Remote Metabolic Effects in Aphasic Stroke Patients

E. Jeffrey Metter and Walter H. Riege
Veteran's Administration Medical Center, Sepulveda, California and
School of Medicine, University of California, Los Angeles

Wayne R. Hanson
Veteran's Administration Medical Center, Sepulveda, California

Catharine A. Jackson, John C. Mazziotta, and Michael E. Phelps
School of Medicine, University of California, Los Angeles

The study of stroke using positron emission tomography (PET) has demonstrated blood flow and metabolic reductions in regions remote from carotid distribution structural lesions. These remote sites included other cortex zones, thalamus, basal ganglia, and contralateral cerebellum (Kuhl, Phelps, Kowell, Metter, Selin and Winter, 1980; Lenzi, Frackowiak, and Jones, 1981; Metter, Wasterlain, Kuhl, Hanson, and Phelps, 1981; Baron, Bousser, Comar, and Castiagne, 1981; Celesia, Polcyn, Holden, Nicles, Koeppe, and Gatley, 1984). Our understanding of mechanisms associated with remote effects is limited, though several explanations seem reasonable (Figure 1). A focal lesion may cause no remote cortical effects and the lesion alone may be responsible for specific behavioral changes. A focal lesion can interact with other brain regions and the combination can result in behavioral dysfunction. A focal lesion can damage white matter resulting in a disconnection of interacting regions (Phelps, Mazziotta, and Huang, 1982) with the distal and proximal changes causing behavioral dysfunction rather than the lesion itself. Alternatively, a lesion can cause diffuse hemispheral changes that may be associated with specific behavioral or other regulatory brain functions.

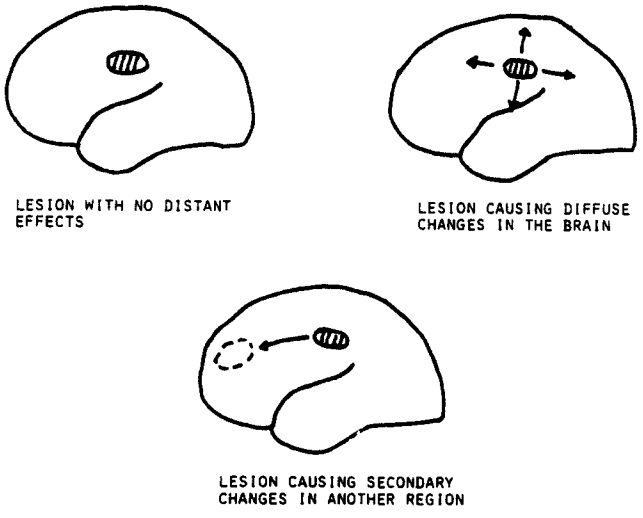


Figure 1. Possible remote metabolic effects associated with a structural lesion. A lesion may have effects limited to the lesion site alone or it may affect adjacent and remote structures. The distant effects may be either diffuse or associated with specific brain regions.

This paper explores possible mechanisms associated with remote effects by examining our experiences with specific stroke patients.

METHOD

Patients. Patients were selected from the stroke cases studied at UCLA as part of a stroke survey, a multi-infarct dementia project, and ongoing aphasia projects. They were included based on the nature of the remote metabolic changes associated with their structural lesions. In addition, 9 control subjects aged 26 to 71 and studied by Kuhl et al. (Kuhl, Metter, Riege, and Hawkins, 1985) and Kling et al. (Kling, Metter, Riege, and Kuhl, 1985) were included for quantitative comparison.

Positron Tomography. Patients and control subjects were studied on the NeuroECAT (CTI, Oakridge, Tenn) with (F18)-fluorodeoxyglucose (FDG). The procedures and techniques have been previously described (Hoffman, Phelps, and Huang, 1981; Huang, Phelps, Hoffman, Sideris, Selin, and Kuhl, 1980; Phelps, Huang, Hoffman, Selin, Sokoloff, and Kuhl, 1979). Patients were studied in the resting state with eyes and ears open for 40 minutes after injection when scanning was begun. The room lights were dimmed and they looked at the ceiling and listened to ambient room noise. For quantitative measurements, the scans were displayed, regions of interest were outlined and local metabolic rates for glucose (LCMRglc) were given in mg/100 gms tissue/minute using the model developed by Phelps and Huang and kinetic constants derived from normal young adults (Huang, Phelps, Hoffman, Sideris, Selin, and Kuhl, 1980; Phelps, Huang, Hoffman, Selin, Sokoloff, and Kuhl, 1979). Left to right ratios were calculated for each of the 15 regions examined (Figure 2), and ranged from .98 to 1.05 for the normal subjects. Z-scores were calculated for each region for aphasic subjects using the regional means and standard deviations from the controls.

