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Effects of Home-Based Working Memory Training on Visuo-Spatial Working Memory in Parkinson's Disease: A Randomized Controlled Trial

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Abstract

Background:

Cognitive impairment is a very frequent and severe nonmotor symptom of Parkinson's disease (PD). Early intervention in this at-risk group for cognitive decline may be crucial for long-term preservation of cognitive functions. Computerized working memory training (WMT) has been proven beneficial in non-PD patient populations, but such evidence is still needed for patients with PD.

Objective:

This study aimed to evaluate the effect of WMT on visuo-spatial working memory (WM) in cognitively unimpaired patients with PD.

Methods:

A single-blind randomized controlled trial encompassing 76 patients with PD but no cognitive impairment according to level II diagnostic criteria was conducted. Thirty-seven patients engaged in home-based adaptive WMT 5 times per week for a period of 5 weeks, whereas the remaining patients were in the waiting list arm of the study (control group [CG]). Working memory performance was evaluated using a computerized task before and after intervention and at 14-week follow-up, allowing to quantify the precision of WM on a continuous scale, ie, to test not only if an item was remembered but also how well the location of this item was retained.

Results:

Coincidently, the WMT group showed slightly worse WM performance compared with the CG at baseline, which was ameliorated after WMT. This training-induced effect remained stable until follow-up.

Conclusion:

Patients showing relatively low WM performance, despite not formally diagnosable as Parkinson's disease with mild cognitive impairment (PD-MCI), seem to benefit from home-based WMT. Thus, WMT could potentially be implemented in future trials as a time- and cost-efficient route to counteract subtle cognitive changes in early disease stages.

Trial registration:

German Clinical Trial Register (drks.de, DRKS00009379)

Keywords: Idiopathic Parkinson's disease, working memory, executive function, working memory training, nonpharmacologic intervention, randomized controlled trial

Introduction

Alongside the cardinal motor symptoms, cognitive impairment is perceived as the greatest burden on quality of life among patients with Parkinson's disease (PD).[1-4] While 25% to 30% of patients fulfill diagnostic criteria for Parkinson's disease with mild cognitive impairment (PD-MCI),[5-7] relevant cognitive deviations in absence of general cognitive deterioration, eg, in executive functions[8] and visuo-spatial working memory (WM),[9] can also be observed in very early disease stages and prodromal cases.[8,10,11] Although these minor cognitive changes may not be objectively captured by standard neuropsychological test batteries, they may still be subjectively perceived by the patient, potentially accompanied by an increasing worry about the preservation of high cognitive function in the future.[12]

Previous reports have shown that cognitive training might be beneficial to maintain cognitive well-being in PD, opening a new window for nonpharmacologic intervention.[13-16] These studies predominantly employed training tasks addressing a great range of cognitive functions but did not focus on a specific cognitive process. Focused working memory training (WMT) however, as opposed to domain-general cognitive training, seemed most promising to enhance cognition in previous studies of young and elderly healthy individuals[17-19] as well as other neurological non-PD populations.[20,21] Considering that executive functions and WM represent the most vulnerable cognitive domains in PD[8,22] and have shown promising improvements due to cognitive training interventions,[13] training focused around WM seems particularly worthwhile in this cohort.

However, studies specifically targeted at WM and WMT in PD are sparse.[13] In addition, studies investigating the efficacy of computerized home-based training as opposed to cost- and time-intensive group training at a clinical facility are largely missing. Recently, the first randomized controlled trial (RCT) employing self-administered home-based WMT in PD was conducted, showing encouraging effects on WM and depressive symptomatology.[23] However, in this trial, the patients' initial cognitive state was evaluated via phone interviews only, leaving the possibility of a relatively heterogenous

cohort in terms of initial cognitive performance, and thus, only cautious conclusions can be drawn about which patients (ie, cognitively intact or PD-MCI) will benefit from a given training regime. In addition, no follow-up (FU) testing was performed.

Here, we conducted a single-blind RCT with the aim to investigate whether WM performance can be improved via self-administered, home-based WMT in patients with PD and whether these effects remain stable until FU at 14 weeks. The WMT was based on the NeuroNation program (http://www.neuronation.com/) and conducted on 5 days per week for a period of 5 weeks. Based on previous results,[17-20] we tailored our intervention to target specifically WM function including WM updating, shifting, and inhibition. Furthermore, because starting an intervention early might be crucial to overcome, delay, or even prevent first signs of cognitive decline, we aimed to elucidate whether WMT can already be beneficial for patients who are still cognitively well preserved and thus only included patients without PD-MCI or dementia.

