RESEARCH ARTICLE

Blind Randomized Controlled Study of the Efficacy of Cognitive Training in Parkinson's Disease

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ABSTRACT: The aim of this study was to analyze the efficacy of a cognitive training program on cognitive performance and quality of life in nondemented Parkinson's disease patients. Participants who met UK Brain Bank diagnosis criteria for Parkinson's disease, with I–III Hoehn & Yahr, aged 50–80, and nondemented (Mini-Mental State Examination $\geq$ 23) were recruited. Patient's cognitive performance and functional and quality-of-life measures were assessed with standardized neuropsychological tests and scales at baseline and after 4 weeks. Subjects were randomly and blindly allocated by age and premorbid intelligence (Vocabulary, Wechsler Adult Intelligence Scale-III) into 2 groups: an experimental group and a control group. The experimental group received 4 weeks of 3 weekly 45-minute sessions using multimedia software and paper-and-pencil cognitive exercises, and the control group received speech therapy. A total of 28 patients were analyzed. Compared with the control group participants (n = 12), the experimental group participants (n = 16) demonstrated improved performance in tests of attention, information processing speed, memory, visuospatial and visuoconstructive abilities, semantic verbal fluency, and executive functions. There were no observable benefits in self-reported quality of life or cognitive difficulties in activities of daily living. We concluded that intensive cognitive training may be a useful tool in the management of cognitive functions in Parkinson's disease. © 2011 *Movement* Disorder Society

Key Words: Parkinson's disease; cognition; cognitive training neuropsychology; cognitive impairment

Cognitive impairment is now recognized as a common feature of Parkinson's disease (PD).[1] The prevalence of dementia in PD is close to 30% and is 6 times higher than that in the general population.[2] In addition, approximately 19%–53% of nondemented PD patients suffer from mild cognitive impairment (MCI).[3–5]

Cognitive impairment in PD is characterized by deficits in executive functions, attention/working memory, speed of information processing, visuospatial abilities, and memory[6] and has important clinical consequences for patient management. MCI and dementia in PD have been linked to difficulties in activities of daily living (ADLs).[7,8] Dementia has also been associated with rapid motor and functional decline,[9,10] increased mortality,[11,12] caregiver stress,[13] and risk of institutionalization.[14]

Because of the strong impact of cognitive disorders on the quality of life (QOL) of patients and their caregivers, it is important to find the necessary tools to manage cognitive decline. Complementary to

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pharmacological treatment, cognitive intervention programs have been shown to be useful in various pathological conditions such as traumatic brain injury,[15] schizophrenia,[16–18] Alzheimer's disease and dementia,[19] and, more recently, MCI.[20,21]

To our knowledge, only 2 studies have assessed the effects of cognitive training (CT) in PD. Results of both studies showed that this therapy had a positive effect on the evolution of cognitive impairment.[22,23]

The first study on CT in PD patients (Sinforiani et al[22]) included a sample of 20 early-stage nondemented PD patients with mild cognitive deficits who underwent a 6-week rehabilitation program (12 one-hour sessions), received CT (performed by neuropsychological training software TNP), and motor rehabilitation. This descriptive study with no control group showed a significant improvement in cognitive measures at the end of the training and after 6 months.

Sammer and colleagues[23] randomized (controlled but not blind) 26 idiopathic PD patients. Twelve subjects participated in a CT regimen (10- to 30-minute sessions) that consisted of working memory tasks requiring executive functions. Fourteen patients received standard treatment, which included occupational therapy, physiotherapy, and physical treatment. The outcome showed improved performance of the group with cognitive treatment in 2 executive tasks, whereas no improvement was seen in the standard-treatment group.

We aimed to overcome previous methodological limitations, conducting a blind, controlled study on a homogeneous group of nondemented PD patients. We performed an intensive CT program[24,25] (three 45-minute sessions per week for 4 weeks) to achieve more clinical and cost-effective results.[20] An extensive and detailed neuropsychological assessment, including mood, QOL, and functional measures commonly used in PD, was obtained at baseline and at the end of training.

The main objective of the present study was to determine the efficacy of a CT program in a 4-week randomized, controlled study of cognitive performance and QOL in nondemented PD patients.

