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Identical sets of $H_2{}^{15}O$-PET brain activation data regarding vibrotactile stimulation and voluntary motion of the fingers in seven young normal subjects, together with the MRI, were analyzed in three PET centers by means of each center's own method of anatomical standardization to Talairach's frame. Every center used a linear or segmentally linear transformation with various number of scaling factors. A variation of 6–8 mm in each axis was observed in the foci localization due to the difference in the transformation principle and the measured brain size. Between-subject variation was similar in all the centers. Since different standardization methods define different coordinate systems, a cautious attitude should be taken to comparing results analyzed at different centers.

Key words: positron emission tomography, regional cerebral blood flow, primary sensorimotor cortex, activation, anatomical standardization

INTRODUCTION

IN MAPPING BRAIN FUNCTIONAL ANATOMY by the PET activation technique, the activation foci are usually identified after each subject's PET images are transformed into a standard brain coordinates system by anatomical standardization followed by inter-subject averaging statistical analysis.[1–3] A brain atlas drawn by Talairach et al.[4] and its revision,[5] which are defined in the stereotactic coordinate system based on the anterior and posterior commissures (AC-PC), have been used to extract the anatomical structure from the coordinates. There is yet, however, no universally agreed standardization philosophy, and the design and implementation of the technique depend on the institute where the study is performed. Because different transformations define different coordinate systems even if the same atlas is used as a template, it is not easy to interpret and compare results from different institutes.[6] An attempt to build a data base of human brain foci maps out of a large number of published results[7] would be groundless if the foci localization significantly depends on the method of analysis. To see how the standardization method affects the final result, a multicenter study was conducted by three PET centers in Japan (Tokyo, Akita and Kyoto) with a common data set and their own standardization methods.

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MATERIALS AND METHODS

Data acquisition

A total of seven right-handed male Japanese normal volunteers with the age 22–33 (average 27) were recruited, three in Tokyo, two in Akita, and two in Kyoto. Informed consent was obtained from each subject in the way approved by the ethical committee of each center. The subject underwent CBF measurements by the $H_2{}^{15}O$-PET autoradiographic method while resting (Re) and during vibrotactile stimulation (Vib), three times for each task in random order at intervals of 12 to 15 minutes. The vibrotactile stimulation was applied to the 2nd to 4th finger pads of the right hand with an electric vibrator (Daito model MD9100, Osaka, Japan). Five out of the seven underwent one or two additional CBF measurements under voluntary flexion-extension of the right 2nd

Table 1 Outlines of the three standardization methods

Method	Kyoto	Tokyo	Akita
Origin	mid-ACPC	mid-FrOc on ACPC	mid-ACPC
Number of scaling factors	1	3	11
Y scaling	AC-PC = 25	Fr-Oc = 171	AC-PC = 25 R: Fr-AC = 73, PC-Oc = 73 L: Fr-AC = 73, PC-Oc = 73
X scaling	same as *Y*	Rt-Lt = 136	Rt- Midsag = 72, Lt-Midsag = 72
Z scaling	same as *Y*	Vx-ACPC = 78	R: Vx-ACPC = 78, ACPC-Base = 43 L: Vx-ACPC = 78, ACPC-Base = 43

AC: Anterior Commissure, PC: Posterior Commissure, Fr: Frontal margin, Oc: Occipital margin, Rt: Right margin, Lt: left margin, Vx: Vertex margin, Base: Temporal base margin, Midsag: Midsagittal plane. Margins are defined in Talairach's orientation based on AC-PC and Midsag. (Length in mm)

to 5th fingers at a frequency of about two Hz (Mot). The eyes were closed and white noise was applied through the earphones in all measurements.

The $H_2{}^{15}O$ was synthesized from $^{15}O_2$ gas and intravenously injected in saline, with the administered dose ranging 1.0–1.8 GBq per scan. The PET data acquisition started immediately after the injection of $H_2{}^{15}O$ (Tokyo and Kyoto) or when radioactivity reached the brain (Akita) and continued for 90 sec (Akita and Kyoto) or 120 sec (Tokyo), to generate a set of 6.5 mm-interval 14-slice images with HEADTOME-IV (Shimadzu Corp., Japan)[8] in Tokyo and Akita and 7 mm-interval 15-slice images with PCT-3600W (Hitachi Medical Corp.)[9] in Kyoto. The attenuation was corrected with the transmission data. The image spatial resolution was 7.5 mm in Tokyo, 8 mm in Akita and 9 mm in Kyoto depending on the intrinsic resolution and reconstruction filter. The axial resolution was 9.5 mm FWHM in Tokyo and Akita, and 7 mm in Kyoto. The parametric images of cerebral blood flow (CBF) were created by the PET-autoradiographic method[10,11] with a look-up table derived from the arterial time activity curve, which was measured by continuous sampling of the arterial blood in Tokyo and Akita, or calculated from the standard arterial activity curve of the institute and the global brain radioactivity of the scan in Kyoto.

