Validation of anatomical standardization of FDG PET images of normal brain: comparison of SPM and NEUROSTAT

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Abstract. *Purpose:* Statistical parametric mapping (SPM) and NEUROSTAT (NS) are widely used for intersubject statistical analysis of brain images. We investigated individual anatomical variations after standardization of ^{18}F-fluorodeoxyglucose positron emission tomography (FDG PET) images of normal brain and compared the differences in the standardized images obtained from SPM and NS.
Methods: Twenty healthy normal subjects were recruited for FDG PET and magnetic resonance imaging (MRI) studies. Sylvian fissures (SF), cingulate sulci (CingS) and central sulci (CtlS) were marked on the brain surface of each individual's co-registered MR images. Then spatial standardization was performed on each subject's PET images using SPM99 and NS with NS's FDG template image, and each subject's MR images (with the SF, CingS, and CtlS marked in advance) were standardized using the sets of parameters obtained from PET standardization by SPM and NS, respectively. The coordinates of each subject's SF, CingS, and CtlS detected on the MR images standardized by the two methods were measured and compared with those on the template images.
Results: The mean individual deviations from the averaged coordinates for the markers on the SF, CingS and CtlS standardized by SPM and by NS were no more than 0.21–1.15 mm. The number of voxels within the brain volume on standardized MR images of all 20 subjects was 88.0% of the total number of brain volume voxels for SPM and 85.3% for NS.
Conclusion: This study demonstrates that SPM and NS yield relatively small differences in standardization and that both methods are effective and valid for PET studies in normal subjects.

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Introduction

A method of anatomical standardization, also called spatial standardization, is commonly used by investigators to compare brain positron emission tomography (PET) images of different subjects voxel by voxel and for intersubject statistical analyses. Although it may seem preferable to obtain morphological information from magnetic resonance (MR) imaging, most investigators standardize PET images by using a software package such as statistical parametric mapping (SPM, The Wellcome Department of Neurology, London, UK) [1] or NEUROSTAT (Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA) [2], rather than using co-registered MR images such as the human brain atlas (HBA, Department of Neuroscience, Karolinska Institute, Sweden) [3]. This is due to the smaller intersubject variation of voxel values and the lower costs when using PET-based standardization compared with MR-based standardization [4]. However, standardization of PET images without the use of co-registered MR images does not guarantee the anatomical correspondence of standardized images. Sugiura et al. [5] examined the anatomical precision of spatial standardization in the localization of the major sulci and brain contours of $H_2{}^{15}O$ cerebral blood flow images with HBA using MR imaging and compared it with SPM95, without use of MR imaging. Their results showed that, despite the lack of use of MR imaging, SPM95 allowed a similar level of precision as HBA, ex-

cept in a few cases where morphological localization varied greatly from that of other subjects.

Recently, spatial standardization of PET images has been used not only in research but also in clinical diagnoses. Minoshima et al. investigated the clinical usefulness of three-dimensional stereotactic surface projections (3D-SSP), in NEUROSTAT [6]. However, there have been no reports on the accuracy of standardization using morphological landmarks of standardized MR images that are transformed with the same parameters as PET images in normal brain. In addition, there have been no reports on the variations in anatomical landmarks of standardized FDG PET images of the normal brain using FDG templates by SPM.

The purpose of this study, therefore, was to assess the morphological accuracy of two commonly used techniques, SPM and NEUROSTAT, in the anatomical standardization of normal brains, by identifying the location of Sylvian fissures, cingulate sulci and central sulci on co-registered MR images.

Materials and methods

Subjects

Twenty healthy normal subjects (19 males, one female; mean age 38.1±18.9 years, range 18–68 years) were recruited for FDG PET and high-resolution T1-weighted MRI studies. Ten (all males, aged 20.5±3.1 years) were recruited from the Institute of Development, Aging and Cancer (IDAC), Tohoku University, Sendai, Miyagi, Japan and ten (nine males and one female, 55.7±7.5 years) from the National Institute for Longevity Sciences (NILS), Obu, Aichi, Japan.

