CHAPTER 8

Tomographic Regional Cerebral Blood Flow Activation During Phoneme Detection in Normal and Aphasic Subjects

Delaina Walker-Batson
Michael D. Devous, Sr.
Kathleen K. Millay
Sharon Reynolds
Ajai J. Ajamani
Dorothy E. Grant
Frederick J. Bonte

Studies of brain metabolism are of particular interest in the study of recovery following stroke and concomitant language disorders. Single-photon techniques, referred to as SPECT, of regional cerebral blood flow (rCBF) have shown much potential for the study of the neural bases for aphasic recovery (Tikofsky, Collier, Hellman, Saxena, Zielonka, Krohn, and Gresch, 1985; Walker-Batson, Wendt, Barton, Devous, and Bonte, 1988) and are providing a starting point of technologies that can objectively measure tissue changes in stroke in response to various therapeutic modalities (Ackerman, 1984). However, resting state blood flow has not been predictive of recovery in several serial aphasia studies (Demmeurisse, Verhas, Capon, and Paternot, 1983; Nagata, Yunoki, Kabe, Suzuki, and Araki, 1986). The current need in all neuroimaging technologies is to develop cognitive activation probes with sensitivity to depict patterns of metabolic activity that are task dependent. Recent methodological criticisms have been made of activation paradigms that use the resting state as the baseline (Hannay, Falgout, Leli, Katholi, Halsey, and Wills, 1987). It has been argued that when normal rest is used as the baseline, focal increases in blood flow associated with cognitive processing cannot be separated from focal increases produced by the sensory input.

In preparation for a serial study of recovery from aphasia, our laboratory has developed an auditory phoneme detection task in an attempt to assess language processing during the xenon-133 SPECT technique. This task, perception of words starting with /b/ from /pa,ta,da,ka,ga,ba/ was selected to tap processing of acoustically complex signals that are perceived categorically (Liberman, Harris, Hoffman, and Griffith, 1957) and have shown strong laterality effects in dichotic listening (Shankweiler and Studdert-Kennedy, 1967). In addition, an auditory control task of passive listening, the same auditory stimuli used in the phoneme detection task, and a resting state with no auditory stimulation were also employed. The purpose of this study was to compare resting state, passive listening, and phoneme detection conditions during the xenon-133 SPECT technique in two subject groups. The following questions were addressed:

1. Are there differences in total hemispheric regional cerebral blood flow uptake between the three conditions in normal and chronic aphasic subjects?
2. Are there regions of interest that are differentially activated by the three conditions in normal and aphasia subjects?

METHODS

Eight normal volunteers and five chronic aphasic subjects were studied. All subjects were male, native English speakers and were right-handed (Oldfield, 1971). Normal subjects had no previous history of neurological injury or disease or psychiatric or learning disorders. The age range of the normal subjects was between 32 and 48 years with a mean age of 45 years and with no more than 14 years of education. All subjects were screened for possible hearing loss at 26 dB.

Aphasic subjects all had history of a single focal infarct verified by computed tomography (CT) scan at least 10 days after stroke (see Table 8-1). Time post-onset ranged from 2 to 10 years. Age range of the aphasic subjects was from 36 to 67 years with a mean of 52 years. Severity and type of aphasia was determined by performance on the Boston Diagnostic Aphasia Examination (BDAE) (Goodglass and Kaplan, 1983). One subject had crossed aphasia from a right-hemisphere infarct.

The stimuli were produced by recording a male speaker saying /ba, pa da, ta, ca, ga/. Waveforms and spectrograms were displayed and all syllables were trimmed to the same duration of 300 ms. Maximum amplitudes of the syllables were equalized according to the peak amplitudes of the vowel /a/. The signals were played in a random order four per second.

The rCBF assessment of means of single-photon emission tomography (SPECT) using the xenon 133 inhalation and washout technique has been described previously, as have the normative studies performed in our laboratory (Walker-Batson, Devous, Bonte, and Oelschlaeger, 1987; Devous, Stokely, Chehabi, and Bonte, 1986). This 4-minute technique provides three-dimensional representations of regional cerebral blood flow noninvasively in three tomographic slices.

All subjects wore inset earphones for all three procedures, and eyes were open. In this pilot study, the same order of tasks was followed for all subjects. The first procedure was the resting state with no auditory input. The subject was instructed to breathe the gas for 1 minute followed by breathing air for a 3-minute period through the breathing apparatus. The second procedure was the auditory control task where the subject was instructed to listen to the sounds while breathing the gas followed by air. Auditory stimuli were adjusted to a comfortable listening intensity and started 30 seconds prior to the initiation of xenon 133. The third procedure was the auditory detection of /ba/ stimuli. Normal and aphasic subjects were instructed to raise the left index finger when a /b/ was heard. Previous studies in our laboratory had shown this small amount of motor finger movement did not cause an increase in regional blood flow. Aphasic subjects had a practice session prior to the initiation of the task to check for understanding of the task directions, not necessarily that they could perform the task. The definition of normal performance was set at an 80-percent criterion level.

