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Original Article

Influence of CT-based attenuation correction on dopamine transporter SPECT with [^{123}I]FP-CIT

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Abstract: Dopamine transporter (DAT) imaging using single-photon emission computed tomography (SPECT) and ^{123}I-labelled radiopharmaceuticals like [^{123}I]FP-CIT is an established part in the diagnostic work-up of parkinsonism. Guidelines recommend attenuation correction (AC), either by a calculated uniform attenuation matrix (calAC) or by a measured attenuation map (nowadays done by low-dose CT; CTAC). We explored the impact of CTAC compared to conventional calAC on diagnostic accuracy and the use of DAT availability as a biomarker of nigrostriatal integrity. Integrated SPECT/CT studies with [^{123}I]FP-CIT were performed in patients with Parkinson's disease (PD; n = 15) and essential tremor (ET; n = 15). SPECT data was reconstructed with calAC, CTAC and without AC (noAC). Regional DAT availability was assessed by uniform volume-of-interest analyses providing striatal binding potential (BP_{ND}) estimates. BP_{ND} values were compared among methods and correlated with clinical parameters. Compared to calAC, both CTAC and noAC provided significantly lower, but highly linearly correlated BP_{ND} estimates (R^2 = 0.96). Diagnostic performance to distinguish between patients with PD and those with ET was very high and did not differ between AC methods. CTAC and noAC data tended so show a stronger correlation with severity and duration of disease in PD and age in ET than did calAC. Defining the reference region on low-dose CT instead of SPECT did not consistently alter findings. [^{123}I]FP-CIT SPECT provides a very high diagnostic accuracy for differentiation between PD and ET that is not dependent on the employed AC method. Preliminary correlations analyses suggest that BP_{ND} estimates derived from CTAC represent a superior biomarker of nigrostriatal integrity.

Keywords: Single-photon emission computed tomography, attenuation correction, dopamine transporter, FP-CIT, Parkinson's disease, essential tremor

Introduction

Pre-synaptic dopamine transporter (DAT) imaging using ^{123}I-labelled radiopharmaceuticals like N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane ([^{123}I]FP-CIT) is an established part in the diagnostic work-up of parkinsonism to distinguish patients with parkinsonism or tremor due to nigrostriatal degeneration (most notably Parkinson's disease, PD) from those without neurodegeneration (e.g., essential tremor, ET) (for a recent review see [1]). Striatal DAT binding in PD is correlated with symptom severity and disease duration at time of imaging (e.g., [2]). [^{123}I]FP-CIT SPECT can also be used to assess the rate of progression in PD, which may be of particular value in therapeutic (e.g., neuroprotective) trials [3]. Beyond changes associated with disease-related nigrostriatal degeneration, DAT availability estimated by [^{123}I]FP-CIT SPECT also exhibits a well-known physiological age-dependent decline (e.g., [4]). Taken together, DAT SPECT may thus not only serve as a differential diagnostic tool but also as a valuable, objective biomarker of nigrostriatal integrity in addition to clinical ratings.

Whereas visual scan interpretation by a trained rater is sufficient in many diagnostic situations, additional quantitative analyses are still helpful to increase the reproducibility of clinical reports and to minimize inter-observer variability [5]. Furthermore, quantitative approaches are in-

dispensable for monitoring of rather subtle effects of disease progression and medical therapies (e.g., [6]). However, accuracy of image quantification and comparability among institutions relies on numerous factors, ranging from actual data acquisition (e.g., time point and camera settings used [7]) to data reconstruction and image analyses (e.g., reconstruction algorithm, corrections for scatters and photon attenuation [8, 9]. Several studies demonstrated that SPECT quantification benefits from (three-dimensional) iterative reconstruction (opposed to filtered back-projection, FBP), resolution recovery (correction for collimator blurring) and the use of scatter and attenuation corrections [8-12]. Attenuation correction (AC) by means of either a calculated uniform correction matrix according to Chang (calculated AC, calAC) or a measured non-uniform attenuation map (nowadays done by low-dose CT, CTAC) is recommended by current European and US guidelines [13, 14]. From a theoretical point of view, CTAC can be assumed to be superior to calAC since it accurately accounts for the individual anatomy that can hardly be approximated by a uniform attenuation matrix (esp. in posterior fossa or close to the base of the skull). Furthermore, calAC may be compromised by errors in head contour definition (usually threshold-based, possibly requiring operator interference) [15], while CTAC is susceptible to possible head movements between transmission and emission scans [12] and causes some, albeit little additional radiation exposure [16].

