Pergamon

PII: S0028–3932(96)00101–7

Neuropsychologia, Vol. 35, No. 4, pp. 519–532, 1997

Printed in Great Britain
0028–3932/97 $17.00+0.00

Spatial and non-spatial working memory at different stages of Parkinson's disease

ADRIAN M. OWEN,*‡ JOANNA L. IDDON,‡ JOHN R. HODGES,§ BEATRICE A. SUMMERS¶ and TREVOR W. ROBBINS†||

†Department of Experimental Psychology, ‡Department of Psychiatry, §Department of Neurology, ||Centre For Brain Repair, University of Cambridge, U.K.; ¶Stafford District General Hospital, Stafford, U.K.

(*Received* 16 *February* 1996; *accepted* 12 *August* 1996)

Abstract—Groups of patients with Parkinson's disease, either medicated or unmedicated, were compared with a matched group of normal control subjects on a computerized battery of tests designed to assess spatial, verbal and visual working memory. In the spatial working memory task, subjects were required to search systematically through a number of boxes to find 'tokens' whilst avoiding those boxes in which tokens had previously been found. In the visual and verbal conditions, the subjects were required to search in exactly the same manner, but through a number of abstract designs or surnames, respectively, avoiding designs or names in which a token had previously been found.

Medicated Parkinson's disease patients with severe clinical symptoms were impaired on all three tests of working memory. In contrast, medicated patients with mild clinical symptoms were impaired on the test of spatial working memory, but not on the verbal or visual working memory tasks. Non-medicated patients with mild clinical symptoms were unimpaired on all three tasks.

These data are compared with the results of a previous study comparing groups of neurosurgical patients with frontal, temporal or amygdalo-hippocampectomy excisions on the same three tests of working memory. Taken together, the findings suggest that working memory deficits in Parkinson's disease emerge, and subsequently progress, according to a defined sequence, the evolution of which may be linked to the likely spatiotemporal progression of dopamine depletion within the striatum. in relation to the terminal distribution of its cortical afferents.

Key Words: dopamine; basal ganglia; cognition; subcortical dementia; frontal lobe.

Introduction

The results of several recent studies suggest that cognitive deficits in Parkinson's disease (PD) emerge, and subsequently progress, according to a defined sequence which begins with deficits on tests that are sensitive to frontal lobe dysfunction, and only later includes impairments on tests that involve more posterior cortical regions [30, 31, 34, 38]. For example, deficits on an attentional set-shifting task, which is known to be sensitive to frontal lobe damage, are observed in PD patients with mild clinical symptoms, whilst these same patients are relatively unimpaired on tests of visuospatial learning and memory, which are known to depend preferentially on the medial temporal lobe structures [30, 31]. In contrast, patients with severe clinical symptoms exhibit a broader range of cognitive impairments which includes deficits in attentional set-shifting and other tasks sensitive to frontal lobe damage and also impaired performance on tests of visuospatial learning and memory that depend on more porterior cortical areas. It seems likely, therefore, that the late emergence of visuospatial learning and memory deficits in PD may reflect a relative sparing of functions associated with the medial temporal lobe structures early in the course of the disease.

In recent years, a number of studies have assessed working memory in patients with PD [5, 7, 8, 16, 25, 30, 31, 34, 52, 43]. Working memory has been described as a "brain system that provides temporary storage and manipulation of the information necessary for such complex tasks as language comprehension, learning and reasoning" [3]. According to Baddeley's cognitive model, a limited capacity 'central executive' acts as controller to a number of slave systems including an 'articulatory loop' and a 'visuo-spatial sketch pad' for the temporary storage of verbal and visual and/or spatial material, respectively. Although methodological differences preclude direct

*Address for correspondence: Dr Adrian M. Owen, Department of Psychiatry, University Of Cambridge Clinical School, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, U.K.; e-mail: amo12@cus.cam.ac.uk; fax: 01223-336968.

comparisons between studies of PD, in general, the results lend further support to the notion that deterioration of cognitive function in these patients progresses in parallel with the degeneration of motor functions that characterizes this disorder. For example, whilst non-medicated patients with mild clinical symptoms have been repeatedly shown to be unimpaired on a test of spatial working memory [25, 30], deficits on this test have been observed in medicated patients, and particularly in those with severe clinical symptoms [30]. Further comparisons between studies also suggest that some aspects of working memory may be affected earlier in the course of PD than others. For example, Bradley *et al.* [5], found that patients with mild to moderate PD were impaired on a test of visuospatial working memory, whilst performance on an analogous test of verbal working memory was unaffected. Similarly, Postle *et al.* [43], demonstrated that, whilst spatial working memory was impaired in medicated patients with mild PD, working memory for visual shapes was relatively preserved.

A plethora of studies has now demonstrated that the lateral frontal cortex is critically involved in certain aspects of working memory. This view emerged primarily from extensive lesion and electrophysiological recording work on nonhuman primates (see [13], for review) and from the study of patients with excisions of frontal cortex (e.g. [42, 29, 33]), although it has been largely confirmed by recent neuroimaging studies in normal human subjects (e.g. [18, 24, 40, 41, 35, 36]). Contemporary accounts, however, view working memory, not as a unitary process, but as a distributed system that depends critically on a close functional relationship between the lateral frontal cortex and more posterior neural structures (see [39], for review). Goldman-Rakic [14] has described several multisynaptic connections between the prefrontal cortex and the hippocampal formation and has speculated that these connections imply a reciprocal functional relationship in working memory [15]. In keeping with this suggestion, it is well established that damage to the hippocampus and related structures in rats produces severe and enduring deficits in spatial working memory tasks [1, 27, 28, 44, 45, 53].

Although it has been possible to implicate specific neural structures in working memory, the relative contributions of these different areas, in functional terms, is less clear. In a recent study, we compared the performance of groups of neurosurgical patients with frontal, temporal or amygdalo-hippocampal excisions on analogous tests of spatial, verbal and visual working memory [37]. The results suggest that both 'executive' (or 'strategic') and mnemonic mechanisms may contribute differentially to performance in tests of working memory and that these dissociable mechanisms may depend most heavily on the frontal cortex and medial temporal lobe structures, respectively. For example, patients with frontal lobe damage were significantly impaired on a spatial self-ordered searching task, making more erroneous returns to locations in which a 'token' had previously been found, even at the simplest levels of task difficulty [29, 33]. In addition, however, these patients were less efficient in the use of a repetitive searching strategy which is known to improve performance on this task, suggesting that at least some of their impairment in spatial working memory arises secondarily from a more fundamental deficit in the use of organizational strategies. The spatial memory task was also sensitive to deficits in patients with temporal lobe damage and in patients with selective amygdalo-hippocampectomy [33, 37], although only at the most extreme level of task difficulty. Moreover, unlike the frontal lobe patients, the temporal lobe groups utilized a normal and effective searching strategy throughout the task suggesting intact executive function accompanied by a more basic dysruption of mnemonic processes. This differential pattern of performance in patients with frontal lobe damage and patients with damage to the medial temporal lobe structures was also evident in a follow-up study, in which the same three patient groups were compared on analogous tests of non-spatial working memory [37]. Thus, in a visual working memory test that placed a considerable load on memory for abstract patterns, but for which no obvious strategy existed to facilitate performance, no deficits were observed in the frontal lobe group. In contrast, significant impairments were observed in the temporal lobe and amygdalo-hippocampectomy groups. Taken together, these findings lend support to the notion that working memory is a widely distributed system which is, consequently, susceptible to damage on a number of different levels.

The results of the study described above also have important implications for the likely progression of cognitive deficits in patients with PD. Given the suggestion, from previous studies, that cognitive deficits in PD progress from 'frontal' to more posterior cortical functions, one might hypothesize that performance on the test of spatial working memory would be affected at an earlier stage of the disease process than performance on the analogous test of visual working memory, given their relative emphasis on frontal and temporal lobe regions, respectively. This study was designed to test this hypothesis explicitly by comparing three sub-groups of patients at different stages of PD on three working memory tests, identical to those used previously to assess neurosurgical patients with frontal or temporal lobe excisions. As well as the spatial and visual working memory tasks described above, all subjects were given a verbal working memory condition, which was insensitive to deficit in either the frontal-lobe or the temporal lobe groups tested previously.

In the present study, an initial group of 21 patients was divided into those with mild clinical symptoms (Hoehn and Yahr Stage I or II; [17]), and those who had more severe physical symptoms (Hoehn and Yahr Stage III or IV). Several recent studies have suggested that frontal lobe deficits in PD may be significantly affected by L-Dopa medication [4, 9, 30, 31, 32]. In fact, in a recent

study of patients with severe PD, performance on the test of spatial working memory described above was improved by L-Dopa medication [22], whereas performance on other non-frontal tests was unaffected. In this study, therefore, the sub-group of patients who were early in the course of PD were divided further into those who had not yet received any medication and those who were already stabilized on dopaminergic therapy. By using precisely the same battery of tests adopted by Owen *et al*. [37] to compare patients with frontal and temporal lobe damage, direct comparisons could be made with this earlier study and, in addition, the likely contributions of both medication and disease severity in PD could be assessed.

