NeuroImage **12,** 326–339 (2000)
doi:10.1006/nimg.2000.0621, available online at http://www.idealibrary.com on IDEAL®

# Intersubject Variability in Cortical Activations during a Complex Language Task

Jinhu Xiong,* Shobini Rao, Paul Jerabek, Frank Zamarripa, Marty Woldorff, Jack Lancaster, and Peter T. Fox

*Research Imaging Center, The University of Texas Health Science Center, San Antonio, Texas; and *Department of Clinical Psychology, National Institute of Mental Health and Neurosciences, Bangalore, India*

Received May 23, 2000

**Intersubject variability in the functional organization of the human brain has theoretical and practical importance for basic and clinical neuroscience. In the present study, positron emission tomography (PET) and anatomical magnetic resonance imaging (MRI) were used to study the functional anatomy of language processes. Intersubject variability in task-induced activations in six brain regions was assessed in 20 normal subjects (10 men and 10 women) for frequency of occurrence, location, intensity, and extent. A complex, but well-studied task (overt verb generation) was compared to a simple baseline (visual fixation) to induce activations in brain areas serving perceptual, motoric, and cognitive functions. The frequency of occurrence was high for all selected brain areas (80–95%). The variability in response location in Talairach space, expressed as the standard deviation along each axis (x, y, z), ranged from 5.2 to 9.9 mm. This variability appears to be uniformly distributed across the brain, uninfluenced by regional differences in the complexity of gyral anatomy or mediated behavior. The variability in response location, expressed as the average Euclidean distances (averaged across subjects) about mean locations of activations, varied from 9.40 to 13.36 mm and had no significant differences by region ($P > 0.05$, $\beta = 0.20$). Intensity variability was also relatively small and homogenous across brain regions. In contrast, response extent was much more variable both across subjects and across brain regions (0.79 to 1.77, coefficient of variation). These findings are in good agreement with previous PET studies of intersubject variability and bode well for the possibility of using functional neuroimaging to study neural plasticity subsequent to congenital and acquired brain lesions.** 

***Key Words:*** **PET; functional human brain mapping; functional anatomy; plasticity; verb generation.**

## INTRODUCTION

Individual variability in the functional organization of the human brain is an issue of relevance for basic neuroscience, for clinical neuroscience and clinical applications of brain-mapping methods. The nature, patterns, and magnitude of intersubject variability in functional pacellation undoubtedly reflect important properties and features of brain development. To investigate the mechanisms underlying the development of cortical functional organization, knowledge of the average organizational pattern is insufficient. The nature and magnitude of normal variations must also be established. Despite the clear need for studies of variability in normal subjects, few such studies have been published.

Functional mapping of the normal human brain is most readily performed with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). A large and rapidly growing literature reports the brain locations of a wide variety of cognitive, perceptual, motoric, and emotional processes. Of the PET studies to date, the majority have relied on intersubject averaging and have reported grand-mean effects. Rather than analyzing and reporting the functional organization for each individual, the individual mappings were averaged across subjects to increase the detection of very subtle (2–3%) neural activations (Fox *et al.*, 1988; Friston *et al.*, 1991). Intersubject averaging is done by spatially normalizing individual brains to a standard orientation, shape, and size, thereby placing all brain images in a common, three-dimensional, stereotactic coordinate space (Talairach and Tournoux, 1988; Fox *et al.*, 1985b). Intersubject averaging has been instrumental in advancing our understanding of the functional organization of the human brain. The grand-averaging strategy, however, extracts only the collective effects of neural activations that are spatially coincident across subjects, providing no information about individual variability in functional organization of the human brain.

Neuroimaging studies that report individual subjects—and, therefore, individual variability—do exist. Unfortunately, a substantial fraction of these studies has not reported their observations within a standardized coordinate space. This is particularly true for



1053-8119/00 $35.00

fMRI, in which the brain is often sampled over too small a volume to allow precise spatial normalization. Furthermore, there is a common impression that spatial normalization is helpful only when data are to be averaged and analyzed for group-mean effects. In our view, studies of individuals that are not reported in standard coordinates do not allow rigorous, quantitative assessment of anatomical variability. While, such studies can (at least in principle) give information on variations in response magnitude and extent, variations in functional anatomy are best quantified relative to a common reference frame.

Previous functional neuroimaging studies quantifying variability within the standard space have been published (for review, see Fox *et al.*, in press). Those studies have reported inter-subject variability in activation locations in the primary visual cortex (Fox *et al.*, 1984, 1985a, 1987b; Belliveau *et al.*, 1991; Schneider *et al.*, 1994; Hasnain *et al.*, 1998), extra-primary visual cortex (Hasnain *et al.*, 1998), primary motor cortex (Fox *et al.*, 1985a; Grafton *et al.*, 1991; Schlaug *et al.*, 1994; Ramsey *et al.*, 1996), primary somatosensory cortex (Schlaug *et al.*, 1994), and the frontal eye fields (Fox *et al.*, 1985a). While providing an important metric of the variability in different cortical regions, these studies have not addressed the variability of language related areas.

Intersubject variability in activation for language has been documented by Herholz *et al.* (1996) using a verb generation task. Their analysis focused on the reproducibility and variation of activation intensity for volumes of interest determined by the gyral anatomy, rather than using Stereotactic coordinates. The reproducibility issue has also been addressed by Poline *et al.* (1996) who pooled data from 12 European PET centers performing the same cognitive activation experiment. Both studies have analyzed and reported the variability in activation magnitude rather than the variability in activation locations.

In this paper, we report on intersubject variability of cortical activations during a semantic (verb) generation task (Petersen *et al.*, 1989). Intersubject variability was assessed in terms of the location (in both Euclidean distances and variation along each coordinate) and magnitude (intensity and extent) of response foci. Cortical areas, both primary and high-order, involved in language perception, comprehension, and production were analyzed. Thus, this work directly addresses the variability in language related areas and the question whether the functional organization in association cortices is similar to that in the primary cortices.

## METHODS

### *Subjects*

Twenty normal healthy volunteers (ten men and ten women), ranging in age from 21–45 years, participated in this study. All subjects were native English speakers and all gave informed consent before the study. PET and MRI scans were acquired with the subject supine and with the head supported in a foam-padded, hemicylindrical head holder. Head position was adjusted for PET imaging with the aid of laser alignment beams to approximate a plane rotated 15° (clockwise, when viewed from the left) from the horizontal plane passing between the anterior and posterior commissures (AC–PC; Talairach and Tournoux, 1988). The subject's head was immobilized within a tightly fitting, thermally molded, plastic facial mask that extended from the hairline to the chin (Fox *et al.*, 1985b).

### *Task Paradigm*

A semantic (verb) generation task (Petersen *et al.*, 1989) was used to assess intersubject variability for language. The task was chosen because it has been extensively published and provides reliable activations. During the task, subjects were asked to generate aloud a verb associated with each of a series of visually presented nouns. A list of 502 concrete nouns was chosen from the list of Paivio *et al.* (1968) and from the lists of frequent words (Francis and Kucera, 1982). Word length ranged from three to seven letters. Three lists of 90 nouns each were constructed to be used during scanning. Two lists of 20 nouns each served as a practice list. Words did not repeat either within or between lists.

Two of three behavioral conditions are reported here: a control state and an activation state. During the control state, the subject was asked to fixate on a cross hair presented in the center of a screen. During the activation state, the nouns were presented to the subject, who was instructed to generate aloud an associated verb for each noun. Words were displayed slightly above the cross hair in the center of a video monitor and subtended approximately 1.2° vertically and, on average, 5.7° horizontally. Words were presented for a duration of 150 ms at the rate of 1/s. Subjects were familiarized with the task by exposure to the practice list before entering the scanner. In the third behavioral condition, which will be reported elsewhere, the subject was asked to name line-drawn pictures. The ordering of the three conditions was pseudo-randomized.

### *Data Acquisition*

PET data were acquired with a GE/Scanditronix 4096 camera. This camera simultaneously acquires 15 parallel slices with a center-center interslice distance of 6.5 mm and a transaxial field of view of 10.5 cm. Images were reconstructed at an in-plane resolution of 7-mm full width at half maximum (FWHM) and an axial resolution of 6.5-mm FWHM. Before emission scanning, a 15-slice tomographic transmission image (68 Ge/68 Ga) was obtained for calculating regional

attenuation coefficients (Fox *et al.*, 1985b). Water labeled with oxygen-15 ($H_2{}^{15}O$, half-life 122 s) was used as a blood-flow tracer. Between 70–75 mCi of $H_2{}^{15}O$ in 5–10 cc of sterile saline was delivered as an intravenous bolus. Data acquisition began as the tracer bolus arrived in the brain (15–20 s after tracer injection) and continued for 40 s. For the activation condition, stimulus presentation and task began at the same time as tracer injection. Each subject underwent a series of nine scans, with three scans each of three behavioral conditions. Two of the three conditions (rest and one task) are reported here. (The analysis of the third condition, a second task, will be reported subsequently elsewhere.) A 10- to 15-min interscan interval (larger than or equal to five half-lives) was sufficient for radioactive decay and to reestablish resting levels of brain blood flow before the subsequent scan.

