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# Effect of eight-week online cognitive training in Parkinson's disease: A double-blind, randomized, controlled trial

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ABSTRACT

*Introduction:* Cognitive training (CT) has been proposed as a treatment option for cognitive impairment in Parkinson's disease (PD). We aimed to assess the efficacy of adaptive, computerized CT on cognitive function in PD.
*Methods:* In this double-blind, randomized controlled trial we enrolled PD patients that experienced substantial subjective cognitive complaints. Over a period of eight weeks, participants underwent 24 sessions of computerized multi-domain CT or an active control intervention for 45 min each (randomized 1:1). The primary outcome was the accuracy on the Tower of London task; secondary outcomes included effects on other neuropsychological outcomes and subjective cognitive complaints. Outcomes were assessed before and after training and at six-months follow-up, and analyzed with multivariate mixed-model analyses.
*Results:* The intention-to-treat population consisted of 136 participants (n = 68 vs. n = 68, age M: 62.9y, female: 39.7%). Multivariate mixed-model analyses showed no group difference on the Tower of London accuracy corrected for baseline performance (n = 130): B: −0.06, 95% CI: −0.27 to 0.15, p = 0.562. Participants in the CT group were on average 0.30 SD (i.e., 1.5 s) faster on difficulty load 4 of this task (secondary outcome): 95% CI: −0.55 to −0.06, p = 0.015. CT did not reduce subjective cognitive complaints. At follow-up, no group differences were found.
*Conclusions:* This study shows no beneficial effect of eight-week computerized CT on the primary outcome (i.e., planning accuracy) and only minor improvements on secondary outcomes (i.e., processing speed) with limited clinical impact. Personalized or ecologically valid multi-modal intervention methods could be considered to achieve clinically meaningful and lasting effects.

## 1. Background

Cognitive impairment is highly prevalent in Parkinson's disease (PD). Even at diagnosis 25% of patients with PD experience deficits in one or more cognitive domains [1] and approximately 50% will have developed PD dementia (PD-D) after ten years [2].

The currently available pharmacological treatments for cognitive impairment in PD have limited efficacy, focus on relieving symptoms but not on delaying decline, and can have negative side-effects [3,4]. There is some evidence that cognitive training (CT) may alleviate cognitive

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impairment and slow down cognitive decline by boosting neuroplasticity [5] and improving the efficiency of global and regional brain networks [6]. A meta-analysis from 2015 found modest positive effects of CT [7], while a more recent Cochrane meta-analysis on the efficacy of CT for PD mild cognitive impairment (PD-MCI) or PD-D did not [8]. Both overviews did, however, show evidence for the efficacy of CT on improving specific cognitive domains, including executive function [7], attention/processing speed [7,8], working memory [7], and verbal memory [8] (mean Hedges' g ranging from 0.30 to 0.74). In addition, two studies showed long-term positive effects of CT, lasting up to 18 months after training [9,10], suggesting its potential in delaying cognitive decline. Nevertheless, the current (aggregated) evidence is imprecise and there is a lack of large-scale trials with active control conditions and adequate double blinding [7,8]. Consequently, there is a need for larger trials that overcome limitations of earlier trials and can provide more reliable evidence on the efficacy of CT.

In this report we present the primary results of the COGnitive Training In Parkinson Study (COGTIPS) [11]. Based on earlier meta-analyses, we hypothesized that our CT that was focused on executive, attentional and processing speed functions would 1) improve executive function (primary outcome), but also other cognitive functions, including attention/processing speed and working memory, 2) reduce subjective cognitive complaints and 3) we expected effects to endure at least six-months.

## 2. Methods

### 2.1. Trial design

COGTIPS is a large mono-center phase-3 double-blind RCT to assess superiority of eight-week computerized CT over an active control condition (AC). Participants were enrolled at the Amsterdam University Medical Centers (Amsterdam UMC), location VUmc. A detailed study protocol article was previously published [11].

COGTIPS was approved by the Medical Ethical Committee of the VU University Medical Center and prospectively registered at ClinicalTrials.gov (NCT02920632; September 30, 2016). The study was carried out in accordance with the Declaration of Helsinki. All participants provided written informed consent.

### 2.2. Participants

We enrolled 140 patients diagnosed by a neurologist with PD and a) Hoehn and Yahr stage <4, b) substantial subjective cognitive complaints (PD Cognitive Functional Rating Scale (PD-CFRS) score >3), and c) home access to a computer or tablet with internet. Exclusion criteria were a) Montreal Cognitive Assessment (MoCA) score <22 [12], b) indications of current drug- or alcohol abuse (CAGE AID-interview score >1), c) moderate or severe depressive symptoms (Beck Depression Inventory (BDI) score >18), d) impulse control disorder (positive screening by diagnostic criteria), e) non-benign psychotic symptoms (positive screening by the Schedule for Assessment of Positive Symptoms – PD), or f) history of traumatic brain injury with loss of consciousness for >15 min and/or posttraumatic amnesia >1 h.

