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ORIGINAL ARTICLE

A double-blind randomized controlled trial of the efficacy of cognitive training delivered using two different methods in mild cognitive impairment in Parkinson's disease: preliminary report of benefits associated with the use of a computerized tool

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Abstract

Background The effectiveness of computer-based cognitive training (CCT) remains controversial, especially in older adults with neurodegenerative diseases.

Aims To evaluate the efficacy of CCT in patients with Parkinson's disease and mild cognitive impairment (PD-MCI).

Methods In this randomized controlled trial, 53 patients were randomized to receive CCT delivered by means of CoRe software, traditional paper-and-pencil cognitive training (PCT), or an unstructured activity intervention (CG). In each group, the intervention lasted 3 consecutive weeks (4 individual face-to-face sessions/week). Neuropsychological assessment was administered at baseline (T0) and post-intervention (T1). Outcome measures at T0 and T1 were compared within and between groups. The Montreal Overall Cognitive Assessment (MoCA) was taken as the primary outcome measure.

Results Unlike the PCT group and the CG, the patients receiving CCT showed significant medium/large effect size improvements in MoCA performance, global cognition, executive functions, and attention/processing speed. No baseline individual/demographic variables were associated with greater gains from the intervention, although a negative correlation with baseline MoCA performance was found.

Conclusion CCT proved effective in PD-MCI patients when compared with traditional PCT. Further follow-up assessments are being conducted to verify the retention of the gains and the potential ability of the tool to delay conversion to PD-dementia.

Trial registration number (ClinicalTrials.gov): NCT04111640 (30th September 2019).

Keywords Computer-based cognitive training · Randomized controlled trial · Neurodegenerative disease · Mild cognitive impairment · Parkinson's disease · Multi-domain stimulation

Introduction

Cognitive training (CT) is a non-pharmacological intervention that has long been used to target cognition in a range of neurological disorders, including age-related cognitive decline [1–3]. CT can be delivered using traditional paper-and-pencil techniques (PCT) or by means of more innovative computer-based solutions (CCT). With respect to traditional PCT, CCT provides real-time feedback, allows modulation of task complexity and response time during and across sessions, requires less exercise preparation (therefore saving therapists time), and allows recording of all session parameters. Finally, CCT, requiring less face-to-face training, can

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be delivered remotely, as a telemedicine intervention, to patients at home [4].

CCT seems to be efficacious in the early phases of cognitive decline, and particularly in cases of mild cognitive impairment (MCI) [5, 6]; however, this evidence refers mainly to MCI due to Alzheimer's disease. To date, few studies have focused on Parkinson's disease (PD) (see [7–13] for review), and even fewer on PD patients with MCI (PD-MCI) [2, 14]. Since motor difficulties can potentially interfere with PD patients' participation in cognitive interventions, CCT may be particularly suitable for them, as the tools used can be developed to be user-friendly even for patients with motor and visuo-spatial difficulties [2, 14]. However, more and better-designed RCTs are needed to examine the usability and usefulness of CCT in PD-MCI patients.

In recent years, we implemented a software tool for cognitive rehabilitation called "CoRe" [4, 15, 16]. CoRe is an adaptive CCT program for individual face-to-face sessions between patient and therapist. In a previous study, we preliminarily tested its usability and safety as a clinical tool in dementia-related disorders with a view to optimizing it and making it easier for patients to use [16]. In another study, we demonstrated its effectiveness in single-domain training targeting logical-executive functions in PD-MCI inpatients [4]. However, considering the importance of multi-domain interventions, designed to produce broader effects across different cognitive domains [2], we here adopted an extended version of CoRe. The new version is a patient-tailored, multi-domain CT tool targeting logical-executive functions, attention/processing speed, working memory, and episodic memory.

