Stability of Regional Cerebral Glucose Metabolism in the Normal Brain Measured by Positron Emission Tomography

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Cerebral glucose utilization (LCMRGl) was measured using the [^{18}F]fluorodeoxyglucose method with PET in two groups of ten healthy young volunteers, each scanned in a resting state under different methodological conditions. In addition, five subjects had a second scan within 48 hr. Mean hemispheric values averaged 45.8 ± 3.3 μmol/100 g/min in the right cerebral hemisphere and 47.0 ± 3.7 μmol/100 g/min in the left hemisphere. A four-way analysis of variance (group, sex, region, hemisphere) was carried out on the results using three different methods of data manipulation: (a) the raw values of glucose utilization, (b) LCMRGl values "normalized" by the mean hemispheric gray matter LCMRGl value, and (c) log transformed LCMRGl values. For all analysis techniques, significantly higher LCMRGl values were consistently seen in the left mid and posterior temporal area and caudate nucleus relative to the right, and in the right occipital region relative to the left. The coefficient of variation of intrasubject regional differences (9.9%) was significantly smaller than the coefficient of variation for regions between subjects (16.5%). No differences were noted between the sexes and no effect of repeat procedures was seen in subjects having multiple scans. In addition, inter-regional LCMRGl correlations were examined both in values from the 20 normal subjects, as well as in a set of hypothetical "abnormal" values. Results were compared with those reported from other PET centers; despite certain methodological differences, the intersubject and inter-regional variation of LCMRGl is fairly constant.

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Attempts to characterize cerebral glucose utilization in normal brain in the so-called "resting state" have ranged from reporting mean LCMRGl values from small numbers of subjects (*1–3*) to more sophisticated correlation analyses with larger data sets (*4,5*). Previous studies using fluorine-18-labeled 2-fluoro-2-deoxy-D-glucose (FDG) have reported the normal mean or regional cerebral metabolic rates for glucose (LCMRG1) obtained at different PET centers (*1–3,6–12*). Despite a growing literature on LCMRGl in the resting normal brain, there appears to be little agreement as to a suitable analysis approach (*13*): while some authors have reported raw data on regional glucose utilization (*1,2*), others have divided regional LCMRGl values by the global brain mean (*15*), used correlational analysis of regional metabolic rates (*4,16*), analysis of variance (*11*), Q-component analysis (*5*) and explicit models of inter-subject variability (*17*). Difficulties in comparing results between and even within centers are encountered due to the use of a wide range of analytic techniques (*2,9,16*). A 30% change in mean gray matter LCMRGl values for the same apparent resting state has been reported from a single center (*2,18,19*). These observations, and demonstrations of stimulus-response related changes in LCMRGl, suggest that a stable resting state for the normal brain with consistency across subjects is difficult to achieve and maintain because it represents one point in a spectrum of cerebral activity (*5,18,20–22*). However, attention has focused recently on the extent to which resting state differences may be a function of methodology or instrumentation (*18,23, 24*) particularly between centers, and on the possibility

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of achieving a stable unstimulated normal brain state (*5,22,25*).

To address these issues before embarking on a range of studies that will rely on a characterization of normal brain states, we examined the data accumulated within this institution from FDG studies for healthy young volunteers. A range of statistical analysis techniques was applied to the data to examine: (a) the consistency and size of inter- and intra-subject variation; (b) the effects of different data transformation strategies on inter- and intra-subject variation; (c) the existence of significant regional LCMRGl differences, and LCMRGl consistency within and between two groups of resting normals without sensory deprivation in which slightly different methodologies were used; (d) male-female differences; (e) reproducibility of results in repeated scans. These results were compared with similar published data sets from other centers in order to examine possible methodological differences in inter-center, inter-subject and inter-regional patterns in the quantitation of normal LCMRGl with PET.

In addition, a correlation analysis was used to investigate LCMRGl relationships occuring between different regions in the two hemispheres, between different regions in the same hemisphere, and between homologous regions in the two hemispheres. The validity of correlations found with raw data and log transformed data was tested by creating a hypothetical "abnormal" LCMRGl data set and searching for spurious correlations.

MATERIALS AND METHODS

Preparation of the Radiopharmaceutical

Fluorine-18- (^{18}F) labeled 2-fluoro-2-deoxy-D-glucose was prepared by reacting ^{18}F-labeled acetyl hypofluorite, prepared by in situ reaction of ^{18}F-molecular fluorine with sodium acetate and triacetyl-D-glucal at room temperature adopting methods described earlier (*26*). The specific activity of the final product was ~25.38 GBg/mmol, or 685 mCi/mmol. The usual dose was ~5 mCi per study, injected intravenously.

Human Subjects

The FDG studies were performed on ten males and ten females under resting conditions. All were healthy volunteers between the ages of 18 and 32 (mean = 25 yr), 19 were strongly right-handed, and one was left-handed. Subjects were screened for a history of medical or neurological diseases, or a history of head trauma. All fasted a minimum of 5 hr prior to the study. Subjects were requested to lie quietly; external stimulation in the room was kept to a minimal level at all times, and the patients did not speak and were not spoken to during the period after FDG injection. Ear and eye patches were not used. Subjects were divided into two groups based on date of scan and PET methodology.

The first group consisted of ten subjects (Group A: five males, five females). For this group, an indwelling intravenous catheter placed in the back of the subjects' hand was used to obtain blood samples, and the hand was warmed in a hot water glove box (*27*) heated to 44°C to arterialize the venous blood. Subjects in Group A were positioned in the scanner at 40 min after FDG administration, after fixation of the deoxyglucose had taken place.

The second group of ten subjects (Group B: five males, five females) was scanned ~1 yr later. For Group B, direct arterial blood sampling was done. Subjects in Group B were positioned in the scanner prior to FDG administration, and remained in the scanner undisturbed until 40 min after the injection, at which time the autoradiographic scans were obtained.

