Elaboration of the SPM template for the standardization of SPECT images with $^{123}$I-Ioflupane


Purpose: Statistical parametric mapping (SPM) is a widely used procedure for normalization of functional images. The aim of this study is the development of a normalization template of $^{123}$I-Ioflupano SPECT-imaging, not available in SPM5, and to validate it by comparing with other quantification methods.

Material and methods: In order to write the template we retrospectively selected 26 subjects who had no evidence of nigrostriatal degeneration and whose age distribution was similar to that of the patients in the usual practice of our Department: 2 subjects (7.6%) were <35 years, 9 between 35 and 65 years (34.6%) and 15 > 65 years (57.7%). All the studies were normalized with the T1-template, available in SPM5, and an average value of the image was obtained for each voxel. For validation we analyzed 60 patients: 30 with idiopathic Parkinson's disease patients (iPD) with right involvement (66.83 ± 12.20 years) and 30 with essential tremor patients (ET) (67.27 ± 8.33 years). Specific uptake rates (SUR) of different striatal regions were compared after image normalization with our template and the application of a semiautomated VOIs-map was created with Analyze v9.0 (© BIR, Mayo Clinic), against two quantification methods: a) manual adjustment of a ROIs-map drawn in Analyze, and b) semi-automated method (HERMES-BRASS) with normalization and implementation of VOIs-map.

Results: No statistically significant differences in the iPD/ET discriminatory capacity among the three methods analyzed were observed ($p < 0.001$). The correlation of SUR after normalization with our “template” was lower than that obtained by method a) ($R > 0.871$, $p < 0.001$). This difference was greater in patients with PD.

Conclusions: Our study demonstrates the efficacy of our SPM “template” for $^{123}$I-Ioflupano SPECT-imaging, obtained from normalization with “T1-template”.

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Palabras clave: Parkinson’s disease
Dopamina
Striatal dopamine transporters
Movement disorders
Statistical parametric mapping

Resumen

Objetivo: El SPM (statistical parametric mapping, mapas estadísticos paramétricos) es un procedimiento de análisis ampliamente utilizado para la normalización de imágenes funcionales. El propósito de este trabajo es elaborar una plantilla (template) para la normalización de imágenes SPECT con $^{123}$I-Ioflupano (DaTSCAN®; GE Healthcare), no disponible en SPM5, y su validación respecto a otros métodos de cuantificación.

Material y métodos: Para la elaboración del template seleccionamos retrospectivamente los estudios SPECT de 26 sujetos sin evidencias de degeneración nigroestrial, con distribución de edad similar a la de los pacientes que se incluyen en la práctica habitual de nuestro servicio: 2 sujetos < 35 años (7,6%), 9 entre 35-65 años (34,6%) y 15 > 65 años (57,7%). Todos los estudios fueron normalizados con el template-T1, disponible en SPM5, obteniendo una imagen promedio del valor para cada vóxel. Para la validación analizamos 60 pacientes: 30 con enfermedad de Parkinson idiopática (EPi) con afectación del hemisferio derecho (66,83 ± 12,20 años) y 30 pacientes con temblor esencial (TE) (67,27 ± 8,33 años). Se compararon los índices de captación específica (ICE) de las distintas regiones estriatales, obtenidos tras la normalización de las imágenes con nuestro template y aplicando un mapa de VOIs semiautomatizado creado en Analyze v9.0 (© BIR, Mayo Clinic), contra otros 2 métodos de cuantificación: a) ajuste manual de un mapa de ROIs elaborado en Analyze, y b) mediante un método semicuantitativo automatizado (HERMES-BRASS) que realiza normalización y aplicación de un mapa de VOIs.
Introduction

The term Parkinsonian syndrome or Parkinsonism refers to a group of diseases clinically characterized by the presentation of tremor, rigidity, bradykinesia and postural disorders. Parkinson disease is characterized by progressive degeneration of the nigrostriatal dopaminergic neurons. This neurodegenerative process is associated with a loss of dopamine transporters in the striate (DaT), as demonstrated in post mortem studies. Thus, in vivo measurement of the density of DaT, either by PET or SPECT, is an early marker of the loss of dopaminergic cells. It should not be forgotten that a series of situations may produce parkinsonian symptoms which are not a consequence of the degeneration of the neuronal nigrostriatal system as occurs with essential tremor secondary to the effect of determined drugs or in cerebrovascular disease, among other diseases.