Whereas several studies employing quantitative analyses and clinical correlations suggest that CTAC is superior to calAC in brain perfusion SPECT [10, 17, 18], its value in DAT imaging is controversial: An early study using [^{57}Co]- and [^{123}I]-transmission scanning showed that non-uniform AC provides higher absolute quantification accuracy than calAC, especially when contour definition for calAC relied on the DAT emission scan. However, absolute errors in the occipital reference and striatal target regions counter-balanced each other to some extent so that the overall diagnostic benefit (PD patients *vs*. healthy controls) of non-uniform AC compared to calAC or even omitting AC was negligible [15]. A more recent study employing SPECT/CT with [^{123}I]FP-CIT in 44 consecutive patients with parkinsonism reported superior image quality for the use of iterative reconstruction and CTAC compared to FBP and calAC. Results by both approaches were highly correlated (r > 0.95). However, they did not contemplate the effect of CTAC *vs*. calAC using the same reconstruction method [11]. Finally, Warwick et al. [12] found that recovery and noise-characteristics were optimal when using CTAC in striatal phantom studies, whereas uniform calAC performed better on actual patient data (compensation for collimator blurring was employed in both settings). According to authors, this discrepancy may be due to subtle patient movements between SPECT and CT. Given the ongoing discussion, aforementioned guidelines do not offer a clear recommendation in favour of CTAC or calAC up to now [13, 14].

Against this background, we explored the impact of CTAC in comparison to conventional calAC and completely omitting AC (noAC) on the diagnostic accuracy of [^{123}I]FP-CIT SPECT for the differentiation between PD and ET. Furthermore, we also investigated the impact of AC on the use of DAT availability as a biomarker of nigrostriatal integrity by assessing the correlations between imaging findings and clinical variables (i.e., duration and severity of disease in PD; age in ET). Finally, the value of a possibly more accurate CT-based delineation of the reference brain region for [^{123}I]FP-CIT SPECT quantification was assessed.

Material and methods

Patients

The data of 15 consecutive patients each with idiopathic Parkinson's disease (PD; 6 female, 9 male, mean ± standard deviation age = 64 ± 12.8 years) and essential tremor (ET; 9 female, 6 male, 61.8 ± 15.8 years-old) (n = 30 in total), who were referred to our department for ^{123}I-FP-CIT SPECT during July to December, 2013, were selected for the present retrospective analyses. Clinical diagnosis was established by a board-certified neurologist specialized in movement disorders who was blinded to imaging results. Information on Hoehn and Yahr (H&Y) stage, Unified Parkinson's Disease Rating Scale Part 3 (UPDRS-3) scores and symptom duration were gathered during clinical routine. PD patients had a mean (± standard deviation) UPRDS-3 score of 38.1 ± 33.7, H&Y stage of 2.91 ± 1.14 and disease duration of 5.8 ± 6.1 years. All patients gave written informed con-

Table 1. Results of regional analyses

	Parkinson's disease				Essential tremor				Area under the ROC curve			
AC Method	calAC	CTAC	CTAC'	noAC	calAC	CTAC	CTAC'	noAC	calAC	CTAC	CTAC'	noAC
BP_{ND} CN	2.35 ± 1.46	1.79 ± 1.08	1.89 ± 1.11	1.52 ± 1.03	4.98 ± 1.04	3.93 ± 0.83	4.01 ± 0.89	3.50 ± 0.71	0.929 ± 0.046	0.942 ± 0.041	0.938 ± 0.047	0.933 ± 0.047
BP_{ND} PUT	1.67 ± 1.10	1.20 ± 0.79	1.29 ± 0.79	1.00 ± 0.80	4.50 ± 1.01	3.49 ± 0.76	3.57 ± 0.82	3.10 ± 0.69	0.982 ± 0.017	0.987 ± 0.015	0.982 ± 0.019	0.982 ± 0.017
C/P ratio	1.45 ± 0.19	1.55 ± 0.20		1.69 ± 0.36	1.12 ± 0.09	1.14 ± 0.10		1.14 ± 0.10	0.964 ± 0.027	0.987 ± 0.015		0.982 ± 0.017
AI%	25.2% ± 24.3%	29.2% ± 33.5%		32.0% ± 30.7%	7.3% ± 5.9%	10.3% ± 7.0%		7.8% ± 5.7%	0.742 ± 0.098	0.627 ± 0.116		0.782 ± 0.106

