New MRI, ^{18}F-DOPA and ^{11}C-(+)-α-dihydrotetrabenazine templates for *Macaca fascicularis* neuroimaging: advantages to improve PET quantification.

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Abstract:

Normalization of neuroimaging studies to a stereotaxic space allows the utilization of standard volumes of interest (VOIs) and voxel-based analysis (SPM). Such spatial normalization of PET and MRI studies requires a high quality template image. The aim of this study was to create new MRI and PET templates of ^{18}F-DOPA and ^{11}C-(+)-α-dihydrotetrabenazine (^{11}C-DTBZ) of the *Macaca fascicularis* brain, an important animal model of Parkinson's disease. MRI template was constructed as a smoothed average of the scans of 15 healthy animals, previously transformed into the space of one representative MRI. In order to create the PET templates, ^{18}F-DOPA and ^{11}C-DTBZ PET of the same subjects were acquired in a dedicated small animal PET scanner and transformed to the created MRI template space. To validate these templates for PET quantification, parametric values obtained with a standard VOI map applied after spatial normalization to each template were statistically compared to results computed using individual VOIs drawn for each animal. The high correlation between both procedures validated the utilization of all the templates, improving the reproducibility of PET analysis. To prove the utility of the templates for voxel-based quantification, dopamine striatal depletion in a representative monkey treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was assessed by SPM analysis of ^{11}C-DTBZ PET. A symmetric reduction in striatal ^{11}C-DTBZ uptake was detected in accordance with the induced lesion. In conclusion, templates of *Macaca fascicularis* brain have been constructed and validated for reproducible and automated PET quantification. All templates are electronically available via the internet.

Introduction

Positron emission tomography (PET) using appropriate radioligands allows imaging of certain components of neurotransmission such as presynaptic transporters and postsynaptic receptors in living brains (Ichise et al., 2001). Accurate quantification of the availability of those transporters or receptors can be obtained using complex mathematical models, which are usually solved with compartmental approaches. The solution of this mathematical problem can be undertaken by kinetic, equilibrium or graphical methods such as Logan (Logan, 2000), Ichise (Ichise et al., 2001) or Patlak Plot (Patlak and Blasberg, 1985). These methods initially require the measurement of radiotracer concentration in arterial plasma, an invasive procedure that introduces additional methodological challenges. In practice, assuming the existence of a reference region without specific uptake of the radiotracer, measurement of plasma concentration is replaced by the definition of a volume of interest (VOI) in that particular reference area and the assessment of its time-activity curve (TAC) (Lammertsma and Hume 1996). Using TAC and dynamic PET study, a parametric image can be generated which represents a specific biological parameter for each voxel. This in turn can be measured by drawing new VOIs in the anatomical areas of interest. Then, in order to obtain the final parametric value, VOIs have to be defined both in the reference area and in the areas of interest. The limited spatial resolution of PET tomographs and the presence of low uptake areas make it quite difficult to delimit VOIs accurately for a given anatomical brain structure. Consequently, the definition of VOIs is probably one of the most critical steps in the quantification procedure and introduces great intra- and inter-operator variability. This process can be standardized with the

definition of a common stereotaxic coordinate system, where a template of VOIs can be defined *a priori*. When images are spatially normalized and hence forced to match such a standardized space, those VOIs can be directly applied reducing observer bias in VOI placement. Moreover, the normalization of functional images to a common stereotaxic coordinate system allows to investigate differences across subjects on a voxel basis using statistical parametric mapping (SPM) (Friston et al., 1995b), a widely extended method for PET analysis.

In order to perform the spatial normalization for VOIs-map or SPM analysis, a 3D template is required, that is, a smoothed image created as the average of several subjects to which any other image can be aligned (Evans et al., 1993). Templates can be created for different image modalities such as magnetic resonance image (MRI) or PET. It must be remarked that the choice of the template and the subsequent normalization strategies may modify the quantification of PET studies (Gispert et al., 2003). The use of a common stereotaxic coordinate system to normalize PET studies is widely extended in human PET analysis (Friston et al., 1995a), but not in the case of primates. In fact, templates required for spatial normalization are rarely found for these animals, although MRI templates have already been developed for some species such as baboons (Black et al., 2001b; Greer et al., 2002) and macaques (Black et al., 2005; Black et al., 2001a; Marenco et al., 2004). PET templates are less usual and only a $H_2{}^{15}O$ PET template has been reported for baboon and *Macaca nemestrina* (Black et al., 2001a; Black et al., 2001b). However, PET imaging in primate animal models is an important and emerging tool to study the pathogenesis and progression of neurological diseases