Patients and Methods

Subjects

This study recruited 46 patients from 2 centers in Barcelona province: the Unit of Parkinson and Movement Disorders from the Centro Médico Teknon and the Parkinson's Association of Mataró. The investigation was conducted in accordance with the Helsinki Declaration of 1964 (2008 revision) and Good Clinical Practice guidelines. All participants gave written informed consent. Subjects were men and women aged 50–80 years diagnosed with PD according to UK PD Society Brain Bank Criteria,[26] with disease severity of Hoehn and Yahr (H&Y) stages I–III,[27] and not receiving any other cognitive, psychological, speech therapy, or physical treatment during the study.

Participants were excluded if they had significant cognitive impairment (Mini-Mental State Examination < 23), below average premorbid intelligence (vocabulary subtest, Wechsler Adult Intelligence Scale-III [WAIS-III] typical score < 40) that would interfere in learning or comprehension of the program, were on cholinesterase inhibitors or had changes in their medication during the study, did not complete 75% of the training program, had major depression (GDS-15 $>$ 10), or had severe auditory or visual deficits or another psychiatric/neurological condition.

Design and Procedures

This was a blind multicenter randomized, controlled trial divided into 5 principal stages (Fig. 1). The first stage was based on the recruitment of the subjects for the study. Sociodemographic data, neurological data, and written informed consent were collected from all subjects enrolled in the study. During the second stage, an expert evaluator, blinded to the patients' group allocation, assessed the cognitive, mood, QOL, and functional status of the participants. In the third stage, subjects were randomly assigned to 2 groups: control (CG) and experimental (CTG). A matched-pairs design was created in which participants were blindly allocated to these 2 groups taking the variables age and vocabulary (WAIS-III) into consideration. In the fourth stage, 2 trained professionals administered the training program to both groups. The treatment group received an individualized CT program, and the CG received speech therapy group sessions. Finally, at the end of the 4-week training, subjects from both groups were administered a blind evaluation, using the same protocol of neuropsychological, mood, QOL, and functional tests. Both evaluations and training were performed during the ON period.

Clinical Assessment

Patients' full clinical histories were collected. Standardized neurological assessment included the Unified Parkinson's Disease Rating Scale (UPDRS)[28] together with the H&Y Staging of Parkinson's Disease.[27]

Aspects of functioning and well-being were assessed using the Parkinson's Disease Questionnaire (PDQ-39),[29] and cognitive difficulties in ADLs were evaluated using the Cognitive Difficulties Scale (CDS).[30] To control the possible influence of mood on cognitive performance, all patients completed the 15-item Yesavage Geriatric Depression Scale (GDS-15).[31]

Neuropsychological Testing

The battery of neuropsychological tests at baseline and retest included cognitive screening assessed by the