In clinical practice SPECT studies of DaT are analyzed according to a visual qualitative evaluation, however, quantitative analysis is useful to differentiate subjects with diffuse decrease of uptake or a focalized loss, albeit of low quantity, which is difficult to evaluate with qualitative analysis. In addition, objective quantification of DaT is especially useful for the development of multicenter studies in the evaluation of disease progression or to assess the efficacy of neuroprotector drugs. I\(^{123}\)-N-omega-fluoropropyl-2\beta-carbomethoxy-3\beta-(4-iodophenyl) nortropane (I\(^{123}\)-FP-CIT) more selectively binds with DaT, which achieves greater concentrations in the striatum. Different studies have demonstrated that I\(^{123}\)-FP-CIT is a reliable, reproducible technique to measure the density of DaT, thereby extending its use.

The density of DaT may be calculated using the index of specific striatal uptake with respect to an unspecific area of uptake (occipital cortex) by manual or automatic delimitation of regions of interest (ROIs). Manual delimitation carries great operator-dependent variability, making reproducibility among centers or subjects difficult. To avoid this bias, the studies may be processed with parametric voxel to voxel study using Statistical Parametric Mapping software (SPM; Wellcome Department of Cognitive Neurology, London, UK), which has demonstrated more precision than the analysis of ROIs. The SPM combines a series of functions of MATLAB (The MathWorks, Inc.) in a complete analysis package available to the neuroimaging community to promote collaboration and the exchange of knowledge (http://www.fil.ion.ucl.ac.uk/spm/).

An essential step for parametric comparison in SPM studies is the individual normalization of the images consisting in the application of linear and non-linear transformations to register each cerebral volume on a standard cerebral template of the Montreal Neurological Institute (MNI; http://www.bic.mni.mcgill.ca) and unify these within a universal anatomical space. Since the template and SPECT must have similar intensities to obtain adequate normalization, the use of SPM for DaT images requires the creation of a specific template not existing in the SPM5 version, with the templates for cerebral perfusion (SPECT.nii) or for gluicidic consumption (PET.nii) offered by the system being of little use.

The objective of our study was to elaborate a template devoted to SPECT studies with \(^{123}\)I-oflupanate from studies without nigrostriatal involvement, with posterior validation by comparison of the application of different methods of quantification in pre- and post-normalization studies.

Material and methods

Patient selection

For the elaboration of the template we retrospectively selected 26 studies of subjects referred to our department for suspicion of essential tremor showing nigrostriatal degeneration. The distribution of the age of the subjects selected was similar to that of the patients included in the usual practice in our department: 2 subjects less than 35 (7.6%) years of age, 9 from 35 to 65 years (34.6%) and 15 older than 65 years (57.7%).

To evaluate the template we analyzed 60 patients: a) 30 patients with involvement of the right hemibody and with clinical diagnosis of initial Parkinson disease using the Hoeh-Yahr scale and the motor score of the Unified Scale of Parkinson Disease (UPDRS-3) at 12 hours after the withdrawal of anti-Parkinsonian medication (mean age: 66.83 ± 12.20 years), and b) 30 patients with a clinical diagnosis of essential tremor (mean age: 67.27 ± 8.33 years).

Image acquisition and processing protocol

All the subjects were administered 500 mg of potassium perchlorate prior to the injection of the radiotracer to avoid the uptake of \(^{123}\)I by the thyroid gland.

