BRAIN COMMUNICATIONS

Working memory training increases neural efficiency in Parkinson's disease: a randomized controlled trial

Kathrin Giehl,[1,2] Anja Ophey,[3] Jochen Hammes,[1] Sarah Rehberg,[3] Thorsten Lichtenstein,[4] Paul Reker,[5] Carsten Eggers,[6] Elke Kalbe[3] and Thilo van Eimeren[1,5,7]

Impairment of working memory and executive functions is already frequently observed in early stages of Parkinson's disease. Improvements in working memory performance in this cohort could potentially be achieved via working memory training. However, the specific neural mechanisms underlying different working memory processes such as maintenance as opposed to manipulation are largely under-investigated in Parkinson's disease. Moreover, the plasticity of these correlates as a function of working memory training is currently unknown in this population. Thus, the working memory subprocesses of maintenance and manipulation were assessed in 41 cognitively healthy patients with Parkinson's disease using a newly developed working memory paradigm and functional MRI. Nineteen patients were randomized to a 5-week home-based digital working memory training intervention while the remaining patients entered a control, wait list condition. Working memory task-related activation patterns and context-dependent functional connectivity, as well as the change of these neural correlates as a function of training, were assessed. While both working memory processes activated an extended frontoparietal–cerebellar network, only the manipulation of items within working memory also recruited the anterior striatum. The intervention effect on the neural correlates was small, but decreased activation in areas relevant for working memory could be observed, with activation changes correlating with behavioural change. Moreover, training seemed to result in decreased functional connectivity when pure maintenance was required, and in a reorganization of functional connectivity when items had to be manipulated. In accordance with the neural efficacy hypothesis, training resulted in overall reduced activation and reorganized functional connectivity, with a differential effect on the different working memory processes under investigation. Now, larger trials including follow-up examinations are needed to further explore the long-term effects of such interventions on a neural level and to estimate the clinical relevance to potentially delay cognitive decline in cognitively healthy patients with Parkinson's disease.

1 Faculty of Medicine and University Hospital of Cologne, Department of Nuclear Medicine, University of Cologne, Cologne, Germany
2 Research Centre Jülich, Institute of Neuroscience and Medicine (INM-2), Jülich, Germany
3 Faculty of Medicine and University Hospital of Cologne, Department of Medical Psychology, Neuropsychology and Gender Studies and Center for Neuropsychological Diagnostics and Intervention (CeNDI), University of Cologne, Cologne, Germany
4 Faculty of Medicine and University Hospital of Cologne, Department for Radiology, University of Cologne, Cologne, Germany
5 Faculty of Medicine and University Hospital of Cologne, Department of Neurology, University of Cologne, Cologne, Germany
6 Faculty of Medicine and University Hospital of Marburg, Department of Neurology and Center for Mind, Brain and Behavior, University of Marburg, Marburg, Germany
7 German Center for Neurodegenerative Diseases (DZNE), Bonn-Cologne, Germany

Correspondence to: Thilo van Eimeren, MD
Department of Nuclear Medicine, University Hospital of Cologne, Kerpener Str. 62, 50937 Cologne, Germany
E-mail: thilo.van-eimeren@uk-koeln.de

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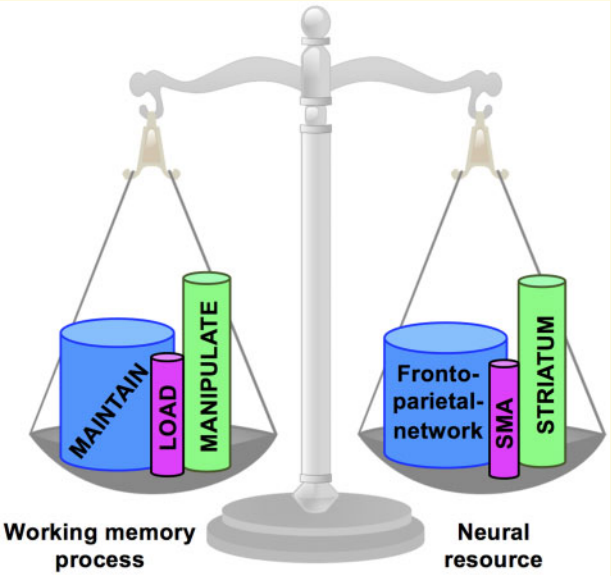
Abbreviations: AS = anterior striatum; CG = control group; dlPFC = dorsolateral prefrontal cortex; FC = functional connectivity; fMRI = functional magnetic resonance imaging; RCT = randomized controlled trial; SMA = supplementary motor area; WM = working memory; WMT = working memory training

Graphical Abstract



Introduction

Cognitive impairment is a very frequent non-motor symptom of Parkinson's disease (Aarsland *et al.*, 2010) with a detrimental effect on quality of life in affected individuals (Lawson *et al.*, 2014). Especially, deficits in working memory (WM) and executive functions are common and reported already in newly diagnosed patients (Muslimović *et al.*, 2005) and even possible prodromal cases of Parkinson's disease (Fengler *et al.*, 2017). For WM, two sub-functions are distinguished: while WM maintenance refers to the pure storage of information, WM manipulation is characterized by the additional demand to operate on this stored information using executive resources (Cowan, 2017; Chai *et al.*, 2018). On a behavioural level, it has been shown that these different facets of WM are variably impacted in Parkinson's disease with greater impairments observed during the manipulation of information with a relative preservation of performance when pure maintenance within WM is needed (Lewis *et al.*, 2003). In line with this, a recent cognitive intervention study in Parkinson's disease resulted in improved performance on a WM manipulation task, but not on a trained task of pure WM maintenance (Fellman *et al.*, 2020). Supporting this dissociation, neurophysiological studies in healthy individuals have shown that the maintenance and manipulation of information in WM rely on different neural substrates (Lewis *et al.*, 2004; Suzuki *et al.*, 2018). Whereas both processes seem to engage a widespread frontoparietal network (Owen *et al.*, 2005; Suzuki *et al.*, 2018), the manipulation of WM content in particular additionally recruits increased anterior striatal contribution (Lewis *et al.*, 2004). Corroborating this, the basal ganglia have been associated with the dopamine-dependent (Gruber *et al.*, 2006) updating of WM and gating of task-relevant information into WM (Awh and Vogel, 2008). Thus, especially in the context of Parkinson's disease marked by substantial dopamine depletion in the basal ganglia (Schapira, 2009; Volpicelli-Daley *et al.*, 2011) and variable behavioural manifestations of WM impairment, the differential examination of WM subprocesses seems necessary. However, MRI-suitable designs targeted at specific cognitive processes of interest (e.g. manipulation in WM) with the aim of understanding the specific neural underpinnings are sparse in Parkinson's disease (Giehl *et al.*, 2019).

Due to the increased vulnerability of patients with Parkinson's disease for cognitive decline, addressing this detrimental process during the early disease phase is crucial to maintain high-level functioning. Previously, cognitive training has been identified as a new route of non-pharmacological intervention to preserve or even improve cognitive function in Parkinson's disease (Leung *et al.*, 2015; Glizer and MacDonald, 2016). However, the

potential of focused interventions on cognitive domains specifically vulnerable in Parkinson's disease—such as WM—is sparse, despite convincing evidence of working memory training (WMT) effects from healthy individuals (Klingberg, 2010; Melby-Lervåg and Hulme, 2013; Karbach and Verhaeghen, 2014; Constantinidis and Klingberg, 2016) and brain-injured non-Parkinson's disease populations (Johansson and Tornmalm, 2012; Aguirre *et al.*, 2019).

