

Subcortical Structures in Aphasia

An Analysis Based on (F-18)-Fluorodeoxyglucose, Positron Emission Tomography, and Computed Tomography

E. Jeffrey Metter, MD; Walter H. Riege, PhD; Wayne R. Hanson, PhD;
Catherine A. Jackson, MA; Daniel Kempler, PhD; Diana van Lancker, PhD

• Subcortical structural damage that includes the anterior and posterior internal capsule, caudate, thalamus, lenticular nuclei, and insula has been shown to cause aphasias. A critical question that has not been resolved is whether the role of these structures on behavior is a direct one or whether it is indirect through the cortex. We have used pathway analysis to evaluate computed tomography, glucose metabolic, and language data from 47 aphasic patients to answer this question. For fluency (from the Western Aphasia Battery), subcortical structural damage had direct and indirect (through frontal lobe) effects on the behavior. For a comprehension task (sequential commands), subcortical damage had no direct effect and only a slight indirect effect through the temporal lobe. Thus, both direct and indirect effects of subcortical damage can be demonstrated for specific behavioral measures.

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Recent interest in aphasia has been on the role of subcortical structures in mediating or supporting language abilities. Reports have shown that subcortical lesions (internal capsule, striatum, globus pallidus, and

thalamus) can result in aphasia.^{1,7} A uniform model of the pathoanatomy of aphasia clearly needs to consider the role of these subcortical structures. This article asks the question whether subcortical structural damage directly causes behavioral symptoms in aphasia or whether it does so indirectly through the cortex?

To understand the association of cortical function to subcortical damage, a measure is needed which reflects the functional integrity of brain tissue independent of structural damage. One such measure is the rate of glucose metabolism demonstrated by positron emission tomography (PET), since glucose metabolism can be shown to increase linearly with increased firing of neurons.⁸ In previous studies of aphasic patients, we have demonstrated that resting patterns of glucose metabolism are distinctly different from structural damage as found by x-ray computed tomography (CT)⁹ or at autopsy.¹⁰ By comparing data obtained from CT and PET, we can better understand the relationship between structure and brain function.

Previously,¹¹ strong correlations were found among prefrontal, posterior-inferior frontal (Broca's region), parietal, caudate, thalamus, and cerebellar glucose metabolism in aphasic patients studied more than four months after the event. A principal components analysis (a technique that examines how variables cluster or group) revealed that these regions constituted the first component accounting for 65% of the variance. A

second component consisted of temporal and parietal metabolism and accounted for 22% of the variance. No other components were found to be important. These observations permit the inference of two brain systems involving the cortical metabolism of aphasic patients: a frontal system linked with subcortical regions, and a temporal system. Parietal metabolism was associated with both systems.

In addition, the left frontal hypometabolism (that included most of the lateral aspect of the lobe) did not necessarily result from direct frontal structural damage. Fifty-seven percent of aphasic subjects¹¹ were found to have left prefrontal hypometabolism (both anterior and superior to Broca's region), while 22% had structural damage in these areas. Subjects with and without left frontal hypometabolism differed on the extent of structural damage to subcortical regions, including the internal capsule (anterior and posterior limbs), caudate, lenticular nuclei, thalamus, and insula. The degree of structural damage in these deep regions was strongly intercorrelated.

The observations on subcortical structural damage suggested that for simplicity in modeling, these regions could be considered as a single measure. This study examines the degree of structural damage to subcortical structures rather than metabolic changes for two reasons: (1) the resolution of PET at present does not allow for accurate analysis of most subcortical structures, and (2) the intent was to compare structural

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From the National Institute of Aging, Gerontology Research Center, Baltimore (Dr Metter); the Veterans Administration Medical Center, Sepulveda, Calif (Drs Riege, Hanson, Kempler, and van Lancker, and Ms Jackson); and the UCLA School of Medicine, Los Angeles (Drs Metter, Riege, and van Lancker).

Reprint requests to Gerontology Research Center, 4940 Eastern Ave, Baltimore, MD 21224 (Dr Metter).

damage with distant metabolic effects, since most current behavioral studies focus on structural damage.

