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Dopamine transporter density in young patients with schizophrenia assessed with [¹²³I]FP-CIT SPECT

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Abstract

Disturbances in the dopamine (DA) system are thought to play a major role in schizophrenia. Amphetamine-induced release of endogenous DA is shown to be enhanced in schizophrenia, as is striatal [¹⁸F]FDOPA uptake in the striatum. It is not clear if the density of DA neurons is altered in schizophrenia. By studying the DA transporter with [¹²³I]FP-CIT single photon emission computed tomography (SPECT), the density of nigrostriatal dopaminergic cells can be studied.

Using [¹²³I]FP-CIT SPECT, DA transporter density in the striatum was studied in 36 young patients with schizophrenia. Ten patients were antipsychotic (AP)-naive, 15 were treated with olanzapine, eight with risperidone and three were AP-free. A control group of 10 age-matched volunteers was included.

Striatal [¹²³I]FP-CIT binding was not significantly different between AP-naive patients (2.87), patients treated with olanzapine (2.76), patients treated with risperidone (2.76), AP-free patients (2.68) and controls (2.82) ($F=0.07$, $p=0.98$). Unexpectedly, striatal [¹²³I]FP-CIT binding in females was significantly higher than in males (3.29 and 2.70, respectively; $t=-2.56$, $p=0.014$).

Concluding, functional changes in the dopaminergic system in schizophrenia are not likely to be reflected in a change in DA transporter density. Moreover, DA transporter density does not seem to be altered by AP medication. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Antipsychotic medication; Dopamine transporter; Gender; Schizophrenia; Single photon emission computed tomography (SPECT)

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1. Introduction

A dysregulation of the dopaminergic neurotransmission system has been thought to contribute to the pathophysiology of schizophrenia (Davis et al., 1991). Pharmacological evidence shows that dopamine antagonists have beneficial effects in patients suffering from schizophrenia, whereas dopaminergic agents exacerbate symptoms (Lieberman et al., 1987).

Recent neuro-imaging studies found significant changes in the presynaptic dopamine (DA) system in schizophrenic patients. First, the endogenous DA release, following an amphetamine challenge, is increased in patients with schizophrenia (Laruelle et al., 1996a; Breier et al., 1997; Abi-Dargham et al., 1998). Second, in two [^{18}F]FDOPA positron emission tomography (PET) studies, an increased [^{18}F]FDOPA uptake in the putamen was found in schizophrenia (Reith et al., 1994; Hietala et al., 1995). In a more recent PET study, an increased [^{18}F]FDOPA uptake was confirmed. Moreover, depressive symptoms were found to correlate negatively with [^{18}F]FDOPA uptake (Hietala et al., 1999). These studies suggest a disturbed presynaptic DA neurotransmission in schizophrenia, which can be detected in the striatum.

The increased striatal [^{18}F]FDOPA uptake and increased drug-induced endogenous DA release could be explained by a higher density of DA nerve terminals and, consequently, DA transporters in the striatum. The DA transporters (or re-uptake sites) are located on nerve terminals and play a role in the re-uptake of DA from the synaptic cleft.

DA transporter density in the human brain can be assessed in vivo with single photon emission computed tomography (SPECT) imaging, using *N*- ω -fluoropropyl-2 β -carbomethoxy-3 β [4-iodophenyl]-tropane (FP-CIT), labeled with ^{123}I , as a radioligand. [^{123}I]FP-CIT SPECT is a highly reproducible technique, which is used in clinical studies to detect presynaptic degeneration of dopaminergic neurons in patients with Parkinson's disease (Booij et al., 1997, 1998).

To examine possible changes in striatal DA transporter density in schizophrenia, we compared

DA transporter density in young patients with schizophrenia with that in age-matched healthy volunteers by using [^{123}I]FP-CIT SPECT.

