Cognitive Impairment and the Brain Dopaminergic System in Parkinson Disease

[18F]Fluorodopa Positron Emission Tomographic Study

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Objective: To investigate the role of the brain dopaminergic system in cognitive impairment in patients with Parkinson disease (PD).

Design: We studied 28 patients with PD and 16 age-matched healthy control subjects using [18F]fluorodopa (fluorodopa F 18) positron emission tomography. Patients with PD showed a variable degree of cognitive impairment, which was assessed using the Mini-Mental State Examination and detailed neuropsychologic assessment, including tests sensitive for frontal lobe function.

Results: [18F]Fluorodopa uptake was reduced in the putamen (to 36% of the control mean; \( P < .001 \)), the caudate nucleus (to 61% of the control mean; \( P < .001 \)), and the frontal cortex (to 45% of the control mean; \( P < .001 \)) in patients with PD compared with controls. There was no significant association between the degree of overall cognitive impairment of patients and [18F]fluorodopa uptake values. The influx constant \( (K_{in}) \) in the caudate nucleus had a negative association with performance in the attention-demanding Stroop interference task, especially with the interference time. The \( K_{in} \) in the frontal cortex had a positive correlation with performance in the digit span (backwards), verbal fluency, and verbal immediate recall tests. Thus, the better the patient performed in tasks demanding immediate and working memory and executive strategies, the better the [18F]fluorodopa uptake in the frontal cortex. In the putamen, no significant correlation was seen between the \( K_{in} \) value and any of the cognitive tests. The severity of the motor symptoms of PD and [18F]fluorodopa uptake showed a negative correlation in the putamen \( (r = -0.38; P = .04) \), and in the caudate nucleus a similar trend was seen \( (r = -0.36; P = .06) \).

Conclusions: Reduced [18F]fluorodopa uptake in PD in the caudate nucleus (and frontal cortex) is related to impairment in neuropsychologic tests measuring verbal fluency, working memory, and attentional functioning reflecting frontal lobe function. This indicates that dysfunction of the dopamine system has an impact on the cognitive impairment of patients with PD. However, our results do not exclude the possibility of more generalized cognitive impairment in PD, the pathophysiology of which is probably different and more generalized.
SUBJECTS AND METHODS

PATIENTS AND CONTROLS

The study population consisted of 28 patients (17 women and 11 men) with idiopathic PD. Patients were diagnosed and regularly followed up at the Department of Neurology, University of Turku, Turku, Finland. All patients had a positive response to levodopa therapy. Mean patient age at the time of PET scanning was 64.1 years (range, 50.0-74.0 years). The mean duration of disease was 14.5 years (range, 5.0-29.0 years). The severity of the disease according to the modified Hoehn and Yahr scale was 1.5 to 4.0 (mean, 2.7). The clinical characteristics of the patients are shown in Table 1. All patients were receiving levodopa. In addition, 14 patients were treated with a dopamine agonist, 9 of whom were also receiving selegiline hydrochloride. None of the patients were taking anticholinergic drugs at the time of neuropsychologic testing or the PET study.

Control subjects (8 women and 8 men; age, mean [SD], 62.4 [6.6] years) were healthy volunteers without any history or signs of neurologic or psychiatric disease. There was no significant difference in demographic characteristics (sex distribution and age) between patients with PD and controls. To rule out any structural lesions, all subjects (patients and controls) underwent brain computed tomography (CT), magnetic resonance imaging (MRI), or both. All the scans were visually inspected and interpreted by an experienced neuroradiologist. All controls had normal findings, and 5 patients showed mild cortical atrophy including the frontal lobes.

The study was approved by the joint ethical committee of University of Turku and University of Turku Hospital. All patients gave written informed consent.

METHODS

Neuropsychologic Assessment

Overall cognitive performance was evaluated using the Mini-Mental State Examination and the Mild Deterioration Battery (MDB) of verbal, visuomotor, and memory tests. The MDB was first used to determine the severity grades of cognitive impairment by comparing values obtained from healthy age-matched controls. If the patient scored below −1.5 SD compared with the control group, he or she received 1 deterioration point; if below −2 SD, then 2 points; and if below −3 SD, then 3 points. Thus, the maximum deterioration score was 24. In addition, in the tasks of object memory and PWA, delayed recall after 1 hour was assessed to evaluate long-term memory function.

