

## Positron Emission Tomography

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We have used positron emission tomography to study brain metabolism using (F-18) fluorodeoxyglucose (FDG); (Hanson, Metter, Kuhl, Phelps, and Wasterlain, 1981). Metabolic activity in the brain is primarily attributed to neuronal metabolic demands, with changes in neuronal function corresponding to changes that occur in local cerebral metabolic rates of glucose (LCMRGlc). Thus, a method for measuring the rate of glucose metabolism is useful in evaluating functional changes as they occur in the brain.

In the initial studies of human brain metabolism investigators have examined normal individuals in a defined "resting" state (Phelps, Huang, Hoffman, Selin, Sokoloff, and Kuhl, 1979; Mazziota, Phelps, Miller and Kuhl, 1981). Normal subjects at rest have consistently demonstrated a strong degree of metabolic symmetry between homologous structures in the left and right cerebral hemispheres. Also, studies in normal aging have demonstrated a small decline in cerebral metabolism with increasing age (Kuhl, Metter, Riege, and Phelps, 1982).

We have studied patients with brain injury and aphasia and have found areas of metabolic depression extending beyond the zone of infarction, suggesting that function in non-structurally-damaged tissue was not normal (Metter, Wasterlain, Kuhl, Hanson, and Phelps, 1981; Metter, Hanson, Riege, Kuhl, and Phelps, 1983; Metter, Riege, Hanson, Kuhl, Phelps, Squire, Wasterlain, and Benson, 1983; Metter, Riege, Hanson, Camras, Phelps, and Kuhl, 1984).

Of particular interest in our findings has been consistent metabolic abnormality in subcortical structures in patients with aphasia. From two cases studied with both CAT scans and PET scans, several specific observations can be made. Figure 1 shows CAT scans, at three levels, of a 57 year old man who had a left CVA and aphasia four months prior to this exam. The illustrations on the left show the lesion outlined on templates prepared from an atlas of the brain. Language evaluation including the Boston Diagnostic Aphasia Examination (BDAE) indicated a moderately severe Wernicke's aphasia. The CAT scan shows a left temporal and parietal lesion with damage to Wernicke's area.

The PET scan (Figure 1) indicated a 67% reduction in glucose metabolism in the area of structural damage. In addition, metabolic depression was noted throughout the left temporal lobe and posterior frontal lobe above Broca's area, as well as the thalamus and basal ganglia.

Figure 2 is a CAT scan of a 48-year-old right-handed male who had sudden onset of mild right hemiparesis and aphasia. The scan shows punctate areas of decreased density in the left and right caudate nucleus, and in the left internal capsule, with normal cortex. Language evaluation six weeks after onset indicated good auditory comprehension except for complex material. Repetition and reading comprehension were unimpaired. He spoke in sentences of normal length and complexity but displayed some anomia, perseveration, and often omitted the endings of words. His Boston indicated a moderately severe aphasia that did not fit any specific pattern. FDG-PET showed a decrease in FDG concentration in the left thalamus, striatum and left middle and inferior



temporal lobe (Figure 2). A more prominent metabolic suppression in the thalamus compared with the cortex (24% vs 15%) suggested that the deeper region was the site of the primary lesion.

This patient demonstrated the features of thalamic aphasia. While an independent cortical lesion cannot be ruled out, we think that the decrease in cortical metabolic rate may be secondary and may indicate a relationship between these subcortical and cortical areas in the genesis of thalamic aphasia. In other patients we have studied, the reduction in metabolic rate was less in thalamic than in cortical areas, suggesting that the thalamic changes were secondary to cortical alterations.

FDG-PET findings have focused attention on the distant effects of a structural lesion. A focal lesion may produce secondary metabolic changes in regions distant from the structural damage as shown in Figure 3.

