics between NMSB groups are showed in Table 1. The PD patients with severe-very severe NMSB showed an older age, older age at onset, and higher PDQ-39 scores ($p<0.05$) than the PD patients with mild-moderate NMSB; while, no significant differences were shown in sex, BMI, disease duration, H-Y stage, MDS-UPDRS III total scores, or MoCA scores ($p>0.05$) (Table 1).

NMS between NMSB groups

The PD patients with severe-very severe NMSB reached significantly higher subscores in the NMSS subcategories "sleep/fatigue" ($p<0.001$), "mood/apathy" ($p=0.041$), "attention/memory" ($p=0.005$), "gastrointestinal tract" ($p=0.028$), "urinary function" ($p=0.003$), "sexual function" ($p=0.005$), and "miscellaneous" ($p=0.003$) than the PD patients with mild-moderate NMSB (Table 1).

Gait parameters between NMSB groups under ST and DT conditions

Differences were revealed in spatiotemporal gait parameters between the NMSB groups in the ST walking condition. The PD patients with severe-very severe NMSB showed slower gait speed ($t=-3.307$, $p=0.002$) and shorter stride length on both sides (MA side $t=-2.443$, $p=0.020$; LA side $t=-2.586$, $p=0.015$) than PD with mild-moderate NMSB (Table 2). Significantly reduced gait speed ($t=-2.210$, $p=0.035$) and stride length on both sides (MA side $t=-2.957$, $p=0.008$; LA side $Z=-2.434$, $p=0.015$) were also shown in PD patients with severe-very severe NMSB under the DT walking condition (Table 2).

The paired-sample t test and Wilcoxon signed-rank test revealed significant effects of the DT on all spatiotemporal gait parameters, with the exception of step length and swing phase on the MA side. The parameters including gait speed ($t=-6.789$, $p<0.001$), cadence ($t=-3.424$, $p=0.002$), stride length (MA side $t=-7.517$, $p<0.001$; LA side $Z=-4.528$, $p<0.001$), gait cycle duration (MA side $Z=-3.487$, $p<0.001$; LA side $Z=-3.282$ $p=0.001$),

Table 2 Gait parameters under ST and DT conditions between NMSB groups

	Mild-moderate NMSB ($n=16$)	Severe-very severe NMSB ($n=17$)	t value; Z value[a]	p value
Single task				
Gait speed (m/s)	1.08 ± 0.15	0.92 ± 0.12	− 3.307	**0.002**
Cadence (steps/min)	114.88 ± 7.67	114.14 ± 11.93	− 0.210	0.835
Stride length (m)				
MA	1.13 ± 0.14	1.00 ± 0.15	− 2.443	**0.020**
LA	1.14 ± 0.15	1.00 ± 0.15	− 2.586	**0.015**
Gait cycle duration (s)				
MA	1.06 ± 0.07	1.09 ± 0.11	0.940[a]	0.363
LA	1.06 ± 0.07	1.10 ± 0.12	1.047[a]	0.309
Step length (% stride length)				
MA	48.94 ± 3.25	48.65 ± 3.41	− 0.256	0.803
LA	51.93 ± 3.18	51.36 ± 3.41	− 0.287	0.776
Swing phase (% gait cycle)				
MA	39.18 ± 2.28	37.24 ± 4.92	− 1.338[a]	0.292
LA	37.97 ± 2.58	39.76 ± 4.62	− 1.063	0.183
Double support phase (% gait cycle)				
MA	22.95 ± 2.90	22.57 ± 3.76	− 0.322	0.750
LA	22.77 ± 3.10	22.60 ± 3.71	− 0.144	0.886
Dual task				
Gait speed (m/s)	0.90 ± 0.17	0.78 ± 0.13	− 2.210	**0.035**
Cadence (steps/min)	105.40 ± 11.94	111.61 ± 14.22	1.357	0.185
Stride length (m)				
MA	1.03 ± 0.13 ±	0.88 ± 0.13	− 2.957	**0.008**
LA	1.03 ± 0.13	0.83 ± 0.29	− 2.434[a]	**0.015**
Gait cycle duration (s)				
MA	1.19 ± 0.15	1.13 ± 0.13	− 1.281	0.210
LA	1.19 ± 0.15	1.13 ± 0.13	− 1.315	0.198
Step length (% stride length)				
MA	48.51 ± 3.81	48.74 ± 3.52	0.176	0.861
LA	51.47 ± 3.84	51.27 ± 3.92	− 0.153	0.879
Swing phase (% gait cycle)				
MA	38.14 ± 3.76	36.43 ± 3.92	− 1.277	0.211
LA	36.63 ± 3.80	37.96 ± 3.19	1.090	0.284
Double support phase (% gait cycle)				
MA	25.09 ± 4.44	25.08 ± 4.83	− 0.002	0.999
LA	25.15 ± 4.38	25.06 ± 4.85	− 0.053	0.958