Method

Subjects

Parkinson's disease patients. The twenty-one parkinsonian patients included in this study were all outpatients at the Maudsley Hospital, London, The Queen Elizabeth Hospital, King's Lynn or Addenbroke's Hospital, Cambridge. Patients were referred consecutively by the consultant neurologist if a diagnosis of idiopathic PD was reached, in the absence of clinical dementia or depression (see below). All patients exhibited a typical akinetic–rigid syndrome with rest tremor and, where medicated, all had shown a significant clinical response. Patients with a significant medical history not related directly to their PD (e.g. stroke, head injury) were not referred for the study. The severity of clinical symptoms was also assessed by the neurologist according to the Hoehn and Yahr, 5 point rating scale [17]. In cases where medicated patients were experiencing response fluctuations, the Hoehn and Yahr rating referred to the 'on' rather than the 'off' condition. All such patients were tested in the 'on' state.

Seven of these patients were early in the course of the disease and had not yet received any medication (NMED PD group). In this group, clinical symptons were rated as Hoehn and Yahr stage I (3 patients) or stage II (4 patients).

The remaining fourteen patients were all receiving L-Dopa preparations either alone, or in combination with other medication. All were responding well and none were suffering from a confusional state at the time of testing. Seven of these individuals (MED PD (mild) group) had mild/moderate clinical; symptoms and were rated as Hoehn and Yahr stage I (2 patients) or stage II (5 patients). In addition to their dopaminergic medication, two of these patients were receiving anti-cholinergic medication (orphenadrine or benzhexanol) at the time of testing seven of the patients in the medicated PD group had more severe clinical symptoms (MED PD (severe) group) and were rated as Hoehn and Yahr stage III (3 patients) or stage IV (4 patients). Two of these patients were receiving anti-cholinergic medication (orphenadrine or benzhexanol) in addition to their dopaminergic medication at the time of testing.

Exclusion criteria for the medicated PD patients included clinical dementia assessed using both the Mini Mental State Examination (MMSE) [11] and the Kendrick Object Learning Test [20]. Specifically, only patients who scored above 24/30 on the MMSE and 23 or above on the KOLT were included. Patients with significant affective disturbance (scoring above 10), were also identified using the Geriatric Depression Scale (GDS) and excluded from this study. This self-administered, 30 item questionnaire [55] is particularly suited for the assessment of depression in parkinsonian patients since it contains relatively few somatic items which may relate directly to the patients' physical disability. The non-medicated group were not given the MMSE, the KOLT or the GDS on a formal basis. However, none of the NMED PD patients included in this study showed any signs of clinical dementia or significant affective disturbance during extensive neurological and neuropsychological evaluations.

Control subjects. Three groups of normal control volunteers were chosen to match the patient groups as closely as possible with respect to age and premorbid verbal IQ, as estimated by the NART [26]. These subjects were recruited from local advertisements in the London and Cambridge areas and from a large pool of control volunteers at the North East Age Research panel in Newcastle Upon Tyne. Exclusion criteria included any history of neurological or psychiatric illness, substance abuse or head injury. Informed consent was obtained from all patients and control subjects prior to the neuropsychological testing session.

Table 1 shows a summary of characteristics for the three groups of patients with Parkinson's disease and for the matched groups of healthy controls.

One way analysis of variance confirmed that the NMED PD group [$F(1,12) = 0.14$], the MED PD (mild) group [$F(1,12) = 0.28$] and the MED PD (severe) group [$F(1,12) = 0.5$], were well matched with their respective control groups in terms of age. Similarly, the three patient groups did not differ significantly from the control groups in terms of estimated verbal IQ ([$F(1,12) = 0.08$, $F(1,12) = 1.19$, $F(1,12) = 0.63$], respectively). It was not possible to match the groups with respect to gender. However, separate analyses of combined control scores and combined PD group scores confirmed that there were no significant effects of gender within the data.

Procedure

Spatial working memory task. This test has been described in detail elsewhere [25, 29–31]. Subjects were required to 'search through' a number of boxes presented on the screen by touching each one with the result that it 'opened up', revealing what was inside [Fig. 1 (i)]. The object of the task was to collect 'blue tokens' hidden inside the boxes and once found, to use them to fill an empty column at the side of the screen. At any one time, there would be a single token hidden inside one of the boxes and the subjects were required to search until they found it, at which point the next token would be hidden. The key instruction was that once a blue token had been found within a particular box, then that box would never be used again to hide a token. Consequently, two types of search error were possible. First, a subject may return to open a box in which a blue counter has already been found during the same trial (a 'between search' error). Second, a subject may return to a box already opened and shown to be empty earlier in the same search sequence (a

Table 1. Subject characteristics

	N	M/F	Age	Verbal IQ (NART)
NMED PD	7	5/2	53.9 (4.7)	112.7 (2.1)
Control	7	2/5	50.9 (6.7)	111.7 (2.7)
MED PD (mild)	7	6/1	59.4 (2.7)	106.4 (3.8)
Control	7	4/3	56.4 (4.9)	112.6 (4.2)
MED PD (severe)	7	5/2	63.9 (2.1)	106.4 (4.3)
Control	7	3/4	62.1 (1.3)	110.9 (3.5)

M/F = male/female (S.E.M in brackets).

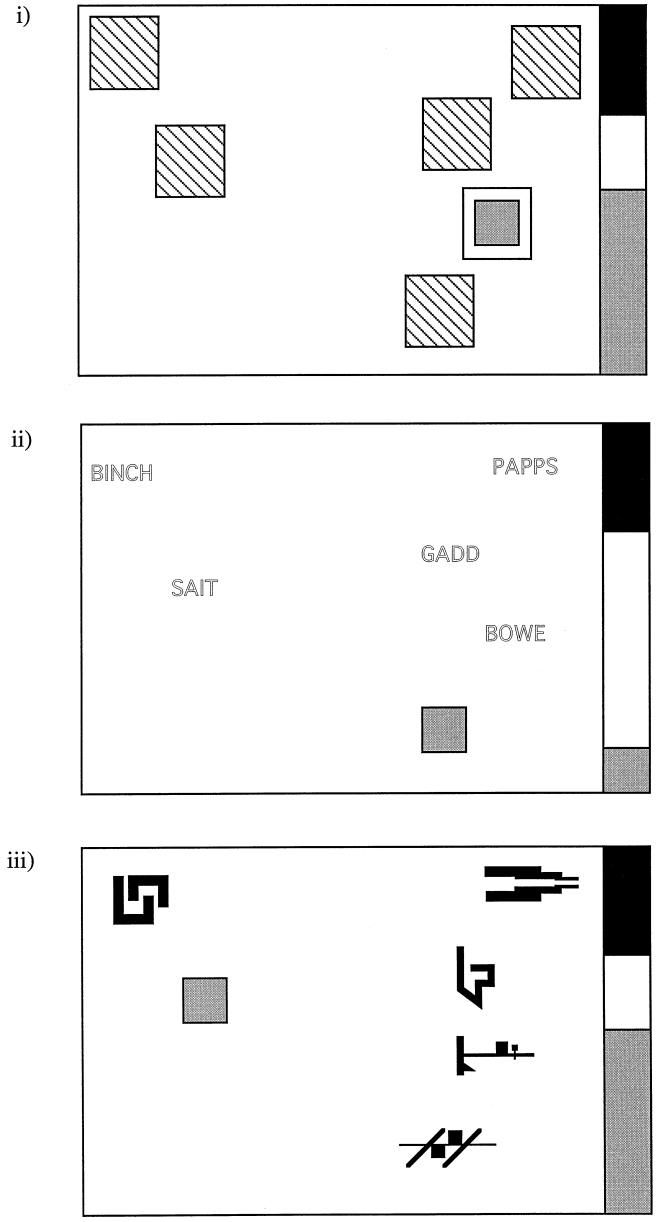


Fig. 1. (i) The spatial working memory task. (ii) The verbal working memory task. (iii) The visual working memory task. In each case, subjects are required to search through each stimulus to find square 'tokens' and then to collect them on the right side of the screen.

'within search' error). Subjects could search the boxes in any order, but for control purposes, the number of empty boxes visited (excluding errors), before a token was found was determined by the computer to be identical for each subject. After four practice trials with three boxes, there were four test trials with each of four, six and then eight boxes. The task was scored according to the number of 'between' and 'within' search errors at each level of difficulty.

The spatial working memory task requires, therefore, a self-ordered, well-organized search to maintain high levels of performance, which presumably depends, to some extent, upon spatial memory capacity. A purely 'mnemonic' deficit, involving reduced capacity, would be expected to affect performance preferentially at those levels of task difficulty where spatial capacity or 'span' were exceeded. However, previous studies have also shown that, in control subjects, performance on this task can be facilitated by the adoption of a repetitive searching strategy, beginning each search with a particular box and then returning to start each new sequence with that same box as soon as a token has been found [29]. Such strategies, when applied to self-ordered search tasks of this type, may serve to reduce the load on active working memory and would, presumably, 'enhance' performance at all levels of task difficulty. The deficit in patients with frontal lobe damage on this task has previously been shown to be related to an inefficient use of this particular searching strategy [29]. This contrasts markedly with the performance of patients with probable Alzheimer's disease who show no impairment in the use of the same strategy, while exhibiting profound deficits in spatial working memory performance at the most demanding levels of task difficulty [48, 49]. Thus, it is apparent that the contribution of both 'strategic' (or 'executive') and 'mnemonic' factors to efficient performance can be differentiated on this task.