Path analysis¹²⁻¹⁴ was adopted for post hoc data analysis. It applies regression and partial correlation techniques to equations developed from a model and differs from multiple regression analysis in (1) a given model may consist of more than one regression equation, and (2) specific criteria need to be met to describe directionality and causality. Figure 1 proposes a model of the relationship between structural damage to subcortical regions, their indirect effects on frontal or temporal regions, and behavior. The presence of an arrow between two boxes implies a causal linkage between the box from which the arrow arises and the box to which it is connected. The "p" is a causal coefficient that, when calculated, indicates how much change occurs in the receiving box when the causative box changes 1 unit. For Fig 1, the model states that subcortical damage can cause changes in behavior directly, or have an effect on the frontal and temporal regions that subsequently effects behavior.

To show causal relationships within the model the following criteria are needed: (1) time precedence (the cause needs to precede the effect); (2) temporal priority or relationship between the two variables (the two variables being considered need to be reasonably associated in time, space, or function and the relationship is not by chance); and (3) nonspuriousness (there must not be a third variable causing the changes in both variables under consideration). Thus, by proposing a reasonable model, equations can be written to solve for the p's, and the p's can be estimated by multiple regression analysis. The model can then be tested by examining how closely the true Pearson correlations between variables can be calculated from the pathways coefficients.

The following observations, made from our aphasic patients, argue that the model in Fig 1 can be considered as a causal one. In normal subjects, local cerebral metabolic rates of glucose (LCMRG1c) for homologous brain regions in each hemisphere are symmetric. Following a left hemisphere cerebral infarction or hemorrhage, many apparently undamaged regions show left/right metabolic asymmetry for homologous regions. Likewise, focal brain damage was accompanied by the development of aphasia. These observations argue for time precedence and an appropriate

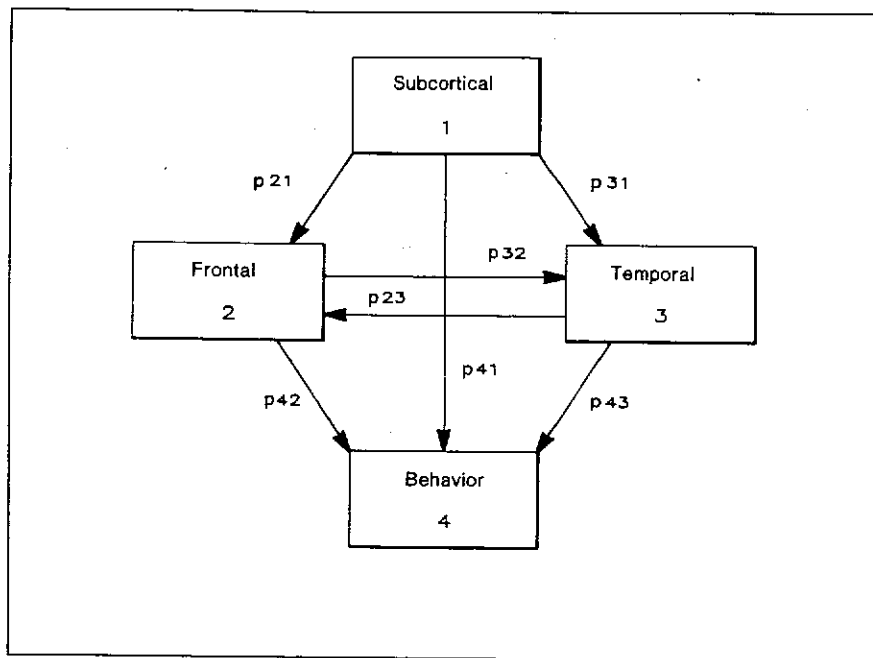


Fig 1.—General model of relationship among subcortical structural damage, metabolism, and behavior. Model states that subcortical damage has direct effects on behavior (arrow p41), frontal (arrow p21), and temporal (arrow p31) lobes. Frontal calculated by averaging frontal metabolic reference ratios. Temporal calculated by averaging posterosuperior temporal and posterior temporal metabolic reference ratios. Both frontal and temporal lobes have effect on behavior. Subcortical damage has indirect effect on behavior based on its effects on frontal and temporal lobes. Relationship between these measures can be expressed based on presence of arrow between boxes. Arrow states that the box being pointed to can be determined by multiplying the box from which arrow comes by the corresponding constant (p). By calculating p's, strength of the relationships in the model can be calculated to determine which relationships are most viable. (For an explanation of "p," see text.)

relationship. The structural damage preceded and was appropriate to cause the metabolic asymmetry and the aphasia. Nonspuriousness is more difficult to argue, but no other variables are likely to have caused the structural damage, metabolic asymmetry, and behavioral changes. Our studies have included patients with cerebral infarctions and hemorrhages, so that general cerebral ischemia secondary to vascular stenosis could not be such a common variable.

