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Neuropsychologia 41 (2003) 645–654

NEUROPSYCHOLOGIA

www.elsevier.com/locate/neuropsychologia

Using executive heterogeneity to explore the nature of working memory deficits in Parkinson's disease

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Received 28 January 2002; received in revised form 26 September 2002; accepted 14 October 2002

Abstract

Idiopathic Parkinson's disease (IPD) is characterised by a triad of motor symptoms, namely bradykinesia, rigidity and resting tremor, although cognitive impairment is a common feature of the disease and has been accepted as one of the strong predictors of quality of life in such patients. Neuropsychological testing in Parkinson's disease often reveals a pattern of cognitive impairment similar to that observed in patients with frontal lobe lesions, although clear differences between the two groups have also often been reported. This apparent inconsistency in the literature may reflect heterogeneity among different groups of patients with Parkinson's disease, although to date this possibility has not been formally addressed. In this study, two groups of patients with Parkinson's disease were assessed on a novel verbal memory task, which allowed different aspects of working memory function such as maintenance, retrieval and manipulation to be tested within the same general paradigm. The two groups were selected according to either good or bad performance on a 'standard', visuospatial test of executive function (The Tower of London Task), but were well matched on all other demographic and cognitive measures tested. The sub-group of Parkinson's disease patients with Tower of London defined executive deficit were specifically impaired at manipulating information within verbal working memory, both compared to controls and to the group of patients with no predefined executive impairments. In contrast, the three groups did not differ in their ability to maintain or retrieve information within verbal working memory. Given the known preferential role of the dorsolateral frontal cortex in higher executive functions, (including both planning and the manipulation of information within working memory), these results suggest that, in a subset of Parkinson's disease patients, it is the frontostriatal circuitry involving this region which is primarily affected, while other components of this circuitry may be relatively spared. The results also suggest that performance on the Tower of London task may prove to be a useful discriminant variable in defining the nature of cognitive heterogeneity in Parkinson's disease.

Keywords: Working memory; Prefrontal cortex; Basal ganglia

1. Introduction

Idiopathic Parkinson's disease (IPD) is a common neurodegenerative condition clinically defined by the motor symptoms of bradykinesia, rigidity and resting tremor. Although only about 20% of IPD patients develop a frank dementia [8], less severe cognitive impairment is a well recognised feature of the disease and has been shown to be an important predictor for the quality of life in most patients [30,55]. The pattern of cognitive impairments seen in the early stages of IPD resembles that produced by frontal-lobe damage and includes deficits of 'executive' functions, such as planning and working memory [16,34,58]. Furthermore, these 'frontal-like' impairments in IPD appear to be related to deficiencies in the dopaminergic system [21,32] although a role for other neurotransmitter systems in the cognitive profile of patients with IPD has also been demonstrated [1,17,35]. Pattern recognition memory and related cognitive processes, which depend more heavily on the medial temporal-lobe structures, are relatively unimpaired in these same patients [32].

In recent years, investigation of the 'frontal-like' pattern of cognitive dysfunction in IPD has focused largely on deficits of working memory [7,11,12,27,38,41–43]. Several

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0028-3932/02/$ – see front matter
PII: S0028-3932(02)00257-9

studies have shown that impairments in working memory are more severe in medicated patients at the later stages of the disease than in non-medicated patients with mild clinical symptoms [38,43]. Moreover, some aspects of working memory are more severely impaired, and appear to be affected at an earlier stage of the disease, than others. For example, spatial working memory deficits have been widely reported in patients with mild to moderate clinical symptoms [7,13,42,49]. In contrast the same patients are unimpaired on analogous tests of verbal and object working memory [7,42], suggesting that spatial tasks may be more vulnerable than equivalent non-spatial tasks early in the course of the disease. While some authors have suggested that PD is accompanied by widespread impairments of spatial processing [33], an alternative possibility is that the spatial tasks used in these studies differ from the non-spatial tasks in terms of their underlying executive requirements. In support of this 'processing-specific' theory, Owen et al. [41], have demonstrated that within spatial working memory, significant impairments are observed in patients with both severe and mild clinical symptoms if the task requires the active manipulation of information within memory. In contrast, in spatial working memory tasks that require only maintenance and retrieval of that information deficits are only observed in the patients with more severe clinical symptoms. On this basis, a model of 'frontal-like' cognitive degeneration in IPD has been formulated which suggests that 'higher-level' executive functions such as manipulation, monitoring and planning which are often assumed to depend critically on the integrity of the dorsolateral frontal cortex [44,47,48], may be more susceptible than basic mnemonic functions such as maintenance and recall, which are assumed to depend on more ventral frontal regions [46].