With the aim to capture even slight variations in WM performance in our cohort of cognitively high-functioning patients, we opted for a recently established task of WM performance as outcome measure. In so-called delayed adjustment tasks, subjects are required to remember one or more objects and to reproduce certain features of one of those objects, eg, its orientation or location on the screen.[24-26] In contrast to discrete and binary measures of pure WM capacity, which can only dissociate between items entirely remembered and entirely forgotten, delayed adjustment tasks also allow to probe how well an item was retained (ie, the quality of a memory trace).[27] Importantly, this type of task has also been shown to be sensitive to very subtle differences in WM, even in newly diagnosed early-stage patients with PD. It was found that the delayed adjustment task performance was significantly worse in patients with PD than in healthy controls, despite scoring in the healthy range of WM capacity according to standard neuropsychological measures such as the digit span and Corsi block-tapping task.[24] Due to this superior sensitivity, these tasks, therefore, provide a great opportunity to identify slight, but relevant, WM deficits and subtle changes in performance due to cognitive decline, pharmacologic therapy, or nonpharmacologic interventions such as WMT.

Based on previous findings,[23] we expected that self-administered, home-based WMT would significantly improve WM function in the trained group as compared to the passive PD control group (CG). Moreover, we hypothesized that a delayed adjustment WM task would be sensitive enough to track even slight performance differences and changes in this cohort of cognitively well-preserved patients.

Methods

Participants

Eighty-five patients were recruited via the Department of Neurology of the University Hospital of Cologne and a PD patient support group network (Deutsche Parkinson Vereinigung e.V.) between September 2016 and July 2018. Patients were included if they fulfilled the diagnostic criteria for idiopathic PD,[28] were between 45 and 85 years old, and had normal or corrected to normal vision and hearing. Patients were excluded if diagnosed with any other neurological or psychiatric disease, including major depression (Geriatric Depression Scale [GDS], score $\geqslant$ 11),[29] suffered from a life-threatening disease, or had received deep brain stimulation. Importantly, patients were also excluded if they fulfilled level II diagnostic criteria for PD-MCI (ie, scoring $\geqslant$1.5 SD below the norm on more than one cognitive test).[6] Thus, all patients included here are considered cognitively healthy. For detailed information regarding patient demographics, see Table 1. The study was performed in accordance with the latest version of the Declaration of Helsinki[30] including the approval of the ethics committee of the Medical Faculty of the University of Cologne (vote no. 16-043) and registered at the German Clinical Trial Register (drks.de, DRKS00009379). All patients provided written informed consent prior to study participation.

Table 1.

Sample characteristics at baseline.

	WMT (n = 36)	CG (n = 36)	*P* value
Age in years	64.36 ± 8.51 (47.9-78.7)	63.90 ± 8.28 (46.3-79.0)	.816[a]
Sex			.814[b]
Female, n (%)	17 (47)	16 (44)	
Male, n (%)	19 (53)	20 (56)	
Education in years	15.32 ± 2.95 (11-22)	15.88 ± 2.58 (10-23)	.399[c]
Global Cognition MoCA score	27 ± 1.72 (24-30)	27.6 ± 1.36 (25-30)	.155[c]
Disease duration in years	6.25 ± 4.40 (0.47-22.05)	6.42 ± 5.99 (0.35-27.04)	.628[c]
UPDRS-III	29 ± 8 (13-53)	29 ± 9 (10-52)	.856[a]
LEDD	675 ± 426 (0-1785.00)	594 ± 433 (100.00-2120.00)	.356[c]
Depression GDS score	2.1 ± 1.8 (0-7)	2.4 ± 2.4 (0-9)	.922[c]

Abbreviations: CG, control group; GDS, Geriatric Depression Scale; LEDD, levodopa equivalent daily dose; MoCA, Montreal Cognitive Assessment; UPDRS-III, Unified Parkinson's Disease Rating Scale Part 3; WMT, working memory training.

Data are mean values ± standard deviation (range), unless stated otherwise.

For baseline comparison between groups, [a]independent sample *t* test, [b]chi-square tests, and [c]*P* values of Wilcoxon rank-sum tests are reported. Variables were inspected statistically by the Shapiro-Wilk tests for normal distribution.

Study design

The study was designed as a single-blind RCT at the University Hospital of Cologne to investigate the effect of WMT on cognitively healthy patients with PD. Our study encompassed 3 testing time points and 1 intervention period.

First, during an initial appointment, patients were screened for eligibility and performed an extensive neuropsychological test battery to ensure cognitive integrity using level II diagnostic criteria for PD-MCI.[6] As a baseline (PRE) measurement, all eligible patients also conducted a delayed adjustment WM task (for details, see below). For the following intervention period, patients were randomly assigned to either the WMT group or the passive CG. The online tool Research Randomizer (www.randomizer.org) was used to generate a blocked randomized allocation sequence with block size = 10 and a 1:1 ratio not stratified for any demographic or clinical variable. To ensure complete blinding for group allocation for the assessor and patient during PRE, the randomization was performed only after initial testing by a researcher not further involved in this RCT. In the following, the assessors remained blinded for group allocation, whereas the patients were not. After completing the WMT or passive waiting, patients' WM performance was re-evaluated (posttesting [POST]: 5.7 ± 0.6 weeks after PRE). Finally, an FU testing was conducted 14 weeks following the end of the WMT/waiting phase with no training in between (FU: 14.0 ± 0.9 weeks after POST). Patients were instructed to continue their regular medication throughout the whole RCT including the intervention and all testing.

