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Short Communication

Working Memory Training Responsiveness in Parkinson's Disease Is Not Determined by Cortical Thickness or White Matter Lesions

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Abstract. Patients with Parkinson's disease are highly vulnerable for cognitive decline. Thus, early intervention by means of working memory training (WMT) may be effective for the preservation of cognition. However, the influence of structural brain properties, i.e., cortical thickness and volume of white matter lesions on training responsiveness have not been studied. Here, behavioral and neuroimaging data of 46 patients with Parkinson's disease, 21 of whom engaged in home-based, computerized adaptive WMT, was analyzed. While cortical thickness and white matter lesions volume were associated with cognitive performance at baseline, these structural brain properties do not seem to determine WMT responsiveness.

Keywords: Working memory training, MRI, cortical thickness, white matter lesion, cognition, Parkinson's disease

INTRODUCTION

The decline of cognitive function in Parkinson's disease (PD) is a common non-motor symptom, which may eventually lead to the development of PD dementia. Cognitive training might be a way of non-pharmacological intervention to preserve a high level of cognitive function and independence [1]. In line with this, our group has previously shown that 5 weeks of computerized working memory training (WMT) could boost cognitive performance for visual-spatial and verbal working memory in a cohort of cognitively healthy patients with PD over a 3-months follow-up period [2–4].

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However, to date it is not clear if and to what extent WMT responsiveness might be affected by preexisting gray and white matter changes in this cohort. In PD, white matter lesion burden has been identified as one of the highest risk factors for the progression of mild cognitive impairment to PD dementia [5]. In addition, increasing gray matter changes are debated as function of cognitive status in PD [6].

In the light of precision medicine working towards tailored treatment approaches, it is essential to understand who can benefit most from WMT. While younger age, higher intelligence and lower cognitive baseline performance seem to predict better training responsiveness [2], it is currently unknown how preexisting structural brain properties might influence training success. While it has previously been shown, that a higher load of white matter lesions was associated with lower training-induced change in processing speed—but no other cognitive domain—in healthy elderly, such evidence is missing in patients with PD [7].

Since gray and white matter changes are closely linked to cognitive status in PD [5, 6], we investigated the association between cortical thickness and white matter lesion volume, respectively, as measured by magnetic resonance imaging (MRI), and cognitive baseline performance in cognitively healthy patients with PD. Furthermore, the relationship between structural brain properties and training success following 5 weeks of computerized WMT was examined in a subgroup of trained patients.

METHODS

Study design

The presented data originate from a single-blind randomized controlled trial (RCT) evaluating the effects of a 5-week computerized WMT compared with a waiting list control group (CG) in patients with PD (for details on WMT see [3]). Clinical and neuropsychological evaluations took place at baseline, the week after the 5-week training/waiting period (posttest, 5.67 ± 0.58 weeks after baseline), and at 3-month follow-up (14.03 ± 0.86 weeks after posttest). While functional neuroimaging was conducted at baseline and post-test, structural MRI was performed at baseline only. For all assessments, patients were evaluated in the ON state.

Participants

For this RCT a total of 76 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. The study was performed in accordance with the latest version of the Declaration of Helsinki 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. For details on inclusion and exclusion criteria see [3]. Here, we present data from a subset of 46 patients with available imaging data.

Neuropsychological data

From all neuropsychological tests within one cognitive domain, equally-weighted composite scores for executive function, verbal working memory, nonverbal working memory, attention, verbal memory and visual construction were calculated on a z-scale [3]. Additionally, we employed an experimental measure of visual-spatial working memory [4]. In short, statistically significant positive training effects in cognitive function due to WMT could be observed for verbal and visual-spatial working memory [3, 4]. These WMT-induced effects could be replicated in this here analyzed, smaller sub-sample (see Supplementary Material). To quantify training gain in these two measures, delta scores between performance at baseline and post-test as well as long-term follow-up, respectively, were calculated for trained participants.

Image preprocessing

To determine cortical thickness, a 3D T1-weighted image was acquired (scan duration = 5 min 55 s, 165 transverse slices, thickness = 1 mm, field of view = $250 \times 230 \times 165$ mm^3, voxel size = $1 \times 1 \times 2$ mm^3, repetition time = 9.6 ms, echo time = 4.8 ms and flip angle = 8°) and processed via the computational anatomy toolbox CAT12 in SPM12 (https://neurojena.github.io/cat/). Preprocessing included normalization into MNI space and image segmentation into gray matter, white matter, and cerebrospinal fluid. After quality control, surfaces were smoothed with a 15x15x15 mm^3 FWHM Gaussian kernel.

