The Use of (F18)-Fluorodeoxyglucose Positron Computed Tomography in the Study of Aphasia

E. Jeffrey Metter and Walter H. Riege
Veterans Administration Medical Center, Sepulveda, California and UCLA School of Medicine

Wayne R. Hanson
Veterans Administration Medical Center, Sepulveda, California

David E. Kuhl and Michael E. Phelps
UCLA School of Medicine

ABSTRACT

(18f)-Fluorodeoxyglucose positron computed tomography in the study of aphasia has demonstrated metabloic changes in the brain extending beyond the region of structural damage as presented by x-ray CAT. Metabolic correlations with language subtests were to more posterior-inferior temporal, inferior parietal, Broca's and caudate regions, which may reflect a shift of language function from perisylvian regions. Further examination of the data in relation to the caudate, suggested that this structure was of particular importance in low level tasks, and appeared to involve the ability of Broca's and inferior frontal regions to interact with other brain areas. Studies from normal subjects have suggested the presence of a second metabolic system involving superior frontal, inferior parietal, and occipital regions which may be important in recognition and decision.

Traditional approaches to the pathoanatomy of aphasia have studied structural brain changes and have assumed that damaged regions were responsible for the language disturbances, ignoring changes which might occur in brain regions without apparent damage. Positron computed tomography (PCT), and the modelling of glucose metabolism using (F18)-fluorodeoxyglucose (FDG) have provided a technique for the study of brain function as indicated by local cerebral metabolic rates of glucose (LCMRGlc). This report will review findings with this technique which reflect on aphasia, by comparing studies in aphasia with findings in normal subjects, and in patients with Huntington's or Parkinson's Disease. Together these observations allow for insight into the role of the basal ganglia, and into the relationships of cortical structures in brain function, particularly how they relate to language processing.

METHOD

Patients. Eleven aphasic patients (Table 1) had FDG PCT, and were administered the Boston Diagnostic Aphasia Examination (BDAE) (1), and the Porch Index of Communicative Ability (PICA) (2). Ten were aphasic from a stroke (either thromboembolic or hemmorrhage), and one was posttraumatic. Three had aphasias secondary to subcortical lesions. All could be classified into major aphasic syndromes, except for two who had mixed patterns. Language data for each patient were handled by reducing the BDAE Z-score profile to eleven language characteristics by calculating means of subtests within each language characteristic (Table 2). The PICA mean subtest scores were reduced to five factors which underly the PICA. These factors (Table 3) were derived from a factor analysis of PICA scores of 118 aphasic subjects (3).

In addition we have studied 12 Huntington's Disease (HD) patients (8 men and 5 women) between the ages of 17 and 62, with a mean of 42 years. All had family histories of HD and typical symptoms. The duration was between 1 and 15 years. Chorea was present in all. Dementia was present in all but two. Seven patients with Parkinson's Disease (PD) were studied (6 men and 1 woman) between the ages of 50 and 73 years, with an average age of 62 years. All PD were being treated with Sinemet. Their severity varied from mild to severe disability on treatment. Prominent bradykinesia was present in all cases, while only one showed mild dementia. We also studied eight patients with Alzheimer's Disease (AD) ages 60 to 83 with a mean age of 69. These subjects had from moderate to severe dementias. Thirty-one control subjects were studied whose ages ranged from 27-78 years. In one study, they were considered as a single group independent of age. When used as a control for the HD, PD, and AD, they were divided into two groups: 14 individuals from 27-50 were controls for the HD, and 17 individuals aged 51-78 were the controls for the PD and AD patients.

X-ray Computed Tomography (CAT). Each aphasic patient had CAT which was evaluated with a five point scale spanning the range of findings in cerebral infarction: 0 = normal; 1 = atrophy with no focal changes; 2 = mild degree of structural damage evidenced by a change in density but no distinct margins; 3 = moderate degree of structural damage with distinct changes in density with margins; 4 = cystic area. The scans were read by area by a neuroradiologist unaware of the purpose or nature of the study.

FDG PCT. The PCT method, FDG isotope preparation, validation of the FDG model, and data analysis have been reported previously (4,5). Patients were studied on the ECAT II positron tomograph (Ortec Inc., Life Sciences, Oakridge, Tn) with a spatial resolution at full-width-at-half-maximum of 1.6 cm in the image plane, and 1.6 cm axially. Throughout the study, patients remained in a relaxed, resting position on the padded ECAT bed with neither eyes nor ears occluded. From the tomograms, thirteen regions from each hemisphere were measured including three of the frontal lobe, two of Broca's, Wernicke's, posterior middle-inferior temporal gyri, and one for the parietal, occipital, head of caudate, and thalamic regions (Figure 1). The regions were taken from transverse scans as illustrated on the right of Figure 1, and then were transposed to a lateral image as shown on the left.