Details on feasibly of the WMT and effect of the intervention on the neuropsychological test battery, which was performed to ensure cognitive integrity, will be discussed in a separate publication. In short, we used WMT completion, motivation to train, and patient satisfaction during WMT as proxy for feasibility. The neuropsychological test battery comprised measures of verbal and nonverbal WM,

executive functions, verbal memory, attention, visuo-constructive functions, and language. WMT was deemed feasible and induced small to medium long-term effects on the WMT group in verbal WM and visuo-constructive abilities only. No other WMT-induced effects on cognitive test and clinical variables were observed.

The intervention

The home-based computerized online training was developed together with the cognitive training provider NeuroNation (Synaptikon GmbH, Berlin, Germany) and consisted of 9 adaptive WM exercises focusing on WM inhibition, updating, and shifting (for details on training tasks, see Supplementary Material). Each training session started with a 4-minute forward block-tapping warm-up task followed by a subset of 4 of the 8 remaining training tasks which were trained for 6.5 minutes each, resulting in a total of 30-minute training time per session. The trained subset on a given day was predetermined with a balanced ratio across all WM exercises. The WMT group was instructed to train 5 days per week for a period of 5 weeks.

Training adherence was monitored remotely via the NeuroNation website, and participants of the WMT group were contacted every week via phone to ensure that no technical problems had occurred. The CG received no intervention but was granted access to the WMT after study completion.

The "What was where"-task and outcome measures

We employed the "What was where"-task ("WwW"-task) identical to the one used by Pertzov and colleagues (see Figure 1).[31-33] In short, on each trial, participants were presented with 1 (presentation time: 1 second) or 3 (presentation time: 3 seconds) colored fractal items on a black background, from which they were instructed to remember their visual properties (identity) and location. Then, a black screen was displayed for either 1 second or 4 seconds (memory delay), followed by the probe array consisting of 2 fractals positioned in the vertical median of the screen on a black background. One of those items was part of the initial memory array (ie, target), whereas the other one was a foil. Participants were required to identify the target and drag it to the location where it was previously seen (during the memory array) using their dominant index finger. Finally, participants logged their responses and self-initiated the next trial by pressing the space bar. Stimuli were drawn from a library of 60 fractal items (http://sprott.physics.wisc.edu/fractals.html) and presented 2 to 3 times each per block. Each participant completed a practice block of 10 trials, before conducting 2 experimental blocks. Each block comprised 50 trials, 10 displaying 1 fractal and 40 displaying 3 fractals with a balanced ratio of 1- or 4-second memory delay. The task was conducted on a touch-sensitive Dell Inspiron One 2320. The experiment code was executed, and responses were recorded using Matlab v.R2015a (MathWorks, Inc).