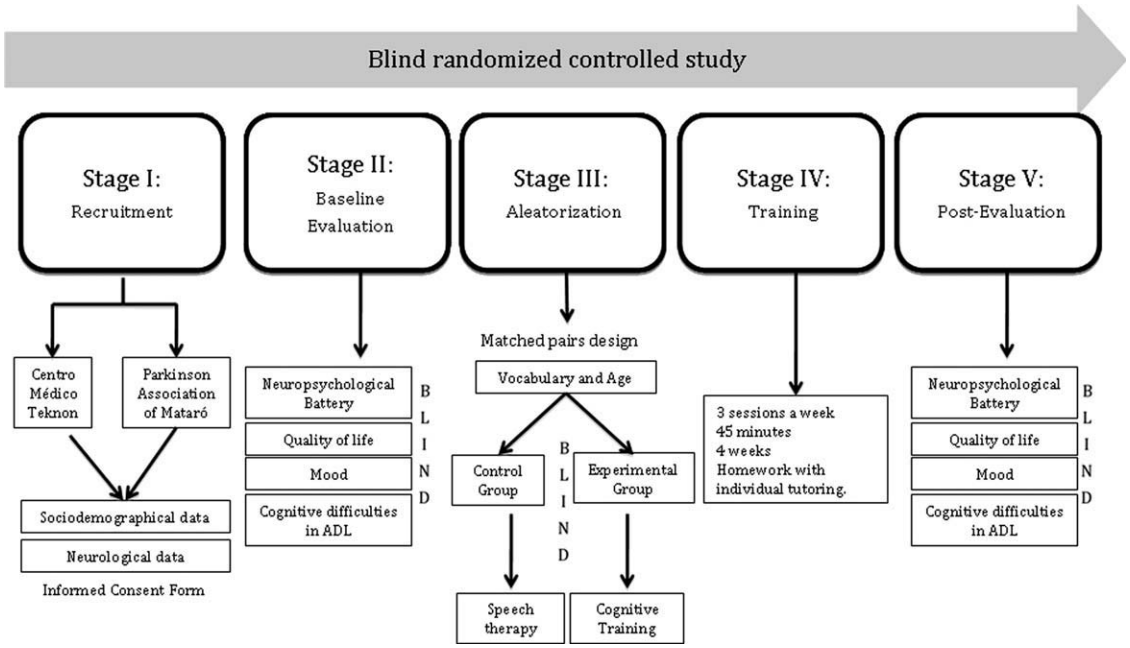

FIG. 1. Stages in the study design.

30-item Mini Mental State Examination[32] and the Addenbrooke Cognitive Examination.[33] Premorbid intelligence was determined by the Vocabulary subtest of the WAIS-III.[34] Attention and working memory were assessed by the Digits subtest (WAIS-III)[34] and the first trial of the California Verbal Learning Test (CVLT-II).[35] Information processing speed was measured using the written modality of the Symbol-Digit Modalities Test (SDMT),[36] Trail Making Test–A (TMT-A),[37] and the Word subtest (Stroop Test).[38] Verbal memory was evaluated using the CVLT-II[35] and the Logical Memory subtest (WMS-III).[39] Learning was also assessed by the CVLT-II.[35] The Rey Osterrieth Complex Figure Test (ROCFT)[40] measured visual memory and visuoconstructive abilities. Visual spatial abilities were measured by the Line Orientation subtest from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).[41] Two verbal fluency tasks were administered: phonemic, using FAS, and semantic, using animals.[42] Frontal lobe–sensitive tasks were also included and were assessed by the Tower of London (TOL),[43] Trail Making Test–B (TMT-B) ,[37] and the Interference subtest of the Stroop Test.[38]

Treatment

Both groups underwent the same rehabilitation program methodology: with a duration of 45 minutes, 3 times a week for 4 weeks (a total of 12 sessions) and, in addition, exercises to do at home, 1 per week, with individual tutored sessions once a week.

CT was performed using different therapeutic modalities, including interactive multimedia software and paper-and-pencil exercises. Computer-aided training was supervised by a trained clinical psychologist using the SmartBrain tool.[44] A platform with 28 activities was designed based on stimulating specific cognitive domains known to be impaired in PD (attention/working memory, memory, psychomotor speed, executive functions, and visuospatial abilities) and nonspecific cognitive exercises (language, simple calculations skills, and culture). Initially, all patients were started at a medium difficulty level (level 7). The software monitored each participant's performance automatically after each correct/incorrect response. Combined with computer-aided training, each week CTG participants received a pack with 20 cognitive homework exercises designed to stimulate specific and nonspecific cognitive areas. The speech therapy received by the CG aimed to make participants' aware of their speech and communication difficulties.

Statistical Analysis

Demographic and clinical characteristics at baseline were compared using a 2-tailed *t* test for independent samples or a 2-sided chi-square test when appropriate. The effect of the CT treatment on neuropsychological performances and daily functional scales was analyzed with repeated-measures ANOVAs (time × treatment interaction), with treatment groups as the between-subject factor and the 2 evaluations (pretest and posttest) as the within-subject factor. To determine the effect of MCI on the dependent variables, we used a 2-way ANOVA (MCI × group) on gain scores of the subjects (posttest/pretest). The level of statistical significance was set at .05.

