Left Prefrontal Glucose Hypometabolism in Aphasia

E. Jeffrey Metter, Wayne R. Hanson, Daniel Kempler, Catherine Jackson, John C. Mazziotta, and Michael E. Phelps

Veterans Administration Medical Center, Sepulveda, California and Laboratory of Nuclear Medicine, UCLA School of Medicine

Left prefrontal hypometabolism has been observed using (F18)fluorodeoxyglucose (FDG) positron emission tomography (PET) in some aphasic patients with focal left hemisphere infarcts and hemorrhages. The prefrontal hypometabolism is independent of focal frontal structural damage. Comparing Broca's, Wernicke's and conduction aphasia patients, we found that differences in prefrontal metabolism tended to differentiate the three syndromes to a greater extent than did temporoparietal metabolism (Metter, Kempler, Jackson, Hanson, Mazziotta and Phelps, 1986). For these reasons, we investigated the role of the prefrontal cortex in aphasia by identifying the cortical and subcortical location of the lesions that cause left prefrontal hypometabolism, and the behavioral differences in patients with and without these changes.

METHOD

Subjects. Forty-five consecutively studied aphasic subjects participated in this study. Twenty-two age-matched control subjects were also studied by PET to determine normal metabolic distributions.

Behavioral Evaluation. The aphasic subjects completed the Western Aphasia Battery (WAB) (Kertesz, 1979), and were classified by aphasia type based on the criteria established for the WAB. In addition, each subject was rated for the degree of hemiplegia (functional disability) in the right arm and leg using a 5-point scale. For the arm, the ratings were 0 = normal, 1 = clumsy but usable, 2 = moderate to good strength but nonfunctional, 3 = minimal movement and nonfunctional, 4 = no movement. For the leg, they were 0 = normal, 1 = mildly spastic gait requiring no equipment, 2 = ambulates independently with cane, 3 = ambulates with assistive devises and with assistance, and 4 = unable to ambulate.

PET. All subjects were studied using (F-18)-fluorodeoxyglucose (FDG) on the NeuroECAT (CTI Inc., Knoxville, Tennessee) (Hoffman, Phelps, and Huang; 1983), in a resting state with eyes and ears unoccluded. They were injected with 5-10 millicuries and lay quietly on the scanner bed for 40 minutes, when scanning was started. Values of LCMRGlc were calculated as previously described (Huang, Phelps, Hoffman, Sideris, Selin and Kuhl, 1980; Phelps, Huang, Hoffman, Selin, Sokologg and Kuhl, 1979).

Fifteen regions of interest were measured in each hemisphere to obtain local cerebral metabolic rates for glucose (LCMRGlc). The approximate regional locations and sizes of each region are presented in Figure 1. Regions were then averaged to make 9 measures. The regions will be referred to as follows: superior frontal = regions 1 and 2, inferior frontal = regions 3 and 4, posterior inferior frontal (Broca's) = regions 5 and 6, parietal = regions 7 and 8, posterior superior temporal (Wernicke's) = regions 9 and 10, posterior temporal = regions 11 and 12, occipital = region 13, caudate = region 14, and thalamus = region 15. Regions were compared by computing a left/right ratio of LCMRGlc for homologous regions in each hemisphere.

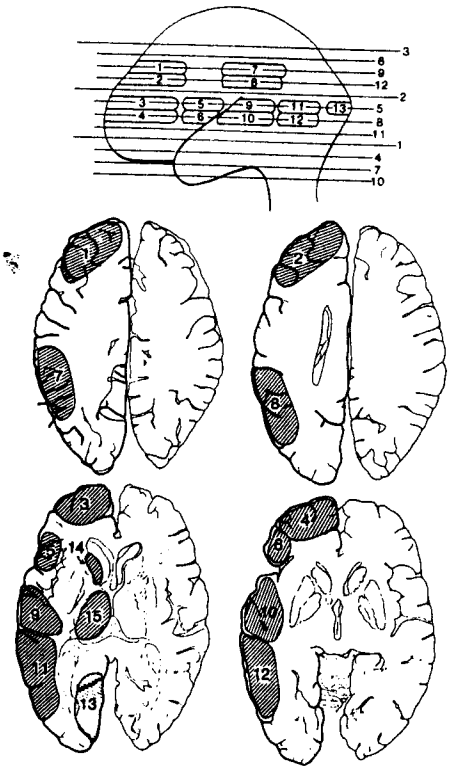

Figure 1. Regions of Interest (ROI) used in the quantitative measures for the study. The lateral section was derived from a rectilinear brain scan of a patient 40 minutes after injection of FDG. These scans are used to align the patient in the tomograph. The initial scanning planes are 1, 2 and 3. After completion, the patient is moved further into the scanner to obtain planes 4, 5 and 6, followed by 7, 8 and 9, then 10, 11 and 12, which represents a full set of scanning planes. ROI were generally obtained from planes 5, 8, 9 and 12 as illustrated. Tomograph sections of these four planes are shown with approximate location and sizes of the measured regions.

