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A computer-based cognitive training in mild cognitive impairment in parkinson's disease

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Abstract.
BACKGROUND: There is no successful pharmacological treatment for cognitive impairment in Parkinson's Disease, therefore treatments capable of slowing down the progression of cognitive dysfunction are needed.
OBJECTIVE: To evaluate the effectiveness of a cognitive training, supported by the CoRe computerized tool, in patients with Parkinson's Disease Mild Cognitive Impairment.
METHODS: This is a prospective, open-unblinded, randomized, controlled study. After baseline cognitive assessment (T0), enrolled patients were randomized to receive motor rehabilitation plus cognitive intervention (G1) or motor rehabilitation only (G2). Follow-up assessments were scheduled 4 weeks (T1) and 6 months after (T2). Global cognitive functioning scores (MOCA and MMSE) were considered as primary outcome. Outcome measures at T0, T1 and T2 were compared within- and between-groups. A percentage change score between T0 and next assessments was calculated to identify patients who improved, remain stable or worsened.
RESULTS: Differently from G2, G1 showed a medium/large effect size improvement in primary (MoCA) and secondary outcome, both between T0 and T1 and T0 and T2. Moreover, within G1, most patients improved their cognitive state compared to the baseline.
CONCLUSIONS: Patients trained with CoRe showed a better evolution of cognitive decline, while untreated patients tended to get worse over time.

Keywords: Cognitive training, executive dysfunctions, parkinson's disease, randomized controlled trial

1. Introduction

Mild Cognitive Impairment (MCI) is used to describe cognitive deficits that appear in the early stage of the neurodegenerative diseases and represents a risk factor for the development of dementia (Petersen et al., 1999). The MCI construct was introduced also in Parkinson's Disease (PD), similarly to what happened in Alzheimer's Dementia (AD) (Caviness et al., 2007; Litvan et al., 2012).

At present, there is no successful pharmacological treatment for cognitive impairment in PD (Emre, Ford, Bilgiç, & Uç, 2014; Orgeta et al., 2015). An extensive literature supports the beneficial effects of cognitive training (CT) in healthy elder people (Lampit, Hallock, & Valenzuela, 2014), in MCI and AD (Andrieu, Coley, Lovestone, Aisen, & Vellas, 2015; Coyle, Traynor, & Solowij, 2015; Rojas et al., 2013). In the case of PD, evidence in favor

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of the effectiveness of CT, using either computers or in-person interventions, is still poor. A systematic review and meta-analysis (Leung et al., 2015) identified only 7 Randomized Controlled Trials (RCTs). Though these studies provided evidence on the effectiveness of CT on cognition in PD patients, they were based on small sample sizes and on different modalities of CT. Therefore, larger RCTs or further confirmatory studies are necessary to examine the usability and usefulness of CT programs as a treatment for cognitive decline in PD. Moreover, it is currently unknown whether CT affects cognition on long term in PD, due to the lack of longitudinal studies. Walton and colleagues (Walton, Naismith, Lampit, Mowszowski, & Lewis, 2017) suggested two options about the potential outcomes from CT in PD: CT may briefly stabilize cognitive decline, by delaying the downward trajectory, or it can attenuate the rate of decline. Furthermore, it is not clear whether long-term effects of CT on both the above outcomes are more likely obtained with booster sessions or with long-term continued CT. In this regard, only one RCT (Petrelli et al., 2015) provided a follow-up assessment after 1 year in PD patients with normal cognitive profile, in order to study the conversion process to MCI. The authors observed that patients who received a 6-weeks CT program maintained their overall cognitive functions, while those in the control group showed a significant decline. Moreover, some studies (Coyle et al., 2015; Walton et al., 2017) suggested that computerized CT may be efficacious at the early phases of PD, or where PD-MCI is present, while it may not be beneficial at the Parkinson's Disease Dementia stage.

Computer-supported CT delivery overcomes some limits of traditional paper-and-pencil approach. In fact, computerized CT uses engaging motivational cues and provides real-time feedback; task complexity and response time demands may change frequently during and across sessions, in accordance with changes in individual performance. This allows avoiding over- or under-stimulation and providing more training time in areas of relative weakness. Computer support also saves time for therapists in the preparation of the exercises and allows to record all session parameters for further statistics.

In the light of this background, we conducted a prospective, open-unblinded RCT in order to assess the effectiveness of a computer-based CT (CoRe system) for the training of logical and executive functions in inpatients with PD-MCI. The study did not include a control group treated with paper-and-pencil approach since, for the advantages of the computer support explained above, we gave for granted the non-inferiority of a computerized rehabilitation program vs a traditional one.

2. Materials and methods

2.1. Participants and measures

Inpatients with idiopathic PD were recruited from the Neurorehabilitation Unit of the IRCCS Mondino Foundation. Inclusion criteria were:

- diagnosis of idiopathic PD according to UKPDBB criteria (Hughes, Daniel, Kilford, & Lees, 1992) and Hoehn & Yahr scale $\leq$4 (Hoehn & Yahr, 1967);
- presence of PD-MCI single-domain (executive) or PD-MCI multiple-domain with executive involvement (Litvan et al., 2012);
- age between 50 and 85 years;
- education level $\geq$5 years.

Exclusion criteria:

- pre-existing cognitive impairment (e.g. aphasia, neglect);
- severe disturbances in consciousness;
- severe sensory or motor disturbances that do not allow the patient to control the trunk or to maintain the sitting position; in particular patients with disturbing resting and/or action tremor (corresponding to score 2–4 in the specific items of Unified Parkinson's Disease Rating Scale (UPDRS III) (Fahn,1987) were excluded;
- concomitant severe psychiatric or neurological conditions;
- patients with Deep Brain Stimulation.

All the patients were treated with dopamine agonists or L-DOPA; the therapy was stable for 3 months and no variations were allowed during the training and follow-up periods. The disease severity was rated according to the Hoehn & Yahr Scale and UPDRS III.

