The effects of online cognitive activity on subjective and objective cognitive functioning in patients with Parkinson's disease

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Abstract

Introduction: The aim of this study was to determine efficacy of a cognitive training (CT) intervention. We investigated whether CT improved objective (neuropsychological tasks) and subjective (self-perceived) cognitive functioning in 19 Parkinson's disease (PD) patients. Furthermore, we investigated whether specific cognitive domains or neuropsychiatric measures showed an association with subjective cognitive complaints (SCCs). **Methods:** During eight weeks, participants completed three 45-minute training sessions a week. Pre- and post-intervention performance and SCCs were compared. **Results**: The intervention did not reduce SCCs. Objective task performance improved on three out of six neuropsychological tests (fluency, attention and verbal episodic memory). The results demonstrated a positive relationship between neuropsychiatric measures and SCCs. **Discussion:** Several objective outcome measures pointed in a positive direction. However, since this was a pilot study, we only investigated a small sample. CT may be a valuable tool in managing cognitive decline in PD, but RCTs in larger patient groups are required.

Keywords: Parkinson's Disease, cognitive deficits, cognitive training, subjective cognitive complaints, objective cognitive functioning.

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Introduction

Idiopathic Parkinson's disease (PD) is a progressive neurodegenerative disease. Rigidity, bradykinesia, tremor at rest and postural instability are considered its cardinal motor features (Jankovic, 2008). Motor symptoms are accompanied by a broad spectrum of non-motor symptoms. These include cognitive and neuropsychiatric disorders, sleep disorders, sensory symptoms and autonomic dysfunction (Jankovic, 2008). The progressive course of the disease and the decline in functional ability over time has a negative influence on daily life and well-being of PD patients and their families. PD is the second-most common neurodegenerative disease in the Netherlands, following Alzheimer's Disease (AD) (De Lau & Breteler, 2006). PD incidence increases steadily with age. Because of the proportional increase of the ageing population, the number of individuals diagnosed with PD is expected to have doubled by 2030 (Dorsey *et al.,* 2007).

Cognitive impairment is recognized as a common feature of PD (Leverenz *et al.,* 2010). Several previous studies reported that especially cognitive and affective disorders negatively influence quality of life (QoL; Klepac, Trkulja, Relja & Babic, 2008). Even a mild reduction in cognitive performance is associated with significantly more neuropsychiatric symptoms and greater disability (Verbaan *et al.,* 2007; Weintraub, Moberg, Duda, Katz & Stern, 2004). In 24% of PD patients, cognitive impairments already coincide with the diagnosis (Muslimović, Post, Speelman & Schmand, 2005). The prevalence of dementia in PD is up to six times higher than in the general population. It is estimated that at least 75% will eventually develop Parkinson's dementia (Aarsland & Kurz, 2010). Cognitive decline in PD is characterized by deficits in the domain of EF (Bosboom, Stoffers & Wolters, 2004). Several executive skills such as planning, problem solving, attentional shifting, verbal fluency and diminished inhibitory functioning are frequently impaired in this patient group (Robbins & Cools, 2014). Furthermore, deficits in attention, working memory (WM), speed of information processing, visuospatial abilities and memory are prominent in PD patients (Muslimović *et al.,* 2005; Bosboom *et al.,* 2004). The frequency of impairment across different cognitive domains is displayed in figure 1.

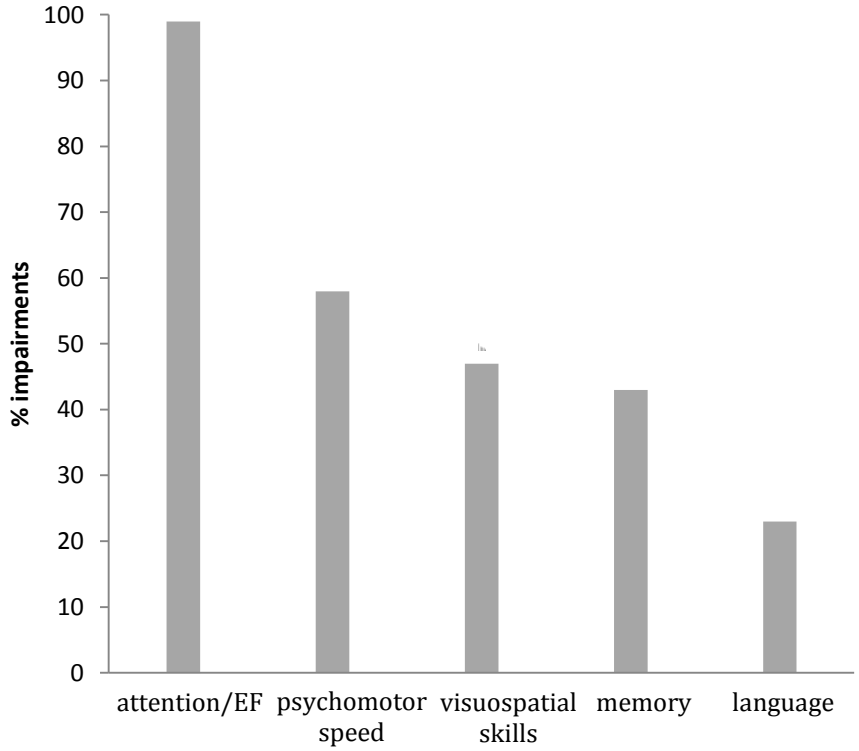

Figure 1. Frequency of cognitive deficits within a group of cognitively impaired PD patients. Adapted from "Cognitive profile of patients with newly diagnosed Parkinson disease", by D. Muslimović, 2005, *Neurology*, 65(8), 1242. Copyright (2005) by AAN Enterprises.

Although several symptomatic therapies alleviate motor symptoms, no current pharmacological intervention is sufficiently efficacious in alleviating cognitive impairments and preventing further cognitive deterioration (Connolly & Lang, 2014). As PD progresses, different cognitive problems insensitive to dopaminergic medication arise due to degeneration of non-dopaminergic systems (Kehagia, Barker & Robbins, 2010; Robbins & Cools, 2014). As cognitive impairment severely affects QoL, development of a therapy is highly necessary. In recent years, there has been an increasing interest in non-pharmacological interventions, such as cognitive training (CT) programs.

The core premise of CT is based on the principle of neuroplasticity – the ability of the brain to restructure itself to adapt to changing circumstances. There are two categories of CT (Sitzer, Twamley & Jeste, 2006). Compensatory strategies aim at overcoming cognitive deficits by learning new ways to accomplish tasks. Restorative strategies focus on improving or maintaining performance in a specific cognitive domain by intensive training of an isolated underlying skill. A meta-analysis of Sitzer et al. (2006) showed that in AD, restorative training yielded larger effects on cognitive functioning than compensatory training. Restorative CT intervention programs were shown to be beneficial in healthy older adults (Rebok *et al.,* 2014),

schizophrenia (Cavallaro *et al.,* 2009), traumatic brain injury (TBI; Cicerone *et al.,* 2011), AD (Olazarán *et al.,* 2010) and mild cognitive impairment (MCI; Simon, Yokomizo & Bottino, 2012). A growing number of studies assessed the effects of CT in PD patients. According to a meta-analysis by Leung et al. (2015), CT interventions appear valuable in PD treatment. Moderate to large effect sizes were found on measures of EF, WM and processing speed. However, the overall effect of CT on cognition was small. These findings are in line with a previous systematic review by Hindle, Petrelli, Clare & Kalbe (2013). According to this review, several CT interventions significantly improved cognitive performance, particularly for EFs. Nonetheless, the authors emphasize the urgent need for methodologically sound randomized controlled trials (RCTs), because many of the reviewed studies lacked power and active control conditions. Petrelli et al. (2015) investigated the long-term effects of CT. PD patients who took part in a CT program retained similar levels of cognitive functioning at 12-month follow-up, whereas patients in the control condition showed a significant decline in cognitive functioning and were three times more likely to develop MCI during this period. Despite the small sample size of this study, these findings rise hope that CT reduces cognitive decline in the long term and might even have the potential to delay PD dementia onset.