(Guilarte et al., 2006; Kito et al., 2001; Strome and Doudet 2007; Venneti et al., 2004) and to test the efficacy of new radiotracers (Halldin et al., 2003; Halldin et al., 2005; Schou et al., 2007; Stone-Elander et al., 1997) or therapeutic agents (Doudet et al., 2004; Melega et al., 2000). These non-human primate models are especially valuable due to these species' similarities to humans.

Our own research focuses on the cynomolgus monkey (*Macaca fascicularis*). This animal is widely used in PET imaging because the size of the brain is appropriate for dedicated animal PET scanners (Martí-Climent et al., 2006; Nagai et al., 2007) and the small size of the animal facilitates its handling and housing. PET images were performed in these animals for the evaluation of the striatal dopaminergic system with two different radiotracers: 6-[^{18}F]-fluoro-L-DOPA (^{18}F-DOPA) and ^{11}C-(+)-α-dihydrotetrabenazine (^{11}C-DTBZ). The aim of this study was to create new MRI template and PET templates for ^{18}F-DOPA and ^{11}C-DTBZ of the *Macaca fascicularis* brain and to demonstrate their usefulness to spatially normalize and quantify PET studies in a fully automated way with a standardized VOI-map, and to perform voxel-by-voxel statistical analysis.

MATERIALS AND METHODS

Animals

Twenty-four healthy cynomolgus monkeys (*Macaca fascicularis*) were studied (twenty males and four females, 3 to 5 years, weight = 3.6 ± 0.9 kg). Fifteen of those animals (eleven males and four females, 3 to 5 years, weight = 3.4 ± 0.7 kg,) were used to create the MRI, ^{18}F-DOPA and ^{11}C-DTBZ templates. PET studies included in the template generation and ^{18}F-DOPA scans of the 9

remaining animals were used for template evaluation. One additional monkey (male, 5 years, 3.5 Kg) treated with the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was studied. MPTP (0.5 mg/kg) was intravenously administered every two weeks to reach a cumulative dose of 7.20 mg.

On the day of each study, anesthesia was initially induced by intramuscular injections of ketamine (10 mg/kg) and imidazolam (1 mg/kg) to allow the animal manage. During the scans anesthesia was maintained with a mixture of ketamine (5 mg/kg) and imidazolam (0.5 mg/kg). To block the peripheral decarboxylation of ^{18}F-DOPA, 50 mg of carbidopa was given orally one hour prior to ^{18}F-DOPA PET scans. All procedures were performed according to the European Council Directive 86/609/EEC as well as in agreement with the Society for Neuroscience Policy on the Use of Animals in Neuroscience Research. The experimental design was approved by the Ethical Committee for Animal Testing of the University of Navarra (ref: 020/05).

MRI images acquisition

Magnetic resonance images were performed in all animals on a 1.5 T Siemens Symphony scanner (Erlangen, Germany). T1 weighted axial images were acquired using a MPRAGE sequence with the following acquisition parameters: TE = 5.03, TR = 2140, flip angle = 15º, slice thickness = 1 mm, image matrix = 192 x 192 x 88 and pixel size = 1 x 1 mm^2.

PET acquisition and analysis

Twenty-four healthy animals underwent ^{18}F-DOPA PET studies and a subgroup of 15 subjects also had ^{11}C-DTBZ PET scans. PET imaging was performed in a dedicated small animal Philips Mosaic tomograph (Cleveland, Ohio, USA), with 2 mm resolution, 11.9 cm axial field of view (FOV) and 12.8 cm transaxial FOV. Under standard anesthesia animals were placed on the bed in prone position with the head centered in the FOV. A transmission study prior to the emission scan was carried out with an external ^{137}Cs source (370 MBq). The radiotracer (79 ± 11.9 MBq for ^{11}C-DTBZ and 82.7 ± 17.1 MBq for ^{18}F-DOPA) was intravenously injected trough the saphenous vein simultaneously to the beginning of a list mode study of 40 minutes for ^{11}C-DTBZ and 100 minutes for ^{18}F-DOPA. For each study, a summed sinogram of the whole emission study was created and reconstructed for visual inspection. Dynamic sinograms were also created with 16 frames for ^{11}C-DTBZ (7 x 30''; 4 x 120''; 5 x 300'') and 23 frames for ^{18}F-DOPA (10 x 90''; 9 x 300''; 4 x 600''). From these sinograms, dynamic images were generated containing the information about the corresponding time intervals. All the images, both summed and dynamic, were reconstructed in a 128 x 128 matrix with a 1 x 1 x 1 mm^3 voxel size using the 3D Ramla algorithm (Surti et al., 2005) with 2 iterations and a relaxation parameter of 0.024. Dead time, decay, attenuation, random and scattering corrections were applied.