RESULTS

Results to question 1 — Are there differences in hemispheric rCBF uptake between the three conditions? — are shown in Table 8-2. Left or right total

TABLE 8-1. DESCRIPTIVE DATA FOR FIVE APHASIC SUBJECTS

Subject	*Age*	*Years post CVA*	*BDAE Comprehension*	*BDAE sentence-paragraph reading*	*Phoneme percentage score*	*Lesion site as described from CT scan*
1	36	6	83	7	71	Left frontal
2	60	6	72	5	28	Left parietotemporal
3	47	2	83	8	95	Left frontal
4	50	6	64	3		Large infarction of most of left middle cerebral artery territory
5	67	14	75	8	95	Large infarction of most of right middle cerebral artery territory

TABLE 8-2. LEFT AND RIGHT NORMALIZED HEMISPHERIC rCBF VALUES FOR RESTING STATE, AUDITORY CONTROL, AND PHONEME DETECTION IN NORMAL AND APHASIC SUBJECTS

	Resting state		*Passive listening*		*Phoneme*	
	LH	*RH*	*LH*	*RH*	*LH*	*RH*
Mean for 8 normals	98	103	98	103	98	103
Aphasic subjects						
1	84	115	86	114	87	112
2	87	112	88	113	85	115
3	89	111	90	112	91	109
4	64	137	58	143	60	140
5 (right CVA)	115	87	—	—	120	79

LH = left hemisphere; RH = right hemisphere.

hemispheric rCBF did not differ between the three conditions — resting state, auditory control, or phoneme detection — in either the normal or aphasic subjects.

Question 2 asked, Are there regions of interest that are differentially activated by the three conditions in normal and aphasic subjects? Figure 8-1 depicts the template 5 to 7 cm above and parallel to the canthomeatal line with 22 regions of interest that was used in the SPECT analysis of brain slice two in this study. Odd numbers reflect left hemisphere, even numbers right hemisphere. In seven of the eight normal subjects that we studied, a pattern of increased rCBF was observed bilaterally in the mesial frontal regions (areas 3 and 4) (Fig. 8-1). Figure 8-2 shows representative rCBF profiles of two normal subjects by hemispheres and regions of interest; note the mesial frontal activation during the auditory probe condition. Comparison of the auditory control and probe conditions across the eight normal subjects revealed considerable intrasubject variability, with the passive listening condition producing as much increase from the resting state as the probe condition in language-related regions in some of the subjects.

Regions of interest differentially activated in the three conditions in the aphasic subjects revealed no distinct patterns in activated rCBF. There was metabolic activity in regions in both left and right hemispheres depending on the condition. Examples of the variability in the aphasic subjects' profiles are shown in Figure 8-3. This figure depicts responses between the two conditions in aphasic subjects one and two. The mesial frontal regions activated in normals decreased slightly in three of the five aphasic subjects that we studied during the phoneme probe condition in the left hemisphere. An unexpected finding in four of the aphasic subjects was regional blood flow increases in cerebellar regions ipsilateral and contralateral to the lesion side during the phoneme probe condition. This information is contained in slice one, which we normally do not analyze in aphasic subjects. Ipsilateral cerebellar increases during the probe condition in the aphasic subjects ranged from 25 to 40 percent, while contralateral cerebellar increases in the aphasic subjects from resting state to probe conditions ranged from 11 to 23 percent. In the eight normal subjects, the right cerebellar mean increase from resting state to probe was 17 percent, while the left cerebellar mean increase was 11 percent.

DISCUSSION

Our finding of no difference between stimulated and unstimulated conditions in total right- and left-hemispheric rCBF uptake in both normal and aphasic subjects was not unexpected and has been reported by other laboratories (Brown, Bartlett, Wolf, Russell, and Brodie, 1985; Hellman, Tikofsky, Collier, Palmer, Hoffman, Igitman, and Krohn, 1987; Tikofsky, Hellman, Collier, Palmer, Hoffman, Krohn, and Gresch, 1986). This suggests that in the subjects we studied and the tasks that we employed, task-induced rCBF differences were subtle intrahemispheric interactions. Lack of clear-cut differences in some of the normal subjects between the auditory control and phoneme probe conditions highlights the complexities of developing cognitive probes and probably represents intersubject variability in language processing. The variability in the aphasic patient's profiles was also not unexpected, as early two-dimensional studies have reported much variability in aphasic activated rCBF patterns (Soh, Larson, Skinjoj, and Lassen, 1978). Mesial frontal activation during various cognitive tracking tasks has been interpreted by some investigators to represent attentional mechanisms (Posner, 1987). We cannot separate attentional and linguistic factors in our task. We have not previously noted cerebellar involvement in recovery from aphasia. The increase in the right cerebellum in the normal subjects during the phoneme probe condition may indicate that our task tapped part of a frontal motor, preplanning system suggested by Metter, Hanson, Kempler, Jackson, Mazziotta, and Phelps (1987) or part of a cortico-cerebellar loop (Wiesendanger, 1983). Our task may also have tapped part of an attending and alerting system in the frontal lobes. To our knowledge, ipsilateral cerebellar activation during linguistic probes has not been reported previously in aphasic subjects. Whether this represents the right hemisphere correlate of a cortico-cerebellar motor planning system is unknown. We are in the process of