In this study, this hypothesis was investigated directly in the verbal domain using a novel working memory task that assessed different inter-related aspects of mnemonic performance, including maintenance, retrieval and manipulation of information, within the same general paradigm. Specifically, patients were required to hold a sequence of four letters in memory (maintenance), across a variable delay period and then either recall that sequence (retrieval) or reorder it (manipulation) according to a pre-learned rule.

Although a number of previous studies have investigated heterogeneity of cognitive deficits in IPD, these investigations have tended to focus on the importance of factors such as disease severity [41,43], medication [32,43], age [2], dominant motor symptom [29,62] and age of onset [23,29]. In this study, the importance of 'executive' impairment as a useful discriminant variable in sub-groups of patients with IPD was assessed. Accordingly, two groups of 'non-demented' patients with IPD were recruited and matched according to all of the variables described earlier. The two groups were selected, however, according to whether their performance was impaired or unimpaired on the Tower of London test (TOL), which has been shown previously to be sensitive to deficit in large groups of patients with IPD [38,43,45]. This division of patients made it possible to test two specific hypotheses. First, that like spatial working memory deficits in IPD, impairments in *verbal* working memory in mild to moderate IPD are psychologically specific and involve the manipulation of information, but not the maintenance of that information, within memory. Second, that deficits in the manipulation of information within verbal working memory will be most severe in patients with 'executive dysfunction' as indexed using an unrelated visuospatial task.

2. Methods

2.1. Subjects

The 41 patients included in this study were all recruited from a larger cohort of cases evaluated in the Parkinson's disease Research Clinic at the Cambridge Centre for Brain Repair (CCBR). All patients satisfied UKPDS Brain Bank criteria [23] and were assessed on their regular medication. All patients underwent careful historical review along with physical examination and neuropsychometric analysis. Each individual assessment took between 1.5 and 2 h and was conducted either in a clinical suite at the CCBR or at the patient's own home. Patients were given appropriate rest periods during the consultation. Permission for the study was obtained from the local research ethical committee and all subjects consented to participation.

All patients were rated as between Hoehn and Yahr stages I–III (mild to moderate disease) and were assessed on sections I–V of the unified Parkinson's disease rating scale, UPDRS [18]. None of these patients showed evidence of clinical dementia and all attained scores $\geq$26/30 on the Folstein Mini-mental State Examination (MMSE) [20]. No patients with overt clinical depression were included and a measure of affective disturbance was also attained using the Beck Depression Inventory, BDI [5]. An estimate of pre-morbid verbal IQ was derived using the National Adult Reading Test (NART) [39]. Neuropsychological testing of verbal and categorical fluency (FAS 60-s [6], animals 90-s [26], pattern and spatial recognition memory tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB), as well as a measure of motor latency (from the CANTAB motor screening test) was performed on all patients. The twenty-four healthy volunteers (eight male) in this study also completed the MMSE, the NART, the BDI and the same CANTAB pattern recognition memory tasks administered to the IPD patients.

The 41 IPD patients were then divided into two groups (Table 1) on the basis of their performance on the Tower of London planning test (TOL), shown previously to be sensitive to deficit in the earliest stages of the disease [38,43]. The TOL was selected as a validated and efficient means of screening executive performance in IPD patients. This planning task clearly utilises aspects of working memory but is not suitable for differentiating between different

Table 1
Disease severity and medications

	Unimpaired IPD ($n = 22$)	Impaired IPD ($n = 19$)
H&Y I	4	2
H&Y II	15	13
H&Y III	3	4
L-dopa	17	14
Antidepressants	4	6
Dopaminergic agonists	9	7
Benzhexol	3	2
Selegiline	2	0

processing components. All patients were pre-tested on the 'one-touch' version of the Tower of London task [45] for full details; see Owen et al., 1995. Performance was assessed according to the number problems solved correctly with the first attempt on 2 one-move problems, 2 two-move problems, 2 three-move problems, 4 four-move problems and 4 five-move problems giving a maximum score of 14. Parallel studies of this 'one-touch' version of the TOL in healthy age and IQ matched control subjects have revealed a mean accuracy score of 10.5 (Sahakian et al., unpublished data). In this study, patients who scored $\geq$11/14 were considered to be unimpaired on the task whereas those scoring $\leq$8/14 were deemed to be impaired. In order to maximize the difference between the two groups, no patients scoring 9/14 or 10/14 were included in the study. This division of patients resulted in one group of 22 patients (10 male) who were considered to be 'unimpaired' on the TOL planning task and a second group of 19 (11 male) who showed clear impairment on this task (Table 1).

