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ORIGINAL ARTICLE

European multicentre database of healthy controls for [^{123}I] FP-CIT SPECT (ENC-DAT): age-related effects, gender differences and evaluation of different methods of analysis

Andrea Varrone · John C. Dickson · Livia Tossici-Bolt · Terez Sera · Susanne Asenbaum · Jan Booij · Ozlem L. Kapucu · Andreas Kluge · Gitte M. Knudsen · Pierre Malick Koulibaly · Flavio Nobili · Marco Pagani · Osama Sabri · Thierry Vander Borght · Koen Van Laere · Klaus Tatsch

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Abstract
Purpose Dopamine transporter (DAT) imaging with [^{123}I] FP-CIT (DaTSCAN) is an established diagnostic tool in parkinsonism and dementia. Although qualitative assessment criteria are available, DAT quantification is important for research and for completion of a diagnostic evaluation.

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A. Varrone (✉)
Karolinska Institutet, Department of Clinical Neuroscience,
Centre for Psychiatry Research,
Karolinska University Hospital, R5:02,
17176 Stockholm, Sweden
e-mail: andrea.varrone@ki.se

J. C. Dickson
Institute of Nuclear Medicine,
UCLH NHS Foundation Trust and University College,
London, UK

L. Tossici-Bolt
Department of Medical Physics,
University Hospitals Southampton NHS Trust,
Southampton, UK

T. Sera
Department of Nuclear Medicine and Euromedic Szeged,
University of Szeged,
Szeged, Hungary

S. Asenbaum
Department of Nuclear Medicine, Medical University of Vienna,
Vienna, Austria

J. Booij
Department of Nuclear Medicine,
Academic Medical Centre, University of Amsterdam,
Amsterdam, Netherlands

O. L. Kapucu
Department of Nuclear Medicine, Faculty of Medicine,
Gazi University,
Ankara, Turkey

A. Kluge
ABX-CRO,
Dresden, Germany

G. M. Knudsen
Neurobiology Research Unit,
Rigshospitalet and University of Copenhagen,
Copenhagen, Denmark

P. M. Koulibaly
Nuclear Medicine Department, Centre Antoine Lacassagne,
University of Nice-Sophia Antipolis,
Nice, France

F. Nobili
Clinical Neurophysiology Unit,
Department of Neuroscience,
Ophthalmology and Genetics,
University of Genoa,
Genoa, Italy

M. Pagani
Institute of Cognitive Sciences and Technologies, CNR,
Rome, Italy

One critical aspect of quantification is the availability of normative data, considering possible age and gender effects on DAT availability. The aim of the European Normal Control Database of DaTSCAN (ENC-DAT) study was to generate a large database of [^{123}I]FP-CIT SPECT scans in healthy controls.

Methods SPECT data from 139 healthy controls (74 men, 65 women; age range 20–83 years, mean 53 years) acquired in 13 different centres were included. Images were reconstructed using the ordered-subset expectation-maximization algorithm without correction (NOACSC), with attenuation correction (AC), and with both attenuation and scatter correction using the triple-energy window method (ACSC). Region-of-interest analysis was performed using the BRASS software (caudate and putamen), and the Southampton method (striatum). The outcome measure was the specific binding ratio (*SBR*).

Results A significant effect of age on *SBR* was found for all data. Gender had a significant effect on *SBR* in the caudate and putamen for the NOACSC and AC data, and only in the left caudate for the ACSC data (BRASS method). Significant effects of age and gender on striatal *SBR* were observed for all data analysed with the Southampton method. Overall, there was a significant age-related decline in *SBR* of between 4 % and 6.7 % per decade.

Conclusion This study provides a large database of [^{123}I]FP-CIT SPECT scans in healthy controls across a wide age range and with balanced gender representation. Higher DAT availability was found in women than in men. An average age-related decline in DAT availability of 5.5 % per decade was found for both genders, in agreement with previous reports. The data collected in this study may serve as a reference database for nuclear medicine centres and for clinical trials using [^{123}I]FP-CIT SPECT as the imaging marker.

Keywords Dopamine transporter · Gender difference · Age effects · SPECT · Scatter correction · Database

Introduction

SPECT imaging of the dopamine transporter (DAT) is a valuable tool for the study of the integrity of the nigrostriatal system in patients with suspected neurodegenerative parkinsonism [1, 2]. [^{123}I]FP-CIT (^{123}I-ioflupane, DaTSCAN; GE Healthcare) is currently one of the most widely used DAT probes in the European Union. The utility of this tracer in the differential diagnosis between essential tremor and idiopathic parkinsonism [3] and its added value in the assessment of patients with an unclear diagnosis [4] are well established. More recently, DaTSCAN has also been approved for the differential diagnosis between dementia with Lewy bodies and Alzheimer's disease [5, 6]. Although [^{123}I]FP-CIT is widely used in Europe, one of its limitations is the lack of quantitative reference values for normal controls. This limitation has become critical considering that clinical trials have shown that approximately 10–15 % of patients satisfying clinical criteria for Parkinson's disease (PD) do not show any signs of a dopaminergic deficit using different PET and SPECT ligands for the nigrostriatal system [7, 8]. This issue is especially relevant when examining patients at an early stage of the disease. In particular, when reporting quantitative results of scans that cannot be interpreted visually as abnormal, no conclusion can be drawn as to whether a (even mild) dopaminergic deficit is present unless normative data for [^{123}I]FP-CIT are available. In addition, if quantitative measures of the DAT deficit in PD patients are of interest, it is not possible to obtain an accurate value without taking into account age and gender effects on DAT availability [9, 10]. Finally, comparison of quantitative results of [^{123}I]FP-CIT SPECT from different centres is difficult without some sort of standardization, taking into account differences in quantitative outcome measures due to different camera sensitivities, scanning protocols, reconstruction algorithms, region of interest analyses, etc. These limitations could be addressed by generating a database of normal control scans.

The Neuroimaging Committee of the European Association of Nuclear Medicine has initiated a cooperative effort among different imaging centres to carry out a multicentre study, the ENC-DAT (European Normal Control Database of DaTSCAN) study, to generate a database of [^{123}I]FP-CIT SPECT scans of healthy controls. The purpose of the project was to collect a large number of

M. Pagani
Department of Nuclear Medicine,
Karolinska University Hospital,
Stockholm, Sweden

O. Sabri
Department of Nuclear Medicine, University of Leipzig,
Leipzig, Germany

T. Vander Borght
Nuclear Medicine Division, Mont-Godinne Medical Center,
Université Catholique de Louvain,
Yvoir, Belgium

K. Van Laere
Nuclear Medicine, University Hospital and K.U. Leuven,
Leuven, Belgium

K. Tatsch
Department of Nuclear Medicine,
Municipal Hospital of Karlsruhe Inc,
Karlsruhe, Germany

SPECT scans of healthy controls to provide reference images and reference values of DAT availability measures obtained with [^{123}I]FP-CIT in order to establish a normal control database of at least 150 scans of healthy controls between 20 and 90 years of age and a male-to-female ratio of approximately 1 to 1 reproducing the gender prevalence of PD [11–13]. Each centre was expected to recruit at least 10–15 healthy controls. The overall endpoint of this database would be to serve as a standard reference for all nuclear medicine departments performing [^{123}I]FP-CIT SPECT studies for reporting both qualitative and quantitative results of the examinations. The database could also provide reference values for clinical trials using [^{123}I]FP-CIT as the imaging probe for DAT.