PET studies

All subjects fasted for at least 6 h before the PET study. Subjects were studied in the resting condition with the eyes blindfolded and ears unplugged in a dimly lit room with minimal noise. An intravenous catheter was inserted in the left antecubital vein and maintained with saline flushing, and 370 MBq of ^{18}F-fluorodeoxyglucose (FDG) was injected. A whole-body PET scanner (SET-2400W, Shimadzu Corporation, Kyoto, Japan) was used at IDAC, with a 20-cm axial field of view, and with acquisition of 63 slices. In-plane spatial resolution was 3.9 mm full-width at half-maximum (FWHM) at the center of the field of view, 4.4 mm FWHM tangentially, and 5.4 mm FWHM radially at 10 cm from the center of the field of view [7]. A two-dimensional data acquisition mode was used, and data acquisition was started 30 s after tracer injection and lasted for 45 min. Images were reconstructed by filtered backprojection with a Butterworth-Ramp filter (cut-off 8 mm, order 2), resulting in an in-plane and an axial resolution of 6.0–6.5 mm FWHM. At NILS, an ECAT EXACT HR47 PET scanner (CTI/Siemens, Knoxville, TN, USA) yielding 47 simultaneous planes with an axial FWHM resolution of 4.8 mm and an in-plane resolution of 3.9×3.9 mm^2 was employed. A two-dimensional data acquisition mode was used, with data acquired from 36 to 60 min after injection. Images were reconstructed by filtered backprojection with a Hanning filter (cut-off frequency at 0.5 cycles/projection element), resulting in an in-plane and an axial resolution of 6.0–6.5 mm FWHM.

MRI studies

For anatomical standardization of PET images, structural MR images for each subject were used. At IDAC, MRI scanning was performed using a Vectra Fast, 0.5-T scanner (GE Yokogawa Medical Systems, Tokyo, Japan) on a separate occasion from, but in close temporal proximity to, the PET study. A regular head coil and conventional T1-weighted, spoiled GRASS (TR 50 ms, TE 12 ms, flip angle 45°, NEX 1, image matrix 160×160) in 3D acquisition mode were used. The voxel size in the final MR image was 0.96×0.96×1.50 mm (x, y and z directions, respectively). At NILS, MRI was performed using a Visart 1.5-T scanner (Toshiba Medical, Tokyo, Japan). The scanning sequence was TR 20 ms, TE 7 ms, flip angle 35°. The voxel size was 0.89×0.89×1.3 mm^3, and the slice gap, 0 mm. The voxels of the obtained MR images were then transformed into a voxel size of 0.89×0.89×0.89 mm^3.

Data analysis

All PET and MR images were transferred to a workstation and image sets were converted to ANALYZE format. We co-registered both PET and MR images for each individual subject using SPM99 and then we removed the extracranial soft tissue from the MR images so the brain surface could be identified by image analysis software (Dr View 5.2; AJS, Tokyo, Japan). Following this, Sylvian fissures, central sulci and cingulate sulci were carefully marked on the brain surface of each subject's MR images on every slice where they were identified by one neuroradiologist referencing the Talairach and Tournoux atlas [8]. Because these sulci are major sulci of the brain and are easy to detect, they have been chosen as landmarks in the previous literature [5].

Anatomical standardization of PET image sets was performed using a program "stereo," which is a part of the program set NEUROSTAT, and a SPM99 normalization program using NEUROSTAT's FDG template image. For SPM anatomical standardization, the number of nonlinear basis functions was set to 7×8×7, the number of iterations to 12 and nonlinear regularization to medium. These default parameters were suggested by SPM. When using a NEUROSTAT template, the bounding box was set to −141.75:145.25, −157.5:129.50, −60.75:73.25; the voxel size was 2.25×2.25×2.25 mm^3, the image size was 128×128×60 and the origin was at (64, 71, 28) [9]. For NEUROSTAT, a total of nine affine transformation parameters were estimated.

Next, we standardized each subject's MR images, on which Sylvian fissures, central sulci and cingulate sulci had been marked in advance, using each parameter obtained from PET standardization by SPM and NEUROSTAT, respectively (Fig. 1). After this procedure, we evaluated the mean individual deviations from the averaged coordinates for each marker on specified planes: Sylvian fissures and cingulate sulci on the resliced coronal plane, central sulci on the axial plane (Fig. 2).

After standardization of the PET image with SPM and NEUROSTAT, the co-registered MRI images without landmarks were standardized with each parameter obtained during the standardization of each PET image. Then the standardized MR images were transformed into binary images inside/outside the brain volume.