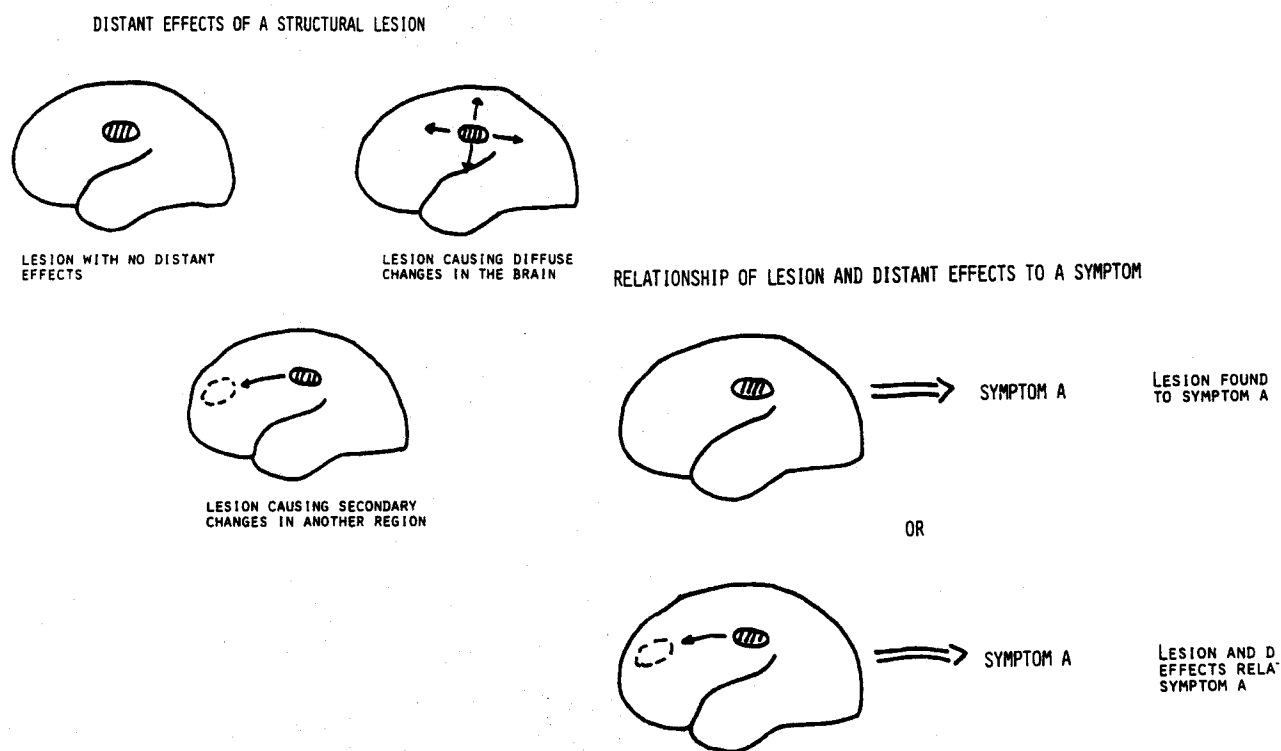


Figure 3. Relationships among structural lesions, distant effects, and symptoms.

When the size and extent of structural and metabolic lesions are similar, traditional anatomic classifications of aphasia are sufficient. Under such circumstance the aphasia will relate directly to the lesion and not to major dysfunction in distant regions. When substantial mismatches occur in structural and metabolic patterns an additional taxonomy based on consideration of both local and distal effects may be required (Figure 3).

To further study the relationships between brain metabolism and aphasia we have taken two approaches. First we have measured metabolic rates for

different brain regions and calculated correlations to identify possible relationships between regions. Of interest here were brain regions in both hemispheres that appear to form functional systems that may be of importance in understanding behavior following brain injury. In our second approach, correlations were calculated between regional metabolism and language test scores from both the Boston and the PICA aphasia examinations.

In a study of 31 normal subjects the local cerebral metabolic rate for glucose was determined for thirteen brain regions in each hemisphere (Metter, Riege, Kuhl, and Phelps, 1984). From the matrix of correlations that were significant at the .01 level two apparently separate functional metabolic systems were identified.

First, there was a higher placed system involving the superior and middle frontal lobe, inferior parietal, and occipital cortex (Figure 4). The high frontal, parietal, and occipital relationships suggest at least three possible functional roles. First these areas are known to be involved with visual function. The occipital lobe includes primary and secondary visual areas while the frontal regions include the frontal eye fields. The inferior parietal relationship to this system may involve attentional aspects of visual awareness. A second possible function may truly be an attentional one -- involved with arousal and ability to attend or focus or follow sequentially presented material. Destruction of the attentional mechanism leads to impairment in these behaviors as seen with superior frontal lesions. A third possibility suggests these areas are importantly involved in normal memory and decision processing. Riege and colleagues (Riege, Metter, Kuhl, Phelps, and Hawkins, 1982) found that the high frontal region metabolism correlated with memory recognition for complex visual items and discrimination of designs.

