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The role of executive processes in working memory deficits in Parkinson's Disease

Abstract: Idiopathic Parkinson's disease (PD) impairs working memory, but the exact nature of this deficit in terms of the underlying cognitive mechanisms is not well understood. In this study patients with mild clinical symptoms of PD were compared with matched healthy control subjects on a computerized battery of tests designed to assess spatial working memory and verbal working memory. In the spatial working memory task, subjects were required to recall a sequence of four locations. The verbal working memory task was methodologically identical except for the modality of the stimuli used, requiring subjects to orally recall a sequence of six digits. In either case, half of the sequences were structured in a way that allowed 'chunking', while others were unstructured. This manipulation was designed to dissociate the strategic component of task performance from the memory-load component. Mild medicated patients with PD were impaired only on the structured versions of the verbal working memory tasks. The analogous deficit in the spatial working memory was less pronounced. These findings are in agreement with the hypothesis that working memory deficits in PD reflect mainly the executive component of the tasks and that the deficits may be at least partly modality-independent.

Key words: Parkinson's disease, spatial working memory, verbal working memory, frontal lobe, executive function

Introduction

Although only about 20% of patients with idiopathic Parkinson's disease (PD) develop frank dementia (Brown & Marsden, 1984), less severe cognitive impairments are common even at the earliest stages of the disease (Downes et al., 1989). It has been suggested that these deficits emerge, and subsequently progress, according to a defined sequence, which evolves in parallel with the motor deficits characterizing the condition (Mortimer, Pirozzolo, Hansch, & Webster, 1982; Owen et al., 1992; Owen, 2004; Palazzini et al., 1995; Taylor, Saint-Cyr, & Lang, 1986). Cognitive deterioration in PD begins with impairments on tests that are sensitive to frontal lobe dysfunction, and then progresses towards deficits on tests that involve more

posterior cortical areas (Owen et al., 1992; Owen et al., 1993; Owen, 2004; Owen, Sahakian, Hodges, Summers, & et al., 1995).

A number of early (Le Bras, Pillon, Damier, & Dubois, 1998; Lange et al., 1992; Owen, Evans, & Petrides, 1996; Owen, Iddon, Hodges, Summers, & Robbins, 1997; Owen, Morris, Sahakian, Polkey, & Robbins, 1996; Postle, Jonides, Smith, Corkin, & Growdon, 1997) and more recent studies (Caminiti, Siri, Guidi, Antonini, & Perani, 2015; Fallon et al., 2015; Foster, Yung, Drago, Crucian, & Heilman, 2013; Lewis, Cools, et al., 2003; Lewis, Dove, Robbins, Barker, & Owen, 2003; Lewis, Slabosz, Robbins, Barker, & Owen, 2005; Possin, Filoteo, Song, & Salmon, 2008; Slabosz et al., 2006; Trujillo et al., 2015) have assessed WM deficits in patients with PD. However, the exact nature of the WM

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deficits in PD remains unclear. It has been suggested that certain aspects of WM can deteriorate earlier than others. For example, in their early study Bradley, Welch and Dick (1989) have found that patients with mild to moderate PD were impaired on a test of visuospatial WM, whilst their performance on an analogous test of verbal WM was unaffected. Similarly, both Postle et al., (1997) and Owen et al., (1997), have demonstrated that whilst spatial WM is impaired in medicated patients with mild PD, WM for visual shapes and verbal material is relatively preserved. As Owen and colleagues concluded, these findings are in agreement with the hypothesis that WM deficits in PD emerge and progress according to a defined sequence that is likely to reflect spatiotemporal progression of dopamine depletion within the striatum, in relation to the terminal distribution of its cortical afferents.