As mentioned above, CT yielded positive effects on objective measures of cognitive performance. Another way to determine efficacy of CT, is to look at the effect on subjective measures. According to a study of Dujardin et al. (2010), approximately one out of three PD patients complains about subjective cognitive difficulties. However, there seems to be a discrepancy between self-reported cognitive problems, commonly referred to as subjective cognitive complaints (SCCs), and objective cognitive impairment. This relation varies between studies and is not always reported (Stewart, 2012). Previous studies suggest that other factors may also influence subjective cognitive functioning. Marino et al. (2009) reported that, in neurological patients and healthy volunteers, subjective cognitive performance was more related to mood and personality traits than objective performance. Dujardin et al. (2010) found that PD patients with and without SCCs, performed equally on an extensive neuropsychological (NP) assessment. However, patients with more SCCs expressed more depressive symptoms. Furthermore, fatigue also seems to influence subjective cognitive performance. This is found in Multiple Sclerosis (MS) (Kinsinger, Lattie & More, 2010) and breast cancer (Pullens, Vries & Roukema, 2010), two clinical conditions where fatigue is highly prevalent. We found no literature on the relationship between fatigue and SCCs in PD. However, since a lot of PD patients experience fatigue as well, the same may be true for PD. The above suggests that psychological factors and fatigue might influence the subjective perception of cognitive performance. Current research on the effects of CT on these factors is limited and lacks power due to small sample sizes. To the best of our knowledge, recent studies did not demonstrate an

effect of CT on QoL, depression or anxiety. Additionally, earlier reviews did not find such an effect (Hindle *et al.,* 2013; Leung *et al.,* 2015). Further research is necessary to investigate the ecological validity of CT, as translation of the effects into everyday function is of great importance for patients.

The main objective of the present study is to determine efficacy of a computer-based cognitive intervention in PD patients. This intervention focusses on training of EFs, since this domain is known to be impaired in PD and impairments often occur already in the early stages of the disease (Bosboom *et al.,* 2004; Muslimović *et al.,* 2005). The intervention is aimed at improving cognitive function in daily life. Therefore, we primarily focus on training-induced improvement of subjective cognitive functioning. We hypothesize that this intervention will lead to a decrease in SCCs. As self-perception of patients regarding their cognitive abilities does not always match objective task performance, it will also be investigated whether this intervention has an effect on objective cognitive functioning, This will be measured with NP tasks for specific cognitive domains, with focus on EF. CT used as an intervention method has yielded positive effects on cognitive functioning in various neurological conditions, including PD (Cavallaro *et al.,* 2009; Cicerone *et al.,* 2011; Olazarán *et al.,* 2010; Simon *et al.,* 2012; Hindle *et al.,* 2013; Paris *et al.,* 2011). Therefore, we expect that this intervention will improve EF. Since this is a pilot study, we also want to explore whether the intervention has an effect on other cognitive domains (attention, episodic memory and WM). To optimize the intervention to the specific needs of PD patients, it will be investigated which factors (objective test scores and neuropsychiatric measures) show an association with SCCs at baseline. Since depressive symptoms and fatigue seem to influence subjective perception of cognitive functioning in various neurological conditions (Marino *et al.,* 2009; Dujardin *et al.,* 2010; Kinsinger *et al.,* 2010; Pullens *et al.,* 2010)), we expect to demonstrate a relationship between subjective cognitive functioning and neuropsychiatric symptoms. We also hypothesize that dysfunction on different cognitive domains will vary in its contribution to the experience of SCCs. To our knowledge, this has not been studied earlier in PD patients. Furthermore, we will assess the association between improvement in subjective cognitive functioning and improvement on NP or neuropsychiatric measures (fatigue and depressive symptoms).

Material and methods

Subjects

The study population comprised 19 idiopathic PD patients. Patients were recruited between January 2016 and January 2017 through (1) the movement disorders outpatient clinic and Centre Neuropsychiatry Parkinson of the VU University Medical Center (VUmc) and (2) advertisements in Parkinson Magazine and the website of the *Dutch Parkinson Association.* To be eligible for inclusion, participants were required to have (1) a clinical diagnosis of idiopathic PD according to the United Kingdom Parkinson's Disease Society Brain Bank criteria (Hughes, Daniel, Kilford & Lees, 1992), (2) objectified cognitive dysfunction (30 ≤ *t*-scores ≤ 43) on at least one EF task (see data analysis for *t*-score explanation), (3) access to a computer with internet and the ability to use a keyboard and mouse, (4) Hoehn & Yahr stadium <4 and stable on dopaminergic therapy, (5) age between 50 and 70 years old and (6) a SAGE score between 14 and 21 (15 ≤ SAGE score ≤ 20). Exclusion criteria were the following: (1) TBI with *contusio cerebri*, (2) drug- or alcohol abuse, (3) patients who were not able to undergo a NP assessment or computer-based intervention, (4) a psychiatric disorder, (5) psychotic symptoms, screened with a Questionnaire for Psychotic Experiences (QPE), except for benign hallucinations, (6), a Montreal Cognitive Assessment score (MoCA) <24, which indicates dementia. For an overview of the screening procedure, see figure 1. Written informed consent form was obtained from all participants. This project was approved by the Medical Ethical Committee (METc) of the VUmc.

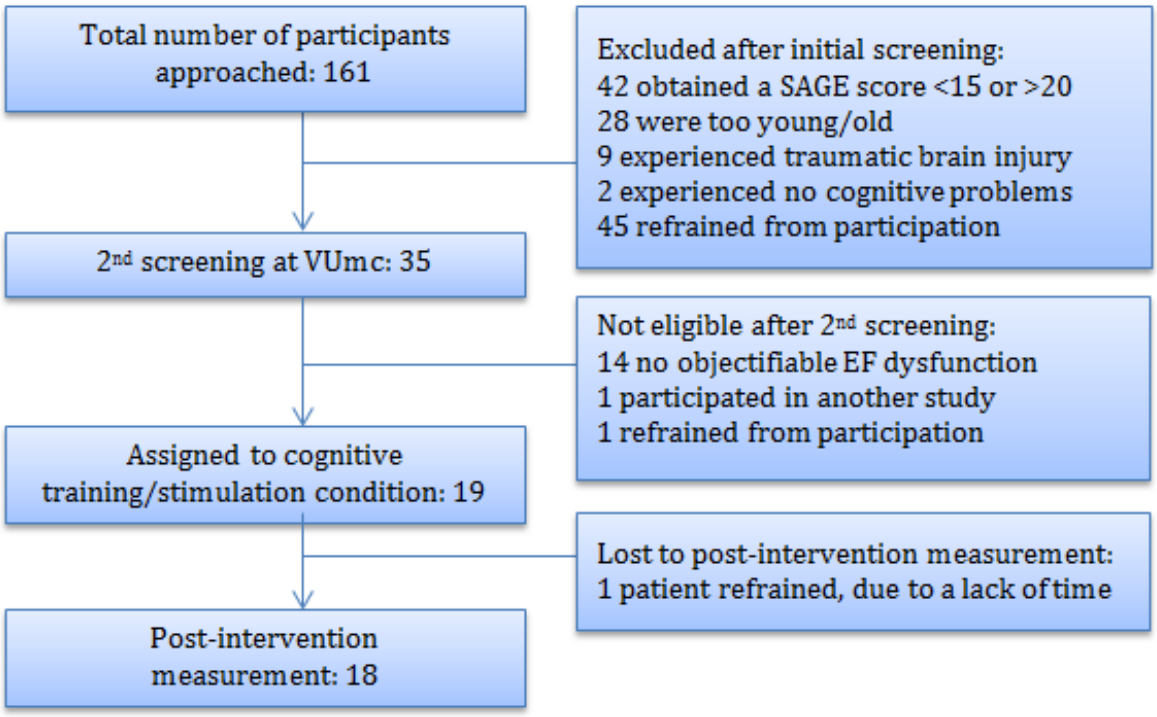

Figure 1. Flowchart of participation in the Online Cognitive Training Study in PD patients

Measurements

Motor symptoms and disease stage. Information about onset of initial symptoms, year of diagnosis and medication was obtained from all of the participants. To evaluate motor symptom severity, the Unified Parkinson's Disease Rating Scale, motor score (UPDRS)-III (Fahn & Elton, 1987) was used. During this clinical examination motor manifestations of PD were rated, including tremor, rigidity, bradykinesia, speech, facial expression, gait and postural instability. Disease stage was assessed using the modified Hoehn & Yahr rating scale (see Appendix 1; Hoehn & Yahr, 1967).

Clinical measures. The Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock & Erbaugh, 1961) was administered to assess severity of depression symptomatology. Scores range from 0 to 63; higher scores indicate greater depression severity. A score of ≥ 15 indicates clinically relevant depressive symptoms in PD patients (Visser, Leentjens, Marinus, Stiggelbout & van Hilten, 2006). The Fatigue Severity Scale (FSS; Krupp, LaRocca, Muir-Nash & Steinberg, 1989) is a 7-item self-report questionnaire to assess severity of disease related fatigue. Higher scores represent more severe fatigue. The QPE was used to rule out psychosis. This is a structured interview on delusions and hallucinations in different modalities.

Subjective cognitive functioning. The Cognitive Failure Questionnaire (CFQ; Broadbent, Cooper, FitzGerald & Parkes, 1982) is designed to assess self-reported cognitive failure in memory, attention and motor function. This questionnaire was used as a measure of subjective cognitive functioning.