Several further assumptions need to be made for the model in Fig 1: (1) The extent of structural damage can be estimated on CT, and the scalar rating system used in this study is linear. (2) Local cerebral metabolic rates of glucose are related to the capability of regions to carrying our specific behaviors. (3) Regional cortical glucose metabolism reflects changes associated with direct damage and/or remote effects; both of which are relevant to behavior. (This issue is tested in Model 2.)

Several related models are tested in this article starting with the model in Fig 1. Two behavioral measures from

the Western Aphasia Battery¹⁵ were selected for study: fluency and sequential commands. In previous studies, reduced fluency was found to correlate strongly with left frontal hypometabolism,¹¹ while impaired comprehension of sequential commands was found to correlate with left temporal hypometabolism. These behavioral measures were not selected to reflect any specific language process, but rather because of their correlations to frontal or temporal functions. In this manner, we optimized our analysis of direct and indirect effects of subcortical structural damage.

SUBJECTS AND METHODS

Subjects

Forty-seven subjects who were studied were aphasic secondary to a cerebral infarct or hemorrhage in the left hemisphere with a history of only a single event. All subjects were right-handed, and five were female. Many were being treated for cardiac disease and hypertension, but none was taking sedatives, tranquilizers, or anticonvulsants. Age ranged from 37 to 73 years with a mean of 62 years. Subjects were tested with the Western Aphasia Battery.¹⁵ All were studied more than six

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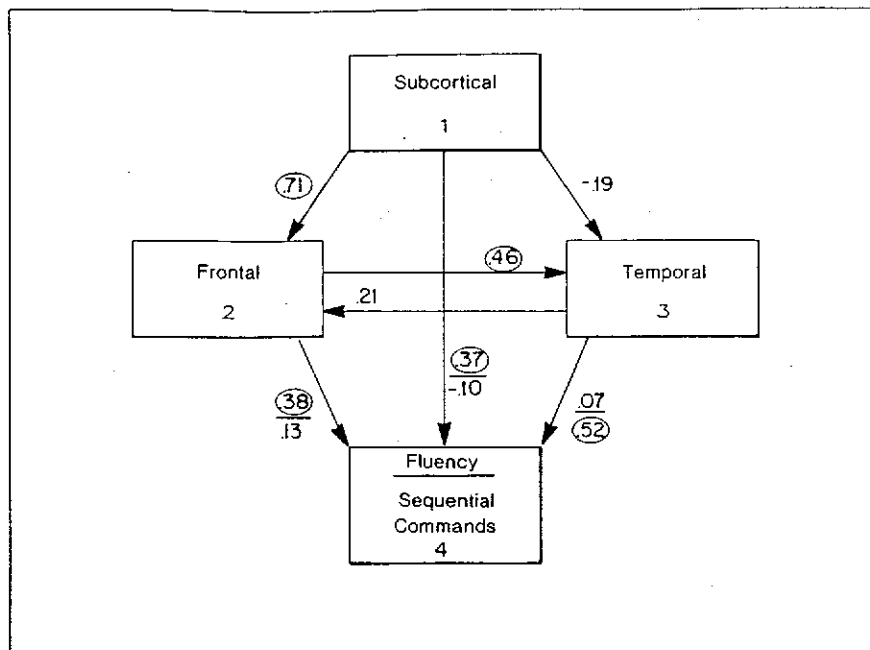


Fig 2.—Model 1. Relationship among structure, metabolism, and fluency or sequential commands from Fig 1. In the model, pathway coefficients for structural and metabolic interrelationships are the same for both behavioral measures. Differences in pathways are from subcortical structural measure, frontal, and temporal metabolism to the behavior. These pathway coefficients (p41, p42, p43) are shown with fluency above the line and sequential commands below. (1) Subcortical structural damage had both direct and indirect effect (through frontal lobe) on fluency. (2) Sequential commands, subcortical damage had no effect on this behavior. Major effect resulted from temporal lobe. (For an explanation of "p," see text.)

