

Published in *Parkinsonism and Related Disorders* 29:24-29 (2016)

©2016. This manuscript version is made available under the CC-BY-NC-ND 4.0 license <http://creativecommons.org/licenses/by-nc-nd/4.0/>

The final publication is available at Elsevier through <http://dx.doi.org/10.1016/j.parkreldis.2016.06.001>

Please cite the published version.

Validation of an automated morphological MRI-based ¹²³I-FP-CIT SPECT evaluation method

Gabor PERLAKI PhD^{a,b,1}, Sarolta SZEKERES MD^{c,1}, Gergely ORSI PhD^{a,b}, Laszlo PAPP MS^d, Balazs SUHA^c, Szilvia Anett NAGY MS^{b,e}, Tamas DOCZI MD PhD^{a,b,f}, Jozsef JANSZKY MD PhD^{a,g}, Katalin ZAMBO MD PhD^{c,2}, Norbert KOVACS MD PhD^{a,g,2,*}

^aMTA-PTE Clinical Neuroscience MR Research Group, H-7623 Pecs, Hungary

^bPecs Diagnostic Centre, H-7623 Pecs, Hungary

^cDepartment of Nuclear Medicine, University of Pecs, H-7624 Pecs, Hungary

^dMediso Medical Imaging Systems, H-1022 Budapest, Hungary

^eMTA-PTE Neurobiology of Stress Research Group, H-7624 Pecs, Hungary

^fDepartment of Neurosurgery, University of Pecs, H-7623 Pecs, Hungary

^gDepartment of Neurology, University of Pecs, H-7623 Pecs, Hungary

***Corresponding author:**

Norbert Kovacs, MD, PhD

Ret str. 2.

Department of Neurology, University of Pecs

H-7623

Pecs

Hungary

phone: +36-72535900 fax: +36-535911

email: kovacs.norbert@pte.hu

¹**Equal contribution in first authorship:** G. P. and S. Sz. contributed equally.

²**Equal contribution in last authorship:** N. K. and K. Z. contributed equally.

Key words: ¹²³I-FP-CIT SPECT; Parkinson's disease; MRI; DATSCAN; dopamine transporter quantification

Main text word count: 2998

Number of tables: 4

Number of references: 30

ABSTRACT

Introduction

Dopamine transporter imaging with ^{123}I -FP-CIT single photon emission computed tomography (SPECT) is helpful for the differential diagnosis between Parkinsonian syndrome (PS) and essential tremor (ET). Although visual assessment and time-consuming manual evaluation techniques are readily available, a fully objective and automated dopamine transporter quantification technique is always preferable, at least in research and follow-up investigations. Our aim was to develop a novel automated magnetic resonance imaging (MRI)-based evaluation technique of dopamine transporter SPECT images and to compare its diagnostic accuracy with those of the gold-standard visual grading and manual dopamine transporter binding quantification methods.

Methods

^{123}I -FP-CIT SPECT and MRI sessions were conducted in 33 patients with PS (15 men; mean age: 60.3 ± 9.7 years) and 15 patients with ET (8 men; mean age: 54.7 ± 16.3 years). Striatal dopamine transporter binding was visually classified by 2 independent experts as normal or abnormal grade I, II and III. Caudal and putaminal specific uptake ratios were calculated by both automated MRI-based and manual evaluation techniques.

Results

We found almost perfect agreement ($\kappa=0.829$) between the visual scores by the 2 observers. The automated method showed strong correlation with the visual and manual evaluation techniques and its diagnostic accuracy (sensitivity=97.0%; specificity=93.3%) was also comparable to these methods. The automatically determined uptake parameters showed negative correlation with the clinical severity of parkinsonism. Based on ordinal regression modelling, the automated MRI-based method could reliably determine the visual grading scores.

Conclusion

The novel MRI-based evaluation of ^{123}I -FP-CIT SPECT images is useful for the differentiation of PS from ET.

1. INTRODUCTION

Dopamine transporter (DAT) single photon emission computed tomography (SPECT) imaging with ^{123}I -FP-CIT radio-ligand is a useful diagnostic tool for the differentiation of PS from ET [1].

In clinical practice the ^{123}I -FP-CIT SPECT images are most commonly interpreted based on careful visual assessment of the striatal tracer binding, which is a simple and straightforward approach with high diagnostic accuracy and excellent interobserver agreement [2, 3]. However, visual classification is subjective and may be strongly dependent on the observer's experience [4]. In addition to visual interpretation, binding quantification based on manual delineation of striatal regions of interest (ROIs) is also readily available. However, this laborious technique is still subjective and dependent on the operator [5, 6]. To overcome such limitations, several automatic or semiautomatic ROI definition techniques were proposed for DAT binding quantification [6-9]. Most of these methods are based on some sort of registration between the DAT SPECT and a standard template image. Unfortunately DAT images contain relatively few anatomic details (i.e. they display a definite amount of uptake only in the striatum), which is further exacerbated by reduced DAT density in patients with advanced PS. Thus, registration to the template image may be inaccurate resulting in reduced accuracy of ROI delineation and subsequent DAT binding quantification [7]. Besides the registration process, generic template based ROIs may yield inaccuracies due to the morphological differences between the generic ROIs and the subject specific ROIs [10].