For six subjects in Group A (four males, two females), it was their initial experience with a PET study ("inexperienced"); the other four (one male, three females) had previously volunteered for an FDG exam ("experienced") as part of a different protocol. For Group B, in addition to the initial study, five subjects (two males, three females) had a second FDG exam within 48 hr.

Blood Sampling and Analysis

After injection of the FDG, 2-ml blood samples were obtained at intervals throughout the study. For Group B subjects, the samples were obtained at shorter intervals than had been used for the sampling of Group A subjects, therefore subjects in Group B were exposed to slightly more tactile stimulation during sampling. Samples were analyzed for plasma glucose level, blood gases, hematocrit, and radioactivity.

Instrumentation and Imaging

The tomographic device used was the Therascan-3128 (*28, 29*) (Atomic Energy of Canada Ltd.), based on a prototype designed at the Montreal Neurological Institute (*30*). The Therascan consists of two rings of 64 bismuth germanate detectors each. Both direct and cross-slice coincidences are acquired, giving three slices simultaneously. Image resolution for the scanning configuration used in all studies reported here is: transverse FWHM = 12 mm; axial FWHM at 8 mm from the center of the field of view = 11 mm (direct slice) and 12.5 mm (cross slice) (unpublished data).

At 40 min after injection of the radiopharmaceutical, 12 tomographic images were obtained, with the center slices of each 3-slice scan located at 10, 42, 48, and 80 mm above the inferior orbitomeatal (OM) line, starting at the lowest position and moving upward. Since the tomograph has a 12-mm slice separation, this scheme gives ~6 mm axial sampling over the range 22–68 mm above the OM line (i.e., scans at 22, 30, 36, 42, 48, 54, 60, and 68 mm above the OM line). Data were collected for 14 min at each position, with 2–5 million total true coincidences per slice.

Image Reconstruction and Analysis

Images were reconstructed using the Therascan software package which includes automatic correction of random coincidences, normalization of detector sensitivity, a projection thresholding procedure for an analytic attenuation correction (*31*), and scatter correction using a deconvolution technique similar to that of Bergström et al. (*32*).

The FDG analysis program is based on the Phelps et al. (*6*) modification of the Sokoloff model (*33*); a rearrangement of the operational equation suggested by Brooks (*34*) has been incorporated. Values for the gray matter rate constants and

for the lumped constant are those reported by Huang et al. ($k_1 = 0.102$, $k_2 = 0.130$, $k_3 = 0.062$, $k_4 = 0.0068$, LC = 0.418) (*8*).

Regions of interest (ROI) 9 mm in diameter were manually placed over eleven cortical gray matter regions, as well as over the cerebellum, caudate, thalamus, and hippocampus. Circular ROI somewhat smaller than the resolution of the images (FWHM 12 mm) were heuristically chosen for image analysis as a simple form of peak averaging. Whenever the estimated size of the anatomic region studied permitted, multiple adjacent ROI were examined and the values averaged. The values for the ROI were expressed in the units of micromoles of glucose utilized per 100 g of tissue per min (μmol/100 g/min) (Fig. 1). Thirty anatomic regions comprised of 15 homologous left-right pairs were examined per subject.

Statistical Analysis

The data were handled in three different fashions, and a four-way analysis of variance (ANOVA) was carried out in each case. The two between-subject variables were "Group" (Group A, Group B) and "Sex" (Males, Females), while the within-subject variables were "Area" (15 areas) and "Side" (Left, Right).

Initially, the mean LCMRGl value in each region was averaged separately over each of the ten subjects in Groups A and B, and a four-way ANOVA was performed. Significant interactions which were found were then analyzed by planned nonorthogonal comparisons (*35*).

Next, the LCMRGl value for each region was divided by the mean glucose utilization rate of the 15 regions of the same hemisphere. This simple normalization technique was used in an attempt to reduce the effects of intersubject variability (*16, 20,22*). An analysis of variance was then carried out on the normalized data. A rationale for such a normalization technique is suggested by the high correlation found between regional LCMRGl values and average glucose metabolic rate for individual subjects (*4*).

The validity of test results depends on the assumption that observations have equal standard deviations and have a normal distribution. Since it has been noted that the standard deviation of LCMRGl values increases with the mean value (*5*), a log transformation of the data, which would also remove the difficulty of a skewed distribution of LCMRGl values might make these assumptions more reasonable (*35*). The analysis was repeated on the log transformed data.

Possible inter-regional correlations were investigated in the following manner. If (X_1,Y_1), (X_2Y_2),. . .,(X_p,Y_p) are pairs of measurements taken on two regions repeated p times, then the correlation between the two regions is estimated by:

$$r = \mathrm{Cor}(X,Y) = \frac{\sum_{j=1}^{p} (X_j - \bar{X})(Y_j - \bar{Y})}{\sqrt{\sum_{j=1}^{p} (X_j - \bar{X})^2 \sum_{j=1}^{p} (Y_j - \bar{Y})}},$$

where $X = \sum_{j=1}^{p} X_j/p$, $Y = \sum_{j=1}^{p} Y_j/p$ are the averages for the two regions. Note that $-1 \le r \le 1$, $r \approx 1$ indicating high positive correlation, and $r \approx 0$ indicating that X and Y are uncorrelated. Repetitions on the same control subject are not available, however, measurements have been taken once on each of p = 20 control subjects. For purposes of statistical comparison we may assume that the correlations are the same for all subjects and that each subject has identical mean glucose utilization levels. They can then be used in place of the p repetitions on the same individual.

In order to detect regions which might be more highly correlated than others, a normalization technique was utilized (see Appendix).