CT. Each aphasic subject had a CT scan done on either a Picker 1200SX or a GE 8800 CT scanner with scanning in the same plane as PET. The same sixteen regions measured for glucose metabolism were rated and reduced to 9 measures. In addition, the anterior internal capsule, posterior internal capsule, insula and lenticular nuclei were rated. Each region was rated on a 5-point scale by a neuroradiologist (blinded to the rest of the data) and a neurologist (EJM). The scale was 0 = normal, 1 = atrophy (sulcal enlargement with no evidence of specific tissue damage), 2 = damage but no loss of tissue (tissue was clearly infarcted but overall regional structure appeared intact), 3 = partial tissue loss, and 4 = complete tissue loss. The two ratings for each region were averaged to obtain an estimate of the degree of structural damage. A 90% agreement was found for all regions by the two raters.

RESULTS

The superior and inferior frontal left/right ratios in the aphasic patients were compared with those of controls. Two groups of aphasic subjects were identified. First, 28 patients were found who had left/right

ratios lower than the controls in the prefrontal regions (95% confidence lower limit = .94). These patients will be referred to as the asymmetric group. Second, 17 patients had prefrontal left/right ratios which were in the normal range (i.e. prefrontal metabolic ratios >.94). These patients will be referred to as the symmetric group.

The two aphasic groups differed significantly in regional left/right ratios (MANOVA F = 12.33, p< .00001) including low values for the asymmetric group in univariate F-tests of the superior and inferior frontal, Broca, parietal, caudate and thalamic measures (Table 1). On stepdown analysis only the superior frontal and caudate ratios remained significant, accounting for most of the differences between the two groups.

Table 1. Left/right metabolic ratios for each region.

	SFR	IFR	PIF	Par	PST	PostT	Occ	Caud	Thal
Symmetric (N=17)	.99	1.03	.92	.78	.67	.65	.98	.93	.88
S.D.	.05	.05	.15	.16	.18	.22	.07	.07	.09
Asymmetric (N=28)	.69	.71	.56	.53	.56	.61	.91	.46	.51
S.D.	.16	.19	.26	.19	.29	.23	.12	.22	.18

Note. SFR=superior frontal, LFR=inferior frontal, PIF=posterior inferior frontal (Broca), Par=parietal, PST=posterior superior frontal (Wernicke), PostT=posterior temporal, Occ=occipital, Caud=caudate, Thal=thalamus.

A principal components analysis was used to examine the patterns of intercorrelations among the 9 regional left/right ratios. Two components were identified (Table 2). The first component accounted for 41% of the variance and was most heavily loaded by the frontal and subcortical metabolic measures. The second component accounted for 26% of the variance and was loaded most heavily by the temporoparietal regions. Thus metabolic changes occurring in the frontal regions were strongly correlated with changes in caudate and thalamic regions. These measures behaved relatively independently of what occurred in the temporal lobe (Component 2).

CT comparisons between the two groups were analyzed using a Mann-Whitney U analysis (Table 3). The asymmetric group showed greater structural damage (p< .01) in the left posterior inferior frontal (Broca's), and subcortical regions.

The demography and patient classification of the two groups was also examined. The asymmetric group included all Broca's aphasia patients (N = 8), while six of eight conduction aphasia subjects were in the symmetric group. Anomic and Wernicke's aphasia patients were found in both groups. No differences were found between the two groups on age (each group averaged 62 years) or duration post stroke (symmetric group 29 months, range 2-81; asymmetric group 19 months, range 1-79).

To examine the behavioral differences between the two groups, WAB scores were compared (Table 4). The asymmetric group was found to have a lower mean WAB aphasia quotient (t = 3.25, p = .003). A MANOVA showed a significant

Table 2. Principal components analysis of left/right ratios.