The PD-MCI diagnosis was formulated on the basis of a comprehensive neuropsychological evaluation (baseline cognitive assessment) according to the guidelines (level II criteria) (Litvan et al., 2012); the following standardized tests assessing different domains were administered:

- global cognitive function: Mini-Mental State Examination (MMSE) (Folstein, Folstein, &

McHugh, 1975) and Montreal Montreal Overall Cognitive Assessment (MoCA) (Nasreddine et al., 2005);
- memory: verbal (Verbal Span, Digit Span) and spatial (Corsi's block-tapping test – CBTT) span (Spinnler, 1987); verbal long-term memory (Logical Memory Test immediate and delayed recall) (Carlesimo, Caltagirone, Gainotti, & Nocentini, 1995), (Rey's 15-word test immediate and delayed recall) (Caffarra, Vezzadini, Dieci, Zonato, & Venneri, 2002); spatial long-term memory (Rey Complex Figure delayed recall – RCF-dr) (Laiacona, Inzaghi, De Tanti, & Capitani, 2000);
- logical-executive functions: non-verbal reasoning (Raven's Matrices 1947 – RM47) (Carlesimo et al., 1995); categorical abstract reasoning (Weigl's Sorting test) (Spinnler, 1987); frontal functionality (Frontal Assessment Battery – FAB) (Apollonio et al., 2005); semantic fluency (animals, fruits, car brands), phonological fluency (FAS) (Carlesimo et al., 1995);
- attention: visual selective attention (Attentive Matrices) (Carlesimo et al., 1995); simple speed processing and complex attention (Trail Making Test parts A - TMTA and part B - TMTB) (Giovagnoli et al., 1996); selective attention/susceptibility to interference (Stroop test) (Amato et al., 2006);
- visuospatial abilities: Rey Complex Figure copy – RCF-copy (Laiacona et al., 2000).

The same battery was also used at follow-up visits; parallel versions were applied when available (verbal long-term memory tests), in order to avoid the learning effect. All the test scores were corrected for age, sex, and education and compared with the values available for the Italian population.

At the baseline, the patients' functional status was assessed using Activities of Daily Living (ADL) (Lawton, 1988), to evaluate basic everyday activities (the score ranges from 0 to 6, with higher scores corresponding to higher levels of independence) and Instrumental Activities of Daily Living (IADL) (Lawton, 1969), to evaluate more complex activities (the score ranges from 0 to 8, with higher scores corresponding to higher levels of independence). Score indicates preserved functions.

Moreover, mood were assessed using the Beck Depression Inventory (BDI) (Beck, Steer, & Brown, 2010) at the baseline and at the follow-up visits, while quality of life were assessed using 8-Item Parkinson's Disease Questionnaire (PDQ-8) (Jenkinson & Fitzpatrick, 2007) at the baseline and six months after training.

The sample size has been calculated on the basis of the global cognitive functioning measured by MoCA, which is more sensitive to executive dysfunction in PD with respect to MMSE. We considered a basal value of MoCA equal to 24.9 ± 3.5, as reported in Hu and colleagues (Hu et al., 2014). We considered as a clinical significant improvement an increase of 3 points. Using a statistical significance threshold of 0.05 for type-1 error and a study statistical power of 80%, we obtained a sample size of 21 patients for group.

The study was approved by the local Ethics Committee and conducted in accordance with the Helsinki Declaration of 1975; all the participants provided written Informed Consent.

2.2. Study design and procedures

This study is a prospective, open-unblinded RCT. All the PD patients recruited underwent baseline cognitive assessment (T0). Patients who met the inclusion and exclusion criteria were enrolled and randomized to receive standard physical rehabilitation plus cognitive intervention with CoRe (intervention group - G1) or standard physical rehabilitation only (control group - G2). The standard physical rehabilitation was the same in the two groups in terms of frequency, duration and number of sessions. Standard physical rehabilitation comprises: cardiovascular warm-up activities, active and passive exercises to improve the joints' range of motion, stretching of the abdominal muscles, strengthening of paravertebral muscles, postural changes, and exercises operating on balance and postural control. Neuropsychological evaluation and CoRe sessions were administered exclusively during "on" status.

The randomization list was generated using a simple randomization method with "random number generator" software. CoRe program consisted of 12 individual sessions (3 sessions/week) each lasting 45 minutes of computer-based logical-executive tasks. All the patients were evaluated at the end of the 4-weeks training (T1) to detect the presence of a training effect (T0 vs T1) and subsequently at six months from the end of CT (T2) to assess the persistence of the training-related improvement (T1 vs T2). We will also evaluate the medium-term impact of CT on the evolution of cognitive decline (comparative changes observed at T2 with respect to T0 in the two groups).

2.3. The CoRe system

CoRe (acronym for Cognitive Rehabilitation) is an ontology-based software tool that allows several degrees of personalization and the possibility to generate different patient-tailored exercises. The stimuli database is created starting from the ontology, which describes every entity trough a set of attributes and its relation with other entities (a detailed description of the ontology can be found in Leonardi, Panzarasa, & Quaglini, 2011). This ontology improves the variety and the personalization of the exercises, which play a vital role in reducing the risk of boredom and increasing the compliance. The exercises administered in this study are the following ones in brackets the specific executive sub-abilities involved are described (for a more detailed description see previous papers (Alloni et al., 2017; Alloni, Quaglini, Panzarasa, Sinforiani, & Bernini, 2018):