Objective cognitive functioning. The Self-administered Gerocognitive Examination (SAGE) (Scharre et al., 2010) was used as an initial screening instrument for mild cognitive deficits. The MoCA was used as a second NP screening, to rule out severe cognitive impairment (Nasreddine *et al.,* 2005). Higher scores on both the SAGE and the MoCA indicate better cognitive performance. Objective cognitive functioning before and after training was assessed as a secondary outcome measure. A battery of NP tasks was administered to the participants, to examine functioning of several cognitive domains. For an overview of all measurement instruments, see table 2.

Table 2. *Overview of the measurement instruments*

Variable	*Measurement instrument*
Motor symptoms	*UPDRS-III*
Disease stage	*Hoehn & Yahr*
Clinical measures	
Depressive symptoms	*Beck Depression Inventory*
Psychotic symptoms	*Questionnaire for Psychotic Experiences*
Fatigue	*Fatigue Severity Scale*
Objective cognitive functioning	
Cognitive screening	*Self-administered Gerocognitive Examination* *Montreal Cognitive assessment*
Executive functioning	
- Mental flexibility	*Trail Making Task -* *part B completion time corrected for part A completion time (Reitan & Wolfson, 1985)*
- Interference susceptibility	*Stroop Color Word Task –* *card III completion time corrected for part II completion time (Hammes, 1971)*
- Verbal fluency	*Letterfluency –* *total number of correctly named words with a specific initial (Schmand, Groenink & van den Dungen, 2008)*
Attention	*WAIS-III digit span forwards –* *total number of correct responses (Wechsler, 2000)*
Working memory	*WAIS-III digit span backwards –* *total number of correct responses (Wechsler, 2000)*
Verbal episodic memory	*15-Word Test –* *total number of correctly retrieved words after 15-minute interval (Saan & Deelman, 1986)*
Subjective cognitive functioning	
Self-reported	*Cognitive Failure Questionnaire*

Procedure

The participants were informed about the study and were asked to sign an informed consent form for a pre-screening at home. The exclusion criteria (TBI, drug- or alcohol abuse, psychiatric disorder) were further checked by phone. Eligible patients were invited to the VUmc for a final screening and intake. Before the intake and intervention participants were asked to sign

informed consent. Subsequently, a second screening was performed to check for mild executive dysfunction (Trail Making Task (TMT), Stroop Color Word Task (SCWT), letterfluency), indication for dementia (MoCA), motor symptom severity (UPDRS-III) and psychotic symptoms (QPE). Participants who met the inclusion criteria proceeded to the pre-intervention measurement (T0). This comprised a NP assessment, conducted by a neuropsychologist or a trained neuropsychology undergraduate, and several questionnaires on SCCs and neuropsychiatric symptoms. The tasks were performed in a fixed order during a time period of 1,5 hour. After T0, participants were randomly assigned to either the *cognitive stimulation* condition (active control condition) or the *cognitive training* condition (experimental condition), stratified by educational level, according to Verhage (1964). The intervention phase started with a brief explanation of either the training or the cognitive stimulation program. This explanation was given by a non-blinded research coordinator. Over the course of eight weeks, participants completed three 45-minute training sessions a week at home. Every week participants were contacted to evaluate progression and answer potential questions. Directly after finishing the training, participants were invited for a post-intervention measurement (T1) in order to evaluate the effects of the intervention. This measurement included another NP assessment (using parallel versions if possible to minimize learning effects), questionnaires on subjective cognitive functioning, questionnaires on neuropsychiatric symptoms and an evaluation of the training program. An overview of the design of the study is depicted in Figure 2. All NP assessments were carried out in clinical offices at the institute or at the subjects' home, if participants were unable to travel to the hospital. PD patients may experience fluctuations in response to medication; motor symptoms oscillate between "off" phases (decreased mobility) and "on" phases (good response to medication and controlled motor symptoms) (Marsden & Parkes, 1976). The evaluations were, if possible, performed during the "on" phase of the medication cycle. Patients were advised to perform the training sessions when they felt most comfortable.

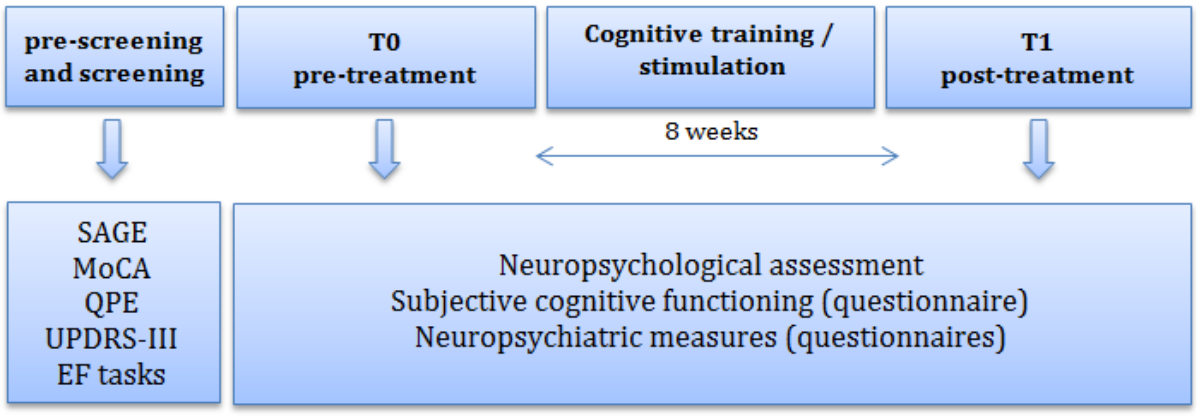

Figure 2. Design of the study.

Intervention

Both intervention methods were performed in an online computer program adapted specifically for PD-related cognitive complaints; *BrainGymmer*. Each training session, participants performed a fixed sequence of cognitive tasks in a challenging game setting. Adherence was monitored and task performance was saved using automatic data upload after each session. Participants in the experimental and the control condition were administered different types of training. For a detailed description of both intervention types, see Appendix 2. This study is part of an overarching project, in which the two intervention types will be compared. Given that the intervention is still in progress, we were not allowed to unblind the data. So, as a first step, it was examined whether being cognitively active in itself had an effect on subjective and objective cognitive functioning in the total sample.

Statistical analysis

The Shapiro-Wilk test was used to assess normality, for all variables. The Shapiro-Wilk test suggested that all variables were approximately normally distributed. However, visual inspection of the data (normal Q-Q plot, histogram and boxplot) carried out that most variables were not normally distributed. Therefore, we analysed the CFQ, BDI, FSS and *t*-scores with non-parametric tests. The change in subjective cognitive functioning, assessed with the CFQ, was used as a primary outcome measure. The Wilcoxon signed-rank test (two-tailed) was used to determine whether there was a statistically significant mean difference between total CFQ score before and after the intervention. NP task scores were converted to *t*-scores, which have a mean of 50 and a standard deviation of 10. These standardized scores are used to correct test scores for the effects of age, gender and education and are based on mean scores obtained by Dutch norm groups (Schmand, Houx & De Koning, 2012). A *t*-score between 30 and 43 (i.e. a below average score) signified mild cognitive impairment. Additional two-tailed Wilcoxon signed-rank tests were performed to determine whether the intervention had an effect on the secondary outcome measures; objective cognitive functioning on several cognitive domains (i.e. EF, attention, episodic memory and WM), measured with NP tasks. The effect sizes of the intervention were calculated using Cohen's D.

To determine which factors are related to SCCs, Spearman's rank correlations were conducted. Missing BDI, CFQ and FSS items were imputed using the average score of valid questionnaire items if 16.7% or less of the items were missing. The relationship between CFQ scores and clinical measures (total BDI and FSS scores) at baseline was assessed. We further investigated correlations between baseline CFQ scores and baseline objective cognitive functioning on various domains (EF, episodic memory, attention and WM), using the *t*-scores on the TMT, SCWT, letterfluency, 15-WT, WAIS-III digit span forwards and backwards respectively.

Spearman correlations were also conducted with uncorrected test scores (i.e. not corrected for age, gender and education). This was done to ensure that a possible effect found is not due to the fact that the BDI and FSS were not corrected for these variables, and the *t*-scores were.

Furthermore, raw pre- and post-measurement data were transformed into change scores. These were expressed in percentages, for better comparison of the results. For the CFQ, BDI and FSS, better intervention response is indicated by negative (at or below zero) percentage change scores. For NP variables (*t*-scores), better intervention response is indicated by positive (at or above zero) percentage change scores, which indicated stable or improved performance after the intervention. Correlations between CFQ percentage change scores and the difference in objective cognitive functioning (*t*-scores) and clinical measures (BDI and FSS percentage change scores) were assessed. The statistical threshold was set at $p < 0.05$. Statistical analyses were performed using IBM SPSS statistics version 22 (Chicago, Il, USA).