Cognitively healthy elderly have frequently been observed to expend more neural resources in order to successfully complete a cognitive task when compared to young individuals, which has often been interpreted as a compensatory mechanism to account for less sufficient processing with increasing age (Li *et al.*, 2015; Suzuki *et al.*, 2018). In addition, WMT studies in healthy individuals have often resulted in decreased neural responses after invention completion (Brehmer *et al.*, 2011; Buschkuehl *et al.*, 2012). Taken together, it seems conceivable that WMT could result in less need for such supposedly compensatory activation, resulting in an overall reduction of neural response. This is in accordance with the neural efficiency idea, stating that highly trained processes require less neural energy (Haier *et al.*, 1988; Neubauer and Fink, 2009). Although first results of WMT in Parkinson's disease show promising behavioural WM improvements (Giehl *et al.*, 2020; Ophey *et al.*, 2020), the neural effects of WMT underlying these effects are currently unknown.

We therefore conducted a single-blind randomized controlled trial (RCT) to investigate the effects of a 5-week home-based WMT in patients with Parkinson's disease without cognitive impairment compared to a no-intervention Parkinson's disease control group (CG) (Ophey *et al.*, 2020). While the clinical and neuropsychological outcomes are reported elsewhere (Giehl *et al.*, 2020; Ophey *et al.*, 2020), this report focuses on the neural effects of the conducted WMT on different aspects of WM using a newly developed WM paradigm and functional magnetic resonance imaging (fMRI). Specifically, activation and functional connectivity (FC) changes with regards to pure maintenance as opposed to manipulation of WM content were examined. Considering the underlying neuropathology of the disease and its variable behavioural manifestation (Lewis *et al.*, 2003; Kudlicka *et al.*, 2011), we hypothesized that WMT would have a differential effect on neural correlates underlying WM maintenance and WM manipulation in Parkinson's disease. Moreover, we expected activation and FC changes resulting in a more efficient underlying neural network similar to long-term WMT effects induced in healthy elderly (Brehmer *et al.*, 2011; Buschkuehl *et al.*, 2012). In addition, presuming that even cognitively healthy patients might experience Parkinson's disease-related inefficient processing, we further hypothesized that WMT might also result in increased activation in those particularly vulnerable areas, as e.g. the striatum, potentially associated with changes in WM performance (Brehmer *et al.*, 2011).

Materials and methods

Study design

The presented neuroimaging data originate from a patient cohort enrolled in a large single-blind RCT conducted at the University of Cologne aiming to investigate effects of WMT in Parkinson's disease (Ophey *et al.*, 2020). The RCT was conducted in accordance with the latest declaration of Helsinki (World Medical Association, 2013), approved by 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, accessed 27 July 2020). All patients gave written informed consent prior to study entry.

In brief, during an initial appointment, all patients were screened for eligibility and performed an extensive neuropsychological test battery (Litvan *et al.*, 2012). Second, eligible patients who agreed to the imaging module of this trial completed the WM-fMRI paradigm on another day within the same week. Third, all included patients entered the 5-week invention period after being randomly assigned to the WMT group or the waiting list arm of the study. The WMT was based on the online cognitive training program NeuroNation (http://www.neuronation.com/, accessed 27 July 2020) and included tasks addressing different WM processes with varying task demands. Finally, all patients were re-evaluated following the invention using the identical fMRI paradigm as for baseline testing. Clinical and neuropsychological examinations were repeated after WMT completion and again after 3 months with no training in-between. Details of the randomization, the WMT intervention, feasibility and immediate as well as long-term clinical and neuropsychological effects of the intervention can be found elsewhere (Giehl *et al.*, 2020; Ophey *et al.*, 2020).

Participants

All patients were diagnosed with idiopathic Parkinson's disease (Hughes *et al.*, 1992), were aged between 45 and 85 years and had normal or corrected to normal vision and hearing. Exclusion criteria were mild cognitive impairment or dementia associated with Parkinson's disease according to level-II diagnostic criteria (Litvan *et al.*, 2012), any other neurological or psychiatric disorder including major depression (geriatric depression score >11) (Yesavage *et al.*, 1982), any other life-threatening disease, deep brain stimulation and, additionally for the imaging study module, the inability to undergo MRI scanning. Patients were instructed to continue their regular medication at all times. For detailed information regarding patient demographics, see Table 1.

Table 1 Final sample characteristics per group at baseline

		WMT (n = 19)	CG (n = 22)	P-value
Age in years		65.3 ± 8.9 (47.9–78.7)	63.5 ± 9.1 (46.3–79.0)	0.54[a]
Sex	Female, n (%)	10 (52.6)	9 (40.9)	0.54[b]
	Male, n (%)	9 (47.4)	13 (59.1)	
Handedness	Right, n (%)	17 (89.5)	22 (100)	0.21[b]
	Left, n (%)	2 (10.5)	0 (0)	
Education in years		15.3 ± 3.4 (11–22)	15.6 ± 2.6 (10–22)	0.34[c]
Global cognition Montreal Cognitive Assessment score		27 ± 1.7 (24–29)	27.7 ± 1.4 (25–30)	0.26[c]
Disease duration in years		5.5 ± 4.1 (0.8–16.1)	5.9 ± 5.8 (0.4–23.2)	0.62[c]
Unified Parkinson's disease Rating Scale-III		28.6 ± 8.0 (13–45)	29.6 ± 7.9 (17–49)	0.69[a]
Hoehn & Yahr scale	Stage 2, n (%)	18 (94.7)	21 (95.5)	0.99[b]
	Stage 3, n (%)	1 (5.3)	1 (4.5)	
Levodopa equivalent daily dose (mg)		667 ± 451 (120–1785)	493 ± 286 (100–1180)	0.29[c]
Depression geriatric depression score		1.7 ± 1.9 (0–7)	2.9 ± 2.7 (0–9)	0.17[c]

Data are mean values ± standard deviation (range), unless stated otherwise. Variables were previously inspected visually by qq-plots and statistically by Shapiro–Wilk tests for normal distribution. CG = control group; WMT = computerized working memory training group.
[a]For baseline comparison between groups, P-values of independent sample t-tests are reported as appropriate.
[b]For baseline comparison between groups, P-values of χ^2-tests are reported as appropriate.
[c]For baseline comparison between groups, P-values of Wilcoxon rank-sum tests are reported as appropriate.

WM-fMRI task

During fMRI, we employed a novel WM paradigm inspired by earlier work from Lewis *et al.* (2004) (see Fig. 1). All letters and signs were displayed in white font against a black background and positioned in the centre of the screen, unless stated otherwise. Name of event and presentation times are given in brackets. Each trial started with a fixation cross and the number '3' or '4' below fixation, indicating how many letters were to follow (load cue, 2.5 s). Accordingly, three or four letters were presented sequentially (presentation phase, 1 s/letter). Then, a cue was presented instructing the patient if these letters had to be remembered (German word: 'merken') or could be discarded (German word: 'verwerfen') (trial cue, 1 s). This cue was followed by an interval marked by another fixation cross in which the patient either had to remember the presented letters (maintain, time window jittered 7–11 s, following 'remember cue') or could rest (rest, time window jittered 7–11 s, following the 'discard cue'). In case of a resting period, a new trial started after the resting time window elapsed. Otherwise the patient was presented with an arrow (arrow cue, 1 s), indicating whether the previously seen letters had to be maintained in the observed, forward order (→) or whether the letter sequence had to be reversed (←) in the upcoming time window [second maintenance phase following (→) or manipulation phase following (←), time window jittered 5–8 s]. This was followed by the sequential presentation of three or four letters in identical/correctly reversed or incorrect order (offered answer, 1 s/letter). Subsequently, the possibilities 'right' or 'wrong' were displayed left and right from the centre of the screen. From those the patient had to choose by pressing the corresponding button on the button box (choice, displayed until button press recorded with a maximum answer period of 3 s). Finally, the patient received feedback about the performance on every trial in form of a smiley or frowny face (feedback, 1 s).

