STUDY DOCUMENTS

Title：	The role of cycling-cognitive dual-task training in early Parkinson’s disease
IRB No.:	201600213A3
PI：	Professor CHIN-SONG LU
Organization:	CHANG GUME MORIAL HOSPITAL at LINKOU
Co-PI：	YA-JU CHANG, CHIUNG-CHU CHEN YI-HSIN WENG
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STUDY PROTOCOL

ABSTRACT

Background: Parkinson's disease (PD) is a neurodegenerative disorder of the basal ganglia in which the production of dopamine is reduced, leading to the motor and non-motor impairment and the loss of automaticity. Recently, the results across studies have indicated that motor-cognitive dual-task deficits in individuals with neurologic disorders appear to be amenable to training. Improvement of dual-task ability in individuals with neurologic disorders holds potential for improving gait, balance, and cognition. The most recent European guideline provides a more graded view, stating that in Hoehn and Yahr stages 2 and 3 DT training may be safe and effective. An overview of current ongoing randomized controlled trials focusing on dual-task rehabilitation, gait training or treadmill training was the major motor-task. However, cycling augmented by cognitive training has not been evaluated. In addition, antioxidant capacity is unclear for PD patients with long-term, regular cycling training.

Study purpose: The purpose of the study will investigate the safety and effectiveness with eight-week cycling-cognitive dual-task training for early Parkinson's disease.

Methods: PD patients will be randomly assigned to cycling training, cycling-cognitive dual task training, and following 8 weeks. All of the subjects will complete 3 assessments at pre-training, post-4 weeks, and post-8 weeks. The outcome measures are clinical severity and disability, performance of gait-cognitive and cycling-cognitive, cognitive-task performance, peripheral-blood oxidative stress, adverse events, etc.

Significance: In this study, evidence-based practice as the foundation, and perspective to design a safe and effective cycling-cognitive dual-task training for early PD patients. It can be verified in the clinical application of these experiments feasibility (practice-based evidence).

INTRODCTION

Parkinson's disease (PD) is a neurodegenerative disorder that is caused primarily by the loss of dopamine neurons, which reduces the amount of dopamine neurotransmitters. PD presents not only with impairment of motor function and automaticity but also with mild cognitive impairment and attention and working memory deficits [1]. PD patients that have a loss of automaticity recruit additional brain networks, specifically the prefrontal areas, even during simple tasks, as a form of compensation [2]. Impairment of the sensorimotor striatum damages automatic control, so PD patients need additional attentional control to perform daily motor behaviors [3]. A study with functional magnetic resonance imaging (fMRI) showed that, at the automatic stage, specific brain regions (such as the anterior putamen, cerebellum, dorsolateral prefrontal cortex, precentral gyrus, and premotor cortex) are more activated in PD patients than in healthy controls, and the posterior putamen region is more activated in controls than in PD patients [4]. This cognitive compensatory mechanism in PD patients may increase the risk of falls [5, 6].

Dual-task (DT) performance is affected by PD. In PD patients, when walking is combined with a cognitive task, spatiotemporal gait parameters worsen [7]; in addition, impaired DT performance has been shown to correlate with an increased risk of falling and diminished quality of life [8]. A previous study showed the occurrence of DT interference during walking in 121 early PD patients and suggested that PD management target DT training in the early stages of PD [9]. There is increasing evidence that integrated or consecutive cognitive-gait DT training improves gait performance [10-16], locomotion automaticity [17], balance, and cognition [16] in patients with PD. However, among the numerous previous DT training studies, only a few studies adopted cycling as a motor task.

Previous studies demonstrated that cycling training improves motor function [20-24], cognition [25, 26], and gait speed [25, 27] in PD patients. Hazamy et al. indicated that patients with PD showed facilitative effects on cognition while performing a cognitive-cycling DT paradigm [28]. A recent study found that aerobic cycling training can improve gait speed, single support time during a self-selected speed condition and cognitive performance in PD patients [29]. We reported that a low-intensity progressive cycling exercise improves motor functions in patients with early-stage PD, especially akinesia. Moreover, the Timed Up and Go (TUG) and double limb support time of these patients significantly decreased after 16 training sessions [30].

In summary, previous reports have indicated that DT training improves gait performance and facilitates cognition during a cognitive-cycling DT paradigm in patients with PD. However, only a few DT training studies adopted cycling as a motor task. By advancing our previous study with cycling single-task (ST) training, we aimed to investigate the efficacy of cognitive-cycling DT training in clinically-matched patients with early-stage PD.