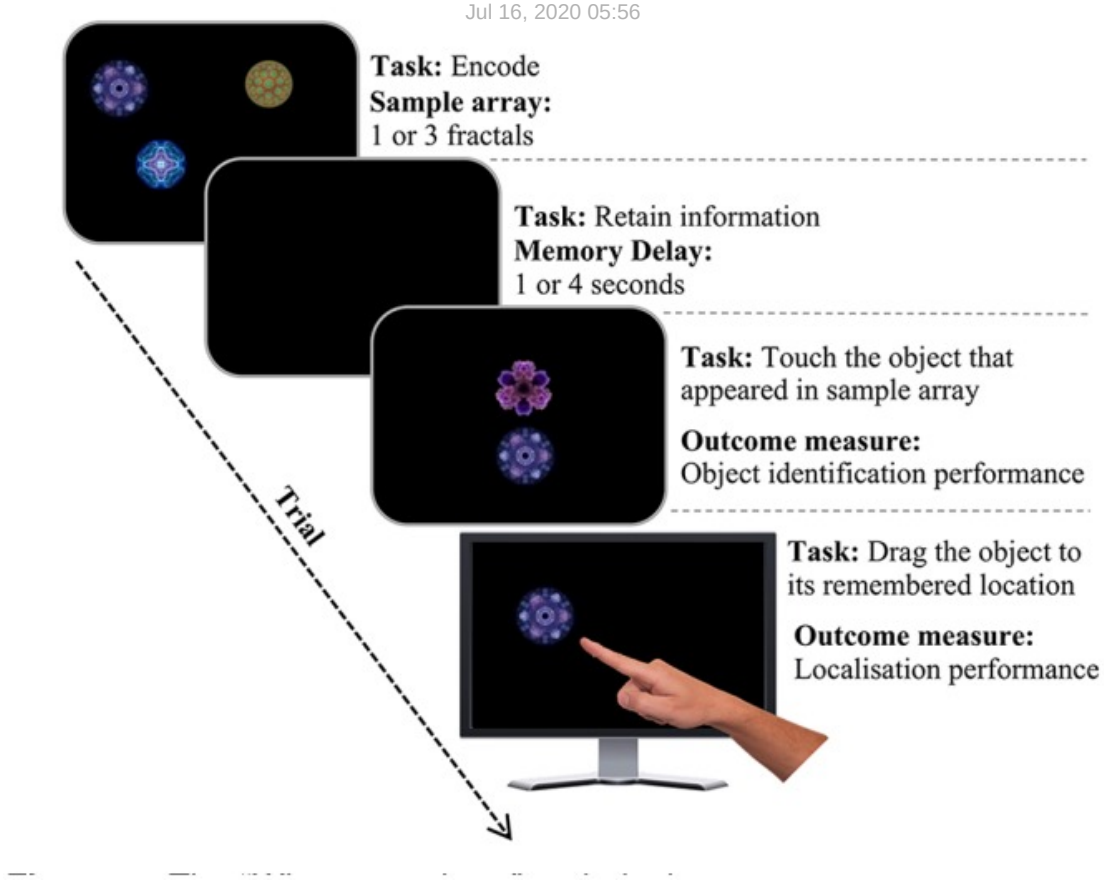

Figure 1.

The "What was where"-task design.

The "WwW"-task provides 2 outcome measures: First, object identification performance, which is determined as the percentage of correctly chosen target items from the probe display. And second, localization error (as a measure of localization performance) for correctly identified targets, which is calculated as the distance between the center of the original target position and the position of the response given by the patient. This parameter has the great advantage of being a continuous measure of memory quality (ie, how precisely a location was remembered) rather than being a discrete measure of whether an item was completely remembered or forgotten.

Determination of sample size

An a priori power analysis was conducted using G*Power.[34] According to a meta-analysis on cognitive training in PD,[13] we expected a medium effect size for measures of WM. Thus, with an α level of .05% and 80% power, the minimum sample size including a 20% dropout was estimated at N = 72.

Statistical analysis

Demographic and clinical data at PRE were compared between groups using Wilcoxon rank-sum tests, independent sample *t* tests, or chi-square tests as appropriate.

To answer our main question regarding the effect of WMT on performance of the task, data from the WM paradigm were entered into repeated measures 2 × 2 analysis of variance (ANOVA) with time as the intrasubject factor (2 levels: PRE and POST training/no intervention) and group (2 levels: WMT vs CG) as the intersubject factor. Then, to estimate whether a significant time × group interaction was

driven by a certain condition (every combination of 1 item or 3 items & 1-second delay or 4-second delay), we calculated the change in performance for each condition within each group expressed by means of effect sizes using Cohen's *d*.[35]

To estimate whether effects were also stable over the FU period, 2 repeated measures 2 × 2 ANOVAs with time as the intrasubject factor (2 levels: PRE vs FU and POST vs FU, respectively) and group (2 levels: WMT vs CG) as the intersubject factor were conducted. In addition, a repeated measures 3 × 2 ANOVA with time as the intrasubject factor (3 levels: PRE, POST, and FU) and group (2 levels: WMT vs CG) as the intersubject factor was performed.

These analysis steps were undertaken for object identification performance and localization error. Data from all conditions (2 levels of set size and delay, respectively) were averaged to create an overall total score for each measure. For this exploratory study, *P* values were not corrected for multiple comparisons. Thus, all results with $P < .05$ were considered statistically significant.

Results

Participant demographics

Initially, 85 patients were screened; however, 9 subjects (≈8%) had to be excluded due to incidental PD-MCI according to level II diagnostic criteria.[6] From 76 eligible patients, 72 completed the "WwW"-task before and after intervention. From those, 36 had been randomized to the WMT group, and 36 had entered the passive no-intervention phase (for details, refer to CONSORT flowchart, Figure 2). At PRE, patients (46% women) had an average age of 64.1 ± 8.3 years and been diagnosed with PD for 6.3 ± 5.2 years. Overall, patients were relatively highly educated with 15.6 ± 2.8 years of education. For demographic and clinical details as well as statistical comparison between the WMT group and CG at PRE, please refer to Table 1. At FU, 67 patients were re-evaluated (2 study dropouts in the WMT group; 3 datasets missing due to technical failure: 1 CG, 2 WMT).