The main aim of this study is to assess the efficacy of this extended version of CoRe in PD-MCI patients using an RCT design. To this end, we compared this CCT intervention with the same stimulation activities delivered using a traditional PCT approach, and with an active control group (CG). The comparison of the CCT with the PCT group was intended to provide evidence on the efficacy of computer-based versus paper-and-pencil activities, and the comparison of these two groups with the CG to provide useful information on the importance of structured versus unstructured cognitive activities. Finally, we also explored the role of individual differences (e.g., age, education, cognitive reserve) in training gains to predict which patients may benefit most from CCT [17].

Materials and methods

Participants and measures

Patients with idiopathic PD were recruited (March 2017–December 2019) from the Neurorehabilitation Unit at the C. Mondino Foundation. The protocol was approved by the local ethics committee and all patients gave written consent before being enrolled in the study. The inclusion criteria were:

- a diagnosis of idiopathic PD according to the UKPDBB criteria and a Hoehn & Yahr scale score ≤ 3 [18, 19];
- the presence of single- or multiple-domain PD-MCI [20];
- age between 50 and 85 years;
- educational level ≥ 5 years.

The exclusion criteria were:

- cognitive impairment due to a pre-existing neurological condition;
- concomitant severe psychiatric disease (e.g. depression, psychosis, behavioral disorders);
- concomitant severe non-neurological comorbidities (e.g. cardiovascular, metabolic and/or endocrinological diseases);
- severe sensory or motor disturbances liable to interfere with the intervention;
- deep brain stimulation.

All patients were treated with dopamine agonists or L-DOPA and had been on a stable therapeutic regimen for at least 3 months. No changes in medication were allowed during the training and follow-up period. In accordance with the Movement Disorder Society Task Force guidelines (level II criteria) [20], the PD-MCI diagnosis was formulated on the basis of a comprehensive neuropsychological evaluation designed to assess, using the instruments listed below, the following five cognitive domains:

1. global cognition: Mini-Mental State Examination (MMSE) and Montreal Overall Cognitive Assessment (MoCA) [21, 22];
2. episodic long-term memory: Logical Memory Test, immediate and delayed recall [23, 24], Rey's 15 word test, immediate and delayed recall [25], and Rey Complex Figure, delayed recall [26];
3. logical-executive functions: Raven's Matrices 1947 [25], the Frontal Assessment Battery [27], semantic fluency [28], phonological fluency [25], and Rey Complex Figure, copy [26];
4. working memory: Verbal Span, Digit Span, Corsi's block-tapping test span [23];
5. attention/processing speed: Attentive Matrices [23], Trail Making Test (A and B) [29].

At post-intervention (T1), we used the same neuropsychological battery; parallel versions were applied when available. All the raw scores were adjusted for age, sex, and

education, and compared with the values available for the Italian population; the adjusted scores were then transformed into equivalent scores [30].

At baseline (T0), we also assessed mood using the Beck Depression Inventory (BDI) [31], functional status using the Instrumental Activities of Daily Living scale (IADL) [32], and cognitive reserve using the Cognitive Reserve Index questionnaire (CRIq) [33].

Study design and procedures

This study is a prospective double-blind 3-arm RCT. All PD-MCI patients recruited underwent T0 assessment performed using the above-listed tests. Patients who met the inclusion criteria were enrolled and randomized to one of three groups: CCT, PCT, or CG. For the patient allocation, we generated random numbers from a uniform distribution in the range 0–1, dividing the range in three equal intervals and assigning each patient to the group corresponding to the sampled number. In all groups, the intervention took place in the Neuropsychology Lab and lasted 3 weeks (4 face-to-face individual sessions/week, each lasting 45 min). Cognitive outcomes were measured at T0 and T1 by a neuropsychologist who was blinded to the patient allocation. Further follow-ups will be conducted by December 2020. All neuropsychological assessments and training sessions were administered exclusively during "on" status.

