Journal of Parkinson's Disease 4 (2014) 37–44
DOI 10.3233/JPD-130321
IOS Press

Research Report

Can Cognitive Remediation Improve Mobility in Patients with Parkinson's Disease? Findings from a 12 week Pilot Study

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Abstract.
Background: Patients with Parkinson's disease (PD) suffer from impaired gait and mobility. These changes in motor function have been associated with cognitive deficits that also commonly co-occur in PD, especially executive function (EF) and attention.
Objective: We hypothesized that a cognitive remediation program would enhance gait and mobility.
Methods: The 18 PD patients in this study were assessed at baseline and again one and four weeks after completion of a 12 week long, home-based computerized cognitive training program. Subjects were asked to "play" computer games designed to improve EF and attention for 30 minutes a day, three times per week for 12 weeks, while seated. The Timed Up and Go (TUG), gait speed, and stride time variability quantified mobility. A previously validated, computerized neuropsychological battery quantified global cognitive function and its sub-domains.
Results: Compared to pre-training values, global cognitive scores and time to complete the TUG significantly improved after the training. TUG components of turning speed and duration also improved. Other TUG components, gait speed, and variability did not change after training.
Conclusions: These initial findings suggest that computerized cognitive training can improve cognitive function and has a beneficial carryover effect to certain aspects of mobility in patients with PD. Additional studies are required to replicate these findings and more fully assess the underlying mechanisms. Nonetheless, the present results underscore the motor-cognitive link in PD and suggest that computerized cognitive training may be applied as a therapeutic option to enhance mobility in patients with PD.

Keywords: Cognitive training, gait, mobility, cognitive function, Parkinson's disease, attention, executive function, instrumented Timed Up and Go, body-fixed sensor

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ISSN 1877-7171/14/$27.50

INTRODUCTION

Gait disturbances and falls are common among patients with Parkinson's disease (PD) [1–4]. While approximately one-third of community-living older adults fall at least one time each year, more than 50–70% of patients with PD experience one or more falls annually [1–3]. Impaired mobility and falls in patients with PD have many negative consequences. They lead to fear of falling, social isolation, depression, self-imposed restrictions on activity, decreased functional independence, morbidity and mortality. Much is known about the multi-factorial nature of falls in PD, however, alternative treatment options are needed for optimal reduction of fall risk [1, 5]. The present study was designed to begin to assess the potential benefits of a cognitive intervention that utilizes computerized training to improve gait and mobility and to reduce fall risk in patients with PD.

The rationale for using a cognitive remediation program to enhance gait and treat fall risk is based on several findings. First, executive function (EF) and attention are generally impaired in PD, even in patients with mild disease [6, 7]. EF refers to higher cognitive processes that use and modify information from posterior cortical sensory systems to modulate behavior, to allocate attention among tasks that are performed simultaneously, and to regulate response inhibition. Second, these cognitive impairments negatively impact mobility, since patients with PD rely on EF and attention to ambulate in complex environs and to compensate for underlying gait disturbances. For example, the ability to walk and carry out another task has been related to EF in PD and the negative effects of a secondary, dual-task on gait are larger among patients with PD compared to age-match controls [8–13]. Further, diminished attention and EF apparently lead to an increased fall risk in PD [14]. From the treatment perspective, a number of studies have shown that cognitive training via computer "games" can enhance cognitive function in aging and in a variety of patient groups including those with PD [15–17]. Preliminary findings also suggest that cognitive enhancing therapy improves gait and mobility in PD [18–21]. Moreover, a small, but very intriguing study reported that 3 months of cognitive remediation markedly improved gait among community-living older adults [22]. The potential of a cognitive remediation program has not yet been studied in PD.

These previous findings raise the question: if PD-related reductions in cognitive function contribute to gait changes and fall risk, can a cognitive intervention that reverses this trend improve gait and reduce the risk of falls in patients with PD? Put differently, will the effects of cognitive therapy "transfer" to mobility in patients with PD? To address these questions, we tested the hypothesis that 12 weeks of computerized cognitive training improves mobility and modifies markers of fall risk.