In the present study, the extent to which a systematic searching pattern was used as a strategy for approaching the problem was estimated from the number of search sequences starting with the same box, within each of the more difficult six and eight box problems. The total of these scores provided a single measure of strategy for each subject, with a high score (many sequences beginning with a different box) representing low use of the strategy, and a low score (many sequences starting with the same box) representing more extensive usage. By focusing on the first response in a given search, this method provides only an estimate of the extent to which the entire search is systematically organized although, importantly, it avoids confounding the strategy score with search errors later in a particular search sequence. The repetitive ordering of choices, as assessed by this strategy measure is by far the most plausible approach to solving this spatial working memory task. Other possible strategies based, for example, on semantic encoding or verbal descriptions of the stimuli are clearly not appropriate, given the spatial nature of the task. Even if such strategies were adopted, one would expect them to manifest as repetitive serial ordering of choices which would, therefore, be detected by the strategy measure described above (for a fuller discussion of this issue, see [37]).

Verbal working memory task. The test was formally similar to the spatial working memory task described above. The subject was required to 'search through' a number of monosyllabic surnames presented on the screen by touching each one to 'find' hidden tokens [Fig. 1 (ii)]. Each name was trial unique and occurred with a similar frequency in the Greater London telephone directory. Names which were considered 'common' (e.g. 'Smith' or 'Jones'), or which were associated with a famous person were avoided, as were names with obvious semantic or visual properties (e.g. 'Green' or 'Long').

Again, the object of the task was to collect blue tokens hidden 'behind' the name and once found, to use them to fill an empty column at the side of the screen. The subjects were instructed that at any one time there would be a single token hidden behind one of the names. Their task was to search until they found it, at which point the next token would be hidden. Again, once a blue token had been found behind a particular name, then that name would never be used again to hide a token. Since every name was used once, on every trial the total number of blue tokens to be found corresponded to the number of names on the screen. In this sense, the task was very similar to the spatial working memory task in that subjects were required to conduct a systematic search through an array, avoiding items in which tokens had previously been found. However, the crucial difference between the two tasks was that in the verbal task, the items to be searched (i.e. the names) altered their spatial locations after each response. Within any given trial, the same fixed number of spatial locations were always used, although after each selection every name moved randomly to a new

location. This provision ensured that the test could not be solved using spatial cues.

A small pilot study of twenty-four control subjects, revealed that this test was considerably more difficult than the spatial working memory task. Therefore, after four practice trials with three names, there were four test trials with each of four and six names. No trials with eight names were included. The task was scored according to the number of 'between search' and 'within search' errors at each level of difficulty.

Since our previous investigation has shown that an efficient, repetitive spatial strategy may be developed to solve the spatial working memory test [29], analogous strategies were monitored in the verbal working memory test. Thus, during all four and six name problems, the extent to which subjects began each search with a particular name and then returned to start each new sequence with that same name, once a token had been found, was calculated. This estimate was rescaled in the range 1–27, with lower scores representing more extensive use of the strategy. The range of scores differed from that in the spatial working memory task since fewer searches are required to complete the four and six box problems than to complete the six and eight box problems. The best possible score of 1 was obtained when, within each problem, the same word stimulus was used to initiate each search sequence. Conversely, if every search within these problems started with a different stimulus, the maximum score of 27 was obtained. As in the spatial working memory task, the repetitive ordering of choices, as assessed by this strategy measure, is the most plausible approach to this non-spatial task. 'Verbal' strategies based, for example, on semantic encoding, are clearly ruled out by the stimulus material, whilst any tendency to code the stimuli according to the first letter was discouraged by including names beginning with the same first letter within each trial. Even if such strategies were adopted, one would expect them to manifest as repetitive serial ordering of choices which would be detected by the strategy measure used.

Visual working memory task. This task was very similar in design to the verbal working memory task described above, although instead of surnames, simple coloured shapes were used as the sample stimuli. Each shape was trial unique and could not easily be described verbally. Within each trial, all the shapes were the same colour, although with each new trial, a different colour was always used [Fig. 1 (iii)].

Again, subjects were required to collect 'blue tokens' hidden 'behind' the shapes and to avoid shapes behind which a blue token had previously been found. As in the verbal working memory task, the items to be searched (i.e. the shapes) altered their spatial locations after each selection. Again, this provision ensured that the test could not be solved using spatial cues. The number of incorrect shapes selected (excluding errors), before a token was found was determined by the computer.

As with the verbal memory task, a pilot study of 24 control subjects had shown this version of the working memory paradigm to be more difficult than the spatial condition and so task difficulty was varied only between 3 and 6 stimuli. Thus, after four practice trials with three shapes, there were four test trials with each of four and six shapes. As in the spatial and verbal analogues of this task, performance was assessed according to the number of 'between search' and 'within search' errors at each level of difficulty.

During all the four and six shape problems, the extent to which subjects began each search with a particular shape and then returned to start each new sequence with that same shape once a token had been found was calculated. This strategy is an exact visual analogue of the one previously shown to increase efficiency in the spatial working memory test [29]. The strategy estimate was rescaled in the range 1–27, with lower scores representing more extensive use of the strategy. The range of scores differed from that in the spatial working memory task since fewer searches are required to complete the four and six box problems than to complete the six and eight box problems. The best possible score of 1 was obtained when, within each problem, the same visual stimulus was used to initiate each search sequence. Conversely, if every search within these problems started with a different stimulus, the maximum score of 27 was obtained. As in the spatial working memory task, the repetitive ordering of choices, as assessed by this strategy measure, is the most plausible approach to this non-spatial task. 'Verbal' strategies were discouraged by adopting stimuli that were difficult to verbalize and even if such a strategy was adopted, one would expect it to manifest as a repetitive serial ordering of choices which would be detected by the strategy measure used.

In general, testing was conducted during two sessions separated by a period of several months. During the first session, all subjects received the spatial working memory test, together with other tests not related to this study. During the second session, subjects received the verbal and visual working memory tests, the order being fully randomized across subjects. In some cases, it was necessary to test a subject on all three tasks during a single session, in which case the order in which they were presented was again randomized.

Data analysis. Since the working memory tasks differed with respect to the number of difficulty levels included, the data were analysed *within* task. Thus, for each of the working memory tests, comparisons were drawn between each of the patient groups and their matched control group. The main variables were the total number of 'between search' errors and the total number of 'within search' errors (summed across the four trials within each level of difficulty) and the single measure of 'strategy' described above. Given the complexity of this design, the analysis of error scores required calculation of both main effects and interactions between the two critical variables, Group (NMED PD versus control, MED PD (mild) versus control and MED PD (severe) versus control) and Difficulty (4 boxes, 6 boxes and for spatial working memory only, 8 boxes). Standard tests of normality and homogeneity of variance across groups confirmed that the data were ideally suited for a parametric analysis. Therefore, for error scores, a two way analysis of variance procedure was employed to assess the relationship between Group and Difficulty. Where significant interactions between the Group and Difficulty factors were identified (usually indicating that a patient group were disproportionately affected by increasing task difficulty), simple main effects were calculated at each level of difficulty and are reported separately. Within each of the working memory tasks, the single 'strategy score' was analysed using one way analysis of variance.

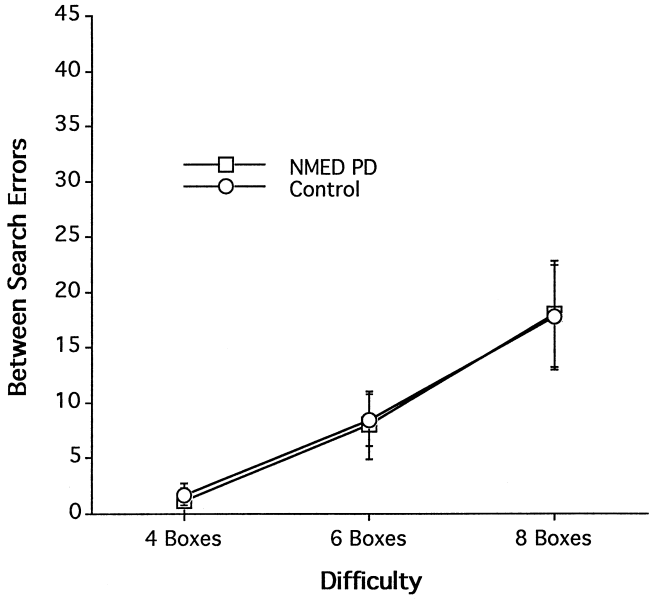
Results

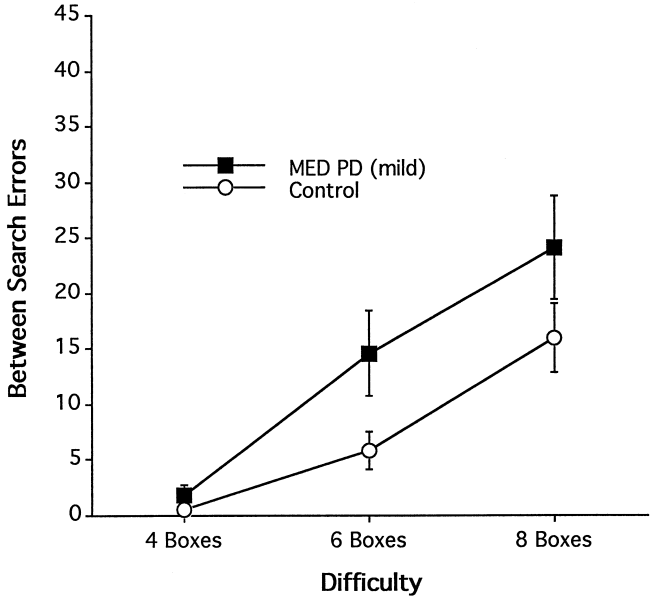
The main results from the three working memory tests are presented in Figs 2–4 and Table 2. Across all tasks there was a uniform effect of difficulty. Thus, as the number of boxes to be searched increased, the number of errors (both 'between' searches and 'within' searches) also increased.