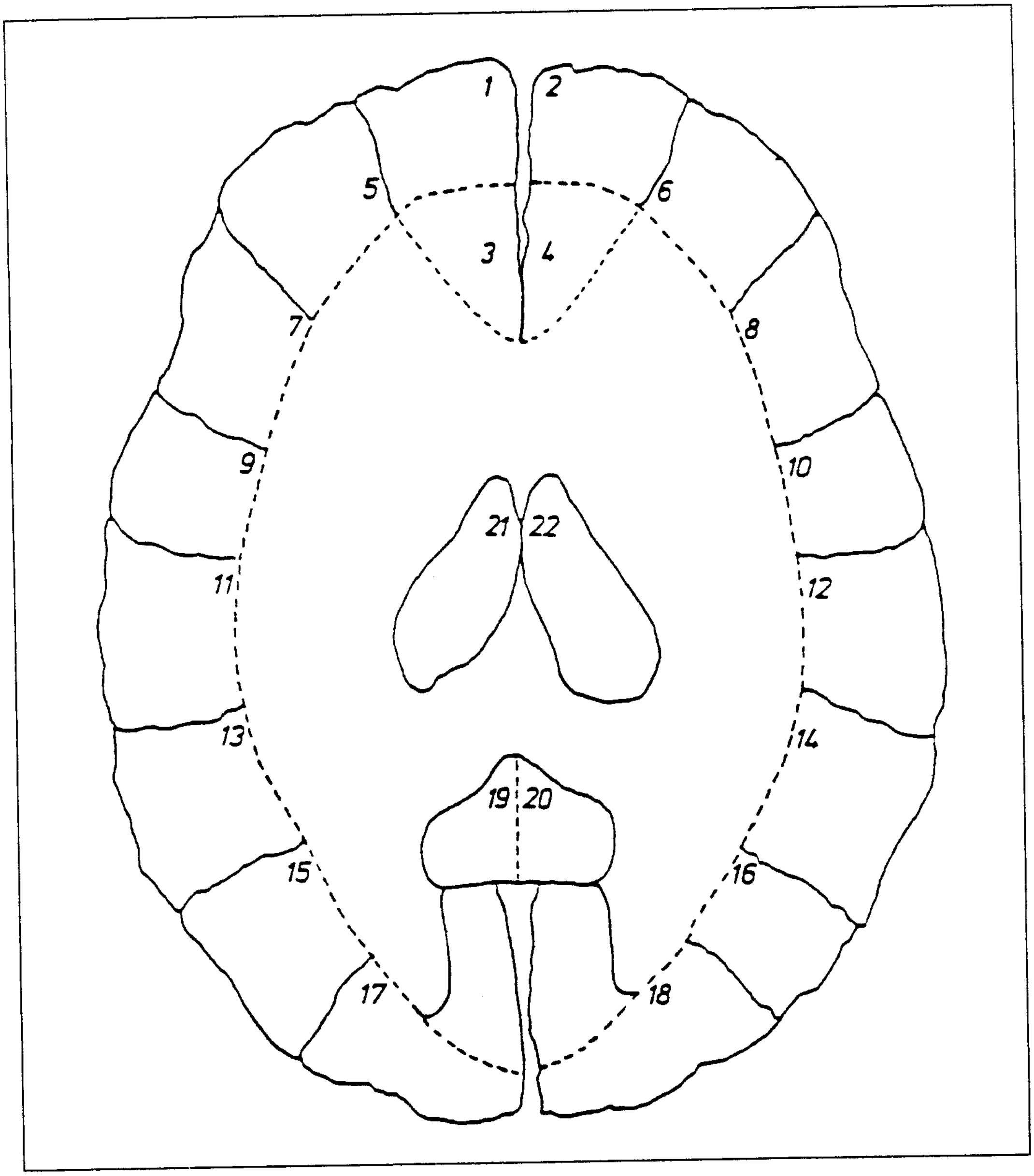
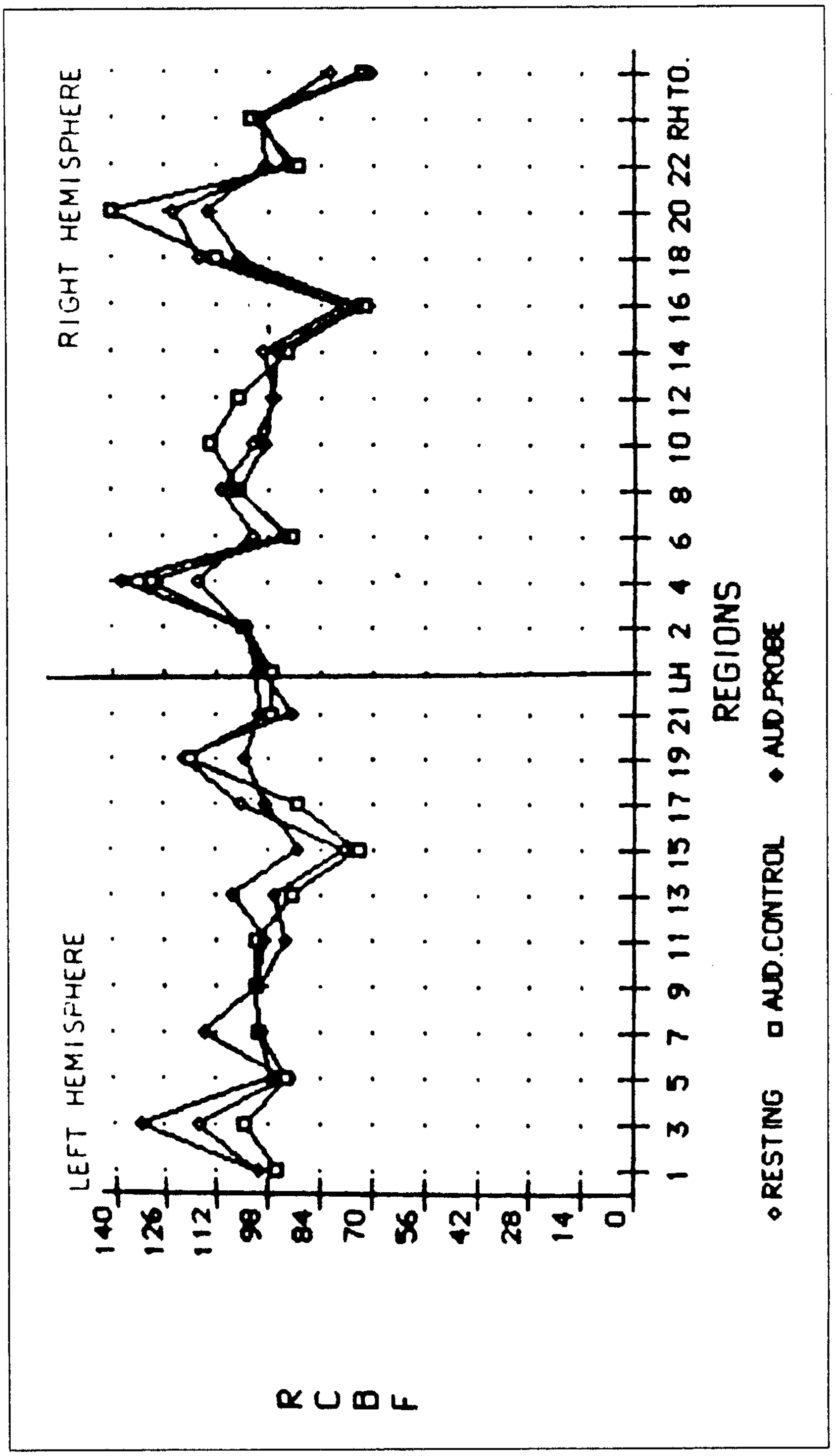