Results

Baseline descriptive sample characteristics

The final sample consisted of 19 PD patients (mean age: 62.05; male: 73.7%; H&Y median: stage 2.5). Demographic and clinical data are presented in table 3. In 3 patients, a missing item was estimated by imputation. This comprised one item on the UPDRS, BDI and CFQ.

Table 3. *Demographic and clinical characteristics at baseline of Parkinson disease patients*

Variable	*N/mean/median*	*SD*	*range*
n	19		
Gender (male/female), n	14/5		
Age, mean	62.05	6.01	53-70
Verhage score, median	6		5-7
UPDRS motor section, mean	20.29	7.19	9-36
Hoehn & Yahr, median	2.5		2-3
Montreal Cognitive Assessment , mean	26.21	1.78	24-29
Beck Depression Inventory, mean	9.22	4.65	3-22

Training effects on SCCs

The Wilcoxon Signed-Ranks Test indicated that post-intervention CFQ scores (Mdn = 38) did not significantly differ from pre-intervention CFQ scores (Mdn = 39), $z = -.501$, $p = .632$. An overview of pre- and post-intervention CFQ scores is provided in figure 6, for each participant. The overall average score remained approximately equal before and after the intervention. However, the majority of the participants had lower post-intervention CFQ scores, indicating less SCCs (black

lines). A number of participants had considerably increased CFQ scores (blue lines). This seems to cause the stable median CFQ score. We explored possible differences between patients that improved on SCCs and patients who did not. Table 4 shows that there were no significant differences on clinical characteristics between the groups.

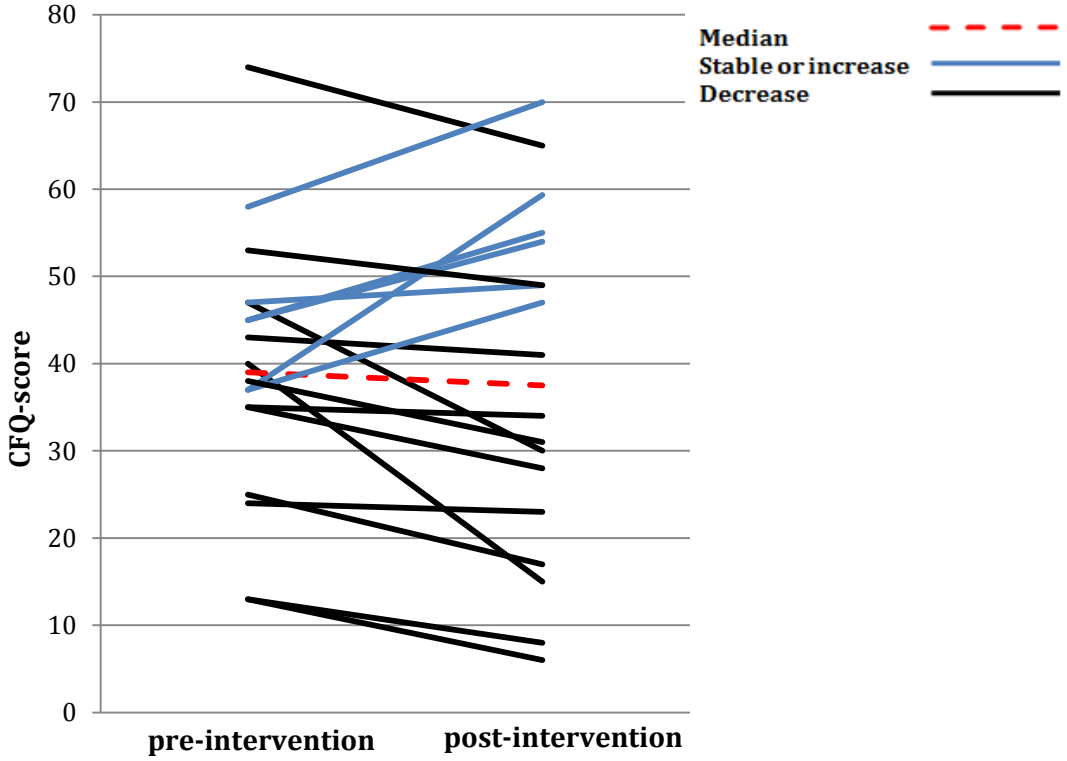

Figure 6. Pre- and post-intervention CFQ scores for each participant.

Table 4. *Comparison between CFQ increase and CFQ decrease group.*

Variable	CFQ increase	CFQ decrease	*P*-value
n	6	12	
Gender (male/female), n	4/2	9/3	.710[a]
Age, median	59.5	66.5	.291[b]
Verhage score, median	6	5	.682[b]
UPDRS motor section, median	17.27	21.5	.250[b]
Hoehn & Yahr, median	2.25	2.5	.755[a]
Montreal Cognitive Assessment, median	25	26.5	.682[b]
Beck Depression Inventory T0, median	8.5	8	.553[b]
Beck Depression Inventory T1, median	11	6.5	.083[b]

[a] Group differences were tested with the two-sided chi-square test

[b] Group differences were tested with the independent samples Mann-Whitney U Test

Training effects on objective cognitive functioning – EF tasks

A Wilcoxon Signed-Ranks Test revealed a statistically significant increase in letterfluency *t*-scores following the intervention, $z = -3.555$, $p < .001$, with a moderate effect size ($r = .59$). The median *t*-score increased from pre-intervention (Mdn = 36) to post-intervention (Mdn = 44). There was an overall increase in letterfluency *t*-scores of 25% after the intervention. Post-intervention TMT *t*-scores (Mdn = 48) were not statistically significant higher than baseline TMT *t*-scores (Mdn = 46), $z = -.071$, $p = .954$ (3% increase). Also, post-intervention SCWT *t*-scores (Mdn = 54) were not significantly higher than baseline SCWT *t*-scores (Mdn = 52), $z = -1.504$, $p = .139$ (1% increase). The individual pre- and post-intervention *t*-scores are displayed in figure 7 and 8 for the letterfluency, TMT and SCWT respectively.

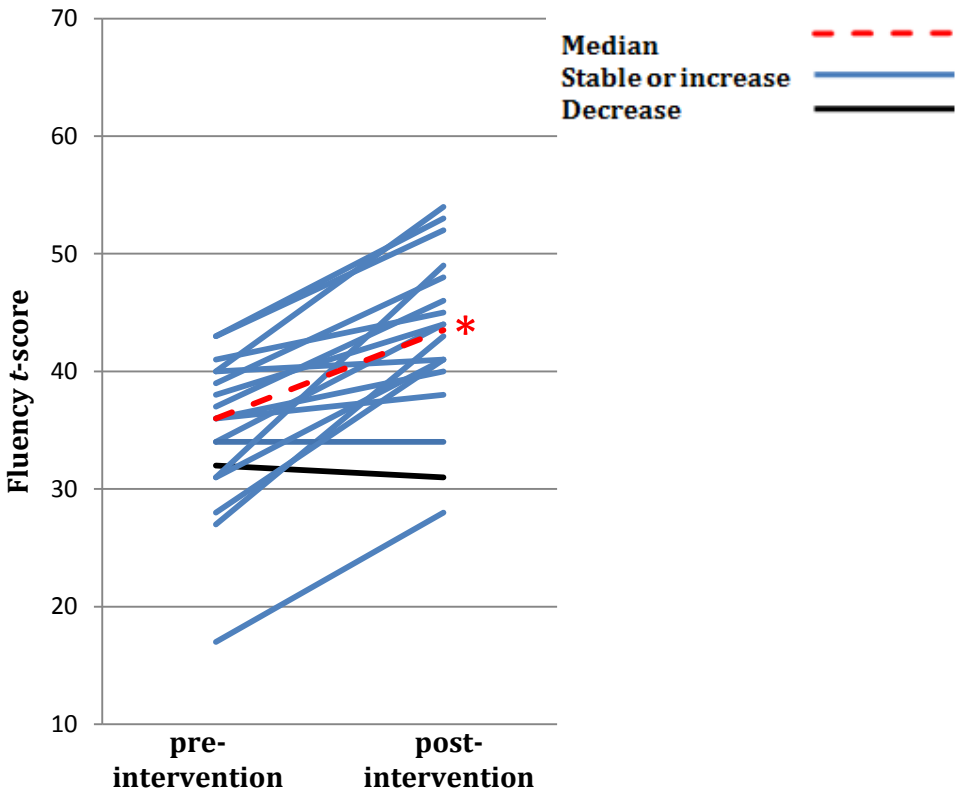

Figure 7. Pre- and post-intervention letterfluency *t*-score for each participant.