### 2.3. Procedures

Participants were randomized over an experimental CT condition and an AC condition in an 1:1 fashion and both participants and outcome assessors were blinded during all assessments (for details see Ref. [11]). In both conditions, participants followed an online home-based intervention during eight weeks, three times a week for approximately 45 min (total duration: 1080 min). The CT consisted of 13 training games that focused on attention, processing speed and executive functions, and had an adaptive difficulty based on the individual participants' performance, based on the 'Braingymmer' online CT platform (www.braingymmer.com; Dezzel Media). Intervention compliance was automatically registered and checked by non-blinded study members and every two weeks we had phone contact with participants to maximize involvement and solve potential issues. The games were not part of the pre- and post-intervention neuropsychological assessments. We corrected for non-specific cognitive engagement by using an AC that consisted of three games without difficulty adjustments (i.e., hangman, trivia questions and solitaire).

At baseline (T0), after training (T1, after approximately nine weeks) and at follow-up (T2, approximately six-months after training) patients underwent an extensive assessment that included neuropsychological tests, questionnaires and interviews (see below and [11] for details).

## 3. Outcomes

The primary outcome measure was the efficacy of CT, relative to the AC, on the percentage correct responses (i.e. accuracy) on a computerized self-paced version of the Tower of London (ToL) task at T1 [13,14]. The ToL covers various executive functions including planning, inhibition, attention and working memory and consists of 100 pseudo-randomized trials with varying difficulty, ranging from one-step to five-step solutions (task-load S1–S5). Participants were excluded from ToL data analysis if they scored <75% on the one-step (S1) trials. We used ToL response time as a secondary outcome. A detailed list of all assessment instruments is provided in Supplementary Material 1.

Additional secondary outcomes were CT effects at T1 and T2 on subjective cognitive complaints and cognitive performance on latent cognitive factors (see Statistical methods). Subjective cognitive complaints were measured with the PD-CFRS and the Cognitive Failures Questionnaire. Latent cognitive factors were defined on the basis of an extensive neuropsychological test battery that mapped global cognitive function and performance on the five cognitive domains.

We additionally classified cognitive function of patients as cognitively normal, cognitive deficits associated with level II Movement Disorder Society (MDS) criteria for PD-MCI [15] or cognitive features of probable PD-D [16] by comparing neuropsychological function with healthy norm groups (see eTable 1 of Supplementary Material 3). Exploratory outcomes included group differences in individual neuropsychological test scores, performance on the CT and AC games, and effects on psychiatric symptoms. No serious adverse events were expected from the interventions and assessments. We therefore only assessed adverse events related to impulse control disorders (including Internet addiction) for which patients with PD are at increased risk.

### 3.1. Statistical methods

Analyses were performed on the intention-to-treat population (i.e., all correctly enrolled and randomized participants). We used a multivariate linear mixed-model analysis to assess differences between groups on the primary outcome measure (ToL accuracy) with z-transformed mean accuracy scores on task-load S1–S5 (modelled together) at T1 as multivariate outcome. We modelled standardized mean accuracy scores of these measures at T0 as covariates, condition as independent variable and a random intercept at participant level to correct for correlation of the multiple variables within participants. In the intention-to-treat analysis, data of ten participants were missing due to failed assessment (n = 4), no follow-up (n = 2) or poor understanding (n = 4) for the primary outcome measure. As this proportion was very small (<5%), we performed the planned analysis without using multiple imputation. All analyses were repeated with adjustment for age, sex and years of education.

We performed similar multivariate mixed-models to assess differences between groups on secondary and exploratory outcomes, i.e., differences on the ToL response time on S1–S5, subjective cognitive complaints, latent cognitive factors and psychiatric symptoms, using Z-scores. Latent cognitive factors were determined using regularized

maximum likelihood factor analysis (for a detailed description, see Supplementary Material 2) to compute individual scores on latent cognitive factors [17]. The effects of CT at six months follow-up were analyzed similarly to the above, but with time as an additional covariate in the mixed-model. Post-hoc, we modelled cognitive status – i.e., cognitively normal (PD-NC), PD-MCI, or PD-D – as an additional covariate in outcomes that showed CT-induced change, to assess differential training effects between subgroups.

We analyzed the change in performance on the CT and AC games using multivariate mixed-model analyses and additionally assessed ceiling effects on the intervention by comparing six phases of training (for a detailed description, see Supplementary Material 2).

We ran statistical analyses in SPSS version 26.0 (Armonk, NY, USA) using two-sided tests with $\alpha = 0.05$ and performed factor analysis using the FMradio package in R (version 3.5.3) [18]. We did not correct for multiple comparisons in our primary and secondary analyses as these involved four multivariate models for separate pre-defined research questions. Exploratory analyses were separately corrected for multiple comparisons using the Benjamini & Hochberg false discovery rate ($q < 0.05$) [19]. During the trial the Clinical Research Bureau of Amsterdam UMC performed two data monitoring visits.

