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CEREBRAL ACTIVATION WITH MEANINGLESS AND MEANINGFUL AUDITORY STIMULI MATCHED FOR ACOUSTIC PARAMETERS: A POSITRON EMISSION TOMOGRAPHY STUDY

A Dissertation
Presented for the
Doctor of Philosophy
Degree
The University of Tennessee, Knoxville

Frances Martin Tucker

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DEDICATION

I dedicate this study to the memory of my mother and father, Katharine Gilman Tucker (1918-1988) and James Martin Tucker, M.D. (1915-1951). Whatever measure of success my attaining this degree represents is surely a reflection of the rich heritage of love they left their children.

I am grateful that my mother, who provided such encouragement for my return to school, lived long enough to be assured that there indeed would be, in her words, "two Dr. Tuckers" in her family. Memories of her courage, strength, and love sustained me during the completion of this dissertation.

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ABSTRACT

The purpose of this study was to determine whether there was a difference in localization and amount of cerebral blood flow (CBF) in specific regions of interest (ROIs), as measured by positron emission tomography, in response to meaningless and meaningful auditory stimuli that were matched for acoustic parameters. Twenty-two meaningless and 22 meaningful consonant vowel consonant (CVC) combinations were matched acoustically for overall duration, fundamental frequency contours, and overall intensity. The stimuli were presented to three neurologically normal, age matched, female subjects in the following conditions: 1) resting baseline; 2) stimulation with either meaningless CVCs or meaningful CVCs; 3) resting baseline; 4) stimulation with CVCs not presented in the first activation condition.

This study was a series of single subject experiments. Correlated t-Tests (for related measures) were done to determine whether significant inter- and intra-hemispheric changes in CBF occurred among the conditions. For one subject, significant intra-hemisphere differences, all in the right hemisphere, were found in three instances: 1) meaningless auditory stimuli elicited greater mean CBF than meaningful auditory stimuli; 2) mean CBF in the first resting baseline was greater than in the first activation with meaningful auditory stimuli; and 3) mean CBF in the second activation with meaningless auditory stimuli was greater than the second resting baseline.

These significant findings as well as the lack of significant differences among the other comparisons were discussed in relation to attention factors, presentation order, hemispheric asymmetries for processing meaningless and meaningful auditory stimuli, subject characteristics, and listener strategy. Possible limitations of the study included: habituation, task and stimuli characteristics, image manipulation, and the effect of error inherent in the measurement procedures. The results of this study indicate that differential

responses in CBF to meaningless and meaningful auditory stimuli may be detected with PET, given refinements in the research protocol.

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CHAPTER I. INTRODUCTION

Introduction

Responses to various types of auditory stimulation have been mapped in the brain by the measurement of regional cerebral blood flow (rCBF) and cerebral metabolism with nontomographic rCBF techniques, single photon emission tomography (SPECT) and positron emission tomography (PET). With these brain imaging techniques neuronal changes during ongoing behavior can be localized because of the closely coupled relationship of rCBF and cerebral metabolism with neuronal activity (Yarowsky & Ingvar, 1981). Whereas the rCBF, SPECT, and PET techniques have this underlying theory in common, the implementation of these techniques results in important differences in temporal and spatial resolution, as well as experimental design. At the present time, PET provides the shortest data collection time and superior spatial resolution of all the techniques (Lassen, 1985; Metter & Hansen, 1985) and, therefore, is the brain imaging technique of choice for mapping physiological responses to auditory stimulation.

Historically, these brain imaging techniques have been used to map responses to auditory stimulation in the normal human brain at the following levels: 1) acoustic (cf. Mazziotta, Phelps, Carson, & Kuhl, 1982; Lauter, Herscovitch, Formby, & Raichle, 1985; 2) phonologic (cf. Bartlett, Brown, Wolf, & Brodie, 1987; Walker-Batson et al., 1988); 3) semantic (cf. Nishizawa, Olsen, Larsen, & Lassen, 1982; Petersen, Fox, Posner, Mintun, & Raichle, 1988), 4) syntactic (Maximillian, 1982), 5) discourse (cf. Mazziotta et al., 1982; Lechevalier et al., 1989), and 6) cognitive (cf. Goldenberg, Podreka, Steiner, & Willmes, 1987; Posner, Petersen, Fox, & Raichle, 1988). The experimental designs of these studies vary in the complexity of stimuli, response, and experimental task, including passive listening, discrimination, meaning and phoneme detection, dichotic listening, comprehension, and memory paradigms.

The possible confounding effects of the complexity of these experimental designs has been addressed in terms of the stimulus, the task, and the response (Mazziotta, et al., 1982; Mazziotta & Phelps, 1985; Lauter et al., 1985; and Raichle, 1987). With regard to the stimulus, Mazziotta and Phelps (1985) suggested beginning studies with simple stimuli and building progressively to more complex paradigms. In the studies mapping physiological changes in the brain to auditory stimuli, the stimuli used in the studies can be categorized as either carrying linguistic meaning or as linguistically meaningless acoustic signals. Although several studies have compared the difference in response between meaningless and meaningful auditory stimuli, the stimuli used to compare the effects of meaningless and meaningful auditory stimulation varied considerably in linguistic and acoustic composition. Therefore, a clear interpretation of these studies is difficult. There has yet to be a systematic study of the changes that occur in rCBF or cerebral metabolism when meaning is added to an acoustic signal.

Characteristics of Auditory Stimuli

Auditory stimuli can be defined according to their acoustic parameters and their linguistic content. The acoustic parameters of an auditory stimulus include the duration, intensity, frequency, and complexity of the frequency spectra of the signal (Hoops, 1969).

The linguistic content of an auditory stimuli can be classified as linguistically meaningless or meaningful. Stimuli which are comprised of an acoustical signal the carries no intrinsic meaning, such as pure tones, clicks, and white noise, as well as variations of these signals related to timing or intensity, may be considered meaningless. In linguistics, the smallest grammatical unit which cannot be divided into smaller meaningful parts is called a morpheme. Therefore, single phonemes or combinations of phonemes, such as /t/, /te/, or /teb/, which do not comprise a morpheme (or meaningful unit), would also be

considered as meaningless. Meaningful auditory stimuli, such as /to/ or /bet/, are those which consist of at least a single morphological unit. Stimuli at the acoustic and phonological levels could be considered meaningless; those at the semantic and discourse level could be considered meaningful.

Importance of Parameters of Auditory Stimuli

Raichle (1987) pointed out that the parameters of the stimulus itself are important in the design of auditory localization studies. Obviously, stimuli are chosen to meet the particular goals and task demands of a study. In the few investigations, however, in which the effects of meaningless and meaningful auditory stimuli on rCBF or cerebral metabolism have been directly compared (Knopman, Rubens, Klassen, Meyer, & Niccum, 1980; and Knopman, Rubens, Klassen, & Meyer, 1982; Roland, Skinhoj, & Lassen et al., 1981; and Nishizawa et al., 1982; Mazziotta, Phelps, Carson, & Kuhl, 1982; and Mazziotta, Phelps, & Carson, 1984) the stimuli have been dissimilar in content and as well as acoustic parameters. Comparisons have been made between the effects of loudness discrimination of noise bursts versus identification of a word of a specific category from a word list (Knopman et al., 1980; Knopman et al., 1982), discrimination of same and different tone rhythms versus passive listening to onomotopoetic words (Roland et al, 1981; Nishizawa et al., 1982), and tests of tonal memory and timbre discrimination versus comprehension of a Sherlock Holmes story (Mazziotta et al, 1982; Mazziotta et al., 1984). No investigation has directly compared the effects of meaningless and meaningful stimuli when both types of stimuli share similar acoustic parameters.