The experiment was divided into five blocks with 16 trials each. Each block was composed of four rest trials and 12 remember trials, of which eight were high-load (four letters) and four were low-load trials (three letters). Half of the high-load trials were pure maintenance trials (arrow cue = right), whereas the other half were manipulation trials (arrow cue = left). Altogether, the experiment comprised 80 trials, which were equally distributed between trial types (20 rest, 20 low-load, 20 high-load maintain and 20 high-load manipulate). The experiment code was executed and responses recorded using Matlab v. R2015a (MathWorks, Inc).

Image acquisition

MRI scanning was performed using a 3-T whole body MRI scanner (Philips Ingenia; Philips Healthcare, Best, the Netherlands) and a 32-channel head coil. An MRI-compatible visual system (SensaVue fMRI, Invivo Corporation, Gainesville, FL) displaying the WM-fMRI paradigm was placed at the head-end of the scanner and viewed by the patients via a mirror-system position on the top of the head coil. Responses were recorded using a button box held in the right hand.

For fMRI, the first five scans of each session were discarded due to non-equilibrium of magnetization, followed by 180 echo planar images with 28 interleaved transversal slices (scan duration = 8 min 2.5 s; field of view = 220 × 220 × 139 mm^3, voxel size = 3.4 × 3.4 × 4 mm^3, slice thickness = 4 mm, gap = 1 mm, repetition time = 2500 ms, echo time = 30 ms and flip angle = 90°).

For spatial normalization and exclusion of gross structural abnormalities, a 3D T_1-weighted image was acquired (scan duration = 5 min 55 s, 165 transverse

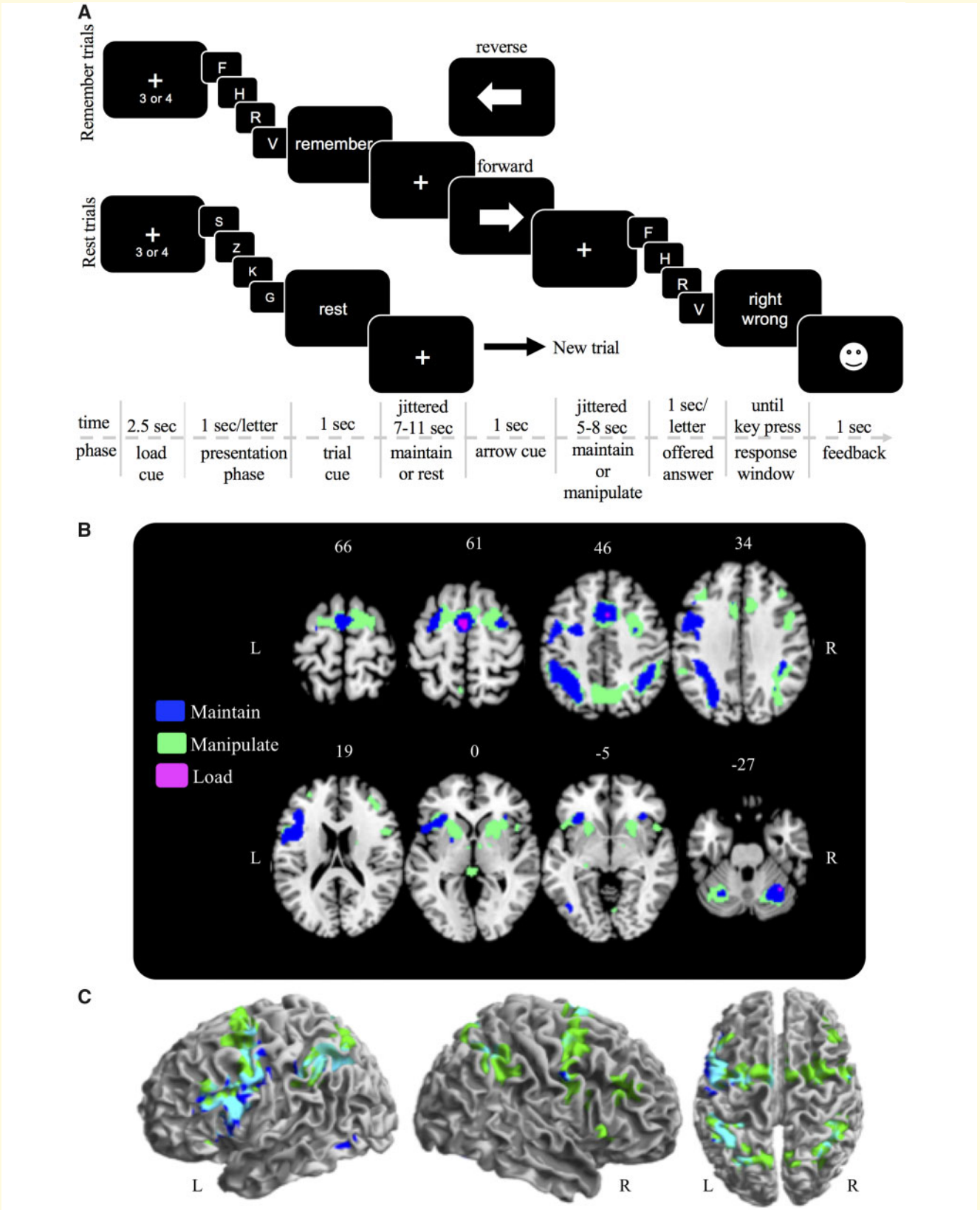


Figure 1 WM-fMRI paradigm and task-related activation pattern. The patient had to remember three or four letters in **A**; following a right arrow, the sequence needed to be maintained in forward order, while the sequence had to be reversed following a left arrow; the offered answer was then judged correct or incorrect via button press. Axial view of baseline activation pattern shown in **B** for maintain versus rest (blue); manipulate versus maintain (green); high load versus low load (pink); surface rendering of maintain versus rest (blue); manipulate versus rest (green); overlap (turquoise) is shown in **C**; binary maps of all voxels with $P < 0.05$ FWE-corrected on voxel-level. L = left; R = right; displayed using MRIcron; surface rendering via SPM12.

slices, thickness = 1 mm, field of view = 250 × 230 × 165 mm^3, voxel size = 1 × 1 × 2 mm^3, repetition time = 9.6 ms, echo time = 4.8 ms and flip angle = 8°). In addition, a 3D FLAIR image was recorded to check for gross vascular lesions (scan duration = 4 min 33.6 s, 326 interleaved transverse slices, thickness = 1.12 mm, field of view = 250 × 250 × 182.6 mm^3, voxel size = 1.12 × 1.12 × 1.12 mm^3, repetition time = 4800 ms, echo time = 281 ms and flip angle= 90°).

Image preprocessing

Preprocessing and statistical analysis of the image data were done using SPM12 (www.fil.ion.ucl.ac.uk/spm/software/spm12/, accessed 27 July 2020) executed in MATLAB version 8.5 (R2015a) (www.mathworks.com, accessed 27 July 2020). To account for movement of the subject, all fMRI image volumes were realigned to the first volume of the corresponding session and subsequently coregistered to the corresponding structural T_1 image using rigid-body transformation. A Volterra expansion was performed on the generated six realignment parameters to model residual movement artefacts (Lund *et al.*, 2005) resulting in 24 movement parameters, which were later entered into the design matrix as regressors of no interest.

For the T_1 image, the origin was set to the AC–PC plane and the images were segmented using the SPM12 segmentation procedure. The produced normalization parameters were then applied to all coregistered fMRI image volumes. Successful normalization to standard Montreal Neurological Institute (MNI) coordinate space was checked at random for each subject using ventricles and brain borders as landmarks. Finally, all fMRI image volumes were smoothed with an isotropic 8-mm full width half maximum Gaussian filter.