	Component 1	Component 2
Eigenvalue	3.69	2.30
Percentage of Variance	40.9	25.6
Superior Frontal	-.80*	.29
Low Frontal	-.85*	.13
Broca's	-.89*	.01
Caudate	-.71*	-.49
Thalamus	-.65*	-.40
Parietal	-.48	.58*
Wernicke's	-.47	.75*
Posterior Temporal	-.32	.81*
Occipital	-.12	.50

Note. The above matrix was calculated without iterations. The loadings for each region represent the correlation of the regional left/right ratio to the component. A * indicates a strong loading to the component.

Percentage of variance represents the amount of the total variance present in the left/right ratios that can be accounted for by the component.

Table 3. Structural differences assessed by Mann-Whitney U test.

	Mean Rank		U	P(1-Tailed)
	Symmetrical	Asymmetrical		
Superior Frontal	20.29	24.64	192	.25
Inferior Frontal	19.24	25.29	174	.054
Post Inf Frontal	17.00	26.64	136	.01
Parietal	19.00	25.43	170	.11
Post Sup Temporal	17.29	26.46	141	.02
Post Temporal	26.53	20.86	178	.16
Occipital	23.91	22.45	222	.54
Caudate	16.41	27.00	126	.004
Thalamus	17.68	26.23	148	.015
Ant Inter Capsule	14.00	28.46	85	.0001
Post Inter Capsule	14.53	28.14	94	.0004
Lenticulate Nuc	12.38	29.45	58	.0000
Insula	14.79	27.98	99	.0009
Body of Caudate	13.29	28.89	73	.0001

multivariate difference between the two groups ($F = 4.63$, $df = 7$, $p = .0009$). Univariate F-tests ($p < .01$) showed them to differ on subtests of writing ($F = 22.2$, $DF = 1,42$, $p = .002$), naming ($F = 11.3$, $p = .002$), reading ($F = 10.3$, $p = .003$), repetition ($F = 10.7$, $p = .002$), information content ($F = 11.2$, $p = .002$) and fluency ($F = 19.3$, $p = .00007$) with the asymmetric group showing lower scores for all measures. Roy-Bargmann stepdown showed that on multivariate analysis only information content ($F = 11.2$, $p = .002$), fluency ($F = 8.7$, $p = .005$) and writing ($F = 7.3$, $p = .01$) were significantly different -- i.e., the other measures showing univariate differences were accounted for by their relations to these three tests. A Mann-Whitney analysis revealed that the asymmetric group had greater arm and leg functional disability than the prefrontal symmetric group ($p < .005$).

Table 4. Language scores on Western Aphasia Battery.

	Info	Fluen	Comp	Nam	Rep	Read	Writ	AQ
Symmetric	8.4	8.4	17.2	7.8	77	83	80	81
S.D.	2.5	1.1	3.1	2.5	16	21	21	16
Asymmetric	5.4	5.2	14.5	4.5	47	57	39	54
S.D.	3.1	2.9	5.3	3.4	35	28	32	28

Note. Info = information content, Fluen = fluency, Comp = comprehension, Nam = naming, Rep = repetition, Writ = writing, Read = reading, AQ = aphasic quotient.

These analyses have considered variables that differentiated two aphasic subgroups. First, glucose metabolism was used to divide patients into symmetric and asymmetric groups. Second, the extent and location of structural damage was demonstrated to be different for the two groups. Third, the two groups were found to differ behaviorally. These observations reveal little about the interrelationships among structure, metabolism and behavior. Clearly, the changes that occur in behavior result from the structural damage caused by stroke. What is not understood is the relationship between the structural changes, what happens elsewhere in the brain, and their combined effect on behavior.

We propose that causal modeling (Duffy, Watt and Duffy, 1981; Asher, 1976) can be used to test the extent to which behavior can be accounted for by structural and metabolic changes. Causal modeling techniques allow for the application of the general linear model using correlation (including partial) and regression methods to predict critical constants and to derive testable equations. For causal modeling to be useful several criteria are necessary. (1) A model needs to be developed *a priori*. (2) Variables have to vary or covary. (3) There must be temporal sequencing between variables. (4) No other causal factors should exist which could account for the covariation. If these assumptions are met, a causal relationship can be argued (Duffy *et al.*, 1981; Asher, 1976).

One such model (Figure 2) represents the effect that structural damage to the subcortical structures (caudate, internal capsule, lenticular nucleus and thalamus) has on frontal metabolism and behavior. The assumption is that when these structures are damaged, they (as well as associated cortical damage) affect metabolism (function) in frontal and temporoparietal regions. Our hypothesis is that the structural damage and functional changes have an additive effect on behaviors. The model allows us to state this quantitatively -- the value of the variable following an arrow can be obtained by multiplying the variable preceeding the arrow by the constant (p) for the arrow.