The T_1-weighted magnetic resonance images (MRI) of each subject were also acquired in multislice 2D spin-echo mode for anatomical reference. Akita used a 1.5 T Shimadzu system to acquire a sagittal image in approximately the midsagittal plane and a set of 2 mm-pitch multi-slice transaxial images. Tokyo and Kyoto used a 1.5 T GE Signa system to take multislice MRI at three angles (sagittal, transaxial, coronal) with a 4.5 or 6.5 mm pitch. The transaxial images were set to be parallel to the anterior and posterior commissure line (AC-PC) in Kyoto and Akita, and parallel to the orbitomeatal line (OM) in Tokyo.

Data analysis

Kyoto used a Macintosh IIfx computer. Tokyo and Akita used "Dr. View" (Asahi Kasei, Japan) and "AVS" (Stardent, USA) running on Stellar GS2000 and GS1000 in Tokyo and on Titan 750 in Akita.

The PET and MRI data for the seven subjects were exchanged among the centers with necessary format conversion together with pixel size, slice pitch and other positional information. The data were then analyzed by the method developed in each center.

First, the PET images were registered to the MRI in each subject by their own technique to locate the activation foci on the MRI for each subject. The registration was generally performed by landmark localization and manual matching of the two image data sets, although it varied from center to center as to details. In Tokyo, the PET and MRI were resliced at 0, ± 10 mm and ± 40 mm apart and parallel to the midsagittal plane, which had been identified as the regression plane of midsagittal points on the original images, and these PET and MRI sagittal images were matched manually with 2D shift and rotation. In Akita and Kyoto, the PET images were registered to the MRI by step-by-step 2D shift and rotation, first matching the midsagittal line in the original transaxial images, then matching the midsagittal line in the resliced coronal images, then matching the estimated AC-PC and brain contour in the resliced sagittal images.

In the next step the PET images were transformed into 2 mm-pixel 4 mm-interval standardized images upon Talairach's frame based on AC-PC and the midsagittal plane by the method of each center described below.

The AC and PC were identified on the MRI, and the PET images were reoriented to the AC-PC line. In Kyoto, the PET images were scaled to adjust the AC-PC distance to that of Talairach's atlas (= 25 mm),[4] and that single scaling factor was applied to all three axes. In Tokyo, the brain size in each axis was measured, and the PET images were scaled to Talairach[4] with a different scaling factor in