Furthermore, meaningless and meaningful auditory stimuli have been used in a variety of other experimental paradigms. Whereas in these studies the acoustic parameters of the meaningless stimuli have been generally well defined, those for the meaningful stimuli have been largely nonspecified. For example, the acoustic parameters of the

stimuli were described in the rCBF and cerebral metabolism studies which used meaningless auditory stimuli (Knopman et al., 1980; Knopman et al., 1982; Roland et al., 1981; Mazziotta et al., 1982; Mazziotta et al., 1984; Lauter et al., 1985, and Lauter, Herscovitch, & Raichle, 1988). Moreover, the investigators clearly defined parameters, such as frequency (Lauter et al., 1985), which were manipulated within each study. This has not been the case in the studies in which meaningful stimuli were used. In those studies, the acoustic complexity of the stimuli within a single study have varied greatly in the complexity of the acoustic parameters. Examples of such stimuli include spoken discourse (Mazziotta et al., 1982; Mazziotta et al., 1984; Reivich, Alavi, & Gur, 1984) and dialogue (Lechevalier et al., 1989). Even in the studies in which single words were used, considerable difference in acoustic complexity can be noted between the stimuli within each study (Knopman et al., 1980; Wood, Taylor, Penny, & Stump, 1980; Knopman et al., 1982; Maximillian, 1982; Nishizawa et al, 1982; Bartlett et al., 1987; Goldenberg et al., 1987; Petersen et al., 1988; Lechevalier, et al., 1989). Evidence is lacking to show that when the brain is stimulated with meaningful auditory stimuli with greatly differing acoustic parameters, the physiological changes in blood flow or metabolism are in response to the meaning of the stimuli rather than to the acoustical complexity of the stimuli.

As noted, auditory stimuli have been used to map physiological responses in the brain in a variety of experimental paradigms, including those comparing the effects of meaningless and meaningful stimuli. The lack of definition of the acoustic parameters of the meaningful stimuli, however, leaves open the question of whether the responses are due to the meaningfulness of the stimuli or to the acoustical complexity of the stimuli.

The purpose to this study is to investigate whether there is a difference in the location and amount of cerebral blood flow as

measured by PET as a response to meaningless and meaningful stimuli that have been matched for acoustic parameters in order to determine whether the linguistic effects of the stimuli can be differentiated from the effects of the acoustical components of the signal.

Review of the Literature

Overview of the History of Cerebral Blood Flow Studies: Rationale for Using PET

Historically, the study of the relationship of language behavior and brain function has been limited to the correlation of brain lesion to resultant behavior. The nineteenth century works of Broca and Wernicke, based on autopsies of patients with speech and language disorders, established many of the principles of localization of communication behaviors that are held to be valid at the present time. Hughlings-Jackson, in the late nineteenth century, warned, however, that "to localize the damage that destroys speech and to locate speech are two different things" (cited in Love & Webb, 1986, p. 171). Until relatively recently the study of ongoing speech and language behavior in the normal human brain was not possible. The emergence of brain imaging techniques that permit the study of brain physiology have enabled such a glimpse into the normal human brain engaged in ongoing behavior.

These new brain imaging techniques are based on the closely coupled relationship between cerebral metabolism and blood flow with neuronal activity (Raichle, Brubb, Gado, Eichling, & Ter-Pogossian, 1976; Yarowsky & Ingvar, 1981). This premise is based on measurements at all levels of the nervous system from single peripheral nerves to the cortical level (Yarowsky & Ingvar, 1981). Yarmowski and Ingvar (1981) state that "the changes in cellular energy metabolism that accompany neuronal activity are to a major extent coupled to the maintenance and restoration of ionic gradients across neuronal membranes" (p. 2353). As Raichle (1987) pointed out, if the "principle always holds, measurements of blood flow or metabolism should allow either an indirect (e.g., blood

flow) or direct (metabolism) assessment of local neuronal work" (p. 654). These relationships generally have been considered to hold true, although some aspects of the exact nature of brain metabolism, blood flow, and neuronal activity remain to be explored (Yarowsky & Ingvar, 1981).

The principles of measurement of cerebral blood flow (CBF) were developed by Kety and Schmidt in 1945 (cited in Lassen, 1985). Using autoradiographic techniques, they demonstrated in studies with monkeys that it was possible to measure whole brain cerebral blood flow using nitrous oxide. The earliest studies in humans were measurements of global hemispheric blood flow. Since that time, a number of refinements have allowed both two dimensional and three dimensional blood flow studies.

For the most part, two dimensional studies have involved the administration of the radioisotope ^{133}Xe, either through inhalation or arterial injection, and the nontomographic measurement of CBF with a scintillation camera or multiple detectors placed over the brain regions. Spatial resolution, especially with the inhalation method is poor. Improvement can be gained by the injection method. With this method, however, for each study the injection is made in one side only. The result is that only one hemisphere can be studied at a time. Therefore, hemispheric comparisons are made between different subjects rather than within the same subjects. In addition, with the injection method only those areas of the brain served by the internal carotid artery, primarily the anterior and middle cerebral arteries receive the tracer (Raichle, 1987). In these studies, activity is measured primarily at the surface of the brain.

Three dimensional imaging and improved spatial resolution became possible with emission tomography. Single photon emission tomography (SPECT) employs a radioisotope, such as ^{131}I, ^{99}Tc, and ^{133}Xe, that emits only a single photon per disintegration. PET uses dual-photon emitters,

such as ^{11}C, ^{13}N, ^{15}O, and ^{18}F. A dedicated cyclotron is usually needed to provide the short-lived radioisotopes used with PET. At this time, the resolution and contrast provided by PET is superior to that of SPECT and both techniques provide better spatial resolution than the nontomographic rCBF techniques (Lassen, 1985; Metter and Hansen, 1985). The use of ^{15}O labeled water to study rCBF with PET has shortened the lengthy data collection time associated with metabolic PET studies from 45 minutes (min) to 40 seconds (s), an important improvement for the study of the effects of acoustic stimuli with durations in milliseconds (ms).

Nontomographic rCBF, SPECT and PET have all been used to investigate the effects of meaningful and meaningless auditory stimulation blood flow or metabolism. PET is the technique of choice, however, for localizing the physiological effects of auditory stimulation because of its short data collection time and superior spatial resolution. In the field of speech-language pathology PET holds great promise as a research tool for the study of brain mechanisms in normal language processing. There is also great potential for PET as a clinical tool for the investigation of how these processes are disrupted and recover after neurological disease and trauma.

Although the purpose of this study is to investigate possible differences in cerebral blood flow between meaningful and meaningless auditory stimuli with PET, studies in which other brain imaging techniques were used to investigate the effects of auditory stimulation will be included in the following literature review. These precursors to the present PET investigations are based on similar premises regarding the relationship of blood flow and metabolism to neuronal activity and share similar goals related to determining cerebral responses to various types of auditory stimulation. Previous investigations of the effects of auditory stimulation on CBF and brain metabolism provide a contextual background for the present study. When

comparing the results from studies using the different techniques, however, one should consider the limitations of spatial and temporal resolution and experimental design inherent in the techniques other than PET (e.g., interhemispheric comparisons between different subjects with the injection method in nontomographic rCBF studies).

Experimental Design Considerations: Control of the Acoustic Parameters of Auditory Stimuli

A number of considerations in the design of neurobehavioral studies with PET were reviewed by Mazziotta et al.(1982), Mazziotta and Phelps, (1985), Lauter et al. (1985), and Raichle (1987). Among these considerations are those that are related to the stimulus itself (e.g. acoustic or linguistic content and complexity); those that are related to the method of presentation (e.g. ear of presentation, intensity level, stimulus and interstimulus durations affecting rate of presentation); and those that are related to the type and complexity of response expected from the subject (e.g. passive listening versus a specific motor, linguistic, or cognitive response, either singly or in combination). In a number of studies the combined effects of stimulus complexity, task, and response mode may be so inextricably interwoven to make questionable the identification of areas of the brain related to specific behaviors. Indeed, some investigators have taken note of this problem. The issue of complexity in experimental designs was addressed by Mazziotta et al. (1982). In their PET study of the effects of auditory stimulation, they acknowledged that complex stimuli involving multiple cognitive functions made interpretation of the stimulus-cognitive process impossible.

The problems of experimental complexity may be addressed at the stimulus level. Mazziotta and Phelps (1985) suggest beginning studies with simple stimuli and building progressively to more complex paradigms. As noted by Raichle (1987), the parameters of the stimulus itself are important in the design of auditory localization studies.

Whether auditory stimuli are classified as linguistically meaningless or meaningful, one way to control stimulus complexity is by careful selection of the acoustic parameters. An auditory signal is defined by the parameters of duration, intensity, frequency, and spectral complexity (Hoops, 1969).