A number of interpretations have been proposed in order to account for the observed pattern of relative impairments of the spatial WM in PD. According to Le Bras et al. (1999), who showed that spatial WM deficit in PD affects not only the maintenance of the information in short term memory, but also its monitoring at the stages of encoding and response programming, this deficit may simply reflect a disproportionate involvement of spatial processing deficits in PD (see also Bradley, Welch, & Dick, 1989). An alternative hypothesis posits that the spatial tasks used in these studies differ from the non-spatial tasks in terms of their underlying executive requirements (Gabrieli, Singh, Stebbins, & Goetz, 1996; Lewis, Cools, et al., 2003; Owen et al., 1996; Owen et al., 1997). For example, Owen and colleagues (1993) have shown that mild PD patients perform as well as healthy control subjects on simple span tasks which require simple remembering of sequences of locations or objects. This intact performance on span tasks contrasts markedly with severely impaired performance on WM tasks that require the flexible updating of WM content (i.e., active manipulation of information within memory), such as the spatial self-ordered search task (Owen et al., 1996; see also Cools, 2006). Successful performance in control subjects on the self-ordered spatial memory task relies heavily upon adoption of a searching strategy that is uncontaminated by overall mnemonic task component (see Robbins, Weinberger, Taylor, & Morris, 1996 for discussion). A similar conclusion was drawn by Pillon et al. (1998), who reported that the memory deficit for spatial location observed in PD under the spatial conditional associative learning results mainly from a disturbance of strategic processes and decreased attentional resources stemming from the dopaminergic depletion and related frontostriatal dysfunction central to the PD.

A study by Lewis and colleagues (Lewis, Cools et al., 2003) has provided more direct evidence that the WM deficits in PD in the verbal domain are specific to manipulation and re-ordering of information, which relies heavily on the integrity of prefrontal cortex (PFC), especially ventro- and dorsolateral PFC cortices (Lewis, Dove, et al., 2003). In this study, a novel verbal WM paradigm was used, allowing dissociation of specific functions of WM, namely retrieval, maintaining, and

manipulating information. The subjects were required to remember a sequence of four letters and, after a period of delay, they were expected to either simply reproduce them, or to reorder them according to the pre-learned rule. When patients with predefined executive deficits were compared to controls the results suggested that they were specifically impaired at manipulating information within verbal WM. However, the patients group and the control group did not differ in terms of memory maintenance or information retrieval. The subsequent functional neuroimaging study by Lewis and colleagues (Lewis, Dove, et al., 2003) of levodopa (l-dopa) withdrawal in groups of patients with PD have led to identification of a neural correlate for these deficits in WM operating loops (Alexander, DeLong, & Strick, 1986). The impairments in information manipulation and re-ordering appeared to be related to the integrity of PFC, especially VLPFC and DLPFC (Lewis, Dove, et al., 2003).

Similarly, with respect to the spatial WM domain, Miah and others (Miah, Olde Dubbelink, Stoffers, Deijen, & Berendse, 2012) compared a group of de novo PD patients with treated PD patients and healthy controls. It has revealed that relative to the other two groups, the de novo patients were significantly impaired at WM strategy use. Together, these findings (Lewis, Cools, et al., 2003; Lewis, Dove, et al., 2003; Lewis et al., 2005; Miah et al., 2012; Owen et al., 1996) support the hypothesis that regardless of the modality, WM deficits in PD stem at least partly from problems in manipulating and reorganizing information and represent high executive or strategic requirements specific to such activity.

Nevertheless, the role of executive component in spatial WM deficits in PD still remains unclear. The meta-analysis run by Siegert, Weatherall, Taylor, & Abernethy (2008) have confirmed that the WM deficits accompanying early PD is small for verbal span and moderate on complex verbal and both simple and complex visuospatial tasks. However, according to the authors these data do not support the notion that WM impairment in PD is related exclusively to the central executive component, but support the view that these deficits are more pronounced for visuospatial than verbal WM.