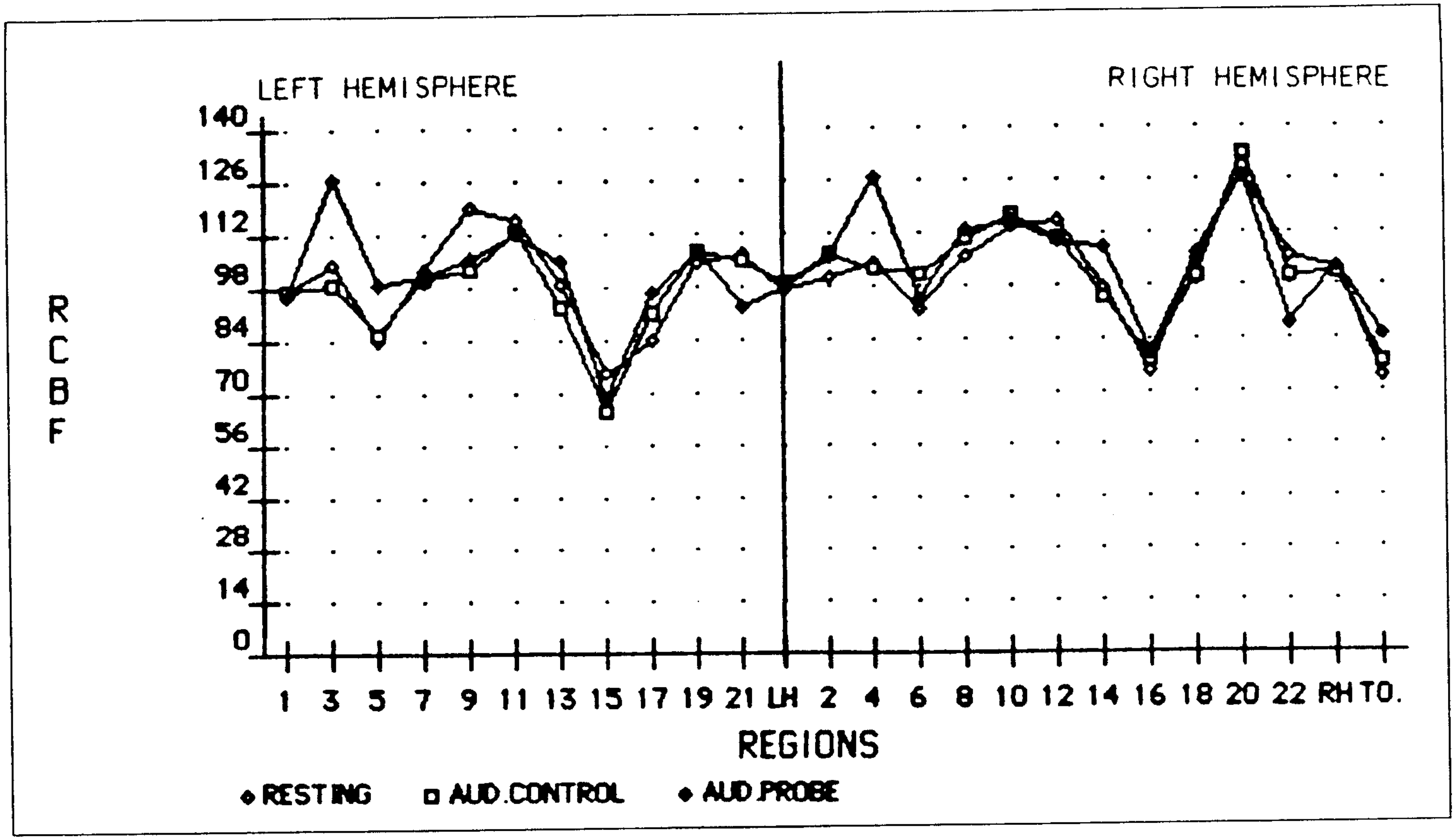


