Validation of a Standardized Normalization Template for Statistical Parametric Mapping Analysis of ^{123}I-FP-CIT Images

Aurélie Kas[1,2], Pierre Payoux[3], Marie-Odile Habert[2,4], Zoulikha Malek[2], Yann Cointepas[5], Georges El Fakhri[6], Philippe Chaumet-Riffaud[7], Emmanuel Itti[8], and Philippe Remy[1,9]

[1]URA CNRS-CEA 2210, Service Hospitalier Frédéric Joliot, Orsay, France; [2]Service de Médecine Nucléaire, CHU Pitié-Salpêtrière, AP-HP, Paris, France; [3]Service de Médecine Nucléaire, CHU Purpan et INSERM U825, Toulouse, France; [4]Université Pierre et Marie Curie-Paris 6, INSERM U678, Paris, France; [5]UNAF-CEA, Service Hospitalier Frédéric Joliot, Orsay, France; [6]Nuclear Medicine Division, Radiology Department, Harvard Medical School and Brigham and Women's Hospital Boston, Massachusetts; [7]Service de Médecine Nucléaire, CHU de Bicêtre, AP-HP et Faculté de Médecine Paris 11, Le Kremlin Bicêtre, France; [8]Service de Médecine Nucléaire, CHU Henri Mondor, AP-HP et Faculté de Médecine Paris 12, Créteil, France; and [9]Département de Neurosciences, CHU Henri Mondor, AP-HP et Faculté de Médecine Paris 12, Créteil, France

^{123}I-FP-CIT (^{123}I-*N*-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane) is a SPECT dopamine transporter (DAT) tracer that probes dopaminergic cell loss in Parkinson's disease (PD). Quantification of ^{123}I-FP-CIT images is performed at equilibrium using a ratio (BR) of specific (striatal) to nonspecific (occipital) uptake with values obtained from regions of interest drawn manually over these structures. Statistical parametric mapping (SPM) is a fully automated voxel-based statistical approach that has great potential in the context of DAT imaging. However, the accuracy of the spatial normalization provided by SPM has not been validated for ^{123}I-FP-CIT images. Our first aim was to create an ^{123}I-FP-CIT template that does not require the acquisition of patient-specific MRI and to validate the spatial normalization procedure. Next, we hypothesized that this customized template could be used by different SPECT centers without affecting the outcomes of imaging analyses. **Methods:** The spatial normalization to the customized template created with SPM (template A1) was validated using ^{123}I-FP-CIT images obtained from 6 subjects with essential tremor (ET) with normal DAT status and 6 PD patients. Variability in BR values due to the normalization was evaluated using striatal volume of interest (VOI). To determine whether different SPECT centers could use a unique ^{123}I-FP-CIT template, we generated 3 other ^{123}I-FP-CIT templates using different subjects and image-processing schemes. The interchangeability of these templates was assessed using (a) putamen BR values analyzed with the intraclass correlation coefficient (ICC) and the Bland–Altman graphical analysis, and (b) SPM analysis comparing the results of group comparisons—that is, ET versus PD, obtained after normalization to each of the 4 templates. **Results:** There was no significant difference between pre- and postnormalization striatal BR values in our study. The mean variability calculated with putamen VOI values after normalization to each template was <10%, with the lowest ICC of 98%. Intergroup analyses performed with VOI and SPM approaches provided similar results independently of the template used. **Conclusion:** SPM normalization was accurate even in subjects with low striatal ^{123}I-FP-CIT uptake, making it a promising approach for automatic analysis of ^{123}I-FP-CIT images using a single customized template at different centers.

Key Words: dopamine transporters; SPECT; statistical parametric mapping; normalization; Parkinson's disease

J Nucl Med 2007; 48:1459–1467
DOI: 10.2967/jnumed.106.038646

Parkinson's disease (PD) is characterized by the progressive degeneration of nigrostriatal dopaminergic neurons. This neurodegenerative process is associated with a loss of striatal dopamine transporters (DATs) as shown by postmortem studies (*1,2*). Therefore, in vivo measurement of DAT density with PET or SPECT is an early marker of the dopaminergic cell loss in subjects with parkinsonian symptoms or in asymptomatic carriers of genetic mutations causing PD (*3–7*). In clinical routine, DAT SPECT images are often analyzed visually. However, quantitative analysis is useful to differentiate subjects with subtle localized or diffuse loss of DATs that can be difficult to sort out by visual inspection alone. Moreover, quantification is mandatory to measure disease progression (*7–11*) and to assess the efficacy of neuroprotective drugs (*12,13*).