One serious confound in the previous designs (Lewis, Cools, et al., 2003; Lewis, Dove, et al., 2003) is that conditions measuring manipulation were inherently more difficult than conditions measuring simple retrieval and therefore much more responsive to any independent variable. For that reason, the present study employs spatial and verbal working memory tasks requiring subjects to simply remember and then reproduce a novel sequence of items (either a sequence of locations in spatial version of the task or a sequence of digits in verbal version), which (i) are methodologically identical except for the modality of the stimuli used, (ii) include the structured and unstructured sequences conditions which allow dissociation of a strategic component (i.e., as reflected by application of 'chunking' strategies in the structured condition) from a mnemonic component, and (iii) allow to compare the two conditions, one of them being subjectively and behaviourally easier

if the extra strategic component is effectively utilized, but at the same time recruiting more of the PFC (especially DLPFC but also VLPFC) than the other (Bor, Cumming, Scott, & Owen, 2004; Bor, Duncan, Lee, Parr, & Owen, 2006; Bor, Duncan, Wiseman, & Owen, 2003; Bor & Owen, 2006). Previous neuropsychological data support the view that the application of 'chunking' strategies (Bor, et al., 2006; Miller, 1956) is supported by PFC contribution. Considering these suggestions that (i) both 'strategic' ('executive') and mnemonic mechanisms may contribute differentially to the performance in tests of WM (Owen et al., 1996), (ii) the 'strategic' component may depend most heavily on frontal cortex (Bor et al., 2004; Bor et al., 2006; Bor et al., 2003; Bor & Owen, 2006), and (iii) assuming that the patients with PD exhibit specific alterations in lateral PFC under the WM manipulation condition (Lewis et al., 2005; Lewis, Cools et al., 2003; Lewis, Dove et al., 2003; Owen et al., 1997), it was hypothesised here that in terms of their behavioural performance the patients will reveal no benefit of the structure regardless of the task modality (spatial or verbal).

Method

Subjects

Patients

Seventeen patients with idiopathic PD (mean age $M=68.21$, $SD=7.88$, 10 male) included in this study were all in the mild stages of the disease. The group was drawn from a pool of the Parkinson's Disease Research Clinic at the Cambridge Centre for Brain Repair where they had undergone careful historical review along with a physical examination and psychometric analysis. This included the National Adult Reading Test (NART; Nelson, 1982) as an estimate of pre-morbid IQ. All patients satisfied UKPDS Brain Bank criteria (Gibb & Lees, 1988). 11 patients were taking L-dopa medication, 10 patients were taking dopamine agonist. The patients were tested when on their usual medications.

Healthy volunteers

A group of eighteen healthy controls performing the same tests of cognitive functioning were recruited from the volunteer panel at the MRC Cognition and Sciences Unit. The group matched the PD group as closely as possible with respect to age (mean age $M=66.8$, $SD=7.9$, 13 male) and pre-morbid verbal IQ as assessed by the NART (Nelson, 1982) and gender. Permission for this study was obtained from the local research ethical committee and all subjects consented to participation.

Table 1 shows a summary of characteristics for the patient group and the healthy control group. There were no significant differences between the two groups with respect to age or NART (see Table 1).

Spatial Working Memory Task (SWMT)

WM for spatial sequences was tested using a modified spatial span task in which participants were required to remember sequences of locations on a 4 by 4 grid (see

Table 1.

Variable	Patients (N=17)	Controls (N=18)
Age (y)	68.21(±)7.88	68.8(±)7.9
NART	115.73(±)8.15	117.40 (±) 8.05
BDI-II	7.36(±)5.20	
UPDRS On	28.18(±)14.17	
H&Y On	1.95(±)0.47	
Years since Diagnosis	5.53(±)2.74	
L-dopa (daily, mg)	594.44(±)417.17	

Acronyms used in Table 1: NART – the National Adult Reading Test (Nelson 1982), BDI-II – Beck Depression Inventory II (Beck 1996), UPDRS 'on' – Unified Parkinson's Disease Rating Scale (1987) tested 'on' medication, H&Y 'on' – Hoehn and Yahr scale (1967) tested 'on' medication. Values represent mean ± standard deviation of the mean. Between-group comparisons using Student's t test revealed no significant differences ($p>0.05$).

Bor et al., 2003 for details). The stimuli were presented on a touch-sensitive screen. Specifically, on each trial, a sequence of red squares flashed blue for 500 ms each, with a 250 ms interval between squares. At the end of the sequence, a short tone prompted the participants to respond by reproducing the same series of locations with the index finger of their dominant hand.

