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VISUOSPATIAL MEMORY DEFICITS AT DIFFERENT STAGES OF PARKINSON'S DISEASE

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Abstract—Groups of patients with idiopathic Parkinson's disease (PD), either medicated or unmedicated, were compared with matched groups of normal controls on a computerised battery of tests designed to investigate spatial working memory, visuospatial recognition memory and learning. The medicated PD patients were subdivided into those with mild and severe clinical disability on the basis of Hoehn and Yahr ratings, thus making three groups of PD patients in all. In a test of spatial recognition memory, a significant impairment was only evident in those PD patients who were medicated and had severe clinical symptoms (Hoehn and Yahr stage III–IV). In contrast, none of the three patient groups were impaired in a complementary test of visual pattern recognition memory.

Whilst all three patient groups performed well in a test of simultaneous visual matching to sample, medicated patients (MED PD) with severe clinical symptoms were significantly impaired when a short (0–12 sec) delay was introduced. In a test of paired associates learning requiring both visual pattern and visuospatial memory, deficits in learning and memory were only evident in the severely impaired MED PD group. In contrast, in a test of spatial working memory known to be sensitive to frontal lobe damage, significant impairments were found in both groups of medicated PD patients and particularly in those patients with more severe clinical symptoms. Taken together, the results suggest that there are multiple memory impairments in PD which may differentially depend on the clinical severity of the disease.

INTRODUCTION

PATIENTS with Parkinson's disease (PD) develop mild neuropsychological deficits across a range of cognitive functions [4, 28, 35, 44, 48, 49, 57–59, 62] (also see Review by BROWN and MARSDEN [7]). Some of these impairments closely resemble those commonly attributed to frontal lobe dysfunction [5, 8, 12, 28, 37, 57–59] although many of the deficits in memory and learning may be more consistent with temporal lobe dysfunction [19, 29, 32, 45–47, 62].

In a previous study, we compared two groups of patients with PD who were all either medicated with L-Dopa (MED PD) or unmedicated (NMED PD), to a group of patients with dementia of Alzheimer type (DAT) on several computerised tests of visuospatial memory and learning [50]. Recognition memory was assessed using complementary tests of visual pattern recognition and visuospatial recognition. Like patients with DAT, the MED PD group were significantly impaired on both tasks, although no impairments were evident

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in the NMED PD group. A simultaneous and delayed matching to sample procedure was also used to assess visual pattern recognition over an ascending series of delays (0–16 sec). Both groups of PD patients were impaired in the simultaneous condition of this matching to sample procedure although only the more severely affected MED PD group were impaired across the delay conditions. In the final test, which required both visual pattern and visuospatial memory, the subject was asked to remember and learn the locations of up to eight different visual patterns. Deficits in learning *and* memory were evident in both the medicated and the non-medicated groups of patients with PD.

Whilst deficits in visual memory and learning have been consistently reported in PD [19, 29, 32, 45–47] these results are by no means unequivocal. Several recent studies have reported normal visual recognition memory performance in PD patients medicated with L-Dopa and/or anti-cholinergics [15] and in unmedicated patients with PD [28]. Much of this disagreement may arise through the progressive nature of PD and the possibility that cognitive defects and specifically, deficits in visuospatial memory, are both qualitatively and quantitatively different at various stages of the disease. In recent years, several studies have emphasised the need to take account of the severity of clinical symptoms when assessing cognitive impairments in PD (e.g. Ref. [57]). Similarly, MORTIMER *et al.* [32] found a relationship between the degree of bradykinesia and visuospatial deficit, whilst in a more recent study of PD patients medicated with L-Dopa, measures of rigidity were shown to correlate significantly with performance on a delayed word recall task [23]. In our previous study of visuospatial memory and learning in PD and DAT, described above [50], there was a significant correlation between the performance in the memory component of the paired associates, pattern learning task and indices of clinical disability. It should be emphasised however, that if such a relationship exists, it is not simply a direct one between impaired motor and cognitive function since many patients can fluctuate between extremes of motor disability whilst aspects of cognitive function remain unaffected [6]. Furthermore, several studies have found insignificant or weak associations between measures of cognitive and motor performance [10, 14, 15, 35, 50].

We have recently investigated the progressive nature of fronto-striatal cognitive deficits in medicated and non-medicated patients with PD [37] using a battery of tests known to be sensitive to localised excisions of the frontal lobes [36, 38]. In tests of attentional set-shifting, spatial working memory and planning, patients medicated with L-Dopa and with both mild and severe clinical symptoms were significantly impaired, although in all three tests, the deficits observed were worse in the subgroup of patients with more severe clinical symptoms. In addition, an impairment in a related test of spatial short-term memory was only evident in the more severely affected group. Non-medicated patients with milder clinical symptoms were only impaired in the test of visual discrimination learning [37].

In the present study, the progression of visuospatial memory deficits in PD was further investigated using a number of computerised tests, similar to those used by SAHAKIAN *et al.* [50]. A much larger group of forty-two patients with idiopathic PD was included, divided into those who were non-medicated with mild–moderate clinical symptoms, those that were medicated with mild or moderate clinical symptoms and those who were medicated with more severe clinical symptoms. Although the tests of visual pattern and spatial recognition memory were identical to those used by SAHAKIAN *et al.* [50], certain modifications were made, particularly to the test of simultaneous and delayed matching to sample, to improve the sensitivity of the test and to discourage the use of mnemonic strategies (see methods section). In addition, these three groups of patients were compared on a test of spatial

working memory previously shown to be sensitive to both mild and severe L-Dopa medicated PD [37] and to localised neurosurgical excisions of the frontal lobes [36]. This task is similar in design to one developed by PETRIDES and MILNER [43] although in the present study, subjects were not required to remember objects by their specific feature, only by their particular locations.

It is important to note that medication may play a key role in the cognitive performance of patients with PD. For example, several studies have reported improved cognitive function in tests of frontal lobe function when L-Dopa is administered [5, 27] although in others, the reverse pattern has been found [20]. However, a recent study has demonstrated that controlled withdrawal of L-Dopa had no effect on identical versions of the tests of pattern and spatial recognition memory, simultaneous and delayed matching to sample and visuospatial paired associates learning included in the current study [27]. The possible role of medication in cognition can also be assessed by studying patients who are "early-in-the-course" of PD and are yet to receive any medication. Using this approach, several studies have now reported specific cognitive deficits in groups of non-medicated patients [12, 28, 37, 57].