1. FIND THE CATEGORY: the patient must choose, between three textual options, the belonging category of the three images displayed (categorical thinking, conceptual abstraction abilities);
2. FIND THE INTRUDER: five words are displayed, four of which belong to the same category, the patient must identify the "intruder" element that belongs to a different category (verbal-logical reasoning, cognitive flexibility, problem solving);
3. UNSCRAMBLE THE SENTENCE: scrambled words are displayed; the patient must select them in the right order to compose a sensible sentence (mental and verbal planning and conceptual abstraction abilities);
4. UNSCRAMBLE THE IMAGES: the same as above, the patient must put the scrambled images in the right order to form a short story (planning of activities, problem solving, temporal sequencing, visual attention);
5. IMAGE AND SOUND: an image (small or big) is displayed and a sound (with low or high volume) is played; the patient must evaluate whether size and volume match (inhibitory control, multi-tasking, working-memory, maintenance of attention over time);
6. WORD COUPLING: eight words are displayed, the patient must associate them in four couples, identifying the relations that exist between the stimuli (verbal-logical reasoning based on previous knowledge);
7. LOGICAL SEQUENCES: a sequence of images is shown, the patient must select, among several options, the one that completes the series (non-verbal reasoning, mental problem solving, decision making);
8. LOGICAL ANALOGIES: a "textual proportion" is shown with one of the four elements missing and named as X (ELEMENT#1 is related to ELEMENT#2 as ELEMENT#3 is related to X); the patient must identify the relation and select the right element among the proposed options (logical reasoning, conceptual abstraction abilities);
9. FIND THE ELEMENTS: a matrix of random text elements (letters or numbers) is displayed, the patient must identify and select the requested ones (sustained and selective attention, visuo-spatial scanning, speed);
10. FUNCTIONAL PLANNING: the patient must select, among the proposed options, the elements needed to perform the action displayed (mental planning, decision making).
11. CoRe was previously tested on healthy volunteers with different education levels and different degree of familiarity with PC (Alloni et al., 2017). Moreover, preliminary data from the trial described in this paper were used to verify the overall system functionality and usability (e.g., in terms of completed sessions), as well as to obtain initial results on its effectiveness (Alloni et al., 2018).

2.4. Statistical analysis

Our hypothesis was that subjects in G1 had a higher probability of maintaining or improving their cognitive level than subjects in G2. The scores of the neuropsychological tests were considered as outcome measures. Particularly, the primary outcome measures were the global cognitive functioning scores (MoCA and MMSE), while the secondary outcome measures were the executive tests scores. Moreover, non-executive test scores were also considered, as explorative outcomes, to assess whether the treatment effect could be transferred even into untrained domains. The effects of the training measured at T0, T1 and T2 were compared within- and between groups. Considering the small sample size, normality tests cannot be expected to give reliable results, so non-parametric tests are to be preferred. Therefore, Friedman's analysis of variance has been used to compare the data obtained in the three cognitive

assessments, while Wilcoxon test was used to perform the group-group evaluations (T0vsT1, T1vsT2, T0vsT2). An effects size index (Cohen's d) was calculated to measure the magnitude of the treatment effect for each significant difference. Contingency tables were used to investigate the association between the intervention and the improvement (Fisher's exact test).

In order to detect the impact of CT on primary outcomes, for both groups, the mean percentage change scores for MMSE and MoCA were calculated and compared between the baseline and the next evaluations (Wilcoxon test). Moreover, as suggested by Binetti and colleagues (Binetti et al., 2013) for each patient, the percentage change of the two primary outcomes at T1 and T2 with respect to the baseline value at T0 were calculated, i.e. 100x(T1 score - T0 score)/(T0 score), and 100x(T2 score - T0 score)/(T0 score). Patients with a percentage change equal to 0 were considered as being stable, those with a percentage change greater than 0 were considered as improved; all the other patients were defined as non-responders, as described also in Petrelli's study (Petrelli et al., 2015). This allowed to identify and compare (Fisher's Test) the number of patients who improved, retained or worsened their cognitive state in the two groups between T0 and T1 and T0 and T2.

When two groups are compared, the results are commonly considered significant for p-values lower than 0.05. However, since we also compared the same variable at different times, and performed a number of tests on multiple endpoint variables, we adopted the FDR (false discovery rate) correction method described in (Benjamini & Yekutieli, 2001). We applied the correction both for the comparisons at different times, and for the three time measures of the multiple endpoints.

All statistical analyses were performed using R (https://www.r-project.org/).

3. Results

Seventy-seven PD patients were recruited. Out of them, 36 were excluded because they did not meet the inclusion/exclusion criteria. The main reasons for exclusion were absence of cognitive impairment, presence of MCI without executive involvement, PD dementia or Deep Brain Stimulation.

Among the 41 patients enrolled, 23 patients were randomly assigned to G1 (7M/16F, mean age 71.18 ± 7.04 years, mean education 9.06 ± 4.51 years) and 18 to G2 (11M/7F, mean age 69.33 ± 7.72 years, mean education 7.67 ± 3.50 years). Within G1, 6 patients dropped-out because they were discharged from the hospital before the end of CT program, therefore statistical analysis considered 17 patients in G1 and 18 in G2 (see CONSORT diagram in Fig. 1). In G1 11/17 and in G2 10/18 patients presented a prevalent rigid-akinetic form, while 6/17 and 8/18 respectively a prevalent tremorigenic form. Four patients (2 in G1 and 2 in G2) presented a moderate freezing. No patients presented impulsive-compulsive disorders or hallucinations. Moreover, patients with executive-single-domain PD-MCI were 2/17 in G1 and 2/18 in G2 respectively, the remaining patients presented multiple-domain PD-MCI with executive involvement.

The demographic and clinical characteristics and the mean neuropsychological scores at T0 are reported in Table 1; no baseline differences were found between the two groups. Table 2 shows the mean (SD) neuropsychological scores and clinical data at T1 and T2; Table 3 shows the results (Wilcoxon test) of the intra-group and inter-group comparisons of the neuropsychological scores at T0, T1, T2. The results are presented with the indication of the significance with correction for the comparisons at different times (*) and for multiple endpoints (**).

Comparison between T0 and T1

– within-group analysis:

G1 showed statistically significant improvements at MoCA, Rey's 15-word test immediate recall, Logical Memory Test immediate recall, Weigl's Test and FAS, while G2 showed no statistically significant changes compared to the baseline scores.

– between-group analysis:

G1 performed significantly better than G2 at MoCA, Rey's 15-word test immediate recall, Logical Memory Test immediate recall, Weigl's Test, TMTA, RM47and Stroop Test time interference.

