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We investigated the neuropsychological correlates of hippocampal atrophy in Parkinson's disease (PD) patients. The memory impaired PD patients had smaller hippocampi than other PD patients. The performance of PD patients in spatial working memory and attentional set-shifting correlated with the severity of motor defect, and not with hippocampal atrophy. Our results suggests that failure of verbal/visual memory may be related to hippocampal atrophy in Parkinson's disease. On the contrast, the defect in spatial working memory and attentional set-shifting may be sensitive to dysfunction of 'fronto-striatal' systems in PD patients *NeuroReport* **9: 1507–1511 © 1998 Rapid Science Ltd.**

Hippocampal atrophy is related to impaired memory, but not frontal functions in non-demented Parkinson's disease patients

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Introduction

Parkinson's disease (PD) even at an early stage impairs performance in tests measuring functions mediated by the 'fronto-striatal' systems, such as spatial working memory (SWM) and attentional set-shifting.[1–3] This impairment may reflect the severity of striatal dopaminergic loss[2,3] and impaired functions of 'fronto-striatal' loops.[4] However, in PD the frontal dopamine projections are also adversely affected,[5] suggesting that the progressive dysfunction of striatal and frontal dopamine transmission may both contribute for the impaired performance in 'frontal' tests.[2] It is relevant to note that more severely disabled PD patients are also less accurate in tests sensitive to dysfunction of hippocampus and anatomically related medial temporal lobe cortical structures, such as delayed matching to sample test (DMTS).[3] Dopaminergic defect may not contribute for impaired DMTS memory accuracy, since L-dopa withdrawal did not further aggravate DMTS defect in PD patients.[3]

We designed the present study to investigate the hypothesis that impaired declarative memory performance in non-demented PD patients is associated with hippocampal atrophy[6,7] and that hippocampal atrophy is not related to the degree of 'fronto-striatal' cognitive defects. Therefore, we compared the volumes of hippocampi of PD patients that had intact or impaired memory performance in two tests that are sensitive to dysfunction of the medial temporal lobe memory systems, DMTS and primacy component of the list learning test.[8] To study the selectivity of the association between hippocampal atrophy and impaired performance in DMTS and list learning tests, we also measured spatial working memory and attentional set-shifting functions of these patients.

Patients and Methods

We included 43 non-demented[9] patients with a diagnosis of idiopathic PD in the study (Table 1). All exhibited a typical akinetic rigid syndrome with rest tremor. The patients were rated while on dopaminergic medication (L-dopa in combination with peripheral decarboxylase inhibitor).[10] Twenty patients were rated I–II (mild PD group) and 23 patients were rated III–IV (severe PD group). None of the patients showed clinical signs of depression (Geriatric Depression scale; GDS), dementia, psychosis or focal cortical pathology. All of the study patients had received dopaminergic medication and

Table 1. Characteristics of different groups of PD patients.

Group	Stage	Age (years)	Duration (years)	MMSE	L-DOPA (mg)	GDS	Hippocampus volume		Number
							Right	Left	
Mild PD	I–II	60 ± 1.2	4.7 ± 1.0	28 ± 1.2	535 ± 49	9 ± 2.2	0.18 ± 0.01	0.17 ± 0.01	20
Severe PD									
Unimpaired memory	III–IV	64 ± 1.4*	7.4 ± 1.2*	26 ± 1.2	658 ± 79	14 ± 1.3*	0.17 ± 0.02	0.17 ± 0.01	15
Impaired memory	III–IV	65 ± 1.1*	8.1 ± 1.3*	25 ± 1.3	699 ± 84	15 ± 1.6*	0.14 ± 0.01*	0.14 ± 0.02*	8

The values are group mean ± s.e.m. The normalized volumes of the right and left hippocampus (volume of the hippocampus/the area of both hemispheres in MRI taken at the level of the anterior commissure) are shown. GDS = geriatric depression scale, duration = disease duration, MMSE = Mini Mental State Examination, number = number of patients/group, stage = classification of Hoehn and Yahr.[10]
*$p < 0.05$ *vs* mild PD group, Bonferroni *post hoc* multiple group comparison.