All gait parameters were expressed as mean ± SD. Statistically significant results are shown in bold

ST single task, *DT* dual task, *MA* more affected, *LA* less affected, *NMSB* non-motor symptoms burden, *SD* standard deviation

[a]Mann–Whitney *U* test

swing phase on the LA side ($t=-2.481$, $p=0.019$), and double support phase (MA side $t=2.837$, $p=0.008$; LA side $t=2.938$, $p=0.006$) substantially reflected gait impairment under DT condition in patients with PD (Table 3).

Stratified by the NMSB, gait was also significantly impaired in the two groups under DT walking condition. In the mild-moderate NMSB group, gait speed ($t=-4.105$, $p=0.001$), cadence ($t=-3.560$, $p=0.003$), bilateral stride length (MA side $t=-3.616$, $p=0.003$; LA side $Z=-2.892$, $p=0.004$), and gait cycle duration (MA side $Z=-3.079$, $p=0.002$; LA side $Z=-3.103$ $p=0.002$) were significantly affected by DT (Table 3). In the severe-very severe NMSB group, gait speed ($t=-7.588$, $p<0.001$), bilateral stride length (MA side $t=-8.638$, $p<0.001$; LA side $Z=-3.443$, $p=0.001$), and double support phase (MA side $t=2.233$, $p=0.041$; LA side

Table 3 Effects of DT on gait parameters in included PD patients

	Total		Mild-moderate NMSB ($n=16$)		Severe-very severe NMSB ($n=17$)	
	t value; *Z* value	*P* value	*t* value; *Z* value[a]	*P* value	*t* value; *Z* value[a]	*p* value
Gait speed (m/s)	−6.789	**<0.001**	−4.105	**0.001**	−7.588	**<0.001**
Cadence (steps/min)	−3.424	**0.002**	−3.560	**0.003**	−1.296	0.213
Stride length (m)						
MA	−7.517	**<0.001**	−3.616	**0.003**	−8.638	**<0.001**
LA	−4.528[a]	**<0.001**	−2.892[a]	**0.004**	−3.443[a]	**0.001**
Gait cycle duration (s)						
MA	−3.487[a]	**<0.001**	−3.079[a]	**0.002**	−1.588[a]	0.112
LA	−3.282[a]	**0.001**	−3.103[a]	**0.002**	−1.212[a]	0.226
Step length (% stride length)						
MA	−0.517	0.609	−0.700	0.495	0.427	0.675
LA	−0.546	0.589	0.715	0.485	−0.397	0.697
Swing phase (% gait cycle)						
MA	−0.867[a]	0.386	−1.138[a]	0.255	−0.118[a]	0.906
LA	−2.481	**0.019**	−1.494	0.156	−1.949	0.069
Double support phase (% gait cycle)						
MA	2.837	**0.008**	1.741	0.102	2.233	**0.041**
LA	2.938	**0.006**	1.913	0.075	2.194	**0.044**

Statistically significant results are shown in bold

NMSB non-motor symptoms burden, *MA* more affected, *LA* less affected

[a]Wilcoxon signed-rank test

$t=2.194$, $p=0.044$) were also significantly affected by DT (Table 3).