To highlight the effects of data transformations, a second set of observations was created from the normal control data in five subjects by halving the LCMRG1 levels in three arbi-

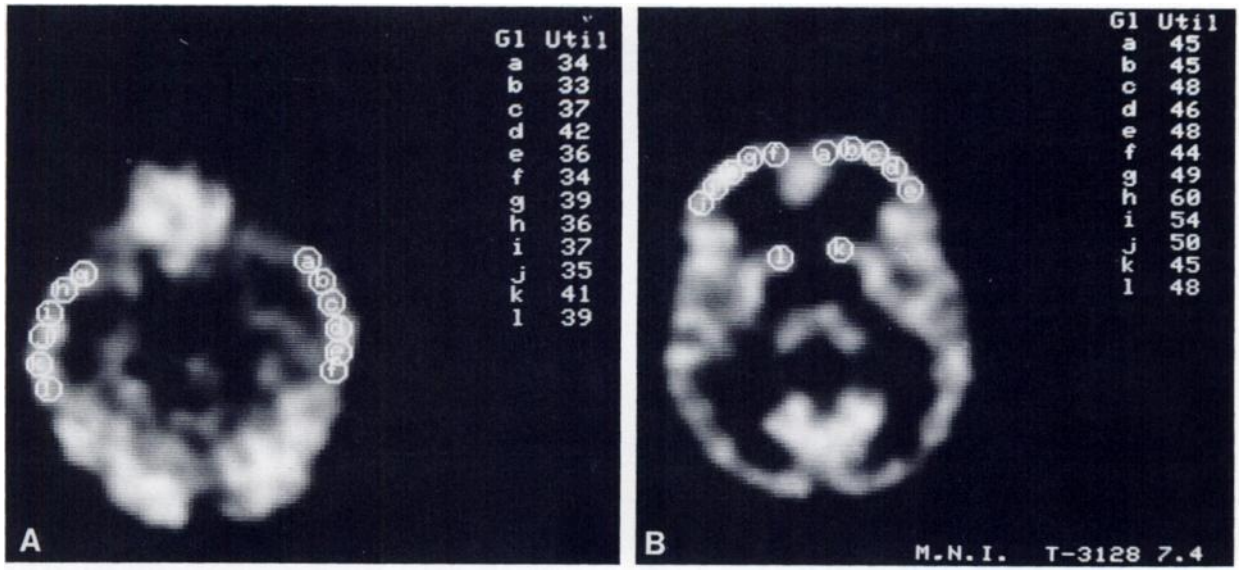

FIGURE 1
A: Regions of interest 9 mm in diameter placed over the temporal regions in a horizontal scan 16 mm above the orbitomeatal line. B: Examples of 9 mm circular ROI placed over the frontal regions and caudate nucleus in a horizontal scan 42 mm above the orbitomeatal line.

trarily chosen bilateral regions, and in three other regions in the left hemisphere alone (Group I). This was designed to simulate abnormal data. Both global LCMRGl values and right-left hemisphere differences were then examined. In an additional three patients, LCMRGl values were decreased by 20%, 40%, and 60%, respectively, in three bilateral regions, and were decreased by 20%, 40%, and 60%, respectively, in three regions in the left hemisphere alone; this was done to simulate a more random distribution of abnormalities (Group II).

RESULTS

LCMRGl Raw Data

The mean raw LCMRGl values for gray matter in each of the 30 regions, averaged separately over each of the ten subjects in Groups A and B, are shown in Figure 2. These values ranged from a minimum of 30.2 ± 6.6 μmol/100 g/min in the hippocampus in Group A, to a maximum of 52.5 ± 8.3 μmol/100 g/min in the upper parietal area in Group B. Coefficients of variation per region (Coefficient of variation in % = (standard deviation/mean) × 100 for LCMRGl values of cortical gray matter) due to inter-subject differences averaged 18% on the right and 20% on the left for Group A, and 15% on the right and 16% on the left for Group B. Assuming a 60:40 gray-to-white matter composition, and if the experimentally derived lumped constant of 0.52 (*36*) were used rather than the lumped constant of Huang et al. (*8*), the whole brain LCMRGl values obtained in this study are in close agreement with values of whole brain glucose utilization obtained with the Kety-Schmidt technique (*37,38*).

The mean hemispheric values of gray matter glucose utilization for each of the 20 subjects are presented in Figure 3. These ranged from values of 31.4 ± 3.0 μmol/100 g/min in Subject 7, to 59.0 ± 5.2 μmol/100 g/min in Subject 17, with the average of the mean values for the two groups being 45.8 ± 3.3 in the right hemisphere, and 47.0 ± 3.7 in the left. The standard deviation of the inter-regional LCMRGl values for each subject, averaged across the 20 subjects, was 4.4 ± 1.1 μmol/100 g/min on the right and 4.7 ± 1.3 μmol/100 g/min on the left, giving coefficients of variation of 9.6% and 10.0%, respectively. The coefficient of variation of the intra-subject variations among regions (mean standard deviation = 5.2, COV = 11.4%) was significantly smaller than the coefficient of variation for regions between different subjects (mean standard deviation = 7.7, COV = 16.9%) ($p < 0.001$).

A four-way analysis of variance was carried out on the mean LCMRGl values in each region. The only significant main effects were Area ($F = 49.20$, $df = 14, 224$, $p < 0.0001$) and Side ($F = 10.45$, $df = 1, 16$, $p < 0.005$). Significant differences in glucose metabolism were seen between the areas, and glucose utilization in the left cerebral hemisphere was statistically significantly higher than in the right despite small differences in the absolute values. No overall significant differences were found between males and females, or between the subjects in Group A and Group B ($p > 0.05$).