ROI delineation based on individual morphology as obtained by image fusion with magnetic resonance imaging (MRI) is also an option recommended by the recent European Association of Nuclear Medicine guidelines, especially when low DAT binding is expected [1]. In a simulation study, Gallego et al. demonstrated that ROIs based on individual morphology as obtained from MRI scan yields more accurate results than using template-

1 based generic ROIs [10]. Although, reliable automated MRI-based brain segmentation
2 methods are available for the striatal structures [11, 12], this type of ROI delineation is not
3 commonly used for DAT SPECT evaluation and even in rare cases where it is applied, the
4 validation is still lacking [13].
5
6
7

8
9 The aim of this study was to develop and validate a novel automated MRI-based
10 evaluation of DAT SPECT images as a tool for the differentiation between PS and ET and to
11 compare the results with a well-established visual grading and DAT binding quantification
12 driven by manual delineation of striatal ROIs. We also investigated for potential associations
13 between DAT binding parameters and clinical measures of PS severity.
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

2. MATERIALS AND METHODS

2.1. Subjects

Thirty-three patients with Parkinsonian syndrome (PS, 15 men and 18 women; mean age: 60.3 ± 9.7 , range: 39-73 years) and 15 essential tremor (ET) patients (8 men and 7 women; mean age: 54.7 ± 16.3 , range: 22-78 years) were included in a prospective study. ET patients served as the control group. Only patients who did not take any medication which could significantly influence striatal DAT binding were included in the study [1].

The diagnosis of PS and ET was confirmed by a movement disorder specialist in accordance with current clinical criteria [14, 15].

The severity of PS was assessed by Hoehn-Yahr scale [16], the Hungarian validated version of Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [17, 18] and the documented disease duration. Demographic and clinical data are presented in **TABLE 1**.

All subjects received detailed information on the investigation and gave written informed consent prior to the examination. The study was approved by the National Ethical Board (36104/2012/EKU).

2.2. SPECT imaging

For thyroid blocking, patients received Lugol's solution (30 drops, 3 times a day, for 3 days) before tracer administration. Three hours after the intravenous administration of 185 MBq of ^{123}I Ioflupane (DaTSCAN, GE Healthcare), brain SPECT examination with low dose computed tomography (CT) was performed. Double head gamma camera (AnyScan, Mediso) with low energy high resolution (LEHR) collimator was used. The imaging parameters were as follows: 128x128 matrix size; 64 frames; 40 sec/frame; angular step 5.6° ; zoom 1.45. Transversal, sagittal and coronal slices were created. Images were reconstructed using a Butterworth brain prefilter.

2.3. Magnetic resonance imaging

Magnetic resonance imaging was performed on a 3T MRI scanner (MAGNETOM Trio a Tim System, Siemens AG, Erlangen, Germany) with a 12-channel head coil. A T1-weighted 3D MPRAGE (TR/TI/TE=2530/1100/3.37ms; Flip Angle=7°; 176 sagittal slices; slice thickness=1mm; FOV=256x256mm²; matrix size=256x256; receiver bandwidth=200Hz/pixel) sequence was obtained to allow automated MR-based evaluation of dopamine transporter (DAT) binding.

2.4. Visual evaluation

SPECT images were visually assessed by 2 independent experts blinded to clinical data and uptake measures provided by the automated (or manual) analysis. Striatal DAT binding was classified as normal or abnormal grade I, II and III in accordance with the criteria of Benamer et al. [2]:

Normal: Tracer uptake bilaterally in putamen and caudate nuclei and largely symmetric.

Abnormal grade I: Asymmetric uptake with normal or almost normal putamen activity in one hemisphere and with a more marked reduction in the contralateral putamen.

Abnormal grade II: Significant bilateral reduction in putamen uptake with activity confined to the caudate nuclei.

Abnormal grade III: Virtually absent uptake bilaterally affecting both putamen and caudate nuclei.

2.5. Automated evaluation

Left and right caudate and putamen were automatically segmented on T1-weighted MPRAGE images using FIRST [12], while occipital cortex was defined by merging the lateral occipital, lingual, cuneus and pericalcarine regions delineated by FreeSurfer 5.3 image

analysis suite [19].

For automated DAT binding quantification, the segmented masks were aligned with each subject's native DAT image, while keeping the original mask resolution of $1 \times 1 \times 1 \text{mm}^3$. The alignment was based on the rigid body (6 degrees-of-freedom) transformation between MR and CT images calculated by FLIRT [20]. Normalized mutual information was used as cost-function. The coregistration process is illustrated in **Supplementary Figure 1**.

Mean ^{123}I -FP-CIT uptake values were extracted for each mask by InterViewTM FUSION version 2.02.055 (Mediso). Specific to nonspecific uptake ratios were calculated separately for the left and right sides of caudate and putamen using the formula:

$$(\text{UPT}_{\text{striatal}} - \text{UPT}_{\text{occ}}) / \text{UPT}_{\text{occ}}$$

, where $\text{UPT}_{\text{striatal}}$ represents the mean uptake in the target region (putamen or caudate) and UPT_{occ} is the mean uptake in the reference region (occipital cortex).

Since, the underlying disease in patients with PS is often asymmetric, the uptake data were defined in terms of the "higher" (less affected) and "lower" specific uptake (more affected) sides, rather than left and right hemispheres. For example, "lower" putamen denotes the lower one from the left and right putaminal specific uptake ratios.

2.6. Manual evaluation

Manual ROI delineation included several steps.