Table 1.—Correlations Model 1*

	Computed Tomography		
	Subcortical	Frontal	Temporal
Frontal	.67 (.67)
Temporal	.14 (.15)	.29 (.32)	...
Fluency	.64 (.67)	.67 (.68)	.22 (.25)
Sequential commands	.05 (.08)	.34 (.23)	.57 (.55)

*Nine of nine comparisons of calculated correlations approximated actual correlations. The first set of correlations given are calculated from pathway analysis, while that within parentheses is the actual correlation. Frontal and temporal refer to the metabolic reference ratios.

weeks after onset of the aphasia. The majority were four to 12 months after a stroke.

PET

Subjects were studied using (F-18)-fluorodeoxyglucose on the PET scanner (NeuroECAT) (CTI Inc, Knoxville, Tenn),¹⁶ in a resting state with eyes and ears unoccluded. They were injected with 5 to 10 mCi of (F-18)-fluorodeoxyglucose, arterialized venous blood samples were drawn to establish an arterial blood curve, and scanning was started 40 minutes later. Values of LCMRG1c were calculated as previously described.^{17,18}

Sixteen regions of interest were measured in each hemisphere to obtain LCMRG1c. The approximate regional locations and sizes have previously been reported.¹¹ A single frontal value was obtained by averaging the six measures of the prefrontal and posteroinferior frontal

(Broca's area) regions. A single temporal value was calculated by averaging the four measures of the posterosuperior temporal (Wernicke's area) and middle and lateral inferior temporal regions. Since left hemisphere LCMRG1c had high variance, the frontal and temporal measures were divided by the average right hemisphere LCMRG1c for each subject. This ratio has been referred to as a "reference ratio."¹⁹ The mean right hemisphere LCMRG1c has been shown to have a normal value in these patients when compared with normal subjects.¹¹

CT

Each aphasic subject had a CT scan done on a CT scanner (Picker 1200SX or a GE 8800) with scanning in the same plane as PET. The same 16 regions as measured for glucose metabolism, as well as the anterior and posterior limbs of the internal capsules, insula, and lenticular nuclei were

rated on a 5-point scale by two evaluators (with a 90% agreement) and averaged out. 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 CT films from eight subjects were used to demonstrate linearity of the above rating scale. Subcortical regions in both the left and right hemispheres were analyzed by densitometry. A left to right ratio was calculated for the densitometric measures. There was a significant correlation by Spearman rho ($r = .62$, $P = .001$) with the CT scale, arguing that at one level the rating scale appears to be linear.

Data Analysis

To reduce skewness in the distribution of the variables, a square root transformation was used for the metabolic data and a log and square root transformation for the CT measures. After transformations, variables were approximately normally distributed and had roughly similar scatter. No outliers were identified with the transformed data, and the regional scores were not highly intercorrelated. The transformed data appeared appropriate for multivariate analysis.²⁰

For the purpose of this study, pathway coefficients greater than .25 were considered important. This level was selected for two reasons (1) at this level more than 5% of the variance was accounted for by the pathway, and (2) for most of the multiple regression equations this level was significant at the .05 level.

RESULTS

The first model examined the pathways in Fig 1. We assumed that cortical structural damage to a region would be totally accounted for by its metabolism. The analytic question was whether the magnitude of pathway coefficients from subcortical structural damage to behavior (fluency and sequential commands) was different from zero (ie, a coefficient of zero implying no causal effect), and how that compared with the coefficients for the indirect paths that included frontal and temporal metabolism.

Figure 2 gives the path coefficients for Model 1 as estimated by regression analysis (standardized beta weights). Subcortical damage directly influenced fluency (p41 = .37). An indirect effect on fluency was also present based on subcortical damage causing left frontal metabolic changes (p21 = .71) that then affected fluency (p42 = .38). The temporal lobe had no direct effect on fluency (p43 = .07), nor did subcortical damage have a major effect on temporal metabolism. Performance on sequential commands

did not result from direct subcortical damage ($p_{41} = -.10$), but rather from the temporal lobe ($p_{43} = .52$).

A close agreement was found for correlations calculated from the path coefficients (eg, the calculated correlation between the subcortical structures and behavior $r_{41} = p_{41} + p_{21} \cdot p_{42} + p_{31} \cdot p_{43} + p_{21} \cdot p_{32} \cdot p_{43} + p_{31} \cdot p_{23} \cdot p_{42}$) and Pearson correlations for both fluency and sequential commands, arguing that the models as presented in Fig 2 cannot be rejected (Table 1).