DAT availability can be estimated using a ratio between specific (striatal) to nonspecific (e.g., occipital) activity (*14,15*) measured using regions of interest (ROIs) drawn manually over these structures in individual images. However, manual ROI delineation is operator-dependent and may be affected by the variability in head positioning and severe signal loss that occurs in the posterior putamen of PD patients. Therefore, manual drawing of ROIs is associated

Received Dec. 8, 2006; revision accepted Jun. 14, 2007.
For correspondence or reprints contact: Aurélie Kas, MD, URA CNRS-CEA 2210, Service Hospitalier Frédéric Joliot, 4, place du Général Leclerc, 91401 Orsay, France.
E-mail: aurelie.kas@psl.aphp.fr

Representative Results:

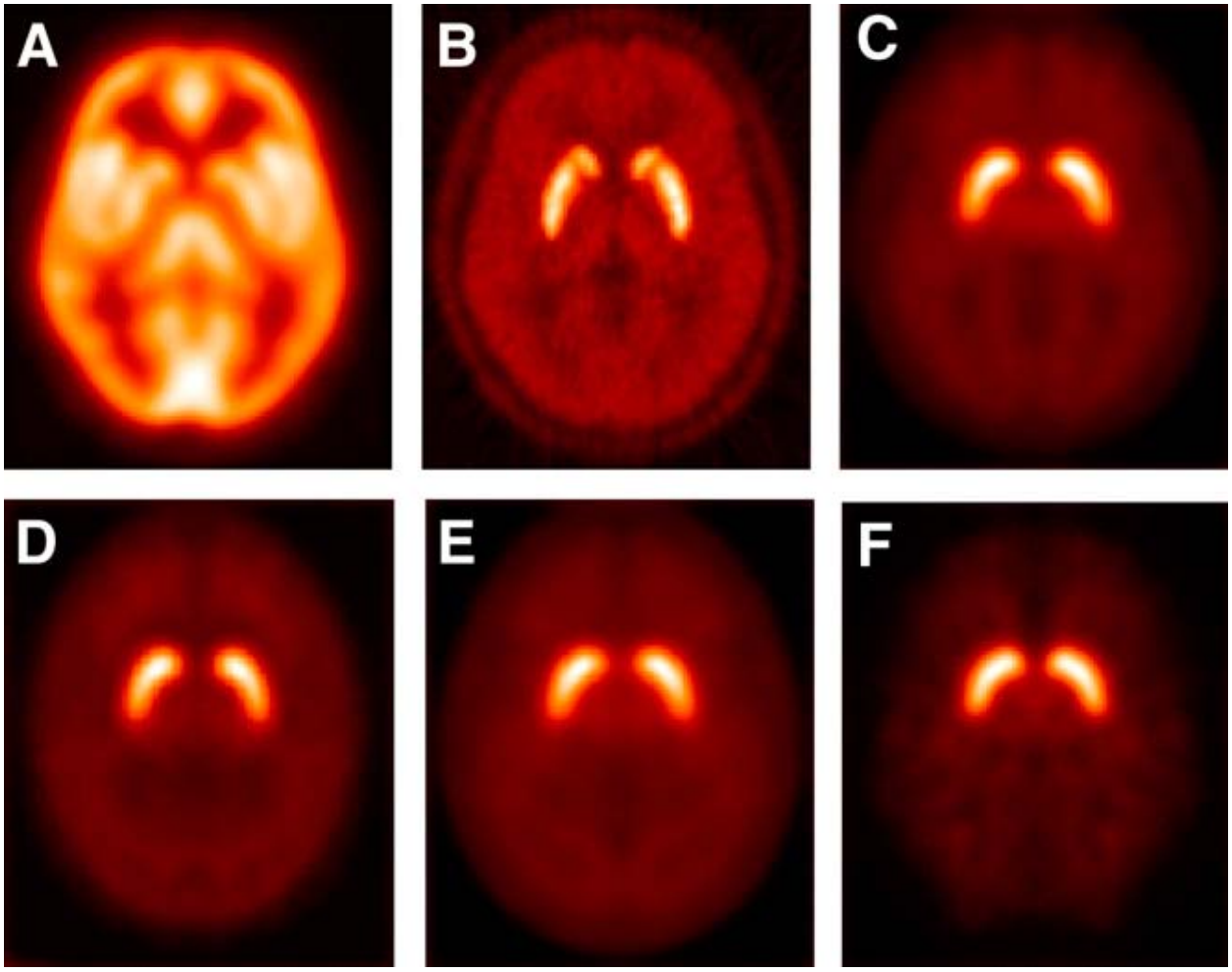

FIGURE 1. Templates: (Top) Regional CBF template (A) available in SPM software package; ^{11}C-raclopride template (B) created in Orsay PET Center from images of healthy subjects; reference template of ^{123}I-FP-CIT (C) created in center A (Template A1). Raclopride template has high specific striatal and low cortical uptake similar to the profile of ^{123}I-FP-CIT images. (Bottom) Three other templates of ^{123}I-FP-CIT (D = template A2, E = template B, and F = template C) constructed with images obtained from different g-cameras or data-processing schemes.

