REGIONAL CEREBRAL BLOOD FLOW DURING VERBAL AUDITORY STIMULATION

A Thesis

Presented to

the Faculty of the Department of Psychology

University of Houston

In Partial Fulfillment

of the Requirements for the Degree

Master of Arts

By

Norma A. Cooke

December, 1978

REGIONAL CEREBRAL BLOOD FLOW DURING VERBAL AUDITORY STIMULATION

An Abstract of a Thesis

Presented to

the Faculty of the Department of Psychology

University of Houston

In Partial Fulfillment

of the Requirements for the Degree

Master of Arts

By

Norma A. Cooke

December, 1978

ABSTRACT

Recent evidence suggests that changes in regional cerebral blood flow (rCBF) are reflections of the levels of functional neuronal activity of the cerebral tissue. The Xenon-133 rCBF technique has been used to examine regional variations in cerebral blood flow at rest and during various forms of behavioral activation, including performance on complex psychological tasks. Unfortunately, the latter studies did not address themselves to the possible role of sensorimotor functions involved in input and output as dictated by modality of task administration and response. The purpose of the present study was to examine possible effects of passive auditory stimulation on rCBF using the noninvasive Xenon-133 inhalation technique. Results suggested that the effects of passive sensory stimulation on rCBF cannot be reliably assessed in isolation, but can only be inferred when examined in the context of a task with cognitive specifications. The reliability, precision and reproducibility of the inhalation technique are also discussed, particularly with regard to the "resting state" baseline procedure.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF TABLES, Cont'd.

LIST OF FIGURES

I. INTRODUCTION

Development of Regional Cerebral Blood Flow Techniques

Regional cerebral blood flow (rCBF) is a radioisotopic measure which is presumed to reflect the rates at which blood is supplied to different regions of the brain via the cerebral vasculature. It is typically measured by one of two techniques (1) the injection, or intracarotid technique, or (2) the inhalation technique. Both use a freely diffusible radioactive gas as a tracer in rCBF measurements, and, by means of external counting detectors ("scintillation detectors") placed against the head, both techniques record rates of photon emission as the isotope traverses different regions of the hemisphere. In each method, rate of blood flow is then calculated from the rate at which the scintillation detectors indicate the radioisotope has cleared from the system. The curve produced from the decreasing number of counts across time at a detector site is called the clearance or desaturation curve.

The forerunner of both the injection and inhalation techniques is the nitrous oxide method (Kety and Schmidt, 1945), in which determinations of total mean cerebral flow were made by measurements of arterial and venous concentrations of inhaled nitrous oxide. The calculations employed in all three techniques are based on the Fick principle (Fick, 1870). Simply stated, the Fick principle

as it relates to circulation is that volume of blood flow is proportional to oxygen consumption and the differences between arterial and venous oxygen levels across time.

The injection technique was first introduced in 1961 by Lassen and Ingvar, who found it to yield the same normal values as the Kety-Schmidt technique. This technique involves the injection of a bolus of radioisotope gas in saline solution into the internal carotid artery and then recording the desaturation curves at chosen regional locations. The first injection studies (Lassen and Ingvar, 1961; Lassen, et al., 1963) used the radioisotope Krypton-85 as a tracer. Xenon-133 is now used predominantly, by virtue of its short half-life (5.3 days) and more limited range of gamma radiations, which are more easily recorded.

The injection technique had a number of advantages over the Kety-Schmidt technique, including a smaller random measurement error (Kety and Schmidt, 1948; Ingvar, et al., 1965; McHenry, et al., 1969; Risberg and Ingvar, 1972) and the availability of regional as well as mean blood flow values. The greatest advantage of the injection technique, however, appeared with the introduction of "two-compartmental analysis" (Lassen and Ingvar, 1963), which made possible the delineation of flow levels into gray matter flow (Fg) and white matter flow (Fw) separately.

Injection technique analysis by the two-compartmental method is based on the fact that gray matter and white

matter are perfused, and consequently the isotope diffused in blood desaturates, at very different rates. Thus, the curve derived from monitoring the washout of the isotope can be separated into a fast component (Fg) and a slow component (Fw). Analysis of injection technique data is now typically done by computer (Sveinsdottir, 1965; Hoedt-Rasmussen, et al., 1966), using an unweighted least-squares method of curve fitting. Computer analysis has made possible simultaneous rCBF measurements at as many as 254 locations on a single hemisphere.

In 1963, Mallett and Veall introduced a method of measuring rCBF which was similar to the injection method, but removed the necessity for carotid puncture, an obvious advantage in both clinical and research applications. Now commonly referred to as the inhalation technique, the Mallett and Veall (1963) method involved administration of the isotope Xenon-133 by allowing the patient to breathe a Xenon-room air mixture for five minutes in a closed-circuit system, and then recording for twenty minutes the rate at which the Xenon was eliminated from the system by use of scintillation detectors, as in the injection technique.

Mallett and Veall (1963) adapted the principles of the two-compartmental analysis used in the injection technique to analyze the clearance curves they obtained. They calculated perfusion rates of gray and white matter based

on their own unpublished observation of the solubility of Xenon-133 in human blood and brain tissues in vitro. The brain/blood coefficients they obtained (.8 and 1.51 for gray and white matter respectively) are the standards now used in inhalation technique analysis.

Mallett and Veall (1963) further reported that blood flow values obtained from the rate of Xenon clearance alone underestimated the true value because the rate of clearance of the arterial Xenon-133 concentration does not fall immediately to zero, due to recirculation of some of the isotope, and this affects the early part of the desaturation curve. They applied a correction to allow for this effect by recording the rate of change of concentration of Xenon-133 in the expired air. Based on their method, Mallett and Veall (1963) reported an average estimated cerebral perfusion rate in normal subjects of 35 ml/100g/min, as compared to an average of 50 ml/100g/min as measured by the injection method.

The validity of the inhalation technique was challenged by Jensen, et al. (1966), who compared clearance rates obtained by each method. Results of paired measurements in eight subjects revealed that the inhalation method not only consistently produced lower cerebral blood flow values than the injection method, but also that statistical analysis failed to show any significant correlation between the two

sets of data. They suggested that the major source of error might lie in the greater absorption of Xenon by extra-cerebral tissues such as scalp and bone in the inhalation method. The extremely slow clearance rates of these tissues was felt to contaminate the clearance curve data to such a degree to "obviate quantitative evaluation of cerebral blood flow by this approach" (p. 485).

The problem of extracerebral contamination in the use of the Xenon inhalation technique was resolved by Obrist and his colleagues (1967). Their findings indicated that it was possible to subtract out the influence of slow-clearing extracerebral tissues into a third component by analysis if the inhalation period was reduced to two minutes and the recording interval was extended to more fully monitor wash-out of extracerebral tissues, about 40 minutes. This "three compartmental analysis" yielded measurements comparable to those obtained by the more established intra-carotid technique.

Obrist, et al. (1967) also included a validation of Mallett and Veall's (1963) substitutions of Xenon activity levels in end-expiratory air for arterial concentrations in calculating flow values by comparisons with results of simultaneous arterial sampling.

The Obrist, et al. (1967) study marks the beginning of the acceptance of the Xenon inhalation technique as a clinically relevant tool for measuring cerebral blood flow. The Xenon inhalation technique possessed two unique properties

which made it highly attractive to researchers: (1) its atraumatic nature and (2) the feasibility of simultaneous bilateral measurements.

Most rCBF research by the inhalation method as it is practiced today is based on a modification of the three compartmental model which Obrist, et al. proposed in 1971 and elaborated on in 1975. Called the "two-compartmental model", it requires only ten minutes of extracranial recording following one minute of Xenon inhalation. The fast component derived from curve analysis provides blood flow estimates of the gray matter which compare favorably with those obtained by three compartmental analysis. White matter and extracerebral clearance rates, however, are treated as a single unit in the slow compartment. The two-compartmental method's frequent use in spite of this limitation is based on (1) the fact that flow rate in the gray matter is often the variable of primary interest, especially in behavioral activation studies, and (2) the obvious convenience of reduced measurement time. With on-line computer analysis, rCBF values are usually available within 30 minutes of the beginning of the measurement.

More recent technical developments in the measurement of rCBF by Xenon-133 inhalation include the development of a new index of rCBF by Risberg, et al. (1975), the Initial Slope Index (ISI). Using the Obrist (1971) modification of the Xenon inhalation technique, Risberg, et al. (1975)

measured rCBF repeatedly in eleven patients with cerebrovascular disorders. Fluctuations in Fg from one measurement to the other in eight of the patients suggested that some pathological tissues fluctuate between the fast and slow compartment, resulting in faulty curve analysis by the bicompartmental method. The ISI was designed to be independent of such fluctuations. Calculated from the two-to-three minute interval of the ten minute recirculation corrected head curve, the ISI is a single index of all tissues recorded rather than compartmentalizing the curve into fast and slow components. This index, however, is highly dominated (84%) by the gray matter flow and very little influenced by extracerebral components. Recalculating their test-retest data using the ISI, Risberg, et al. (1975) found a maximum observed variability of 4%. The authors suggested that the ISI showed potential as a more useful tool in the evaluation of patients with cerebrovascular disorders than traditional measures. A similar parameter, $rCBF_{init}$ or f_{init}, has been developed for the injection technique.

Methodological Research: Reliability of the rCBF Technique

Recent evidence suggests that problems with test-retest reproducibility may not be limited to patients with cerebrovascular disorders. In particular, researchers have begun to examine the "resting state" so often used as a basis for comparison in rCBF "activation" studies. Among them are Lassen, et al. (1977), who reported the inter-individual variations in mean CBF in 49 selected neurological patients by the injection technique to be so wide (32 - 82 ml/100g/min) that the rest condition could not be considered a well-defined cerebral state. In addition, repeated measurements revealed a consistent tendency toward decreased mean flow or "diffuse deactivation" (right hemisphere 7%, left hemisphere 3%). However, the overall pattern usually associated with the resting state, with higher values anteriorly, was found to be highly reproducible.

Baluenstein, et al. (1977) performed test-retest serial resting measurements on 35 healthy right-handed volunteers using the Obrist (1971) modification of the Xenon inhalation technique. They also found a wide range of variability in mean hemispheric CBF values both from subject to subject and in serial measurements in the same subject. However, the interhemispheric correlation of changes from first to second resting measurements was statistically significant both regionally and even moreso

in terms of hemispheric mean flow. This was true for all CBF parameters calculated, including ISI and Fg.

For all measures examined, however, the variability was higher than the standard error of measurement of 4% obtained by Obrist and his colleagues (1975) in comparisons of pairs of computer-simulated clearance curves. Blauenstein, et al. (1977) felt that their data suggested that this additional variability was predominantly of physiological origin. However, others (Ingvar, et al., 1965; McHenry, et al., 1969; Risberg and Ingvar, 1972) who analyzed their use of the injection technique found a total random measurement error ranging from only 3.5 to 5% between repeated measurements.

