Effect of age and gender on dopamine transporter imaging with [^{123}I]FP-CIT SPET in healthy volunteers

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Abstract. Dopamine transporter imaging is a valuable tool to investigate the integrity of the dopaminergic neurons. To date, several reports have shown an age-associated decline in dopamine transporters in healthy volunteers. Although animal studies suggest an effect of gender on dopamine transporter density, this gender effect has not yet been confirmed in human studies. To study the influence of age and gender on dopamine transporter imaging in healthy volunteers, we performed single-photon emission tomography imaging with [^{123}I]FP-CIT to quantify dopamine transporters. Forty-five healthy volunteers (23 males and 22 females) were included, ranging in age from 18 to 83 years. SPET imaging was performed 3 h after injection of ±110 MBq [^{123}I]FP-CIT. An operator-independent volume of interest analysis was used for quantification of [^{123}I]FP-CIT binding in the striatum. The ratio of specific striatal to non-specific [^{123}I]FP-CIT binding was found to decrease significantly with age. Moreover, we found a high variance in [^{123}I]FP-CIT binding in young adults. Finally, females were found to have significantly higher [^{123}I]FP-CIT binding ratios than males. This effect of gender on [^{123}I]FP-CIT binding ratios was not related to age. The results of this study are consistent with findings from previous studies, which showed that dopamine transporter density declines with age. The intriguing finding of a higher dopamine transporter density in females than in males is in line with findings from animal studies.

Key words: Dopamine transporter imaging – Single-photon emission tomography – [^{123}I]FP-CIT – Age – Gender

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Introduction

Dopamine transporter imaging with [^{123}I]FP-CIT single-photon emission tomography (SPET) is a valuable tool in the diagnostic process for patients with parkinsonian symptoms. However, confounding factors have to be taken into account when using dopamine transporter imaging as a diagnostic tool. For example, an age-related decline in dopamine transporter density in healthy volunteers has been reported [1, 2, 3, 4, 5]. Most of these studies described a linear pattern of decline, although one study proposed a broken stick model with a faster decrease in young adults than in old age [2].

A gender effect on dopamine transporter heterogeneity has been reported in humans, with females having a higher heterogeneity in the striatum than males [6]. Furthermore, a gender effect on dopamine transporter density has been reported in animals [7]. However, a gender effect has not been described in humans so far. We used *N*-ω-fluoropropyl-2β-carbomethoxy-3β-[4-iodophenyl] tropane (FP-CIT), labelled with iodine-123, to evaluate the effect of both age and gender on [^{123}I]FP-CIT binding to dopamine transporters in healthy volunteers, including a relatively large group of young adults. To exclude operator-dependent variability, we used automated data analysis of [^{123}I]FP-CIT SPET images.

Materials and methods

[^{123}I]FP-CIT SPET imaging was performed in 45 healthy volunteers, 23 males and 22 females, aged 18–83 years (mean 47.7 years, SD 21.4). All volunteers were free from any neurological or psychiatric disease and were not on medication or using drugs of abuse. Seven were left-handed and 38 were right-handed. All subjects gave their written informed consent for the study, which was approved by the medical ethical committee of the Academic Medical Center.

SPET procedure. For SPET imaging a brain-dedicated camera was used (Strichman Medical Equipment Inc, Medfield, Mass., USA). This camera consists of 12 individual crystals each equipped with a focussing collimator. The transaxial resolution is 7.6 mm full-width half-maximum of a line source in air. The energy window

was set at 135–190 keV. All subjects received potassium iodide to block thyroid uptake of free radioactive iodide. [^{123}I]FP-CIT (specific activity of >185 MBq/nmol; radiochemical purity of >95%) was injected intravenously at an approximate dose of 110 MBq. ^{123}I labelling of FP-CIT was performed by Amersham Cygne (Eindhoven, The Netherlands) with the trimethylstannyl precursor of FP-CIT. SPET acquisition was performed at 3 h p.i. [8]. Images were acquired during periods of 150 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 [8]. The measured concentration of radioactivity was expressed as Strichman Medical Units (SMUs; 1 SMU = 100 Bq/ml as specified by the Strichman Medical Equipment Inc.).

Data analysis. Assessment of [^{123}I]FP-CIT binding in the whole striatum, caudate nucleus and putamen was performed with a recently developed fully automated three-dimensional technique [9]. Briefly, this method automatically places volumes of interest (VOIs) over the brain areas, instead of manually placing predefined two-dimensional regions of interest, as in traditional SPET 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. Occipital cortex (OCC) was used as a reference region for non-specific binding. Ratios of specific to non-specific [^{123}I]FP-CIT binding were calculated as: [^{123}I]FP-CIT binding = (VOI–OCC)/OCC, in which VOI represents the mean radioactivity (in SMU) in the VOI (striatum, caudate nucleus or putamen).

Statistics. Stepwise linear regression analyses were performed in the total group of all 45 subjects, with [^{123}I]FP-CIT binding in the striatum, caudate nucleus and putamen as dependent variables. Age, gender and the product of age and gender were used as independent variables. A significance level of $P<0.05$ was used. All statistical analyses were carried out with SPSS 9.0 for Windows.

