SHORT REPORT

Hippocampal and prefrontal atrophy in patients with early non-demented Parkinson's disease is related to cognitive impairment

A Brück, T Kurki, V Kaasinen, T Vahlberg, J O Rinne

J Neurol Neurosurg Psychiatry 2004;**75**:1467–1469. doi: 10.1136/jnnp.2003.031237

Background: Early stage patients with Parkinson's disease (PD) show cognitive impairment in frontal lobe functions and memory tests. Hippocampal atrophy is seen in medicated patients with advanced PD.

Objectives: To examine whether prefrontal or hippocampal atrophy are already present in early stage PD, and whether such atrophy is associated with cognitive impairment.

Methods: Twenty non-medicated, non-demented patients with early stage PD and 22 neurologically healthy age matched controls were studied. All subjects underwent magnetic resonance imaging to study hippocampal and prefrontal atrophy. Atrophy was evaluated by a neuroradiologist using a five point scale. In addition, the patients underwent a neuropsychological test battery sensitive to frontal lobe functions and memory.

Results: Patients with PD had atrophy in the right and the left prefrontal cortex. In the right hippocampus, the mean atrophy score was 1.15 in PD and 0.45 in controls. Corresponding figures for the left hippocampus were 1.05 for PD and 0.64 for controls. In PD, the left hippocampus atrophy correlated with verbal memory and prefrontal atrophy correlated with impaired performance in a test measuring vigilance.

Conclusions: Non-medicated, non-demented patients with early stage PD show hippocampal and prefrontal atrophy. Impaired memory is related to hippocampal atrophy, whereas sustained attention is related to prefrontal atrophy.

It is known that patients at the early stage of Parkinson's disease (PD) already have impairments in cognitive performance. These impairments can be found especially in tests measuring frontal lobe functions and memory but, as the disease proceeds, they can lead to an overall cognitive decline and dementia.[1–3]

The pathophysiological basis of the cognitive deficits in PD is unclear. A magnetic imaging (MRI) study found that non-demented patients with PD had more global brain volume loss than controls, and this was related to global measures of cognitive decline.[4] MRI studies reporting hippocampal volumes have shown that PD is associated with hippocampal atrophy,[5] and related to impaired memory.[6 7] However, the patients in these studies were on antiparkinsonian medication and had suffered from the disease for at least five years. There has been no information about the possibility of hippocampal atrophy in the early unmedicated stages of PD. Furthermore, because PD is associated especially with impaired frontal lobe functions, we hypothesised that if there was prefrontal atrophy it would be related to impairment in tests requiring frontal lobe functions.

SUBJECTS AND METHODS

The patient sample consisted of 20 non-demented patients (seven women and 13 men) with idiopathic PD at an early stage of the disease. The patients were diagnosed at the department of neurology, University of Turku and had at least two of the main symptoms of PD: tremor, rigidity, and hypokinesia. None of the patients exhibited atypical symptoms.[8] All patients fulfilled the UK Parkinson's disease brain bank criteria for definite PD. None of the patients had received antiparkinsonian medication before the examinations. After the MRI and the neuropsychological tests, all the patients were treated with dopaminergic medication with a positive response. The control population included 22 healthy volunteers (13 women, nine men); they had no history of neurological or psychiatric diseases. The patients and the controls did not differ in education level. Table 1 shows the clinical characteristics of the patients with PD and the controls. All patients and controls gave their written informed consent. The study protocol was approved by the joint ethics committee of Turku University and Turku University Hospital, Finland.

All patients and controls were scanned with a 1.5 Tesla MRI device (GE Signa Horizon LX EchoSpeed, Milwaukee, Wisconsin, USA). 3D FSPGR (fast spoiled gradient echo) sequencing was used for image analysis. Imaging parameters were as follows: TR 11.3 ms, TE 4.2 ms, flip angle 20, one acquisition, data acquisition matrix 256 × 192, the slice thickness was 1.2 mm, FOV 22 × 17.6 cm; 124 contiguous axial slices with no interslice gap were obtained. The visual analysis was performed by using reconstructed coronal and axial images. The degree of atrophy was evaluated separately on both sides by an experienced neuroradiologist (TK) on a SUN workstation monitor. The evaluator was blinded to the identity, sex, age, and diagnosis of the subjects. The rater was instructed that the subject population consisted of neurological patients and healthy controls in a random order. Hippocampal atrophy was evaluated from coronal T1 images according to Scheltens *et al*,[9] a highly reliable method for hippocampal atrophy rating.[10] Atrophy of the prefrontal cortex was similarly evaluated by a zero to four visual scale from axial T1 images. The visual evaluation of atrophy has previously been used in the frontal cortex and has been found to be reliable.[11] In both scales zero corresponded to no

