Clinical Evaluation of Interictal Fluorine-18-Fluorodeoxyglucose PET in Partial Epilepsy

Thomas R. Henry, Jerome Engel, Jr. and John C. Mazziotta

Department of Neurology, University of Michigan, Ann Arbor, Michigan; and Departments of Neurology, Anatomy and Cell Biology and Radiological Sciences, UCLA, Los Angeles, California

Interictal [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography (PET) is useful in presurgical evaluation of medically refractory partial epilepsies. Limited replicability of image interpretation may restrict this application. We investigated interpretation replicability in 241 ^{18}F-FDG studies performed with three different tomographs in partial epilepsy patients. Two investigators independently interpreted the studies with a standardized evaluation protocol and without knowledge of the subjects. Replicability of these unbiased interpretations in detection of regional hypometabolism was best for studies performed with the highest performance tomograph. Interictal ^{18}F-FDG studies performed with this tomograph revealed regional hypometabolism in 62% of patients who had normal cerebral magnetic resonance imaging (MRI). Replicability of interpretations in detecting regional hypometabolism was adequate for clinical application of interictal ^{18}F-FDG studies performed with any of the tomographs.

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Regional glucose hypometabolism is reported to occur in the majority of partial epilepsy patients, a group in which temporal lobe epilepsy predominates, with interictal [^{18}F]fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) (*1–17*). The region of interictal hypometabolism almost always includes the electrophysiologically recorded ictal onset zone in limbic and neocortical partial epilepsies, but is usually much larger than the electrophysiological ictal onset zone (*2–4,6,18*). These observations support clinical application of FDG PET in presurgical evaluation of medically refractory complex partial seizures to: (1) provide a high degree of confidence in performing anterior temporal lobectomy in the mesial temporal lobe epilepsy syndrome based on concordance of noninvasively acquired information, and (2) assist in selecting high-probability sites for intracranial electrode placement when invasive ictal electrophysiological monitoring is necessary (*18–20*).

Current clinical applications of cerebral FDG PET are based on qualitative visual interpretation analysis of tomographic images. Mathematical models of FDG kinetics support reliable PET quantification of local cerebral glucose metabolic rate (*21,22*). Quantitative analysis of FDG PET in pathologic and normal conditions may be expected to increase the sensitivity and accuracy of detecting regional metabolic dysfunction, as well as to reliably measure the severity of this dysfunction. Despite intensive development of automated routines for PET-MRI coregistration to support determination of standardized functional imaging coordinates, there is no consensus across PET centers on how to perform quantitative PET analysis (*23*).

Qualitative evaluation remains the only agreed-upon means by which to apply interictal FDG PET in epilepsy surgery programs (*20*). A survey of epilepsy surgery programs participating in the 1992 Palm Desert International Conference on Surgical Treatment of the Epilepsies indicated that among programs which use FDG PET clinically, none relied entirely on any form of quantitative PET analysis for clinical decision-making (though quantification of metabolism was prevalent in research applications). Most programs relied exclusively on qualitative PET interpretations made by epileptologists and nuclear medicine specialists who were fully aware of each patient's non-PET data.

Replicability of these qualitative evaluations of regional cerebral metabolism has not been adequately demonstrated. We suspect that knowledge of an individual's clinical data can easily bias interpretation of subtle variations in FDG image intensity. It also remains unclear whether differences in spatial resolution among FDG image sets affect replicability of qualitative PET analysis. We designed this study to resolve the issues of reproducibility of unbiased FDG PET interpretations and whether image resolution influences replicability of interpretation.

METHODS

Subject Selection and Correlative Data

Partial epilepsy patients studied with FDG PET were aged 16–55 yr. Between 1978 and 1990, medically refractory complex partial seizures in each patient led to referral to the UCLA Clinical Neurophysiology Program for consideration of surgical treatment. Definite diagnosis of partial epilepsy, with exclusion of generalized epilepsies and of psychogenic seizures, was based on ictal scalp-sphenoidal EEG-videomonitoring in each patient. Among 249 such patients, eight had FDG studies that were excluded due

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For correspondence and reprints contact: Dr. Thomas R. Henry, Epilepsy Laboratory, University of Michigan Hospital 1B340/0036, 1500 E. Medical Center Dr., Ann Arbor, MI 48109.