One of the most serious and pertinent criticisms of the Xenon inhalation technique appeared recently in an article by Eichling and Ter-Pogossian (1977). They report results of phantom studies which indicate approximately 60% of a typical scintillation detector's response is noise, originating from scatter or extracerebral tissues. They further charge that such scatter coupled with the large field of view provided at depth by typical collimators results in regionality being essentially lost.

It would appear from the results of the foregoing studies that, although noninvasive, the inhalation technique may be less precise than the injection technique. Certainly the typical inhalation clearance curve has less

"counts" or data points than a curve produced by the injection method, simply because the tracer follows a less direct route to the cerebral vasculature. As a result, scintillation detectors used in the inhalation method must have a larger field of view in order to obtain sufficient data for curve analysis. The regionality issue would thus appear unresolvable with inhalation equipment currently available. Both techniques, however, are equally vulnerable to the inter- and intra-individual variations in rCBF, which, whatever their source, combine to present difficulties in making inferences from rCBF group results.

Cerebral Blood Flow and Behavior

Observations of the apparent coupling of cortical activation as recorded by EEG desynchronization and increases in the cortical circulation was reported by Ingvar (1954, 1955), in a study in which the ascending reticular activating system was electrically stimulated and flow changes observed visually at low magnification. Recent evidence suggests that changes in EEG and blood flow are reflections of the levels of functional neuronal activity of the cerebral tissue (Ingvar 1976), by virtue of the fact that carbon dioxide, a powerful vasodilator, is generated by the oxidative metabolism of the neurons. It follows that if different kinds of mental "work" are characterized by discrete changes in local as well as global levels of neuronal

activity, then these "patterns" of activation might well be marked by regional variations in cerebral blood flow. In this section we will review some of the studies which have examined changes in regional cerebral blood flow during various forms of behavioral activation.

Behavioral activation studies typically compare an individual's rCBF pattern at rest with eyes closed to a test condition in which rCBF measured are obtained simultaneously with the individual's participation in some task. The inference is, of course, that any differences noted in the two rCBF measurements can be attributed to the changes in the demands imposed on the nervous system by the task requirements.

Psychological Activation

The earliest rCBF activation studies (Ingvar and Risberg, 1967; Risberg and Ingvar, 1968, 1970, 1973) addressed themselves to the very general notion of "psychological activation", as represented by such tasks as the digit-span-backward test (Wechsler, 1959), picture memory test (Thurstone, 1938) mental arithmetic, and Raven's Standard Matrices (Raven, 1938). Ingvar and Risberg referred to the small regional changes (5 - 10%) seen as "functional landscapes" and related them to the content of psychic activity during task performance. Unfortunately, they did not address themselves to the possible role of sensorimotor functions involved in input and output as

dictated by modality of task administration and response. Ingvar and Risberg's inference that changes in rCBF were a result of mental activity would seem unwarranted in view of the methodological inadequacy of these early studies.

Ingvar and Risberg did, however, make some observations that were later relevant to other researchers. Of major impact has been their introduction to rCBF analysis of Luria's (1966, 1973) conceptualization of the functional organization of the brain. The Luria framework has been found to be highly compatible with descriptions of "patterns of change" during behavioral activation. Noting the consistency of frontal rCBF increases across tasks, Risberg and Ingvar (1973) proposed that frontal cortical flow increases during mental activity represented a nonspecific, or general arousal component of activation. Frontal increases in subsequent activation research have been ascribed to "behavioral programming" (Ingvar and Philipson, 1977), "general control and organization of behavior" (Risberg, et al., 1977) and "programming of movements" (Roland, et al., 1977b, 1977c).

Risberg and Ingvar (1973) also reported that in two subjects in which parallel versions of the Raven's Matrices were administered in succession, the second session showed more clearcut focal changes and less indication of diffuse increase. Results of a more extensive investigation (Risberg, et al., 1977) indicated the second session was also characterized by an absence of the focal increase

usually seen in the frontal region during activation. It was suggested that this "restriction" of rCBF augmentations and apparent decreased participation of the frontal regions during the second testing was due to adaptation or learning on the part of the subject. Subsequent behavioral activation studies (Ingvar and Schwartz, 1974; Roland and Larsen, 1976; and others) have followed the procedure of initiating activation prior to the beginning of the rCBF measurement in response to Risberg and Ingvar's (1973) observation.

Lastly, Risberg and Ingvar (1973) were the first researchers to describe what they felt was a "typical" rCBF pattern during resting conditions, characterized by flow values about ten per cent above the hemispheric mean in frontal and prerolandic regions, and lower flows in inferior temporal and parieto-occipital regions. Ingvar and Schwartz (1974) and Ingvar and Philipson (1977) concurred with this observation.

Sensory-Motor Activation

The Oleson (1971) behavioral activation study was the first to focus on a more discrete behavioral function than "psychological activation". Oleson (1971) examined changes in rCBF at rest and during vigorous hand exercise ("arm work").

In a group of ten patients, rCBF was determined in 35 small areas of a hemisphere by the Xenon-133 intra-arterial

injection method. For each patient, a drawing of detector placement was superimposed on a lateral x-ray or arteriogram for individual localization of the probes.

"Arm work" required the patient to open and close his hand 1-2 times per second, to a beat indicated verbally by a nurse. Measurement of rCBF began two to three minutes after initiation of exercise to that maximal innervation effort was necessary to continue and so that sensory input from the arm was intense Resting and test measurements were obtained in alternating order. A focal increase averaging 54% was found in 9 of 10 patients. The localization of the rCBF increase corresponded to the cortical representation of the hand. These findings were later replicated by Ingvar and Schwartz (1974), Ingvar and Philipson (1977), and Lassen, et al. (1977).

As Oleson notes, his task did require auditory input (the timing of the hand movements) in addition to the "arm work" being examined. Although the pacing of the task presented would appear to be a desirable control measure in terms of the amount of "work" being performed, it is not possible to assess the impact of this additional input on the rCBF values he obtained.

Further studies of voluntary motor movements have been made by Roland, et al. (1977b, 1977c). They found that a single sustained static contraction increased rCBF 30 - 40% in the Rolandic sensory-motor hand and arm area in the

contralateral hemisphere. They also compared rCBF patterns during the organization and execution of motor sequences. During the execution measurement ("motor sequences"), patients touched different fingers with their thumb in a prearranged order and as quickly as they were able. During the organization measurement ("internal motor sequences"), the patient was instructed to follow the finger sequence internally but was not allowed to execute the movements. A comparison of results suggested the possibility that Brodmann's area 6 of the frontal region might be involved in the programming of movements in temporal sequences.

Roland and Larsen (1976), in reporting increases in rCBF during stereognostic testing, gave the most complete account of specifications for the resting condition to appear in the literature up to that time:

> ...The ears were plugged and the eyes were closed with cotton wool pads that reduced the ocular movements. The subject was awake and relaxed. He was told to lie comfortably, not to move, and to think of nothing. The EEG was recorded with bipolar leads according to the 10-20 system. The galvanic skin response (GSR) was recorded with a galvanometer. Intra-arterial blood pressure and pulse were recorded with another galvanometer. Within the first minute after the injection, an arterial blood sample was taken from the internal carotid artery for determination of PaCO2.
>
> The purpose of these measurements of autonomic variables (EEG, GSR, pulse, blood pressure, PaCO2) was as follows: (1) the condition of the subject should approximate ideal rest in which the EEG recordings showed a regular alpha-type activity in the posterior leads; (2) the galvanic skin conductance should remain stable; (3) the mean arterial blood pressure and the pulse

> frequency should approximate the clinically measured mean blood pressure and pulse frequency on the ward; and (4) the PaCO2 should be close to 40 mm Hg. (p. 552)

Regional cerebral blood flow measurements were made at rest and during stereognostic testing in three modalities in eighteen right-handed neurological patients using the Xenon injection method and 254-channel recording with a dynamic gamma camera. Initial slope index blood flow values were reported. The stereognostic task consisted of a two alternative forced-choice tactual discrimination by hand, mouth, or foot; in each trial, the subject responded as to which of two objects was the most oblong. The test started 20 seconds before the start of injection and stopped 120 seconds after the start of the injection. Less than one second after the subject had answered, a new object was given to him. Instruction and learning trials were given five minutes prior to the injection.

Results of paired t-tests indicated significant increases as follows: during had discrimination, a contralateral increase in mean flow, the sensory-motor hand area, and premotor frontal regions. During mouth and foot discrimination, similar patterns were seen, with changes in the appropriate sensory-motor region. Increases were always seen in Brodmann's area 6 and 8 of the premotor frontal regions.

It is important to note that Roland and Larsen (1976)

found no indication from rCBF results for the participation of the parietal lobules during somatosensory shape discrimination, despite the clear spatial nature of the stimuli used. In this connection, the authors also note that the rCBF procedure does not permit a study of the time relations between the activation of different cortical areas, and as a result, regions (such as perhaps the parietal areas) with a brief activation might be missed.

Automatic Speech

Ott, et al.(1977) examined rCBF patterns at rest and during automatic speech. Regional CBF was measured in six neurologically normal subjects using the intra-arterial technique and 16 scintillation detectors placed on the lateral aspect of a single hemisphere. The speech test consisted of repeating the names of the weekdays and months and counting from 1 to 20 repeatedly. Their findings confirmed those of others using the same task (Ingvar and Schwartz, 1974; Ingvar, 1975; Larsen, et al., 1977) that during speech, rCBF in the dominant hemisphere increases in the premotor, rolandic, and sylvian regions.

Auditory Input

The following limited series of rCBF studies have special relevance to the present research in that they examine the stimulus parameter of interest here, auditory input.

Carmon, et al. (1975) measured rCBF at rest and during two auditory listening tasks. Using the intracarotid technique and 24 scintillation detectors placed over a single hemisphere, regional cerebral blood flow was measured in nine right-handed subjects without major focal or diffuse hemispheric disease, using a rest, test, test design. Order of presentation of a verbal and a nonverbal task was counterbalanced between subjects. On the verbal task (a Hebrew translation of passages from the Wechsler Memory Scale), subjects were instructed to listen carefully, remember each passage and report them after the session was completed. On the nonverbal task the patient simply listened to two passages of melodic music. Each rCBF measurement, lasting two minutes, was performed during the last two minutes of a five minute task presentation.

During the nonverbal task, mean hemispheric blood flow increased bilaterally, moreso on the right (right mean increase = 7-19%; left mean increase less than 7%). During the verbal task, mean hemispheric CBF increased on the left and decreased on the right.

Regional analyses were evaluated by two different methods: (1) by percentage deviation from the resting mean and (2) by the percentage deviation of each region from that region's resting value. These two methods yielded different results. By method one, increases during the verbal task were seen in the left frontal and left anterior/mid temporal regions. By

method two, however, increases were seen in left temporal, left temporo-parietal, and right anterior fronto-temporal regions.