Metabolic data were expressed as a ratio of left LCMRglc to right LCMRglc for homologous regions called the "metabolic ratio," because of large between subject variation in LCMRglc, and as an attempt to balance partial volume effects. Also, a ratio of each measurement was calculated to the mean of the thirteen right hemisphere LCMRglc for the aphasic subjects and to the mean of all 26 measures for other groups. This was referred to as the "reference ratio." This approach was similar to the "cerebral metabolic landscape" used by Mazziota et al. (6), assuming the mean right hemisphere value was a representative estimate of normal mean metabolism. This assumption seemed reasonable as no differences were found in comparing mean and regional right hemisphere LCMRGlc from these aphasic subjects, and 11 age matched controls (unpublished data).

Table 1. Patient characteristics.

Patient	AGE	Lesion	Location (Left)	Aphasia	Severity*	Time of Eval Post Onset
AA	44	Trauma	Temporal	Global	Severe	20 mos
SA	48	Lacunes	Int Capsule Caudate	Anomic	Mild	6 wks
JH	54	Hemorrhage	Putamen	Mixed	Moderate	2 mos
RH	71	Infarction	Frontal Parietal	Global	Severe	5 yrs
WJ	61	Infarction	Perisylvian	Broca	Moderate	14 yrs
RM	69	Infarction	Frontal Parietal	Transcorti-cal Sensory	Severe	10 mos
Mpa	57	Infarction	Temporal	Wernicke	Moderate	4 mos
Mpe	57	Infarction	Perisylvian	Wernicke	Moderate	10 mos
JR	60	Multiple Infarctions	Atrophy	Mixed	Moderate	2 mos** 2 yrs
JV	63	Hemorrhage	Thalamic	Anomic	Mild	6 mos
GW	64	Infarction		Anomic	Moderate	2 mos

*Based on BDAE Severity Scale (0-1=Severe, 2-3=Moderate, 4-5=Mild).
**2 mos represented time following most recent stroke; 2 years following first stroke.

Table 2. Eleven language characteristics used to rate patients. (BDAE)

1. Severity Rating
2. Fluency
3. Auditory Comprehension
4. Naming
5. Oral Reading
6. Repetition
7. Paraphasia
8. Automatic Speech
9. Reading Comprehension
10. Writing
11. Music

Table 3. Factors derived from Porch Index of Communicative Ability.

Factor I (Speaking)
- I Describe Function
- IV Name Object
- IX Sentence Completion
- XII Repetition

Factor II (Writing)
- A. Write Function
- B. Write Names of Objects
- C. Write Names When Heard
- D. Write Name, Spelling Dictated

Factor III (Comprehension
- V Read Function and Position
- VI Point Object by Function
- VII Read Name and Position
- X Point Object by Name

Factor IV (Gestural)
- II Pantomime Function
- III Pantomime Function, Ordered

Factor V (Copying)
- E. Names Copied
- F. Geometric Forms Copied

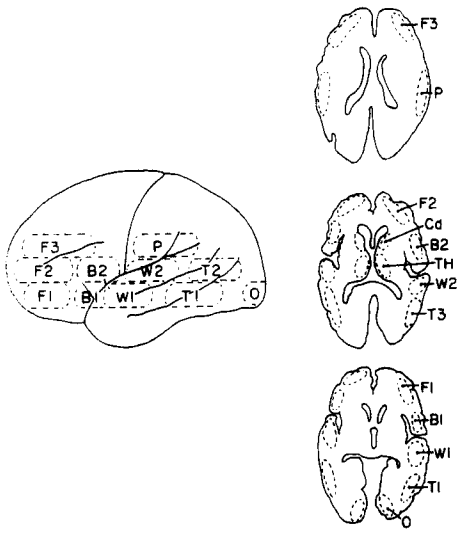

Figure 1. Demonstration of regions from which LCMRGlc were determined on FDG tomograms. Regions were outlined on transverse sections displayed on video, with the computer calculating LCMRGlc for the designated region. Corresponding transverse illustrations (right part of the figure) were derived from the atlas of Matsui and Hirano (17) at zero degrees to the canthomeatal line. The metabolic regions from transverse sections were projected onto the lateral brain surface (left part of figure). Areas B1, B2, and W2 fold into the Sylvian fissure, and do not cross it. F = frontal, B = Broca's, W = Wernicke's, T = posterior middle inferior temporal, O = occipital, Cd = Caudate, and TH = thalamic areas.