OUTCOME MEASURES

The primary outcomes were changes in the results of clinical assessments including the unified Parkinson's disease rating scale part III (UPDRS III) and modified Hoehn and Yahr staging (mHYS) for both off- and on-states, on-state total UPDRS, TUG test, new freezing of gait questionnaire (NFOGQ), Schwab and England Activities of Daily Living (SE-ADL, %), 39-item Parkinson's disease questionnaire (PDQ-39), and spatiotemporal gait performance during a cognitive-walking DT paradigm. Secondary outcomes were changes in cognitive performance and CMI patterns during the cognitive-walking DT paradigm. We measured accuracy and reaction time and computed a composite score that accounted for speed–accuracy trade-offs [31]. Cognitive performance was reported as a composite score (%). DTI of cognitive and motor performances were accounted for by the composite score and gait speed, respectively. Possible adverse events (AE) were recorded during the study.

MATERIAL AND METHODS

Participants

These patients with idiopathic PD were diagnosed by a neurologist specialized in movement disorders according to the diagnostic criteria proposed by Gelb et al.[32]

Inclusion Criteria:

(1) idiopathic Parkinson's disease
(2) an age between 45 to 70 years
(3) asymmetrical onset of at least 2 of 3 cardinal sign
(4) mHYS from 1 to 2.5 during off state
(5) MoCA score of 26 or greater

Exclusion Criteria: The patients were ineligible if they had

(1) a neurological history other than PD
(2) ever undergone neurosurgery for PD
(3) had moderate to severe dyskinesia
(4) been unstable with medical or psychiatric co-morbidities, orthopedic conditions restricting exercise
(5) done more than 20 min of aerobic exercise over 3 sessions per week on their own

Each patient initially received a baseline (pretraining, T0) test and a midterm (T1) test after 8 sessions of the cognitive-cycling DT training. After all 16 sessions of the cognitive-cycling DT training and 2-3 days of a wash-out period, each participant received a posttraining (T2) test.

Clinical assessments

All clinical assessments were performed after 12 hours of overnight withdrawal of anti-Parkinsonian medications. Twenty-four hours of withdrawal was needed for patients taking prolonged-release dopaminergic agonists. The UPDRS III and mHYS assessments were conducted the subsequent morning while patients were in the off state. Each patient self-administered the medications. The total UPDRS, mHYS, TUG test, NFOGQ, SE-ADL, PDQ-39, and spatiotemporal gait analysis were assessed the patients during their best on-state. The UPDRS subscores were analyzed as follows: akinesia (items 23-26; finger taps, hand movements, rapid alternating movements of the hands and leg agility), and PIGD (items 29-30; gait and postural stability).

Intervention

Patients were scheduled to perform cognitive tasks simultaneously with the cycling training twice per week for 8 weeks for a total of 16 sessions during their on-states.

The cycling activity included an initial phase of dose titration for 2 weeks and a late phase of dose maintenance for 6 weeks. Each session included a 5-min warm-up, the main cycling activity and a 5-min cool down. A standard stationary bicycle was used. The cycling activity started with 15 min of a self-selected cadence in the titration phase, and the speed increased by 5 to 10 revolutions per min (rpm) in increments of 5 min. The intensity of cycling reached at least 40 rpm and was maintained for 30 min in the 4^{th} session. The duration for which the intensity was maintained and the total cycling time was extended by 5 min every 4 sessions; the total cycling time was 30 min for 5-8 sessions, 35 min for 9-12 sessions, and 40 min for 13-16 sessions. Blood pressure (BP), heart rate (HR), rating of perceived exertion (RPE, Borg scale) [33], and saturation of peripheral oxygen (SpO_2) were monitored before, during, and after each training session. If an individual's HR exceeded 50~55 % of the individual's target heart rate (THR, defined as 220 minus the individual's age, which is the maximum heart rate using the Karvonen formula) [34], the trainer required the patient to decrease his or her cycling cadence to below the THR.

The cognitive activity included an initial phase of 2 weeks and a late phase of 6 weeks. The three cognitive tasks, calculation task, spatial memory task, and Stroop inhibition task, were integrated into the cycling training program. The timing of the cognitive tasks was evenly arranged. During the initial phase, cognitive training started with 15 min, and the same level of complexity was maintained for 4 sessions. During the last phase, the cognitive training time was extended by 5-10 min every 4 sessions; the cognitive training time was 20 min for 5-8 sessions, 30 min for 9-12 sessions, and 35 min for 13-16 sessions. In addition, the complexity of the cognitive tasks was increased progressively every 4 sessions.