Antipsychotic (AP) medication is the cornerstone of therapy in patients with schizophrenia. However, the influence of AP on striatal [^{123}I]FP-CIT binding has not been elucidated in humans. Therefore, in our study, patients who had never been treated previously with AP (AP-naive) were compared with patients treated with the atypical AP olanzapine or risperidone, and with patients previously treated with AP who were now AP-free. Finally, we studied correlations between clinical symptoms of schizophrenia and DA transporter density.

2. Methods

2.1. Subjects

SPECT imaging was performed in 38 first-admitted patients at the Adolescent Clinic of the Academic Medical Center. All patients were suffering from a first or second psychotic episode and had a diagnosis of schizophrenia according to DSM-IV (American Psychiatric Association, 1994), which was confirmed during outpatient follow-up. Two patients were left out of the analysis because of a different diagnosis during follow-up (i.e. substance-induced psychotic disorder and obsessive-compulsive disorder). Therefore, 36 patients were studied, divided into four subgroups (characteristics are listed in Table 1). The first group consisted of 10 AP-naive patients. Moreover, at the time of SPECT imaging, no other medication was being taken. A second group of 15 patients was treated with 5–30 mg of olanzapine (mean 16.3 mg, S.D. 7.2). A third group of eight patients was treated with 2–6 mg of risperidone (mean 3.5 mg, S.D. 1.3). AP type and dose were stable from at least 6 weeks before SPECT imaging in both AP-treated groups. A fourth group consisted of three patients who did not take AP medication for more than 4 weeks before SPECT imaging. Six patients in the medicated group were co-medicated with SSRI antidepressant medication at the time of SPECT imaging

Table 1
Composition of groups of schizophrenic patients and controls

Groups	<i>n</i>	Age in years (S.D.)	Sex	Illness duration ^a	Subtype ^b	Medication in mg (S.D.)
AP-naive	10	22.1 (3.7)	9M, 1F	33.5 (8.5)	5 Par, 1 Dis, 3 Und, 1 Sch-aff	
Olanzapine	15	21.0 (2.5)	12M, 3F	16.5 (17.0)	6 Par, 8 Und, 1 Sch-aff	16.3 (7.2)
Risperidone	8	22.8 (4.1)	8M	18.5 (20.5)	4 Par, 2 Und, 2 Sch-aff	3.5 (1.3)
AP-free	3	19.0 (2.0)	3M	13.7 (7.0)	1 Par, 1 Und, 1 Sch-aff	
Control	10	20.3 (0.5)	7M, 3F			

^a Illness duration in months at the time of SPECT imaging (median).

^b Subtype: paranoid (Par), disorganized (Dis) and undifferentiated (Und) subtype of schizophrenia; and schizoaffective disorder (Sch-aff).

(four with paroxetine 20–30 mg, one with fluvoxamine 150 mg, one with venlafaxine 300 mg), one was co-medicated with amitriptyline 225 mg and one with lithium 1000 mg.

A group of 10 healthy volunteers, with a mean age comparable to that of the patient groups, was included in this study. Volunteers were free from any neurological or psychiatric disease and were not taking any drugs.

All patients and controls participated after informed consent. The research protocol was approved by the Medical Ethical Committee of the Academic Medical Center in Amsterdam.

2.2. SPECT procedure

For SPECT imaging, a brain-dedicated camera was used (Strichman Medical Equipment Inc., Medfield, MA, USA). This camera consists of 12 individual crystals each equipped with a focussing collimator. The transaxial resolution of this camera is 7.6 mm full-width half maximum (FWHM) of a line source in air, and the axial resolution is 13.5 mm FWHM. The energy window was set at 135–190 keV.