Statistical analysis

Demographic, clinical and behavioural data

Demographic and clinical data at baseline were compared between groups using Wilcoxon rank-sum tests, independent sample *t*-tests or χ^2-tests as appropriate. fMRI-task performance was determined as percentage of correct answers during the forced-choice period of the paradigm. Data were entered in a 2 × 2 repeated measure ANOVA with time (baseline testing versus post-testing) as intra-subject and group (WMT versus CG) as inter-subject factor.

Statistical analysis of fMRI data

Activation analysis. First-level analysis was performed using a general linear model with 12 regressors of interest (all events) and 34 regressors of no interest (all 10 events of a remember trial preceding an erroneous response of the patient plus 24 realignment parameters). On a single subject level, we then computed four contrast images for events of interest: maintain versus rest, manipulate versus rest, manipulate versus maintain and high load versus low load.

On the second level, we computed the main effects of condition at baseline across both groups by means of a one sample *t*-tests with the respective first-level contrast images. Group differences following WMT were assessed using a full-factorial ANOVA design with time and group as factors and masked using a binarized grey matter mask implemented in SPM (mask thresholded at >0.2).

Reported clusters for main effects of task are significant on $P < 0.05$ (family wise error (FWE)-corrected on voxel-level), whereas comparisons between groups over time, i.e. effect of WMT, are reported at $P < 0.001$ uncorrected. Anatomical labelling was conducted using the Harvard–Oxford brain atlas. If locations could not be determined the AAL atlas was consulted.

Functional connectivity analysis: psycho-physiological interaction. In order to understand the effect of WMT on FC observed for the different experimental contexts, i.e. WM maintenance and manipulation, we opted for the psycho-physiological interaction analysis approach as implemented in SPM12.

Based on the task activation patterns observed during the activity analysis of our data, we chose areas displaying the highest activity across the task as seed regions. Thus, a sphere of 8 mm was drawn around three peak voxels in the left dorsolateral prefrontal cortex (dlPFC) (−42/8/26), left supplementary motor area (SMA) (−2/2/62) and left anterior striatum (AS) (−18/14/−2). In order to understand whether those regions interacted differently during the pure maintenance or a pure manipulation process, we calculated the interaction term between contrast 1 (maintain versus rest) and all seeds separately, and contrast 3 (manipulate versus maintain) and all seeds separately, resulting in six different models.

Each first-level general linear model included the following regressors: psycho-physiological interaction-interaction term, the activity time course of the seed (physiological regressor), the contrast of interest (psychological regressor) as well as nuisance regressors (24 movement and one session regressor).

On a group-level, we submitted the contrast images of all patients derived from the according first-level psycho-physiological interaction–interaction term to a full-factorial ANOVA design with time and group as factors to test for effects of WMT on FC in different psychological contexts. Masking, determination of significance and anatomical location were conducted as for the WMT-induced change of activation. Results of the baseline FC analysis can be found in Supplementary material.

Behaviour–brain correlations of WMT-induced changes. Since the fMRI paradigm used here was not designed to pick up small variations in behaviour, we used results from more sensitive measures of WM from the neuropsychological test battery to calculate correlations between behaviour and WMT-induced neural change. Thus, change

scores for significantly improving neuropsychological measures including a verbal WM composite score (Ophey *et al.*, 2020) and an experimental measure of visuospatial WM function (Giehl *et al.*, 2020) were calculated. These were then correlated with the mean blood oxygen level dependent signal change associated with each task condition showing a significant WMT effect (maintain versus rest; manipulate versus rest; manipulate versus maintain), extracted from an 8-mm sphere around the overall WMT-induced peak corresponding to the left AS (−4/4/−4).

Data availability

The data generated during this study are available on reasonable request.

Results

Participant characteristics

Initially 85 patients were screened for this trial from which 76 were eligible. Nine patients (9%) had to be excluded due to incidental Parkinson's disease with mild cognitive impairment. A subset of 48 patients agreed to the imaging module of this study. From those, 22 were randomized to the WMT group, and 25 entered the waiting phase. One patient declined post-intervention scanning. Six data sets had to be excluded for various reasons (excessive movement = 2; scanner artefact = 2; incidental finding = 2; for details refer to CONSORT flow chart, Fig. 2), leaving 41 data sets for analysis (WMT = 19; CG = 22).

At baseline, patients (46.34% female; two left-handed) included in the final analysis had an average age of 64.34 ± 8.96 years and an average disease duration of 5.71 ± 5.12 years. The majority was mild to moderately affected (mainly Hoehn & Yahr stage II) with an average Unified Parkinson's disease Rating Scale-III score of 29.12 ± 1.23. Patients received a levodopa equivalent daily dose of 573 ± 377 mg. Overall, patients were relatively highly educated with 15.46 ± 2.94 years of education, achieved a high average Montreal Cognitive Assessment score of 27.4 ± 1.6 and showed only minor symptoms of depressed mood (average geriatric depression score: 2.37 ± 1.58). Importantly, no significant difference on any demographic or clinical measure was evident between groups at baseline (see Table 1).

In-scanner task performance

There was no significant main effect of time [$F(1,39) = 3.56$, $P = 0.067$, $\eta^2 = 0.08$] or group [$F(1,39) = 0.38$, $P = 0.540$, $\eta^2 = 0.01$] on task performance, nor an interaction [$F(1,39) = 1.26$, $P = 0.269$, $\eta^2 = .03$]. Across groups and time, participants reached on average 88.1 ± 10.62% accuracy.

General task activation

In order to examine whether this newly designed paradigm indeed targeted WM as hypothesized, we first examined task activation at baseline across both groups for our four contrasts of interest (see Fig. 1 and Table 2). During maintain versus rest extensive frontal activation was observed encompassing the orbitofrontal cortex, inferior and middle frontal gyrus, SMA and precentral gyrus. In addition, strong activation was observed in the superior parietal lobe and supramarginal gyrus, inferior temporal gyrus, thalamus and the cerebellum. The manipulate versus rest contrast relied on very similar brain regions, however, additional strong activation of the precuneus and bilateral AS was observed. A similar activation pattern was found when contrasting manipulate versus maintain. When comparing the high-load versus low-load memory condition, only two clusters of increased activation were observed in the SMA and paracingulate gyrus.

Effects of WMT

Neural activation change

No activation increases following WMT could be observed in the training group for any of the investigated contrasts (see Fig. 3 and Table 3). In contrast, clusters of decreased activation following WMT were located in the middle frontal and precentral gyrus, precuneus, brainstem, cerebellum and AS for the pure maintenance process. Stronger and more spatially extended WMT-induced decreased activation clusters were found when manipulation was required. The largest cluster was observed in the midline area encompassing the bilateral AS and subcallosal cortex. In addition, clusters of decreased activation were located in the SMA, bilateral insular cortex, precuneus, superior temporal and lateral occipital gyrus, brainstem and cerebellum. For the specific manipulation contrast, only two small clusters of decreased activation, one encompassing the subcallosal cortex, thalamus and lateral ventricle as well as one in the anterior cingulate gyrus were observed. The differential effect of load did not change as a function of WMT. Since dopamine replacement therapy could potentially impact cortical activation patterns (Nombela *et al.*, 2014), we conducted an additional analysis including levodopa equivalent daily dose as covariate in the full-factorial model to account for variations in medication. However, only marginal changes could be observed.