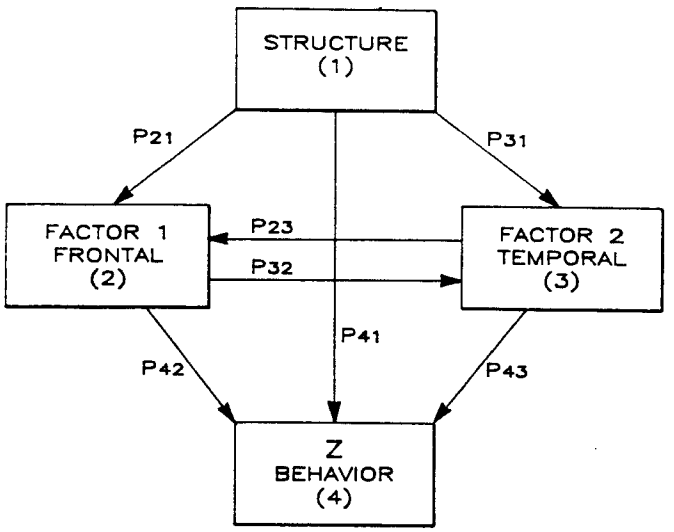

Figure 2. Model of the relationship between structure, metabolism and behavior. This figure is a general model. Structure refers to damage occurring in the subcortical regions secondary to cerebral infarction or hemorrhage in the aphasic patients that were studied. Factor 1 - Frontal was calculated by averaging the frontal left/right ratios and reflects Factor 1 (Table 2). Factor 2 - Temporal was calculated by averaging the posterior superior temporal and posterior temporal left/right metabolic ratios. Z refers to behavior that is to be explained by the model. The relationship between these measures can be expressed based on the presence of an arrow between boxes. The arrow states that the box being pointed to can be determined by multiplying the box from which the arrow comes by the corresponding constant (p).

For the model in Figure 2, the following assumptions were made.

(1) The metabolic asymmetries found in aphasic patients compared with normal subjects are caused by the structural damage associated with cerebral infarction and/or hemorrhage.

(2) The extent of structural damage to a brain region can be estimated on CT, and the scalar rating system used for this study is linear. Evidence to support this statement was derived by examining CT by densitometry and showing a good correlation to the scalar system (unpublished data).

(3) The degree of functional capabilities of specific brain regions are reflected in the metabolic ratio.

(4) The extent of structural damage and metabolic asymmetries are responsible for some aspects of the behavioral abnormalities.

To test the model, structural damage in the deeper structures (those regions that most strongly distinguished the two metabolic asymmetric groups) was estimated by averaging the CT ratings for the caudate, thalamus, lenticular nucleus and insula to create a single score. A prefrontal metabolic measure was estimated by averaging metabolic left/right ratios of the superior, inferior prefrontal, and posterior inferior frontal ratios to represent Factor 1 (Table 2). A posterior temporal measure was derived by averaging the posterior superior and posterior temporal ratios to reflect Factor 2 (Table 2). Two behavioral measures (Z, Figure 2) were examined -- fluency and sequential commands from the WAB.

The results of the analysis are presented in Figures 3 and 4. Using regression analysis, the constants (p's which show the strength of associations within the model) were estimated and are shown. Using these constants, the accuracy of the model can be tested by predicting the correlation coefficients. The model in Figure 3 reasonably predicted the correlation coefficients, except for the correlation between Factor 1 and Fluency where the predicted coefficient = .51 and the actual coefficient was .67. This demonstrated that the model accounted for the relationship between structure, metabolism and fluency in these patients (r^2 = .47). However, another factor appears to be needed to account for the correlation between Factor 1 and fluency.