Methods

Subjects

Included in the study were 151 healthy controls (80 men, 71 women; age range 20 to 83 years, mean 53 years) recruited in 13 different centres (Table 1). The study was approved by the local institutional review boards of the participating centres and was performed in accordance with the ethical standards of the Declaration of Helsinki. All subjects gave written informed consent to participation in the study. All subjects were Caucasians. They were healthy according to medical history, blood chemistry, neurological examination, including the Unified Parkinson's Disease Rating Scale (UPDRS) score, and psychiatric evaluation, including the following self-assessment scales: the Symptom Checklist-90 revised (SCL-90 R; score <63) [14]; and the Beck Depression Inventory (BDI; score <9) [15]. The neurological and psychiatric evaluations were performed at each centre by a movement disorder specialist with specific training in the administration of these scales. The UPDRS was administered as part of the assessment to rule out a diagnosis of movement disorder. Subjects had no evidence of cognitive impairment as assessed by a Mini-Mental State Examination (MMSE; score ≥28). Furthermore, subjects had no history of parkinsonism in first-degree relatives (sibling, parent or children, either diagnosed by a neurologist or established retrospectively using information obtained from the unaffected relatives). Nonconsanguineous spouses of PD patients were eligible if they fulfilled the inclusion criteria.

All subjects underwent a structural MR scan according to the imaging protocol of the recruiting centre to rule out the presence of pathology. In subjects <60 years of age, no abnormalities were allowed. In subjects ≥60 years of age white matter hyperintensities on T2-weighted images, corresponding to a white matter lesion score of ≤2 (of 3) on the Fazekas scale were acceptable as normal for age in these subjects [16]. Handedness was assessed with the Edinburgh Inventory [17]. On the day of the SPECT scans, a

Table 1 Details of the healthy controls recruited in each centre (in alphabetical order) and the SPECT system used for imaging. The numbers refer to the subjects and scans included in the analysis of the SPECT data

Centre	Men (*n*)	Women (*n*)	Age (years)		SPECT system (no. of subjects)	
			Mean±SD	Range	At 3 h	At 4 h
Amsterdam	3	3	63±5	56–70	Neurofocus	ECAM (*n*=6)
Ankara	5	5	38±16	21–74	GE Infinia (*n*=10)	
Copenhagen	10	6	43±17	21–69	IRIX (*n*=16)	
Genoa	7	7	54±19	27–82	GE Millennium (*n*=14)	
Leipzig	4	4	56±17	25–79	Ceraspect (*n*=8)[a]	Symbia (*n*=8)
Leuven	8	7	52±17	20–78	ECAM (*n*=15)	IRIX (*n*=11)[a]
London	6	4	61±17	25–78	GE Infinia (*n*=10)	
Munich	7	7	52±17	23–74	Symbia (*n*=14)	PRISM 3000 (*n*=14)[a]
Nice	5	7	51±20	22–80	PRISM 3000 (*n*=12)	
Southampton	3		57±20	34–72	Mediso (*n*=3)	
Stockholm	7	6	54±21	23–83	Trionix (*n*=13)	
Vienna	2	2	39±8	31–43	IRIX (*n*=4)	GE Millennium (*n*=4)[a]
Yvoir	7	7	55±19	21–81	IRIX (*n*=14)	TRIONIX (*n*=14)[a]
Total[b]	74	65	53±19	20–83	*N*=125	*N*=14

[a] Data acquired with these SPECT systems were only used for comparison of specific binding ratio values between 3 h and 4 h.

[b] The total refers to the SPECT data included in the final analysis.

urine pregnancy test was performed in female subjects under the age of 50 years, and a urine drug test was performed in all subjects.

SPECT imaging

In each centre a rigorous QC protocol was applied for site certification [18]. The protocol included a quality assurance programme to ensure that the longitudinal uniformity and centre of rotation of all SPECT systems used were maintained. In addition, ^{123}I SPECT images of an anthropomorphic striatal phantom (Radiology Support Devices Inc., Long Beach, CA) were acquired in each of the participating centres on 17 imaging systems: 4 Siemens ECAM, 3 GE Infinia, 3 Philips IRIX, 2 Siemens SYMBIA, 2 Trionix Triad XLT 20, 1 GE Millennium VG, 1 Siemens Multispect, and 1 Mediso x-Ring/4HR. The main data of all the SPECT systems used in this study have already been reported as has the protocol for filling of the phantom [19]. The purpose of the phantom study was to assess the different imaging systems for both their SPECT uniformity and the linearity of their response to ^{123}I. Finally, the phantom data were used to generate calibrated quantitative values for each SPECT system. The outcome measures obtained for each SPECT system were corrected by the corresponding linear calibration factors as previously described by Tossici-Bolt et al. [19].

Prior to injection of [^{123}I]FP-CIT, the thyroid was blocked according to the local routine procedure for each centre. [^{123}I]FP-CIT (180±16 MBq) was injected intravenously as a bolus in a volume of 2±0.6 mL. Scans were obtained at 3±0.3 h and 4±0.6 h (optional) after tracer injection. Subjects were allowed to rest for 15–30 min between scans. For logistic reasons, SPECT scans were performed in 151 subjects at 3 h after injection and only in 61 of them also at 4 h after injection. In Leipzig and Amsterdam the scans at 3 h after injection were performed with the brain-dedicated systems Ceraspect and Neurofocus, respectively, and at 4 h with the dual-head systems Symbia and ECAM, respectively. Because of the unique features of the SPECT data from the Neurofocus (Amsterdam) and Ceraspect (Leipzig) brain-dedicated systems, it was decided to include only the data acquired at 4 h after injection from the ECAM and Symbia SPECT systems at these sites for all further evaluations of the database. All other data from the SPECT systems in the remaining centres included in the final analysis were acquired at 3 h after injection. From the original number of 151 subjects recruited, SPECT data from 139 subjects were included in the final analysis (Table 1). SPECT data from 12 subjects were not available for the final analysis for technical reasons. In Leipzig, in only 8 of the 15 subjects were the data acquired on the Symbia system. Therefore, data from the remaining 7 subjects from Leipzig were excluded from the final analysis because the 3-h acquisition was performed on the Ceraspect system. Data from 4 subjects from Amsterdam and 1 subject from Leuven were not included in the final analysis because of the positioning of the subject in the SPECT system (incomplete coverage of the whole brain). The age distribution of the subjects included in the different centres in the final analysis is shown in Supplementary Fig. 1.

Imaging devices included in this study were multiple detector (triple or dual head) or other dedicated SPECT systems for brain imaging. Collimators were used that met our specification for SPECT spatial resolution (<15 mm at 15 cm radius of rotation), which included LEHR, LEUHR and fan-beam collimators, and one system with LEGP collimators. The acquisition parameters were as follows: rotational radius fixed for all SPECT studies between 13 and 15 cm with appropriate patient safeguard for LEHR, LEUHR and LEGP collimators; >15 for triple-head cameras with fan-beam collimators; matrix 128 × 128; angular sampling ≤3° (360° rotation); and hardware zoom (1.23–2) to achieve a pixel size of 2–3 mm. Besides the photopeak imaging window (159 keV ±10 %, 143–175 keV), two additional scatter energy windows were also acquired, below (138 keV ±3.5 %, 133–143 keV) and above (184 keV ±3 %, 178.5–189.5 keV), in order to assess the value of scatter and septal penetration correction using the triple energy windows method [20]. The small gap between the photopeak and the upper scatter windows was aimed to ensure that no primary photons were detected in the latter, given the limited energy resolution of the systems. For technical reasons scatter windows were not used in Vienna and were used only in the scans of four subjects recruited in Nice. In Leipzig, data were acquired on the Symbia system using a narrower window for the photopeak and the scatter. The weight of the scatter windows was adjusted accordingly for the triple energy windows scatter correction.