Functional connectivity change

Following WMT, no clusters of increased FC could be observed in the context of maintenance for any of the seeds. However, reduced FC was evident between the dlPFC seed and the left middle frontal gyrus, right superior frontal gyrus, right cingulate, left lingual gyrus and left AS (see Table 4). The AS seed showed decreased FC

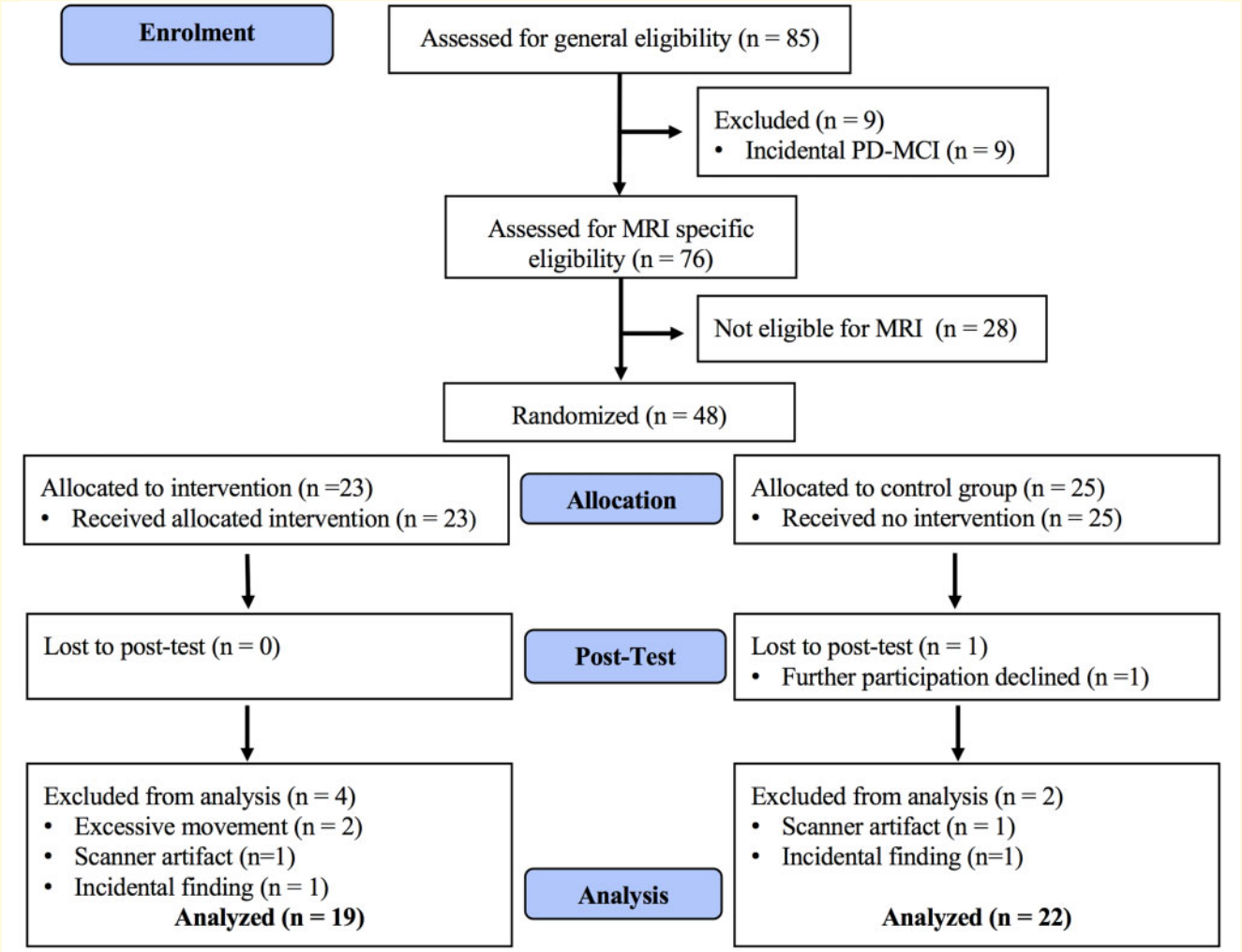


Figure 2 CONSORT flow chart. Participant enrolment, allocation and analysis.

towards white matter adjacent to the lateral ventricle, parahippocampal gyrus and precuneus.

Following WMT, a redistribution of FC in the context of manipulation was observed with a tendency towards reduced FC from the dlPFC and increased FC from SMA and AS.

More precisely, from the left dlPFC seed, one cluster of increased FC was evident in the left parietal operculum, while a widespread reduction of FC was observed towards the right superior, right middle and bilateral inferior frontal gyrus, left frontal pole, right cingulate, right insula, right precentral gyrus and right cerebellum. In contrast, from the left SMA, several clusters of increased FC towards the left postcentral gyrus, left planum polare, left angular, fusiform, lingual, supramarginal gyrus and right SMA were observed, accompanied by only one cluster of reduced FC located near the left lateral ventricle. From the AS, increased FC was observed towards the superior frontal gyrus, lateral ventricle, superior parietal lobe and hippocampus. No decreased FC from the AS was evident.

Brain–behaviour correlations of WMT-induced changes

When investigating the relationship between WMT-induced activation change in the AS and the observed significant post-testing–baseline testing-change in cognition as operationalized via a neuropsychological composite score of verbal WM (Ophey *et al.*, 2020) and a measure of visuospatial WM (Giehl *et al.*, 2020), a moderate positive correlation between both WM measures and blood oxygen level dependent signal change could be observed for the maintain versus rest contrast [$r(17) = 0.48$, $P = 0.039$ for verbal WM, and $r(17) = 0.50$, $P = 0.029$ for visuospatial WM, respectively]. For the manipulate versus rest contrast, there was a moderate positive correlation for verbal WM only [$r(17) = 0.56$, $P = 0.013$]. No correlations could be observed for the specific manipulate versus maintain contrast (see Fig. 4). When including levodopa equivalent daily dose as a covariate into the brain-behaviour correlation analyses, again only marginal changes could be observed.

Table 2 Task-associated activation

Brain region	Side	MNI peak coordinate			Cluster size (voxel)	Peak t-values	*P*-value
		x	*y*	*z*			
Contrast 1: maintain versus rest							
Inferior/middle frontal gyrus/precentral gyrus	L	−42	8	26	2695	10.13	<0.001
Cerebellum/fusiform gyrus	R	28	−64	−26	716	9.41	<0.001
Supplementary motor area	L	−2	0	62	985	9.15	<0.001
Supramarginal gyrus	R	38	−48	40	722	8.88	<0.001
Superior parietal lobule	L	−30	−58	40	1756	8.64	<0.001
Middle frontal gyrus	R	30	0	56	199	7.35	<0.001
Inferior temporal gyrus	L	−44	−54	−14	180	6.85	0.001
Orbitofrontal cortex	R	34	28	−6	47	6.45	0.002
Precentral gyrus	R	56	−4	40	40	6.23	0.004
Thalamus	L	−10	−16	4	39	6.23	0.004
Cerebellum	L	−2	−50	−20	97	6.01	0.007
Cerebellum	L	−28	−64	−28	39	5.78	0.014
Contrast 2: manipulate versus rest							
Middle frontal gyrus/supplementary motor area	R	30	−2	54	5603	10.55	<0.001
Superior parietal lobule	R	38	−48	42	1510	9.58	<0.001
Superior parietal lobule/lateral occipital cortex/supramarginal gyrus	L	−32	−52	42	2289	9.17	<0.001
Orbitofrontal cortex	R	34	28	−4	281	8.88	<0.001
Orbitofrontal cortex	L	−32	26	−4	259	7.94	<0.001
Cerebellum/fusiform gyrus	R	28	−66	−26	519	7.69	<0.001
Middle frontal gyrus	R	38	34	26	283	7.36	<0.001
Precuneus cortex	R	10	−68	50	204	7.23	<0.001
Anterior striatum	R	16	14	−4	176	7.14	<0.001
Anterior striatum	L	−16	14	−4	147	6.57	0.001
Cerebellum	L	−28	−64	−28	150	6.35	0.002
Inferior frontal gyrus	L	−52	12	0	63	6.04	0.006
Cerebellum	R	2	−50	−18	50	5.98	0.006
Inferior temporal gyrus	L	−48	−56	−14	27	5.81	0.010
Thalamus	R	8	−20	−4	34	5.67	0.015
Contrast 3: manipulate versus maintain							
Middle frontal gyrus	R	38	32	26	441	9.31	<0.001
Middle and inferior frontal gyrus	L	−36	32	36	752	9.29	<0.001
Anterior striatum	R	22	12	−4	629	9.11	<0.001
Paracingulate gyrus/middle and superior frontal gyrus	R	10	14	46	4077	8.86	<0.001
Insular cortex/anterior striatum/thalamus	L	−40	20	−2	848	8.82	<0.001
Supramarginal gyrus/lateral occipital cortex	R	46	−46	48	1210	8.41	<0.001
Lateral occipital cortex/superior parietal lobule/precuneus	L	−26	−68	34	2534	8.23	<0.001
Cerebellum/lingual gyrus	R	38	−60	−30	969	8.15	<0.001
Cerebellum	L	−34	−58	−28	337	7.49	<0.001
Thalamus	L	−2	−28	4	243	6.82	0.001
Precentral gyrus	R	44	10	30	227	6.62	0.001
Inferior frontal gyrus	R	52	10	16	52	6.34	0.003
Frontal pole	L	−32	50	18	20	6.24	0.004
Temporal pole	R	48	16	−6	82	6.18	0.004
Lingual gyrus	L	−2	−72	6	38	6.08	0.006
Cerebellum	R	2	−50	−20	20	5.87	0.010
Thalamus	L	−14	−14	8	16	5.63	0.019
Contrast 4: high load versus low load							
Supplementary motor area	L	−4	0	60	47	6.75	0.001
Paracingulate gyrus	R	2	12	46	13	5.70	0.021

