Impact of aging on semiquantitative uptake parameters in normal rated clinical baseline [^{123}I]Ioflupane single photon emission computed tomography/computed tomography

Rudolf A. Werner[a,b,c,*], Constantin Lapa[c,*], Sara Sheikhbahaei[a], Charles Marcus[a], Lilja B. Solnes[a], Yong Du[a], Jeffrey P. Leal[a], Andreas K. Buck[c], Takahiro Higuchi[c,d], Steven P. Rowe[a] and Mehrbod S. Javadi[a]

Objectives **Studies investigating the age-related impact on dopamine transporter binding have previously omitted the use of attenuation correction by computed tomography (CT). We aimed to explore the impact of age and gender on dopamine transporter binding on [^{123}I] Ioflupane single photon emission CT (SPECT) imaging with simultaneously acquired CT.**

Methods **Three hundred forty-two patients with clinically uncertain parkinsonian syndrome underwent [^{123}I]-Ioflupane SPECT/CT with CT-based attenuation correction. Two nuclear medicine physicians independently performed a visual evaluation of all scans and only visibly normal scans were included for further analysis. Moreover, the results of a fully automatic semiquantitative evaluation method were recorded. Thereafter, the obtained [^{123}I] Ioflupane binding ratio and the hemispheric asymmetry index were correlated with age and sex.**

Results **Patient age range was 41–80 years with a balanced distribution over decades. Of 342 patients, 133 (38.9%, 66 females, median age, 64 years) were considered visually normal by both observers on the SPECT/CT images. A significant inverse correlation between age and [^{123}I]Ioflupane binding ratios in the striata (R=−0.38; P<0.001), putamina (R=−0.39; P<0.001) and caudate nuclei (R=−0.3; P<0.001) was demonstrated. Linear regression of all included subjects demonstrated an average decrease of 0.19 per decade in the striatal binding ratio (6.6%). No significant sex differences were found in striatal binding ratios (P=0.86). Moreover, no significant correlation was observed between age and striatal asymmetry index (r=0.12; P=0.16).**

Conclusion **In the present largest single-center analysis investigating [^{123}I]Ioflupane SPECT/CT in patients with clinical uncertain parkinsonian syndrome, a dopamine transporter loss of 6.6% per decade in visually normal scans was recorded.**

[a]Division of Nuclear Medicine and Molecular Imaging, The Russell H Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, [b]Department of Nuclear Medicine, Hannover Medical School, Hannover, [c]Department of Nuclear Medicine/Comprehensive Heart Failure Center, University of Wuerzburg, Wuerzburg, Germany and [d]Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

Correspondence to Rudolf A. Werner, MD, Department of Nuclear Medicine, University Hospital Würzburg, Oberdürrbacherst 6, 97080 Würzburg, Germany
Tel: +49 931 201 35905; fax: +49 931 201 6 555 00;
e-mail: rudolfwerner2015@gmail.com

*Dr. Rudolf A. Werner and Dr. Constantin Lapa contributed equally to the writing of this article.

Introduction

[^{123}I]-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane ([^{123}I]Ioflupane; DaTscan [GE Healthcare, Waukesha, Wisconsin, USA]) serves as a powerful tool to identify degeneration in dopaminergic neurons and to separate patients with parkinsonism caused by nigrostriatal degeneration from those without neurodegeneration [1,2]. Nigrostriatal and dopaminergic neurons are one of the most age-sensitive neurotransmitter systems [3,4] and an extensive body of evidence has reported on an age-related decline on dopamine transporter binding using either single photon emission computed tomography (SPECT) or PET [5–8]. All of these previous studies had been performed in relatively small patients cohorts (from n = 23 to n = 51) [5,9] or collected data from multiple sites (up to 13 different centers) using a variety of different SPECT systems [10]. Moreover, although recommended by current guidelines [1], even recently published studies investigating the age-related impact on dopamine transporter binding omitted the use of attenuation correction by computed tomography (CT) [11]. Therefore, in the present largest single tertiary care center investigation, we aimed to define the decrease of dopamine transporter loss using baseline [^{123}I]Ioflupane SPECT/CT in a large cohort of visually normal scans.