The initial sample size calculation was based on a repeated-measures ANOVA corrected for a moderate correlation between pre- and post-intervention outcomes ($r = 0.6$) and an effect size $f = 0.12$ of CT on global cognitive function as reported in an earlier meta-analysis in PD patients [7]. Due to obscurity in the parameter definition in G*Power, we erroneously estimated the sample size needed to detect the effect (with $\alpha = 0.05$ and $\beta = 0.80$) at $n = 112$. Unfortunately, after trial completion we discovered that this sample size is insufficient to detect the expected effect on global cognition (for details, see the Supplementary Material 2). Based on our sample size ($n = 136$) and analysis method (revised from the initial planned analysis for higher sensitivity; linear mixed-model analysis with baseline covariate) the minimal effect size detectable in this study was $f = 0.19$, which should be sufficient to detect effects of CT on working memory ($f = 0.31$; [7]), and approaches earlier reported effects on executive function and processing speed ($f = 0.15$-$f = 0.16$).

### 3.2. Role of the funding organization

Two members of the Dutch Parkinson's Disease Patient Association made a contribution to the design of the study. The funding bodies and Dezzel Media B.V. had no role in the collection, analysis, and interpretation of data, writing the manuscript, or the decision to submit the manuscript for publication.

## 4. Results

### 4.1. Participants

We enrolled 140 patients with PD between September 15th, 2017 and May 23rd, 2019 with six-month follow-up assessments until January 29th, 2020. A flowchart is provided in Fig. 1. Four participants were wrongfully enrolled and excluded. One-hundred-and-thirty-six participants remained (mean age 62.9 ± 7.6 years; 39.7% female).

Groups showed similar demographic and clinical characteristics (Table 1), except for small differences in sex distribution, education and baseline cognitive complaints. Compliance was excellent with the