Given are mean values ± standard deviation of regional binding potential (BP_{ND}; side-averaged) values and secondary measures (C/P ratio, caudate/putamen BP_{ND} ratio, side-averaged; striatal asymmetry index, AI%) for caudate nucleus (CN) and putamen (PUT) for the different attenuation correction (AC) methods (calCAL, calculated AC according to Chang; CTAC, computer tomography [CT]-based AC; CTAC', CTAC with reference region defined on CT; noAC, no AC performed); area (± standard error) under the receiver operating characteristics (ROC) curve for the differentiation between patients with Parkinson's disease (PD; n=15) and those with essential tremor (ET, n=15). Mean regional BP_{ND} values were significantly lower in patients with PD compared to those with ET for each AC method (all $p < 0.001$), whereas mean C/P ratio (all $p < 0.001$) and mean AI% (all $p < 0.05$) were significantly higher in PD compared to ET. There were no significant differences between the areas under the ROC curves provided by the different AC methods (all $p > 0.1$); note that ROC analyses were performed with BP_{ND} values contralateral to the clinically most affected side in PD *vs*. side with lower binding in ET.

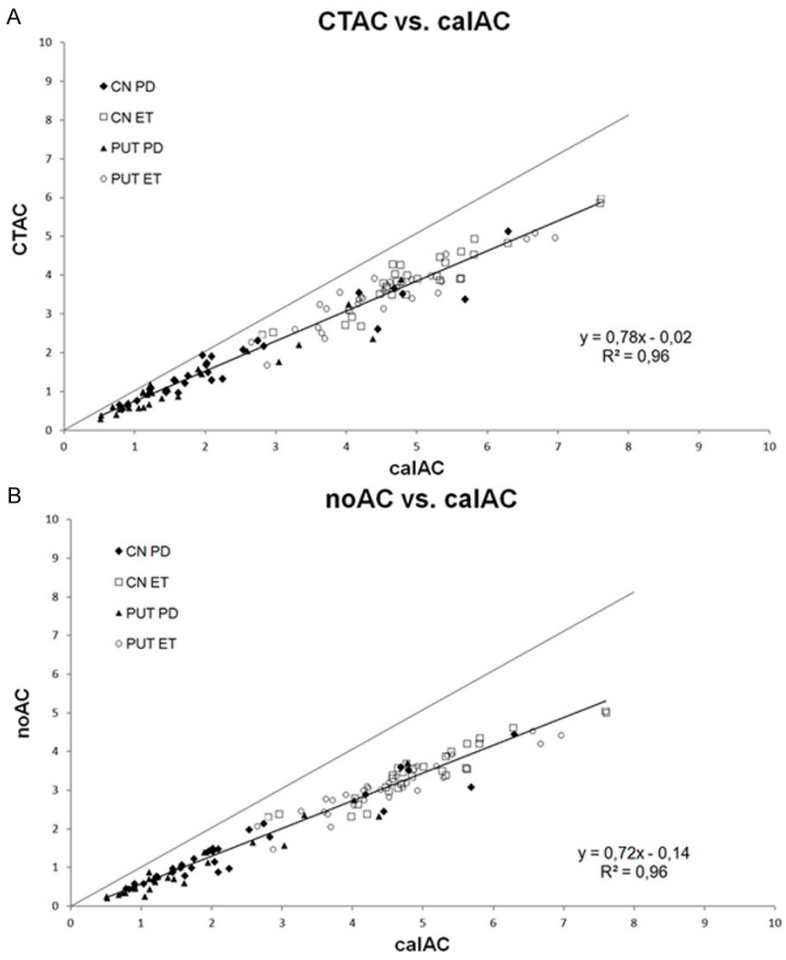

Figure 1. Scatter plots and linear regression analyses between regional binding potential (BP_{ND}) estimates derived from SPECT analyses with CT-based attenuation correction (CTAC; A) and without attenuation correction (noAC; B) in comparison to calculated AC (calCAC). Data points depict BP_{ND} estimates of left and right caudate nucleus and putamen in 15 patients each with Parkinson's disease (closed symbols) and essential tremor (open symbols), respectively. Linear regression lines are given.

sent. As all data were acquired in the clinical routine as part of the diagnostic work-up, additional approval was waived by the local ethics committee.