More specific tests for frontal lobe function were conducted. First, 2 tasks on verbal fluency demanding executive strategies were studied. On the phonological fluency task, patients were asked to generate within 60 seconds as many words as possible beginning with the letter s. On the semantic fluency task, they were asked to name as many animals as possible within 60 seconds. Second, attentional functioning was measured using Stroop tasks with 4 colors. On the control task, patients were instructed to name the color of the ink of 100 rectangles as quickly as possible. On the interference task, patients named the color of the ink of 100 written words in which the color and the meaning were contradictory (eg, the word blue printed in red). This task requires continuous suppression of automatic processing of word meaning. A practice round preceded the interference task. The color naming times on the 2 tasks and the difference between them (interference time) served as variables in the Stroop test, which was performed by 18 patients.

The Beck Depression Inventory was also administered to all patients.

Positron Emission Tomography

[18F]Fluorodopa investigation was performed according to a protocol described previously by Ruottinen et al. Positron emission tomographic investigations were performed using a scanner (Siemens/CTI 931/12/8; CTI, Knoxville, Tenn). This camera provides 15 transaxial planes, with an observed in-plane resolution of 8 mm after reconstruction. Patients were lying in the tomograph and positioned by an individual head holder with 3-dimensional laser beam alignment according to the orbitomeatal plane.

The [18F]fluorodopa synthesis was carried out according to the method of Namavari et al and Bergman et al. At the end of synthesis, the specific radioactivity was at least 44.4 MBq/µmol. The radiochemical purity exceeded 98% in every case. On average, a mean (SD) of 127.3 (28.9) MBq of [18F]fluorodopa was injected intravenously.

A dynamic study with 37 time frames and a total duration of 90 minutes was performed. Regions of interest were drawn on the head of the caudate nucleus, putamen, medial frontal cortex, and lateral occipital cortex on 2 consecutive planes on integrated (20-90 minutes) PET images. The regions of interest were identified by visual inspection with the help of a neuroanatomic atlas and CT or MRI. The radioactivity concentrations were calculated for each region of interest, and the values of the corresponding anatomical structures on the 2 consecutive planes were averaged. The influx constant ($K_{\text{in}}$) was calculated with a multiple time graphical analysis approach, modified using a nonspecific tissue (occipital cortex) rather than plasma input function, with a procedure previously described. The $K_{\text{in}}$ reflects mainly decarboxylation of [18F]fluorodopa to [18F]fluorodopamine and the function of presynaptic dopaminergic terminals. Before statistical analysis, the $K_{\text{in}}$ values of the left and right structures were averaged.

Continued on next page
tamen and caudate nucleus. The putamen might be more involved with motor behavior, whereas the caudate nucleus also participates in behavioral functions.13

The main biochemical consequence of the progressive loss of nigrostriatal dopamine neurons in PD is a deficiency of dopamine in the striatum. When the dysfunction of the nigrostriatal dopamine system becomes more severe, the motor disability worsens.14-16 Brain dopamine systems other than the nigrostriatal projections, such as those projecting directly to the cortical areas, are also affected in PD, as is indicated by a widespread reduction in dopamine content.17 Patients with PD were impaired after withdrawal from levodopa therapy, especially in cognitive tests sensitive to frontal lobe function,5,18,19 suggesting that dopamine is associated with frontal cognitive functions in PD. Some investigators,20 however, have found levodopa therapy to be ineffective for cognitive symptoms. On the other hand, performance in tests measuring long-term memory, primarily reflecting medial temporal lobe functions, has been reported to improve in PD with dopaminergic therapy (for a review see Yanagisawa20). Therefore, the dopamine system in different brain areas seems to be involved in many cognitive functions in PD, especially in those thought to be related to the function of the frontal lobes.

The aim of this study was to investigate in vivo, using positron emission tomography (PET), whether the brain dopamine system is involved in cognitive functions in patients with PD. Our hypothesis was that there is an association between reduced [18F]fluorodopa (fluorodopa F 18) uptake and defects in performance on cognitive tests sensitive to frontal lobe functions.

RESULTS

The mean (SD) mini-mental state examination score of patients with PD was 26.0 (3.3) points (range, 18.0-30.0 points), and the mean (SD) MDB score was 6.3 (6.2) (range, 0-20.0). Six patients fulfilled clinical criteria (Diagnostical and Statistical Manual of Mental Disorders, Third Edition*) for dementia, whereas 10 had only mild cognitive impairment. The remainder of the patients with PD (n = 12) were cognitively preserved.

Mean [18F]fluorodopa uptake values are presented in Table 2. There was a significant reduction in Kᵢocc values in the putamen (to 36% of the control mean; P<.001) and the caudate nucleus (to 61% of the control mean; P<.001) in patients with PD compared with controls. In the frontal cortex, Kᵢocc values in patients with PD were reduced to 45% of the control mean (P<.001).