For lesion segmentation, a 3D FLAIR image was acquired (scan duration = 4 min 33.6 s, 326 interleaved transverse slices, thickness = 1.12 mm, field of view = $250 \times 250 \times 182.6$ mm^3, voxel size = $1.12 \times 1.12 \times 1.12$ mm^3, repetition time = 4800 ms, echo time = 281 ms and flip angle = 90°) and processed using the SPM Lesion segmentation toolbox (LST). The FLAIR image was co-registered to the corresponding T1 image and subsequently the lesion prediction algorithm was applied using a binary classifier in the form of a logistic regression model. Lesion volume [in ml] was determined [8]. The Fazekas score indicating lesion severity was determined for all participants upon visual inspection [9]. FLAIR data of 3 participants were excluded due to insufficient image quality.

Statistical analyses

Demographic and clinical data. Group means and standard deviations were calculated for age, disease duration, levodopa equivalent dose (LEDD), Unified PD Rating Scale part III (UPDRS III), years of education, Montreal Cognitive Assessment (MoCA), Geriatric Depression Scale (GDS), and lesion volume. For Fazekas score, we calculated median and interquartile range. All analyses were performed in SPSS.

Cortical thickness. In order to investigate the relationship between cortical thickness and cognitive performance at baseline, we performed voxel-wise regression analyses between cortical thickness maps and all composite scores derived from the neuropsychological test battery (all participants).

In order to examine whether cortical thickness had an influence on training responsiveness (trained subgroup), the delta scores of the verbal working memory composite and the experimental visual-spatial working memory measure were correlated with cortical thickness. p-values below $p < 0.05$ FWE-corrected on cluster-level were considered as significant. All analyses were corrected for age and sex.

White matter lesions. Normal distribution of lesion volume was examined by Shapiro-Wilks-Test using SPSS. Due to non-normal distribution, non-parametrical analyses were performed. Cognitive composite scores at baseline were correlated with lesion volume to examine whether lesion severity was associated with cognitive performance. In order to examine whether lesion volume had an influence on training responsiveness (trained subgroup), the delta scores of the verbal working memory composite and the experimental visual-spatial working memory measure were correlated with lesion volume. Bonferroni correction for multiple comparisons was applied to control the family wise error rate to $\alpha = 0.05/7 = 0.007$ for cognitive performance at baseline, and $\alpha = 0.05/4 = 0.0125$ for WMT-induced cognitive changes, respectively. All correlation analyses were corrected for age and sex by using partial rank correlations in SPSS.

RESULTS

The distribution of demographical, cognitive, and clinical data for the complete group and the trained subgroup is shown in Table 1.

Table 1
Demographical, clinical and cognitive data of all participants and participants with training

	All participants ($n = 46$)	Participants with training ($n = 22$)
Age, y	64 ± 9	65 ± 9
Male in %	52	55
Years since diagnosis	5.8 ± 5.5	6.1 ± 5.3
LEDD in mg	568 ± 359	650 ± 425
UPDRS III "ON"	29 ± 8	29 ± 8
Years of education	15.5 ± 2.9	15.1 ± 3.3
MoCA	27.5 ± 1.6	27.3 ± 1.8
GDS	2.5 ± 2.3	1.8 ± 1.8
Fazekas Score	1 ± 1	1 ± 1
Lesion Volume in ml	4.6 ± 6.5	4.94 ± 6.27
Executive Baseline	0.35 ± 0.54	0.23 ± 0.58
○ ΔPost-Baseline	0.13 ± 0.37	0.17 ± 0.42
○ ΔFollowUp-Baseline	0.10 ± 0.38	0.15 ± 0.42
Verbal WM Baseline	–0.05 ± 0.66	–0.27 ± 0.58
○ ΔPost-Baseline	0.22 ± 0.46	0.35 ± 0.50
○ ΔFollowUp-Baseline	0.24 ± 0.47	0.40 ± 0.43
Nonverbal WM Baseline	–0.15 ± 0.63	–0.33 ± 0.57
○ ΔPost-Baseline	0.21 ± 0.47	0.35 ± 0.43
○ ΔFollowUp-Baseline	0.18 ± 0.43	0.24 ± 0.42
Verbal Memory Baseline	0.08 ± 0.82	–0.12 ± 0.89
○ ΔPost-Baseline	0.69 ± 0.70	0.64 ± 0.60
○ ΔFollowUp-Baseline	0.77 ± 0.77	0.82 ± 0.73
Attention Baseline	0.36 ± 0.74	0.27 ± 0.78
○ ΔPost-Baseline	0.12 ± 0.45	0.16 ± 0.51
○ ΔFollowUp-Baseline	0.20 ± 0.45	0.22 ± 0.53
Visual-Construction Baseline	–0.28 ± 0.91	–0.66 ± 0.76
○ ΔPost-Baseline	0.03 ± 1.06	0.29 ± 1.14
○ ΔFollowUp-Baseline	–0.11 ± 1.03	0.30 ± 1.00
Visual-spatial WM Baseline in %	91.05 ± 4.09	89.52 ± 4.09
○ ΔPost-Baseline	1.77 ± 3.69	3.14 ± 3.42
○ ΔFollowUp-Baseline	1.30 ± 4.68	2.63 ± 4.27

Means and standard deviations were calculated, when possible, for each group. For all cognitive domains, composite z-scores are provided, the scores of the experimental visual-spatial WM measure are expressed in %. LEDD, Levodopa equivalent daily dose; UPDRS III, Unified Parkinson's Disease Ranking Scale Part III; MoCA, Montreal Cognitive Assessment; GDS, Geriatric Depression Scale; WM, Working Memory.