If ^{123}I -FP-CIT accumulation was apparent bilaterally in the putamen and caudate then manual delineation was performed as follows: left and right caudate and putamen were manually labelled in three axial SPECT slices; the slice showing most intense striatal tracer uptake and the most caudal and cranial slices in which the tracer uptake was still evident for the given brain structure. Using InterViewTM FUSION version 2.02.055 (Mediso), the user-defined two-dimensional (2D) ROIs were automatically extended between these three slices to form a three-dimensional (3D) ROI for each structure. Finally, using the CT images, each

3D ROI was manually corrected according to the anatomical landmarks.

If ^{123}I -FP-CIT accumulation was present only in one hemispheric putamen or caudate, then the 3D ROI around the best preserved putamen or caudate was outlined based on the above. The mirror image of this tracing was used as an initial label for the contralateral side, which was adjusted manually based on the CT image to fit individual anatomy.

If ^{123}I -FP-CIT accumulation was visually absent bilaterally in the caudate or the putamen, the delineation of the 3D ROI covering the corresponding anatomical structure was based on the CT image exclusively.

Three dimensional ROIs of the occipital reference region were drawn in a way to avoid the inclusion of any bone tissue or cerebrospinal fluid.

Similarly to the automated evaluation, specific to nonspecific uptake ratios were calculated separately for the “higher” (less affected) and “lower” specific uptake (more affected) sides of the putamen and caudate. For these calculations, the average of the mean uptake values from left and right occipital ROIs was used as the nonspecific uptake reference (i.e. UPT_{occ}).

2.7. Statistical analysis

Statistical analyses were performed using SPSS 20.0 software (IBM Corp., Armonk, NY).

Agreement between the visual uptake scores (normal=0; grade I=1; grade II=2, grade III=3) by the 2 observers was evaluated by Cohen’s kappa coefficient (κ). Kappa values were interpreted as follows: 0.00-0.20 indicates slight, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 substantial and 0.81-1.00 almost perfect agreement.

The abilities of visual, automated and manual evaluation methods to differentiate between ET and PS patients were assessed by receiver operating characteristic (ROC) analysis with clinical diagnosis (PS vs. ET) as reference standard. To describe the

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

discriminative properties, area under the ROC curve (AUC), specificity, sensitivity, positive and negative predictive values (PPV and NPV, respectively) were calculated.

Spearman correlations were performed to assess the relationships among visually, manually and automatically determined uptake parameters. The strength of Spearman correlations was interpreted based on the value of the correlation coefficient (ρ): $|\rho| \geq 0.7$ =strong; $0.3 \leq |\rho| < 0.7$ =moderate; $|\rho| < 0.3$ =weak.

Subsequently, regression analysis was performed to evaluate how efficiently the automated method can predict the grade of abnormality rated by visual observers. In this part of the study, only the scans of those patients were included where visual scores agreed between the 2 observers ($n=42$). Ordinal regression was used to model the dependence of visual scores on specific uptake ratios derived from automated method. This analysis was performed only for the “lower” putamen; the region providing the best diagnostic accuracy (see the results of ROC analysis). After obtaining a significant regression model, Kappa analysis was performed to assess the agreement between predicted and actual visual categories.

In the PS group, Spearman correlations were used to assess the correlations of visually/manually/automatically determined uptake parameters with clinical measures. In these analyses, the visual scores were used as the average between the two observers.

Results were considered significant at $P \leq 0.05$ for all statistical tests.

3. RESULTS

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Almost perfect agreement was found between the visual scores by the 2 observers (complete agreement in 42/48 cases; only one grade difference was found in 6 cases; $\kappa=0.829$). Most of the disagreement happened at higher grades (grades 3 vs. 2 in two occasions, grades 2 vs. 1 in three occasions, grade 1 vs. 0 in one occasion). All of the patients with a clinical diagnosis of PS were visually classified as abnormal (grade \geq I) by both observers.

To demonstrate the diagnostic accuracy (PS vs. ET) of each method, AUC, sensitivity, specificity, PPV and NPV are presented in **TABLE 2**. The best AUC (=0.988) was achieved for the “lower” putaminal uptake ratio derived from the automated method, which was comparable to AUCs for the human observers (0.961-0.980) and the putaminal uptake ratios derived from the manual method (0.984-0.986). Frequencies of the estimated outcomes (PS vs. ET) by each method are presented in **Supplementary Table 1**.

The automatically determined specific uptake ratios showed strong correlation with the manually determined ones in all 4 regions (“lower” putamen: $\rho=0.931$; $P<0.001$; “higher” putamen: $\rho=0.897$; $P<0.001$; “lower” caudate: $\rho=0.814$; $P<0.001$; “higher” caudate: $\rho=0.821$; $P<0.001$). Visual ratings showed strong negative correlation with both manually and automatically determined specific uptake ratios, which was more remarkable in the putamen (**TABLE 3**). The best correlation with visual scores was obtained for the “lower” putaminal uptake ratio derived from automated method.