TABLE 1
Protocol for Qualitative Evaluation of Fluorine-18-FDG PET Studies

I. The examiner reviews the entire image set at least twice, first to exclude artifacts that would preclude reliable evaluation and to mentally assign boundaries to lobar and subcortical regions, and again to detect abnormal alterations in image intensity within these regions.

II. First Review: The examiner briefly views every image plane to:

  A. Exclude from further evaluation studies with major artifacts, including:

    1. Detectably asymmetric cranial positioning (i.e., excessive lateral head tilt).

    2. Artifacts of computerized tomographic reconstruction.

    3. Other artifacts that prevent reliable recognition of each region within each image. (Mild anteroposterior or rotational cranial malpositioning does not preclude reliable scan evaluation.)

  B. Assign boundaries on each relevant image plane for the frontal, lateral temporal, mesial temporal, parietal, occipital, anterior and posterior cingulate, basal ganglial, thalamic, cerebellar and brainstem regions bilaterally (Fig. 1). It is usually useful to compare adjacent image planes in assigning these boundaries.

III. Second Review: Image intensity is evaluated within each plane, noting zones of apparent hypointensity or hyperintensity with respect to the standardized regions.

  A. Areas of decreased (or increased) intensity on an image plane are compared with similar planes on normal FDG studies performed with the same tomograph and technique that were used for the scan under evaluation.

  B. Focal abnormalities (if any) noted on individual images are compared in location and intensity to generate an overall evaluation of the study. To constitute definite regional hypometabolism (or hypermetabolism), a zone of abnormally decreased (or increased) intensity must be located in the same region on at least two adjacent planes. The most inferior plane on which the mesial and lateral temporal regions appear should not be used in assessing intensity asymmetries of the mesial and lateral temporal regions; the same holds for the frontal and occipital regions on the most inferior plane on which they appear and for the cerebellum on the most superior plane on which it appears. (These rules are intended to exclude partial volume effects of averaging with normal sulcal spaces, subcortical white matter and the base of the skull for structures that have relatively flat contours in the axial plane.)

  C. Any equivocal findings with regard to abnormal image intensity on one image plane or to adjacency of the zone of intensity alteration between planes are rejected in the final evaluation of the study (i.e., "equivocally abnormal" = "normal").

to imaging artifacts, resulting in an epilepsy group of 241 for this study.

Correlative cerebral magnetic resonance imaging (MRI) data were consistently available only for the patients who were evaluated after 1986. Among the entire partial epilepsy group, the subgroup of patients who had PET studies performed with the CTI-Siemens 831 (Siemens Medical Systems, Hoffman Estates, IL) scanner all had cerebral MRI studies prior to epilepsy surgery. These MRI studies were performed with several different 1.5-tesla scanners at several centers, under various scanning protocols that did not always include gadolinium administration, but always provided axial and coronal views with T1, proton density and T2 weighting. In each case, the MRI study was interpreted by a neuroradiologist who did not have knowledge of the patient's ictal EEG or PET data. The neuroradiologists' MRI interpretations were used to exclude MRI-detectable cerebral lesions in order to examine the replicability of PET interpretation in "nonlesional" partial epilepsy. Among the 56 patients who had PET with the 831 scanner, 14 had cerebral abnormalities on MRI and three had MRI studies of suboptimal quality, leaving 39 patients with high-quality cerebral MRI that was normal.

The 25 control subjects were 18–50 yr old, had no history of neurologic or psychiatric illness, and had normal neurologic examinations. None was receiving any medication at the time of PET.