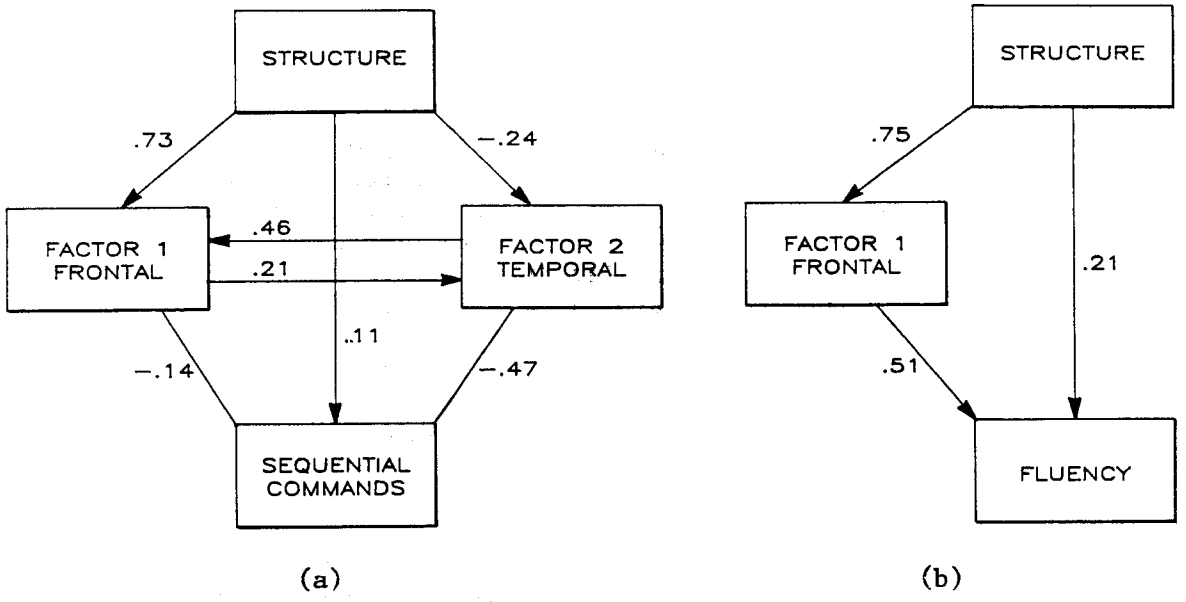

Figure 3. Model to explain the relationship between structure, metabolism and fluency (WAB). (a) The entire model with P constants calculated by using regression analysis. The model was tested by predicting correlations calculated between each pair of variables. The model was accurate except in explaining the correlation between Factor 1 and Fluency where the actual correlation was .67. (b) Simplified model with slightly better accuracy than in (a) and demonstrating the minor affect of the temporal metabolic ratio in explaining fluency.

The analysis of sequential commands showed a very different structural relationship (Figure 4). In this case, structural damage and Factor 1 contributed to the behavioral measure (r^2 = .26), while Factor 2 was of much less significance.