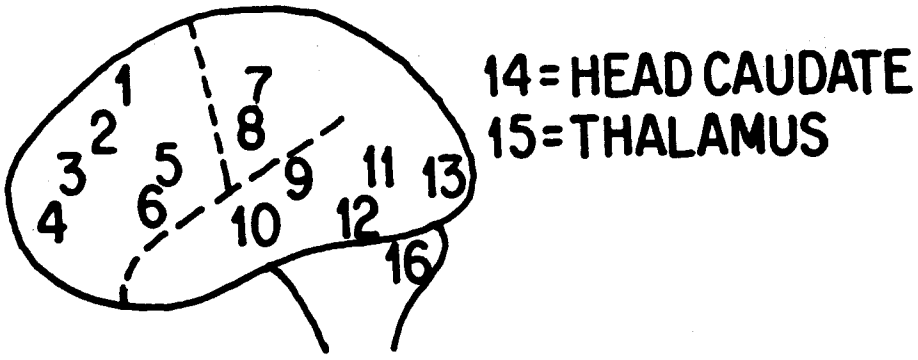
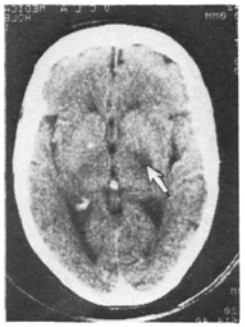


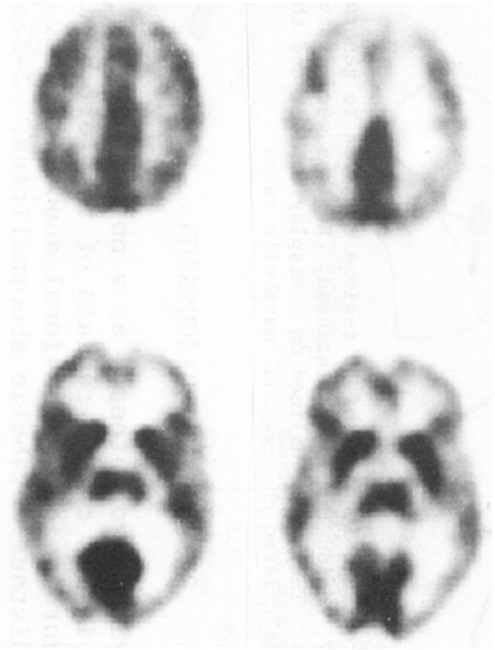
Figure 2. Approximate location of 15 regions measured to generate the data presented. Region 16 was not included. Regions were derived from four FDG planes. They were outlined on a display monitor and the computer then calculated the regional metabolic rate.

RESULTS AND DISCUSSION

Case 1. This individual volunteered as a normal subject but was found to have a small infarct in the corona radiata of the left hemisphere on X-ray CT (Figure 3) with no neurologic or behavioral abnormalities. The FDG PET study did not show any distant metabolic abnormalities. Z-scores were within 1 standard deviation of the mean for all measured brain regions.

Identifying small infarcts with no clinical disability has become a common occurrence with the wide use of X-ray CT. These are typically lacunar infarctions in deep white or grey matter. Patients are unaware of their