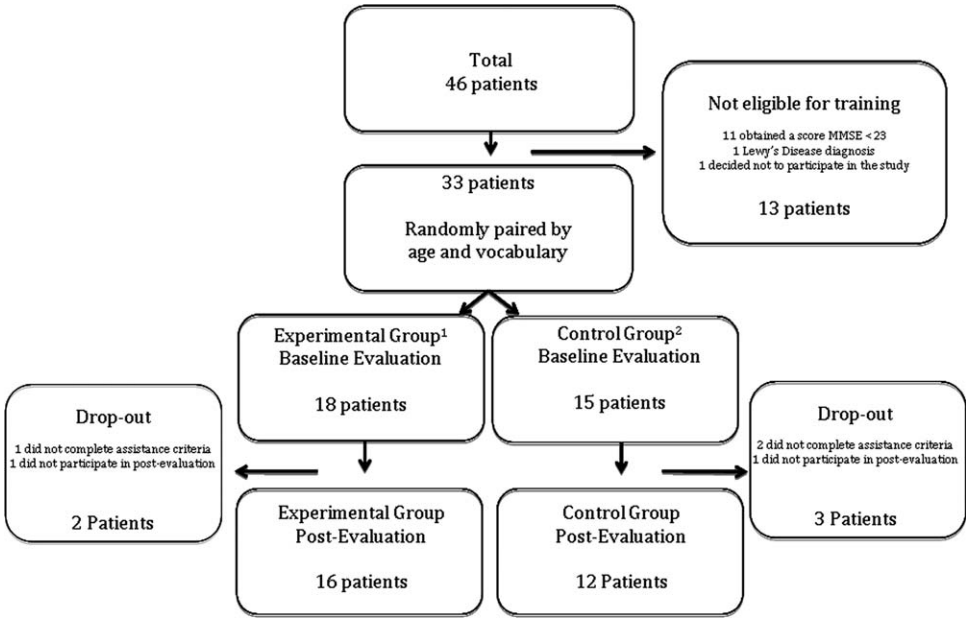

FIG. 2. Flow diagram of subject recruitment and participation in the study. (1) The experimental group participated in an individualized cognitive training program; (2) the control group received group speech therapy reeducation. Randomization was performed after baseline assessment to blind investigators.

Furthermore, to compare the magnitude of the treatment effects on the CTG, standardized effect sizes (Cohen's *d*) were calculated for each variable following the Thalheimer and Cook[45] methodology. Following to the recommendation of Wilson et al,[46] we subtracted the CG posttest score from the CTG posttest score, and divided this term by the standard deviation of the whole sample at retest. The following cutoff scores applied: $\geq$1.10 to $<$1.45, very large effect; $\geq$0.75 to $<$1.10, large effect; $\geq$0.40 to $<$0.75, medium effect; $\geq$0.15 to $<$0.40, small effect.

Results

From the initial sample of 46, a total of 33 subjects were randomly assigned to treatment. Only 5 participants dropped out (2 in the CTG and 3 in the CG) during the study. Reasons for the dropping out were not completing the attendance criteria or not participating in the postevaluation. Among completers, 16 patients received the CT program (CTG) and 12 the speech therapy program (CG). The diagram flow of participation can be seen in Figure 2.

The sample included participants from both sexes (50% male). Their mean age was 65 $\pm$ 9.19 years, mean duration of the disease was 7.5 $\pm$ 6.8 years, and mean years of education was 9 $\pm$ 2.9 years. Of the studied sample, 50% (14 of 28 patients) met Petersen et al criteria for MCI.[47,48] Subjects classified as having MCI demonstrated a decrement of more than 1.5 SD on any cognitive test or subtest. There were no statistically significant differences between groups at baseline observation for any of the variables studied (Table 1).

The repeated-measures ANOVA showed a significant time $\times$ treatment interaction in favor of the CTG for several neurocognitive variables. The CTG had an improved performance in 1 of the attention and working memory measures, the WAIS-III Digit Span Forward ($F = 5.58$, $P = .026$). Also, 1 of the measures of information processing speed showed this expected interaction, the Stroop Word subtest ($F = 16.46$, $P = .000$). Both measures of visual memory showed the expected time $\times$ treatment interaction, Immediate ($F = 7.02$, $P = .014$) and Delayed ($F = 4.31$, $P = .048$) Recall of the ROCFT. The measure of visuoconstructive abilities, the Copy of the ROCFT, also showed our hypothesized interaction ($F = 8.95$, $P = .006$), as did the measure of visuospatial abilities, the RBANS–Line Orientation subtest, ($F = 10.80$, $P = .003$). Moreover, 1 of the verbal fluency measures, the Semantic–Animals, showed the expected improvement for the CTG ($F = 9.53$, $P = .005$), as well as 3 of the executive function measures, the TMT-B ($F = 6.44$, $P = .018$), the TOL–Total Moves ($F = 12.17$, $P = .002$), and the TOL–Total Correct ($F = 12.21$, $P = .002$). However, QOL and functional scales did not show the expected significant time $\times$ treatment interaction (Table 2).

