Increased frontal $[^{18}\text{F}]$fluorodopa uptake in early Parkinson’s disease: sex differences in the prefrontal cortex

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Summary
Previous imaging studies in Parkinson’s disease have focused mainly on the striatum, a region with very high dopaminergic activity. Using modern high-sensitivity 3D $[^{18}\text{F}]$fluorodopa (Fdopa)-PET, mesocortical monoamine projections can be studied. To study the frontal monoaminergic system in unmedicated early Parkinson’s disease patients (10 women, 10 men) and 16 healthy subjects (nine women, seven men) with 3D Fdopa-PET, using standard region-of-interest-based analysis with MRI co-registration. Women with Parkinson’s disease had 87% higher Fdopa uptake in the right dorsolateral prefrontal cortex (area 46) compared with men with Parkinson’s disease, whereas there was no sex difference in the control group (sex $\times$ disease interaction, $P = 0.03$). The uptake in the right dorsolateral prefrontal cortex was 82% higher in men with Parkinson’s disease and 219% higher in women with Parkinson’s disease compared with control groups (effect of disease, $P < 0.0001$). Also in the left dorsolateral prefrontal cortex and in the medial frontal cortex, early Parkinson’s disease patients had significantly (18–94%) higher Fdopa uptake compared with healthy controls. In the putamen, both men and women with Parkinson’s disease had a significantly lower (27–46%) uptake compared with healthy controls. These results indicate that frontal monoaminergic activity is increased and that there is a sex difference in the prefrontal monoaminergic system in early Parkinson’s disease. The reported sex difference may be linked to clinical sex differences in the symptoms and treatment response in Parkinson’s disease.

Keywords: Parkinson’s disease; sex; frontal; $[^{18}\text{F}]$fluorodopa

Abbreviations: ROI = region-of-interest; Fdopa = 6-$[^{18}\text{F}]$fluoro-L-dopa; SPM = statistical parametric mapping; UPDRS = Unified Parkinson’s Disease Rating Scale

Introduction
In Parkinson’s disease, the degeneration of the mesostriatal pathway leads to progressive loss of presynaptic dopaminergic nerve terminals in the striatum. The loss of striatal dopaminergic activity in Parkinson’s disease can be quantified in vivo using PET with 6-$[^{18}\text{F}]$fluoro-L-dopa (Fdopa) as radioligand (Nahmias et al., 1985; Firnau et al., 1986). The decline in Fdopa uptake is pronounced in the putamen contralateral to the clinically more affected side in Parkinson’s disease (Nahmias et al., 1985) and the uptake decreases with increasing motor disability (Leenders et al., 1986a, b; Brooks et al., 1990). Striatal Fdopa uptake seems to reflect, among other things, the number of functioning nerve terminals in the striatum (Snow et al., 1993).

The relatively low sensitivity and spatial resolution of early PET scanners focused the main interest in dopaminergic PET studies on the striatum, a region with very high dopaminergic activity. Recently, Rakshi and colleagues, using modern 3D Fdopa-PET and statistical parametric mapping (SPM), reported that extrastriatal changes in the monoaminergic function can also be localized in Parkinson’s disease patients (Rakshi et al., 1999). In a sample of seven hemiparkinsonian early Parkinson’s disease patients, they made an unexpected finding of a possible compensatory 32–36% increase in Fdopa uptake in the anterior cingulate gyrus of the medial frontal cortex. The significance of the finding is not clear, but because five of the seven patients had been medicated with levodopa, a medication effect in early Parkinson’s disease cannot be excluded.

To find out if the paradoxical increase in frontal Fdopa uptake in early Parkinson’s disease is drug-induced or disease-
related, we studied 20 drug-naive early Parkinson’s disease patients using standard region-of-interest (ROI)-based analysis and 3D-mode PET with MRI co-registration. Because Parkinson’s disease (Kuopio et al., 1999) and many other disorders (Brown and Gershon, 1993; Di Paolo, 1994; Epperson et al., 1999) with a known or proposed association with dopaminergic neurotransmission exhibit sex differences at the clinical level, we studied men and women separately.

