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Original Article

Effects of dual-task on gait and cognition in patients with advanced Parkinson's disease during 'on' or 'off' medication state

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Abstract: Background: In the present study, we investigated the effects of dual-task on cognitive and motor functions in patients with advanced Parkinson's disease (PD) during "on" or "off" state, and evaluated the degrees of movement disorder during dual-task performance under different status of medication. Objective: The present study was designed to investigate the effects of dual-task on cognitive and motor functions in patients with advanced Parkinson's disease (PD) during "on" or "off" state, and evaluate the degrees of movement disorder during dual-task performance under different status of medication. Methods: We evaluated motor functions including step velocity, step length, and rotation velocity in 20 patients with advanced PD in "on" or "off" state during the performance of a dual-task. Results: Both motor and cognitive task performance (i.e., correct calculation efficiency of concurrent serial addition of 3 additions or subtraction of 7) were reduced during dual-task when compared to single task (i.e., walking only). While concurrent serial addition or subtraction impaired motor functions to a similar degree in patients during "off" or "on" state after L-DOPA treatment, correct calculation efficiency of concurrent serial subtraction of 7 was reduced, relative to that of concurrent serial addition of 3, and correct calculation efficiency of concurrent serial subtraction of 7 and serial addition of 3 was reduced, relative to the single task condition. Such impairment in cognitive task performance became more severe when patients were in "off" state of L-DOPA. Conclusions: Our results suggested that neurological functions involved in gait adjustment might be different during "on" or "off" state after L-DOPA treatment. The complexity of cognitive task in dual task test can significantly impact performances of motor and cognitive tasks in patients with advanced PD.

Keywords: Parkinson's disease, dual-task, cognition, gait

Introduction

Gait dysfunction in Parkinson's disease (PD) is one of the most common movement disorders. As the disease progresses, the incidence and severity of gait disorders gradually increase. In the first three years of PD diagnosis, more than 85% of PD patients face clinical gait dysfunction [1]. Gait disorders seriously affect the quality of life of PD patients [2]. In daily life, the situation of walking while performing an additional movement or cognitive tasks often occurs, such as walking while talking to family members, or with a cup of coffee in hand. A large number of studies have shown that walking while performing another task negatively affects gait performance and is closely related to fall [3-5]. When there is no clear indication of which task has the priority, performing two tasks at the same time leads to the competition of attention resource. In addition, the brain needs to evaluate and determine which task has the priority, which may be decided by motivation to minimize danger and maximize pleasure [6]. Based on previous studies, age, neurological disorders, and cognitive decline are the key factors affecting the dual-task gait function [7-12]. However, it is still unclear about how dual-task gait function in PD patients was affected by L-DOPA treatment, a gold standard treatment for PD.

While turning is one of the most important and frequently-occurred movements in daily life, reports about the characteristics of turning movement when PD patients perform dual-tasks are rare. Thus, the similarities and differences between PD patients turning and walking in PD patients when performing dual-tasks worth further investigation. Furthermore, advanced PD patients often have more severe gait disorders and larger difference in movement disorders during medication "on" and "off" states. With the progression of the disease, fluctuations in symptoms, reduced efficacy of L-DOPA, and medication wearing-off effect are inevitable, which are similar to off-state. This is the scenario that each patient with advanced PD has to face. In this phase, PD patients are most likely to fall. Therefore, it is particularly important to understand the relationship between cognitive task and motor task during medication on and off states, and study how cognitive resources are assigned to these two tasks.