Spatial working memory

The mean numbers of 'between search' errors made by the three patient groups and the three control groups at each level of difficulty are presented in Fig. 2.

Two-way analysis of variance confirmed that there was





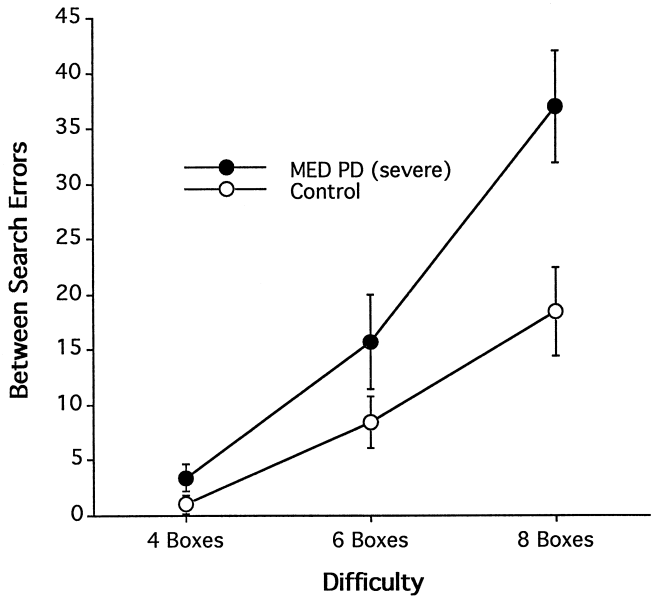
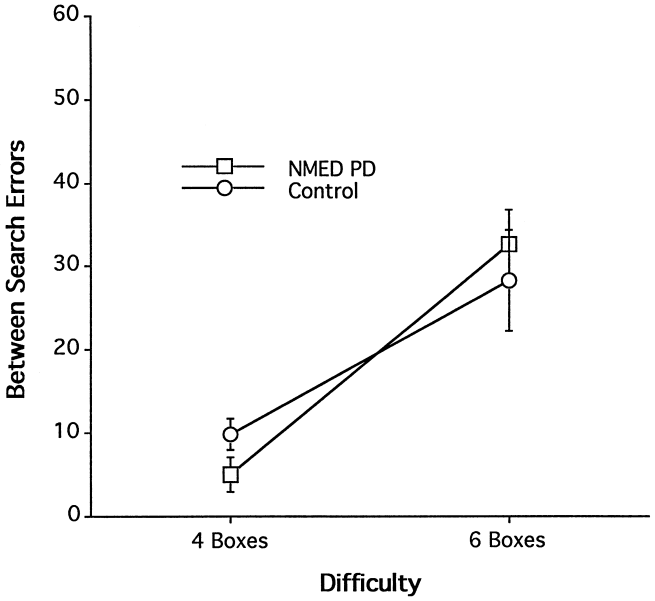
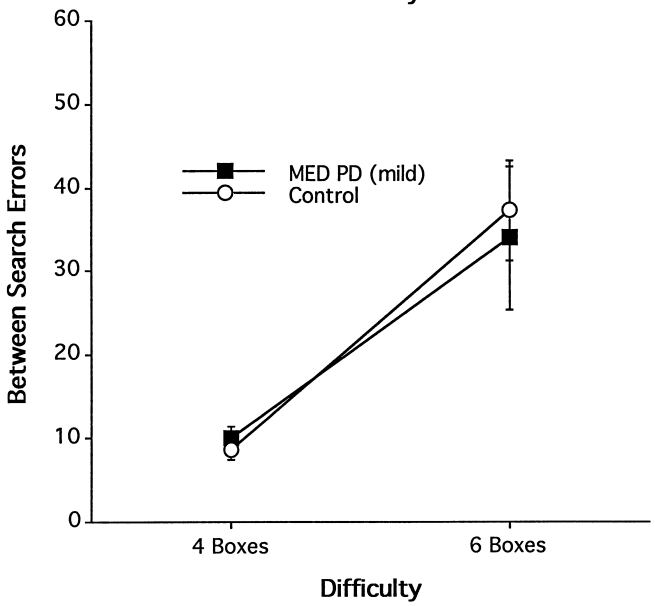


Fig. 2. Spatial working memory. The mean number of 'between search' errors at each level of difficulty in the three groups of patients with PD and their matched groups of control subjects.





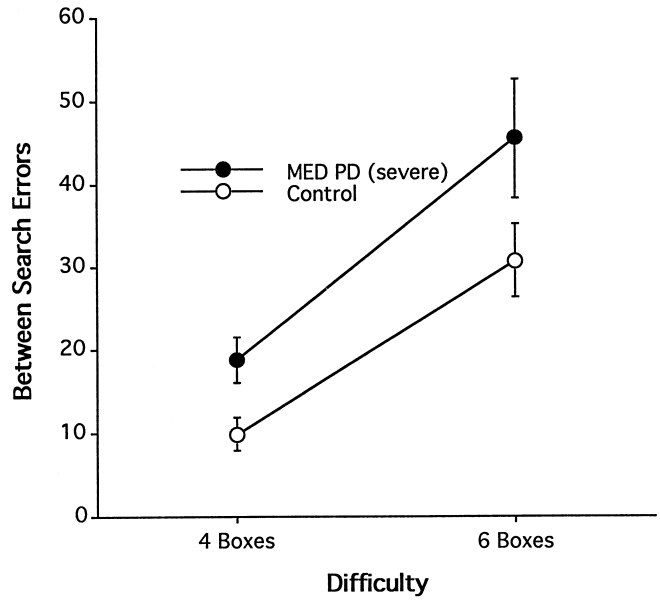


Fig. 3. Verbal working memory. The mean number of 'between search' errors at each level of difficulty in the three groups of patients with PD and their matched groups of control subjects.

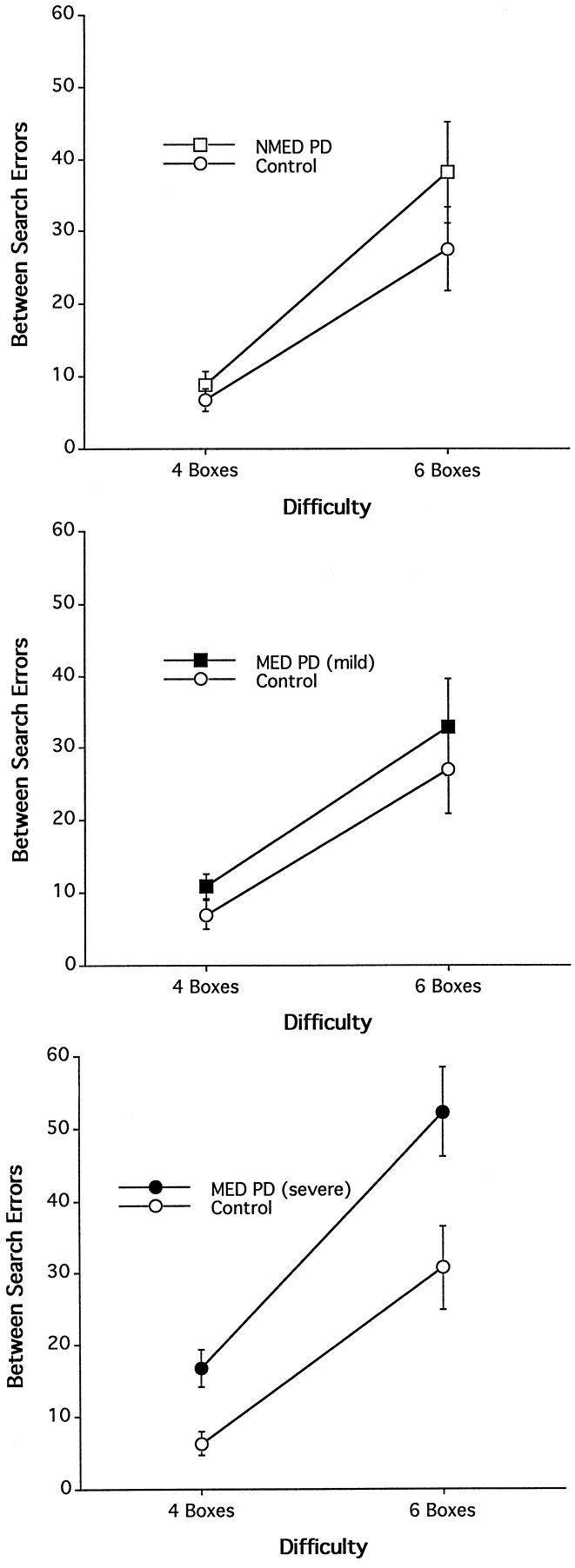


Fig. 4. Visual working memory. The mean number of 'between search' errors at each level of difficulty in the three groups of patients with PD and their matched groups of control subjects.

