Automatic Versus Semi-Automatic method for the striatum specific uptake ratio quantification based on [^{123}I]FP-CIT SPECT images

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***Abstract*—The aim of this work was to implement an automatic application (AA) for the quantification of the striatum transaxial slices based on [^{123}I]FP-CIT SPECT (Single Photon Emission Tomography) images.**

A sample of 68 subjects with and without pathology was collected from the nuclear medicine department of the Hospital Particular de Almada.

In order to compare the striatum specific uptake ratios (SUR), a semi-automatic application (SAA) was also developed allowing manual adjustments by a specialist operator. The obtained results were compared with the DaTSCAN® V4 application, from General Electric Healthcare. The experimental results based on SUR demonstrate that the AA can successfully discriminate the healthy patients from the pathological subjects. Additionally, a strong correlation was verified between the AA and the semi-automatic methods (DaTSCAN® V4 and the SAA). These methods also evidence intra and inter-operator variability, suppressed by the AA.

The proposed methodology for segmentation and quantification of the striatum transaxial images obtained by [^{123}I]FP-CIT SPECT demonstrated that the developed application can accurately complement the visual analysis, requiring future optimization.

I. Introduction

Parkinsonian syndrome (SP) or Parkinsonism is a group of pathologies with symptoms such as bradykinesia, rigidity, rest tremor and postural instability, causing movement disorders. The most common cause of Parkinsonism is Parkinson's disease (PD), a progressive neurological disorder associated with the progressive degeneration of nigrostriatal dopaminergic neurons [1].

Imaging of the dopamine transporters density with ^{123}I-Ioflupane ([^{123}I]FP-CIT), available under the label DaTSCAN™ (GE Healthcare, UK), using single photon emission computed tomography (SPECT) is the most widely used nuclear medicine (NM) technique for routine assessment of patients with suspected degenerative Parkinsonism. This method allows *in vivo* visualization of pre-synaptic dopaminergic transporters function. Using this technique it is possible to confirm PD and exclude the diagnosis of other diseases without pre-synaptic neurodegeneration, such as essential tremor, with sensitivity and specificity values of 95% and 93%, respectively [1,2]. The routine assessment of [^{123}I]FP-CIT SPECT images is mostly performed through visual analysis by experienced NM physicians. Since this visual subjective inspection depends on the observer´s experience, intra and interoperative variability occurs, especially in cases of doubtful and early PD patients. In order to improve the diagnostic accuracy, this evaluation should be based on both visual and quantitative results [3-7]. The quantification of these images can be obtained using semi-automatic or fully automatic methods [1,5]. These methods use specific to non-specific uptake ratios (SUR) between striatum and background uptake (e.g occipital region) [1].

Currently, in the clinical field, there are commercial software packages that use mainly semi-automatic methods for image quantification. Considering that the automatic quantification reveals the best reproducibility results [1,5], as well as the lack of automatic clinical applications for SUR quantification, an automatic methodology adapted to the NM department should be proposed. Consequently, the main goal of this work was to implement an automatic application for the SUR quantification of the striatum transaxial slices based on [^{123}I]FP-CIT SPECT images. Furthermore, a comparison with the two semi-automatic methods – commercial DaTSCAN® V4 (GE Healthcare, UK) and the developed semi-automatic application – was performed.

II. Methods

A. Subjects

Sixty-eight subjects with clinical indication for [^{123}I]FP-CIT SPECT were selected from the database of the NuclearMed Institute, Hospital Particular Almada (HPA) (Portugal). The studies were divided into three groups by a non-probability sampling technique, according to the diagnosis attested in the patients' clinical report: Group I (GI): 32 with subjects with normal uptake in the striatum, used as healthy control reference values; Group IIP (GIIP): 26 subjects with qualitative reduced uptake in the striatum compatible with PD; and Group IIS (GIIS): 10 subjects with normal uptake pattern. GI (training set) was used to create a normal reference model and both GIIP and GIIS were used as a test set to analyse the SUR of subjects with "normal" or "abnormal" uptake in striatum.