The images were obtained at 3–4 h after the intravenous injection of 185 MBq de \(^{123}\)I-FP-CIT (DaTSCAN, GE Healthcare). All the studies were carried out with a Siemens Symbia T6 tomograph, equipped with a Fan-Beam collimator with a matrix of 128 × 128, applying a zoom of 1.23 and a rotation radium of 14 cm. The reconstructed volume (voxel size: 2.3 × 2.3 × 2.3 mm\(^3\)) was filtered using a Butterworth filter (order: 5; slice frequency: 0.50) without correction of attenuation. A total of 128 images were acquired per study with an image timing of 30 s. The number of total counts was greater than 3 million in all the cases.

All the images were converted from the DICOM format into NIfTI using the dcm2nii software of the MIRicron platform (MCCausland Center, University of South Carolina, USA; available at http://www.mccauslandcenter.sc.edu/mriicro/mricron/).

Template elaboration

Basal normalization of the 26 studies considered for the elaboration of the template was initially performed with the aim of unifying these within a common anatomical space. This initial normalization was performed with the SPM5 software taking the template for magnetic resonance in T1-weighted sequences available in the program as a reference on considering that this sequence provides greater spatial resolution and anatomical detail. On normalization of all the studies in this single anatomical environment, the average spatial image or template was obtained in which the value for each voxel was the result of its mean value in the normalized studies based on T1-weighted and the application of a gaussian filter. The presence of correct spatial normalization of each of the studies was visually verified.
Validation of the template

A map of volumes of interest (VOI) was elaborated using the Analyze version 9.0 software (©BIR, Mayo Clinic) in a study of cerebral magnetic resonance in T1-weighted sequence. Five volumes were determined: right caudate, left caudate, right striatum, left striatum and occipital cortex. In this way the quantification of the SPECT-DaT studies after normalization with our template could be obtained by the application of this VOI map and the calculation of the specific striatal uptake index ([striatal VOI counts – occipital VOI counts]/occipital VOI counts).

For the validation of our template we used another 2 quantification methods in the studies with any type of spatial normalization. The first consisted of a ROI map also elaborated with Analyze v. 9.0, with individualized manual adjustment of the image summing 4 frames (15.6 mm) including practically all the striatal volume of each subject. The second method consisted of a method of semi-quantification (Brass v3.5, Hermes Medical Solutions Inc.) which was based on totally automated normalization and application of a VOI map.

On obtaining the template for spatial Image123I-labeled I-flupane, the 60 studies selected for the validation (30 patients diagnosed with Parkinson disease of right predominance and 30 patients diagnosed with essential tremor) were spatially normalized with our template and the automatized VOI map was applied, obtaining the quantitative values for posterior comparison with those obtained in the studies without normalization using the other 2 quantification methods.

Statistical analysis

The mean value of the uptake index was calculated for each VOI and the typical deviation for each method. To analyze the concordance of the mean values between the different methods the Student’s t test for paired data (α = 0.05) and analysis of correlation (Pearson’s r) were used, estimating the relationship between the values by linear regression analysis. Likewise, the Bland–Altman method was performed to evaluate the concordance of the different methods. For the parametric analysis with SPM, the two simple t-test was used; p < 0.05 not corrected and K cluster value >20 voxels.

Results

The quantitative values obtained with the 3 quantification methods indicated a low specific striatal uptake in patients diagnosed with Parkinson disease in all the ROI (Table 1), being especially significant at the level of the left putamen compared to the control group (Table 2).

Likewise, the parametric image demonstrated significant differences in the group with Parkinson disease compared to the controls [essential tremor, (ET)], especially localized in the left putamen, although significant differences were also observed at the level of the right putamen (two simple t-tests; p < 0.05 not corrected, K cluster value >20 voxels) (Fig. 1).

These results corroborated those obtained with the automated semiquantitative method, the manual application of the VOI map

Table 1
Statistical analysis of the related samples in the pathological group (idiopathic Parkinson disease).