Fluorine-18-FDG PET Techniques

The deoxyglucose method, with intravenous injection of approximately 10 mCi of FDG, was employed (*21*). Axial cerebral imaging was obtained with one of three tomographic instruments: (1) ECAT scanner (Ortec, Knoxville, TN), operating with spatial resolution of approximately 13 mm in-plane and 19 mm axially (full width at half maximum), providing seven or eight brain images with 12 mm spacing, acquired in two sets of four images with one vertical shift in cranial position between sets (*24*); (2) NeuroECAT scanner (CTI, Knoxville, TN), with approximately 9 mm in-plane and 11 mm axial resolution, providing 12 images with 8 mm spacing, acquired in three sets of four images with vertical shifts between sets (*25*); and (3) 831 scanner (CTI-Siemens, Knoxville, TN), with approximately 6 mm in-plane and 7 mm axial resolution, providing simultaneous acquisition of 15 images with 6.75 mm spacing (unpublished results). Scanning began 30–40 min after FDG injection in every study, but continued for 60–90 min with the ECAT, 60 min with the NeuroECAT and 45 min with the 831 scanner. Subjects were scanned under ambient waking conditions, with eyes open and ears unoccluded in a dim, quiet environment (*26*). Interictal scanning in epilepsy patients was assured by continuous observation and scalp EEG from 30 min before to 60 min following FDG injection, in addition to the patient's denial of subjective ictal phenomena during this period. Correction for attenuation was performed by the geometric method, in which a cranial average linear attenuation coefficient (*27*) is used to correct the measured emission activity based on an ellipse carefully placed around the area of maximal activity within each image plane of each study (*28*).

Qualitative Evaluation of Fluorine-18-FDG PET

Two neurologists with prior experience in PET interpretation (T.R.H. and J.E., Jr.) evaluated each PET study independently and unaware of the identity of the PET subject. The protocol for evaluation (Table 1) was used in conjunction with the regional

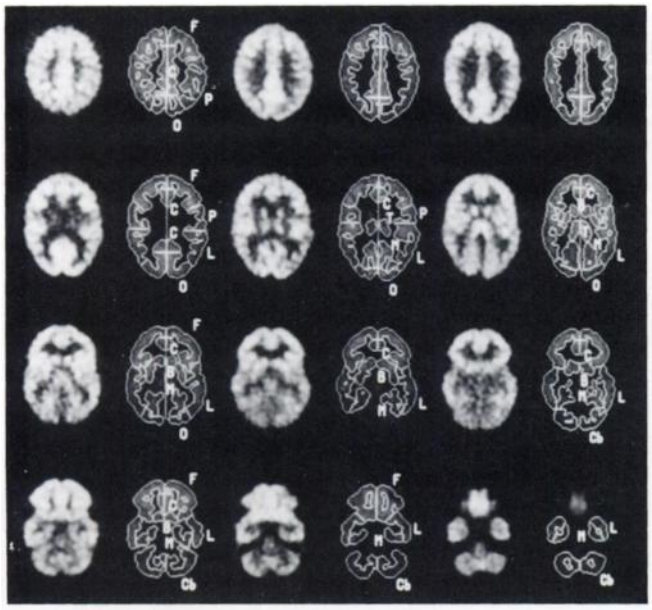

FIGURE 1. Template for metabolic regions. This FDG PET study of a normal control subject, performed with the CTI-Siemens 831 tomograph, is displayed in rows of adjacent pairs of the same image without and with boundaries of the standardized lobar and subcortical regions. Images without regional boundaries are displayed in full gray scale. Images with regional boundaries are displayed in truncated gray scale to enhance visualization of the boundary lines. These axial images are displayed in descending order from the upper left. Regions on the right image are labeled with adjacent letters as F (frontal), P (parietal), O (occipital), L (lateral temporal), M (mesial temporal), C (cingulate), B (basal ganglial), T (thalamic) or Cb (cerebellar). Regions on the right that do not have labels are the same region as that labeled on an adjacent image plane.

template FDG study (Fig. 1). A gray scale displayed image intensity for each study (Figs. 2–4).

Each investigator was first shown 10 FDG studies of normal control subjects that were identified to the investigator as normal, with examples from each of the three tomographs used in the study. After reviewing the identified normal studies, the investigator then evaluated 264 FDG studies that were not identified with any information on the scan subject, including 15 scans of normal adults and 249 scans of patients with partial epilepsy. Evaluations generated an interpretation of "normal" or "abnormal" for each reliably imaged region of every image and for the image set as a whole.