* Significant at the .001 level

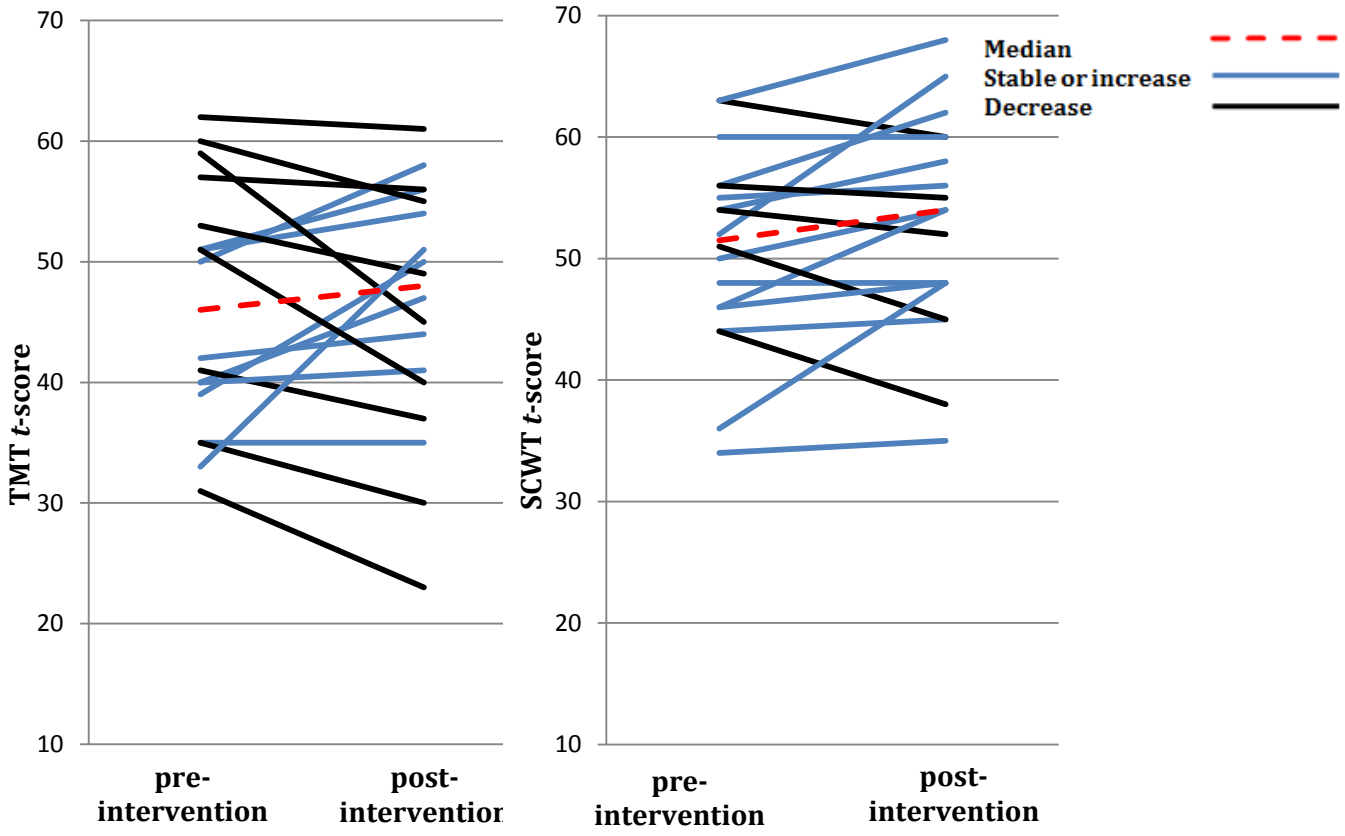

Figure 8. Pre- and post-intervention TMT and SCWT *t*-score for each participant.

Attention, working memory and verbal episodic memory

Figure 11, 12 and 13 in appendix 3 present an overview of the individual pre- and post-intervention scores on the remaining NP tasks. Post-intervention WAIS-III digit span forwards *t*-scores (Mdn = 34), a measure of attention, were significantly higher than baseline *t*-scores (Mdn = 31), z = -2.618, p < .050, with a moderate effect size (r = .45). There was an overall increase of 15%. The median WAIS-III digit span backwards *t*-score, a measure of WM, decreased from pre-intervention (Mdn = 52) to post-intervention (Mdn = 48). However, the overall decrease of -5% was non-significant, z = -1.569, p = .122. Post-intervention 15-WT *t*-scores (Mdn = 40), a measure of verbal episodic memory, were significantly higher than baseline *t*-scores (Mdn = 35), z = -2.110, p < .050, with a small effect size (r = .35). There was an 18% increase in 15-WT *t*-scores after the intervention. A comparison of NP test performance before and after the intervention is shown in table 5.

Table 5. *Cognitive test performance before and after the intervention*

Variable	Baseline Median *t*-score	Post-intervention Median *t*-score	Percentage change scores	P-value, Wilcox-Signed Ranks test
Executive functioning				
Mental flexibility	46	48	3%	$p = .954$
Interference susceptibility	52	54	1%	$p = .139$
Verbal fluency	36	44	25%	$p < .001$
Attention	31	34	15%	$p < .050$
Working memory	52	48	-5%	$p = .122$
Verbal episodic memory	35	40	18%	$p < .050$

Baseline correlations - CFQ and neuropsychiatric measures

A Spearman correlation was computed to assess the relationship between CFQ scores and clinical measures (BDI and FSS scores) at baseline. There was a strong, positive significant correlation between CFQ and BDI score, $r(18) = .654$, $p = .002$. There was a moderate, positive significant correlation between CFQ and FSS score, $r(18) = .511$, $p = .025$. The scatterplots in figure 9 summarize the results. Overall, higher CFQ scores were correlated with higher BDI and FSS scores.

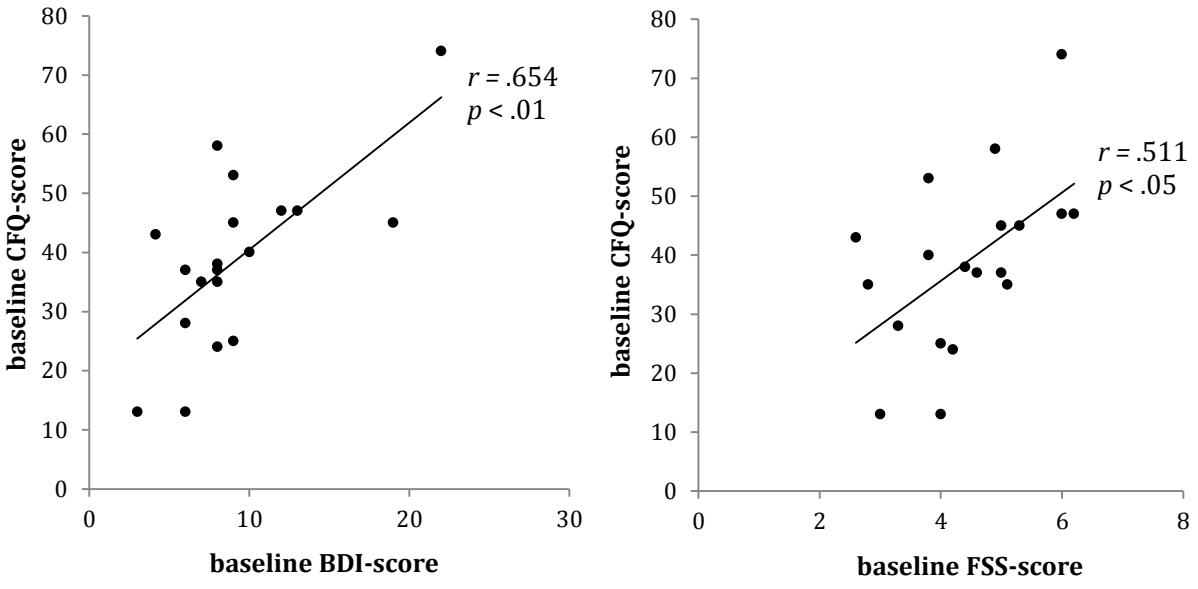

Figure 9. The correlation between baseline CFQ scores and baseline BDI and FSS scores.

Baseline correlations - CFQ and NP task scores

Spearman correlations revealed no significant correlations between CFQ scores and NP task performance. However, there was a weak, negative relationship between CFQ score and SCWT *t*-score: higher CFQ scores – non-significantly – correlated with lower SCWT scores, $r(19) = -.34$, $p = .154$. An overview of all baseline correlations is depicted in table 6. In contrast to NP task scores, BDI and FSS scores were not corrected for the confounding effects of age, gender and education. To ensure that observed correlations between CFQ scores and clinical measures (BDI and FSS score) were not influenced by correcting for these variables, we conducted Spearman correlations on the uncorrected data (i.e. raw test scores) as well. This yielded similar results.

