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SERIAL-ORDER recall in working memory across the cognitive spectrum of Parkinson's disease and neuroimaging correlates

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We sought to determine if Parkinson's disease (PD) with mild cognitive impairment (MCI) is associated with a greater SERIAL-ORDER (mental manipulation) than ANY-ORDER (auditory span, storage) deficit in working memory (WM). We investigated WM combining neuropsychological measures with the study of brain functional connectivity. A cohort of 160 patients with idiopathic PD, classified as PD-MCI (n = 87) or PD with normal cognition (PD-NC; n = 73), and 70 matched healthy controls were studied. Verbal WM was assessed with the Backward Digit Span Task (BDT; Lamar et al., 2007, *Neuropsychologia*, 45, 245), measuring SERIAL-ORDER and ANY-ORDER recall. Resting-state MRI data were collected for 15 PD-MCI, 15 PD-NC and 30 controls. Hypothesis-driven seed-based functional connectivity of the dorsolateral prefrontal cortex (DLPFC) was compared between the three groups and correlated with BDT performance. We found the main effect of the test (impairment in SERIAL ORDER > ANY ORDER) and group ((NC = PD-NC) > PD-MCI) in BDT performance that was even more pronounced in SERIAL ORDER when controlling for ANY ORDER variability but not vice versa. Furthermore, PD-MCI compared to other groups were characterized by the

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functional disconnection between the bilateral DLPFC and the cerebellum. In functional correlations, DLPFC connectivity was positively related to both SERIAL- and ANY-ORDER performance. In conclusion, PD-MCI patients evidenced greater SERIAL-ORDER (manipulation and cognitive control) than ANY-ORDER (storage) working memory impairment than PD-NC and controls with a disrupted DLPFC resting-state connectivity that was also related to the verbal WM performance.

Lashley (1951) is often credited as the first to comprehensively discuss 'The Problem of Serial Order' processing of information (Emrani *et al.*, 2018; Hurlstone, Hitch, & Baddeley, 2014). For Lashley (1951), SERIAL-ORDER processing was central to understand all higher-order motor and cognitive behaviour including recalling sequentially presented items (words, numbers, syllables, etc.) in either forward or backward order (Kahana, 2014) and fundamental to higher-order cognitive operation in everyday life (Anderson, 1983). 'The problem of serial order recall' continues to be at the heart of psychological research investigating human memory (Anderson & Matessa, 1997; Baddeley, 1986; Brown, Preece, & Hulme, 2000; Burgess & Hitch, 1992; Burgess & Hitch, 1999; Conrad, 1964; Ebbinghaus, 1885; Estes, 1973; Hurlstone, Hitch, & Baddeley, 2014; Lewandowsky & Murdock, 1989; Murdock, 1993; Page & Norris, 1998; Shiffrin & Cook, 1978; Wickelgren, 1965a, 1965b).

Research into the psychology of short-term and working memory (WM) has revealed much about SERIAL-ORDER recall (Kahana, 2014; Long & Kahana, 2019). For example, auditory span in serial recall is severely limited by the amount of information (Miller's 'magical' number seven or Cowan's number four) (Cowan, 2001; Miller, 1956); modality effects, e.g. auditory vs. visual (Drewnowski & Murdock, 1980); and latency or the time taken to pronounce the words (word-length effect) (Baddeley, Thomson, & Buchanan, 1975). By using the conceptual framework of the working memory (WM) model of Baddeley and Hitch (1974), the aim of the present study was to investigate how a basal ganglia disorder, such as Parkinson's disease (PD) known for higher-order sequencing deficits, may be used to define what mechanisms and neuroanatomic networks that are involved in SERIAL-ORDER recall (Baddeley, 2012; D'Esposito & Postle, 2015; Miyake & Shah, 1999).

PD, well-known for the typical motor phenotype (Litvan *et al.*, 2003), has recently been associated with neuropsychological deficits (Aarsland *et al.*, 2017). For example, problems with WM in PD are common (Dalrymple-Alford *et al.*, 2011) and have been linked to alterations involving both the prefrontal cortex and basal ganglia (Chatham & Badre, 2015; Gratwicke, Jahanshahi, & Foltynie, 2015; O'Reilly & Frank, 2006). Considerable research on verbal WM SERIAL-ORDER recall has been conducted with dementia patients presenting with Alzheimer's disease (AD), subcortical vascular dementia (VaD), and mild cognitive impairment (MCI) as operationally defined using the Backward Digit Task (BDT; see Emrani *et al*, 2018; Lamar *et al*, 2007, 2008).

Prior research suggests that PD impairs more than just the maintenance or retrieval of information, but also negatively impacts higher-level mental manipulation/WM skills, and that these deficits might be improved by dopaminergic medications (Costa, Peppe, Dell'Agnello, Caltagirone, & Carlesimo, 2009; Lewis, Slabosz, Robbins, Barker, & Owen, 2005; Morris *et al.*, 1988) and by different task demands (Lewis, Cools, *et al.*, 2003; Lewis, Dove, *et al.*, 2003). However, recent work by Ma *et al.* (2018, 2019) might contradict this notion as these researchers reported evidence for backward, but not forward, SERIAL-ORDER deficits in early stages of PD based upon observations of greater number of anticipations and fill-in errors (the tendency to recall the item displaced by the error).

Other research has shown that WM deficits are already present in early stages of PD (Kensinger, Shearer, Locascio, Growdon, & Corkin, 2003). Non-demanding WM tasks (e.g., recall of spatial sequence) are only impaired in patients with severe clinical symptoms. By contrast, WM tasks requiring considerable neurocognitive resources (e.g., changing spatial sequence with differential difficulty within WM) have been shown to be already impaired in patients with mild symptoms (Gabrieli *et al.*, 1996; Owen, 2004). Based on findings in early PD patients, Kensinger *et al.* (2003) hypothesized that WM impairment in PD is associated with disrupted inhibitory processes from dopaminergic prefrontal–striatal projections.

PD molecular pathology is characterized by dopaminergic depletion and fronto-striatal alterations (Lewis, Slabosz, Robbins, Barker, & Owen, 2005; Owen, 2004). Gabrieli, Singh, Stebbins, and Goetz (1996) showed in drug-naïve patients with PD a correlation between WM deficits and poor performance on tasks measuring strategic memory and perceptual-motor speed. The authors suggest that the dopaminergic-dependent fronto-striatal memory network facilitates WM performance by mediating perceptual-motor processing speed, which in turn influences the capacity of WM. Interestingly, PD patients showed deficits in the paired associate recall condition but demonstrated intact recognition performance on these tasks. In comparison, Lewis *et al.* (2005) showed that dopaminergic drugs improved WM behaviour measuring mental manipulation, but not other cognitive processes like retrieval. Owen (2004) also concluded that loss of dopamine in dorsolateral/ventrolateral frontal cortices results in WM mental manipulation but not retrieval deficits. Moreover, it was found that recall and long-term memory retrieval activity activate ventrolateral frontal cortex, while active manipulating and organizing information relies on the dorsolateral frontal cortex.