Table 1. Mean distance from the center of traced points in applicable slices

	rt. SF	lt. SF	rt. CngS	lt. CngS	rt. CtlS	lt. CtlS
NEUROSTAT	3.65 (2.45–5.05)	3.83 (3.14–4.52)	3.98 (2.66–5.13)	3.34 (2.73–6.10)	5.04 (4.25–5.69)	4.97 (3.61–6.14)
SPM	3.44 (2.92–5.06)	3.2 (2.74–3.64)	3.34 (2.18–5.38)	2.96 (2.18–3.71)	4.12 (3.89–4.45)	3.82 (3.30–4.68)
Mean difference between NEUROSTAT and SPM	0.21	0.63	0.61	0.38	0.92	1.15

Units are mm; the range of individual distances from the center of traced points is shown within parentheses
rt., Right; lt., left; SF, Sylvian fissure; CngS, cingulate sulcus; CtlS, central sulcus

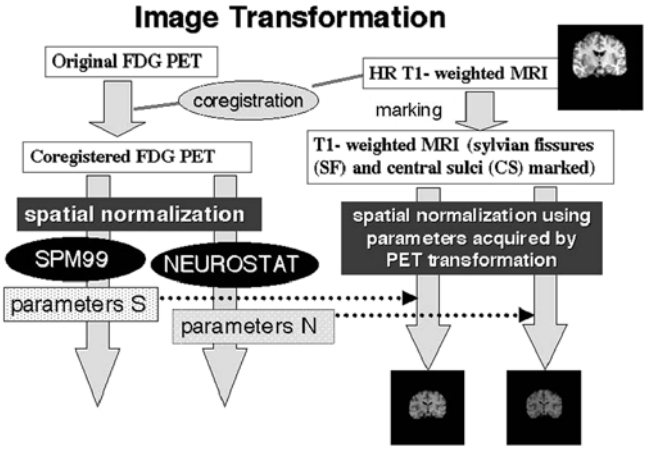

Fig. 1. Process of image transformation in this study. Note that MRI was not used in the process of anatomical standardization but was used for anatomical evaluation. *Parameters S*, image transformation parameters obtained by SPM anatomical standardization; *parameters N*, image transformation parameters obtained by NEUROSTAT anatomical standardization; *HR*, high resolution

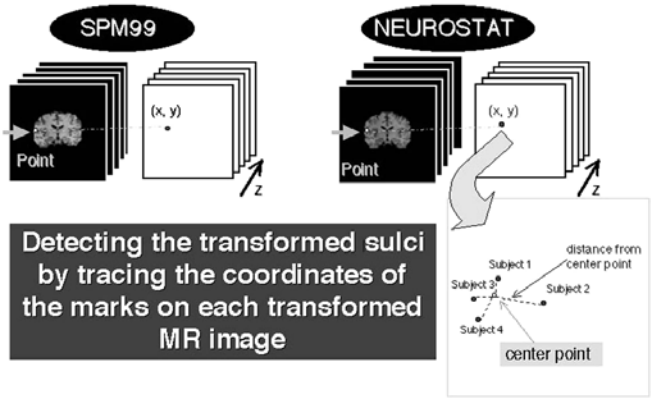

Fig. 2. Definition of center point for each sulcus and definition of each individual distance from the center point on each slice. Center points were defined as the coordinates averaged across subjects

All binary images were summed, and we counted the number of pixels and calculated the overlap ratio; perfect standardization between SPM and NEUROSTAT would result in 100% overlap, and we calculated the ratio in relation to the whole brain area (Fig. 3).