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's Disease; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; PD, Parkinson's disease; DEL, WMS-R test for delayed memory; WMS-R, Wechsler Memory Scale-Revised; VEM, WMS-R test for verbal memory; VIM, WMS-R test for visual memory

Table 1 The clinical characteristics and the atrophy values for patients with Parkinson's disease and controls

	N	Sex (F/M)	Age (years)*	UPDRS*	Duration (years)†	MMSE‡	PFC right‡	PFC left‡	Hippocampus right‡	Hippocampus left‡
Patients	20	7/13	61.3; 7.0	29.7 (6.3)	1.7; 0.8; 0.7–4	26.7; 1.5; 26.5; 24–29	1.90; 0.64; 2; 0–3	1.90; 0.64; 2; 0–3	1.15; 0.81; 1; 0–2	1.05; 0.89; 1; 0–3
Controls	22	13/9	65.7; 9.3	–	–	28.8; 1.1; 29; 27–30	1.73; 0.88; 2; 0–4	1.73; 0.88; 2; 0–4	0.45; 0.67; 0; 0–2	0.64; 0.66; 1; 0–2
p Value		0.12	0.09			<0.0001	0.02	0.02	0.001	0.01

*Values are mean and SD; †values are mean, SD, and range; ‡values are mean, SD, median, and range.
F, female; M, male; MMSE, Mini-Mental State Examination; PFC, prefrontal cortex; UPDRS, Unified Parkinson's Disease Rating Scale.

atrophy and four to very severe atrophy. Subjects with massive white matter changes were excluded from our study.

The patients with PD underwent a neuropsychological test battery to evaluate cognitive performance. The tests included Consortium to Establish a Registry for Alzheimer's Disease (CERAD), Wechsler Memory Scale-Revised (WMS-R), and a vigilance test. CERAD consisted of nine different tasks, namely: verbal fluency, modified Boston naming, Mini-Mental State Examination (MMSE), Word-List Memory, Word-List Recall, Word-List Savings, Word-List Recognition, Praxis Recall, and Praxis Savings. WMS-R tests for verbal memory (VEM), visual memory (VIM), and delayed memory (DEL) were administered. The controls performed only the MMSE.

The stratified Mann-Whitney U test was used to compare the atrophy scores between the patients with PD and the controls. Stratification was made by three groups (48–59 years, 60–68 years, and 69–78 years) to adjust for the confounding effect of age. Exact p values were used in stratified Mann-Whitney U tests. The age differences were tested with the *t* test and the differences in sex distribution with the χ^2 test. MMSE scores between groups were compared with the Mann-Whitney U test. p Values less than 0.05 were considered significant. Correlations were calculated using the Spearman rank order. Our correlation analyses were hypotheses driven (hippocampal atrophy associated with memory impairment and prefrontal atrophy with impairment in frontal lobe functions) and thus $p < 0.05$ was considered significant despite several correlation calculations. Statistical computations were done with the SAS System for Windows, version 8.02 and StatXact, version 5.0.

RESULTS

We found that the patients with PD had more atrophy in the hippocampus and the prefrontal cortex compared with controls. These differences were seen in both hemispheres. Table 1 shows the mean atrophy scores.