In the following review of brain imaging studies in which auditory stimuli were used, the differences in design of the meaningless and meaningful stimuli will be demonstrated. The acoustic parameters of the meaningless auditory stimuli used in the rCBF and cerebral metabolism studies were well defined by the investigators. Examples of such stimuli include noise bursts (Knopman et al., 1980; Knopman et al., 1982), tone rhythms (Roland et al., 1981), tones and chords (Mazziotta et al., 1982; Mazziotta et al., 1984), pure tones (Lauter et al., 1985), and consonant vowel (CV) combinations (Lauter et al., 1988; Walker-Batson et al., 1988). In addition, parameters, such as frequency (Lauter et al., 1985), which were manipulated in the experiment were clearly defined.

The meaningful auditory stimuli, however, were primarily described according to linguistic characteristics, such as their phonetic (Knopman et al., 1982; Bartlett et al., 1987), semantic (Knopman et al.,1980; Knopman et al., 1982; Wood et al., 1980; Goldenberg et al., 1987), syntactic (Maximillian, 1982), and discourse content (Mazziotta et al., 1982; Mazziotta et al., 1984; Reivich et al., 1984; Lechevalier, et al., 1989). The acoustic parameters of these stimuli were largely nonspecified. The stimuli within a study could vary considerably in acoustic complexity. In the case of a spoken story (Mazziotta et al., 1982; Mazziotta et al., 1984; Reivich et al., 1984) or dialogue (Lechevalier et al., 1989), specifically defining the acoustic components of the stimuli would be difficult. This might also be the case for single word stimuli which had been chosen to meet criteria such as "varying in concreteness" (Wood et al., 1980) or which were described

as "onomotopoetic words" (Nishizawa et al., 1982) or "phonotactically correct meaningless words" (Goldenberg et al., 1987). Single word stimuli used within a study, such as "two syllable Swedish words" (Maximillian, 1982), "monosyllabic English words" (Bartlett et al., 1987), "frequent English nouns" (Petersen et al., 1988), "nouns and transitive verbs" (Lechevalier et al., 1989), might vary considerably between themselves along parameters such as duration, intensity, spectral complexity, and fundamental frequency. In these studies, it would be difficult to determine whether the responses to the stimuli were to the meaning of the stimuli or to the varying acoustic complexity of the stimuli.

Studies Comparing the Evvects of Meaningless and Meaningful Auditory Stimuli

Differential electrophysiological responses to meaningless and meaningful auditory stimuli have been reported for consonant vowel consonant (CVC) combinations (Molfese, 1979) and for sentences (Hume, 1984). In these studies, subjects were required to attend to and make a judgment about the nature of the stimulus. The results of electrophysiological studies are useful for clarification of the "timing and organization of cerebral processes by which words are recognized and their meanings extracted" (Hillyard & Picton, 1987, p. 559), but brain activity during language processing can be localized in studies of metabolism and CBF (Mateer, 1989; Finitzo & Pool, 1987; Hillyard & Picton, 1987).

Investigators have studied the location of the physiological response to auditory stimulation in a variety of experimental paradigms using brain imaging techniques. In a limited number of studies, the effects of meaningless and meaningful auditory stimulation on brain physiology have been directly compared. As can be seen in the following review of the literature, however, the effects of these types of stimuli have not been compared when the stimuli share similar acoustic features.

A summary of these studies is contained in Table 1 (All Tables and Figures are contained in the Appendix).

Regional blood flow patterns were studied by Knopman, et al., (1980), using the 133-xenon inhalation method, to determine whether there was a difference between blood flow patterns elicited by meaningless and meaningful auditory stimuli. Three conditions were administered: 1) resting baseline, 2) listening for word meaning and 3) listening for a reduction in intensity in a series of noise bursts. The meaningful stimuli consisted of a list of nouns generated from the Thorndike-Lorge word book (1944) from which the subject was to identify "something to eat." The target and nontarget stimuli were matched for word frequency and initial first letter. The meaningless stimuli were 0.5 s noise bursts which contained a frequency range of 250-4000 Hz and a 10 ms rise/decay time. Presentation of both types of stimuli was at the rate of 2.5 s. Subjects responded by pressing a button with the index finger of the right hand. Both conditions produced a greater rCBF in the left than right posterior Sylvian region, with the meaningful activation condition producing a wider distribution of flow than the meaningless. The authors noted that the number of variables (i.e. signaling, altered states of attention and the act of concentration) changed between the resting and activation conditions which complicated comparisons between the states.

The effects of meaningless and meaningful auditory stimuli on rCBF were compared in two companion studies by Roland et al. (1981) and Nishizawa et al.(1982), respectively. In the first, the effects of a tone rhythm discrimination task on rCBF were investigated using the ^{133}Xe injection method (Roland, et al., 1981). The meaningless auditory stimuli consisted of pairs of rhythms from the Seashore test series B. Tone pulses were 500 Hz bursts of 50 ms duration. In order to "avoid artifacts from the organization of motor activity" subjects were requested not to respond motorically or verbally with a decision about

the similarity of the stimuli. Compared to a resting baseline, the auditory discrimination task increased the rCBF bilaterally in the auditory areas, the posterior inferior frontal regions (Broca area), the frontal eye fields, the frontal polar regions, and the superior frontal regions close to the midline. Differences in right and left hemisphere activation were: 1) activation of the inferior and midparietal region on the right but not on the left, 2) a more intense rCBF increase in the right auditory area than in the left, 3) activation of areas adjacent to the mid and inferior temporal region on the right, but not significantly on the left, 4) greater activation of the right posterior inferior frontal area on the right side, 5) a small activation of the right temporal operculum. The authors concluded that most of the analysis of complex nonverbal auditory signals occurs in the right temporal and parietal lobe and in the right posterior inferior frontal area. They noted that superior frontal activation may occur when the subject followed a plan of action according to prior instruction. Eight out of 12 subjects demonstrated diffuse increase in rCBF in the association cortex but not in the Rolandic strip. The authors suggested that selective facilitation occurs for areas that potentially could be included in information processing.

The purpose of a the second study (Nishizawa et al., 1982) was to compare the effects on rCBF of stimulation with meaningful auditory stimuli with the effects of stimulation with meaningless auditory stimuli (Roland, et al., 1981). The ^{133}Xe injection method was used to study cerebral blood flow during a resting baseline and a passive listening task. The stimuli were 20 onomotopoetic words, presented live voice by a male speaker, with interstimulus intervals averaging 2 s at a distance of about 1 m from the subject's unplugged ear. A 10% increase in hemispheric blood flow was demonstrated bilaterally, particularly in the temporoparietal and frontal regions. A marked increase appeared in the posterior part of the superior temporal regions (Brodmann areas 41,

42, and posterior part of area 22) which are the primary and associative auditory areas. Significant asymmetries were found in these area with the left side showing a more widespread and intense increase, averaging 29% compared to 18% on the right. A similar asymmetry was found in a more anterior part of the superior temporal region. In some instances, cortical activation extended upward to the inferior part of the parietal region corresponding to the supramarginal region and laterally in the temporal region corresponding to Brodmann area 21. Frontal activation included the anterior part of the upper frontal region (prefrontal region), the frontal eye field and the anterior part of the lower frontal region (orbitofrontal region). There was a significantly greater right side activation in the prefrontal region. The authors conclude that the results of this study, compared to those of Roland et al. (1981) indicate that different neural events occur in the right and left temporoparietal regions during nonverbal and verbal auditory perception, respectively. They attributed the increase in right hemisphere prefrontal activation to enhanced attention and mental effort. A major drawback of the study cited by the authors was the inability of this technique to perform simultaneous bilateral studies. They suggest that emission tomography will be necessary "to settle the question of cortical activation of sound versus word perception more definitely."