Comparison between T1 and T2

– within-group analysis:

G1 showed a significant worsening at MoCA and FAS.

G2 showed significant worsening at MoCA and FAS similarly to G1, but also at MMSE and FAB.

– between-group analysis: – there were no significant differences in the test scores variations between the groups.

Comparison between T0 and T2

– within-group analysis:

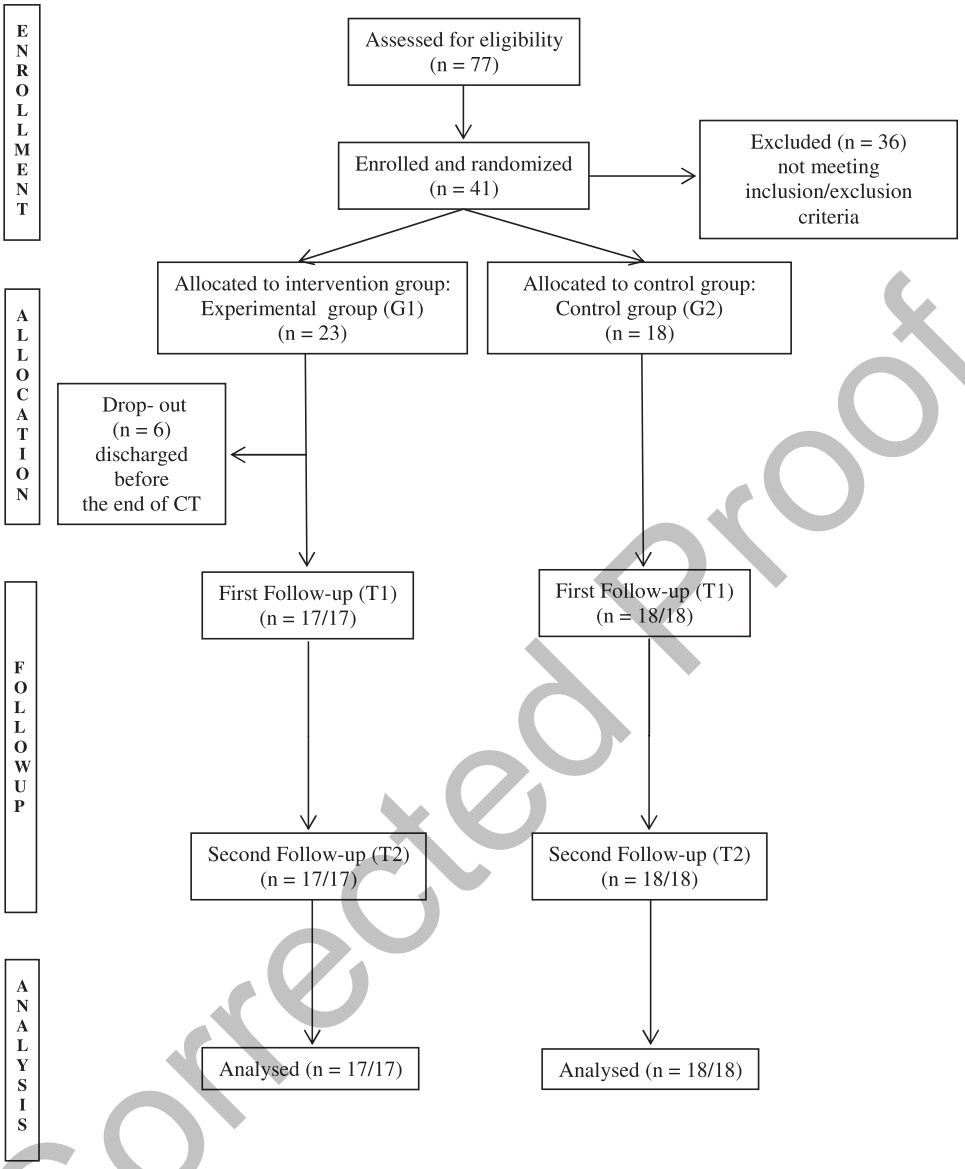

Fig. 1. CONSORT flowchart with the follow-up information.

G1 showed statistically significant improvement at MoCA, Rey's 15-word test immediate and delayed recall and Weigl's Test.

G2 showed significant worsening at MoCA, MMSE and FAB.

– between-group analysis:

G1 performed significantly better than G2 at MoCA, Rey's 15-word test immediate and delayed recall, Weigl's Test, FAB, TMTA and Stroop Test time interference and error interference.

The mean percent change in MMSE and MoCA scores between T0 and T1 and between T0 and T2 were calculated for G1 and G2 (Table 4).

Regarding MoCA, G1 improved both between T0 and T1 and between T0 and T2, while G2 worsened. Regarding MMSE, G1 slightly improved, while G2 slightly improved between T0 and T1 but worsened between T0 and T2.

In particular, there was no significant group difference in the mean percentage change scores at

Table 1
Mean and standard deviation of demographic data and neuropsychological scores at T0