no significant difference between the NMED PD group and their group of matched controls in terms of the number of 'between search' errors [$F(1,12)=0.00$], and no significant interaction between the group and difficulty factors [$F(2,24)=0.02$]. As expected, there was a highly significant effect of task difficulty [$F(2,24)=25.5$, $P<0.0001$]. 'Within search' errors were analysed in a similar way (Table 2). No significant differences were observed between the NMED PD group and the controls in terms of this measure [$F(1,12)=3.07$], and there was a non-significant interaction between the group and difficulty factors [$F(2,24)=1.51$]. The effect of task difficulty did not reach significance [$F(2,24)=0.18$].

Unlike the NMED PD group, the MED PD (mild) patients made significantly more 'between search' errors than their control subjects [$F(1,12)=5.49$, $P<0.05$], although the interaction between the group and difficulty factors did not quite reach significance [$F(2,24)=2.58$, $P=0.097$]. There was a highly significant effect of task difficulty [$F(2, 24)=33.07$, $P<0.0001$]. No significant differences were observed between the MED PD (mild) group and the controls in terms of the number of 'within search' errors [$F(1,12)=0.27$], and there was a non-significant interaction between the group and difficulty factors [$F(2,24)=0.56$]. There was a significant effect of task difficulty [$F(2,24)=5.56$, $P=0.01$].

The MED PD (severe) patients were also impaired in terms of the number 'between search' errors in the spatial working memory task [$F(1,12)=6.58$, $P=0.025$], and there was a significant effect of task difficulty [$F(2,24)=48.99$, $P<0.001$]. In addition, the interaction between the group and difficulty factors was highly significant [$F(2, 24)=5.08$, $P=0.01$], and further analyses of simple main effects revealed that the MED PD (severe) group were only significantly impaired at the most difficult, eight-box level of task difficulty [$F(1,12)=25.5$, $P<0.001$]. No significant differences were observed between the MED PD (severe) group and their controls in terms of the number of 'within search' errors [$F(1,12)=0.25$], and the interaction between the group and difficulty factors did not approach significance [$F(2,24)=0.97$]. There was a significant effect of task difficulty [$F(2,24)=7.67$, $P<0.01$].

The estimate of strategy employed in this task was scored on a scale of 1–37 with lower scores representing more extensive use of the strategy (see [29]). The best possible score of 1 was obtained when, within each of the more difficult 6 and 8 box problems, the same box was used to initiate each search sequence. Conversely, if every search within each of these problems started with a different box, the maximum score of 37 was obtained. The mean spatial 'strategy scores' for each of the patient groups and the controls are presented in Table 2. Because of the small number of subjects in each group, the three PD groups were combined, as were the three control groups, for correlational analyses. In both the combined control group and in the combined PD group there was a significant and similar level of correlation between the

Table 2. Mean performance data for 'within search' errors and strategy scores

Within Search errors	4 Boxes	6 Boxes	8 Boxes	Strategy Score
Spatial Working Memory				
NMED PD	0.14(0.14)	1.14(0.70)	0.14(0.14)	31.57(2.40)
Control	3.00(2.24)	0.86(0.55)	2.43(0.65)	34.43(2.14)
MED PD (mild)	0.14(0.14)	2.43(1.38)	2.71(1.34)	34.86(1.35)
Control	0.14(0.14)	1.00(0.49)	2.71(0.97)	34.71(0.81)
MED PD (severe)	0.57(0.57)	0.57(0.30)	5.00(2.16)	34.86(1.47)
Control	0.57(0.57)	1.14(0.55)	3.00(0.87)	36.14(1.39)
Verbal Working Memory				
NMED PD	2.71(1.02)	14.00(4.11)		26.63(1.31)
Control	4.57(1.32)	16.43(6.14)		22.57(1.32)
MED PD (mild)	6.86(1.22)	19.43(6.21)		26.17(0.87)
Control	4.14(0.88)	22.86(5.78)		23.14(1.60)
MED PD (severe)	12.4(3.94)	23.29(7.36)		27.20(0.80)
Control	5.50(1.31)	18.00(5.26)		23.43(1.67)
Visual Working Memory				
NMED PD	4.29(1.39)	19.73(4.98)		20.43(2.61)
Control	3.71(1.19)	14.43(4.44)		24.14(1.06)
MED PD (mild)	6.00(1.60)	16.01(4.21)		23.83(0.95)
Control	3.57(1.67)	16.57(6.04)		22.71(1.04)
MED PD (severe)	5.14(1.14)	19.61(5.55)		26.00(0.77)
Control	3.43(1.39)	14.14(4.64)		23.43(1.29)

(S.E.M. in brackets.)

extent to which this strategy was adopted and the number of 'between search' errors on the more difficult six and eight box problems ($r=0.59$, $P<0.01$ and $r=0.74$, $P<0.001$, respectively). However, one-way analyses of variance confirmed that none of the three PD groups were significantly impaired on this measure relative to their matched controls (NMED PD [$F(1,12)=0.79$], MED PD (mild) [$F(1,12)=0.05$], MED PD (severe) [$F(1,12)=0.52$]).

Verbal working memory

The mean numbers of 'between search' errors made by the three patient groups and the control group at each level of difficulty are presented in Fig. 3.

Two-way analysis of variance confirmed that there was no significant difference between the NMED PD group and their group of matched controls in terms of the number of 'between search' errors [$F(1,12)=0.00$], and no significant interaction between the group and difficulty factors [$F(1,12)=1.44$]. As expected, there was a highly significant effect of task difficulty [$F(1,12)=35.61$, $P<0.0001$]. 'Within search' errors were analysed in a similar way (Table 2). No significant differences were observed between the NMED PD group and the controls in terms of this measure [$F(1,12)=0.32$], and there was a non-significant interaction between the group and difficulty factors [$F(1,12)=0.01$]. There was a significant effect of task difficulty [$F(1,12)=9.25$, $P=0.01$].

Like the NMED PD group, the MED PD (mild) patients were not significantly impaired on the verbal working memory task. Thus, this group made no more 'between search' errors than their control subjects [$F(1,12)=0.03$], and there was no significant interaction between the group and difficulty factors [$F(1,12)=0.21$]. There was a highly significant effect of task difficulty [$F(1,12)=27.59$, $P<0.0001$]. Similarly, no significant differences were observed between the MED PD (mild) group and the controls in terms of the number of 'within search' errors [$F(1,12)=0.01$], and the interaction between the group and difficulty factors was not significant [$F(1,12)=0.57$]. There was a significant effect of task difficulty [$F(1,12)=14.7$, $P=0.01$].

Unlike the other two patient groups, the MED PD (severe) patients were impaired in terms of the number of 'between search' errors in the verbal working memory task [$F(1,12)=5.92$, $P<0.05$], although there was no significant interaction between the group and difficulty factors [$F(1,12)=0.47$]. There was a significant effect of task difficulty [$F(1,12)=32.51$, $P<0.0001$]. No significant differences were observed between the MED PD (severe) group and their controls in terms of the number of 'within search' errors [$F(1,12)=1.34$], and the interaction between the group and difficulty factors did not approach significance [$F(1,12)=0.06$]. There was a significant effect of task difficulty [$F(1,12)=7.31$, $P<0.05$].

The mean verbal 'strategy scores' for each of the patient groups and the controls are presented in Table 2. In both the combined control group and in the combined PD group the correlation (Pearson's r) between the extent to which this strategy was adopted and the total number of 'between search' errors on the four and six box problems failed to reach significance ($r=0.21$ and $r=0.34$, respectively). One-way analyses of variance confirmed that none of the three PD groups were significantly

impaired on this measure relative to their matched controls (NMED PD [$F(1,12)=0.92$], MED PD (mild) [$F(1,12)=2.5$], MED PD (severe) [$F(1,12)=3.17$]).

Visual working memory

The mean numbers of 'between search' errors made by the three patient groups and the control group at each level of difficulty are presented in Fig. 4.