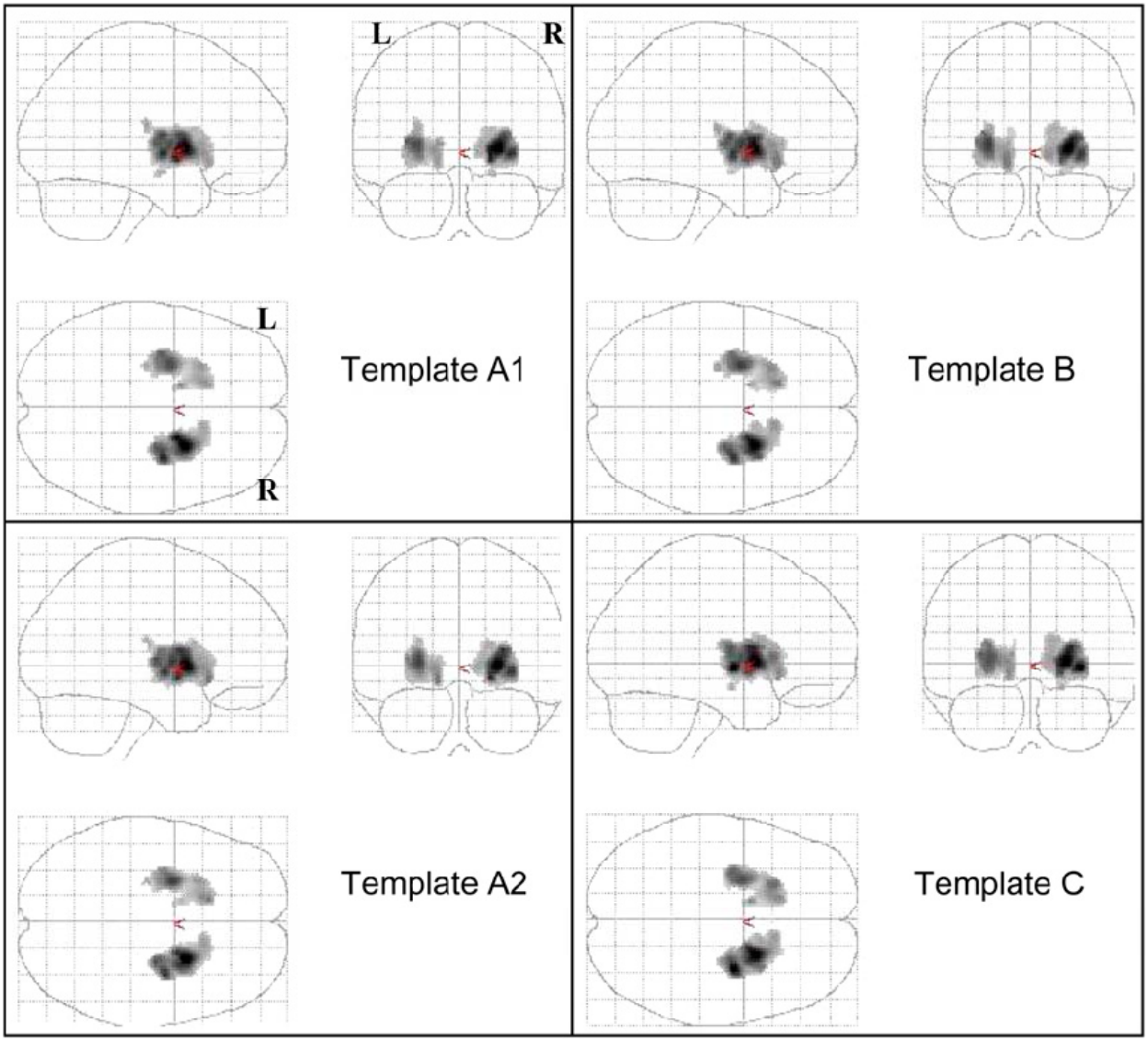

FIGURE 5. SPM t maps ($P_{uncorrected} < 0.001$) obtained by comparing ET patients with PD patients (6 PD < 6 ET) after normalization to each template. Four statistical maps reveal similar significant differences between the 2 groups for 4 different templates. R = right; L = left.