The total scan time which was dependent on system type was determined as the time by which 2 million photopeak counts were detected in the photopeak window. Typically this was at least 25 min. Projection data from fan-beam collimators were rebinned to parallel projection data. Raw SPECT projection data in DICOM or interfile format were analysed by a centre core laboratory. Reconstruction was performed using the ordered-subset expectation-maximization (OSEM) algorithm [21], with ten iterations and ten subsets for sets of 120 projections [22], and with 12 iterations and eight subsets for sets of 128 projections to maintain an equivalent number of total EM iterations. The number of iterations and subsets were selected so as to

achieve a balance between convergence and a quantitatively accurate value of striatal uptake [22]. Three-dimensional postfiltering was applied to the reconstructed slices using a Butterworth filter (defined as $1/B = \sqrt{1+(f/f_c)^{2n}}$ where f_c is the cut-off frequency and n the order), with a cut-off of 0.50 cm^{-1} and order 10. This filter was selected so as to provide the best balance between image accuracy and image noise.

Three OSEM reconstructions were performed without attenuation or scatter correction (NOACSC), with calculated attenuation correction only (AC), and with both attenuation and scatter and septal penetration corrections (ACSC). The latter was implemented according to the triple energy windows method [20, 23], as previously reported [19]. The broad and narrow beam attenuation coefficient for 159 keV gamma rays in water were set to μ=0.11 cm^{-1} and μ=0.143 cm^{-1} to correct data with and without the scatter and septal penetration contribution, respectively [19].

The reconstruction data were quantified using two methods. The first method used the BRASS software (Hermes Medical Solutions, Stockholm), a validated semiautomatic analysis package [24]. In essence this package uses a two-stage registration algorithm to register the image data to a template in a standard space before applying volumes of interest (VOI) over the caudate, putamen and posterior occipital cortex. The posterior occipital cortex is used as a reference region to determine nonspecific binding. The outcome measure was the specific-to-nondisplaceable binding ratio (*SBR*) calculated as $(VOI_{CAUorPUT} - VOI_{OCC})/VOI_{OCC}$. The second method (Southampton method) consisted of collecting the whole radioactivity from the striatum of each hemisphere and estimating the background radioactivity from the whole brain minus that from the striatum, as previously described [25]. The *SBR* is then calculated as follows:

$$\frac{Vol_{StrVOI}}{Vol_{Str}}\left(\frac{Counts_{StrVOI}}{counts\,per\,pixel_{Bkg}\times Vol_{StrVOI}}-1\right)$$

In the present work, we used the original method with slight modification. We calculated the *SBR* using not a fixed striatal volume for Vol_{Str}, but introducing the percentage difference for the right and left striatum as described in men and women by Gunning-Dixon et al. [26] (3.7 % between the right and left striatum in men; 7.1 % and 6.6 % between men and women for the right and left striatum, respectively). The volumes used (based on the striatal phantom volume of 11.4 ml) were as follows: right striatum 11.4 mL, left striatum 10.99 mL, in men; right striatum 10.59 mL, left striatum 10.26 mL, in women. For both methods, data are presented for reconstruction with NOACSC, with AC, and with ACSC. The primary outcome measure was measured at 3 h after injection.

Statistical analysis

The differences in the *SBR* measured at 3 h and 4 h in those centres in which the subjects were examined on two SPECT systems were evaluated with a paired *t* test. Differences in the number of right- and left-handed subjects were evaluated with the chi-squared test. A multivariate analysis was performed to investigate the effects of age, gender and imaging site on *SBR*. The dependent variable was the *SBR* calculated in the different striatal regions of both hemispheres. For the BRASS analysis, the caudate-to-putamen ratio was also entered as a dependent variable. Differences between right and left striatal regions were evaluated with a paired *t* test. Linear regression analysis was performed to investigate the relationship between age and *SBR* in both genders. Differences between *r* values were evaluated according to the following formula [27]:

$$z = \frac{r_1' - r_2'}{\sqrt{\frac{1}{n_1-3}+\frac{1}{n_2-3}}}$$

where r'_1 and r'_2 are the Fisher's *r* to *z* transformation of the coefficients r_1 and r_2 and n_1 and n_2 are the corresponding sample sizes. Significance was set at p=0.05. Statistical analysis was performed with SPSS (IBM SPSS Statistics, v20).

Results

Representative SPECT images of healthy controls aged from 23 to 82 years and acquired in different imaging centres are shown in Fig. 1.

Comparison between specific binding ratio at 3 h and 4 h

Calibrated SPECT data obtained from five of the six centres in which the healthy controls were imaged at 3 h and 4 h after injection were used for a within-subject comparison of *SBR*. For simplicity, only the data analysed with the BRASS method were used for this comparison. In this analysis, only a subset of the data from Leipzig was used, since not all subjects were imaged with the Symbia system, and data from Amsterdam were not included because only uncorrected data could be obtained with the Neurofocus system. Calibrated SPECT data from Leipzig (Fig. 2) showed a consistently higher striatal *SBR* at 3 h (Ceraspect) than at 4 h (Symbia): for the AC data (7.86±0.61 vs. 5.94±0.83, $p<0.001$, paired *t* test) and ACSC data (7.75±0.53 vs. 5.88±0.68, $p<0.001$, paired *t* test). Calibrated data from the other