The three significant interactions found were Group × Area ($F = 3.77$, $df = 14, 224$, $p < 0.0001$), Area × Side ($F = 5.39$, $df = 14, 224$, $p < 0.0001$) and Area × Side × Group × Sex ($F = 2.47$, $df = 14, 224$, $p < 0.003$). Because of the complexity of the four-way interaction, it was not broken down further by means of post-hoc tests. However, inspection of the data suggested that this interaction could be attributed to the female subjects in Group B who appeared to have smaller left-right asymmetries in the LCMRGl in certain regions. However, none of these contrasts proved significant. Only the two-way interactions were further analyzed. Planned nonorthogonal comparisons were carried out on the Area × Side interaction, comparing

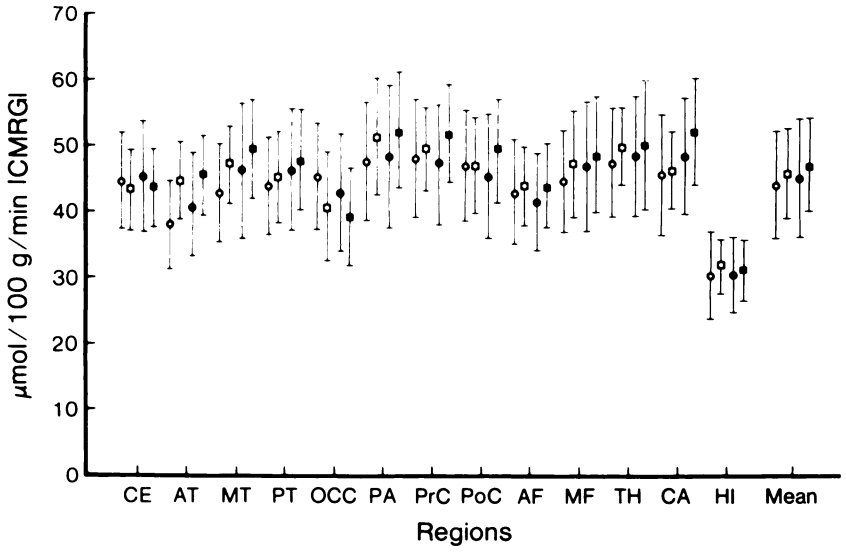

FIGURE 2
LCMRG1 values and standard deviations in each of 30 regions averaged over Groups A and B. Open symbols represent right hemisphere values, closed symbols represent left hemisphere values. Circles demonstrate the values in Group A, squares demonstrate the values in Group B. Key to regions: CE = cerebellum, PT = posterior temporal, PP = posterior parietal, OC = occipital, SM = supramarginal, MT = mid-temporal, AT = anterior temporal, PoC = postcentral, PrC = precentral, MF = midfrontal, AF = anterior frontal, TH = thalamus, CA = caudate, HI = hippocampus.

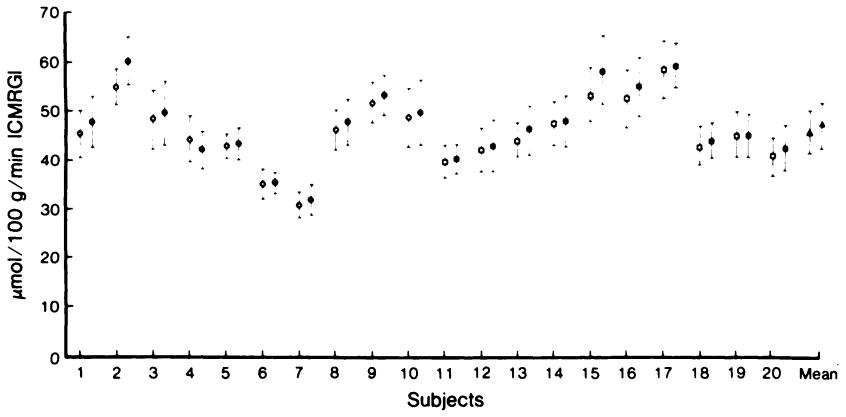

FIGURE 3
Hemispheric LCMRG1 values with standard deviations for each of 20 subjects. Open circles demonstrate right hemispheric values, and closed circles represent left hemispheric values. Mean values for the right (open triangle) and left (closed triangle) LCMRGl values across all subjects are also shown.

the left with the right side for each cortical region (*38*). The significance level was set at 0.05 for these comparisons. The only significant differences found were the following: glucose metabolism was higher in the left cerebral hemisphere as compared with the right for the anterior, mid- and posterior temporal regions (5%, 7%, and 5% differences), for the inferior mid-frontal region (4% difference) and for the caudate nucleus (10% difference). In contrast, the glucose metabolic rate was higher in the right occipital lobe as compared with the left (5% difference). For the remaining cortical regions the glucose metabolism was found to be symmetric.

Planned nonorthogonal comparisons were also performed in an attempt to analyze the Group × Area interaction. Group A was compared with Group B for each regional area. Although the overall LCMRGl values did not differ between the two groups, it was found that glucose utilization was higher for certain areas in Group B as compared with Group A. Significant differences (at least $p < 0.05$) were found for the anterior and mid-temporal regions, superior and inferior parietal regions, as well as the inferior, mid-frontal, and postcentral regions. In only one cortical area, the occipital lobe, was the value significantly lower in Group B than in Group A.

The number of significant ($p < 0.05$) inter-regional correlations found on the untransformed, or LCMRGl raw data are presented in line one of Table 1. At this level of significance, 13 correlations were found between the average values, however, when a Bonferroni correction was applied, only one significant correlation, between the anterior and mid-frontal regions, remained ($0.01 < p < 0.05$).

TABLE 1
Number of Significant Correlations*

	Between averages	Between differences	Between averages and differences
Normal data			
Untransformed	13 (1)	17 (0)	14 (0)
Transformed to logarithms	14 (2)	14 (0)	12 (0)
"Abnormal" data			
Untransformed			
(I)†	29 (5)	17 (2)	30 (3)
(II)	21 (3)	13 (3)	29 (4)
Transformed to logarithms			
(I)	14 (2)	14 (0)	12 (0)
(II)	14 (2)	14 (0)	12 (0)
Expected number	5.25 (0.05)	5.25 (0.05)	11.25 (0.05)

* Number of correlations significant at 5% level and in brackets the number significant at the 5/(No. of correlations) level (see Appendix).
† Groups I and II of simulated abnormal data (see text).