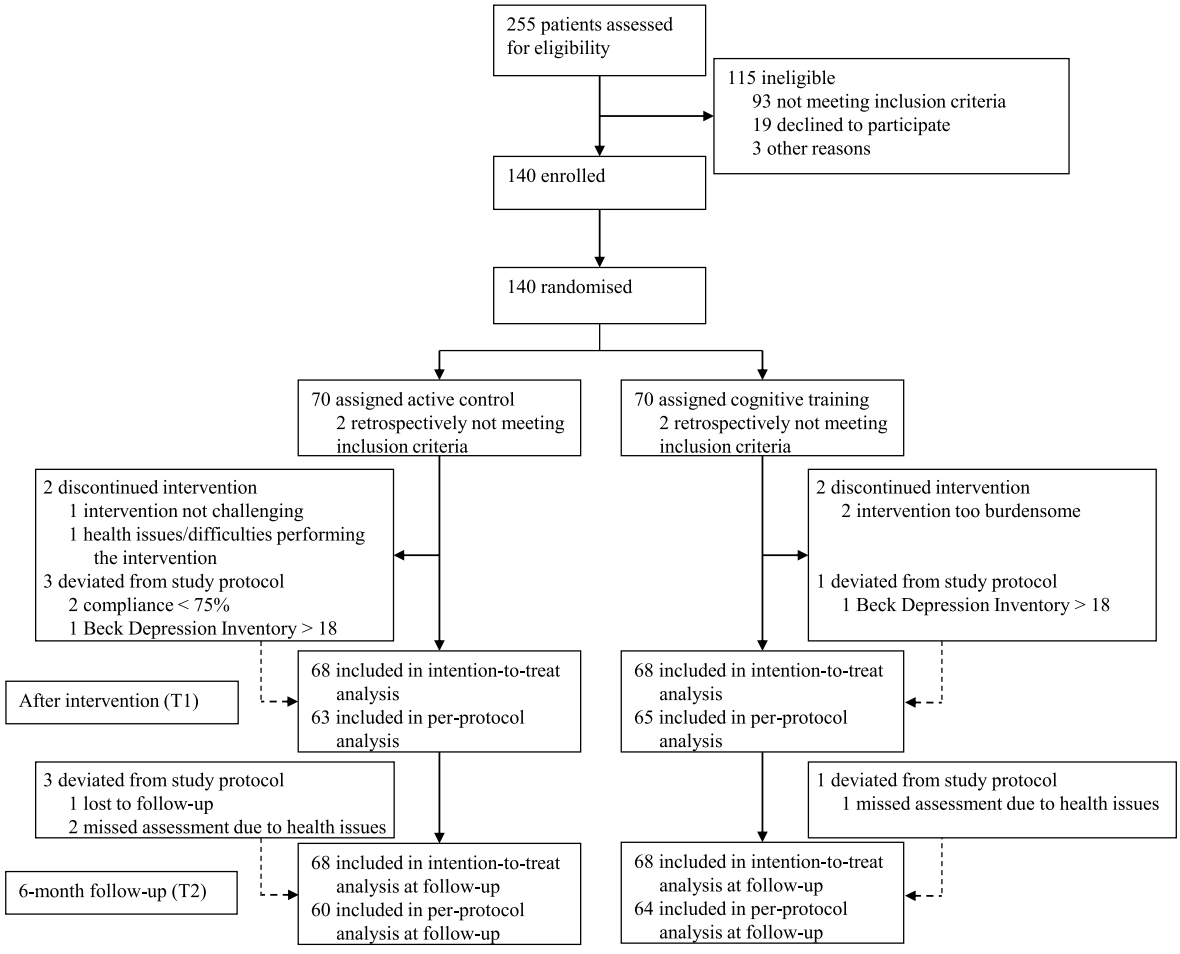


**Fig. 1.** CONSORT flow diagram of the enrollment procedure.

**Table 1**
Demographic and clinical characteristics of the intention-to-treat population.

| | Active control (n = 68) | Cognitive training (n = 68) |
|---|---|---|
| **Sex (Female N (%))** | 21 (31%) | 33 (49%) |
| **Age (years)** | 62.9 (7.0) | 62.9 (8.1) |
| **Education (years)** | 16.7 (4.4) | 15.5 (3.3) |
| **Education classification (N (%))**[a] | | |
| **3** | 1 (1.5%) | 1 (1.5%) |
| **4** | 4 (5.9%) | 4 (5.9%) |
| **5** | 16 (23.5%) | 17 (25.0%) |
| **6** | 26 (38.2%) | 29 (42.6%) |
| **7** | 21 (30.9%) | 17 (25.0%) |
| **Disease duration (years, median [range] )** | 5 [1-26] | 5 [0–22] |
| **UPDRS-III** | 21.0 (9.5) | 20.2 (8.3) |
| **Hoehn & Yahr stage (N (%))** | | |
| **1** | 5 (7.4%) | 4 (5.9%) |
| **1.5** | 2 (2.9%) | 7 (10.3%) |
| **2** | 34 (50.0%) | 28 (41.2%) |
| **2.5** | 18 (26.5%) | 18 (26.5%) |
| **3** | 9 (13.2%) | 11 (16.2%) |
| **LEDD (median [range] )** | 650 [0–2100] | 737 [0–1665] |
| **Medication change during study (N (%))** | 15 | 11 |
| **LEDD T1 (median [range] , N=132)** | 710 [0–1981] | 762 [0–1530] |
| **MoCA** | 25.9 (2.3) | 26.3 (2.0) |
| **Global cognitive function classification (N (%))** | | |
| **Normal cognition** | 13 (19.1%) | 15 (22.1%) |
| **Single-domain MCI** | 7 (10.3%) | 9 (13.2%) |
| **Multi-domain MCI** | 35 (51.5%) | 34 (50.0%) |
| **PD dementia** | 13 (19.1%) | 10 (14.7%) |
| **BDI** | 7.87 (4.1) | 8.21 (4.0) |
| **QUIP-RS (N=125)** | 19.2 (12.7) | 15.8 (12.8) |
| **PAS (N=135)** | 10.5 (6.8) | 10.3 (6.6) |
| **AS (N=135)** | 13.4 (4.5) | 13.2 (4.5) |
| **Credibility-Expectancy (N=135)** | 32.7 (7.6) | 33.9 (6.0) |
| **PD-CFRS (median [range] )** | 9.0 [3.3–22] | 7.0 [3.3–19] |
| **Compliance (%, median [range] )** | 100 [25–100] | 100 [39–100] |
| **T0-to-T1 interval (days)** | 64.3 (6.5) | 63.6 (4.8) |
| **T0-to-T2 interval (days)** | 253 (14) | 250 (10) |

Data are mean (SD) unless otherwise specified. .
*Abbreviations*: AS = Apathy Scale; BDI = Beck Depression Inventory; PAS = Parkinson Anxiety Scale; PD-CFRS = Parkinson's Disease – Cognitive Functional Rating Scale; LEDD = Levodopa equivalent daily dosage; MCI = mild cognitive impairment; MoCA = Montreal Cognitive Assessment; QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease – Rating Scale; UPDRS = Unified Parkinson's Disease Rating Scale.
[a] According to Dutch Verhage education classification (range 1: lower than primary school, to 7: university).

majority of participants completing 100% of the intervention. Compared with healthy norm groups, the participants showed below average cognitive performance on attention and processing speed tasks, but normal for other cognitive domains (see Supplementary Material 3).

## 5. Primary outcome

The intention-to-treat analysis (reported below) showed similar results to the per-protocol sample (Supplementary Material 4–5). There was no difference between groups on ToL accuracy after training across all task-loads S1–S5 adjusted for baseline performance: B[SE]: −0.06 [0.10], 95% CI: −0.27 to 0.15, p = 0.562 (crude model), or adjusted for baseline performance, age, sex and education level: B[SE]: −0.07 [0.10], 95% CI: −0.28 to 0.14, p = 0.229 (adjusted model; see Fig. 2a). The groups also showed no significant differences on the individual ToL accuracy task-loads (see Table 2).