In a meta-analysis of 1,653 healthy subjects, functional MRI studies have shown that WM deficits are consistently found on a wide range of tests and are related to a broad fronto-parietal network (Rottschy *et al.*, 2012). Results were superimposed in a conjunction analysis to reveal core WM hubs including bilateral intraparietal cortex, bilateral anterior insula, bilateral inferior frontal gyrus pars opercularis, bilateral caudal lateral prefrontal gyrus, left posterior medial frontal cortex and right posterior medial frontal cortex.

In study 1, we hypothesize that the WM dysfunction in PD with normal cognition (PD-NC) with stable dopaminergic medication would be associated with greater SERIAL-ORDER (mental manipulation) than ANY-ORDER (short-term auditory storage) deficits than PD-NC on the Backward Digit Span Task (BDT; Lamar *et al.*, 2007, 2008). Furthermore, we aimed to show that SERIAL-ORDER deficits are more pronounced in PD with mild cognitive impairment (PD-MCI). In study 2, the WM network(s) were defined using data obtained from healthy controls. This information was subsequently applied to investigate the underlying selective connectivity changes in PD using resting-state functional connectivity (rs-fMRI). Additionally, we investigated rs-fMRI connectivity to find putative neural correlates of verbal WM impairment across the PD cognitive spectrum. We performed hypothesis-driven seed-based functional connectivity analyses of the dorsolateral prefrontal cortex (DLPFC) as the hub of the WM brain functional network (Mattay *et al.*, 2002; Rottschy *et al.*, 2012). We hypothesized more severe changes in DLPFC connectivity in PD-MCI compared to PD-NC and controls and a preferential correlation between SERIAL-ORDER recall and DLPFC alterations.

Materials and methods

Study 1: Design and participants

Since neuroimaging data were available only for a subgroup of the total sample, we split the research into two main parts: 'Study 1,' where we report detailed neuropsychological assessment, and 'Study 2,' where we describe the results obtained from neuroimaging data.

Study 1: Participants

We included 160 patients with PD and 71 demographically matched healthy controls (Table 1 and Table S1). The patients were recruited from the Movement Disorders Center, Department of Neurology. All patients were examined by a neurologist specialized in movement disorders and met the UK PD Society Brain Bank criteria (UKPDSBB) (Hughes *et al.*, 1992). Exclusion criteria were as follows: PD dementia according to IPMDS criteria (Emre *et al.*, 2007), atypical or secondary parkinsonism, severe or moderate depression according to Beck Depression Inventory (BDI-II), psychotic manifestations (hallucinations or delusions), anticholinergic medications and other medical or neurological conditions potentially resulting in cognitive impairment (e.g., epileptic seizure, tumour, stroke or head trauma). All participants (patients and controls) underwent a comprehensive clinical evaluation that included medical history, evaluation of functional abilities, medication status, and motor status by the Unified Parkinson's Disease Rating Scale (UPDRS-III). All PD patients were treated with dopaminergic therapy, consisting of levodopa, dopamine agonists or a combination of them, during cognitive and MRI examinations. Levodopa equivalent daily dose for each patient was calculated (Table 1 and Tables S1 and S2) (Tomlinson *et al.*, 2010). Controls were recruited from the general community through advertisements (non-random sampling), and brief medical history was obtained by telephone.

Seventy-one healthy subjects met the following criteria: interviews excluded the history of head trauma with loss of consciousness, cerebrovascular accident, abuse of alcohol or other psychoactive substances, history of neurological or psychiatric diseases or ongoing delirium. We excluded persons currently undergoing radio- or chemotherapy, with a major medical condition (e.g., myocardial infarction, diabetes mellitus), or sensory deficits. We excluded control subjects with cognitive impairment, that is Mattis Dementia Rating Scale, Second Edition (DRS-II) $\leq$ 139/144 points (Jurica, Leitten, Mattis, & Schmidt, 2001), and moderate/severe depression on the BDI-II score, that is >13/64 points (Beck, Steer, & Brown, 1996). The study was approved by the ethics committee of the University Hospital and the Declaration of Helsinki. All participants provided signed informed consent.

Study 1: Neuropsychological Assessment

MCI classification

Cognitive assessment was performed using a standard neuropsychological protocol at Level I, as recommended by the IPMDS task force for the definition of PD-MCI (Litvan *et al.*, 2012). MCI was defined using the DRS-II. The cut-off for MCI classification was based on the previous normative and discriminative validity data studies, that is $\leq$139/144 points (Jurica *et al.*, 2001). Eighty-seven PD patients fulfilled PD-MCI criteria (Table 1), while the remaining 73 patients were classified as having normal cognition (PD-NC).

Table 1. Characteristics of PD-MCI, PD-NC and control samples and their comparison (controls vs. PD-NC/controls vs. PD-MCI/PD-NC vs. PD-MCI)

Variables (*M* ± *SD*)	Controls (*n* = 70)	PD-NC (*n* = 73)	PD-MCI (*n* = 87)	*p*-values* (*t*-test/ANOVA, Tukey HSD)
Age	61.03 ± 10.61	58.03 ± 9.01	61.49 ± 8.66	.139/.949/.055
Education (years)	15.05 ± 3.19	14.45 ± 2.63	13.51 ± 2.99	.438/.004*/.112
Sex (% male; m/f)	51 (36/34)	59 (43/30)	72 (63/24)	.133†/.020*,[a]/103[a]
PD duration (years)	–	10.69 ± 5.80	11.65 ± 4.85	.517
UPDRS-III 'on' state	–	12.74 ± 6.86	18.41 ± 8.85	<.001*
Hoehn & Yahr stage	–	1.95 ± 0.49	2.11 ± 0.62	.435
L-Dopa equivalent (mg)	–	1,196.62 ± 603.32	1,209.93 ± 550.81	.768
DRS-II (min-max; 0–144)	141.91 ± 1.53	142.05 ± 1.33	133.85 ± 5.35	.968/<.001*/<.001*
BDI-II (min-max; 0–64)	6.33 ± 4.28	10.21 ± 6.25	10.25 ± 5.78	<.001*/<.001*/.998

Notes. ANOVA = one-way between-groups analysis of variance with *post hoc* comparisons using the Tukey HSD; BDI-II = Beck Depression Inventory, Second Edition; DRS-II = Mattis Dementia Rating Scale, Second Revision; f = female; m = male; *M* = mean; PD = Parkinson's disease; PD-MCI = Parkinson's disease with mild cognitive impairment; PD-NC = Parkinson's disease with normal cognition; *SD* = standard deviation; *t* test (independent-samples *t* test); UPDRS = Unified Parkinson's Disease Rating Scale.