In the present study, both medicated and non-medicated PD patients with mild and severe clinical symptoms were included such that the likely contribution of *both* medication and disease severity could be assessed.

METHOD

Subjects

The 42 PD patients included in this study were all outpatients at the Maudsley Hospital and the National Hospital for Neurology and Neurosurgery, London. In all cases, idiopathic Parkinson's disease was diagnosed by a consultant neurologist who also assessed the severity of clinical symptoms according to the HOEHN and YAHR rating scale [22]. In cases where patients were experiencing response fluctuations the Hoehn and Yahr rating referred to the "on" rather than the "off" condition. On the basis of this assessment, and depending on whether anti-Parkinsonian medication had already been received, each patient was assigned to one of three groups.

Eighteen patients were "early in the course" of the disease (mean = 1.38 years) and had not received any medication (NMED PD). In this group, clinical symptoms were rated either as Hoehn and Yahr stage I (nine patients), stage II (seven patients) or stage III (two patients).

The remaining 24 patients were all receiving L-Dopa preparations either alone or in combination with anticholinergic medication. Eleven of these individuals had mild/moderate physical symptoms [MED PD (mild)] and were rated as either Hoehn and Yahr stage I (two patients) or stage II (nine patients). In addition to their dopaminergic treatment, three of these patients were receiving anticholinergic medication (orphenadrine or benzhexol) at the time of testing.

The remaining 13 patients [MED PD (severe)] had more severe physical symptoms and were rated as stage III (seven patients) or stage IV (six patients). Two of these patients were receiving anticholinergic (orphenadrine or benzhexol) as well as dopaminergic medication at the time of testing.

Exclusion criteria for the two groups of medicated PD patients included clinical dementia and all patients were above the cut-off score for dementia on both the Mini Mental State Examination (MMSE) [16] and the Kendrick Object Learning Test (KOLT) [25]. To assess the incidence of affective disturbance in these patients, the Geriatric Depression Scale (GDS) [63] was also administered. This is a self-administered, 30-item questionnaire designed specifically for elderly subjects. It is particularly suited for the assessment of depression in PD patients since it contains relatively few somatic items which may relate directly to the patients' physical disability. In the present study, data from the GDS were analysed twice, including and excluding somatic items. Since no qualitative difference was found between the two analyses only the results from the initial, fully inclusive analysis are presented. The non-medicated patients were not given the MMSE, the KOLT or the GDS although none of these patients were regarded as demented or depressed by their consultant neurologist.

Three groups of healthy control subjects were chosen to match the groups of PD patients as closely as possible with respect to age and pre-morbid verbal IQ as assessed using the National Adult Reading Tests (NART) [33]. These subjects were drawn from a large pool of control volunteers at the North East Age Research panel in Newcastle upon Tyne.

Table 1 shows a summary of characteristics for the three patient groups and their controls. One-way analysis of

variance confirmed that the NMED PD group, the MED PD (mild) group and the MED PD (severe) group were all well matched with their respective control groups in terms of age [$F(1, 34) = 1.19$, $F(1, 20) = 0.35$, $F(1, 24) = 0.64$, respectively) and NART IQ estimate [$F(1, 34) = 2.53$, $F(1, 20) = 1.36$, $F(1, 24) = 0.36$, respectively). Since all 42 chosen control subjects had not performed the test of spatial working memory, three similar (but not identical) groups of controls (total $N = 42$) were chosen to match the three patient group for this test. Again, one way analysis of variance confirmed that the NMED PD group, the MED PD (mild) group and the MED PD (severe) group were all well matched with these control groups in terms of age [$F(1, 18) = 0.29$, $F(1, 20) = 0.09$, $F(1, 24) = 0.89$, respectively) and NART IQ estimate [$F(1, 18) = 1.2$, $F(1, 20) = 2.65$, $F(1. 24) = 1.04$, respectively).

The two medicated groups did not differ significantly in terms of their Mini Mental State Examination scores [$F(1, 22) = 0.31$). There was, however, a significant difference between these two groups in their scores on both the Kendrick Object Learning Test [$F(1, 20) = 5.06$, $P < 0.05$] and the GDS [$F(1, 20) = 7.28$, $P < 0.025$] and this will be discussed in detail later.

Materials and procedure

The main testing procedures were taken from the Cambridge Neuropsychological Test Automated Battery (CANTAB), a series of computerised paradigms run on an IBM PS/2 Model 30 286 personal computer with a high resolution Taxan 770+ colour monitor fitted with a Mellordata touch sensitive screen. Subjects were seated at a comfortable height approximately 0.5 m from the monitor. It was explained that they would have to respond to stimuli by touching the screen. They were introduced to the apparatus by way of a "motor screening task" in which they were asked to respond to a series of flashing crosses on the screen by placing the index finger of their preferred hand on the centre point of each cross. Once each cross had been accurately touched the next cross appeared after a brief delay. Following a short demonstration by the experimenter, in which three consecutive crosses were touched, subjects were presented with a series of 10 crosses to touch at 6-sec intervals. After satisfactorily completing the introductory motor screening task, subjects were given the following tests in the order described below.

Pattern recognition [*Fig.* 1(*i*)]. This test was presented in two phases. Initially, subjects were shown a series of 12 coloured patterns (set 1) appearing one at a time inside a white box located in the centre of the screen (presentation phase). Each of these "target" patterns was presented for 3 sec, the screen was then cleared and the next pattern appeared. In the second (recognition) phase, 12 pairs of coloured patterns appeared on the screen (one pair at a time) and the subject was required to respond to each pair by touching the pattern they had already seen during the presentation phase. Each of the target patterns were presented in reverse order and paired with distractor patterns that differed in form but not in colour from the targets. Each response was accompanied by an auditory tone and visual feedback was automatically provided by the computer in the form of green ticks and red crosses. This procedure was then repeated with 12 new patterns (set 2) and the subject's total score (maximum possible = 24) was expressed as a percentage correct.