MATERIALS AND METHODS

Study design

To evaluate the effects of 12 weeks of computerized cognitive training on mobility and markers of fall risk, a baseline assessment (pre) was performed at the initial visit, before training commenced. This was followed by 12 weeks of training in each subject's home. Afterwards, two more evaluations took place one week after the conclusion of the intervention (post) and about 4 weeks later (follow-up), to begin to evaluate long-term retention.

Study participants

Patients with PD were recruited from Clalit Health Services clinics and were evaluated at the Lin Medical Center in Haifa, Israel. Ethics approval from the local human studies committee was obtained and all participants provided written informed consent. The study was registered with clinicaltrials.gov, registration number NCT01121627. Subjects were included if they were diagnosed by a movement disorders specialist as having idiopathic PD, were between 50 and 80 years of age, had a score between I and III on the Hoehn & Yahr scale, were ambulatory, had access to a computer and the internet at home, were taking anti-parkinsonian medications, and had a Mini Mental State Examination (MMSE) score above 24 points. Subjects were excluded if their health status or medications were not stable, if they had brain surgery (including deep brain stimulation implants) or if they had significant co-morbidities likely to affect gait, e.g., acute illness, orthopedic disease, significant visual problems, or a clinical history of stroke. Subjects who could not comply with the training protocol were also excluded. Patients with dementia, as determined by DSM IV and ICD 10 criteria, were excluded.

Clinical assessment

Parkinsonian symptoms, disease duration, and disease severity were assessed based on interview and the Unified Parkinson's Disease Rating Scale (UPDRS)

[23]. All testing was conducted in the ON medication state by a physical therapist who was not blinded to the study aims. Age, gender, and years of education were also recorded. The PDQ-39 evaluated quality of life [24].

Assessment of cognitive function

The Mindstreams® (NeuroTrax Corp., TX) battery of computerized neuropsychological tests was used to measure cognitive function at baseline and after the completion of the training [25, 26]. Multiple domains were assessed: executive function, attention, memory and visual-spatial function. The executive function and attention indices were computed based on computerized versions of the traditional Go-NoGo and Stroop tests. These are well-established cognitive tests that evaluate the facility with which an individual is able to inhibit a response and to continue with an activity in the face of competing stimuli. The Mindstreams computerized battery has been validated in PD and has been described elsewhere in detail [10, 25, 26]. Briefly, the cognitive battery includes a practice component before each test. A global cognitive score (mean across all cognitive domains) and indices in each domain are scored on an age and education normed IQ-like scale where 100.0 represents the value for healthy controls and lower numbers reflect worse performance.

Assessment of gait and mobility

The Timed Up and Go (TUG) test was used to assess functional mobility and fall risk [27–29]. This functional-performance based test has been widely used in older adults, in PD, and in other patient populations to characterize and quantify mobility; the American and British Geriatric Society's task force on falls recommend using this test as a screen for fall risk [27]. Subjects were asked to stand up from a standard chair, walk at their normal pace for 3 meters, turn around, and return to a seated position. As per standard procedures, the second of two trials was used to minimize any practice effects. Subjects performed the TUG while wearing a small body-fixed sensor on the lower back (3D accelerometer and 3D gyroscope, Dynaport, hybrid, McRoberts, The Netherlands). Sensor-derived measures were used to determine the time to complete the TUG, the time to carry out individual sub-tasks of this test (e.g., sit-to-stand, turn), and to further characterize performance using previously described methods [30, 31, 48]. Longer times to complete the TUG indicate poorer mobility and an increased risk of falls [27–29].

To evaluate gait, subjects walked at their normal pace on level ground under three conditions (1 minute under each condition): 1) usual-walking; 2) while performing serial 3 subtractions (starting with a 3 digit number); and 3) while performing a test of verbal fluency. These walks took place after a practice condition to familiarize the subjects with the protocol. Previously established methods [10, 32] were used to quantify gait speed (i.e., the time taken to walk the middle 10 meters of the second lap of each condition) and the variability of stride time (using the coefficient of variation, CV). Higher CV values reflect decreased rhythmicity and reduced automaticity and are associated with an elevated fall risk in PD and other populations [10, 33–35].