All subjects received potassium iodide orally to block thyroid uptake of free radioactive iodide. [¹²³I]FP-CIT (specific activity of >185 MBq/nmol; radiochemical purity of >95%) was injected intravenously at an approximate dose of 110 MBq. ¹²³I-labeling of FP-CIT was performed by Amersham Cygne (Eindhoven, The Netherlands) with the trimethylstannyl precursor of FP-CIT obtained from Research Biochemicals International (Natick, MA, USA). SPECT

acquisition was performed at 3 h p.i. (Booij et al., 1999). Images were acquired during periods of 210 s from the orbitomeatal line to the vertex with an interslice distance of 5 mm. Data acquisition took place in a 128 × 128 matrix.

Attenuation correction and reconstruction of the images were performed as described previously (Booij et al., 1997). The measured concentration of radioactivity was expressed as Strichman Medical Units (SMUs; 1 SMU = 100 Bq/ml, as specified by Strichman Medical Equipment Inc.).

2.3. Data processing

Assessment of [¹²³I]FP-CIT binding in the entire striatum, caudate nucleus, putamen and occipital cortex (non-specific binding) was performed with a recently developed fully automated three-dimensional technique. This technique has been described in detail by Habraken et al. (1999). Briefly, this method automatically places volumes of interest (VOI) over the brain areas instead of manually placing predefined two-dimensional regions of interest (ROI), as in traditional SPECT data analysis. Binding activity is compared on a voxel-by-voxel base to achieve the best fit. This automated arranging of volumes is operator-independent and repeatable. Caudate nucleus and putamen were defined as sub-regions of the striatum and occipital cortex (OCC) was used as a reference region. Specific to non-specific [¹²³I]FP-CIT binding was calculated as: [¹²³I]FP-CIT binding = (VOI – OCC)/OCC, where VOI represents the mean radioactivity (in SMU) in the VOI (striatum, caudate nucleus or putamen).

Asymmetry of striatal [^{123}I]FP-CIT binding ratios was calculated with the Asymmetry Index (AI): (right – left)/(right + left). If the index is positive, the binding ratio is higher on the right than on the left side.

2.4. Clinical measurements

Psychotic symptoms were assessed in all patients during the week of imaging by one of the investigators (J.L.) who was blind to the results of SPECT imaging. All AP-naive patients were interviewed on the day of imaging. Psychotic symptoms were rated with the structured clinical interview of the PANSS (Positive And Negative Symptoms Scale for schizophrenia; Kay et al., 1986). Depression was rated with the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979). Akathisia was assessed with the Barnes' akathisia rating scale (Barnes, 1989).

2.5. Statistics

Differences between groups were calculated with one-way ANOVA. Linear regression was performed in the total group of all subjects under study, and separately in one group with all patients, and in the group of medicated patients. Striatal [^{123}I]FP-CIT binding was used as dependent variable. Correlations between variables were measured using a two-tailed Spearman's rho (ρ). A significance level of $p < 0.05$ was used if not otherwise indicated. All statistical analyses were carried out with SPSS 9.0 for Windows.

3. Results

3.1. [^{123}I]FP-CIT SPECT imaging

Visually, striatal [^{123}I]FP-CIT binding was not different among the five groups (Figs. 1 and 2). No significant differences in specific to nonspecific [^{123}I]FP-CIT binding ratios were found between patient groups and controls (Table 2). This was true for binding ratios in the entire striatum ($F = 0.07$, $P = 0.98$), caudate nucleus ($F = 0.04$, $p = 0.99$) and putamen ($F = 0.15$, $p = 0.93$).

The Asymmetry Index was low in all groups (Table 2). No significant difference in Asymmetry Index was found between groups in the entire striatum, caudate nucleus or putamen.

The AP-free group was left out of the analysis because of the small number of subjects. However, as shown in Fig. 2, the striatal [^{123}I]FP-CIT binding ratios in this group were comparable to the binding ratios of the other groups, which was also true for binding ratios in the caudate nucleus and the putamen.