Spatial recognition [*Fig.* 1(*ii*)]. This procedure was also presented in two phases. In the presentation phase, subjects were shown a series of five unfilled 1 in. white squares, appearing one at a time, at different locations on the screen. Each square was presented for 3 sec before the screen was cleared and the next square appeared. In the second (recognition) phase, two squares appeared simultaneously on the screen and the subject had to select which location had been used before in the presentation phase. The target squares were presented in reverse order and paired with distractor squares which appeared in novel locations which had never been used as target locations. Again, each response was accompanied by an auditory tone and visual feedback was provided in the form of green ticks and red crosses. This procedure was then repeated three more times using new target and distractor locations on each occasion. The subject's total score (maximum possible = 20) was expressed as a percentage correct.

Simultaneous and delayed matching to sample [*Fig.* 1(*iii*)]. At the beginning of each trial, a complex abstract (sample) pattern consisting of four quadrants, each differing in colour and form, appeared in the centre of the screen for a presentation period of 4.5 sec. Subjects were told to study the pattern, since they would later be required to identify it from among three "distractor" patterns. In the *simultaneous* condition, four choice patterns then appeared, located under the sample pattern. The subject was required to respond by touching the choice pattern that corresponded exactly (in both colour and form) to the sample pattern above. Only one of the choice patterns was identical to the sample. One of the other choice patterns was a novel distractor, differing in both colour and form from the sample. The remaining two choice patterns were "partial distractors" in that one had the colours of the sample but the form of the novel distractor whilst the other was the same shape as the sample but had the colours of the novel distractor. In addition, each of the four choice patterns had one (random) quadrant in common to discourage mnemonic strategies based on remembering the colour and shape of a single quadrant [see Fig. 1(iii)]. The subject's response was accompanied by an auditory tone and visual feedback was provided in the form of green ticks and red crosses. After an incorrect response, the subject had to continue to choose until the correct (target) stimulus had been touched.

The *delay* condition was identical to the *simultaneous* condition in every way except that after the initial 4.5-sec presentation period, the sample stimulus disappeared from the screen. There then followed a 0-, 4- or 12-second delay before the four choice stimuli appeared and the subject was required to make their selection. Following three practice trials (one of each simultaneous, 0 and 12 sec), there were a total of 10 test trials in each of the four simultaneous and delay conditions presented sequentially, and in a pseudo random order (total test trials = 40).

Table 1. Subject characteristics

Group	Stage	*N*	M/F	Age	NART	Disease duration (years)	Levodopa (mg)	MMSE	GDS	KOLT
Non-medicated PD	I III	18	11/7	61.39 (2.38)	109.2 (2.4)	1.75 (1.25)				
Controls		18	9/9	64.33 (1.26)	113.6 (1.3)					
Medicated PD (mild)	I–II	11	7/4	63.27 (3.01)	106.2 (3.2)	9.73 (1.20)	575 (248)	28.50 (0.67)	11.13 (1.22)	39.10 (2.2)
Controls		11	5/6	65.36 (1.83)	110.5 (1.8)					
Medicated PD (severe)	III–IV	13	8/5	66.54 (1.95)	109.8 (2.4)	10.6 (1.21)	779 (273)	28.55 (0.37)	14.36 (1.61)	33.17 (1.6)
Controls		13	7/6	67.15 (1.46)	111.5 (1.6)					

Standard errors are shown in brackets.

Each subject was scored according to the number of trials correct on the first choice in each of the simultaneous and delay conditions. Mean response latencies in each condition were also calculated, including only those trials in which the first choice was the correct one.

Paired associates learning [*Fig.* 1(*iv*)]. In this test, subjects were required to remember up to eight pattern-location associations. Initially, six white boxes were presented around the screen [see Fig. 1(iv)] and subjects were told that each of them would "open up" in turn, showing them what was inside. Their task was to look for coloured patterns in the boxes and to remember which pattern belonged in which box. Each of the boxes opened up (i.e. became "unfilled") for 3 sec and then closed again in a randomised sequence. In the first trial, only one of the boxes contained a coloured pattern. Immediately after the last box had opened, this pattern was presented in the centre of the screen and the subject was required to respond by touching the box in which it had appeared. Feedback was *not* provided after each response although if the choice was correct, the words "ALL CORRECT" appeared in the centre of the screen and the subject proceeded to the next trial. If the choice was incorrect, the boxes were successively reopened (*reminding* phase) for 2 sec each, and the subject was then given a second attempt to correctly locate the pattern. On each trial, the subject was allowed up to nine *reminding* phases, making 10 attempts in all, before the test was prematurely aborted. After the initial trial with one pattern, there was one more trial with a single pattern, then two trials with two patterns each, two trials with three patterns each and then one trial with six (one in every box) patterns to locate. Finally, two extra boxes were added to the array on the screen and the subject was required to correctly locate a total of eight patterns. The subject automatically moved from one trial to the next by correctly locating all of the patterns, either after the initial *presentation* phase or after one of the nine *reminding* phases.

Performance was assessed according to four main measures. (i) *Trials* represented the total number of presentations required (maximum score = 10 presentations per trial) to correctly locate all the patterns summed across each of the eight trials. Subjects were assigned the maximum score of 10 for trials not attempted due to failure at an earlier stage. (ii) *Errors* represented the total number of errors (incorrect placements) summed across the eight trials. Subjects not reaching a particular set, were assigned the worse score obtained by a subject actually attempting that set. (iii) The *memory* score was calculated according to the total number of patterns correctly located after the first presentation, summed across the eight trials (range = 0 to 26). (iv) *First correct* corresponded to the total number of trials that were completely correct after just one, initial presentation (range = 0 to 8).

Spatial working memory

This test has been described in detail elsewhere [36, 37] and only a brief description will be given here. Subjects were required to "search through" a number of boxes presented on the screen in order to collect "blue tokens" hidden inside. At any one time, there would be a single token hidden inside one of the boxes and subjects were 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. On each trial, every box was used once to hide a token such that the total number of blue tokens to be found corresponded to the number of boxes on the screen. Errors were scored according to the number of occasions on which a subject returned to open a box in which a blue counter had already been found. After four practice trials with three boxes, there were four test trials, with each of four, six and eight boxes making a total of 12 test trials in all.