DTEs of gait parameters

The DTE of each gait parameter was used to assess the effect of DT on spatiotemporal gait parameters in PD patients with mild-moderate NMSB or severe-very severe NMSB. The DTE on cadence ($t=2.615$, $p=0.038$) and DTE on bilateral gait cycle duration (MA side $Z=-2.234$, $p=0.025$; LA side $Z=-2.558$, $p=0.010$) were significantly larger in the mild-moderate NMSB group than in the severe-very severe group (Table 4). Overall, in the DT condition, both groups showed reduced gait speed, cadence, stride length, and swing phase and showed increased gait cycle duration and double support phase by Student's *t* test and the Mann–Whitney *U* test (Table 4).

Correlation analysis between DTEs and NMSB

Correlation analysis revealed certain correlations between DTEs of gait parameters and NMSS scores and that are presented in Fig. 1. The DTE of bilateral gait cycle duration was significantly correlated with NMSS scores (MA side $r_{Sp}=-0.404$, $p=0.020$; LA side $r_{Sp}=-0.420$, $p=0.015$). A significant correlation was also shown between the DTE of swing phase on the MA side and NMSS scores

Table 4 DTEs (%) of gait parameters between NMSB groups

	Mild-moderate NMSB ($n=16$)	Severe-very severe NMSB ($n=17$)	*t* value; *Z* value[a]	*p* value
Gait speed	−16.46 ± 14.30	−15.27 ± 7.62	0.301	0.765
Cadence	−8.18 ± 9.04	−2.22 ± 6.67	2.165	**0.038**
Stride length				
MA	−7.83 ± 8.61	−13.17 ± 7.06	−1.954	0.060
LA	−8.76 ± 9.05	−17.89 ± 22.32	−1.658[a]	0.102
Gait cycle duration				
MA	12.45 ± 14.37	2.91 ± 7.13	−2.234[a]	**0.025**
LA	12.36 ± 13.24	2.23 ± 6.82	−2.558[a]	**0.010**
Step length				
MA	−0.84 ± 5.00	0.18 ± 1.74	−0.720[a]	0.488
LA	0.90 ± 4.84	−0.16 ± 1.68	−1.009[a]	0.326
Swing phase				
MA	−2.72 ± 6.93	−1.51 ± 8.35	−1.009[a]	0.326
LA	−3.37 ± 9.94	−3.82 ± 9.27	−0.136	0.892
Double support phase				
MA	10.46 ± 21.32	12.31 ± 20.91	0.247	0.806
LA	11.82 ± 21.71	12.02 ± 21.15	0.026	0.980

Statistically significant results are shown in bold

DTE dual task effect, *NMSB* non-motor symptoms burden, *MA* more affected, *LA* less affected