MRI experiments were performed on an Elscint Gyrex 2-T whole-body MRI scanner (Elscint Ltd., Haifa, Israel) operating at 1.9 T. For every volunteer participating in the PET study, a three-dimensional (3-D) T1-weighted anatomical image was acquired for the entire brain with a voxel size of $1.0 \times 1.0 \times 1.2$ mm for PET-MRI coregistration to facilitate precisely determining the structures corresponding to the functional activation foci.

### *Data Analysis*

*Image normalization.* The PET and the 3-D MRI T1-weighted images were spatially normalized into registration with the Talairach brain atlas (Talairach and Tournoux, 1988) using the software package "SN" developed by Lancaster *et al.* (1995). This algorithm uses a nine-parameter fit and interactive denotation of the AC–PC line. Images were resliced into 60 slices using trilinear interpolation, with image matrix size $60 \times 128 \times 128$ and each voxel $2 \times 2 \times 2$ mm$^3$. Brain volume was defined by a intensity-thresholding of 30% maximum voxel value of the individual data. Voxels with values lower than the threshold were considered as nonbrain region. PET blood-flow images were then value-normalized to a whole brain mean voxel value of 1000.

*Grand-mean analysis.* The PET images were grouped into activation and control states. A voxel-by-voxel group *t* test was performed to create a statistical parametric image (SPI). The SPI was then thresholded using both an intensity threshold and a cluster-size threshold to delimit the activation foci (Xiong, 1995, 1996). An intensity threshold of $z = 2.06$ was used to produce a significant activation signal at the $P = 0.02$ level (uncorrected for multiple comparisons). Activation foci with a spatial extent less than 16 voxels (128 mm$^3$) were eliminated from final activation images to further suppress random noise (Friston *et al.*, 1994; Xiong *et al.*, 1995). The location of each activation focus was determined as the center-of-mass for that focus (Mintun *et al.*, 1989). The *x*-, *y*-, and *z*-coordinates of the center-of-mass were calculated in Talairach-atlas coordinates (Talairach and Tournoux, 1988). The center-of-mass is likely to be stable over a reasonable range of intensity and extent thresholds.

*Volume of interest (VOI).* Intersubject variability was assessed based on the significant activations for selected regions. The regions were selected based on the literature and confirmed by our grand-mean analysis. These included two left inferior frontal cortices [Brodmann area (BA) 44 and BA 47], left primary motor and premoter cortices in the mouth region (BA 4/6), supplementary motor area (BA 6), anterior cingulate (BA 32/24), and left posterior superior temporal cortex (BA 22). The selected brain regions were known to be involved in language processing and language production (Petersen *et al.*, 1988, 1989; Posner *et al.*, 1988; Wise *et al.*, 1991; Paulesu *et al.*, 1993; Raichle, 1994; Warburto *et al.*, 1996; Xiong *et al.*, 1998). Activation in BA 44 has been postulated for articulatory encoding; and activation in BA 47 has been interpreted as mediating lexical semantic processing, especially for words meaning retrieval (Penfield and Roberts, 1959; Petersen *et al.*, 1988, 1989; Paulesu *et al.*, 1993; Demb *et al.*, 1995; Warburton *et al.*, 1996). The anterior cingulate (BA 32) has been implicated in response selection (Posner *et al.*, 1988) and the SMA in motor programming (Rao *et al.*, 1993; Petersen *et al.*, 1989; Fox *et al.*, 1996). The left superior temporal gyrus (BA 22) is thought to associate with phonological processing (Wise *et al.*, 1991; Demonet *et al.*, 1992). BA 4 and BA 6 are the primary motor cortex and premotor cortex in the mouth region and mediate movement.

*Occurrence.* Individual analyses of the PET images were performed using the same procedure and the same parameters described above to defined significant activation foci. The occurrences of activations were indexed by two different methods: a region-based and a voxel-based frequency of activation. The region-based frequency is an index of how may subjects show at least one activation in a particular VOI. A voxel-based frequency (or "penetrance" image) was created by computing the frequency of significant activation across subjects for each voxel (Fox *et al.*, 1996). Penetrance images reveal spatial consistency of activations among subjects.

*Location variability.* For each region, more than one activation focus was possible. The location of significant activation for each region was computed as the center-of-mass of the largest activation focus located in the region. A standard deviation along each of the *x*-, *y*-, and *z*-coordinates was computed for each selected VOI. Euclidean distance value, *d*, about the mean lo-

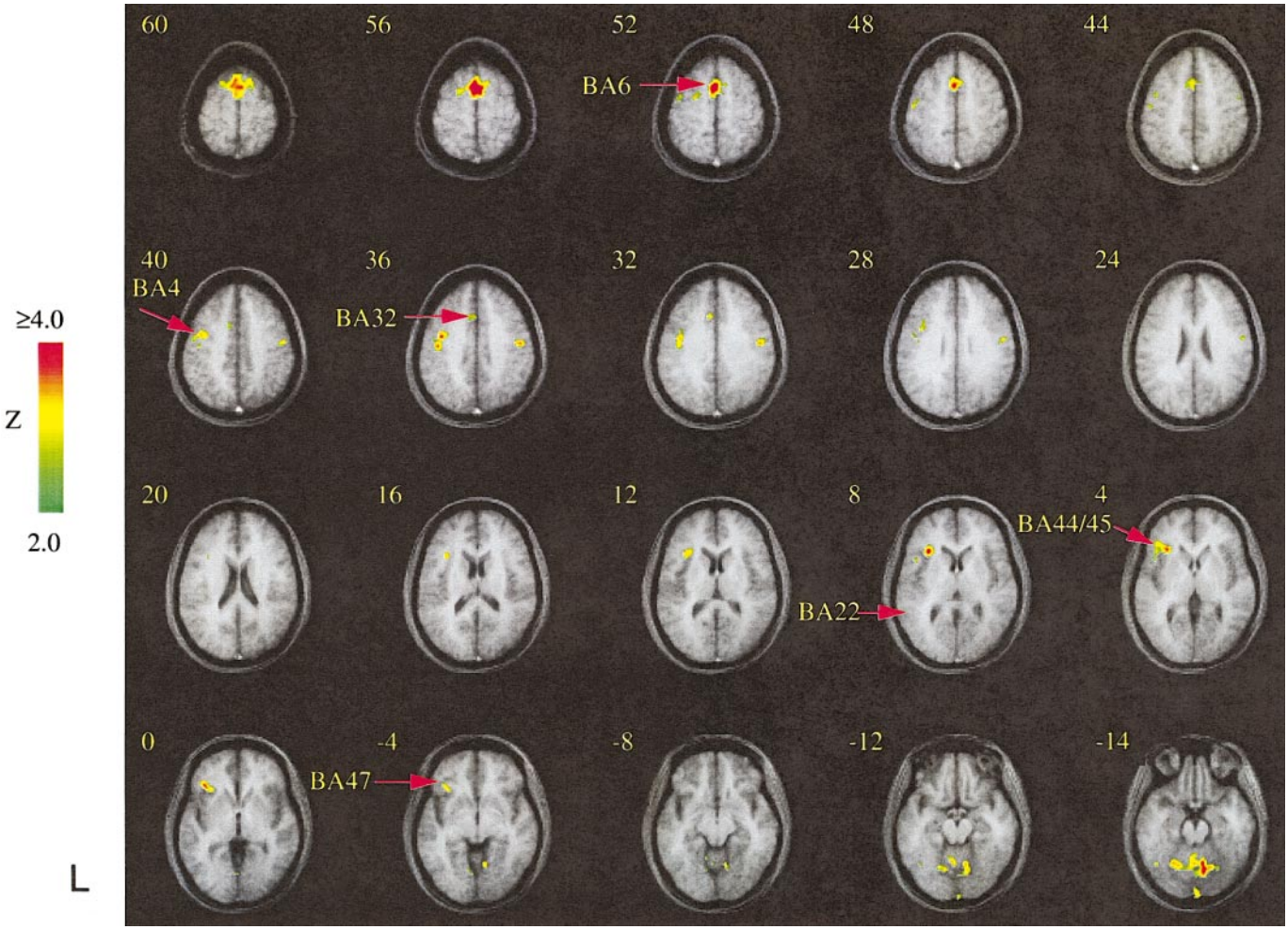


**FIG. 1.** PET activations during verb generation relative to fixation rest. The activation information has been transformed into stereotactic space, averaged across 20 subjects, and overlaid on the spatially normalized, averaged anatomical T1-weighted MRI images. The color scale represents the *z* value of each voxel. The number in the upper-left of each panel refer to distance in millimeters from the AC-PC plane. L, the left hemisphere.

cation ($x_0$, $y_0$, $z_0$) for each selected VOI was also calculated for each subject using the following equation:

$$d = \sqrt{(x - x_0)^2 + (y - y_0)^2 + (z - z_0)^2},$$

where *x*, *y*, and *z* are location in Talairach space for an activation focus. Intersubject variability in the location of activation for each region was then calculated across subjects.