There were four locations presented in each trial. Spatial span of each participant was calculated as the mean number of locations that could be recalled successfully following a single presentation. The sequences were either structured, using an algorithm which tended to produce sequences containing familiar shapes, such as right angled triangles and parallelograms, or unstructured, using an alternative algorithm that produced sequences with less symmetry and fewer parallel sides. Structured and unstructured sequences were presented in a pseudo-random order. There were 14 trials in each condition presented over two runs of the task. Participants were not informed that trials differed in any way.

Verbal Working Memory Task (VWMT)

The VWMT for digit sequences was tested using the test described in detail elsewhere (Bor et al., 2004). The subjects were presented with a sequence of digits to be remembered and reproduced. For each trial they were firstly presented with a cross on a screen, followed by the auditory presentation of the novel sequence of six digits. Each digit was presented for 0.75 s. After a short period of delay (4 to 8 s.), a visual presentation of the word 'RECALL' indicated that the subject was to respond by repeating the sequence just heard. Subjects' responses were recorded and scored in order to be able to analyze response times and accuracy.

All sequences were six digits in length. Two different types of sequence were presented in a pseudo-random order. Structured sequences were made up of proportions of up to four digits in length of runs of either ascending or descending adjacent, even or odd numbers. An example of structured sequence is: 8, 6, 4, 2, 3, 5. Unstructured sequences were designed to appear to be as random as possible, i.e., they had no runs of adjacent, even or odd numbers, or any other kind of pattern. An example of structured sequence is: 4, 7, 1, 5, 2, 9. There were 14 trials in each condition. Participants were not informed that there were two types of trials.

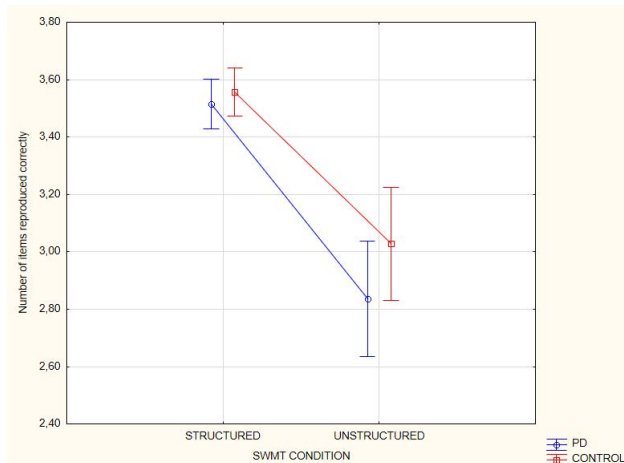
Results

SWMT

The PD and control groups were compared in terms of the number of locations reproduced correctly (see Fig. 1). The two-way analysis of variance of group (PD or control) and type of sequence (structured or unstructured sequences) revealed no main effect of group ($p=0.556$) and a highly significant main effect of type of sequence ($F(1,33)=41.73$, $p<0.001$), with more errors being committed in the unstructured condition compared to the structured condition. The interaction between group and type of sequence was insignificant ($p=0.424$).

Figure 1. Spatial working memory task

The mean number of correctly reproduced locations for two types of sequences in the group with Parkinson's disease and the control group. Error bars represent standard errors