On the nonverbal task, there were also differences in results obtained by each analysis method. By method one, increases were seen in right frontal, right anterior/mid temporal, right temporo-occipital, left fronto-parietal, and left posterior temporal regions. Method two yielded increases in right fronto-temporal, left frontal, and left mid/posterior temporal regions.

Understandably, Carmon, et al. (1975) emphasized primarily the mean hemispheric flow differences on the two tasks, which they viewed as further evidence for hemispheric specialization in processing of verbal and nonverbal input. Failure to find clearcut regional changes was attributed to the nature of the task, in that the procedure did not enforce the subject's attention to the task. As also later suggested by Roland and Larsen (1976) and Roland, et al. (1977b), Carmon, et al. (1975) were of the opinion that measurements with a higher temporal resolution might do much to alleviate this problem.

Using the intra-arterial technique and 254 channel recording, Larsen, et al. (1977b) examined rCBF changes in 20 neurologically normal patients at rest and during passive listening. In the listening condition, patients were instructed to just listen to simple words consisting of ono-

matopoeia. Results were based on 10 left and 10 right hemisphere studies. Left hemisphere mean CBF was found to increase 10% during listening, and statistically significant regional increases were noted in the posterior temporal region (14%), inferior parietal region (8%) and Broca's area (7%) of the left hemisphere. Consistent results for the right hemisphere were not obtained.

Roland, et al. (1977a) examined rCBF at rest and during nonverbal auditory input in an unreported number of neurological patients with normal arteriograms and normal rCBF resting patterns. Regional CBF measurement was by the intracarotid technique and 254 channel recording. The stimulus material used was Series B of the Seashore Test, which is a two alternative discrimination test of a pair of sequences of pure tones. Stimulus presentation was to the subject's left ear. The patient was instructed to listen to the tone sequences and decide whether the pair was identical or different, but not to respond unless asked. No responses were requested during the measurement procedure. To assure that the subject had been attending, however, a request for response was made at the end of the procedure.

Focal increases were reported in four regions of the right hemisphere: inferior parietal/posterior superior temporal, inferior frontal, frontal polar and middle prefrontal. Roland, et al. (1977b) report the same results based on ten patients, but it is unclear whether the studies are the same.

Neither study reports magnitude of increase.

Roland, et al. (1977b) proposed an explanation for the pattern of rCBF increases seen. It was felt that those frontal regions with elevated rCBF were the areas receiving first order afferents from the auditory projection area, the exact localization depending on whether the initial input was through the auditory or somatosensory channel.

Lastly, Lassen, et al. (1977) briefly state that listening to music results in an increase in the posterior part of the superior temporal gyrus bilaterally.

Based on the foregoing studies (all of which use the intracarotid technique), it appears possible that auditory input increases rCBF in the inferior frontal, inferior parietal, and/or posterior temporal regions. It is also possible that the nature of the auditory input may affect lateralization of increase. With the exception of the Carmon, et al. (1975) study (which was unable to produce positive regional findings), however, the poor quality of methodological and statistical reporting in these studies renders valid critical analysis of results virtually impossible. In addition, where regional magnitude of increase is reported (Larsen, et al., 1977b), it is less than 15%, a change perhaps too small to be reliably detected by the inhalation method.

A number of questions remain unresolved with regard to the effects of stimulus conditions, i.e., possible inter-

actions between stimulus characteristics and laterality of input. The neuroanatomical structure of the auditory system is such that there are bilateral connections from each ear to the cortical projection areas. However, the majority of these projection fibers (about 80%) travel to the auditory projection area (Heschl's gyrus) in the contralateral hemisphere (Rosenzweig, 1951). Furthermore, the expected contralateral site of increase on unilateral stimulation is complicated by results of research on laterality of function in the human brain, which suggest that verbal material is primarily processed by the left hemisphere, and nonverbal material by the right hemisphere in right-handed individuals (Kimura, 1967).

An interaction effect between input and processing would predict maximal rCBF changes in the left hemisphere (particularly increases in the region of Heschl's gyrus) with unilateral right ear stimulation. Binaural stimulation might show the same rCBF pattern in a context of diffuse increase, and the changes seen during left ear stimulation would depend on whether the effects of laterality of input or processing predominated. It is suggested that processing requirements might best be held constant across subjects by use of a passive listening task in which no response or attention is required.

The present study, then, examines regional and hemispheric changes in CBF at rest and during verbal auditory

passive stimulation using the Xenon inhalation technique. Special emphasis has been placed on control of stimulus conditions in order to better determine the source of any changes observed.

II. METHODS

Subjects

The subjects were fifteen selected male volunteers aged between 19 and 28 years (mean age 24.5, SD 2.97) who met the following screening criteria for participation in the study: (1) normal hearing-threshold levels in the speech range, (2) right hand dominance, and (3) right ear dominance on a dichotic listening task. The purpose of the screening tasks was to control inter-subject variability during the rCBF measurement due to auditory acuity deficits or differences in hemispheric dominance for speech.

In order to rule out deficits in auditory acuity, each subject received a brief pure tone audiometric evaluation while seated in an anechoic chamber. Auditory thresholds were obtained for each ear at 250, 500, 1000, 2000 and 4000 Hz, using an Allison 22 audiometer and TDH-39 audiometric headphones. Criteria for normal hearing in the speech range was defined as threshold at or below 20 dB at 500-2000 Hz. Equipment and instruction for auditory screening were provided by the University of Texas Speech and Hearing Institute through the cooperation of Dr. Albert Yonovitz.

Right hand dominance and right ear dominance were the criteria selected to control for left hemisphere dominance for speech. The Hand Preferences portion of the Harris Tests of Lateral Dominance was administered to confirm

right hand dominance. Ear dominance was determined by performance on a dichotic listening task. The dichotic listening tape was provided by the University of Florida Neuropsychology Laboratory through the cooperation of Dr. Paul Satz. The tape consisted of thirty trials, a trial being six digits, three presented to each ear at .5 second intervals. Each presentation lasted for 1.5 seconds. An 8.5 second blank space for the subject to respond followed. The subject was requested to report all of the digits he had heard in any order, and was given five practice trials prior to testing. After trial fifteen, the earphones were reversed to counterbalance for possible channel differences. The digits were presented via a TEAC A-2300SX tape recorder and TDH-39 audiometric headphones. Ear dominance was determined by the number of digits reported correctly for each ear.

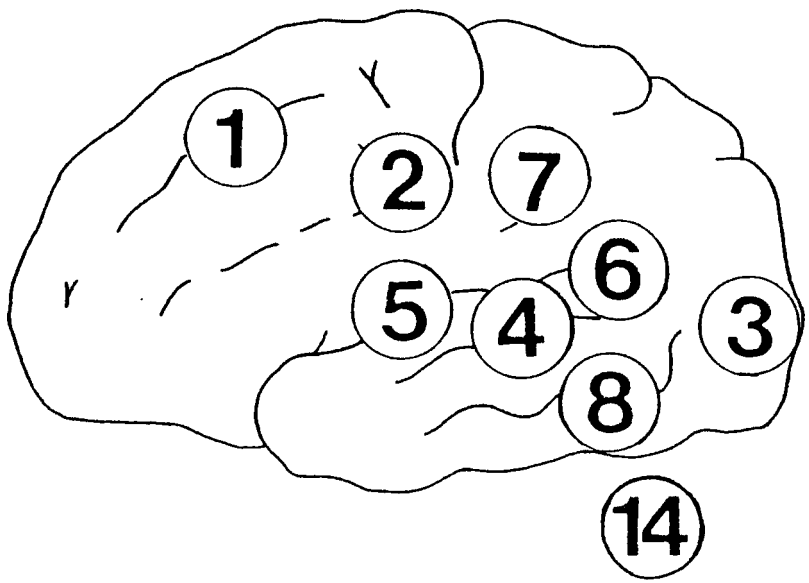
Following screening, subjects were assigned to one of three stimulus conditions for the rCBF measurement in rotating order: right ear monaural auditory input, left ear monaural auditory input, or binaural auditory input.

Procedures

After the study was explained and a signed consent form was obtained (Appendix A), the subject was taken to the Noninvasive Regional Cerebral Blood Flow Laboratory, introduced to the lab personnel, and shown the equipment to be

used in the experiment. In order to obtain a gross measure of arousal during the rCBF procedure, frontal (F3 & F4), temporal (T3 & T4) and occipital (O1 & O2) electrodes were attached to the subject's scalp following the International 10-20 electrode system. Electrodes were also attached for EMG and EOG activity recording. Vertex was marked at this time with a pad of cotton for later verification of correct positioning of the scintillation detectors. Electrode impedance was checked, with criterion level set at 1500 ohms.

A close-fitting anesthesia-type face mask to be used for Xenon administration was then adjusted to the subject's face and a surgical cap was placed over the head to protect the electrodes. The subject was asked to recline on an examining table adjacent to the blood flow equipment complex and his head was positioned in the rCBF helmet in which the scintillation detectors for extracranial recording of rCBF levels are mounted. Vertex was checked and the sixteen scintillation detectors were lowered into place against the subject's scalp and secured by set screws. Figures 1 and 2 show the detector placement for the right and left hemispheres for all subjects. Retractable earphones situated in the helmet were fitted snugly to the subject's ears and also secured by set screws. The face mask was then attached to the Xenon delivery system. Simultaneous recordings of temperature, blood pressure, and respiration rate were begun at this time. The stimulus tape was then calibrated via a Grason Stadler



1 - Area 8
2 - Precentral
3 - Occipital
4 - Heschl's Gyrus
5 - Broca's Area
6 - Inferior Parietal Lobule
7 - Post Central
8 - Inferior Temporal/ Midbrain
14 - Cerebellum

Figure 1.

Probe Locations: Left Hemisphere and Cerebellum

9 - Area 8
10 - Precentral
11 - Post Central
12 - Broca's Area
13 - Inferior Parietal Lobule
15 - Inferior Temporal/ Midbrain
16 - Heschl's Gyrus

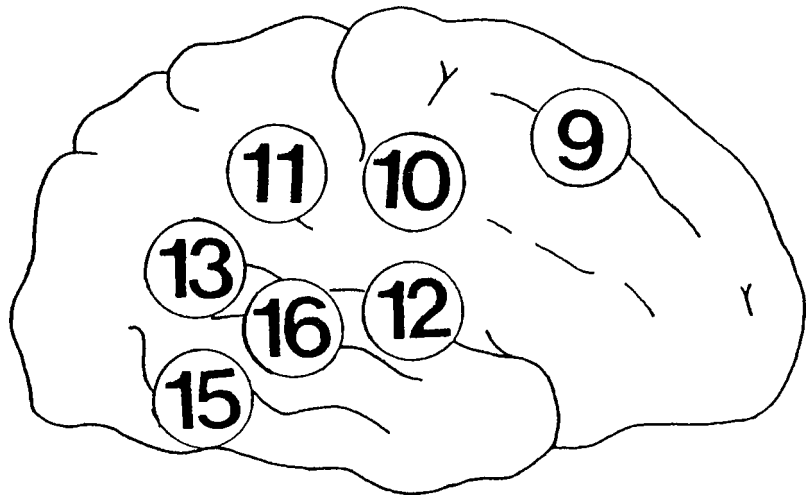


Figure 2.