## 6. Secondary outcomes

Statistics on the secondary outcomes are depicted in Table 2. Multivariate analysis of the ToL response times across task loads S1–S5 (n = 126) showed that the CT group was on average 0.17 standard deviation faster after training compared with the AC group: B[SE]: −0.17 [0.10], 95% CI: −0.36 to 0.03, p = 0.087 (crude model); B[SE]: −0.12 [0.10], 95% CI: −0.31 to 0.08, p = 0.232 (adjusted model). The CT group showed an improvement of 0.30 standard deviation (i.e., 1.5 s) on task-load S4 relative to the AC group: B[SE]: −0.30 [0.12], 95% CI: −0.55 to −0.06, p = 0.015 (crude model); B[SE]: −0.25 [0.12], 95% CI: −0.50 to 0.01, p = 0.042 (adjusted model; see Fig. 2b). Estimates of the other ToL task-loads indicated numerically similar but non-significant positive effects of CT compared with the AC. Subjective cognitive complaints (n = 133) showed no between-group differences.

Factor analysis on all cognitive outcomes resulted in five latent factors, that represented episodic memory (F1), executive and visuo-spatial function (F2), planning ability (F3), processing speed (F4), and attention and working memory (F5). After the intervention, there were no between-group differences on any of the factors (Table 2). Further details are reported in Supplementary Material 6.

At six-months follow-up, no between-group differences were present (see Supplementary Material 11–13).

### 6.1. Exploratory and post-hoc analyses

Results on exploratory univariate analyses of individual neuropsychological test outcomes are reported in Supplementary Material 7, and suggest improvement in the CT group on the Stroop Color-Word Test card II and III and improvement in the AC group on the Rey Complex Figure Test, that, however, did not survive correction for multiple comparisons. Exploratory analyses of improvement on the intervention games are provided in Supplementary Material 8–9. Participants improved significantly on the training in both conditions and on all separate training games. Comparison of six sequential phases of the training showed that the CT group no longer improved after phase IV, while the AC group no longer improved after phase I (eFigure 5). There was a significant association between improvement on the CT games and pre-to-post training change on the Stroop Color-Word Test card II and card III. Analyses of the effect of CT on psychiatric symptoms are reported in Supplementary Material 10.

Lastly, we performed post-hoc analyses of the differential effects of CT in separate cognitive diagnostic groups (PD-NC (n = 28), PD-MCI (n = 85) and PD-D (n = 23)). The differential effects are illustrated in Fig. 2 (ToL outcomes) and eFigure 6 (Stroop Color-Word Test), and statistics are reported in Supplementary Material 14. Briefly, CT effects were largest in the PD-D group both after training and at six-months follow-up.

## 7. Discussion

In the COGTIPS double-blind RCT we assessed the efficacy of online, home-based, adaptive multi-domain cognitive training (CT) in the largest sample of PD patients to date. Our results showed no effect of eight-week CT on planning task accuracy (primary outcome) in PD patients, nor did CT improve subjective cognitive complaints. Secondary study outcomes showed tentative positive effects on measures of processing speed during executive functioning that reached statistical significance for ToL response time only. No effects were found in other cognitive domains and no CT effects were present at six-months follow-up.

The negative results of this trial are in line with earlier aggregated findings of a Cochrane meta-analysis that described no clear evidence of CT on general cognitive function (and more specifically executive function) and activities of daily living in individuals with PD-MCI and PD-D [8]. While we a priori expected CT to primarily improve executive function, our study did not confirm this. In line with previous meta-analyses [7,8], we did observe tentative positive effects of CT on processing speed. However, this mental acceleration does not seem to