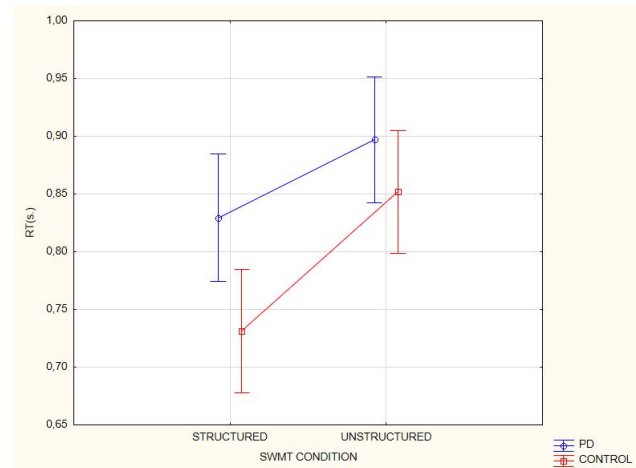


In terms of reaction times, the two-way analysis of variance of group and type of sequence revealed no main effect of group ($p=0.349$) and a highly significant main effect of type of sequence ($F(1,33)=48.35$, $p<0.001$), with faster reaction times for the structured condition compared to the unstructured condition. The interaction between group and type of sequence was approaching the required level of significance ($F(1,33)=3.828$, $p=0.0588$; see Fig. 2). Considering the directional nature of the hypothesis concerning the relationship between the

strategic component of the WM performance and PD, this interaction can be considered as significant at the p level $p=0.025$. This effect suggests that in terms of response times, although both groups benefitted from the structured pattern of stimuli, the PD patients might have benefitted less than the matched controls.

Figure 2. Spatial working memory task

The mean RT (for correct responses only) for two types of sequences in the group with Parkinson's disease and the control group. Error bars represent standard errors



VWMT

The PD group and the control group were compared in terms of the number of digits reproduced correctly. The two-way analysis of variance of group (PD or control) and type of sequence (structured or unstructured sequences) revealed the main effect of group ($F(1,33)=4.1897$, $p=0.048$), with the patients group reproducing significantly less items. The main effect of structure was insignificant ($p=0.35$). Although the interaction of group x structure was approaching a required level of significance ($F(1,33)=2.26$, $p=0.07$, unidirectional test; see Fig. 3), a closer examination by contrast analysis revealed that the PD group remembered significantly less items than the control group, but only in the structured item condition ($F(1,33)=6.26$; $p=0.017$) and not for the unstructured condition ($F(1,33)=1.70$; $p=0.20$). Again, the PD patients benefitted less from the structured pattern of the memorized material, compared to controls.

When reaction times were analyzed, the two-way analysis of variance of group and type of sequence revealed no main effect of group ($p=0.1$), no main effect of type of sequence ($p=0.11$) and no interaction between group and type of sequence ($p=0.25$; see Fig. 4). However, a contrast analysis revealed that the RT's of the control group were significantly shortened under the structured condition as compared to the PD group ($F(1,33)=4.80$, $p=0.04$). It may suggest that the patients with PD were less able to take advantage of the structured material.

Figure 3. Verbal working memory task

The mean number of correctly reproduced digits for two types of sequences in the group with Parkinson's disease and the control group. Error bars represent standard errors

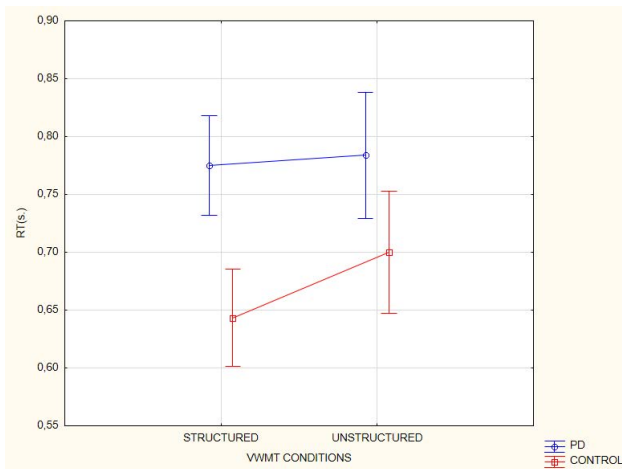
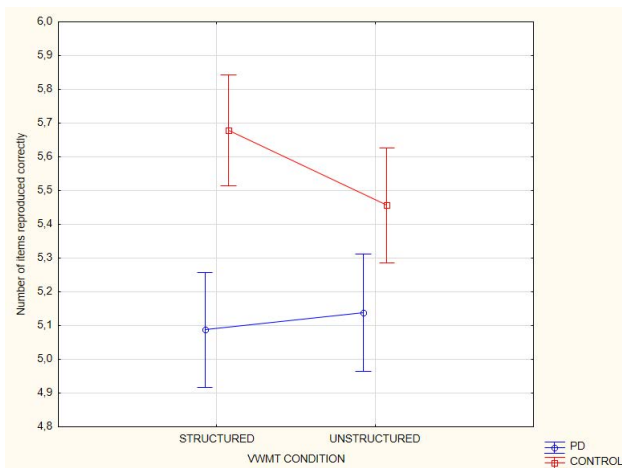