Material and methods

For this retrospective evaluation, 342 subjects with clinically uncertain Parkinsonian syndrome who had undergone a baseline [^{123}I]Ioflupane SPECT/CT were included. Parts of this patient cohort had been investigated previously [12]. Patients had been clinically referred from our institutional Movement Disorders Center and were analyzed as part of an Institutional Review Board-approved retrospective protocol of the Johns Hopkins School of Medicine (Baltimore, Maryland, USA). For further details of the patient cohort refer to Ref. [12].

Imaging procedure

Integrated SPECT/CT using a Symbia T2 (Siemens, Erlangen, Germany) equipped with a low energy, high-resolution collimator was performed in all patients. A SPECT brain scan was acquired 3 hours after the intravenous administration of 111–185 MBq (3–5 mCi) [^{123}I] Ioflupane. Imaging parameters included a 128 × 128 matrix, 30 s projection time (120 projections) and a photopeak energy window of 159 keV ± 20%. The obtained data were reconstructed at the acquisition terminal and analyzed using a Xeleris Workstation (DaTQUANT 4.0, GE Healthcare, Waukesha, Wisconsin, USA). Reconstruction was carried out using ordered-subset expectation maximization iterative reconstruction (four subsets and eight iterations). CT-based attenuation correction was applied per routine clinical protocol.

Fully automatic semiquantitative analysis

All images were compared with brain scans of 118 healthy volunteers through the multicenter Parkinson's Progression Markers Initiative project provided with DaTQUANT on Xeleris 4.0 [13]. Region of Interests (ROIs) were automatically defined over the caudate nuclei, putamina and striata bilaterally, as well as over the occipital cortex (background nonspecific uptake reference region). The following equation was used to determine binding ratios: [(mean counts of striatal ROI – mean counts of background ROI)/mean counts of background ROI] [14]. Semiquantitative parameters were obtained in all subjects.

Imaging interpretation

Two experienced nuclear medicine physicians performed a visual evaluation of all scans independently. Binary reporting was performed by visual analysis of radiotracer uptake and morphology within the putamen and caudate in each hemisphere. Readers were blinded to relevant clinical information. Only those scans deemed visually normal by both readers were included for further analysis.

Statistical analysis

Continuous variables are presented as mean ± SD. Paired sample *T*-tests were used to assess the differences in dopamine transporter availability between left and right striata, caudate nuclei, and putamina. A hemispheric asymmetry index derived for the striata, caudate nuclei, and putamina was calculated using the following equation:

$$\text{Asymmetry Index (AI)} = (\text{Right} - \text{Left}) / (\text{Right}/2 + \text{Left}/2) \times 100 \text{ [15].}$$

The effect of age on the striatal [^{123}I]Ioflupane binding ratio (dopamine transporter availability in striata, caudate nuclei, and putamina) and hemispheric asymmetry index were evaluated by the Pearson correlation coefficient (R) analysis and linear-regression analysis with age as the independent variable. The striatal [^{123}I]Ioflupane binding ratio in relation to age was displayed in a scatter plot. Statistical analysis was performed using IBM SPSS Statistics (version 22, Chicago, Illinois, USA). The statistical significance level was set at $P < 0.05$.

Results

Of 342 patients, 133 (38.9%, 66 females, median age, 64 years, range, 41–80 years) were determined to be visually normal by both observers [distribution over decades: (41–50 years: $n = 18/133$, 13.5%); (51–60 years: $n = 30/133$, 22.6%); (61–70 years: $n = 49/133$, 36.8%); (71–80 years: $n = 36/133$, 27.1%)]. The mast vajority of the enrolled subjects suffered from tremor (98/133, 73.7%), followed by gait abnormality (40/133, 30.1%).

Comparisons between left and right striatal regions showed significantly higher dopamine transporter availability in the left than in the right striata (mean difference of +0.04, $P < 0.011$) and caudate nuclei (+0.13, $P < 0.001$). There was no significant difference in dopamine transporter uptake in the left and right putamina (Table 1).