Cognitive training

Attengo® software was used to provide cognitive training. The computer-based cognitive remediation program was developed to improve cognitive function in a variety of patient populations such as children and adults with ADHD. After an automated, personalized assessment of the subject's cognitive abilities in several domains, the cognitive training program was tuned to each patient's needs. For this study, we specified that the training would focus on executive function and attention (Attenfocus®). Games challenged subjects with problem solving, information processing, response inhibition, and dividing attention. Subjects were asked to use the system for at least 30 minutes a day, three times a week for 12 weeks. Subjects used the cognitive remediation software on their own computer in their own home. In each session, a variety of "games" were presented that taxed different tasks of attention and executive function. The level of difficulty was automatically increased following the standard implementation of the software. The time spent using the software (i.e., a measure of compliance) was recorded automatically by the software and sent to the research team via the internet.

Statistical analysis

Descriptive statistics are reported as mean ± SD. Given the range in the outcome measures and non-normal distributions, we used the Related-Samples Two-way Analyses of Variance by Ranks test, the non-parametric equivalent of repeated measures ANOVA, to assess the response of the dependent variables (e.g., time to complete the TUG, cognitive function) to the training (e.g., pre vs. post vs. follow-up 4 weeks later).

Table 1
Subject characteristics

Age (yrs)	67.7 ± 6.4*
Gender (men/women)	11/7
Years of Education	15.5 ± 3.3
Mini Mental State Exam	29.2 ± 1.1
Disease duration (yrs)	8.9 ± 6.6
Hoehn &Yahr Stage	1.67 ± 0.59
UPDRS Motor Part III	17.6 ± 7.5
Quality of life (PDQ-39)	48.7 ± 27.8
Timed Up and Go (sec)	11.7 ± 3.3
Gait speed (m/sec)**	1.0 ± 0.2
Stride time variability (%)**	2.3 ± 0.8

*Entries are mean ± SD except for gender. **These values are for usual walking.

If the ANOVA Rank test model indicated a significant effect of time or tended to be significant ($p < 0.01$), Wilcoxon Signed Ranked tests were performed *post-hoc* to compare the baseline, pre-intervention values to the post and follow-up values. Baseline values of cognitive function were compared to those of age-matched norms using one sample Wilcoxon Signed Rank tests. A p-value ≤ 0.05 was considered statistically significant. Statistical analyses were performed using SPSS (version 21).

RESULTS

Subject characteristics

Subject characteristics are shown in Table 1. In general, the 18 subjects (7 women) had mild to moderate disease severity and they scored high on the MMSE (mean score of 29.2), a general test of cognitive function. The time to complete the TUG (mean of 11.7 seconds) was below the threshold that corresponds to a high fall risk (13.5 sec), indicating a moderate, but not high level of impaired mobility and fall risk. Similarly, gait speed was reduced compared to the values expected among age-matched healthy controls, but was still above the threshold suggested as marking significant impairment (i.e., 1.0 m/sec).

Effects of cognitive training on cognitive function

On average, the subjects trained less than the desired goal of 18 hours (12 weeks × 1.5 hours per week). Mean training time on the computer intervention was 13.84 ± 4.47 hours. Prior to training, scores on the computerized cognitive battery were significantly below the values expected of healthy age-match controls (see Table 2). Recall that 100.0 represents the age and education normed mean for healthy subjects for the global cognitive score and for each individual cognitive domain. Cognitive remediation significantly improved the global cognitive score, as assessed using the Mindstreams battery (see Fig. 1 and Table 2). Performance on each of the other cognitive domains also tended to improve after the training, however, the overall repeated measures statistical models were not significant for the individual domains.