The TOL-unimpaired group of 22 cases (10 male) included 4 H&Y stage I (combined H&Y 1 and 1.5), 15 H&Y stage II (combined H&Y 2 and 2.5) and 3 H&Y stage III patients (mean 2.0). The mean UPDRS was 38.4 and mean BDI was 9.6. Of these patients, 17 were taking L-dopa (mean daily dose 342.3 mg) while 9 were taking dopaminergic agonists (pergolide, ropinirole or cabergoline) in isolation or combination with L-dopa therapy. Three were taking anticholinergic medication (benzhexol or orphenadrine), two were on selegiline and four were on an antidepressant (selective serotonin reuptake inhibitor or tri/tetracyclic antidepressant).

In the group of 19 patients showing impairment on the TOL planning task (11 male), 2 were H&Y stage I, 13 were H&Y stage II and 4 were H&Y stage III. The mean UPDRS was 37.2 and mean BDI was 8.9. Fourteen were taking L-dopa (mean daily dose 431.6 mg) while seven were taking dopaminergic agonists in isolation or combination with L-dopa therapy. Two were taking anticholinergic medication (benzhexol or orphenadrine), none were on selegiline and six were on an antidepressant (selective serotonin reuptake inhibitor or tri/tetracyclic antidepressant).

Summary characteristics for the two patient groups are shown in Table 2 along with the data obtained from the healthy group of controls.

One-way analysis of variance (ANOVA) between the two patient groups revealed no significant differences in age, age of disease onset, duration of illness, H&Y stage, UPDRS, duration of disease, motor latency, MMSE, NART, letter and categorical fluency, pattern recognition, spatial recognition nor BDI. The laterality of disease was also found to be non-significantly different between the two groups using a Mann-Whitney *U*-test.

Furthermore, no significant differences were observed on one-way ANOVA between control subjects and patients for age, MMSE, NART, pattern recognition although BDI was significantly lower in controls (F (2, 62) =3.943, $P = 0.025$). Since controls were not tested, it was not possible to compare the mean accuracy scores for spatial recognition memory and words generated in tests of verbal and categorical fluency directly. However, the scores attained in the patient groups were similar to those that have been reported previously in age matched control samples [51,59].

2.2. Verbal working memory task

All subjects were tested by the same investigator (SJGL), in a clinical suite at the CCBR or in the subject's own home. The test was presented on a *Dell Inspiron* 3800 portable computer with a 14 in. screen and three labelled keys on the keyboard were used to monitor subject responses. The test was

Table 2
Group characteristics

Group	Age (year)	Onset age (year)	Duration (year)	H&Y	UPDRS	BDI	MMSE	NART	FAS	Animals	Pattern	Spatial	Latency (ms)	L-dopa (mg/day)
Controls ($n = 24$)														
Mean	65.3					5.4	29.5	115.1			20.7			
S.D.	8.2					3.7	0.7	6.9			1.3			
Unimpaired IPD ($n = 22$)														
Mean	63.7	56.2	7.5	2.0	38.4	9.6	29.2	116.5	41.2	22.7	19.3	15.4	1232.5	342.3
S.D.	8.4	8.0	4.9	0.6	14.9	7.0	0.9	5.7	9.9	5.8	3.0	2.0	430.5	289.5
Impaired IPD ($n = 19$)														
Mean	66.6	60.6	6.0	2.2	37.2	8.9	28.8	114.6	37.4	19.7	20.2	14.8	1301.0	431.6
S.D.	7.7	9.5	6.0	0.6	13.2	5.1	1.3	7.2	11.4	3.9	2.1	2.1	373.2	384.1