[a]Chi-square test with Yates Continuity Correction; **p*-value (controls vs. PD-NC; controls vs. PD-MCI; and PD-NC vs. PD-MCI).

Table 2. Backward Digit Span Task performance in general linear model three-way mixed between–within ANCOVA (n = 70 controls; 73 PD-NC; and 87 PD-MCI) with depression and education as covariates

BDT	F	p-Value	η^2
Between-subjects			
Group (Ctrl vs. PD-NC vs. PD-MCI)	16.14[a]	<.001	.125
Within-subjects			
Test (SER vs. ANY)	38.93[a]	<.001	.147
3-span; 4-span; 5-span trials	12.33[b]	<.001	.052
Interactions			
Test*345 (Wilks' λ = .954)	5.35[b]	.006	.023
Group*345 (Wilks' λ = .865)	11.97[b]	<.001	.096
Group*Test (Wilks' λ = .904)	11.95[a]	<.001	.096
Group*Test*345 (Wilks' λ = .918)	5.15[a]	.001	.044

Notes. Ctrl = Controls; PD = Parkinson's disease; PD-MCI = Parkinson's disease with mild cognitive impairment; 345 = 3-span; 4-span; 5-span trials; PD-NC = Parkinson's disease with normal cognition.
[a]Sphericity assumed; [b]Greenhouse–Geisser correction.

Backward Digit Span Task (BDT)

The BDT (Table 2) consists of seven trials of 3-, 4- and 5-digit span lengths for a total of 21 trials. All 4- and 5-span trials were constructed so that contiguous numbers were placed in strategic positions. For example, in 4-span trials contiguous numbers were placed in either the first- and third- or second- and fourth-digit positions, for example 5 269 or 1 493. In 5-span trials, contiguous numbers were also placed in the middle three-digit positions, for example 16 579. Specifically, subjects were required to hold a sequence of numbers in memory (maintenance), with no delay period, then immediately repeat the sequence (retrieval) and reorder it in backward order (manipulation), a task involving multiple executive abilities. Three-span test trials were not constructed in this fashion because of primacy and recency effects. The BDT was administered using standardized WAIS-III Digit Span Backward procedures with the exception that the discontinuation rule was not applied as all patients received all 21 test trials of the BDT. The following dependent variables were scored from the same corpus of BDT trials in which patients were instructed to say the digits they heard in reverse order:

1. Percent of BDT correct SERIAL ORDER. This score reflects the total number of digits correctly recalled in accurate serial position divided by the total possible correct multiplied by 100, [(total # correct digits SERIAL ORDER)/(total possible correct)] × 100. This variable is believed to measure the more executively demanding aspects of WM associated with mental manipulation such as disengagement and temporal reordering.
2. Percent of BDT correct ANYORDER. This score reflected the sum total of every digit correctly recalled regardless of serial position divided by the total possible correct multiplied by 100 [(total # correct digits ANY ORDER)/(total possible correct)] × 100. By eliminating the importance of serial position during digit recall despite instruction, this variable is believed to reflect less complex aspects of working memory characterized mainly by short-term or immediate storage and rehearsal mechanisms. The BDT has been described in detail by Lamar *et al.* (2007, 2008) and Emrani *et al.* (2018).

Statistical analyses on neuropsychological variables

All analyses were performed using IBM software (SPSS 22.0 for Windows; IBM Corp, Armonk, NY, USA). Normality was evaluated by visual inspection of Q-Q plots and the Shapiro–Wilk test. Differences among PD-MCI, PD-NC, and controls on demographic and clinical variables were explored using analyses of variance (ANOVA) models.

Concerning the specific hypothesis on WM impairment, we have three factors of interest: Factor 1 (WM test condition, that is 3-, 4- and 5-digit span lengths within-subjects trials); Factor 2 (two within-subjects levels SERIAL ORDER and ANY ORDER); and Factor 3 (with three between-subjects levels: PD-MCI, PD-NC, and controls). A 2 × 3 × 3 mixed between–within ANCOVA with depression level (BDI-II) and education as covariates was implemented to study the main effects of WM task and group, as well as their interactions in Study 1 and Study 2. The effect size was determined by eta-squared (η^2). The significance level was set at $\alpha = .05$. Cohen classifies η^2 of .01 as a small effect, .06 as a medium effect and .14 as a large effect (Cohen, 1988). Subsequently, separate ANOVAs were performed for each difficulty level (3-, 4-, 5- span) accompanied by post hoc tests with Games–Howell adjustment for multiple comparisons. The hypotheses based on GLM mixed between–within ANCOVA were (1) main effect of the factor test: impairment in SERIAL ORDER > ANY ORDER; (2) main effect of factor group: performance in PD-MCI < PD-NC < controls; and (3) a significant interaction with greater SERIAL-ORDER than ANY-ORDER deficits in PD-MCI patients compared to other groups.

Study 2: Design and participants

Study 2 included a subsample of subjects from Study 1 with available neuroimaging measures. This additional inclusion criterion led to the creation of an imaging subsample including 30 patients with PD (15 PD-NC and 15 PD-MCI) and 30 demographically matched controls (Table S2).

Clinical characteristics and BDT performance

Demographic and clinical data were analysed in the subcohort with neuroimaging data as in the main group reported in Study 1. We did not find any differences in demographics between controls, PD-NC and PD-MCI. Table S3 summarizes the results of the repeated-measures mixed between–within ANOVA.

Study 2: MRI Acquisition

MRI acquisition

3T MRI scans of patients and controls were acquired with a Magnetom Skyra scanner (Siemens, Erlangen, Germany) at the Radiology Department. Functional connectivity without external input was assessed by resting-state functional magnetic resonance imaging (rs-fMRI) sequence (T2*-weighted gradient-echo echo-planar imaging (EPI); flip angle = 90°, TR = 2000 ms, TE = 30 ms, resolution = 3×3 × 3.45 mm, repetitions = 300). Patients and controls were presented a white fixation cross on a black background in a task-free resting-state. To control for pathological changes, T2-weighted sequence (TR = 3.2 s, TE = 9 ms, resolution = 0.9 × 0.9 × 3 mm) were investigated.

Study 2: MRI Analysis

Seed-based analysis

To identify the neural correlates of WM impairment in PD, we implemented a seed-based functional connectivity analysis. To target the WM-related functional network in the brain, we created two seeds in the left and right DLPFC, namely located at the coordinates ± 42 38 28 in the Montreal Neurological Institute—MNI—stereotactic space as reported by Curtis and D'Esposito (2003) (see Figure 1). The analysis was run using an in-house script in MATLAB R2017b (9.3).