Peak coordinates of significant clusters following voxel-wise FWE correction ($P < 0.05$) exceeding 10 continuous voxels are reported; L = left; R = right.

Discussion

Using a newly designed WM-fMRI paradigm, we were able to identify specific neural correlates underlying WM maintenance and WM manipulation in patients with Parkinson's disease without cognitive impairment. While both WM processes relied on a network of increased left-dominant frontoparietal–cerebellar activation, only WM manipulation seemed to evoke additional, rather bilateral neural responses including the right precuneus and bilateral AS. Following WMT, generally less activation and FC was observed for the WMT group as compared to the CG, mainly focused around the AS. Activation change in this region was also correlated with neuropsychological performance gains.

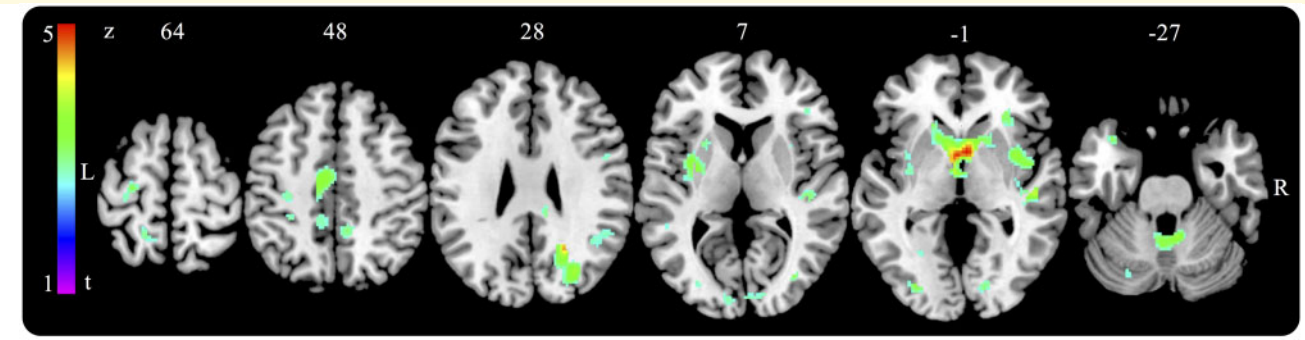


Figure 3 Neural WMT-induced effect. Axial view of WMT-induced activation decreases for the manipulate versus rest contrast. Illustratory threshold $P < 0.005$ uncorrected. L = left; R = right; displayed using MRIcron.

Table 3 WMT-induced activation changes

Brain region	Side	MNI peak coordinate			Cluster size (voxel)	Peak t-values	*P*-value
		x	*y*	*z*			
Contrast 1: maintain versus rest							
Negative group × time interaction							
Middle frontal gyrus	R	30	−4	54	75	4.21	<0.001
Anterior striatum/lateral ventricle	L	−6	4	0	36	4.04	<0.001
Cerebellum	R/L	0	−54	−26	38	4.01	<0.001
Precuneus	R	22	−58	28	26	3.97	<0.001
Brainstem	L	−2	−18	−22	14	3.92	<0.001
Precentral gyrus	L	−36	0	28	33	3.6	<0.001
Contrast 2: manipulate versus rest							
Negative group × time interaction							
Anterior striatum (including bilateral nucleus accumbens and subcallosal cortex)	L	−4	4	−4	311	4.99	<0.001
Precuneus	R	22	−58	28	137	4.46	<0.001
Superior temporal gyrus	R	50	−22	0	29	4.09	<0.001
Brainstem	L	−6	−38	−8	36	3.95	<0.001
Lateral occipital cortex	R	28	−72	26	35	3.76	<0.001
Cerebellum	R	8	−50	−26	42	3.76	<0.001
Insular cortex	R	36	4	0	49	3.72	<0.001
Insular cortex	L	−32	−2	10	68	3.66	<0.001
Lateral occipital cortex	R	32	−74	14	16	3.54	<0.001
Supplementary motor area	L	−6	−10	48	51	3.54	<0.001
Contrast 3: manipulate versus maintain							
Negative group × time interaction							
Subcallosal cortex, thalamus, lateral ventricle	R	2	4	0	40	3.78	<0.001
Anterior cingulate gyrus	L	−2	−4	42	27	3.64	<0.001
Contrast 4: high load versus low load							
No group × time interaction							

Peak coordinates of significant clusters exceeding 10 continuous voxels ($P < 0.0001$ uncorrected) are reported; L = left; R = right.

The identified frontoparietal–cerebellar network associated with the WM task is in accordance with previous meta-analyses on neural correlates underlying WM in healthy individuals (Owen *et al.*, 2005; Emch *et al.*, 2019). While we observed that both WM processes relied on roughly similar neural networks (Veltman *et al.*, 2003), the additional neural responses elicited during manipulation only are in line with previous studies showing increased activation of the parietal lobe in relation to WM manipulation (Veltman *et al.*, 2003; Koenigs *et al.*, 2009; Emch *et al.*, 2019) and the role of the striatum in gating information to and updating of WM (Lewis *et al.*, 2004; Gruber *et al.*, 2006; Dahlin *et al.*, 2008; McNab and Klingberg, 2008; Baier *et al.*, 2010; Yu *et al.*, 2013). Using recurrent neural network models, it has recently been proposed that pure WM maintenance can be achieved via low-activity synaptic short-term plasticity, while the WM manipulation process cannot. For the manipulation operation, persistent neural activity is needed, even scaling with increasing manipulation complexity