RESULTS AND DISCUSSION

FDG tomographs from aphasic patients (7,8) revealed areas of metabolic depression extending beyond the zone of infarction determined by CAT as demonstrated in the case in Figure 2, twenty-eight days after his injury. Note that metabolic depression is present throughout the left hemisphere as compared to the right, while structural changes are restricted to the mesial frontal region. A comparison between structural and metabolic abnormalities can be seen for the eleven aphasic cases from this study in Table 4. Of interest were the presence of metabolic abnormalities in the caudate, thalamus, and frontal regions where there was no evidence of structural damage. This suggested that function in undamaged tissue was aberrant, and might account for some aspects of the aphasic language disturbance.

To examine functional relationships correlations were calculated between metabolic ratios, reference ratios, CAT, and language scores from the PICA and BDAE (9,10). Reliable correlations ($r > 0.73$ for comparison of two measures this represents $p < 0.01$) are presented in Table 5. These correlational values, however, do not meet the significance level adjusted for family wise error (18). What can be seen are two sets of clustering of correlations. First, there is a cluster to posterior brain regions including Wernicke's, parietal, and posterior temporal regions. Secondly there is a cluster to bilateral frontal

Table 4. This table demonstrates a comparison of metabolic and CAT data for the 11 aphasic patients. The CAT values were derived as described in the methods. FDG regional measures were considered as abnormal if there were a 15% left to right difference in any measure taken of the particular region (for example three measurements were taken of the frontal lobe). The data are presented by region with the left column representing FDG and the right CAT. The number of abnormal scans for each region have been totaled at the bottom

Patient	Frontal	Broca	Parietal	Wernicke	Temporal	Occipital	Caudate	Thalamus
AA	+ 0	+ 0	+ 3	+ 3	+ 2	+ 0	+ 0	+ 0
SA	- 0	- 0	- 0	- 0	- 0	- 0	+ 0	+ 0
JH	+ 0	+ 0	+ 0	+ 0	+ 1	- 0	+ 0	+ 0
RH	+ 0	+ 0	+ 2	+ 0	+ 0	+ 0	+ 0	+ 0
WJ	+ 0	+ 4	+ 4	+ 4	+ 4	- 0	+ 0	+ 0
RM	+ 0	+ 3	+ 4	+ 4	+ 0	- 0	+ 0	+ 0
MPa	- 0	+ 0	+ 3	- 1	+ 2	+ 2	+ 3	+ 0
MPe	+ 0	+ 4	+ 4	+ 4	+ 4	+ 0	+ 0	+ 0
JR	+ 0	+ 0	- 0	- 0	- 0	- 0	+ 0	+ 0
JV	- 0	- 0	- 0	- 0	- 0	- 0	+ 0	+ 0
GW	+ 0	+ 2	+ 4	+ 2	+ 0	- 0	+ 0	+ 0
	8 0	9 4	8 7	7 7	8 5	4 1	11 1	11 0

CAT Scores are on a 0-4 scale (see Methods). This number is the left hemisphere reading. 0 implies either a normal region or equal atrophy for the region in both hemispheres.

FDG PCT + represents greater than a 15% left right difference for any measure in that region e.g. three measures were taken of the frontal lobe (see Figure 2). A - implies no left right differences.

Table 5. Summary of reliable correlation ($p < 0.01$, $r > 0.73$ unadjusted) between LCMRGlc, CAT and Language Measures.

	BDAE						PICA		
	Auditory Comp	Naming	Oral Reading	Repetition	Reading	Automatic Speech	Write	Copy	Speak
Frontal	-	-	-	RRR	-	RRR	LCT RCT	LCT RCT LRR RRR	-
Broca	-	-	-	-	RRR	-	LCT RRR	RRR	MR LRR RRR
Wernicke	-	-	LCT	LCT	-	-	-	-	LCT
Parietal	MR	MR	MR	MR	-	-	-	-	-
Posterior Temporal	MR LRR	MR LRR	MR LRR	LCT MR LRR	RRR	-	RRR	-	-
Occipital	-	-	-	-	-	-	-	RRR	-
Caudate	-	-	-	-	MR LRR	-	LRR	RCT	MR LRR
Thalamus	-	-	-	-	-	-	-	-	-

Correlations were calculated between language score, (11 BDAE mean score and 5 PICA factor scores), and metabolic and CAT measures. Only those language tests showing significant correlations are included in the table. The metabolic measures were reduced to 8 regions for this chart and include:

MR = Metabolic Ratio - Ratio of left to right hemisphere LCMRGlc for any region.