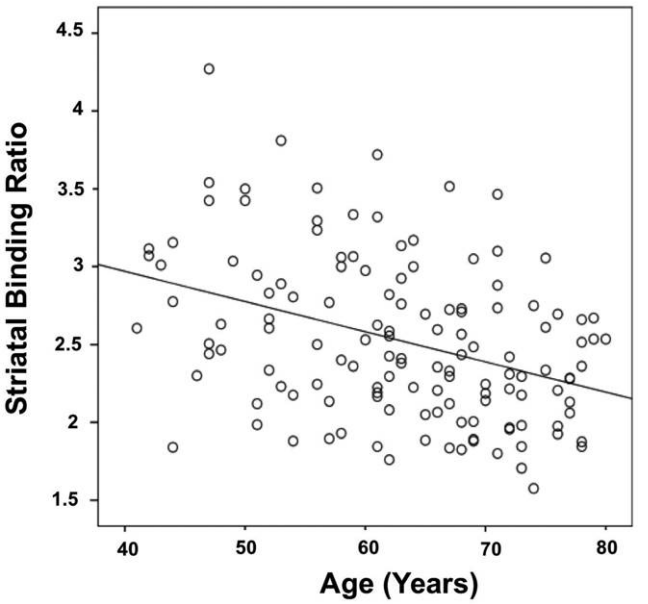
Significant inverse correlations between age and [^{123}I] Ioflupane binding ratios in the striata ($R = -0.38$), putamina ($R = -0.39$), and caudate nuclei ($R = -0.3$) were demonstrated ($P < 0.001$, respectively). Linear regression analysis demonstrated a significant effect of age on striatal binding ratio ($B = -0.19$ per decade, $t = -4.68$, $P < 0.001$), with an estimated 6.6% [95% confidence interval (CI) = 3.7–9.5%) loss in the striatal binding ratio per decade (Fig. 1). No significant sex differences were found in striatal binding ratios ($P = 0.86$). There was no significant correlation between age and the striatal

Table 1 Comparison between left and right striatal binding regions

	Mean	SD	Mean difference (left versus right)	*P* value
Striatum right	2.5057	0.51235	+0.04	0.011
Striatum left	2.5434	0.53360		
Putamen right	2.2905	0.54809	+0.03	0.324
Putamen left	2.3186	0.53345		
Caudate right	2.8495	0.61005	+0.13	<0.001
Caudate left	2.9812	0.68665		

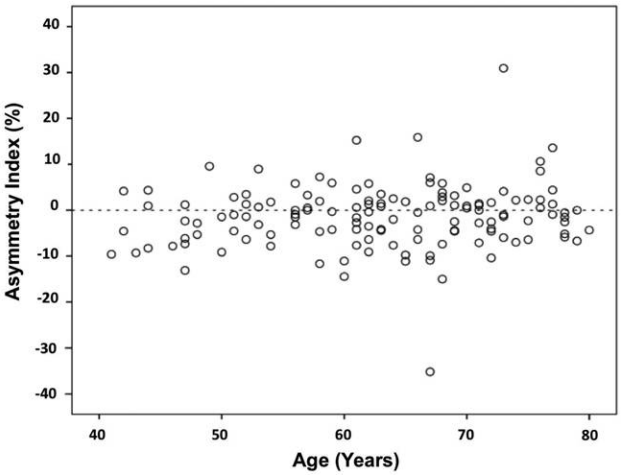
A significantly higher dopamine transporter availability in the left than in the right striatum and caudate could be observed.

Fig. 1



Correlation between striatal binding ratio and age (in years) in 133 subjects rated normal by two observers (correlation coefficient −0.38; $P<0.001$). An average decrease of 6.6% per decade in the striatal binding ratio was recorded.

Fig. 2



Asymmetry index of striatal binding ratio (%) in relation to age (years). No relation to age could be observed.

asymmetry index ($R=0.12$; $P=0.16$), caudate asymmetry index ($R=0.11$; $P=0.21$), or putamen asymmetry index ($R=0.02$; $P=0.82$). Asymmetry index of the striatal binding ratio in relation to age is displayed in Fig. 2.