All subjects were scanned about 2 to 4 hours after intravenous administration of 185 MBq of [^{123}I]FP-CIT (DaTSCAN™). The SPECT images were acquired using a dual-head gamma camera (*Infinia*, GE Healthcare) equipped with a low-energy, high-resolution (LEHR) collimator. The total acquisition orbit was a full 360º rotation (120 views with a 3º angular step, 35 seconds per projection). A 128 x

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128 matrix with a zoom factor of 1.2 was used. The radius of rotation was 15 to 16 cm depending on the morphological characteristics of the subjects. Images were acquired in a step and shoot mode. The energy window (20%) was centred on 159 KeV.

The SPECT data was reconstructed using the Brain SPECT™ tool from a Xeleris Workstation (version 3, GE Healthcare). To obtain the transaxial, sagittal and coronal slices, a filtered back projection (FBP) algorithm (pre-filtering butterworth window, order of 10 and a cut-off frequency 0.6 cycles.cm^{-1}) was applied. Chang´s attenuation correction was utilized (coefficient of 0.11 cm^{-1}). The images were exported in the standard DICOM (Digital Imaging and Communication on Medicine) protocol.

B. Automatic and semi-automatic applications

The automatic and semi-automatic applications for analysis of striatum transaxial slices based on [^{123}I]FP-CIT SPECT images were implemented in Python® programming language (version 3.6.1) using specific toolboxes for image processing and mathematical calculation.

The developed computational methodology can be divided into the following steps: (1) creation of the normal SPECT striatum template, for both left and right sides; (2) alignment of the generated striatum template with the obtained post-reconstruction image of each subject; (3) computation of the SUR.

(1) Normal SPECT striatum template (Fig. 1A): All DaTSCAN™ studies with normal uptake in striatum were selected (42 subjects, from GI and GIIS). These images were aligned based on the centroid of the striatum (left and right) of each transaxial slice. Finally, all the aligned slices were normalized as a function of the intensity scale to obtain the striatum template, based on their contours (Region of Interest – ROI).

(2) Image registration: the alignment of the normal SPECT striatum template with the post-reconstruction image of each subject was performed by two different methods: automatic and semi-automatic. In both methods, a threshold method was used to segment the region of the striatum in each slice of each DaTSCAN™ study.

Regarding the automatic method, the template was automatically aligned in the striatum region of each DaTSCAN™ study, based on both centroids (Fig. 1B), without the interaction of operator.

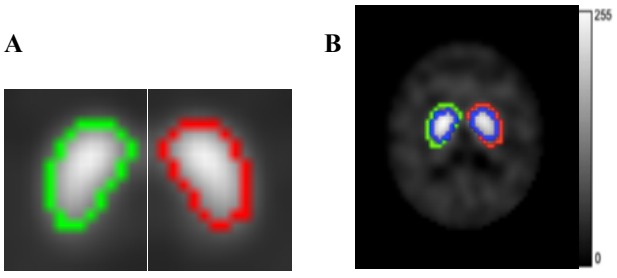

Figure 1. A) Normal SPECT striatum template from left (red) and right (green) striatum. B) Automatic placement of the normal templates (red and green) based on the centroids of each striatum of a DaTSCAN™ study (blue)

Relatively to the semi-automatic method, the same previous automatic method was applied to align the template. However, if necessary, a fine adjustment (translation operation) was made by a specialist operator.

For both methods, the reference region (occipital region) was automatically defined by the application.

(3) Computation of specific uptake ratios (SUR): the computation method was based on the mean intensities of the pixels of each region defined by the aligned templates (ROI) for the left/right striatum and for the occipital region using the two alignment methods (automatic and semi- automatic). The SUR were calculated according to the formulas presented in Table I, where LS, RS and OCC, correspond to the mean intensities of the pixels of the left striatum, right striatum and occipital region, respectively.