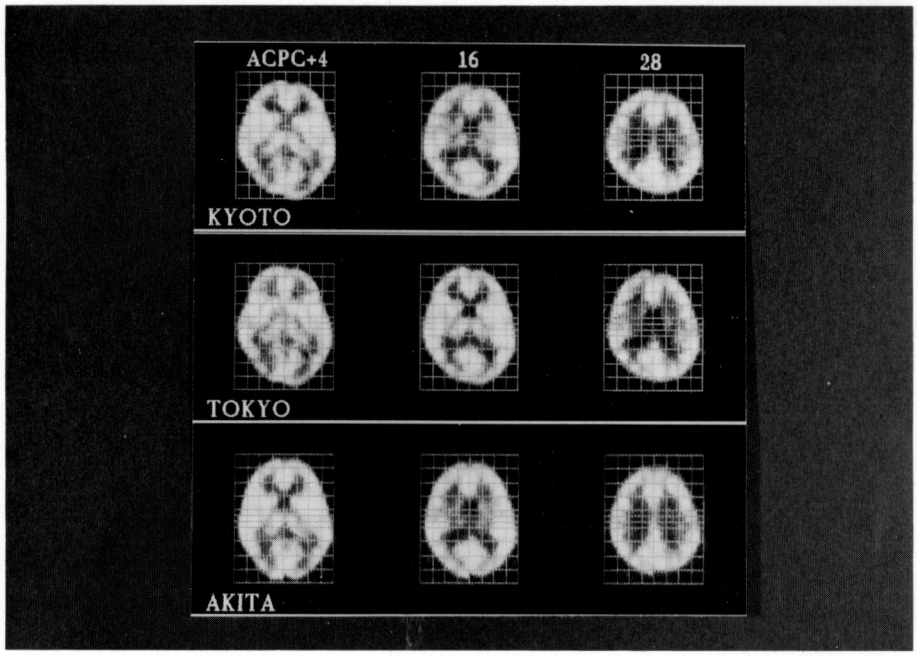

Fig. 1 CBF images of a normal subject standardized into Talairach's frame using three different methods and displayed at ACPC + 4, 16 and 28 mm with Talairach's grids overlayed. Although the original images are identical, the standardized images look quite different. The Kyoto images look roundish due to the preserved $X : Y : Z$ proportion of the typical Japanese brain, while the Tokyo and Akita images are oval like Talairach's atlas. The Akita images, using different scaling factors in right and left, are more symmetrical than Kyoto and Tokyo. (See text for detail of the method in each center.)

each axis, from right to left pole on the X-axis, from frontal to occipital pole on the Y-axis, and from ACPC to vertex on the Z-axis, making a total of three scaling factors. In Akita, the brain was divided into two segments on the X-axis (right and left), three on the Y (Frontal-AC-PC-Occipital) and two on the Z (above and below ACPC) based on the original idea of Talairach,[4] and the scaling factors were determined in each segment: two X-axis factors (from midsagittal to right and left pole), five Y-axis factors (from right and left frontal pole to AC, from AC to PC, and from PC to right and left occipital pole), four Z-axis factors (from ACPC to right and left temporal base, and from ACPC to right and left vertex), making a total of eleven scaling factors. The scaling methods are summarized in Table 1.

Assessment

The standardized CBF images were transferred to Tokyo for further assessment and comparison. After normalization by the global CBF, which is set to 50 ml/min/100 ml, and 7×7 pixel smoothing, the transformed images were processed to create the subtraction images between Vib and Re as well as between Mot and Re in each subject to find the peak in the left Rolandic area. With automatic peak searching and region determining software, a 10 mm-diameter spherical region was placed around the peak pixel in the subtraction images, and the peak coordinates were expressed as the center-of-gravity within the region.

An intersubject averaging statistical analysis was also performed pixel by pixel with a general linear model: $CBF_{ij} = \mu + \alpha_i + \beta_j + Error_{ij}$, where CBF_{ij} constitutes the observed value for CBF in subject i and task j, $(\mu + \alpha_i + \beta_j)$ is the population mean with μ, α_i and, β_j being the grand mean, subject effect and task effect, respectively, and the $Error_{ij}$'s are identically and independently distributed normal errors with mean zero and an unknown variance σ^2. The least squares estimate (mean ΔCBF) and the t value (df = 10) for $(\beta_{Vib} - \beta_{Re})$ and $(\beta_{Mot} - \beta_{Re})$ were mapped. The peak point was identified in the ΔCBF images and t maps in the same manner as in the intrasubject analysis.

RESULTS

The data acquired at the various centers were transferred through magnetic tapes and floppy disks, and were also processed without much difficulty by proper formatting.

One of the authors in each center (MS in Tokyo, HF in Akita, HL in Kyoto) analyzed the data. The computing and interactive process for registration and anatomical standardization of one subject data took approximately two hours in Tokyo, four hours in Akita and five to six hours in Kyoto.

The PET-MRI registration was accomplished satisfactorily at each center, and the registered subtraction images