Imaging

Datasets were acquired on a dual-headed integrated SPECT/CT system (Symbia T2; Siemens, Erlangen, Germany) equipped with a MELP (medium-energy low penetration) collimator at exactly 180 min after injection of 177 ± 5 MBq of [^{123}I]FP-CIT (GE Healthcare, Munich, Germany). Acquisition parameters were as follows: 60 projections of 40 s each, photopeak window of 159keV ± 15%, matrix 128 × 128, zoom factor 1.23. Reconstruction was performed using OSEM 3D (including resolution recovery) with 8 subsets, 8 iterations and 8 mm Gaussian filtering as previously described [9]. Triple energy window scatter correction was applied. In addition to omitting attenuation correction (noAC), we employed Chang's calculated AC (calAC; μ = 0.12/cm) and CT-based AC (CTAC) using low-dose CT (Care dose modulation; 130 kV, slice thickness 0.5 cm, acquisition time 0.8 s; reconstructed using a B08s kernel). These analyses were done using the manufacturer software (e.soft, Siemens Healthcare, Erlangen, Germany).

Data analysis

All subsequent analyses were performed using the commercial software package PMOD (Version 3.2; PMOD Technologies Ltd, Adliswil, Switzerland). All three datasets per patient (noAC, calAC and CTAC) were summed to give a single unified SPECT dataset, which was used for re-alignment to AC-PC orientation and volume of interest (VOI) delineation employing a standardized VOI set. The latter comprised paired VOI for bilateral caudate nucleus, putamen and whole striatum and a large bilateral occipital lobe reference VOI (each placed on the three consecutive slices with maximum striatal uptake). Striatal VOI were adjusted for position and rotation, while the occipital reference VOI was also adjusted for configuration of the occipital lobe. The re-alignment parameters and adjusted VOI set were then applied to each individual dataset (9). In addition to the conventional definition of the occipital reference region on SPECT (used for noAC, calAC and CTAC), we also investigated the effect of low-dose CT-based reference region definition (blinded for SPECT data) for