There was no significant association between the degree of overall cognitive impairment (Mini-Mental State Examination or MDB score) of the patients and the [18F]fluorodopa uptake values. However, there was a trend toward reduced caudate Kᵢocc values in patients with more severe overall cognitive impairment (MDB score vs Kᵢocc; r = −0.35; P = .07). In addition, prolonged reaction time in the interference task (r = −0.51; P = .03) and prolonged interference time (r = −0.50; P = .03) in the attention-demanding Stroop test were related to reduced [18F]fluorodopa uptake in the caudate nucleus. Similar association also was seen in the frontal cortex (Table 3). Moreover, there was a positive correlation between performance in the verbal fluency task (phonological fluency: r = 0.44; P = .04; semantic fluency: r = 0.44; P = .04) and [18F]fluorodopa uptake in the frontal cortex. Performance in the verbal test of 30 PWAs for immediate recall was also better in patients with higher frontal [18F]fluorodopa uptake (r = 0.39; P = .04). In contrast, performance on the Benton Revised Visual Retention Test and the delayed recall tasks of 30 PWAs and 20 objects did not have a significant correlation with [18F]fluorodopa uptake in the caudate nucleus or the frontal cortex.

Results of the regression analysis for correlations between Kᵢocc values in different brain areas and results of cognitive tests after correcting for the effect of duration and severity of disease are shown in Table 3. In the Stroop test, there was a negative association between Kᵢocc in the caudate and the Stroop interference test (r = −0.44; P = .044; Table 4).

Table 1. Clinical Characteristics of Patients With Parkinson Disease and Controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Parkinson Disease Group (n = 28)</th>
<th>Control Group (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, F/M</td>
<td>17/11</td>
<td>8/8</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>64.1 (6.9)</td>
<td>62.4 (6.6)</td>
</tr>
<tr>
<td>Disease duration, mean (SD), y</td>
<td>14.5 (7.3)</td>
<td></td>
</tr>
<tr>
<td>Modified Hoehn and Yahr stage*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1.5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>3.0</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>4.0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>5.0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*According to Fahn et al.21

Table 2. [18F]Fluorodopa Uptake Values in 28 Patients With Parkinson Disease and 16 Controls

<table>
<thead>
<tr>
<th>Group</th>
<th>Putamen</th>
<th>Caudate Nucleus</th>
<th>Frontal Cortex</th>
</tr>
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<tbody>
<tr>
<td>Parkinson disease</td>
<td>4.20 (1.73)†</td>
<td>7.45 (2.42)†</td>
<td>1.10 (0.65)†</td>
</tr>
<tr>
<td>Control</td>
<td>11.74 (0.66)</td>
<td>12.23 (0.89)</td>
<td>2.42 (0.85)</td>
</tr>
</tbody>
</table>

*Kᵢocc indicates influx constant. †P<.001.
in our study, the regions of interest were not placed directly on PET images. In the frontal cortex, the signal-to-noise ratio of [18F]fluorodopa uptake is clearly lower than that in the striatum. Thus, there is a certain degree of uncertainty in the determination of [18F]fluorodopa uptake in the frontal lobes. In addition, possible atrophy of the frontal lobes might be related to cognitive impairment of the patients. However, only 6 of our patients ful-

Table 3. Results of Multiple Regression Analysis of [18F]Fluorodopa Uptake in 28 Patients With Parkinson Disease

<table>
<thead>
<tr>
<th>Brain Area</th>
<th>Test</th>
<th>Regression Coefficient</th>
<th>SE</th>
<th>t</th>
<th>P</th>
<th>R², %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudate nucleus</td>
<td>Stroop</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interference task, time</td>
<td>−14.6</td>
<td>5.77</td>
<td>−2.53</td>
<td>.02</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>Interference time</td>
<td>−7.6</td>
<td>3.67</td>
<td>−2.07</td>
<td>.06</td>
<td>26</td>
</tr>
<tr>
<td>Frontal cortex</td>
<td>Digit span (backwards)</td>
<td>0.68</td>
<td>0.28</td>
<td>2.43</td>
<td>.02</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Verbal fluency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phonological memory</td>
<td>5.16</td>
<td>2.76</td>
<td>1.87</td>
<td>.08</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Semantic memory</td>
<td>3.70</td>
<td>1.82</td>
<td>2.03</td>
<td>.06</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Paired word associates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immediate recall</td>
<td>3.61</td>
<td>1.99</td>
<td>1.81</td>
<td>.08</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Stroop</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interference task, time</td>
<td>−39.4</td>
<td>22.2</td>
<td>−1.77</td>
<td>.09</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Interference time</td>
<td>−25.8</td>
<td>17.1</td>
<td>−1.97</td>
<td>.07</td>
<td>24</td>
</tr>
</tbody>
</table>