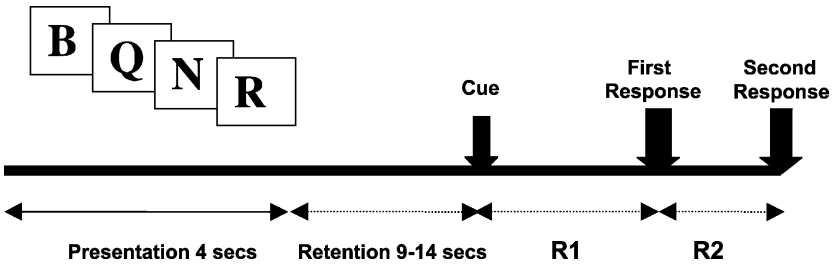

Fig. 1. A single trial from the working memory task. Following presentation of four letters and a retention interval of 9–14 s, a cue signalled one of three conditions, 'same', 'ends' or 'middle'. The subject responded with a key press ('first response') once the correct solution had been generated and a second key press ('second response'), to select from two alternative possibilities.

conducted with the subject positioned sitting comfortably in front of the screen with the first three fingers of the dominant (right) hand overlying the three response keys. All subjects were trained on the task using a purpose written working demonstration program (*PowerPoint* 2000) and before testing, 35 practice conditions were presented. All subjects demonstrated their understanding of the task and adequate use of the keyboard responses prior to being presented with a further 90 trials.

A modified version of the verbal working memory task developed by Bublak et al. [9] was used and the structure of a trial is shown in Fig. 1. In each of three conditions, four different consonants (drawn from the set B, H, J, N, Q, R, X), were presented sequentially during a study phase of 4 s (one per second). The participant was then required to retain the letters in memory and was explicitly instructed to sub-vocally rehearse the sequence in the order presented. In all conditions, the length of the retention phase varied randomly between 9 and 14 s. At the end of this period, a cue word was presented in the centre of the screen for 1 s. This cue informed the subject whether the letter sequence was to be recalled verbatim (maintenance only condition), or whether the letters had to be reordered in one of two pre-learned ways.

- *Maintenance*: When the word '**same**' was presented as the cue, the participant's task was to recall the letters in the same order as they were presented during the study phase. For example, the list "B Q N R" had to be recalled as "B Q N R".
- *Manipulation* 1: When the word '**ends**' was presented as the cue, the participant's task was to recall the digits in the following order: the 3rd, 4th, 1st and 2nd digit of the original memory list. For example, the list "B Q N R" had to be recalled as "N R B Q".
- *Manipulation* 2: When the word '**middle**' was presented as cue, the participant's had to recall the letters in a different order from presentation. The task was to reorder the middle letters, thus to recall the 1st, then the 3rd, then the 2nd and then the 4th letter of the original memory list. For example, the list "B Q N R" had to be recalled as "B N Q R".

Following the cue, a blank screen was presented until the subject indicated, by pressing the response button under their ring finger, that they had the required sequence of letters 'in mind'. This response was taken as an approximate measure of when the trial 'thinking time' terminated and is referred to as R1. Immediately following this response, two sets of four letters appeared above and below the centre of the screen. These alternative solutions were composed of the same four letters and were constructed such that identification of the correct answer from the incorrect foil required the subject to check through the sequences fully. The subject was required to select the correct answer by pressing one of the two response keys under their index and middle fingers. The response keys were arranged in such a way that the location of the correct response was spatially compatible with the location of the correct response alternative. This (second) response was taken as an approximate measure of 'motor response' time and is referred to as R2, although it is clear that this period may also include some degree of cognitive processing. Following the second response, the participants were informed automatically whether the trial was correct or incorrect.

Accuracy and response time data were treated using repeated measures analysis of variance (SPSS-PC), or where appropriate, one-way analysis of variance (O-ANOVA). In the analysis of response time data, only 'correct' trials were included.

3. Results

3.1. Accuracy

The mean number of correct responses in each condition are presented in Fig. 2 and were analysed using a repeated measures ANOVA, with one within-subject factor (condition, 3 levels) and one between-subject factor (group, 3 levels). Across groups, subjects performed more poorly as the conditions became more difficult (see Fig. 2), as indexed by a significant main effect of condition (F (2, 62) = 89.18, $P < 0.001$). Moreover, there was a significant main effect of group (F (2, 62) = 12.791, $P < 0.001$), but