Spatiotemporal gait analysis

Gait performance was analyzed using GAITRite (CIR Systems, Inc., Franklin NJ, USA) with a 3.66-meter long and 0.9-meter wide instrumented walkway [35] while patients performed the DT paradigm. The DT paradigm comprised four sections: 1) motor single-task (ST), 2) cognitive ST, 3) cognitive-motor DT without task prioritization, and 4) cognitive-motor DT with task-specific prioritization. During the ST cognitive and DT sections, the three cognitive tasks, the calculation, spatial memory, and visual Stroop inhibition tasks, were randomly assigned.

In the motor ST section, the patients were instructed to walk at their "preferred speed" and "fast speed" twice. The outcome measures of the gait assessments were gait speed (cm/sec), step length (cm), step width (cm), step time (sec), and double limb support time (DLST, sec).

In the cognitive ST section, all patients performed three cognitive tasks (i.e., the calculation, spatial memory, and visual Stroop inhibition tasks) while sitting on a chair located approximately 6 meters from a projection screen. The outcomes of cognitive performance were reaction time (millisecond, msec), accuracy (%), and a composite score [31].

In the cognitive-motor DT section, the patients walked at their preferred speed and simultaneously performed a cognitive task. Three cognitive tasks were each performed twice. No instructions were provided regarding the prioritization of a task. Afterwards, instructions regarding the prioritization of a specific task were provided when patients performed the calculation-walking DT paradigm.

Data analysis

The effect of the DT was described as DTI and calculated as the difference between ST and DT performance expressed as a percentage of ST performance, as follows:

$$\text{Dual-task interference (DTI, \%)} = \frac{\text{DT performance} - \text{ST performance}}{\text{ST performance}} \times 100$$

The cognitive performance was described as a composite score, as follows: Composite score (%) $= \frac{\text{Accuracy (\%)}}{\text{Reaction time (ms)}} \times 100$

Statistics

All statistical analyses were performed using SPSS version 22.0 software. Descriptive statistics are reported as the mean ± standard deviation (SD). The Friedman test was used to compare the UPDRS III and TUG test results between T0, T1 and T2. The Wilcoxon signed rank test was used once a significant difference was detected. Repeated measures ANOVA with 1 within-subjects factor was used to compare the gait parameters (gait speed, step length, step width, step time, and double limb support time), accuracy, reaction times, and composite scores between T0, T1 and T2. Fisher's LSD (least significant difference) was used when a significant difference was detected. The significance level was set at $p < 0.05$.

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PRELIMINARY RESULTS

GENERAL INFORMATION

During study period form 2016/06/01 to 2017/05/31, thirteen eligible patients (31 % women) were enrolled and completed the study. The mean age was 60.64±5.32 years (range, 53-67), and the mean age at the onset of PD was 53.62±6.46 years (range, 45-63). The mean disease duration was 7.02±3.23 years (range, 2-14). The mean MoCA test result was 28.69±1.11 (range, 26-30). A total of 12 PD patients completed the training program and all assessments. One subject withdrew from this study due to personal reasons.

OUTCOME MEASURES

The UPDRS III scores improved predominantly from T0 to T2 during both the off- and on-states. Notably, the UPDRS III scores ($p= 0.027$), akinesia subscores ($p= 0.007$), and PIGD subscores ($p= 0.025$) improved significantly from T0 to T1 in the off-state. The observed effect sizes (ES) of the primary outcomes, such as the off-state UPDRS III scores, both the off- and on-states akinesia subscores and the PIGD subscores, TUG, and PDQ-39, were large after 16 sessions of DT training.

While the patients walked at their “preferred speed”, gait speed, step time and double limb support time improved significantly at T1 and T2 compared to T0. Under the calculation-walking DT situation, gait speed, step length, step time, and double limb support time improved significantly at T1 (except step length) and T2 compared to T0. During the spatial memory-walking DT, gait speed and double limb support time improved significantly at T1 (except gait speed) and T2 compared to T0. During the Stroop inhibition-walking DT situation, gait speed, step length, step time, and double limb support time improved significantly at T1 (except step length) and T2 compared to T0. During the DT with prioritization of walking, gait speed, step time, and double limb support time improved significantly at T1 and T2 compared to T0. During the DT with prioritization of the calculation task, gait speed improved significantly at T1 and T2 compared to T0; step time and DLST improved significantly at T2 compared to T0. In summary, gait performance improved significantly after 16 sessions of cognitive-cycling training.

During the cognitive ST and DT sections, the composite score of spatial memory significantly increased at T2 compared to T0.

The adverse events did not recur afterwards.

CONCLUSION

Our study demonstrated that 16 sessions of cognitive-cycling DT training not only improves motor functions of PD patients in off- and on-states but also improves the gait and cognitive performance of PD patients during a DT paradigm. We suggest that cognitive-cycling DT training may be beneficial to include cognitive-cycling DT training as part of the rehabilitation of patients with very early-stage PD.