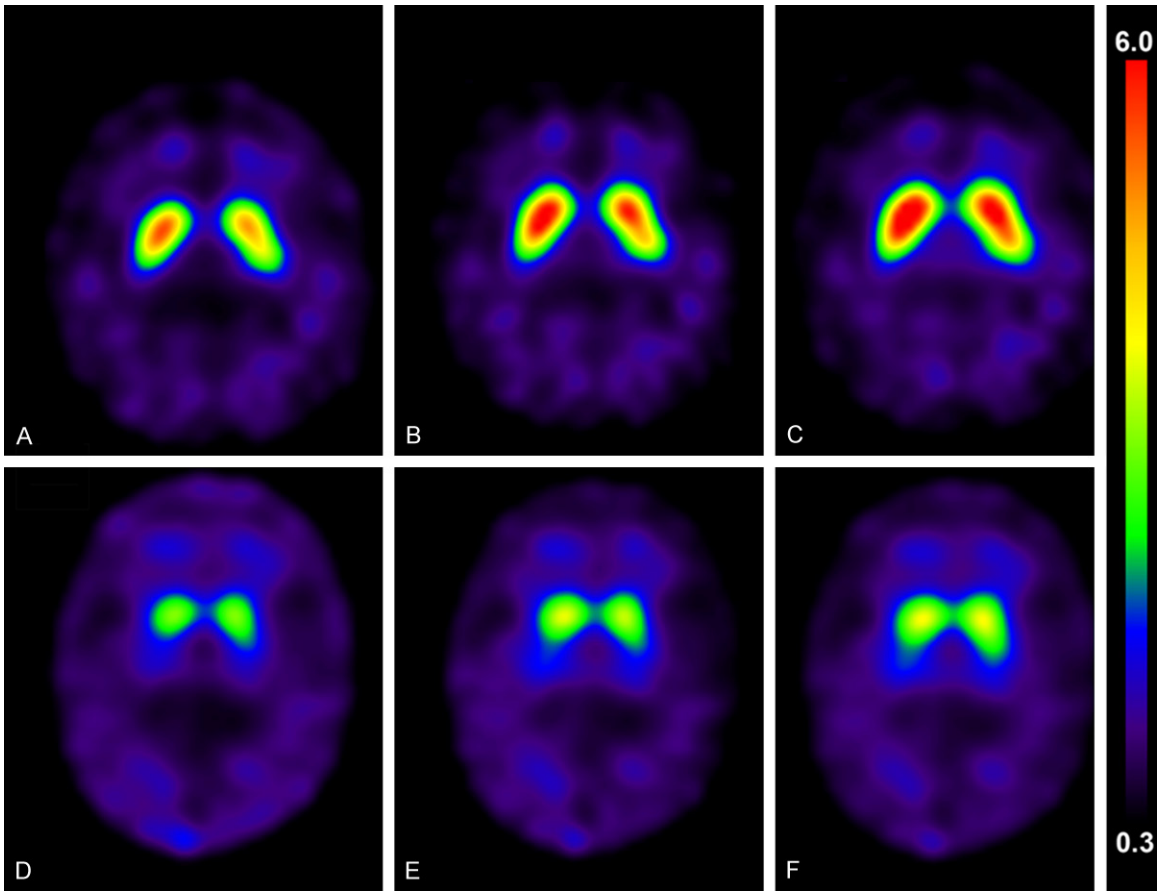

Figure 2. Representative SPECT images given by the different attenuation correction (AC) methods in a patient with essential tremor (ET; A-C) and Parkinson's disease (PD; D-F). Upper (A-C) and lower rows (D, E) give representative transaxial SPECT images of striatal dopamine transporter binding in a patient with ET and PD, respectively. (A and D) no AC; (B and E) CT-based AC; (C and F) calculated AC. Parametric images scaled to occipital tracer uptake.

CTAC data (referred to as CTAC'). Of note, CT-based striatal VOI definition was not pursued since low-dose CT scanning does not allow for a reliable definition of striatal structures. Average regional uptake values from VOI analyses were used to calculate regional estimates of the binding potential (BP_{ND}; equal to distribution volume ratio - 1) for caudate nucleus (CN), putamen (PUT) and whole striatum (STR) (for both hemispheres) using the occipital cortex as a reference region (*19*). Additionally, the CN to PUT BP_{ND} ratio (C/P ratio) and the asymmetry index of whole striatal DAT availability were assessed. The latter was calculated as the BP_{ND} difference ($STR_{ipsilateral}$ - $STR_{contralateral}$) relative to the mean value of both striata (AI%, expressed as percent), whereby ipsilateral and contralateral refer to the clinically most affected body side in PD. In ET, the side with lower striatal uptake was defined as contralateral.

Statistical analysis

The commercial software packages SPSS 20.0 (IBM Corp., Armonk, NY) and MedCalc (V12.4; MedCalc Software, Ostend, Belgium) were used for statistical analyses. Linear regression analyses were employed to explore the association between BP_{ND} estimates provided by the different AC methods. Differences in mean regional BP_{ND} values and secondary measures (side-averaged C/P ratio and striatal AI%) were assessed by paired (between different AC methods) and unpaired (between patient groups) Student's t tests. Receiver operating characteristics (ROC) curves were plotted and analyzed for differences in the areas under the curves (AUC) to compare the diagnostic performance of the different AC methods to differentiate between patients with PD and those with ET. ROC analyses were performed with BP_{ND} values contralateral to the clinically most

Table 2. Association between striatal dopamine transporter availability and clinical parameters

	Parkinson's disease			Essential Tremor
Para-meter	UPDRS Part 3 (motor score)	Hoehn & Yahr stage	symptom duration	age
calAC	-0.34	-0.49	-0.48	-0.55*
CTAC	-0.59*	-0.61*	-0.49	-0.74‡
CTAC'	-0.52	-0.51	-0.76‡	-0.68‡
noAC	-0.58*	-0.53*	-0.52	-0.64†

Spearman's correlation coefficients *rho* between mean putaminal binding potential (BP_{ND}) and clinical parameters in patients with Parkinson's disease (n=15; UPDRS-3, Hoehn & Yahr stage and disease duration data were available in 12, 11 and 14 patients, respectively), and between mean striatal BP_{ND} and age in patients with essential tremor (n=15). UPDRS, Unified Parkinson's Disease Rating Scale; for additional abbreviations see **Table 1**; *$p < 0.05$, †$p \leq 0.01$, ‡$p \leq 0.005$.

affected side in PD *vs*. side with lower binding in ET. Finally, the association between striatal BP_{ND} estimates and clinical parameters (H&Y, UPDRS-3 and disease duration) in PD and age in ET was explored by Spearman's non-parametric correlation coefficient *rho*. *P* values < 0.05 were considered statistically significant.

Results

Assessment of regional striatal dopamine transporter availability

Table 1 summarizes regional estimates of BP_{ND} and secondary measures calculated thereof (i.e., C/P ratio and AI%). As depicted in **Figure 1**, regional results provided by SPECT analyses with CTAC and noAC exhibited highly significant linear correlations with corresponding regional results obtained with calAC over the full range of BP_{ND} values encountered in PD and ET (linear regression results: CTAC = 0.78 * calAC - 0.02, $R^2 = 0.96$, $p < 0.001$; noAC = 0.72 * calAC - 0.14, $R^2 = 0.96$, $p < 0.001$). Compared to calAC, both CTAC and noAC gave consistently lower BP_{ND} values (mean relative difference: -23.5% ± 9.8% and -35.2% ± 10.6%, respectively) with noAC providing lower BP_{ND} values than CTAC (-15.1% ± 10.1%; all $p < 0.001$).