In brief, the intensity signal was extracted from the bilateral DLPFC for each time frame in the rs-fMRI images, that is for each of the 300 volumes acquired during the 10-minute MRI measurement. The procedure was iterated for each subject, using the single-voxel coordinates as seeds to prevent the incorporation of intensity signal out of the target. Indeed, the smoothing step during image preprocessing had already mixed part of the neighbouring signal intensities in the selected seed voxels. This extraction phase produced, for each subject, two vectors with 300 values containing the signal intensity fluctuations over time for the left and right DLPFC. These vectors were then correlated within subjects with the time-courses from all the other voxels in the brain. This second step of the procedure generated correlation maps, where each voxel value (Pearson's r coefficient) expresses the correlation between that voxel and the seed in the DLPFC.

Meta-analysis based seed validation

In order to show that the chosen seeds in the DLPFC are part of the broader WM network, we extracted the controls' DLPFC network and ran term-based, automated meta-analysis of fMRI studies using Neurosynth (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011)

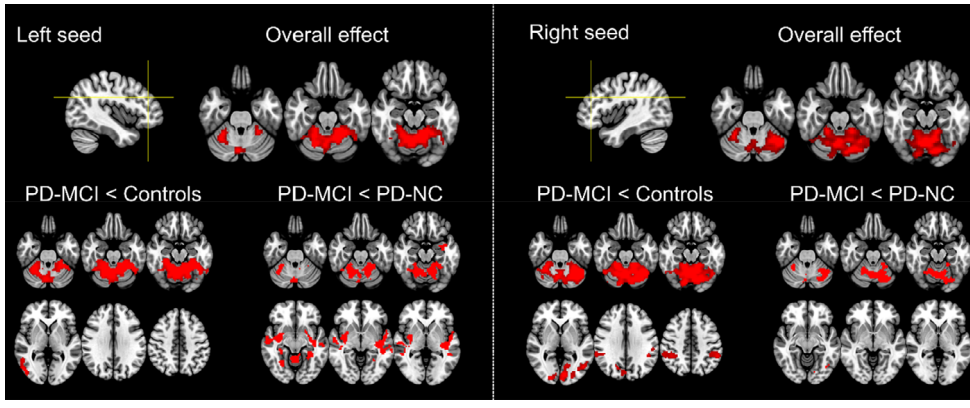

Figure 1. DLPFC functional connectivity differs among groups.

Notes. In both the left and right panels, the top rows display the seed locations in the left/right DLPFC (MNI −/+42 38 28), and the result of the one-way ANOVAs comparing the three groups. The lower panels show the significant pairwise differences, comparing PD-MCI to controls and PD-MCI to PD-NC. All the differences are FWE corrected at the cluster level ($p < .05$). Images are shown in the radiological convention: left of the brain on the right of the image.

Abbreviations: DLPFC = dorsolateral prefrontal cortex; FWE = family-wise error rate; PD-NC = Parkinson's disease with normal cognition; PD-MCI = Parkinson's disease with mild cognitive impairment. [Colour figure can be viewed at wileyonlinelibrary.com]

to overlay these results with our identified network. First, we defined the network of the left and right DLPFC seeds in our healthy controls by running a one-sample t test with age and gender as covariates in SPM12. Clusters were detected using a voxel threshold of $p < .05$ family-wise error rate (FWE) corrected. We combined the resulting network of the left and right seeds to obtain a map of the whole network. Second, a term-based, automated meta-analysis was carried out by means of Neurosynth (Yarkoni *et al.*, 2011) using the term 'working memory.' We downloaded the uniformity test map consisting of *z*-scores from a one-way ANOVA, which shows the convergence of activated peaks loading high on the term 'working memory.' Results are false discovery rate (FDR) corrected at $p < .01$. Third, to assess the degree of overlap between the independent meta-analytical WM network and the network obtained from the seeds of our cohort in the DLPFC, we computed the Sørensen–Dice similarity coefficient for image segmentation (Dice, 1945) in MATLAB R2017b (9.3):

$$\mathrm{dice}(\mathrm{A},\mathrm{B}) = 2 * |\mathrm{intersection}(\mathrm{A} \cap \mathrm{B})|/(|\mathrm{A}|+|\mathrm{B}|).$$

The coefficient ranges from 0 to 1, where 1 applies for high similarity. To test that our network mostly corresponds to the WM network, we also searched other memory-related networks in the Neurosynth database and acquired the meta-analytical maps of episodic, autobiographical, semantic, recollection and retrieval memory. Again, we computed the Sørensen–Dice similarity coefficient of the overlap of the aforementioned meta-analytical maps and our DLPFC network.

Group comparisons

Group comparisons were performed to test whether DLPFC functional connectivity differs between controls, PD-NC and PD-MCI. First, an ANOVA model including all the three groups was implemented to compare the correlation maps for both the left and right DLPFC functional connectivity. Then, pairwise group differences were investigated comparing PD-MCI with controls, PD-MCI with PD-NC, and PD-NC with controls. Age and gender were included in all models as nuisance covariates. The results were first

Table 3. Backward Digit Span Task performance in general linear model three-way mixed between–within ANCOVA (n = 30 controls; 15 PD-NC; and 15 PD-MCI) with depression and education as covariates

BDT	*F*	*p*-Value	η^2
Between-subjects			
Group (Ctrl vs. PD-NC vs. PD-MCI)	1.40[a]	.256	.048
Within-subjects			
Test (SER vs. ANY)	6.48[a]	.140	.105
3-span; 4-span; 5-span trials	1.39[b]	.253	.025
Interactions			
Test*345 (Wilks' λ = .812)	8.00[b]	.001	.127
Group*345 (Wilks' λ = .825)	2.36[b]	.057	.079
Group*Test (Wilks' λ = .958)	1.20[a]	.310	.042
Group*Test*345 (Wilks' λ = .871)	1.61[b]	.001	.055

Notes. Ctrl = controls; PD = Parkinson's disease; PD-MCI = Parkinson's disease with mild cognitive impairment; 345 = 3-span; 4-span; 5-span trials; PD-NC = Parkinson's disease with normal cognition.
[a]Sphericity assumed; [b]Greenhouse–Geisser correction.

thresholded at the uncorrected voxel level ($p < .005$) and were then deemed significant after applying a cluster-level FWE correction.

Correlation analysis

We performed a whole-brain correlation analysis to investigate the association between DLPFC functional connectivity and WM performance in the BDT. Specifically, we used the scores from the BDT condition with five numbers, which represents a more challenging task for both patients and controls, thus generating a larger performance variability. For this reason, patients and controls were included in a single model to capture the relationship between test performance and DLPFC functional connectivity. The correlations were performed for both left and right DLPFC with either the SERIAL- or ANY-ORDER recall and including age as a nuisance covariate. Results were first thresholded at the uncorrected voxel level ($p < .005$) and were then deemed significant after applying a cluster-level FWE correction.

Results

Study 1: Behavioral Results

Clinical characteristics

Although age was not significantly different between groups, PD-MCI had a significantly lower level of education, and there were more men in comparison with controls (Table 1). As expected, global cognitive performance in DRS-II was lower in PD-MCI compared with both controls and PD-NC; concurrently, PD-NC and controls did not differ. Controls differed significantly from PD-NC and PD-MCI on the BDI-II. However, there were no differences between PD-NC and PD-MCI. Further, PD-MCI had greater motor symptoms than PD-NC as using the UPDRS-III (Table 1).