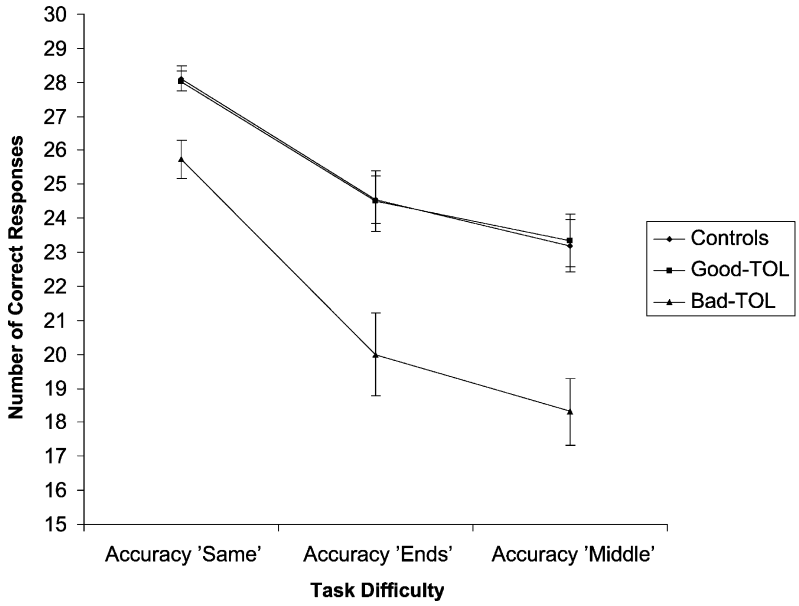

Fig. 2. Performance accuracy. The number of correct responses at each level of task difficulty. Bars represent S.E. of the mean.

no significant interaction between the two factors (F (2, 62) = 2.1, P = 0.085). Further analysis of the group main effect revealed that the TOL-impaired IPD group were significantly less accurate over all conditions when compared with the TOL-unimpaired group ('same' F (2, 62) = 10.415, $P < 0.001$, 'ends' F (2, 62) = 7.454, P = 0.001, 'middle' F (2, 62) = 10.935, $P < 0.001$).

3.2. Response times

Response times R1 and R2 are presented as a function of group and task difficulty in Fig. 3 and were analysed using a repeated measures ANOVA with 2 within-subject factors ('task difficulty' (3 levels) and 'response time' (2 levels; R1 versus R2) and one between-subject factor (group (3 levels)).

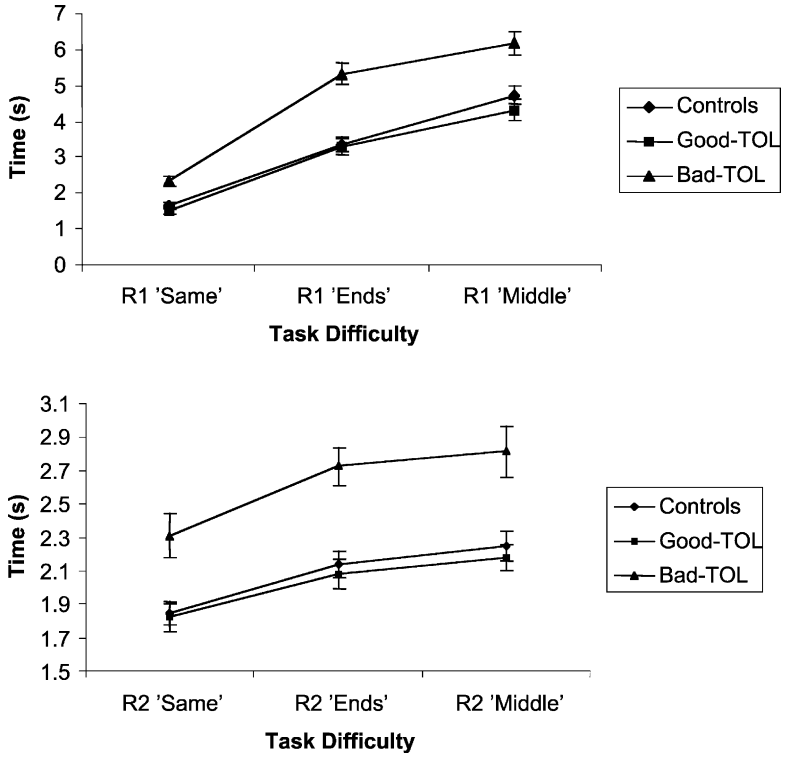

Fig. 3. Performance latency. Top: the latency to generate a solution (correct solutions only) at each level of task difficulty ('R1'). Bottom: the latency to select from two alternatives (correct solutions only) at each level of task difficulty ('R2'). Bars represent S.E. of the mean.