Table 1 also lists the results yielded by defining the reference region on CT (CTAC') instead of using conventional SPECT-based reference region definition. Regional estimates of BP_{ND} were slightly, albeit significantly higher than the results from CTAC (+6.2% ± 15.6%, $p < 0.001$) and still highly linearly correlated with calAC (CTAC' = 0.78 * calAC + 0.07, $R^2 = 0.93$, $p < 0.001$).

Discrimination accuracy between PD and ET

As would be expected, mean regional BP_{ND} values were significantly reduced in patients with PD compared to those with ET. Likewise, mean values of AI% and C/P ratio were significantly higher in PD than ET (**Table 1**). Regardless of the parameter employed to differentiate between PD and ET, diagnostic performances as assessed by the AUC of the ROC curves did not differ among AC methods, being particularly high for putamen BP_{ND} (AUC-ROC 0.98-0.99) and the C/P ratio (0.96-0.99). Representative SPECT images given by the different AC methods in patients with PD and ET are given in **Figure 2**.

Association between striatal DAT availability and clinical parameters

Preliminary correlation analyses between DAT availability and clinical parameters (UPDRS-3, H&Y stage and disease duration; data available in 12, 11 and 14 patients, respectively) in PD patients and age in ET patients are summarized in **Table 2**: Mean BP_{ND} of putamen (selected for analyses as the most affected striatal sub-region) showed a significant negative correlation with UPDRS motor score and H&Y stage when using CTAC or noAC and with symptom duration when using CTAC' (i.e., the higher the impairment, the lower the DAT availability). Of note, clinical parameters showed no significant correlation with results from calAC. Mean striatal BP_{ND} exhibited a significant negative correlation with age in ET patients for all AC methods, albeit being weakest for calAC and strongest for CTAC.

Discussion

The present study demonstrates that CTAC provides significantly lower, albeit highly linearly correlated striatal BP_{ND} estimates than the conventional method relying on calAC ($R^2 > 0.96$; mean difference -23.5% ± 9.8%). As expected, omitting AC (noAC) yielded even lower BP_{ND} estimates (-35.2% ± 10.6%). However, these differences did not affect overall discrimination accuracy between PD and ET in the present study population: In line with a large multi-cen-

ter study including patients with established PD and ET [20], we found a close to perfect discrimination of both groups using putaminal BP_{ND} (ROC AUC > 0.98 for all analyses). Furthermore, our results are in general agreement with aforementioned earlier studies comparing non-uniform AC or CTAC with calAC [11, 15] (see Introduction) and with own phantom studies: Despite severe underestimation of target-to-background radioactivity concentration ratios by 40-60% regardless of the AC method applied (see also [7]), calAC provided concentration ratios that were 20-30% higher than those given by CTAC (data not shown in detail).

Besides allowing for an accurate and reproducible diagnosis, regional DAT availability is also of growing importance as an objective biomarker to assess disease progression and possible effects of therapeutic (e.g., neuroprotective) interventions [3, 6]. This is supported by earlier studies showing a negative correlation of DAT availability with severity and duration of symptoms and disease progression [2, 3]. Moreover, [^{123}I]FP-CIT SPECT is well capable to detect the age-dependent DAT loss in humans (e.g., [4]). Thus, we also explored the associations between aforementioned parameters and BP_{ND} provided by the different AC methods, which has not been contemplated before: Regarding clinical parameters in PD, BP_{ND} yielded by CTAC tended to show a higher correlation with UPDRS-3, H&Y and disease duration than those given by calAC (actually not reaching statistical significance). In ET, all methods gave significant correlations of BP_{ND} with age. However, this association tended to be stronger for CTAC than calAC. It is intriguing to note that omitting AC (noAC) did not noteworthy affect the overall results, neither the diagnostic group discrimination nor the correlations with clinical parameters. This underlines that [^{123}I]FP-CIT SPECT is a very robust method with a strong biomarker signal, compared to which AC is only of minor importance.

Stronger tracer binding or higher injected activity increase the number of counts detected by the gamma camera. However, ignoring possible minor effects on automatic contour definition for calAC, these factors are independent of the attenuation correction method applied. As stronger attenuation and more inhomogenously distributed attenuation coefficients are expected for deeper structures in the central region of the brain, the role of the corrections is also less pronounced for the brain regions studied with [^{123}I]FP-CIT.