Results

No significant differences were found between left and right striatum, caudate nucleus or putamen (Table 1). A decrease in specific to non-specific striatal [^{123}I]FP-CIT binding ratios with age was found (Fig. 1). In young adults, aged 18–30 years, the variance in [^{123}I]FP-CIT binding ratios was 0.25, compared with 0.08 and 0.18, respectively, in the age groups 30–60 and 60–90 years. Linear regression analysis demonstrated a significant effect of both age and gender on striatal [^{123}I]FP-CIT binding ratios (β=–0.62, t=–4.96, $P<0.001$ and β=–0.33, t=–2.62, P=0.012, respectively), but the interaction between age and gender was not found to have a significant effect (β=0.20, t=0.64, P=0.53). Because of the number of included subjects and visual assessment of our data (Fig. 1), a linear model was used to investigate the correlation between [^{123}I]FP-CIT binding and age.

Striatal [^{123}I]FP-CIT binding ratios were significantly higher in females than in males. Linear regression showed a decrease of 4.1% per decade.

Table 1. Specific to non-specific [^{123}I]FP-CIT binding ratios in 45 healthy volunteers

	Left (SD)	Right (SD)	Mean (SD)
Whole striatum	2.56 (0.48)	2.55 (0.47)	2.55 (0.47)
Caudate nucleus	2.62 (0.55)	2.60 (0.54)	2.61 (0.54)
Putamen	2.53 (0.45)	2.51 (0.44)	2.52 (0.44)

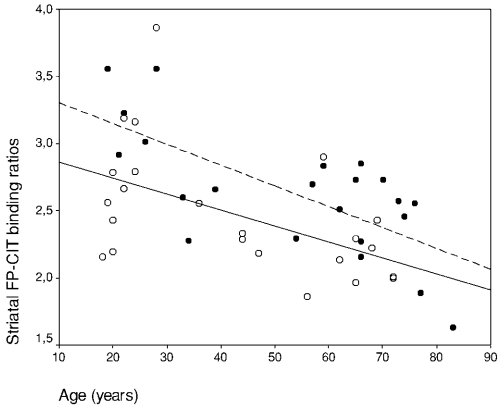

Fig. 1. Specific to non-specific striatal [^{123}I]FP-CIT binding ratios versus age in 45 healthy volunteers. *Closed circles* represent females (*dotted line*), *open circles* represent males (*unbroken line*)

[^{123}I]FP-CIT binding ratios in both the caudate nucleus and the putamen decreased significantly with age (β=–0.61, t=–4.77, $P<0.001$ and β=–0.62, t=–4.99, $P<0.001$, respectively), with a significant gender effect (β=–0.27, t=–2.14, P=0.039 and β=–3.66, t=–2.95, P=0.005, respectively). The interaction between age and gender was not a significant variable in either the caudate nucleus or the putamen.

No significant increase in the ratio of caudate over putamen was found with age. [^{123}I]FP-CIT binding ratios in the putamen were not significantly lower than in the caudate nucleus.

Discussion

The results of this study show that [^{123}I]FP-CIT binding in the striatum in healthy volunteers decreases significantly with age. The decline in [^{123}I]FP-CIT binding with age (4.1% per decade) is consistent with published studies [1, 2, 3, 5]. To describe the influence of age on dopamine transporter density, a linear model gave the best fit for our data, which is in agreement with earlier studies.

Furthermore, the high variance in [^{123}I]FP-CIT binding in a relatively large group of young volunteers is in line with the results of a previous study [2]. However, the pattern of a relatively rapid rate of decline during young adulthood followed by a less rapid decline during middle age was not confirmed in our study.

It has to be kept in mind that there are no large prospective studies to date on decline in dopamine transporter density with age. The findings from cross-sectional studies of volunteers in various age groups may differ from individual longitudinal findings.

All subjects were imaged at 3 h p.i. Although peak time of [^{123}I]FP-CIT binding may be earlier with higher age, specific striatal to non-specific binding ratios are stable between 3 and 6 h p.i., independent of the density of striatal dopamine transporters.

The higher density of dopamine transporters in females is in line with studies in rats [7], but not with a previous [^{123}I]β-CIT SPET study [1]. In female rats, the oestrogen hormone was found to be a crucial factor in the expression of dopamine transporters, which might explain the gender difference in dopamine transporter density in humans as well. Studying the postsynaptic side of the synapse, gender differences in dopamine D_2 receptor affinity have been reported by Pohjalainen et al. [10]. In their study, females were found to have a lower affinity, suggesting an increased endogenous striatal dopamine concentration in women. This may be related to the higher number of dopaminergic nerve terminals in females, as found in our study.

In conclusion, both age and gender should be taken into account in dopamine transporter imaging studies, especially in neuropsychiatric disorders with involvement of the dopaminergic system and established gender differences. For example, female patients with schizophrenia have a higher age of onset than males and in general a less invalidating course of disease. Interestingly, changes in dopamine transporter density have also been described in alcoholism. It may be of interest to study whether the lower occurrence of alcoholism in females is related to gender differences in dopamine transporter density.

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