Mazziotta et al. (1982) and Mazziotta et al. (1984) investigated the effects of both meaningless and meaningful auditory stimuli on cortical and subcortical metabolism using PET with ^{18}F fluorodeoxyglucose. Two types of meaningless stimuli were used. The first consisted of tone sequence pairs, in which each sequence consisted of three, four, or five tones of different frequencies but equal intensity, duration, and interval. The second type of meaningless stimulus consisted of single chords having complex harmonic composition, which were either identical or differed in their harmonic composition

and were prepared in the same way as the tonal stimuli. In both instances, during the scan the subjects were requested to identify the pairs that were different by pressing a switch with a finger. The meaningful stimulus was described as a Sherlock Holmes story which had been recorded by a professional male narrator. The stimuli were presented monaurally to 20 subjects; two subjects received binaural stimulation. After the data collection, the subjects were given questions to answer about the content of the story. In the monaural listening condition, the chords elicited bilateral parietotemporal activation with right greater than left frontotemporal asymmetries. Tone sequence pairs, presented monaurally, produced asymmetries depending on the subject's listening strategy. Musically naive listeners demonstrated right greater than left frontoparietal asymmetries whereas musicians demonstrated left greater than right asymmetries. Binaural presentation of a story and music elicited diffuse bilateral activations of frontal and temporal cortex. Mazziotta et al. (1984) found that the thalamus was activated bilaterally when the subjects listened to a story and were asked to remember the content for later recall. The head of the left caudate was activated for subjects listening to tone pairs who used visual imagery to assist in discriminating the differences. Mazziotta et al. (1982), acknowledging the complexity of the experimental paradigm, recommended that more discrete stimuli be used in future studies as a way to produce more focal changes in metabolic activity.

Wise, Hadar, Howard, and Patterson (1991), in a PET study with ^{15}O, found significant activation of both superior temporal gyri when normal subjects heard words played backwards (described as sounds with the frequency transitions of speech but without recognizable phonemes), listened to non-words (described as words with no meaning but with normal English phonological structure), and performed category judgments on pairs of real words. No difference in activation was found among

these conditions. Two possibilities were offered by the investigators for this lack of differences: 1) an overlap of the neural networks involved in the processes of 2) the activity produced by these different conditions was below the threshold of the technique to distinguish signal from background noise.

To summarize these studies, greater left than right hemisphere activation was found in the temporoparietal regions for meaningful auditory stimuli (Knopman et al., 1980; Nishizawa et al., 1980). In some studies meaningless auditory stimuli produced greater right than left activation (Roland et al., 1981; Mazziotta et al., 1982). In the study by Wise et al., (1991), however, no hemispheric differences were found between listening to stimuli with unrecognizable speech-like stimuli, non-words, or words. Listening strategies influenced hemispheric activation to meaningless stimuli (Mazziotta et al., 1982; Mazziotta et al., 1984). Comparison of the results of these studies may be confounded, however, by the differences in acoustic complexities both between and within the groups of stimuli.

Studies Involving Meaningless Stimuli Only

Meaningless auditory stimuli were used in two PET regional cerebral blood flow (rCBF) studies reported by Lauter et al. (1985) and Lauter et al. (1988). A summary of these studies is contained in Table 2. In the first study (Lauter et al., 1985), tonotopic organization of the human auditory cortex was demonstrated in response to pure tone stimuli. The stimuli were tones of 500 Hz and 4000 Hz, pulsed with a duty cycle of 50%, approximately 500 ms on/off, with a rise/fall time of 50 ms. Activation occurred in two different regions of the left superior temporal plane, contralateral to stimulation, according to the frequency of the stimulus. In the second study, Lauter et al. (1988) observed response to synthetic consonant vowel (CV) syllables occurring in the area of the angular gyrus for their subjects. These stimuli consisted of tape recorded synthetic syllables comprised of the phonemes

/pa, ta, ka, ba, da, ga/ with 50 ms durations. In this experiment, rate, overall intensity level, and ear of presentation were manipulated. Increased rCBF corresponded to increased rate and level. Ear of presentation affected contralateral response with suggestion of asymmetrical responses.

To summarize, in these studies, Lauter et al. (1985) and Lauter et al. (1988) have begun to show a continuum of response to auditory stimulation from the discrete pure tone to acoustically complex speech stimuli. It is clear that at the level of meaningless acoustic stimuli the changes in CBF become wider as the acoustical complexity increases. In addition, the passive listening design of the studies have limited confounding factors related to task and response complexity. These studies can serve as basis for mapping the physiological response to increasingly complex auditory stimuli.

Studies Involving Meaningful Stimuli Only

A number of investigators used auditory stimuli in studies of a variety of cortical functions. A summary of the following review of these studies is contained in Table 3.

Recognition and semantic classification memory were investigated by Wood et al. (1980) using meaningful auditory stimuli to study rCBF changes during two conditions. The authors proposed that semantic memory involves cortical processing, whereas episodic memory involves subcortical processing. The ^{133}Xe inhalation method was used. The stimuli were 40 common words which varied in "concreteness." One task involved listening for words which had been presented previously and the other task involved listening for words that represented a concrete object. The response was to lift the left index finger. The semantic classification task induced significantly greater increase in left hemisphere activation than the recognition memory task. An inverse relationship was demonstrated between the accuracy of the subject's recognition memory and blood flow in the occipital and temporo-occipital

(angular gyrus) regions of the left hemisphere. The results were considered to "support the anatomical basis for the distinction between episodic and semantic memory and to suggest that occipital flow may diminish with accurate memory performance because of an upstream demand of blood in the medial temporal lobes" (p. 113).

Knopman et al., (1982) investigated the effect of handedness on motoric responses and the rCBF correlates of phonological processing of meaningful auditory stimuli, using the ^{133}Xe inhalation technique in a companion study to the Knopman et al. (1980) study of auditory activation with meaningless and meaningful auditory stimuli. Four conditions were presented. The meaning detection (semantic) and loudness discrimination (acoustic) conditions had been used in the previous study (Knopman et al., 1980). In the meaning condition, the subjects were given a list of words and were to listen for types of food; in the loudness condition, they were to listen for the less intense tone. Two new conditions, both considered phonologic, were added. In the rhyme condition, the stimuli were single words and the target was a word that rhymed with "-ate," with the remainder of the words having final syllables close in sound to "-ate," such as "detain." In the last condition, subjects were asked to discriminate between "pan" and "tan," with the target being "tan." Taped auditory stimuli were presented binaurally at a comfortable listening level through insert earphones to each subject. The subjects were instructed to press a button with their left index finger when they heard the target word. Left-right hemispheric comparisons revealed no difference in hemispheric means except for the rhyme condition in which nine of the ten subjects had greater left than right rCBF. Comparison was made between the baseline and activation conditions. Baseline conditions showed increased activation frontally. In the meaning condition, an increase in rCBF occurred in the right posterior Sylvian area. In the loudness condition, the increase occurred in the left Sylvian area. In the rhyme

condition, there was an increase in rCBF in the left Sylvian regions as well as the right temporal region. No significant changes occurred in the left hemisphere in the "pan-tan" discrimination condition. The authors conclude that 1) changes in rCBF are due to differences in listening tasks, not necessarily to the stimuli, 2) processing of single words for sound (rhyme condition) appears to be a function of the left posterior Sylvian area, 3) processing single words for meaning may be carried out bilaterally, and 4) mechanisms for auditory short term memory may be localized in the left posterior Sylvian region.

Whether lateralized verbal input affects differently the neural activity in the ipsi- versus contralateral hemisphere was investigated by Maximillian (1982) in a dichotic listening paradigm. The ^{133}Xe inhalation method was used to study cortical blood flow during repeated monaural stimulation with meaningful auditory stimuli. The stimuli were parallel lists of two syllable meaningful Swedish words presented monaurally. Subjects were asked to give a nonspecified affirmative response to least common Swedish plural endings. The findings were: 1) no asymmetry in the resting state; 2) verbal stimulation lead to significant interhemispheric asymmetry with higher flows in the left temporoparietal area with both right and left ear stimulation; 3) with left ear stimulation, higher flows occurred in the right frontotemporal area. These findings were interpreted as demonstrating a posterior temporal language area of the left hemisphere regardless of laterality of the stimulus and possibly indicating cross-hemisphere transfer of partially processed verbal material from the right frontotemporal region. Task complexity was cited as having a possible effect on the results.

In a study of physiological response in perceptual tasks, Reivich et al. (1984) examined factors affecting metabolic responses using PET. They studied attentiveness of listeners to a factual story presented during a scan by testing recall at the end of the study. With monaural

stimuli, elevated metabolic rates were found in the temporal cortex contralateral to the stimulated ear in each subject. The effect of vigilance was studied by having the subjects listen to a verbal discourse in an unfamiliar language (Hungarian) and identify a specified word ("vonat") by pressing a bar with both hands. Significantly greater activation occurred in the right inferior parietal lobes in this task. In addition, for those subjects with a higher level of anxiety during the testing, a greater activation in the right than the left hemisphere was demonstrated.