* Only explanatory variables that were significant in this analysis are shown.

date nucleus and speed in the interference task. Furthermore, a similar trend was seen between caudate $K_{iocc}^K$ and the Stroop interference time. That is, the lower the $K_{iocc}^K$ in the caudate nucleus, the more time it took to perform the interference task compared with the control task. A similar trend between speed in the interference task and interference time in the Stroop test and $K_{iocc}^K$ was seen in the frontal cortex (Table 3). In addition, $K_{iocc}^K$ in the frontal cortex had a positive correlation with the performance in the digit span backwards, phonological fluency, and PWA immediate recall tests (Table 3). Thus, the better the patient performed on the tasks demanding immediate and working memory, the better the [18F]fluorodopa uptake in the frontal cortex. In contrast, in the putamen, no significant correlation was seen between the $K_{iocc}^K$ value and any of the cognitive test results.

The degree of depression, evaluated by the Beck Depression Inventory score, did not show any significant correlation with [18F]fluorodopa uptake in any of the brain areas examined.

As predictable, there was a significant negative correlation between the severity of the motor symptoms of PD and [18F]fluorodopa uptake in the putamen ($r = −0.38$; $P = .04$). In the caudate nucleus, a similar trend was seen ($r = −0.36$; $P = .06$).

**COMMENT**

Our results show that dysfunction of the dopamine system in the caudate, but not in the putamen, is related to certain characteristics of cognitive impairment in PD. This association was seen only in neuropsychologic tests thought to be sensitive for frontal lobe function. Another factor emphasizing the selectivity of our findings is that no correlation between neuropsychologic test results reflecting temporal lobe function and [18F]fluorodopa uptake was seen.

Holthoff et al37 studied 7 pairs of twins discordant for PD. They found a significant correlation between scores obtained in Buschke's selective reminding task and striatal [18F]fluorodopa uptake. Both the twins with PD and their clinically asymptomatic cotwins were combined in a single group, which might have, at least partially, contributed to the high correlation found between the verbal memory test score and fluorodopa uptake ($r = 0.8$ and $0.9$ for caudate and putamen, respectively). These verbal memory test scores comprised episodic memory, including delayed recall. These scores might focus on temporal rather than frontal lobe function. They found an association between performance in a selective reminding task and [18F]fluorodopa uptake in the caudate nucleus and putamen. This might be explained to some extent by the combination of patients with PD and unaffected cotwins in a single group.

In a subsequent study, Holthoff-Detto et al38 found a correlation in patients with advanced PD (Hoehn and Yahr stage 2–4) between reduction in caudate uptake of [18F]fluorodopa and impaired performance in delayed recall of the selective reminding task (a verbal task of episodic memory demanding medial temporal lobe function39). In the putamen, no such correlation was seen. Our findings are in line with those of Holthoff-Detto et al38 in that there was a correlation between some cognitive functions in PD and [18F]fluorodopa uptake. However, our findings indicate that this association is seen not only in the caudate nucleus but also in the frontal cortex. Moreover, in our study, the significant association between [18F]fluorodopa uptake and cognitive performance was seen in tests demanding working memory and attention, ie, in tests thought to be sensitive for frontal lobe functions. In contrast to previous results,37,38 no significant association was seen for test variables primarily reflecting medial temporal lobe function, such as delayed recall performance. This does not exclude the possibility that there might be a relationship between temporal lobe dopamine function and performance in episodic memory tests in PD.

In our study, the regions of interest were not placed using anatomical reference based on MRIs but were drawn directly on PET images. In the frontal cortex, the signal-to-noise ratio of [18F]fluorodopa uptake is clearly lower than that in the striatum. Thus, there is a certain degree of uncertainty in the determination of [18F]fluorodopa uptake in the frontal lobes. In addition, possible atrophy of the frontal lobes might be related to cognitive impairment of the patients. However, only 6 of our patients ful-
filled the clinical criteria for dementia, and only 1 showed mild frontal atrophy on CT or MRI indistinguishable from that seen in the rest of the patients. Altogether, only 5 patients had mild atrophy of the frontal lobes after visual inspection of the CT or MRI scans by an experienced neuroradiologist. However, our results concerning the frontal lobes should be interpreted as preliminary. Thus, in future studies on frontal cortex [18F]fluorodopa uptake, it is important to coregister the PET scans with anatomical scans.