Probe Locations: Right Hemisphere

speech audiometer for presentation at 90 dB SPL and a five second portion of the tape was played with the subject asked to report the ear (right, left, or both) in which he heard the stimulus. The subject was then instructed to lie quietly with eyes closed for the duration of the measurement. The laboratory was darkened and kept as quiet as possible to minimize extraneous auditory input and the subject's respiration rate was monitored until he had relaxed and respiration became steady and regular.

Xenon 133 was administered through the face mask in a room air mixture for one minute, followed by a ten minute recording of clearance activity. Simultaneous recordings of EEG, EMG, EOG, end-tidal PCO2 and PO2 were also obtained during this time.

At the end of the first measurement period, the room was illuminated and the mask was removed from the subject's face. Inter-trial time was approximately 20 minutes in order to allow most residual Xenon to clear from the subject's system, and to permit on-line computer processing and analysis of the data obtained during the measurement.

The second rCBF measurement, or stimulus condition, followed the same procedures as the first with the addition of stimulus material presentation. The presentation of the stimulus tape began approximately one minute prior to Xenon inhalation and continued throughout the second rCBF measurement. The subject was instructed simply to listen to the

words presented. The stimulus material consisted of a tape containing 32 spondaic words (Appendix B), each approximately 800 msec. in length. The spondees were presented in random groups of three at one second intervals, each group separated by a five second interval of silence.

The words were presented via a Sony tape recorder and TDH 39 earphones with an MX 41/AR cushion mounted in the rCBF helmet.

After another 20 minute inter-trial interval, the third, or post stimulus measurement was obtained, following the same procedures as the first rCBF measurement. Prior to each measurement, vertex was again checked to insure that the subject's head had not shifted in the helmet during the 20 minute washout interval.

Apparatus

The apparatus used in the measurement of rCBF can be divided into four functional components: (1) the Xenon delivery system, (2) equipment for simultaneous recording of other measures known to influence rCBF levels, (3) Xenon activity recording, and (4) on-line computer analysis.

Xenon Delivery System. The Ventil-Con (RADX Corporation, Houston) is a three-way gas delivery system which allows the subject to breathe room air through the face mask prior to the inhalation procedure and maintains 0_2 and $C0_2$ levels of inspired air constant in a closed system during Xenon-133

delivery and recirculation. Xenon inhalation is via a close-fitting anesthesia-type face mask connected to the Ventil-Con. The Ventil-Con contains a vacuum pump which draws expired air from the face mask at the rate of 1.5 liters per minute. The end-tidal air is passed over a scintillation detector for monitoring of end-expiratory $C0_2$ ($PEC0_2$). Partial pressure end-tidal oxygen ($PE0_2$) is measured by a Clark oxygen electrode. Xenon activity, $PEC0_2$ and $PE0_2$levels are all continuously recorded on a polygraph. For recirculation, $PEC0_2$ is removed by a Baralyme $C0_2$ filter.

The Xenon concentration of the system is manually maintained at 5 - 7 millicuries/liter prior to each inhalation procedure and is displayed on an analog meter on the control panel of the Ventil-Con. The Ventil-Con has a 40 liter capacity.

Simultaneous Recording. Blood pressure and pulse rate are simultaneously recorded on the polygraph by use of a finger plethysmograph. Continuous EEG, EMG, and EOG activity are recorded to give a gross measure of the subject's level of arousal during each rCBF measurement.

Xenon Activity Recording. Extracranial recording of rCBF levels was obtained by means of sixteen scintillation detectors or probes mounted in ports drilled in a modified motorcycle helmet, as shown in Figure 3. The placement of the ports was designed for monitoring of Xenon activity in the frontal (Area 8), precentral, post central, inferior

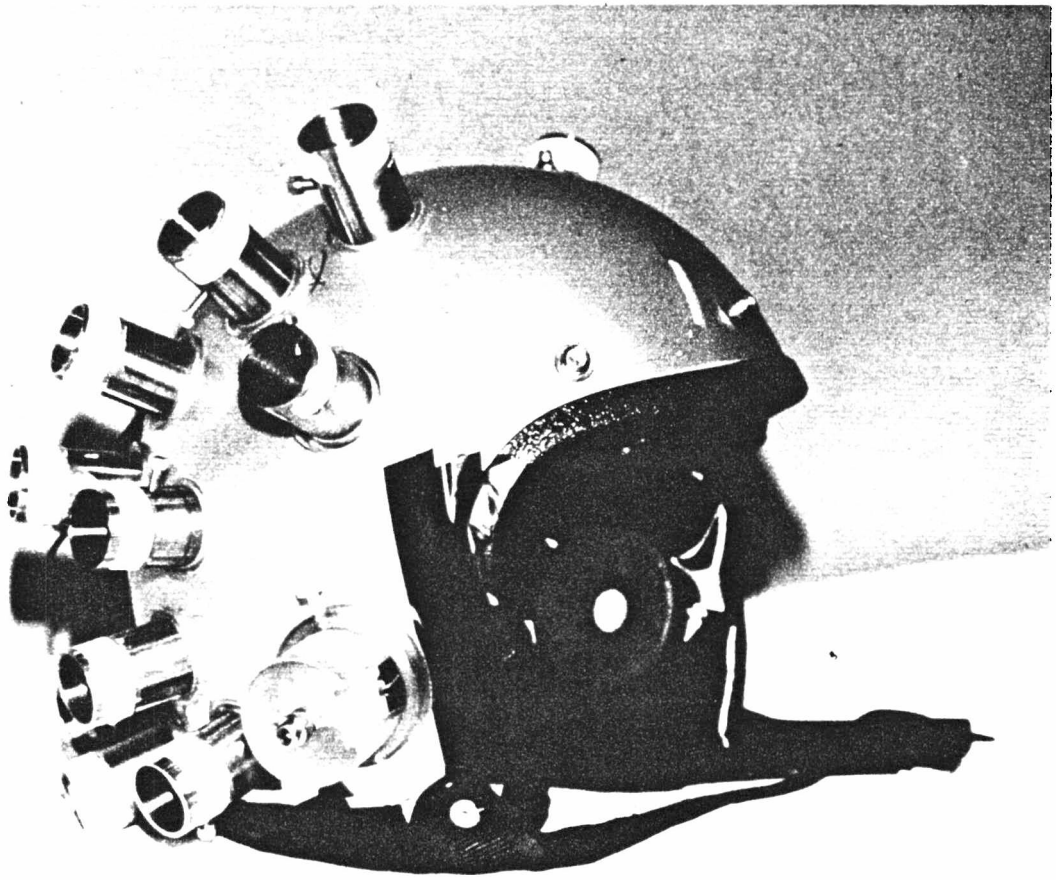


Figure 3.

rCBF Helmet with Ports for Placement of Probes

frontal (Broca's area), posterior superior temporal (Heschl's gyrus), inferior parietal lobule, and inferior temporal/ midbrain regions bilaterally, and the left occipital region and cerebellum. Accuracy of localization of port placement (Stump, 1978) was confirmed by a lateral skull x-ray with the helmet centered at vertex and the proposed port locations marked with lead tabs. Accuracy to .5 cm. was confirmed by cadaver studies at a later date. As previously mentioned, a scintillation detector is also mounted in the Ventil-Con for monitoring end-tidal Xenon activity.

Each probe contains a collimator which determines its optical circle of resolution and relative efficiency. Length of collimation in inversely proportional to area of resolution. In the present study, collimators of one inch length and .5 inch internal diameter were used for all regions except Area 8 and Heschl's gyrus bilaterally. To reduce the optical circle of resolution and minimize contamination from the nasopharyngeal air passages and sinuses, longer collimators (1.58 inches) were chosen for placement over Area 8 and Heschl's gyrus.

Each probe also contains a thallium-activated sodium iodide crystal which converts the photon energy produced by the Xenon activity in the area beneath that probe into visible light, or scintillation. The probe also contains a photomultiplier which converts this scintillation into electronic pulses. Like every other radionuclide, Xenon-133 has

a "pulse-height spectrum", or voltage range of pulses, which is unique to that radionuclide. Pulses from the probe not in this range may be assumed to be due to background activity or scatter. By means of an electronic processing unit, each pulse from the photomultiplier is amplified and submitted to pulse height analysis. By rejecting photons not in the pulse-height spectrum for Xenon-133, recording is limited to those primary photons coming from Xenon activity in the region beneath the probe. Pulse data from all seventeen scintillation detectors is then modified for computer analysis by a multiprobe Dynamic Function Analyzer.

On-Line Computer Analysis. All rCBF data acquisition, analysis and storage is under PDP11-5 computer control. Display, editing, and recall of data is by means of a Tektronix Graphic Display unit.

The computer program used in the present study is a modification of Obrist, et al's (1975) ten minute two-compartmental analysis method. Using an unweighted least-squares method of curve fitting, fast and slow component values are obtained from the desaturation curve from each probe. Recirculation of Xenon is corrected by fitting these curves with the desaturation curve of the radioactivity of the expired air.

Analysis yields a number of rCBF parameters, including values for gray matter flow (Fg; derived from the fast component), white matter flow (Fw; derived from the slow com-

ponent), and the Initial Slope Index (ISI2; derived from the first two minutes of clearance). The program will also provide confidence intervals for Fg and Fw indicating the goodness-of-fit of each curve if desired. Should the fit be poor due to incomplete rejection of scatter, an "edit" option allows alteration of data points on the clearance curve. Total analysis time is about twenty minutes, depending on the number of iterations required for an acceptable "fit" on each curve.

III. RESULTS

Three rCBF measurements were performed on each subject: pre-stimulus resting state (pre), auditory stimulus presentation (stim) and post stimulus resting state (post). The mean hemispheric Fg during each measurement for each of the stimulus presentation conditions, Right Ear Stimulation (R Stim), Left Ear Stimulation (L Stim) and Binaural Stimulation (B Stim) is shown in Figure 4.

Mean Hemispheric Fg: An increase in mean hemispheric Fg is usually regarded as an indication of increased level of activation, even in the absence of clearcut focal findings (i.e., Carmon, et al., 1975). As seen in Figure 4, only the L Stim condition shows a tendency toward increased mean hemispheric Fg during stimulus presentation. R Stim and B Stim appear unchanged and/or mildly decreased during stimulus presentation, depending on the resting state (pre or post) used for comparison. Results of paired t-tests (Tables 1 and 2) indicate that mean hemispheric Fg during stimulus presentation is not statistically significantly different from either pre or post in any of the stimulus presentation conditions.