Table 4 WMT-induced connectivity changes

Brain region	Side	MNI peak coordinate			Cluster size (voxel)	Peak t-values	*P*-value
		x	y	z			
dlPFC × contrast 1: maintain versus rest							
No positive group × time interaction							
Negative group × time interaction							
Middle frontal gyrus	L	−34	20	46	23	3.824	<0.001
Cingulate gyrus, posterior division	R	4	−44	16	31	3.811	<0.001
Anterior striatum/insula	L	−34	0	−4	13	3.524	<0.001
Lingual gyrus	L	−12	−44	−12	10	3.483	<0.001
Superior frontal gyrus	R	20	44	30	14	3.443	<0.001
Cingulate gyrus, anterior division	R	10	30	24	10	3.375	0.001
dlPFC × contrast 3: manipulate versus maintain							
Positive group × time interaction							
Parietal operculum cortex	L	−38	−34	18	50	4.117	<0.001
Negative group × time interaction							
Middle frontal gyrus	R	24	38	26	62	4.202	<0.001
Cerebellum crus 1	R	32	−70	−34	19	4.192	<0.001
Frontal pole	L	−26	50	20	13	4.185	<0.001
Cingulate gyrus, anterior division	R	4	−10	34	39	4.146	<0.001
Inferior frontal triangularis	L	−34	30	16	12	3.977	<0.001
Inferior frontal gyrus, pars triangularis	R	48	28	−2	72	3.929	<0.001
Cingulate	R	12	14	32	13	3.751	<0.001
Insula	R	34	2	8	43	3.726	<0.001
Superior frontal gyrus	R	16	−18	68	13	3.702	<0.001
Cingulate gyrus, anterior division	L/R	0	26	28	35	3.670	<0.001
Inferior frontal gyrus, pars triangularis	L	−46	34	−2	13	3.643	<0.001
Insula	R	40	−24	2	13	3.630	<0.001
Middle frontal gyrus	R	42	34	26	17	3.557	<0.001
Precentral gyrus	R	46	8	32	12	3.422	<0.001
SMA × contrast 1: maintain versus rest							
No group × time interaction							
SMA × contrast 3: manipulate versus maintain							
Positive group × time interaction							
Postcentral gyrus	L	−34	−28	52	98	4.266	<0.001
Angular gyrus	L	−46	−52	30	105	4.098	<0.001
Fusiform gyrus	L	−36	−42	−8	61	4.094	<0.001
Lingual gyrus	L	−4	−48	−4	35	4.008	<0.001
Planum polare	L	−46	2	−16	87	3.813	<0.001
Fusiform gyrus	L	−32	−62	−8	20	3.767	<0.001
SMA	R	12	−8	42	24	3.761	<0.001
Supramarginal gyrus, posterior division	L	−48	−48	42	23	3.645	<0.001
Negative group × time interaction							
Lateral ventricle	R	4	8	−2	10	3.838	<0.001
AS × contrast 1: maintain versus rest							
No positive group × time interaction							
Negative group × time interaction							
Lateral ventricle	R	20	−24	26	16	3.821	<0.001
Parahippocampal gyrus, anterior division	R	20	−18	−24	18	3.765	<0.001
Precuneus	L	−4	−52	8	14	3.567	<0.001
AS × contrast 3: manipulate versus maintain							
Positive group × time interaction							
Superior frontal gyrus	L	−20	36	30	22	3.723	<0.001
Lateral ventricle	L	−12	−28	22	15	3.649	<0.001
Superior parietal lobe	L	−30	−58	52	27	3.633	<0.001
Hippocampus	L	−36	−36	−8	10	3.439	<0.001
No negative group × time interaction							

Peak coordinates of significant clusters exceeding 10 continuous voxels ($P < 0.0001$ uncorrected) are reported; AS = anterior striatum; dlPFC = dorsolateral prefrontal cortex; L = left; R = right; SMA = supplementary motor area.

(Masse *et al.*, 2019). This might be a potential explanation for the generally increased activation observed in our manipulation contrast. Moreover, it might also account for the rather weak effect that we observed when introducing a slightly higher load in the pure maintenance condition evident in the SMA.

Following WMT, several clusters of decreased activation in WM associated regions were observed, implying

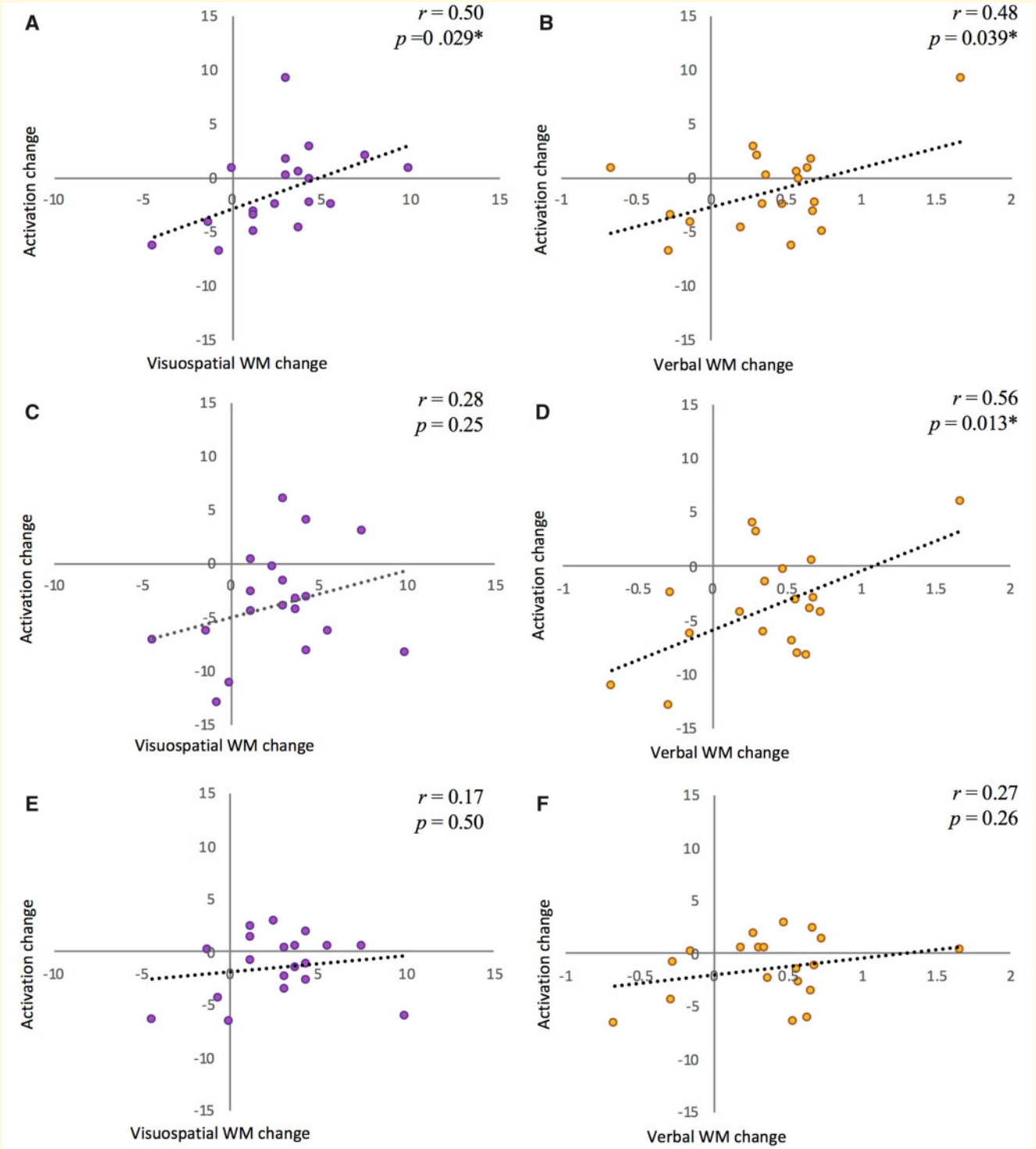


Figure 4 Behaviour–brain correlations. Correlations between neuropsychological WM change scores (visuospatial WM in **A**, **C** and **E**; verbal WM in **B**, **D** and **F**) and blood oxygen level dependent signal change (maintain versus rest contrast in **A** and **B**; manipulate versus rest contrast in **C** and **D**; manipulate versus maintain contrast in **E** and **F**) derived from an 8-mm sphere around WMT-induced activation change peak at the AS (4/−4/4).