had shown adequate clinical anti-parkinsonian response. The PD patients were on optimal dopaminergic medication during testing that had been stable for at least 2 months. No subjects received anticholinergic medication during the study period or for 12 months before the initiation of the study. In addition to cognitive testing and routine clinical MRI analysis, the investigation of the subjects included clinical neurological examination and laboratory tests to exclude medical conditions that could impair cognitive functioning.

Cognitive testing included computerized neuropsychological tests (SWM, intra- dimensional/extra dimensional (ID/ED) attentional set shifting, DMTS, motor screening).[11] A computerized system with a touch sensitive video screen was used. These tests provide non-verbal stimuli and record responses using the touch sensitive screen. The subjects were first familiarized with the testing procedure by letting them perform a motor screening task in which they were trained to point accurately at the screen. A standard 'paper and pencil' word list learning test was alsi assessed. SWM[12] is a self ordered test of working memory, which also incorporates a strategic search component to tax central executive function. Subjects had to search through a number of boxes (four, six or eight) tor a hidden token without returning to a box which they had already examined on the same trial (to avoid within-search errors) or which had already contained a token on the previous trial (to avoid between-search errors). Tokens were hidden one at a time, and were never hidden in the same box twice. The main measure of this test was between-search errors at each level of the test, as this has been shown to separate mild and severe PD patients.

ID/ED[13] is a test of attentional set-shifting based in part on the Wisconsin card sort test (WCST). There are nine stages in which a subject has to learn a visual discrimination to criterion (six consecutive trials correct). The first two stages required a simple visual discrimination (SD), followed by a reversal of this discrimination upon reaching criterion (SDR). Another visual dimension is then introduced which the subject must learn is irrelevant (compound discrimination with stimuli separated (C–D) or superimposed (CD)), even in the face of a reversal of the original discrimination (compound discrimination reversal; CDR). An intra-dimensional shift is then introduced, at which point new exemplars of the two dimensions are given, and the subject must now learn a new discrimination to criterion (intra-dimensional shift; IDS) followed by a reversal of this rule (intra-dimensional reversal; IDR). The penultimate stage of the test introduces an extra-dimensional shift (EDS), where again new exemplars of the two dimensions are presented, but this time the subject must shift his or her attention to the dimension which was previously irrelevant (EDS), followed finally by a reversal of this rule (extra-dimensional reversal; EDR). The EDS is akin to a category shift in the WCST. For each stage of the test, the main measure was the stage successfully attainted. The main measures were the IDR and EDS stages that cannot and can separate, respectively, the performance accuracy of mild and severe PD patients.

Visual memory was tested with the DMTS.[14] In the DMTS, the subject must match patterns in either a delayed or simultaneous condition. In the simultaneous condition the sample and all of the choice stimuli are present on the screen simultaneously, and the subject must select the choice pattern that matches the sample exactly. In the final condition there are delays of 1, 4, 8 and 16 s between the 40 presentations of the sample pattern and the choice stimuli. The subjects must touch the choice stimulus that exactly matches the sample. If the first response is incorrect, the subject may choose again until the correct answer is reached or all choice stimuli have been selected. There are three practice trials, and then 40 test trials during which delay condition (0, 4, 8 or

16 s delay) are counterbalanced. A short break is allowed after 20 test trials. To discourage subjects from encoding the sample pattern on the basis of one quadrant only, all four choice patterns have one quadrant in common with the sample. The outcome measure is the percentage of correct responses at different delays.