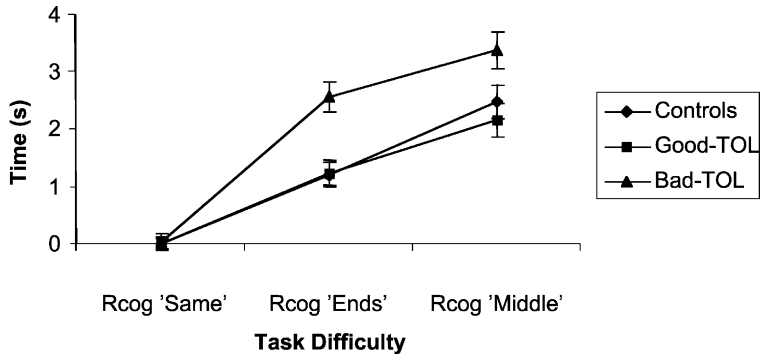

Fig. 4. Corrected performance latency. The ('cognitive') latency to generate a solution minus the ('motor') latency to select from two alternatives (correct solutions only) at each level of task difficulty ('R1–R2'). Bars represent S.E. of the mean.

The analysis revealed significant main effects of task difficulty (F (2, 62) = 495.995, $P < 0.001$), response time (F (2, 62) = 178.647, $P < 0.001$ and group (F (2, 62) = 22.66, $P < 0.001$). Moreover, there was a significant three-way interaction between the variables (F (2, 62) = 3.823, $P = 0.006$), and this was investigated further by examining the two-way interaction effects for response times R1 ('thinking time') and R2 ('motor time') separately. A significant group by condition effect was observed for variable R1 (F (2, 62) = 6.19, $P < 0.001$), but not for variable R2 (F (2, 62) = 0.941, $P = 0.443$). The significant two-way interaction for variable R1 was investigated further by examining the one-way group effects at the three levels of task difficulty, separately. These analyses revealed significant results across all conditions ('same' (F (2, 62) = 16.629, $P < 0.001$, 'ends' (F (2, 62) = 20.822, $P < 0.001$) and 'middle' (F (2, 62) = 10.47, $P < 0.001$)).

Since the 'thinking time' (R1) and 'motor time' (R2) variables were operationally defined and undoubtedly overlap to some extent in terms of the cognitive and motor processes involved in each (e.g. R1 also involved a button push), a new variable, Rcog, was computed by subtracting R2 from R1 at each level of the task. The period of 'motor time' (R2) doubtless included cognitive elements such as mentally checking the answer derived during R1 and was also susceptible to delays, for example, if a subject became confused or lost focus before confirming their selection. Thus, the variable Rcog was assumed to represent a more conservative estimate of 'thinking time'. For the two manipulation conditions ('ends' and 'middle') Rcog was significantly longer in the TOL-impaired IPD group than in either the TOL-unimpaired group ('ends' F (1, 39) = 15.381, $P < 0.001$, 'middle' F (1, 39) = 8.089, $P = 0.007$) or in the healthy control volunteers ('ends' F (1, 41) = 17.524, $P < 0.001$, 'middle' F (1, 41) = 4.629, $P = 0.037$), see Fig. 4. In contrast, there were no significant group effects for the variable Rcog during the maintenance condition.

4. Discussion

In this study, a novel letter manipulation task was employed to differentiate aspects of verbal working function in patients with IPD. Specifically, the task provided independent measures of the ability to maintain information within working memory and to manipulate that information according to one of several pre-specified rules uncontaminated by factors such as simple motor movement times. Moreover, performance on this task was examined in two groups of patients who differed according to their performance on an independent visuospatial test of executive function (TOL), but were well matched according to performance on other non-executive cognitive tasks as well as on various demographic variables.

In terms of task accuracy, the TOL-impaired group were significantly less accurate than control volunteers on the verbal working memory task, although this effect was generalised across all conditions and not specific to those trials requiring the manipulation of information within memory.

In terms of estimated thinking times *for correct responses only*, patients in the TOL-impaired sub-group were also significantly impaired on measure R1 of the verbal working memory task, specifically in those conditions where they were required to manipulate information within memory. Thus, while thinking times were not different from controls when the patients were required simply to retrieve a previously maintained sequence of four letters, they were significantly prolonged when they were required to re-order those letters according to either of the two pre-learned rules. The fact that the motor requirements for the maintenance and manipulation conditions were identical and that selection time (R2) was not disproportionately longer for the manipulation conditions in the TOL-impaired group suggests that this deficit in the speed of manipulating information within working memory is not a direct result of differences in clinical (motor) symptoms between the two patient groups. Moreover, an additional control for the effects of any residual differences in motor execution time was extracted by

subtracting R2 from R1 and re-analysing the response data. The overall pattern of results was unchanged. Since only correct trials were included in the analysis, it appears unlikely that this deficit in thinking time during manipulation is related directly to the observed accuracy deficits across all three types of trials.