that the WMT group performed the WM task using fewer neural resources than the CG after training completion. In line with our results, long-term WMT as implemented here has often been associated with decreased activation in healthy young (Schneiders *et al.*, 2011; Clark *et al.*, 2017) and elderly (Brehmer *et al.*,

2011; Miró-Padilla *et al.*, 2019) as well as neurological non-Parkinson's disease patients (Aguirre *et al.*, 2019). These findings all align with the neural efficacy idea, postulating that better or as in this case 'trained' cognitive performers need less neural resources in order to successfully complete a task (Haier *et al.*, 1988; Neubauer and Fink, 2009). Interestingly, the observed effect was located in and close to the anterior striatal area, the region uniquely contributing to the additional activation observed for the manipulation process in our study. In addition, another major WMT-induced change was observed in the right precuneus, which also contributed majorly to the manipulation contrast. One might speculate that these areas were recruited as a compensatory strategy prior to the intervention in order to maintain high cognitive performance. Similar supporting activation has already been described during WM tasks for the dlPFC in healthy elderly (Suzuki *et al.*, 2018), and for the striatum in patients with Parkinson's disease (Poston *et al.*, 2016; Simioni *et al.*, 2017). Thus, since both groups performed behaviourally on comparable levels on the WM-fMRI task for both time points, it is conceivable that most trained patients were able to produce the same cognitive performance, however using less neural resources (Clark *et al.*, 2017).

Within the trained group, the change in activation correlated with the observed change in neuropsychological measures of WM, indicating that the greatest increase in blood oxygen level dependent signal was associated with the greatest cognitive improvements. Importantly, only the verbal WM task required the maintenance and manipulation of WM (Ophey *et al.*, 2020), while the visuospatial WM task relied on WM maintenance only (Giehl *et al.*, 2020). Accordingly, both tasks correlated with the activation change extracted from the maintain contrast, but only the verbal WM task (i.e. the task also requiring manipulation) correlated with the activation change for the manipulation condition, supporting the idea that the observed specific neural changes support these specific cognitive processes. Interestingly, no correlation was found between the specific manipulation contrast and behaviour. Thus, one might speculate that the neural change was more associated with the pure maintenance of information in WM, rather than the executive demand of operating on this information.

This observed positive relationship between behaviour and brain activation might first seem at odds with the results of our WMT analysis showing decreased activation clusters only. However, despite the inclusion of a rather homogenous cohort of cognitively unimpaired patients with Parkinson's disease, considerable variation within this group regarding cognitive performance is theoretically still possible. Assuming this, one might speculate that the majority of patients recruited additional neural resources in order to produce high cognitive performance prior to WMT. WMT could have potentially made this compensatory hyperactivation redundant while keeping cognitive performance stable, resulting in a more efficient underlying neural network and ultimately in an overall reduction of persistent activation. The observed positive correlations between activation change and behavioural improvements in the WMT group on the other hand could be driven by a subgroup of patients who did not perform at their optimal level prior to WMT, potentially related to early insufficient processing or an incomplete compensatory coping mechanism. Supporting this idea, increased activation following cognitive training in patients with MCI has frequently been observed (Belleville *et al.*, 2011; Rosen *et al.*, 2011). Also, in our study, a true performance increase (as opposed to maintaining the same close-to-optimal cognitive level) could be associated with a net increase in activation in the AS, as shown previously (Brehmer *et al.*, 2011).

In accordance with the intervention effect observed for our activity analysis, WMT had some effects on FC of the three seed regions towards other regions of the brain. For the pure maintenance context, either no (SMA) or small clusters of negative interaction (dlPFC, AS) could be observed, again supporting the idea of increased neural efficiency of the WM network. However, in the context of manipulation decreased FC, especially from the dlPFC, and increased FC from the SMA and the AS were observed, pointing to a general reorganization of FC when the manipulation of WM was required. While previous research has mainly focused on the investigation of task-independent FC in healthy individuals, our results support the general notion that WMT could have the potential to alter the FC of the brain (Buschkuehl *et al.*, 2012; Jolles *et al.*, 2013; Takeuchi *et al.*, 2013).

Strengths and limitations

Our results should be interpreted taking the strengths and limitations of our study design into consideration. To the best of our knowledge, this is the first RCT on WMT in Parkinson's disease implementing neuroimaging methods with the aim to elucidate the underlying neural mechanism of effects induced by such an intervention. In addition, we used a new fMRI paradigm, which was designed to distinguish between different processes in WM as they could potentially be variably affected in Parkinson's disease. Utilizing a robust sample size, our analyses are sufficiently powered resulting in highly reliable results for our WM task.

Next to understanding how WMT could work on a neural level, it is important to know who would benefit from such an intervention and thus the thorough characterization of the sample is essential. Therefore, patients enrolled in this RCT were limited to individuals without MCI to understand whether benefits could already be observed at this early stage before major cognitive decline has occurred. While the inclusion of such a homogeneous cohort enables to draw specific conclusions for this patient group, potentially informing clinicians how to

optimize preventive interventions for patients in stages before the dopaminergic deficit has had an impact on cognition, it limits the generalizability of our results towards patients with Parkinson's disease in other cognitive states. Therefore, more RCTs should be conducted including well characterized patients regarding cognitive stages (Parkinson's disease versus Parkinson's disease with mild cognitive impairment versus Parkinson's disease with dementia) and other variables, e.g. demographic groups (e.g. higher versus lower educated). Moreover, longitudinal studies including follow-up examinations over several years are urgently needed to understand whether WMT could have clinical relevance to delay or even prevent cognitive decline for patients with Parkinson's disease at this early stage.

While some beneficial effects were evident on a behavioural level (Giehl *et al.*, 2020; Ophey *et al.*, 2020), WMT-induced change on underlying neural correlates could only be observed in an exploratory analysis not corrected for multiple comparisons and should thus be interpreted with caution. However, due to our target group of cognitively healthy patients, large effects were not expected since similar findings in healthy and thus cognitively healthy adults have been observed previously (Ripp *et al.*, 2019).

It is important to note that both groups performed the fMRI task equally well across time points. Although the lack of behavioural change in the fMRI task could potentially indicate a lack of transfer from the WMT towards the in-scanner task, it might also just reflect the low sensitivity of the task to pick up behavioural change (i.e. as half the answers are correct simply by chance). In contrast, the absence of behavioural change speaks for the suitability of this task for fMRI. If behavioural performance had been different between time points, it would have been impossible to discriminate whether the observed neural effect was due to a change in behaviour per se or a change induced by WMT. Considering that neuropsychological improvements were observed using more sensitive neuropsychological measures (Giehl *et al.*, 2020; Ophey *et al.*, 2020) and that these changes were correlated with the observed change in activation is seems plausible that the observed neural effects relate to WMT and are thus meaningful.

Conclusion

Using a new WM paradigm, we were able to successfully differentiate between different WM processes in patients with Parkinson's disease and shed light onto the potential effect of home-based WMT on the neural correlates underlying these in this patient group. While WM maintenance and manipulation relied on a widely distributed frontoparietal–cerebellar network, only manipulation of information relied on additional activation of the AS.

WMT led to the reduction of activation and reorganization of context-dependent FC, especially when manipulation of WM content was required suggesting increased neural efficiency after WMT in Parkinson's disease. Activation changes were correlated with behavioural training gains.

This RCT is the first to explore the neural effects of WMT in Parkinson's disease. Although results should be considered with caution, our findings are promising in that WMT may enhance neural efficiency in early phases of Parkinson's disease. More research in this area should be highly encouraged in order to understand if such interventions have clinically relevant potential to delay or prevent cognitive impairment in early Parkinson's disease and elucidate the underlying neural mechanism of action.

Supplementary material

Supplementary material is available at *Brain Communications* online.

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Competing interests

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