Metabolic changes related to covariance of brain regions during a phoneme monitoring task was investigated by Bartlett et al. (1987) in a PET study with ^{11}deoxyglucose. In this discrimination task, the subjects listened to tape recorded meaningful monosyllabic English words spoken by a female and were requested to respond by foot movement to words beginning with a /b/ or /s/. The words were presented in 5 min blocks with an 8-s pause between blocks at a rate of 3.7 per s. Fifteen percent of the stimuli began with the target sounds. A pattern of cross hemisphere symmetry was found at rest and asymmetry during stimulation. Within-hemisphere correlations for the left but not the right hemisphere were shown during activation. These included the left inferior frontal, left superior temporal, and left transverse temporal cortical regions. In addition, significant correlations were found between the left regions and the right superior temporal region. In general, the results of this study show a pattern of cross-hemispheric symmetry at rest and asymmetry with stimulation superimposed on the resting symmetry.

In a rCBF SPECT study, Goldenberg et al., (1987) investigated memorization of high and low imagery meaningful words. The aim of the study was to investigate whether an anatomically distinct "imagery system" was activated by concrete nouns. Concrete and abstract meaningful words and meaningless words were used in the study. The meaningless words were described as "phonotactically correct," derived

from exchanging syllables and letters within real German words. On a seven point scale of imaginability of German nouns, the abstract nouns rated no more than three points whereas the concrete nouns rated no less than six points on the same scale. The frequency of occurrence of both concrete and abstract nouns showed a normal distribution when plotted on a logarithmic scale of word frequency. Subjects were asked to memorize the nouns under two conditions, with and without visual imagery. Subjects listened to a list of words presented through earphones. After an interval they heard another word and flashed a lamp held in the left hand if they thought the word had been presented in the previous list. Performance on all memory tasks activated the hippocampal and inferior temporal regions of both hemispheres. The occipital regions were activated as well when concrete nouns were memorized; when subjects were instructed to use imagery, the left inferior occipital lobe of some of the subjects showed increased blood flow. The imagery instruction led to increased count rates bilaterally in the superior frontal lobes, with the highest count in all conditions in the left middle frontal lobe. The authors suggest that the imagery instructions placed cognitive demands on subjects to follow a prescribed strategy resulting in prefrontal activation. In the resting state, asymmetry of greater right than left hemisphere blood flow was observed which was attributed to attention paid the surroundings. Right greater that left hemispheric asymmetry occurred in memorization of concrete nouns without imagery. Analysis of correlational structures, however, suggest that in both of the memorization conditions, activation occurs primarily in the left hemisphere and that the difference in hemispheric asymmetries may be related to "different modes of hemispheric collaboration."

Meaningful auditory stimuli were used in a complex rCBF PET study of single word auditory and visual processing by Petersen et al. (1988). The investigators used a three level stepwise paradigm to demonstrate brain regions activated during passive sensory processing of single

words, repetition of words, and production of semantic associations. Stimuli were described as "frequent English nouns." Stimuli were presented both auditorily and visually. Visual words were presented on a color monitor. The auditory stimuli were tape recorded and presented through earphones at a rate of 1 per s. Of the three levels in this paradigm, the passive listening task is the most comparable to the other studies in this review. During the listening task, areas of activation were found bilaterally in the primary auditory cortex, and lateralized to the left hemisphere in the temporoparietal cortex, anterior superior temporal cortex, and inferior anterior cingulate cortex. It should be noted that as the task complexity increased, at the level of semantic associations, the activation increased to include an area in the inferior anterior frontal cortex (Brodmann area 47). These data were used to develop a model for cognitive operations in the brain (Posner et al., 1988). In later related studies with visual stimuli only, Peterson, Fox, Snyder, & Raichle (1990) and Raichle (1991) reported increased activation in the left frontal area with word stimuli but not word-like stimuli.

Cerebral blood flow during phoneme detection was assessed in both normal and aphasic subjects with SPECT using the ^{133}Xe inhalation method (Walker-Batson et al., 1988). Three conditions were presented, resting, passive listening, and phoneme detection. The stimuli consisted of the meaningless syllables /pa,ta,da,ka,ga,ba/ recorded by a male speaker. Each syllable was 300 ms duration, with maximum amplitudes equalized according to the peak amplitudes of the vowel /a/. [The phonetic symbol /a/ was used by Walker-Batson et al. (1988). It is unclear whether this symbol represented the typed /a/ described by Pickett (1980). In the remainder of this document, the vowel symbols used are those used by the authors quoted.] The randomized syllables were presented at the rate of 4 per s. In the phoneme detection condition, the subjects were instructed to lift the left index finger when /ba/ was heard. No

difference was detected in total right and left hemispheric rCBF uptake in either the normal or aphasic group in each of the three conditions. Considerable intrasubject variability was demonstrated in the normal subjects. For some of the subjects the passive listening condition produced as much increase from the resting state as the phoneme detection task in language related regions. Seven of the eight normal subjects demonstrated activation of the mesial frontal regions during the phoneme detection condition. The authors noted that they were unable to separate the linguistic and attentional factors which might contribute to that effect.

No distinct pattern of activation in regions of interest were noted in the aphasic subjects, although in four of the five subjects an unexpected finding was rCBF increases in cerebellar regions ipsilateral and contralateral to the lesion side during the phoneme detection task. The authors cautioned that their results might reflect the small number of subjects and the limited resolution of their "first generation" SPECT machine.

Lechevalier et al., (1989) used meaningful auditory stimuli in their rCBF investigation of comprehension of spoken discourse and production of speech, using the ^{133}Xe inhalation method. In the comprehension part of this study, subjects listened to a tape recorded story consisting of a dialogue between a female and a male speaker. At the conclusion of the stimulus presentation and measurement of the rCBF, the subjects were asked to select three pictures, from an array of nine, that were related to the text. In the speech production part of the study, the stimuli consisted of a list of 17 nouns and 8 transitive verbs of high frequency, presented by live voice, which the subjects were to define orally or to use in an appropriate context. The authors noted that the auditory-verbal component of this task was "reduced to a minimum and standardized (1 word per 30 s)" (p.3). For the comprehension task, rCBF increased significantly in the right but not

the left hemisphere compared to the resting state. Increases occurred in both inferior parietal areas, with the main increase on the left side. Other increases included: left prerolandic and opercular regions, as well as on the right prerolandic, midrolandic, superior rolandic, and posterior parietal zones. The speech task induced diffuse increase in mean hemispheric rCBF bilaterally, with regional increases in both inferior parietal, left opercular, and right upper motor and premotor areas. The authors offered possible explanations for the right hemisphere activation in the comprehension task. The content of test material could have elicited emotional response from the subjects resulting in right hemisphere activation. In addition, attention may have induced increased right hemisphere blood flow. The authors indicated, however, that their results may point to the role of the nondominant hemisphere in complex verbal listening tests.

The studies reviewed in this section represent the use of auditory stimuli in a number of different experimental paradigms. In summary, these studies generally support greater left than right hemispheric activation for meaningful auditory stimuli (Wood et al., 1980; Maximillian, 1982; Bartlett et al., 1987; Petersen et al, 1988; Lechevalier, 1989). Meaningless stimuli were found to be processed in the right hemisphere, although activation contralateral to the ear of stimulation was found for meaningful stimuli (Reivich et al., 1984). Whereas Knopman et al. (1982) found that meaningful stimuli produced bilateral activation, Wise et al. (1991) found bilateral activation for speech-like sounds, non-words, and words alike. The results reported by Walker-Batson et al. (1988) were equivocal in that the authors were unable to separate linguistic and attentional factors. Goldenberg et al. (1987) concluded that memorization occurs primarily in the left hemisphere. It must be noted that considerable variability of the acoustic parameters of the meaningful auditory stimuli was evident in these studies. Although the investigators reported differential results

to the task demands of the studies, the confounding effect of the varying acoustic complexity of the auditory stimuli cannot be ruled out.