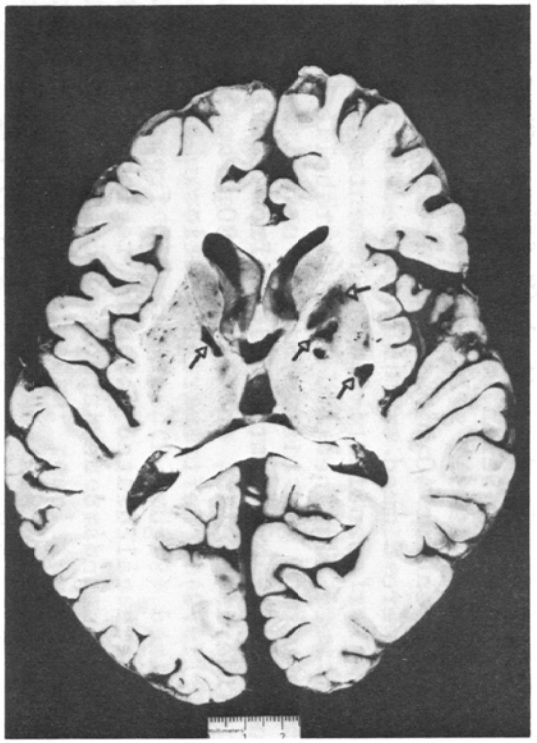




REGIONAL Z-SCORES

REGION	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
	.1	-.7	-.3	-.2	-1.0	-.2	-1.0	.2	-.1	0.0	.3	-.6	.1	-.7	-.9

Figure 3. X-ray CT, FDG scans, and Z-score profile of Case 1. CT scan demonstrates a lacunar infarct in the left internal capsule (arrow). No structural changes are apparent in the cortical regions. The FDG scan shows four levels with no evidence of any cortical metabolic abnormalities. The Z-score profile is the number of standard deviations away from the mean value for the left/right ratio from nine control subjects for each region of interest as numbered in Figure 2. The normal range is +2 to -2 for each region. The Z-scores of the left to right ratios were within the normal range for control subjects.



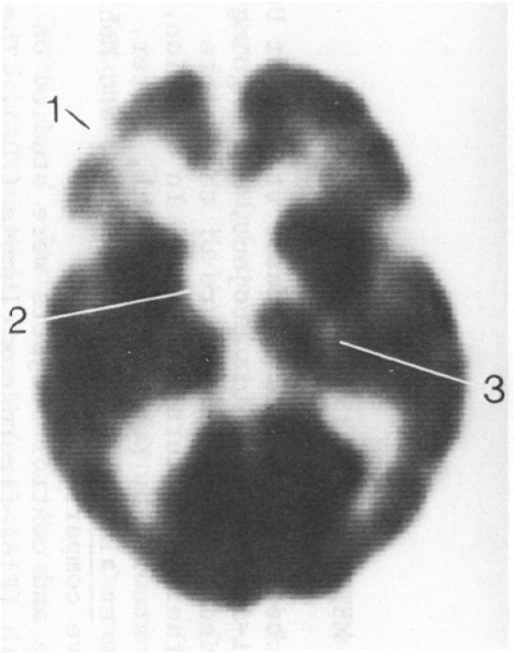


Figure 4. FDG and corresponding brain section from Case 2. (a) Brain section demonstrating multiple lacunar infarctions in the basal ganglia bilaterally (arrows). Of particular interest is the lacune in the genu of the left internal capsule which is associated with degeneration of the anterior limb of the capsule. (b) FDG scan of brain section which shows striking hypometabolism in the left inferior frontal cortex, an area found to be structurally normal.

presence. If lesions are appropriately situated and associated with minimal axonal or deep grey damage no functional changes may result. This case illustrates such a lesion in a clinically normal individual, who was studied extensively, including a neuropsychologic battery. The FDG study showed normal cortical, thalamic and caudate metabolism. We have seen this pattern in several individuals with silent deep infarcts and normal appearing gray matter metabolism. We propose that for a deep lacunar white matter lesion to be symptomatic, remote cortical or deep gray hypometabolism must be present, i.e. the deep lesion needs to disrupt gray matter function to the point of altering glucose metabolism.