Interventions

CoRe (acronym for cognitive rehabilitation) is a software tool developed within a research project. The extended version of CoRe (with respect to [4]) used in the present study administers 11 tasks targeting several cognitive abilities (e.g., logical-executive functions, attention/processing speed, working memory, and episodic memory; for details see Online Resource 1). Most of these tasks are computerized versions of existing paper-and-pencil exercises. Others were created to meet specific requirements expressed by the therapists and to exploit computer functionalities that would be particularly difficult to reproduce with a paper-and-pencil approach. During the dynamic generation of the exercises, the individual patient's performance data (accuracy and number of clues required) were analyzed to set the appropriate difficulty level. For each exercise and each level, thresholds are defined so as to allow difficulty levels to be progressively increased. Moreover, CoRe computed a performance indicator, the weighted score (WS) [16], which was calculated taking into account different parameters: type of exercise, difficulty level, accuracy, response time. The WS, used to assess both the overall outcome of a session and the global trend of the rehabilitation, served to summarize each patient's performance in a single value.

The PCT group followed the same training program as the CCT group, but using the paper-and-pencil version of the tasks. Computer tasks not reproducible in the context of the PCT approach were substituted by equivalent tasks training the same skills. In PCT, the dynamic aspect of the training (i.e. the increasing levels of difficulty) was managed by the therapist (who spent around 4 h/patient on preparation of appropriate PCT material).

The CG subjects did unstructured activities (e.g., reading magazines, chatting, drawing) that served as a behavioral placebo treatment.

Statistical analysis

The primary outcome measure was global cognitive functioning assessed using the MoCA, while the secondary outcome measures were performances in the five cognitive domains. To obtain a score for each domain, we calculated, in each group, the sum of the equivalent scores of all the tests and then divided the total by the number of tests. The sample size was based on the primary outcome. A power analysis indicated that a total sample size of 39 patients would be sufficient to detect an effect size of 0.3, with 90% power at 5% level of statistical significance. The data were analyzed according to the intention-to-treat principle and including only those of participants who completed the study. Considering the small sample size, normality tests could not be expected to give reliable results, so non-parametric tests were preferred. The Kruskal–Wallis test was used for inter-group comparisons of participant characteristics and training gains (i.e., T1 minus T0). Significant differences were then evaluated using the Wilcoxon signed-rank test, which was also used for intra-group comparisons between T0 and T1. An effect size index (Cohen's d) was calculated to measure the magnitude of the training effect for each significant difference within each group. The Wilcoxon signed-rank test was also used within the CCT group to evaluate changes in the WS from session 1 to session 12. Finally, Spearman's correlations were used to detect associations between individual characteristics and training gains in global cognitive functioning, as reflected in the MoCA score, our primary outcome measure. To this end, only the CCT and PCT groups were considered, given that the CG did no structured activity. All statistical analyses were performed using SPSS software ver. 23.0.

Results

Fifty-three PD patients were enrolled. Of these, 21 were randomly assigned to CCT, 14 to PCT, and 18 to CG activities. In the CCT and PCT groups, 3 and 2 patients, respectively, dropped out because they were discharged before the end

Fig. 1 CONSORT flow chart

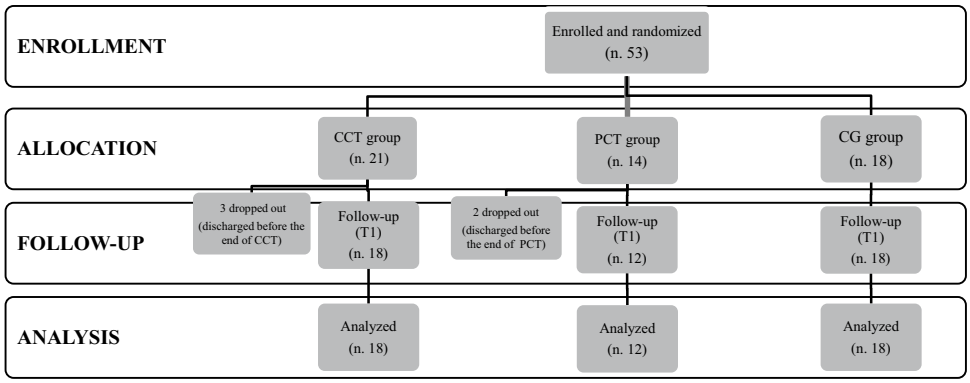


Table 1 Participant characteristics (means ± standard deviations) as a function of group