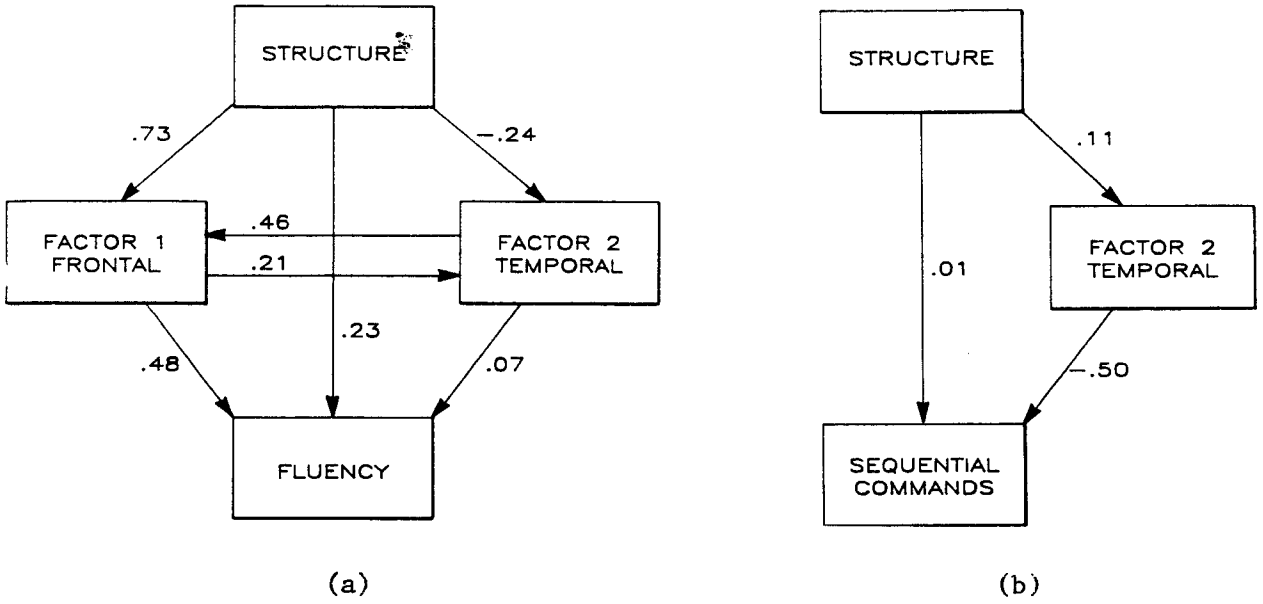

Figure 4. Model to explain the relationship between structure, metabolism and sequential commands (WAB). (a) The entire model. (b) A simplified model. This model demonstrates that changes in sequential commands is related to the effect of structural damage on temporal metabolism with little additive effect from either structural damage directly or from frontal function.

DISCUSSION

The study demonstrates that prefrontal metabolic asymmetry is a common finding in aphasic patients, and the asymmetry does not require direct structural damage to this area. The prefrontal asymmetry was strongly associated with metabolic ratios for Broca's, parietal, caudate and thalamic regions (Factor 1, Table 2). Temporal lobe left/right ratios were independent of the prefrontal measures. All subjects had left temporoparietal hypometabolism. In fact, it has been our experience (unpublished observations) that all aphasic patients have metabolic abnormalities in the left temporoparietal region.

The presence of frontal asymmetry differences is a striking observation in aphasic subjects. These findings raise questions about the role of the frontal asymmetry in aphasia. One hypothesis is that the prefrontal relationships are a reflection of an integrated brain system specialized for motor behavior extrinsic to language functioning (DeLong, Georgopoulos

and Crutcher, 1983; Eccles, 1979; Wiesendanger, 1983). Evidence for such a "motor" system comes from behavioral comparisons between the two aphasic groups. The prefrontal asymmetric group had greater motoric disability (i.e., poor functioning of leg and arm), and greater deficits in language output (writing and spontaneous speech) than the symmetric metabolic group. Whether these behavioral observations reflect only motor performance or a combination of motor and other frontal functions (e.g. the ability to shift sets) cannot be established at present. The modeling in Figures 2 to 4 is consistent with a motor factor where the frontal lobe functions are relatively independent of the posterior temporal language areas in the execution of speech (as reflected by the fluency measure). In Figure 3, fluency can be accounted for directly by the presence of structural damage to subcortical structures and to the action of frontal regions (Factor 1).

The two aphasic groups did not differ on specific measures of auditory comprehension and repetition. The uniformity of these language performances parallels the uniformity observed in temporal lobe metabolic measures in the two groups. These findings are also consistent with our previous report showing a strong correlation of comprehension, naming and repetition to temporal and parietal measures (Metter, Riege, Hanson, Camras, Kuhl and Phelps, 1984). The model in Figure 4 is consistent with this conclusion, as comprehension of sequential commands was found to be strongly associated with the posterior temporal measures.

Behavioral differences across aphasic syndromes may relate to metabolic differences in the frontal regions and those structures that change metabolically with it (i.e., Factor 1). FDG PET studies of Wernicke's, Broca's and conduction aphasias suggested this possibility, because the three syndromes differed in prefrontal cortical metabolism while showing similar metabolic abnormalities in temporoparietal regions (Metter, Kempler et al., 1986; Metter, Jackson, Kempler, Camras, Hanson, Mazziotta, and Phelps, 1986). The observations from this study suggest that (1) aphasia relates to changes that occur in temporoparietal regions, (2) prefrontal asymmetry resulting from subcortical structural damage is a common occurrence in aphasia and (3) specific syndromes are related to the extent of the aphasia and modification of behavior by what happens in frontal lobes.

ACKNOWLEDGMENT

Funded in part by Veterans Administration Medical Research, Department of Energy Contract #DE-AM03-76-SS00012 and U.S. Public Health Service Research Grants R01-GM-24839 and P01-NS-15654. Dr. Mazziotta is the recipient of Teacher Investigator Award 1K07-NS-0058805 from NINCDS.

REFERENCES

Asher, H.B. Causal Modeling. Beverly Hills, CA: Sage, 1976.

DeLong, M.R., Georgopoulos, A.P., and Crutcher, M.D. Cortico-basal ganglia relations and coding of motor performance. In Massion, J., Paillard, J., Schultz, W., and Wiesendanger, M., (Eds.), Neural Coding of Motor Performance. Berlin: Springer-Verlag, 1983.