*Intensity and extent variability.* Intersubject variability in intensity and extent of activation for each VOI was assessed. The mean and standard deviation of the peak *Z* scores for each VOI were calculated and used as indices of the intensity variability. The mean and coefficient of variation (COV) of the volumes for each VOI was computed as extent variability. Here, the COV is defined as a ratio of the standard deviation to the mean.

## RESULTS

### *Subject Performance*

All twenty subjects performed well on the verb-generation task. The rate of correct responses was higher than 90% for every subject, on every trial.

### *Grand-Mean Analysis*

Our grand-mean analysis confirmed the activations reported previously in the literature for the verb generation task (Petersen *et al.*, 1988, 1989; Wise *et al.*, 1991). Significant activations were presented in the cortical areas subserving motoric, visual, and languagistic functions. Primary motor cortex (M1 mouth/BA 4) and premotor cortex (BA 6) were activated bilaterally, with activation in the left hemisphere stronger than that in the right hemisphere.

Significant activations were observed in the supplementary motor area (SMA/BA 6) and anterior cingulate (BA 32/24). Strong activations were also observed in the left inferior frontal gyrus (BAs 45 and 47), left Broca's area (BA 44), providing evidence for left hemispheric dominance. Additional activations were also seen in the inferior temporal gyrus (BA 37), occipital gyri (BAs 18, 19), and cerebellum (Fig. 1). Activation locations and peak *Z* score values for the selected VOIs were summarized in Table 1.

*Occurrence*

The region-based detection frequency of task-specific activation was high for each selected region (Fig. 2). Activation foci in the supplementary motor area (SMA/BA 6) and the left M1 mouth region were detected in 19 of 20 subjects (95%). The detection frequency in the left superior temporal gyrus (BA 22) was 90% (18 of 20 subjects). Activation foci in the left inferior frontal gyrus (BA 44 and BA 47) and anterior cingulate (BA 32/24) were detected in 16 of 20 subjects (80%). The voxel-based detection frequency varied from one brain region to another, as revealed by the penetrance image (Fig. 3) and the bar graphs (Fig. 2). A penetrance image is a measurement of the spatial consistency of significant activations and shows how many subjects activated in a particular voxel. The maximal spatial overlaps of the task-specific activation areas were in SMA (BA 6) (95%). Also activated consistently were cerebellum, Broca's area (BA 44), bilateral M1 mouth regions (BA 4), inferior frontal gyrus (BAs 45 and 47), and bilateral inferior temporal gyrus regions (BA 37). Activations within superior temporal gyrus (BA 22), brain stem, insula, thalamus, and anterior cingulate (BA 32/24) tended to overlap less but to still spatially cluster. Activation in extra striate gyri (BAs 18 and 19) appeared to be widely spread. Infrequent activations, with locations varying across subjects, were also found in the basal ganglia and some subcortical structures.

**TABLE 1**

Location and Peak *Z* Score of Significant Activation for the Selected Brain Regions for the Grand-Mean Image

| Brain region | Peak *Z* score | Talairach coordinates *X* (mm) | *Y* (mm) | *Z* (mm) |
|---|---|---|---|---|
| SMA, BA6 | 5.3 | −1.2 | 5.9 | 55.1 |
| Anterior cingulate, BA 32/24 | 3.3 | −5.4 | 16.3 | 34.1 |
| Left M1 mouth, BA4/6 | 4.2 | −39.1 | −6.3 | 35.4 |
| Left superior temporal gyrus, BA22 | 2.6 | −48.0 | −32.3 | 6.0 |
| Left inferior frontal gyrus, BA44 | 4.4 | −32.6 | 21.1 | 5.5 |
| Left inferior frontal gyrus, BA47 | 3.2 | −41.9 | 21.0 | −5.5 |

*Location Variability*

Our assessment in intersubject variability in locations of activations was focused in the left hemisphere because frequencies of activations in the right hemisphere were typically low. The intersubject variability in locations of activations in the left hemisphere (Fig. 4A) ranged from 5.2 mm (BA 44, the *x*-coordinate) to 9.9 mm (BA 32/24, the *y*-coordinate) and is consistent with the previous findings (Fox *et al.*, 1985a, 1987b; Belliveau *et al.*, 1991; Grafton *et al.*, 1992; Schlaug *et al.*, 1994; Ramsey *et al.*, 1996; Hasnain *et al.*, 1998). The variability in locations of activations was calculated as the standard deviation for the *x*-, *y*-, and *z*-coordinates of the significant activation foci for each selected region. When each coordinate is treated as independent, a Bartlett's test for equality of variance revealed that no significant difference was present in the variability across brain structures and across the different coordinates ($P > 0.10$). The average locations, average *Z* scores, and average intensity-weighted volumes of significant activations for selected brain regions were listed in Table 2.

In addition, Euclidean distance value about the mean location for each selected VOI was also calculated for each subject. The mean Euclidean distance values varied from 9.40 mm (BA 6) to 13.36 mm (BA 32) (Fig. 4B). A Kruskal–Wallis test showed no significant difference in Euclidean distances across brain structures ($P > 0.05$). The Kruskal–Wallis test provided a stronger evidence for the homogeneity of the location variability because the test is insensitive to the assumption of independence of each coordinate and the normal distribution of population and less sensitive to sample size. Based on the experimental data presented in Fig. 4B and the procedure described by Zar (1996) for estimating power in analysis of variance, the power for our statistical test (Kruskal–Wallis) was more than 80%, at a significance level $\alpha = 0.05$. That is, there was a less than 20% chance of having a Type II error in this analysis.

*Intensity and extent variability.* The intersubject variability in magnitude of activations was assessed by intensity and extent of the activation. The averaged peak *Z* scores (averaged across subjects) ranged from 4.58 (BA 22) to 5.41 (BA 6) for the selected VOIs (Fig. 5A), and did not show any significant change across the brain regions ($F = 0.99$, $P > 0.50$, ANOA test). The variations of the peak *Z* scores (indexed by the standard deviation) were also relatively uniformly distributed ($P > 0.10$, Bartlett's test). In contrast, the response volume *did* show a significant change across different brain regions ($F = 4.71$, $P < 0.002$, ANOVA). The variability of the response extent (measured by the coefficient of variation) also shown a significant change ($P < 0.05$, Bartlett's test). The coefficients for the selected brain regions were in a range of 0.79 to 1.77,

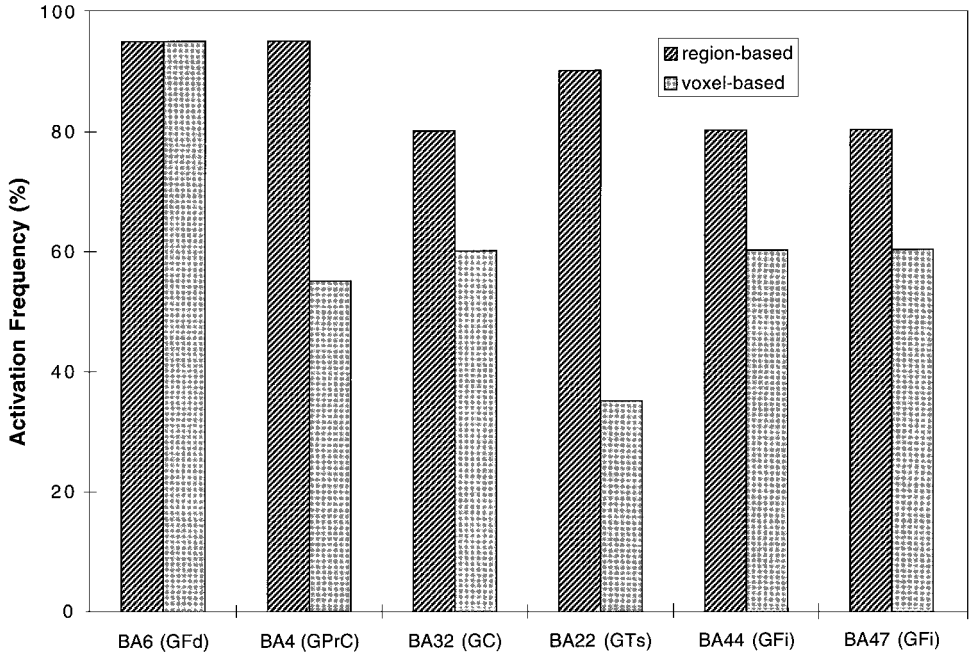


**FIG. 2.** Region-based and voxel-based frequency of task-specific activations for the selected brain regions.

with the smallest variation in SMA (BA 6) and the largest in the left posterior superior temporal cortex (BA 22) (Fig. 5B).