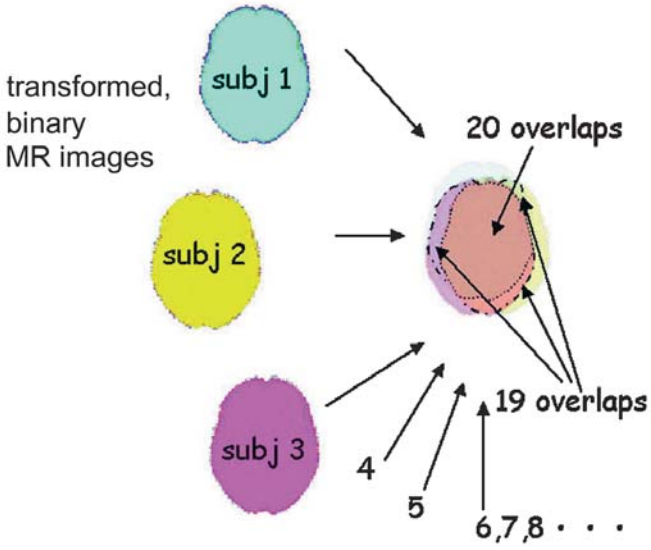

Fig. 3. Method for obtaining the overlap ratio of standardized images of 20 subjects (see text for details)

Results

The mean distance of the subjects' sulcus localization from the center points for each slice in the standardized images differed by no more than 1.15 mm between SPM and NEUROSTAT.

As shown in Table 1, the distance of the Sylvian fissure for each individual subject from the center point ranged from 2.45 mm (on the 62nd slice) to 5.05 mm (on the 68th slice) for NEUROSTAT, and from 2.74 mm (on the 62nd slice) to 5.06 mm (on the 68th slice) for SPM (Fig. 4a). The distance of the cingulate sulci from the center point ranged from 2.66 mm (on the 70th slice) to 6.10 mm (on the 73rd slice) for NEUROSTAT, and from 2.18 mm (on the 73rd slice) to 5.38 mm (on the 53rd slice) for SPM (Fig. 4b). The distance of the central sulci from the center point in the axial slice ranged from 3.61 mm (on the 76th slice) to 6.14 mm (on the 82nd slice) for NEUROSTAT, and from 3.30 mm (on the 80th slice) to 4.68 mm (on the 82nd slice) for SPM (Fig. 4c).