Demographic data and neuropsychological scores	T0		(W)p
	G1 M(DS)	G2 M(DS)	
PATIENTS (M/F)	17 (6/11)	18 (11/7)	0.11
AGE	71.18 (7.04)	69.33 (7.72)	0.36
SCHOOL ATTENDANCE (years)	9.06 (4.51)	7.67 (3.50)	0.36
DISEASE DURATION (years)	7.18 (3.19)	10.67 (7.36)	0.15
HOEHN & YAHR SCALE	2.8 (0.96)	2.9 (0.47)	0.46
UPDRS III	37.82 (13.93)	36.50 (12.82)	0.74
PDQ-8 (Summary Index)	41.7 (20.9)	40.9 (21.2)	0.51
BDI	3.1 (1.7)	3.2 (1.5)	0.33
ADL	5.5 (0.2)	5.4 (0.4)	0.36
IADL	7.1 (1.2)	7.2 (1.1)	0.79
MMSE	25.32 (2.26)	25.35 (2.68)	0.96
MoCA	20.82 (3.34)	19.17 (3.49)	0.16
DIGIT SPAN	4.32 (0.32)	4.13 (0.90)	0.70
CBTT	3.74 (1.12)	3.81 (0.82)	0.96
VERBAL SPAN	3.62 (0.55)	3.42 (0.48)	0.32
REY'S 15 WORD TEST-ir	33.99 (7.05)	29.33 (7.39)	0.06
REY'S 15 WORD TEST—dr	6.25 (2.89)	5.86 (2.04)	0.49
LOGICAL MEMORY TEST-ir	4.06 (2.61)	4.66 (2.41)	0.60
LOGICAL MEMORY TEST-dr	4.62 (2.67)	5.39 (2.19)	0.50
RM47	23.32 (5.95)	21.02 (4.70)	0.33
WEIGL'S TEST	6.41 (2.77)	5.85 (2.06)	0.57
FAB	13.21 (1.86)	12.58 (2.06)	0.27
TMT A	144.47 (61.51)	121.71 (53.90)	0.20
TMT B	236.71 (104.09)	216.94 (119.21)	0.61
ATTENTIVE MATRICES	39.93 (11.77)	38.95 (9.07)	0.70
STROOP TEST TIME	28.26 (19.95)	21.52 (11.07)	0.43
STROOP TEST ERROR	8.56 (6.55)	5.88 (5.05)	0.28
PHONOLOGICAL FLUENCY (FAS)	27.25 (10.66)	24.38 (9.30)	0.39
SEMANTIC FLUENCY	32.71 (5.79)	29.15 (8.61)	0.06
RCF copy	26.54 (8.11)	24.01 (9.00)	0.43
RCF-dr	13.54 (5.61)	10.51 (6.49)	0.15

Abbreviations: G1 = Intervention Group; G2 = Control Group; M = mean; SD = standard deviation; (W)p = Wilcoxon test p values for inter-group comparisons; UPDRS III = Unified Parkinson's Disease Rating Scale III; PDQ-8 = 8-Item Parkinson's Disease Questionnaire; BDI = Beck Depression Inventory; ADL = Activities of Daily Living; IADL = Instrumental Activities of Daily Living; MMSE = Mini-Mental State Examination; MoCA = Montreal Montreal Overall Cognitive Assessment; CBTT = Corsi's block-tapping test; ir = immediate recall; dr= delayed recall; RM47 = Raven's Matrices 1947; FAB = Frontal Assessment Battery; TMT A and B = Trail Making Test parts A and B; RCF = Rey Complex Figure.

MMSE both between T0 and T1 ($p = 0.5$) and T0 and T2 (although at the limit of significance: p 0.058); while there was significant group difference at MoCA both between T0 and T1 ($p < 0.0001$) and T0 and T2 ($p < 0.0001$), where G1 performed significantly better than G2.

Contingency tables (Table 5) display for each group the number and percentage of patients that improved, remained stable or worsened respectively in MoCA and MMSE between the baseline and the next evaluations; the Fisher's Exact test p-values show whether there is a significant association between groups (G1 and G2) and performance (improved, stable and worsened).

No significant difference between the performance of the two groups at MMSE was observed between T0 and T1 (F p-value = 0.838), while between T0 and T2 there was significant group difference (F p-value = 0.043), since in G1 most patients improved or remained stable, while in G2 most patients worsened. Moreover, at MoCA there was a significant difference in the two groups both between T0 and T1 (F p-value < 0.0001) and between T0 and T2 (F p-value <0.0001), since in G1 most patients improved while

Table 2
Mean and standard deviation of clinical data and neuropsychological scores at T1 and T2

Clinical data and neuropsychological scores	T1		T2	
	G1 M(DS)	G2 M(DS)	G1 M(DS)	G2 M(DS)
UPDRS III	29.05 (10.18)	28.3 (11.71)		
PDQ-8 (Summary Index)			39.7 (21.4)	39.2 (21.6)
BDI	3.1 (1.5)	3.1 (1.4)	3.0 (1.5)	3.1 (1.6)
MMSE	25.51 (2.02)	25.38 (2.09)	25.59 (1.99)	24.49 (2.08)
MoCA	23.52 (2.78)	19.11 (3.32)	22.58 (2.95)	17.61 (4.08)
DIGIT SPAN	4.51 (0.62)	4.11 (0.47)	4.27 (0.30)	3.79 (0.90)
CBTT	4.16 (0.82)	3.77 (7.39)	3.98 (0.60)	3.56 (0.58)
VERBAL SPAN	3.85 (0.62)	3.55 (0.78)	3.69 (0.49)	3.37 (0.58)
REY'S 15 WORD TEST-ir	39.54 (9.06)	29.71 (6.24)	37.84 (9.03)	28.55 (5.27)
REY'S 15 WORD TEST-dr	7.68 (2.32)	5.24 (2.05)	7.90 (1.68)	5.06 (2.09)
LOGICAL MEMORY TEST-ir	5.35 (2.04)	4.37 (4.70)	4.72 (1.56)	4.37 (1.98)
LOGICAL MEMORY TEST-dr	4.52 (1.38)	5.81 (1.52)	5.75 (1.50)	5.29 (1.69)
RM47	25.57 (3.92)	20.45 (4.44)	23.80 (4.81)	19.22 (6.21)
WEIGL'S TEST	9.32 (2.64)	6.15 (2.44)	8.32 (1.98)	5.62 (2.29)
FAB	14.48 (2.25)	12.35 (1.68)	14.09 (1.53)	11.13 (1.37)
TMT A	108.82 (58.33)	124.82 (59.54)	121.94 (53.21)	145.64 (77.68)
TMT B	212.11 (74.28)	213.94 (112.53)	227.05 (94.76)	182.70 (122.70)
ATTENTIVE MATRICES	43.29 (5.89)	39.90 (7.97)	41.89 (9.07)	38.48 (8.64)
STROOP TEST TIME	19.66 (13.13)	24.66 (11.44)	24.63 (15.84)	29.40 (14.50)
STROOP TEST ERROR	5.16 (4.20)	5.67 (4.34)	5.64 (4.55)	8.47 (10.77)
PHONOLOGICAL FLUENCY (FAS)	33.15 (11.10)	24.87 (7.67)	28.17 (8.71)	23.43 (7.24)
SEMANTIC FLUENCY	32.88 (4.58)	28.96 (6.49)	33.64 (5.72)	29.83 (5.50)
RCF copy	28.05 (6.95)	24.84 (8.82)	26.16 (7.34)	23.76 (8.20)
RCF-dr	15.91 (4.39)	12.19 (5.33)	14.54 (5.54)	10.75 (7.26)