The apparent difference between the two groups of patients with IPD could simply reflect a global difference in cognitive capacity between patients in the TOL-impaired and TOL-unimpaired sub-groups. This seems unlikely, however, since the two IPD groups could not be distinguished in terms of their performance on other neuropsychological tasks, including a test of pattern recognition memory, which is sensitive to temporal-lobe and not frontal-lobe lesions [32]. The two patient groups were also very well matched with respect to clinical measures such as their age, age of disease onset, disease duration, Hoehn and Yahr scores, UPDRS, daily L-dopa dose, concomitant medications, simple motor latency, MMSE, NART, and BDI.

The results suggest, therefore, that there may be two clear sub-groups of patients with IPD, who are differentially impaired on tests of 'executive dysfunction' across multiple stimulus domains (e.g. spatial and verbal). Previous studies have divided patients according to factors such as age [2], dominant motor symptom [29,62] and age of onset [23,29] divisions which may prove to be wholly orthogonal to the TOL-defined 'executive impairment' factor identified here. Of course, one obvious criticism of this approach is that the patient group was sub-divided according to performance on one test of 'executive' dysfunction and the sub-groups were simply found to differ on another test that ostensibly measures a closely related set of cognitive processes. However, it is important to consider that the Tower of London task is a visuospatial task that places a significant load on *planning* processes, while the novel task employed in this study taps aspects of *verbal working memory*. In addition, the patients were subdivided according to their *accuracy* scores on the Tower of London task, yet the primary dissociation reported here is in the *speed* (i.e. response time), of manipulating information within verbal working memory. Although, 'thinking time' deficits have been reported previously in IPD, they do not generally correlate with accuracy deficits even on the same test [43]. Moreover, a recent large-scale factor analysis in healthy controls has demonstrated that measures of thinking time and response accuracy across a range of planning and working memory tasks load on different factors [50].

The results of the present study confirm and extend previous investigations that have attempted to define the precise nature of the executive impairment in patients with Parkinson's disease. For example, spatial working memory deficits have been widely reported in patients with mild to moderate clinical symptoms [7,13,49], but only in tasks that require the active manipulation of information within memory; no deficits are observed in such patients in spatial tasks that require only maintenance and retrieval of the remembered information. Using a single task, the present results confirm that, as in the spatial domain, verbal working memory deficits in response time are only observed in mild IPD if the task requires the manipulation of information within working memory, but not if the task requires only the maintenance and retrieval of that information. On the other hand, deficits in accuracy were observed in all three conditions, and this impairment was not significantly greater in the manipulation conditions. Slowed thinking time in patients with IPD, a possible correlate of 'bradyphrenia' may reflect a state of psychomotor retardation characteristic of Parkinson's disease and depressed patients. Rogers et al. [53] proposed that bradyphrenia in IPD and psychomotor retardation in primary depressive illness may be closely related and that the dopaminergic system may be involved in both. Importantly however, although cognitive impairment in IPD is known to be associated with depression [57], in the current study the two groups of patients did not differ significantly in terms of their scores on the BDI suggesting that depression did not contribute to the specific deficits seen in the TOL-impaired group. It also seems unlikely that the thinking time deficit in the TOL-impaired group reflects a speed error trade off since similar accuracy deficits were observed in this group in all three types of trials and the analysis of thinking time scores included only correct trials. Prolonged thinking time in the manipulation trials may be attributed to mental activity that is not devoted to solving the problem at hand, resulting in 'mind wandering' or 'blanking' [60]. The latter may be likened to so-called 'psychic akinesia' occasionally reported in IPD [28,52]. Finally, slowed thinking may reflect delays in switching between internal representations of the sequence of stimuli to be remembered. This latter hypothesis is relevant to theories of cognitive dysfunction in IPD that have focussed on deficits in attentional set-shifting ability, possibly resulting from frontal–striatal dysfunction (e.g. [38,41,43]).