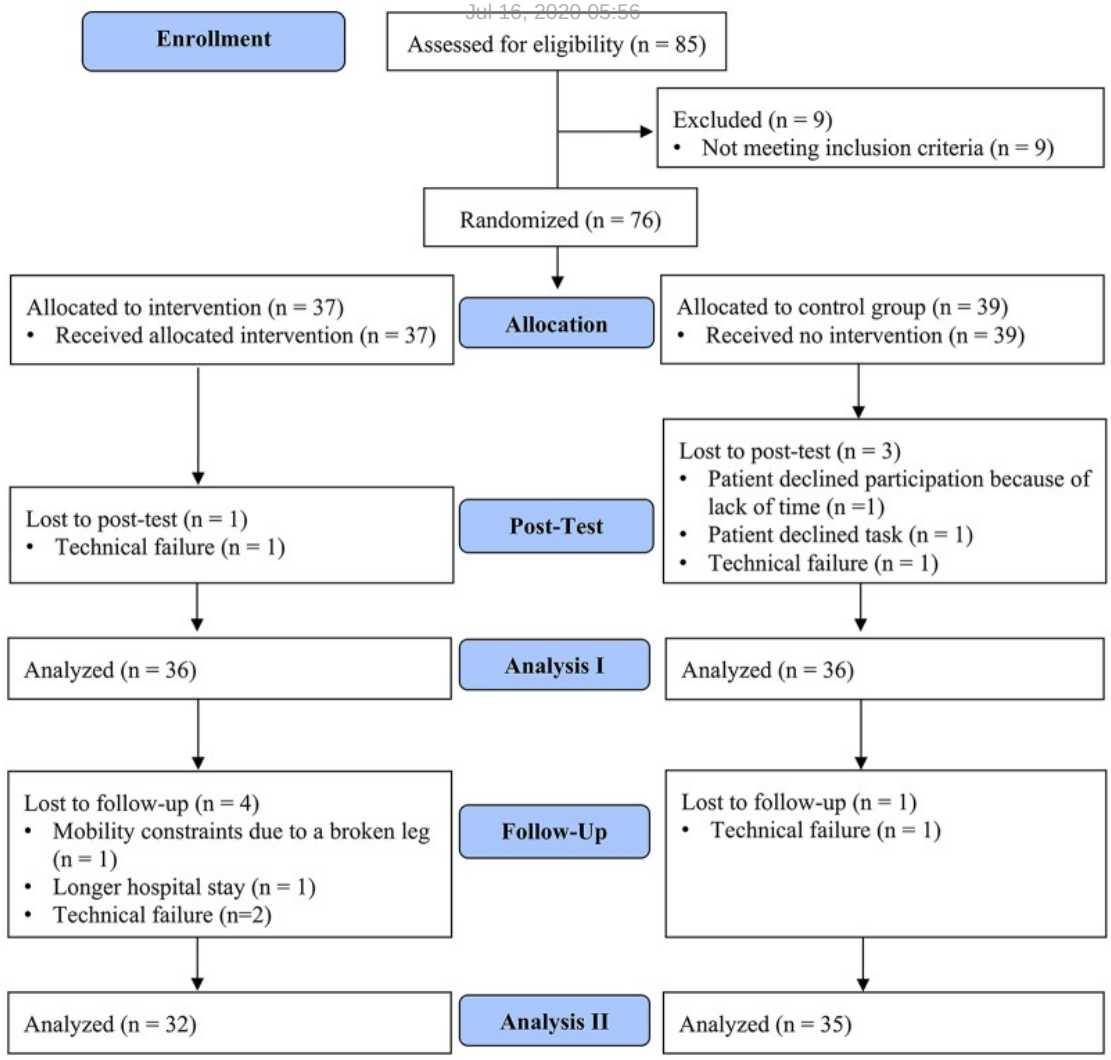

Figure 2.

Enrollment, study arm allocation, posttest, and follow-up of study participants.

Immediate effects of WMT on WwW-task

Object identification performance For object identification performance, measured as the percentage of correctly chosen items during the forced-choice phase of the experiment, there was a significant main effect of time indicative of a practice effect ($P = .022$) but no significant effect of group. However, the time × group interaction reached significance ($P = .034$) indicating that the trained group improved significantly more over time than controls (see Table 2 and Figure 3 for details). Indeed, before WMT, the training group only reached 90.5 ± 4.2% accuracy, while the CG performed at 92.1 ± 3.6%. This performance difference was ameliorated following the intervention with both groups on average reaching just above 92% (see Table 3).

Table 2.

Effects of WMT.

ANOVA	Effect of time	Effect of group	Time × group interaction
	PRE-POST comparison: F(1, 70)		
Object identification	F = 5.46	F = 0.60	F = 4.70
	***P* = .022**	*P* = .441	***P* = .034**
	η_p^2 = .07	η_p^2 = .01	η_p^2 = .06
Localization error	F = 11.41	F = 0.19	F = 0.24
	***P* = .001**	*P* = .667	*P* = .623
	η_p^2 = .14	η_p^2 = .00	η_p^2 = .00
	PRE-FU comparison: F(1, 65)		
Object identification	F = 1.16	F = 0.03	F = 4.62
	P = .285	*P* = .866	***P* = .035**
	η_p^2 = .03	η_p^2 = .00	η_p^2 = .07
Localization error	F = 1.07	F = 0.07	F = 0.05
	P = .305	*P* = .789	*P* = .818
	η_p^2 = .02	η_p^2 = .00	η_p^2 = .00
	POST-FU comparison: F(1, 65)		
Object identification	F = 1.69	F = 1.05	F = 0.06
	P = .198	*P* = .310	*P* = .805
	η_p^2 = .03	η_p^2 = .02	η_p^2 = .00
Localization error	F = 3.98	F = 0.00	F = 0.53
	***P* = .050** η_p^2 = .06	*P* = .956	*P* = .468
		η_p^2 = .00	η_p^2 = .01
	PRE-POST-FU comparison: F(2, 130)		
Object identification	F = 2.89	F = 0.04	F = 3.51
	P = .059	*P* = .836	***P* = .033**
	η_p^2 = .04	η_p^2 = .00	η_p^2 = .05
Localization error	F = 4.91	F = 0.01	F = 0.31
	***P* = .009**	*P* = .917	*P* = .733
	η_p^2 = .07	η_p^2 = .00	η_p^2 = .01

Abbreviations: ANOVA, analysis of variance; FU, follow-up; POST, posttesting; PRE, baseline; WMT, working memory training.