Normalized Data

As in the previous analyses, the main effect of Area was significant ($F = 56.30$, $df = 14, 224$, $p < 0.0001$). There were also three significant interactions; Group × Area ($F = 4.27$, $df = 14, 224$, $p < 0.000$), Area × Side ($F = 5.45$, $df = 14, 224$, $p < 0.0001$), and Area × Side × Group × Sex ($F = 2.31$, $df = 14, 224$, $p < 0.006$). The two-way interactions were further analyzed by planned nonorthogonal comparisons. It was found that the glucose utilization was significantly higher (at least $p < 0.05$) in the left cerebral hemisphere as compared with the right in the mid-temporal and posterior temporal areas (3% differences) as well as in the caudate nucleus (7% difference). However, in the occipital lobe the reverse pattern was again found; the metabolic rate was higher on the right side (7% difference). In addition, in the right anterior frontal region the glucose utilization was higher than in its homotopic area on the left (4% difference). Planned nonorthogonal comparisons were again carried out for the Group × Area interaction. The significant differences were that the metabolic rate was higher in Group B than Group A in the anterior-temporal and in the mid-frontal region; it was lower, however, in Group B in the occipital region and in the cerebellum.

Log Transformed Data

The analysis of variance on the logarithmically transformed values yielded the following results. There were two significant main effects: Area ($F = 68.47$, $df = 14$,

224, $p < 0.001$) and Side ($F = 11.33$, df = 14, 224, $p < 0.004$). In addition, the same regional interactions as in the previous analysis of variance of normalized data were observed: Area × Group ($F = 4.40$, df = 14, 224, $p < 0.001$), Area × Side ($F = 5.67$, df = 14, 224, $p < 0.001$), Area × Group × Side × Sex ($F = 2.16$, df = 14, 224, $p < 0.01$).

At the 5% level, log-transformed LCMRGl values were significantly higher in the left mid- and anterior temporal areas than on the right, and in the right mid- and anterior frontal areas compared with the left. These correlations were not significant at the 1% level.

Simulation of "Abnormal" Data

The results of the correlation analysis performed on the simulated "abnormal" data set is shown in Table 1. Five regions in the "abnormal" data show significant but spurious correlations in the untransformed data. However, in the log transformed observations (rows 5 and 6, Table 1), the results show no spurious correlations when compared with those seen in the normal data (row 2, Table 1), because decreasing by a fixed percentage is equivalent to subtracting a constant on the log scale, and this constant is removed by the normalization (see Appendix).

Because the standard deviation of LCMRGl values increased as the mean LCMRGl absolute values increased, the results were also analyzed after transforming each score logarithmically. The analysis of variance that was carried out on the transformed values yielded results which were not statistically different from those found in the previous analysis of the data. A probability plot showed a slightly skewed distribution which was corrected by the log transformation. The analysis repeated on the log transformed data gave the results in the second row of the table. The conclusions were essentially unchanged.

Possible Effects of Repetitive Scanning

The effects of habituation have been discussed in other work (*2,25*). In order to assess the possible effects of repetitive scanning, the metabolic activity of the 6 experienced and the 4 inexperienced subjects in Group A was compared. The global value for the "inexperienced" group was 42.7 ± 4.5 μmol/100 g/min compared with 47.2 ± 4.2 μmol/100g/min for the "experienced" group, which is not significantly different ($p > 0.05$).

Five subjects in Group B had two FDG studies under resting conditions; in four instances these studies were 24 hr apart, and in one case the studies were 48 hr apart. Although a tendency was seen for the LCMRGl values to decrease on the second study, no statistically significant effect of a prior PET scan was seen. An analysis of variance was performed on the data of the five subjects who received two FDG studies. No significant difference was found between the mean LCMRGl values of the first and the second study ($p > 0.15$), nor was there any significant interaction involving the replication factor. This suggests that the glucose utilization remained relatively constant between the two studies. As in the analyses described above, significant effects of Area, and Area × Side were observed. Regional changes in LCMRGl are presented in Table 2.

In order to correct for day-to-day fluctuations in LCMRGl values within one subject, ratios of frontal cortex to parietal cortex, and frontal cortex to temporal cortex were examined. No significant differences were found in these ratios between the "inexperienced" (N = 4) and "experienced" (N = 6) subjects in Group A, or between the first and second studies in the five subjects in Group B who had two scans. There were no differences between the ratios in the "inexperienced" members of Group A and in the first studies of the members of Group B, or between the ratio in the "experienced" members of Group A and the repeat studies in subjects in Group B.

DISCUSSION

The use of an extension (*38*) of the Sokoloff deoxyglucose model (*33*) to study cerebral glucose metabolism in pathologic states has demonstrated the need to document and report the findings in healthy control populations. The raw regional LCMRGl value obtained from an FDG study of a normal awake brain at rest is a complex function of many interacting variables.

TABLE 2
Percentage Change in Regional LCMG1 Values in Five Subjects Having Successive FDG Studies

	R	L
Cerebellum	−3.0	−1.5
Hippocampus	−8.0	−5.3
Ant. temporal	−2.3	−1.6
Mid-temporal	−5.7	−4.9
Post-temporal	−4.9	−6.1
Parietal upper	−9.0	−8.7
Parietal lower	−6.8	−8.4
Occipital	−13.6	−7.0
Postcentral	−11.3	−8.0
Precentral	−9.6	−12.5
Mid-frontal upper	−3.7	−10.2
Mid-frontal lower	+2.3	−5.1
Ant.-frontal	−3.9	−8.5
Caudate	−4.6	−8.6
Thalamus	−13.8	−8.7
Mean change	−6.5	−7.0
LCMRGl first study*	45.4 ± 4.3	47.0 ± 5.9
second study	42.4 ± 3.1	43.7 ± 3.6

* LCMRGl in μmol/100 g/min.