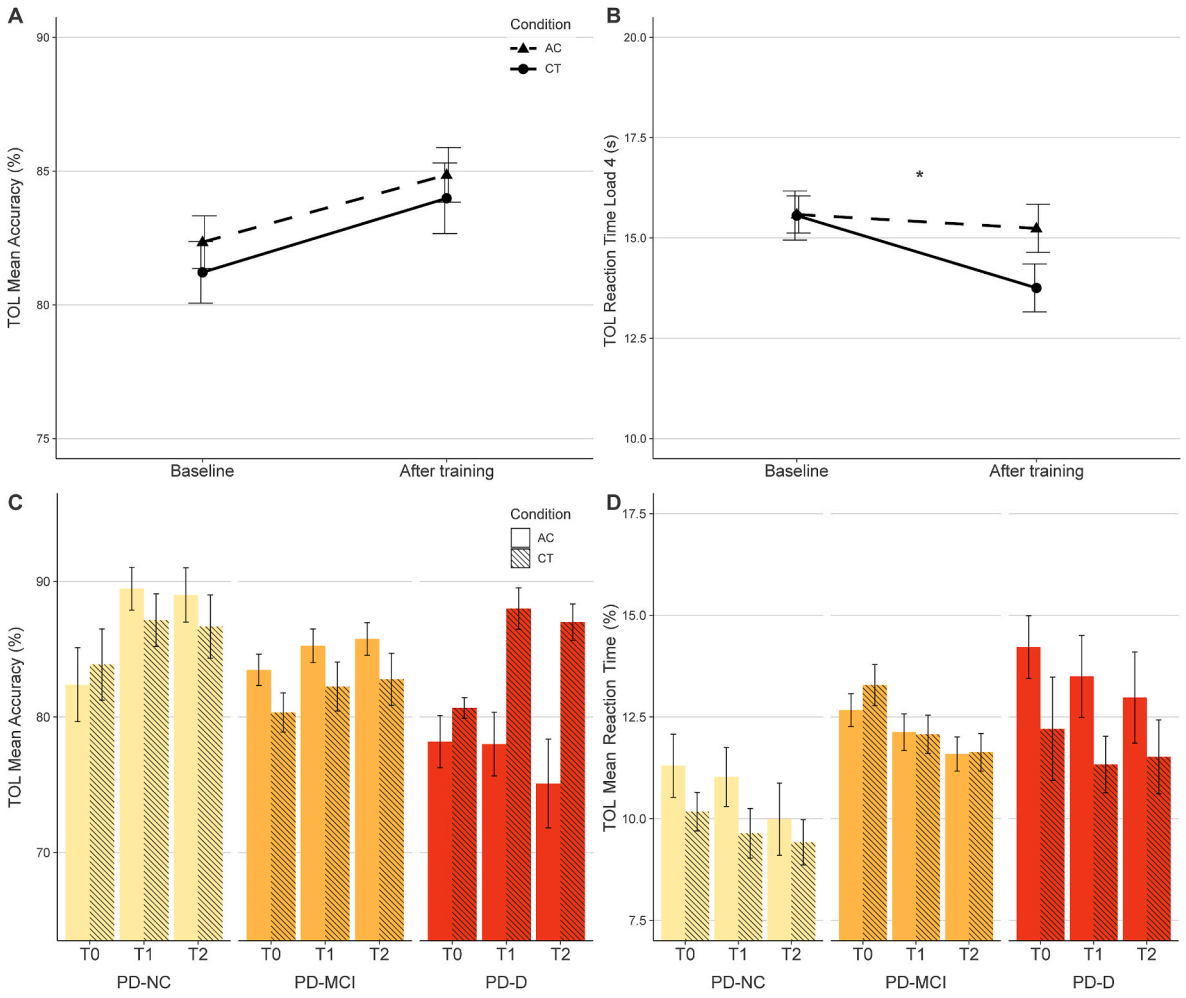


**Fig. 2.** Intervention effect in the cognitive training (CT) and active control (AC) groups. The upper panels show effects on the Tower of London (TOL) mean accuracy of S1–S5 **(A)** and response time **(B)**. *Indicates significant difference after training adjusted for baseline performance in the crude model. The lower panel shows results of the post-hoc analyses – the difference between intervention effects on the Tower of London (TOL) mean accuracy **(C)** and response time **(D)**, separated for participants with normal cognition (PD-NC), PD-mild cognitive impairment (PD-MCI) and PD dementia (PD-D). Data shown are observed means ± standard error.

translate to daily function as patients in both conditions reported minor subjective improvement after the intervention, but without group differences. Previous studies that assessed the effects of CT on subjective complaints in PD found small improvements [9,20] or null results [21–23]. The sensitivity of the PD-CFRS in measuring treatment effects – as opposed to its sensitivity to measuring clinically relevant cognitive decline [24,25] – has not yet been studied and our PD sample showed little variation in the total score at baseline. Limited transfer to 'real-world' cognitive function has previously been reported to be a shortcoming of CT and remains an important topic for future research [26]. At six-months follow-up the group differences on the ToL response time and Stroop Color-Word Test that were present after training had levelled out. As yet, this does not support two earlier smaller studies that assessed long-term CT effects [9,10].

The results of this clinical trial do not substantiate the use of CT (in its current form) in clinical practice. While we show that computerized CT is a highly feasible intervention, its effects do not transfer to everyday life. Effects of CT could be enhanced by individualization of training protocols, i.e., adjusting the training to the individuals' impairments. Transfer may additionally be more viable when CT resembles everyday life situations, for example by using virtual reality training interventions. This fast-developing technology is already being studied in psychiatric disorders [27,28] and may combine the easy administration and low cost of CT with ecological validity of cognitive rehabilitation. Tentative, targeted effects of CT on processing speed can additionally be enhanced by combining CT with aerobic or high intensity interval training [29,30], or neurostimulation [31]. Lastly, CT may be more effective for specific sub-populations within PD. Our post-hoc tests suggested larger CT effects in PD-D patients compared with PD-NC and PD-MCI patients. Earlier studies did not differentiate CT effects between PD-NC, PD-MCI or PD-D patients. Our results were contrary to our expectation that an intervention in early-stage PD – when compensatory neural mechanisms may still be able to counteract progressive PD pathology – would be more efficacious [11], although we must stress that the PD-D sub-group was small, making these results less reliable. An explanation could also be that PD-NC participants performed at a ceiling level on cognitive tasks with little room to quantify improvement.