Regional Fg: Risberg and Ingvar (1967) have noted the possibility of regional increases being counterbalanced by areas of reduced activity to produce different rCBF patterns in

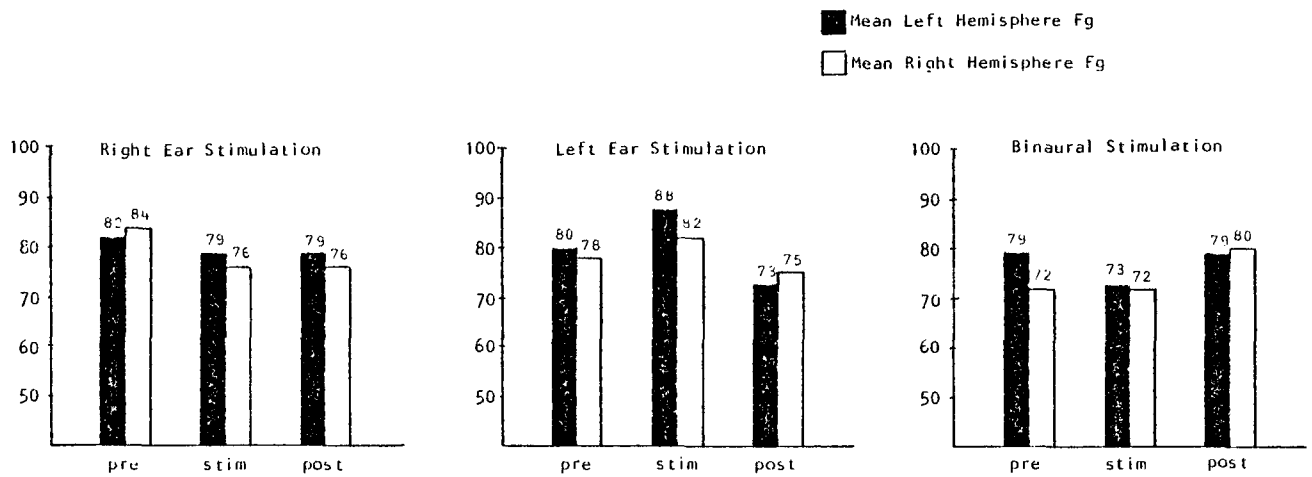


Figure 4.

Mean Hemispheric Fg by Stimulus Presentation Groups

Table 1.

Fg Analysis

Results of Paired t-tests for Ho: Pre = Stim

Condition	R. Ear Stim (N = 5)		L. Ear Stim (N = 5)		Binaural Stim (N = 5)	
Hemisphere	L	R	L	R	L	R
Region						
Area 8	n.s.	n.s.	n.s.	n.s.	n.s.	.05
Precentral	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Post Central	n.s.	.05	n.s.	n.s.	n.s.	n.s.
Broca	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Heschl	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Inferior Parietal	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Mean Flow	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Table 2.

Fg Analysis

Results of Paired t-tests for Ho: Stim = Post

Condition	R. Ear Stim (N = 5)		L. Ear Stim (N = 5)		Binaural Stim (N = 5)	
Hemisphere	L	R	L	R	L	R
Region						
Area 8	n.s.	n.s.	n.s.	n.s.	.05	n.s.
Precentral	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Post Central	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Broca	n.s.	n.s.	.05	n.s.	.01	.05
Heschl	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Inferior Parietal	n.s.	n.s.	n.s.	n.s.	n.s.	.05
Mean Flow	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

the absence of mean flow differences. Regional Fg for the R Stim condition is shown in Figure 5. All regions except Heschl's gyrus in the left hemisphere show a tendency to decrease from pre to stim. Broca's area in the left hemisphere, the precentral region bilaterally, Heschl's gyrus in the right hemisphere and the inferior parietal region bilaterally show a tendency to decrease from stim to post. Results of paired t-tests (Tables 1 and 2) indicate a statistically significant decrease in Fg from pre to stim in the right post central region ($p<.05$). No other significant changes in Fg occurred in any region between pre and R Stim, or between R Stim and post.

Regional Fg for the L Stim condition is shown in Figure 6. All regions except right post central and right Heschl's gyrus show a tendency to increase from pre to L Stim and to decrease from L Stim to post. Results of paired t-tests (Tables 1 and 2) indicate that Fg in the left inferior frontal region (Broca's area) was significantly higher ($p<.05$) during L Stim than during post. No other statistically significant changes in Fg occurred in any region between pre and L Stim, or between L Stim and post.

Regional Fg for the Binaural Stimulation condition is shown in Figure 7. Results of paired t-tests (Tables 1 and 2) differed depending on whether stimulus presentation Fg was compared to the pre or post resting measurement. Fg increased significantly from pre to B Stim in the right pre-

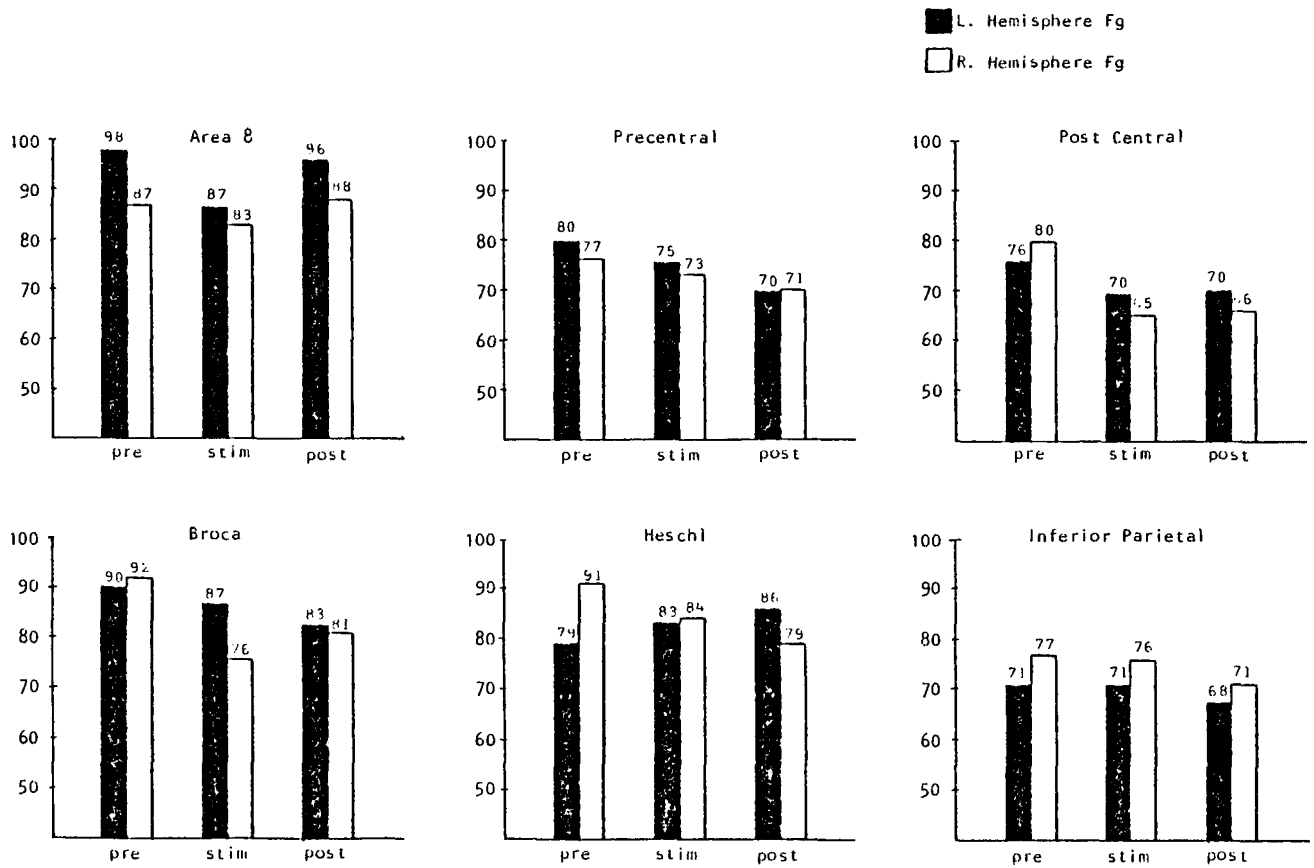


Figure 5.

Fg Regional Values for Right Ear Stimulation (N = 5)

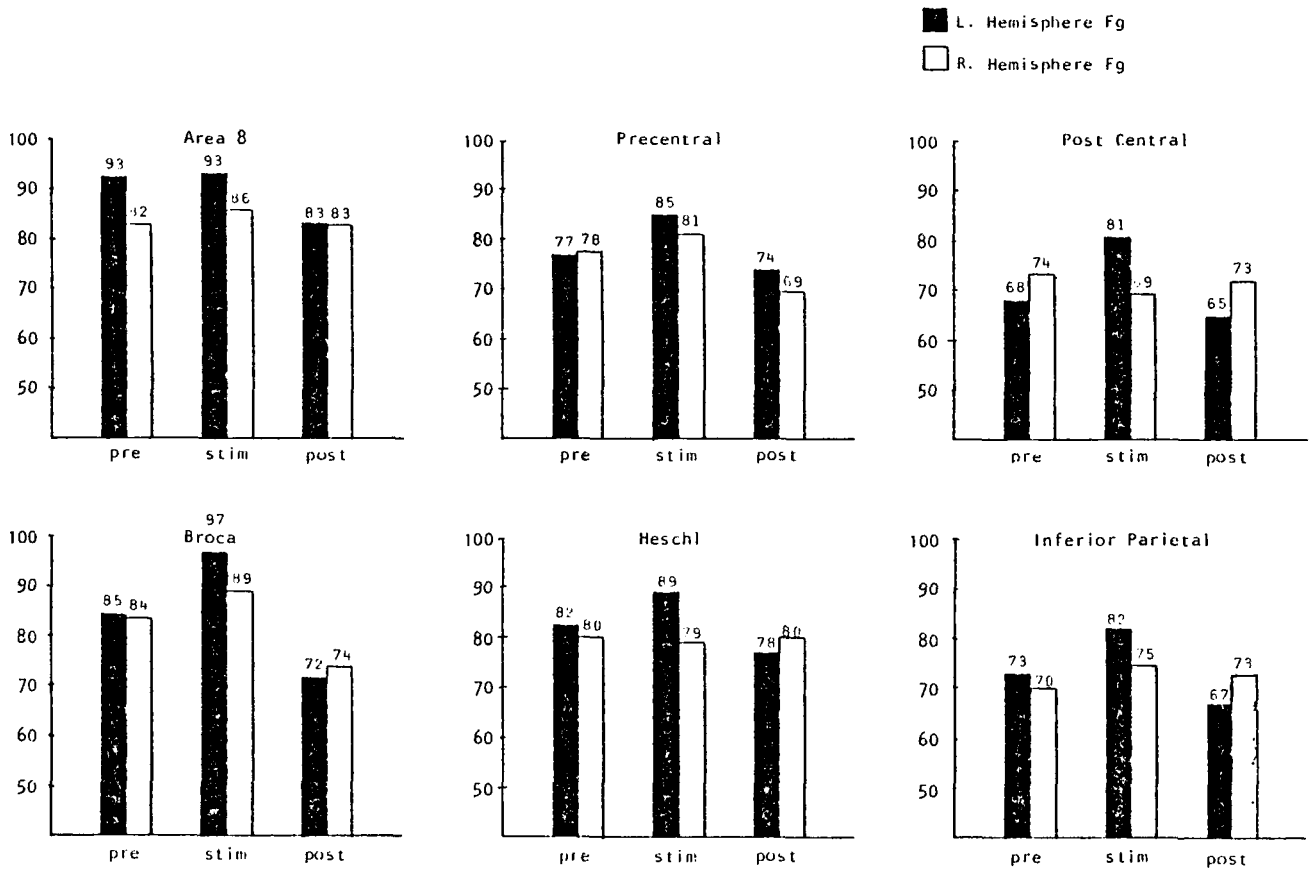


Figure 6.