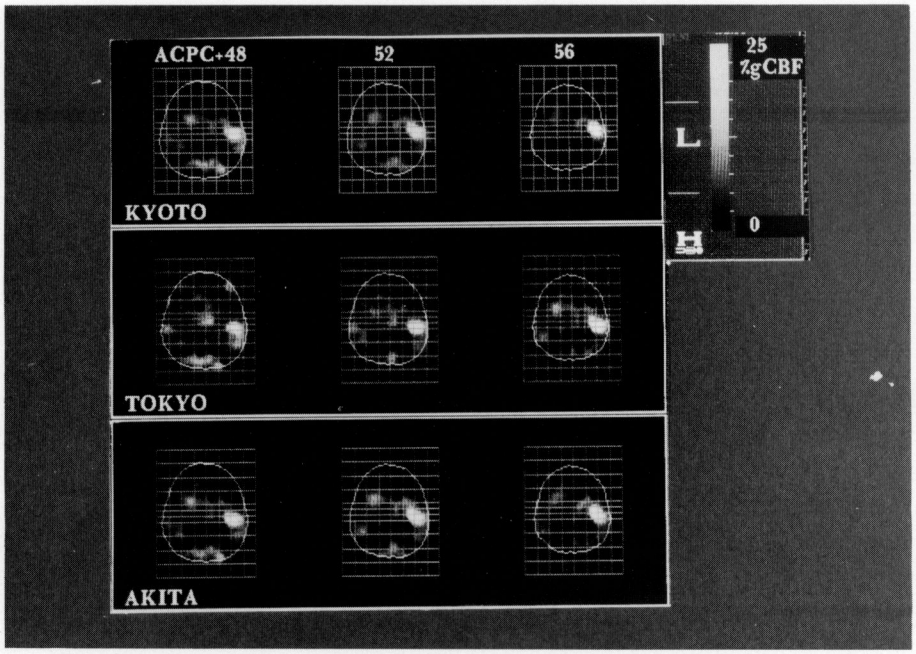

Fig. 2 CBF subtraction images between the right finger vibration and the resting state in a single normal subject, which are anatomically standardized into Talairach's frame using three different methods (Kyoto, Tokyo, and Akita. See text for detail). The foci localization in terms of Talairach's coordinates system depends on the standardization method, even though the identical data are analyzed.

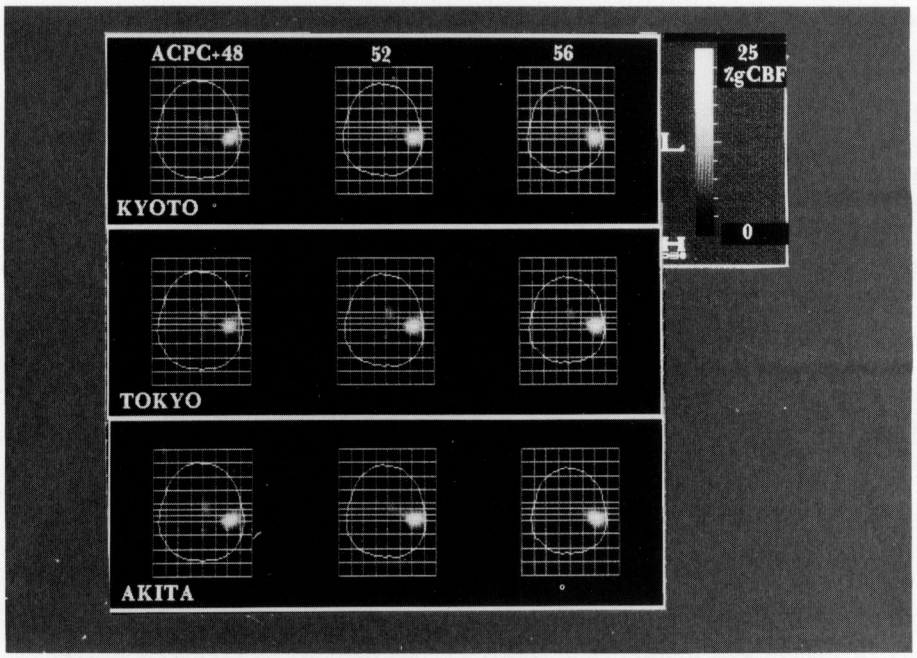

Fig. 3 Intersubject-averaged CBF subtraction images between the right finger vibration and the resting state. The CBF images have been anatomically standardized into Talairach's frame using three different methods (Kyoto, Tokyo, and Akita. See text for detail) and averaged among seven normal subjects. The foci localization in terms of Talairach's coordinates system depends on the standardization method, even though the identical data are analyzed.

showed hot spots covering or touching the left central sulcus in every subject.