Figure 8-1. This template is 5–7 cm above and parallel to the canthomeatal line with 22 regions of interest labeled; odd numbers are left hemisphere, even numbers are right hemisphere. (Template was derived from T. Matsui and A. Hirano [1978] *An atlas of the human brain for computerized tomography*. Tokyo: Igaku-Shoin. Structures are labeled as follows: 1, left superior frontal gyrus; 2, right superior frontal gyrus; 3, left cingulate; 4, right cingulate; 5, left middle frontal gyrus; 6, right middle frontal gyrus; 7, left inferior frontal gyrus; 8, right inferior frontal gyrus; 9, pre- and post-central gyri; 10, right pre- and post-central gyri; 11, left supramarginal, superior temporal gyri; 12, right, supramarginal superior temporal gyri; 13 left middle temporal gyrus; 14, right middle temporal gyrus; 15, left inferior temporal gyrus; 16, right inferior temporal gyrus; 17, left occipital lobe; 18, right occipital lobe; 19, left cingulate and precuneas; 20, right cingulate and precuneas; 21, left thalamus; 22, right thalamus.

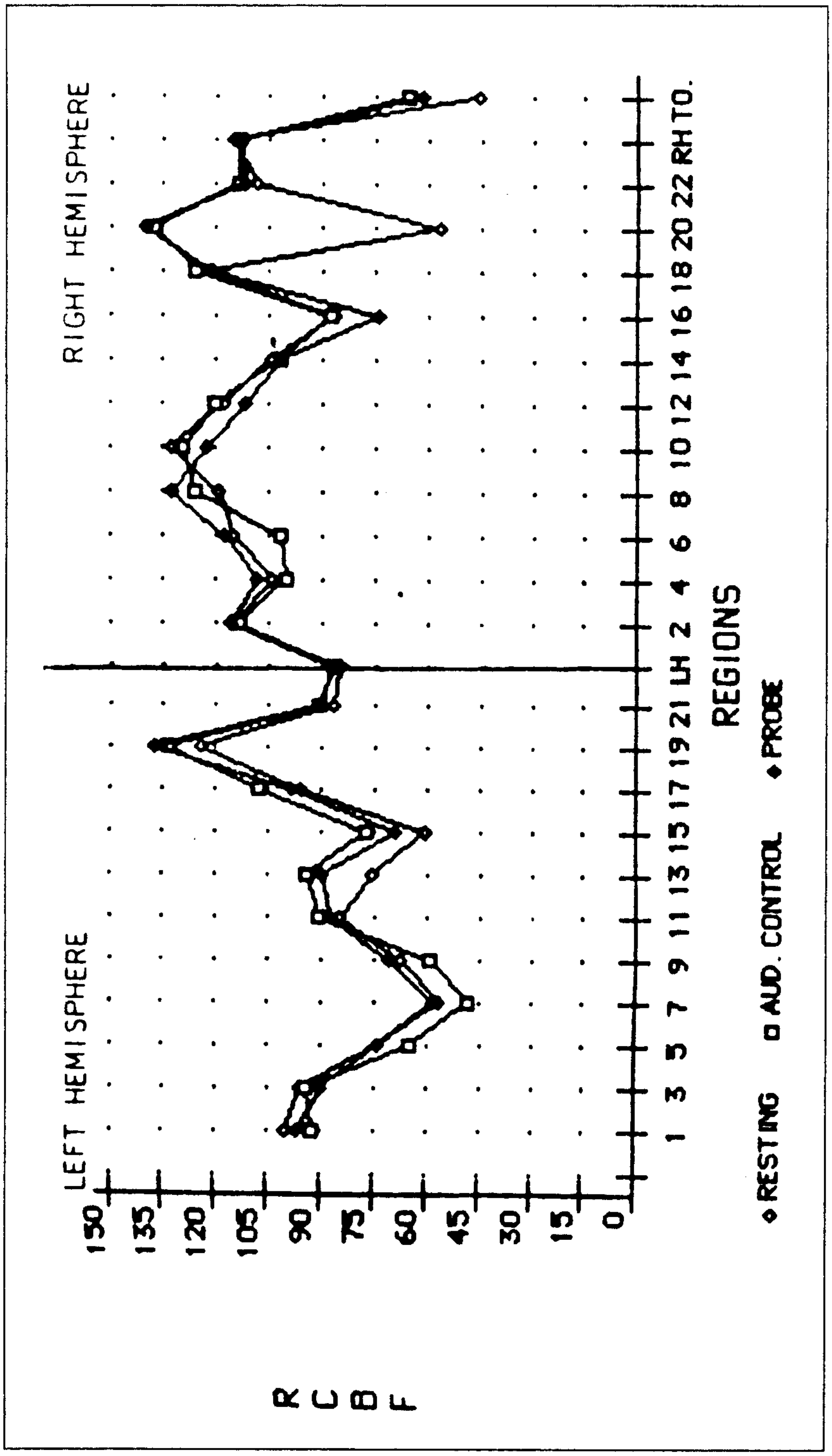

R C B F
LEFT HEMISPHERE
RIGHT HEMISPHERE
140
126
112
98
84
70
56
42
28
14
0
1 3 5 7 9 11 13 15 17 19 21 LH 2 4 6 8 10 12 14 16 18 20 22 RH TO.
REGIONS
◇ RESTING
▫ AUD.CONTROL
◆ AUD.PROBE