Three patients (one AP-naive, one treated with olanzapine and one with risperidone), were found to have a high striatal [^{123}I]FP-CIT binding ratio (5.42, 4.20 and 3.82, respectively). These individual ratios were more than 2 S.D. above the mean of controls. The AP-naive patient was actively psychotic (acoustic hallucinations and paranoia) and disorganized at the time of SPECT imaging, with PANSS scores of positive symptoms that were higher than in all other patients. The patient treated with olanzapine was a female and was co-medicated with fluvoxamin which may have influenced [^{123}I]FP-CIT SPECT imaging.

3.2. Symptoms and [^{123}I]FP-CIT SPECT imaging

In the AP-naive group, PANSS rates of positive and negative symptoms of schizophrenia and general psychopathology (Table 3), did not correlate with [^{123}I]FP-CIT binding ratios in the entire striatum ($\rho = 0.40$, $p = 0.26$; $\rho = 0.13$, $p = 0.71$; $\rho = 0.49$, $p = 0.16$, respectively). These PANSS rates were also not significantly correlated with [^{123}I]FP-CIT binding ratios in the caudate nucleus or putamen.

Also, these symptoms did not correlate with [^{123}I]FP-CIT binding ratios in both of medicated patient groups. In all patient groups, depression rates did not correlate with [^{123}I]FP-CIT binding ratios in all three regions.

Both duration of illness and duration of untreated psychosis were positively correlated with striatal [^{123}I]FP-CIT binding. However, this correlation was caused by outliers. Specifically, the three patients with exceptionally high striatal [^{123}I]FP-CIT binding also had longer duration of illness