However, in line with current guidelines [13, 14] we also refrain from completely omitting AC in clinical routine since this compromises image quality (e.g., non-physiological inward gradient complicating visual readings and VOI analyses) and renders regional data susceptible to artifacts (e.g., head size, gender, [re-] positioning). Nevertheless, this study underlines that it may be worthwhile to consider noAC data to confirm findings given by AC data.

In addition to AC, we explored if the anatomical information provided by CT is of benefit for VOI definition. Anatomical details given by low-dose CT are usually not sufficient for delineating striatal (sub-) structures. However, low-dose CT can still be used to define the reference region by securely including the entire occipital lobe and strictly avoiding enlarged CSF spaces (e.g., sulci or ventricle). With increasing age and/or disease duration or structural brain abnormalities (e.g., infarcts, normal-pressure hydrocephalus), the latter may introduce a relevant positive bias and variability into BP_{ND} estimates. Albeit correlation between BP_{ND} and disease duration was indeed highest for CTAC', the possible advantage of CTAC' could not be verified for overall group discrimination or correlations with other parameters (including age in ET). One reason for this could also be that reconstruction parameters were initially selected for optimal visualization of both the reference and the target regions [9]. Thus, particularly if more iterations and/or less image filtering are employed, it may be advantageous to use the low-dose CT data not only for CTAC but also for verification of the reference region.

Some limitations of the present study need to be acknowledged: First, we used a MELP collimator, although many investigators use LEHR collimators. However, as stated by the EANM guideline [14], the use of medium-energy collimators can be advantageous to reduce septal penetration. In fact, our phantom studies also showed a reduced scatter contribution when using the MELP collimator and no relevant influence on regional measurements. Second, we only enrolled a limited number of patients (n = 30 in total), and clinical parameters were not available in all of these. Thus, aforementioned

correlation analyses and apparent differences need to be contemplated with cautions. Replication in a larger patient cohort is warranted. Finally, in the majority of cases we included patients with established diagnoses of PD or ET, some of which were scheduled for deep brain stimulation (SPECT for exclusion of alternative diagnoses). Thus, the diagnostic performance of the different AC methods may have been overestimated and narrowed in range compared to their performance in earlier, clinically more questionable cases. However, even in these cases, [^{123}I]FP-CIT SPECT usually shows an excellent diagnostic accuracy [1]. On the other hand, the present sample allowed us to compare the different AC methods across a wide range of BP_{ND} values (see **Figure 1**).

Conclusion

[^{123}I]FP-CIT SPECT provides a very high diagnostic accuracy for differentiation between PD and ET that is not dependent on the employed AC method. Preliminary correlations analyses suggest that BP_{ND} estimates derived from CTAC represent a superior biomarker of nigrostriatal integrity.

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Disclosure of conflict of interest

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References

[1] Meyer PT, Hellwig S. Update on SPECT and PET in parkinsonism - part 1: imaging for differential diagnosis. Curr Opin Neurol 2014; 27: 398-404.

[2] Benamer HT, Patterson J, Wyper DJ, Hadley DM, Macphee GJ, Grosset DG. Correlation of Parkinson's disease severity and duration with ^{123}I-FP-CIT SPECT striatal uptake. Mov Disord 2000; 15: 692-698.

[3] Winogrodzka A, Bergmans P, Booij J, van Royen EA, Janssen AG, Wolters EC. [^{123}I]FP-CIT SPECT is a useful method to monitor the rate of dopaminergic degeneration in early-stage Parkinson's disease. J Neural Transm 2001; 108: 1011-1019.

[4] Varrone A, Dickson JC, Tossici-Bolt L, Sera T, Asenbaum S, Booij J, Kapucu OL, Kluge A, Knudsen GM, Koulibaly PM, Nobili F, Pagani M, Sabri O, Vander Borght T, Van Laere K, Tatsch K. 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.

[5] Söderlund TA, Dickson JC, Prvulovich E, Ben-Haim S, Kemp P, Booij J, Nobili F, Thomsen G, Sabri O, Koulibaly PM, Akdemir OU, Pagani M, van Laere K, Asenbaum-Nan S, George J, Sera T, Tatsch K, Bomanji J. Value of semiquantitative analysis for clinical reporting of ^{123}I-2-β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)nortropane SPECT studies. J Nucl Med 2013; 54: 714-722.

[6] Parkinson Study Group. Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression. JAMA 2002; 287: 1653-1661

[7] Meyer PT, Sattler B, Lincke T, Seese A, Sabri O. Investigating dopaminergic neurotransmission with ^{123}I-FP-CIT SPECT: comparability of modern SPECT systems. J Nucl Med 2003; 44: 839-845.