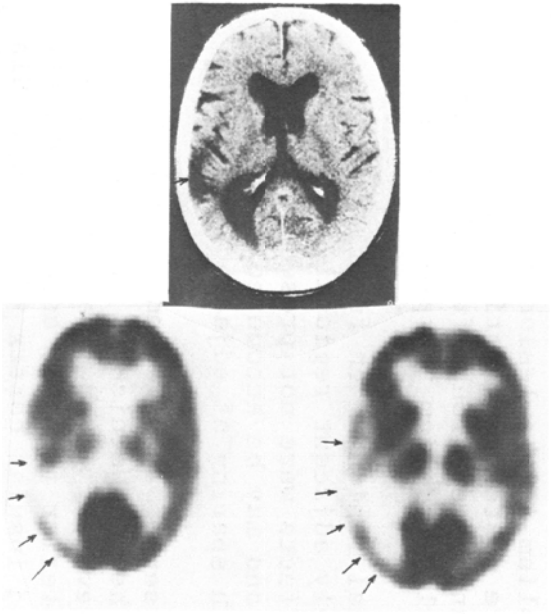
Case 2. A 69-year-old man had a stroke with a right hemiparesis, mild anomia, and dementia. He was studied 1 month post onset and died 10 days later from a gastrointestinal hemorrhage (Metter, Mazziotta, Itabashi, Mankovich, Phelps, and Kuhl, 1985). His autopsy demonstrated multiple infarcts (Figure 4a, arrows). Of major interest was an infarct in the genu of the left internal capsule. It was associated with degeneration of the anterior limb of the internal capsule which, among other regions, innervates the left lateral inferior frontal cortex. The frontal cortex was normal structurally by X-ray CT and gross post-morten examination. The FDG scan (Figure 4a), on the other hand, showed a marked metabolic reduction in the left inferior frontal region. Histologic examination of the frontal region showed normal structure and cell count. Lacunar infarcts were present in the right basal ganglia, but the right internal capsule was spared and no overlying cortical metabolic changes were found. These infarcts were clinically silent, as this man had no evidence of a left hemiparesis or hemisensory loss.

This case demonstrated a functionally significant lacunar infarct that disconnected the left frontal region from deep structures by destroying principle fiber tracts. As is illustrated by the first two cases, the structures damaged are critical for remote effects associated with lacunar infarctions and clinically significant lacunae are associated with cortical hypometabolism.

Case 3. A 55-year-old man had sudden onset of aphasia. He was studied six months later when he had a mild conduction aphasia based on the Western Aphasia Battery. His X-ray CT scan showed a left superior temporal gyrus infarct, while his PET demonstrated hypometabolism in the lesion and in adjacent temporoparietal regions including more posterior-inferior temporal and inferior parietal areas. No metabolic changes were found frontally (Figure 5). Regional Z-scores confirmed normal frontal metabolism and prominent left temporoparietal hypometabolism.

This case demonstrated a localized cortical lesion which functionally affects only the lesion site and the immediately adjacent regional cortex in a man with only a mild aphasia. Far remote effects were not present, as seen by sparing of left frontal cortex metabolism, and may be accounted for by the strictly cortical location of the infarct, with sparing of adjacent deep white matter.

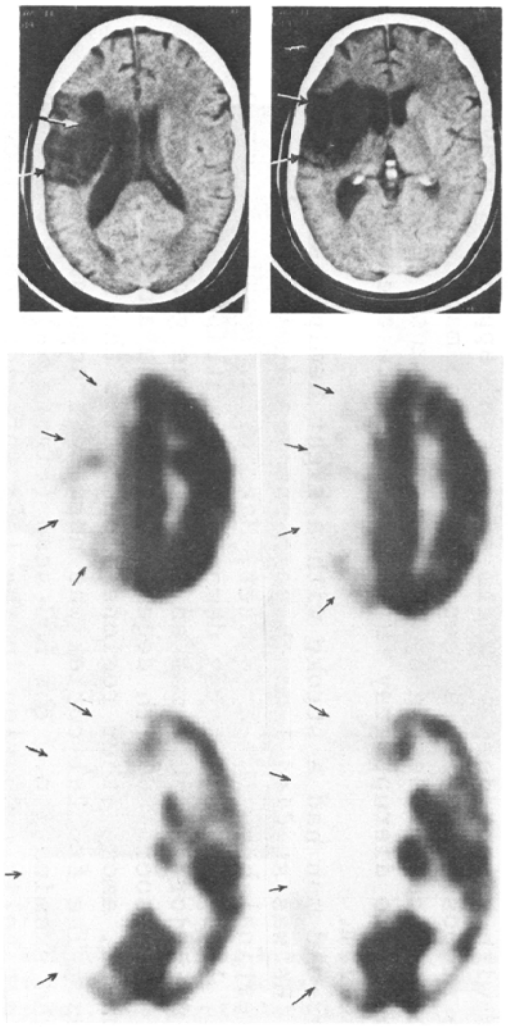
Case 4. A 65-year-old man with sudden onset of aphasia and right hemiplegia was studied at 6 months postonset when he had Wernicke's aphasia as indicated by the Western Aphasia Battery and severe right hemiparesis. His X-ray CT showed a large lesion of the left posterior frontal, anterior parietal cortex, caudate, putamen, deep white matter and insular cortex (Figure 6). His FDG study demonstrated diffuse left hemisphere hypometabolism except for visual cortex. Z-scores calculated for the 15 brain regions (Figure 2) demonstrated two levels of metabolic regional involvement, with 9 regions showing Z-scores less than 10 and 6 showing scores higher than 10. The higher scores are primarily associated with structurally damaged regions and those adjacent,