Study 1

General linear model mixed between–within ANCOVA with the Bonferroni adjustment for multiple comparisons (Table 2) (PD-MCI < PD-NC, p <.001; PD-MCI < Ctrl, p <.001; PD-NC = Ctrl, $p = .442$), separate ANOVA for each difficulty level (3-, 4-, 5-digit span; SERIAL and ANY ORDER together) and post hoc tests with Games–Howell adjustment for multiple comparisons showed the following: 3-span (PD-MCI < PD-NC, p <.001; PD-MCI < Ctrl, $p = .003$; PD-NC = Ctrl, $p = .888$); 4-span (PD-MCI = PD-NC; $p = .209$; PD-MCI < Ctrl, $p = .006$; PD-NC = Ctrl, $p = .278$); 5-span (PD-MCI < PD-NC $p < .001$; PD-MCI < Ctrl, p <.001; PD-NC < Ctrl, $p < .018$).

Study 2

General linear model mixed between–within ANCOVA with the Bonferroni adjustment for multiple comparisons (Table 3) (PD-MCI = PD-NC, $p = .374$; PD-MCI = Ctrl, $p = .496$; PD-NC = Ctrl, $p = 1.000$) and post hoc tests with Games–Howell adjustment for multiple comparisons showed the following: 3-span (PD-MCI = PD-NC, $p = .064$; PD-MCI = Ctrl, $p = .427$; PD-NC = Ctrl, $p = .138$); 4-span (PD-MCI = PD-NC; $p = .618$; PD-MCI = Ctrl, $p = .725$; PD-NC = Ctrl, $p = .962$); 5-span (PD-MCI = PD-NC, $p = .067$; PD-MCI = Ctrl, $p = .036$; PD-NC = Ctrl, $p = .934$).

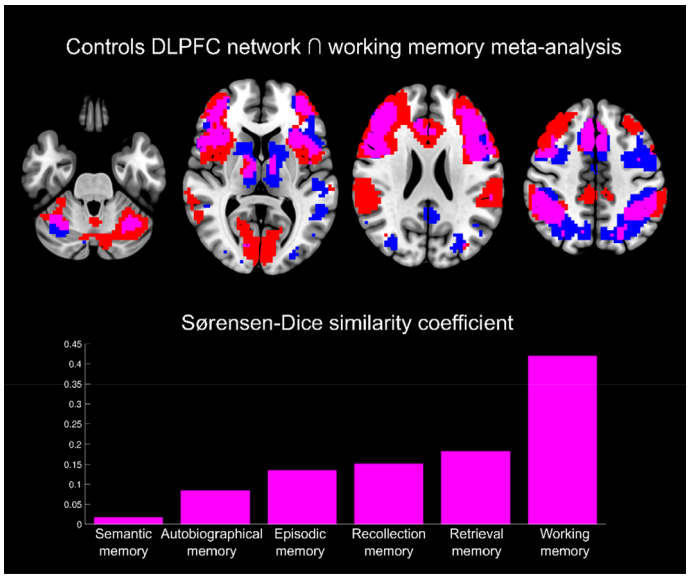

Figure 2. The healthy control DLPFC network is part of the working memory network.
Notes. The upper panel displays the conjunction (violet clusters) of the network of the DLPFC seeds left/right combined in the healthy controls cohort (red clusters, DLPFC: MNI -/+42 38 28) and the automated meta-analysis of 1091 WM network fMRI studies from Neurosynth (blue clusters). The lower panel shows the Sørensen–Dice similarity coefficients between the controls' DLPFC network and the meta-analytical memory-related networks from Neurosynth. Results for the controls' DLPFC network are corrected for multiple comparisons with voxel-level FWE $p > .05$. The meta-analysis of the WM network from Neurosynth applied an FDR $p < .01$. Images are shown in the radiological convention: left of the brain on the right of the image.
Abbreviations: DLPFC = dorsolateral prefrontal cortex; FDR = false discovery rate; FWE = family-wise error rate; WM = working memory; ∩ = conjunction. [Colour figure can be viewed at wileyonlinelibrary.com]

Analyses of demographic variables were repeated for the MRI sample (Table S2). Descriptive statistics of WM measures included in the analyses with BDT SERIAL ORDER and ANY ORDER in Study 1 and BDT SERIAL ORDER and ANY ORDER with Digit Span forward and backward and Letter Number Sequencing in Study 2 and all other types of correlational and inferential analyses, such as general linear model one-way ANCOVA with post hoc tests and depression, education and either SERIAL ORDER or ANY ORDER as covariates (Study 1), can be found in Supporting information (Tables S3 to S10. and Figures S1 and S2).

Study 2: Neuroimaging results

Meta-analysis based seed validation

The resting-state network of the DLPFC seeds in our healthy controls consists of bilateral DLPFC, insulae, inferior/middle/superior frontal gyri, frontal eye fields, anterior/middle/posterior cingulate cortex, posterior inferior/superior parietal lobules, middle temporal lobe and lobule I–V in the cerebellum (Figure 1). The right hemisphere showed additional involvement of precuneus and cuneus. The left hemisphere also included the calcarine cortex, orbital gyrus, putamen, supplementary motor cortex, middle occipital gyrus and