The MCI group did not show any significant effect in the multivariate tests. In the tests of the within-subjects effects, we found a significant interaction MCI $\times$ group in the dependent variables RBANS–Line Orientation ($F = 6.264$, $P < .05$), TOL–Total Movements ($F = 4.441$, $P < .05$), and Trail Making Test–B ($F = 4.323$, $P < .05$). This significant interaction occurred because the experimental treatment more improved

TABLE 1. Demographic and clinical data at baseline of patients in the CTG and CG groups

	Group		Statistics	
Variable	CTG	CG	χ^{2a}	*P*
Sex (male/female), n	7/9	7/5	0.58	.45
			t[b]	*P*
Age, mean (SD)	64.75 (9.19)	65.42 (9.60)	−0.19	.85
Year of diagnosis, mean (SD)	2002.06 (4.58)	2001.17 (9.63)	0.33	.75
Years of evolution, mean (SD)	6.94 (4.58)	8.25 (9.22)	−0.50	.62
Hoehn & Yahr, mean (SD)	2.37 (0.76)	2.25 (0.78)	0.49	.63
Years of education, mean (SD)	9.88 (2.94)	9.50 (3.09)	0.33	.75
WAIS-III Vocabulary,[c] mean (SD)	58.19 (6.57)	55.33 (8.38)	1.42	.17
			χ^{2a}	*P*
Mild cognitive impairment,[d] n (%)	8 (50%)	6 (50%)	0	1

[a]Two-sided chi-square test;
[b]2-tailed *t* for independent samples;
[c]adjusted by age;
[d]according to Petersen's et al.[45] Criteria: (1) presence of a subjective memory complaint, (2) preserved general intellectual functioning as estimated by performance on a vocabulary test, (3) decrement of more than 1.5 SD on any cognitive test or subtest, (4) intact ability to perform activities of daily living, and (5) absence of dementia. CTG, cognitive training group; CG, control group; WAIS-III Vocabulary, Wechsler Adult Intelligence Scale–III, Vocabulary subtest.

the performance of the subjects with MCI than those without MCI.

Complementary analysis including the center from where the subjects were recruited as a second between-subject factor showed that the differences between the subjects from both centers did not affect the significant time × treatment interaction found.

Effect Sizes of Improvement

Table 2 also shows the effect sizes of improvement for the differences between groups. Cohen's *d* value confirmed the significant interaction found in Semantic–Animals, TOL–Total Correct, and TOL–Total Moves, indicating a very large effect from CT. The Stroop Word subtest, and the WAIS-III Digit Span Forward, which also showed a significant time × treatment interaction, showed a large effect from CT. The significance found with the TMT-B was confirmed by a medium effect size, and the RBANS–Line Orientation test only showed a small effect after CT.

Discussion

Cognitive impairment is frequent in nondemented PD. Similar to in other studies,[3–5] in our sample 50% met criteria for MCI. CT has proved to be a useful and efficient tool in the management of cognitive impairment of other pathological conditions. As very few studies have been conducted in PD, we aimed to determine the efficacy of a CT program on cognitive performance and QOL in nondemented PD patients.

Our findings suggest that an intensive CT program (3 times a week for 4 weeks) can be a useful tool in improving cognitive performance in PD patients. Improved cognitive performance was observed in CTG participants compared with controls in attention, information processing speed, memory, visuospatial and visuoconstructive abilities, semantic verbal fluency, and executive functions. Thus, our study supports theories that suggest CT may activate mechanisms of cerebral plasticity and slow down the progression of cognitive manifestations of the disease.[49,50] Future investigations with functional neuroimaging methods such as positron emission tomography and functional magnetic resonance should be encouraged. Such studies may be useful in assessing CT effectiveness and explaining the cerebral consequences of plasticity associated with PD.