Rationale

Brain imaging studies of cerebral blood flow and metabolism have been shown to provide information about the localization of cerebral activation in response to auditory stimulation. The results of these studies of localization of auditory function in which meaningful stimuli were used may be difficult to interpret, however, because of the acoustic variability of the stimuli used within the different studies. Responses considered to be related to the meaningful content of the stimuli might be related, instead, to the complex acoustical characteristics of the stimuli. Comparisons between responses to meaningless and meaningful auditory stimuli have yet to be made when the acoustic characteristics of the stimuli have been controlled. Without consistency of the acoustic parameters for each of the stimulus items, it may not be possible to separate brain activation related to linguistic effects of the stimuli from those that may be more properly interpreted as related to the acoustical components of the signal. Until more data are available about the effects of controlling acoustic parameters of meaningful auditory stimuli, interpretation and generalization of the results of these studies may be inconclusive.

Statement of Purpose

The purpose of this study is to determine whether there is a difference in localization and amount of increased cerebral blood flow as a response to meaningless and meaningful auditory stimuli that have been matched for acoustic parameters. This study attempted to answer the following research question: is there a significant difference in amount of cerebral blood flow as measured by PET for specific inter- and intra-hemispheric regions of interest (ROIs) during the presentation of meaningless and meaningful auditory stimuli matched for acoustic parameters.

CHAPTER II. METHODS

This chapter describes the research methods used to answer the question of whether there is a significant difference in cerebral blood flow as measured by PET for specific ROIs during presentation of meaningless and meaningful auditory stimuli.

Subjects

Three female, native speakers of American English, aged 32 years, 8 months to 39 years, 10 months, with no history of speech, hearing, language, learning or neurological problems served as subjects in this study. The subjects were drawn from a pool of normal healthy adult volunteers for the project. These volunteers were faculty or staff in the Department of Audiology and Speech Pathology at the University of Tennessee, Knoxville or staff at the University of Tennessee Medical Center, Knoxville. Because differences have been found between female and male subjects in repeated CBF measurements (Gur et al., 1982; Warach et al., 1987) and age differences in glucose utilization have been reported (Kuhl, Metter, Riege, & Hawkins, 1984), the subjects were the same gender and within a ten year age range of each other. The first individual to volunteer for the study was the 32 year old female. This was the determining factor for the selection of the gender and age range of the remaining subjects.

Each subject underwent a brief neurological examination by a neurologist to verify a neurological status within normal limits. This examination consisted of a family and personal health history, evaluation of general mental status (e.g. orientation and short term memory), cranial nerve status, and overall motor and sensory systems. Each subject was judged to be within normal limits by the examining neurologist.

Subjects were right handed, according to report. Hearing threshold were no greater than 20 dB HL at 250, 500,1000, 2000, 4000, and 8000 Hz for each ear. Two subjects were speech-language

pathologists and one subject was a certified occupational therapy aid. Table 4 contains a summary of the subject data.

Prior to participating in this study, each subject signed a Statement of Informed Consent form approved by the University of Tennessee Medical Center Knoxville (UTMCK) and the University of Tennessee Knoxville (UTK). Appendix C contains the Statement of Informed Consent.

Stimuli

The stimuli for this study consisted of one syllable consonant vowel consonant (CVC) combinations that differed minimally in acoustic characteristics, yet could be clearly differentiated as meaningful or meaningless. The primary criteria for the selection of stimuli were 1) that there be an equal number of meaningful and meaningless stimuli and 2) that they could be matched acoustically as closely as possible according to the parameters of overall duration, overall intensity, and fundamental frequency contours. In order to control these parameters, it seemed advisable to choose stimuli with minimal acoustic complexity. The CVC combinations represented the least acoustically complex unit with which a sufficient number of stimuli could be generated to meet these criteria.

Twenty-two meaningless and twenty-two meaningful CVC speech stimuli comprised of six consonant phonemes /p,t,k,b,d,g/ and four vowel phonemes / ε / as in "pep", / $\wedge$ / as in "pup", / æ / as in "pap", and / α / as in "pop" were generated by natural speech and were eventually matched as closely as possible according to the acoustic characteristics of overall duration, overall intensity, and fundamental frequency contours. The stimuli were selected from the 144 possible CVC combinations of these phonemes and generated according to criteria described in the next sections. Table 5 contains all the possible CVC combinations.

Description of the Stimuli

General Acoustic Properties of the Consonants and Vowels

The following description of the acoustic properties of the stimuli is included in order to provide a context for the selection of the particular consonants and vowels for the study and for the manipulation of the acoustic parameters of these stimuli in the study. The six selected consonants (/p,t,k,b,d,g/) are considered to be similar in terms of the manner in which they are produced and thus share similar acoustic characteristics (Miller & Nicely, 1955). These consonants are classified as stop consonants. For production of these consonants, air flow in the oral cavity is trapped and rapidly released by the articulators. The consonants differ according to the place in the oral cavity in which the constriction and release of the air flow occurs (Minifie, 1973). The consonants /p,b/ are produced by closure and release of the lips; /t,d/ are produced by closure and release of the tongue tip against the alveolar ridge; /k,g/ are produced by closure and release of the back of the tongue against the soft palate. The consonants also differ in the characteristic of voicing. The consonants /p,t,k/ are called voiceless consonants in that no vocal cord vibration is involved in their production. The consonants /b,d,g/ are called voiced consonants because vocal cord vibration occurs during their production. The acoustic correlates of the stop consonants include a period of silence, a burst of noise, and a transition if the consonant precedes a vowel and a transition, a silence, and a noise burst if it follows a vowel (Halle, Hughes, & Radley, 1957). The energy concentration in the spectra differ according to the place of articulation (Halle et al., 1957). For /p/ and /b/ the primary concentration of energy is in the low frequencies (500-1500 Hz). For /t/ and /d/, the energy is in the region of 500 Hz and either have a "flat" spectrum or a concentration of energy above 4000 Hz. For /k/ and /g/ the energy of the burst is in the mid range (1500-4000 Hz).

The four vowels (/ɛ , ʌ , æ, ɑ /) are also closely related acoustically. They share similar frequency spectra. When the frequency of the first formant is plotted against the frequency of the second formant for each of the vowels, the vowels occupy adjacent positions on the resulting graph (Peterson & Barney, 1952). The vowels would be expected to differ in duration, fundamental frequency, and intensity since these parameters are dependent on the surrounding consonants (House & Fairbanks, 1953). In a study of vowel duration, Umeda (1975) studied the production of three speakers reading aloud. She found that for monosyllabic words, similar to the CVC stimuli of this study, the durations of the vowels / ɛ / and / ʌ / were shorter than those for / æ / and / ɑ /. She also noted that vowels are shorter before voiceless stop consonants than voiced stop consonants irrespective of the consonant preceding the vowel. Fundamental frequencies of vowels differ according to their consonant environments; in voiceless environments fundamental frequencies are higher than those in voiced environments (House & Fairbanks, 1953). Similarly, House and Fairbanks (1953) found that the intensity of vowels in voiced environments was greater than for those in voiceless environments. According to that study, vowels surrounded by voiced consonants will have longer durations, lower fundamental frequencies, and greater intensity than those vowels in a voiceless environment.

Stimuli Selection Criteria

The stimuli for this study were selected from the possible 144 CVC combinations according to the following criteria: 1) that there be an equal number of meaningful and meaningless stimuli; 2) that no first or last names, trade names (e.g. /kɛd/, "Ked"), slang or obscure words (e.g. /tɛt/, "tet," which might carry meaning to someone of an age to remember the Tet Offensive in the Vietnam War) be included in the meaningful stimuli; and 3) that the two sets of stimuli be balanced so that each initial consonant and vowel would be equally represented in

both sets of stimuli. To meet the first two criteria, the investigator made preliminary judgments about the meaningful and meaningless nature of the 144 CVCs and eliminated any CVC that appeared to be a first or last name, a trade name, a slang word, or have an obscure meaning. This was done in an effort to create easily recognizable meaningful stimuli. The constraints of stimuli selection, related to the need to match the stimuli according to acoustic parameters, precluded much flexibility in stimuli selection according to features such as semantic content, syntactic category, or frequency of occurrence. In addition, with regard to possible habituation effects, as many stimuli as possible were accepted into the stimulus pool so that each stimulus would be presented a minimal number of times. In a study of electrophysiological response to meaningful and nonmeaningful sentences, Hume (1984) noted that, though not statistically significant, the peaks of the waveforms were generally reduced during the second presentation of a stimulus. This indication of habituation to the stimulus after one presentation suggests that limiting the number of presentations of each stimulus would be desirable.