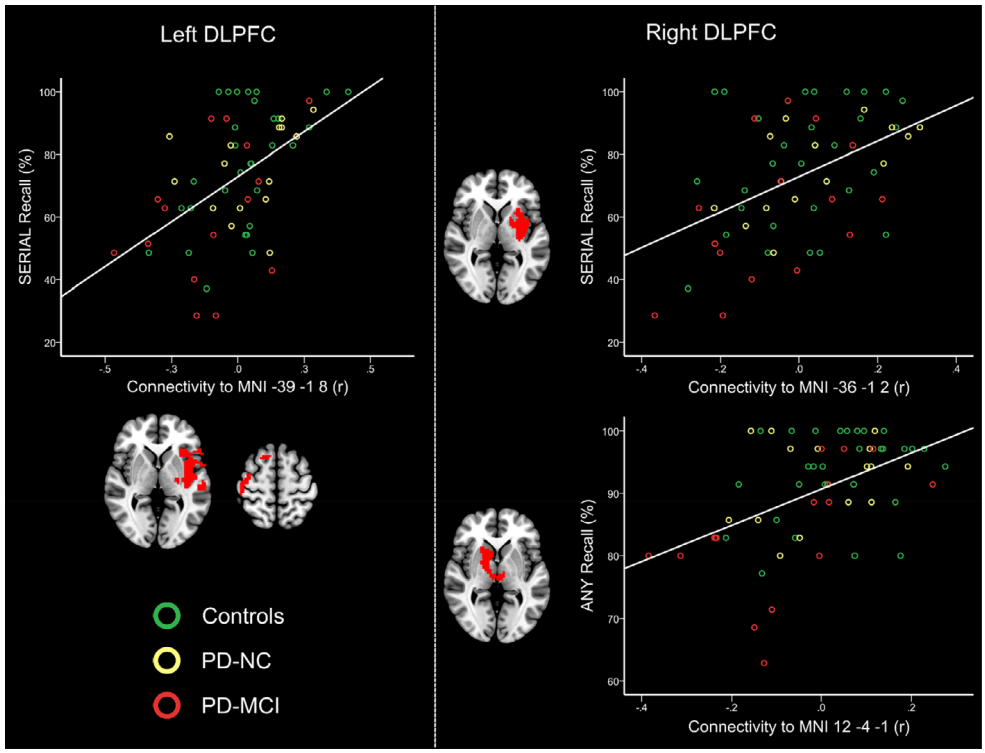

Figure 3. Correlations between Backward Digit Span Task (BDT) performance and DLPFC functional connectivity.

Notes. On the left: Significant correlation between the functional connectivity of the left dorsolateral prefrontal cortex (MNI: −42 38 28) and the performance in the SERIAL recall (5-span test condition). On the right: significant correlations between the functional connectivity of the right dorsolateral prefrontal cortex (MNI:42 38 28) and the test performance in the SERIAL (upper panel) and ANY (lower panel) recall. Both SERIAL and ANY recall conditions are from the test session with five numbers. The correct percentage of recalled items is reported on the y-axis. The *x*-axis reports as Pearson's r coefficients the functional connectivity between the seeds and the peak of the significant whole-brain correlations. Coloured circles in the scatterplots stratify the subjects into controls (green), PD-NC (yellow) and PD-MCI (red). Significant cluster are FWE-corrected at the cluster level ($p < .05$). Images are shown in radiological convention: left of the brain on the right of the image.

Abbreviations: DLPFC = dorsolateral prefrontal cortex; few = family-wise error rate; MNI = Montreal neurological institute; PD-NC = Parkinson's disease with normal cognition; PD-MCI = Parkinson's disease with mild cognitive impairment. [Colour figure can be viewed at wileyonlinelibrary.com]

supramarginal gyrus. The automated meta-analysis of WM comprised 1,091 studies from Neurosynth database encompassing the regions of the thalamus, posterior cingulate cortex and middle/superior frontal gyrus, all bilateral. In the left hemisphere, the precuneus, superior temporal gyrus and superior parietal gyrus were identified. On the right side, the caudate nucleus, middle/inferior occipital gyrus and middle temporal gyrus showed convergence (Figure 1).

The Sørensen–Dice similarity coefficient of the overlay of our network of both DLPFC seeds and the meta-analysis of WM was .42 (Figure 2). When computing the coefficients

for all other memory-related networks available on Neurosynth, results show the highest value for the meta-analysis of WM and our network of both DLPFC seeds (Figure 2). The comparison between our network and the network of autobiographic memory yielded the lowest value with a coefficient of .018. This supports the choice of the DLPFC as seeds and its contribution to the WM network.

Group comparisons

The seed-based group comparison analysis showed significant differences among groups for both the left and right DLPFC seeds (Figure 2, Table S6 and S7). When testing group differences for the left DLPFC seed, a significant overall effect was found across the three groups. In particular, a change in functional connectivity was found between the seed and external cerebellar regions with the maxima in the left Lobule V, extending to the contralateral Lobule V, to the bilateral Lobules VI, and the vermis. The pairwise group comparisons showed that this effect reflected lower functional connectivity between the cerebellum and the left DLPFC in the PD-MCI group compared to both controls and PD-NC. Additionally, the PD-MCI < controls comparison showed reduced connectivity with a cluster in the right inferior/middle temporal gyrus extending to the inferior parietal lobule, while the PD-MCI < PD-NC contrast revealed additional connectivity reductions in the bilateral superior temporal gyri, in the fusiform gyri and in the putamen. The comparison between PD-NC and controls did not show any significant difference.

As for the right DLPFC seed, the 3-group ANOVA showed a significant effect in the bilateral cerebellum, similar to the one observed for the contralateral seed. Specifically, the right DLPFC showed a disconnection with the left cerebellar Lobule VIIa, extending to the bilateral Lobules VI and V and the vermis. A reduction in the functional connectivity between the cerebellum and the right DLPFC was found in the PD-MCI group compared to both controls and, to a lower extent, PD-NC. Moreover, the PD-MCI < controls comparison indicated further connectivity decreases in the former group in the bilateral inferior parietal lobules, and the occipital cortex, extending dorsally to the cuneus and the superior parietal cortex. Comparing PD-NC and controls, we were not able to show significant differences.

Correlation analysis

The seed-based correlation analysis revealed a significant positive association between the SERIAL-ORDER recall performance and the functional connectivity between the left DLPFC and two clusters (Figure 3). The first cluster encompasses the entire left insula, the left inferior frontal gyrus (both pars opercularis and pars triangularis) and the tail of the left putamen. The second cluster, located in the right hemisphere, includes the superior frontal gyrus, the precentral gyrus and the posterior medial frontal gyrus. There were no significant correlations between test performance in the ANY-ORDER condition and the functional connectivity of the left DLPFC. SERIAL-ORDER recall showed a positive correlation with the connectivity between the right DLPFC and the left insula. Furthermore, the ANY-ORDER recall condition showed a positive correlation with the functional connectivity between the right DLPFC and the left caudate nucleus, the pallidum and the bilateral thalamus, especially in the ventromedial nuclei.

Discussion

Study 1 examined WM measured by the Backward Digit Span Task (BDT; Lamar *et al.*, 2007, 2008) obtained from a large cohort of 160 PD patients hypothesizing greater SERIAL ORDER (mental manipulation) versus ANY ORDER (auditory span, storage) in PD-MCI as a pre-dementia state when compared to PD-NC and healthy participants. We show that there is the main effect of group (PD-MCI are more impaired than PD-NC and controls) in WM/SERIAL ORDER rather than the short-term store (ANY ORDER) and that this difference increases with WM task difficulty (from 3-span to 5-span). This deficit is not simply related to the increasing task difficulty, but clinical status, as illustrated by the presence of the test vs. group interaction (Lewis *et al.*, 2005). Despite a statistically significant WM test condition vs. group interaction, these data should be interpreted with caution. We surmise that the interaction effect arises consistent with WM being a fundamental factor in cognitive processing (i.e. interrelated with the clinical, cognitive status) in these patient groups.