We could build a significant ordinal regression model between the automated results and the visual grades determined by the observers. Our model showed that the “lower” putaminal uptake ratio derived from automated method was inversely associated with visual scores ($P<0.001$; Nagelkerke’s $R^2=0.839$). The obtained Nagelkerke’s R^2 value was considerably high, suggesting a very good fit of the model. The subsequent Kappa analysis

1 indicated substantial ($\kappa=0.635$) agreement between the predicted visual scores by the ordinal
2 regression model and the actual visual scores by the observers. Complete agreement was
3 found in ~74% of the cases and only one grade difference was observed in the discrepant
4 cases.
5
6
7

8
9 Concerning the correlation between uptake parameters and the severity of PS (**TABLE**
10 **4**), all of the examined uptake measures were moderately correlated ($|\rho|>0.5$; $P<0.001$) with
11 disease duration. Hoehn-Yahr score was also significantly correlated with all uptake
12 measures, except the “higher” putaminal uptake ratio derived from the manual method. Scores
13 on MDS-UPDRS Part I did not correlate with any uptake measures, while the other MDS-
14 UPDRS scores showed trends or even significant correlations with most of the uptake
15 parameters. Correlation coefficients were negative between clinical severity and the uptake
16 ratios and positive between clinical severity and the visual scores.
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

4. DISCUSSION

Visual assessment of DAT binding is an effective tool in the differential diagnosis between PS and ET [2]. However, an objective DAT quantification technique is warranted for both clinical and research applicability (e.g. monitoring subtle changes during the progression of PS). DAT quantification based on conventional manual ROI delineation is still subjective, therefore more complicated methods were proposed to provide objective information on tracer binding [6-9]. While the objectivity is improved by these methods, the accuracy may be biased by the fact that striatal ROIs are delineated by using DAT SPECT images rather than incorporating relevant morphological information (CT or MRI images).

In this study, we tested a novel automated morphological MRI-based evaluation of DAT binding – as applied to the differentiation of PS from ET – and compared it with the gold-standard visual grading and conventional manual ROI delineation techniques.

Our results showed almost perfect interobserver agreement between the two observers in visually interpreting ^{123}I -FP-CIT SPECT images, which is consistent with an earlier study using the same 4-point visual rating scale [21]. Other studies are also reported a high interobserver agreement for visual analysis when using only a dichotomous division of normal versus abnormal SPECT images [22, 23]. All of the patients with the clinical diagnosis of PS were visually classified as abnormal by both observers, therefore none of our patients could be considered as so-called SWEDD (Scans Without Evidence of Dopaminergic Deficit) patient; a small specific entity of patients clinically diagnosed with Parkinson's disease but having normal DAT imaging [22].

The ROC analysis suggests that the automated MRI-based evaluation of the putaminal region is appropriate for the differentiation of PS from ET with similarly high discriminatory ability as the visual grading technique or the manual evaluation of the putaminal region (for AUCs see **TABLE 2**). Actually, the best general discriminability of PS and ET was observed

1 for the “lower” putaminal uptake ratio derived from the automated method (AUC=0.988). The
2 high sensitivity (97.0%) and specificity values (93.3%) observed for the automated evaluation
3 of the putaminal region were also comparable to those observed for the validated visual
4 grading or the manual evaluation of the putaminal region, but please note that these values are
5 highly dependent on the actual cutoff points used. Uptake ratios derived from the caudal
6 region showed lower diagnostic performance for both the automated and the manual
7 evaluation techniques, which is consistent with earlier studies [6, 24]. The lower diagnostic
8 accuracy for caudate could be due to partial volume effect and anatomical variability between
9 subjects [10], or due to the pattern of Parkinson disease degeneration (i.e. the putamen is more
10 affected than the caudate nucleus) [25].
11
12
13
14
15
16
17
18
19
20
21
22
23

24 Uptake scores obtained from the three different methods were strongly intercorrelated.
25 Additionally, when the “lower” putaminal uptake ratio derived from the automated method
26 was regraded into predicted visual scores, substantial agreement was observed with the actual
27 visual scores by the observers. Because in our automated method the “lower” putaminal
28 uptake ratio can be reliably transformed into the visual grading scores by an ordinal
29 regression model, our automated evaluation technique seems to be valid, reliable and
30 congruent with the gold-standard visual evaluation.
31
32
33
34
35
36
37
38
39
40

41 In patients with PS, the automated method showed decreased striatal DAT binding
42 with increased disease duration in accordance with the other two evaluation techniques and
43 earlier studies [26, 27]. The “lower” putaminal uptake ratio derived from the automated
44 method was inversely correlated with clinical measures such as Hoehn-Yahr score, MDS-
45 UPDRS Total and MDS-UPDRS Parts II, III and IV scores, suggesting that the automated
46 evaluation may be effective not only in the diagnosis of PS, but also in the assessment of
47 disease severity. Most of the other uptake parameters examined in this study also showed
48 trends or even significant correlations with clinical severity, consistently with previous studies
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 [7, 27]. Scores on MDS-UPDRS Part I did not correlate with any uptake measures, which is
2 not surprising because MDS-UPDRS Part I describes the disability mainly caused by non-
3 motor symptoms [17, 28].
4
5

6
7 Our study has some inherent limitations. The clinical diagnosis used as a reference
8 standard in the ROC analyses may be imperfect [29, 30]. Although in the absence of
9 postmortem confirmation of the diagnosis this uncertainty cannot be totally eliminated, but to
10 minimize the possibility of any misdiagnosis, all of our patients were examined by the same
11 neurologist specialized in movement disorders. Moreover, we tried to reduce chance of
12 diagnostic inaccuracy of ET by having patients with disease duration ≥ 5 years. Another
13 potential limitation is that the AUC, sensitivity, specificity, positive and negative predictive
14 values may be affected by both the size and the composition of our sample. However, since all
15 the three evaluation techniques were tested on the same sample, our results still provide a fair
16 representation of their relative performance.
17
18
19
20
21
22
23
24
25
26
27
28
29
30