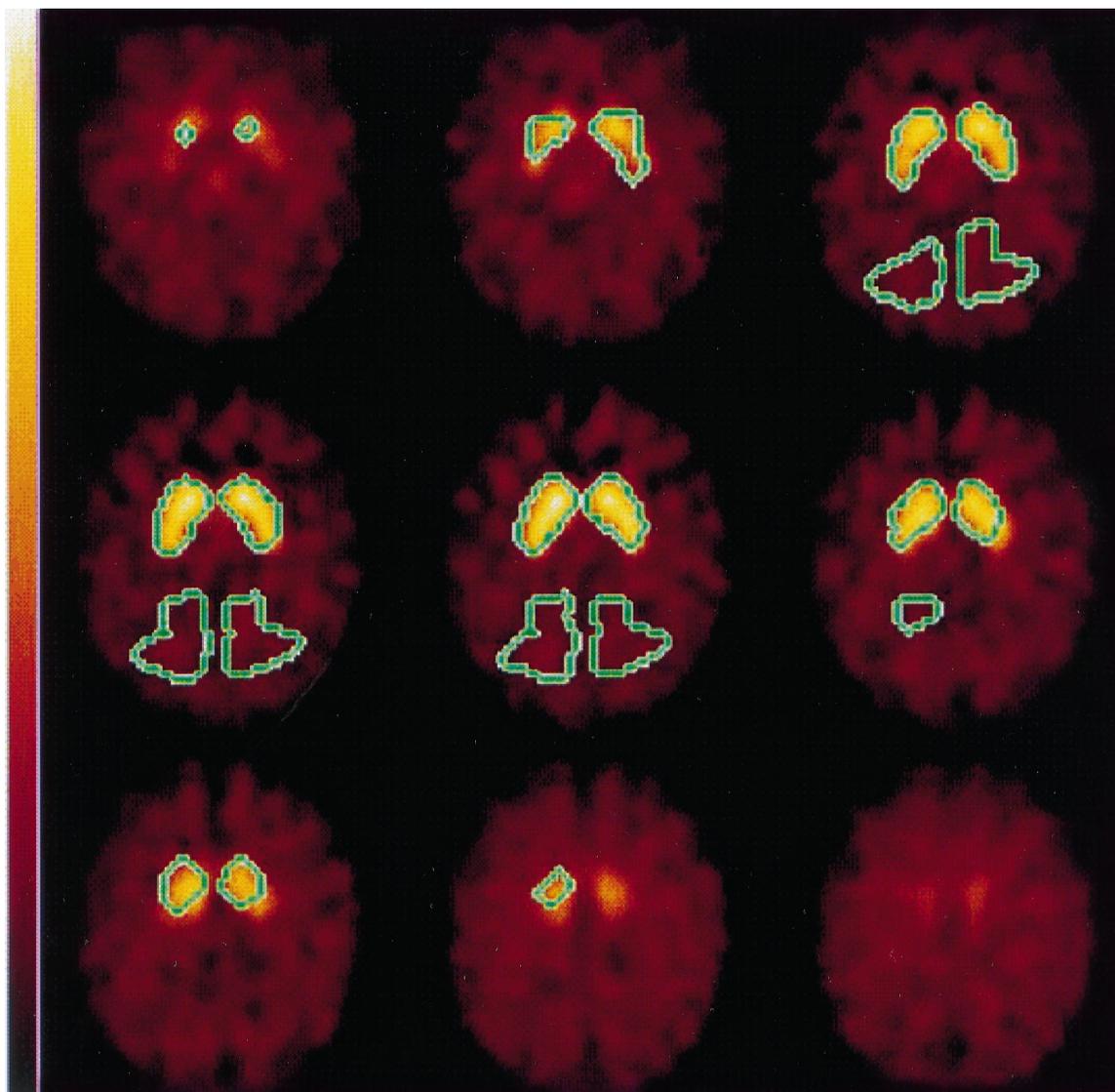


Fig. 1. [^{123}I]FP-CIT SPECT images of an antipsychotic-naive patient with schizophrenia. Transverse slices of the striatum with overlaid Volumes of Interest for striatum and occipital cortex. The level of radioactivity is color-coded from low (black) to high (white).

(60, 35 and 98 months) and duration of untreated psychosis (60, 29 and 85 months), compared with the median of all four patient groups (16 and 6.5 months for duration of illness and duration of untreated psychosis, respectively).

Age of onset of psychotic symptoms and subtype of schizophrenia were not significantly correlated with [^{123}I]FP-CIT binding ratios.

3.3. Medication and [^{123}I]FP-CIT SPECT imaging

In the group of patients with present or previous AP medication ($n=26$), linear regression showed no significant influence of duration of AP treatment and of SSRI co-medication on striatal [^{123}I]FP-CIT binding ratios. Furthermore, no correla-

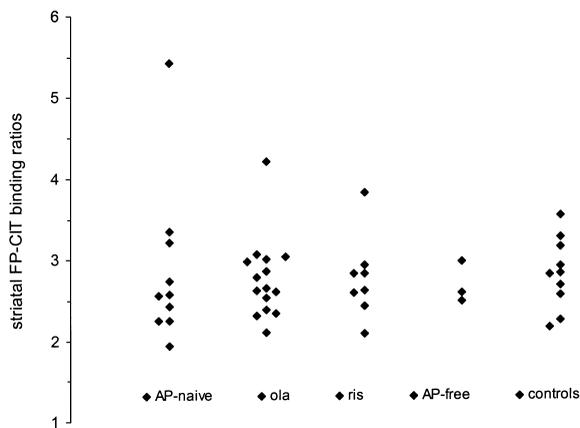


Fig. 2. Specific striatal to non-specific striatal [^{123}I]FP-CIT binding ratios (mean left and right side) in schizophrenic patients and normal controls. At the time of imaging patients were AP-naive, treated with olanzapine (ola), treated with risperidone (ris), or AP-free.

tion was found between daily dose of olanzapine or risperidone and [^{123}I]FP-CIT binding ratios ($n=15$, $\rho=-0.099$, $p=0.725$; $n=8$, $\rho=-0.210$, $p=0.618$, respectively).