The effect of task difficulty, and the relevance of repetitive searching strategies on this test have previously been investigated in both medicated and non-medicated patients with PD [37]. Therefore, in the present study, only the total number of errors summed across the 12 test trials will be presented.

Data analysis

The data were analysed using the Statistical Package For The Social Sciences (SPSS/PC) [34]. One- and two-way multivariate analysis of variance (MANOVA) were conducted, and where approprite Pearson product moment correlation coefficients were calculated.

Preliminary analyses confirmed that there were no significant differences between the three control groups in terms of age, NART IQ or any of the tests of spatial working memory, visuospatial memory and learning. For each test, the normal controls were therefore, collapsed into a single group of 42 subjects and an orthonormal contrast analysis was performed, comparing each of the MED PD (mild), MED PD (severe) and NMED PD groups with the single group of normal controls.

RESULTS

Pattern and spatial recognition

Mean values and corresponding standard errors for the pattern and spatial recognition tests are shown in Fig. 2. for the three PD groups and the combined ($N = 42$) group of controls. A one-way analysis of variance showed that the four groups did not differ

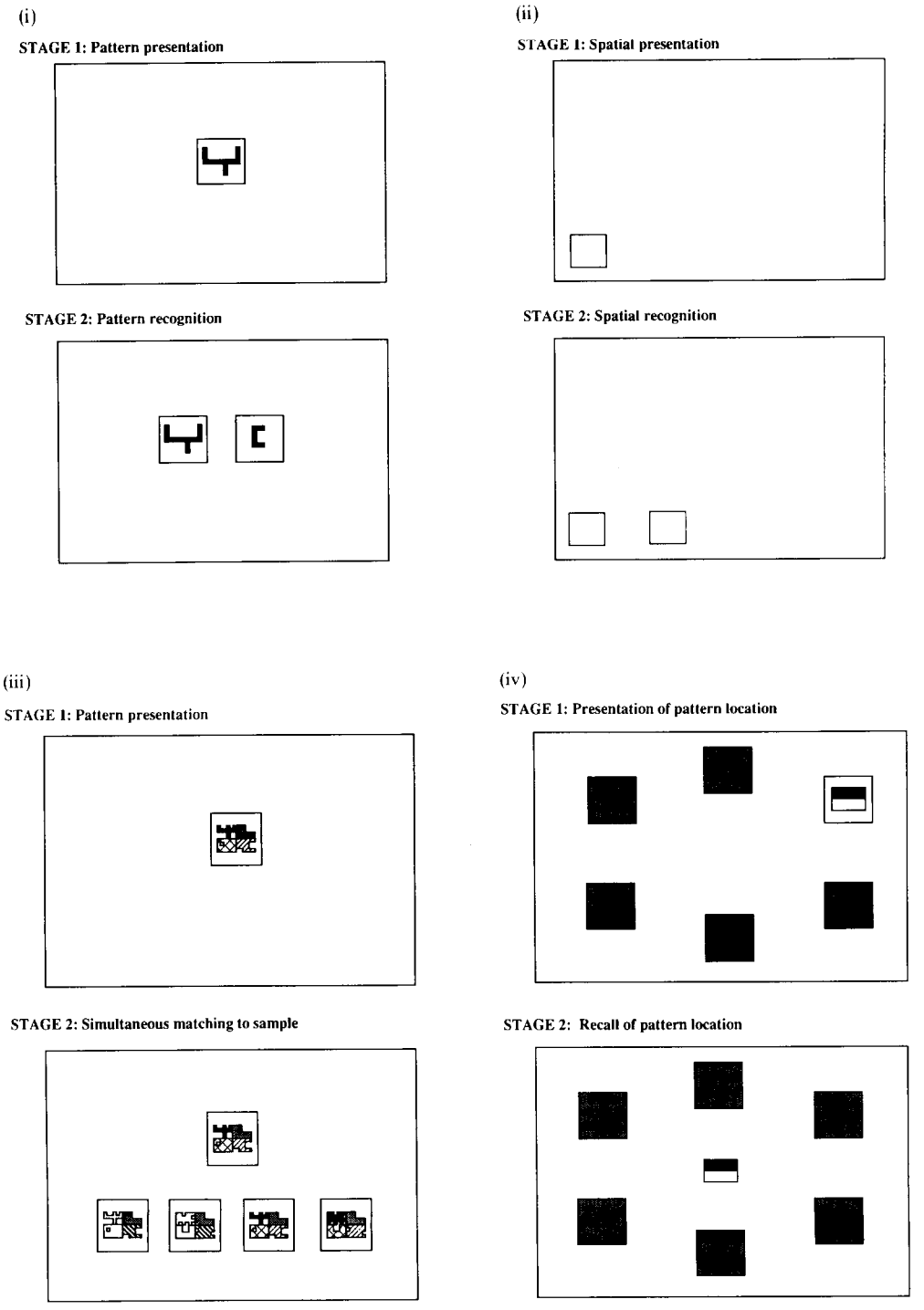

Fig. 1. (i) The pattern recognition memory test. (ii) The spatial recognition memory test. (iii) Simultaneous and delayed matching to sample. (iv) Paired associates learning.

significantly on the test of pattern recognition [$F(3, 62) = 0.465$]. In contrast, there was a significant difference between the groups in the test of spatial recognition [$F(3, 62) = 3.12$, $P < 0.05$] and a between group, orthonormal contrast analysis confirmed that only the MED PD (severe) group were significantly impaired on this measure compared to the combined control group [$t(62) = 2.96$, $P < 0.005$]. A similar deficit was not evident in either the NMED PD group or the MED PD (mild) group [$t(62) = 0.77$ and $t(62) = 1.27$, respectively].

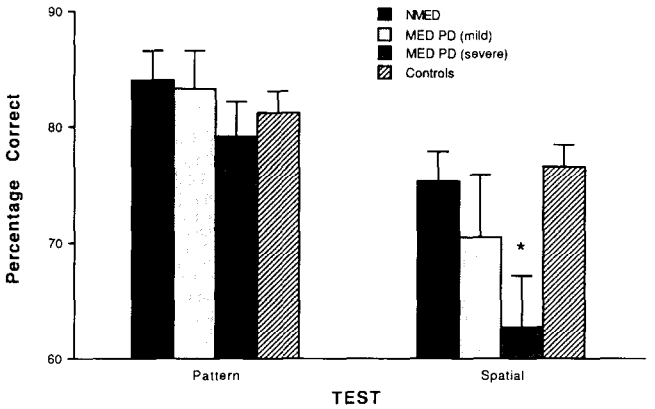

Fig. 2. The mean percentage correct scores for the pattern and spatial recognition memory test. Bars represent standard errors. *$P < 0.05$.