An amended list of 80 CVCs was then presented to five native speakers of American English to be judged as meaningful or meaningless. Appendix D contains the response form which lists the CVCs for this task. The judges listened to this list of CVCs read aloud and indicated which of those sounded like a recognizable English word (even if it were a slang or obscure word, which they were asked to note). The CVCs judged to be English words were considered meaningful and the remainder meaningless. Those identified slang or obscure words were deleted from the meaningful group. The three PET subjects were included in this group of judges. This was done to avoid including a CVC in the group of meaningless stimuli that might contain a meaning idiosyncratic to a PET subject, such as a nickname or the name of a pet. Two examples of otherwise meaningless CVCs which held meaning idiosyncratic to the PET

subjects were one that represented a subject's initials and another that was an utterance made by a subject's child. Such CVCs were omitted from the stimulus pool. Of the 80 CVCs presented to the judges, 33 were judged to be meaningful and 38 were judged to be meaningless with 100% agreement. The remaining 9 CVC were meaningful for some judges and meaningless for others. These CVCs were omitted from further consideration as stimuli.

The third stimulus selection criterion, that the stimuli be phonemically balanced, was based on the results of electrophysiological studies that showed differences in cortical response to CVC and CV stimuli related to voicing and place of production of the consonants (Mateer & Cameron, 1989; Molfese, 1979). Molfese (1979) found that auditory evoked responses were sensitive to the time of voice onset of voiced and voiceless consonants, /b,g/ and /p,k/, as well as to the place of articulation, whether in the back, /k,g/ or front, /p,b/, of the mouth. Mateer and Cameron (1989) recorded cortical potentials directly from the human cortex in response to auditory stimulation with the CVs /ba/ and /pa/ and found that the latencies of the waves differed according to the onset of voicing for the consonants. Therefore, effort was made in this study to ensure that both sets of stimuli shared similar phonemic characteristics so that any differences in the subjects responses to the stimuli could not be attributed to phonemic differences in the stimuli.

The selected CVC stimuli, therefore, were grouped into eight subgroups according to the voicing of the initial and final consonants (voiced, V, /b,d,g/ or voiceless, VL, /p,t,k/) and expected duration of the vowel (short, S, /ɛ and ʌ / or long, L, /æ and ɑ /). The CVCs within these subgroups were then balanced according to the criteria, so that each subgroup contained an equal number of meaningful and meaningless CVCs and the phonemic composition was balanced for initial consonants and vowels. Although these criteria precluded a balance of

final consonants in a similar manner, both sets of stimuli contained an equal number of voiced and voiceless final consonants (Table 6 a,b,c). During this process a number of CVCs were rejected from the stimulus pool if they could not be matched for phonemic composition with a comparable meaningful or meaningless CVC.

Because of the acoustic characteristics of the individual phonemes and contextual influences, clearly variations were expected among the CVCs. Durations of the stimuli could vary depending on vowel duration and the voicing of the final consonant according to Umeda (1975). Therefore, in order to match the stimuli according to their acoustic parameters, the eight groups were reduced to four groups based on expected vowel duration (S or L) and final consonant voicing of the CVC (V or VL): a short vowel preceding a voiceless consonant (S-VL), a long vowel preceding a voiceless consonant (L-VL), a short vowel preceding a voiced consonant (S-V), and a long vowel preceding a voiced consonant (L-V). Within each group the overall durations of the stimuli would be within 50 ms of each other; the overall intensity of each stimulus would be within 2 dB of the other stimuli; and each of the CVCs would have a falling fundamental frequency contour with approximately a 100 Hz range from the beginning and ending fundamental frequencies. These values were selected based on the investigator's experience analyzing natural speech samples of CVCs from a pilot study related to synthetic speech stimuli.

Generation of Stimuli

The stimuli were generated by a female, native speaker of standard American English. Each stimulus was recorded three times, in an acoustically treated booth, on a Sony APR 2003 reel to reel audio recorder, with a Realistic microphone, model 33-1080, held 8" from the speaker's mouth. Because fundamental frequency was the only parameter that could not be modified in some way after production, the fundamental frequency contours were monitored during actual production with the Kay

Visi-Pitch 6087 DS (Kay Elemetrics) to ensure that each token of the stimuli contained a falling fundamental frequency pattern.

Each of the tape recorded CVCs was then recorded to an AT-compatible computer (386 system) and digitalized for analysis and stimulus manipulation with the Canadian Speech Research Environment, version 3.0 (CSRE). The overall durations and fundamental frequency contours of the three tokens of each CVC were analyzed. The durations (in ms) were measured from the beginning of the waveform to the last point appearing on the waveform after the aspiration of the final plosive consonant. An example can be seen in Figure 1. The CSRE Pitch Extraction program was used to establish the fundamental frequency contours. The highest point of the contour was measured (in Hz) closest to the onset of voicing and the lowest point was measured at the point were the voicing of the vowel appeared to end. The fundamental frequency contour was taken to be the subtracted difference in these two points. From the three tokens, one CVC was chosen as the stimulus based on the clarity of the phonemes (in particular the consonants), the overall duration, and the fundamental frequency contour.

Analysis of the Stimuli Items

Overall Analysis of Acoustic Parameters

The criterion that the overall durations of the stimuli within each of the groups (S-VL, S-V, L-VL, L-V) be within 50 ms of each other was approximately achieved in three of the groups. The differences in durations of the stimuli of three groups were 54, 51, and 49 ms for the S-VL, S-V, and L-VL groups, respectively. For the L-V group, the durations of two stimuli were modified with the Waveform Paste Editor of CSRE which allows portions of the waveform to be deleted from or added to the overall waveform. The modifications to stimulus duration were made in the portion of the waveform representing the point of articulatory closure prior to the burst of the final consonant. In one instance, /dɑg/, the duration was increased by the addition of a period

of silence (57 ms) during the closure. In the other instance, /kæg/, the duration was shortened by removing a portion of the signal (12 ms) during the closure. Even with these modifications, the difference in overall durations for this group was 63 ms.

Of the three tokens of each CVC, the one most approximating a 100 Hz falling fundamental frequency contour was chosen, secondary to considerations of the duration and quality of the CVC. No effort was made to match the CVCs according to the beginning and ending frequencies of the frequency contours. For all groups, the fundamental frequency contours ranged from 75 to 124 Hz.

Normalization of the overall intensity of the stimuli was achieved with a specialized computer program (Z. Czyzewski, personal communication, 1991). This program also permitted reduction of the intensity of portions of the audio signal which contained extraneous computer generated noise in some stimuli (particularly in stimuli with a voiceless final consonant) as a result of digitalization during the CSRE program. To compare the intensities of the each of the CVCs, the overall amplitudes of the CVC signals were expressed as root-mean-square (RMS) voltage. RMS is derived by taking the square of the amplitude of the wave in every point in time, finding the average mean of the squared values, then finding the square root of the mean. The resulting value is directly proportional to the energy in the signal (Baken, 1984; Z. Czyzewski, personal communication, 1991). The range of RMS amplitudes, in relative dB, for all groups was 42.0 to 43.5.

A sample waveform, amplitude and fundamental frequency contours, and frequency spectrum for the CVC /pæb/, generated by a Kay DSP 5500 Sonograph, are displayed in Figure 1. (The zero crossing line is not relevant to this study; the display set up does not include an option to delete it from the display.) Spectrograms for all the CVCs are contained in Appendix I.

Comparisons of Acoustic Parameters of the Meaningless and Meaningful Groups

Table 7 contains the ranges of the declination of the fundamental frequencies, overall durations, and intensity measurements of all the stimuli. The stimuli have been separated into meaningful and meaningless categories and according to the previously described groupings. The means, standard deviations, ranges of the fundamental frequency changes, overall durations, and overall intensities are presented for the meaningless and meaningful CVCs. As can be seen from this table, the means for all the acoustic parameters were very closely matched for the meaningless and meaningful stimuli in each of the groups.

The t-Test for Independent Means was performed for the fundamental frequency declinations, overall durations, and overall intensities to determine if there were differences in these acoustic parameters between the meaningless and meaningful stimuli. No significant differences were found for these acoustic parameters between the two types of stimuli with respect to duration ($t = 0.218$, $df = 42$, $p > 0.05$), fundamental frequency contour ($t = 0.259$, $df = 42$, $p > 0.05$), or intensity ($t = 0.063$, $df = 42$, $p > 0.05$). These results indicate that the goal of matching the stimuli for the two conditions according to their acoustic parameters was successfully achieved.