A

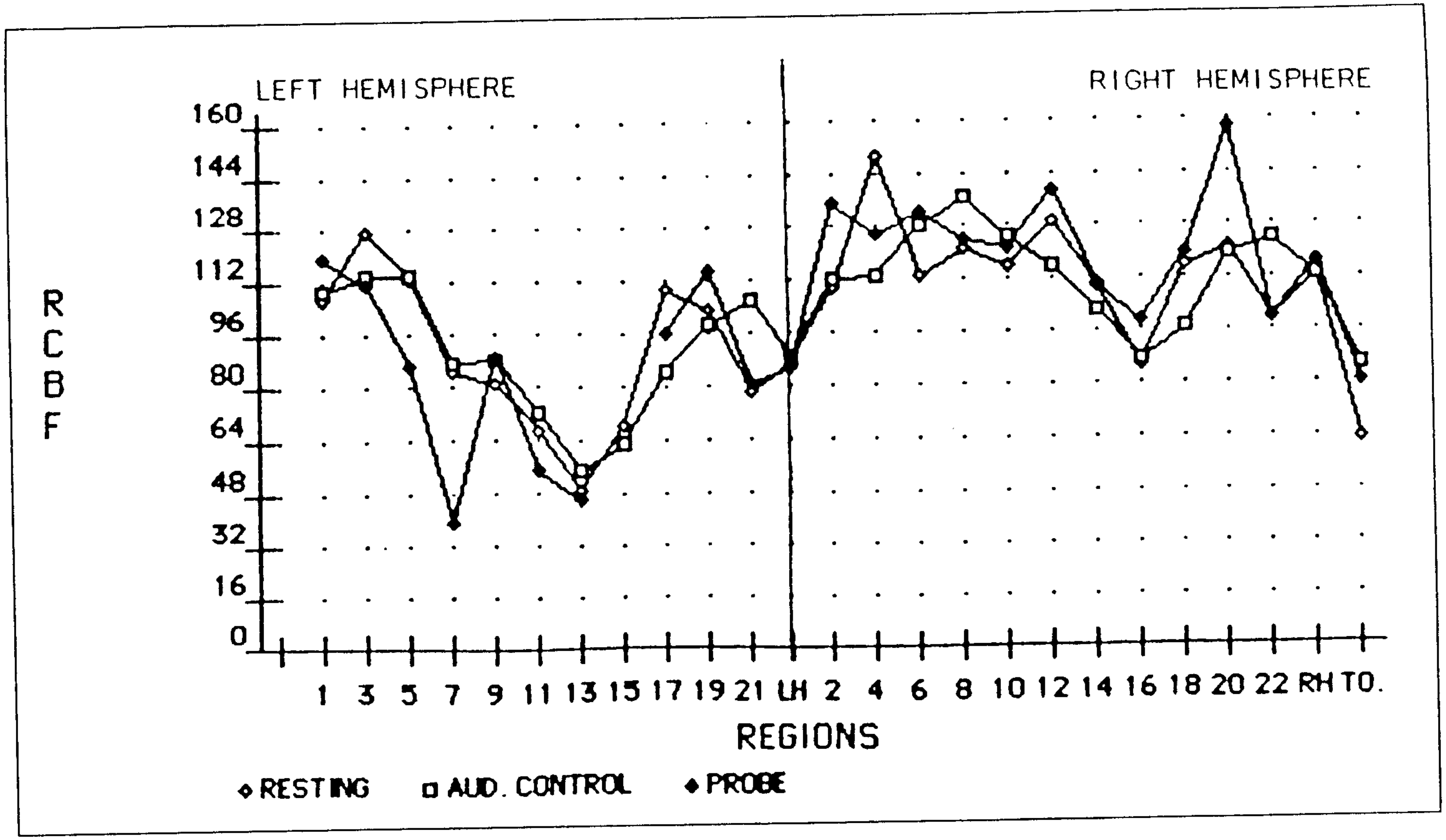


B

Figure 8-2. Examples of rCBF uptake of two normal subjects during the three conditions. *A.* Case 1. *B.* Case 2. Refer to Figure 8-1 for regions of interest by numbers on template. Note elevation of pericingulate regions bilaterally during the phoneme detection task. This figure demonstrates patterns of metabolic variability that are greater for some regions than for others with resting conditions as opposed to cognitive probe.


RCBF
150
135
120
105
90
75
60
45
30
15
0
LEFT HEMISPHERE
RIGHT HEMISPHERE
1 3 5 7 9 11 13 15 17 19 21 LH 2 4 6 8 10 12 14 16 18 20 22 RH TO.
REGIONS
◇ RESTING
▫ AUD. CONTROL
◆ PROBE

A



B

Figure 8-3. Examples of rCBF uptake of two chronic aphasic subjects during the three conditions. *A.* Case 1. *B.* Case 2. All aphasic subjects displayed great metabolic variability for regions in both left and right hemispheres, depending on the condition.

developing a passive listening task with stimuli from the probe condition for comparison to these results.

Our results should be interpreted cautiously because of the small number of subjects studied and the limited resolution of a first-generation SPECT machine. This was a first attempt to develop a cognitive activation task in normal subjects eventually to aid in determining viable neural tissue in aphasic recovery. With the improved sensitivity of the newer SPECT systems, careful attention to task development, and study of acute stages of stroke, single-photon techniques hold promise to enhance our understanding of neural mechanisms of recovery from aphasia.

REFERENCES

Ackerman, R. (1984). Of cerebral blood flow, stroke, and SPECT. *Stroke, 15,* 1–4.

Brown, J. W., Bartlett, E. J., Wolf, A. P., Russell, J., and Brodie, J. (1985). Metabolic correlates of language processing in healthy male adults. *Neurology, 18,* 119.

Demmeurisse, G., Verhas, M., Capon, A., and Paternot, J. (1983). Lack of evolution of the cerebral blood flow during clinical recovery of a stroke. *Stroke, 14,* 77–81.