LRR = Left Reference Ratio = The ratio of left hemisphere region's LCMRGlc to the mean LCMRGlc of the right hemisphere for the subject.

RRR = Right Reference Ratio = Ratio right hemisphere region's LCMRGlc to mean right hemisphere LCMRGlc for the subject.

The CAT correlations are: LCT = Left CAT Measure. RCT = Right CAT Measure.

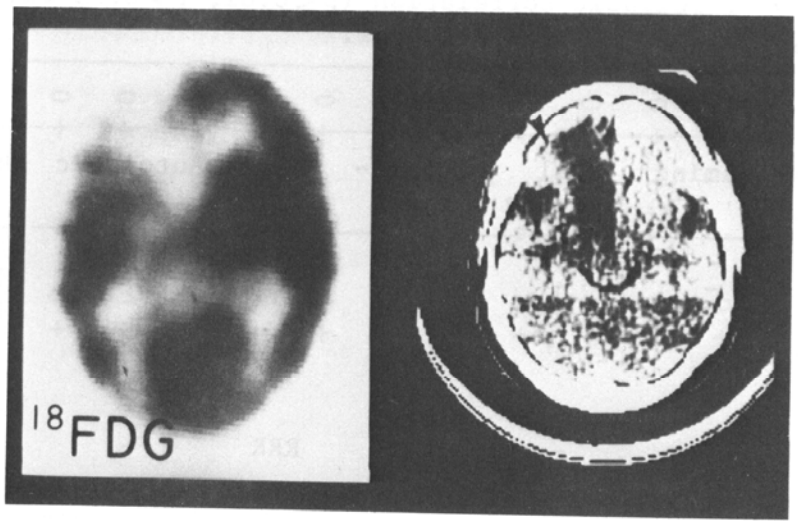

Figure 2. FDG Tomograph and corresponding CAT scan from a twenty-two year old male who had a traumatic occlusion of the left carotid artery. The patient developed a mild right hemiplegia, and aphasia. The details of his aphasia were unknown. He was not part of the series of patients presented here, but his scan is shown to illustrate FDG and CAT differences. The CAT demonstrates an area of infarction in the anterior cerebral artery distribution in the mesial frontal area on the left. In the FDG tomograph, the darker the region, the higher is the LCMRGlc. Note the decrease in LCMRGlc throughout the left hemisphere as compared to the right.

regions including frontal, Broca's and caudate regions. These clusters involved both structural and metabolic abnormalities. In the first cluster, the structural damage from Wernicke's region and not its metabolism showed high correlations to aspects of impaired language. The association of structural damage to Wernicke's region with language dysfunction is consistent with traditional structural models (1). Interestingly, high metabolic correlations with language in the same cluster were to more posterior-inferior temporal, and inferior parietal regions. Metabolic intercorrelations from normal subjects have shown strong correlations between all regions in the left hemisphere involved with these two clusters, including left inferior frontal, Broca's, Wernicke's, and posterior temporal regions, suggesting a functional relationship (15). All these regions are likewise activated in normal young adults when stimulated with auditory signals, as are corresponding regions in the right hemisphere (6). Together these data suggest that the perisylvian region forms a unit involved with language function, and when structural damage occurs particularly in Wernicke's region the remaining adjacent language areas attempt to assume language function.

Of interest were correlations of caudate metabolism with PICA Speaking and Comprehension factors and BDAE Writing and Reading scores ($p < 0.02$ not adjusted for multiple comparisons). To better understand these relationships, the twenty subtests making up these factors and scores (from Tables 2 and 3) were correlated with caudate metabolism (11). The correlations which were significant at $p < 0.01$ ($r > 0.73$ not adjusted for multiple comparisons) are shown in Table 6.

Table 6. Caudate correlation to 20 subtests from Porch Index of Communicative Ability (PICA) and Boston Diagnostic Aphasia Examination (BDAE) ($p < 0.01$).