In order to obtain parametric images, PET studies were analyzed by suitable tracer kinetic models using PMOD software (PMOD Technologies Ltd., Adliswil, Switzerland). The computed parameters were the uptake rate (Ki) for

^{18}F-DOPA and the binding potential (BP) of VMAT2 transporter for ^{11}C-DTBZ. For parametric images generation the kinetic model requires the PET dynamic data and a TAC obtained by drawing VOIs over the reference areas. The ^{18}F-FDOPA Ki was calculated using the Patlak graphical analysis, considering the occipital cortex as the reference area (Whone et al., 2004). The Ichise Multilinear Reference Tissue Model (Ichise et al., 1996) was used for ^{11}C-DTBZ quantification, using the striatum as transporter-rich region and occipital cortex as transporter-poor region.

MRI template construction

Construction of a MRI template has been previously reported (Black et al., 2001b; Greer et al., 2002) and is described in detail next. All MRI were skull-stripped using the Brain Surface Extractor (BSE) within BrainSuite 2 (University of South Carolina, Columbia, South Carolina, USA) (Shattuck et al., 2001). One of the individual MRI scan was selected as the representative brain, in terms of the size of the animal (4.3 Kg), the brain size and general shape. This MRI was reoriented parallel to the orbitomeatal axis and, in order to remove unnecessary background data, matrix size was reduced to 88 x 88 x 60, maintaining the voxel size (ANALYZE software, Mayo Clinic, Rochester, Minnesota, USA). Each individual MRI was then registered to the reference scan using Automated Image Registration software (AIR 5.0, University of California, Los Angeles, California, USA) (Woods et al., 1998). For this alignment, the intramodality registration tool was used with the standard deviation of ratio image as cost function and the 3D affine transformation as spatial model (Greer et al., 2002). The registered images were averaged voxel-wise and spatially smoothed using

a gaussian filter (FWHM = 2 mm) to get a preliminary template (SPM, Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). Then each original MRI was automatically normalized to this preliminary template, to obtain transformed images that were much more similar to each other. These ones were again averaged and smoothed in order to achieve a higher quality template. To obtain the final template this process was repeated one more time (third iteration) without visually appreciable changes.

^{18}F-DOPA and ^{11}C-DTBZ template construction

For each PET study, a summed PET image across frames was generated and registered with the corresponding MRI (with skull and scalp) using an automated algorithm based on mutual information (PMOD fusion tool).

Normalization of each individual PET image to the standard stereotaxic space was performed, calculating the geometric transformation for MRI normalization and applying that transformation over the registered PET. Normalized PET images were averaged and smoothed (FWHM = 2 mm) to obtain the ^{18}F-DOPA template and the ^{11}C-DTBZ template (SPM2) in the common stereotaxic space.

VOI-map definition

To create a standard VOI-map, anatomical structures were identified over the reference MRI with the help of a *Macaca fascicularis* brain atlas (Martin et al., 2000). VOIs were hand drawn in the striatum (VOI size 400 mm^3) and occipital lobe (VOI size 310 mm^3) on axial MRI slices based on anatomical

borders (striatum) or position (occipital region). These VOIs were drawn by common consent between two skilled operators.

Templates evaluation

Templates were evaluated by performing a comparison analysis of regional values of BP (n=15) and Ki (n=24) measured with ^{11}C-DTBZ and ^{18}F-DOPA PET respectively. This PET quantification was performed using the manual method used regularly in our center and the automated methods using different templates for spatial normalization. The different quantification methods are described in detail below:

1. Manual method without spatial normalization: Summed PET study was registered automatically to its original MRI (PMOD fusion tool) and the transformation was applied over the dynamic study. Individual VOIs were drawn manually for each subject over its PET summed image, with the anatomical reference of the MRI.