Subjects and methods

Subjects
Ten female patients with early Parkinson’s disease, 10 male patients with early Parkinson’s disease, nine healthy female subjects and seven healthy male subjects were studied. The severity of Parkinson’s disease was assessed according to the motor part of the Unified Parkinson’s Disease Rating Scale (UPDRS) (Fahn et al., 1987). There were no significant differences in the severity measured with UPDRS between men and women with Parkinson’s disease (Table 1). Five of the women with Parkinson’s disease and two of the men with Parkinson’s disease had predominantly left-sided symptoms. The rest had predominantly right-sided symptoms. Three of the 32 subjects were left-handed (two female controls, one female Parkinson’s disease patient) and one subject was ambidextrous (male control). None of the Parkinson’s disease patients had received any anti-parkinsonian medication. All female participants were over the age of normal menopause except one control woman (age 50 years) and one woman with Parkinson’s disease (age 47 years). None of the subjects had major depression. However, because no quantitative measurements of the affective state were carried out, a mild dysthymic state cannot be ruled out. The main clinical characteristics of the subjects are shown in Table 1. All participants gave their informed consent after the procedures had been fully explained according to the Declaration of Helsinki. The joint Ethical Committee of the University of Turku and Turku University Central Hospital approved the study.

PET imaging
Electrophilic [18F]F2 was produced according to Bergman and Solin (Bergman and Solin, 1997). Fdopa was synthesized according to the method of Namavari and colleagues (Namavari et al., 1992) and Bergman and colleagues (Bergman et al., 1994). The radiochemical purity exceeded 98% in every case. For premedication, to block peripheral decarboxylation of Fdopa, all subjects received carbipoda. Dynamic 90-min PET scans were performed with a GE Advance PET Scanner (General Electric Medical Systems, Milwaukee, Wis., USA) in the 3D scanning mode (septa retracted). The 3D performance of the scanner has been described elsewhere (Lewellen et al., 1996). The subjects were positioned in the scanner with 3D laser alignment with reference to the orbitomeatal line. Before scanning, a cannula was placed in an antecubital vein for radioligand injection. A sterile solution containing on average 168 MBq (SD = 24 MBq) of Fdopa was injected intravenously as a bolus.

Data analysis
The ROI analysis was carried out by delineating the medial frontal cortex [including the anterior cingulate gyrus (Brodmann areas 24 and 32)], mid-dorsolateral prefrontal cortex (area 46), caudate nucleus, putamen, ventral striatum and occipital cortex in each hemisphere as separate ROIs. To exclude structural lesions and for anatomical reference, each individual underwent a brain MRI scan (Magnetom 1.5 T; Siemens, Erlangen, Germany). PET and MRI planes were realigned with a surface-fit computer program (Pelizzari et al., 1989) so that the planes corresponded in the axial and transaxial positions. After realignment, ROIs were drawn on the MRI and transferred to the corresponding PET images. Fdopa influx rate constants (Kiocc) were calculated with a multiple time graphical analysis method (Patlak and Blasberg, 1985), modified to use a non-specific tissue (occipital cortex) rather than the plasma input function, with a procedure described previously (Brooks et al., 1990; Burn et al., 1992; Ruottinen et al., 1997). The visual examination of the Patlak plots indicated that the Patlak method could also be used for the extrastriatal regions.

The statistical computations were performed with SAS System for Windows 6.10 (SAS, Cary, NC, USA). The differences between age, UPDRS and Fdopa Kiocc were analysed by two-way analysis of variance with respect to sex differences. Differences in the average level of corresponding measurements on opposite hemispheres were tested with the matched pairs t test. The associations of striatal Fdopa Kiocc with extrastriatal Fdopa Kiocc and of UPDRS scores with Fdopa Kiocc were studied by linear regression analysis and with Pearson’s correlation coefficient. P values less than 0.05 were interpreted as statistically significant.