Abbreviations: G1 = Intervention Group; G2 = Control Group; ir = immediate recall; dr= delayed recall; M = mean; SD = standard deviation; UPDRS III = Unified Parkinson's Disease Rating Scale III; PDQ-8 = 8-Item Parkinson's Disease Questionnaire; BDI = Beck Depression Inventory; ADL = Activities of Daily Living; IADL = Instrumental Activities of Daily Living; MMSE = Mini-Mental State Examination; MoCA = Montreal Montreal Overall Cognitive Assessment; CBTT = Corsi's block-tapping test; ir = immediate recall; dr= delayed recall; RM47 = Raven's Matrices 1947; FAB = Frontal Assessment Battery; TMT A and B = Trail Making Test parts A and B; RCF = Rey Complex Figure.

in G2 most patients maintained their performance between T0 and T1 and worsened between T0 and T2.

As by the UPDRS III, both groups showed statistically significant motor improvement between T0 and T1 (G1 $p < 0.04$; G2 $p < 0.05$), while there was no significant difference in the scale variations between the groups at T1 (Table 1). With regard to the mood, there was no significant group difference in BDI score between the baseline and the follow-up visits. No differences have been reported at PDQ-8 both at baseline and after six months within each group.

4. Discussion

This prospective, open-unblinded RCT aimed to evaluate the effectiveness of a CT supported by a computerized tool (CoRe system) in PD-MCI. The analysis of the results allows to draw several considerations.

Cognitive intervention had positive effects immediately after the end of training. G1 patients showed a medium/large effect size improvement in the overall cognitive performance score measured by MoCA (a primary outcome measure) and in many executive tests (secondary outcome measures). Furthermore, inter-group analysis confirmed that the improvement in G1 was statistically different from G2 in several executive and non-executive tests. Since the training tasks differed from the tests used during the neuropsychological assessments and parallel test versions were used, when available, on post-assessment, these results may reflect learning of appropriate strategies rather than simple practice effects.

A follow-up evaluation was scheduled 6 months after the end of the training, with the aim of detecting (1) if post-training improvement was maintained over time and (2) how CT affects the evolution of cognitive decline in medium-term. About the first aim, comparing the post-training assessment with the last follow-up assessment, G1 behaved as G2 and no post-training improvement was maintained six months later. We can conclude that the benefits of the training are evident immediately afterward but not at the six-month follow-up. The reason is probably related to the duration of the training program.

Table 3
Z-value differences of T0vsT1, T1vsT2 and T0vsT2. Intra-group comparisons (Wilcoxon signed-rank test (W) and Cohen's d effect sizes (d)) as well as inter-group comparisons using the Wilcoxon signed-rank test (W) are shown. Underlined numbers represent positive results (improvement), *italic* numbers represent negative results (worsening)

	Intervention Group (G1)			Control Group (G2)			Inter-g	
	Z	(W)p Intra-g	d	Z	(W)p Intra-g	d	Z	(W)p
NpsTests (T0 vs T1)								
MMSE	0.43	0.661		0.21	0.836		0.40	0.684
MoCA	3.47	**0.0005****	0.87	0.22	0.821		4.27	**0.00001****
DIGIT SPAN	1.13	0.258		0.19	0.850		1.29	0.196
CBTT	1.41	0.158		0.26	0.792		1.33	0.181
VERBAL SPAN	1.37	0.169		1.19	0.234		0	1.00
REY'S 15 WORD TEST-ir	3.42	**0.0006****	0.68	1.18	0.237		3.32	**0.0008****
REY'S 15 WORD TEST-dr	1.43	0.151		0.96	0.332		1.65	0.098
LOGICAL MEM- ir	2.57	**0.010***	0.55	0.35	0.724		2.66	**0.007****
LOGICAL MEM- dr	1.54	0.123		1.13	0.255		0.59	0.550
RCF-dr	1.80	0.071		1.71	0.087		0.52	0.6
RM47	2.30	0.021		1.21	0.225		2.49	**0.012***
WEIGL'S TEST	2.93	**0.003***	1.07	0.98	0.325		2.66	**0.007****
FAB	2.17	0.029		0.52	0.601		2.17	0.029
TMT A	2.32	0.020		0.56	0.569		3.17	**0.001****
TMT B	1.55	0.120		0.18	0.856		0.87	0.379
ATTENTIVE MATRICES	1.25	0.208		0.59	0.553		0.52	0.596
STROOP TIME	2.35	0.018		1.67	0.093		3.11	**0.001***
STROOP ERROR	2.27	0.022		1.33	0.182		2.26	0.023
PHON FLUENCY (FAS)	2.65	**0.007***	0.54	0.65	0.516		2.33	0.019
SEMANTIC FLUENCY	0.09	0.923		1.05	0.293		0.64	0.516
RCF copy	0.62	0.53		0.44	0.660		0.21	0.829
NpsTests (T1 vs T2)								
MMSE	0.53	0.596		3.62	***0.0002****	–0.42	1.83	0.066
MoCA	2.40	***0.016****	–0.32	3.22	***0.001****	–0.40	1.09	0.274
DIGIT SPAN	1.51	0.129		1.92	0.054		00.14	0.887
CBTT	0.83	0.40		1.33	0.182		0.22	0.821
VERBAL SPAN	0.93	0.350		1.33	0.182		0	1.0
REY'S 15 WORD TEST-ir	1.72	0.084		1.33	0.182		0.54	0.582
REY'S 15 WORD TEST-dr	0.35	0.721		0.51	0.608		0.84	0.398
LOGICAL MEM- ir	1.73	0.083		0.99	0.319		0.79	0.427
LOGICAL MEM- dr	0.99	0.319		2.15	0.031		0.76	0.447
RCF-dr	1.61	0.106		1.23	0.217		0.21	0.829
RM47	2.38	0.017		0.94	0.346		0.86	0.386
WEIGL'S TEST	1.58	0.113		2.33	0.019		0.03	0.972
FAB	1.06	0.287		2.82	***0.004****	–0.79	1.31	0.189
TMT A	1.32	0.187		2.09	0.036		0	1.0
TMT B	0.97	0.328		0.85	0.394		1.74	0.081
ATTENTIVE MATRICES	0.39	0.697		1.68	0.092		0.64	0.518
STROOP TIME	1.78	0.074		1.71	0.087		0.22	0.822
STROOP ERROR	1.66	0.096		1.87	0.0612		0.29	0.768
PHON. FLUENCY (FAS)	2.63	***0.008****	–0.49	2.42	***0.015****	–0.19	1.61	0.107
SEMANTIC FLUENCY	0.54	0.588		0.43	0.666		0.629	0.529
RCF copy	1.03	0.299		1.37	0.168		0	1.0
NpsTests (T0 vs T2)								
MMSE	0	1.0		2.33	***0.019****	–0.35	1.87	0.060
MoCA	2.38	**0.017***	0.71	3.22	***0.001****	–0.41	3.69	**0.0002****
DIGIT SPAN	0	1.0		2.15	0.031		2.13	0.032
CBTT	1.18	0.236		1.42	0.154		1.60	0.107
VERBAL SPAN	0.44	0.656		0.18	0.850		0.72	0.468
REY'S 15 WORD TEST-ir	2.70	**0.006***	0.47	0.97	0.329		2.70	**0.006****
REY'S 15 WORD TEST-dr	2.40	**0.016***	0.69	1.64	0.099		2.79	**0.005****
LOGICAL MEM- ir	1.18	0.236		1.18	0.234		1.45	0.145
LOGICAL MEM- dr	1.18	0.234		0.31	0.756		1.24	0.214
RCF-dr	1.37	0.170		0.65	0.513		0.41	0.679