Figure 4. Verbal working memory task

The mean RT (for correct responses only) for two types of sequences in the group with Parkinson's disease and the control group. Error bars represent standard errors



Discussion

One major issue surrounding the nature of the WM impairment in PD concerns whether the spatial WM underperformance reflects a disproportionate involvement of spatial processing deficits (Le Bras et al., 1999), or whether it is rather modality unspecific, reflecting underlying additional executive task requirements (Owen et al., 1996; Owen et al., 1997). The results of the present study demonstrate that, relative to healthy control subjects, the patients with mild PD were significantly less accurate and slower than controls on the verbal WM task, specifically on the structured condition, revealing executive demands of the task. The analogous deficit was less pronounced in the case of the spatial WM task performance. It was reflected by the response time data, revealing that the patients with PD – relative to the control group – were

unable to benefit (i.e., shorten their responses) from the structured component while performing SWMT. Several recent studies have shown that the performance of groups of patients at different stages of PD on spatial memory tests can be differentiated in terms of executive demands of the tasks (Morris et al., 1988; Owen et al., 1992; Owen et al., 1993). Thus, when the task simply involved the retention and recall of a spatial sequence within WM, deficits were apparent only in patients with severe clinical symptoms. By contrast, when the task required the active manipulation of spatial information within WM and the implementation of organizational strategies, deficits were observed in medicated patients with both mild and severe clinical symptoms. Taken together, these results are indicative of a primary role of modality unspecific, executive deficits on verbal and spatial WM task performance in PD.

The neural correlates of the executive component of the tasks used here have been recently investigated (Bor et al., 2003, Bor et al., 2004, Bor et al., 2006). Bor et al. (2003) presented healthy control participants with SWMT. They have observed that structured sequence trials were recalled significantly better, with concomitant activation increases in LPFC. In the subsequent study Bor and colleagues (2004) examined the neural correlates of VWMT performance. Again, better performance of the healthy volunteers for the structured sequences was accompanied by higher activity in the LPFC (see also Bor & Owen, 2006). Finally, the role of DLPFC in the processing of executive component of the task was also confirmed in a study with patients with DLPFC lesions (Bor et al., 2006). It is widely accepted that the prefrontal cortex plays a critical role in various aspects of WM (Cabeza & Nyberg, 2000; Fletcher & Henson, 2001; Goldman-Rakic, 2011; Owen et al., 1998; Pochon, 2001; Prabhakaran, Narayanan, Zhao, & Gabrieli, 2000; Wager & Smith, 2003), and a number of neuroimaging studies in healthy control participants have suggested that the manipulation of information within WM preferentially involves the mid-dorsolateral prefrontal cortex (Owen et al., 1999; Owen, Evans, & Petrides, 1996). This conclusion corresponds to the recent findings revealing that in PD the impairments in information manipulation within WM is related to the integrity of PFC, especially DLPFC and VLPFC (Lewis, Dove et al., 2003). Taken together, these findings suggest that it is the DLPFC component of frontostriatal circuitry that is primarily responsible for the WM strategic deficits observed in the patients with PD in the current investigation.