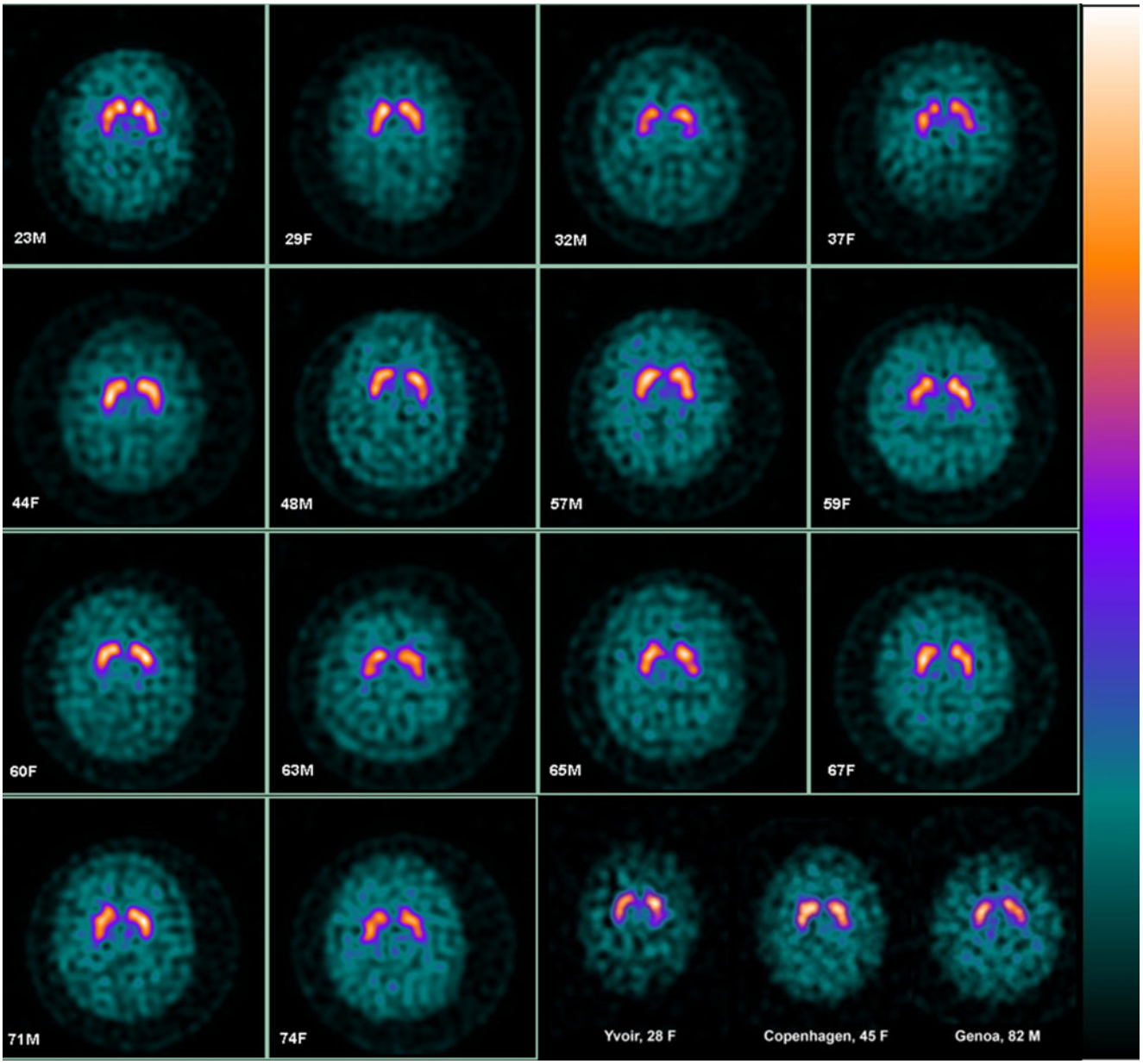

Fig. 1 Representative images of healthy controls acquired with the PRISM system in Munich, and in the lower right corner, three representative images from three other centres in three subjects of different ages

centres (Fig. 2) showed a lower striatal *SBR* at 3 h than at 4 h after injection: NOACSC data (6.10±1.01 vs. 6.59±1.23, $p<0.001$, paired *t* test), AC data (6.17±1.01 vs. 6.97±1.03, $p<0.05$, paired *t* test), and ACSC data (6.43±1.10 vs. 7.25±1.16, $p<0.001$, paired *t* test).

Effects of age, gender and imaging site on the *SBR*

There were 66 men and 59 women who were right-handed and 7 men and 6 women who were left-handed. There was no difference in the proportions of right- and left-handedness between men and women. The *SBR* values for all striatal regions calculated with the BRASS and the Southampton methods are presented in Tables 2 and 3, respectively. In all regions examined with the BRASS analysis, a significant effect of age on *SBR* values was observed in all striatal regions examined with each method (NOACSC, AC and ACSC; Table 2). A significant effect of gender was observed for the NOACSC and the AC data, but only for the left caudate for the AC data (Table 2). Imaging site had either no effect or a marginally significant effect on the *SBR* for the NOACSC and AC data. A significant effect of imaging site was observed for the uncalibrated ACSC *SBR* values. This effect was related mostly to the

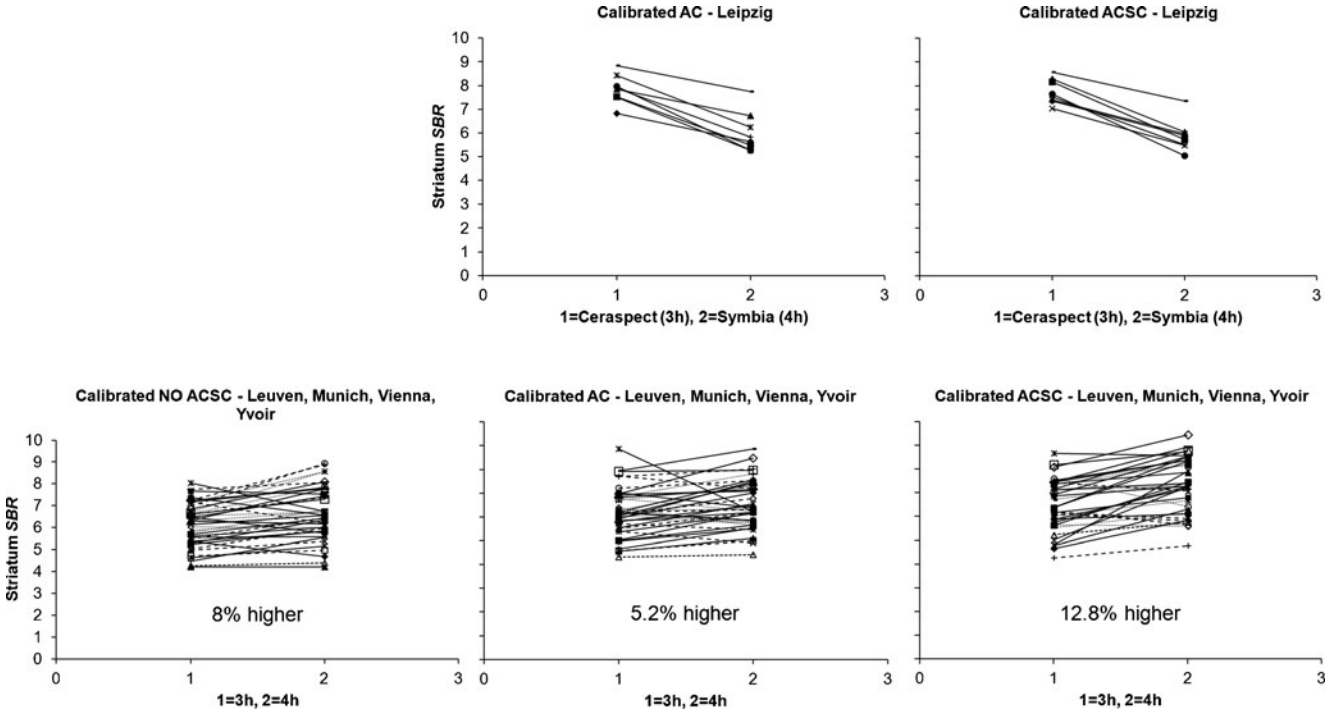

Fig. 2 Comparison of *SBR* in the striatum obtained with two different SPECT systems at 3 h and 4 h after injection in Leipzig, Leuven, Munich, Vienna, and Yvoir. For simplicity only the data analysed with the BRASS method are presented. The data have been calibrated with the phantom data

higher *SBR* values obtained at the Copenhagen site that were significantly higher than those from Leipzig, Leuven, Munich, Stockholm and Yvoir (Table 4). The caudate-to-putamen ratios in men were as follows (mean ± SD): *NOACSC* right 1.13±0.13, left 1.09±0.13; *AC* right 1.10±0.12, left 1.07±0.12; *ACSC* right 1.09±0.13, left 1.06±0.12. The caudate-to-putamen ratios in women were as follows: *NOACSC* right 1.12±0.11, left 1.09±0.10; *AC* right 1.09±0.10, left 1.08±0.8; *ACSC* right 1.07±0.10, left 1.09±0.11. There were no effects of age, gender or imaging site on the caudate-to-putamen ratio.

In the case of the Southampton method, a significant effect of age and gender on striatal *SBR* was found for the NOACSC, AC and ACSC data (Table 3). The imaging site had a significant effect only on the uncalibrated and calibrated ACSC data as a result of higher *SBR* values measured at the Copenhagen site (*uncalibrated ACSC* right striatum 10.88±2.2, left striatum 11.17±2.3; *calibrated ACSC* right striatum 10.35±2.1, left striatum 10.62±2.2) as compared with the Nice site (*uncalibrated ACSC* right striatum 9.05±2.70, left striatum 8.93±2.52; *calibrated ACSC* right striatum 6.60±1.98, left striatum 6.51±1.84), with the Stockholm site (*uncalibrated ACSC* right striatum 7.90±1.46, left striatum 8.54±1.59; *calibrated ACSC* right striatum 8.08±1.49, left striatum 8.72±1.62), and with the Yvoir site (*uncalibrated ACSC* right striatum 8.52±0.82, left striatum 8.63±0.87; *calibrated ACSC* right striatum 8.84±0.85, left striatum 8.96±0.90) (for all values, $p<0.05$ by post-hoc analysis with Bonferroni correction).