Figure 1 shows the CBF images for one subject (No. 3) that were transformed into Talairach's coordinate system at the three centers. The standardized brain images from Kyoto looked roundish due to the preserved $X : Y : Z$ proportion of the typical Japanese brain. The images from Tokyo and Kyoto had right-left asymmetry in most cases,

Table 2 Foci localization and variation

Method	Intra-Subject				Inter-Subject Averaging							
	Peak location and inter-subject variation				Peak location and intensity							
					ΔCBF				t-map			
	Mean			SD (mm)	Peak			Intensity	Peak			Intensity
	x	y	z	distance	x	y	z	ΔCBF_{max}	x	y	z	t_{max}
Vibration focus												
Kyoto	37.9	−8.2	53.2	8.0	39	−9	48	9.4	41	−13	52	13.5
Tokyo	35.3	−6.1	56.1	6.1	37	−5	56	10.1	33	−7	56	10.5
Akita	33.9	−8.2	55.2	7.9	35	−9	52	10.2	39	−9	52	11.5
Motor focus												
Kyoto	36.2	−9.9	55.1	6.4	39	−11	52	13.3	41	−13	52	14.2
Tokyo	33.5	−8.2	57.4	6.7	33	−9	59	12.1	33	−7	56	9.6
Akita	33.4	−9.0	55.3	7.4	33	−9	56	12.1	37	−11	59	9.8

The (x, y, z) coordinates are expressed in mm left lateral (x), anterior (y) and superior (z) from mid-ACPC.

whereas the Akita images that had used different scaling factors on the right and left were more symmetrical.

Figure 2 shows standardized CBF subtraction images between vibrotactile stimulation and the resting state in another subject (No. 2) and compares the three analyzing methods (Kyoto, Tokyo, and Akita). The same gray scale is used throughout the figure, and the brain contour is derived from the mean CBF images averaged among seven normal subjects by the Tokyo method. The standardized subtraction images looked different and the foci localization in terms of Talairach's coordinate system varied from center to center, even though identical raw data were analyzed.

Figure 3 shows intersubject averaged CBF subtraction (vibrotactile minus rest) images for the seven subjects and compares the three analyzing methods. Like the single subject analysis, the peak location varied from center to center even though identical raw data were analyzed. As the noise was suppressed by inter-subject averaging, the foci were clearly visualized with greater contrast but with lower peak values than in the single subject analysis in Figure 2.

The foci localization was taken as the center of gravity within the spheric area 1 cm in diameter surrounding the peak point both in the standardized subtraction images in each subject and in the inter-subject averaged ΔCBF and t-map images. Table 2 summarizes the localization and the variation in the foci as well as the intensity of ΔCBF and the t value at the peak point.

According to the intra-subject analysis, inter-subject variation in the foci localization ranged 3–6 mm in x, 4–6 mm in y, 2–4 mm in z, and 6.1–8.0 mm in 3D distance. Although the degree of inter-subject variation was comparable at all the centers, the Tokyo method showed the smallest variation in the sensory foci (SD = 6.1 mm in 3-D distance) and the Kyoto method showed the smallest variation in the motor foci (SD = 6.4 mm).

The intersubject averaging analysis indicated that the foci coordinates derived at the three centers lay on and around the central sulcus in Talairach's atlas. The motor focus was localized upper and medial to the sensory focus, consistent with the relationship between the pre- and post-central gyrus in the atlas, as it happens that the y axis of Talairach's atlas has a large angle both to the central sulcus and to the contour of the brain near the primary sensorimotor hand area. Comparison of peak localization in ΔCBF and t maps for the three methods showed a variation of 4–8 mm in x, 2–6 mm in y, and 4–8 mm in z due to the standardization methodology. The peak ΔCBF and t-value was comparable at all three centers.

Table 3 shows some of the brain size data measured at each center. Although identical data were analyzed, a considerable difference was observed in the measured brain size in some subjects.

DISCUSSION

The foci localization in PET activation studies have been described after transformation into Talairach's frame. The transformation method is designed and implemented by each institute, some using linear and others using non-linear transformation.[12-14] A different transformation method should define a totally different coordinate system even if the same atlas is used as a template. Therefore the foci coordinates derived at one center may not be compared with those derived at another if the standardized foci coordinates strongly depend on the transformation method. The present study was conducted to evaluate the effect of the transformation method on sensorimotor foci localization by means of a common data set. The data acquired at the different centers were processed equally without much difficulty. The results revealed a variation

Table 3 Brain size measured in each center (mm)

