

¹⁸FDG Positron Emission Computed Tomography in a Study of Aphasia

E. Jeffrey Metter, MD,*† Claude G. Wasterlain, MD,*† David E. Kuhl, MD,*
Wayne R. Hanson, PhD,† and Michael E. Phelps, PhD*

Positron emission computed tomography (PECT) using ¹⁸F-2-fluoro-2-deoxy-D-glucose (FDG) was used to investigate the correlations between clinical status, anatomy (as described by CT), and metabolism in five patients with stable aphasia resulting from ischemic cerebral infarction. Local cerebral metabolic activity was diminished in an area larger than the area of infarction demonstrated by CT. In one patient, FDG PECT revealed a metabolic lesion that probably caused the aphasic syndrome and was not apparent by CT. The data suggest that reliance on CT in delineating the extent of the brain lesion in aphasia or other neuropsychological defects can be misleading; FDG PECT may provide important additional information. Two patients with similar metabolic lesions had very different clinical syndromes, showing that even when currently available methods are combined, major gaps remain in clinicoanatomical correlations in aphasia.

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Recent developments allow clinical evaluation of the local cerebral metabolic rate for glucose (LCMRglc) using ¹⁸F-2-fluoro-2-deoxy-D-glucose (FDG) [8, 17, 30, 32, 33]. This method is derived from the autoradiographic technique devised by Sokoloff et al [39]. FDG is transported between blood and brain by the same carrier system as glucose. Once inside the cell, it is phosphorylated by hexokinase; but since FDG is a poor substrate for hexose isomerase, it cannot be transformed to fructose-6-phosphate and further metabolized. The FDG-6-phosphate is trapped within the cell, where its accumulation is proportional to the rate of glucose utilization. With the use of an isotopic label (radioactive ¹⁸F), the distribution of FDG can be quantified by positron emission computed tomography (PECT) to give maps of LCMRglc in humans.

PECT is a noninvasive scanning method using positron-emitting radionuclides [28, 29] and is similar to the emission computed tomographic technique developed previously for use with single-photon-emitting radionuclides [14, 15]. It produces quantitative cross-sectional images of brain radioactivity in humans following intravenous injection of a radioactively labeled compound. The LCMRglc method has been extended to humans [17, 32, 33], corrected for dephosphorylation of FDG-6-phosphate [8],

validated [30], and shown applicable to the study of patients with stroke and epilepsy [16, 18].

Since the metabolic rate for glucose has been directly correlated with neuronal firing rates [38] and with brain function [7, 18, 30, 31, 37], FDG PECT might add another dimension to the many recent studies correlating aphasic syndromes with anatomical localization as determined by computed tomography (CT) [11, 22, 26], pertechnetate brain scanning [2, 10, 12, 40], angiography [35], pathology [24], and regional cerebral blood flow [37]. We studied five stable aphasic patients by FDG PECT and CT to investigate the relationships between the clinical syndrome, CT, and LCMRglc.

Methods

Five patients were selected from the stroke rehabilitation unit at the VA Medical Center, Sepulveda, CA. In each case, aphasia had resulted from what appeared to be a single ischemic event, diagnosed clinically and by laboratory investigation including, where appropriate, lumbar puncture, electroencephalogram (EEG), and isotope brain scan. The interval between stroke and the study varied from six weeks to fourteen years, and the patients' clinical deficits were stable. Each patient was clinically evaluated by one of us (E. J. M.). Patient selection was based on availability, cooperativeness, and apparent expressive/receptive dichotomy. Testing consisted of a full neurological exam-

From the *UCLA School of Medicine, Los Angeles, CA 90024, and the †Veterans Administration Medical Center, Sepulveda, CA 91343.

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Address reprint requests to Dr Metter, Department of Neurology, Veterans Administration Medical Center, 16111 Plummer St, Sepulveda, CA 91343.

ination and the Boston Diagnostic Aphasia Examination (BDAE) [6]. Each patient also had a CT scan, with and without contrast, performed at 15 degrees to the canthomeatal line. Informed consent was obtained from the patient or family before the study.

Methods of radionuclide preparation, positron emission computed tomography (PECT), and data analysis are described in detail elsewhere [18, 30]. PECT was performed with the ECAT positron tomograph (ORTEC, Inc., Life Sciences, Oakridge, TN) [28, 29]. The spatial resolution employed was 1.7 cm in the image plane and 1.8 cm in the axial direction.

Five to 10 mCi of FDG was injected intravenously, and blood samples were obtained over time from a hand vein to determine FDG and glucose concentrations [30]. Six brain levels were scanned sequentially, parallel to the canthomeatal plane, from upper cerebellum to above the cerebral ventricles starting 40 minutes after injection. A normal scan is presented in Figure 1; it represents the radioactivity measured in each area (i.e., ^{18}F tissue concentrations). Calculation of local cerebral metabolic rate for glucose (LCMRglc), in milligrams per 100 mg of tissue per minute, required measurement of the time course of plasma ^{18}F activity, glucose concentration, and local ^{18}F tissue concentration. LCMRglc was calculated using the model of Huang, Phelps, and associates with the rate constants determined from normal young adults [8, 18, 30]. Regions of interest were selected on the tomograph display screen, local values of ^{18}F tissue concentration or LCMRglc were determined, and comparisons were made between selected zones and corresponding contralateral zones. The final value was expressed as percentage difference between the corresponding areas.

Areas of abnormality were determined from FDG and CT. These lesions were then plotted on templates prepared from the atlas of Matsui and Hirano [21]. The templates for CT utilized cross sections at 15 degrees to the canthomeatal line, while those for FDG were at zero degrees to the line. These templates represent our best estimate of lesion extent as determined from the original scans. For selected areas from the FDG tomographs, differences were calculated for LCMRglc.

Results

Patient 1

A 48-year-old man with a previous history of hypertension and adult-onset diabetes mellitus had sudden onset of right-handed weakness and aphasia. When studied six weeks later, he demonstrated mild right central facial weakness, mild weakness and incoordination of his right hand, normal sensation to pain, touch, vibration, and position, and mild astereognosis on the right. He had marked difficulty in following pictorially presented directions and in constructional tasks. He had no neglect, right-left disorientation, or finger agnosia. His hypertension was adequately controlled with a diuretic and clonidine. His diabetes was being treated by diet alone. An EEG demonstrated bifrontal intermittent delta activity, more prominent on the left, suggestive of a deep lesion. Per technetate brain scan, skull roentgenogram, electrocardiogram, and routine laboratory evaluation were normal.