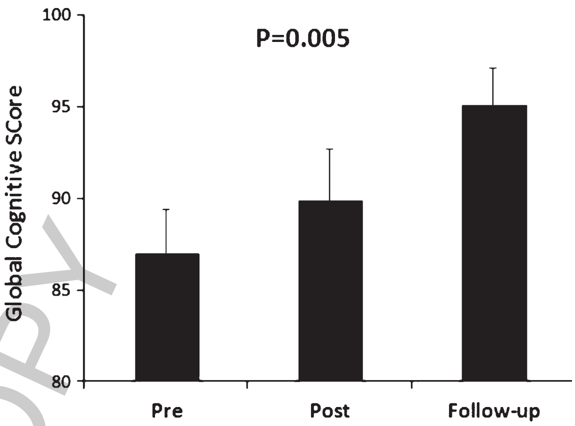

Fig. 1. Effects of cognitive training on global cognitive scores. Error bars reflect the SD.

Effects of cognitive training on mobility and gait

The time to complete the Time Up and Go was lower (i.e., improved) after the training (see Fig. 2). Examination of the individual components of the Time Up and Go using measures derived from the body-worn sensor indicates that performance on the turn improved, while other aspects of this test (e.g., sit-to-stand, stand-to-sit, walking) did not change significantly in response to the training. Specifically, the angular velocity during the turn increased from 130.7 ± 29.8 deg/sec at baseline to 145.9 ± 32.1 deg/sec at post testing ($P = 0.014$) and to 160.1 ± 37.1 deg/sec at follow-up testing ($P = 0.002$). Correspondingly, turn duration decreased from 2.23 ± 0.46 seconds at baseline to 1.91 ± 0.49 ($P = 0.008$) seconds and to 1.70 ± 0.38 seconds ($P = 0.003$) at follow-up testing. Usual walking gait speed did not change in response to the training ($P = 0.975$). Gait speed during both dual task conditions ($P \geq 0.103$) and stride time variability tended to improve, but the changes were not statistically significant ($P \geq 0.105$).

To further assess the link between change in cognitive function and change in TUG performance, we ranked the subjects based on the degree of changes in the global cognitive score and the TUG (change at

Table 2
Effects of cognitive training on cognitive function as assessed using the computerized battery. Entries are mean ± SD with the range shown in parentheses

	Pre	Post	Follow-up	*P*-Value*
Global cognitive Score	87.3 ± 9.2	89.6 ± 11.1	95.1 ± 7.8	0.005
	(61.2–103.1)	(58.7–105.1)	(80.7–112.3)	
	P < 0.001**	*P* = 0.085***	*P* = 0.001***	
Executive function	87.7 ± 12.8	91.5 ± 15.7	94.6 ± 9.3	0.087
	(52.1–106.3)	(54.3–114.6)	(77.4–114.7)	
	P = 0.001	*P* = 0.163	*P* = 0.005	
Attention	88.8 ± 18.5	94.6 ± 16.1	98.2 ± 13.7	0.080
	(35.1–112.4)	(48.9–113.9)	(58.4–116.1)	
	P = 0.022	*P* = 0.094	*P* = 0.017	
Memory	82.7 ± 10.9	82.4 ± 12.8	92.2 ± 10.3	0.079
	(67.1–106.9)	(58.8–110.2)	(77.2–110.9)	
	P = 0.001	*P* = 0.501	*P* = 0.039	
Visial-spatial	93.5 ± 12.3	95.1 ± 11.3	101.2 ± 12.8	0.062
	(76.0–127.2)	(79.1–116.6)	(69.2–113.6)	
	P = 0.022	*P* = 0.518	*P* = 0.033	

*The *p*-values shown in this column are the results of the Related-Samples Two-way Analyses of Variance by Ranks tests. **The *p*-values in this column are the result of a one sample Wilcoxon Signed Rank test comparing the median values with the values of healthy, age-matched controls (i.e., 100.0). *** The *p*-values in these columns are the *post-hoc* comparisons to the baseline, pre-intervention values.

follow-up compared to baseline values for each measure, separately). Subjects with larger changes in the global cognitive score (top 50%) were more likely to also be among those who had larger reductions (top 50%) (i.e., improvements) in TUG times (*P* = 0.030, Chi-square test). Interestingly, subjects who had larger improvements in the global cognitive score and subjects who had larger improvements in the TUG times tended to spend more time training (above the median) (*P* = 0.092, Chi-square test for both tests), compared to those who showed less improvements in these two measures. These associations suggest that there may have been a "dosing" effect; subjects who trained more tended to improve more.