31 In conclusion, observer-independent automated DAT quantification methods are
32 preferable, at least in research. We developed and validated a novel MRI-based evaluation
33 technique of ^{123}I -FP-CIT SPECT images that was useful for the differentiation of PS from ET.
34 Main advantages of this technique are that it is fully objective and that the ROIs used for the
35 evaluation are delineated based on individual morphology rather than using generic template-
36 based ROIs or the DAT binding itself. Our new approach showed strong correlation with the
37 gold-standard visual and conventional manual evaluation techniques and its diagnostic
38 accuracy was also similarly good. Additionally, the uptake parameters derived from this new
39 method showed correlation with the clinical severity of parkinsonism. The promising nature
40 of our results should be further investigated in larger samples and in follow-up studies.
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

5. Author roles

1) A. Conception and design of the study, B. Acquisition of data, C. Analysis and interpretation of data

2) A. Drafting the article, B. Revising it critically for important intellectual content

3) Final approval of the version to be submitted

GP: 1A, 1B, 1C, 2A, 2B, 3

SS: 1A, 1B, 1C, 2A, 2B, 3

GO: 1B, 2B, 3

LP: 1A, 1C, 2B, 3

BS: 1C, 2A, 3

SAN: 1B, 2B, 3

TD: 1A, 2B, 3

JJ: 1A, 2B, 3

KZ: 1A, 1B, 1C, 2A, 2B, 3

NK: 1A, 1B, 1C, 2A, 2B, 3

6. ACKNOWLEDGMENTS

Our study was supported by the Hungarian Brain Research Program (KTIA_13_NAP-A-II/10) government-based fund. N.K., G.P. and G.O. were supported by the Bolyai Scholarship of the Hungarian Academy of Science. N.K. was supported by the OTKA PD103964. S.A.N. was supported by the Hungarian Brain Research Program “B” (KTIA_NAP_13-2-2014-0019). The present scientific contribution is dedicated to the 650th anniversary of the foundation of the University of Pecs, Hungary.

7. DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

J.J. received a research grant from Hungarian Brain Research Program (KTIA_13_NAP-A-II/9) and honoraria from UCB Magyarország and Valeant Pharma Magyarország. N.K. received a research grant from Hungarian Brain Research Program (KTIA_13_NAP-A-II/10) and consultation fees from Hungarian subsidiaries of Medtronic, Boehringer Ingelheim, Novartis, GlaxoSmithKline, UCB, Krka and Abbvie.

Regarding this study the authors did not receive any corporate funding.