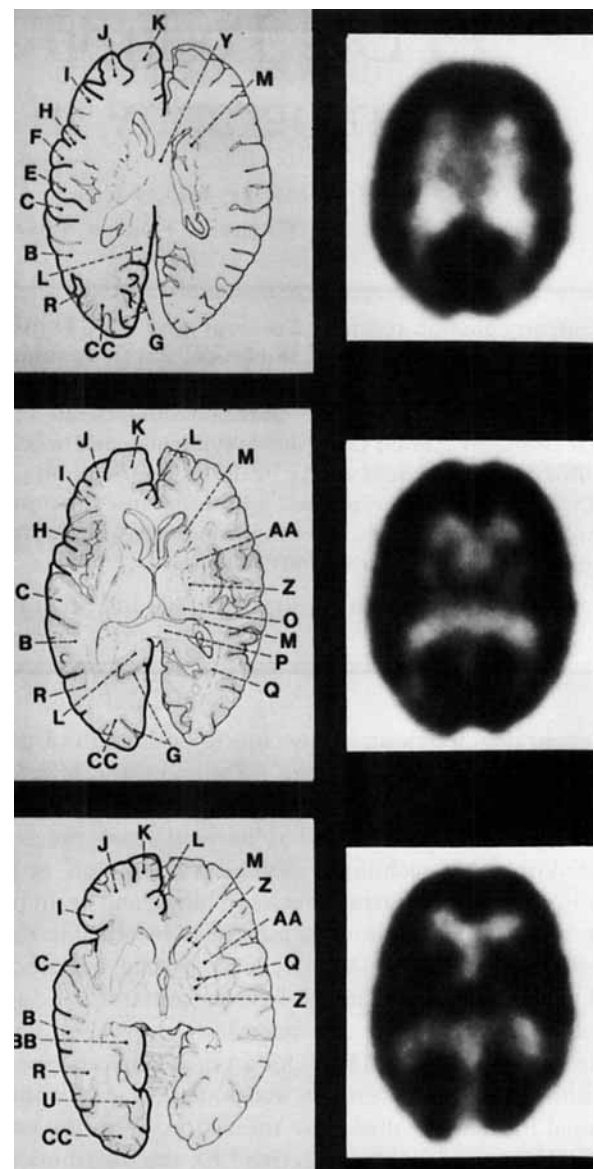


Fig 1. Normal FDG PECT. The scans were obtained at zero degrees to the canthomeatal line in a normal individual (as described under Methods) and depict tissue ^{18}F FDG concentrations. The templates on the left are traced drawings of zero-degree sections from Matsui and Hirano [21] with their labeling changed to letters. These templates were used for all FDG PECT. (Templates derived from Matsui T, Hirano A: *An Atlas of the Human Brain for Computerized Tomography*. Tokyo, Igaku-Shoin, 1978.)

For this and subsequent figures, structures are labeled as follows: A, lateral occipital gyrus; B, middle temporal gyrus; C, superior temporal gyrus; D, sylvian fissure; E, supramarginal gyrus; F, postcentral gyrus; G, calcarine sulcus; H, precentral gyrus; I, inferior frontal gyrus; J, middle frontal gyrus; K, superior frontal gyrus; L, cingulate gyrus; M, caudate nucleus; N, precuneus; O, thalamus; P, splenium; Q, globus pallidus; R, inferior temporal gyrus; S, angular gyrus; T, lingual gyrus; U, fusiform gyrus; V, pars opercularis; W, pars triangularis; X, cuneus; Y, body of corpus callosum; Z, internal capsule; AA, putamen; BB, hippocampal gyrus; CC, occipital lobe, DD, insula; EE, Ammon's horn.

Language evaluation demonstrated good comprehension of conversational speech and single words but difficulties in understanding complex messages and relational terms. Repetition of single words and phrases was good. Reading comprehension was good, but when reading aloud he would omit or substitute words. Writing was adequate for one-syllable words, but he misspelled more complex words. He spoke in sentences of adequate length and complexity but had word-finding difficulties, occasionally perseverated, and often omitted the ends of words. On the BDAE (Table), he had moderately severe aphasia but did not fit any specific pattern.

CT demonstrated two punctate areas of decreased density in the left caudate nucleus and possibly the left internal capsule, and one punctate area in the right caudate (Fig 2). The overlying cortex appeared normal. FDG PET (Fig 3) demonstrated a 24% decrease in LCMRglc in the left

Individual Scores on the Boston Diagnostic Aphasia Examination

Determination	Range	Patient No.				
		1	2	3	4	5
Severity rating	0-5	3	2	2	1	4
Articulatory rating	1-7	2	6	3	3	6
Phrase length	1-7	7	6	1	2	6
Verbal agility	0-14	7	6	9	6	11
Word discrimination	0-72	70	52	72	45	30
Body part identification	0-20	19	6	19	19	16
Commands	0-15	12	3	14	6	8
Complex material	0-12	8	1	6	5	6
Responsive naming	0-30	26	11	18	16	19
Confrontation naming	0-105	97	74	89	60	82
Animal naming	0-23	5	4	6	3	9
Body part naming	0-30	26	15	19	6	21
Word reading	0-30	30	20	23	27	30
Sentence reading	0-10	7	0	3	4	4
Repetition (words)	0-10	10	8	8	9	9
Repetition—high probability	0-8	7	0	2	6	5
Repetition—low probability	0-8	4	0	1	5	2
Neologisms	0-12	0	12	2	1	1
Literal paraphasias	0-16	1	3	3	16	2
Verbal paraphasias	0-24	3	2	17	1	8
Extended paraphasias	0-16	0	...	0	0	0
Reading—symbols	0-10	10	8	10	9	10
Word recognition	0-8	7	6	8	5	8
Comprehension of oral spelling	0-8	5	1	6	2	3
Word-picture matching	0-10	10	6	10	2	10
Reading sentences and paragraphs	0-10	7	2	7	3	6

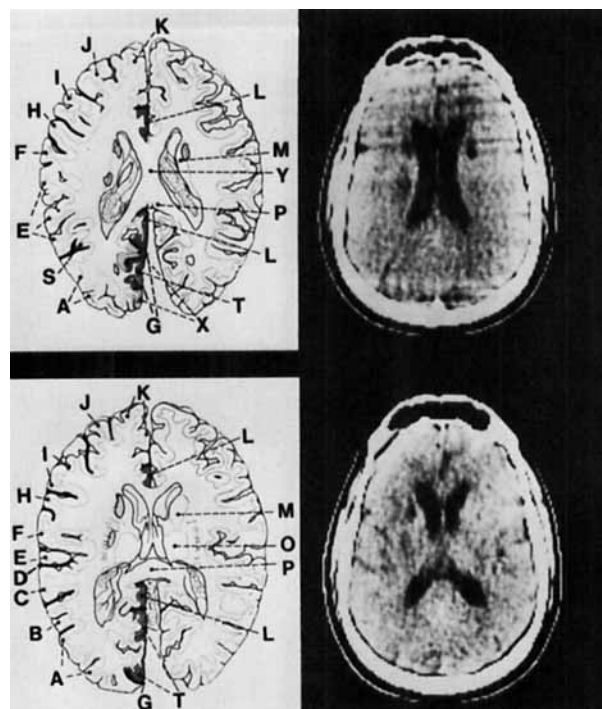


Fig 2. (Patient 1) CT demonstrates lucent areas in both internal capsules and the left caudate. All CT scans were obtained at 15 degrees to the canthomeatal line. The templates are directly from Matsui and Hirano [21] with labeling changed to letters as described in Figure 1. These templates will be used for all CT. (Templates derived from Matsui T, Hirano A: *An Atlas of the Human Brain for Computerized Tomography*. Tokyo, Igaku-Shoin, 1978.)

thalamus and major depression in the left striatum. In addition, there was a 15% decrease in the left middle and inferior temporal gyri.

COMMENTS. This patient demonstrated many of the characteristics of a thalamic aphasia, with anomia, perseveration, and sparing of comprehension. Thalamic lesions have been associated with several clinical presentations of aphasia [5, 19, 25, 34, 36]. Acutely, most of these patients demonstrate reduction of spontaneous speech, anomia, perseveration, trailing off of words, decreased voice volume, and paraphasias. Repetition is intact, and variable changes are noted in comprehension. This syndrome resolves over weeks to months, with improvement in spontaneous speech and frequently clearing of the entire syndrome. Thalamic aphasia has many features in common with transcortical [5] or anomic aphasia. Lesions in cortical gray or subcortical white matter are believed responsible for transcortical and anomic aphasias, while most reported cases of thalamic aphasia have been secondary to hemorrhagic thalamic lesions with no evidence of cortical involvement [5, 11, 25, 34, 36].