Discussion

The results of this study are concordant with previous investigations using either ROI settings or voxel-based analysis (reported dopamine receptor uptake loss per decade (4.1–8.9%) [7,9–11]). A similar finding was also derived in a recently published meta-analysis (3.7–14%) including both PET and SPECT compounds [15]. However, the present largest single-center investigation differs from prior reports in that the SPECT camera and its acquisition parameters were consistent across all included scans and all scans were reconstructed using CT-based attenuation correction [10,12]. Given the similar rate of dopamine transporter loss per decade among these different types of studies, the molecular imaging specialist should consider an age-related impact on dopamine transporter binding, in particular while interpreting [^{123}I]Ioflupane SPECT/CT examinations of older patients or when comparing longitudinally acquired scans in the same patient.

In the present study, patients had been clinically referred from our institutional Movement Disorders Center to assist in diagnosis. Thus, instead of including definitive healthy subjects, the baseline [^{123}I]Ioflupane SPECT/CT of patients with clinically uncertain Parkinsonian syndromes were analyzed. Consequently, the design of the present investigation might reflect a more common clinical 'real-world' scenario. Notably, in concordance with studies investigating other neuroimaging SPECT (^{123}I-2beta-carbomethoxy-3beta-(4-iodophenyl)tropane, [^{123}I]beta-CIT) or PET ([^{11}C]threo-methylphenidate) probes, an identical decrease of 6.6% in striatal binding per decade of life was observed [5,16]. Taken together, our findings should not be interpreted as results obtained in healthy subjects, but in patients with clinically uncertain Parkinsonian syndrome but visually normal striatal dopaminergic function at baseline. This may have direct applicability to the clinical setting: before any clinical symptoms of Parkinson Disease (e.g., motor signs) may become apparent, about 50% (or even up to 70%) of dopamine neurons must have been lost [17–19]. Thus, given the findings of the present study, an age-dependent decline should be taken into account, especially when interpreting borderline cases.

The dopamine transporter availability among different sexes is still a point of controversy. Studies in Japan and Europe had reported on a higher [^{123}I]Ioflupane binding in women compared to men [10,11], but similar to our findings, Jakobson *et al.* [20] found no significant sex difference. Indeed, in contrast to other studies [11], the ratio between male and female in the present cohort was rather balanced across decades (e.g., 40–49 years, ratio female versus. male, 1:1).

van Dyck *et al.* [16] reported on the hemispheric asymmetry index using [^{123}I]beta-CIT and, similar to the findings in this study, no correlation between striatal asymmetry index and age was found (Fig. 2). One might speculate that the observed higher dopamine transporter availability in the left than in the right striatum and caudate

(Table 1) is primarily a function of left cerebral dominance [21,22]. Consequently, the handedness (e.g., derived by the Edinburgh Inventory) in the setting of [^{123}I]Ioflupane imaging should be the subject of future studies [23].

Conclusion

An age-induced dopamine transporter loss of 6.6% was observed in visually normal baseline [^{123}I]Ioflupane SPECT/CT scans of patients with clinically uncertain Parkinsonian syndrome.

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Conflicts of interest

There are no conflicts of interest.