<table>
<thead>
<tr>
<th></th>
<th>Mean ISU</th>
<th>N</th>
<th>Standard deviation</th>
<th>Standard error of the mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-normalization VOI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right caudate</td>
<td>1.2557</td>
<td>30</td>
<td>0.39396</td>
<td>0.07193</td>
</tr>
<tr>
<td>Left caudate</td>
<td>1.0770</td>
<td>30</td>
<td>0.39885</td>
<td>0.07282</td>
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<tr>
<td>Right putamen</td>
<td>0.8801</td>
<td>30</td>
<td>0.27703</td>
<td>0.05058</td>
</tr>
<tr>
<td>Left putamen</td>
<td>0.6686</td>
<td>30</td>
<td>0.25824</td>
<td>0.04715</td>
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<tr>
<td>Manual VOI</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Right caudate</td>
<td>1.1551</td>
<td>30</td>
<td>0.38760</td>
<td>0.07077</td>
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<tr>
<td>Left caudate</td>
<td>0.9595</td>
<td>30</td>
<td>0.36604</td>
<td>0.06683</td>
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<tr>
<td>Right putamen</td>
<td>0.4822</td>
<td>30</td>
<td>0.22274</td>
<td>0.04067</td>
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<tr>
<td>Left putamen</td>
<td>0.3099</td>
<td>30</td>
<td>0.17164</td>
<td>0.03134</td>
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<td>Automated semiquantification</td>
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<td>Left caudate</td>
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<td>Right putamen</td>
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<td>30</td>
<td>0.32676</td>
<td>0.05966</td>
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<tr>
<td>Left putamen</td>
<td>0.6127</td>
<td>30</td>
<td>0.27018</td>
<td>0.04933</td>
</tr>
</tbody>
</table>

ISU: index of specific uptake; N: sample size

Table 2
Statistical analysis of related samples in the control group (essential tremor).

<table>
<thead>
<tr>
<th></th>
<th>Mean ISU</th>
<th>N</th>
<th>Standard deviation</th>
<th>Standard error of the mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-normalization VOI</td>
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<td></td>
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<tr>
<td>Right caudate</td>
<td>1.7087</td>
<td>30</td>
<td>0.20979</td>
<td>0.03830</td>
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<tr>
<td>Left caudate</td>
<td>1.6708</td>
<td>30</td>
<td>0.24705</td>
<td>0.04521</td>
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<tr>
<td>Right putamen</td>
<td>1.4301</td>
<td>30</td>
<td>0.14726</td>
<td>0.02689</td>
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<tr>
<td>Left putamen</td>
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<td>30</td>
<td>0.24907</td>
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<td>Manual VOI</td>
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<tr>
<td>Right caudate</td>
<td>1.5699</td>
<td>30</td>
<td>0.40424</td>
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<tr>
<td>Left caudate</td>
<td>1.6132</td>
<td>30</td>
<td>0.37609</td>
<td>0.06866</td>
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<td>Right putamen</td>
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<td>30</td>
<td>0.32281</td>
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<td>Left putamen</td>
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<td>0.36965</td>
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<td>Automated semiquantification</td>
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<tr>
<td>Right caudate</td>
<td>1.9300</td>
<td>30</td>
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<tr>
<td>Left caudate</td>
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<td>30</td>
<td>0.34632</td>
<td>0.06323</td>
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<td>Right putamen</td>
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<td>30</td>
<td>0.29387</td>
<td>0.05365</td>
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<tr>
<td>Left putamen</td>
<td>1.7473</td>
<td>30</td>
<td>0.30618</td>
<td>0.05590</td>
</tr>
</tbody>
</table>

ISU: index of specific uptake; N: sample size
**Fig. 1.** Comparative parametric image of the pathologic group (idiopathic Parkinson disease, iPD) respect to the group with essential tremor (two simple t-test; \( p < 0.05 \) not corrected, \( K \) cluster value >20 voxels). In the lower part, image co-registered with magnetic resonance which localizes the volumes with significant differences in both putamens, being more notable in the left putamen.

and the automated post-normalization calculation \( p < 0.05; \) Student’s \( t \) test for unpaired data).

We also compared the correlation of the existing related sample for the indexes of specific uptake obtained by the 3 methods and observed an excellent correlation in all the cases, although the highest correlation value was obtained with the automated semiquantitative method (Table 3).