To test whether hippocampal atrophy was related to performance in tests related to memory, we calculated the correlation between hippocampal atrophy and the performance in Word-List Memory, Word-List Recall, Word-List Savings, Word-List Recognition, Praxis Recall, Praxis Savings, DEL, VEM, and VIM. Similar correlations were calculated between prefrontal cortex atrophy and verbal fluency, attention/concentration, and vigilance, functions thought to be mainly under frontal control. We found a significant negative correlation between left hippocampal atrophy and VEM ($r = -0.56$, $p = 0.01$). A similar, although borderline, result was seen between left hippocampal atrophy and DEL ($r = -0.47$, $p = 0.05$). In the right hippocampus, no significant correlations were seen between neuropsychological tests and atrophy. A clear positive correlation was found in both hemispheres between prefrontal cortical atrophy and the increased reaction time in the test measuring vigilance (right: $r = 0.49$, $p = 0.02$; left: $r = 0.51$, $p = 0.02$). No other significant correlations were seen in the prefrontal cortex. Table 1 shows the mean MMSE results. Even though the patients had significantly lower MMSE scores, none had a value that would indicate dementia, and the results of a comprehensive neuropsychological test showed that none of the patients was demented. In addition, none of the patients with PD met the clinical criteria for dementia defined by the Diagnostic and Statistical Manual of Mental Disorders. The MMSE scores of the controls and the patients were not associated with the atrophy scores probably because of the narrow range values in both groups.

DISCUSSION

Our study indicates that non-demented patients at the early stage of PD already have atrophy in the hippocampus and the prefrontal cortex. Our study also suggests that left hippocampal atrophy is related to impaired memory and prefrontal cortex atrophy is associated with the prolonged reaction time in tests measuring vigilance.

Our study is in agreement with previous studies that showed patients with PD to have atrophy in the hippocampus[6 7] and medial temporal lobe structures,[12] when compared with controls. However, we found similar results in the prefrontal cortex also, although the difference was smaller than in the hippocampus. In addition, we found these differences in patients with an average disease duration of 1.7 years, whereas in the previous studies the patients had had PD for a considerably longer time.[6 7 12]

Previous studies have indicated that brain atrophy in PD is related to cognitive impairment. This has been shown in medicated patients with PD using volumetric MRI between global brain volume loss and global measures of cognitive decline,[4] between hippocampal atrophy and impaired memory,[6] and between hippocampal atrophy and impaired recognition memory and MMSE.[7] The association between brain atrophy and cognitive impairment is further supported by a previous study[5] in which the hippocampal volumes of patients with Alzheimer's disease, vascular dementia, PD with dementia, and PD without cognitive impairment were compared. It was found that the cognitively unimpaired patients with PD had atrophy when compared with controls, but to a lesser extent than patients with PD who also had dementia. Our study supports the previous studies and shows similar results in a larger PD patient sample with a significantly shorter mean disease duration (5.1 years[7] and 5.4 years,[5] our current study 1.7 years) and without antiparkinsonian medication.

We found an interesting relation between the prolonged reaction time in a test measuring vigilance (sustained attention) and prefrontal atrophy. Attention is considered to be part of the prefrontal executive functions and, in particular, the dorsolateral prefrontal cortex is more active in sustained attention.[13 14] There is little information about the relation between attention and frontal atrophy in PD, but an earlier study showed that right superior frontal atrophy predicted a poor performance in tests requiring attention in multiples sclerosis.[15] We found the correlation in PD in both

hemispheres, but with a more accurate atrophy evaluating method a lateralisation might be seen between prefrontal cortex atrophy and sustained attention.

Wahlund and Scheltens have compared visual rating to volumetry. Visual evaluation of brain MRI scans was shown to be as useful as volumetric measurement in evaluating hippocampal atrophy.[10 16] A similar technique was used in our present study to evaluate atrophy of the prefrontal cortex. Visual evaluation of the frontal lobes has been shown to have good inter-rater reliability.[11]

In our study, the patient group consisted mainly of men, whereas the controls were predominantly women. However, this difference was not significant. It is possible that the differences in the sex distribution in patients and controls could affect the degree of atrophy as a result of the larger intracranial volumes and possibly larger hippocampus seen in men.[7] However, even with the current study groups the difference remained significant and the relative predominance of men in the PD group would, if anything, dilute the differences seen.

In conclusion, our study indicates that non-medicated and non-demented patients at the early stage of PD already have atrophy in the prefrontal cortex and in the hippocampus, as compared with controls. The prefrontal cortical atrophy seems to be related to the prolonged reaction time in tests measuring vigilance and the hippocampal atrophy to impaired memory.