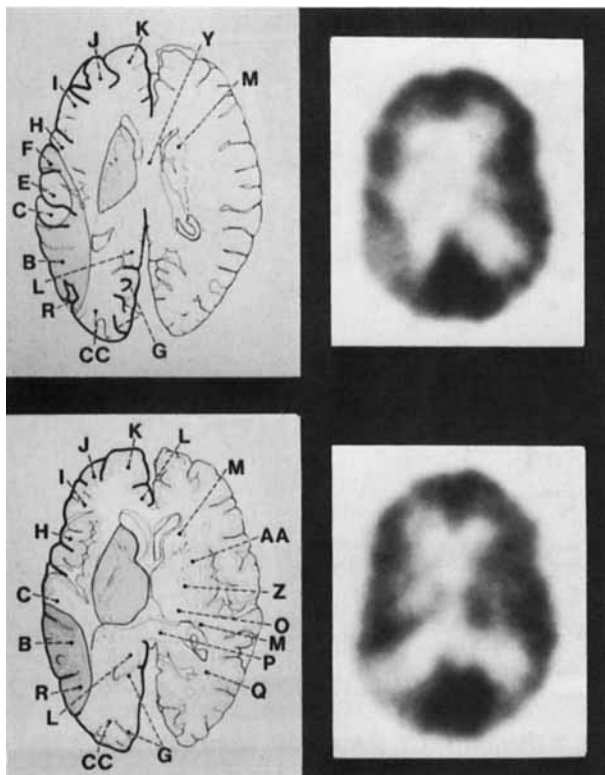


Fig 3. (Patient 1) FDG PET shows areas of decreased FDG concentration in the left thalamus and left temporal lobe, particularly the middle and inferior temporal gyri.

Our patient demonstrated the features of a thalamic aphasia except for the expected reduction of spontaneous speech and decreased voice volume. This difference may be due to the more limited extent of the lesion than usually occurs in hemorrhage. The more prominent metabolic suppression in the thalamus and striatum as compared to cortex suggested that these deeper regions were the site of the primary lesion. While an independent cortical lesion cannot be ruled out, we suggest that the decrease in cortical metabolic rate may be secondary and may indicate a relationship between these subcortical and cortical areas in the genesis of thalamic aphasia. This is consistent with the suggestion of Cappa and Vignolo [5] that "the linguistic role of the thalamus is related to that of the marginal language areas" rather than the "central language zones," which are perisylvian in location.

Patient 2

A 57-year-old, right-handed, bilingual Mexican-American man had sudden onset of right hemiparesis and aphasia. He was competent in English, had been educated in the United States, and before his illness worked as an engineer. Past medical history included hypertension, gout, and medullary sponge kidney. Examination ten months after onset demonstrated an incomplete right homonymous hemian-

opia, right central facial weakness, minimal drift of his right hand, hyperactive reflexes on the right with no Babinski sign, a mild right hemisensory loss, and normal blood pressure.

Language evaluation in English demonstrated difficulty in understanding more than simple spoken statements and simple conversation. He was able to carry out one-part instructions but was unable to follow more complex ones. He could read single letters and match printed words to pictures but was unable to follow written directions. He was unable to write words except by copying. He spoke English fluently in complete, complex sentences; however, much of the speech lacked content and meaning. Paraphasia was only occasionally noted and there were few, if any, neologisms. Word-finding difficulties were frequent. He was able to ask and answer simple questions and could carry on a limited conversation. He had an orofacial apraxia and early in his course was unable to repeat syllables or words modeled for him. The BDAE (Table) demonstrated a pattern consistent with severe Wernicke's aphasia. The patient was noted to have similar problems in Spanish.

CT showed a large perisylvian infarction involving much of the territory of the middle cerebral artery (Fig 4). The precentral gyrus appeared to be partially spared, while damage was present in the pars triangularis, Broca's area, the temporal and parietal areas, and the underlying white matter. Higher and lower sections showed damage to most of the parietal and much of the middle and inferior temporal gyri. FDG PET demonstrated a 79% reduction in LCMRglc in the left parietal and posterior temporal regions (Fig 5). At the level of Broca's area the frontal lobes showed 65% reduction of LCMRglc. At levels higher than the pars triangularis the frontal lobe appeared normal. Depression of FDG was noted also in the left occipital area and basal ganglia. The left thalamus showed 44% reduction in LCMRglc but appeared intact by CT.

COMMENTS. Based on the extensive structural and metabolic changes throughout the major language areas, including Broca's, this patient would be expected to have a mixed aphasia with marked expressive difficulties, yet his speech was fluent. His fluency might be explained by preservation of function in the island of tissue in the vicinity of the precentral gyrus noted on CT and FDG PET, but one wonders how this area could be connected to other cortical regions since it appears to be entirely surrounded by infarcted tissue. Alternatively, fluency could be based on altered cortical organization, with greater right hemisphere involvement, related to his bilinguality [1].

Decreased metabolic activity was present in the basal ganglia and thalamus (intact by CT), reflecting either reduction in the activity of thalamocortical circuits or retrograde degeneration of thalamic neurons. Cortical areas adjacent to the infarction also demonstrated some depression of LCMRglc, suggesting loss of corticocortical interactions.

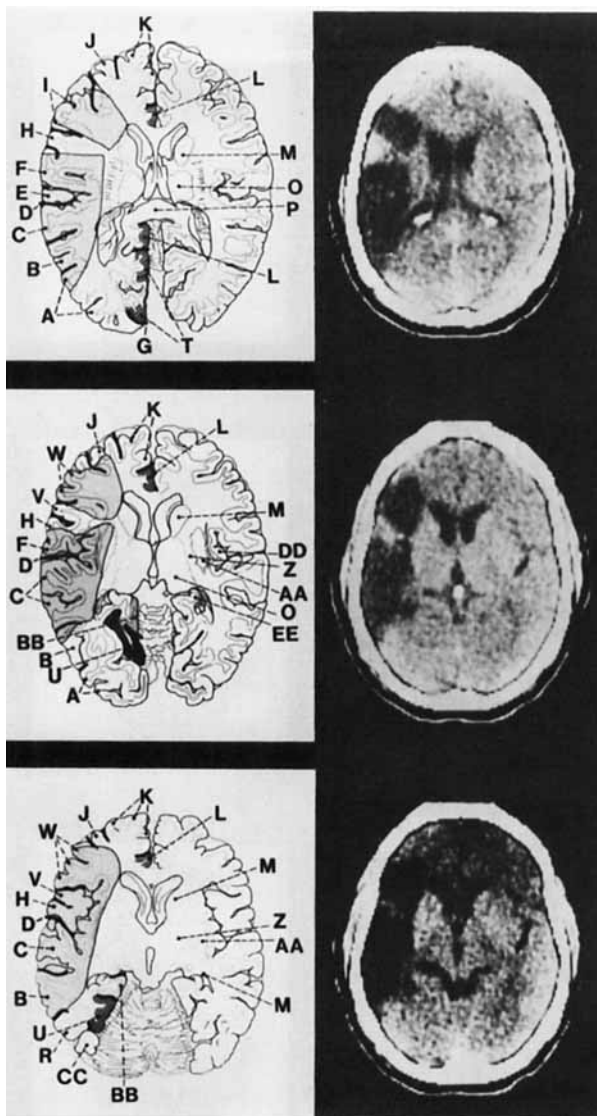


Fig 4. (Patient 2) CT demonstrates a large left perisylvian infarct. The bifrontal hypodensity noted on the lowest scan is artifactual. (Templates derived from Matsui T, Hirano A: *An Atlas of the Human Brain for Computerized Tomography*, Tokyo, Igaku-Shoin, 1978.)