Statistical analysis via repeated measures ANOVA: Effect of time, treatment group, and time × group interaction. Note: Bold values signifies significant *p* values.

Table 3.

Task performance and group comparison.

Performance	**PRE**		**POST**		**FU**	
	WMT	**CG**	**WMT**	**CG**	**WMT**	**CG**
Object identification (%)	90.5 ± 4.2	92.1 ± 3.6	92.4 ± 4.3	92.2 ± 3.8	92.6 ± 3.7	91.6 ± 4.3
Localization (°)	5.8 ± 1.3	5.6 ± 1.3	5.4 ± 1.3	5.3 ± 1.3	5.5 ± 1.6	5.4 ± 1.4
Group comparison	**PRE**		**POST**		**FU**	
Object identification	$t(70) = -1.68$ $P = .097$		$t(70) = 0.25$ $P = .800$		$t(65) = 0.99$ $P = .327$	
Localization	$t(70) = 0.56$ $P = .560$		$t(70) = 0.21$ $P = .831$		$t(65) = 0.31$ $P = .759$	

Abbreviations: CG, control group; FU, follow-up; POST, posttesting; PRE, baseline; WMT, working memory training.

Mean performance ± standard deviation is reported. Statistical group comparison via 2-sample *t* test for each time point.

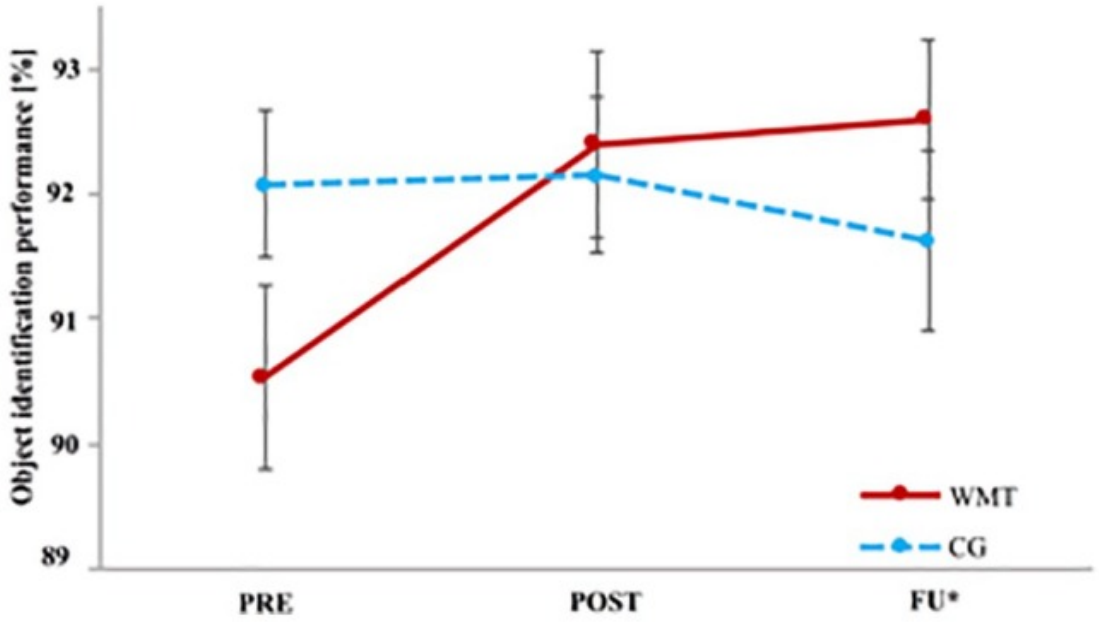

Figure 3.

Mean and standard error of total object identification performance (%) per group before and after intervention/waiting and at 14-week follow-up. *Subset available for follow-up (WMT: n = 32; CG: n = 35). CG, control group; WMT, working memory training; FU, follow-up.

To investigate whether this change was driven by a certain condition (1 item/1 s, 1 item/4 s, 3 items/1 s, and 3 items/4 s), we compared the PRE and POST data within each group using a paired sample *t* test for the total score as well as each condition separately and calculated the effect sizes expressed as

Cohen's *d* for both groups between these time points (see Table 4). Working memory training had a moderate effect on total object identification performance in the training group ($t(35) = 3.05$, $P = .004$; $d = 0.51$), which was mainly driven by improvements in the easiest (1 item/1 s: $t(35) = 2.36$, $P = .024$; $d = 0.39$) and most demanding condition (3 items/4 s: $t(35) = 3.43$, $P = .002$; $d = 0.57$), whereas performance in the CG remained unchanged.