Duffy, J.R., Watt, J., and Duffy, R.J. Path analysis: A strategy for investigating multivariate causal relationships in communication disorders. Journal of Speech and Hearing Research, 24, 474-490, 1981.

Eccles, J.C. Introductory remarks. In J. Massion and K. Sasaki (Eds.), Cerebro-cerebellar Interactions. Amsterdam: Elsevier/North-Holland Biomedical, 1979.

Hoffman, E.J., Phelps, M.E., and Huang, S.C. Performance evaluation of a positron tomograph designed for brain imaging. Journal of Nuclear Medicine, 24, 245-257, 1983.

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, 69-82, 1980.

Kertesz, A. Aphasia and Associated Disorders: Taxonomy, Localization, and Recovery. Orlando, FL: Grune and Stratton, 1979.

Metter, E.J., Riege, W.R., Hanson, W., Camras, L., Kuhl, D.E., and Phelps, M.E. Correlations of cerebral glucose metabolism and structural damage to language function in aphasia. Brain and Language, 21, 187-207, 1984.

Metter, E.J., Jackson, C.A., Kempler, D., Camras, L., Hanson, W.R., Mazziotta, J.C., and Phelps, M.E. Glucose metabolic asymmetries in chronic Wernicke's, Broca's and conduction aphasias. Neurology, 36, 317, 1986.

Metter, E.J., Kempler, D., Jackson, C.A., Hanson, W.R., Mazziotta, J.C., and Phelps, M.E. Cerebral glucose metabolism: Differences in Wernicke's, Broca's and conduction aphasia. In R.H. Brookshire (Ed.), Clinical Aphasiology: Conference Proceedings, 1986. Minneapolis, MN: BRK Publishers, 1986.

Phelps, M.E., Huang, S.C., Hoffman, E.J., Selin, C.S., Sokoloff, L., and Kuhl, D.E. Tomographic measurement of local cerebral metabolic rate in humans with (F-189 2-fluoro-2-deoxyglucose): validation of method. Annals of Neurology, 6, 371-388, 1979.

Wiesendanger, M. Cortico-cerebellar loops. In J. Massion, J. Paillard, W. Schultz, and M. Wiesendanger (Eds.), Neural Coding of Motor Performance. Berlin: Springer-Verlag, 1983.

DISCUSSION

Q: Would you explain why there can be an abnormality in metabolism when there is no visible structural damage as in one of the slides you have shown?

A: Please turn on the slide projector and we'll look at the next slide. This slide was shown by Dr. Michael Weinrich on Sunday and was from the paper by Damasio et al. in the Archives of Neurology (1982). The slide shows the corticospinal connections of the prefrontal region and their relationship to the striatum, globus pallidus and thalamus. Fiber tracts going and coming from the prefrontal areas course through the internal capsule. These fibers represent a major output and input to the prefrontal areas. They allow prefrontal regions to communicate with the brainstem, thalamus, cerebellum, basal ganglia and to some extent other parts of the cortex. When subcortical structures are damaged these pathways can be injured or destroyed, disrupting normal

communication networks of the prefrontal region. In a previous study (Metter et al., Neurology 1985; 35, 1695-1701), we were able to study a patient's brain and compare structural and metabolic changes. The patient died one week after having a resting FDG PET scan. On pathologic examination, the patient had a left lacunar infarct that destroyed the anterior limb of the left internal capsule. On histologic examination, no apparent structural damage was found in comparing the left and right prefrontal regions. However, glucose metabolism was decreased by about 25% in the left compared with the right prefrontal region. The reason for the metabolic change was related to the destruction of the internal capsule, which disrupted prefrontal inputs and outputs. If you look at it as circuitry, by cutting the wires you have a direct and indirect effect on cortical function that is reflected in metabolism.

Q: Is it that there is indeed some cortical damage but you just can't see it? Do you have to have some structural damage to have altered metabolic uptake in a region?

A: No you don't.

Q: Then what do you mean by saying that some of the pathways are destroyed or disturbed? What is the nature of that damage if it is not structural?

A: A neuron has a cell body and a long axon. If you cut the axon, the cell body remains alive. What is lost is connections to elsewhere in the brain. The structural integrity of the cortex can remain. Are there subtle structural changes in dentritic arborization and cellular biochemistry? That is much harder to evaluate. With deep lesions, the dendritic firing pattern changes because of fewer dendrites; the metabolic demand of the cortex will decrease and be reflected in decreased glucose metabolism.