Results
Women with Parkinson’s disease had 87% higher Fdopa values in the right dorsolateral prefrontal cortex (area 46) compared with men with Parkinson’s disease, while there was no sex difference in the control group (sex × disease interaction, P = 0.03) (Table 1). The values in the right dorsolateral prefrontal cortex were higher in both men with Parkinson’s disease (82% higher) and women with Parkinson’s disease (219% higher) than in the control groups (Fig. 1 and Table 1). Also in the left dorsolateral prefrontal cortex and in the medial frontal cortex, early Parkinson’s disease patients had 18–94% higher Fdopa uptake compared with healthy controls (Table 1). In the contra- and ipsilateral putamen and in the contralateral caudate, both men and women with Parkinson’s disease had 27–46% lower Fdopa Kiocc values compared with healthy controls (Table 1).
In the Parkinson’s disease group, the Fdopa $K_i^{occ}$ values in the striatal regions contralateral to the predominant symptoms of Parkinson’s disease were lower compared with the corresponding ipsilateral regions (17% lower in the contralateral putamen, $P = 0.0007$; 8% lower in the contralateral caudate, $P = 0.004$; 6% lower in the contralateral ventral striatum, $P = 0.002$) (Table 1). In the extrastriatal regions, no significant differences were seen between the contra- and ipsilateral hemispheres. Fdopa $K_i^{occ}$ in the contra- or ipsilateral putamen did not correlate with cortical Fdopa $K_i^{occ}$ in the Parkinson’s disease group (Fdopa $K_i^{occ}$ in the contralateral putamen versus Fdopa $K_i^{occ}$ in the right dorsolateral prefrontal cortex, $r = -0.09$, $P = 0.72$). In the control group, the mean putaminal Fdopa $K_i^{occ}$ did not correlate with cortical Fdopa $K_i^{occ}$ (Fdopa $K_i^{occ}$ in the putamen versus Fdopa $K_i^{occ}$ in the right dorsolateral prefrontal cortex, $r = -0.02$, $P = 0.95$). Striatal Fdopa $K_i^{occ}$ in the contra- or ipsilateral regions (17% lower in the contralateral putamen, $P = 0.0007$; 8% lower in the contralateral caudate, $P = 0.004$; 6% lower in the contralateral ventral striatum, $P = 0.002$) (Table 1). In the extrastriatal prefrontal cortex, $r = -0.02$, $P = 0.95$). Striatal Fdopa $K_i^{occ}$ in the contra- or ipsilateral hemispheres did not correlate significantly with unilateral motor UPDRS scores (contralateral putamen Fdopa $K_i^{occ}$ versus motor UPDRS on the side of the predominant symptoms, $r = 0.04$, $P = 0.88$). Healthy women had higher Fdopa $K_i^{occ}$ values in the left dorsolateral prefrontal cortex (mean 0.71, SD 0.54) compared with the right dorsolateral prefrontal cortex (mean 0.48, SD 0.48) ($P = 0.02$). No other significant differences between left and right hemispheres were seen.

**Discussion**

This study documents an increase in Fdopa uptake in the frontal cortex in early Parkinson’s disease. The increase was significant in all frontal cortical regions studied in early Parkinson’s disease compared with healthy controls. The Fdopa uptake in the right dorsolateral prefrontal cortex was 87% higher in women with early Parkinson’s disease compared with men with early Parkinson’s disease.

**Increased frontal monoaminergic activity in Parkinson’s disease**

Using SPM analysis and 3D Fdopa-PET, Rakshi and colleagues (Rakshi et al., 1999) reported increased Fdopa uptake in the putamen contralateral to the predominant symptoms of Parkinson’s disease and in the right dorsolateral prefrontal cortex (DLPFC) (area 46) in men and women with Parkinson’s disease. The values are percentages of the control mean (dashed line). Contralateral putaminal values in the Parkinson’s disease groups were compared with mean values for the left and right putamen in the control groups.

**Table 1 Main clinical characteristics and Fdopa uptake ($K_i \times 10^{-3}$) in men and women in the early Parkinson’s disease and control groups**