Although mechanisms underlying the phenomenon of dual-task interference are still unclear, dual-task interference can occur in any population, including young people, the elderly, people with mild cognitive impairment, people with dementia, as well as people suffering from PD and other neurological disorders [13, 14]. Some studies have shown that patients with cognitive dysfunction or neurological disorders, such as dementia and PD, are more susceptible to additional cognitive tasks [15, 16]. Currently, there are three hypotheses to explain the dual-task phenomenon. First, capacity theory suggests that cognitive resources can be flexibly assigned when execution of the two tasks limits the total amount of resources. Motor task will occupy part of the cognitive resources. When two tasks are simultaneously performed, tasks will compete with each other for limited cognitive resources, resulting in decreased performance in one or two tasks [17, 18]. Second, Bottleneck theory indicates two similar tasks that were simultaneously performed may need to compete for the same neurological pathway. Thus, the performance of one of the two tasks may be impaired [19]. According to this theory, dual-task performance requires serial or sequential processing of the two concurrent tasks, which can compete for the same processing resources. Therefore, in order to complete one task, processing of the second task is temporarily postponed, resulting in decrements of performance in the second task. Last, cross-talk theory suggests that competition of two tasks simultaneously for the same neurological pathway will instead reduce the extent of dual-task interference [20]. However, it is still unclear whether these theories would help to explain the mechanisms underlying the effects of dual-task performance on cognitive and motor functions in patients with advanced Parkinson''s disease (PD) during "on" or "off" states.

Therefore, the present study was designed to investigate the effects of dual-task on cognitive and motor functions in patients with advanced Parkinson's disease (PD) during "on" or "off" states, and evaluated the degrees of movement disorder during dual-task performance under different status of medication. To this end, we evaluated motor functions including step velocity, step length, and rotation velocity in 20 patients with advanced PD during "on" or "off" states after L-DOPA treatment when simultaneous cognitive tasks with different levels of cognitive load were performed.

Method

Subjects

Twenty patients with idiopathic PD were recruited by Department of Neurosurgery, Tangdu Hospital, The Fourth Military Medical University in Xi'an, China to meet the following criteria: diagnosis of idiopathic PD, disease severity of Hoehn and Yahr stages II-IV [21], the ability to perform walking and rotation movements on their own during the 'off' state of medication. Patients were excluded when the following criteria was met: (1) have a variety of secondary PD and PD plus syndromes; (2) have a history of neurological disorders (such as vestibular and central nervous system trauma, cerebrovascular disease, etc.; (3) had brain surgery or brain gamma knife radiosurgery treatment; (4) concurrent mental illness; (5) severe depression and anxiety (Hamilton anxiety Scale score >29 points; Hamilton depression scale score >35 points; (6) previous history of drug and alcohol abuse; (7) poor adherence to complete a full assessment; (8) have muscle-related diseases, peripheral nervous system disorders, and bone and joint diseases, which may cause gait disorders; (9) possibility of Parkinson's disease-mild cognitive impairment (PD-MCI) and Parkinson's

Table 1. Clinical characteristics of PD participants (n = 20)

	Mean	SD
Male (%): 15 (75%)		
Age (year)	61.9	7.9
Education	12.1	3.2
Duration	7.1	2.7
H-Y scale	3.1	0.8
UPDRS III	25.6	7.8
LEED (mg/day)	530.2	271.8
MoCA	27.4	1.3

Disease Dementia (PDD) in accordance with PD-MCI level I by Movement Disorder Society (MDS) [22] and PDD diagnostic criteria [23]; (10) have obvious panic gait. Experiments were within-subject designed, and the same PD patients in different states of medication (i.e., off-state, or on-state) underwent all the experiments. Ethical approval for the study was granted by the Research Ethics committee at the Fourth Military Medical University in Xi'an, China.

Data collection of general information

The collected general information of PD patients included age, sex, disease duration, age of onset, education, levodopa equivalent daily dose (LEDD) [24], Hoehn and Yahr Staging of PD, UPDRSIII, Hamilton anxiety Scale scores, and Hamilton depression Scale scores.

Cognitive assessment

The cognitive function of PD patients was assessed using Montreal Cognitive Assessment (MOCA) Beijing Version recommended by MDS. Comprehensive cognitive assessment (not including cognitive testing tasks) was conducted in the early morning during the on-state of medication. On-state was defined as one hour after 1.5 times of daily dose of Levodopa, and was clinically confirmed in the morning. Off-state was defined as over 12 hours after stopping L-DOPA intake [25].