The lower relationship (shown in Figure 5) involved inferior frontal, Broca's, and posterior temporal regions. The posterior temporal regions are known to be important for language recognition, and for the reception and initial processing of language, while anterior regions are important in further sequential processing and motor programming for verbal output. Perisylvian regions appear to form a functional metabolic system where metabolism within one region very much depends on metabolism in associated regions involved with language processing. The high degree of symmetry between regional metabolism in left and right hemispheres appears to reflect their yoked activities through callosal connections. In aphasic patients we have studied, the regional metabolic interrelationships just described were not evident in the damaged hemisphere but were present in the contralateral hemisphere.

As previously mentioned, in our second approach, correlation analyses were used to examine the relationships between language, brain metabolism and structural damage. Eleven aphasic patients had resting FDG-PET, CAT scans, and were administered the Boston Diagnostic Aphasia Examination (BDAE) and the Porch Index of Communicative Ability (PICA).

Two clusters of correlations between specific language skills and regional metabolic measures became apparent. One cluster of correlations involved the frontal areas, Broca's area, and the caudate with speaking and copying factors from the PICA (Hanson, Riege, Metter, and Inman, 1982). Also, it can be seen in Figure 6 that these correlations provide further evidence for a right hemisphere role in language function in aphasia.

The second cluster (Figure 7) is apparent in the posterior middle-inferior temporal areas which correlated with several language subtests from the Boston (auditory comprehension, naming, oral reading, and repetition).

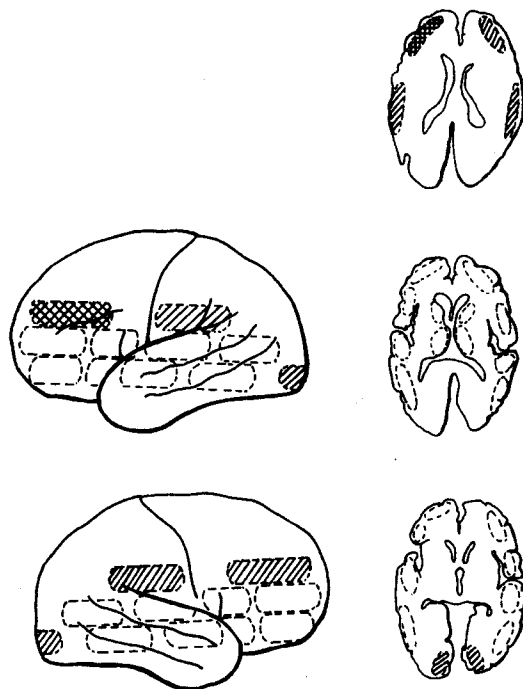


Figure 4. Frontal, parietal, and occipital metabolic relationships.

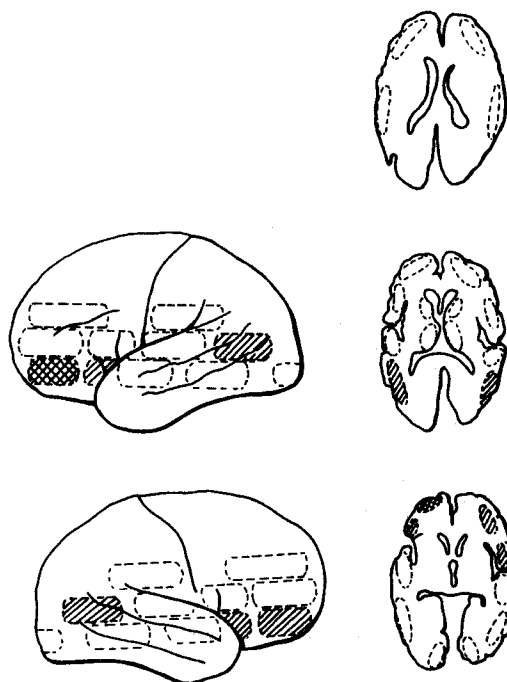


Figure 5. Frontal, posterior temporal metabolic relationships.