Patient 3

A 61-year-old, right-handed man with a history of rheumatic heart disease and mitral stenosis had sudden onset of a right hemiplegia and aphasia in 1964. At the time of examination in 1978 he had a spastic right hemiplegia, increased stretch reflexes, Babinski sign, and decreased sensation to pain, touch, position, and vibration on the right. He walked with a cane and was independent in activities of daily living.

Language evaluation demonstrated mild impairment in auditory comprehension. Reading and writing were moderately impaired. His speech was nonfluent and telegraphic and was characterized by word-finding difficulties, paraphasias, and moderate orofacial apraxia. The BDAE (Table) demonstrated Broca's aphasia of marked severity.

CT (Fig 6) showed a large area of decreased density in-

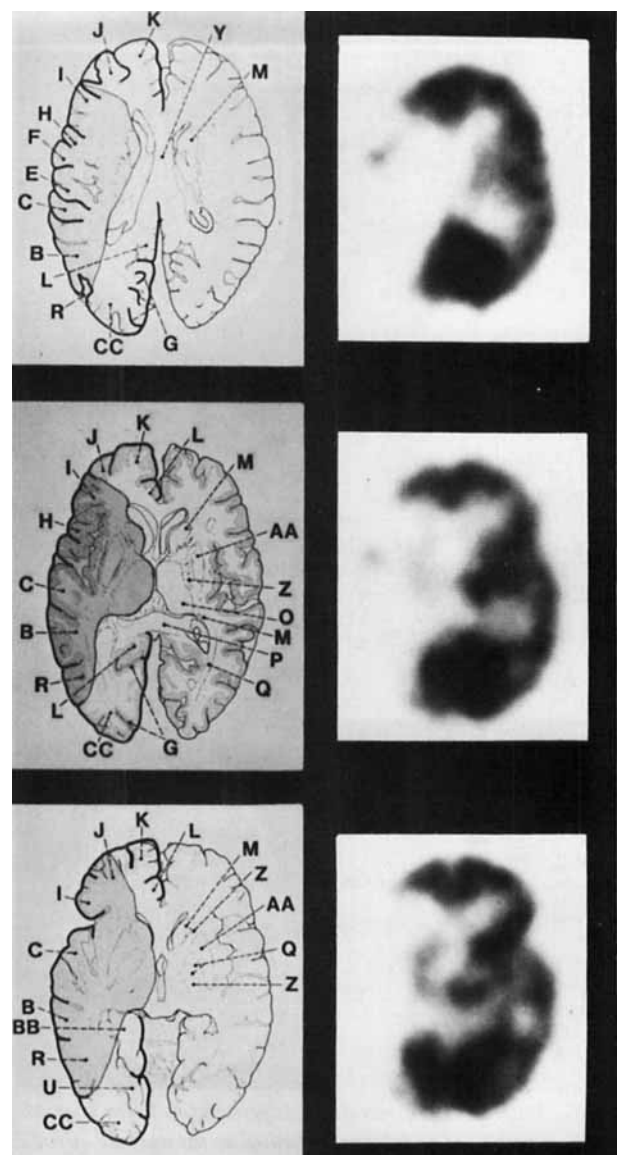


Fig 5. (Patient 2) FDG PECT demonstrates extensive decrease in FDG concentration in much of the left hemisphere, including major subcortical structures.

volving the left temporal, parietal, and frontal regions and the basal ganglia. The involvement in the temporal lobes seemed to spare much of the middle and inferior temporal gyri, while extensive damage to the inferior parietal lobule extended through all higher sections (not shown). The frontal involvement included much of the posterior aspect of the inferior frontal gyrus but spared the middle and superior frontal gyri. FDG PECT (Fig 7) correlated well with CT, showing 73% reduction of LCMRglc in the frontotemporal area. Decreased LCMRglc was noted in the left thalamus (63% reduction), where no structural lesion was observed by CT.

COMMENTS. CT and FDG PECT demonstrated a large lesion in the left perisylvian area. Given the extent of cortical damage, it is surprising that this pa-

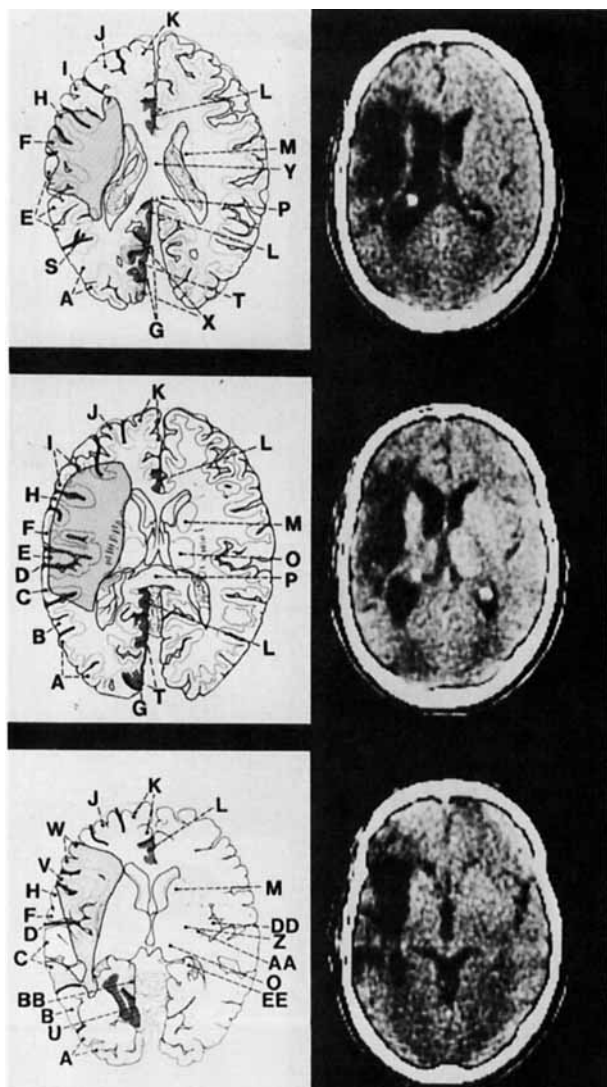


Fig 6. (Patient 3) CT reveals a left perisylvian lesion that is not as extensive or as posteriorly located as the one in Patient 2. There appears to be a relatively preserved cortical strip in the middle and lower figures. (Templates derived from Matsui T, Hirano A: *An Atlas of the Human Brain for Computerized Tomography*. Tokyo, Igaku-Shoin, 1978.)

tient had only mild impairment in auditory comprehension. This patient's CT and FDG scans showed lesions similar to those of Patient 2, yet the two men presented very different abnormalities of language and speech, one with Wernicke's and one with Broca's aphasia. The major difference on CT and FDG PECT between the patients was sparing of the middle and inferior temporal gyri in Patient 3. Whether these two gyri are part of Wernicke's area is unclear [4], but they are generally considered to be a secondary language area.