(*continued next page*)

Table 3
(*Continued*)

	Intervention Group (G1)			Control Group (G2)			Inter-g	
	Z	(W)p Intra-g	d	Z	(W)p Intra-g	d	Z	(W)p
RM47	0.49	0.623		1.97	0.048		1.75	0.078
WEIGL'S TEST	2.96	**0.003***	0.79	0.40	0.684		3.15	**0.001****
FAB	1.82	0.068		3.14	***0.001****	–0.82	3.38	**0.0007****
TMT A	2.17	0.029		2.20	0.027		2.96	**0.003****
TMT B	1.26	0.205		1.62	0.105		0.03	0.972
ATTENTIVE MATRICES	0.65	0.513		0.76	0.447		0.57	0.562
STROOP TIME	0.90	0.365		2.35	0.018		3.11	**0.001****
STROOP ERROR	0.56	0.573		2.55	0.010		2.66	**0.007****
PHON. FLUENCY (FAS)	0.94	0.343		0.88	0.378		1.38	0.164
SEMANTIC FLUENCY	0.85	0.390		0.55	0.582		0.23	0.816
RCF copy	0.85	0.393		0.64	0.522		0.16	0.868

Abbreviations: Nps = neuropsychological; ir = immediate recall; dr = delayed recall; MMSE = Mini-Mental State Examination; MoCA = Montreal Montreal Overall Cognitive Assessment; CBTT = Corsi's block-tapping test; ir = immediate recall; dr = delayed recall; RM47 = Raven's Matrices 1947; FAB = Frontal Assessment Battery; TMT A and *B* = Trail Making Test parts A and B; RCF = Rey Complex Figure; *Z* = z-value differences between T0vsT1 or T1vsT2 or T0vsT2 intra-groups and inter groups; (W)p intra-g = Wilcoxon test p values for intra-group comparisons; (W)p inter-g = Wilcoxon test p values for inter-group comparisons; *d* = Cohen's d effect size intra-groups with *d* = .2 small effect, *d* = .5 moderate effect, *d* = .8 large effect; *p*-values that resulted still significant after corrections for the comparisons at different times (*) or for multiple endpoints (**).

Table 4
Mean percentage change scores at MMSE and MoCA for G1 and G2 between T0 and T1 and between T0 and T2

	T0 vs T1			T0 vs T2		
	G1	*G2*	*p*	*G1*	*G2*	*P*
MoCA *M(SD)*	17.18 (12.09)	– 0.036 (4.67)	<0.001	9.96 (13.57)	–8.78 (8.5)	<0.0001
MMSE *M(SD)*	1.02 (6.12)	0.54 (6.63)	0.5 (n.s.)	1.96 (11.19)	–3.02 (5.16)	0.058 (n.s.)

Abbreviations: G1 = Intervention Group; G2 = Control Group; *p* = values of statistical significance; *M* = mean; SD = standard deviation; n.s. = not significant.

Table 5
Performance at MMSE and MoCA in G1 and G2 between T0 and T1 and between T0 and T2

MoCA

	T0 vs T1			T0 vs T2		
	Improved	Stable	Worsened	Improved	Stable	Worsened
G1	16 (94.1%)	0	1 (5.9%)	13 (76.5%)	0	4 (23.5%)
G2	3 (16.7%)	10 (55.5%)	5 (27.8%)	1 (5.5%)	3 (16.7%)	14 (77.8%)
	Fp-values:<0.0001			Fp-values:<0.0001		

MMSE

	T0 vs T1			T0 vs T2		
	Improved	Stable	Worsened	Improved	Stable	Worsened
G1	7 (41.2%)	5 (29.4%)	5 (29.4%)	6 (35.3%)	7 (41.2%)	4 (23.5%)
G2	6 (33.3%)	6 (33.3%)	6 (33.3%)	2 (11.1%)	4 (22.2%)	12 (66.7%)
	Fp-values: not significant (0.838)			Fp-values:=0.043		

Abbreviations: G1 = Intervention Group; G2 = Control Group; Fp-values = Fisher's Exact test p values; *M* = mean; SD = standard deviation; n.s. = not significant.