Experimental protocol

PD patients were asked to perform a single motor task, during which patients walked straight from a starting point for 5 meters, turned 180 degrees, walked straight back to the starting point, and ended with turning 180 degrees. The same patients were also asked to perform a single cognitive task, during which the subjects were tested in a sitting state and were asked to perform either concurrent serial additions of 3 or subtractions of 7 task. In order to avoid the reduction of cognitive load due to putative learning effects in subsequent assessments, addition of 3 task started from 10, and subtraction of 7 task started from 90. The task lasted for 30 seconds, and question interval was 2 seconds, in order to keep the stable cognitive load in unit time. If the patients could not give the answer, same questions were repeated until the correct answers were provided.

To test the effects of dual tasks on motor and cognitive functions, PD patients were also asked to perform a dual task, which consisted of simultaneous performance of motor and cognitive tasks as described above. Specifically, patients walked straight from a starting point for 5 meters, turned 180 degrees, walked straight back to the starting point, and ended with turning 180 degrees, while performing either on current serial 3 additions or 7 subtractions task. During dual-task, addition of 3 task started from 3, and subtraction of 7 task started from 100. Question interval remained the same as single task. In order to improve the sensitivity of the test, once calculation errors occurred, the same question was repeated until patients calculated correctly.

Participants were evaluated at our testing site in a quiet environment. The patients were fully informed before the test regarding test processes and precautions by allowing patients watch a video demonstrating the testing process. The order of the tasks was randomized among patients. Patients were asked to keep length and speed of steps at their daily comfortable level. The whole testing process was recorded by video. Close monitor and rear side protection were provided to patients with PD in off-state during testing in order to prevent putative injuries.

Date analysis

Data of gait parameters were acquired based on recorded testing videos. Data entry was double checked by additional experimenters. The definitions of the gait parameters are described as follows: walking time was defined

Table 2. Gait outcomes in PD participants during "on" or "off" states

Group	Step Speed (m/s)	Step length (m)	Rotation velocity (rad/s)	Berg Score
On-state	0.76 ± 0.15	0.46 ± 0.07	108.75 ± 41.55	54.00 ± 2.73
Off-state	0.48 ± 0.26	0.30 ± 0.11	64.06 ± 49.62	38.70 ± 14.22
P value	P < 0.05	P < 0.05	P < 0.05	P < 0.05

as time used in walking straight in 10 meters (excluding time used for rotation); walking steps was defined as the number of steps used in walking straight in 10 meters (excluding time used for rotation); rotation time was defined as the sum of time used in two rotations (rotate 180°); rotation steps was defined as the sum of steps used in two rotations; Step length = total distance (10 m)/Walking steps; Step speed = total distance (10 m)/Walking time; and Rotation velocity = 360°/Rotation time(s). Relative change in performance between task conditions was also calculated and described as the interference effect using the following equations: (the effect of dual-task on cognitive performance was described as dual-task interference). Dual-task interference = dual-task performance-single-task performance [26]. The effect of the dual-task on gait performance was described as dual-task cost. Dual-task cost (percentage) = (dual-task performance-single-task performance)/single-task performance × 100% [27].

In literature, correct rate alone or total number of correct calculations were often used to assess arithmetic task performance [28]. However, these methods do not count the time factor. Thus, they may not reflect the total performance of arithmetic task. Therefore, in order to assess the cognitive performance, we used the correct calculation efficiency, which was calculated as follows: test time/the number of correct calculations (s/n). It represents the length of time required to complete a correct calculation.

Statistical analysis

All statistical analyses were performed using SPSS19.0 statistical software. Paired comparisons were evaluated using a two-tailed t-test, while multiple comparisons were evaluated by an analysis of variance (ANOVA) followed by Bonferroni post-test when appropriate. Data were expressed as mean ± standard deviation (Mean ± SD). Alpha for statistical significance was 0.05.

Results

Participant characteristics

Participants' demographic and clinical details are shown in **Table 1**. Fifteen men and 5 women presented with moderate to severe PD.

Gait outcomes in PD participants during "on" or "off" states

The gait outcomes in PD participants during "on" or "off" states after L-DOPA treatment are shown in **Table 2**. The step length, step speed, rotation velocity, and Berg scores were reduced when PD participants were in off-state, relative to on-state.