Two-way analysis of variance confirmed that there was no significant difference between the NMED PD group and their group of matched controls in terms of the number of 'between search' errors [$F(1,12)=1.44$], and no significant interaction between the group and difficulty factors [$F(1,12)=1.07$]. As expected, there was a highly significant effect of task difficulty [$F(1,12)=58.68$, $P<0.0001$]. Although the NMED PD group had a higher mean 'between search' error score than their controls at the 6 box level of task difficulty, this group difference failed to approach significance even when a supplementary comparison was performed between these patients and a larger group ($N=35$) of age and IQ matched controls [$F(1,40)=1.6$, $P>0.05$]. 'Within search' errors were analysed in a similar way (Table 2). No significant differences were observed between the NMED PD group and the controls in terms of this measure [$F(1,12)=0.56$], and there was a non-significant interaction between the group and difficulty factors [$F(1,12)=0.64$]. There was a significant effect of task difficulty [$F(1,12)=19.7$, $P=0.001$].

Like the NMED PD group, the MED PD (mild) patients were not significantly impaired on the visual working memory task. Thus, this group made no more 'between search' errors than their control subjects [$F(1,12)=1.21$], and there was no significant interaction between the group and difficulty factors [$F(1,12)=0.00$]. There was a highly significant effect of task difficulty [$F(1,12)=26.65$, $P<0.0001$]. Similarly, no significant differences were observed between the MED PD (mild) group and the controls in terms of the number of 'within search' errors [$F(1,12)=0.04$], and the interaction between the group and difficulty factors was not significant [$F(1,12)=0.22$]. There was a significant effect of task difficulty [$F(1,12)=12.84$, $P=0.01$].

Unlike the other two patient groups, the MED PD (severe) patients were impaired in terms of the number 'between search' errors in the visual working memory task [$F(1,12)=11.80$, $P<0.01$], although there was no significant interaction between the group and difficulty factors [$F(1,12)=1.68$]. There was a significant effect of task difficulty [$F(1,12)=48.66$, $P<0.0001$]. No significant differences were observed between the MED PD (severe) group and their controls in terms of the number of 'within search' errors [$F(1,12)=0.87$], and the interaction between the group and difficulty factors did not approach significance [$F(1,12)=0.26$]. There was a significant effect of task difficulty [$F(1,12)=12.13$, $P<0.05$].

The mean visual 'strategy scores' for each of the patient groups and the controls are presented in Table 2. In both the combined control group and in the combined PD group the correlation (Pearson's r) between the extent to which this strategy was adopted and the total number of 'between search' errors on the four and six box problems failed to reach significance ($r=0.23$ and $r=0.16$, respectively). One-way analyses of variance confirmed that none of the three PD groups were significantly impaired on this measure relative to their matched controls (NMED PD [$F(1,12)=1.74$], MED PD (mild) [$F(1,12)=0.61$], MED PD (severe) [$F(1,12)=2.36$]).

Discussion

The results of this study have considerable significance for the staging of cognitive decline in PD. The findings demonstrate that groups of patients at different stages of PD can be differentiated in terms of their performance on tests of spatial, verbal and visual working memory. Thus, non-medicated patients with mild clinical symptoms were unimpaired on all three tasks. In contrast, medicated patients with mild clinical symptoms were impaired on the test of spatial working memory, but not on the verbal or visual working memory tasks. Finally, medicated PD patients with severe clinical symptoms were impaired on all three tests of working memory.

The neural substrates responsible for deficits in these tests of spatial, visual and verbal working memory have recently been investigated in groups of neurosurgical patients with excisions of the frontal cortex or of the temporal lobe and the medial temporal lobe structures [29, 33, 37]. Although a simple mapping between a given memory tasks and a particular neural structure is unlikely to exist, the results suggest that performance on the test of spatial working memory may be affected by damage to either the frontal lobes or to the medial temporal lobe structures, whilst the test of visual working memory may be particularly sensitive to damage to the temporal lobe but not to the frontal lobe. Moreover, it appears likely that both 'executive' (or 'strategic') and mnemonic mechanisms may contribute differentially to performance on these tests of working memory and that these mechanisms may depend most heavily on the frontal cortex and medial temporal lobe structures, respectively.

The results of this study suggest that non-medicated patients in the earliest stages of PD are unimpaired on this type of working memory task, regardless of the type of stimuli used. In part, this result confirms our previous findings in an unrelated group of non-medicated patients with mild PD who were also unimpaired on the test of spatial working memory [30, 31]. The present study extends these previous findings, however, to demonstrate sparing of function on analogous tests of visual and verbal working memory. This sparing of working memory function contrasts markedly with the severe deficit observed on tests of sorting or attentional set-formation

and shifting in de novo patients with PD [9, 23, 30, 32]. Like the spatial working memory tests, these tasks are also known to depend on the integrity of the prefrontal cortex. Together, therefore, the results suggest a limited anatomical focus, within the prefrontal cortex, for the cognitive impairments occurring early in the course of PD. Thus, performance on one test sensitive to frontal-lobe damage is impaired (attentional set-shifting), whilst performance on another is not (spatial working memory). An alternative possibility, which has been addressed in a recent study, is that working memory may be affected in early PD but that the deficits remain undetected, if the tasks used to test these abilities are insufficiently challenging for these patients [34]. In that study, a novel spatial sequencing task was used to measure the capacity of active (spatial) working memory in patients with PD and in a group of neurosurgical patients with frontal lobe excisions. The results of that study demonstrate that, like other tests of frontal lobe function, spatial working memory may be vulnerable in non-medicated patients with mild PD if the task used exceeds the normal limit of working memory capacity in these patients. Whether this general pattern also applies to tests of non-spatial working memory remains to be seen.

Unlike the NMED PD group, the medicated patients with mild clinical symptoms were impaired on the test of spatial working memory, but not on the verbal or visual working memory tasks. This result cannot be explained by differences in task difficulty since examination of control performance (Figs 2–4), confirms that the spatial working memory task was, in fact, somewhat easier than either the verbal, or the visual, working memory conditions. The result is also unlikely to reflect a more fundamental perceptual deficit for spatial material among these medicated patients with mild PD because a larger study that involved most of the cases included here, has shown that these patients exhibit no deficits on a test of spatial span [30]. It seems likely, therefore, that the deficit observed in the MED PD (mild) group reflects a genuinely selective impairment in a test of spatial working memory, whilst performance on tests of verbal and visual working memory are unaffected. The same general pattern of findings has been found previously among neurosurgical patients with frontal lobe excisions [37] and, in this sense, these results are particularly relevant to two recent studies that have examined the relationship between 'frontal' and 'non-frontal' cognitive deficits in PD patients [30, 31]. In the former study, medicated and non-medicated patients at different stages of PD, were compared on three tests known to be sensitive to frontal-lobe damage, whilst in the latter study, their performance on these tasks was compared with that on tests of visuospatial memory and learning which are sensitive to temporal lobe, but not to frontal lobe, damage [33]. The results clearly demonstrate that 'frontal' tests are more sensitive to deficit in patients with mild PD than 'non-frontal' tests, although, importantly, both types of task may be sensitive to deficit in patients with more severe clinical symptoms. On one level, the results of the present study also suggest that in early PD, it is those tests that are most selectively sensitive to frontal lobe damage, in this case the spatial working memory task, that are most likely to be affected. However, close inspection of the pattern of deficits observed in the patients with frontal-lobe damage studied previously [29, 34] and in the MED PD (mild) group included in this study, suggests that important differences may exist between the two groups in terms of the precise cognitive mechanisms involved. For example, like frontal lobe patients, significant spatial working memory deficits were observed in the PD group in terms of the overall number of 'between search' errors, although unlike frontal lobe patients, no concomitant increase in the number of 'within search' errors was observed. In addition, the PD patients exhibited a normal searching pattern according to a measure of 'strategy' that is known to be sensitive to deficit in the patients with frontal lobe excisions. There are two possible explanations for this difference; First, the spatial working memory deficits observed in the MED PD (mild) group may, in fact, represent significant temporal-lobe, rather than frontal-lobe, involvement early in the course of the disease, since similar deficits in 'mnemonic', but not 'strategic' aspects of performance on this task were observed previously in patients with damage to the temporal lobe or to the medial temporal lobe structures [33, 37]. This seems unlikely, however, since medicated PD patients with mild clinical symptoms are not impaired on tests of pattern recognition memory, delayed matching to sample and paired associates learning, all of which are known to be particularly sensitive to temporal lobe damage [33]. In addition, unlike patients with neurosurgical removals from the temporal lobe region [33], the deficit observed in the MED PD (mild) group included in this study was not obviously dependent on task difficulty and consequently, is less likely to reflect disruption of purely mnemonic processes. An alternative explanation for the difference between patients with frontal-lobe damage and medicated patients with mild PD is that the beneficial effects of dopaminergic therapy effectively 'mask' some of the 'frontal' cognitive deficits in these patients. This possibility is strengthened by the results of three recent studies which have shown that, under certain conditions, L-Dopa can selectively improve performance on tests, or aspects of tests, that are specifically sensitive to frontal lobe dysfunction [22, 32, 34]. In the current study, therefore, some of the 'executive' or 'strategic' spatial working memory impairments in the MED PD (mild) group may be ameliorated by dopaminergic medication, rendering the group rather less similar to the patients with localized excisions of the frontal cortex.