ACKNOWLEDGEMENTS

This study was supported by the clinical grants (EVO) of Turku University Hospital, the Research Foundation of Orion Corporation, the Finnish Parkinson Foundation, the Emil Aaltonen Foundation, the Finnish Neurology Foundation, and the Turku Finnish University Society.

Authors' affiliations

A Brück, V Kaasinen, J O Rinne, Turku PET Centre, University of Turku, POB 52, FIN-20521, Turku, Finland
T Kurki, Department of Radiology, University of Turku
T Vahlberg, Department of Biostatistics, University of Turku
V Kaasinen, Department of Neurology, University of Turku

Competing interest: none declared

Correspondence to: Dr J O Rinne, Turku PET Centre, University of Turku, PO Box 52, FIN-20521 Turku, Finland; juha.rinne@pet.tyks.fi

Received 28 October 2003
In revised form 19 December 2003
Accepted 21 December 2003

REFERENCES

1 **Dubois B**, Pillon B. Cognitive deficits in Parkinson's disease. *J Neurol* 1997;**244**:2–8.
2 **Pillon B**, Deweer B, Vidailhet M, *et al*. Memory for spatial location in Parkinson's disease. *Neurology* 1997;**48**:4039.
3 **Owen AM**, Doyon J, Dagher A, *et al*. Abnormal basal ganglia outflow in Parkinson's disease identified with PET—implications for higher cortical functions. *Brain* 1998;**121**:949–65.
4 **Hu MT**, White SJ, Chaudhuri KR, *et al*. Correlating rates of cerebral atrophy in Parkinson's disease with measures of cognitive decline. *J Neural Transm* 2001;**108**:571–80.
5 **Laakso MP**, Partanen K, Riekkinen P, *et al*. Hippocampal volumes in Alzheimer's disease, Parkinson's disease with and without dementia, and in vascular dementia: an MRI study. *Neurology* 1996;**46**:678–81.
6 **Riekkinen P Jr**, Kejonen K, Laakso MP, *et al*. Hippocampal atrophy is related to impaired memory, but not frontal functions in non-demented Parkinson's disease patients. *Neuroreport* 1998;**9**:1507–11.
7 **Camicioli R**, Moore MM, Kinney A, *et al*. Parkinson's disease is associated with hippocampal atrophy. *Mov Disord* 2003;**18**:784–90.
8 **Hughes AJ**, Daniel SE, Blankson S, *et al*. A clinicopathological study of 100 cases of Parkinsons-disease. *Arch Neurol* 1993;**50**:140–8.
9 **Scheltens P**, Leys D, Barkhof F, *et al*. Atrophy of medial temporal lobes on MRI in ''probable'' Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. *J Neurol Neurosurg Psychiatry* 1992;**55**:967–72.
10 **Wahlund LO**, Julin P, Johansson SE, *et al*. Visual rating and volumetry of the medial temporal lobe on magnetic resonance imaging in dementia: a comparative study. *J Neurol Neurosurg Psychiatry* 2000;**69**:630–5.
11 **Victoroff J**, Mack WJ, Grafton ST, *et al*. A method to improve interrater reliability of visual inspection of brain MRI scans in dementia. *Neurology* 1994;**44**:2267–76.
12 **Cordato NJ**, Halliday GM, Harding AJ, *et al*. Regional brain atrophy in progressive supranuclear palsy and Lewy body disease. *Ann Neurol* 2000;**47**:718–28.
13 **Faw B**. Pre-frontal executive committee for perception, working memory, attention, long-term memory, motor control, and thinking: a tutorial review. *Conscious Cogn* 2003;**12**:83–139.
14 **Cabeza R**, Nyberg L. Imaging cognition II: an empirical review of 275 PET and fMRI studies. *J Cogn Neurosci* 2000;**12**:1–47.
15 **Benedict RHB**, Bakshi R, Simon JH, *et al*. Frontal cortex atrophy predicts cognitive impairment in multiple sclerosis. *J Neuropsychiatry Clin Neurosci* 2002;**14**:44–51.
16 **Scheltens P**, Launer LJ, Barkhof F, *et al*. Visual assessment of medial temporal lobe atrophy on magnetic resonance imaging: interobserver reliability. *J Neurol* 1995;**242**:557–60.