Effects of dual task on motor functions in PD participants during "on" or "off" states

The effects of dual task on motor functions in PD participants during "on" or "off" states are shown in **Table 3**. Repeated ANOVA showed that step speed, step length, and rotation velocity were reduced in patients who had dural task of addition of 3 or subtraction of 7 as compared to those who had single task during either on-state or off-state of L-DOPA. Furthermore, PD participants in "off" state exhibited reduced step speed, step length, and rotation velocity as compared to those when were in "on" state when performing either single task or dual tasks.

Effects of dual task on cognitive functions in PD participants during "on" or "off" states

The effects of dual task on cognitive functions in PD participants during "on" or "off" states are shown in **Table 4**. Repeated ANOVA showed that dual task decreased the efficiency of correct calculation as compared to single task. Furthermore, PD participants in "off" state exhibited decreased efficiency of correct calculation as compared to "on" state when performing dual tasks with either additions of 3 or subtraction of 7. Additionally, dual task interference was enhanced during off-state, as compared with on-state. Finally, dual task interfer-

Table 3. Effects of cognitive task on motor functions in PD participants during "on" or "off" states

Characteristics	State	Single Task	Dual Task With 3 Addition	Dual Task With 7 Subtraction	*P* values
Step Speed	On	0.76 ± 0.15	0.67 ± 0.16*	0.62 ± 0.20*	$P_{task} < 0.05$
	Off	0.48 ± 0.26#	0.40 ± 0.21*,#	0.36 ± 0.21*,#	$P_{group} < 0.05$
Step Length	On	0.46 ± 0.07	0.41 ± 0.09*	0.38 ± 0.10*	$P_{task} < 0.05$
	Off	0.30 ± 0.11#	0.25 ± 0.12*,#	0.21 ± 0.09*,#	$P_{group} < 0.05$
Rotation velocity	On	108.75 ± 41.55	88.50 ± 38.39*	77.15 ± 35.24*	$P_{task} < 0.05$
	Off	64.06 ± 49.62#	44.00 ± 29.29*,#	33.25 ± 21.5*,#	$P_{group} < 0.05$

P values represent the group or task main effects and the interaction effect. *: Represent significant effect relative to single task. # Represents significant effect relative to on-state.

Table 4. Effects of dual task on cognitive functions in PD participants during "on" or "off" state

Characteristics	Task	On State	Off State
3 Addition	Single	2.60 ± 0.64	2.66 ± 0.69
	Dual	2.89 ± 0.72#	4.83 ± 2.84#
7 Subtraction	Single	5.45 ± 0.99	5.66 ± 1.54
	Dual	7.82 ± 4.84#	13.50 ± 10.53#
Dual Task Interference	3 Addition	0.29 ± 0.39	2.16 ± 2.82+
	7 Subtraction	2.37 ± 4.64*	7.83 ± 10.44*,+

*: Represents significant effect relative to 3 addition tasks. #: Represents significant effect relative to single task. +: Represents significant effect relative to on-state.

ence was robustly increased in dual task with subtraction of 7, relative to dual task with addition of 3 in either on-state or off-state.

Effects of cognitive task on dual task costs (DTCs) of motor functions

The state of L-DOPA treatment and concurrent serial additions of 3 or subtraction of 7 task differentially influenced the DTCs of step length, step speed, and rotation velocity. Specifically, in on-state, concurrent serial subtraction of 7 task, but not addition of 3 tasks, increased DTCs of rotation velocity, relative to step speed and step length (**Figure 1A**). Furthermore, in off-state, concurrent serial subtraction of 7 task and addition of 3 tasks similarly increased DTCs of rotation velocity, relative to step speed, but not step length (**Figure 1B**).

Discussion

The present study investigated the effects of dual-task on cognitive and motor functions in patients with advanced Parkinson's disease (PD) during "in" or "off" states, and evaluated the degrees of movement disorder during dual-tasks performance under different status of medication. We found that both motor and cognitive task performance (i.e., efficiency of correct calculation during concurrent serial addition of 3 or subtraction of 7) were reduced in patients during dual-task, relative to single task (i.e., walking only). Such impairments became increased when patients were walking and performing concurrent serial subtractions of 7, relative to addition of 3. While concurrent serial subtraction of 7 impaired motor functions to a similar degree in patients during "off" or "on" states after L-DOPA treatment relative to addition of 3, efficiency of correct calculation was reduced during concurrent serial subtraction of 7 when compared to that of concurrent serial addition of 3. Such impairment in performance of cognitive task became more severe when patients were in L-DOPA off-state, relative to on-state. Generally, our results are consistent with previous studies that PD patients exhibited reduced gait parameters including step speed, step length and rotation velocity, and impaired cognitive performance during the performance of dual task [27-29].