The medicated PD patients with severe clinical symptoms were worse than either of the other PD groups on almost all aspects of task performance. Thus, significant increases in the number of 'between search' errors were observed in all three working memory tests, and in the spatial condition, this increase was particularly severe

at the most challenging levels of task difficulty. 'Within search' errors and strategy scores were unaffected throughout. Because of the controlled nature and design of these tests, the impairments observed cannot simply be explained in terms of the concurrent deterioration of motor function in these patients. The results do, in fact, concur fully with more extensive neuropsychological evaluations of these same patient groups which suggest that the pattern of cognitive impairment in PD emerges and subsequently progresses according to a defined sequence which evolves in parallel with the motor deficits that characterize the disorder [30, 31]. This apparent 'progression' on tests which are known to emphasize different aspects of working memory function and appear to depend critically on different cortical regions could simply reflect intellectual deterioration akin to that observed in patients with dementia of the Alzheimer type. This seems unlikely, however, since the MED PD patients included in this study were clinically diagnosed as non-demented and were screened for dementia using both the Mini Mental State Examination [11] and the Kendrick Object Learning Test [20]. Furthermore, three PD groups similar to those included in this study, could not previously be distinguished in terms of their performance on a test of pattern recognition memory (see [31]). Significant deficits on this test have been observed in patients with both mild and moderate dementia of the Alzheimer type [46, 47].

It may also be argued that some of the cognitive deficits observed in this study, particularly in those patients with severe clinical symptoms can be attributed to various aspects of medication, as both L-Dopa [16] and scopolamine [10], have been shown to affect cognitive performance in PD patients. It is unlikely that dopaminergic medication disrupts performance on the spatial working memory task since a recent study has demonstrated that controlled withdrawal of L-Dopa significantly *improved* performance on an identical version of this task in patients with severe PD [22]. Anti-cholinergic medication is also unlikely to play a significant role in the pattern of cognitive deficits observed in this study since only 4 of the 14 medicated patients included were receiving such preparations. A supplementary examination of performance confirmed no obvious differences between these patients and the remainder of the medicated PD group.

The question therefore arises, as to whether a plausible neural account might be formulated for the progression of working memory deficits in PD. Non-dopaminergic forms of pathology in PD, including noradrenergic, serotonergic and cholinergic: deafferentation of the cortex [2], may play a significant role in some of the cognitive deficits observed. Similarly, cortical Lewy bodies, which may occur even in the early stages of PD, may play a contributory role [6, 12]. However, recent anatomical and neuropathological evidence suggests that the sequence may be linked to what is known about the spatio-temporal progression of dopamine depletion within the striatum in relation to the terminal distribution of its cortical afferents. Of particular importance are several recent studies which have redefined the way in which the cerebral cortex innervates the striatum in primates. Previous findings had suggested a topographic mapping of the neocortical regions upon the striatum, such that frontal regions of neocortex projected to the most rostral areas, parietal regions to the intermediate sectors and the temporal lobes to the most caudal regions, including the tail of the caudate [19]. More contemporary studies, however, have shown the pattern to be more complicated, with a longitudinal medial–lateral organization superimposed upon the principle of topographic mapping by spatial proximity [54, 51, 50], such that the temporal lobe, for example, also projects strongly to the head of the caudate nucleus [50]. Nevertheless, these authors have emphasized that the inferotemporal cortex (area TE) in non-human primates mainly innervates the more posterior regions of the head of the caudate nucleus, whilst regions of the prefrontal cortex tend to innervate rostral portions of the head of the caudate [51]. Thus, it appears that there is still a degree of topographic representation of these regions of association cortex within the head of the caudate nucleus, which could potentially be relevant to explaining the progressive nature of working memory deficits in PD. This is highlighted by a detailed post-mortem neurochemical analysis which showed uneven patterns of striatal dopamine loss in patients dying with idiopathic PD [21]. The study confirms the well-known finding that the putamen appears to more severely depleted than the caudate nucleus, although in view of anatomical and electrophysiological evidence, the putamen is generally implicated in the motor deficits associated with PD. Dopamine levels in the caudate nucleus, which appears to be a more serious candidate for mediating the cognitive sequelae of PD, are also substantially depleted in PD, and importantly, this depletion is significantly greater in the most rostral extent of the head of this structure (to a maximum of about 90%), an area which is heavily connected with dorsolateral regions of the frontal lobe [56]. It seems likely, therefore, that these rostral regions of the caudate nucleus are subjected to greater disruption by the disease, and probably at an earlier stage of its progression. This may concur with the present finding that the visual working memory task, which is sensitive to temporal lobe, but not frontal lobe, damage is a relatively insensitive indicator of cognitive impairment in PD. It is important to point out that the neurodegenerative model described above may not only apply to the apparent increase in severity of impairments observed in patients with severe PD. For example, a similar model has recently been proposed to account for the general broadening of impairments *within* frontal lobe functions observed during the earliest stages of PD [38].

Acknowledgements—This research was supported by a Program Grant from the Wellcome Trust to Drs T. W. Robbins, B. J. Everitt, A. C. Roberts and B. J. Sahakian. We thank Prof. P.

Rabbitt for allowing us access to control subjects drawn from the North East Age Research panel at Newcastle University. During the preparation of this manuscript, Dr A. M. Owen was supported by the McDonnell–Pew Program in Cognitive Neuroscience at the Montreal Neurological Institute, Montreal, Canada and by the Pinsent Darwin Research Scholarship at the University of Cambridge, Cambridge, U.K.

References

1. Aggleton, J. P., Hunt, P. R. and Rawlins, J. N. P. The effects of hippocampal lesions upon spatial and non-spatial tests of working memory. *Behavioural Brain Research* **19,** 133–146, 1986.
2. Agid, Y., Ruberg, M., Dubois, B. and Pillon, B. Anatomoclinical and biochemical concepts of subcortical dementia. In *Cognitive Neurochemistry*, S. M. Stahl, S. D. Iversen and E. C. Goodman (Editors), pp. 248–271. Oxford University Press, Oxford, 1987.
3. Baddeley, A. D. Working memory. *Science* **255,** 556–559, 1992.
4. Bowen, F. P., Kamienny, M. A., Bums, M. M. and Yahr, M. D. Parkinsonism: Effects of Levodopa treatment on concept formation. *Neurology* **25,** 701–704, 1975.
5. Bradley, V. A., Welch, J. L. and Dick, D. J. Visuospatial working memory in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry* **52,** 1228–1235, 1989.
6. Byrne, E. J., Lennox, G., Lowe, J. and Godwin-Austin, R. B. Diffuse Lewy body disease: Clinical features in 15 cases. *Journal of Neurology, Neurosurgery and Psychiatry* **52,** 709717, 1989.
7. Cooper, J. A., Sagar, H., Jordan, N., Harvey, N. S. and Sullivan, E. V. Cognitive impairment in early, untreated Parkinson's disease and its relationship to motor disability. *Brain* **114,** 2095–2122, 1991.
8. Cooper, J. A., Sagar, H., Doherty, S. M., Jordan, N., Tidswell, P. T. and Sullivan, E. V. Different effects of dopaminergic and anticholinergic therapies on cognitive and motor function in Parkinson's disease: A follow-up study of untreated patients. *Brain* **115,** 1701–1725, 1992.
9. Downes, J. J., Roberts, A. C., Sahakian, B. J., Evenden, J. L., Morris, R. G. and Robbins, T. W. Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease: evidence for a specific attentional dysfunction. *Neuropsychologia* **27,** 1329–1343, 1989.
10. Dubois, B., Danze, F., Pillon, B., Cusimano, G., Lhermitte, F. and Agid, Y. Cholinergic-dependent cognitive deficits in Parkinson's disease. *Annals of Neurology* **22,** 26–30, 1987.
11. Folstein, M. F., Folstein, S. E. and McHugh, P. R. 'Mini-Mental State': A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* **12,** 189–198, 1975.
12. Gibb, W. R. G., Luthert, P. J., Janota, I. and Lantos, P. L. Cortical Lewy body dementia: clinical features and classification. *Journal of Neurology, Neurosurgery and Psychiatry* **52,** 185–192, 1989.
13. Goldman-Rakic, P. S. Circuitry of primate prefrontal cortex and the regulation of behavior by representational memory. In *Handbook of Physiology, Sec* 1, *The Nervous System*, F. Plum and V. Mountcastle (Editors). Vol. 5, pp. 373–417, 1987.
14. Goldman-Rakic, P. S. Cellular and circuit basis of working memory in prefrontal cortex of nonhuman primates. In *Progress in Brain Research*, Vol. 85, H. B. M. Uylings, C. G. Van Eden, J. P. C. De Bruin, M. A. Corner and M. G. P. Feenstra (Editors), pp. 325–336. Elsevier Science Publishers B.V. (Biomedical Division), 1990.
15. Goldman-Rakic, P. S., Selemon, L. D. and Schwartz, M. L. Dual pathways connecting the dorsolateral prefrontal cortex with the hippocampal formation and parahippocampal cortex in the rhesus monkey. *Neuroscience* **12,** 719–743, 1984.
16. Gotham, A. M., Brown, R. G. and Marsden, C. D. 'Frontal' cognitive functions in patients with Parkinson's disease 'on' and 'off' levodopa. *Brain* **111,** 299–321, 1988.
17. Hoehn, M. M. and Yahr, M. D. Parkinsonism: onset, progression and mortality. *Neurology* **17,** 427–442, 1967.
18. Jonides, J., Smith, E. E., Koeppe, R. A., Awh, E., Minoshima, S. and Mintun, M. A. Spatial working memory in humans as revealed by PET. *Nature* **363,** 623–625, 1993.
19. Kemp, J. M. and Powell, T. P. S. The cortico-striate projection in the monkey. *Brain* **93,** 525–546, 1970.
20. Kendrick, D. C. *Kendrick Cognitive Tests for the Elderly*. NFER-NELSON Publishing Company Ltd, Windsor, Berks, 1985.
21. Kish, S. J., Shannak, K. and Hornykiewicz, O. Uneven patterns of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathophysiologic and clinical implications. *New England Journal of Medicine* **318,** 876–880, 1988.
22. Lange, K. W., Robbins, T. W., Marsden, C. D., James, M., Owen, A. M. and Paul, G. M. L-Dopa withdrawal in Parkinson's disease selectively impairs cognitive performance in tests sensitive to frontal lobe dysfunction. *Psychopharmacology* **107,** 394–404, 1992.
23. Lees, A. J. and Smith, E. Cognitive deficits in the early stages of Parkinson's disease. *Brain* **106,** 257–270, 1983.
24. McCarthy, G., Blamire, A. M., Puce, A., Nobre, A. C., Bloch, G., Hyder, F., Goldman-Rakic, P. and Shulman, R. G. Functional magnetic resonance imaging of human prefrontal cortex activation during a spatial working memory task. *Proceedings of the National Academy of Sciences, U.S.A.* **91,** 8690–8694, 1994.
25. Morris, R. G., Downes, J. J., Sahakian, B. J., Evenden, J. L., Heald, A. and Robbins, T. W. Planning and spatial working memory in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry* **51,** 757–766, 1988.
26. Nelson, H. E. *National Adult Reading Test* (*NART*) *Test Manual*. NFER-Nelson, Windsor, 1982.