BDAE	Symbol Discrimination	PICA	I - Tell Function
	Word Recognition		IV - Naming
	Primer Dictation		VI - Point to One Used For
	Serial Writing		X - Point to Named Object

These subtests tended to be the simplest of the tasks when comparing these significant subtests to the other subtests making up the PICA Speaking and Comprehension factors, and the BDAE Writing and Reading scores. Principal components analysis of the twenty subtests identified three factors (Table 7). Only the third factor correlated significantly ($p < 0.01$) with caudate metabolism, and included four of the six subtests loading most strongly to the caudate. These correlations suggested a caudate language role related to phonetic recognition for simple, overlearned materials, including simple syntax, low levels of abstraction, and identification or sequencing of phonetic and semantic material. This role appeared related to, but independent of Broca's area and inferior frontal lobe function.

Table 7. Factors derived from principal components analysis of twenty subtests related to caudate metabolism with most highly loaded subtests.

Factor 1.	BDAE Comprehension of oral spelling
	Read - sentences and paragraphs
	Writing to confrontation naming
	Spelling to dictation
	Sentences to dictation
	PICA V - Read function and position
Factor 2.	BDAE Word recognition
	Mechanics - writing
	Serial writing
	Primer dictation
Factor 3.	BDAE Symbolic discrimination
	PICA I - Describe function
	IV - Name object
	VI - Point to object by function
	XII - Repetition

Alternatively, caudate function may involve cortical organization of planned movement. Each language subtest correlating with caudate metabolism involved movement, and most were to the PICA which emphasizes behavioral differences. To examine caudate function further, two basal ganglia diseases, Parkinson's (PD) and Huntington's (HD), were compared to a cortical disease, Alzheimer's (AD) (12). We speculated that the two basal ganglia diseases would differ metabolically from the cortical disease and controls, reflecting upon the loss or alteration of basal ganglia function. As compared to normals, LCMRglc was markedly decreased only in AD, and in the caudate in HD. Cortical metabolism in HD was normal, and mild to moderately decreased in PD

(approximately 22%). We asked the question whether metabolism between two regions varied linearly across the subjects with a single illness (Figure 3).

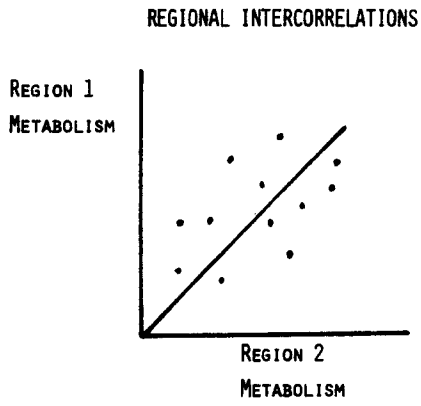

Figure 3. Relationship between metabolism in Region 1 and metabolism in Region 2.

Examining regional correlation matrices for each disease, the number of cortical, regional reliable correlations (r values selected for $p < 0.02$ unadjusted) decreased in HD and PD compared to age matched controls (Table 8). This differed from AD where an increase was found in cortical to cortical correlations. These findings suggested a loss in focusing of cortical activity related to basal ganglia pathology, and evidence for the role of these structures in relation to cortical function which may account for some clinical features in HD and PD. In addition with cortical pathology a reorganization occurs in regional cortical metabolic relationships. From our studies, the head of the caudate appeared to be of particular importance for the relationship of Broca's and inferior frontal to other cortical brain regions, which may reflect on the caudate's role in speech and language.

Table 8. Metabolic intercorrelations in Huntington', Parkinson's, and Alzheimer's Diseases.

	Cortical Intercorrelations
Control (AD, PD)	17
Parkinson's Disease	8
Alzheimer's Disease	43
Control (HD)	35
Huntington's Disease	23

The numbers represent how many reliable region to region correlations were present between cortical areas for each group.

Separate age matched controls were used for the three groups. Alzheimer's patients had an average age of 68, Parkinson's patients were 62, the control (AD, PD) were 64, while Huntington's patients averaged 44, and the control (HD) were 42.