Patient 4

A 71-year-old, right-handed man experienced sudden onset of right hemiparesis and aphasia in 1973. He had a

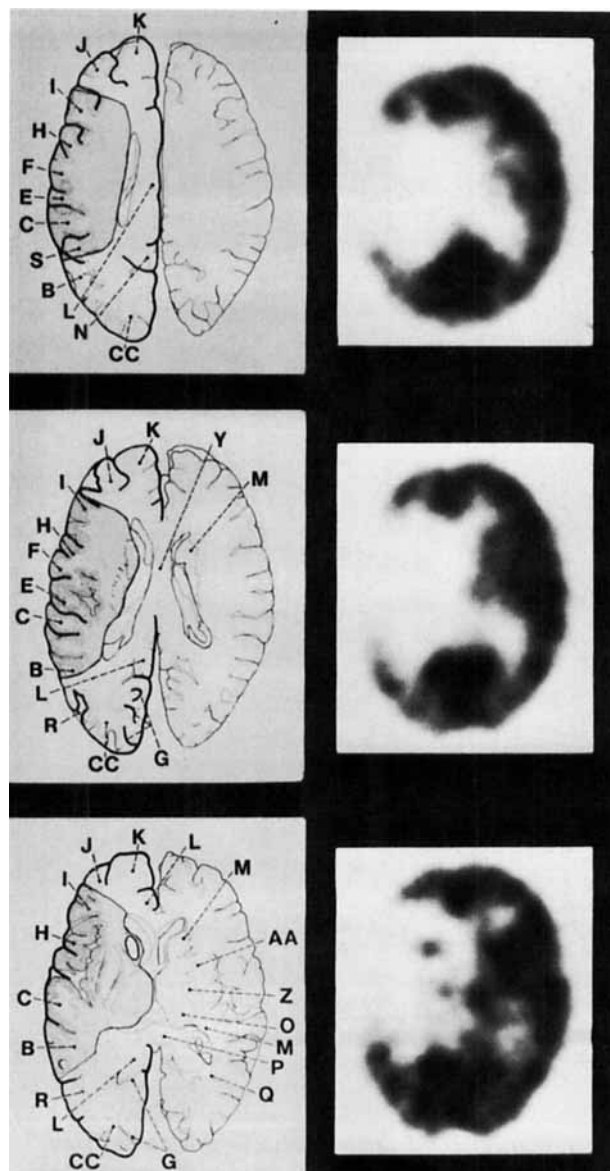


Fig 7. (Patient 3) FDG PECT shows severe metabolic depression in the left temporal and parietal regions extending beyond the area of structural damage noted in Figure 6. Marked depression is noted in the relatively preserved cortical rim.

history of prior myocardial infarction. Since the stroke, he suffered occasional generalized seizures for which he took phenytoin. Examination at the time of this study in 1978 demonstrated an incomplete right homonymous hemianopia, right central facial weakness, spastic right hemiparesis with minimal voluntary movement, hyperactive reflexes on the right with a right Babinski sign, decreased sensation to pain, touch, and stereognosis on the right, and orofacial apraxia. In addition, he had paratonic resistance on the left and incoordination of the left leg. He was mildly to moderately demented and had severe memory dysfunction in addition to his language problem.

Language evaluation demonstrated moderate impairment in auditory comprehension. Naming, repetition, and reading comprehension were poor, and he was unable to

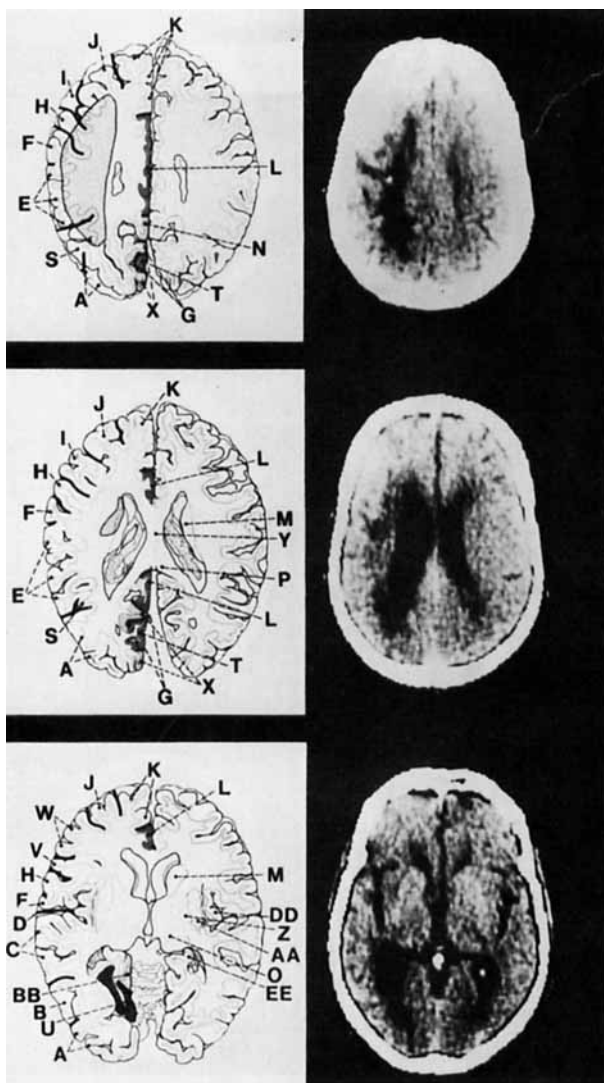


Fig 8. (Patient 4) CT shows no structural abnormalities in either Wernicke's or Broca's areas but a subcortical lesion at levels higher than the lateral ventricles. Dilatation is prominent in the left lateral ventricle. (Templates derived from Matsui T, Hirano A: *An Atlas of the Human Brain for Computerized Tomography*. Tokyo, Igaku-Shoin, 1978.)

write. He could not protrude his tongue voluntarily or repeat vowels. His speech was agrammatical and telegraphic. He spoke in one- and two-word phrases. The BDAE (Table) demonstrated severe aphasia that included all the features of a Broca's aphasia plus some deficit in auditory comprehension.

CT (Fig 8) showed an enlarged left ventricular system and a region of decreased density high in the left parietooccipital area (mainly above the level of the ventricles) extending into the left thalamus. Broca's and Wernicke's areas appeared intact. FDG PECT (Fig 9) demonstrated more extensive abnormalities than CT had shown. A 47% reduction of LCMRglc was noted in the entire cortex of the left hemisphere at all levels higher than the lateral ventricles. Reduced FDG concentration was also seen in the posterior temporal lobe (involving the superior, mid-