	CCT ($n=18$)	PCT ($n=12$)	CG ($n=18$)
Age	74.61 ± 5.68	69.83 ± 9.66	69.33 ± 7.72
Years of education	9.50 ± 3.94	8.08 ± 3.63	7.67 ± 3.50
% Female	33	40	33
Disease duration	8.44 ± 4.30	14.88 ± 7.75	10.67 ± 7.36
UPDRS III	34.93 ± 9.31	30.86 ± 10.35	36.50 ± 12.82
BDI	10.22 ± 6.00	13.83 ± 6.63	3.20 ± 2.68
IADL	6.28 ± 1.57	6.50 ± 1.68	7.00 ± 0.71
Cognitive reserve	104.22 ± 15.98	99.60 ± 14.98	104.60 ± 18.74
MoCA baseline	19.09 ± 2.84	20.83 ± 3.15	19.17 ± 3.49
MMSE baseline	25.01 ± 2.62	25.68 ± 1.91	25.35 ± 2.68

UPDRS III = Unified Parkinson's Disease Rating Scale III; BDI = Beck Depression Inventory; IADL = Instrumental Activities of Daily Living scale; MoCA = Montreal Cognitive Assessment; MMSE = Mini-Mental State Examination

of the intervention (CONSORT diagram in Fig. 1). The CCT and PCT groups, thus, comprised 18 and 12 patients, respectively.

Demographic and clinical characteristics at T0 are reported in Table 1. No baseline difference was found between the three groups: age ($\chi^2=4.68$, $p=0.10$, df = 2), education ($\chi^2=1.90$, $p=0.38$, df = 2), gender ($\chi^2=1.04$, $p=0.59$, df = 2), disease duration ($\chi^2=4.52$, $p=0.10$, df = 2), UPDRS III ($\chi^2=0.67$, $p=0.72$, df = 2), IADL ($\chi^2=0.71$, $p=0.70$, df = 2), cognitive reserve ($\chi^2=0.56$, $p=0.76$, df = 2), MMSE ($\chi^2=0.20$, $p=0.91$, df = 2), MoCA ($\chi^2=1.35$, $p=0.51$, df = 2). The only exception was BDI ($\chi^2=11.13$, $p=0.004$, df = 2); the CG had significantly lower scores than the CCT ($Z=2.617$, $p=0.009$) and PCT ($Z=2.964$, $p=0.003$) groups, whose scores were similar ($Z=1.634$, $p=0.10$).

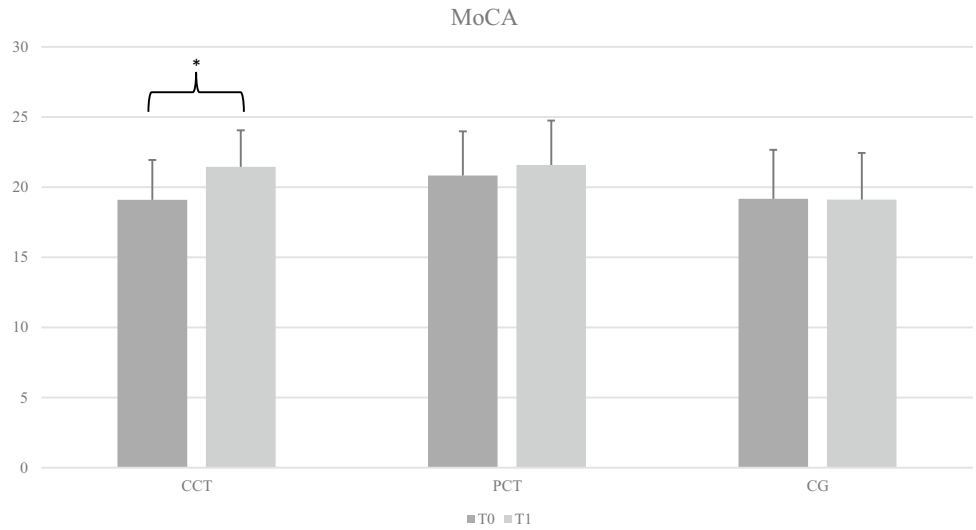
Analysis of T0 data was carried out on mean performance scores for the five cognitive domains considered. Internal consistency for these domains (Cronbach's α) was moderate, probably due to the multifaceted complexity of each ability: global cognition (α = 0.54), episodic long-term memory (α = 0.47), logical-executive functions (α = 0.51), working memory (α = 0.69), and attention/processing speed (α = 0.58). No baseline differences were found between groups: global cognition ($\chi^2=2.38$, $p=0.31$, df = 2), episodic long-term memory ($\chi^2=3.50$, $p=0.17$, df = 2), logical-executive functions ($\chi^2=4.99$, $p=0.08$, df = 2), working memory ($\chi^2=3.59$, $p=0.17$, df = 2), and attention/processing speed ($\chi^2=1.99$, $p=0.37$, df = 2).