Metabolism associated with the cingulate gyrus, cerebellum and brainstem must be identified in order to be excluded from adjacent regions (Fig. 1). The size and shape of the cingulate gyrus and brainstem fall below the recovery coefficient of the ECAT scanner, so glucose metabolism of these areas cannot be reliably evaluated in FDG studies performed with this tomograph (*29*). Cranial positioning within the field of view of each tomograph

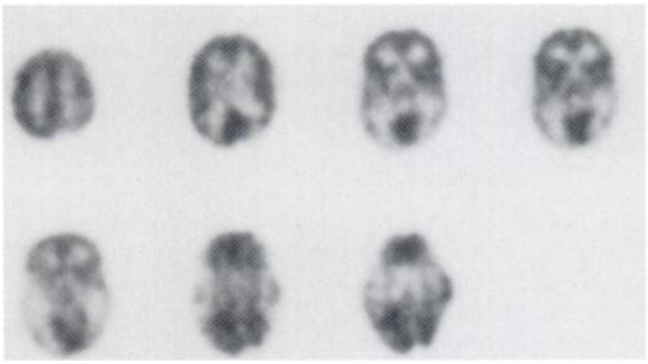

FIGURE 2. FDG study with the ECAT tomograph. This interictal study of a partial epilepsy patient is displayed with the subject's right hemisphere on the right side of each image. Both investigators reported left lateral temporal hypometabolism (seen on the three most inferior image planes). One investigator reported left mesial temporal hypometabolism, but the other did not. Other areas of possible hypometabolism (e.g., the right parietal area on the image plane to the right of the upper row) were not considered clearly abnormal.

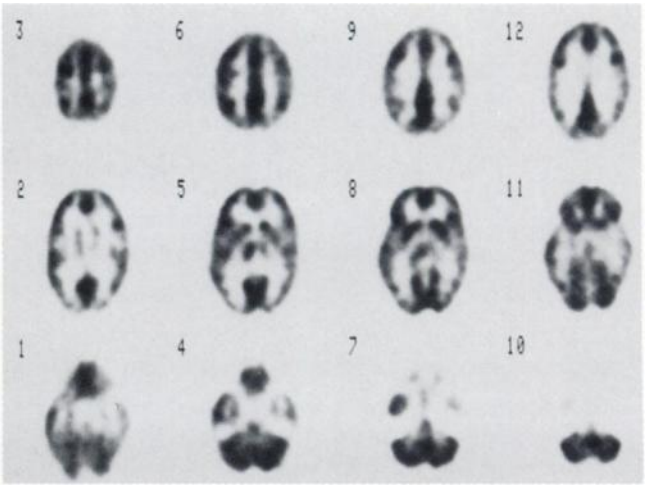

FIGURE 3. FDG study with the NeuroECAT tomograph. This interictal study of a partial epilepsy patient is displayed with the subject's right on the images' right. Both investigators reported right mesial temporal, lateral temporal and thalamic hypometabolism.

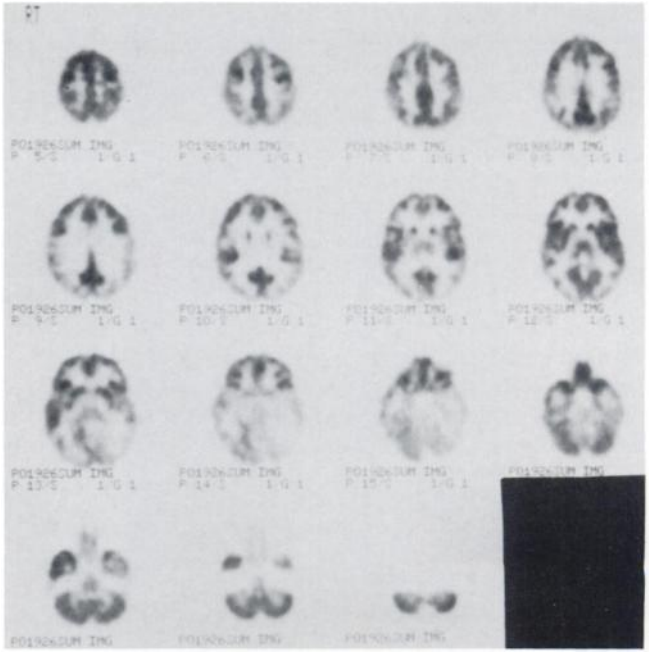

FIGURE 4. FDG study with the 831 tomograph. This interictal study of a partial epilepsy patient is displayed with the subject's right on the images' left. Both investigators reported left mesial temporal, lateral temporal and occipital hypometabolism.