In Model 2, cortical structural damage to frontal and temporal regions (as measured by CT ratings for these regions) was separated from brain metabolism and considered as separate variables. Model 1 assumed for simplicity that metabolism would account for all structural damage effects. It is clear though that metabolic asymmetry occurs in aphasic patients in regions that are not structurally damaged,¹¹ and this is particularly frequent in the prefrontal regions. Likewise, there was a tendency for co-occurrence of subcortical and Broca's area damage. These observations argue that the subcortical effect on frontal metabolism in Model 1 might be explained by the co-occurrence of subcortical and frontal structural damage caused by a common vascular distribution.

For these reasons Model 2 examined whether the indirect effect of subcortical damage was related to structural or functional (metabolic) changes in frontal and temporal regions (Fig 3). The double-headed lines between the three structural regions imply an unanalyzed, noncausal relationship between structures that is dependent on what has caused the structural damage in each area. This relationship was estimated by partial correlations (covarying for the structural damage to the third region). The remaining paths were calculated by regression.

Figure 3 presents the calculated coefficients. A strong partial correlation was found between subcortical and frontal structural damage. Both structures showed a combined effect through the frontal metabolism on fluency. In addition, a direct effect of subcortical damage still existed on fluency; frontal lobe damage alone does not appear explanatory, since it exerted little direct effect on the behavioral measures. Direct structural damage to temporal lobe clearly affected temporal metabolism. The temporal lobe effects on fluency were minimal and indirect through the frontal complex. For sequential com-

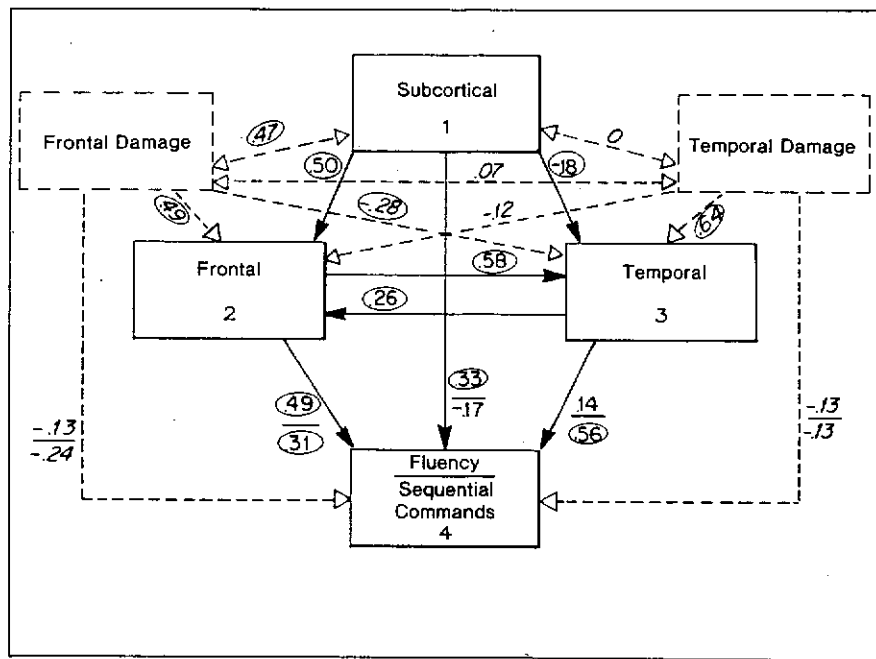


Fig 3.—Model 2 for fluency and sequential commands that includes effect of frontal and temporal lobe structural damage on Model 1. Pathway coefficients shown for both fluency and sequential commands. On paths where two behaviors have different coefficients, fluency is above the line and sequential commands below the line. Note, basic structure of Model 1 is unchanged. Subcortical damage has direct and indirect (through frontal lobe) effect on fluency. Subcortical damage affected sequential commands through its actions on frontal lobe.

Table 2.—Correlations Model 2*

	Computed Tomography				
	Subcortical	Frontal	Temporal	Frontal	Temporal
Frontal	.73 (.74)	.66 (.72)	.08 (.03)
Temporal	-.02 (.15)	.06 (.11)	.57 (.68)	.08 (.31)†	...
Fluency	.69 (.67)	.39 (.38)	-.02 (.03)	.74 (.68)	.07 (.25)†
Sequential commands	.02 (.08)	.02 (.00)	.21 (.27)	.24 (.23)	.62 (.54)

*Fifteen of 17 comparisons of calculated correlations approximated actual correlations. The first set of correlations given are calculated from pathway analysis, while that within parenthesis is the actual correlation. Frontal and temporal refer to the metabolic reference ratios.