Notably, we also demonstrated that the state of L-DOPA treatment and the level of cognitive load could differentially influence the DTCs of step length, step speed, and rotation velocity. Specifically, high cognitive load (i.e., subtraction of 7), but not low cognitive load (i.e., addition of 3), increased DTC of rotation velocity, relative to DTCs of step length and step speed when PD participants were on medication. However, when PD participants were in "off"

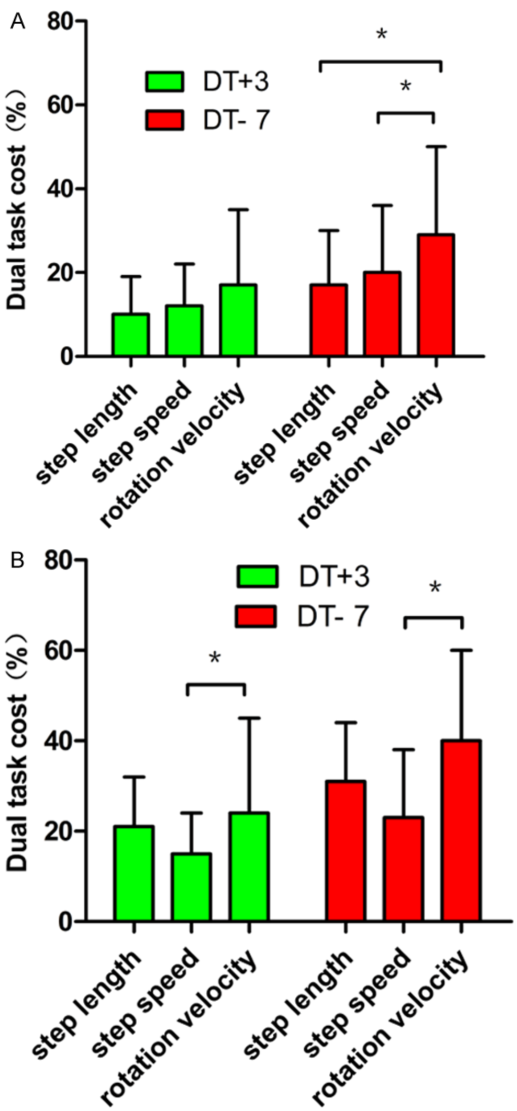

Figure 1. Percentage of dual-task interference for step velocity, step length, and rotation velocity during (A) on-state and (B) off-state. Asterisks represent significant effects in dual-task cost between motor function characteristics ($P < 0.05$).

state, low cognitive load increased DTC of rotation velocity relative to DTC of step speed, which is similar to high cognitive load. These results suggested that rotation was more complex than straight walking, which may require more cognitive resources and motion effort than walking straight. Interestingly, when comparing DTCs of step length and step speed, we found that cognitive load did not alter DTC of step speed relative to step length, when PD participants were in "on" state after treatment. However, cognitive load produced a trend toward lower DTC of step speed relative to step length, when PD participants were in "off" state after treatment. These results indicate that gait adjustment strategies may be different in on-state and off-state, and dual-task gait adjustment might mainly focus on step length rather than step speed in off-state.

Additionally, the present study demonstrated that the state of L-DOPA treatment could differentially influence the dual task interference for cognitive performance. Specifically, concurrent serial addition of 3 task during off-state (dual task interference: 2.16 ± 2.82) increased dual task interference about 10 times, relative to on-state (dual task interference: 0.28 ± 0.35). Additionally, concurrent serial subtraction of 7 task during off-state (dual task interference: 7.83 ± 10.44) increased dual task interference only about 3 times relative to on-state (dual task interference: 3.12 ± 2.82). Our previous hypothesis was that dual task interference on motor or cognitive task would be similar during either on-state or off-state, when cognitive load is same. However, the present study showed that, for the same PD participant dual task interference on motor task (i.e., step length, step speed, and rotation velocity) was not different between on-state and off-state, but dual task interference on cognitive task was significantly increased during off-state, relative to on-state.