[a]Mann–Whitney *U* test

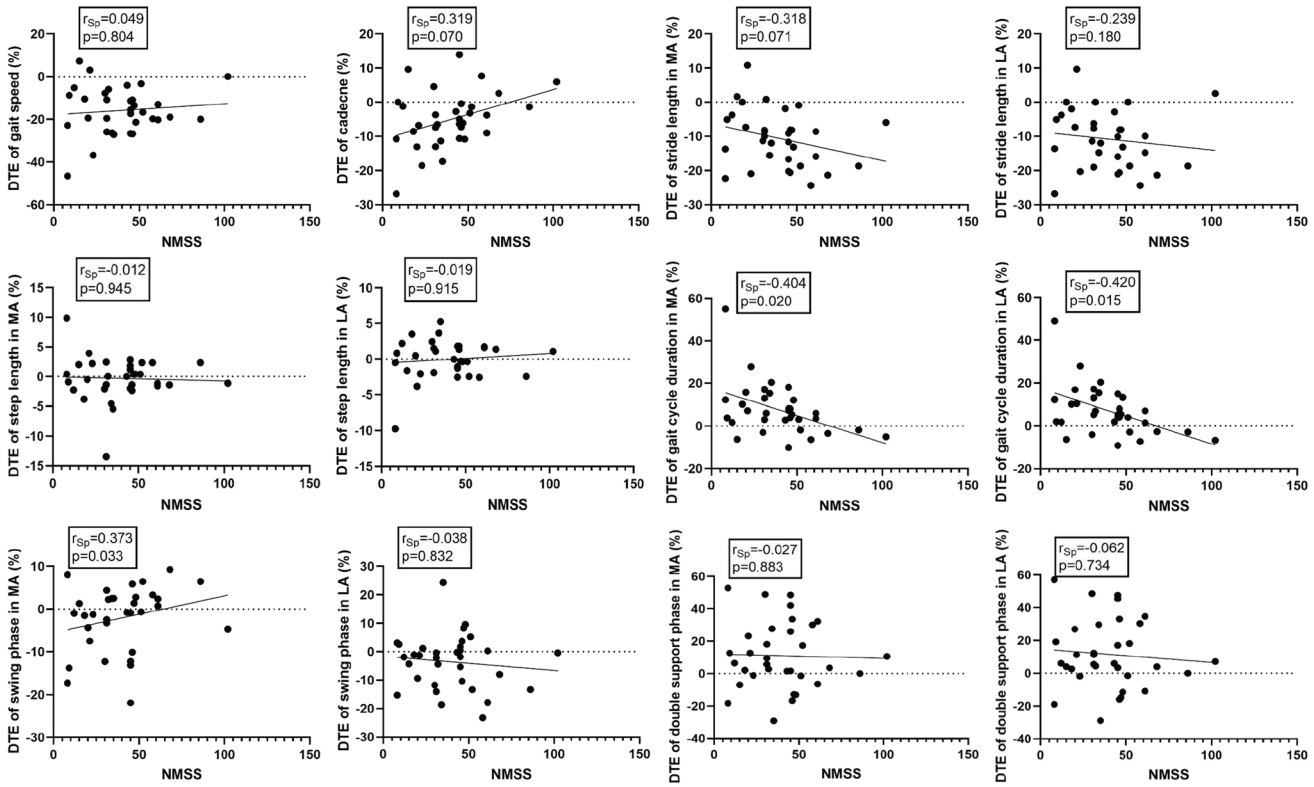

Fig. 1 Correlation analyses between NMSS and DTEs of spatiotemporal gait parameters in PD. DTE, dual task effect; NMSS, Non-motor Symptoms Scale; MA, more affected; LA, less affected; r_{Sp}, Spearman's rank correlation

($r_{Sp} = 0.373$, $p = 0.033$). More relevant but not significant correlations were detected in the DTEs of cadence ($r_{Sp} = 0.319$, $p = 0.070$) and DTEs of stride length on MA side ($r_{Sp} = -0.318$, $p = 0.071$). The correlations between spatiotemporal gait parameters and NMSS scores under the ST and DT conditions are showed in Supplementary Table 1.

Regression analysis

DTEs of gait parameters (cadence, stride length on the MA side, bilateral gait cycle duration, and swing phase on the MA side) that showed correlation coefficients $|r_{Sp}| \geq 0.3$ were included in a linear regression analysis. Multicollinearity was observed in DTEs of gait cycle duration on the MA side-LA side, as the variance inflation factor was above 10. Thus, we included DTEs of cadence, stride length on the MA side, gait cycle duration on the LA side, and swing phase on the MA side as the independent variables in the following linear analysis on NMSS scores (dependent variable), and showed that the DTE of gait cycle duration on the LA side ($\beta = -1.306$ 95%CI -3.985 to -0.927, $p = 0.003$) was significantly associated with NMSS scores (Model 1) (adjusted $R^2 = 0.440$, $p < 0.001$) (Table 5). When further adjusted for variables including sex, age, BMI, H-Y stage, LEDD, and MoCA, and PDQ-39 scores (dopamine receptor agonists were used in all study participants and were not included in the regression model as a confounding variable), a significant association was also shown between the DTE of gait cycle duration on the LA side and NMSS scores (Model 2) ($\beta = -1.095$ 95%CI -4.061 to -0.058, $p = 0.044$; adjusted $R^2 = 0.434$, $p = 0.010$) (Table 5).