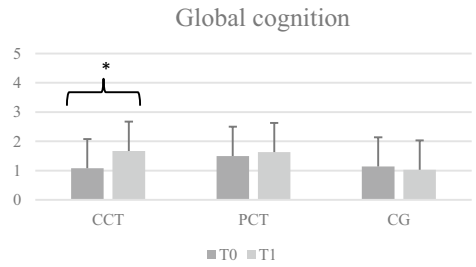
Table 2 and Figs. 2 and 3 report descriptive characteristics for the neuropsychological assessments performed at T0 and T1. The corresponding statistics are reported in Table 3.

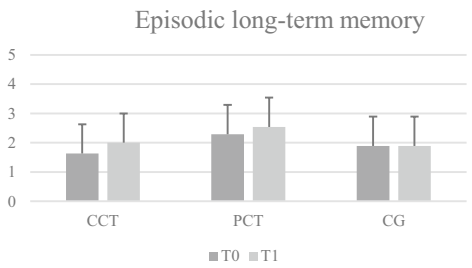
At T1, the CCT group showed significant improvements on T0 in the following scores: MoCA, global cognition,

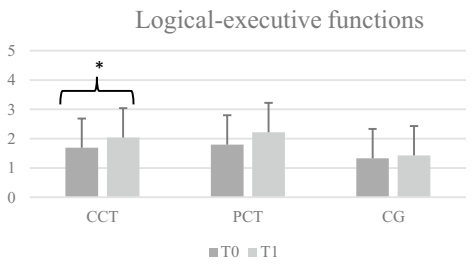
Table 2 Mean values ± standard deviations recorded for cognitive evaluations at T0 and T1 as a function of group

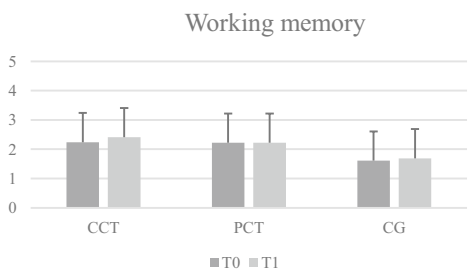
	CCT		PCT		CG	
	T0	T1	T0	T1	T0	T1
Montreal Cognitive Assessment	19.09 ± 2.84	21.45 ± 2.60	20.93 ± 3.42	21.50 ± 3.39	19.17 ± 3.49	19.11 ± 3.32
Mini-Mental State Examination	25.01 ± 2.62	24.89 ± 2.49	26.05 ± 1.88	25.82 ± 2.21	25.35 ± 2.68	25.38 ± 2.10
Global cognition	1.08 ± 0.75	1.67 ± 0.75	1.55 ± 0.60	1.60 ± 0.57	1.14 ± 0.78	1.03 ± 0.70
Episodic long-term memory	1.63 ± 0.94	2.00 ± 1.10	2.20 ± 1.08	2.40 ± 1.06	1.89 ± 0.81	1.89 ± 0.74
Executive functions	1.69 ± 0.81	2.04 ± 1.06	1.80 ± 0.58	2.30 ± 0.89	1.33 ± 0.69	1.43 ± 0.82
Working memory	2.24 ± 0.99	2.41 ± 1.03	2.33 ± 0.99	2.20 ± 0.92	1.61 ± 1.06	1.69 ± 1.05
Attention/processing speed	0.83 ± 0.97	1.33 ± 0.93	1.37 ± 1.11	2.15 ± 1.36	1.04 ± 069	1.14 ± 0.75