C. DaTSCAN V4 Software (GE Healthcare™)

All DaTSCAN™ studies were also processed using the DaTSCAN V4 software, available at the Xeleris™ workstation (GE Healthcare), in the NM department of HPA. This commercial application is used in clinical practice and has a semi-automatic methodology. The pre-computed templates of the striatum, caudate nucleus, putamen and occipital regions are loaded and placed in the transaxial slice of each DaTSCAN™ study. The position of templates does not take into account the local information of the striatum uptake of each slice image and, the operator needs to adjust them to each study. For the calculation of the SUR (Table I), the mean intensity of the pixels is extracted in each ROI.

TABLE I. FORMULAS OF SUR FOR QUANTIFICATION OF DATSCAN™ SPECT STUDIES

Specific Uptake Ratios	Formulas	Code
Striatum / Occipital	$\frac{[(LS - OCC) + (RS - OCC)]/2}{OCC}$	A
Left Striatum / Occipital	$\frac{LS - OCC}{OCC}$	B
Right Striatum / Occipital	$\frac{RS - OCC}{OCC}$	C
Left Striatum / Right Striatum	$\frac{LS - OCC}{RS - OCC}$	D

D. Statistical analysis

The Statistical Package for Social Sciences® (SPSS), (version 22) software was used for the statistical analysis of the collected data. In all the statistical tests, a significance level confidence interval of 95% was used.

For the three applications (automatic, semi-automatic and DaTSCAN® V4 software), SUR reference values (RV), mean ± standard deviation ($\bar{x} \pm \delta$), from Group I (GI) studies were computed. In order to analyse the SUR values obtained from GIIS and GIIP, control charts were created comparing the A-D SUR relative to the RV. In order to obtain the Area Under the Curve (AUC), Receiver Operating Characteristics (ROC) curves were generated from the control charts. Intra and interoperative variability was also studied in the semi-automatic applications.

III. RESULTS

A. Automatic Application

For the automatic application, the following RV were obtained: A (3.78 ± 0.58), B (3.79 ± 0.57), C (3.77 ± 0.60), D (1.01 ± 0.03). The distribution of the SUR values of GIIS and GIIP relatively to the RV, revealed that 83% of the subjects without pathology are within the established limits and that 76% of the subjects with pathology are outside these limits. The ROC curves are represented on Fig. 2, with the associated AUC values, sensitivity and specificity on Table II. Intra and interoperative variability was not analysed, since it is an automatic application.

B. Semi-Automatic Application

For the semi-automatic application, the following RV were obtained: A (3.61 ± 0.58), B (3.62 ± 0.57), C (3.60 ± 0.60), D (1.01 ± 0.05). The distribution of the SUR values of GIIS and GIIP relatively to the RV, indicate that 73% of subjects without pathology are within established limits and that 78% of subjects with pathology are outside these limits. The ROC curves are represented on Fig. 3, with the associated AUC values, sensitivity and specificity on Table III. Intra and interoperative variability was verified in DaTSCAN^{TM} studies of subjects with and without pathology ($p<0.05$).

C. DaTSCAN V4 Software (GE Healthcare)

For the DaTSCAN V4 software (GE Healthcare) the following RV were obtained: A (3.43 ± 0.46), B (3.46 ± 0.49), C (3.40 ± 0.43), D (1.02 ± 0.04). The distribution of the SUR values of GIIS and GIIP relatively to the RV, revealed that 85% of subjects without pathology are within the established limits and that 72% of subjects with pathology are outside these limits. The ROC curves are represented on Fig. 4, with the associated AUC values, sensitivity and specificity on Table IV. In this application, only interoperative variability was verified in DaTSCAN^{TM} studies of subjects with pathology ($p<0.05$), and intraoperative variability was not verified ($p>0.05$).