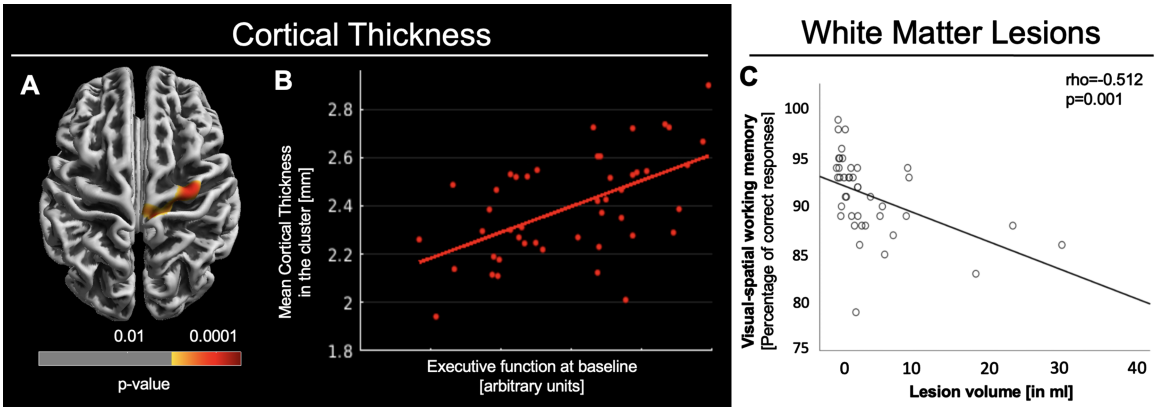

Fig. 1. A) Multiple regression between executive function at baseline and cortical thickness. Positive contrast on executive function at baseline corrected for age and sex. $p < 0.05$ FWE corrected on cluster level. B) Plot of the linear regression between mean cortical thickness (in mm) extracted from the cluster and executive function at baseline (arbitrary units) corrected for age and sex. C) Scatter plot of visual-spatial working memory at baseline and lesion volume [in ml] with linear fitline. Rho and p-value of the partial rank correlation corrected for age and sex.

Cortical thickness

There was a positive correlation between executive function at baseline and cortical thickness in the right precentral gyrus ($x = 35, y = -14, z = 66, T = 4.18$) (see Fig. 1A, B). Cortical thickness did not affect any other cognitive domain at baseline. No relationship was observed between cortical thickness and training responsiveness in any cognitive domain.

White matter lesions

There was a negative correlation between the experimental visual-spatial working memory measure at baseline and lesion volume ($p = 0.001$, rho = –0.512) (see Fig. 1 C). Lesion volume did not affect any other cognitive domain at baseline nor the training responsiveness in any cognitive domain.

DISCUSSION

Here, we demonstrate that neither cortical thickness nor white matter lesions were associated with the responsiveness to WMT. However, cognitive performance at baseline was influenced to some extent by brain structure. Particularly, better executive function performance was associated with higher cortical thickness in the precentral gyrus, which is consistent with prior findings showing a positive correlation between cortical thickness and executive function operationalized with the Wisconsin Card Sorting Test [10]. Additionally, here higher white matter lesion volume was associated with decreased visual-spatial working memory performance, which has previously been shown for other neuropsychological domains [11].

While this study is the first in PD to take structural brain properties as a potential determining factor for WMT responsiveness into account, the results need to be interpreted with caution. Since this RCT focused on a specific group of cognitively healthy patients with PD and the sample comprised mainly subjects with mild to moderate severity of white matter lesions, our results cannot be generalized to patients with baseline cognitive dysfunction or a higher load of white matter lesions. However, our results are in line with a recent publication showing that WMT success was not hampered by the presence of mild white matter lesions in healthy individuals [12].

To conclude, WMT seems effective in cognitively healthy patients with PD [3, 4]. While WMT responsiveness might be predicted by age, intelligence and baseline performance [2], it was independent of cortical thickness or volume of white matter lesions in this cohort. Now, more research in larger samples is needed, especially focusing on patients with severe cerebral small vessel disease as well as apparent cognitive impairment in order to confirm these findings and extent our knowledge on intervention responsiveness, ultimately aiming to improve tailored treatment.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY

Data will be made available upon reasonable request.

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