Five major areas of interaction have been identified and discussed in the literature. First, the establishment of a stable resting state in the awake brain should be as reproducible as possible (*2,18,40,41*). Second, the relationship of partial volume effects due to slice orientation and the scanner's three-dimensional resolution volume to the measurement of localized radioactivity in brain structures must be appreciated (*2,19,42*), since some of the inconsistencies in results from various positron emission tomography (PET) centers may be explained by variability of scanner resolution (*2,19*). Third, the ability of a particular PET scanner to accurately measure localized radioactivity concentrations must be known, with particular reference to errors caused by attenuation, deadtime, changes in detector sensitivity, and random and scattered coincidences (*27, 43,44*). Fourth, the physiologic model used to calculate metabolic rates from in vivo radioactivity measurements must be verified, especially in regard to parameters of the FDG model, such as the kinetic rate constants and lumped constants (*8,11,36,45,46*). Finally, methodology for selecting anatomic regions based on functional maps must be standardized (*2,9,47,48*). Variations in these factors are possible sources of inter- and intra-center differences in the measurement of LCMRGl values.

It has been suggested that it is necessary to scan patients under conditions of sensory deprivation (ear plugs, eye patches) in order to achieve a stable, reproducible, resting state (*2*), and the degree to which sensory input is limited varies from center to center (Table 3). However, the consistency of intrasubject standard deviations for regional LCMRGl values (Figure 2, Group A = 8.5 ± 1.2, Group B = 7.0 ± 1.9) supports the argument that apart from global inter-subject variation, a relatively stable resting state can be achieved without the imposition of significant limitations on sensory input if inter-regional variation of the order of 10% is acceptable. This relative stability of the resting state is further supported by the repeat scanning results in Table 2. The reduction of both auditory and visual input has been reported to introduce a left-greater-than-right metabolic asymmetry in the inferior frontal, perisylvian, and lateral occipital cortex (*18*). In the present study, subjects in Group B underwent a relative visual deprivation, their field of view being largely limited to the plain inner surface of the scanner aperture. This resulted in a 10% lower LCMRGl in the occipital lobes of Group B subjects relative to Group A, but no other changes in left-right LCMRGl values were seen, and no overall differences in LCMRGl were seen between Groups A and B. Also, as detailed above, certain left-greater-than-right asymmetries were consistently found in this series of 20 subjects without sensory deprivation. In contrast to other reports of left-right LCMRGl ratio not differing significantly from unity (*9–11*) or of left-tright asymmetry only in the associative visual cortex (*2*), significant left-greater-than-right differences were found for the raw data in the anterior, mid-, and posterior temporal regions, for the lower mid-frontal area, and for the caudate. In the occipital region, however, LCMRGl was consistently higher on the right than on the left. These differences were small in absolute terms (<8%), but were statistically significant when viewed across the sample group of 20 subjects. This small but significant asymmetry may be a reflection of the true "basal state" in a strongly right-handed population at rest, exposed to limited auditory and visual stimulation. These findings are similar to the asymmetries in the frontal, lateral occipital, and posterior superior temporal cortex reported in a group exposed to verbal stimuli (*21*).

TABLE 3
Repeated Normal Gray Matter Mean Glucose Metabolic Rates Measured with Fluorodeoxyglucose*

	Age range	No. subjects	No. regions	Sensory eyes	Deprivation ears	LCMRG1 (μmol/100 g/min)
Reivich et al. (1979) (7)†	24–26	2	8	–	–	27.1 ± 3.6
Schwartz et al. (1983) (6)	21–33	10	23	+	+	33.9 ± 2.9
Horwitz et al. (1984) (4)	21–83	40	59	+	+	27.8 ± ?
Duara et al. (1983) (15)	21–83	21	31	+	+	29.2 ± 6.7
Duara et al. (1984) (10)	21–83	40	50	+	+	29.5 ± 6.7
Heiss et al. (1984) (11)	28–38	7	10	+	–	38.1 ± 3.0
Herholz et al. (1985) (48)	28–38	7	28	+	–	37.5 ± 5.3
Mazziotta et al. (1981) (2)	21–27	7	20	+	–	37.4 ± 3.4
de Leon et al. (1984) (49)	(26.1 ± 5.1)‡	15	12	+	–	20.2 ± 3.5
Huang et al. (1980) (8)	?	13	8–10	–	–	40.9 ± 7.4
Kuhl et al. (1980) (1)	18–30	8	5	–	–	36.9 ± 1.1
Kuhl et al. (1982) (9)	18–27	10	6	–	–	38.5 ± 1.5
M.N.I. (1987)	18–32	20	30	–	–	45.4 ± 7.7

* Excluding primary visual cortex and small structures such as hippocampus.
† All studies except this used rate constants reported by Huang (*3*).
‡ Mean age, range not given.

The ANOVA results for both the main effects and for the interactions were similar with the use of raw data, normalized data, and log transformed data. It seems reasonable to assume that the Group × Area and Area × Side interactions, which were seen in all forms of the data, may indeed have physiologic importance. However, the relevance of interactions, such as Group × Area for the cerebellum and parietal area, which only appear with and without normalization, respectively, is questionable. They may fulfill the numerical criteria for significance without being functionally relevant. Such results demonstrate the difficulties inherent in interpreting the significance of small regional patterns that are statistically identified as being characteristic of a group of subjects' LCMRGl measurements. In particular, the interaction of transformation such as normalization with the statistical analysis technique being used must be carefully considered to avoid spurious results (*17*).

To test for significant interactions between brain regions it is necessary to know whether or not pairwise LCMRGl measurements would be correlated if many repeat measurements were available from the same subject (*4,5,15*). A novel approach was developed by noting that the availability of only single data sets from different subjects with different mean LCMRGl levels implies that at least uniformly significant correlations will be obtained. Therefore, the question was not whether any significant regional correlations existed, but whether there was enough evidence to indicate a significantly non-uniform pattern of correlations (i.e., some correlations significantly different from others) if repeated measurements were carried out on a single subject. To test this, a null hypothesis was set up in which three possible correlations due to different global, hemisphere and homologous region random effects were removed by data transformation (see Appendix). The hypothesis that significant differences existed between regional correlations could then be tested. It can be seen in Figure 2 that for a valid analysis, it was necessary to transform the observations to the log scale. The importance of carefully choosing data transformations to prevent the appearance of spurious inter-regional correlations is demonstrated with this data set (Table 1).