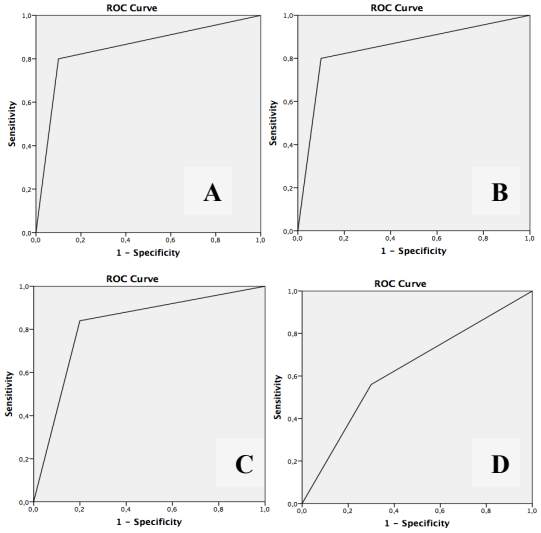

Figure 2. ROC curves for A-D ratios (Automatic Application)

TABLE II. AUC, SENSITIVITY AND SPECIFICITY VALUES FOR AUTOMATIC APPLICATION

	A	B	C	D
AUC	0.85	0.82	0.85	0.63
Sensitivity	0.80	0.84	0.80	0.56
Specificity	0.90	0.80	0.90	0.70

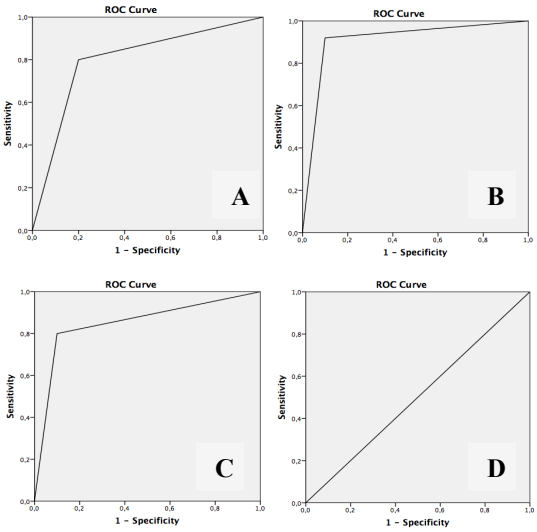

Figure 3. ROC curves for A-D ratios (Semi-Automatic Application)

TABLE III. AUC, SENSITIVITY AND SPECIFICITY VALUES FOR SEMI AUTOMATIC APPLICATION

	A	B	C	D
AUC	0.80	0.91	0.85	0.50
Sensitivity	0.80	0.92	0.80	0.60
Specificity	0.80	0.90	0.90	0.60

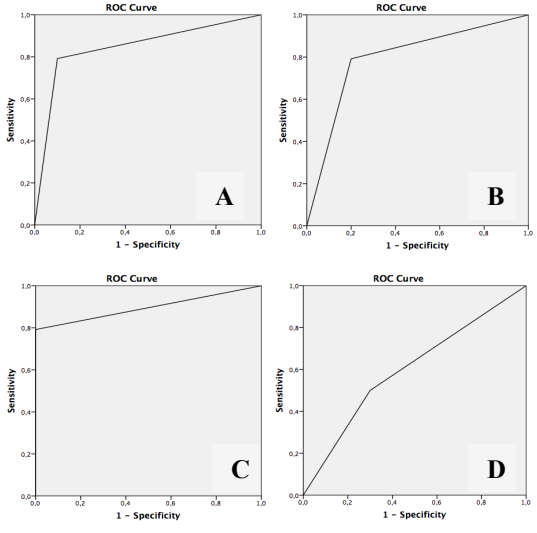

Figure 4. ROC curves for A-D ratios (DaTSCAN V4 software)

TABLE IV. AUC, SENSITIVITY AND SPECIFICITY VALUES FOR DATSCAN V4 SOFTWARE

	A	B	C	D
AUC	0.846	0.896	0.796	0.60
Sensitivity	0.792	0.792	0.792	0.50
Specificity	0.90	1.00	0.80	0.70

IV. DISCUSSION

Considering all the applications, it was possible to observe that the RV for the B and C SUR are similar, since they correspond to the homologous symmetrical structure of the uptake on the striatum; the RV for the A SUR is the mean value between the left and right striatum; and the D SUR, as a symmetry ratio, presents a value of approximately 1. However, relative to the DaTSCAN V4 software, the difference between the RV of the B and C SUR was higher, compared to the other applications, and consequently a higher value of the D SUR was obtained, mainly due to a superior left-right asymmetry.