REGIONAL Z-SCORES

REGION	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
	-.2	-.7	-1.7	.2	1.8	.7	-2.2	-2.6	-3.4	-3.5	-6.8	-13.3	0.0	1.3	-.2

Figure 5. X-ray CT, FDG scan, and Z-score profile for Case 3. The CT shows a focal cortical lesion in the temporal lobe. FDG scan shows hypometabolism at the site of the structural lesion and extends to adjacent temporal and parietal regions. Z-scores demonstrate normal values for the frontal regions while temporoparietal regions all showed prominent asymmetry.



REGION Z-SCORES

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
-7.0	-8.6	-8.9	-7.9	-14.3	-8.0	-7.9	-14.7	-10.1	-7.9	-8.2	-12.9	-3.3	-10.7	-14.0

Figure 6. X-ray CT, FDG scan, and Z-score profile of Case 4. The CT shows a moderately large infarct in the posterior frontal, insular, and anterior parietal regions with deep extension. The FDG scans show hypometabolism in the region of the infarct and extends to adjacent frontal cortex and to more remote temporal cortex. The Z-scores were abnormal in both frontal and temporoparietal regions.

while the lower scores are from more remote regions (Region 12, z=-12.9 is incongruous because the standard deviation for the control subjects was extremely small compared with the other regions).

This case illustrated local hypometabolism as observed in case 4, but also more distant temporal hypometabolism (Z-scores less than 10). The appearance of the temporal changes seems to depend on deeper white matter disruption, the presence of larger lesions, involvement of insular cortex or basal ganglia. At present we have no data to distinguish these possibilities. The presence of a larger lesion and more diffuse metabolic abnormality tend to be associated with more severe clinical disability.

Case 5. A 54-year-old man had a putamenal hemorrhage associated with aphasia in 1980. Over the next 5 years his aphasia improved. His continuing problems were central pain syndrome and depression. When studied 4 years postonset, his X-ray CT demonstrated a slit-shaped lesion in the left lateral basal ganglia. His FDG study showed hypometabolism involving the entire left hemisphere (Figure 7), with a 16% left<right asymmetry of hemispheric metabolic rate for glucose. LCMRglc was also markedly decreased in temporoparietal areas as can be seen from the high Z-scores in regions 8, 9, and 12, and in the caudate and thalamus.

The case demonstrated prominent left hemisphere hypometabolism in the absence of major persisting language impairment. Compare this case to Case 6.

Case 6. A 72-year-old man had sudden onset of severe global aphasia and right hemiplegia secondary to a putamenal hemorrhage. When studied 6 months postonset, he continued to have severe aphasia and hemiplegia. His X-ray CT scan (Figure 8) demonstrated a large putamenal lesion which extended more medially than in case 5. The FDG study demonstrated diffuse hypometabolism throughout his left hemisphere (29% asymmetry compared to the right) with focal severe metabolic changes in the temporoparietal region and mild to moderate reduction in frontal regions (Z-scores, Figure 8).