Six out of 15 patients treated with olanzapine experienced questionable to moderate akathisia, as did four out of eight patients treated with risperidone. Akathisia rates were not significantly

correlated with striatal [^{123}I]FP-CIT binding in patients treated with olanzapine or risperidone.

3.4. Gender and [^{123}I]FP-CIT binding

In females, the striatal [^{123}I]FP-CIT binding ratios were significantly higher than in males, 3.29 and 2.70, respectively ($t=-2.56$, $p=0.014$). This difference was found in the three female controls compared with male controls, as well as in the four female patients compared with the male patients, though the latter only at a trend level ($p=0.07$). Moreover, in a linear regression analysis including all subjects ($n=45$), gender was the only variable with a significant effect on striatal [^{123}I]FP-CIT binding ratios ($R^2=0.341$, $\beta=-0.565$, $P<0.001$). Group, handedness and age were of no significant influence on [^{123}I]FP-CIT binding ratios. One AP-naive patient was left out of the regression analysis because the [^{123}I]FP-CIT binding ratio was more than 3 S.D. above the mean.

4. Discussion

4.1. DA transporter density in schizophrenia

In this study we found no significant difference in specific to nonspecific striatal [^{123}I]FP-CIT

Table 2
Mean [^{123}I]FP-CIT SPECT binding ratios in patients with schizophrenia and controls^a

Group	Striatum (S.D.)	Putamen (S.D.)	Caudate nucleus (S.D.)	Asymmetry Index (S.D.) ^b
AP-naive	2.87 (0.99)	2.97 (1.09)	2.81 (0.94)	-0.001 (0.018)
Olanzapine	2.76 (0.49)	2.76 (0.51)	2.76 (0.49)	-0.013 (0.014)
Risperidone	2.76 (0.50)	2.83 (0.52)	2.73 (0.50)	-0.009 (0.031)
AP-free	2.68 (0.26)	2.71 (0.30)	2.66 (0.25)	-0.016 (0.006)
Control	2.82 (0.43)	2.86 (0.45)	2.79 (0.44)	0.000 (0.017)

^a [^{123}I]FP-CIT binding ratio is determined as (Region of Interest – occipital binding)/occipital binding.

^b Asymmetry Index is (right – left)/(right + left) of the striatal binding ratios.

Table 3
Mean psychotic and depressive symptoms at [^{123}I]FP-CIT SPECT imaging (S.D.)

Group	PANSS positive	PANSS negative	PANSS general	MADRS
AP-naive	22.8 (3.8)	18.9 (6.7)	43.5 (8.1)	22.5 (9.5)
Olanzapine	11.2 (4.4)	14.7 (6.1)	27.0 (4.8)	9.3 (8.3)
Risperidone	11.7 (4.9)	14.0 (4.2)	27.7 (7.7)	10.6 (10.4)
AP-free	11.0 (2.0)	15.0 (8.9)	24.3 (7.6)	2.0 (2.0)

binding ratios between young AP-naive patients with schizophrenia, medicated patients with schizophrenia, and controls. This was also true for [^{123}I]FP-CIT binding ratios in the two subdivisions of the striatum, the caudate nucleus and the putamen. These findings, in a large group of schizophrenic patients, may indicate that there are no significant changes in striatal DA transporter density in schizophrenia.

Our findings are in line with a study by Laruelle et al. (1996b), which showed no change in striatal DA transporter density in schizophrenia assessed by [^{123}I]FP-CIT SPECT. Our findings are also in line with post-mortem studies, in which no change in DA transporter density in schizophrenia was found (Hirai et al., 1988; Joyce et al., 1988; Czudek and Reynolds, 1989; Pearce et al., 1990; Chinaglia et al., 1992; Knable et al., 1994).