Literature suggests that the executive functions need to be continuously stimulated over time since training has a strong impact in the short term but not probably enough to maintain efficient functioning in the long term (Moro et al., 2015). A possible solution would be to increase the number of weekly sittings during the period of treatment and then encourage the patient to continue the treatment at home (Alloni et al., 2018). To this concern, Walton and colleagues (Walton et al., 2017) highlighted the possible role of boosters or additional CT after completion to maintain the CT benefit. Regarding the second aim, both the intra- and the inter-group comparisons showed that after seven months G1 performance was

significantly better than the baseline in global cognitive functioning measured by MoCA and in several executive and non–executive test. As PD is a chronic progressive disease, the worsening observed in G2 can be interpreted as a cognitive profile modification due to natural disease evolution, while G1 showed a better evolution of cognitive decline, probably as a result of the cognitive intervention.

Moreover, we can observe that, even if CoRe focused on executive functions, the post-training effects observed in our patients seem to be transferred also into untrained domains, such as memory, thus suggesting the presence of a generalization effect. In fact, as suggested by Moro and colleagues (Moro et al., 2015), a training concerning cognitive strategies (e.g. task planning, inhibition of interference, and divided attention) seems to have some impact on the organization of the information that a patient must remember, with a positive secondary effect on memory.

In order to have a global measure of cognitive functioning we used both MMSE and MoCA. While the former is the most commonly used test in the literature, it is known that the latter is more sensitive and adequate to investigate logical-executive dysfunctions in PD (Burdick et al., 2014; Dalrymple-Alford et al., 2010). As a matter of fact, in our study we observed a change in MOCA but not in MMSE. In fact, comparing the baseline with the post-training assessments, within G1 the global cognitive functioning measured by MoCA significantly improved, as opposed to the decline in the control group. This improvement was more consistent immediately after the end of the training and decreased over time, but even after seven months the performance was higher than the baseline. Furthermore, the percentage of patients that improved, remained stable, or worsened at MoCA between the baseline and the next evaluations, was significantly different in the two groups: in G1 most patients improved their global cognitive level, while in G2 most patients maintained their global cognitive level between T0 and T1 and worsened between T0 and T2.

A comparison of our results with the literature is difficult because, to date, few studies used a global measure of cognitive functioning in the analysis of CT effects. París (París et al., 2011) did not find significant effects on overall cognitive functions, measured by ACE and MMSE, while Petrelli (Petrelli et al., 2015) reported long-term effect after one year using MMSE and Dem Tect. Further RCTs with comparable global cognitive tests and longer follow-up intervals are needed.

Moreover, some studies explored the interplay between motor and cognitive aspects in PD rehabilitation. For example, a study suggested that rehabilitative approaches involving cognition appear to be the most effective and permit to achieve motor benefits (Ferrazzoli et al., 2018). Other studies suggested that the combination of physical activity and cognitive exercises may improve cognitive function (memory and executive functions) in MCI (Teixeira et al., 2012). A systematic review (Murray, Sacheli, Eng, & Stoessl, 2014) suggested that physical exercise improved not only motor symptoms, but also cognitive impairments in PD; but the extent to which physical exercise specifically impacts cognition in PD, and how, is unclear. In our study, comparing the UPDRS III scores between the baseline and the end of physical rehabilitation program, both groups significantly improved and the size of this improvement was similar; so we can conclude that no significant effect of CT on motor performance was observed. Furthermore, in our study only patients who also received CT showed a better evolution of cognitive decline, while patients who received motor rehabilitation only tended to get worse over time. Therefore, our results do not allow to hypothesize the presence of correlation between motor and cognitive performances.

In conclusion, CoRe seems to be an effective treatment in PD-MCI in the attempt of briefly stabilizing cognitive decline, delaying the downward trajectory as suggested by Walton (Walton et al., 2017).

We are aware that this study has some limitations. First of all, we were not able to analyze the number of patients (also because of drop-outs) calculated from the sample size estimation. Thus, the statistical power of the study slightly decreased. On the other hand, our study is a prospective, open-unblinded RCT performed on a homogeneous sample and we believe that these characteristics balance the relatively small sample size.

The follow-up interval was limited to 6 months; however, to date few RCTs published follow-up data of CT intervention in PD (Leung et al., 2015) and only one with a longer (12 months) follow-up (Petrelli et al., 2015). Therefore, the present data provide a solid stepping stone for future RCTs and appear to be largely confirmatory that CT is safe and modestly effective on cognition in patients with PD as also suggested by Leung et al (Leung at al., 2015).

It should also be clarified that the goal of this study is not to demonstrate that computerized cognitive

training with CoRe is better than traditional paper and pencil cognitive training. Our results, in addition to confirming that cognitive training is helpful in PD, allow to suggest that, in the hospital setting, the use of a computerised version of the exercises offers benefits both for the operator and the patient: first, the possibility for an operator to follow more patients simultaneously, with consequent saving in time and costs; second, the availability of all the data, stored in electronic format, related to the rehabilitation sessions, which allow to perform sound statistics both at individual and aggregated level; third, the possibility for the patients to continue the treatment even after discharge.

In the light of an approach characterized by combination treatments for neurodegenerative disorders, our data suggest that CoRe could be incorporated into clinical routine and recommended as a non-pharmacological complementary therapy, to be implemented also at home in order to maintain its benefits over time (Alloni et al., 2018). Core is currently a research tool, open for sharing experiences with other health professionals. Our next step is to use it as a telerehabilitation tool, for the provision of remote rehabilitation treatments to home-patients.

Conflict of interest

The authors declare that they have no conflict of interest.

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