Table 6. *Spearman's rank correlations (rs) between baseline CFQ scores and clinical measures (BDI and FSS score), and CFQ scores and objective cognitive functioning (t-scores)*

Variable	BDI	FSS	TMT	SCWT	fluency	15WT	WAIS-III forwards	WAIS-III backwards
CFQ (N=19)	*rs = .654 P < .01*	*rs = .511 P < .05*	*rs = -.056 P = .820*	*rs = -.341 P = .154*	*rs = -.279 P = .248*	*rs = .186 P = .447*	*rs = .289 P = .230*	*rs = -.010 P = .976*

Abbreviations: CFQ = Cognitive Failure Questionnaire, BDI = Beck Depression Inventory, FSS = Fatigue Severity Scale, TMT = Trail Making Task, SCWT = Stroop Color Word Task, 15WT = 15-Word Test, WAIS = Wechsler Adults Intelligence Scale.

Correlates of SCC change

Subsequently, the relationship between change in subjective cognitive functioning and BDI- and FSS-score change was assessed. Analyses revealed no significant correlations between proportional CFQ score change and proportional BDI- and FSS-score change. However, there was a weak, positive relationship between CFQ score change and BDI score change: improvement in subjective cognitive functioning was – non-significantly – correlated with less depressive symptoms on the BDI, $r(18) = .39$, $p = .170$. Spearman correlations revealed no significant relationship between change in subjective (CFQ percentage change score) and objective cognitive functioning (NP task percentage change scores). Table 7 displays the percentage change score correlations. We observed a moderate, trend-significant relationship between CFQ and WAIS-III forwards percentage change score in the unexpected direction: increased proportional CFQ change scores (i.e. deterioration), correlated with increased proportional WAIS-III forwards change scores (i.e. improvement), $r(18) = .45$, $p = .063$. A scatterplot is displayed in figure 10.

Table 7. *Spearman's rank correlations (rs) between CFQ and BDI/FSS percentage change scores, and CFQ and objective measures percentage change scores*

Variable	BDI	FSS	TMT	SCWT	fluency	15WT	WAIS-III forwards	WAIS-III backwards
CFQ (N=18)	*rs* = .338 *P* = *.170*	*rs* = -.014 *P* = *.955*	*rs* = .022 *P* = *.932*	*rs* = -.171 *P* = *.496*	*rs* = .263 *P* = *.291*	*rs* = .022 *P* = *.932*	*rs* = .448 *P* = *.063*	*rs* = -.198 *P* = *.432*

Abbreviations: BDI = Beck Depression Inventory, FSS = Fatigue Severity Scale, TMT = Trail Making Task, SCWT = Stroop Color Word Task, 15WT = 15-Word Test, WAIS = Wechsler Adults Intelligence Scale.

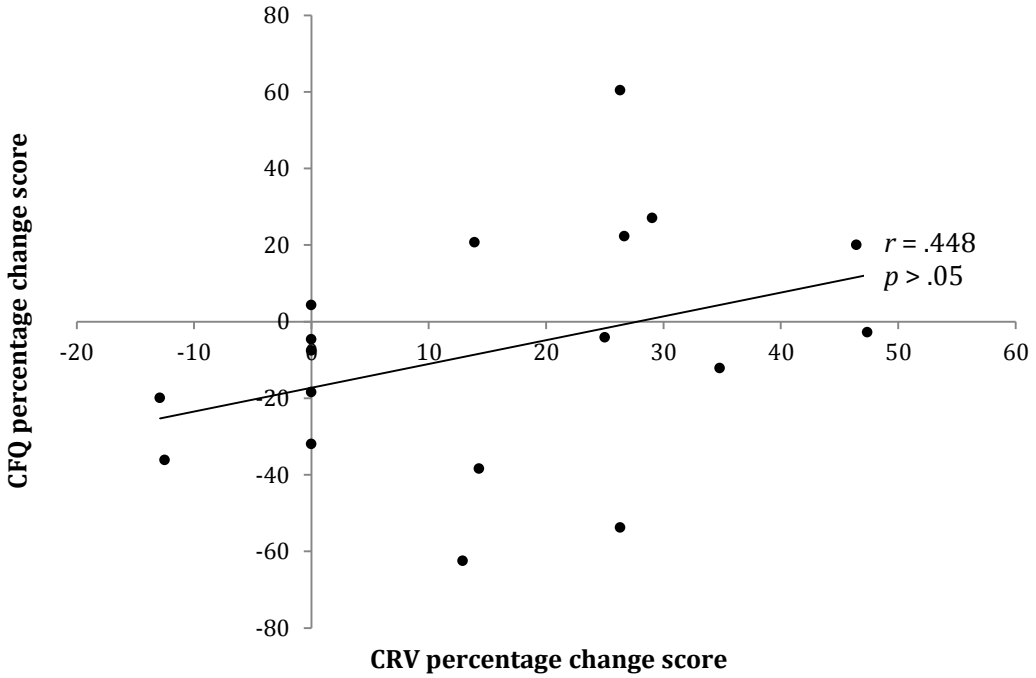

Figure 10. The correlation between proportional CFQ change scores and proportional WAIS-III forwards change scores.

Post-hoc analyses – correlations between BDI/FSS and NP task scores

To assess whether there was a direct relationship between BDI/FSS scores and NP task performance, we computed a Spearman correlation for this variables. These results (see Appendix 4, table 8) show that there were no significant correlations between either BDI/FSS scores and NP task scores.

Discussion

Cognitive dysfunction occurs abundantly in PD (Muslimović *et al.,* 2005), and is one of the most disabling features of the disease (Klepac *et al.,* 2008). Thus far, there is no intervention to slow down the underlying neurodegenerative process of cognitive decline in PD. This study aimed to investigate the possible benefits of cognitive activity on subjective and objective cognitive performance in PD patients, using a CT intervention program. Our study did not show effect of cognitive activity on SCCs. This contradicts our hypothesis that CT would reduce self-perceived cognitive complaints in PD patients. However, improved performance was observed on several objective measures of cognitive functioning. Although we hypothesized that EF in particular would benefit from the intervention, only on the verbal fluency task performance did improve. The intervention additionally improved verbal episodic memory and attention. Consistent with previous research and our hypothesis, a relationship was observed between neuropsychiatric symptoms and SCCs. SCCs could not be attributed to cognitive dysfunction. Furthermore, CFQ score change was not associated with a reduction in fatigue, reduced depressive symptoms and improvements on any of the cognitive tasks.

Subjective cognitive complaints

We found no significant difference in overall CFQ scores pre- and post-intervention. Concerning the individual results, SCCs decreased in the majority of participants. However, six out of 18 patients reported more SCCs following the intervention. Although we found no significant differences in clinical characteristics between the group of patients improving and those declining, there was a trend-significant difference in BDI scores between the groups after training. Patients who experienced more SCCs after training, tended to score higher on the BDI. Mood may have been a confounding factor. An increase in depressive symptoms throughout the training may have led to the experience of more SCCs or vice versa.

A topic to consider is the psychometrics of our subjective functioning outcome measure. No cut-off scores for the CFQ are available, which makes it hard to deduce when scores indicate clinically relevant SCCs. In trials with healthy subjects, participants obtained similar CFQ scores to the PD patients in our study (Wallace, Kass, & Stanny, 2002; Middleton *et al.,* 2006; Preiss, Lukavský, & Steinová, 2010). In a group known to be cognitively impaired, we expected higher scores. Previous reports are inconclusive on the exact constructs measured by the CFQ. Wallace et al. (2002) proposed a four-factor solution, consisting of distractibility, memory lapses, blunders (i.e. social blunders and poor motor control) and forgetting people's names. The CFQ is developed to assess cognitive failures in everyday routine activity. However, in movement disorders, it is sometimes less evident if failures are due to cognitive or motor impairment. It is conceivable that PD patients express more failures on the "blunder" subscale (e.g. "do you bump

into people?" or "do you drop things?"), due to poor motor control. When motor symptoms cause these problems, positive ratings on these items do not represent an actual cognitive problem. Therefore, it is debatable whether this questionnaire is a suitable tool for SCCs in PD patients. The Parkinson's Disease – Cognitive Functional Rating Scale (PD-CFRS, Kulisevsky *et al.,* 2013) is designed for PD specifically. Besides, cut-off scores indicating clinically relevant decline in cognitive functional status are available for this questionnaire. It might be better to add the PD-CFRS as an outcome measure, in order to identify more PD-specific problems. This scale appeared to be a valid and reliable measure of cognitive impairment in PD, sensitive for subtle cognitive changes (Kulisevsky *et al.,* 2013).