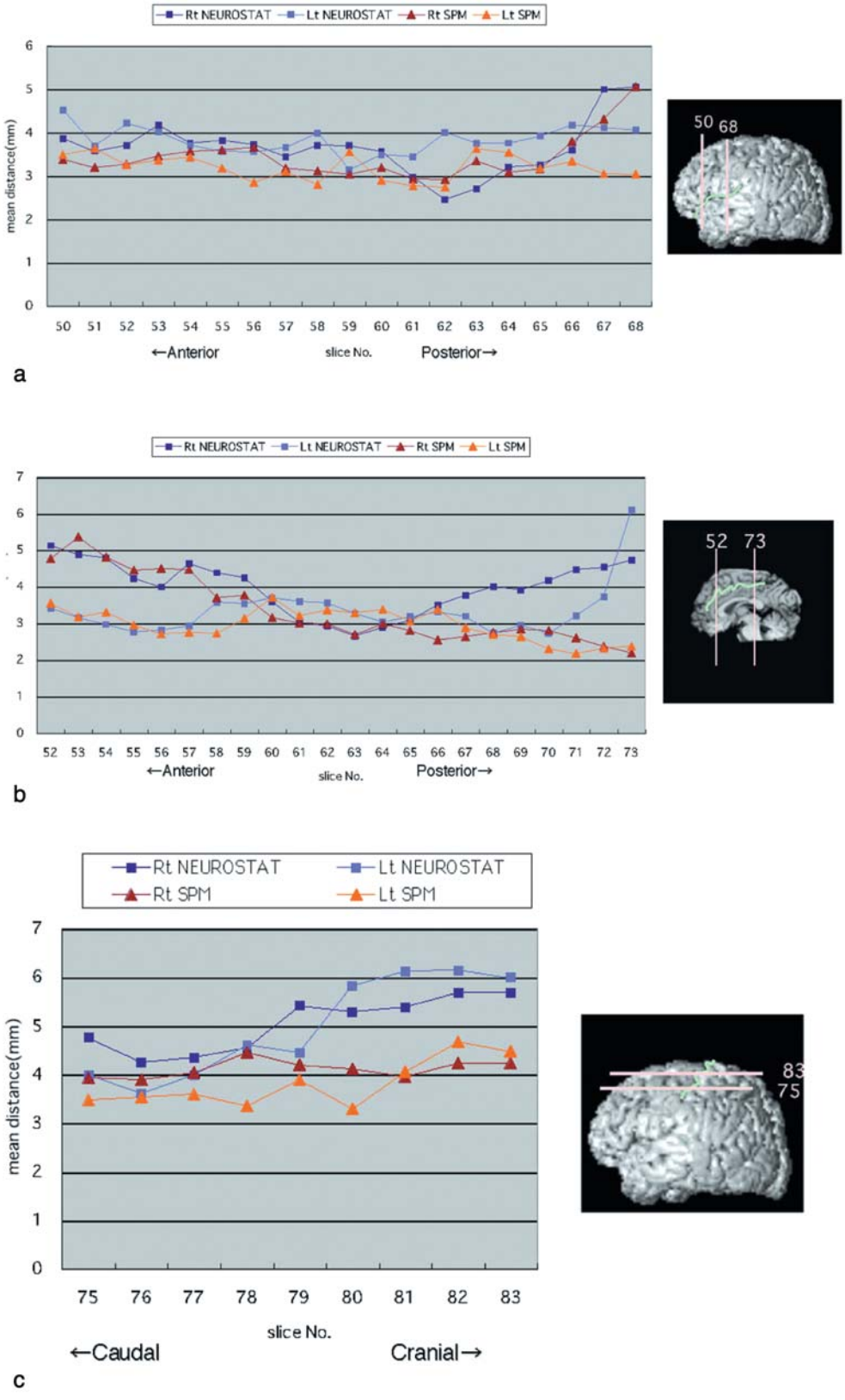

Fig. 4. a The mean distance of the subjects' Sylvian fissure localization from the center points for each slice in the standardized images. **b** The mean distance of the subjects' cingulate sulcus localization from the center points for each slice in the standardized images. **c** The mean distance of the subjects' central sulcus localization from the center points for each slice in the standardized images

The 100% overlap ratio of the pixels within the brain volume for the 20 subjects was 83.1% for NEUROSTAT and 84.9% for SPM. The area of the 95% (=19/20) overlap ratio occupied 4.6% with NEUROSTAT and 3.8% with SPM. The area of 70–95% overlap ratio with NEUROSTAT was a little larger than that with SPM (Fig. 5). There was no significant difference in the area of the 20–60% overlap ratio between NEUROSTAT and SPM.

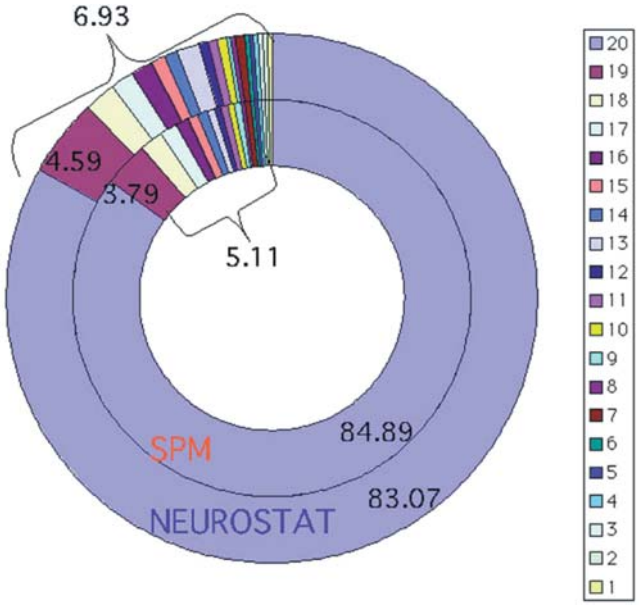

Fig. 5. Percentage of overlap of standardized images for 20 subjects. *The blue area* shows percentage of overlap area for all 20 standardized images

Discussion

In a previous validation of anatomical standardization for atrophied brain that included both healthy volunteers and Alzheimer's disease (AD) patients, the investigators concluded that NEUROSTAT and SPM yielded grossly similar patterns in FDG PET images of AD [9]. In our study we focused only on the brains of healthy volunteers, and we also found no major differences between the standardized FDG PET images with SPM and NEUROSTAT. We examined normal subjects because no study has been done on this topic and because such investigations should first be performed in normal subjects. SPM and NEUROSTAT are expected to be and are actually used for patients, but it is well known that there are some cases where normalization does not work satisfactorily. How the anatomical correspondence matches or varies for patients is an important issue and will be a target of future work.