The mean percentage correct scores in the tests of pattern recognition and spatial recognition for the combined control group were 81.34 and 76.54%, respectively. A paired t-test confirmed that overall, the control group performed significantly better on the pattern recognition test than on the spatial recognition test [$t(41) = 2.77$, $P < 0.008$]. Similar results have been observed when a large group of normal control volunteers ($N = 265$) are compared on these two recognition memory tests [$t(264) = 7.89$, $P < 0.0001$, ROBBINS *et al.*, unpublished observations] suggesting that for control subjects, the test of spatial recognition is significantly more difficult than the test of pattern recognition. Therefore, the apparent difference in pattern and spatial recognition memory in the PD patients may simply be an artifact of task difficulty. However, further analysis shows this to be unlikely. Thus, mean percentage correct scores for set 1 and set 2 of the pattern recognition test for the combined control group were 88 and 79%, respectively. Further analyses confirmed that whilst pattern recognition, set 1 and spatial recognition differed significantly [$t(37) = 4.33$, $P < 0.001$], there was no difference between pattern recognition set 2 and spatial recognition score [$t(37) = 0.74$]. Therefore, in order to investigate the specificity of the spatial recognition memory deficit in the MED PD (severe) group further, a supplementary analysis was performed, assessing performance separately for pattern recognition sets 1 and 2. Compared to the combined group of normal controls, the MED PD (severe) group were unimpaired at pattern recognition set 1 [$t(53) = -0.63$] and set 2 [$t(53) = -1.18$]. This confirms that the observed difference in pattern recognition memory (unimpaired) and spatial recognition memory (impaired) in the group of medicated patients with severe clinical symptoms does not simply reflect the effects of task difficulty.

Simultaneous and delayed matching to sample

Data for this test were analysed separately for the simultaneous and delayed matching conditions. Since performance accuracy was expressed as a proportion correct score (maximum possible in each condition = 10), an arcsin transformation of the data was performed before one- and two-way analyses of variance were conducted. The (transformed) proportion correct scores for the three PD groups and the combined control group within each of the four conditions are presented in Fig. 3.

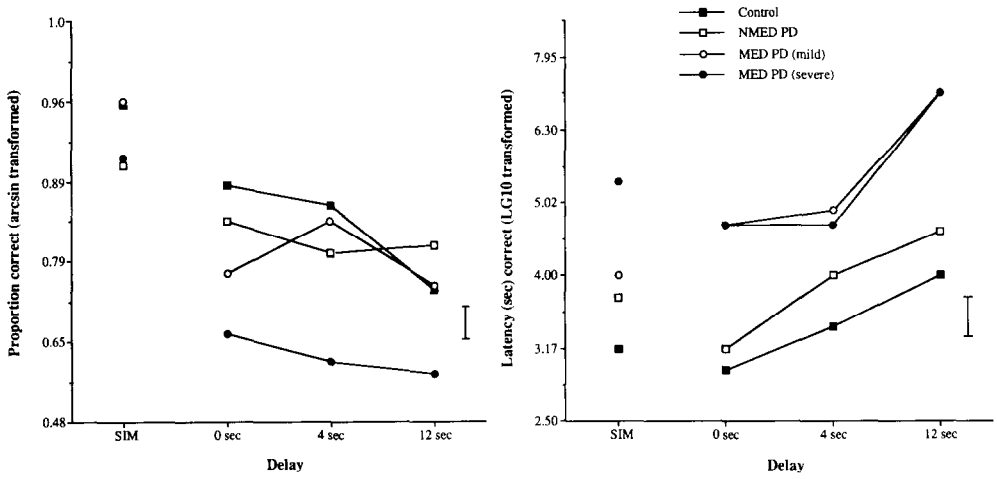

Fig. 3. Simultaneous and delayed matching to sample (i) proportion correct and (ii) mean latency for correct solutions. Bars represent one *standard error of the difference between the means*. This is an appropriate index of variation for computing *post-hoc* tests of significance between the mean values of the groups and is calculated according to the formulae provided by COCHRAN and COX [9].

There was no significant difference between the four groups in terms of the proportion of items correctly recalled in the *simultaneous* matching condition [$F(3, 79) = 1.42$]. In contrast, a group X delay, two-way MANOVA across the three *delay* conditions revealed a highly significant difference between the four groups [$F(3, 79) = 7.10$, $P < 0.0001$] in terms of the overall proportion of items recalled. However, an orthonormal contrast analysis confirmed that, compared to the combined group of normal controls, only the MED PD (severe) group were significantly impaired [$t(79) = -4.55$, $P < 0.0001$] across these delay conditions. In addition, there was a significant main effect of delay [$F(2, 158) = 3.71$, $P < 0.05$], although there were no significant interactions between the group and the delay factors.

Response latencies for the simultaneous and delayed conditions were also analysed using separate one- and two-way MANOVA's. In all cases, latencies were recorded in milliseconds and then transformed into logarithms (Base 10) to reduce skewness in the distribution. The transformed data are presented in Fig. 3. In the simultaneous condition, there was a highly significant difference between the four groups [$F(3, 79) = 5.98$, $P = 0.001$]. An orthonormal contrast analysis confirmed that only the MED PD (severe) group were significantly slower than controls in this condition [$t(79) = 4.16$, $P < 0.0001$].