Devous, M. D., Stokely, E. M., Chehabi, H. H., and Bonte, F. J. (1986). Normal distribution of regional cerebral blood flow measured by dynamic single-photon emission tomography. *Journal of Cerebral Blood Flow and Metabolism, 6,* 95–104.

Goodglass, H., and Kaplan, E. (1983). *Assessment of aphasia and related disorders.* Philadelphia: Lee & Febiger.

Hannay, H. J., Falgout, J. C., Leli, D. A., Katholi, C. R., Halsey, J. H., and Wills, E. L. (1987). Focal right temporo-occipital blood flow changes associated with judgment of line orientation. *Neurospychologia, 25,* 755–763.

Hellman, R. S., Tikofsky, R. S., Collier, B. D., Palmer, D. W., Hoffman, R. G., Igitman, A. T., and Krohn, L. (1987). Quantition of regional cerebral I-123 iodoamphetamine (IMP) distribution in normal subjects undergoing a cognitive challenge. *The Journal of Nuclear Medicine, 28,* 592.

Liberman, A. M., Harris, K. S., Hoffman, H. S., and Griffith, B. C. (1957). The discrimination of speech sounds within and across phoneme boundaries. *Journal of Experimental Psychology, 54,* 358–368.

Metter, M. J., Hanson, W. R., Kempler, D., Jackson, C., Mazziotta, J., and Phelps, M. E. (1987). Left prefrontal glucose hypometabolism in aphasia. *Clinical Aphasiology, 17,* 300-313.

Nagata, K., Yunoki, K., Kabe, S., Suzuki, A., and Araki, G. (1986). Regional cerebral blood flow correlates of aphasia outcome in cerebral hemorrhage and cerebral infarction. In F. Duffy (Ed.), *Brain electrical activity mapping.* Boston: Cambridge Publishers.

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh Inventory. *Neuropsychologia, 9,* 97–113.

Posner, M. (1987, November). *Selective attention and its neural basis.* Presidential Symposium, 17th Annual Meeting, Society for Neuroscience, New Orleans, LA.

Shankweiler, D. P., and Studdert-Kennedy, M. (1967). Identification for consonants and vowels presented to left and right ears. *Quarterly Journal of Psychology, 19,* 59–63.