In accordance with previous studies (Ma *et al.*, 2018; Ma *et al.*, 2019), we show that PD-MCI patients scored lower for SERIAL-ORDER recall suggesting impaired WM skills necessary for successful mental manipulation, temporal ordering and disengagement. To support this conclusion, we also analysed the data using general linear model one-way ANCOVA with post hoc tests and depression, education and either SERIAL ORDER or ANY ORDER as covariates (Study 1; Table S4). The results show that filtering the influence of ANY from SERIAL ORDER leads to pronounced deficits (Ctrl = PD-NC) > PD-MCI (in 3- and 5-span); however, filtering SERIAL from ANY ORDER does not lead to any differences in any group comparison.

Nonetheless, PD-MCI patients also evidenced at least mild ANY-ORDER recall impairment. We interpret these findings as consistent with the *dual* syndrome hypothesis with more pronounced deficits involving SERIAL-ORDER impairment driven by a progressive lack of dopaminergic input; hence, we see PD-NC > PD-MCI, as compared to ANY ORDER (associative memory impairment) driven by presumably cortical cholinergic dysfunction (Kehagia, Barker, & Robbins, 2010, 2013), and hence, we see PD-NC = PD-MCI regarding the fact that cholinergic input disruption comes into play in later stages of the disease.

The rs-fMRI imaging results described in Study 2 showed significantly compromised DLPFC functional connectivity in PD-MCI. In particular, we observed a disconnection between bilateral DLPFC seeds and the cerebellum in PD-MCI as compared to both healthy controls and PD-NC. The conjunction analysis of our controls' DLPFC network along with the WM meta-analysis supports that our chosen seed is part of the WM network. Further, we identified clinical–functional correlations between both SERIAL- and ANY-ORDER performances with functional connectivity of the DLPFC, confirming that the integrity of these functional WM networks is related to WM performance.

The rs-fMRI analysis aimed to uncover the relationship between WM impairment in PD and the functional connectivity of the WM-related functional network. Given our specific hypothesis, we implemented a seed-based analysis focused on the bilateral DLPFC. Indeed, the DLPFC has been often described among the main hubs of the WM-related functional network (Barbey, Koenigs, & Grafman, 2013; Rottschy *et al.*, 2012). In our healthy control cohort, the bilateral DLPFC defined a resting-state network that included the bilateral DLPFC, the insulae, the inferior frontal gyri, the frontal eye fields, the anterior, and middle cingulate cortex, the posterior inferior/superior parietal lobules and the Lobule V in the cerebellum. On a qualitative level, this topographic pattern closely

resembles previous descriptions of the WM-related activation network from meta-analyses of activation studies, independently from task modality (Rottschy *et al.*, 2012; Wager & Smith, 2003). Of note, the seminal study from Smith *et al.* (2009) has highlighted that the functional architecture of the brain is very similar when studied either during activation or during rest, thus making it possible to draw meaningful parallels between activation and resting-state networks (Smith *et al.*, 2009). Moreover, to quantitatively validate the chosen seeds and the related resting-state network, we performed an overlap analysis between our DLPFC functional network and meta-analytically defined brain systems related to different memory functions. As expected, the maximum overlap was observed between the DLPFC network and the meta-analytical network for WM. This confirms that the chosen seeds in the DLPFC represent key structures in the WM network (Lara & Wallis, 2015; Miller, Lundqvist & Bastos, 2018; Rottschy *et al.*, 2012; Smith *et al.*, 2009).

The group comparison showed that the functional connectivity of the bilateral DLPFC seeds was impaired in PD-MCI compared to controls and PD-NC. Given the lack of significant difference between PD-NC and controls, we suggest that major changes in the WM-related functional networks are an important feature that characterizes PD-MCI but not necessarily all patients with PD. The main effect identified in our study was a functional disconnection in the PD-MCI patients between the bilateral DLPFC and the cerebellum, specifically in the Lobules VI, V, and, to a lesser extent, VII. Resting-state connectivity between cerebral and cerebellar structures at rest (Buckner, Krienen, Castellanos, Diaz, & Yeo, 2011; O'Reilly *et al.*, 2009), as well as co-activations during task performance, has been described elsewhere (Salmi *et al.*, 2010).

Recent functional imaging studies have highlighted the relevance of the cerebellum not only for motor performance, as in the traditional view, but also higher-order cognitive tasks (Stoodley, 2012). A review by Stoodley (2012) summarizes evidence of cerebellar functional activations related to WM tasks. More specifically, the activation of the cerebellar-frontal loop seems to be mainly associated with the encoding and rehearsal of the presented verbal stimuli (Chen & Desmond, 2005a,b). The association between verbal WM and the cerebellum is additionally supported by a meta-analysis showing that WM specifically activates the bilateral lobules VI and Crus I (Stoodley & Schmahmann, 2009).

Furthermore, activation of the VI and VII cerebellar lobules was also observed during tasks requiring spatial processing (Stoodley, 2012). This observation could be linked to the BDT to the extent that mental manipulation of test stimuli likely underlies successful test performance. Finally, functional activation studies have also related the cerebellar Lobules V/VI to language processing, that is to sustain motor control during speech articulation (Stoodley, 2012). Of note, the interaction between these cerebellar lobules in the right hemisphere and left prefrontal regions has been associated with a successful performance involving both WM tasks and speech production (Ackermann, Mathiak, & Riecker, 2007). This similarity might arise from the subvocal rehearsal mechanisms adopted to maintain the verbal information during a WM task. Overall, the evidence from activity-based studies suggests that the interplay between specific cerebellar subregions and the prefrontal cortex supports many cognitive functions that are relevant to BDT performance.

The group comparison between PD-MCI and controls showed additional disrupted functional connectivity in the former group between the DLPFC and the temporoparietal associative cortex. In particular, the inferior and superior parietal lobules are known to be part of the functional brain network associated with WM and BDT performance (Curtis & D'Esposito, 2003; Gerton *et al.*, 2004; Schlosser, Wagner, & Sauer, 2006) with increasing

activity after WM training (Olesen, Westerberg, & Klingberg, 2004). Finally, the contrast between PD-MCI < controls revealed additional disconnections between the DLPFC and the middle occipital gyrus that has been associated with performance in the BDT, possibly associated with the adoption of a visual imagery strategy (Gerton *et al.*, 2004).

To specifically investigate the association between WM performance and prefrontal functional connectivity, we assessed for correlation between ANY- and SERIAL-ORDER recall and DLPFC connectivity. The results showed that a better SERIAL-ORDER recall performance positively correlated with increased functional connectivity between the bilateral DLPFC and the left insula, inferior frontal gyrus and putamen. The lateralization on the left side of the brain is consistent with the content of the BDT, mainly relying on language. Indeed, previous studies have reported a differential hemispheric lateralization of the brain networks supporting verbal and spatial WM (Nagel, Herting, Maxwell, Bruno, & Fair, 2013; Smith & Jonides, 1997; Smith, Jonides, Marshuetz, & Koeppe, 1998). In line with the results from our correlation analysis, verbal WM was mainly related to locations within the left hemisphere including the insular cortex and the inferior frontal gyrus. Recent research has associated left insular cortex with attention processes (Menon & Uddin, 2010) and auditory processing (Bamiou, Musiek, & Luxon, 2003). Past research has also shown links between the inferior frontal gyrus with increasing demands in phonological processing and subvocal rehearsal of WM contents (Burton, Small, & Blumstein, 2000; Paulesu, Frith, & Frackowiak, 1993).