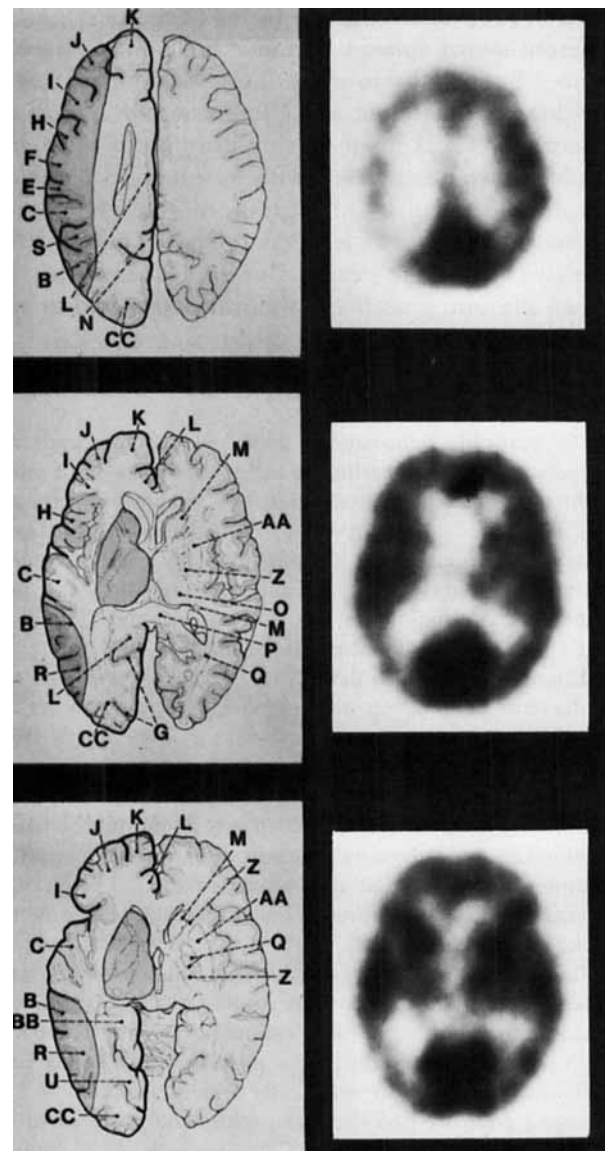


Fig 9. (Patient 4) FDG PET demonstrates an extensive decrease in FDG concentration at levels above the left lateral ventricles. Metabolic depression is also present in the thalamus and posterior temporal region, where no lesion was visible on CT (see Fig 8).

dle, and inferior gyri), the left thalamus, the supramarginal gyrus, the angular gyrus, and possibly Wernicke's area.

COMMENTS. This patient showed all the features of Broca's aphasia plus poor auditory comprehension. Based on the deficit in comprehension, he was classified as a mixed aphasic. The most impressive aspect of this patient's clinical syndrome was his severe expressive difficulties, yet there was no evidence of damage to Broca's area on CT or FDG PET. Mohr et al [24] have argued that a large perisylvian lesion, which includes damage to Broca's area but extends beyond it, is required for Broca's aphasia. Luria and

Hutton [20] described two forms of motor aphasia: efferent motor aphasia, a kinetic breakdown characterized by inability to make the transition from one articuleme to another; and afferent motor aphasia, a kinesthetic breakdown causing inability to form articulemes and associated with an orofacial apraxia. According to Luria and Hutton, this "afferent syndrome" results from a lesion in the postcentral gyrus. Perhaps our patient's expressive difficulties are based on an afferent, kinesthetic abnormality related to his parietal lobe damage.

Patient 5

A 57-year-old, right-handed man had sudden onset of aphasia. One month earlier he had had an episode of mild right-sided weakness, dysarthria, and swallowing difficulties that lasted less than a day. Past medical history was otherwise unremarkable. Examination demonstrated a mild drift of the right upper extremity. The remainder of his neurological examination was normal, including stereognosis, graphesthesia, and tactile localization.

Language evaluation demonstrated that he was able to understand simple, but not complex, directions and conversation. Repetition was poor even for single words. He was incapable of reading sentences but could match printed words to pictures. He was able to write only a few letters to dictation. His spontaneous speech was fluent, but he used neologisms and jargon in syntactically and grammatically complete sentences that gave no information. The BDAE results (Table) can be interpreted as showing severe Wernicke's aphasia.

CT demonstrated an area of decreased density on the left side involving the superior and middle temporal, angular, and supramarginal gyri and extending deep to involve periventricular structures by the posterior horn of the lateral ventricle. The left ventricular system appeared to be enlarged compared to the right, with mild posterior displacement (Fig 10). FDG PET demonstrated more extensive metabolic damage (Fig 11). In areas where the CT showed destructive lesions there was a 67% reduction of LCMRglc. In addition, a mild reduction of FDG concentration was seen in the left basal ganglia and a 15% reduction of LCMRglc in the left thalamus.

COMMENTS. The clinical syndrome in this patient correlated well with CT and FDG PET. He had Wernicke's aphasia with a major structural defect in Wernicke's area. The metabolic abnormality, as measured by FDG PET, involved a larger area of brain than the abnormalities in tissue x-ray density noted on CT. It is not known whether the ventricular enlargement on CT reflected more diffuse loss of hemispherical brain substance. Several studies have noted similar ventricular enlargement following cerebral infarction [9, 13, 25]. In the late stages following infarction, dilation of the ipsilateral ventricular system may occur with displacement toward the infarction [9, 25]. These observations do

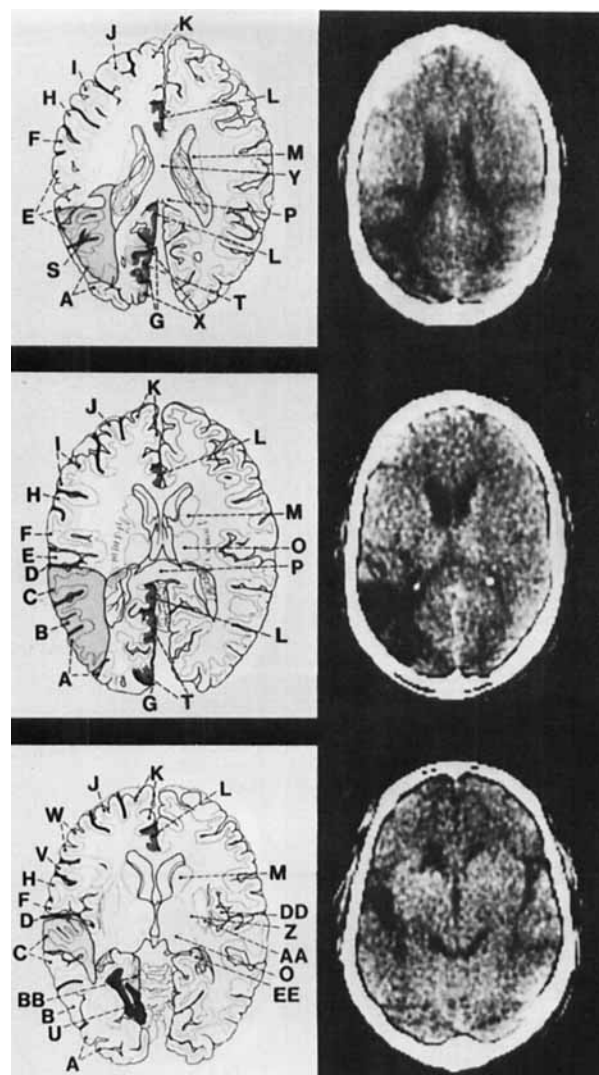


Fig 10. (Patient 5) CT demonstrates a left temporal and parietal lesion with extensive damage to Wernicke's area. There is some dilatation of the left ventricular system. (Templates derived from Matsui T, Hirano A: *An Atlas of the Human Brain for Computerized Tomography*. Tokyo, Igaku-Shoin, 1978.)

not eliminate the possibility of more diffuse damage, but they demonstrate that such an explanation is not necessary in our patient.