Across delay conditions, there was also a highly significant group difference

[$F(3, 79) = 7.63$, $P < 0.0001$] and a significant interaction between the delay and group factors [$F(6, 158) = 2.32$, $P < 0.05$]. Simple main effects were therefore calculated for each of the three PD group comparisons at each level of delay. At the shortest, 0 sec delay, both groups of MED PD patients were impaired, compared to the combined PD group [$t(79) = 6.38$, $P < 0.001$ and $t(79) = 6.19$, $P < 0.001$, respectively] although no deficit was observed in the NMED PD patients [$t(79) = 0.74$]. In contrast, at 4-sec delay and 12 sec delay, all three PD groups were significantly impaired in terms of latency to make correct responses [4 sec; NMED PD, $t(79) = 2.19$, $P < 0.05$, MED PD (mild), $t(79) = 5.19$, $P < 0.001$, MED PD (severe), $t(79) = 4.34$, $P < 0.001$; 12 sec; NMED PD, $t(79) = 2.05$, $P < 0.05$, MED PD (mild), $t(79) = 7.99$, $P < 0.001$, MED PD (severe), $t(79) = 8.04$, $P < 0.001$]. There was also a significant main effect of delay [$F(2, 158) = 56.07$, $P < 0.0001$] with latency to make correct responses tending to increase in all groups with increasing delay.

Paired associates learning

The three PD groups and the combined control group were compared in terms of four indices of learning and memory; total *trials* to criterion, total *errors* committed, total number of patterns correctly located after a single presentation (*memory score*) and total number of trials entirely correct after a single presentation (*first correct*). The data are presented in Fig. 4.

Separate orthonormal contrast analyses between the four groups confirmed that the MED PD (severe) group were significantly impaired on each of these four measures. In terms of learning performance, this group with more severe clinical symptoms required more trials to complete the test [$t(62) = 3.07$, $P < 0.005$] and made significantly more errors in doing so [$t(62) = 2.78$, $P < 0.01$]. In terms of the two indices of memory performance, the MED PD (severe) group correctly located significantly fewer patterns on the first attempt [$t(62) = -2.73$, $P < 0.01$] and successfully completed fewer trials after a single presentation of the pattern locations [$t(62) = -4.6$, $P < 0.0001$]. The NMED PD group and the MED PD (mild) group were unimpaired on any of these four measures.

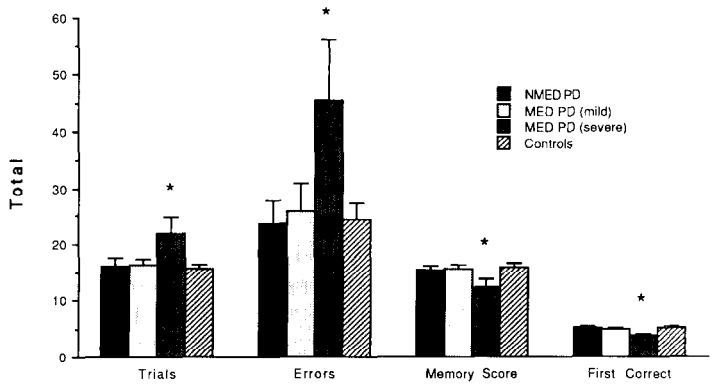

Fig. 4. The paired associates pattern-location learning task. Bars represent standard errors. *$P < 0.05$.

Spatial working memory

Mean total errors and the corresponding standard errors for the spatial working memory test are shown in Fig. 5. for the three PD groups and the combined ($N=42$) group of controls. A one-way analysis of variance showed that the four groups differed significantly on this test [$F(3, 64)=8.18$, $P<0.0001$] and a between group, orthonormal contrast analysis confirmed that both the MED PD (mild) group [$t(64)=3.07$, $P<0.05$] and particularly the MED PD (severe) group [$t(64)=4.55$, $P<0.0001$] were significantly impaired on this measure compared to the combined control group. Whilst the NMED PD group made over 25% more errors than controls on this measure, this trend did not reach statistical significance [$t(64)=1.61$].

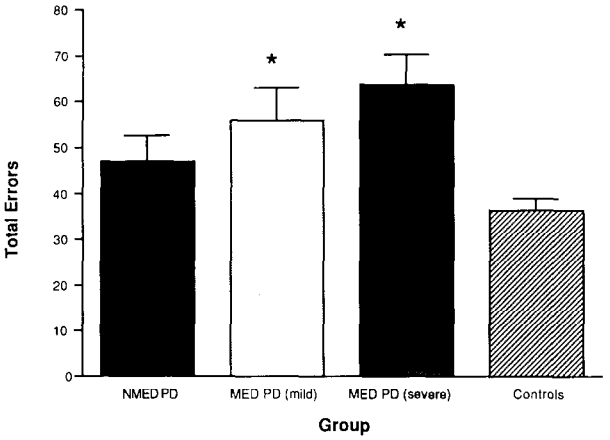

Fig. 5. The total number of errors in the spatial working memory test. Bars represent standard errors. *$P<0.05$.

DISCUSSION

The results of this study have considerable significance for the staging of cognitive decline in PD and are particularly relevant to recent work on the progression of fronto-striatal cognitive defects in PD [37]. In that study, tests sensitive to frontal lobe damage, including planning, attentional set-shifting and spatial working memory were used to differentiate groups of patients at different stages of PD. In the present study, the relationship between the spatial working memory deficit and other forms of visual memory impairment were explored in the same patient groups of medicated and non-medicated patients at different stages of PD. The main results suggest that the spatial working memory deficit was more sensitive in detecting deficits in these patients than tests of pattern and spatial recognition, delayed matching to sample and a test of visuospatial learning, although most of these tests showed impairments in the patients with the most severe clinical symptoms.

Specifically, in a test of spatial recognition memory, a significant impairment was only evident in those PD patients who were medicated and had the most severe clinical symptoms (Hoehn and Yahr stage III–IV). In contrast, none of the three patients groups were impaired in a complementary test of visual pattern recognition memory. Although the spatial task was shown to be considerably more difficult than the visual pattern task, this factor does not

adequately account for the deficit in the severely disabled PD patients. Thus, pattern recognition memory was still preserved in this group when only those patterns from set 2 were considered, which, in terms of task difficulty, was comparable with the spatial recognition memory task.