As for the ANY ORDER, we found that better performance was associated with higher functional connectivity between the right DLPFC and the left caudate nucleus and the ventromedial thalamic nuclei. It is well established that both the caudate nuclei and the ventromedial thalamus are structurally and functionally connected with the prefrontal cortex (Johansen-Berg *et al.*, 2005; Lara & Wallis, 2015; Di Martino *et al.*, 2008; Postuma & Dagher, 2006). Several previous studies showed a link between fronto-striatal dysfunctions in PD and a poorer WM performance (Kehagia, Barker, & Robbins, 2013). Moreover, this result is in line with the evidence of a complex interplay between dopaminergic modulation and WM performance in both healthy subjects (Chatham & Badre, 2015; Robbins & Arnsten, 2009) and PD patients (Lewis *et al.*, 2005).

The dissociation between the neural correlates of SERIAL- and ANY-ORDER recall suggests that patients with PD are still able to cope with less demanding cognitive operations necessary for successful WM performance. When demand for neurocognitive resources increases, as required for SERIAL-ORDER recall, patients' WM performance worsens. Further, the altered DLPFC networks might influence the difference in performance between the SERIAL and ANY ORDER. The DLPFC is responsible for very demanding cognitive operations as related to successful WM test performance (Owen, 2004).

These results need to be seen within the context of several study limitations. First, we did not analyse error patterns (anticipations, postponements, and repetitions), which could provide additional information regarding WM impairment in PD-NC and PD-MCI. Second, response latencies are a significant factor regarding sequencing and short-term store performance. However, these data were not available for this study. Third, dopaminergic medication might influence WM performance and WM network itself, leading to a bias in the behavioural test and imaging results; however, as noted above, both patient cohorts were medicated. Thus, despite this potential limitation, we were able to show that patients with MCI performed worse than PD-NC. Furthermore, we could not replicate the significant differences in BDT test results (interaction) in the imaging subcohort. This might be due to smaller sample size and resulting in lower statistical

power. Fourth, PD MCI group in Study 2 differs from the comparison groups in Study 1 (education, sex and BDI). This is not the case in the group in Study 2, where groups are almost equal. Effects found in Study 1 might therefore be ascribed to education, depression or sex that we tried to minimize by ANCOVA. Nevertheless, one might acknowledge that the trends of the BDT results are similar to Study 1. Fifth, because ANY-ORDER performance is close to ceiling there may be no differences in recall (see Table S6 where we look at the differential contribution of SERIAL without ANY and vice versa, showing a pervasive impairment in SERIAL ORDER but not in ANY ORDER). Sixth, we should also acknowledge the limitations of the integrated meta-analysis given that Neurosynth is based on an automatized text search strategy as opposed to a human-conducted systematic search.

In conclusion, our results on the behavioural level suggest a *dual* impairment in WM, that is more impaired sequencing (SERIAL ORDER) than the short-term store (ANY ORDER). This effect is more pronounced in PD-MCI than PD-NC and is critically dependent on the difficulty level of the WM task. Overall, the imaging findings in the subcohort showed that the WM-related resting-state functional network is impaired in PD-MCI as compared to both PD-NC and controls. In particular, this impairment targeted the functional connections between the DLPFC and cerebellar lobules associated with cognitive performance. We additionally showed that the DLPFC functional connectivity either to the left insula and inferior frontal gyrus or to the thalamus and caudate nucleus correlated, respectively, with performance in the SERIAL- and ANY-ORDER BDT recall performance. These findings suggest a relationship between the disruption of the DLPFC resting-state functional network specific to PD-MCI and the impairment in the BDT.

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Conflicts of interest

All authors declare no conflict of interest.

Author contributions

Ondrej Bezdicek, Ph.D. (Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Visualization; Writing – original draft) Tommaso Ballarini (Data curation; Formal analysis; Methodology; Software; Visualization; Writing – original draft) Franziska Albrecht (Data curation; Formal analysis; Methodology; Software; Writing – original draft) David J. Libon (Conceptualization;

Methodology; Supervision; Writing – original draft) Melissa Lamar (Conceptualization; Methodology; Supervision; Writing – original draft) Filip Růžička (Conceptualization; Data curation; Project administration; Writing – original draft) Jan Roth (Conceptualization; Data curation; Funding acquisition; Project administration; Writing – original draft) Mark J. Hurlstone (Conceptualization; Formal analysis; Methodology; Writing – original draft) Karsten Mueller (Data curation; Formal analysis; Investigation; Methodology; Software; Writing – original draft) Matthias Schroeter (Conceptualization; Data curation; Formal analysis; Funding acquisition; Supervision; Writing – original draft) Robert Jech (Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Writing – original draft).

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

The following supporting information may be found in the online edition of the article:

Figure S1. General Linear Model repeated measures mixed between-within ANOVA Backward Digit Span Task performance across trials 3,4,5-Span ANY/SERIAL-ORDER.

Figure S2. Backward Digit Span Task performance across trials 3,4,5-Span SER and 3,4,5-Span ANY based on the multiple comparisons results from General Linear Model three-way repeated measures ANOVA.

Table S1. Characteristics of the Clinical sample (PD) and Controls (Study 1).
Table S2. Characteristics of PD-MCI, PD-NC, and Control Samples (Controls vs. PD-NC/Controls vs. PD-MCI/PD-NC vs. PD-MCI) included in Study 2 (MRI analyses)
Table S3. Backward Digit Span Task performance based on the multiple comparisons results from General Linear Model three-way repeated-measures ANOVA with post-hoc tests (Study 1).
Table S4. Backward Digit Span Task performance based on the multiple comparisons results fromGeneral Linear Model one-way ANCOVA with post-hoc tests and depression, education and either SER or ANY as covariates (Study 1).
Table S5. Significant clusters for the controls imaging group DLPFC network.
Table S6. Significant clusters for the imaging group comparisons (left DLPFC).
Table S7. Significant clusters for the imaging group comparisons (right DLPFC).
Table S8. Significant clusters for the imaging correlation analysis.
Table S9. Descriptive statistics of working memory measures included in the analyses with BDT SERIAL and ANY in Study 1 and BDT SERIAL and ANY with Digit Span forward and backwards and Letter Number Sequencing in Study 2.
Table S10. Correlation analysis of standardized clinical measures of WM (Digit Span forward and backwards and Letter Number Sequencing) with BDT SERIAL and ANY (3-, 4-, 5-span) in Controls (n = 30), PD-NC (n = 15) and PD-MCI (n = 15).