Q: I don't understand the difference between structural and functional change.

A: By structural change, I mean that the overall anatomic organization of the region is altered, with loss of neurons. A change in function can mean a lot of things since it is a general term. Physiologically, it can mean a decrease in the amount of dendritic activity, or an alteration in inhibition or excitation within the cortex. That doesn't require structural alterations to the area, but changes in firing patterns of fibers coming into the area. Structurally, we cannot say that there is no ischemic damage, but we can only say that we have no evidence for it. In the one pathologic case we studied, there was no evidence of pathologic ischemic changes in the metabolically depressed left prefrontal area. When you take cortex and examine it histologically, there are typical changes that occur with ischemia. These were not seen in the patient studied.

Q: You studied your patients at 6 months post-onset or longer. Are there data demonstrating when the hypometabolism first occurs?

A: Yes there are. Hypometabolism can be demonstrated within the first twenty-four hours. I am not aware of studies which have examined patients within the first 4 to 6 hours. Diaschesis appears within the

first 24 hours and then improves over time. In our studies, the earliest patient studied was about one week post event.

Q: Is it important to correlate findings from for example positron emission tomography with behavior such as fluency? If we are going to establish such relationships, is it important for us to know when both phenomena occur? Is it crucial to know that those phenomena occur simultaneously?
A: The answer to both questions is yes.

Q: As I recall my internal capsule anatomy, there are fibers from other parts of cortex coursing through that area. Do you find hypometabolism in other areas of cortex? Other areas for example that are connected to subcortical structures by fibers coursing through that area?
A: Yes.

Q: As I recall, there are parietal fibers in that area. Do you find hypometabolism in the parietal region and you did not feature that in your slides or did I somehow miss it some other way?
A: Basically, in the anterior internal capsule almost all the fibers go to the frontal lobes. The fibers going to the parietal lobe tend to be more posterior in the internal capsule. In the population we studied, there was much less damage to the posterior internal capsule. We have seen cases with focal small posterior internal capsule or posterior lenticular nuclei lesions that are associated with parietal hypometabolism.

Q: So patients with more posterior lesions do show hypometabolism in the parietal lobe?
A: Yes. In this study, we did not see consistent damage to more posterior parts of the internal capsule. In the way we read the CT scans, focal damage this far posterior, may not have been completely expressed. We were more interested in the region closer to the genu and mid portion. When we have seen lesions more posterior and when they have been behaviorally significant, they are associated with parietal hypometabolism. We have seen several patients where lesions were in this area and were clinically silent. In such instances, no cortical hypometabolism was found. We have raised the hypothesis that for a lesion to be clinically important with persistent behavioral consequences, it has to have remote metabolic effects. We have seen about seven patients with "silent" lesions and the lesions have not shown remote metabolic effects. In fact, in our CAC paper 1985, one such patient was presented.

Q: What is known about the permanency of the remote hypometabolism? Does it last, or at what rate does it reduce if it does reduce?
A: In our experience, we have studied 10 patients 1 to 2 months post onset and again 6 months later. Most patients will show a general improvement. The left/right ratios, though, remain pretty much the same. What changes is the overall level of metabolism throughout the brain. All regions tend to shift up, down or stay about the same. Other groups looking at blood flow have shown improvements in flow over the first six weeks to three months which represent diaschesis. We have studied

patients out to 16 years and the scans look the same as those that I have shown you. Many of the hypometabolic patterns are persistent and represent a persistent marker.

Q: I think that the use of path analysis with data like these is a perfect application of that technique because it forces you to hypothesize a model that explains behavior. I think it is a nice way to blend anatomic and physiologic data into a model, and then to test the model explicitly with a statistical technique. I have one question. When you use path analysis there is a procedure that can be used at the end to regenerate the correlations. If you can do that accurately it lends credence to the model, and if you cannot do it accurately it should lead you to reject the model. Did you do that regeneration and how did that come out?

A: Yes I did. The two models predicted correlations very well. Only the correlation between the frontal measure and fluency was approximate. The predicted correlation based on sample size and how variables were arranged varied from .49 to .57 while the actual correlation was between .65 and .69. That was the only correlation that was not carefully predicted, and it suggested that in the frontal region there are one or two compartments that need to be separated. We averaged many measures into the frontal value, so that overall the prediction was good.

Q: What it suggests is that you cannot reject those models.

A: No, we can't.