8. REFERENCES

- [1] J. Darcourt, J. Booij, K. Tatsch, A. Varrone, T. Vander Borgh, O.L. Kapucu, K. Nagren, F. Nobili, Z. Walker, K. Van Laere, EANM procedure guidelines for brain neurotransmission SPECT using (123)I-labelled dopamine transporter ligands, version 2, *Eur. J. Nucl. Med. Mol. Imag.* 37 (2010) 443-50.
- [2] T.S. Benamer, J. Patterson, D.G. Grosset, J. Booij, K. de Bruin, E. van Royen, J.D. Speelman, M.H. Horstink, H.J. Sips, R.A. Dierckx, J. Versijpt, D. Decoo, C. Van Der Linden, D.M. Hadley, M. Doder, A.J. Lees, D.C. Costa, S. Gacinovic, W.H. Oertel, O. Pogarell, H. Hoeffken, K. Joseph, K. Tatsch, J. Schwarz, V. Ries, Accurate differentiation of parkinsonism and essential tremor using visual assessment of [123I]-FP-CIT SPECT imaging: the [123I]-FP-CIT study group, *Mov. Disord.* 15 (2000) 503-10.
- [3] N. Papathanasiou, P. Rondogianni, P. Chroni, M. Themistocleous, E. Boviatsis, X. Pedeli, D. Sakas, I. Datseris, Interobserver variability, and visual and quantitative parameters of (123)I-FP-CIT SPECT (DaTSCAN) studies, *Ann. Nucl. Med.* 26 (2012) 234-40.
- [4] C. Scherfler, M. Nocker, Dopamine transporter SPECT: how to remove subjectivity?, *Mov. Disord.* 24(suppl 2) (2009) S721-4.
- [5] A. Kas, P. Payoux, M.O. Habert, Z. Malek, Y. Cointepas, G. El Fakhri, P. Chaumet-Riffaud, E. Itti, P. Remy, Validation of a standardized normalization template for statistical parametric mapping analysis of 123I-FP-CIT images, *J. Nucl. Med.* 48 (2007) 1459-67.
- [6] W. Koch, P.E. Radau, C. Hamann, K. Tatsch, Clinical testing of an optimized software solution for an automated, observer-independent evaluation of dopamine transporter SPECT studies, *J. Nucl. Med.* 46 (2005) 1109-18.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
- [7] A. Ciarmiello, G. Giovacchini, C. Guidotti, M. Meniconi, P. Lazzeri, E. Carabelli, L. Mansi, G. Mariani, D. Volterrani, M. Del Sette, Weighted registration of ¹²³I-FP-CIT SPECT images improves accuracy of binding potential estimates in pathologically low striatal uptake, *J. Cell. Physiol.* 228 (2013) 2086-94.
- [8] F.P. Oliveira, D. Borges Faria, D. Campos Costa, J.M. Tavares, A robust computational solution for automated quantification of a specific binding ratio based on [¹²³I]fp-cit SPECT images, *Q. J. Nucl. Med. Mol. Imaging* 58 (2014) 74-84.
- [9] P.S. Jensen, M. Ziebell, G. Skouboe, U. Khalid, R. de Nijs, G. Thomsen, G.M. Knudsen, C. Svarer, Validation of a method for accurate and highly reproducible quantification of brain dopamine transporter SPECT studies, *J. Nucl. Med. Technol.* 39 (2011) 271-8.
- [10] J. Gallego, A. Ninerola-Baizan, A. Cot, P. Aguiar, C. Crespo, C. Falcon, F. Lomena, J. Sempau, J. Pavia, D. Ros, Validation of semi-quantitative methods for DAT SPECT: influence of anatomical variability and partial volume effect, *Phys. Med. Biol.* 60 (2015) 5925-38.
- [11] B. Fischl, D.H. Salat, E. Busa, M. Albert, M. Dieterich, C. Haselgrove, A. van der Kouwe, R. Killiany, D. Kennedy, S. Klaveness, A. Montillo, N. Makris, B. Rosen, A.M. Dale, Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain, *Neuron* 33 (2002) 341-55.
- [12] B. Patenaude, S.M. Smith, D.N. Kennedy, M. Jenkinson, A Bayesian model of shape and appearance for subcortical brain segmentation, *Neuroimage* 56 (2011) 907-22.
- [13] L. Passamonti, M. Salsone, N. Toschi, A. Cerasa, M. Giannelli, C. Chiriaco, G.L. Cascini, F. Fera, A. Quattrone, Dopamine-transporter levels drive striatal responses to apomorphine in Parkinson's disease, *Brain Behav.* 3 (2013) 249-62.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
- [14] I. Litvan, K.P. Bhatia, D.J. Burn, C.G. Goetz, A.E. Lang, I. McKeith, N. Quinn, K.D. Sethi, C. Shults, G.K. Wenning, Movement Disorders Society Scientific Issues Committee report: SIC Task Force appraisal of clinical diagnostic criteria for Parkinsonian disorders, *Mov. Disord.* 18 (2003) 467-86.
- [15] R.J. Elble, Diagnostic criteria for essential tremor and differential diagnosis, *Neurology* 54(suppl 4) (2000) S2-6.
- [16] M.M. Hoehn, M.D. Yahr, Parkinsonism: onset, progression and mortality, *Neurology* 17 (1967) 427-42.
- [17] C.G. Goetz, B.C. Tilley, S.R. Shaftman, G.T. Stebbins, S. Fahn, P. Martinez-Martin, W. Poewe, C. Sampaio, M.B. Stern, R. Dodel, B. Dubois, R. Holloway, J. Jankovic, J. Kulisevsky, A.E. Lang, A. Lees, S. Leurgans, P.A. LeWitt, D. Nyenhuis, C.W. Olanow, O. Rascol, A. Schrag, J.A. Teresi, J.J. van Hilten, N. LaPelle, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results, *Mov. Disord.* 23 (2008) 2129-70.
- [18] K. Horvath, Z. Aschermann, P. Acs, E. Bosnyak, G. Deli, E. Pal, I. Kesmarki, R. Horvath, K. Takacs, S. Komoly, M. Bokor, E. Rigo, J. Lajtos, P. Klivenyi, G. Dibo, L. Vecsei, A. Takats, A. Toth, P. Imre, F. Nagy, M. Herceg, E. Hidasi, N. Kovacs, Validation of the Hungarian Mds-Updrs: Why Do We Need a New Parkinson Scale?, *Ideggyogy. Sz.* 67 (2014) 129-34.
- [19] B. Fischl, A. van der Kouwe, C. Destrieux, E. Halgren, F. Segonne, D.H. Salat, E. Busa, L.J. Seidman, J. Goldstein, D. Kennedy, V. Caviness, N. Makris, B. Rosen, A.M. Dale, Automatically parcellating the human cerebral cortex, *Cereb. Cortex* 14 (2004) 11-22.
- [20] M. Jenkinson, P. Bannister, M. Brady, S. Smith, Improved optimization for the robust and accurate linear registration and motion correction of brain images, *Neuroimage* 17 (2002)

825-41.

1
2
3 [21] J.T. O'Brien, S. Colloby, J. Fenwick, E.D. Williams, M. Firbank, D. Burn, D. Aarsland,
4
5 I.G. McKeith, Dopamine transporter loss visualized with FP-CIT SPECT in the differential
6
7 diagnosis of dementia with Lewy bodies, Arch. Neurol. 61 (2004) 919-25.
8
9

10
11 [22] V.L. Marshall, C.B. Reininger, M. Marquardt, J. Patterson, D.M. Hadley, W.H. Oertel,
12
13 H.T. Benamer, P. Kemp, D. Burn, E. Tolosa, J. Kulisevsky, L. Cunha, D. Costa, J. Booij, K.
14
15 Tatsch, K.R. Chaudhuri, G. Ulm, O. Pogarell, H. Hoffken, A. Gerstner, D.G. Grosset,
16
17 Parkinson's disease is overdiagnosed clinically at baseline in diagnostically uncertain cases: a
18
19 3-year European multicenter study with repeat [123I]FP-CIT SPECT, Mov. Disord. 24 (2009)
20
21 500-8.
22
23
24