### 7.1. Limitations and strengths

The main limitation of this study was that we retrospectively discovered (i.e. after trial completion) that our sample size fell short of the intended statistical power (see Supplementary Material 2). Even though this study enrolled more than twice the participants compared with previously published computerized CT studies, we were underpowered to detect effects on global cognitive function. Our study was adequately powered to detect effects on specific cognitive domains, however not including the executive function domain [7,8]. Secondly, our study did not include an additional waiting-list control group. Thirdly, despite our eligibility criterion to exclude PD patients with

**Table 2**
Group differences from the multivariate linear mixed-model analyses on the primary and secondary outcome measures for the crude and adjusted analysis models.

| | Baseline | | T1 | | Group difference (crude model) | | | Group difference (adjusted model)[a] | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Active control M (SD) | Cognitive training M (SD) | Active control M (SD) | Cognitive training M (SD) | B [SE] | 95% CI | *P* value | B [SE] | 95% CI | *P* value |
| **Primary outcome measure** | | | | | | | | | | |
| Overall ToL accuracy (%)[b] | 82.3 (7.9) | 81.2 (9.1) | 84.9 (8.2) | 84.0 (10.4) | −0.060 [0.104] | −0.266 to 0.145 | 0.562 | −0.070 [0.103] | −0.275 to 0.135 | 0.501 |
| S1 | 96.5 (5.1) | 96.0 (5.9) | 96.9 (4.9) | 96.2 (4.7) | −0.118 [0.162] | −0.435 to 0.200 | 0.466 | −0.127 [0.161] | −0.444 to 0.190 | 0.430 |
| S2 | 92.0 (8.7) | 90.6 (9.1) | 92.5 (8.5) | 90.6 (11.6) | −0.140 [0.162] | −0.458 to 0.177 | 0.385 | −0.151 [0.161] | −0.468 to 0.166 | 0.350 |
| S3 | 87.7 (10.9) | 86.8 (12.0) | 88.8 (9.1) | 89.0 (13.2) | 0.039 [0.162] | −0.278 to 0.357 | 0.808 | 0.030 [0.161] | −0.287 to 0.347 | 0.852 |
| S4 | 75.9 (13.5) | 75.0 (15.2) | 80.8 (14.1) | 78.7 (17.2) | −0.112 [0.162] | −0.429 to 0.206 | 0.490 | −0.121 [0.161] | −0.437 to 0.196 | 0.455 |
| S5 | 59.7 (20.4) | 57.6 (20.0) | 65.3 (21.4) | 65.3 (22.2) | 0.029 [0.162] | −0.289 to 0.346 | 0.859 | 0.019 [0.161] | −0.298 to 0.336 | 0.906 |
| **Secondary outcome measures** | | | | | | | | | | |
| Overall ToL reaction time (s)[c,d] | 12.7 (2.7) | 12.4 (3.2) | 12.1 (2.9) | 11.4 (2.9) | −0.167 [0.097] | −0.359 to 0.025 | 0.087 | −0.116 [0.097] | −0.308 to 0.076 | 0.232 |
| S1 | 6.4 (1.9) | 5.9 (1.8) | 5.9 (2.1) | 5.3 (1.6) | −0.198 [0.124] | −0.443 to 0.046 | 0.111 | −0.150 [0.124] | −0.394 to 0.094 | 0.227 |
| S2 | 8.3 (2.6) | 8.1 (2.9) | 7.4 (2.1) | 7.1 (2.4) | −0.108 [0.124] | −0.352 to 0.135 | 0.382 | −0.057 [0.124] | −0.301 to 0.186 | 0.644 |
| S3 | 11.0 (2.7) | 11.0 (3.5) | 10.6 (3.3) | 10.0 (3.5) | −0.157 [0.124] | −0.401 to 0.086 | 0.204 | −0.105 [0.124] | −0.348 to 0.138 | 0.397 |
| S4 | 15.6 (3.7) | 15.6 (4.8) | 15.2 (4.8) | 13.8 (4.7) | −0.304 [0.124] | −0.548 to −0.060 | 0.015 | −0.252 [0.124] | −0.495 to −0.009 | 0.042 |
| S5 | 22.0 (4.9) | 21.5 (4.8) | 21.5 (4.3) | 20.9 (4.5) | −0.067 [0.124] | −0.312 to 0.177 | 0.588 | −0.016 [0.124] | −0.260 to 0.228 | 0.897 |
| Overall subjective cognitive complaints[c,e] | | | | | −0.06 [0.11] | −0.28 to 0.15 | 0.560 | −0.03 [0.11]* | −0.25 to 0.20 | 0.821 |
| PD-CFRS | 9.7 (4.7) | 8.0 (4.0) | 8.0 (5.1) | 6.9 (4.3) | −0.06 [0.14] | −0.33 to 0.22 | 0.689 | −0.02 [0.14]* | −0.30 to 0.26 | 0.880 |
| PD-CFRS inf. | 5.6 (4.3) | 6.0 (5.0) | 5.7 (4.3) | 5.3 (3.6) | 0.00 [0.17] | −0.34 to 0.34 | 0.981 | 0.04 [0.17]* | −0.30 to 0.39 | 0.798 |
| CFQ | 38.5 (11.5) | 38.2 (10.6) | 38.0 (12.7) | 36.9 (10.5) | −0.11 [0.14] | −0.38 to 0.17 | 0.437 | −0.07 [0.14]* | −0.34 to 0.21 | 0.635 |
| Overall cognitive factors[b] | | | | | 0.024 [0.068] | −0.110 to 0.158 | 0.722 | 0.002 [0.070] | −0.135 to 0.138 | 0.983 |
| Factor 1 | −0.035 (0.993) | 0.100 (1.125) | −0.002 (1.194) | 0.076 (0.947) | −0.002 [0.152] | −0.301 to 0.298 | 0.992 | −0.023 [0.152] | −0.322 to 0.276 | 0.879 |
| Factor 2 | −0.005 (1.252) | 0.117 (1.204) | −0.075 (1.236) | 0.134 (1.072) | 0.137 [0.152] | −0.162 to 0.437 | 0.368 | 0.116 [0.152] | −0.183 to 0.415 | 0.448 |
| Factor 3 | 0.025 (0.935) | −0.025 (0.905) | 0.096 (0.734) | −0.048 (1.081) | −0.115 [0.152] | −0.414 to 0.185 | 0.452 | −0.138 [0.152] | −0.437 to 0.161 | 0.365 |
| Factor 4 | 0.054 (1.065) | −0.002 (0.917) | −0.068 (1.080) | 0.081 (1.016) | 0.182 [0.152] | −0.118 to 0.481 | 0.234 | 0.158 [0.152] | −0.141 to 0.457 | 0.299 |
| Factor 5 | 0.042 (1.096) | −0.069 (1.107) | 0.087 (1.050) | −0.061 (1.062) | −0.081 [0.152] | −0.381 to 0.218 | 0.594 | −0.105 [0.152] | −0.404 to 0.194 | 0.490 |
| MoCA | 26.0 (2.3) | 26.4 (1.9) | 26.0 (2.2) | 26.2 (2.3) | 0.04 [0.35] | −0.66 to 0.74 | 0.918 | −0.10 [0.35] | −0.78 to 0.59 | 0.781 |