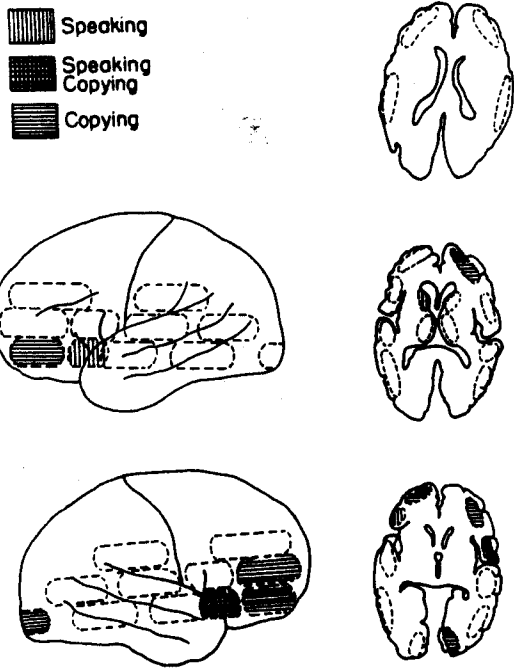


Figure 6. Correlations of PICA scores with regional metabolism.

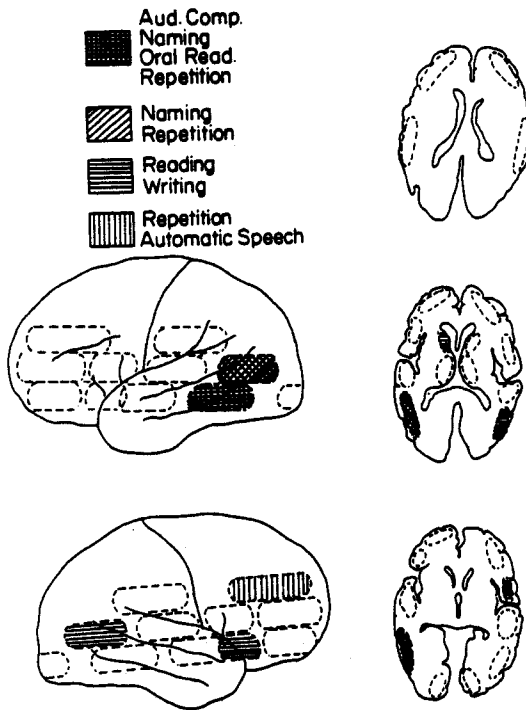


Figure 7. Correlations of BDAE scores with regional metabolism.

Several right hemisphere areas also correlated with Boston language tasks (reading, writing, automatic speech, and repetition). Interestingly, there were no correlations of language subtests, from either Boston or PICA, to Wernicke's area with FDG-PET. However, the CT comparisons with language tests indicated a significant correlation of the PICA verbal score with the degree of damage to Wernicke's area. Boston subtests correlating with Wernicke's aphasia included oral reading and repetition.

The metabolic correlations are distinct from the structural (CT) correlations with Wernicke's area, suggesting that when Wernicke's area is damaged the so-called secondary language areas assume some aspects of the resulting aphasic language. This may mean there is a relative "turning off" of Wernicke's area secondary to structural damage which serves to release from inhibition the more posterior temporal areas.

The caudate appears to work in collaboration with frontal areas as a functional unit in the motor activities of speech. The head of the caudate may aid the inferior frontal and Broca's region to work together with other regions to accomplish a planned or sequenced response. Mazziotta (personal communication), recently found that the head of the caudate in normal subjects can be activated metabolically by using an automatic writing task, such as writing one's name. The meaning of this finding at present is unknown, but suggests a role in sequential planning of a well organized behavior.

A number of physiologic stimulation studies have been completed using FDG-PET with normal subjects. By measuring the regional metabolic rate in response to a given stimulus it is possible to map areas of the brain activated by that stimulus. For example, Greenberg and colleagues (1981) have shown that when left visual fields are stimulated, significantly greater glucose utilization is noted in the right striate cortex than in the left. Conversely, with stimulation of the right visual hemifield increased metabolic rates were noted in the left visual cortex. Visual stimulation studies have shown that as the complexity of the visual stimulus is increased from simple white light, to a checkerboard pattern, to an outdoor park scene, there is a concomitant increase in metabolic response in the visual cortex. The visual interpretations associated with complex visual scenes appear to progressively increase the involvement of the associative visual cortex as indicated by its metabolic response. Deprivation of sensory input may also influence brain metabolism. In a subject who was first tested with both eyes open and then again with both eyes blindfolded, there was a 23% decrease in glucose utilization in both left and right occipital cortices with the blindfolds (Phelps, Kuhl, and Mazziotta, 1981).