2. Automated method with anatomical normalization to the MRI template: Summed PET study was registered automatically to its MRI (before skull-stripping) using PMOD fusion tool and the transformation parameters were applied over the dynamic study. Individual PET study was spatially normalized using the skull-stripped MRI for the estimation of the geometric transformation (SPM2). The normalized VOI-map previously defined in the standard stereotaxic coordinate system was directly applied, with slight repositioning in some cases.

3. Automated method with functional normalization to the PET template: Spatial normalization of each PET image to the PET template was performed in

two steps: an initial rigid alignment to the PET template (PMOD fusion tool) and the SPM2 non-rigid normalization. The normalized VOI-map was directly applied, and in only a few cases VOIs were slightly repositioned over the normalized PET.

In all methods, parametric images were generated (PMOD) using the suitable reference regions and the biological parameter was calculated in the striatal regions. As a final value, the data of both striata were averaged. Therefore, for each PET study three different parametric values were obtained and statistically compared (SPSS Inc, Chicago, USA). First, parametric values obtained for each method were checked for normality using the Kolmogorov–Smirnov test. Further, statistical differences between methods were evaluated by means of the paired Student's t-test in the case of normally distributed variables, and the Wilcoxon rank test for paired samples with no normal distribution. A p-value less than 0.05 was considered to indicate statistically significant differences between samples. Correlation between samples was also assessed by the Pearson's correlation coefficient.

Lastly, a SPM analysis was performed using a ^{11}C-DTBZ PET image of a monkey with severe dopaminergic depletion after MPTP systemic treatment. A two-sample t-test was performed in order to assess regional differences between this animal and the ^{11}C-DTBZ control group used for the creation of the templates. For this purpose, the parametric PET image of MPTP-treated monkey was normalized using both MRI and ^{11}C-DTBZ templates. All PET images were smoothed using a 6 mm Gaussian kernel.

RESULTS

Templates construction

Using the methodology described above, we created a high resolution MRI template of the *Macaca fascicularis* brain (Fig. 1). The MRI template obtained allows spatial normalization to a common space of individual MRI studies, obtaining an excellent spatial fit between images with automatic procedures. PET templates of summed images were also constructed in the same stereotaxic space with two different radiotracers (^{11}C-DTBZ and ^{18}F-DOPA). Representative sections of the templates are shown in Fig 1. The ^{11}C-DTBZ and ^{18}F-FDOPA templates were excellent in quality based on visual inspection. Although ^{18}F-FDOPA template presents some extracerebral uptake, this pattern is representative of all the summed PET images that were averaged. These templates are also available on the internet and can be downloaded from:

http://www.cima.es/labs-en/instrumental-techniques-micropet/technologies/1.

Templates evaluation: Normalization

All PET studies were spatially normalized by two different automated methods: anatomical normalization using the MRI template after PET to MRI registration, and functional normalization using the corresponding PET template. Most normalization operations worked correctly in one iteration, showing good spatial alignment to the common stereotaxic space. Only in 2 out of 39 images was the normalization carried out twice because the first alignment was considered inaccurate. As an example, MRI and summed ^{18}F-DOPA and ^{11}C-DTBZ PET images acquired for the same monkey and spatially

normalized to the MRI template are shown in Fig 2. The MRI template is also presented in order to demonstrate the correct spatial alignment between them. The VOI-map for striatum and occipital cortex, predefined over the standard coordinates system, was directly applied over the MRI or PET images of this particular monkey. A precise matching between the VOI-map and the anatomical structures of interest can be noticed. A similar, accurate normalization was also carried out using PET templates (data not shown). In some cases, using both modality templates, minor VOIs repositioning was needed.

Templates evaluation: comparison of quantification values

PET studies permitted calculation of the Ki for ^{18}F-DOPA and BP for ^{11}C-DTBZ in the striatum for each subject. The three different quantification approaches described previously were used for each PET study. Mean and standard deviation of data obtained for each procedure are shown in Table 1.