Fg Regional Values for Left Ear Stimulation (N = 5)

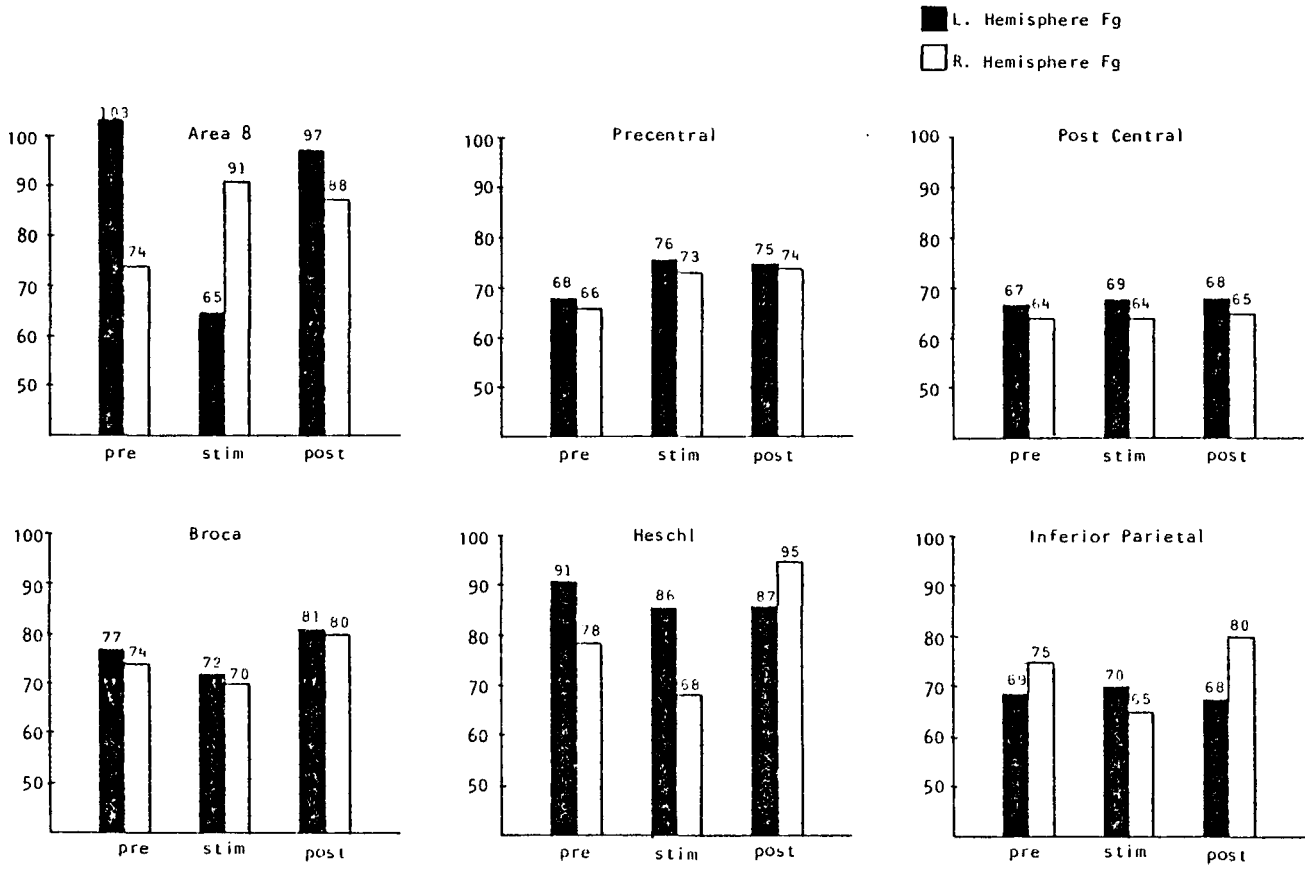


Figure 7.

Fg Regional Values for Binaural Stimulation (N = 5)

frontal region (Area 8). However, Fg decreased significantly during B Stim compared to post in the left prefrontal region, the right inferior parietal region, and Broca's area bilaterally.

The Sign Test was employed to determine if, on a regional basis, direction of change in Fg between trials was significantly different. Postitive results of the Sign Test might reveal very small but consistent changes during stimulus presentation of too small a magnitude to attain statistical significance by means of the paired t-test.

Results of the Sign Test inidicate that Fg in the right inferior frontal region (Broca's area) changed consistently from the pre resting state to right ear stimulus presentation (Table 3). No other changes from pre to stim were consistent for any region. During binaural stimulus presentation, Fg in the right inferior frontal region (Broca's area) and the right inferior parietal region changed consistently from stimlus presentation to the post resting state (Table 4). No other changes from stim to post were significantly consistent for any region. Table 5 shows that no changes from pre to post were significantly consistent for any region.

Regional ISI2: The possibility that a different CBF parameter, ISI2, might be less vulnerable to fluctuations due to scatter, and thus provide a more reliable measure of changes in rCBF, was investigated. Results of paired t-tests are shown in Table 6 and Table 7. As in the analysis of regional

Table 3.

Sign Test for Direction of Change in Fg
from Pre to Stimulus Conditions

Condition	R. Ear Stim (N = 5)		L. Ear Stim (N = 5)		Binaural Stim (N = 5)	
Hemisphere	L	R	L	R	L	R
Region						
Area 8	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Precentral	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Post Central	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Broca	n.s.	.05	n.s.	n.s.	n.s.	n.s.
Heschl	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Inferior Parietal	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Table 4.

Sign Test for Direction of Change in Fg
from Stimulus to Post Conditions

Condition	R. Ear Stim (N = 5)		L. Ear Stim (N = 5)		Binaural Stim (N = 5)	
Hemisphere	L	R	L	R	L	R
Region						
Area 8	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Precentral	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Post Central	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Broca	n.s.	n.s.	n.s.	n.s.	n.s.	.05
Heschl	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Inferior Parietal	n.s.	n.s.	n.s.	n.s.	n.s.	.05

Table 5.

Sign Test for Direction of Change in Fg
from Pre to Post Conditions

Region	Left Hemisphere (N = 15)	Right Hemisphere (N = 15)
Area 8	n.s.	n.s.
Precentral	n.s.	n.s.
Post Central	n.s.	n.s.
Broca	n.s.	n.s.
Heschl	n.s.	n.s.
Inferior Parietal	n.s.	n.s.

Table 6.

ISI2 Analysis
Paired t-tests for Ho: Pre = Stim

Condition	R. Ear Stim (N = 5)		L. Ear Stim (N = 5)		Binaural Stim (N = 5)	
Hemisphere	L	R	L	R	L	R
Region						
Area 8	n.s.	n.s.	n.s.	n.s.	n.s.	.05
Precentral	n.s.	n.s.	n.s.	n.s.	.05	n.s.
Post Central	n.s.	.05	n.s.	n.s.	n.s.	n.s.
Broca	n.s.	.05	n.s.	n.s.	n.s.	n.s.
Heschl	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Inferior Parietal	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Table 7.

ISI2 Analysis
Paired t-tests for Ho: Stim = Post

Condition	R. Ear Stim (N = 5)		L. Ear Stim (N = 5)		Binaural Stim (N = 5)	
Hemisphere	L	R	L	R	L	R
Region						
Area 8	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Precentral	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Post Central	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Broca	n.s.	n.s.	.05	n.s.	.05	n.s.
Heschl	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Inferior Parietal	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

changes in Fg (Tables 1 and 2), statistically significant changes in ISI2 during stimulus presentation are very different when compared to pre and when compared to post. This is also true for results of the Sign Test for direction of change in ISI2, as shown in Table 8 and Table 9.

Test-Retest Reliability: The Fg values obtained in the present study were pooled with those of a nonverbal auditory study (Stump, 1978; same design and rCBF procedures) to determine the statistical equivalence of the pre and post resting states. Test-retest reliability of Fg (Table 10) indicated that on a regional basis, only three probe locations showed statistically significant correlations between pre and post resting states: left prefrontal (Area 8), left inferior frontal (Broca's area) and right precentral. Mean Fg was reliable for the left hemisphere, but not for the right.

Interhemispheric Correlation: The three stimulation conditions in the verbal auditory study were pooled and interhemispheric correlations performed for each resting state and stimulus presentation (Table 11). It was hoped that such a procedure might indicate regions affected by laterality of stimulus input. However, the three regions showing poor interhemispheric correlation during stimulus presentation (Area 8, Broca's area, and Heschl's gyrus) also correlated poorly during the pre and/or post resting states. In addition, interhemispheric correlation of mean Fg was statistically

Table 8.

Sign Test for Direction of Change in ISI2
from Pre to Stimulus Conditions

Condition	R. Ear Stim (N = 5)		L. Ear Stim (N = 5)		Binaural Stim (N = 5)	
Hemisphere	L	R	L	R	L	R
Region						
Area 8	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Precentral	n.s.	n.s.	n.s.	n.s.	.05	n.s.
Post Central	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Broca	n.s.	.05	n.s.	n.s.	n.s.	n.s.
Heschl	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Inferior Parietal	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Table 9.

Sign Test for Direction of Change in ISI2
from Stimulus to Post Conditions

Condition	R. Ear Stim (N = 5)		L. Ear Stim (N = 5)		Binaural Stim (N = 5)	
Hemisphere	L	R	L	R	L	R
Region						
Area 8	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Precentral	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Post Central	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Broca	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Heschl	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Inferior Parietal	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.

Table 10.