In the striatum, [18F]fluorodopa uptake reflects the function of presynaptic dopaminergic neurons. [18F]Fluorodopa is converted by aromatic amino acid decarboxylase to [18F]fluorodopamine, which is stored in vesicles in presynaptic terminals. However, the exact proportion of [18F]fluorodopa uptake in the frontal cortex that is related to dopaminergic neurons cannot be estimated because amino acid decarboxylase is also present in the noradrenergic and serotonergic neurons, and thus cortical [18F]fluorodopa signal does not necessarily reflect solely the activity of dopaminergic cortical terminals.

A correlation does not necessarily imply a causal relationship. An association between cognitive impairment and reduced [18F]fluorodopa uptake might be due to an overall decline in dopaminergic function with increasing severity of disease. It might be accompanied also by cognitive impairment because it has been shown that in PD the probability of having cognitive impairment and the severity of this impairment increase with advanced disease, although the duration of developing cognitive impairment might vary individually. However, in our statistical analyses, we took into consideration the duration and severity of the disease and still found an association between [18F]fluorodopa uptake in the caudate nucleus and frontal cortex and cognitive performance of patients. More important, the correlations between [18F]fluorodopa uptake and cognitive impairment were seen in the caudate nucleus (and frontal cortex), but in the putamen, which is thought to be related mainly to motor function, we did not see any significant correlations between [18F]fluorodopa uptake and cognitive performance of patients. Pathological studies have shown a correlation between neuronal loss in those areas of the SN projecting to frontal areas and caudate nucleus and the degree of cognitive impairment of patients.

The neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) causes a selective dopaminergic lesion in people exposed to MPTP, cognitive symptoms similar to those seen in PD were noted, ie, deficits in visuospatial and executive functions (such as the verbal fluency task). Similar but less severe impairment was also found in asymptomatic (in the motor sense) persons with limited exposure to MPTP. In addition, patients with PD show already at an early stage of the disease difficulties in performing tasks demanding executive functions (Wisconsin Card Sorting Test) and attentional functioning (Stroop test). In this very early phase, the biochemical defect in PD is thought to be restricted to the dopaminergic system, at least in a subgroup of patients. These observations support the view that the brain dopaminergic system is involved with planning and internal control that is supposed to be under control of the frontal lobes. A key question is why dopaminergic therapy in the long run does not alleviate the cognitive impairment in PD as it does for the motor symptoms. There is evidence that especially those cognitive symptoms thought to be related to frontal lobe function improve with dopaminergic therapy, whereas temporal lobe functions, for instance, do not change. It is evident that dopaminergic defects alone cannot explain all the various cognitive symptoms and the possible development of dementia in PD. The pathophysiological basis of generalized cognitive impairment in PD might include concomitant Alzheimer pathologic features or the presence of cortical Lewy bodies and defects in neurotransmitter systems other than the dopaminergic system.

This multifactorial basis of generalized cognitive impairment and dementia in PD involves various cortical areas and their connections. Therefore, ligands reflecting general metabolic activity such as [18F]fluorodeoxyglucose understandably correlate with the degree of cognitive impairment in PD. Frankly demented patients with PD show a pattern of reduced [18F]fluorodeoxyglucose typically seen in Alzheimer disease, with posterior parietal and temporal areas being most affected. This pattern is even described in one patient with PD showing at autopsy only Lewy body pathologic evidence and no Alzheimer-type lesions.

The severity of motor symptoms of our patients with PD correlated with reduced [18F]fluorodopa uptake in the putamen, in accordance with pathological studies showing preferentially ventrolateral loss of neurons in the SN correlating with the severity of motor symptoms of patients. Similar correlations have been found with PET or single photon emission CT studies using various dopaminergic ligands. In our study in the caudate nucleus, the correlation between [18F]fluorodopa uptake and motor performance was nonsignificant, although a trend for reduced [18F]fluorodopa uptake with more severe motor symptoms was seen. One possible explanation for the modest correlation between motor symptoms and striatal [18F]fluorodopa uptake is that in our patients the motor severity, assessed by the modified Hoehn and Yahr scale, was mainly 2, 2.5, or 3; only 1 patient was in stage 1.5 and 2 patients were in stage 4.

In conclusion, our results show that reduced [18F]fluorodopa uptake in the caudate nucleus and the frontal cortex is related to impairment in neuropsychologic tests for working memory, attentional, and executive functioning probably linked to frontal lobe function. This indicates that dysfunction of the dopamine system has an impact on cognitive impairment of patients with PD. However, our results do not exclude the possibility of more generalized cognitive impairment in PD, the pathophysiologic basis of which is probably also more generalized.

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