TABLE 2
Fluorine-18-FDG PET Evaluations* in Epilepsy

	Any	LT	MT	Th	F	P	O	BG
ECAT:								
Normal	0.32	0.32	0.36	0.84	0.90	0.96	0.90	0.98
Abnormal	0.46	0.44	0.36	0.02	0.04	0.02	0.08	0.00
Disagree	0.22	0.24	0.28	0.14	0.06	0.02	0.02	0.02
Kappa† (n = 50)	0.55	0.52	0.44	0.17	0.54	0.66	0.88	0.00
NeuroECAT:								
Normal	0.26	0.36	0.42	0.60	0.87	0.96	0.94	0.96
Abnormal	0.53	0.44	0.40	0.16	0.05	0.02	0.03	0.01
Disagree	0.21	0.20	0.18	0.24	0.08	0.02	0.03	0.03
Kappa† (n = 135)	0.54	0.60	0.65	0.43	0.54	0.66	0.65	0.32
831:								
Normal	0.29	0.29	0.30	0.77	0.95	0.93	0.95	0.96
Abnormal	0.70	0.70	0.66	0.21	0.05	0.05	0.05	0.04
Disagree	0.01	0.01	0.04	0.02	0	0.02	0	0
Kappa† (n = 56)	0.96	0.96	0.92	0.95	1.00	0.86	1.00	1.00
831: No Lesion								
Normal	0.36	0.36	0.36	0.77	0.95	0.95	0.97	0.97
Abnormal	0.62	0.62	0.59	0.23	0.05	0.05	0.03	0.03
Disagree	0.03	0.03	0.05	0	0	0	0	0
Kappa† (n = 39)	0.94	0.94	0.88	1.00	1.00	1.00	1.00	1.00
Any Tomograph:								
Normal	0.28	0.34	0.38	0.69	0.90	0.95	0.93	0.97
Abnormal	0.55	0.50	0.45	0.15	0.05	0.03	0.05	0.01
Disagree	0.17	0.16	0.17	0.16	0.05	0.02	0.02	0.02
Kappa† (n = 241)	0.63	0.66	0.67	0.54	0.62	0.72	0.81	0.52

*The first column (labeled "Any") lists the proportions of each set of FDG studies that had any one or more regions considered abnormal versus studies that had "not any" abnormal regions (i.e., normal studies); the other columns are for individual regions, abbreviated as LT (lateral temporal), MT (mesial temporal), Th (thalamic), F (frontal), P (parietal), O (occipital), and BG (basal ganglia). Rows labeled normal specify the proportion of each group that were considered normal by both investigators; abnormal specifies the proportion considered abnormal by both investigators; and disagree specifies the proportion which one investigator considered normal and the other considered abnormal. The upper three sets of evaluations are grouped by the tomograph used for each group of FDG studies; the next set (831: No Lesion) includes 39 FDG studies of epilepsy patients who had normal cerebral MRI studies; the bottom set (Any Tomograph) includes all 241 FDG studies of epilepsy patients.

†Kappa statistics are calculated for each set of regional evaluations by tomograph. The number of PET studies are specified for each group.

excluded most of the cerebellum and brainstem from the available image sets. We therefore did not evaluate cingulate, cerebellar or brainstem metabolism, but did evaluate metabolism in the remainder of the identified regions.

Statistical Analysis of Fluorine-18-FDG PET Evaluations

The kappa statistic (*30*) was used to measure shared discrimination of the two investigators' PET evaluations. This statistical measure differs from simple calculation of percent agreement, in that kappa represents agreement corrected for chance. A kappa value of 1.00 represents complete shared discrimination and a value of 0.00 represents total absence of shared discrimination.

RESULTS

Replicability of Fluorine-18-FDG PET Interpretations

Both investigators considered each of the 15 normal control FDG studies to be entirely normal. (These scans were not identified during scan evaluation as those of normal control subjects and were intermixed with scans of epilepsy patients.) There was also complete agreement in excluding eight epilepsy studies from evaluation because of major artifacts (as defined in Table 1).

Comparison of investigators' evaluations of the 241 epilepsy studies are shown in Table 2. Despite adherence to conservative criteria, frequent disagreements occurred in evaluating individual regions, and even in rating an entire image set as normal or abnormal ("global evaluations"). Many regions have higher kappa values with NeuroECAT than ECAT data. Global evaluations and all regional evaluations have their highest kappa values for scans produced by the latest generation tomograph, the Siemens-CTI 831. When the investigators agreed in finding a regional abnormality, they always agreed on the side of the abnormality and the abnormality was always considered to be hypometabolism (never hypermetabolism). Nearly all regional hypometabolism was unilateral, to the point that if a scan had multiple hypometabolic regions, these regions were almost always in one hemisphere. Among 241 epilepsy scans, only four had bilateral hypometabolism (with no disagreements between investigators as to bilaterality of hypometabolism).