**Fig. 2** shows the correlation between the indexes obtained with our template in the left putamen post-normalization compared with the automated semiquantitative method in the 60 patients \( (r = 0.871, \ p < 0.001) \). Linear regression: index obtained post-normalization \( = 0.3284 + 0.5675 \), automated semiquantitative method.

Using Bland Altman analysis (Fig. 3) we obtained the difference of the means between the indexes in the left putamen obtained post-normalization with our template compared with the automated semiquantitative method, showing an increasing trend to greater values of uptake with the automated semiquantitative method \( (r = 0.669, \ p < 0.001) \) with a relationship of \( y = 0.449x − 0.308 \ (p < 0.001) \), with \( y \) being \( = ( \) automated semiquantitative index \( − \) post-normalization index \( ) \) and \( x \) \( = ( \) automated semiquantitative index \( + \) post-normalization index \( )/2 \).

As shown in Table 4, on comparing the control and pathologic groups separately we found that the correlation obtained was greater, albeit not significantly, in the group with degeneration of the dopaminergic neuronal system.
The application of ROI maps allows relative
In a serial study of 20 patients with Parkinson disease
post-normalization = 0.3284 + 0.5675 automated semiquantitative method.
physician. Semiquantitative evaluation as additional data should
being largely dependent on the experience of the nuclear medicine
syndrome. Nonetheless, visual evaluation carries a certain degree
uptake in the left putamen obtained by the automated semiquantitative methods
Bland–Altman graph showing the relationship between the indexes of
normalization with our template with respect to the automated semiquantitative
Fig. 2. Correlation between the indexes obtained in the left putamen post-

Semiquantitative vs. post-normalization 60 0.768 0.000
Semiquantitative vs. manual 60 0.848 0.000

Table 3 Correlations of related samples.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Correlation</th>
<th>Significance</th>
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<td><strong>Right caudate</strong></td>
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<tr>
<td>Semiquantitative vs. manual</td>
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<td>0.755</td>
<td>0.000</td>
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<td>Post-normalization vs. manual</td>
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<td>0.847</td>
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<td>0.810</td>
<td>0.000</td>
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<td>Semiquantitative vs. post-normalization</td>
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<td>0.868</td>
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<td><strong>Right putamen</strong></td>
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<tr>
<td>Semiquantitative vs. manual</td>
<td>60</td>
<td>0.802</td>
<td>0.000</td>
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<tr>
<td>Post-normalization vs. manual</td>
<td>60</td>
<td>0.782</td>
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<td>Semiquantitative vs. post-normalization</td>
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<td>0.895</td>
<td>0.000</td>
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<td>Semiquantitative vs. manual</td>
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<tr>
<td>Post-normalization vs. manual</td>
<td>60</td>
<td>0.768</td>
<td>0.000</td>
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<tr>
<td>Semiquantitative vs. post-normalization</td>
<td>60</td>
<td>0.871</td>
<td>0.000</td>
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</table>

**Discussion**

In many cases visual evaluation of the SPECT images allows
the decision if a neurodegeneration of the presynaptic neurons is
present and confirm or rule out a neurodegenerative parkinsonian
syndrome. Nonetheless, visual evaluation carries a certain degree
of intrinsic subjectivity which limits its efficacy and reproducibility,
being largely dependent on the experience of the nuclear medicine
physician. Semiquantitative evaluation as additional data should
be taken into account, especially for early diagnosis, the detection
of subtle changes in the DaT in subregions of the striatum and
to monitor disease progression or the beneficial effects of the
neuroprotector drugs. The application of ROI maps allows relative
semiquantitative measurement of the putamen regions which
represent the specific uptake of the tracer to the dopaminergic
transporter with respect to the background uptake (generally
occipital cortex which represents the non specific binding of the
radiotracer) allowing comparison with the reference values for
each age range in a cohort of healthy individuals, thereby increasing
the confidence in the correct evaluation of the individual study.

Visual evaluation and semiquantitative analysis of ROI provide
a similar diagnostic performance, perhaps because experienced
observers are able to identify subtle patterns of abnormality.