Differences in specific binding ratio between hemispheres

Differences between right and left sides of the brain (Table 2) were observed in men and women for the putamen (right lower than left) for uncorrected data. For the ACSC data, a significant difference was observed only in the caudate (right higher than left) in men. There were no differences in the caudate-to-putamen ratio between hemispheres.

Similar results were obtained with the Southampton method (Table 3). In all subjects, the calculated *SBR* for the right striatum was significantly lower than that for the left striatum.

Age-related decline in specific binding ratio

The relationship between age and *SBR* in men and women is shown in Fig. 3 for the AC and ACSC data analysed with the BRASS method and in Fig. 4 for the corresponding data analysed with the Southampton method. Data from linear regression analysis of *SBR* vs. age and corresponding values of the percentage decline in *SBR* per year are presented in Tables 5 and 6 for the data analysed with the BRASS method and in Table 7 for the data analysed with the Southampton method.

Table 2 Caudate and putamen *SBR* in men and women in both hemispheres. Data from the BRASS analysis are presented. Uncalibrated and calibrated NOACSC data, AC data and ACSC data (means ± SD) are shown. *F* values and corresponding *p* values are presented for the effects of age, gender and imaging site on *SBR*

Correction			Uncalibrated				Calibrated			
			Right caudate	Left caudate	Right putamen	Left putamen	Right caudate	Left caudate	Right putamen	Left putamen
NOACSC (n=139)	Men (n=74)		2.1±0.5	2.0±0.5	1.8±0.4*	1.9±0.5	6.0±1.1	6.0±1.1	5.4±1.1*	5.6±1.1
	Women (n=65)		2.3±0.5	2.3±0.5	2.0±0.5*	2.1±0.5	6.5±1.3	6.6±1.4	5.9±1.3*	6.0±1.2
	F-value	Age	70.4 ($p < 0.001$)	65.5 ($p < 0.001$)	76.3 ($p < 0.001$)	63.1 ($p < 0.001$)	73.3 ($p < 0.001$)	70.5 ($p < 0.001$)	73.7 ($p < 0.001$)	60.6 ($p < 0.001$)
		Gender	6.7 ($p = 0.01$)	8.7 ($p = 0.004$)	7.1 ($p = 0.008$)	6.4 ($p = 0.01$)	9.1 ($p = 0.003$)	12.1 ($p = 0.001$)	8.8 ($p = 0.003$)	8.7 ($p = 0.004$)
		Imaging site	0.0 (n.s.)	0.2 (n.s.)	0.1 (n.s.)	0.5 (n.s.)	5.1 ($p = 0.05$)	3.7 (n.s.)	0.8 (n.s.)	0.3 (n.s.)
AC (n=139)	Men (n=74)		2.4±0.5	2.4±0.5	2.2±0.5	2.2±0.5	5.9±1.1**	5.8±1.1	5.6±1.2	5.6±1.2
	Women (n=65)		2.6±0.5	2.6±0.5	2.4±0.5	2.5±0.5	6.4±1.3	6.4±1.3	6.1±1.2	6.1±1.2
	F-value	Age	74.8 ($p < 0.001$)	70.7 ($p < 0.001$)	73.8 ($p < 0.001$)	81.1 ($p < 0.001$)	65.1 ($p < 0.001$)	62.9 ($p < 0.001$)	53.0 ($p < 0.001$)	58.1 ($p < 0.001$)
		Gender	7.1 ($p = 0.009$)	11.0 ($p = 0.001$)	7.2 ($p = 0.008$)	6.5 ($p = 0.01$)	8.4 ($p = 0.004$)	13.3 ($p < 0.001$)	7.3 ($p = 0.008$)	7.1 ($p = 0.009$)
		Imaging site	0.5 (n.s.)	0.5 (n.s.)	0.5 (n.s.)	1.6 (n.s.)	3.8 ($p = 0.03$)	3.9 ($p = 0.05$)	1.8 (n.s.)	0.5 (n.s.)
ACSC (n=127)	Men (n=69)		3.2±0.6*	3.1±0.6	3.0±0.6	2.9±0.6	6.3±1.2*	6.1±1.2	6.0±1.2	6.0±1.2
	Women (n=58)		3.3±0.6	3.4±0.6	3.1±0.6	3.1±0.6	6.7±1.2	6.7±1.2	6.5±1.2	6.4±1.2
	F-value	Age	38.2 ($p < 0.001$)	34.7 ($p < 0.001$)	45.1 ($p < 0.001$)	39.4 ($p < 0.001$)	30.1 ($p < 0.001$)	27.9 ($p < 0.001$)	30.3 ($p < 0.001$)	31.4 ($p < 0.001$)
		Gender	1.5 (n.s.)	6.2 ($p = 0.01$)	2.9 (n.s.)	3.3 (n.s.)	2.3 (n.s.)	8.0 ($p = 0.005$)	3.3 (n.s.)	3.3 (n.s.)
		Imaging site	7.6 ($p = 0.007$)	4.0 ($p = 0.05$)	6.2 ($p = 0.01$)	5.0 ($p = 0.03$)	2.2 (n.s.)	0.7 (n.s.)	0.3 (n.s.)	0.0 (n.s.)

*Significantly different from the left side; $p<0.05$, paired t test.

**Different from the left side; $p=0.042$, paired t test.

Table 3 Striatal *SBR* in men and women in both hemispheres. Data from the Southampton method are presented. Uncalibrated and calibrated NOACSC data, AC data and ACSC data (means ± SD) are shown. *F* values and corresponding *p* values are presented for the effects of age, gender and imaging site on *SBR*

Correction			Uncalibrated		Calibrated	
			Right striatum	Left striatum	Right striatum	Left striatum
NOACSC (n=139)	Men (n=74)		5.5±1.1*	5.7±1.2	7.7±1.4*	7.9±1.5
	Women (n=65)		6.1±1.4*	6.3±1.4	8.4±1.8*	8.5±1.7
	F value	Age	78.6 ($p < 0.001$)	66.9 ($p < 0.001$)	58.2 ($p < 0.001$)	47.1 ($p < 0.001$)
		Gender	8.7 ($p = 0.004$)	7.2 ($p = 0.008$)	9.1 ($p = 0.003$)	7.5 ($p = 0.007$)
		Imaging site	1.3 (n.s.)	0.7 (n.s.)	0.0 (n.s.)	0.1 (n.s.)
AC (n=139)	Men (n=74)		6.5±1.3*	6.7±1.3	7.9±1.5*	8.1±1.5
	Women (n=65)		7.1±1.4*	7.2±1.4	8.7±1.7*	8.9±1.8
	F value	Age	75.1 ($p < 0.001$)	67.9 ($p < 0.001$)	62.2 ($p < 0.001$)	53.4 ($p < 0.001$)
		Gender	10.5 ($p = 0.002$)	9.0 ($p = 0.003$)	13.1 ($p < 0.001$)	11.2 ($p = 0.001$)
		Imaging site	0.8 (n.s.)	1.0 (n.s.)	0.7 (n.s.)	0.8 (n.s.)
ACSC (n=127)	Men (n=69)		8.8±1.7*	9.0±1.7	8.6±1.6*	8.8±1.5
	Women (n=58)		9.7±2.1*	9.9±2.1	9.6±1.9*	9.8±2.0
	F value	Age	60.8 ($p < 0.001$)	49.1 ($p < 0.001$)	45.7 ($p < 0.001$)	37.1 ($p < 0.001$)
		Gender	9.7 ($p = 0.002$)	8.8 ($p = 0.004$)	11.4 ($p = 0.001$)	10.8 ($p = 0.001$)
		Imaging site	12.8 ($p < 0.001$)	10.0 ($p = 0.002$)	5.8 ($p = 0.02$)	4.0 ($p = 0.05$)