Previous studies of memory function in stroke have noted differences in decision criteria of aphasic patients, compared to normal and right hemisphere stroke subjects (13,14). The aphasic patients were less willing to guess, took longer to respond and used fewer processing steps. We have not been able to examine these observations in relationship to glucose metabolism in aphasia. In 31 normal individuals, we have identified reliable intercorrelations ($p < 0.01$ unadjusted) between reference ratios of high frontal, inferior parietal, and occipital regions (15). In addition, when correlations were calculated between metabolism and memory and decision criteria derived from a twenty-two subtest memory battery analyzed using Signal Detection measures, high frontal metabolism correlated ($p < 0.02$ unadjusted) with the correctness of immediate memory tasks, while the occipital area correlated ($p < 0.02$ unadjusted) with decision criteria (16). This superior frontal, parietal, occipital metabolic system appeared to involve decisional factors and memory in visual processing, and included visual cortex and frontal eye fields. It may rely upon connections through the superior longitudinal fasciculus, and could relate to the postulated attentional system which includes frontal, inferior parietal and cingulate cortex (16). The memory and decision abnormalities noted in stroke patients may involve functional abnormalities in this metabolically noted system.

These data suggest that language requires the interaction of a number of highly integrated systems of the brain. This interaction involves both hemispheres as well as cortical and subcortical structures. Subcortical areas associated with arousal, attention, and sequenced planning of response seem particularly important in language and speech. Improved treatment for aphasia may be developed as our understanding of these physiologic measures improves. The best treatment may not depend only on the nature of the patient's symptomatology, but also on the brain regions and functional strategies that are being used in attempting to overcome the disability. Tailoring some aspects of treatment toward these latter factors may further improve the recovery of communicative ability in the aphasic patient.

REFERENCES

1. Goodglass, H., and Kaplan, E. The Assessment of Aphasia and Related Disorders. Philadelphia: Lea & Febiger, 1972.
2. Porch, B.E. Porch Index of Communicative Ability. Volume 1: Theory and Development. Palo Alto: Consulting Psychologist Press, 1967.
3. Hanson, W.R., Riege, W.H., Metter, E.J., and Inman, V. Factor derived categories of chronic aphasia. Brain and Language, 15, 369-380, 1982.
4. Huang, S.C., Phelps, M.E., Hoffman, E.J., Sideris, K., Selin, C.J. and Kuhl, D.E. Noninvasive determination of local cerebral metabolic rate of glucose in man. American Journal of Physiology, 238, E69-E82, 1980.
5. Phelps, M.E., Huang, S.C., Hoffman, D.J., Selin, C.S., Sokoloff, L., and Kuhl, D.E. Tomographic measurement of local cerebral metabolic rate in humans with (F-18) 2-fluoro-2-deoxyglucose: Validation of method. Annals of Neurology, 6, 371-388, 1979.
6. Mazziotta, J.C., Phelps, M.E., Carson, R.E., and Kuhl, D.E. Tomographic mapping of human cerebral metabolism: Auditory stimulation. Neurology, 32, 921-937, 1982.
7. Kuhl, D.E., Phelps, M.E., Kowell, A.P., Metter, E.J., Selin, C., and Winter, J. Effect of stroke on local cerebral metabolism and perfusion: Mapping by emission computed tomography of 18FDG and 13NH3. Annals of Neurology, 8, 47-60, 1980.

8. Metter, E.J., Wasterlain, D.G., Kuhl, D.E., Hanson, W.R. and Phelps, M.E. 18FDG positron emission computed tomography in a study of aphasia. Annals of Neurology, 10, 173-183, 1981.
9. Metter, E.J., Riege, W., Hanson, W., Phelps, M.E., and Kuhl, D.E. Correlation of language and metabolic abnormalities in aphasia. Transactions of the American Neurologic Association, 106, 328-330, 1981.
10. Metter, E.J., Riege, W., Hanson, W., Camerus, L., Phelps, M., and Kuhl, D. Metabolic and structural comparisons to language function in aphasia. Abstracts, Society for Neuroscience, 7, 240, 1981.
11. Metter, E.J., Riege, W.H., Hanson, W.R., Phelps, M.E., and Kuhl, D.E. Role of the caudate in aphasic language: Evidence from FDG positron emission computed tomography. Neurology (NY) 32(2), A94, 1982.
12. Metter, E.J., Riege, W.H., Kameyama, M., Phelps, M.E., and Kuhl, D.E. Correlational differences of regional glucose metabolism in Huntington's, Parkinson's, and Alzheimer's Diseases. Annals of Neurology, 12, 88, 1982.
13. Riege, W.H., Metter, E.J. and Hanson, W.R. Verbal and nonverbal recognition memory in aphasic and nonaphasic stroke patients. Brain and Language, 10, 60-70, 1980.
14. Riege, W.H., Klane, L.T., Metter, E.J. and Hanson, W.R. Decision speed and bias during nonverbal recognition in patients after unilateral stroke. Cortex, 18, 345-355, 1982.
15. Metter, E.J., Riege, W.H., Kuhl, D.E. and Phelps, M.R. Relations among measures of local cerebral glucose metabolism in healthy adults. Abstract to Society for Neuroscience, 8, (2)917, 1982.
16. Riege, W.H., Metter, E.J., Kuhl, D.E., Phelps, M.E. and Hawkins, R.A. Relation among measures of local cerebral glucose utilization and memory or decision functions. Abstract to Society for Neuroscience, 8, (2)918, 1982.
17. Matsui, T. and Hirano, A. An Atlas of the Human Brain for Computerized Tomography. Tokyo: Igaku-Shoin, 1978.
18. Games, P.A. Multiple comparisons of means. American Educational Research Journal, 8, 531-565, 1971.