Discussion

At present there are limitations in the use and interpretation of FDG PET. First, the determination of LCMRglc with FDG is based on an operational equation of a model of the biochemical behavior of glucose and deoxyglucose in brain. The equation is dependent on empirically derived rate constants and a lumped constant. Those used in this study were measured from normal young adults. LCMRglc has been found to be quite insensitive to severalfold changes in rate constants when determinations are

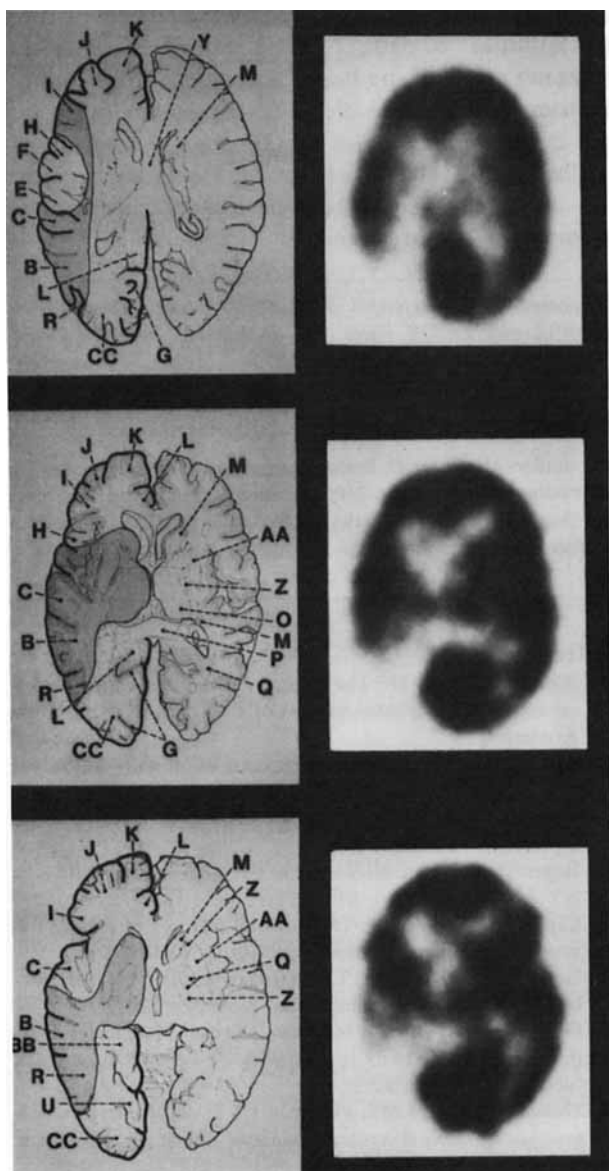


Fig 11. (Patient 5) FDG PECT demonstrates depression of FDG concentration throughout the left temporal lobe and possibly in parts of the inferior frontal lobe. The middle figure exemplifies some of the problems in localization that result from limitations in photographic reproduction. The lesion outlined on the template encompasses the area of decreased FDG concentration observed on the original scan, which is produced on x-ray film. After printing, the decrease in FDG concentration is no longer visible in some temporal and posterior frontal areas.

made in a near steady state, as was done in our patients [8, 36]. With pathological states, large changes may occur in the constants and lead to errors in calculated LCMRglc. Hawkins et al (in preparation) have estimated the rate and lumped constants for infarcted brain tissue following thromboembolism. Major differences were found in the rate constants, while the lumped constant was unaffected in patho-

logical tissue. A 20 to 40% difference in the estimate of LCMRglc can occur when these constants are compared to those from normal young adults. The normal constants tend to overestimate the degree of depression, particularly in areas of very low LCMRglc. These errors in calculated LCMRglc are important to keep in mind but do not detract from the use of tissue ^{18}F concentration as an index of glucose metabolism.

A second limitation to the FDG PECT method is that normative data for LCMRglc are currently available only for young adults. This makes it difficult to compare our patients to a normal population. For this reason, emphasis has been placed on right-left differences, and no inferences have been drawn with regard to the activity of the noninfarcted hemisphere. Third, the spatial resolution of the positron tomographs was less than that obtained with CT, making delineation less precise for anatomical structure. The hatched areas of the templates are estimates of lesion extent conservatively drawn from the original scans, explaining the minor discrepancies between the illustrated scans and templates.

Despite these limitations, our study demonstrates that FDG PECT can reveal the location of lesions not detected by other methods and provides an improved assessment of the degree and extent of the metabolic deficit in aphasia. This was most evident in Patient 1, whose metabolic scan revealed the location of a lesion that was not observed by CT and that explained the clinical picture. In this case, had the study been done with CT alone, the caudate lesions might have been interpreted as causing the aphasia while the metabolic suppression in the thalamus went undetected.

The metabolic abnormalities demonstrated by PECT were more extensive than the CT evidence of structural damage in all five patients. The finding of suppression of metabolism in noninfarcted brain is consistent with xenon 133 studies of regional cerebral blood flow, which have shown reduced flow throughout the involved hemisphere both acutely and chronically following ischemic stroke [23], and with the observations of Kuhl et al [18], who found extensive cortical, striatal, and thalamic hypometabolism in stroke patients by FDG PECT in the absence of any CT abnormality. Reduced cerebral metabolism in noninfarcted tissue suggests cortical suppression or deactivation, which may be secondary to a functional decrease in metabolic activity of intact cells, to neuron loss, to undercutting of cortical fiber tracts with wallerian degeneration, or to persistent ischemia [18].

These metabolic data add a new dimension to the study of anatomicoclinical correlations in aphasia. Infarcted tissue may have widespread effects on

structurally intact tissue, as demonstrated by decreased LCMRglc in areas synaptically connected to the damaged area. These metabolic changes may have functional importance. For example, the decreased LCMRglc in the thalamus in patients whose primary lesion appears cortical, and the reduced cortical activity in Patient 1, whose primary lesion appears thalamic, suggest that thalamocortical circuits have functional importance in language. Admittedly, the small number of patients and lack of pathological correlation make it impossible to exclude multiple lesions accounting for these changes. However, the consistency of the thalamocortical metabolic interaction suggests a true relationship, since none of our patients showed normal LCMRglc in the left thalamus when the cortex was extensively damaged and since the involved cortical areas and thalamus have a different vascular supply. Whether these thalamocortical connections are involved in language storage, retrieval, and conception or in some of the motor or sensory feedback circuits can be determined only by further studies.

Our findings also suggest a possible relationship between the left thalamus and posterior portions of the middle and inferior temporal gyri in aphasia. Each of our patients demonstrated abnormalities in LCMRglc in these areas, with no other cortical areas being consistently involved. In Patients 2 through 5 the reduction of LCMRglc was less in thalamic than in cortical areas, suggesting that the thalamic changes were secondary to cortical alterations.

In this study, clinicopathological correlations were made in aphasia by classifying patients using the BDAE, which allows for separation of aphasias in a classification using traditional anatomical considerations. The assumption is that particular patterns of language involvement are associated with damage to specific cortical structures [3]. Patients 1 and 5 demonstrate the success of this approach in some patients. In Patient 1, metabolic suppression was noted in the middle and inferior temporal lobes, areas considered to be responsible for some cases of anomic aphasia. Patients 2, 3, and 4 demonstrate limitations in our current understanding of the pathological anatomy of aphasia. Each showed large lesions with extensive suppression of LCMRglc, yet their clinical syndromes could not be predicted from the anatomical or metabolic abnormalities. Other factors that could affect the clinicoanatomical correlation include bilinguality, dementia, and recovery.

Our investigation suggests that one reason for the failure of clinicoanatomical correlations may be technical, i.e., the result of limitations in present methods. For example, Patient 1 failed to show clinicoanatomical correlation on CT, but FDG PECT resulted in excellent correlation, accurately showing

the lesion at the site predicted by the clinical picture. In addition to structural anatomy, a chemical anatomy exists in the brain. At present this chemical anatomy is not accessible to imaging techniques, and the current precision of PECT does not permit visualization of small structures. If the latter becomes possible, improved correlation may provide a more accurate theory of language.