Table 4.

Effect sizes for object identification performance change within groups.

PRE-POST change					
	Total	**1 item 1 second**	**1 item 4 second**	**3 items 1 second**	**3 items 4 second**
WMT *t*(35)	$t = 3.05$	$t = 2.36$	$t = -0.21$	$t = 1.07$	$t = 3.43$
	$P = .004$	$P = .024$	$P = .838$	$P = .294$	$P = .002$
	$d = 0.51$	$d = 0.39$	$d = -0.03$	$d = 0.02$	$d = 0.57$
CG *t*(35)	$t = 0.13$	$t = 0.37$	$t = -1.41$	$t = 0.36$	$t = 0.77$
	$P = .902$	$P = .711$	$P = .169$	$P = .722$	$P = .448$
	$d = 0.00$	$d = 0.01$	$d = -0.02$	$d = 0.06$	$d = 0.01$

Abbreviations: CG, control group; *d*, Cohen's *d* calculated from mean and standard deviation difference between 2 time points within groups (paired sample *t* test); WMT, working memory training.

Note: Bold values signifies significant *p* values.

Localization error For localization error, there was a significant main effect of time ($P = .001$) indicative of a practice effect, however no main effect of group nor an interaction (see Table 2).

Effects of WMT on WwW-task at FU

Object identification performance When comparing total object identification performance at PRE with performance at FU, there was no significant main effect of time or group; however, the time × group interaction reached significance ($P = .035$) indicating that the WMT group was able to retain the WMT-induced effect over time. No further significant changes between POST and FU testing could be observed. Finally, taking all 3 time points into account, there was no main effect of time or group, but a significant interaction between time × group ($P = .033$) was confirmed (see Table 2 and Figure 3).

Localization error When comparing total localization performance at PRE with FU, there was no significant main effect of time or group, nor an interaction. Only when comparing the POST to FU data, a trend towards a significant effect of time ($P = .050$) could be observed. Finally, taking all 3 time points into account, a significant effect of time ($P = .009$), but neither significant effect of group nor an interaction, was observed (see Table 2 for details).

Discussion

Using a randomized single-blind controlled design, we sought to examine whether self-administered, home-based adaptive WMT could positively influence WM performance in cognitively well-preserved patients with PD. Due to the high cognitive capabilities of this cohort, we opted for a continuous measure of WM performance, namely, the "WwW"-task.[36] In comparison to the passive CG, we observed improved memory for object identity in the training group as indicated by a significant time × group interaction which remained stable until FU testing. However, there were no effects on object location memory.

Only one other study applied self-administered, home-based WMT in PD.[23] It was observed that WM performance improved on the trained WM updating tasks as well as tasks structurally similar to the once trained, but not for the trained pure WM maintenance task, structurally different WM tasks, or tasks of other cognitive functions. Our study complies with these results, but critically extends these findings: first, we observed improvements for WM tasks structurally different to the ones trained yielding the possibility of an extended transfer effect of our WMT; second, we ensured that all included patients were cognitively well preserved according to level II diagnostic criteria for PD-MCI; and finally, we conducted a FU examination showing stability of the positive training effect after 14 weeks.

Studies examining the neural mechanism underlying such training-induced changes in PD are rather sparse and marked by small samples; however, first results point toward plasticity in networks involving the dorsolateral prefrontal cortex (dlPFC) as a major plastic hub. In PD, increased functional activation in the dlPFC and superior parietal lobe following attention-focused training[37] and increased connectivity between the dlPFC and inferior temporal lobe following domain-general training were observed during resting-state functional magnetic resonance imaging (fMRI).[38] Using electroencephalogram (EEG), increased alpha-band oscillations have been observed following time-estimation training in PD.[39] Task-based fMRI, however, has shown decreased cortical activation and increased subcortical activation in the basal ganglia following training in healthy elderly[40] and a single PD case report.[41] While increased activity in the striatum has been associated with alterations in dopamine levels[42] and WMT-induced dopaminergic changes have been observed in healthy young individuals,[43] the potential benefit for patients with PD remains currently unknown but should certainly be explored in future research.

Whether the trend-significant suboptimal performance of the WMT group for object identification at PRE in this study was due to an encoding or retrieval failure of the desired information cannot be fully answered using the present design. However, because both groups showed similar performance for object location (ie, similar localization error) at PRE, one might speculate that once an item has been properly encoded, the memory for both features (ie, its identity and location) is rather stable. It is, therefore, plausible that the impaired performance for simple object identification was not a failure to maintain encoded information within WM, but rather an encoding failure per se. This could be due to attentional changes which are well described in patients with PD and are a predictor for cognitive impairment and quality of life in patients with PD-MCI.[44]

It is important to note that the lower PRE performance in the WMT group was coincidental. That suggests that although all patients were regarded as cognitively intact according to diagnostic criteria, they did not all perform equally well on this precision measure of WM. This might indicate lower cognitive abilities potentially pointing to subthreshold deficits which could eventually develop to cognitive impairment. This stresses the need for sensitive measurement tools, such as the "WwW"-task, to identify patients with an elevated risk for cognitive decline.[24] Using such tasks as outcome may, therefore, be of special importance when studying (yet) cognitively unimpaired individuals during early disease stages to identify cognitively vulnerable patients and to track subtle cognitive changes.