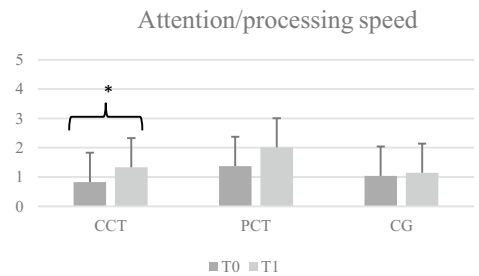


Fig. 2 Montreal Cognitive Assessment (MoCA) scores as a function of group and timing

Fig. 3 Performances in the five cognitive domains as a function of group and timing

logical-executive functions, and attention/processing speed. No significant differences were found in the episodic long-term memory or working memory domains.

The PCT group showed no significant differences between T0 and T1 in any of the domains, and the same stable pattern was also found in the CG.

The analysis of training gains is reported in Table 4 (see Online Resource 2 for corresponding means and standard deviations).

The three groups differed significantly in the MoCA, global cognition, and attention/processing speed domains. The CCT group, compared with the PCT patients, recorded significantly better MoCA and global cognition domain performances, whereas they showed similar training gains in the other domains. Compared with the CG, the CCT group recorded greater training gains on the MoCA and global cognition and attention/processing speed. These pairs of groups showed similar training gains in episodic long-term memory, logical-executive functions, and working memory. When comparing the PCT group and the CG, no significant differences emerged, with the exception of attention/processing speed, where the PCT patients did better than the CG.

With regard to the WS, computed by the CoRe software, the CCT group showed a significant improvement from session 1 to session 12 ($Z = 3.724$, $p < 0.001$) (see Fig. 4).

On analysis of possible correlations between individual patient characteristics and training gains, MoCA gains correlated negatively with baseline performance ($r = -0.54$,

Table 3 Intra-group T0 vs T1 comparisons as a function of group allocation

T0 vs T1	CCT			PCT			CG		
	Z	W(p)	Intra-g d	Z	W(p)	Intra-g d	Z	W(p)	Intra-g d
Montreal Cognitive Assessment	**3.70**	**0.001**	**1.15**	0.63	0.53	–	0.30	0.76	–
Global cognition	**3.07**	**0.002**	**1.03**	0.91	0.37	–	1.41	0.16	–
Episodic long-term memory	1.35	0.18	–	1.18	0.24	–	0.19	0.85	–
Logical-executive functions	**2.21**	**0.027**	**0.57**	1.66	0.10	–	1.05	0.29	–
Working memory	0.70	0.49	–	0.09	0.93	–	0.49	0.62	–
Attention/processing speed	**2.41**	**0.016**	**0.73**	1.71	0.09	–	1.15	0.25	–

Significant differences are shown in bold

W = Wilcoxon signed-rank test; d = Cohen's d effect size

Table 4 Inter-group comparisons of training gains (T1-T0) evaluated for significant differences using the Kruskal–Wallis test (H) and then the Wilcoxon signed-rank test (W)