This phenomenon may indicate that off-state PD patients might give priority to maintain the stability of the posture balance. From another perspective, it is more likely that bad movement and balance ability in off-state may force patients to reduce or even suspend cognitive tasks (e.g., some patients were asked many times without answering). The saved cognitive resources are used to compensate the poor motion and balance in order to avoid falling. This also indicated that the allocation strategy for the cognitive resources was altered during on-state or off-state.

Generally, our findings suggest that PD patients may take up cognitive resources to compensate for controlling gait movement. In fact, PD patients may need to rely on increased cognitive resources to keep moving balance partly because disorders of basal ganglia function may lead to reduced capacity of motor function automatically. Functional magnetic resonance imaging studies have showed that brain activity levels in supplementary motor area and prefrontal cortex were significantly increased in PD patients during simultaneously performing dual tasks, as compared to healthy people. These brain areas may be associated with compensatory activities related to movement [30]. Similarly, PD patients may require more cognitive resources to control the walk and carry out the task along with walking [31, 32]. Specifically, negative factors in off-state, such as lower limb muscle rigidity, tremor and slow and postural balance disorder, may make patients spend additional cognitive resources to compensate these negative factors, so that cognitive task performance is likely reduced in these PD patients.

While the neurological mechanisms underlying the effects of states of L-DOPA treatment on dual task performance of motor and cognitive tasks are still not clear, L-DOPA treatment may affect the neurological pathways that control rhythmic movement. Rhythmic exercise is executed without the need for a skill or conscious control to direct the movement [33]. While walking *per se* is a rhythmic movement, the important role of attention and cognitive functions in control walking has been gradually realized [18, 34]. The reduction of basal ganglia function in PD patients may result in a reduction in control for rhythmic movement, which requires cognitive resources [35]. Therefore, in the same PD patient, basal ganglia function disorder would require more cognitive resources for movement control, thus available cognitive resources would be attenuated, leading to interference on the performance of both motor and cognitive tasks. L-DOPA treatment may help maintain the same requirement of cognitive resources for controlling movement, and save additional cognitive resources to complete cognitive tasks. Thus, the performance of motor tasks and cognitive tasks may be improved when PD patients are in on-state. Secondly, L-DOPA treatment may help improve the executive function in PD patients. Basal ganglia dysfunction affects the projections of basal ganglia to the dorsolateral prefrontal cortex, leading to executive dysfunction in PD patients [36, 37]. Previous studies have shown that executive dysfunction is highly correlated to impaired dual-task performance [38]. Last but not least, in recent years, it has been increasingly realized that the pathological process of PD is not limited to the dopamine system. Other neurotransmitter systems, such as serotonin, norepinephrine and acetylcholine, also play a critical role in PD [39-41]. Importantly, L-DOPA treatment can affect the release or reuptake of these neurotransmitters [42]. Therefore, it will be necessary to dissect these putative mechanisms in future studies.

In summary, the present study demonstrated that there is a close and direct interaction between cognitive function and gait adjustment. Consistent with previous studies, the present study indicated that gait adjustment and cognitive task performance may share the same cognitive resources at least partly and dual tasks likely compete for the same cognitive resource. The more complex the cognitive tasks become, the greater impairment in gait adjustment occurs. The more complex the motion tasks are (turning is more complex than the straight walking), the greater the change in gait is. In dual-task, not only gait changes, but the performance of cognitive tasks decreases as the complexity of cognitive task increases. The more complex the cognitive task is, the more obvious the performance declines. Our findings suggested that cognitive function may compensate the impairment of motor functions in PD patients. These findings may facilitate our understanding of the relationship between cognition and movement of PD patients in different states of medication treatment, and may shed light on the intervention of advanced PD and prevention of fall injury.

Disclosure of conflict of interest

None.

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