Data obtained using the three different methods (manual, MRI template and PET template) were analyzed statistically to examine the correspondence between them. The Ki values for ^{18}F-DOPA obtained with the manual method were not normally distributed ($p<0.05$ in the Kolmogorov-Smirnov test), whereas for the other two methodologies data followed a normal distribution. For ^{18}F-DOPA, significant differences were found using the Wilcoxon non-parametric test in comparisons between the automated and the manual methods ($p<0.05$), while there were not statistical differences between MRI and PET templates methods. Data obtained with different methods were highly correlated (Fig. 3), with a Pearson's coefficient higher that 0.87. On the other hand, the BP values

obtained for ^{11}C-DTBZ with any of the considered methods were normally distributed across subjects, allowing the use of a parametric t-test. Comparisons yielded non-significant differences between all methods. The correlation between data was also evaluated, showing a very high Pearson's coefficient, greater than 0.95 (Fig. 3).

As an illustration of statistical voxel-based analysis, a SPM comparison of the MPTP-treated monkey *versus* the control group was performed using the MRI template or ^{11}C-DTBZ template for normalization (Fig. 4). A symmetric reduction in ^{11}C-DTBZ uptake in the striatum was detected in both analyses, but the significant cluster observed using the ^{11}C-DTBZ template had a greater extension. The ^{11}C-DTBZ uptake in the MPTP PET study was also assessed using VOIs-map analysis, showing a clear dopaminergic depletion (BP = 0.28). The SPM results were thus in agreement with the VOIs analysis.

DISCUSSION

The objective of this study was to create *Macaca fascicularis* brain templates in order to quantify PET studies in an automated and reproducible manner. Particularly, to study the dopaminergic system we utilize two PET radiotracers: ^{18}F-DOPA and ^{11}C-DTBZ. ^{18}F-DOPA estimates the synthesis and storage capacity of dopamine and is classically used in clinical studies of Parkinson's disease (Morrish et al., 1996; Volkow et al., 1996). ^{11}C-DTBZ is a marker for monoamine transporter VMAT2, located in the presynaptic vesicles of the dopaminergic neurons (Koeppe et al., 1996) and is also used to assess presynaptic dopaminergic terminals (Collantes et al., 2008; Kumar et al., 2003; Lee et al., 2000). Both radiotracers are very useful tools for evaluating the

striatal dopamine deficit caused by MPTP in monkeys, which is one of the best animal models of Parkinson's disease (Emborg, 2007).

MRI templates for other primate species such as baboons and *Macaca nemestrina* have been previously reported and they are digitally available (Black et al., 2001a; Black et al., 2001b; Greer et al., 2002). Black developed a MRI template for the *Macaca fascicularis* (Black et al., 2005) but with some limitations. Firstly, the template has to be created from a representative group of the population under study and in Black's abstract the general characteristics of the animals are not well described. Furthermore, a MRI template without extracerebral structures should be used for an accurate registration of subsequent MRI. Black's template was created as average of T1-weighted MRI including skull and scalp and a mask was later offered in order to extract non-brain structures from the template. This mask was drawn manually over the template, resulting in a loose mask which does not eliminate completely the undesired anatomical structures. In our template, the extraction was performed automatically for each scan using BrainSuite 2 software, which provides a mask that closely fits the brain surface. Consequently, non-brain structures are completely removed in the final MRI template.

Regarding the procedure of creation of templates we have used several programs widely extended and already validated. For inter-subject registration without template we have used AIR, which has been proven to be even better than SPM for this application (Zhilkin and Alexander 2004). For intra-modality registration, we have used the normalized mutual information method of PMOD, which is already experimentally validated (Studholme et al., 1999). For non-

linear spatial normalization to the template SPM was used because it is clearly the standard software to this aim (Friston et al., 1995a).

Although normalization based on MRI templates is better than for any other template due to their high-quality anatomical information and high spatial resolution, the main limitation of this kind of template is that its utilization requires the acquisition of a MRI for each animal and the MRI-PET registration. The creation of PET templates for specific radiotracers allows the normalization of individual PET images directly to the PET template, avoiding the MRI-PET registration. However, we were unable to find any published PET template for *Macaca fascicularis*. This fact prompted us to develop our own PET templates for the two radiotracers that are being used most frequently in our animal studies: ^{18}F-DOPA and ^{11}C-DTBZ. Moreover, images used for the creation of these PET templates were obtained in a dedicated small animal PET scanner with a 2 mm resolution, resulting in high quality templates.