Concordance in visual detection of interictal hypometabolism in epilepsy also rises across the three tomographs. For example, both investigators found hypometabolism in one or more regions on 46% of ECAT scans, 53% of NeuroECAT scans and 70% of 831 scans. Some regions

showed this trend more clearly than others. In particular, concordant visual detection of thalamic hypometabolism increased with each increase in tomographic resolution (Table 2). No regions showed consistent trends toward increasing or decreasing concordance in "normal" ratings across the three levels of tomographic performance. Thus, the increasing concordance in finding regional hypometabolism and the relatively unchanging rate of concordantly finding normal metabolism, as tomographic performance increases, are associated with decreasing discordance in detection of regional hypometabolism by both investigators.

The replicability of PET interpretations appeared similar in the 39 patients without cerebral MRI abnormalities to the replicability in all 56 patients on whom PET scans were obtained with the 831 tomograph (Table 2). Among the 14 patients with cerebral abnormalities on MRI, both investigators reported normal metabolism in one patient (who had a small left anterior-lateral temporal MRI lesion most consistent in appearance with a vascular malformation estimated at 1.5 cm in greatest dimension) and both agreed in lateralizing a region of hypometabolism in 13 patients. Among these 13 patients, the side of the unilateral hypometabolic region and the side of the single MRI lesion agreed in 12. One patient had a right anterior-lateral temporal MRI abnormality most consistent in appearance with a vascular malformation (estimated at 2 cm in greatest dimension) and widespread left mesiolateral temporal hypometabolism on PET; epilepsy surgery was not performed because ictal EEG recordings showed multiple seizures with ictal onsets independently over both temporal lobes.

The 39 patients with normal cerebral MRI and PET performed with the 831 tomograph included 24 (62% of this subgroup) who had concordantly reported regional hypometabolism. Among these 24 patients, four did not have epilepsy surgery because the zone of ictal onset could not be adequately localized with intracranial EEG monitoring, while the other 20 went on to temporal lobectomy based on multimodality presurgical evaluations. In each of these 20 patients PET detected hypometabolism of the temporal lobe that was resected. Postoperative follow-up is too brief to permit definitive comparison of PET findings with the efficacy of these surgical procedures, but all 20 patients appear to have improved or complete seizure control at early (1–2 yr postoperatively) review.

Observations Regarding the Protocol for Qualitative Evaluation of Fluorine-18-FDG PET Studies

The investigators observed several aspects of the protocol in comparison with less formalized PET interpretation.

Normal FDG PET studies show overall symmetry of intensity between homologous functional divisions. However, normal control subjects' studies often have small areas of apparent decreases in image intensity along the cortical ribbon on single-image planes. Similar single-plane hypointensities also are frequently observed in many areas on epilepsy patients' studies. Because these small hypointensities are not seen on adjacent images, under this protocol they are not considered abnormal. The investigators occasionally noted marked decreases in small areas of cortical metabolism of normal control and epilepsy studies, which were sufficiently hypointense that the studies would have been considered abnormal except for the fact that the hypointensity appeared only on a single image plane. In most of the 14 such cases, the marked single-plane hypointensity would have been considered abnormal (except for the multiplanar requirement for abnormality) by one of the investigators but not by the other. These 14 studies were performed with the ECAT (one of five normal and three of 50 epilepsy studies), NeuroECAT (none of five normal and seven of 135 epilepsy studies) and 831 (one of five normal and two of 56 epilepsy studies) tomographs; the two such epilepsy studies with the 831 scanner were the same two that were performed on patients who had small MRI lesions consistent with vascular malformations, and the "normal" (single-plane) regional decrease in cortical FDG activity corresponded to the location of the MRI abnormality in both patients according to both investigators. (We suspect but have not demonstrated that most of the single-plane cortical hypointensities represent sulcal spaces. The fact that small MRI lesions were not associated with qualitatively definite hypometabolism in two of our cases, however, suggests that conservative PET interpretation may generate false-negative results.)