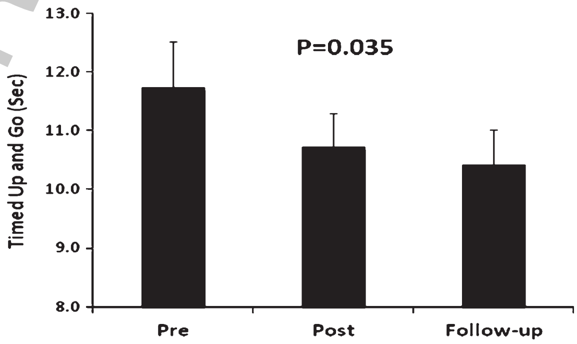

Fig. 2. Effects of cognitive training on Timed Up and Go times. Error bars reflect the SD.

DISCUSSION

The results of this study confirm that cognitive remediation can improve cognitive function in patients with PD. This finding is consistent with a previous study in PD [16] and reports in other populations [15, 17]. Moreover, we found evidence that the 12 weeks of cognitive training, carried out while sitting in front of a computer, appears to have positively impacted certain aspects of mobility. Performance on the TUG, a highly reliable [28], widely used test of mobility and fall risk [27–29], significantly improved in response to the training. This finding lends further support to the provocative notion that cognitive interventions can enhance gait and mobility in PD, similar to what has been demonstrated using other therapeutic modalities [18, 36] and in other populations [18, 21, 22, 37–40].

Two previous studies examined the effects of computerized cognitive remediation on balance and gait in older adults. Li et al. [41] reported that cognitive training while seated enhanced balance in a group of older adults, while the outcomes were unchanged in a control group. The authors explained that balance in aging is influenced by executive control and that the training improved this cognitive domain, with carryover effects to the "motor" task. Similarly, Verghese et al. found that 3 months of computerized cognitive remediation enhanced usual walking and dual-tasking gait speed in a pilot study among older adults [22]. In some sense, the present findings agree with those reports and extend their findings by showing that computerized cognitive training enhances mobility even in the presence of a neurodegenerative disease that affects both cognitive and motor function, i.e., PD. However, in contrast to the study by Verghese et al. the TUG improved, but gait speed did not respond to the training in the present study.

This disparity between the responsiveness of the TUG and lack of a change in gait speed could be explained in several ways. Previous work in older adults has suggested that the TUG is related to executive function and utilizes cognitive resources in part because of the challenges involved with planning and negotiating the turn that takes place about halfway through this test [42–44, 49]. Further, the cognitive demands of usual, straight line walking and curved walking, like a turn, differ [45]. The cognitive remediation program apparently enhanced the cognitive domains needed for turning and the TUG, while it had less of an impact on the cognitive domains utilized during straight line walking. The improvements observed in the turn, but not other aspects of this test, are consistent with this idea.

Alternatively, perhaps, the magnitude of the cognitive change needed to affect on the TUG and straight line walking are not the same. In a previous study that examined the effects of methylphenidate in PD, gait speed, TUG and executive function all significantly improved [18]. Perhaps the pharmacologic intervention had a more widespread or more potent effect. Another potential factor that may have impacted these results relates to the severity of the disease. Most patients in this study had disease severity of I-II based on the Hohen and Yahr scale, scores that reflect mainly a unilateral disease with some axial involvement. Perhaps for these participants, the primary mobility impairment is seen in tasks that are asymmetrical by nature (such as turns) and represent a challenge that requires more cognitive resources. Impairment and hence improvement may be less evident when the tasks are symmetrical (i.e., straight line walking), Future studies, perhaps with more intense or specific training and with a group of patients with a wider disease representation, could tease out the differences between these mobility tasks and their sensitivity to cognitive remediation.