[8] Soret M, Koulibaly PM, Darcourt J, Hapdey S, Buvat I. Quantitative accuracy of dopaminergic neurotransmission imaging with ^{123}I SPECT. J Nucl Med 2003; 44: 1184-1193.

[9] Winz OH, Hellwig S, Mix M, Weber WA, Mottaghy FM, Schäfer WM, Meyer PT. Image quality and data quantification in dopamine transporter SPECT: advantage of 3-dimensional OSEM reconstruction? Clin Nucl Med 2012; 37: 866-871.

[10] Shimosegawa E, Fujino K, Kato H, Hatazawa J. Quantitative CBF measurement using an integrated SPECT/CT system: validation of three-dimensional ordered-subset expectation maximization and CT-based attenuation correction by comparing with O-15 water PET. Ann Nucl Med 2013; 27: 822-833.

[11] Bieńkiewicz M, Górska-Chrzastek M, Siennicki J, Gajos A, Bogucki A, Mochecka-Thoelke A, Płachcińska A, Kuśmierek J. Impact of CT based attenuation correction on quantitative assessment of DaTSCAN (^{123}I-Ioflupane) imaging in diagnosis of extrapyramidal diseases. Nucl Med Rev Cent East Eur 2008; 11: 53-58.

[12] Warwick JM, Rubow S, du Toit M, Beetge E, Carey P, Dupont P. The role of CT-based attenu-

ation correction and collimator blurring correction in striatal SPECT quantification. Int J Mol Imaging 2011; 2011: 195037.

[13] Djang DSW, Jannsen MJR, Bohnen N, Booij J, Henderson TA, Herholz K, Minoshima S, Rowe CC, Sabri O, Seibyl J, Van Berckel BN, Wanner M. SNM practice guideline for dopamine transporter imaging with ^{123}I-ioflupane SPECT 1.0. J Nucl Med 2012; 53: 154-163.

[14] Darcourt J, BooiJJ, Tatsch K, Varrone A, Vander Borght T, Kapucu OL, Någren K, Nobili F, Walker Z, Van Laere K. EANM procedure guidelines for brain neurotransmission SPECT using 123I-labelled dopamine transporter ligands, version 2 Eur J Nucl Med Mol Imaging 2010; 37: 443-450.

[15] Rajeevan N, Zubal IG, Ramsby SQ, Zoghbi SS, Seibyl J, Innis RB. Significance of nonuniform attenuation correction in quantitative brain SPECT imaging. J Nucl Med 1998; 39: 1719-1726.

[16] Brix G, Nekolla EA, Borowski M, Noßke D. Radiation risk and protection of patients in clinical SPECT/CT. Eur J Nucl Med Mol Imaging 2014; 41 Suppl 1: S125-136.

[17] Ishii K, Hanaoka K, Okada M, Kumano S, Komeya Y, Tsuchiya N, Hosono M, Murakami T. Impact of CT attenuation correction by SPECT/CT in brain perfusion images. Ann Nucl Med 2012; 26: 241-247.

[18] Farid K, Petras S, Poullias X, Caillat-Vigneron N. Clinical Impact of Nonuniform CT-Based Attenuation Correction in Brain Perfusion SPECT/CT Using ^{99m}Tc-ECD. Clin Nucl Med 2014; 39: 343-345.

[19] Innis RB, Cunningham VJ, Delforge J, Fujita M, Gjedde A, Gunn RN, Holden J, Houle S, Huang SC, Ichise M, Iida H, Ito H, Kimura Y, Koeppe RA, Knudsen GM, Knuuti J, Lammertsma AA, Laruelle M, Logan J, Maguire RP, Mintun MA, Morris ED, Parsey R, Price JC, Slifstein M, Sossi V, Suhara T, Votaw JR, Wong DF, Carson RE. Consensus nomenclature for in vivo imaging of reversibly binding radioligands. J Cereb Blood Flow Metab 2007; 27: 1533-1539.

[20] Benamer TS, Patterson J, Grosset DG, Booij J, de Bruin K, van Royen E, Speelman JD, Horstink MH, Sips HJ, Dierckx RA, Versijpt J, Decoo D, Van Der Linden C, Hadley DM, Doder M, Lees AJ, Costa DC, Gacinovic S, Oertel WH, Pogarell O, Hoeffken H, Joseph K, Tatsch K, Schwarz J, Ries V. Accurate differentiation of parkinsonism and essential tremor using visual assessment of [^{123}I]-FP-CIT SPECT imaging: the [^{123}I]-FP-CIT study group. Mov Disord 2000; 15: 503-510.