One solution to these problems of subjectivity is automated
voxel to voxel quantification which has greater objectivity on being
independent of the operator. This voxel to voxel quantification is
especially useful for the development of multicenter studies or in
the assessment of disease progression. Cuberas-Borrós et al. studied
60 patients using parametric images: 20 patients with idiopathic
Parkinson, 20 with parkinsonism caused by drugs and 20 with
essential tremor, demonstrating the index of striatal uptake to be
significantly greater in patients with essential tremor or Pharma-
cologic parkinsonism compared to those diagnosed with Parkinson
disease. In a serial study of 20 patients with Parkinson disease
(mean interval of 36 months) Tamayo et al. reported a significant
reduction in DaT in the second study with respect to the first,
directly related to the time of disease evolution. Bellesi et al. studied
a population of 64 patients with movement disorders and
demonstrated the usefulness of SPM in the differentiation between
subjects with and without Parkinson disease as well as between the
initial stages of the disease compared to more advanced stages.

This automated voxel to voxel comparison represents a series
of steps including spatial normalization, smoothed results or the
application of an appropriate linear statistical model. The SPM
provides several specific templates for spatial normalization of
nuclear studies but only 2 (PET.nii and SPECT.nii) are applied in
nuclear medicine. Both templates are useful for perfusion studies.
Unfortunately, it is difficult to normalize a SPECT study with
I-123-Ioflupane in a template of metabolism. Thus, the elaboration of a
specific template is essential for the normalization of SPECT images
of dopaminergic transporters. The medical literature has described
that the initial normalization of these studies with the template
provided by SPM for the normalization of metabolic resonance in
T1-weighted sequence may be useful as a starting point for the
elaboration of a specific template.8,14–17

In our study, with the T1.nii template we obtained the first
spatial normalization for the 26 studies without nigrostriatal
degeneration which we considered for the creation of the template.
In all the cases adequate spatial normalization was visually con-
firmed. In a posterior step the template was obtained calculating
the average value for each voxel.

In the evaluation of the template the correlation between the
indexes of specific uptake obtained by the 3 different methods was
verified: 2 of the images without applying our method of normal-
ization and the third after normalization with our template. The
first consisted in the individualized manual application of a stan-
dardized ROI map on the summed image of 4 frames (15.6 mm)
which included practically the total striatal volume of each sub-
ject. The second method in the studies without normalization with
our template consisted in an automated method of semiquanti-
fication (Brass v3.5, Hermes Medical Solutions Inc.) which, in turn, is
based on the normalization and application of a VOI map. The third
and last method was based on the automated application of a VOI
map independent of the operator in the studies normalized with
our template.

Our results indicate the utility of the template for the discrimi-
nation between patients with and without Parkinson disease, with
a high correlation of the indexes with respect to other reference methods.

The quantitative values obtained with the 3 quantification methods of the images with and without normalization with our template indicated less specific striatal uptake in the patients diagnosed with Parkinson disease in all the ROI, being especially significant in the left putamen with respect to the control group (clinical diagnosis of essential tremor). The parametric image corroborated these data, demonstrating a significant difference localized in the left putamen in the group with Parkinson disease compared with the controls, although a significant difference was also observed in the right putamen.

On comparing the correlation of the existing related samples for the indexes of specific uptake obtained for the 3 methods of validation we observed an excellent correlation in all the cases. The greatest correlation was obtained with the automated semiquantitative method. Rocha et al. showed great concordance between the findings observed by two nuclear medicine experts and those obtained with the parametric SPM software (84.37% and 71.18%, respectively).

Recent studies seem to indicate that it is time for the clinical application of these methods of parametric quantification after having demonstrated elevated precision in the differential diagnosis and to improve the consistence of the quantitative measurements in multicenter studies not involving operator-dependent variability.  

Conclusions

Our study demonstrates the efficacy of the SPM template in the normalization of SPECT images with 123I-Ioflupane, elaborated from initial normalization with the T1-template (T1.nii) in a population with no evidence of nigrostriatal degeneration, obtaining adequate spatial normalization and an excellent correlation with the other methods of quantification analyzed.

Conflict of interests

The authors report no conflict of interests.

References