## DISCUSSION

Intersubject variability of brain activations associated with a widely used language task—overt verb generation—was assessed in 20 normal volunteers (10 men and 10 women). Grand-mean analysis confirmed that the regions activated in our subject group were in good agreement with that reported in the literature. For each brain area, the frequency of occurrence was sufficiently high (80–95%) to allow a meaningful assessment of variability for a variety of response parameters within and between regions. Parameters assessed included response location, intensity and extent. Variability in location and intensity were both small and relatively homogeneous across brain regions, in good agreement with prior human imaging studies. Variability in response extent was quite large and varied widely across brain regions, in good agreement with a limited literature on human cytoarchitectonics.

### *Occurrence*

Frequency of occurrence was assessed both by region and by voxel. Region-based detection frequencies were high, ranging from 80 to 95% (Fig. 2). That is, the activations observed in the group (Fig. 1) were observed in the great majority of individuals. A theoretical implication of this observation is to argue against the idea that individuals might vary significantly in the strategy used to perform this complex task: each region was used by virtually all subjects. A practical implication of this observations is that in no region was variability assessed in fewer than 16 subjects. This was of particular importance for assessment the homogeneity of variance across brain regions (below). Another practical implication is to contradict the widespread impression that PET is not a suitable technology for assessing individual variability. In fact, it appears that failure to detect activations in individual subjects may be higher for fMRI than for PET. In this study, every subject recruited was reported.

Voxel-based analysis gave slightly lower values for occurrence (penetrance) than region-based: peak values ranging from 35 to 95% (Figs. 2 and 3). These values the point of maximum overlap across individual. The voxel-based penetrance fell off rapidly from the point of maximum overlap, closely following the intensity profile in the group-mean image. This suggests that the intensity profile in a group-mean image is chiefly a function of intersubject spatial overlap, rather than being a true expression of the shape of the activation. Note that present data were not smoothed, as is commonly done, so that the spatial resolution was higher than many previously reported PET studies (approximately 7 mm), although still lower than the majority of fMRI studies (~3 mm in-plane resolution). Smoothing will likely increase the voxel-based frequency.

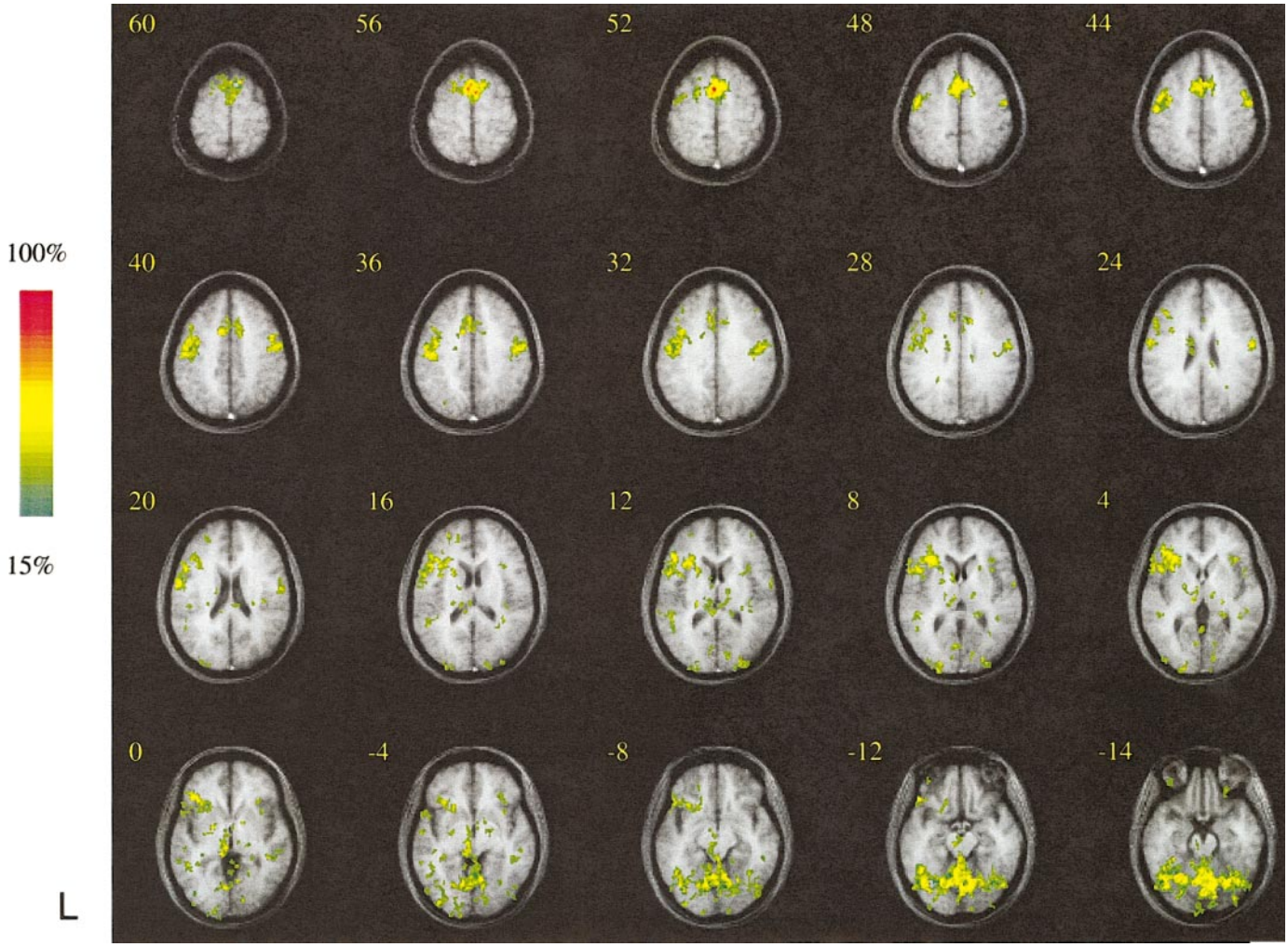


**FIG. 3.** Penetrance image to show the consistency in locations of significant activations. The image has been transformed into stereotactic space. The color scale represents the percentage of subjects activated for each voxel. The number in the upper-left of each panel refer to distance in millimeters from the AC–PC plane. L, the left hemisphere.

*Location Variability*

*Homogeneity of variance.* Previous human imaging studies have reported intersubject variability in functional organization (indexed as standard deviations in millimeters along each axis) to be 2–10 mm for primary cortices (Fox *et al.*, 1985a, 1987b; Belliveau *et al.*, 1991; Fox and Pardo, 1991; Grafton *et al.*, 1992; Schlaug *et al.*, 1994; Ramsey *et al.*, 1996; Hasnain *et al.*, 1998; Fox *et al.*, in press). Our findings, with standard deviations ranging from 5.2 to 9.9 mm, are in excellent agreement with this literature. In addition, our findings are among the first to extend these observations to nonprimary brain areas, including BA 44, BA 47, BA 22, and BA 32. Surprisingly, location variability was relatively uniform across brain regions, rather than being higher in regions of higher gyral or cognitive complexity. This finding (of location variability homogeneity) is consistent with the findings of Fox and Pardo (1991), who also found similar location variability for higher-order and for primary cortices, although this was in a patient population (temporal-lobe epilepsy). A statistical caution can be raised, however, regarding the assertion that location variance was homogenous across brain areas. This caveat derives from the common practice of quantifying location variability as the standard deviation along each axis. Using this metric, the uniformity of variance is assessed by testing the equality of variance. Tests for equality of variance, however, are very sensitive to sample size. Although the sample size of our study is relatively large (20 subjects), it may still be a concern whether there was sufficient power to detect a true difference in the variances across regions. To address the concern, a new parameter, Euclidean distance value about the mean location for each selected VOI, was calculated for each subject. The homogeneity of variability in location was then be assessed by test-