Abbreviations: CFQ = Cognitive Failures Questionnaire; inf. = informant version; MoCA = Montreal Cognitive Assessment; PD-CFRS = Parkinson's disease – Cognitive Functional Rating Scale; ToL = Tower of London.

[a] Corrected for age, sex and education in years.
[b] Positive estimates indicate effects in favor of CT.
[c] Negative estimates indicate effects in favor of CT.
[d] Reaction time of correct responses.
[e] Model additionally corrected for credibility/expectancy questionnaire score.

severe cognitive impairments by using previously reported screening criteria on the MoCA for PD-D [12], still a substantial proportion of patients showed cognitive deficits associated with PD-D after applying the more elaborate diagnostic criteria. Lastly, we used the ToL as primary outcome and – although executive function that is measured with the ToL task is the most often reported (subjective) cognitive impairment related to PD – this task focuses on only one of the cognitive domains that can be affected by PD. Importantly, participants underwent short- and long-term extensive neuropsychological assessments that encompassed the *full* spectrum of cognitive function, thereby conforming to the MDS Task Force guidelines [15,16], with additional assessment of motor and non-motor symptoms. A major strength of our study was the randomized, double-blind controlled trial design with an adaptive CT with excellent intervention compliance and study protocol adherence. We performed a prospectively registered study, designed based on recommendations of earlier reviews [7,32].

## 8. Conclusions

This randomized, double-blind controlled trial in a large sample of patients with PD showed that multi-domain CT did not improve accuracy on an executive function measure (primary outcome) or subjective cognitive complaints. We found tentative effects of CT on processing speed during executive functioning. The intervention was suitable for

patients with PD considering the high compliance, and participants showed large improvement on the training tasks. In its present form, however, eight-week computerized CT does not seem clinically applicable due to the subtle and targeted improvement with no translation to everyday function. Future studies may investigate personalized or ecologically valid, multi-modal intervention methods to achieve clinically meaningful and lasting effects.

## Authors' roles

1) Research project: A. Conception: TvB, HB, YvdW, RH, TB, OvdH, CV; B. Organization: TvB, HB, YvdW, OvdH, CV; C. Execution: TvB, OvdH, CV.
2) Statistical Analysis: A. Design: TvB, HB, YvdW, JT, CP, AH, OvdH, CV; B. Execution: TvB, CV; C. Review and Critique: TvB, HB, YvdW, JT, CP, AH, OvdH, CV.
3) Manuscript: A. Writing of the first draft: TvB, OvdH, CV; B. Review and Critique: TvB, HB, YvdW, JT, CP, AH, RH, TB, OvdH, CV.

All authors approved the final version of the article.

## Data availability statement

The data used in the analyses described in this paper are available upon reasonable request.

## Declaration of competing interest

None.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2022.02.018.

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