<table>
<thead>
<tr>
<th></th>
<th>Men: mean (SD)</th>
<th>Women: mean (SD)</th>
<th>Sex × diagnosis: $P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early PD</td>
<td>Controls</td>
<td>Early PD</td>
</tr>
<tr>
<td>$n$</td>
<td>10</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Age</td>
<td>59.5 (7.0)</td>
<td>61.7 (7.5)</td>
<td>61.3 (8.0)</td>
</tr>
<tr>
<td>UPDRS score</td>
<td>32.4 (5.0)</td>
<td>–</td>
<td>30.8 (4.8)</td>
</tr>
<tr>
<td>UPDRS range</td>
<td>25–39</td>
<td>–</td>
<td>21–36</td>
</tr>
<tr>
<td>Basal ganglia*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caudate contralateral</td>
<td>9.57 (1.64)</td>
<td>10.6 (1.0)</td>
<td>9.17 (0.95)</td>
</tr>
<tr>
<td>Caudate ipsilateral</td>
<td>10.4 (1.4)</td>
<td>10.6 (1.0)</td>
<td>10.1 (1.1)</td>
</tr>
<tr>
<td>Putamen contralateral</td>
<td>6.61 (3.40)</td>
<td>10.7 (1.4)</td>
<td>6.23 (1.72)</td>
</tr>
<tr>
<td>Putamen ipsilateral</td>
<td>7.79 (2.59)</td>
<td>10.7 (1.4)</td>
<td>7.61 (1.89)</td>
</tr>
<tr>
<td>Ventral striatum contralateral</td>
<td>9.73 (2.18)</td>
<td>10.0 (2.1)</td>
<td>9.21 (1.33)</td>
</tr>
<tr>
<td>Ventral striatum ipsilateral</td>
<td>10.5 (2.1)</td>
<td>10.0 (2.1)</td>
<td>9.77 (1.73)</td>
</tr>
<tr>
<td>Frontal lobe cortical regions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial frontal cortex right</td>
<td>2.10 (0.72)</td>
<td>1.69 (0.32)</td>
<td>2.36 (0.45)</td>
</tr>
<tr>
<td>Medial frontal cortex left</td>
<td>1.84 (0.51)</td>
<td>1.56 (0.34)</td>
<td>2.38 (0.39)</td>
</tr>
<tr>
<td>Dorsolateral prefrontal cortex right</td>
<td>0.82 (0.30)</td>
<td>0.45 (0.17)</td>
<td>1.53 (0.62)</td>
</tr>
<tr>
<td>Dorsolateral prefrontal cortex left</td>
<td>1.04 (0.45)</td>
<td>0.62 (0.19)</td>
<td>1.38 (0.68)</td>
</tr>
</tbody>
</table>

*PD = Parkinson’s disease; UPDRS = motor part of the Unified Parkinson’s Disease Rating Scale. *For the basal ganglia in the control groups, means of left and right hemisphere regions are given.
uptake in the left medial frontal cortex (Brodmann areas 24 and 32) and in the dorsal midbrain in seven early Parkinson’s disease patients. In the present study, using a standard ROI-based analysis and 3D Fdopa-PET, we similarly report increased uptake in the medial frontal cortex (areas 24 and 32) and additionally in the dorsolateral prefrontal cortex in 20 Parkinson’s disease patients. It is not clear why, in the study by Rakshi and colleagues, no differences were seen in the dorsolateral prefrontal cortex. A possible reason is the relatively high variability of Fdopa $K_r^{ECC}$ in the dorsolateral prefrontal cortex compared with other cortical regions (Table 1) and the smaller number of subjects in the earlier study. Moreover, five of the seven early Parkinson’s disease patients in the earlier study had been medicated and the sex of the subjects is not reported. The main finding, however, is the same in the present study and in the study by Rakshi and colleagues: increased frontal Fdopa uptake in early Parkinson’s disease. Parkinson’s disease is neurochemically characterized by a dopamine loss in the striatum. The increased frontal Fdopa uptake is paradoxical in the sense that Parkinson’s disease is considered a hypodopaminergic syndrome.

Although the Fdopa uptake in the right dorsolateral prefrontal cortex was increased by up to 219% in early Parkinson’s disease compared with controls in the present study, it should be noted that the mean striatal Fdopa uptake in healthy individuals was over 20 times higher than in the prefrontal cortex Fdopa uptake. Thus, the largest absolute change in Fdopa uptake in early Parkinson’s disease was seen in the putamen, where the absolute decline was five times greater than the absolute increase in Fdopa uptake in the prefrontal cortex. Nevertheless, the relative increase in the prefrontal areas was robust and statistically significant and has potential functional importance. The significance of increased frontal Fdopa uptake in early Parkinson’s disease is unclear, but there are several possibilities, which were discussed earlier by Rakshi and colleagues (Rakshi et al., 1999). One possibility is a compensatory mechanism in the mesofrontal monoaminergic projections secondary to the degeneration of the mesostriatal projections. The results of the present study indicate, however, that there is no inverse relationship with frontal and striatal Fdopa uptake in early Parkinson’s disease or in healthy controls. Furthermore, the motor disability was not associated with frontal or striatal Fdopa $K_r^{ECC}$. This is not surprising because, although striatal Fdopa uptake correlates well with the motor disability in advanced Parkinson’s disease patients (Brooks et al., 1990), the correlation is often small in early Parkinson’s disease as a result of the narrow range of motor disability in the patient sample. However, in the present study both men and women with early Parkinson’s disease had lower Fdopa uptake in the putamen, caudate and ventral striatum contralateral to the predominant symptoms of the disease.