DISCUSSION

Q: Are there any major differences between metabolic studies and blood flow studies as they relate to brain-behavior relationships?

A: There are several differences. First, one has to consider differences in techniques used for blood flow and metabolic studies. Most blood flow studies which have examined brain-behavior relationships have used xenon with from 8 to 256 detectors. Each detector measures a region that is directly under the crystal, and measures primarily surface activity, with relatively limited resolution. The positron technique looks at any region within the brain. Its resolution is also quite a bit higher than with the xenon method. Secondly, there may be major differences in looking at metabolism and blood flow in brain damaged individuals. In stroke, mismatches have been found between metabolism and blood flow. Most mismatches occur early and are present during the first month following a stroke, and typically are gone after a month. In our early studies, we tried using ammonia as a measure of blood flow. It is moderately reliable measure in some ranges of flow. We did find mismatches, but these tended to occur early following stroke. Other centers using the positron technique study flow and metabolic measures with 015. In normal individuals there is a

close coupling between blood flow and metabolism. In the brain damaged individual this relationship is not necessarily maintained; the two measure different phenomena.

Q: What happens after 1 month post ictus?
A: After 1 month post ictus, the comparison between blood flow and metabolism tends to become more consistent.

Q: Does that mean that the remote effects of a lesion as indicated by PCT are gone by a month?
A: No, they are not. In the patients presented here, one individual was 15 years post stroke with a Broca's aphasia and he still shows the same types of distant changes as the rest of the group. In our series of stroke patients, including the aphasic patients presented today, most of the cortical lesions tended to be large. Of the aphasic series, three of the patients had subcortical lesions, one with a lacunar state, and two had hemorrhages. Even in the subjects with deep, more discrete, smaller lesions, and 4 to 6 months post ictus, extensive cortical depression was found as a distant effect.

Q: I have to tell you how pleased I am that this paper was presented this afternoon, because I think the information you have presented is directly related to a couple of papers to be presented tomorrow, including Donald Robin's and Steven Scheinberg's paper on the thalamus, and John Tonkovich and my paper on subcortical lesions. With your extensive presentation here, I think that this is a good introduction into some of the thinking that we might be able to discuss tomorrow about what it means when we see these subcortical lesions. There is a whole school now that feels the basal ganglia in and of itself contributes to language function, and there have been other studies implicating the role of disconnections, certainly I think that Norman Geschwind would be happy with these findings. However, this presents good evidence to begin thinking that when we see a patient following involvement of these particular structures (the basal ganglia, thalamus and so forth) are we looking at language, words, or aphasia which follow from specific involvement of those structures, or are we looking at the distant effects? To respond to Joe's question about the duration of these types of things, certainly, I think that when you see aphasias that become chronic following subcortical lesions, that would be good evidence that these distant effects, these disconnections, however you want to describe them, do not go away. In those cases where aphasia is only short lived and then clears within the first few weeks, these distal changes may clear. The cases that we are dealing with are maybe a year or two post onset of their strokes, and are demonstrating moderate to marked aphasia probably retain the distal effects.
A: I agree. I think these distant effects in many instances remain as a permanent marker on these individuals, and what we are seeing in a number of stroke patients suggest that we need to consider not only the structural lesion, but also the lesion's effect on the whole brain. Frequently the effects on other brain regions may be of real importance, and may be amenable to more direct therapy than when the region is directly damaged. If we think of the effect of a subcortical lesion as creating a difficulty for cortical areas to work together, perhaps strategies of trying to use alternate techniques to allow these cortical regions to

better function together, may improve our treatment effectiveness in some aphasia patients. For example, we see aphasic patients who if you keep things very, very simple they understand perfectly and will communicate with you for hours. If the material becomes a litte difficult, or if they become tired they start to have a great deal of difficulty in understanding or putting together complex types of ideas. From a physiologic point of view, the problem may be that if things are kept simple you may restrict the number of brain regions that actively have to be involved in processing the information. Whereas as things get more complex, the complexity of whole brain interrelations may need to be expanded greatly. Based on these possible physiological considerations, we may be able to mold performance by using techniques which may selectively activate or restrict specific regions.