A more surprising aspect of the current results relates to the fact that more profound impairments of the WM performance in the PD group were observed in the verbal domain rather than in the spatial domain. This result is unexpected considering that spatial WM deficits have been widely reported in patients with mild to moderate clinical symptoms, whilst the same patients were reported as unimpaired on analogous tests of verbal and object WM (Bradley et al., 1989; Owen et al., 1996; Owen et al., 1997; see also Siegert et al., 2008). Considering that both SWMT and VWMT used here were methodologically identical

except for the modality of the stimuli used, it remains to be established what factor may account for the discrepancy between the current results and the previous findings. One possible reason may be related to the fact that in SWMT, the subjects were required to reproduce a sequence of only four locations and the overall performance (for both the patients with PD and the control healthy volunteers) was high. This methodological factor could lead to the scale attenuation. In contrast, in VWMT, the subjects were required to repeat a sequence of six digits, making the task slightly more difficult.

One possible confound in the current study is that the patients were on dopamine replacement therapy at the time of testing (Costa et al., 2003; Fournet, Moreaud, Roulin, Naegel, & Pellat, 2000; Lange et al., 1992), whilst the selective influence of dopamine depletion on manipulation of information within WM rather than information retrieval or maintenance has been observed. For example, in the study reported by Slabosz et al. (2006), L-dopa administration in patients with PD selectively improved manipulation within WM relative to other cognitive processes such as maintenance and retrieval (see also Lewis et al., 2005). Moreover, L-dopa administration ameliorates dysfunction of circuitry involving the mid-dorsolateral and/or the mid-ventrolateral frontal cortices observed in the patients on the same WM task as used by Slabosz et al. (2006) and Lewis et al. (2005), while performing the WM manipulation condition (Lewis, Dove et al., 2003; Lewis, Dove, Robbins, Barker and Owen, 2004). As indicated above, the same areas are responsible for executive component of VWMT and SWMT (Bor et al., 2003, Bor et al., 2004, Bor et al., 2006; Bor & Owen, 2006). Taken together, these results suggest that in the current study L-dopa may have specifically undermined the impairment of the patients relative to the control group observed under the structured condition of VWMT and SWMT. The effects of L-dopa on the patients performance under the unstructured condition of the tasks were presumably less pronounced.

A final point to consider is that dopaminergic medication may have differentially affected the performance of the patients with PD on the VWMT and SWMT. Only a few studies have directly compared the effects of L-dopa on verbal and spatial WM tasks well matched in terms of all requirements except for the modality of materials used. For example, Beato et al., (2008), using three variants of the 'n-back' task (spatial items, faces and letters), have shown that L-dopa had a positive effect only on spatial WM task (and no effect on faces or letters performance). In contrast, Kraft, Binder, Lulé, Storch and Gruber (2012) using phonological and visuospatial variants of delayed matched to sample paradigm have demonstrated that in PD reduced brain activity during verbal WM task performance was normalized by L-dopa, whilst altered brain activity accompanying visuospatial WM task performance

was insensitive to dopaminergic manipulation.¹ Taken together, these findings suggest that modality specific WM performance can show different responses to L-dopa in PD. As to the current results, it may indicate that the performance of the patients on VWMT and SWMT was differentially affected by L-dopa. However, due to the mixed findings of the previous studies, at the moment it is difficult to speculate on the exact nature of these influences and further research is needed to disentangle this issue.

In sum, our findings support the view that in PD deficits in verbal WM modality (and plausibly in spatial WM modality as well) may be at least partly attributed to a primary executive dysfunction present even at the early stages of the condition. These findings concur well with the notion that WM is susceptible to damage on a number of different levels. Moreover, current observations suggest that seemingly simple span tasks may actually be not so simple for the patients with PD, when requiring a considerable contribution of executive resources. However, even with this requirement, span tasks are still easier than Tower of London or spatial self-ordered searching tasks, which are too difficult for patients with more advanced PD. The conclusions stemming from the current task could be used as a starting point for developing a new test diagnostic for executive deficits in PD: a 'simple' simple span task with a strategic component.

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¹ However, it should be noted that while the patients with PD tested by Beato et al., (2008) performed less well on the WM tasks than the controls, Kraft and colleagues (Kraft, Binder, Lulé, Storch & Gruber, 2012) reported no significant behavioural difference between the PD group and the healthy controls.

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