Soh, K., Larson, B., Skinjoj, E., and Lassen, N. A. (1978). Regional cerebral blood flow in aphasia. *Archives of Neurology, 35,* 625–632.

Stokely, E. M., Sveinsdottir, E., Lassen, N. A., and Rommer, P. (1980). A single photon dynamic computer assisted tomograph (DCAT) for imaging brain function in multiple cross-sections. *Journal of Computer Assisted Tomograhy, 4,* 230–240.

Tikofsky, R. S., Collier, B. D., Hellman, R. S., Sapena, V. K., Zielonka, J. S., Krohn, L., and Gresch, A. (1985). *Cerebral blood flow patterns determined by SPECT 1-123 iodoamphetamine (IMP) imaging and WAB AQs in chronic aphasia: A preliminary report.* Paper presented at the Academy of Aphasia, Pittsburgh.

Tikofsky, R. S., Hellman, R. S., Collier, B. D., Palmer, D. W., Hoffman, R. G., Krohn, L., and Gresch, A. (1986, October). Differences in rCBF determined by SPECT/IMP between chronic aphasics and normals under baseline condition and while performing the Boston Naming Test: A preliminary report. Poster presented at the Academy of Aphasia, Nashville, TN.

Walker-Batson, D., Devous, M. D., Bonte, F. S., and Oelschlaeger, M. (1987). Single-photon emission tomography (SPECT) in the study of aphasias: A preliminary report. *Clinical Aphasiology, 17,* 313–319.

Walker-Batson, D., Wendt, J., Barton, M., Devous, M. D., and Bonte, F. J. (1988). A longterm follow-up case study by these authors of crossed aphasia assessed by single-photon emission tomography (SPECT) language and neuropsychological measures. *Brain and Language, 33,* 311–322.

Wiesendanger, M. (1983). Cortico-cerebellar loops. In J. Massion, J. Paillard, W. Schultz, and M. Wiesendanger (Eds.), *Neural coding of motor performance.* Berlin: Springer-Verlag.

DISCUSSION

Q = question; A = answer; C = comments.

Q. Could you give us your notion of the crucial need or needs for research in this area? Do we need better methodology, better task control, more subjects? Are there certain of those and perhaps others that are more important, as this work advances, than others?

A. I would say all of the above; certainly second-generation machines with better resolution. It is very difficult to develop tasks on these first-generation machines that have poor resolution. We have tried to replicate some of the two-dimensional blood flow tasks and could not get activation. Cognitive challenges show functional brain areas that are not observed during resting state rCBF. I think it is important to develop linguistic tasks carefully and to look at patients from acute to chronic stages of recovery.

Q. How strongly should we believe in the hypotheses about brain function based on these kinds of studies? Have we studied enough patients with the right number of tasks, with the right instrumentation to begin to be confident about the hypotheses that are stated at the end of the papers, or do we still need to be careful, and if so, what do we need to do?

A. I feel that we still need to be very careful about interpretation; run many more subjects and develop linguistic tasks because of the great variability among subjects both normal and aphasic. I feel that we have a long way to go yet.

Q. Why don't you see general increases in blood flow in your data with either task which you did not see in normal and pathological states? If you don't see in normal individuals identifiable reasons of altered brain blood flow specific to the task of the phoneme, what does that tell us? Is the technology insensitive to the processes that differentiate those two, or is the technology limited in terms of your machine?

A. We could use auditory click stimuli and get very obvious differences. We wanted to try to tap linguistic processing. This was a beginning step. It was disappointing. We were hoping that the auditory control would be differentiated from the probe condition, and both show more activation. Interestingly, two or three of the normals and one of the aphasic subjects treated the control like the probe condition and started segmenting the syllables. With a 4-minute window, an individual could be doing different types of mental processing across this time period. We have thought of making the control condition only a vowel sound with no consonant so that there is not a syllable. We did not randomize our tasks because of the small number of subjects. Ideally, we would like to run at least 30 subjects, but with the relatively high cost of the procedure, this is not possible.

Q. Do you have any thoughts as to what difference in mechanisms may be going on? Is it because, with some of these more complex procedural things, we're going through many synapses where the balance of positive and negative types of signals are bouncing out, and we don't see changes?

A. I would like to state hypotheses about something and have adequate data. I believe with the newer scanners we will be able to pick up subtle changes. I do think some of our problems have been the technology and its limitations.

Q. It seems that no matter what task you use you still have that attentional effect. How are you planning to sort that out with selecting different stimuli and different methods?

A. I really haven't thought that through. When I think about language processing and attentional mechanisms, I think it is very difficult to know which factors to say are linguistic and which are attentional. Phoneme segmentation may be most likely attentional; we don't really know.

Q. Did you get cerebellar activation in the resting condition as well as the other conditions?

A. No. Only in the probe condition and much more in the aphasic subjects in the ipsilateral (to the lesion) cerebellum than in any of the other conditions.

Q. Are the subjects given instructions not to move their heads and that sort of matter?

A. Yes they are.