In order to analyse the distribution of the A-C SUR relatively to the calculated RV, the control chart limit of $(\bar{x} \pm \delta)$ (-1SV) was considered the value that distinguishes a study with pathology from a non-pathological one. This was based in the potential usefulness that may contribute to assist the clinical diagnosis and in order to increase the accuracy of the established RV. It is expected that the DaTSCAN^{TM} studies of subjects without pathology are above this limit, and the studies of subjects with pathology are below it. Regarding the analysis of the distribution of the D SUR, as a symmetry ratio, allocated to the RV, the limit $(\bar{x} \pm \delta)$ was used. The DaTSCAN^{TM} studies of subjects with pathology revealed to be outside this limit.

With reference to the SUR values, the ROC curves obtained for the automatic application, considering the AUC values, indicate that the A, B and C SURs can be a good measure of discrimination between subjects with and without pathology [8]. Based on the results obtained, there is 85% (A and C SUR) and 82% (B SUR) of probability that a study with pathology present a lower uptake value than a non-pathological study [3-7]. This fact is consistent with our results, demonstrating higher values of sensitivity and specificity. In the semi-automatic application, the B SUR was considered an excellent discriminator, and the A and C SUR good discrimination measures, with 91% (B SUR) of probability that a study with pathology presented a lower uptake value than a study without pathology [3-8]. For the DaTSCAN V4 software, A and B SUR revealed to be good discrimination measures, and C SUR is a moderate measure; with 89.6% (B SUR), 84.6% (A SUR) and 79.6% (C SUR) of probability that a study with pathology would have a lower catch value than a non-pathological study [3-8]. Moreover, when this application is used, the B SUR presents 100% specificity value and is considered an excellent parameter to ensure that a patient is truly healthy [8]. Contrary, the sensitivity values obtained by this commercial method were lower than those achieved when using the developed applications, which seems to be a good indicator. For all studied applications, the D SUR was considered a bad discriminator [8] that can infer about the left-right asymmetry verified in the striatum of the sample used.

When semi-automatic applications were applied, intra intra and interoperative variability was verified, as reported in the literature. It is important to note that in the DaTSCAN V4 software there was no intraoperative variability, nor interoperator, when the studies without pathology were considered. This can be justified by the fact that it's an application that separates the two substructures from the striatum, and the manual adjustments of the ROI allow their rotation as well as a finer adjustment compared to the current version of the semi-automatic application developed. Intra and interoperative variability is more pronounced in the group of patients with pathology, since the images present defects at the level of specific uptake of [^{123}I]FP-CIT and therefore the adjustment of the ROI around the striatum is a complex process given the difficulty in finding the geometric limits of the objects being studied [3-7].

V. CONCLUSION

It was possible to verify that the automatic application developed successfully discriminates the healthy subjects of the pathological ones in the SUR A, B and C. Additionally, this method also exhibits a strong correlation with the semi-automatic methods, except for the SUR D. Regarding the values of sensitivity and specificity of each method, high and identical values were obtained in the three methods, except for the symmetry SUR D. The automatic application, being independent of an operator, does not have inherent intra and interoperator variability, something that was verified when semi-automatic methods were applied. Even though the intra and interoperator are removed, some degree of variability is expected, despite the fact this phenomenon was not evaluated. It is possible to conclude that the implementation of this automatic method for segmentation and quantification of transaxial slices of the striatum in images obtained by [^{123}I]FP-CIT SPECT demonstrated promising results, with the potential to accurately complement the visual analysis, despite the need for future optimization and validation.

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