Table 5 Regression analysis for NMSS

	Adjusted R^2	Standardized β coefficient (95% CI)	p value
Model 1	0.440	−1.306 (−3.985, −0.927)	**0.003**
Model 2	0.434	−1.095 (−4.061, −0.058)	**0.044**

Model 1 was adjusted for DTEs of cadence, stride length in MA side, gait cycle duration on the LA side and swing phase on the MA side; model 2 was further adjusted for sex, age, BMI, H-Y stage, LEDD, MoCA and PDQ-39 scores. Statistically significant results are shown in bold

DTE dual task effect, *NMSB* non-motor symptoms burden, *MA* more affected, *LA* less affected, *BMI* body mass index, *H-Y staging* Hoehn–Yahr staging, *LEDD* levodopa equivalent daily dosage, *MoCA* Montreal Cognitive Assessment, *PDQ-39* 39-item Parkinson's disease Questionnaire, *95% CI* 95% confidence intervals

Discussion

The present study investigated the interplay between NMS and gait performance in patients with PD under DT walking condition by the widely used serial subtraction 7 paradigm and used DTE to quantitatively assess the influence of DT condition. The main results revealed that NMSs were significantly associated with gait impairment in patients with PD during DT condition and that NMSB was reflected in the DTEs of spatiotemporal gait parameters. Significant effects of DT on gait speed and bilateral stride length, gait cycle duration, and double support phase were related to degree of NMSB. The PD patients with mild-moderate NMSB showed larger DTEs on cadence and bilateral gait cycle duration. NMS and DTEs on bilateral gait cycle duration were significantly correlated. Furthermore, the DTE on gait cycle duration on the LA side explained 43% of the variance in NMSS scores. In conclusion, NMS and gait impairment interacted in PD patients while performing DT walking.

We found that DT had significant effect on gait speed, cadence, stride length, gait cycle duration, and double support phase on both sides and swing phase on the LA side in our total PD population. A similar significant effect from DT was also showed in PD patients with varying extents of NMSB. The effects of DT interference on gait parameters have been previously described in patients with PD, and our study was consistent with previous findings that DT interference has significant effect on quantitative spatiotemporal gait parameters such as gait velocity, stride length, cadence, step width, and stance time [8, 9, 22, 23]. Interestingly, the effects on gait speed and stride length were present in both NMSB groups, which may suggest that gait speed or stride length was not suitable as a quantitative gait parameter to differentiate the burden of NMS in PD patients.

Intriguingly, we found that the PD patients with mild-moderate NMSB showed larger DTEs of cadence and bilateral gait cycle duration than the patients with more severe NMSB, which means that DT had greater impacts on cadence and gait cycle duration in PD patients with mild-moderate NMSB. However, two studies compared DTEs of gait parameters between PD patients with and without cognitive impairment and showed that PD patients with cognitive impairment had larger DT costs on gait velocity, stride time, and gait variability [12, 14]. These contradictory results may be attributable to the fact that we used the NMSS as a holistic scale to assess NMS, without assessing the weights of each of the NMS. More investigation is needed to explore the differences in DTEs of gait parameters among patients with varying degrees of NMS impairments to further clarify the influence of NMS on gait performance under DT walking condition. In addition, the phenomenon of larger DTEs on gait parameters shown in the mild-moderate NMSB PD group may indicate that PD patients with mild-moderate NMSB prioritize cognition task over gait while performing motor-cognitive task. It has been suggested that the posture-second strategy might be an effective DT strategy to reduce the negative effects from DT in early-stage PD [24]. Another possible hypothesis was that PD patients with more severe NMSB were unable to consider the secondary task during DT walking. Additional investigations that include different DT tasks and activities in brain regions are required to confirm this hypothesis.