Training gains	Kruskal–Wallis test			CCT vs PCT		CCT vs CG		PCT vs CG	
	χ^2	df	H (p)	Z	W(p)	Z	W(p)	Z	W (p)
Montreal Cognitive Assessment	**13.69**	**2**	**0.001**	**2.04**	**0.041**	**3.87**	**0.001**	0.39	0.69
Global cognition	**14.55**	**2**	**0.001**	**2.17**	**0.03**	**2.64**	**0.008**	1.39	0.16
Episodic long-term memory	1.49	2	0.48	–	–	–	–	–	–
Logical-executive functions	2.68	2	0.26	–	–	–	–	–	–
Working memory	0.28	2	0.87	–	–	–	–	–	–
Attention/processing speed	**7.84**	**2**	**0.02**	1.50	0.13	**2.13**	**0.038**	**2.30**	**0.022**

Significant differences are shown in bold

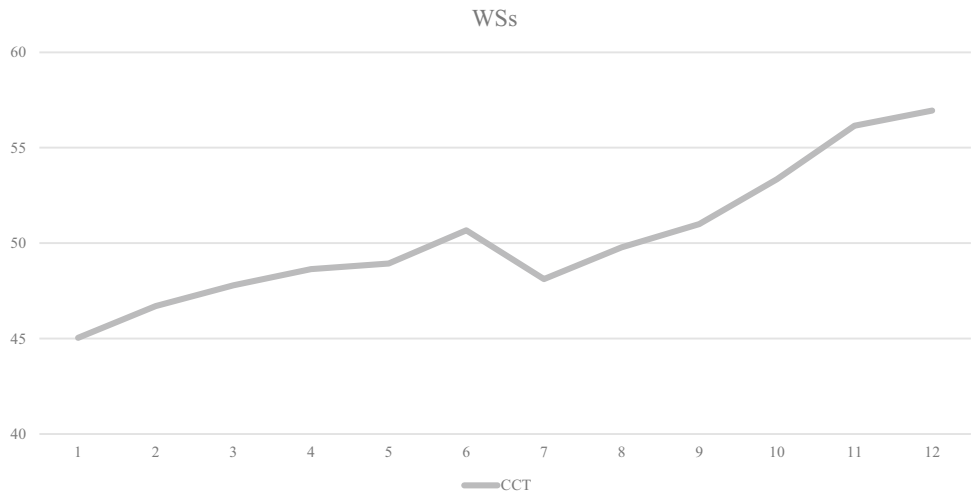


Fig. 4 WSs calculated by CoRe across the 12 sessions

$p = 0.004$), whereas no associations were found for the other variables (age: $r = -0.25$, $p = 0.19$; education: $r = -0.10$, $p = 0.60$; disease duration: $r = -0.14$, $p = 0.52$; UPDRS III: $r = -0.26$, $p = 0.24$; IADL: $r = 0.14$, $p = 0.47$; BDI: $r = 0.07$, $p = 0.73$; cognitive reserve: $r = -0.06$, $p = 0.78$).

Discussion

Our results showed positive effects of CCT compared with other interventions. On within-group analysis, the CCT patients showed medium/large effect size changes from T0 to T1 both in global cognitive functioning (MoCA score), which was our primary outcome measure, and in some secondary outcomes. No significant improvement was observed in the PCT or CG patients. Furthermore, the between-group analysis confirmed that the CCT-induced improvements were statistically different from the trends recorded in the other groups. In particular, the CCT patients had significantly larger training gains than the PCT ones on the MoCA and in the global cognition domain. When compared with the CG intervention, CCT induced significantly larger gains on the MoCA, and in the global cognition and attention/processing speed domains. On the other hand, the comparison of the PCT with the CG results confirmed the importance of structured cognitive activities with respect to unstructured ones, given that PCT was associated with significantly larger training gains in the attention/processing speed domain.