Our analysis of the inter-regional correlations (see Appendix) attempted to take into account both the total number of correlations as well as the possible effects of random variability in the mean glucose levels across subjects. Thus, using this somewhat conservative statistical approach, it appears that there is little evidence in our data set to support the notion of interrelated regions whose metabolic rates are strongly coupled, or to support the hypothesis that such interrelations correspond to functional systems.

We noted that, over a period of about 1 year, there was no significant change in the LCMRGl measurements obtained in the laboratory. This stability in quantitation existed despite small technical changes in data collection (change from arterialized venous blood to arterial samples), scanning (patients placed in camera gantry before or 40 min after FDG injection), and small changes in tactile sensory input (slightly more frequent blood sampling in later studies), as has been seen elsewhere (*20*) in regards to the effects of hand-warming and the performance of minor manual tasks. This serves as additional evidence that the technique is not threatened by small, incidental factors. The present study thus demonstrates the consistency and stability of test conditions not only within a group of subjects, but over time, in two groups of subjects.

The mean coefficients of variation for LCMRGl values reported by various centers (*1,2,6–11,48,49*) are also fairly consistent (Table 4); if one study (*6*) is excluded from this group, the mean coefficient of variation for LCMGRl values for the remainder is 19 ± 4. This may be taken as presumptive evidence that there is a consistent global effect operating within and across PET centers (*4,20*). This intercenter consistency also suggests the existence of a consistent characteristic of inter-subject variation in the resting state.

In the 20 controls scanned in the present study, intra-subject variation in LCMRGl was significantly lower than the inter-subject variation (coefficient of variation = 11.4% versus 16.9%). In contrast, one recent study (*11*) has reported the reverse, i.e., that in a group of seven control subjects, inter-regional differences accounted for 74% of the total variation, as compared with 11% contributed by variation among subjects. However, this latter study included large predominantly gray matter regions, as well as small regions in the brain stem and regions in white matter.

TABLE 4
Mean Coefficient of Variation* for Regional† Cerebral Glucose Metabolic Rates

	Mean coeff. of variation	No. subjects
Huang et al. (1980) (*8*)	18.1 (mean k's)	13
Huang et al. (1980) (*8*)	16.2 (kinetic)	13
Kuhl et al. (1980) (*1*)	13.9	8
Mazziotta et al. (1981) (*2*)	23.5	7
Kuhl et al. (1982) (*9*)	23.8	10
Reivich et al. (1983) (*47*)	22.5	6
Duara et al. (1983) (*15*)	23.0	21
Schwartz et al. (1983) (*6*)	6.6	10
Heiss et al. (1984) (*11*)	20.7 (mean k's)	7
Heiss et al. (1984) (*11*)	13.9 (kinetic)	7
M.N.I. (1987)	16.5	20

* Coeff. of variation = (std. deviation/mean).
† All regions including white and gray.

Although the overall LCMRGl values did not vary between Groups A and B, and no significant differences in the right-left asymmetries were seen between the groups, the values in Group B tended to be higher bilaterally in the anterior and mid-temporal, parietal, and lower mid-frontal and postcentral regions. These regional differences between Groups A and B, though small (5–15%), were statistically significant. The reasons for these differences are unclear, but we speculate that higher LCMRGl values in selected bilateral regions in subjects in Group B may reflect heightened anxiety, or increased awareness and attention to environment due to the partial visual input deprivation. The slight but significant increase in the standard deviation of LCMRGl values in Group A compared with Group B is probably due to small errors in the blood curve obtained with the arterialized-venous-blood sampling technique.

Despite a trend for lower LCMRGl values on a second FDG study in the same patient, no statistically significant difference was seen with repeat studies (Table 2). The tendency to obtain lower LCMRGl values in a second PET study (mean decrease = 6.8%) reflects a mild global decrease in metabolism, rather than a change confined to one specific region, such as the frontal lobes (Table 2). Previous reports have noted relative increases in blood flow (*6*) and glucose metabolism (*2*) in frontal cortex; this increased frontal blood flow pattern seemed to disappear as subjects became accustomed to the scanning procedure (*44*). In the present study, no such "hyperfrontal" state was found, and no significant changes in frontal lobe metabolism were seen with repeat studies. However, in light of a trend for decreasing LCMRGl values on a repeat scan (Tables 3 and 4), results from data on only five subjects may be insufficient to demonstrate subtle small signal effects of repeated scanning as significant.

In conclusion, despite the use of various scanning methodologies, instrumentation, and data-analysis techniques, the inter-regional variation of LCMRGl is typically of the order of 10%. This suggests that it is possible to establish a relatively stable "resting state" within one center, and potentially across centers. The inter-subject variation of LCMRGl is also fairly consistent, being ~20% for most centers, further implying the existence of consistent baseline conditions. However, the size of the coefficient of variation for inter-regional differences across subjects defines a large normal range. This implies a limited usefulness of "normal" ranges as an index of comparison when evaluating pathologic states.

Normalization represents a widely used attempt to overcome the problem of large inter-subject variability. However, there is no clearly demonstrated statistical advantage, and there are some inconsistencies in identifying significant regional effects when comparing our raw data and normalized data ANOVA results. This suggests that predictions of improved statistical power based on the reduced coefficient of variation for normalized regional data do not necessarily hold for statistical analyses more complex than t-tests. Statistical techniques such as multiple-way ANOVAs and correlation analyses may be required to obtain consistent, reproducible functional information from the relatively small regional signal often found in LCMGRl data sets. The impact of data transformations used with such tests must be carefully considered and tested to ensure that reproducible results are being obtained.

APPENDIX

Investigation of Correlation of Glucose Utilization Between Regions of the Brain

If measurements of glucose utilization are taken on a subject in, for example n = 15 regions in each cerebral hemisphere, it is possible to test whether measurements between regions are correlated.