Q: Do you think that this procedure would resolve some questions about the nature of recovery if it were administered over time, and resolve some questions like whether recovery occurs through functional substitution or functional reorganization of brain structures?

A: Yes, I think these techniques would be useful in recovery. The big difficulty with the positron studies from a practical point of view is their expense. It is a very expensive technique, and to study people repeatedly, you need to find funding agencies which are willing to finance such projects.

Q: Do you think that there are not too many confounds or anything like that?

A: With FDG, difficulties in studying somebody early would include whether they were able to lay still for the required period of time. A second issue is radiation exposure. Repeated studies of a patient are within the radiation limits set by institutions. The limiting factor is going to be the cost. An alternative approach that I imagine in the next few years will become more practical and probably cheaper is single photon emission computed tomography. This procedure does not require a cyclotron at the site that you are doing the studies, since the isotopes used have much longer half-lives. I think recovery studies will more likely be done with this type of study.

Q: If I can follow Alvin's question a little bit. In your correlational studies you said that you took the metabolic level of the right hemisphere as the normal level. Across subjects, be they normal or brain damaged how consistent is the level of the metabolism that you see? In other words when you are calling it normal how confident are you that it is not increased or decreased?

A: This is a problem in many of these studies. In the brain damaged individuals, we find a large variance between subjects. This is why we have used relative measures. When comparing the eleven aphasic patients presented to age matched controls, the mean right hemisphere values were essentially normal, but if you looked at the variance there was a much greater variance between subjects in the aphasic group.

Q: Have you looked at the consistency of the rate across the right hemisphere? How consistent from site to site are the right hemisphere values?

A: The metabolic values between sites in a single individual are quite consistent, within 5%.

Q: You found that consistently in your lesioned population?
A: Yes, within the same individual it tends to be quite consistent.

Q: Don't you think that the requirement for such a long analysis window presents a problem for this localized study? Forty-five minutes didn't you mention?
A: Yes, the equilibrization time was 45 minutes with the subject in a resting state with neither eyes nor ears occluded.

Q: So, the patient just sits there while this test is performed? It is certainly possible that different kinds of activities which different patient might perform during that time could cause confounding variability in further analysis. For example, trying to correlate that data with language performance on other tests, the interpretation of those results may be difficult don't you say?
A: Yes, I agree. This is a problem for FDG with these types of studies. You were initially referring to the stimulation studies done by Mazziotta and Phelps et al.?

Q: Yes, after considering that data, I realize that different activities will produce different patterns of activation. So an uncontrolled 45 minutes, anything could occur.
A: Yes, anything can, and probably does occur. In our studies, we assume that the level of function that a region is capable of is reflected in its metabolic activity, independent of what the individual is doing during the FDG study. In this way, we can try to study that metabolism in relationship to language function. This is similar to the assumptions made in correlating structural damage to behavior. What was surprising in our aphasia study, was how consistent these clusters appeared. That is really as far as I think we can go in these statements. I try not to focus very closely on what the individual correlations might mean. You must realize that we are talking about an enormous matrix. The number of correlations computed were over 500, and based on that every correlation is not reliable, but what I think is reliable is that we are seeing some verydefinite clustering, and in a very consistent manner. That is the key. I don't think that we can say the data here is of a true statistical significance for each correlation, but there is inferential information suggesting thatwe have to expand our scope, when consdiering lesions in relationship to brain functions. We need to expand our goals and sights in trying to understand what else is happening in the brain at a distance from the lesion. As far as stimulation studies, I think that shorter scanning times are required to reduce the time required to activate and decrease individuals from wandering. One approach is to use a different isotope and molecule, such as 015-water to measure blood flow or metabolism. With that molecule, a study can be done in one to two minutes, and a number of studies can be done at a single sitting. Currently, that technique is being developed in normals in the UCLA laboratory. We are hoping that we can get funding to do it in aphasic patients. The difficulty with the approach may be mismatches between flow and metabolism. When you look at flow, are you getting a true measure of brain function as is obtained with metabolism in brain damaged subjects? The best evidence at present is that you should, but that is always difficult to prove.