*Significantly different from the left side; $p<0.05$, paired *t* test

BRASS method No differences in *r* values were observed between men and women for both uncalibrated and calibrated data. No differences in *r* values were observed for the NOACSC, AC and ACSC data. In men, the age-related decrease in striatal *SBR* was 0.42–0.58 %/year and 0.41–0.49 %/year for uncalibrated and calibrated data, respectively. In women, the age-related decrease in striatal *SBR* was 0.48–0.67 %/year and 0.44–0.60 %/year for uncalibrated and calibrated data, respectively.

Southampton method Similar to the data analysed with the BRASS method, there was no difference in *r* values between men and women and for the NOACSC, AC and ACSC data. The decline in striatal *SBR* was 0.48–0.56 %/year in men and 0.55–0.66 %/year in women for uncalibrated data and 0.41–0.48 %/year in men and 0.50–0.57 %/year in women for calibrated data.

Discussion

This study was designed to generate a large database of [^{123}I]FP-CIT SPECT scans of healthy controls across a wide age range and using different SPECT systems. The database generated by the ENC-DAT study included data obtained from 13 different European centres. The SPECT data were collected using mainly dual-head SPECT systems and also triple-head SPECT systems, representing the most typical systems currently available in nuclear medicine departments. Dedicated SPECT systems including the Ceraspect and the Neurofocus were also used, but in the final analysis only the data from dual- and triple-head systems (with the exception of the Mediso Nuclide Xring 4HR) were used. Therefore, a total of 139 healthy subjects with ages ranging from 20 to 83 years were included.

SPECT scans were acquired with triple energy windows to apply scatter correction and analysed centrally by a core

Table 4 Striatal *SBR* values obtained with the BRASS method at different imaging sites. Uncalibrated ACSC data are shown

*Significantly higher than from the other centres; $p<0.05$ post-hoc analysis with Bonferroni correction.

Imaging site	Right caudate	Right putamen	Left caudate	Left putamen
Copenhagen	3.95±0.61*	3.63±0.69*	3.87±0.69*	3.65±0.65*
Leipzig	2.75±0.43	2.57±0.20	2.77±0.44	2.43±0.27
Leuven	3.03±0.37	2.78±0.46	2.86±0.46	2.72±0.44
Munich	3.25±0.54	3.08±0.46	3.18±0.51	3.03±0.44
Stockholm	3.09±0.60	3.00±0.57	3.17±0.52	2.93±0.50
Yvoir	2.92±0.61	2.68±0.41	2.87±0.47	2.79±0.41

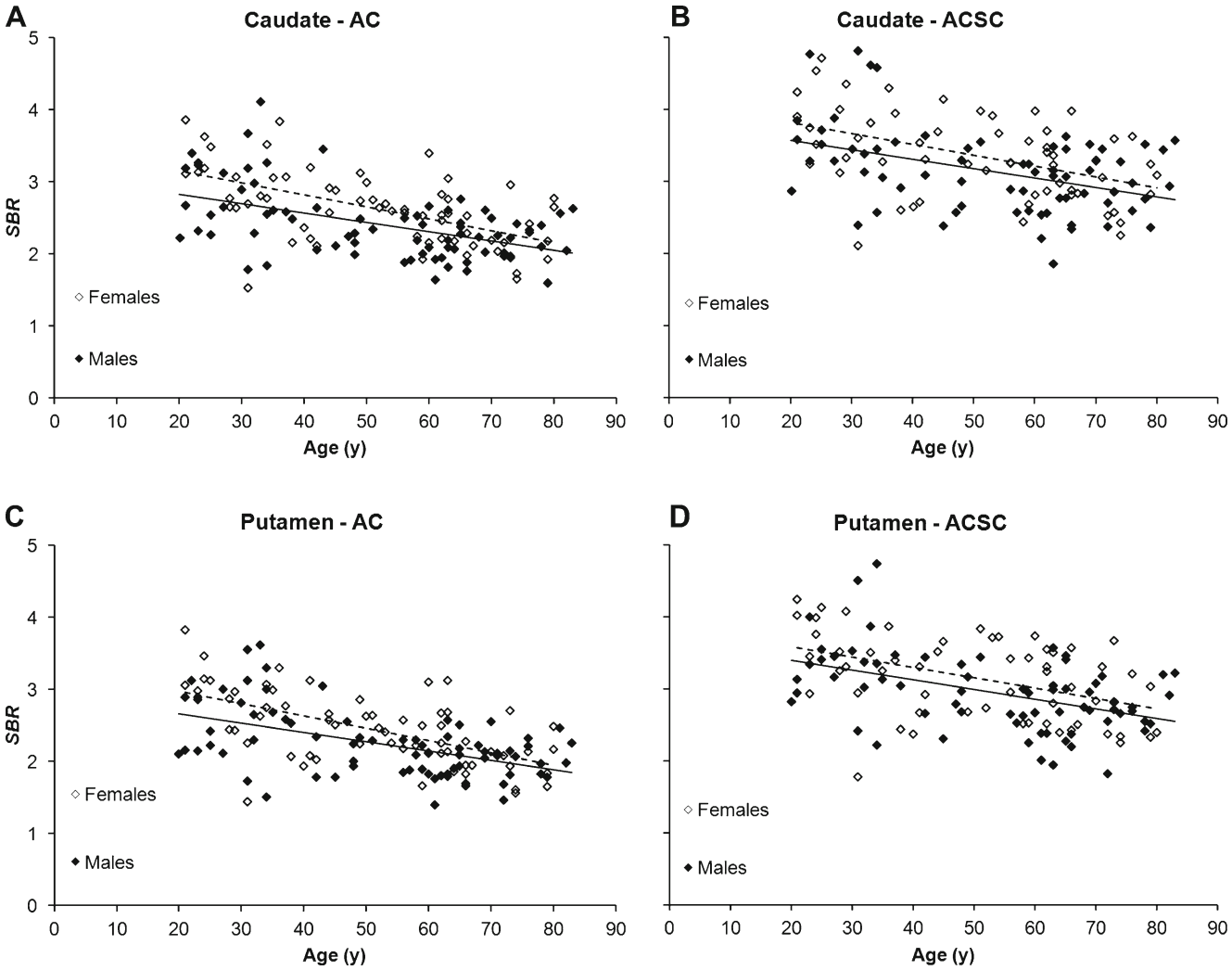

Fig. 3 Caudate (**a**, **b**) and putamen (**c**, **d**) *SBR* values in men and women as a function of age calculated using the BRASS method for corrected (AC and ACSC) data. Data are the average of right and left side

laboratory using two different quantification methods. The first method involved the BRASS analysis, which is commonly used for the quantification of [^{123}I]FP-CIT SPECT in the clinical setting and also includes a regional