If $(X_1,Y_1), (X_2,Y_2), \ldots, (X_p,Y_p)$ are pairs of measurements taken on two regions repeated p times, then the correlation between the two regions is estimated by:

$$r = \mathrm{Cor}(X,Y) = \frac{\sum_{j=1}^{p} (X_j - \bar{X})(Y_j - \bar{Y})}{\sqrt{\sum_{j=1}^{p} (X_j - \bar{X})^2 \sum_{j=1}^{p} (Y_j - \bar{Y})^2}},$$

where $\bar{X} = \sum_{j=1}^{p} X_j p$, $\bar{Y} = \sum_{j=1}^{p} Y_j p$ are the averages for the two regions. Note that $-1 \le r \le 1$, $r \approx 1$ indicating high positive correlation, and $r \approx 0$ indicating that X and Y are uncorrelated.

Such repetitions on the same control subject are not available, however, measurements have been taken once on each of p = 20 control subjects. If we assume that the correlations are the same for all subjects and that each subject has identical mean glucose utilization levels, then they can be used in place of the p repetitions on the same individual.

Since the subjects do not have identical mean glucose levels, we shall assume that these mean levels are taken at random from a normally distributed population. The fact that the mean level for a randomly chosen subject is itself a random variable common to all regions of that subject induces equal positive correlations between regions on the sample of p subjects. Since the magnitude of this correlation depends on the standard deviation of the observations about the subject mean, and the standard deviation of the subject mean in the population of all subjects which are unknown, no statistical method can detect significant correlations between regions if all the correlations are equal. However, the hypothesis of interest is that some regions are more highly correlated than others. In order to detect this, we can remove the equal correlation by normalizing the observations so that the resulting correlations between the normalized observations will have known pre-determined values if the original unnormalized observations were equally correlated. Any departures from

these pre-determined values will indicate different correlations between the regions, which is what we wish to detect.

The situation is complicated by the possible presence of two other random effects: (a) one for each cerebral hemisphere in the subject, which induces equal correlations between observations on the same side of the brain above the correlation between observations on different sides, and (b) one for each region of the subject that induces equal correlations between right and left measurements in the same region of a subject. Thus, our final null model is that there are possibly three different correlations between observations in an individual.

1. Between observations on different side and different regions, e.g., right cerebellum and left hippocampus;
2. Between observations on the same side, e.g., right cerebellum, right hippocampus;
3. Between observations on different sides but on the same region, e.g., right cerebellum, left cerebellum.

All these three unknown correlations, induced by the fact that the subjects are drawn at random from a population, rather than repeated observations on the same subject, can be removed by appropriate normalization.

The appropriate normalization is as follows. Let R_{ij} and L_{ij} be right and left observations for the i-th region on the j-th patient, i = 1, ..., n, j = 1, ..., p. The correlation between R_{ij} and L_{ij} is removed by transforming to averages and differences: $A_{ij} = (R_{ij} + L_{ij})/2$ and $D_{ij} = R_{ij} - L_{ij}$. If R_{ij} and L_{ij} have equal standard deviations, then A_{ij} and D_{ij} are uncorrelated (r = 0). Let $\bar{A}_{.j}$ and $\bar{D}_{.j}$ be the average over all regions:

$$\bar{A}_{.j} = \sum_{i=1}^{n} A_{ij}/n,\ \bar{D}_{.j} = \sum_{i=1}^{n} D_{ij}/n\,.$$

The correlations between regions are removed by subtracting the means:

$$A^*_{ij} = A_{ij} - \bar{A}_{.j},\ D^*_{ij} = D_{ij} - \bar{D}_{.j}\,.$$

If A_{ij} and D_{ij} are equally correlated, then A_{ij}^* and D_{ij}^* have correlations -1/(n-1) between regions.

Calculations of Correlations

For two regions i and k say, let

$$r_{ik}^{AA} = \mathrm{Cor}\,(A_i^*, A_k^*) = \frac{\sum_{j=1}^{p} (A_{ij}^* - \bar{A}_{i.})(A_{kj}^* - \bar{A}_{k.}^*)}{\sqrt{\sum_{j=1}^{p} (A_{ij}^* - \bar{A}_{i.}^*)^2 \sum_{j=1}^{p} (A_{kj}^* - \bar{A}_{k.}^*)^2}}$$

and similarly let

$$r_{ik}^{DD} = \mathrm{Cor}\,(D_i^*, D_k^*),$$

$$r_{ik}^{AD} = \mathrm{Cor}\,(A_i^*, D_k^*)\,.$$

Then if the observations are equally correlated r_{ik}^{AA} and r_{ik}^{DD} should be $\sim \rho = -1/(n-1)$ and r_{ik}^{AA} should be approximately $\rho = 0$. If the observations are normally distributed with correlation ρ then it can be shown that the t-statistics:

$$T = \frac{\sqrt{p-2}\,(r-\rho)}{\sqrt{(1-r^2)(1-\rho^2)}}$$

has an approximate t-distribution with p-2 degrees of freedom if ρ (rho) is small, and exactly if $\rho = 0$ (*50*). Let T_{ik}^{AA}, T_{ik}^{DD}, and T_{ik}^{AD} be the t-statistics with $\rho = -1/(n-1)$, $-1(n-1)$, and 0, respectively. We can now test the hypothesis of equal correlations by comparing the t-statistics to the t-distribution with p-2 degrees of freedom.

Significance Levels

We are interested in detecting abnormally high or low correlations and so for a 5% level test the critical value of T is ±2.1009.

The first row of Table 1 summarizes the number of significant correlations. Since there are n(n-1)/2 = 105 possible correlations r_{ik}^{AA} and 105 r_{ik}^{DD}'s, then we expect 105 × 5% = 5.25 falsely significant statistics in the first two columns, and 15 × 15 × 5% = 11.25 in the third. To counteract this we must reduce the significance level by the number of tests that are made, to 5/105%, 5/105% and 5/225% giving critical values of ±4.2551, ±4.2551 and ±4.6001, respectively (*51*). At this level one t-statistic was significant, indicating that there was some evidence to show an abnormally large correlation between the mid and anterior frontal regions of the brain. This correlation was not significant at the 1% level.

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