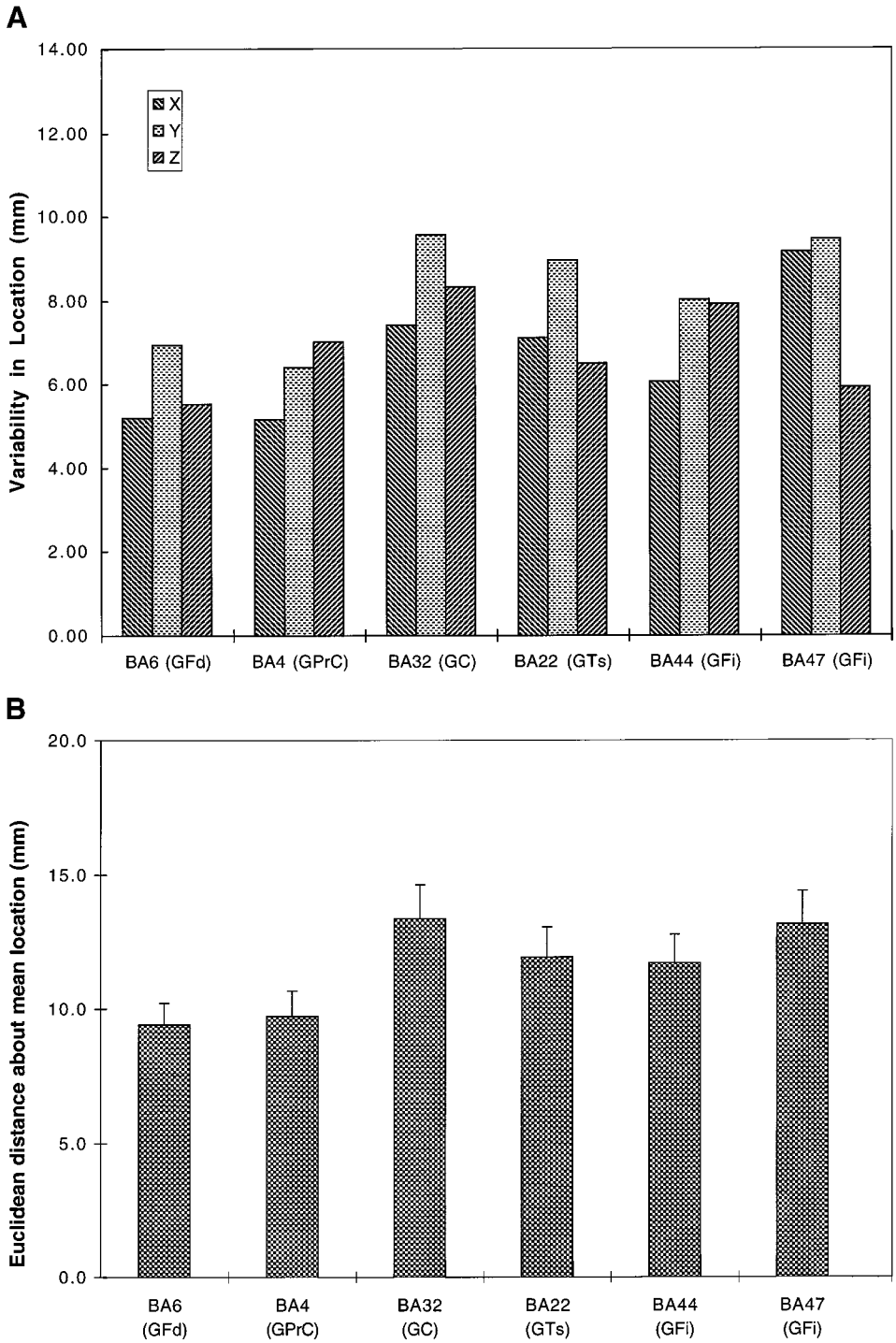


**FIG. 4.** Intersubject variability in locations of activations for selected brain regions, which include BAs 4, 6, 22, 32, 44, and 47. In A, each bar graph represents one standard deviation in x-, y-, and z-coordinates. In B, each bar graph represents the average Euclidean distance about the mean location for each brain region. The error bar represents one standard error.

ing the null hypothesis that the mean Euclidean distance values were the same for all regions. That is, a test about equality of variance was converted into a test about the equality of means, which are less sensitive to sample size. The nonparametric test we used here (Kruskal–Wallis) is also insensitive to assumptions of independence (of each axis) and normality. The test for the equality of means provided, therefore, still stronger evidence for the homogeneity of variance across brain regions. When indexed by the average

**TABLE 2**

Average Location, *Z* Score, and Volume of Significant Activation for the Selected Brain Regions

| Brain region | Peak *Z* score | Volume ($mm^3$) | Talairach coordinates | | |
|---|---|---|---|---|---|
| | | | *X* (mm) | *Y* (mm) | *Z* (mm) |
| SMA, BA6 | 5.41 | 4326 | −1.20 | 7.58 | 50.60 |
| Anterior cingulate, BA 32/24 | 4.84 | 1078 | 1.11 | 19.77 | 31.30 |
| Left M1 mouth, BA4/6 | 5.12 | 1906 | −42.44 | −11.44 | 36.75 |
| Left superior temporal gyrus, BA22 | 4.58 | 1459 | −51.50 | −34.90 | 8.71 |
| Left inferior frontal gyrus, BA44 | 4.97 | 2489 | −43.87 | 17.63 | 11.11 |
| Left inferior frontal gyrus, BA47 | 4.92 | 920 | −35.99 | 29.45 | −10.58 |

Euclidean distances (averaged across subjects) about mean locations of activations, the variability for the selected brain regions varied from 9.40 to 13.36 mm and also had no significant differences ($P > 0.05$, $\beta = 0.80$, Kruskal–Wallis test).

While our results indicated a uniform distribution of location variability, it has long been believed that functional organization of the human brain is more variable in the association cortices than in the primary cortices. Brodmann (1909) noted that the principle sulci bounded the primary sensory and motor cortices. These areas evidenced relatively little individual variability. Areas dedicated to higher-order processes—for example, the inferior frontal lobe—appeared to have greater individual variations (Brodmann, 1909; Ono *et al.,* 1990; Zilles *et al.,* 1997). The gyral foldings of the frontal operculum, in particular, are notorious complex, whereas gyration of the dorsal, lateral frontal lobe is of intermediate complexity, and the medial surface of the frontal lobe has rather simple, stereotypic gyral anatomy (Ono *et al.,* 1990). Despite these variations in the complexity of gyration and the complexity of the behavior that the brain regions were mediating, intersubject variability in locations was effectively uniform for all areas. Gyral complexity and functional complexity appeared not to influence the variability in locations of brain functional activations, when the variability is indexed by stereotactic coordinates.

*Standardized coordinates as a location metric.* In keeping with a widespread practice, we have reported and analyzed the locations of brain activations relative to a 3-D coordinate space (i.e., in "Talairach coordinates"), without explicit reference to gross anatomical landmarks. This was done for several reasons. First, spatial coordinates are the anatomical terminology which is best standardized and most widely used. The great majority of functional brain mapping studies have used standardized coordinates to report their results. Thus, reporting variability within this space gives present results the greatest relevance for this community. Second, standardized coordinates are a numerical data format readily amenable to precise quantification and parametric statistical testing. As yet, there is no quantitative equivalent using gross anatomy as the reference frame. Thus, most descriptions of anatomical variability are qualitative, being chiefly verbal descriptions of specific features. Third, identification of specific gross anatomical landmarks is inconsistent even among highly trained individuals and for prominent features, such as the central sulcus (Sobel *et al.,* 1993). Fourth, there is significant interindividual variability in the relationship of brain functional areas to sulcal anatomy. Brodmann repeatedly cautions that many functional zones (cytoarchitectonic areas) bear no consistent relation to visible landmarks (translated by Garey, 1994, pp. 120). Even for the primary visual cortex (BA 17), "The borders of this area, especially laterally, are extraordinarily variable . . . . Even medially there are no regular and constant relationship with "limiting sulci" (Garey, 1994, pp. 120). Subsequent studies of human cytoarchitecture continue to confirm Brodmann's warnings (Clark, 1993; Gebhard *et al.,* 1993). Based on electrical stimulation mapping of 117 epileptic patient, Ojemann and his colleagues (1989) also stated "Considered over the entire population, essential areas for language do not correspond to any described cytoarchitectonic areas of cortex." For this reason, gross anatomical landmarks cannot be regarded as a reliable framework within which to report functional variability. A more reasonable strategy is to use the standardized space to describe the location and location variability of both structure and function. In fact, this is likely the most appropriate strategy for quantifying structure–function covariance. In this way, the reliability with which a particular surface feature predicts a particular functional area could be expressed as cross-correlation. Unfortunately, this strategy has not yet been used to address this fundamental question.