25
26 [23] I. McKeith, J. O'Brien, Z. Walker, K. Tatsch, J. Booij, J. Darcourt, A. Padovani, R.
27
28 Giubbini, U. Bonuccelli, D. Volterrani, C. Holmes, P. Kemp, N. Tabet, I. Meyer, C. Reininger,
29
30 Sensitivity and specificity of dopamine transporter imaging with 123I-FP-CIT SPECT in
31
32 dementia with Lewy bodies: a phase III, multicentre study, Lancet Neurol. 6 (2007) 305-13.
33
34
35
36

37
38 [24] A. Skanjeti, G. Castellano, B.O. Elia, M. Zotta, F. Dazzara, M. Manfredi, A. Galati, S.
39
40 Grimaldi, M. Balma, R.E. Pellerito, V. Podio, Multicenter Semiquantitative Evaluation of I-
41
42 FP-CIT Brain SPECT, J. Neuroimaging 25 (2015) 1023-9.
43
44
45

46
47 [25] L. Filippi, C. Manni, M. Pierantozzi, L. Brusa, R. Danieli, P. Stanzione, O. Schillaci,
48
49 123I-FP-CIT semi-quantitative SPECT detects preclinical bilateral dopaminergic deficit in
50
51 early Parkinson's disease with unilateral symptoms, Nucl. Med. Commun. 26 (2005) 421-6.
52
53

54
55 [26] W. Pirker, S. Djamshidian, S. Asenbaum, W. Gerschlager, G. Tribl, M. Hoffmann, T.
56
57 Brucke, Progression of dopaminergic degeneration in Parkinson's disease and atypical
58
59 parkinsonism: a longitudinal beta-CIT SPECT study, Mov. Disord. 17 (2002) 45-53.
60
61

1 [27] H.T. Benamer, J. Patterson, D.J. Wyper, D.M. Hadley, G.J. Macphee, D.G. Grosset,
2 Correlation of Parkinson's disease severity and duration with 123I-FP-CIT SPECT striatal
3 uptake, *Mov. Disord.* 15 (2000) 692-8.
4
5
6

7
8 [28] K. Horvath, Z. Aschermann, P. Acs, E. Bosnyak, G. Deli, E. Pal, J. Janszky, B. Faludi, I.
9 Kesmarki, S. Komoly, M. Bokor, E. Rigo, J. Lajtos, P. Klivenyi, G. Dibo, L. Vecsei, A. Takats,
10 A. Toth, P. Imre, F. Nagy, M. Herceg, A. Kamondi, E. Hidasi, N. Kovacs, Is the MDS-UPDRS
11 a Good Screening Tool for Detecting Sleep Problems and Daytime Sleepiness in Parkinson's
12 Disease?, *Parkinsons Dis.* November 17, 2014 [Epub ahead of print]
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

[29] A.J. Hughes, S.E. Daniel, L. Kilford, A.J. Lees, Accuracy of clinical diagnosis of
idiopathic Parkinson's disease: a clinico-pathological study of 100 cases, *J. Neurol.*
Neurosurg. Psychiatry 55 (1992) 181-4.

[30] S. Jain, S.E. Lo, E.D. Louis, Common misdiagnosis of a common neurological disorder:
how are we misdiagnosing essential tremor?, *Arch. Neurol.* 63 (2006) 1100-4.

9. FIGURE LEGENDS

Supplementary Fig. 1. Figure illustrating the coregistration process of the automated evaluation in a patient with normal **(a)** and in a patient with abnormal grade II **(b)** tracer uptake as graded by both observers. The pink, light blue and yellow indicate the automatically segmented masks of the putamen, caudate and occipital cortex, respectively. The masks were generated in the native space of the acquired T1-weighted MR images (shown on the left), and were aligned to the space of DAT SPECT images based on the 6 degrees-of-freedom (DOF) rigid body transformation between MR and CT images. The aligned masks and MR images overlaid with DAT SPECT images are shown on the right.

Table 1. Demographic and clinical data of patients

	PS (n=33)	ET (n=15)
Gender (M/F)	15 M; 18 F	8 M; 7 F
Age (years)	60.3±9.7 [39-73]	54.7±16.3 [22-78]
H&Y	stage 1: 1 case stage 2: 16 cases stage 3: 12 cases stage 4: 3 cases stage 5: 1 case	n.a.
Disease duration (years)	6.5±6.1 [1-24]	9.5±3.1 [5-19]
MDS-UPDRS I	14.1±7.6 [2-27]	n.a.
MDS-UPDRS II	15.0±9.8 [1-37]	n.a.
MDS-UPDRS III	37.0±13.0 [15-62]	n.a.
MDS-UPDRS IV	5.1±3.0 [0-15]	n.a.
MDS-UPDRS Total	71.2±26.4 [26-120]	n.a.