Another possible explanation for the absence of a significant effect on SCCs is our study design. The current experiment lacked a follow-up measurement. A longer period of time might be needed for the intervention to take effect on a subjective level. We applied an intervention period comparable to other studies, as reviewed by Leung et al. (2015). These also struggled to demonstrate a transfer of CT improvements into everyday function. Therefore, longer training might be necessary. Transfer effects into everyday life are of major importance for CT to be clinically relevant, but most previous CT studies mainly found improvements in NP task performance Hindle *et al.,* 2013; Leung *et al.,* 2015). However, it has repeatedly been found that physical exercise programs have beneficial effects on both cognitive functioning and instrumental activities of daily living performance (Paillard, Rolland & De Souto Barreto, 2015). Reuter, Mehnert, Sammer, Oechsner and Engelhardt (2012) investigated a multi-modal CT intervention, combined with motor skill training. The authors reported an effect on cognitive performance in daily life of PD patients as well. The above suggests that capabilities to perform domestic tasks benefit more from a multi-modal approach than cognitive training alone.

Objective cognitive performance

Tasks on which patients performed below-average at baseline showed larger training effects compared to those on which patients performed average. A possible explanation is that low pre-treatment scores for these tasks, leave maximal opportunity for a training effect. Some degree of cognitive dysfunction might be required in order to detect cognitive improvement with NP tasks. Alternatively, a phenomenon to take into consideration is regression toward the mean (Barnett, Van Der Pols & Dobson, 2005). This implies that if a pre-intervention score is extreme, the post-intervention score tends to be closer to the average score. However, visual inspection of the pre- and post-measurement figures indicated that this is not a plausible scenario. The tasks with below-average baseline scores showed no clear pattern of regression toward the mean.

As EF is frequently impaired in PD patients, we expected to find more impairment across EF measures. However, EF is associated with impulse control, planning and prioritising, organisation and flexible thinking. Therefore, in this domain specifically, it is conceivable that the somewhat artificial setting in which a NP assessment takes place failed to reflect a real-life situation. The addition of more ecologically valid tests may be a solution. In comparison to standard EF tests, the Behavioral Assessment of the Dysexecutive Syndrome is more sensitive to everyday executive dysfunction (Bennet, Ong & Ponsford, 2005). Furthermore, we expected larger EF improvement, since the emphasis of the training was on this domain. Our finding deviates from other studies, where improvement in EF after CT has repeatedly been found (Hindle *et al.,* 2013; Leung *et al.,* 2015). However, since the baseline scores in our sample on two out of three tasks were already average prior to training, there may have been less room for improvement. Remarkably, all participants except one showed improvement on the letterfluency task. As both the cognitive training and the cognitive activity condition comprised linguistic tasks, this may have led to actual improvement. Harrison, Buxton, Husain and Wise (2002) concluded that the letterfluency task has acceptable levels of test-retest reliability and is appropriate for use in repeated measurement studies. Still, this result must be interpreted cautiously, whereas the best measure to eliminate a practicing effect is a control group, which this study lacked. Also, significant improvement on our attention measure could have influenced the fluency results. NP task performance generally relies on multiple areas of cognition, instead of single domains. The letterfluency task measures, apart from EF, difficulties in word retrieval, speed, WM and attention (Rosen, 1980). In our sample, 16 of 18 patients showed improved attention which may have automatically lead to improved verbal fluency.

Baseline and change score correlations

Psychological factors appear important contributors to the experience of SCCs. In our study, patients who experienced more fatigue and depressive symptoms tended to report more SCCs. Contrary, we found no significant relationship between objective cognitive functioning and SCCs. This agrees with several studies that demonstrated a limited relationship between subjectively perceived and objectively measured cognitive performance (Middleton *et al.,* 2006; Marino *et al.,* 2009; Slavin *et al.,* 2010). Thus, SCCs seem to reflect mood and psychological state, rather than actual cognitive performance. This would also provide a possible explanation for the increased CFQ scores after training in some participants. If patients were fatigued or in a negative mood during the post-measurement, they may have been more likely to report SCCs. In that case, we would also expect a relationship between BDI and SCC change scores. This was indeed found, although non-significantly.

Limitations

Several limitations should be taken into account when interpreting the results. A major study limitation was the absence of a control group. As not all patients completed the intervention, it was not allowed to unblind the data by the time this report was written. Therefore, the cognitive training- and activity group were analysed as one group. Stronger effects of CT on subjective and objective cognitive functioning may appear when both groups will be analysed separately. A control condition is also important in order to control for test-retest effects. The current experiment is also hampered by its small sample size. However, CT intervention studies reviewed by Hindle et al. (2013) generally used similar sample populations and many still reported positive results. Finally, the fact that training sessions were fulfilled at home made it harder to judge how devoted patients performed their training. Although this is beyond control with the current design, the high compliance, the small number of drop-outs and patient's positive evaluations allow the conclusion that patients were sufficiently motivated.

Future research

First, for future research it might be interesting to further explore differential clinical characteristics and baseline task performance between patients who improve after the intervention and those who do not. Our results indicate that lower baseline scores leave more room for improvement. Patient characteristics at baseline may predict the potential benefit of the intervention. Secondly, it would be interesting to compare a CT intervention group to a control group without any training. Cognitive performance could then be assessed at 1- or 2-year follow-up. In the present study, not all participants improved on NP tasks. However, patients may maintain a similar level of cognitive functioning over a longer period of time due to training. CT could prove to be of vital importance if cognitive decline could be delayed. Thirdly, follow-up studies could compare efficacy of domain-focused training sessions (i.e., one specific function is trained every session) versus mixed sessions. A study of Petrelli et al. (2014) reported positive effects of the former variant. Also, the effect of more ecologically relevant training tasks could be investigated. Interventions that explicitly address everyday tasks may yield larger effects on everyday-like activities.

The issue how to evaluate effectiveness of CT is complicated and still needs to be addressed more explicitly in future research. Self-perceived cognitive functioning is not always a reliable measure, since it can be influenced by mood. Therefore, it is desirable to include a hetero-anamnesis by a close relative, to obtain a more objective view. It is conceivable that NP assessments and subjective questionnaires measure different constructs. A NP assessment reflects a subject's abilities to perform structured tasks in a quiet test setting at a specific moment in time. This is not a completely accurate depiction of how patients function in everyday

life, but it provides a controlled and independent view. Subjective measures refer more to a patient's capacities to function and adapt to changing circumstances in the real world. A disadvantage of subjective measures is that these are more likely to be influenced by for instance mood or placebo effects. However, the most important outcome for patients is that CT eventually leads to noticeable changes in daily life. For future research, we would recommend to evaluate effectiveness of CT with a core set of outcome measures, that comprises both objective and subjective measures. This combination is essential to obtain a comprehensive impression of cognitive functioning.

Conclusions

The cognitive intervention yielded – marginal – positive results, although the sample size was limited. CT was mainly effective in improving performance on tasks with below average baseline scores. This suggests that there has to be some decline in cognitive functioning in order for CT to be effective. Furthermore, our intervention has not produced the expected effect on subjective cognitive functioning. However, high compliance to the intervention and positive feasibility ratings are promising. The observed relationship between neuropsychiatric symptoms and SCCs suggests that it is important to address psychological well-being as well. The concept of CT remains worth investigating, but RCTs in larger patient groups are required. CT may be beneficial for PD patients and would be a cost-effective, non-invasive and easy to administer intervention to improve cognitive functioning and manage cognitive decline.

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Appendix 1. Stages of the modified Hoehn & Yahr rating scale.

Table 1. *Modified Hoehn &Yahr rating scale*

Stage	*Description*
0	*No signs of Parkinson's Disease*
1	Unilateral involvement only
1.5	Unilateral and axial involvement
2	Bilateral involvement without impairment of balance
2.5	Mild bilateral disease with recovery on pull test
3	Mild to moderate bilateral disease; some postural instability, physically independent
4	Severe disability, still able to walk or stand unassisted
5	Wheelchair bound or bedridden unless aided

Appendix 2. Detailed description of both intervention types.

Cognitive training

This intervention is aimed at training specific cognitive domains known to be impaired in PD. The exercises are designed to improve EF, attention, memory and speed of information processing. Each training session consisted of 13 exercises, with a duration varying between one and five minutes. The processes being trained in the cognitive training condition of *BrainGymmer* corresponded well to what is being trained during traditional face-to-face cognitive training tasks. The exercises included memorizing sequences, discrimination of confusable items, counting correct items between distractor items, reconstruction of sequences, matching of correct pairs and solving complex puzzles. Correct responses were rewarded with points and positive feedback. Participants were challenged to improve themselves through dynamic difficulty adjustment: the degree of complexity of the task adjusted to the subjects individual performance. Furthermore, *BrainGymmer* is an interactive platform. Participants got to see an overview of their own score in comparison to the mean score of the other participants, and their own previous achievements. To prevent participants from being discouraged, this comparison was only shown when their performance was equal or better than the average score on that specific task.

Cognitive stimulation

This intervention matched the cognitive training condition for time, computer use and being cognitively active. The intervention comprised exercises that were designed to increase cognitive functioning in a nonspecific manner. That is, the participants were cognitively active, but were not training specific cognitive domains. The tasks (Trivia, Hangman and Solitaire) rely on general knowledge and vocabulary. The degree of complexity remained the same throughout the training. Every session, participants performed the same three tasks for 12 minutes each. Participants received no feedback on their performance and did not get to see a comparison with other participants.