*Sources of variability.* The observed intersubject variability in location of activations reported here actually includes the combined effects of three sources of variation: anatomical variability, functional variability, and normalization error. By anatomical variability, we mean the intersubject variation of a particular brain structure (sulcus, gyrus, nucleus, etc.), within

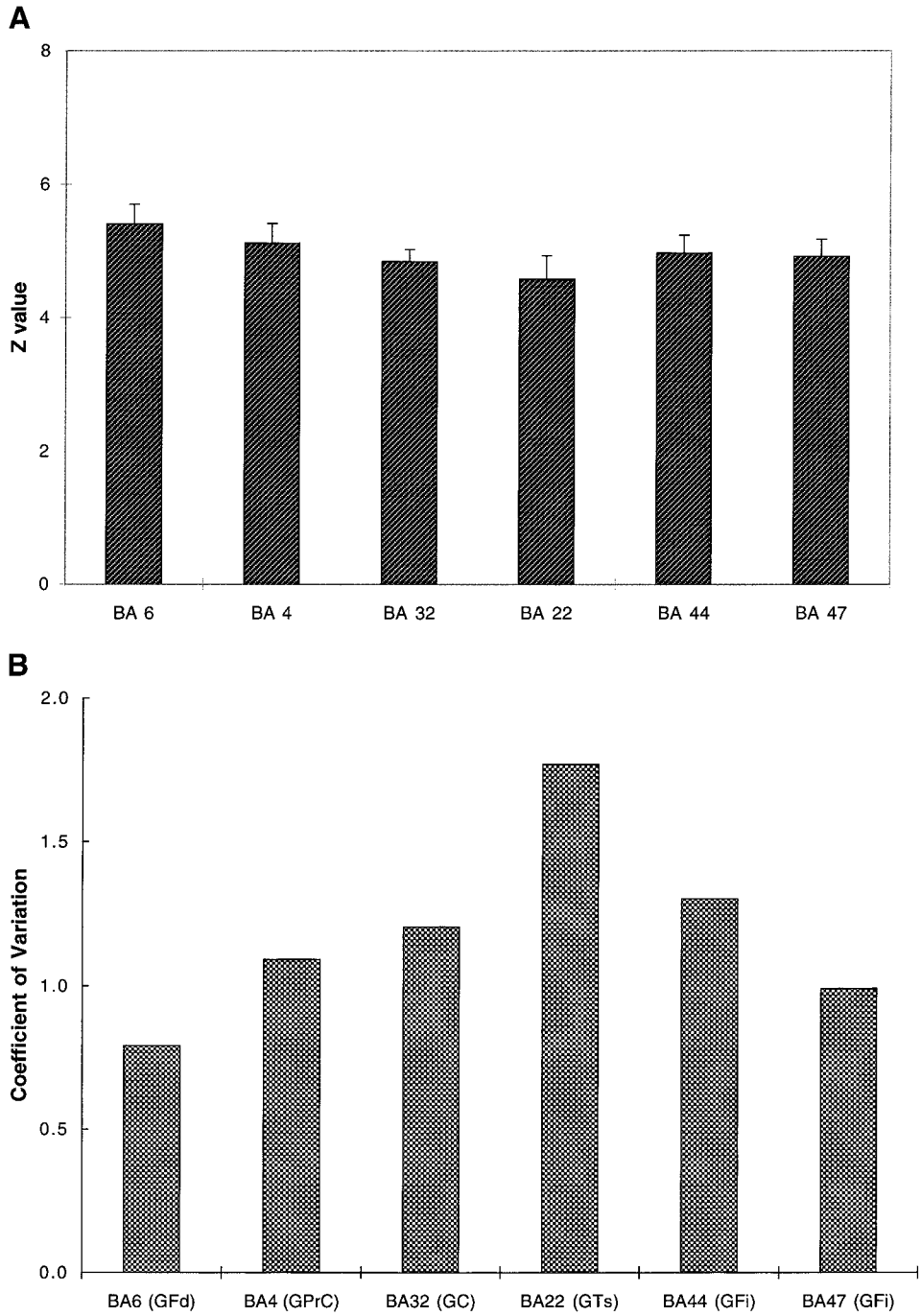


**FIG. 5.** The intensity (*Z* score) (A) and the coefficient of the variation for the volumes (B) of the significant activations in the selected brain regions. The error bar represents one standard error.

the standardized coordinate space. Functional variability refers to variations in the location of an functional area relative to a local landmark, such as a specific sulcus or gyrus. Normalization error is the intersubject variation due to imprecision in the spatial normalization process. It has been shown that normalization error is about 2 mm for the procedure we used here (Lancaster *et al.,* 1995). Anatomical variability has been reported to be about 3 mm for most brain structures (Downs, 1994). Similarly, Woods *et al.* (1998) reported a 1.4 mm normalization error and about a 5 mm variation in combined anatomical and normalization error. Given the factor of total variability is 5.2 to 9.9 mm for our data and assuming the variability from the three different sources (normalization error, anatomical variability, and functional vari-

ability) are uncorrelated, the functional variability can be estimated to be 3.7–9.2 mm. This calculation indicates that the functional variability is a major source of intersubject variation in the locations of activations.

The spatial normalization algorithm used here (Lancaster *et al.*, 1995) is a semiautomatic, nine-parameter method. Fully automatic algorithms using more than nine parameters have been reported and are now in wide use (Friston *et al.*, 1995; Woods *et al.*, 1998; Lancaster *et al.*, 1998). A more traditional algorithm (Lancaster *et al.*, 1995) was used here because it is well validated (Lancaster *et al.*, 1995) and less prone to occasional large errors than fully automatic algorithms. Further, many fully automatic algorithms, when applied directly to functional images, confound anatomical and functional variability, which we are seeking to dissociate. Regardless of these considerations, the choice of spatial normalization algorithms is unlikely to have a major impact on the location variability data reported here, because normalization error is not a dominant error source and because reported normalization errors are similar across algorithms (Friston *et al.*, 1995; Lancaster *et al.*, 1995; Woods *et al.*, 1998).

### *Intensity and Extent Variability*

Response intensity was remarkably consistent across brain areas. Intensity, measured as the peak $Z$ score with each functional area, did not vary significantly across regions ($F = 0.99$, $P > 0.5$, ANOVA; Fig. 5). Similarly, the intensity variability was small and consistent across brain areas (Fig. 5). This observation argues against the common impression that primary areas respond more robustly than higher-order areas. Note, however, that some of the intersubject variability in response magnitude was reduced by removing trials lacking a response from the analysis.

Volume of activation, by contrast, varied greatly between regions and between subjects. The mean volume of activation varied among regions ($F = 4.71$, $P < 0.002$, ANOVA). Further, the variability in volume of activation (expressed as the coefficient of variation) varied significantly among brain regions ($P < 0.05$, Bartlett's test). The coefficients of variation for response volume ranged from 0.79 to 1.77. (That is, the maximum standard deviation was 1.77 times the mean.) Imaging data on intersubject variability in response volume, to our knowledge, have not been reported previously. Thus, there is not standard of comparison within the imaging literature. However, the variability of the volumes of cytoarchitectonic areas does provide some reasonable basis for comparison. In human striate cortex, Stensaas *et al.* (1974) reported up to a fourfold difference in total area across individuals. A similar degree of intersubject variability was reported in macaque visual cortex (Van Essen *et al.*, 1984).

Extent, therefore, was the only response characteristic, among the three measured here (i.e., location, intensity, and extent), showing large variability among brain areas and among subjects. Interindividual variability in the extent of cortical cytoarchitectonic areas has been repeatedly put forward as an argument against the use of standardized coordinates. Thus, it is important to note that despite confirming that interindividual variability in extent is large, we have also demonstrated that extent variability does not contaminate location variability. That is, the variability of location of functional areas was effectively independent of variations in extent. This observation lends further support to the arguments presented above for the use of stereotactic coordinates in preference to gross anatomy as a reference frame for functional brain mapping and for quantification of intersubject location variability.

### *Human Electrophysiology*

Nonimaging data on intersubject location variability of human language areas are scant. The largest and most influential study is that of Ojemann *et al.* (1989), in which brain locations at which speech interruption was produced by cortical electrical stimulation were reviewed for 177 epileptic patients who had undergone presurgical mapping. In this nonquantitative study, Ojemann reported substantial individual variability in the exact location of language function. "This variability in language localization outside the inferior frontal gyrus exceeds even the considerable variability in gross anatomy of the human perisylvian gyri" (Ojmann *et al.*, 1989). Although this study did not quantify intersubject variability, the impression of the investigators—that is, of large variability in location—is clearly at odds with that of the present study. Four reasons which may account for this inconsistency can be posed, as follows.

First, while we studied normal subjects, Ojemann and colleagues studied patients with chronic, medically intractable epilepsy. It is entirely plausible, even likely, that the underlying disease induced functional reorganization that was variable from subject to subject. Disease-induced reorganization has been demonstrated using functional imaging to be substantial, even *trans*-hemispheric (Belin *et al.*, 1996; Weiler *et al.*, 1995; Booth *et al.*, 1999; Muller *et al.*, 1999). Second, electrical stimulation mapping may well interrupt the activity of areas remote from the stimulated site, via interregional connections such as the arcuate fasciculus or transcortical $U$ fibers. For example, stimulation of Wernicke's area may interrupt speech production by means of its projections onto Broca's area. This influence on remote regions by electrical-magnetic stimula-

tion has been reported by several research groups using transcranial magnetic stimulation combined with positron emission tomography (Fox *et al.*, 1997; Paus *et al.*, 1997). This effect would produce a strong tendency for observations with direct cortical stimulation to be more variable than those with functional brain imaging. Third, unlike PET data analysis, electrical stimulation mapping did not normalize the brain of each subject within a standardize space. Differences in the shape and size of the brains among subjects would contributed to the impression of variability. Fourth, in the electrical stimulation study intersubject variability was not quantified. The subjective impression gained by viewing the interruption-locations plotted onto a brain template is of the range of dispersions for multiple areas simultaneously, rather than the standard deviation of each area individually, as was reported here. For these reasons, a direct comparison between present results and Ojemann's electrical stimulation mapping is difficult. Future studies will be necessary to make a valid comparison between these two techniques.