Subject	AC-PC distance			*X*-size (Right-Left)		*Z*-size (ACPC-Vertex)		
	Kyoto	Tokyo	Akita	Tokyo	Akita	Tokyo	Akita	
1	25.0	25.3	24.2	147.5	147.0	71.5	R 70.0	L 71.0
2	24.5	23.5	22.0	138.7	140.0	71.1	R 69.0	L 71.0
3	24.0	23.2	22.0	142.9	143.0	75.1	R 74.0	L 72.0
4	24.0	28.6	24.0	143.6	149.5	72.1	R 73.0	L 73.5
5	25.0	29.1	25.0	134.0	139.0	69.5	R 70.0	L 72.0
6	25.5	25.3	23.5	140.8	136.0	72.2	R 69.3	L 70.2
7	24.0	25.4	22.0	141.0	135.0	71.0	R 71.0	L 71.0

of 4–8 mm in x, 2–6 mm in y, and 4–8 mm in z due to the standardization method, indicating that the sensorimotor foci in the hand area at the three centers are comparable allowing a center-induced variation of up to one centimeter. Considering the difference in the scaling principle and in the measured brain sizes at the various centers, this between-center variation is remarkably small. It is a matter of course that the degree of center-induced variation depends on the foci location in the brain, which is determined by the paradigm, as well as on the transformation method, especially its nonlinearity nature. In the case of a focus located near the frontal or occipital pole, where a small error in the AC-PC angle would produce a large error in the x- or z-coordinate, the between-center variation might be larger. A cautious attitude should always be taken when comparing results analyzed at different centers.

The sensory foci for finger vibration were reported by Fox et al.[15] to be (42, −7, 48) and by Meyer et al.[16] to be (35, −7, 56). This difference is explained by the difference in their method of AC-PC localization as well as by the population difference. Although all our subjects are of the Japanese race, the foci localization obtained at each center in the present study is consistent with these two reports and fell on or around the central sulcus in Talairach's atlas, which was based on the brain of a French woman.

The between-center variation in general is caused by (a) the variation due to method and operator in registering PET to MRI, (b) the variation due to method and operator in brain size measurement and anatomical landmark identification, as well as (c) the difference in the transformation principle including the number of scaling factors.

In the present study all three centers used a linear or segmentally linear transformation. Different results might have occurred if a nonlinear transformation had been applied. Regarding the scaling principle, the Tokyo method is the one most widely used in the world. The Akita method, although not as popular, is most loyal to the principle adopted in Talairach's atlas. The Kyoto method, with the uniform scaling factor across the space to preserve the $X : Y : Z$ proportion, may be logical in dealing with Japanese subjects that have a different brain shape from Europeans.

We must also consider the variation in the process of PET-MRI registration, landmark identification and brain size measurement. The measured AC-PC distance and brain size showed considerable variation among the centers (Table 3). This suggests that part of the between-center variation in this study was caused by variation in landmark identification and brain size measurement. The AC and PC are easily identified in sagittal MRI in most subjects but not in all. We often encounter cases with unclear commissures, which may be identified differently by different observers. Moreover, brain size measurement is not straightforward in some cases. The brain surface is not smooth and it is not easy to identify the most distant point along the axis, which, on the other hand, depends on the AC-PC. In the present study, the entire data analysis was left to each center, and no consultation was conducted between the centers about landmark identification and brain size measurement. Therefore Table 3 represents the degree to which the brain is measured differently when a PET center performs the measurement in its own way just as they do in their own research projects.

Those institutes that use MRI for anatomical landmark measurement have a variety of techniques to register PET to MRI,[17–20] which would cause center-induced variation in their foci localization. Greater variation could result if AC-PC is not localized in MRI but estimated in x-ray film[1] or from PET images alone.[21]

The between-center variation observed in this study is partly due to the operator. This factor, which would be assessed by a multi-operator study with the same method of analysis, was not addressed quantitatively in this study. The variation due to the operator may strongly depend on the method itself, especially the practical way of using the software as well as the principle of the method.

The inter-subject variation in the foci localization in the standardized images is caused partly by the anatomical variation not accounted for by the standardization technique and partly by the individual variation in the anatomico-functional relations. Since the activation foci covered the central sulcus in every subject at every center in the present study, most of the observed inter-subject variations are considered to be caused by the anatomical variation. The Akita method, which divided the brain into segments and applied different scaling factors to each segment, transformed each subject's brain to make it

more like the Talairach's and accounted for the individual morphological variation over the whole brain better than the other two methods. In fact, it proved to be valid in subjects with an asymmetrical brain or with the frontooccipital disproportion frequently observed in Japanese. However, the Akita method, as compared to the other two, did not reduce the inter-subject variation in foci localization nor significantly augment the peak magnitude in the ΔCBF and t map images. Since the sensorimotor foci are located close to the origin on the *Y* axis, it may not be affected by how to scale the *Y* axis.

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