Verbal memory was measured with a list learning test. The list learning test consisted of a nine-word list that was read aloud to patients three times. Immediately after the tester had finished reading the words, the patient repeated as many words as possible (immediate recall). This was repeated three times and a maximum correct score was 27 (9 words × 3 repetitions = 27 words). The patient was asked to again repeat the words 6 min later (delayed recall, maximum correct score nine words). During this break other cognitive tests were assessed. The number of total correct and false words was measured. Furthermore the word list was divided into three parts to study the serial position effect (primacy words 1–3; intermediate words 4–6 and recency words 7–9) and to examine in detail what component of word list learning is affected by PD.

The subjects were scanned with a 1.5 T Magnetom (Siemens, Erlagen, Germany) using a standard head coil and coronal 3D gradient echo sequence (MP-RAGE: TR 10sms, TE 4 ms, TI 250 ms, flip angle 120°, FOV 250 mm, matrix 256 × 192, one acquisition).[8] This resulted in 128 T1-weighted partitions with slice thickness of 1.5–1.8 mm. The partitions covering the hippocampus were reformatted into 1 mm contiguous slices perpendicular to the long axis of the hippocampus. The term hippocampus included the dentate gyrus, the hippocampus proper and the subicular complex. The uncal portion of the rostral hippocampus that is located ventral to the caudal amygdala was included into the hippocampus. The caudal end of the hippocampus was determined from the section in which the fornices were still detectable in their full length. The fornices were not, however included in the volume of the hippocampus. We used standard anatomical atlases of the human brain as guidelines to determine the boundaries of the amygdala auld hippocampus on oblique coronal MRI sections. The boundaries of the region of interest were outlined by a trackball-driven cursor. The number of voxels within the region was integrated by using a program developed in-house for standard work console. Every second 1 mm slice was included in the analysis, which reduced the number of slices to 20–23 for hippocampus. We calculated the results using normalized volumes of the amygdala and hippocampus (volume of the hippocampus/the area of both hemispheres in MRI taken at the level of the anterior commissure).

The group and task difficulty effects and group × difficulty interaction were analyzed with repeated measures ANOVA. The *t*-test, one-way ANOVA and Bonferroni *post hoc* test, χ^2 and Wilcoxon signed ranks tests were used.

Results

Eight PD patients performed ⩾ 1 s.d. below the mean of all the patients at the longest delay of DMTS test and at the primacy component of the list learning test measured after a 6 min forgetting interval. These patients were called memory impaired (MI) PD patients and all of them were suffering from severe PD (III–IV). The rest of the patients ($n = 35$) were called memory unimpaired (MU) PD patients (20 mild PD: I–II; 17 severe P; Fig. 1A,B).

The performance of MI PD patients was at long delays impaired compared with the MU PD patients (delay × group interaction: $F(1.41) = 12.1$, $p < 0.001$; Fig. 1A). The MI PD group was not impaired at simultaneous matching, or at a 0 or 4 s delay ($p > 0.1$) but they scored less well at 8 and 16 s delays ($p < 0.001$). In the list learning test, MI PD patients after 6 min forgetting interval recalled fewer primacy words ($p < 0.001$), but were as accurate as the MU PD patients in recalling intermediate and recency words ($p > 0.1$, for both; Fig. 1B).

The number of between-search errors at the level of 6 and 8 boxes did not differ between the MI and MU PD patients (group: $F(1.41) = 1.0$, $p > 0.1$; difficulty: $F(1,41) = 95.1$, $p < 0.001$; group × difficulty: $F(1.41) = 3.3$, $p = 0.08$; Table 2). Furthermore, the number of MU and MI PD groups that reached IDR, EDS or EDR stages did not differ ($\chi^2 > 1.0$, $p > 0.1$; for all).