Our different templates allow spatial normalization by automatic procedures of all PET studies to a common space, obtaining a very good spatial fit between images (Fig. 1). Once PET images are spatially normalized, we are able to use a standard VOI-map (Fig. 2) permitting totally automated quantification of PET studies and reducing the processing time. This standardization reduces intra- and inter-operator variability derived from the uncertainty in drawing VOIs manually, not only because the position can be slightly different but also because VOIs may have different shape and size. Although we are working with healthy animals, it must be noted that the application of the pre-defined VOIs-map would be especially useful in injured

animals, due to the fact that regions of interest have a deficit in the radiotracer uptake and the definition of VOIs is more uncertain.

Results obtained comparing manual and automated quantification were strongly correlated. Although we are unable to check which method yields more real quantitative values, we have validated the utilization of any of the methodologies on an equal basis in healthy animals. Moreover, ^{11}C-DTBZ analysis exhibited no statistical differences between methods, demonstrating the equivalence between them. The statistical differences between methods observed for ^{18}F-DOPA might be explained by the possible inaccurate registration of these PET images with different extrastriatal uptake. As previously noted, the complete inhibition of the peripheral aromatic L-amino acid decarboxylase enzyme with carbidopa is not attainable in primates because of their high levels of this enzyme (Chan et al., 1995).

Another important advantage of the normalization is that the definition of a standard coordinate system gives us the chance to statistically compare images on a voxel basis (Fig. 4). As an example, we have compared the dopaminergic activity in an MPTP-treated monkey with the control group using SPM. As expected, a decrease was detected in the striatum using both anatomical and functional normalization with MRI and ^{11}C-DTBZ templates respectively. However, using MRI template, the decreased uptake areas were less extended and more adjusted to the anatomical areas of interest. The highest spatial specificity of SPM analysis using anatomical normalization was already recognized (Gispert et al., 2003) and can be justified by the fact that MRI spatial normalization is more accurate than that performed using functional PET images, given the better anatomical information and higher spatial

resolution of MRI. In any case, quantification of ^{11}C-DTBZ uptake in MPTP-treated monkeys using the VOIs-map analysis also revealed a clear reduction in dopaminergic activity in the same area, supporting the SPM results.

The main limitation of our study is that the three templates and consequently all normalized images are not aligned to any atlas such as that published by Martin *et al* (Martin et al., 2000). In fact, images are oriented parallel to the orbitomeatal axis, for analogy with the usual human orientation. The development of a digital atlas is therefore a convenient next step.

In summary, templates of *Macaca fascicularis* brain have been constructed for MRI and PET and have been used to spatially normalize ^{18}F-DOPA and ^{11}C-DTBZ PET studies. This spatial normalization allows the utilization of an automated and reproducible procedure for PET quantification using a pre-defined VOI-map, and has been validated by comparison with manual methods used previously. Furthermore, the utilization of spatial normalization offers the chance to conduct image analysis further by means of SPM. These templates are available for the scientific community on the website of our institution:

http://www.cima.es/labs-en/instrumental-techniques-micropet/technologies/1.

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Legend for Figures

Figure 1. Representative axial, sagital and coronal slices of MRI template (A), ^{18}F-DOPA PET template (B) and ^{11}C-DTBZ PET template (C) of the *Macaca fascicularis* brain obtained in the common stereotaxic coordinate space. A volume of interest, drawn as an iso-contour over MRI, has been applied over three images to show the correspondence between the three templates.

Figure 2. MRI template image showing the standardized VOI-map on the striatum and occipital regions (A). The same VOIs were applied over MRI (B) and summed ^{18}F-DOPA(C) and ^{11}C-DTBZ PET (D) images from the same monkey spatially normalized to the MRI template. For graphical purposes, skull from ^{18}F-DOPA image was removed in Figure 2, using the brain mask obtained from the registered MRI of the animal.

Figure 3. Correlation analysis of Ki and BP values for ^{18}F-DOPA and ^{11}C-DTBZ studies comparing the three different methods: manual vs. automated using MRI template, manual vs. automated using PET template and automated method using MRI template or PET template. r: Pearson´s correlation coefficient.

Figure 4. Effect of MPTP-induced dopaminergic depletion. Statistical parametric maps showing significant reduction of ^{11}C-DTBZ uptake in the striatum rendered over the normalizated MRI template. Results of the SPM analysis were obtained using MRI template (A) or ^{11}C-DTBZ template (B) for images normalization.