Even mild lateral cranial malpositioning (lateral head tilt) during image acquisition is commonly associated with asymmetric hypointensities of temporal areas bilaterally on qualitative evaluation, as well as on quantitative analysis (*5*). Since such asymmetric bilateral temporal lobe hypointensities never occurred in our 241 epilepsy and 25 control studies that had symmetric cranial positioning during scanning, this suggests that lateral cranial malpositioning creates unacceptable imaging artifacts. The protocol excludes such studies from definitive interpretation. (Image realignment can be performed to correct for lateral cranial malpositioning, but image resolution declines for a re-sliced axial data set compared with the original data set acquired by tomographs that have better in-plane than axial resolution; we did not perform image realignment for this study because we intended to compare replicability of scan interpretation in tomographs of differing intrinsic resolution.) Mild lateral cranial malpositioning is often most clearly recognized by inspection of the basal ganglia, i.e., when noting that a basal ganglial region appears one plane superior to the most superior plane on which its contralateral homologue appears, and the contralateral homologue extends one plane below the most inferior plane on which the first basal ganglial region appears.

DISCUSSION

Our results strongly suggest that replicability of qualitative PET interpretation increases as tomographic perfor-

mance increases. Effective image resolution is determined by the intrinsic physical resolution of the tomograph, image statistics, object size and object contrast (*22,28,29*). Intrinsic tomographic resolution rose with successive generations of tomographs used in our study. Image statistics are determined in part by the dose and biophysical properties of the radiotracer and by the timing from radiotracer administration to initiation of image acquisition (all of which remained constant across our PET studies), and also by the efficiency of the tomographic system (which increased with each generation of tomograph used in our study) and duration of image acquisition. We cannot retrospectively measure object size in our epilepsy subjects using currently available magnetic resonance volumetry techniques (*31*).

We cannot directly measure object contrast in our patients because there is no method for in vivo determination of interregional glucose metabolic contrast which is independent of FDG PET. It is therefore possible that mean size and mean contrast of hypometabolic regions varied between the groups of patients studied with the three tomographs. We doubt that intergroup regional sizes and contrasts varied in any systematic fashion such that the current generation tomograph had a series of more easily detectable hypometabolic objects, because patient selection criteria and characteristics did not change across time and each group consisted of 50 or more patients. We required that regional hypointensity be noted on at least two adjacent image planes in order to be considered abnormal.

It is possible that this requirement favored detection of abnormality by the latest generation tomograph, which produced the most image planes per brain volume. However, we noted that failure to require adjacent multiplanar hypointensity as a criterion of abnormality would have decreased agreement and shared discrimination for studies performed with any of the three tomographs. Further, the availability of more image planes per object volume with the latest tomograph is itself a reflection of the greater axial resolution of this instrument. Thus, increased tomographic efficiency and intrinsic resolution are the likely explanations of the greater replicability of FDG PET interpretation in our most recently imaged patient group.

Our findings support the reliability of qualitative interpretation of interictal FDG PET for presurgical epilepsy evaluation or other purposes. Some experience in PET image evaluation, gained by reviewing studies of normal subjects, is required to recognize the heterogeneity of normal region-specific glucose metabolism. Replicability of qualitative interpretation was excellent for the current generation tomograph used in our study, though less impressive for older tomographs. This is important because most epilepsy surgery programs mandate clinical application only of unequivocal localizing findings with PET, MRI, ictal scalp-sphenoidal electroencephalographic-video monitoring and other techniques (*32,33*); when one interpreter observes a localizing finding that is not appreciated by another, this potential finding is usually disregarded. Thus, if a higher performance tomograph makes regional hypometabolism more clear, then this hypometabolism can become more useful for clinical application. Even with lower resolution tomographs, however, concordantly recognized regional hypometabolism is useful in presurgical evaluation (*34,35*). We also noted that the higher performance tomograph supported a high rate of concordance in detecting regional hypometabolism among patients whose high-quality cerebral MRI studies were normal.

CONCLUSIONS

Replicability of unbiased interpretations in detecting regional hypometabolism on interictal FDG PET studies was adequate for clinical application to presurgical evaluation of partial epilepsy, even in the absence of cerebral lesions detected by MRI. Replicability of interpretation was best for studies performed with a current generation tomograph and was somewhat poorer in detection of cortical and particularly of subcortical hypometabolism with lower performance tomographs.

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