Even though classic tests of executive functions, such as the TMT, have been widely accepted as good predictors of functional status,[51–53] the observed cognitive changes were not shown in a change of functional measures. It is worth noting that specific functional scales sensitive to detecting subtle cognitive change for PD do not exist. However, a recent study demonstrated how a functional scale designed for Alzheimer's disease could also be used to assess functional changes in PD with MCI.[8] Our functional scale was a self-administered measure designed to assess cognitive difficulties

TABLE 2. Neurocognitive performances, measures of functional scales, and effect size of improvement in the CT and CG groups at baseline and retest

Neurocognitive areas	Baseline				Retest						
	CTG (n = 16)		CG (n = 12)		CTG (n = 16)		CG (n = 12)		Statistics (ANOVA)		
Test—measure	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	F^a	P^a	d^b
Cognitive screening											
MMSE	28.13	(1.31)	27.58	(1.44)	28.56	(1.03)	27.42	(1.93)	1.21	.28	0.8
ACE	89.56	(8.05)	84.58	(9.03)	92.88	(6.64)	84.92	(6.02)	3.00	.09	1.29
Attention and working memory											
WAIS III–Digit Span	15.44	(3.55)	14.00	(5.01)	16.44	(3.27)	13.08	(3.75)	2.28	.14	1
WAIS III–Digit Span Forward	5.75	(1.18)	5.67	(1.07)	6.38	(0.96)	5.25	(1.54)	5.58	.03	0.94
WAIS III–Digit Span Backward	4.75	(1.12)	4.08	(0.67)	58.06	(11.16)	53.67	(7.57)	1.12	.30	0.47
CVLT II–List A1	4.75	(1.77)	5.58	(1.51)	7.25	(1.81)	6.83	(1.40)	3.86	.06	0.26
Information processing speed											
SDMT	29.75	(14.23)	27.36	(12.33)	31.13	(11.75)	26.09	(11.73)	.62	.44	0.45
TMT-A	66.38	(39.47)	60.55	(34.31)	54.44	(22.79)	62.55	(38.84)	3.50	.07	0.28
Stroop Test–Word subtest	98.88	(18.22)	101.00	(21.99)	105.94	(15.77)	88.45	(21.45)	16.46	.00	1
Verbal memory											
CVLT-II–Short-Delay Free Recall	9.88	(3.26)	8.00	(1.41)	57.50	(8.56)	50.42	(8.38)	2.87	.10	0.87
CVLT-II–Long-Delay Free Recall	9.88	(2.91)	8.50	(1.68)	11.69	(2.24)	10.25	(2.56)	0.00	.95	0.63
WMS-III–Logical Memory I	34.38	(12.53)	29.83	(5.73)	40.13	(12.96)	31.67	(7.85)	1.63	.21	0.79
WMS-III–Logical Memory II	20.56	(7.34)	16.83	(5.61)	25.63	(7.84)	19.42	(7.44)	1.53	.23	0.84
Learning											
CVLT-II–List A Total	42.94	(10.59)	41.00	(6.69)	53.63	(9.97)	48.42	(8.67)	1.22	.28	0.57
Visual memory											
ROCFT–Immediate Recall	15.38	(5.17)	18.54	(5.53)	20.34	(7.10)	20.04	(5.17)	7.02	.01	0.05
ROCFT–Delayed Recall	12.84	(7.47)	17.25	(5.06)	18.84	(8.47)	19.83	(5.65)	4.31	.05	0.14
Visuoconstructive abilities											
ROCFT –Copy	30.75	(6.39)	33.88	(4.05)	33.00	(5.30)	33.13	(3.02)	8.95	.01	0.03
Visuospatial Abilities											
RBANS–Line Orientation	16.25	(3.42)	17.83	(1.85)	17.88	(2.19)	16.92	(3.48)	10.80	.00	0.35
Verbal fluency											
Phonemic–FAS	38.69	(12.34)	33.33	(11.44)	42.25	(9.79)	33.92	(10.51)	3.43	.08	0.86
Semantic–Animals	16.06	(5.21)	15.42	(3.00)	20.94	(4.65)	14.75	(5.51)	9.53	.01	1.28
Executive functions											
TMT-B	141.56	(96.42)	149.30	(131.22)	114.81	(66.45)	161.20	(147.02)	6.44	.02	0.46
TOL–Total Moves	43.56	(22.72)	35.90	(17.54)	22.25	(12.69)	37.10	(15.74)	12.17	.00	1.11
TOL–Total Correct	3.25	(1.81)	3.70	(2.00)	5.50	(1.93)	3.20	(2.30)	12.21	.00	1.15
TOL–Rules Violations	1.36	(1.79)	1.40	(2.84)	0.56	(1.09)	0.70	(1.06)	0.01	.91	0.13
Stroop Test–Interference	4.00	(5.15)	3.00	(6.02)	5.44	(7.92)	6.20	(6.43)	0.37	.55	0.11
Functional Scales											
Quality of life											
PDQ-39	47.94	(21.36)	42.83	(20.67)	50.25	(26.72)	34.08	(20.57)	2.20	.15	0.69
Mood											
GDS-15	2.69	(2.15)	2.42	(2.31)	2.56	(2.48)	2.17	(1.95)	0.02	.90	0.18
Cognitive difficulties in ADLs											
CDS	44.63	(25.51)	40.83	(22.38)	41.63	(24.24)	39.42	(24.91)	0.06	.81	0.09