We also compared the performance of severe and mild PD patients in SWM and ID/ED tests. The severe PD group was impaired at the arduous 8 box level of SWM test compared with the mild PD (20 MU patients) group (group: $F(1,41) = 2.8$, $p = 1.0$; difficulty: $F(1,41) = 139.8$, $p < 0.001$; group × difficulty: $F(1,41) = 11.8$, $p < 0.001$; Table 2). The ID/ED set-shifting performance of the mild and severe PD was as accurate at easy IDR level ($\chi^2 = 0.15$, $p > 0.1$), but the proportion of the severe PD patients that solved the difficult EDR and EDS levels was lower ($\chi^2 = 10$, $p < 0.01$; for both). Importantly, comparison of the MU and MI severe PD patients showed no difference in SWM (group: $F(1,21) = 3.3$, $p = 0.5$; difficulty: $F(1,21 = 91.4$, $p < 0.001$; group × difficulty: $F(1,21) = 0.18$, $p > 0.1$) or attentional set-shifting performance (IDR, EDS, EDR stages: $p > 0.1$ for all).

The MU and MI severe PD patients were older, had suffered from the disease for a longer period and had higher GDS scores than mild PD patients

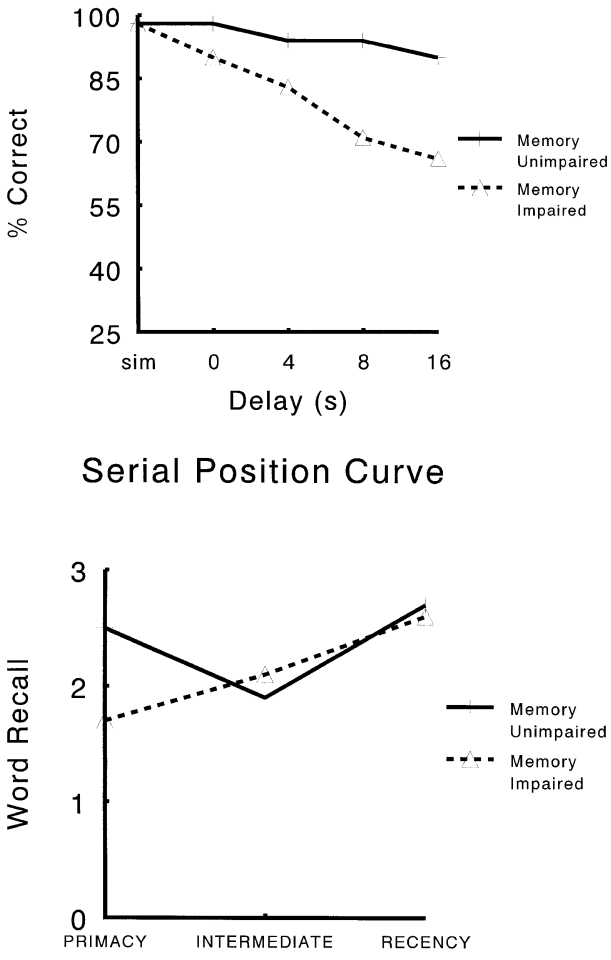

FIG. 1. Delayed matching to sample memory performance (**A**) and word list after a 6 min forgetting interval (**B**) of PD patients. The group mean percentage correct at different delays is shown in (A). The group mean of primacy (words 1–3), intermediate (words 4–6) and recency (words 7–9) are shown in (B).

Table 2. Spatial working memory (between-search errors at 6 and 8 box level) and ID/ED attentional set shifting (number of patients that reached the stage/total number of patients) performance in PD: memory unimpaired ($n = 35$) and memory impaired groups ($n = 8$).

Group	Errors	6 boxes errors	8 boxes IDR stage	reach EDS stage
Mild PD	12.8 ± 3.7	20.0 ± 4.5	15/20	11/20
Severe PD				
Unimpaired memory	13.2 ± 5.4	25.7 ± 7.4*	11/15	2/15**
Impaired memory	9.9 ± 2.6	24.0 ± 5.6*	6/8	1/8**

*$p < 0.05$ *vs* mild PD group, Bonferroni *post hoc* multiple group comparison.
**$p < 0.05$ Severe *vs* mild PD group, Kruskal-Wallis one-way ANOVA

($F(2.40) > 4$, $p < 0.05$ for all; $p < 0.05$ *vs* mild PD; Table 1). The MU and MI Severe PD patients did not differ in these measures ($p > 0.05$). MMSE and dopaminergic medication did not significantly differ between the mild and severe PD groups ($F(2,40) < 1$, $p > 0.1$ for both comparisons).