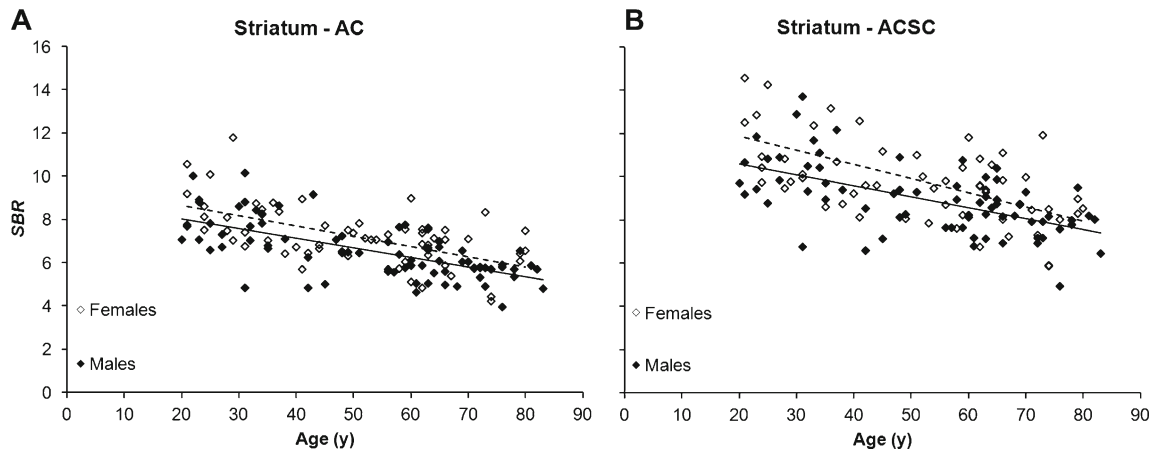

Fig. 4 *SBR* values obtained in men and women as function of age calculated using the Southampton method for corrected data (**a** AC data, **b** ACSC data). Data are the average of right and left side

Table 5 Linear regression analysis (*r* values, intercepts and slopes) of DAT availability vs. age in the caudate, putamen and whole striatum in men and women. NOACSC data, AC data and ACSC data from the BRASS analysis are shown. Values in parentheses are 95 % confidence intervals for the intercepts and slopes

Correction			Uncalibrated			Calibrated		
			Caudate	Putamen	Striatum	Caudate	Putamen	Striatum
NOACSC	Men	*r*	−0.58	−0.57	−0.59	−0.58	−0.53	−0.57
		Intercept	2.80 (2.54–3.07)	2.59 (2.33–2.84)	2.68 (2.43–2.94)	7.79 (7.14–8.43)	7.11 (6.44–7.78)	7.43 (6.80–8.05)
		Slope	−0.014 (−0.019–0.010)	−0.014 (−0.018–0.009)	−0.014 (−0.019–0.009)	−0.035 (−0.047–0.023)	−0.032 (−0.044–0.020)	−0.033 (−0.044–0.022)
	Women	*r*	−0.60	−0.62	−0.62	−0.63	−0.66	−0.67
		Intercept	3.16 (2.84–3.47)	2.97 (2.66–3.28)	3.05 (2.74–3.35)	8.95 (8.16–9.73)	8.25 (7.66–8.93)	8.59 (7.89–9.29)
		Slope	−0.017 (−0.023–0.012)	−0.018 (−0.023–0.012)	−0.018 (−0.023–0.012)	−0.047 (−0.061–0.032)	−0.044 (−0.057–0.032)	−0.046 (−0.059–0.033)
AC	Men	*r*	−0.58	−0.57	−0.59	−0.54	−0.47	−0.52
		Intercept	3.19 (2.91–3.47)	3.01 (2.73–3.28)	3.09 (2.82–3.36)	7.40 (6.77–8.03)	7.13 (6.42–7.85)	7.30 (6.65–7.94)
		Slope	−0.015 (−0.020–0.010)	−0.015 (−0.020–0.010)	−0.015 (−0.020–0.010)	−0.031 (−0.042–0.019)	−0.029 (−0.042–0.016)	−0.030 (−0.042–0.019)
	Women	*r*	−0.63	−0.66	−0.65	−0.64	−0.65	−0.67
		Intercept	3.57 (3.27–3.88)	3.39 (3.10–3.68)	3.47 (3.18–3.76)	8.66 (7.92–9.39)	8.34 (7.65–9.03)	8.54 (7.86–9.22)
		Slope	−0.018 (−0.024–0.013)	−0.019 (−0.024–0.013)	−0.018 (−0.024–0.013)	−0.045 (−0.058–0.031)	−0.044 (−0.056–0.031)	−0.045 (−0.057–0.032)
ACSC	Men	*r*	−0.48	−0.53	−0.53	−0.44	−0.46	−0.48
		Intercept	3.95 (3.58–4.33)	3.77 (3.43–4.11)	3.85 (3.51–4.19)	7.69 (6.90–8.47)	7.51 (6.77–8.25)	7.64 (6.91–8.36)
		Slope	−0.015 (−0.022–0.009)	−0.016 (−0.022–0.009)	−0.015 (−0.021–0.009)	−0.028 (−0.042–0.014)	−0.028 (−0.041–0.015)	−0.029 (−0.041–0.016)
	Women	*r*	−0.54	−0.54	−0.56	−0.50	−0.50	−0.52
		Intercept	4.26 (3.86–4.66)	4.01 (3.62–4.40)	4.12 (3.74–4.50)	8.35 (7.53–9.18)	8.01 (7.23–8.80)	8.24 (7.46–9.02)
		Slope	−0.018 (−0.025–0.010)	−0.017 (−0.024–0.010)	−0.018 (−0.025–0.011)	−0.033 (−0.048–0.017)	−0.031 (−0.046–0.017)	−0.033 (−0.047–0.018)

Table 6 Age-related decline in DAT availability in the caudate, putamen and whole striatum expressed as percentage change per year in men and women. NOACSC data, AC data and ACSC data from the BRASS analysis are shown

Correction		Uncalibrated			Calibrated		
		Caudate	Putamen	Striatum	Caudate	Putamen	Striatum
NOACSC	Men	0.56	0.61	0.58	0.49	0.49	0.49
	Women	0.61	0.69	0.67	0.59	0.60	0.60
AC	Men	0.52	0.55	0.54	0.46	0.44	0.45
	Women	0.56	0.64	0.58	0.58	0.59	0.59
ACSC	Men	0.41	0.46	0.42	0.39	0.40	0.41
	Women	0.46	0.46	0.48	0.43	0.42	0.44

analysis of caudate and putamen specific binding ratios. The second method is the Southampton method which measures the *SBR* in the whole striatum, but also accounts for partial volume effects by measuring the whole striatal radioactivity normalized by the volume of the striatum. Data were analysed without any correction (NOACSC), with attenuation correction (AC), and with attenuation and scatter correction (ACSC). In addition, phantom data measured with different striatum-to-background ratios were used to obtain calibrated data for each SPECT system and for each method of analysis.

The main objectives of this study were to examine: (1) gender differences in DAT availability; (2) the age-related decline in DAT availability; (3) potential differences among the NOACSC, AC and ACSC data. The two main findings of this study were that women had significantly higher DAT availability than men and that there was an age-related decline in DAT availability of 5.5 % per decade.

Imaging site and DAT availability

SPECT data acquired at 3 h and 4 h in five centres showed a slight (9 %) but significantly higher *SBR* measured at 4 h than at 3 h, mainly in the ACSC data (12.8 %). This effect might have been related to the fact that a perfect transient equilibrium condition had not been achieved at 3 h, and thus DAT availability might have been slightly underestimated. Only in two centres, Amsterdam and Leipzig, were data at 4 h included in the final analysis. We do not believe that these data significantly influenced the results, since we did not find any effect of imaging site on *SBR* obtained from NOACSC and AC data. However, we did observe a significant effect of imaging site on the ACSC uncalibrated data, mainly due to higher values of *SBR* measured in the data from the Copenhagen site. The reason of this difference is not clear, but it might have depended on the effect of scatter correction on the data acquired on the IRIX SPECT system at the Copenhagen site, probably related to lower estimation of the scatter fraction in the higher energy window relative to the photopeak window using the triple energy window method.