Many investigators are interested in whether they can find hypometabolic changes in target regions, e.g., hippocampus in AD. The question is, "Which is larger, the size of the hypometabolic area or the degree of the individual variation for the spatial normalization?" We did not examine the variation for the hippocampus in the present study, but found the variation for the central sulcus and cingulate sulcus to be <1 cm on average; this result may be extrapolated to other regions. Because the hypometabolic area in the target regions in focal cortical neurodegenerative disorders is usually sufficiently larger, it will be visualized by either SPM or NEUROSTAT.

In a methodological study, use of a single scanner is usually preferable. The present study, however, used two different scanners because many investigators currently use them together with SPM or NEUROSTAT [5, 9] and we did not want the results to be applicable only to a specific scanner. In fact, there is a trend toward establishing a normal database acquired with a certain scanner, with which patient images acquired with a different scanner will be compared. Because both scanners provide sufficient image quality that allows spatial normalization by SPM or NEUROSTAT and because the most important part of the analysis was done for each subject before summarizing the results in the present study, use of two different scanners is not likely to have affected the results significantly.

In the NEUROSTAT algorithm, differences in brain size between the individual brain and the standard template are removed by linear scaling. Then, to adjust the individual brain shape to the stereotactic atlas proposed by Talairach and Tournoux [8], nonlinear warping along the directions of major neuronal fiber bundles within the brain is performed [2]. This process is the most characteristic feature of the NEUROSTAT algorithm. In contrast, in SPM99 the first step of the standardization is to determine the optimum 12-parameter affine transformation. Next, nonlinear deformation of the individual brain shape is performed by a linear combination of three-dimensional discrete cosine transform basis functions. Matching involves simultaneous minimization of membrane energies from the deformation fields and the residual squared difference between the images and template [10]. In spite of the difference in the algorithm between these two programs, only a small difference in the morphological correspondence was observed in this study. The mean distance from the center point in each fissure was no more than 6.14 mm. While the mean distance from the center point in each fissure standardized by NEUROSTAT was a little larger than that observed with SPM in all six fissures, the difference was no more than 1.15 mm. Considering the resolution of PET images, we believe this will not cause any serious errors.

The mean distance from the center point of the central sulcus was the largest among the three fissures. This may be because the distance between the AC–PC plane and the sulcus is larger than that between the AC–PC plane and the Sylvian fissure or cingulate sulcus. The mean distance from the center point bilaterally of the cingulate sulcus and Sylvian fissure standardized by two different techniques had a similar value in each slice. Therefore, it is supposed that the difference mainly depends on individual variation in the shape of the sulcus rather than on the algorithm of standardization. There is wide variation in individual fissures or sulci even in normal healthy subjects [5, 9]. Therefore, it is natural that variations remain after anatomical standardization.

We supposed that the overlap ratio is one of the indicators of precise anatomical standardization and re-

flects cortical mismatches among the individual standardized images. In programming a study with SPM or NEUROSTAT, before voxel-by-voxel statistics, precise anatomical standardization is needed. If the overlap ratio is small, the voxel-by-voxel statistics will lead to mistakes, especially at the voxels of cortical ribbons.

The complete overlap area of the 20 brains standardized by SPM was slightly larger than that standardized by NEUROSTAT. However, the difference was very small and we expect that this difference will not exceed the variance in individual brain contours. With NEUROSTAT, after anatomical standardization, peak cortical activities are extracted and are projected to surface pixels, and then statistics are performed [8]. This procedure (3D-SSP) has merit in compensating for the small mismatch of cortical regions in anatomical standardization, though SMP performs voxel-by-voxel statistics directly.

Theoretically, NEUROSTAT's anatomical standardization seems superior to SPM's mathematical standardization and it was validated in the study of atrophied brain [9]. However, the results showed that SPM is slightly superior in transforming FDG images to the same anatomical space in the brains of normal subjects. Sugiura's study [5] reported the superiority of SPM 95, which is an old version of SPM 99, compared with HBA, though HBA uses anatomical images while SPM 95 does not. As no perfect standardization technique currently exists, we believe that these two anatomical standardization programs provide acceptable results.

In conclusion, we found that differences in FDG distribution after anatomical standardization with SPM and NEUROSTAT were very small. Both techniques are effective and valid for FDG PET studies in normal subjects.

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