In contrast with our findings, Tatsch et al. (1999) recently found a lower density of striatal DA transporters in patients with schizophrenia than in controls, assessed by [^{123}I]IPT SPECT. However, their preliminary results were obtained in a relatively small group of patients, and it is not clear whether data were analyzed with an operator-independent analysis technique. SPECT imaging with [^{123}I]FP-CIT, using an operator-independent three-dimensional analysis technique, has been shown to be a sensitive and reproducible technique to visualize and quantify the DA transporter density in vivo (Booij et al., 1998; Habraken et al., 1999). Therefore, the lack of changes we found in striatal DA transporter density in schizophrenia is a reliable observation.

Earlier studies showed a higher striatal [^{18}F]DOPA uptake in schizophrenic patients (Hietala et al., 1999). Taking into account the results of the present study, the increased [^{18}F]DOPA uptake may be explained by an increased decarboxylase activity instead of an increased number of DA terminals.

4.2. AP medication and the DA transporter

In patients treated with olanzapine or risperidone, the [^{123}I]FP-CIT binding ratios in all striatal regions measured were not significantly different from those in AP-naive patients and those in

controls. Therefore, it can be presumed that treatment with atypical AP medication does not change DA transporter density. Chronic administration of the classic AP haloperidol showed different effects on DA transporter density in two animal studies. In one study, a reduced presynaptic DA re-uptake was found (Vander Borght et al., 1995) in rats with chronic administration of antipsychotic medication, whereas no difference with controls was found in another study (Rivest et al., 1995). Chronic administration of olanzapine and risperidone induced no significant effect on striatal [^{123}I]FP-CIT binding in rats (Lavalaye et al., 2000).

Unexpectedly, we found a higher striatal [^{123}I]FP-CIT binding in women than in men. This was found both in patients and in controls. Higher DA transporter density in females than in males has been reported in animal studies (Rivest et al., 1995), but no effect of gender on DA transporter density was found in a human study (van Dyck et al., 1995). In addition, an [^{18}F]DOPA PET study performed in patients with attention deficit hyperactivity disorder (ADHD) and controls, showed higher striatal uptake ratios in women compared with men (Ernst et al., 1998). This was found both in patients and controls. The higher striatal [^{18}F]DOPA uptake may imply a higher number of dopaminergic terminals and, consequently, of DA transporters in females, which is in line with our findings.

In general, DA transporter imaging studies are performed in groups of a wide age range, mostly including subjects who are older than the subjects in this study. Therefore, gender-related differences might easily be overlooked. Nevertheless, gender differences in the DA system play an important role in schizophrenia (Szymanski et al., 1995). This is closely related to hormonal influence, which is of influence in schizophrenia, and which has been extensively discussed (Seeman, 1997). However, it has to be kept in mind that the number of females in this study was limited. Therefore, it would be of interest to confirm our finding of a higher DA transporter density in women in a larger study, or by using a meta-analytical approach.

The small age range of the subjects in the present study is an important feature, since aging

is associated with a clear loss of DA transporters, according to several PET and SPECT studies (van Dyck et al., 1995; Volkow et al., 1998). Therefore, a wide age range is a relevant confounding factor in many imaging studies.

Three patients in this study were found to have a very high striatal [^{123}I]FP-CIT binding, compared with controls. In these three patients the duration of untreated psychosis was more than 2 years. It is not clear whether this could explain the high [^{123}I]FP-CIT binding, because a large variability in the number of striatal DA transporters has been observed in controls (van Dyck et al., 1995). In addition, a high density of DA D_2 receptors was found in a subgroup of AP-naive schizophrenics (Hietala et al., 1994).

5. Conclusion

Striatal DA transporter density in young patients with schizophrenia is not different from that in controls, as assessed with [^{123}I]FP-CIT SPECT. Moreover, DA transporter density is not significantly different in drug-naive compared with medicated patients. In controls, as well as in patients, we observed a higher striatal density of DA transporters in women than in men. Further exploring the DA system in schizophrenia, and the possible involvement of presynaptic changes, may lead to a better understanding of this devastating disease, and finally to a more causal therapy.

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