The severe aphasia in this patient suggested the absence of proper left cortical function in the presence of diffuse cortical hypometabolism. Cases 5 and 6 had very similar lesions and cortical metabolic changes, but had very different outcomes. Case 5 had been also studied two months post onset and had a very similar metabolic picture, so that the differences between the two cases cannot be accounted for by time course (6 months versus 4 years). The difference in the degree of aphasia seems to relate mostly to the difference in degree of hypometabolism in the posterior temporal regions. Comparing the regional Z-scores (Figures 7 and 8), the most striking differences are in regions 7, 8, 11, 12, and 13; i.e., the parietal, posterior middle temporal, and occipital areas. There is no evidence from X-ray CT in either case for structural damage in these regions, but the severely aphasic patient (Case 6) had a 20% greater asymmetry than case 5. Note that the superior temporal (Wernicke's) region is quite similar in the two cases (Regions 9, 10). Other cases with persisting moderate-to-severe aphasias also have severe metabolic asymmetry in the left posterior middle temporal region similar to case 6, while mild aphasic patients seem to have higher metabolic rates. This agrees with our previous reports (Metter, Riege, Hanson, Camras, Kuhl, and Phelps, 1984) of a correlation between posterior middle temporal gyri metabolic activity and language functions.

Case 7. A 24-year-old man had onset of right sided sensory loss and weakness in association with abnormal eye movements. X-ray CT showed a thalamic hemorrhage, while FDG study done 1 week postonset showed mild diffuse left-sided hypometabolism as demonstrated by the consistent negative Z-scores (Figure 9). Only 3 of the regions had scores greater than 2, but 14 of 15

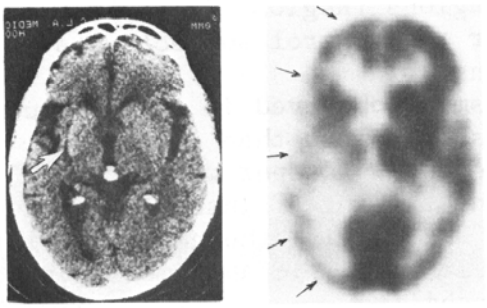


Figure 7. X-ray CT, FDG scan, and Z-score profile of Case 4. The CT shows a moderately large infarct in the posterior frontal, insular, and anterior parietal regions with deep extension. The FDG scans show hypometabolism in the region of the infarct and extends to adjacent frontal cortex and to more remote temporal cortex. The Z-scores were abnormal in both frontal and temporoparietal regions.

REGIONAL Z-SCORES

REGION														
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
-.6	-2.4	-3.3	-2.5	-3.3	-2.3	-2.5	-5.2	-4.6	-2.9	-2.5	-6.7	-1.0	-4.3	-9.5

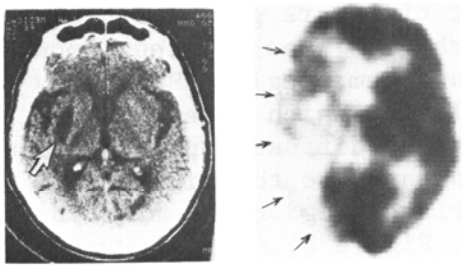


Figure 8. X-ray CT, FDG scan, and Z-score profile of Case 6. The CT shows a slit-shaped lesion in the putamen with no evidence of cortical damage. The FDG scan shows diffuse cortical left hypometabolism most prominent in temporoparietal regions. Z-score profile shows significant hypometabolism in the left hemisphere for all regions, most prominently in Regions 8, 12, 13, and 15 (Figure 2).

REGION Z-SCORES

REGION														
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
-2.0	-3.6	-5.2	-2.3	-3.5	-2.3	-6.3	-8.8	-5.3	-3.9	-6.8	-15.7	-7.8	-5.0	-8.7

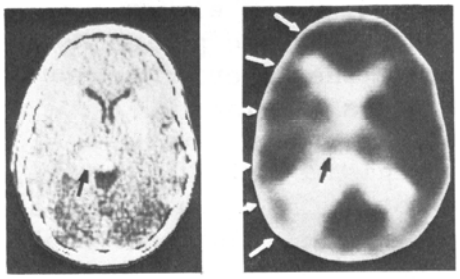


Figure 9. X-ray CT, FDG scan, and Z-score profile of Case 7. The CT shows a small thalamic hemorrhage. The FDG scan shows prominent hypometabolism in the left thalamus, and a diffuse cortical hypometabolism throughout the left hemisphere. Z-score profile demonstrates that Z-scores for all regions except visual cortex (13) are negative. Most regions were only mildly reduced in the left, compared with the right hemisphere.