VERBAL & NONVERBAL AUDITORY STUDIES

Fg Test - Retest Reliability

* p<.05

	Left Hemisphere		Right Hemisphere	
	r	df	r	df
Region				
Area 8	*.3962	27	.0119	26
Precentral	.2599	27	*.4068	27
Post Central	.2989	24	.1667	25
Broca	*.4799	24	.1132	26
Heschl	-.0912	25	.1124	27
Inferior Parietal	.3090	27	.2096	26
Mean Fg	*.3690	28	.2239	28

Table 11.

Interhemispheric Correlation of Fg

* p <.01
** p <.005
*** p <.001

Condition	Resting Pre Stim		Auditory Stim		Resting Post Stim	
	r	df	r	df	r	df
Region						
Area 8	.4906	12	.3372	12	.4477	12
Precentral	***.7617	13	***.9424	13	***.8908	12
Post Central	*.6531	13	*.6784	13	*.6765	12
Broca	***.8096	12	.4752	12	.4471	11
Heschl	.2837	13	.1601	13	.1237	12
Inferior Parietal	.2727	12	*.6418	13	**.7754	12
Mean Flow	***.7876	13	***.8883	13	**.7250	13

significant across all trials (resting pre stim, $p<.001$; auditory stim, $p<.001$; resting post stim, $p<.005$).

IV. DISCUSSION

The purpose of the present study was to determine if passive verbal auditory stimulation would produce significant and reliable changes in mean hemispheric or regional cerebral blood lfow in comparison to resting state hemispheric and/or regional flow values. The present results, summarized in Table 12, indicate that statistically significant changes in regional CBF, but not mean hemispheric CBF, did indeed occur during stimulus presentation, but that locus of significant regional change was entirely dependent on the resting measurement (pre or post) used to make the comparison. In no case was a given region significantly different from both pre and post. In addition, locus of significant regional change was also dependent on the rCBF measure (Fg, Fg%, or ISI2) from which the comparison data was drawn. Furthermore, no consistent pattern across stimulus presentation groups (R Stim, L Stim, and B Stim) could be demonstrated for Fg, Fg% or ISI2.

The present results raise two possibilities: (1) passive verbal auditory stimulation does not produce consistent changes in mean hemispheric or regional cerebral blood flow, or (2) the present methodology, despite its widespread use in the field of rCBF research, inadequately controls a number of sources of variability, such that consistent changes are masked by "noise" in the data. It is to the latter of these

Table 12.

SUMMARY OF STATISTICALLY SIGNIFICANT

rCBF CHANGES DURING VERBAL AUDITORY STIMULATION

Condition	Region	Comparison	% Change During Stim
		1. Fg	
L Stim	L Broca	stim to post	26% increase
R Stim	R Post Central	pre to stim	19% decrease
B Stim	R Area 8	pre to stim	19% increase
	L Area 8	stim to post	33% decrease
	R Broca	stim to post	12% decrease
	L Broca	stim to post	12% decrease
		2. Fg%	
L Stim	R Broca	stim to post	11% increase
R Stim	none		
B Stim	R Area 8	pre to stim	24% increase
	L Precentral	pre to stim	17% increase
		3. ISI2	
L Stim	L Broca	stim to post	12% increase
R Stim	R Post Central	pre to stim	12% decrease
B Stim	R Area 8	pre to stim	21% increase
	L Precentral	pre to stim	12% increase
	L Broca	stim to post	3% decrease

possibilities that we now turn.

Sources of Variability

Much discussion has appeared in the literature regarding both variability in rCBF data in general and variability which is specific to the Xenon inhalation technique alone. Difficulties in obtaining "analyzable" data which were anticipated in the present study from reviews of prior rCBF research include inter- and intra-subject variability and error of measurement.

Inter- and intra-subject variability. One of the major difficulties with traditional statistical treatment of group rCBF data is the wide range of flow values considered to be within the range of normal variation. That this has been troublesome to researchers in the past is apparent in the wide array of approaches that have been undertaken to control it. These approaches have included the development and use of new rCBF measures (i.e., ISI2), manipulation of existing measures (i.e., Fg%), and efforts to standardize measurement conditions (i.e., the "resting state"), each of which were incorporated into the present study.

Meyer, et al. (1978) have recently published norms for regional values in resting subjects. They report a variation in regional Fg from the hemispheric mean must exceed 24.8% for the left hemisphere and 23.2% for the right hemisphere to be regarded as a significant deviation from normal.

Presumably these values consider the combined effects of error of measurement, intra- and inter-subject variability.

An examination of the individual Fg% data in the present study reveals only eight of the fifteen subjects had completely "normal" rCBF values during the pre stim resting measurement, according the Meyer, et al. (1978) criteria; in four of the fifteen subjects all rCBF values were within normal limits during the post stim resting measurement. These results are summarized in Table 13. It is extremely unlikely that between seven and eleven of the fifteen normal volunteers had pathology affecting their cerebral blood flow, and it can only be supposed that (1) the ideal "resting state" was not achieved in the subjects; or (2) the inhalation method's variability is even greater than the Meyer, et al. (1978) estimate.

Lassen, et al. (1977) suggest that, although flow ranges during the resting state are highly variable, the hyperfrontal pattern is a consistent feature of rCBF measurements in a quiet laboratory with the subject's eyes closed. In the present study, however, this hyperfrontality was not obtained consistently, although it is seen in group data. On the average, 4 of 5 subjects in each stimulus presentation group demonstrated high frontal Fg values in the left hemisphere and 3 of 5 subjects in each stimulus presentation group demonstrated high frontal values in the right hemisphere. This was true for both pre and post stim resting

Table 13.

SUMMARY OF ATYPICAL rCBF VALUES

DURING PRE AND POST RESTING MEASUREMENTS

Normal Range for Fg%:*

Left Hemisphere 75.2 - 124.8
Right Hemisphere 76.8 - 123.2

Subject #:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Area 8															
pre				L			R					L	L		
post				L R	R				L R		L	L	R		R
Precentral															
pre										L	L				
post				L											
Post Central															
pre				R						L	R				
post		R		L							R	R			
Broca															
pre				L R											
post	L														
Heschl															
pre										L R		L	R		
post					L	L				L	L	R	R		
Inferior Parietal															
pre				L R	L										
post												L			

* from Meyer, et al. (1978)

measurements. The resting state as defined by the presence of the hyperfrontal pattern is clearly a more difficult state to obtain than would appear evident from the rCBF literature.

Error of measurement. "Error of measurement" refers to variability which can be attributed to the technique itself, i.e., scattered radiation, extracerebral contamination, and overlap in spatial sampling, or to the analysis technique. Blauenstein, et al. (1977) conservatively estimate the error of measurement for regional Fg to be 6-8% using the inhalation technique. The upper limit of this range (twice that for the injection technique) is currently in use at the laboratory where the present study was conducted.

Thus the limitation imposed by the inhalation technique's error of measurement alone is perilously close to the average magnitude of change of about 10% reported in the current injection method auditory activitation literature. For this reason, the activation procedure in the present study was designed to maximize possible responsive changes in rCBF to passive stimulation. It was hoped that the choice of stimulus intensity at 90 dB SPL, a level of somewhat higher intensity than normal conversational levels, would provoke a clearcut focal change in rCBF in the auditory projection area by virtue of auditory stimulation alone, i.e., without cognitive or attentional components to the task. The results of the present study fail to rule out the

possibility that the inhalation technique does not have the resolution power to view the magnitude of rCBF changes during passive auditory stimulation.

However, a re-examination of Table 13 suggests that error of measurement may have contributed to the variability in the present data on a more limited basis. A brief inspection reveals that over 50% of the atypical Fg values were obtained in Area 8 and Heschl's gyrus, the two regions where longer collimators were used in rCBF measurement in order to restrict the field of view to the small cortical areas of interest. It seems likely that such restriction decreased the number of "counts" obtained for the clearance curves in these areas to such a degree that the error of measurement was much greater in these two regions. This notion was supported by an examination of the confidence intervals for Fg in these regions, which revealed markedly poorer goodness-of-fit than for the other probe positions. In some cases, the confidence inerval for an obtained Fg value was as wide as $\pm$ 50% of that value. That such a range would be capable of masking any activation effects in these regions is readily apparent.

A final consideration concerns the possibility that passive auditory stimulation may in fact not produce consistent changes in rCBF. The likelihood of this possibility has to do with the passive nature of the task during stimulus presentation in the present study. A possible point of

similarity between the resting state and passive auditory stimulation is that both measurements, rather than being free of a cognitive component, in practice merely inadequately specify what the subject is doing cognitively during the measurement period. The individual's "cognitive leeway" may then cover a wider response range, introducing additional variability to the measurement. If such is the case, then the effects of passive sensory stimulation on rCBF cannot be reliably assessed in isolation, but can only be inferred when examined in the context of a task with cognitive specifications. At this time it appears that the use of a subtractive technique where comparisons of rCBF patterns during a cognitive task executed with and without accompanying auditory stimulation may best reveal the differences sought in the present study.

BIBLIOGRAPHY

Blauenstein, U.W., Halsey, J.H., Wilson, E,M,, Wills, E.L., and Risberg, J. ^{133}Xenon method analysis of reproducibility: some of its physiological implications. Stroke, 1977, 8 (1), 92-102.

Carmon, A., Lavy, S., Gordon, H., and Portnoy, Z. Hemispheric differences in rCBF during verbal and nonverbal tasks. In Brain Work, Alfred Benzon Symposium VIII, Munksgaard, 1975, pp. 414-423.

Deshmukh, V.D., and Meyer, J.S. Noninvasive measurement of regional cerebral blood flow in man. New York: Spectrum, 1977.

Eichling, J.O. and Ter-Pogossian, M.M. Methodological shortcomings of the ^{133}Xenon inhalation technique of measuring rCBF. Acta Neurologica Scandinavica, 1977, 56, supplementum 64, 262-263.

Hoedt-Rasmussen, K. and Skinhoj, E. In vivo measurements of the relative weights of gray and white matter in the human brain. Neurology, 1966, 16, 515-520.

Ingvar, D.H. Discussion. In Brain Mechanisms and Consciousness, E.D. Adrian, F. Bremer and H.H. Jasper, eds. Blackwell Scientific Publications: Oxford, 1954, p. 342.

Ingvar, D.H. Extraneuronal influences upon the electrical activity of isolated cortex following stimulation of the reticular activating system. Acta Physiologica Scandinavica, 1955, 33, 169-193.

Ingvar, D.H. Functional landscapes of the dominant hemisphere. Brain Research, 1976, 107, 181-197.

Ingvar, D.H., Cronquist, S., Ekberg, R., Risberg, J., and Hoedt-Rasmussen, K. Normal values of regional cerebral blood flow in man, including flow and weight estimates of grey and white matter. Acta Neurologica Scandinavica, 1965, 41, supplementum 14, 72-78.