Although no consensus has been reached regarding the fractionation of functions within the prefrontal cortex it is widely accepted that this region plays a critical role in aspects of working memory [22,25,56]. A number of relevant studies have suggested that the manipulation of information within working memory involves the mid-dorsolateral frontal cortex, while more basic mnemonic functions such as encoding and retrieval preferentially involve more ventral regions (for review, see [40]). The question arises, therefore, as to whether a plausible neural account might be formulated for the specific 'executive' impairment observed in the TOL-impaired sub-group of patients with IPD. Non-dopaminergic forms of pathology, including noradrenergic, serotoninergic and cholinergic deafferentation of the cortex [3], may play a significant role in some of the cognitive deficits observed in IPD. Similarly, cortical Lewy bodies, which may occur even in the early stages of IPD, may play a contributory role [10,24]. However, the fact that working memory deficits have been shown previously to be extremely sensitive to the effects of controlled L-dopa withdrawal in groups of patients with IPD [32] suggests a

predominantly dopaminergic substrate for the deficits observed in the current study. IPD is characterised by dopamine depletion within the frontal cortex itself [54] (via degeneration of the mesocortical dopamine system), which may play a significant role in the 'frontal-like' cognitive deficits observed in this study. However, this system is known to be far less severely affected (50% depletion) than the nigrostriatal dopamine system in IPD [3], which therefore, appears to be a more plausible neural candidate for the deficits observed. Recent anatomical and neuropathological evidence suggests that in IPD, executive impairments of this type may be linked to the spatiotemporal progression of dopamine depletion within the striatum in relation to the terminal distribution of its cortical afferents. A central model for much of this work has been the concept of cortico-striatal loops [4], which emphasises the functional inter-relationships between the neocortex and the striatum. Of particular interest is the fact that the principal target of basal ganglia outflow appears to be the frontal lobes and that different sectors of the striatum project to specific frontal regions via a number of distinct intermediate stations. For example, neural connections have been mapped in non-human primates using a technique of retrograde transneuronal viral uptake and suggest that the dorsolateral frontal cortex (areas 9/46) may be part of a distinct neural network to that which includes the ventrolateral frontal cortex (area 12) [36,37]. Furthermore the results of this work show that cortical regions receive fibres in a highly ordered topographical fashion and those projections from distinct regions of the basal ganglia nuclei remain topographically mapped in the cortex. In IPD, neuronal loss is most pronounced in the pars compacta region of the substantia nigra and specific regions within the pars compacta are differentially sensitive, with the greatest neuronal loss in the ventrolateral tier (60–70% at the onset of clinical symptoms [15,19]). As the nigrostriatal projection is topographically organised, this variable loss of dopaminergic neurons within the pars compacta leads directly to an uneven pattern of dopamine depletion within the striatum [31]. The putamen is more severely depleted than the caudate nucleus, although anatomical and electrophysiological evidence generally implicates this structure in the motor, rather than cognitive, deficits associated with IPD. Dopamine depletion in the caudate nucleus, which appears to be a more serious candidate for mediating the cognitive sequelae of IPD, is greatest (to a maximum of about 90%) in the most rostrodorsal extent of the head of this structure, an area which is heavily connected with dorsolateral regions of the frontal lobe [61]. It seems likely, therefore, that these rostrodorsal regions of the caudate nucleus are subjected to greater disruption by the disease and perhaps more severely in some patients than in others. By contrast, ventral regions of the caudate, which are preferentially connected with more ventral regions of the frontal lobe [61], are relatively spared in early IPD, which may leave functions that are maximally dependent on this neural circuitry relatively intact in many patients.

This model of 'frontal-like' cognitive degeneration in IPD has received some support recently from PET activation studies in patients with IPD performing tasks that are known to recruit specific regions of the lateral frontal cortex [13,14]. In one study, regional cerebral blood flow was measured in six patients with moderate Parkinson's disease and in six age-matched controls while subjects performed easy and difficult versions of a modified Tower of London planning task and a mnemonic variant of this task that required short-term retention and reproduction of problem solutions. Both the planning task and the working memory task were associated with abnormal cerebral blood flow in the patients centred on the internal segment of the globus pallidus, but normal blood flow in the frontal lobes. The results again suggest that striatal dopamine depletion disrupts the normal pattern of basal ganglia outflow in IPD and consequently, affects the expression of dorsolateral frontal-lobe functions by interrupting normal transmission of information through frontostriatal circuitry.

Acknowledgements

This study was made possible by a Parkinson's Disease Society Project Grant.

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