Appendix 3. Individual pre- and post-intervention *t*-scores.

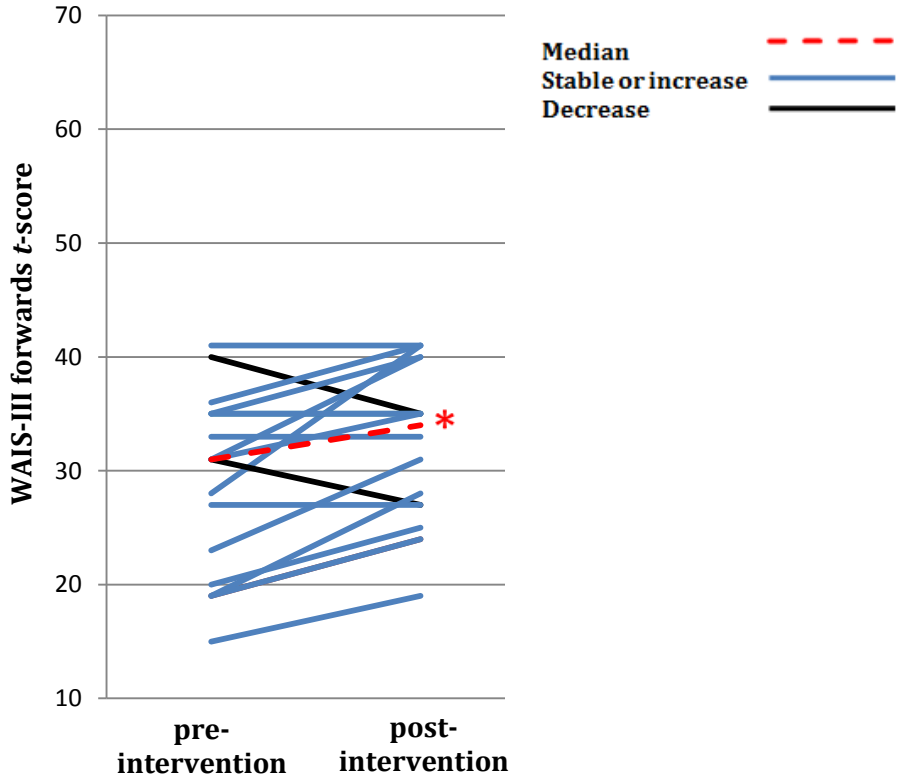

Figure 11 . Pre- and post-intervention WAIS-III digit span forwards *t*-score for each participant.

* Significant at the .05 level

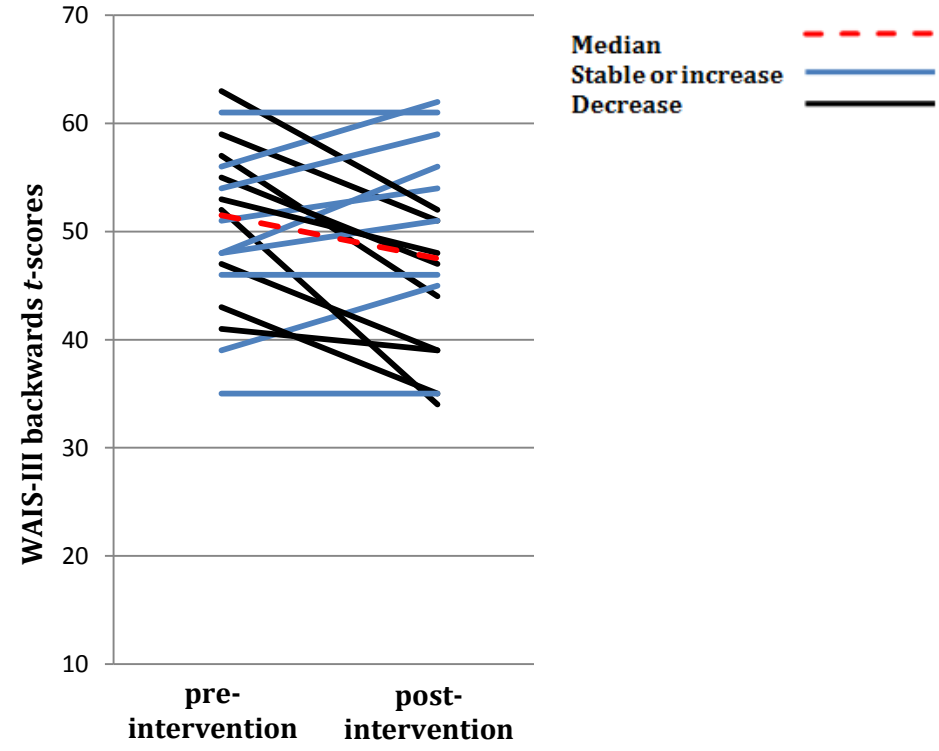

Figure 12 . Pre- and post-intervention WAIS-III digit span backwards *t*-score for each participant.

Appendix 3. Individual pre- and post-intervention *t*-scores (continued)

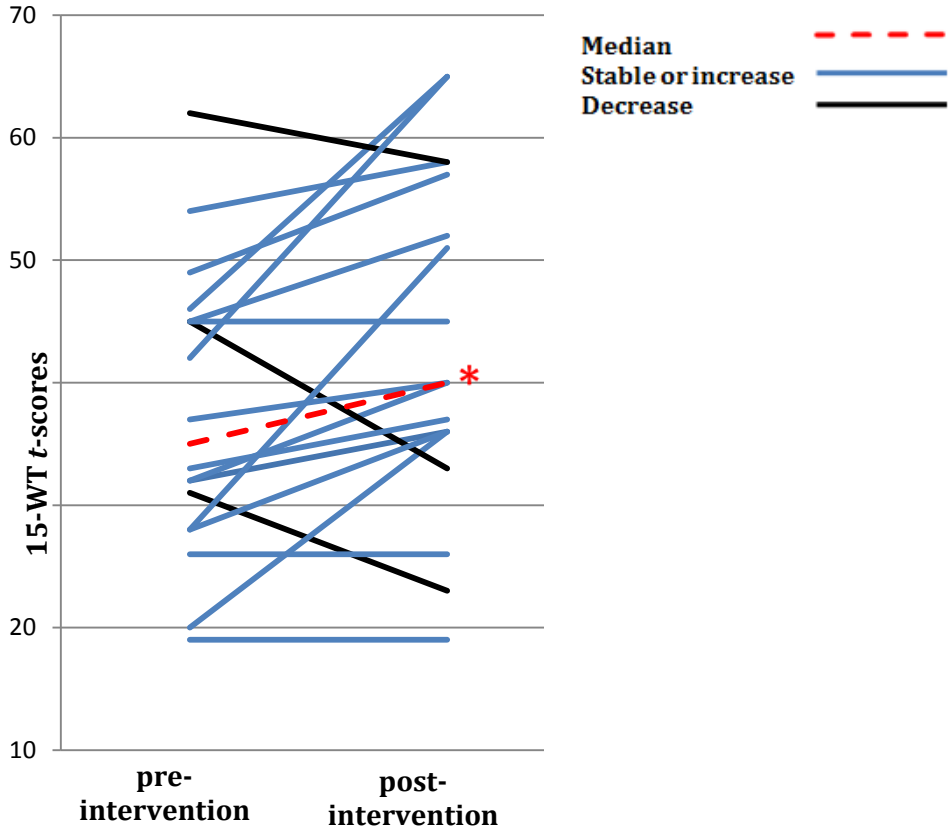

Figure 13. Pre- and post-intervention 15-WT *t*-score for each participant.

* Significant at the .05 level

Appendix 4. Overview of correlations between BDI/FSS and NP task scores.

Table 8. *Spearman's rank correlations (rs) between clinical measures (BDI and FSS score) and objective cognitive functioning (t-scores)*

Variable	TMT	SCWT	fluency	15WT	WAIS-III forwards	WAIS-III backwards
BDI (N=19)	r_S = -.180 P = .461	r_S = -.267 P = .269	r_S = -.110 P = .655	r_S = .237 P = .329	r_S = .120 P = .626	r_S = .081 P = .742
FSS (N=19)	r_S = -.098 P = .690	r_S = .139 P = .571	r_S = .095 P = .698	r_S = .230 P = .345	r_S = -.146 P = .552	r_S = .328 P = .170

* Correlation is significant at the 0.05 level (2-tailed)

** Correlation is significant at the 0.01 level (2-tailed)

Abbreviations: BDI = Beck Depression Inventory, FSS = Fatigue Severity Scale, TMT = Trail Making Task, SCWT = Stroop Color Word Task, 15WT = 15-Word Test, WAIS = Wechsler Adults Intelligence Scale.