Ingvar, D.H. and Philipson, L. Distribution of cerebral blood flow in the dominant hemisphere during motor ideation and motor performance. Annals of Neurology, 1977, 2(3), 230-237.

Ingvar, D.H. and Risberg, J. Increase of regional cerebral blood flow during mental effort in normals and in patients with focal brain disorders. Experimental Brain Research, 1967, 3, 195-211.

Ingvar, D.H. and Schwartz, M.S. Blood flow patterns induced in the dominant hemisphere by speech and reading. Brain, 1974, 97, 273-288.

Jensen, K.B., Hoedt-Rasmussen, K., Sveinsdottir, E., Stewart, B.M. and Lassen, N.A. Cerebral blood flow evaluated by inhalation of 133Xe and extracranial recording: a methodological study. Clinical Science, 1966, 30, 485-494.

Kety, S.S. and Schmidt, C.F. The determination of cbf in man by the use of nitrous oxide in low concentration. American Journal of Physiology, 1945, 143, 53-65.

Kety, S.S. and Schmidt, C.F. The nitrous oxide method for the quantitative determination of cerebral blood flow in man: theory, procedure and normal values. Journal of Clinical Investigation, 1948, 27, 476-483.

Kimura, D. Functional asymmetry of the brain in dichotic listening. Cortex, 1967, 3, 163-178.

Larsen, B., Skinhoj, E. and Endo, H. Localization of basic speech functions as revealed by rCBF measurements in normal subjects and patients with aphasia. In Cerebral Vascular Disease, J.S. Meyer, H. Lechner and M. Reivich, eds. Excerpta Medica: Amsterdam-Oxford, 1977a, 49-51.

Larsen, B., Skinhoj, E., Soh, K., Endo, H. and Lassen, N.A. The pattern of cortical activity provoked by listening and speech revealed by rCBF measurements. Acta Neurologica Scandinavica, 1977b, 56, supplementum 64, 268-269.

Lassen, N.A. and Ingvar, D.H. The blood flow of the cerebral cortex determined by radioactive Krypton-85. Experientia, 1961, 17, 42-50.

Lassen, N.A. and Ingvar, D.H. Regional cerebral blood flow measurements in man. Archives of Neurology and Psychiatry, 1963, 9, 615-622.

Lassen, N.A., Roland, P.E., Larsen, B., Melamed, E., and Soh, K. Mapping of human cerebral functions: a study of the regional cerebral blood flow pattern during rest, its reproducibility and the activations seen during

basic sensory and motor functions. Acta Neurologica Scandinavica, 1977, 56, supplementum 64, 262-263.

Lassen, N.A., Hōedt-Rasmussen, K., Sorensen, S.C., Skinhoj, E., Cronquist, S., Bodforss, B. and Ingvar, D.H. Regional cerebral blood flow in man determined by Krypton^{85}. Neurology, 1963, 13, 719-727.

Luria, A.R. Higher Cortical Functions in Man. Tavistock Publications: London, 1966.

Luria, A.R. The working brain: an introduction to neuropsychology. (B. Haigh trans.) New York: Basic Books, 1973.

McHenry, L.C., Jaffe, M.L. and Goldberg, I.H. Regional cerebral blood flow measurements with small probes. I. Evaluation of the method. Neurology, 1969, 19, 1198-1206.

Mallett, B.L. and Veall, N. Investigation of cerebral blood flow in hypertension using radioactive Xe inhalation and extracranial recording. Lancet, 1963, i, 1081-1082.

Meyer, J.S., Sakai, F., Yamaguchi, F., Yamamoto, M. and Shaw, T. Regional changes in cerebral blood flow during standard behavioral activation in patients with disorders of speech and mentation compared to normal volunteers. Brain and Language, in press, 1978.

Obrist, W.D., Thompson, H.K., King, C.H. and Wang, H.S. Determination of regional cerebral blood flow by inhalation of 133 Xenon. Circulation Research, 1967,

20, 124-135.

Obrist, W.D., Thompson, H.K., Wang, H.S. and Cronquist, S. A simplified procedure for determining fast compartment rCBFs by ^{133}Xenon inhalation. In Ross Russell, R.W. (ed.): Brain and Blood Flow. London: Pitman Publishing, 1971, 11-15.

Obrist, W.D., Thompson, H.K., Wang, H.S. and Wilkinson, W.E. Regional cerebral blood flow estimated by 133 Xenon inhalation. Stroke, 1975, 6, 245-256.

Oleson, J. Contralateral focal increase of cerebral blood flow in man during arm work. Brain, 1971, 94, 635-646.

Ott, E.O., Lechner, H., Perry, P.J., Aranibar, A., Ladurner, G., Gypser, G., and Schreyer, H. Patterns of regional cerebral blood flow induced by speech in normals and in patients with aphasia. In Cerebral Vascular Disease, J.S. Meyer, H. Lechner and M. Reivich, eds. Excerpta Medica: Amsterdam-Oxford, 1977, 45-48.

Risberg, J., Ali, Z., Wilson, E.M., Wills, E.L. and Halsey, J.H. Regional cerebral blood flow by 133 Xenon inhalation. Stroke, 1975, 6(2), 142-148.

Risberg, J. and Ingvar, D.H. Regional changes in cerebral blood volume during mental activity. Experimental Brain Research, 1968, 5, 72-78.

Risberg, J. and Ingvar, D.H. Regional variations in cerebral blood volume during mental activity in normals and in psychiatric patients. In Charles C. Thomas (ed.),

Research on the Cerebral Circulation, 1970, Springfield, Ill.

Risberg, J. and Ingvar, H. Increase of blood flow in cortical association areas during memorization and abstract thinking. European Neurology, 1972a , 6, 236-241.

Risberg, J. and Ingvar, D.H. Multibolus technique for measuring the distribution of cerebral blood flow over short intervals in man. Circulation Research, 1972b, 31, 889-898.

Risberg, J. and Ingvar, D.H. Patterns of activation in the gray matter of the dominant hemisphere during memorizing and reasoning. Brain, 1973, 96, 737-756.

Risberg, J., Maximilian, A.V., and Prohovnik, I. Changes of cortical activity patterns during habituation to a reasoning test. Neuropsychologia, 1977, in press.

Roland, P.E. and Parsen, B. Focal increase of cerebral blood flow during stereognostic testing in man. Archives of Neurology, 1976, 33, 551-558.

Roland, P.E., Larsen, B., Skinhoj, E., and Lassen, N.A. Regional cerebral blood flow increase due to treatment of somatosensory and auditive information in man. Acta Neurologica Scandinavica,1977 a, 56, supplementum 64, 540-541.

Roland, P.E., Skinhoj, E., Larsen, B., and Endo, H. Perception and voluntary action: Localization of basic input and output functions as revealed by regional cerebral

blood flow increases in the human brain. In Cerebral Vascular Disease, J.S. Meyer, H. Lechner and M. Reivich, eds. Excerpta Medica: Amsterdam-Oxford, 1977b, 40-44.

Roland, P.E., Skinhoj, E., Larsen, B., and Lassen, N.A. The role of different cortical areas in the organization of voluntary movements in man. A regional cerebral blood flow study. Acta Neurologica Scandinavica, 1977c, 56, supplementum 64, 542-543.

Rosenzweig, M.R. Representations of the two ears at the auditory cortex. American Journal of Physiology, 1951, 167, 147-158.

Stump, D. Focal regional cerebral blood flow responses to simple auditory stimuli. Unpublished doctoral dissertation, University of Houston, 1978.

Sveinsdottir, E. Clearance curves of Kr^{85} or Xe^{133} considered as a sum of mono-exponential outwash functions. Acta Neurologica Scandinavica, 1965, 41, supplementum 14, 69.

Appendix A

Subject Consent Form

STUDY OF HEMISPHERIC LATERALITY OF FUNCTION DETERMINED BY NON-INVASIVE MEASUREMENTS OF REGIONAL CEREBRAL BLOOD FLOW DURING BEHAVIORAL ACTIVATION

Normal Consent Form

I, _____, authorize Dr. Francisco I. Perez, Dr. John Stirling Meyer or such other authorized personnel as they may designate, to perform the following investigational procedure.

Purpose: The purpose of the test is to study brain-behavior relationships by measuring regional cerebral blood flow and electrophysiological changes as seen in selected regions of the brain. This provides information on the regional functional activity of the brain during normal brain "work" of mental processes.

Description: You will be given some auditory tests to assess your hearing. You will be presented with a series of auditory tasks including tones, digits or words to either one or both ears. You will be asked to report what you have heard. Following this, three regional cerebral blood flow measurements will be made, each lasting 12 minutes.

Run #1: No auditory stimulation. During this run the auditory tasks will not be presented. This measures your regional cerebral blood flow during the resting state. To measure brain blood flow, no sedative or incision is required. Eight Geiger counters will be placed on each side of the head prior to breathing ^{133}Xenon, a radioisotope gas, for inhalation for 1 minute only. Xenon is a radioisotope used for medical diagnostic procedures, e.g. lung scans. Tracer amounts of ^{133}Xenon will be mixed with air in a special gas delivery machine and inhaled for one minute through a face mask. The face mask is worn for about 12 minutes for each measurement. The administered concentration of the Xenon isotope gas is at a level considered safe. For measurement of the electrical activity or EEG of the brain, eight electrodes will be attached to your scalp following conventional procedures.

Run #2: Auditory stimulation. After an interval of 30 minutes from Run #1 brain blood flow and electrical activity will be measured again but you will be requested to listen to sounds or words.

Run #3: No auditory stimulation. This is similar to Run #1 and will be conducted 30 minutes after Run #2, to prove that Run #2 change was not fortuitous.

Discomfort, danger and safeguards: This causes little or no discomfort from wearing a face mask and virtually no danger. Xenon 133 is delivered through a closed circuit well shielded gas delivery system. Exposure to radioisotope is kept at minimum. At the present time, this procedure is investigational. No beneficial results are assured or guaranteed. You will not be charged a fee for this procedure.

I grant this authority voluntarily, upon my own initiative, and with no assurance from anyone as to the results that may be obtained. I am aware that this procedure is investigational and may not benefit me.

I understand that I may withdraw from the procedure at any time. I have received verbal explanation from the investigator and his associates. They have indicated their willingness to discuss any information available or to answer any questions I may have at any future time. I understand that, within the legal control of the investigators, my identity in this study will be kept confidential.

Subject Name	Date
Subject Signature	Witness

Appendix B

Stimulus Materials: Spondaic Words

Spondaic Words

grandson	pancake
mousetrap	workshop
eardrum	woodwork
daybreak	armchair
hot dog	iceberg
railroad	headlight
schoolboy	sunset
northwest	stairway
doormat	horseshoe
hardware	sidewalk
toothbrush	cowboy
padlock	airplane
mushroom	greyhound
grandson	birthday
doormat	baseball
oatmeal	playground