†Poor fit of the calculated with actual correlation.

mands, both the frontal complex and temporal lobe had an effect on the behavior. The more critical factor on sequential commands was the direct effect of damage to temporal cortex on temporal glucose metabolism (ie, temporal lobe function). Subcortical structural damage had no direct effect on sequential commands.

Calculated correlations for Model 2 agreed with Pearson correlations for 15 of 17 determinations (Table 2). The model underestimated the correlation between frontal and temporal metabolism, and the correlation of temporal metabolism with fluency. With the complexity of the model these two inconsistencies did not seem to be severe enough to reject the model as a whole, but argue for refinements. The findings from Model 2 argue that the simpler Model 1 was reasonable to

test our intended hypothesis.

Model 3 examined each subcortical region making up the subcortical measure in Model 1 where it was an average of the damage to the anterior and posterior limbs of the internal capsule, the caudate, thalamus, lenticular nuclei, and insula. Care needs to be taken in interpreting Model 3 because of the large number of comparisons. The data are presented because of interest in knowing what regions might be most important in causing the subcortical effect. For simplicity, only fluency was studied.

Table 3 shows the results of Model 1 for each subcortical structure. The strongest direct effect on fluency was from the posterior limb of the internal capsule. Note that as p_{41} (the effect of subcortical damage on fluency) declines, p_{42} (the effect of frontal

Subcortical Region in the Model	p21	p31	p32	p23	p42	p43	p41
Anterior limb of internal capsule	.70	-.34	.54	.27	.48	.10	.24
Posterior limb of internal capsule	.52	-.04	.33	.23	.48	.07	.33
Head of caudate	.56	-.40	.51	.39	.56	.11	.18
Thalamus	.39	.09	.27	.22	.60	.04	.17
Lenticular nuclei	.54	-.07	.34	.24	.59	.06	.11
Insula	.42	.19	.21	.18	.60	.03	.14

Region	sr • r *
Frontal metabolism	.040
Temporal metabolism	.006
Computed tomography	
Anterior limb of internal capsule	.000
Posterior limb of internal capsule	.067†
Caudate	.011
Thalamus	.000
Lenticular nuclei	.003
Insula	.016
Unique variance	.143
R ²	.578
Shared variance = R squared - Unique variance	.435

* $sr \cdot r = (F/df) \text{ Residuals} / (1 - R^2) = (F/38) / (1 - .58) = F \cdot .011$
 † $P < .05$ for the regression of posterior limb of the internal capsule on fluency.

metabolism on fluency) increases. Also, p21 (the effect of subcortical damage on frontal metabolism) is strongest for the anterior limb of the internal capsule. The anterior and posterior limbs of the internal capsules appeared to contribute most strongly to the strength of the model.

In these models, the pathway coefficients consistently underestimated the Pearson correlation between temporal lobe and fluency (Pearson $r_{43} = .26$, while calculated r_{43} ranged from .03 to 0.21 from the equation $r_{43} = p_{43} + p_{23} \cdot p_{42} + p_{31} \cdot p_{41} + p_{31} \cdot p_{21} \cdot p_{42}$. This observation suggests that influences between regions are needed to adequately explain the Pearson correlations.

To examine independent and shared variance for the subcortical regions, a multivariate regression was analyzed for fluency by frontal and temporal metabolism and all six subcortical regions. Table 4 gives squared semipartial correlations calculated for each regional measure (this is the amount that the total variance is reduced if each region was not included

in the equation).²⁰ Only the posterior limb of the internal capsule was significant ($F = 6.06$; $df = 8,38$; $P = .018$) in explaining fluency, though frontal lobe metabolism approached significance ($F = 3.646$; $df = 8,38$; $P = .064$). Unique variability represents the total amount of variance independently accounted for by all the regional measures. Shared variance is that contributed by two or more regions. Sixty-one percent of the variance was shared. This is consistent with the size, location, and regional interrelationships of the structural lesions in these patients.