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References

1. Albert ML, Obler LK: The Bilingual Brain: Neuropsychological and Neurolinguistic Aspects of Bilingualism. New York, Academic, 1978
2. Benson DF: Fluency in aphasia: correlation with radioactive scan localization. *Cortex* 3:373-394, 1967
3. Benson DF: Aphasia, Alexia, Agraphia. New York, Churchill/Livingstone, 1979
4. Bogen JE, Bogen GM: Wernicke's region—where is it? *Ann NY Acad Sci* 280:834-843, 1976
5. Cappa SF, Vignolo LA: Transcortical features of aphasia following left thalamic hemorrhage. *Cortex* 15:121-130, 1979
6. Goodglass H, Kaplan E: The Assessment of Aphasia and Related Disorders. Philadelphia, Lea & Febiger, 1972
7. Greenberg JH, Reivich M, Alavi A, et al: Mapping of functional neuronal activity in man with ^{18}F -fluorodeoxyglucose. *Neurology* 29:545, 1979
8. Huang SC, Phelps ME, Hoffman EJ, et al: Noninvasive determination of local cerebral metabolic rate of glucose in man. *Am J Physiol* 238 (Endocrinol Metab 1):E69-E82, 1980
9. Huk W, Schiefer W: Computerized tomography (Siretom) of acute cerebrovascular events. In Lanksch W, Kazner E (eds): *Cranial Computerized Tomography*. New York, Springer-Verlag, 1976, pp 264-272
10. Karis R, Horenstein S: Localization of speech parameters by brain scan. *Neurology (Minneapolis)* 26:226-230, 1976
11. Kertesz A, Harlock W, Coates R: Computer tomographic localization, lesion size and prognosis in aphasia and nonverbal impairment. *Brain Lang* 8:34-50, 1979
12. Kertesz A, Lesk D, McCabe P: Isotope localization of infarcts in aphasia. *Arch Neurol* 34:590-601, 1977
13. Kinkel WR, Jacobs L: Computerized axial transverse tomography in cerebrovascular disease. *Neurology (Minneapolis)* 26:924-930, 1976
14. Kuhl DE, Edwards RQ: Image separation radioisotope scanning. *Radiology* 80:653-662, 1963
15. Kuhl DE, Edwards RQ, Ricci AR, et al: Quantitative section scanning using orthogonal tangent correction. *J Nucl Med* 14:196-200, 1973
16. Kuhl DE, Engel J Jr, Phelps ME, Selin C: Epileptic patterns of local cerebral metabolism and perfusion in humans determined by emission computed tomography of ^{18}F FDG and $^{13}\text{NH}_3$. *Ann Neurol* 8:348-360, 1980

17. Kuhl DE, Hoffman EJ, Phelps ME, et al: Design and application of the Mark IV scanning system for radionuclide tomography of the brain. In *Medical Radionuclide Imaging: Proceedings of the International Atomic Energy Agency Symposium on Medical Radionuclide Imaging*, Los Angeles, CA, Oct 25–29, 1976. Vienna, IAEA, 1977, vol 1, pp 309–320
18. Kuhl DE, Phelps ME, Kowell AP, et al: Effects of stroke on local cerebral metabolism and perfusion: mapping by emission computed tomography of ^{18}F FDG and ^{13}N H $_3$. *Ann Neurol* 8:47–60, 1980
19. LoVerme SR, Alexander M: Language and neurobehavioral deficits following thalamic and putaminal hemorrhages of the left hemisphere. *Neurology* 29:599, 1979
20. Luria AR, Hutton JT: A modern assessment of the basic forms of aphasia. *Brain Lang* 4:129–151, 1977
21. Matsui T, Hirano A: *An Atlas of the Human Brain for Computerized Tomography*. Tokyo, Igaku-Shoin, 1978
22. Mazzocchi F, Vignolo LA: Localization of lesions in aphasia: clinical–CT scan correlation in stroke patients. *Cortex* 15:627–653, 1979
23. Meyer JS, Kanda T, Fucuchi Y, et al: Clinical prognosis correlated with hemispheric blood flow in cerebral infarction. *Stroke* 2:383–394, 1971
24. Mohr JP, Pessin MS, Finkelstein S, et al: Broca aphasia: pathological and clinical. *Neurology* 28:311–324, 1978
25. Mohr JP, Watters WC, Duncan GW: Thalamic hemorrhage and aphasia. *Brain Lang* 2:3–17, 1975
26. Naeser MA, Hayward RW: Lesion localization in aphasia with cranial computed tomography and the Boston Diagnostic Aphasia Exam. *Neurology* 28:545–551, 1978
27. New PFJ, Scott WR: *Computed Tomography of the Brain and Orbit (EMI Scanning)*. Baltimore, Williams & Wilkins, 1975, pp 332–361
28. Phelps ME, Hoffman EJ, Huang SC, et al: ECAT: A new computerized tomographic imaging system for positron-emitting radiopharmaceuticals. *J Nucl Med* 19:635–647, 1978
29. Phelps ME, Hoffman EJ, Mullani NA, et al: Application of annihilation coincidence detection to transaxial reconstruction tomography. *J Nucl Med* 16:210–224, 1975
30. Phelps ME, Huang SC, Hoffman EJ, et al: Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18)2-fluoro-2-deoxy-D-glucose: validation of method. *Ann Neurol* 6:371–388, 1979
31. Phelps ME, Kuhl DE, Mazziotta JC: Metabolic mapping of the brain's response to visual stimulation: studies in man. *Science* 211:1445–1448, 1981
32. Reivich M, Kuhl DE, Wolf A, et al: Measurement of local cerebral glucose metabolism in man with 18-F-2-deoxy-D-glucose. In Ingvar DH, Lassen N (eds): *Cerebral Function, Metabolism and Circulation (A CBF symposium in Copenhagen, Denmark, June 1977)*. *Acta Neurol Scand* 56 [Suppl 64]: 190–191, 1977
33. Reivich M, Kuhl DE, Wolf A, et al: The ^{18}F -fluoro-deoxyglucose method for the measurement of local cerebral glucose utilization in man. *Circ Res* 44:127–137, 1979
34. Reynolds AF, Turner PT, Harris AB, et al: Left thalamic hemorrhage with dysphasia: a report of five cases. *Brain Lang* 7:62–73, 1979
35. Rosenfield DB, Goree JA: Angiographic localization of infarcts in aphasia. *Arch Neurol* 34:590–601, 1977
36. Samarel A, Wright TL, Sergay S, et al: Thalamic hemorrhage with speech disorder. *Trans Am Neurol Assoc* 101:283–285, 1976
37. Soh K, Larsen B, Shinhøj E, et al: Regional cerebral blood flow in aphasia. *Arch Neurol* 35:625–632, 1978
38. Sokoloff L: Relationship between functional activity and energy metabolism in the CNS. *Trans Am Soc Neurochem* 11:171, 1980
39. Sokoloff L, Reivich M, Kennedy C, et al: The ^{14}C deoxyglucose utilization: theory, procedure and normal values in conscious and anesthetized albino rat. *J Neurochem* 28:897–916, 1977
40. Verkas M, Schoutens A, Demol D, et al: Study in cerebrovascular disease: brain scanning with technetium 99m pertechnetate; clinical correlation. *Neurology (Minneapolis)* 25:553–558, 1975