The sum of the available information indicates that the increase in frontal monoaminergic activity in Parkinson’s disease is restricted to recently diagnosed Parkinson’s disease patients and to studies using Fdopa as radioligand. We have seen no significant changes in the frontal dopaminergic $D_2/D_3$ receptors (Kaasinen et al., 2000) or in the frontal presynaptic dopamine reuptake sites (Rinne et al., 1999) using 3D PET in unmedicated early Parkinson’s disease patients. Moreover, in advanced Parkinson’s disease no significant change (Rakshi et al., 1999) or decline (Rinne et al., 2000) in the frontal Fdopa uptake has been seen. Striatal Fdopa accumulation can reflect the transport of Fdopa into nigrostriatal nerve terminals, the activity of dopa decarboxylase, the storage of 6-[18F]fluorodopamine within vesicles (Firnau et al., 1987; Hoshi et al., 1993) and/or the number of functioning nerve terminals (Snow et al., 1993). The increase in frontal Fdopa uptake in early Parkinson’s disease may most likely be a reflection of increased aromatic amino acid decarboxylase activity (Rakshi et al., 1999). Because aromatic amino acid decarboxylase is also present in serotonergic and noradrenergic neurones, cortical Fdopa uptake cannot be considered specific to the dopamine system.

**Sex difference**

In addition to the overall increase in Fdopa uptake in the frontal cortex in early Parkinson’s disease, we report a sex difference in prefrontal monoaminergic activity in early Parkinson’s disease. Dopamine neurotransmission is modulated by sex steroids (Di Paolo, 1994) and ovarian hormones may have a role maintaining the normal balance between the neurotransmitter systems in the dorsolateral prefrontal cortex (Kritzer and Kohama, 1999). There are conspicuous sex differences in disorders that have been linked to a dysfunction in the dopaminergic system (Di Paolo, 1994). In Parkinson’s disease, a recent epidemiological study revealed a substantial increase in the occurrence of Parkinson’s disease in men, whereas the prevalence among women remained stable (Kuopio et al., 1999). There are indications that clinical sex differences in Parkinson’s disease emerge as the disease progresses, men exhibiting more severe parkinsonian motor features and women experiencing more levodopa-induced dyskinesia (Lyons et al., 1998). Sex may also play a role in determining the frequency and treatment of behavioural problems in nursing home residents with Parkinson’s disease (Fernandez et al., 2000). Depression occurs in ~40% of patients with Parkinson’s disease and the female sex may be a risk factor for depression in Parkinson’s disease (Cummings, 1992). Diminished drive and motivation seem to be associated with lesions of the cingulate or dorsolateral prefrontal cortex (Fuster, 1999). Neuro-psychological, metabolic, clinical, pharmacological and anatomical studies support the involvement of frontal monoaminergic projections in patients with Parkinson’s disease and depression. Our study was carried out with early Parkinson’s disease patients with no antiparkinsonian medication or major depression. We hypothesize that the sex difference in the prefrontal cortex monoamine system in early Parkinson’s disease is linked to clinical sex differences.
in the disease and treatment complications as the disease progresses.

Conclusion
Using a standard analysis method for 3D Fdopa-PET studies, we have demonstrated an increase in the frontal cortex Fdopa uptake in unmedicated early Parkinson’s disease patients, which is pronounced in the right dorsolateral prefrontal cortex in female patients. Because unmedicated patients were studied, the increase seems to be disease-related rather than a medication effect. The significance of the increase and of the sex difference is unclear. Sex differences in the clinical picture and treatment response in Parkinson’s disease indicate, however, that underlying neurotransmitter function may be different in men and women with Parkinson’s disease. The results of the present study support the need to investigate neuropsychology and emotion in Parkinson’s disease together with 3D Fdopa PET, with the focus on the extrastriatal regions.

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