COMMENT

The three models demonstrated that subcortical damage had an important effect on fluency but not on sequential commands. The subcortical effect on fluency was both direct and indirect through its actions on the frontal lobe. The analysis presented a general model that reduced the number of regional measures to the bare minimum based on strong intercorrelations.

Lacunar lesions to posterior putamen and internal capsule have been shown to affect glucose metabolism in temporoparietal cortex.¹⁹ In this study, subcortical lesions acted through the frontal lobes. The two observations are not inconsistent. As a general rule, damage to subcortical structures result from middle cerebral artery infarctions with extensive damage. In our study, the effects of smaller, less frequent, lacunar lesions would be masked, and are averaged out in the general considerations of the model. The effects of such lesions could be incorporated by subdividing the subcortical measure, or by specifically modeling a large number of patients who show such lesions. As a general rule, however, subcortical damage involving the internal capsule, corpus striatum, globus pallidus, and thalamus tends to exert its major effect, as measured by resting glucose metabolism, on frontal lobe, the strongest effect being from the poste-

rior limb of the internal capsule. This finding is consistent with an observation that the extent of structural damage to the posterior limb of the internal capsule differed between Broca's aphasic patients and other aphasic patients who had similar structural lesions.²¹

Another aspect of the model examined the effects of frontal metabolism and temporal metabolism on each other (p32 and p23). This part of the model was included because of known and theoretical relationships between the regions. Traditional aphasia models argue that information flow in language is from temporal to frontal regions, ie, language information needs to be received and analyzed before a motoric response develops. For our models, we would have predicted that the temporal lobe effect on frontal regions would have been greater than frontal on temporal, but this was not the case. The observation suggests the importance of frontal lobe function on behavioral performance in aphasia. The functional importance may have to do with arousal, attention, and planning that are needed to respond when tested.

In evaluating the model several assumptions were made and where possible were tested. For the basic model (Model 1), we assumed that any structural damage to frontal and temporal lobes would be reflected in the glucose metabolic rates and would not interfere with the goal of the experimental question. Model 2 clearly showed that this was the case, and that Model 1 was reasonable but not completely descriptive. We assumed that the extent of structural damage could be estimated using a rating scale and that this rating could be considered to be of equal interval and linear rather than ordinal for the purpose of analysis. This assumption is clearly difficult to test since no standards exist to judge the extent of structural damage. We have compared our scalar ratings with changes in regional density on the x-ray film using a densitometer, and found a strong linear correlation, suggesting the reasonableness of the linearity assumption.

A third assumption was that regional glucose metabolism controls and precedes the language behavior. At present, the implications of remote hypometabolism are not well understood. For a complete picture, changes at a cellular, neuronal network, and regional level need to be considered, as well as how such processes are integrated to allow for performance.

Clearly, our knowledge of these factors is limited. Some speculation may be worthwhile to understand the implications of remote changes. At one level, when a remote region becomes hypometabolic, several possible mechanisms could be occurring: (1) loss of input from other regions could decrease dendritic activity, and/or (2) decrease in neuronal firing patterns may result. At a higher level, the loss of input could imply that a region is able to perform "normally" but without information supplied from other regions. Alternatively, if neuronal activity is turned off, the region itself may not function despite the lack of structural damage. The models studied in this article do not address such issues, but they need to be considered to establish a more sophisticated and complete model. Besides these limitations, the strength and consistencies of the model developed here demonstrate

the value of such modeling approaches.

Subcortical damage can be seen as having both direct and indirect effects on behavioral changes in aphasia. The observations that the strongest links in the model were the anterior and posterior limbs of the internal capsule argue that damage to these structures results in disconnection of frontal regions from deeper structures. We have previously reported a case showing this relationship.¹⁰ The connections of internal capsule damage with frontal function are not unexpected but emphasize that the frontal lobes rostral to Broca's area need to be considered in modeling of the pathophysiology of aphasia. This has been done, to some degree, in analyses of transcortical motor aphasias when damage occurs in these more anterior areas. The frontal regions beyond Broca's area also seem to come into play (even though not structurally

damaged) when structural lesions extend deep to the cortex and involve the subcortical structures included in this study, and particularly the internal capsule. The models bring together such ideas and argue that cortical and subcortical circuitry are critical for the aphasias as proposed by others.^{22,23} Positron emission tomography is now allowing us to more carefully evaluate such models and to present a more complete picture of what occurs in the brain of aphasic patients.

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