### *Limitations*

It may be argued that PET is not the ideal technique for the study of intersubject variability, both by reason of its intrinsic limitation of the number of studies than can be performed on each subject and by reason of its limited spatial resolution (here, 7 mm). Even if the number of PET scans that can be performed on a single subject is limited, it has been well demonstrated that signal-to-noise ratio of PET is sufficient for single-subject analysis (Fox *et al.*, 1985a, 1985c, 1987a, 1987b, 1991; Grafton *et al.*, 1991; Silbersweig *et al.*, 1993; Watson *et al.*, 1993; Ramsey *et al.*, 1996; Xiong *et al.*, 1998; Hasnain *et al.*, 1998). In the present study, the frequency of observation of individual functional areas and the magnitude (*Z* score) of the responses is quite comparable to fMRI data. Limited spatial resolution (7 mm), moreover, is a serious limitation only for our absolute estimate of response extent and intensity, but not for our estimates of their relative variabilities and not for our estimates of absolution location or location variability. Specifically, it has been shown that when the location of an activation focus is indexed by the center-of-mass, the localization accuracy is several-fold higher than the spatial resolution of the image (Mintun *et al.*, 1989; Ramsey *et al.*, 1996), minimizing the significance of the resolution limitation of PET. Similarly, the effects of low spatial resolution on the coefficient of variation of extent and intensity will be much smaller than on their absolute values, because the coefficient of variation is a relative measurement and the low spatial resolution has similar effects on all subjects and all regions. Thus, our results on intersubject variability and homogeneity of variance should be expected to hold generally, for fMRI as well as for PET.

### *Applications*

Present data form a basis for developing models of the spatial probability distributions of brain functional area, i.e., for "functional volumes modeling" (Fox *et al.*, 1997, 1999, 2000). Precise description of spatial probability distributions should be extremely valuable for detection and quantification of disease-induced cerebral plasticity. With a uniform distribution over different types of cortices and a relatively narrow range in the variability, anatomical locations identified by functional studies of normal subjects could be used to identify changes in this functional pattern occurring in patient populations. Extrapolating the data derived from normals onto patient populations would enable the PET technique to be used for clinical evaluations regarding reorganization and recovery of brain functions following brain damage.

## ACKNOWLEDGMENTS

This work has been financially supported by the EJLB Foundation, the National Institute of Mental Health (P20 DA52176), and the National Library of Medicine (1 RO1 LM06858-01). The authors thank Betty Heyl and Sergio Leal for their technical support.

## REFERENCES

Belin, P., Van Eeckhout, P., Zilbovicius, M., Remy, P., Francois, C., Guillaume, S., Chain, F., Rancurel, G., and Samson, Y. 1996. Recovery from nonfluent aphasia after melodic intonation therapy: A PET study. *Neurology* **47**(6):1504–1511.

Belliveau, J. W., Kennedy, D. N., Jr., McKinstry, R. C., Buchbinder, B. R., Weisskoff, R. M., Cohen, M. S., Vevea, J. M., Brady, T. J., and Rosen, B. R. 1991. Functional mapping of the human visual cortex by magnetic resonance imaging. *Science* **254:**716–719.

Booth, J. R., Macwhinney, B., Thulborn, K. R., Sacco, K., Voyvodic, J., and Feldman, H. M. 1999. Functional organization of activation patterns in children: Whole brain fMRI imaging during three different cognitive tasks. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **23**(4):669–682.

Brodmann, K. 1909. *Brodmann's 'Localisation in the Cerebral Cortex'* (L. J. Garey, translated, 1994), pp. 107–174. Lodon. Smith-Gordon.

Clark, S. 1993. Callosal connections and functional subdivision of the human occipital cortex. In *Functional Organization of Human Visual Cortex* (B. Gulyas, D. Ottoson, and P. E. Roland, Eds.), pp. 137–149. Pergamon Press, New York.

Demb, J. B., Desmond, J. E., Wagner, A. D., Vaidya, C. J., Glover, G. H., and Gabrieli, J. D. 1995. Semantic encoding and retrieval in the left inferior prefrontal cortex: A functional MRI study of task difficulty and process specificity. *J. Neurosci.* **15**(9):5870–5878.

Domonet, J. F., Chollet, F., Ramsey, S., Cardebat, D., Nespoulous, J. L., Wise, R., Rascol, A., and Frackowiak, R. 1992. The anatomy of phonological and semantic processing in normal subjects. *Brain* **115:**1753–1768.

Downs, J. H. 1994. *A Convex Hull Method for Surface Based Spatial Normalization of the Brain.* Ph.D. Dissertation, University of Texas Health Science Center at San Antonio.

Fox, P. T., and Raichle, M. E. 1984. Stimulus rate dependence of regional cerebral blood flow in human striate cortex, demonstrated by positron emission tomography. *J. Neurophysiol.* **51:**1109–1120.

Fox, P. T., Fox, J. M., Raichle, M. E., and Burde, R. M. 1985a. The role of cerebral cortex in the generation of saccadic eye movements: A positron emission tomographic study. *J. Neurophysiol.* **52:**348–368.

Fox, P. T., Perlmutter, J. S., and Raichle, M. E. 1985b. A stereotactic method of anatomic localization for positron emission tomography. *J. Comput. Assist. Tomogr.* **9:**141–153.

Fox, P. T., Raichle, M. E., and Thach, W. T. 1985c. Functional mapping of the human cerebellum with positron emission tomography. *Proc. Natl. Acad. Sci. USA* **82:**1–5.

Fox, P. T., Burton, H., and Raichle, M. E. 1987a. Mapping human somatic sensory cortex with positron emission tomography. *J. Neurosurg.* **63:**34–43.

Fox, P. T., Miezen, F. M., Allman, J. M., Van Essen, D. C., and Raichle, M. E. 1987b. Retinotopic organization of human visual cortex mapped with positron-emission tomography. *J. Neurosci.* **7:**913–922.

Fox, P. T., Mintun, M. A., Reiman, E. M., and Raichle, M. E. 1988. Enhanced detection of focal brain responses using intersubject averaging and change-distribution analysis of subtracted PET images. *J. Cereb. Blood Flow. Metab.* **85:**642–653.

Fox, P. T., and Pardo, J. V. 1991. Does inter-subject variability in cortical functional organization increase with neural "distance" from the periphery? In *Exploring Brain Functional Anatomy with Positron Tomography,* pp. 125–144. Wiley, New York.

Fox, P. T., Ingham, R. J., Ingham, J. C., Hirsch, T. B., Downs, J. H., Martin, C., Jerabek, P., Glass, T., and Lancaster, J. L. 1996. A PET study of the neural systems of stuttering. *Nature* **382**(6587):158–161.

Fox, P., Ingham, R., George, M. S., Mayberg, H., Ingham, J., Roby, J., Martin, C., and Jerabek, P. 1997. Imaging human intra-cerebral connectivity by PET during TMS. *Neuroreport* **8**(12):2787–2791.

Fox, P. T., Lancaster, J. L., Parsons, L., and Xiong, J. 1997. Functional volumes modeling: Theory and preliminary assessment. *Hum. Brain Mapp.* **5:**306–311.

Fox, P. T., Huang, A., Parsons, L. M., Xiong, J., Rainey, L., and Lancaster, J. L. 1999. Functional volumes modeling: Scaling for group size in averaged images. *Hum. Brain Mapp.* **8:**143–150.

Fox, P. T., Huang, A., Parsons, L. M., Xiong, J., Zamarripa, F., Rainey, L., and Lancaster, J. L. 2000. Location-probability profiles for the mouth region of human primary motor cortex: Metanalysis and validation. *NeuroImage,* in press.

Francis, W. N., and Kucera, H. 1982. *Frequency Analysis of English Usage: Lexicon and Grammar Boston.* Houghton Mifflin.

Friston, K. J., Frith, C. D., Liddle, P. F., and Frackowiak, R. S. J. 1991. Comparing functional (PET) images: The assessment of significant change. *J. Cereb. Blood Flow Metab.* **11:**690–699.

Friston, K. J., Ashbumer, J., Frith, C. D., Poline, J.-B., Heather, J. D., and Frackowiak, R. S. J. 1995. Spatial registration and normalization of images. *Hum. Brain Mapp.* **3:**165–189.

Friston, K. J., Worsley, K. J., Frackowiak, R. S. J., Mazziotta, J. C., and Evans, A. C. 1994. Assessing the significance of focal activations using their spatial extent. *Hum. Brain Mapp.* **3,** 210–220.

Garey, L. J. 1994. Brodmann's "Localisation in the cerebral cortex," pp. 109–129. Smith-Gordon, London.

Gebhard, R., Zills, K., and Armstrong, E. 1993. Gross anatomy and gyrification of the occipital cortex in human and non-human primates. In Functional Organization of Human Visual Cortex (B. Gulyas, D. Ottoson, and P. E. Roland, Eds.), pp. 101–110. Pergamon Press.