Figures 1 and 2 illustrate another interesting outcome of the present study. In the presence of a progressive neurodegenerative disease like PD, one might anticipate that after the cessation of therapy, outcome measures would return toward the baseline, pre-training values. However, the global cognitive score and TUG times (both the overall time and the performance on the turn) continued to improve when tested 4 weeks after the patients stopped training. Although somewhat counter-intuitive, another cognitive-motor intervention study also observed similar behavior in PD [46]. In that study, gait speed significantly increased after 6 weeks of training delivered via a virtual reality program that targeted walking under complex and cognitively challenging conditions. In addition, gait further improved when subjects were examined 4 weeks after the intervention was completed. The authors of that study offered several explanations for this phenomenon that may also be applicable here. To briefly restate, the cognitive training may have created learning opportunities and fostered additional development of new movement strategies that prompted behavioral changes [46]. Alternatively, perhaps the training empowered increased attention to environmental characteristics, a feature of motor learning that depends in part on cerebellar activation, and, thereby, promoted new strategies to at least partially circumvent impaired basal ganglia loops [47]. More generally, perhaps the training fostered compensatory responses via other neural pathways that lead to further improvements. Another possibility is that this simply reflects practice effects; however, previous studies showing test re-test reliability of the TUG in PD [28] and the fact that only a subset of measures improved would suggest that this may not be the full explanation. Additional work is needed to better understand the encouraging time course seen in Figs. 1 and 2.

The present study has a number of limitations. A major limitation is the absence of a control group. Because of this limitation, the placebo effect cannot be ruled out. Nonetheless, several factors suggest that the placebo effect may not have been fully responsible for the observed effects: 1) The improvements were observed only in specific measures (e.g., the turning portion of the Timed Up and Go) and not globally to. 2) The time spent training the time (i.e., compliance) was associated with improvements on the Timed Up and Go and cognitive function, consistent with a dosing effect. 3) The results are consistent with two previous studies conducted among older adults (i.e., subjects who did not have PD, where the placebo effect is typically smaller) [22, 41]. The study by Li et al. observed an effect in the training group, but not in the control group. 4) Certain measures continued to improve four weeks after the completion of the training, whereas one might expect that the placebo effect would wear off. While the placebo effect cannot be completely dismissed, these observations support the possibility that the cognitive remediation played an important role in achieving the observed improvements.

Other limitations of the present study include the small sample size, the open-label nature of the study, and the lack of assessor and patient blinding. The subjects were generally well educated, had their own computer which was used to deliver the cognitive remediation, and had access to the internet. Thus, generalizability of these preliminary findings may be limited. We used the TUG as a measure of mobility and a proxy for fall risk, but did not follow subjects prospectively to investigate the effects on fall frequency. We can only speculate about the effects on fall frequency. Finally, the average time spent training with the cognitive remediation was, on average, about 4 hours less than the recommended training time over the 3 month intervention period. We suspect that this discrepancy may have been due to the fact that all of the subjects trained in their own homes, without constant supervision. Home-based training offers certain advantages compared to training that takes place in specialized centers. In the future, however, it might be interesting to compare training in the home to training in a center.

Additional investigations are needed to more fully explore the potential of cognitive remediation in the presence of PD and the degree to which the training effects transferred beyond tasks that were directly practiced. We fully agree with the motor learning concept that practice and training should be closely related to the task that is being trained. In this case, cognitive training for mobility appears to violate, in a sense, the principle of task specificity of learning. Perhaps the motor component that improved relied on the cognitive features that were trained and/or perhaps this motor improvement reflect a form of transfer across tasks. Regardless of the exact explanation, we suggest that these initial results demonstrate that cognitive remediation may, perhaps, have merit as an adjunct therapy to enhance motor control and mobility in patients with PD. This form of therapy is safe, does not place the patient at risk, and can be performed in the home-setting, without the need for an expert trainer. For some patients, perhaps cognitive function can be combined with motor training to form an optimal treatment.

ACKNOWLEDGMENTS

We thank the participants for their time and effort and Marina Brozgol for invaluable assistance.

CONFLICT OF AUTHORS

The authors declare that they have no conflicts of interests.

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