Gender differences in DAT availability

Previous studies have already shown higher DAT availability in women than in men [10, 28, 29], whereas other studies have not shown such a gender difference [9, 30]. A previous study with [^{123}I]β-CIT SPECT on DAT availability and age included a similar number of healthy controls as our study, but did not report any gender differences [31]. Therefore, to our knowledge, this is the largest study showing that women have higher DAT availability than men. This finding might be related to higher expression of the DAT in the striatum of the women (i.e. higher density), which might be related to higher dopamine transmission or turnover in women than in men due for instance to hormonal effects [32]. Alternatively, gender differences might also be related to differences in the volume of the striatum [26]. Therefore, it is possible that the total number of striatal DAT binding sites is the same in men and women, but because of the larger volume of the striatum in men, the concentration of DAT binding sites is higher in women than men. This hypothesis is supported by the fact that if the SPECT data analysed with the Southampton method were expressed relative to a standard volume of the striatum as in the original method [25] rather than taking into account the gender difference in volume reported [26], no differences between men and women were seen (data not shown). Therefore, it is likely that the difference in DAT availability between men and women is related to differences in striatal volumes between genders.

An accurate estimation of *SBR* in men and women using the Southampton method would require a detailed volumetric assessment of the striatum using T1-weighted MR images obtained in the same subjects, which was beyond the scope of the present study. The gender differences in DAT availability were significant in all cases except for the ACSC data of the right caudate and the putamen bilaterally

Table 7 Linear regression analysis (*r* values, intercepts and slopes) of DAT availability vs. age and age-related DAT decline in the whole striatum using the Southampton method expressed as percentage change per year in men and women. NOACSC data, AC data and ACSC data from the BRASS analysis are shown. Values in parentheses are 95 % confidence intervals for the intercepts and slopes

Correction		Uncalibrated				Calibrated			
		r	Intercept	Slope	DAT decline (%/year)	*r*	Intercept	Slope	DAT decline (%/year)
NOACSC	Men	−0.62	7.65 (7.03–8.28)	−0.038 (−0.050–0.027)	0.56	−0.51	9.88 (9.02–10.74)	−0.040 (−0.055–0.024)	0.44
	Women	−0.65	8.78 (7.99–9.58)	−0.051 (−0.066–0.036)	0.66	−0.60	11.43 (10.37–12.50)	−0.059 (−0.078–0.039)	0.57
AC	Men	−0.64	8.90 (8.21–9.59)	−0.044 (−0.057–0.032)	0.55	−0.59	10.43 (9.61–11.26)	−0.046 (−0.061–0.031)	0.48
	Women	−0.61	9.63 (8.78–10.47)	−0.048 (−0.063–0.032)	0.56	−0.57	11.62 (10.53–12.71)	−0.056 (−0.076–0.036)	0.53
ACSC	Men	−0.58	11.60 (10.62–12.57)	−0.050 (−0.068–0.033)	0.48	−0.51	10.94 (9.97–11.91)	−0.041 (−0.058–0.024)	0.41
	Women	−0.58	13.18 (11.84–14.52)	−0.065 (−0.090–0.041)	0.55	−0.55	12.65 (11.39–13.91)	−0.057 (−0.081–0.034)	0.50

analysed with the BRASS method. This lack of significance might have been related to the effect of scatter correction on the slope of the regression line between DAT availability and age. In the case of the NOACSC (data not shown) and AC data (Fig. 3), the regression lines in women and men showed greater separation at earlier decades, whereas in the case of ACSC this effect was not visible. This effect could have influenced the statistical power of the analysis. In addition, since this effect was not evident in the data analysed with the Southampton method, which included the whole striatum, it could have been related to the effect of scatter correction on the quantification of the regional DAT availability in the smaller regions of interest of the caudate and putamen.

Men tended to have higher DAT availability in the right striatum than in the left striatum, whereas no such difference was found in women. Analysis with the BRASS method showed a difference between the right and left putamen in the NOACSC data and between the right and left caudate in the AC and ACSC data. This apparent discrepancy could have been related to small inaccuracies in the attenuation correction procedure related to the placement of the elliptical region of interest on reconstructed SPECT scans, in which the brain contour might be difficult to accurately identify.

Age-related decline in DAT availability

The age-related decline in DAT availability measured in this study was between 4 % and 6.7 % per decade, depending on the method of analysis used. This value is in agreement with those found in previous studies that have shown values ranging from 4 % to 8 %. The other large study of DAT availability and age performed with [^{123}I]β-CIT SPECT showed an average 6.5 % decline in DAT per decade, which was slightly higher than that found in our study (5.6 % per decade) using AC data [31]. This slight difference might have been related to the fact that our study included data from many centres. The fact that the data came from different SPECT systems could have contributed to a slightly higher variability in the estimation of the regression line and the percentage decline per decade. In this regard, the calibration of the data using factors obtained from phantom data did not have any visible effect on the estimate of the regression line or on the variability of the outcome measures. Therefore, we believe that our results are quite representative of the decrease in DAT availability in the striatum, although the data were acquired with different SPECT systems. The type of analysis also seemed to have an effect on the estimate of the age-related DAT decline. The ACSC data showed on average lower *r* values and lower percent decline in DAT availability with age than the NOACSC and AC data. This effect could have been related to slightly higher

noise introduced by the triple energy window scatter correction method that could have affected the overall variability of the outcome measures across all subjects. Alternative methods of scatter correction could be investigated to assess whether similar differences between outcome measures of DAT availability with and without scatter correction in relation to age are found.

The differences between the data with and without scatter correction and the lack of differences between the uncalibrated and the calibrated data suggest that in multicentre studies, even if the data are processed consistently by a core laboratory, simple approaches applied to data corrected for attenuation or even without any correction could be sufficient for the quantification of DAT availability with SPECT. Improved accuracy would require more complex approaches based for instance on the delineation of the contour for attenuation correction on the projection data [33] and on alternative methods of scatter correction (e.g. convolution subtraction) to reduce the noise of the data. These methods could be explored in the future using the same dataset as used in this study.

In this study, we calculated linear regression parameters and their confidence intervals for the age-related decline in DAT availability in both men and women. With the help of the parameters (intercept and slope) displayed in Table 5, it would be possible to calculate the expected *SBR* in relation to age and gender if the BRASS analysis and similar hardware and processing algorithm were applied. For example, the 95 % confidence interval of the expected uncalibrated *SBR* in the putamen for a 50-year-old man using the BRASS analysis and AC data would range between $(50\times-0.020+2.73)=1.73$ and $(50\times-0.010+3.28)=2.78$, with a mean of $50\times-0.015+3.01=2.26$.

Conclusion

A large database of [^{123}I]FP-CIT SPECT scans of healthy controls aged between 20 and 83 years was generated. The analysis of the data with methods used in the clinical setting confirmed previous findings of higher DAT availability in women than in men and an age-related DAT decline of 5.5 % per decade. These SPECT data can be used as reference data for nuclear medicine departments performing [^{123}I]FP-CIT imaging, as a dataset for the evaluation of additional methods of quantification, and for future clinical trials using [^{123}I]FP-CIT as an imaging biomarker for DAT quantification. Finally, the implementation of this dataset in commercially available image analysis software is currently underway.

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