Whilst all three patient groups performed accurately in a test of simultaneous visual matching to sample, thus showing no obvious perceptual impairment, medicated patients with severe clinical symptoms were significantly impaired when a delay of between 0 and 12 sec was introduced. In addition, although all three groups of PD patients were slower to respond correctly in the longer delay conditions, only the more severe PD patients were slower to respond in the simultaneous condition. In the final test of visuospatial learning, which required subjects to remember where particular visual stimuli were located on the computer screen, deficits in learning *and* memory were also evident only in the severely impaired MED PD group. In contrast, in the test of spatial *working memory*, previously shown to be sensitive to frontal lobe damage [36] medicated PD patients with *both* mild and severe clinical impairments were significantly impaired and a non-significant trend towards impairment was also observed in the non-medicated group. These combined results confirm that there are multiple memory impairments in PD which may differentially depend on the clinical severity of the disease.

The results of this investigation extend the findings of SAHAKIAN *et al.* [50] in several ways, although there are also a number of discrepancies between the two studies which should be addressed. In the present study, a counterbalanced sequence of trials was employed in the delayed matching to sample task, rather than the gradually increasing length of delay that had been previously adopted [50]. In that comparative study of PD and Alzheimer's disease, the sequencing of the trials was simplified in this way to make the test more amenable to demented patients. In the present study, the test was also made more sensitive by including one (random) common quadrant in each of the matching stimuli to discourage the use of encoding strategies based on remembering only a limited proportion of the sample stimulus. The effects of this modification may be seen by comparing the relatively poorer performance of control subjects in this study to those studied by SAHAKIAN *et al.* [50], using the earlier version of the task. Thus, the controls in the present study exhibited a clearly significant delay-dependent decline in performance accuracy, which was not consistently observed in the previous study [50]. The findings from the previous study have also been extended in terms of the differential pattern of deficits observed in the three groups of patients with PD. Specifically, although the unimpaired performance accuracy of the NMED PD group in the delayed matching condition essentially repeats the findings of SAHAKIAN *et al.* [50], among the medicated patients in this study, deficits were only evident in those patients *with severe clinical symptoms*. In addition, although neither the NMED PD or the MED PD (mild) group were impaired in terms of performance accuracy on this task, both groups exhibited significantly prolonged response latencies for correct responses. As this increase in latency in PD varied as a function of delay, it is clearly not related simply to a basal slowing of reaction time but represents a cognitive deficit in short-term visual retention. Response latencies were not reported in the previous study. In this study, and in the previous one by SAHAKIAN *et al.* [50], the impairment in the MED PD (severe) group was not delay dependent; that is, in comparison with controls, the PD patients performed equally poorly at each delay over the range 0–12 sec. This pattern of impairment contrasts with the delay-dependent deficits seen in patients with mild DAT who have recently been shown to exhibit disproportionately inferior performance at 12-sec delay, using an identical version of this task [53].

In the present study, the results from the visuospatial paired associates learning task also help to clarify the findings from the previous investigation by demonstrating that only severely disabled MED PD patients are consistently impaired on this task. This confirms the previously observed relationship between disease severity and both memory score and errors to criterion on an identical version of the test [50] although in that study, small groups sizes precluded any formal comparison betwen subgroups of PD patients. In addition, in the previous study, a small number of NMED PD patients (3/12) failed to reach criterion on this task, although the overall group performance (errors and trials to criterion) was not significantly impaired. The present study effectively confirms this result; only 1/18 NMED PD patients failed to complete the test and as a group, they were unimpaired on any of the performance indices.

Of the two serial recognition memory tests, the results for spatial recognition also extend previous results by showing that a deficit is only apparent in medicated PD patients with severe clinical disability. In contrast, none of the three PD groups were impaired in the test of pattern recognition memory, a result which appears to contradict the findings of both SAHAKIAN *et al.* [50] and LANGE *et al.* [27]. However, a retrospective analysis reveals that several of the medicated PD patients studied by SAHAKIAN *et al.* [50], showed strikingly low scores on the Kendrick Object Learning Score (two were actually in the dementing range) although all of the patients were clinically diagnosed as not having dementia. If these patients are excluded from the analyses of pattern recognition performance, no significant group deficit is observed. Similar factors appear to account for the significant deficit reported by LANGE *et al.* [27]. In that study, again, the performance of two patients on the Kendrick Object Learning test was actually within the dementing range although all patients were clinically diagnosed as not having dementia. Importantly, in the present investigation, as well as being clinically diagnosed as non-demented, all prospective medicated PD patients were *screened* for dementia using both the Mini Mental State Examination and the Kendrick Object Learning Test. Therefore, on the basis of these three studies, it appears likely that impaired pattern recognition performance may be observed in PD patients whose scores on traditional clinical scales place them in the dementing range, although not in non-demented patients with PD. In support of this, when the medicated PD patients from the three studies are combined ($N=45$), a significant positive correlation is observed between the Kendrick Object Learning Test score and performance on the pattern recognition test ($r=0.46$, $P=0.001$). Since the pattern recognition test is sensitive to deficits in DAT [49, 51], it is suggested that this test may be a useful instrument for detecting dementia, but not for characterising the cognitive deficits associated directly with PD. This late manifestation of visual memory deficits that are comparable to those observed in DAT may reflect the non-dopaminergic neuropathological changes also observed in PD, including for example, cortical Lewy bodies [19a] or deficits in the functioning of cortically-projecting cholinergic and monoaminergic systems [2].

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 [20] and scopolamine [13] have been shown to affect cognitive performance in PD patients. However, it is unlikely that dopaminergic medication disrupts performance in medicated PD patients included in this investigation since a recent study [27] has demonstrated that controlled withdrawal of L-Dopa had *no effect* on identical versions of the tests of pattern and spatial recognition memory, simultaneous and delayed matching to sample and visuospatial conditional associative learning. In contrast, performance on other

tests of cognitive function, particularly those sensitive to frontal lobe damage (including the spatial working memory reported here) actually deteriorated following withdrawal of L-Dopa medication.

Anti-cholinergic medication is also unlikely to play a significant role in the pattern of cognitive deficits observed in the present study since only five of the 24 medicated PD patients included were receiving such preparations. In addition, a supplementary analysis confirmed no obvious differences between these five patients and the remainder of the medicated PD group.