The normalized right and left hippocampal volumes of the MI severe PD group were smaller than those of the MU mild or severe PD patients ($F(1.42) > 5.9$, $p < 0.019$ for both comparisons; $p < 0.05$ *vs* the other two groups of PD patients; Table 1). The volume of right and left hippocamppi correlated with DMTS accuracy at 16 s delay ($r > 0.7$, $p < 0.001$ for both analyses), but not at shorter delays ($r < 0.2$. $p > 0.1$ for all). Hippocampal volume correlated nearly significantly with recall of primacy words after the 6 min forgetting interval ($r = 0.26$, $p = 0.088$). Hippocampal volumes, and DMTS or list learning accuracy did not correlate with measures of SWM or ID/ED set shifting tests, age, disease duration, dose of dopaminergic medication and GDS scoring ($r < 0.15$, $p > 0.05$ for all analyses).

Discussion

Hippocampal atrophy correlated with impaired memory scoring in PD patients. We also confirmed previous evidence suggesting that dopaminergic dysfunction may cause impaired SWM and attentional set-shifting accuracy, as the severity of motor symptoms correlated with these fronto-striatal functions.[2,3]

Previous clinical and experimental results support our finding that impaired memory performance in DMTS and list learning tests in PD patients is at least partly due to hippocampal dysfunction. First, humans may employ verbal strategies to perform in the DMTS test and actually form associations between verbal cues and the sample figures employing a paired associates learning strategy that requires hippocampal processing.[15,16] Second, a supra-span list learning test and recall of these memory items after a delay filled with distracting activity (other cognitive tests) depends on hippocampal processing.[8] Indeed, surgical excision of the medial temporal lobe structures during epilepsy surgery[17] and neurodegeneration in Alzheimer's disease[18] disrupts list learning and impairs the ability to retrieve the words from the beginning of the list.[8,19] However, the defective DMTS and word list test scoring may not be only due to degeneration of the hippocampus, as several neurotransmitter systems are affected during the progression of PD.[5] For example, dysfunction of cholinergic cells of the basal forebrain or noradrenergic locus coeruleus may impair attention and certain forms of declarative memory functions in more advanced PD patients.[5]

Some non-specific factor, such as disease duration, depression, medication or age is unlikely to explain the inferior delayed memory performance, as the MI severe PD patients did not differ in these measures

from the MU severe PD patient. Furthermore, no correlation was observed between depression scoring, dopaminergic medication, disease duration or age and memory performance.

In conclusion, our present data described that some PD patients that suffered from a severe motor disability also had a delay-dependent visual and verbal memory failure that was associated with mild atrophy of the hippocampus. On the contrary, the defect in fronto-striatal measures did not correlate with the hippocampal atrophy, but was related to the severity of motor dysfunction. This and earlier evidence suggests that the dopamine cell loss in the midbrain contributes for the defect in fronto-striatal functions in PD patients. Furthermore, failure of memory retention occurs less frequently in PD patients and this is at least to some extent due to hippocampal dysfunction.

Conclusion

Parkinson's disease is characterized by impaired function of fronto-striatal loops that results from loss of dopaminergic cells in the substantia nigra. Impaired activity of the fronto-striatal systems disrupts spatial working memory, planning and attentional set-shifting at an early stage of the disease. However, some PD patients suffer from a retention delay-dependent impairment (i.e. the longer the delay is, the worse memory) of memory that is not likely to result from dopaminergic dysfunction. Our results found that the severity of hippocampal atrophy correlated with impaired memory accuracy in PD patients.

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