References

1 Djang DS, Janssen MJ, Bohnen N, Booij J, Henderson TA, Herholz K, *et al*. SNM practice guideline for dopamine transporter imaging with 123I-ioflupane SPECT 1.0. *J Nucl Med* 2012; **53**:154–163.
2 Lapa C, Spehl TS, Brumberg J, Isaias IU, Schlögl S, Lassmann M, *et al*. Influence of CT-based attenuation correction on dopamine transporter SPECT with [(123)I]FP-CIT. *Am J Nucl Med Mol Imaging* 2015; **5**:278–286.
3 Branch SY, Chen C, Sharma R, Lechleiter JD, Li S, Beckstead MJ. Dopaminergic neurons exhibit an age-dependent decline in electrophysiological parameters in the mitopark mouse model of Parkinson's disease. *J Neurosci* 2016; **36**:4026–4037.
4 Volkow ND, Wang GJ, Fowler JS, Ding YS, Gur RC, Gatley J, *et al*. Parallel loss of presynaptic and postsynaptic dopamine markers in normal aging. *Ann Neurol* 1998; **44**:143–147.
5 Volkow ND, Ding YS, Fowler JS, Wang GJ, Logan J, Gatley SJ, *et al*. Dopamine transporters decrease with age. *J Nucl Med* 1996; **37**: 554–559.
6 van Dyck CH, Seibyl JP, Malison RT, Laruelle M, Wallace E, Zoghbi SS, *et al*. Age-related decline in striatal dopamine transporter binding with iodine-123-beta-CITSPECT. *J Nucl Med* 1995; **36**:1175–1181.
7 Lavalaye J, Booij J, Reneman L, Habraken JB, van Royen EA. Effect of age and gender on dopamine transporter imaging with [123I]FP-CIT SPET in healthy volunteers. *Eur J Nucl Med* 2000; **27**:867–869.
8 Shingai Y, Tateno A, Arakawa R, Sakayori T, Kim W, Suzuki H, Okubo Y. Age-related decline in dopamine transporter in human brain using PET with a new radioligand [^{18}F]FE-PE2I. *Ann Nucl Med* 2014; **28**:220–226.
9 Eusebio A, Azulay JP, Ceccaldi M, Girard N, Mundler O, Guedj E. Voxel-based analysis of whole-brain effects of age and gender on dopamine transporter SPECT imaging in healthy subjects. *Eur J Nucl Med Mol Imaging* 2012; **39**:1778–1783.
10 Varrone A, Dickson JC, Tossici-Bolt L, Sera T, Asenbaum S, Booij J, *et al*. European multicentre database of healthy controls for [123I]FP-CIT SPECT (ENC-DAT): age-related effects, gender differences and evaluation of different methods of analysis. *Eur J Nucl Med Mol Imaging* 2013; **40**:213–227.
11 Yamamoto H, Arimura S, Nakanishi A, Shimo Y, Motoi Y, Ishiguro K, *et al*. Age-related effects and gender differences in Japanese healthy controls for [123I] FP-CIT SPECT. *Ann Nucl Med* 2017; **31**:407–412.
12 Werner RA, Marcus C, Sheikhbahaei S, Solnes LB, Leal JP, Du Y, *et al*. Visual and semiquantitative accuracy in clinical baseline 123I-ioflupane SPECT/CT imaging. *Clin Nucl Med* 2019; **44**:1–3.
13 Parkinson Progression Marker Initiative. The Parkinson progression marker initiative (PPMI). *Prog Neurobiol* 2011; **95**:629–635.
14 Van Laere K, Varrone A, Booij J, Vander Borght T, Nobili F, Kapucu OL, *et al*. EANM procedure guidelines for brain neurotransmission SPECT/PET using dopamine D2 receptor ligands, version 2. *Eur J Nucl Med Mol Imaging* 2010; **37**:434–442.
15 Karrer TM, Josef AK, Mata R, Morris ED, Samanez-Larkin GR. Reduced dopamine receptors and transporters but not synthesis capacity in normal aging adults: a meta-analysis. *Neurobiol Aging* 2017; **57**:36–46.
16 van Dyck CH, Seibyl JP, Malison RT, Laruelle M, Zoghbi SS, Baldwin RM, Innis RB. Age-related decline in dopamine transporters: analysis of striatal subregions, nonlinear effects, and hemispheric asymmetries. *Am J Geriatr Psychiatry* 2002; **10**:36–43.
17 Marsden CD. Parkinson's disease. *Lancet* 1990; **335**:948–952.
18 Lang AE, Lozano AM. Parkinson's disease. First of two parts. *N Engl J Med* 1998; **339**:1044–1053.
19 Fearnley JM, Lees AJ. Ageing and Parkinson's disease: substantia nigra regional selectivity. *Brain* 1991; **114** (Pt 5):2283–2301.
20 Jakobson Mo S, Larsson A, Linder J, Birgander R, Edenbrandt L, Stenlund H, *et al*. ^{123}I-FP-cit and 123I-IBZM SPECT uptake in a prospective normal material analysed with two different semiquantitative image evaluation tools. *Nucl Med Commun* 2013; **34**:978–989.
21 Isaacs KL, Barr WB, Nelson PK, Devinsky O. Degree of handedness and cerebral dominance. *Neurology* 2006; **66**:1855–1858.
22 Annett M. Handedness and cerebral dominance: the right shift theory. *J Neuropsychiatry Clin Neurosci* 1998; **10**:459–469.
23 Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 1971; **9**:97–113.