Strengths and limitations

Previous research on cognitive training in PD has produced mixed results because training regimes employed and cohort studies varied greatly.[45] Therefore, we aimed to focus on one specific, well-characterized, and homogeneous patient subgroup, namely, patients with PD but no signs of cognitive impairment, to understand whether such an intervention can already be beneficial at this early stage.

Furthermore, to investigate whether the observed positive effect was stable over time, we included an FU examination. Moreover, we have studied a cohort with a relatively high level of education. Previous studies have shown that patients with higher education benefit more from cognitive training.[23] However, it is important to note that the educational level of trained patients and the CG was similar. Limiting our sample to such a specific subgroup of patients may reduce the generalizability of our results to other patient groups. Therefore, future studies should also include thoroughly characterized patients of various cognitive stages (PD-MCI and PD-dementia) and different levels of education.

In addition, a few methodological shortcomings of our study design should be addressed. Gender was not balanced within groups, which however corresponds to the natural incidence of PD with more men being affected than women.[46] Importantly, gender distribution, however, was equal between groups. Note that we cannot rule out that the observed group × time interaction was partly driven by a ceiling effect in the CG. In addition, increased motivation in the WMT group due to the weekly technical check-up calls from research staff or increased experience and/or reduced anxiety in the WMT groups for using a computer due to the computerized nature of the WMT could play a role. For future trials, the inclusion of an additional active CG may help to overcome those potential confounds.

Moreover, because the training effect on the WMT group was stable until FU, a second re-evaluation after a longer interval would have been desirable. Future longitudinal studies should, therefore, investigate whether the home-based WMT effect observed here is stable over a longer period of time and, thus, might have a clinically relevant potential to delay cognitive decline in those today cognitively well-preserved patients.

Despite reservations regarding training compliance, home-based cognitive interventions have previously been shown to, nonetheless, elicit training benefits in healthy elderly[47] and patients with PD.[23] Considering that home-based training is a much more cost-effective option and entails a rather low logistic burden for the patient, long-term implementation of home-based WMT in daily life seems realistic. In addition, via telemedicine techniques, sufficient and accurate execution of training could be ensured and remotely monitored by experts.[48] Taking the positive feedback from patients into account, we consider self-administered, home-based WMT a promising option for patients with PD which should receive more attention in future trials.

Conclusions

By using a precision measure of WM, we were able to identify subtle cognitive deviations in cognitively healthy patients with PD. Self-administered and home-based adaptive WMT significantly improved performance on this sensitive and specific WM measure, and this positive effect was retained until FU. Thus, we suggest that future clinical trials—ideally including long-term FU and larger samples—should further validate WMT as a time- and cost-efficient route to preserve high cognitive function in PD. If these studies corroborate potential clinical utility for patients with PD, more attention should be given to home-based WMT as a possible treatment option.

Supplemental Material

CONSORT_2010_Checklist_Giehl_et-al_CNSD_rev1 – Supplemental material for Effects of Home-Based Working Memory Training on Visuo-Spatial Working Memory in Parkinson's Disease: A Randomized Controlled Trial:

Click here for additional data file. (65K, pdf)

Supplemental material, CONSORT_2010_Checklist_Giehl_et-al_CNSD_rev1 for Effects of Home-Based Working Memory Training on Visuo-Spatial Working Memory in Parkinson's Disease: A Randomized Controlled Trial by Kathrin Giehl, Anja Ophey, Paul Reker, Sarah Rehberg, Jochen Hammes, Michael T Barbe, Nahid Zokaei, Carsten Eggers, Masud Husain, Elke Kalbe and Thilo van Eimeren in Journal of Central Nervous System Disease

Supplementary_material_CNSD – Supplemental material for Effects of Home-Based Working Memory Training on Visuo-Spatial Working Memory in Parkinson's Disease: A Randomized Controlled Trial:

Click here for additional data file. (33K, pdf)

Supplemental material, Supplementary_material_CNSD for Effects of Home-Based Working Memory Training on Visuo-Spatial Working Memory in Parkinson's Disease: A Randomized Controlled Trial by Kathrin Giehl, Anja Ophey, Paul Reker, Sarah Rehberg, Jochen Hammes,

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Author Contributions: KG developed the research idea of this study. SR and EK designed the intervention. NZ and MH developed the WwW-task. KG and JH implemented the experimental set-up. KG, AO, SR, CE, MTB, EK and TvE helped in the recruitment of patients. PR conducted the UPDRS-III ratings. KG, AO and SR acquired data. KG and TvE analyzed and interpreted data, prepared figures and tables and wrote the manuscript. All authors critically revised the manuscript and approved its final version.

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