Grafton, S. T., Woods, R. P., Mazziotta, J. C., and Phelps, M. E. 1991. Somatotopic mapping of the primary motor cortex in humans: Activation studies with cerebral blood flow and positron emission tomography. *J. Neurophysiol.* **66**(3):735–743.

Herholz, K., Thiel, A., Wienhard, K., Pietrzyk, U., von Stockhausen, H. M., Karbe, H., Kessler, J., Bruckbauer, T., Halber, M., and Heiss, W. D. 1996. Individual functional anatomy of verb generation. *Neuroimage* **3:**185–194.

Hasnain, M. K., Fox, P. T., and Woldorff, M. G. 1998. Intersubject variability of functional areas in the human visual cortex. *Hum. Brain Mapp.* **6:**301–315.

Lancaster, J. L., Glass, T. G., Lankipalli, B. R., Downs, H., Mayberg, H., and Fox, P. T. 1995. A modality-independent approach to spatial normalization of tomographic images of the human brain. *Hum. Brain Mapp.* **3:**209–223.

Lancaster, J. L., Kochunov, P. V., Fox, P. T., and Nickerson, D. 1998. K-tree method for high-speed spatial normalization. *Hum. Brain Mapp.* **6**(5–6):358–363.

Mintun, M. A., Fox, P. T., and Raichle, M. E. 1989. A highly accurate method of localizing regions of neuronal activation in the human brain with positron emission tomography. *J. Cereb. Blood Flow Metab.* **9:**96–103.

Muller, R. A., Rothermel, R. D., Behen, M. E., Muzik, O., Chakraborty, P. K., and Chugani, H. T. 1999. Language organization in patients with early and late left-hemisphere lesion: A PET study. *Neuropsychologia* **37**(5):545–557.

Ojemann, G., Ojemann, J., Lettich, E., and Berger, M. 1989. Cortical language localization in left, dominant hemisphere. *J. Neurosurg.* **71:**316–326.

Ono, M., Kubik, S., and Abernathey, C. D. 1990. *Atlas of the Cerebral Sulci.* Thieme Medical Publishers, New York.

Paivio, A., Yuille, J. C., and Madigan, S. A. 1968. Concreteness, Imagery, and Meaningfulness Values for 925 Nouns. *J. Exp. Psychol. Monograph. Suppl.* **76:**1–25.

Paulesu, E., Frith, C. D., and Frackowiak, R. S. J. 1993. The neural correlates of the verbal component of working memory. *Nature* **362:**342–345.

Paus, T., Jech, R., Thompson, C. J., Comeau, R., Peters, T., and Evans, A. C. 1997. Transcranial magnetic stimulation during positron emission tomography: A new method for studying connectivity of the human cerebral cortex. *J. Neurosci.* **17**(9):3178–3184.

Penfield, W., and Roberts, L. 1959. *Speech and Brain-Mechanisms.* Princeton Univ. Press, Princeton, NJ.

Petersen, S. E., Fox, P. T., Posner, M. I., Mintun, M., and Raichle, M. E. 1988. Positron emission tomographic studies of the cortical anatomy of single-word processing. *Nature* **331:**585–589.

Petersen, S. E., Fox, P. T., Posner, M. I., Mintun, M., and Raichle, M. E. 1989. Positron emission tomographic studies of the processing of single words. *J. Cogn. Neurosci.* **1:**153–170.

Poline, J. B., Vandenberghe, R., Holmes, A. P., Friston, K. J., and Frackowiak, R. S. 1996. Reproducibility of PET activation studies: Lessons from a multi-center European experiment. EU concerted action on functional imaging. *Neuroimage* **4**(1):34–54.

Posner, M. I., Petersen, S. E., Fox, P. T., and Raichle, M. E. 1988. Localization of cognitive operations in the human brain. *Science* **240:**1627–1631.

Ramsey, N. F., Kirkby, B. S., Van Gelderen, P., Berman, K. F., Duyn, J. H., Frank, J. A., Mattay, V. S., Van Horn, J. D., Esposito, G., Moonen, C. T., and Weinberger, D. R. 1996. Functional mapping of human sensorimotor cortex with 3D BOLD fMRI correlates highly with H2(15)O PET rCBF. *Cereb. Blood Flow Metab.* **16**(5):755–764.

Raichle, M. E. 1994. Images of the mind: Studies with modern imaging techniques. *Annu. Rev. Psychol.* **45:**333–356.

Rao, S. M., Binder, J. R., Bandettini, P. A., Hammeke, T. A., Yetkin, F. Z., Jesmanowicz, A., Lisk, L. M., Morris, G. L., Mueller, W. M., Estkowski, L. D., Wong, E. C., Haughton, V. M., and Hyde, J. S. 1993. Functional magnetic resonance imaging of complex human movements. *Neurology* **43:**2311–2318.

Schlaug, G., Knorr, U., and Seitz, R. J. 1994. Inter-subject variability of cerebral activations in acquiring a motor skill: A study with positron emission tomography. *Exp. Brain Res.* **98:**523–534.

Schneider, W., Casey, B. J., and Noll, D. C. 1994. Functional MRI mapping of stimulus rate effects across visual processing stages. *Hum. Brain Mapp.* **1:**117–133.

Silbersweig, D. A., Stern, E., Frith, C. D., Cahill, C., Schnorr, L., Grootoonk, S., Spinks, T., Clark, J., Frackowiak, R., and Jones, T. 1993. Detection of thirty-second cognitive activations in single subjects with positron emission tomography: A new low-dose H2(15)O regional cerebral blood flow three-dimensional imaging technique. *J. Cereb. Blood Flow Metab.* **13**(4):617–629.

Sobel, D. F., Gallen, C. C., Schwartz, B. J., Waltz, T. A., Copeland, B., Yamada, S., Hirschkoff, E. C., and Bloom, F. E. 1993. Locating the central sulcus: Comparison of MR anatomic and magnetoencephalographic functional methods. *AJNR Am. J. Neuroradiol.* **14**(4): 915–925.

Stensaas, S. S., Eddington, D. K., and Dobelle, W. H. 1974. The topography and variability of the primary visual cortex in man. *J. Neurosurg.* **40:**747–755.

Talairach, J., and Tournoux, P. 1988. *Co-Planar Stereotactic Atlas of the Human Brain.* Theime Medical, New York.

Van Essen, D. C., Newsome, W. T., Maunsell, J. H., and Bixby, J. L. 1986. The projections from striate cortex (V1) to areas V2 and V3 in the macaque monkey: Asymmetries, areal boundaries, and patchy connections. *J. Comp. Neurol.* **244**(4):451–480.

Warburton, E., Wise, R. J., Price, C. J., Weiller, C., Hadar, U., Ramsay, S., and Frackowiak, R. S. 1996. Noun and verb retrieval by normal subjects. Studies with PET. *Brain* **119**(Pt 1):159–179.

Watson, J. D. G., Myers, R., Frackowiak, R. S. J., Hajnal, J. V., Woods, R. P., Mazziotta, J. C., Shipp, S., and Zeki, S. 1993. Area V5 of the human brain. *Cereb. Cortex* **3:**79–94.

Weiller, C. 1998. Imaging recovery from stroke. *Exp. Brain Res.* **123**(1–2):13–17.

Wise, R., Chollet, F., Hadar, U., Friston, K., Hoffner, E., and Frackowiak, R. 1991. Distribution of cortical neural networks involved in word comprehension and word retrieval. *Brain* **114:**1803–1817.

Woods, R. P., Grafton, S. T., Watson, J. D. G., Sicotte, N. L., and Mazziotta, J. C. 1998. Automated image registration: II. Intersubject validation of linear and nonlinear models. *J. Comput. Assist. Tomogr.* **22:**253–265.

Xiong, J., Gao, J. H., Lancaster, J. L., and Fox, P. T. 1995. Clustered pixels analysis for functional MRI activation studies of the human brain. *Hum. Brain Mapp.* **3:**287–301.

Xiong, J., Gao, J.-H., Lancaster, J. L., and Fox, P. T. 1996. Assessment and Optimization of functional MRI analyses. *Hum. Brain Mapp.* **4:**153–167.

Xiong, J., Rao, S., Gao, J. H., Woldorff, M., and Fox, P. T. 1998. Evaluation of hemispheric dominance for language using functional MRI: A cross-validation with positron emission tomography. *Hum. Brain Mapp.* **6:**42–58.

Zar, J. 1996. *Biostatistical Analysis.* Prentice-Hall, Upper Saddle River, NJ.

Zilles, K., Schleicher, A., Langemann, C., Amunts, K., Morosan, P., Palomero-Gallagher, N., Schormann, T., Mohlberg, H., Burgel, U., Steinmetz, H., Schlaug, G., and Roland, P. 1997. Quantitative analysis of sulci in the human cerebral cortex: Development, regional heterogeneity, gender difference, asymmetry, intersubject variability and cortical architecture. *Hum. Brain Mapp.* **5:**218–221.