The "baseline" and "retest" columns show the raw scores of evaluations and the differences between pretest and posttest calculated with ANOVA.
[a]ANOVA;
[b]Cohen's effect-size test. CTG, cognitive training group; CG, control group; ACE, Addenbrooke's Cognitive Examination; MMSE, Mini–Mental State Examination; WAIS-III, Wechsler Adult Intelligence Scale–III; CVLT-II, California Verbal Learning Test–II; SDMT, Symbol Digit Modalities Test; TMT-A, Trail Making Test, part A; WMS-III, Wechsler Memory Scale–III; ROCFT, Rey-Osterrieth Complex Figure Test; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status. TMT-B, Trail Making Test, part B; TOL, Tower of London; PDQ-39, Parkinson's Disease Questionnaire; GDS-15, 15-item Geriatric Depression Scale; CDS, Cognitive Difficulties Scale.

in ADLs. The finding of deficits in meta-memory found in PD patients[54] may suggest questioning the accuracy of these measures.[55] Asking a caregiver or family member to fill out questionnaires could be useful in future investigations. In addition, CT programs focused specifically on the training of more ecological tasks could also help improve ADLs of PD patients.[56]

No significant statistical improvements were observed in terms of self-reported QOL in CTG subjects. This outcome could have resulted from QOL

being a multidimensional construct affected by various factors[57–59] that were not controlled in this study. Alternatively, the outcome may be because of the short duration of the treatment. An extended training program may be needed to have a meaningful impact on well-being and QOL. Likewise, improvement in mood was not observed, but this was not expected in our study because most of our patients were not depressed at baseline.

Our main study limitation was its relatively small sample size, which may have subtracted external validity from the obtained results. However, our blind, randomized, controlled trial design ensured internal validity of the results. Previous studies of CT in PD have also achieved positive results with a similar or smaller sample size.[21,22]

Another important limitation to the study was that we were not able to establish mid- and long-term effects (>6 months). Because this follow-up evaluation was not performed, it was not possible to observe if the effects of this training persisted over time or if the effect of improvement was mainly associated with the CT program.

Despite the methodological limitations described above, several major strengths distinguish this study. First, we used a comprehensive standardized battery that included well-known instruments used in PD. Second, there were no biased researchers in this study, protecting against selection bias. Third, based on previous investigations, we conducted a brief and intensive training program to improve clinical outcomes and cost effectiveness.[19] Finally, the small number of dropouts indicates high adherence to therapy in the intensive training program, proving it to be practical and of easily implemented in nondemented PD patients.

Further studies are necessary to evaluate the efficacy of CT and at which moment in the course of the disease it is better to start CT programs in PD patients. These studies should also determine which strategies and techniques are more efficient in the management of cognitive deficits in PD and if these skills translate to improvements in daily life and QOL. Larger studies with follow-up periods are needed to verify if the effects of this training persist over time. Nonetheless, our findings suggest that intensive CT may be an effective tool for improving cognitive functions in nondemented PD patients. ■

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