Data are presented as mean ± standard deviation [range]; PS=parkinsonian syndrome; ET=essential tremor; M=male; F=female; H&Y=Hoehn-Yahr score; MDS-UPDRS= Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; n.a.=not available

Table 2. Diagnostic accuracy for the various methods of ^{123}I -FP-CIT uptake analysis

Analysis method	Region	AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Automated	PUT _{lower}	0.988	97.0 (84.2-99.9)	93.3 (68.1-99.8)	97.0 (84.2-99.9)	93.3 (68.1-99.8)
	PUT _{higher}	0.978	97.0 (84.2-99.9)	93.3 (68.1-99.8)	97.0 (84.2-99.9)	93.3 (68.1-99.8)
	CAUD _{lower}	0.871	78.8 (61.1-91.0)	86.7 (59.5-98.3)	92.9 (76.5-99.1)	65.0 (40.8-84.6)
	CAUD _{higher}	0.859	78.8 (61.1-91.0)	86.7 (59.5-98.3)	92.9 (76.5-99.1)	65.0 (40.8-84.6)
Manual	PUT _{lower}	0.984	97.0 (84.2-99.9)	93.3 (68.1-99.8)	97.0 (84.2-99.9)	93.3 (68.1-99.8)
	PUT _{higher}	0.986	93.9 (79.8-99.3)	100 (78.2-100)	100 (88.8-100)	88.2 (63.6-98.5)
	CAUD _{lower}	0.931	81.8 (64.5-93.0)	100 (78.2-100)	100 (87.2-100)	71.4 (47.8-88.7)
	CAUD _{higher}	0.893	75.8 (57.7-88.9)	100 (78.2-100)	100 (86.3-100)	65.2 (42.7-83.6)
Visual ₁	–	0.961	100 (89.4-100)	80.0 (51.9-95.7)	91.7 (77.5-98.3)	100 (73.5-100)
Visual ₂	–	0.980	100 (89.4-100)	86.7 (59.5-98.3)	94.3 (80.8-99.3)	100 (75.3-100)

AUC= area under the curve; PPV= positive predictive value; NPV= negative predictive value; PUT=putamen; CAUD=caudate; *lower* means the more affected side with lower specific uptake ratio; *higher* means the less affected side with higher specific uptake ratio; sensitivity, specificity, PPV and NPV values at the optimal cutoff point (closest to the upper left corner of the ROC space) are given for the diagnosis of Parkinsonian syndrome; values in parentheses represent 95% confidence intervals; Visual₁=visual grades by Observer₁; Visual₂=visual grades by Observer₂

Table 3. Correlations of visual scores with specific uptake ratios

Analysis method	Region	Visual ₁		Visual ₂	
		ρ	P	ρ	P
Automated	PUT _{lower}	-0.889	<0.001	-0.887	<0.001
	PUT _{higher}	-0.833	<0.001	-0.853	<0.001
	CAUD _{lower}	-0.760	<0.001	-0.781	<0.001
	CAUD _{higher}	-0.721	<0.001	-0.731	<0.001
Manual	PUT _{lower}	-0.839	<0.001	-0.846	<0.001
	PUT _{higher}	-0.810	<0.001	-0.829	<0.001
	CAUD _{lower}	-0.791	<0.001	-0.808	<0.001
	CAUD _{higher}	-0.743	<0.001	-0.770	<0.001

PUT=putamen; CAUD=caudate; *lower* means the more affected side with lower specific uptake ratio; *higher* means the less affected side with higher specific uptake ratio; ρ =Spearman's correlation coefficient; P=statistical P-value; Visual₁=visual grades by Observer₁; Visual₂=visual grades by Observer₂

Table 4. Correlations between uptake parameters and the severity of Parkinsonian syndrome

Analysis method	Region	H&Y		Disease duration		MDS-UPDRS I		MDS-UPDRS II		MDS-UPDRS III		MDS-UPDRS IV		MDS-UPDRS Total	
		ρ	P	ρ	P	ρ	P	ρ	P	ρ	P	ρ	P	ρ	P
Automated	PUT _{lower}	-0.433	0.012	-0.638	<0.001	-0.002	0.991	-0.349	0.047	-0.390	0.025	-0.359	0.040	-0.370	0.034
	PUT _{higher}	-0.396	0.022	-0.648	<0.001	-0.028	0.876	-0.287	0.106	-0.303	0.087	-0.301	0.089	-0.325	0.065
	CAUD _{lower}	-0.497	0.003	-0.601	<0.001	-0.080	0.659	-0.343	0.051	-0.288	0.104	-0.395	0.023	-0.356	0.042
	CAUD _{higher}	-0.445	0.010	-0.597	<0.001	-0.094	0.603	-0.340	0.053	-0.275	0.121	-0.380	0.029	-0.353	0.044
Manual	PUT _{lower}	-0.361	0.039	-0.655	<0.001	-0.093	0.608	-0.362	0.038	-0.362	0.039	-0.340	0.053	-0.395	0.023
	PUT _{higher}	-0.300	0.090	-0.643	<0.001	-0.099	0.585	-0.368	0.035	-0.275	0.121	-0.260	0.144	-0.363	0.038
	CAUD _{lower}	-0.446	0.009	-0.676	<0.001	-0.190	0.290	-0.404	0.020	-0.310	0.079	-0.379	0.029	-0.404	0.020
	CAUD _{higher}	-0.384	0.027	-0.635	<0.001	-0.189	0.291	-0.341	0.052	-0.230	0.198	-0.319	0.071	-0.336	0.056
Visual _{mean}	–	0.411	0.018	0.693	<0.001	0.115	0.525	0.366	0.036	0.469	0.006	0.458	0.007	0.448	0.009

H&Y=Hoehn-Yahr score; MDS-UPDRS= Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; ρ =Spearman's correlation coefficient; P=statistical P-value; PUT=putamen; CAUD=caudate; *lower* means the more affected side with lower specific uptake ratio; *higher* means the less affected side with higher specific uptake ratio; Visual_{mean}=the visual grades averaged between the two observers