Since our neuropsychological assessments included tests that were not part of the training activities, our results may reflect training-related effects rather than consequences of simple practice. With regard to the neuropsychological test, we used as the primary outcome, it is worth remarking that the MoCA is considered the most appropriate screening test for detecting global cognitive functioning in PD [34]. Some authors used the MMSE [35, 36], others the ACE-R [37, 38]. In this research, we administered both the MMSE and the MoCA, which were considered as separate measures and also combined in a composite index of global cognition. Our results showed an overall effect of CoRe on global cognitive level (both on the MoCA and on the composite index of global cognition), as also observed in [4]. It is noted that the baseline MoCA score in the CCT group was slightly, although not significantly, lower than that of the PCT group. The fact that the CCT also showed greater gains in other cognitive domains further reinforces the superiority of the computer-based training. Another consideration is that the CCT patients tended to have a shorter (albeit not significantly shorter) disease duration. It could, therefore, be argued that these patients might be more likely to show greater gains from cognitive training, independently of the treatment. However, the fact that disease duration was not found to correlate with training gains seems to confute this hypothesis.

CoRe is a multi-domain training tool. Our analysis revealed training gains with large effect size mainly in the logical-executive functions and attention/processing speed domains, but less impact of the training on memory. In PD-MCI patients, executive functions are the most affected and probably the most sensitive to treatment effects. Furthermore, different domains need different degrees of stimulation, in terms of duration and frequency. From this perspective, it would be interesting to explore the effect of this CCT approach in other patients with different cognitive dysfunction profiles.

As for the influence of demographic/individual differences [17], none of the variables considered correlated with training gains, except for a negative association with baseline cognitive status measured by MoCA. This is in line with the "compensation model", which postulates that people with lower initial cognitive status tend to benefit more from the intervention because it allows them to compensate for their difficulties. In other words, participants with lower baseline performance and cognitive resources would have more room for improvement [39].

Our experience with CCT highlighted its multiple advantages, for therapists and patients, over traditional approaches. First, CCT allows more adaptive and patient-tailored training. Second, it is time-saving for the therapist—the CCT tool was ready to use, whereas the therapists spent 20 min/session per PCT patient on setting exercises, which amounts to about 48 h for just 12 patients. CoRe also records session parameters, whereas PCT per se does not allow recording of any session parameter. The time saved with CCT could be used to intensify the training sessions, or to provide more patients with treatment. Third, as CCT automatically records data, it offers the possibility of calculating a performance indicator (the WS) that summarizes the performance of a single patient or group. It is also worth noting the very high percentage of completed sessions, the good usability of the tool, and the patients' confidence when using it, reported during the sessions. All these are points in favor of the system [16].

This study has some limitations. First, the number of patients randomized to the three groups was unbalanced. This is due to the relatively small total number of patients enrolled ($n = 53$). Randomized allocation of 53 cases to three groups is inherently very likely (the probability is around 26%) to result in such an imbalance. Second, the study lacks follow-up assessments; therefore, we could not verify the retention of the effects of the treatment or the potential ability of CCT to delay conversion of PD-MCI into PD-dementia. Follow-up data are currently being collected and will be the topic of a future publication. Third, we observed selective drop-out in the CCT and PCT groups, due to the

discharge of some patients before the end of the treatment. This might be considered a violation of the intention-to-treat principle, which may have biased the results. However, these discharges were linked to routine clinical practice procedures or to personal reasons unrelated to the patients' cognitive problems, and they were not due to the desire to discontinue the treatment.

CoRe is currently a research tool, available for use by other health professionals with a view to sharing experiences. Cognitive training performed using the CoRe software could usefully be incorporated into routine clinical protocols as a non-pharmacological complementary therapy. With adequate adaptations, CoRe-based CCT could be repeated over time and also used remotely at home, thereby broadening its therapeutic potential and the number of beneficiaries.

Author contributions SBe and SBo: Study conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript. All authors: interpretation of data. SQ and SP: Analysis and interpretation of data. MB: acquisition of data. ES and CT: Critical revision of the manuscript for important intellectual content.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was performed in accordance with the guidelines of the Declaration of Helsinki. The study was approved by local ethics committee (San Matteo Hospital, Pavia, Italy).

Informed consent Written informed consent was collected from all of the participants.

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