Mazziotta and colleagues (1982) have shown that auditory stimulation produces metabolic changes that are determined in part by the nature of the stimulus and the analysis strategy of the subject. Verbal stimuli produced diffuse metabolic changes in the left hemisphere and bilateral activation of the transverse and posterior temporal lobes. Nonverbal auditory stimulation using chords demonstrated bilateral parietotemporal activations and diffuse right greater than left frontotemporal asymmetries. Tone sequence pairs presented monaurally produced asymmetries that differed by the subjects' analysis strategy. Nonanalytical, musically naive subjects had right greater than left frontotemporal asymmetries, whereas analytic or musically sophisticated subjects demonstrated left greater than right temporal asymmetries. Binaural presentation of a factual story and music produced diffuse bilateral activations of the temporal and frontal cortex.

With tactile stimulation, using brush stroking of the hand, the contralateral postcentral cortex became more metabolically active compared with the

ipsilateral side (Alavi, Reivich, Greenberg, Hand, Rosenquist, Rintelmann, Christman, Fowler, Goldman, MacGregor, and Wolf, 1981). Our studies of aphasic patients were done at rest, which does not directly reflect brain activity or metabolism during language performance. A difficulty with the FDG method in stimulation studies has been that it requires 30 minutes of stimulation, over which time it is difficult to constantly control mental activity. In the future, shorter scans using other isotopes will prove more suitable.

In speculating about the future, positron emission tomography should aid in the clinical management of patients with aphasia. Our descriptions of input and output behaviors in aphasia will be augmented by parallel studies of activities going on inside the brain. The "black box" will become much less opaque. Metabolic measures will add to our understanding of how the brain reorganizes itself following injury. By studying patients repeatedly, over time, with metabolic and language measures, we will learn more about the physiological substrate associated with recovery of behavioral competence. More attention will be focused on a patients' personal cognitive processing "style" as revealed by physiologic measures. These data, combined with our behavioral studies, may improve our selection of the most appropriate and timely intervention strategies. For example, in some aphasic patients, language reorganization may reflect the existence of an alternate store of learning on the opposite side of the brain, which has remained dormant until the dominant side was injured. If these patients could be identified by the degree of right hemisphere metabolic activation during language performance, treatment directed toward tapping right hemisphere function may more likely benefit those with prominent activation than those without. A patient with such activation may be one for whom the treatment of choice is an indirect, thought oriented approach, consistent with the preferred cognitive style attributed to the right hemisphere. Other specific treatments which engage the right hemisphere, such as melodic intonation therapy or other treatments yet to be described, may be of value.

In some aphasic patients association areas in the dominant hemisphere may retain secondary capacity for a specific language function after injury to the primary area. Our finding of a shift of some language tasks away from Wernicke's area is consistent with this theory. For patients in whom left hemisphere activation is predominant a more direct, sequential, specific task-oriented treatment may be the most appropriate. Treatment approaches will be more comprehensive, with the aphasiologist taking advantage of what is known about the patient's neurophysiology to focus therapy and to increase the amount of language recovery. Knowledge of the pattern of metabolic depression following injury and the brain's regional response to stimulation measured over time should have a positive influence on the rehabilitation of patients with aphasia. This may include the prudent use of neuropharmacological agents for the treatment of some aspects of communicative disabilities. Samuels, at the 1980 Academy of Aphasia meeting, discussed two cases with subcortical lesions and difficulties in speech initiation that responded to Sinemet with improved speech. As part of the improvement, each case was able to increase the grammatical complexity of their speech. Based on physiologic changes in the brain, subjects who might respond to drug treatment could be identified. For example, considering Samuels' study, perhaps patients who show speech abnormalities and absence of caudate activation may respond to Sinemet, while subjects showing caudate activation might not, and, in fact, might respond to an antagonist. Applications to therapy are far off, but the



present work may indicate new directions for therapy based on brain physiology. If nothing else, the bringing together of multivariate methods for language analysis and the ability to identify regional changes in both structure and function in the brain should lead to a more complete understanding of aphasic behavior.

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