27. Olton, D. S. and Papas, B. C. Spatial memory and hippocampal function. *Neuropsychologia* **17,** 669–682, 1979.
28. Olton, D. S., Walker, J. A. and Gage, F. H. Hippocampal connections and spatial discrimination. *Brain Research* **139,** 295–308, 1978.
29. Owen, A. M., Downes, J. D., Sahakian, B. J., Polkey, C. E. and Robbins, T. W. Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia* **28,** 1021–1034, 1990.
30. Owen, A. M., James, M., Leigh, P. N., Summers, B. A., Quinn, N. P., Marsden, C. D. and Robbins, T. W. Fronto-striatal cognitive deficits at different stages of Parkinson's disease. *Brain* **115,** 1727–1751, 1992.
31. Owen, A. M., Beksinska, M., James, M., Leigh, P. N., Summers, B. A., Marsden, C. D., Quinn, N. P., Sahakian, B. J. and Robbins, T. W. Visuo-spatial memory deficits at different stages of Parkinson's disease. *Neuropsychologia* **31,** 627–644, 1993.
32. Owen, A. M., Roberts, A. C., Hodges, J. R., Summers, B. A., Polkey, C. E. and Robbins, T. W. Contrasting mechanisms of impaired attentional set-shifting in patients with frontal lobe damage or Parkinson's disease. *Brain* **116,** 1159–1179, 1993.
33. Owen, A. M., Sahakian, B. J., Semple, J., Polkey, C. E. and Robbins, T. W. Visuo-spatial short term recognition memory and learning after temporal lobe excisions, frontal lobe excisions or amygdalo-hippocampectomy in man. *Neuropsychologia* **33,** 1–24, 1995.
34. Owen, A. M., Sahakian, B. J., Hodges, J. R., Summers, B. A., Polkey, C. E. and Robbins, T. W. Dopamine-dependent fronto-striatal planning deficits in early Parkinson's disease. *Neuropsychology* **9,** 126–140, 1995.
35. Owen, A. M., Evans, A. C. and Petrides, M. Evidence for a two-stage model of spatial working memory processing within the lateral frontal cortex: A positron emission tomography study. *Cerebral Cortex* **6,** 31–38, 1996.
36. Owen, A. M., Doyon, K., Petrides, M. and Evans, A. C. Planning and spatial working memory examined with positron emission tomography (PET). *European Journal of Neuroscience* **8,** 353–364, 1996.
37. Owen, A. M., Morris, R. G., Sahakian, B. J., Polkey, C. E. and Robbins, T. W. Double dissociations of memory and executive functions in working memory tasks following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. *Brain*, **119,** 1597–1615, 1996.
38. Owen, A.M. and Robbins, T.W. Attention and working memory in movement disorders. In *The Neuropsychology of Movement Disorders*, M. Jahanshahi and R. Brown (Editors), 1997.
39. Petrides, M. Frontal lobes and working memory: evidence from investigations of the effects of cortical excisions in nonhuman primates. In *Handbook of Neuropsychology*, F. Boller and J. Grafman (Editors), Vol. 9, pp. 59–82. Elsevier, Amsterdam, 1994.
40. Petrides, M., Alivisatos, B., Evans, A. C. and Meyer, E. Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. *Proceedings of the National Academy of Sciences, U.S.A.* **90,** 873–877, 1993.
41. Petrides, M., Alivisatos, B., Evans, A. C. and Meyer, E. Functional activation of the human frontal cortex during the performance of verbal working memory tasks. *Proceedings of the National Academy of Sciences, U.S.A.* **90,** 878–882, 1993.
42. Petrides, M. and Milner, B. Deficits on subject-ordered tasks after frontal- and temporal-lobe lesions in man. *Neuropsychologia* **20,** 249–262, 1982.
43. Postle, B. R., Corkin, S. and Growdon, J. H. Dissociation between two kinds of visual working memory in Parkinson's disease. *Society For Neuroscience Abstracts* **409.10,** 1002, 1993.
44. Rawlins, J. N. P. and Olton, D. S. The septo-hippocampal system and cognitive mapping. *Behavioural Brain Research* **5,** 331–358, 1982.
45. Rawlins, J. N. P. and Tsaltas, E. The hippocampus, time and working memory. *Behavioural Brain Research* **10,** 233–262, 1983.
46. Sahakian, B. J., Downes, J. J., Eagger, S., Evenden, J. L., Levy, R., Philpot, M. P., Roberts, A. C. and Robbins, T. W. Sparing of attentional relative to mnemonic function in a subgroup of patients with dementia of the Alzheimer type. *Neuropsychologia* **28,** 1197–1213, 1990.
47. Sahgal, A., Sahakian, B. J., Robbins, T. W., Wray, C. J., Lloyd, S., Cook, J. H., McKeith, I. G., Disley, J. C. A., Eagger, S., Boddington, S. and Edwardson, J. A. Detection of visual memory and learning deficits in Alzheimer's disease using the Cambridge Neuropsychological Test Automated Battery. *Dementia* **2,** 150–158, 1991.
48. Sahgal, A., Lloyd, S., Wray, C. J., Galloway, P. H., Robbins, T. W., Sahakian, B. J., McKeith, I. G., Cook, J. H., Disley, J. C. A. and Edwardson, J. A. Does visuospatial memory in Alzheimer's disease depend on severity of the disorder? *International Journal of Geriatric Psychiatry* **7,** 427–436, 1992.
49. Sahgal, A., McKeith, I. G., Galloway, P. H., Tasker, N. and Steckler, T. Do differences in visuospatial ability between senile dementias of the Alzheimer's and Lewy body types reflect differences solely in mnemonic function? *Journal of Clinical and Experimental Neuropsychology* **17,** 35–43, 1995.
50. Saint-Cyr, J. A., Ungerleider, L. G. and Desimone, R. Organization of visual cortical inputs to the striatum and subsequent outputs to pallido-nigral complex in the monkey. *Journal of Comparative Neurology* **298,** 129–156, 1990.
51. Selemon, L. D. and Goldman Rakic, P. S. Longitudinal topography and interdigitation of corticostriatal projections in the rhesus monkey. *Journal of Neuroscience* **5,** 776–794, 1985.
52. Singh, J., Gabrieli, J. D. E. and Goetz, C. G. Impaired working memory in unmedicated Parkinson's disease. *Society For Neuroscience Abstracts*, **17,** 1991.
53. Sziklas, V. and Petrides, M. Memory impairments following lesions to the mammary region of the rat. *European Journal of Neuroscience* **5,** 525–540, 1993.
54. Van Hoesen, G. W., Yeterian, E. H. and Lavizzo-

Mourey, R. Widespread corticostriate projections from temporal cortex of the rhesus monkey. *Journal of Comparative Neurology* **199,** 205–219, 1981.
55. Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M. and Leirer, V. O. Development and evaluation of a geriatric depression screening scale. *Journal of Psychiatric Research* **17,** 37–49, 1982.
56. Yeterian, E. H. and Pandya, D. N. Prefrontostriatal connections in relation to cortical architectonic organisation in rhesus monkeys. *The Journal of Comparative Neurology* **312,** 43–67, 1991.