REGIONAL Z-SCORES

REGION														
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
-1.1	-1.6	-1.3	-.5	-2.5	-1.1	-.9	-2.6	-1.3	-1.1	-1.3	-4.3	0	-.8	-1.6

regions were negative. In the nine controls, a mean of 7 of the 15 measured regions had negative Z-scores, with a standard deviation of 2.6. Thus 14 negative scores, as observed in Case 7, would be quite unusual in normal persons.

The FDG study in this case demonstrates a mild uniform reduction of left hemisphere metabolism for all regions except the visual cortex. The consistency of the asymmetry, region by region, suggests that some mechanism has been altered that acts on the overall level of cortical activity. This mechanism may act as a gain control set by deep grey structures. The overall functional level can be adjusted downward without major persisting clinical problems.

The seven cases demonstrate the variability that can be found in remote metabolic effects caused by infarcts and hemorrhages. A number of observations have been presented which require further investigation. (1) Structural damage can be associated with normal cortical metabolism and behavior (Case 1). (2) Structural damage involving white matter fiber tracts can result in disconnection of remote areas. It is the disruption of regional communication that is critical to account for behavioral changes (Geschwind, 1965) (Case 2). (3) Cortical infarcts, when symptomatic, consistently result in metabolic abnormalities not only at the site of damage but also in adjacent brain regions (Case 3). (4) Cerebral infarctions can result in metabolic abnormalities not only in regions adjacent to the lesion, but also at a distance. The latter regions are not as severely involved and may or may not be directly associated with the aphasic syndrome. The comparison of Cases 5 and 6 demonstrates this difference where both show the same degree of left frontal asymmetry but are very different in residual aphasia. Their FDG studies differ primarily in the degree of metabolic depression in parietal and posterior middle temporal regions. (5) Focal structural damage, particularly in deep nuclei, can result in functional disruption of the entire hemisphere (Case 7) with a generalized decrease in metabolism. Such changes may or may not be associated with residual behavioral abnormalities.

It is clear that complex relationships exist between the distribution of metabolic lesions and their relationship to behavior. A better understanding of the variability of brain metabolism in aphasic patients should improve our understanding of pathoanatomy and its relationship to behavior. This paper has presented some possible explanations for the sources of the variability.

ACKNOWLEDGMENT

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DISCUSSION

Q: What is the reliability of the scanning procedure?

A: If you do a PET scan and retest the patient 3 to 4 days later in the same state, there is up to 10 to 15% variability. The left to right ratios as used in this study, though, remain very constant. In a sample of 40 normals that we had previously studied with the ECAT II (our earlier scanner), the left to right ratios were very solid. If you examine local cerebral metabolic rates of glucose (LCMGGlc), you can get 10 to 15% changes, but when you examine the ratios, they remain very tight. If you take the same scan and determine the metabolic rates for the same region on two different days you can get a 5 to 15% variation. The changes that I have shown are outside of these ranges.

Q: Are you correlating some of those results with some of the language data?

A: That is the long-term plan. Right now we have done 33 cases in our current series. We have about 150 variables. I plan to wait another year. At

that point we should have about 70 cases and then we'll do some factoring to reduce the number of variables.

Q: What is the contribution or potential contribution of stimulation during the PET scanning and how might that or those conditions influence your present hypotheses?

A: In terms of your first question, stimulation is very important. All the studies I have shown you are done in the resting state, and the question is, "What is the individual doing during those studies?" If it is a college student they may be doing their homework. A housewife may be planning her evening meal. If it is an aphasic individual, I am not sure what they are thinking. The advantage of stimulation is that you can control a few more of the variables. The difficulty is that it is very hard, at least in my mind, to control enough variables to totally predict what the results might be.

Q: These seem to be important data for your first hypothesis.

A: Yes. The only data that I am aware of that has looked at this issue are John Mazziotta's with Huntington's patients. These are individuals who have lost their caudate nucleus. He has shown with several motor tasks (particularly a handwriting task where he has the individual write their name repeatedly while blindfolded) that normal subjects produce very little cortical activation. The major activation was in the caudate nuclei. When you looked at Huntington's disease patients without caudate nuclei, the writing task was driven by cortex.