Studies have suggested that NMS largely contributed to gait impairments in PD. PD patients with the postural instability and gait disorder (PIGD) subtype had more severe NMS, such as sleep, fatigue and urinary symptoms and cognitive and mood disorders [25, 26]. Cognitive impairment or sleep or mood disorder also could influence gait parameters under ST or DT condition [14, 15, 27, 28]. Here, we used the regression model to explore whether DTEs of gait parameters could reflect the NMSB and revealed that the DTE of gait cycle duration on the LA side was negatively correlated with NMSS scores, independent of sex, age, BMI, H-Y stage, LEDD, MoCA, and PDQ-39 scores. In other words, a greater impact of DT on gait cycle duration on LA side means a lighter NMSB.

Gait cycle duration, one of the temporal gait parameters, was thought to be controlled by brainstem and spinal cord mechanisms [29, 30]. According to the Braak's hypothesis, the spread of α-synuclein pathology via the vagal nerve and the dorsal motor nucleus of the vagus in the medulla oblongata and the spread of pathology within the central nervous system from lower brainstem regions, towards the substantia nigra, and eventually the neocortex, lead to motor and non-motor symptoms in PD [31, 32]. Thus, we hypothesized that the brainstem or the nuclei in it was crucial brain area involved in the relationship between NMS and gait cycle duration. Additional imaging studies, such as multimodal magnetic resonance imaging (MRI) or 7 Tesla MRI, are needed in the future to further clarify the neural mechanisms.

The effects of DT condition on gait parameters and the correlations between DTEs of gait parameters and NMSS provided some inspiration for clinical management of PD patients. First, deteriorated gait parameters under the DT conditions could provide rehabilitation strategies for PD patients like DT training, especially motor-cognitive DT training. Second, our study showed larger DTEs of gait cycle duration and cadence in the mild-moderate NMSB group, which indicated that a reasonable intervention to improve the negative effects of DT on gait impairment was more needed in PD patients with mild-moderate NMSB.

Third, clinicians should pay more attention to the NMS management when a PD patient had smaller DTE of gait cycle duration on the LA side.

The study has several strengths. First, to the best of our knowledge, this is the first study to quantitatively compare gait performance between groups with differing NMSB and investigate whether NMSB could be reflected by gait performance under DT condition. We revealed a novel association between NMS and DTE of gait cycle duration on the LA side in PD. Second, we used a portable and lightweight wearable device to evaluate gait parameters in a relatively natural environment. Third, we assessed the gait parameters from both the MA and LA sides, which could better reflect the clinical features of asymmetric onset of PD.

Our study has certain inherent limitations. The first limitation was that the sample size was small. Further studies with larger samples are needed to draw more robust conclusions. Second, we used only one motor-cognitive DT paradigm to investigate the correlation between NMS and gait performance during DT, and additional investigations are needed to understand the role of different DT paradigms to address their sensitivity for detecting NMSB in PD. Third, the DT cost of the cognitive task (incorrect answers while counting) was not recorded in this study, so an assessment of the priority of the gait task or counting task during DT walking was unavailable. Fourth, drugs to alleviate NMS, such as antidepressants, anxiolytics, and cholinesterase inhibitors, were not considered in our study, although a previous study indicated that antidepressants were independently associated with gait deficits in ST and DT conditions in older adults[33].

Conclusion

In conclusion, the results of the current study indicate that DT gait performance could reflect the NMSB in PD patients, and that gait cycle duration is a valuable gait parameter to further investigate. Patients with mild or severe NMSB were equally challenged by the DT, and the effects in the mild-moderate NMSB group were more pronounced. In summary, there are many unsolved mysteries in the relationship between gait and NMS to be explored in the future that will provide more evidence for clinical management in patients with PD.

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Author contribution All the authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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Declarations

Ethical approval The studies involving human participants were reviewed and approved by the Ethics Committee of the Beijing Tiantan Hospital. The participants provided their written informed consent to participate in this study.

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

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