It has previously been suggested that depression may contribute to the cognitive profile of patients with PD [56]. In the present study, although none of the patients were described as clinically depressed, the medicated patients with severe clinical symptoms performed more poorly than the patients with mild clinical symptoms on the Geriatric Depression Scale [63] suggesting that affective disturbance may contribute, at least in part, to the more severe pattern of cognitive deficits observed in this group. However, two lines of evidence refute this suggestion; First, the depression score was not significantly correlated wth any aspect of learning or memory in the medicated patients with PD. In fact, *only* severity of motor symptoms, assessed according to the Hoehn and Yahr rating scale correlated with depression in this group. Second, in a recent study, the pattern of deficits observed in a group of elderly depressed patients, using very similar versions of these tests, was not the same as that observed in medicated patients with PD [1]. For example, the depressed patients were significantly impaired in the tests of both spatial *and* pattern recognition memory and exhibited a marked delay-dependent deficit in the delayed matching to sample procedure. Therefore, it seems most likely that in the present study, subclinical affective disturbance does not contribute to the observed pattern of learning and memory deficits.

It may also be argued that task complexity or test difficulty may contribute to the pattern of deficits observed in patients with PD in this study. However, such explanations cannot adequately account for the entire pattern of results. Thus, although the paired associates learning task is far more complex in design than the test of spatial recognition memory, the two tests are equally sensitive in differentiating between groups of medicated patients with PD. Similarly, when the pattern and spatial recognition memory tests were equated for task difficulty according to control performance (see results), the pattern of results was unchanged.

The results of this cross-sectional study therefore have considerable significance for the possible progression of cognitive impairments as patients show increasing clinical disability (reflected in their Hoehn and Yahr ratings) which may merit further investigation in a longitudinal design. Because of the controlled nature and design of these tests, discussed above, these cognitive deficits cannot simply be explained in terms of motor dysfunction. Moreover, it seems likely that some cognitive deficits progress in parallel with the motor deficits characteristic of PD, and may reflect differing forms of neuropathological involvement.

The neural substrates underlying these deficits in tests of spatial working memory, visual memory and learning have recently been investigated in groups of neurosurgical patients with excisions of the frontal and temporal cortices [36, OWEN *et al.*, in preparation]. It should be made clear that a simple mapping between a given memory task and a particular neural structure is unlikely to exist. However, our preliminary results suggest that performance on the tests of pattern recognition, spatial recognition and delayed matching to sample is more impaired following temporal lobectomy than following excisions of the

frontal cortex, whereas the tests of paired associates learning and spatial working memory are more affected by frontal lobe damage than by lesion of the temporal lobe structures.

Of course, many of these correlations between particular anatomical structures and cognitive functions have been presaged by early studies of patients [30, 42] and by experimental studies of infra-human primates. The latter are particularly relevant to the present study, as many of the tests employed here are based directly on procedures developed for testing non-human species. For example, the delayed matching to sample procedure (in its "non-matching" format) has been used extensively by Mishkin and his co-workers to define a neural system for mediating visual recognition memory. This includes, as major components, the inferotemporal cortex and medial temporal lobe structures although particular sectors of the frontal lobe have also been implicated [3, 18, 39]. In the case of the spatial working memory test and the test of paired associates learning, similar parallels may be drawn with studies by PASSINGHAM [40] and PETRIDES [41], respectively, which investigated the effects of frontal lobe ablations in monkeys.

It therefore seems likely that the late emergence of deficits in delayed matching to sample and pattern recognition memory in PD may reflect a relative sparing of functions associated with temporal lobe structures, early in the course of the disease. This sparing contrasts markedly with the susceptibility of these same PD patients to tasks sensitive to frontal, but not temporal, lobe damage [37]. It is important to note that performance on the test of short-term spatial span is unaffected by either frontal or temporal lobe lesions [36], although spatial span is significantly reduced in patients with severe PD [37]. Deficits in spatial span have previously been associated with damage to right posterior regions including the parietal cortex [11] and it therefore seems likely that the frontal lobe-like deficits in PD also precede deficits in parietal lobe functioning [4].

In summary, the pattern of results for this and related papers suggests that cognitive deficits in PD emerge and subsequently progress according to a defined sequence, which begins with frontal type deficits and only later includes more posterior cortical functions. This contrasts with the reverse pattern observed in most patients with dementia of the Alzheimer type [21, 50, 51] which corresponds to the typical progression of regional neuropathological signs in the cortex of DAT patients [60, 21].

The question therefore arises, as to whether a plausible neural account might also be formulated for the specific sequence of cognitive deficits accompanying the motor symptoms that are characteristic of patients with PD. Recent anatomical and neuropathological evidence suggests that the sequence can indeed be linked to what is known about the likely spatiotemporal 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 [24]. However, more contemporary studies 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, 55, 61], such that the temporal lobe, for example, also projects strongly to the head of the caudate nucleus [54]. Nevertheless, these authors have emphasised that the inferotemporal cortex (area TE) mainly innervates the more posterior regions of the head of the caudate nucleus, in contrast to other areas of the temporal lobe, such as TA, which projects more anteriorly,

whilst regions of the prefrontal cortex tend to innervate rostral portions of the head of the caudate [55]. 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 cognitive deficits in PD, as well as other basal ganglia disorders. This is highlighted by a recent, detailed post-mortem neurochemical analysis which shows uneven patterns of striatal dopamine loss in patients dying with idiopathic PD [26]. The study confirms the well-known finding that the putamen appears to be more severely depleted than the caudate nucleus, and extends the analysis to show that the caudal putamen is more affected than the more rostral portions. However, 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, but importantly, this depletion is significantly greater in the most rostral extent of the head of this structure (to a maximum of about 90%) compared to its more caudal limits (to a maximum of about 60%). Consequently, it seems likely that the more rostral regions are subjected to greater disruption by the disease, and probably at an earlier stage of its progression. This may concur with the present findings that pattern recognition and delayed matching to sample deficits, which are sensitive indicators of temporal lobe dysfunctions, are relatively insensitive indicators of cognitive impairment in PD. Alternatively, the apparent lack of effect of L-Dopa withdrawal on impaired visual memory and learning in severely affected PD patients [27] may suggest a predominantly non-dopaminergic (and hence probably non-striatal) substrate for these cognitive deficits, perhaps related to the presence of cortical Lewy bodies [19a]. Further studies are clearly required before this issue can be fully resolved, but the present study suggests that it will be particularly interesting to focus on certain impairments in visual memory and learning found in the more advanced stages of PD, in order to test between these possibilities.

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