Comparisons of the Acoustic Parameters of the Four Groups (S-VL, S-V, L-VL, L-V)

Initially, the stimuli had been grouped into four groups according to expected differences in the acoustic parameters related to vowel durations and consonant environments (S-VL, S-V, L-VL, L-V). An equal number of meaningless and meaningful stimuli were represented in each group so that the groups were balanced. To determine whether these balanced groupings were justified, additional t-Tests were performed between the four groups themselves for the parameters of duration and

fundamental frequency. Intensity was not considered in these analyses because the intensities of the stimuli were modified to be within 2 dB of each other and were not dependent on the phonemic content of the stimuli. Table 8 contains the means, standard deviations, and ranges of each group for each acoustic parameter.

With respect to overall duration, a significant difference was found between the two short vowel (S-VL plus S-V) and the two long vowel groups (L-VL plus L-V) ($t = 17.201$, $df = 42$, $p < 0.001$) and between the two long vowel groups (L-VL and L-V)($t = 4.250$, $df = 18$, $p < 0.001$). In the first instance, the "long vowel" groups had longer overall durations than the "short vowel" groups; in the second instance the durations of the stimuli with voiced final consonants were longer than those with voiceless final consonants. Although the stimuli had been chosen for inclusion within the groups according to specific selection criteria and could not be considered random samples, they did appear to fit the observations of Umeda (1974) about vowel durations and the effect of consonant environment. In this study, the overall durations of the stimuli containing /ɛ/ and /ʌ/ were shorter than those containing /æ/ and /ɑ/ and the overall durations of stimuli with long vowels and voiced final consonants were longer than for those with long vowels and voiceless final consonants. No other significant differences were found between the group comparisons for overall duration.

For the fundamental frequency contours, a significant difference was found in the mean declination of the frequency contours between those stimuli with long vowels and voiceless final consonants (L-VL) and those with voiced final consonants (L-V)($t = 2.126$, $df = 18$, $p < 0.05$). Those stimuli ending in voiceless consonants had a greater frequency contour declination than those ending in voiced consonants which was not found to be the case for the CVCs with short vowels. The reason for this is unclear.

The rationale for grouping the stimuli according to vowel duration and final consonant voicing was supported by these differences found in the parameters for the groups. Grouping the stimuli in this manner facilitated matching the meaningless and meaningful stimuli for acoustic parameters because the stimuli had been group according to both phonemic and acoustic criteria.

Reliability of Measurements for Acoustic Analysis

To assess the reliability of the measurements of the acoustic parameters, the investigator remeasured ten percent, or five, of the stimuli six months after the initial measurements were made. The stimuli were composed of 44 CVCs. Therefore, the duration and fundamental frequency declinations were remeasured for five randomly selected stimuli. Table 9 contains the original and repeated measurements. Percent difference was calculated between the means for each set of measurements [(x-y)/(x+y)*100)] For the duration measurements there was 0.08% difference between the mean of the first measurements (mean = 589 ms, SD = 71.8) and the second set of measurements (mean = 588 ms, SD = 71.6). For the fundamental frequency declination measurements, the percent difference was 1.01% between the first set of measurements (mean = 107.6 Hz, SD = 9.6) and the second set of measurements (mean 109.8 Hz, SD = 11.3).

Perceptual Assessment

To ensure identifiability, a perceptual assessment was made of each stimulus. An audio tape recording containing a sample of each of the 44 stimuli was presented individually to three listeners. The stimuli were presented through the insertion ear phones to be used in the PET study (E.A.RTONE 3A Insert Earphones, Cabot Corporation) at a comfortable listening level to each listener's right ear. The right ear was chosen as the ear of presentation for this study. In previous studies, stimuli have been presented monaurally to either the right or left ear or binaurally. No particular precedent has been set for ear of

presentation. Whereas increased effects of stimulation to the contralateral ear have been demonstrated (Lauter et al., 1985; Lauter et al., 1988; Reivich et al., 1984) and asymmetries in these responses have been noted (Lauter et al., 1988), in this study, the right ear was chosen for presentation of the stimuli because it is the ear contralateral to the left auditory cortex.

The listener was instructed to repeat the stimulus to the investigator who transcribed the responses. Only those stimuli which were identified with 100% agreement were included in the study. All stimuli were identified correctly by the listeners.

Final Preparation of the Audio Tape

Originally, a presentation rate of one stimulus per 1 s was selected. After that rate was judged by two listeners to be too rapid for comfortable listening, a second presentation rate of one syllable per 1.6 s was arbitrarily selected and judged comfortable by the two listeners. A period of silence was added by a computer program at the end of each stimulus to permit an approximate 1 s interstimulus interval.

The modified CVCs were randomized and recorded from the computer onto an audio tape using the Sony APR 2003 reel to reel tape recorder. For each condition, each of the twenty two stimuli was randomly presented five times for a total presentation time of 2 min 54 s. This list was then repeated to create an audio tape 5 min 48 s long. Although the overall stimulation time was expected to be no greater than three minutes, the tape was made long enough to ensure that stimuli would be presented in case of an unforeseen interruption in the scanning protocol. For the purpose of calibration, a thirty second segment of speech spectrum noise at the overall level of the speech stimuli was attached to the beginning of each tape.

Neuroimaging Techniques

The protocol developed for this study at the University of Tennessee Medical Center Knoxville (UTMCK) utilized magnetic resonance imaging (MRI) for the purpose of increasing the accuracy of identification of the regions of interest (ROIs). Magnetic resonance imaging produces images related to anatomy, whereas PET images are based on physiology. The PET images represent cerebral activity and as such do not necessarily define the underlying anatomy. In fact, because of the lower spatial resolution of PET, compared to MRI, the identification of underlying structures by PET is problematic. This problem has been addressed in the literature (cf. Evans, Beil, Marrett, Thompson, & Hankin, 1988; Fox, Perlmutter, & Raichle, 1985; Levin, Pelizzari, Chen, Chen, & Cooper, 1988).

According to the protocol for ROI identification and localization developed for this study, each subject underwent an MRI scan prior to her PET scans. The MRI images for each subject were superimposed on that subject's PET images in a series of steps described in later sections of this chapter. In this way, ROIS that were identified on the MRI images then could be transferred to the PET scans. The basic principles underlying MRI and PET will be described in the following sections.

Magnetic Resonance Imaging

MRI utilizes the principle that the nuclei of selected elements react to magnetic fields. In a strong magnetic field the nuclei will align themselves either parallel or antiparallel to the magnetic field. When a radiofrequency wave is applied to the field the nuclei will be temporarily misaligned. As the nuclei return to alignment, radiowaves are emitted in the process. Detectors measure these signals and a computer constructs an image from the signals. The digital MRI images consist of a grid of picture elements, or pixels. Each pixel can be located by x,y coordinates (S. McClain, personal communication, 1992).

MRI can show differences in tissues that have different chemical compositions such as gray matter and white matter in the brain. It provides a superior image to computed tomography (CT) images for these tissues (Brookshire, 1992; Metter, 1986). The MRI scans for this study were done on an Elscint Gyrex 2T housed in the Department of Radiology at UTMCK.

Positron Emission Tomography

Positron emission tomography (PET) is an imaging technique that measures the location and amount of physiological activity in a body. In PET studies, radiotracers are injected intravenously or administered by inhalation and are distributed in the body according to their biochemical or physiological properties. In this particular study, blood flow to the brain was measured with the radioisotope ^{15}O. This isotope was used because of its short half life which permits the short scanning time. PET images are obtained by computerized reconstruction of events occurring within the body from the decay of positron emitting radioisotopes.

The radioisotopes used in PET are produced in a cyclotron. In this device an extra positive charge is added to a stable element by bombarding the nucleus with protons or deuterons (a composite of a proton and neutron having a positive charge). This excess positive charge is emitted from the nucleus in the form of a positron (positive electron) (Jacobson, 1988). In the body, when positrons are emitted during the radioisotope decay, they quickly combine with electrons. This causes an annihilation reaction to occur, during which both the positron and electron are converted into energy. As a result, two 0.511 MeV photons emerge at 180 degree angles from each other. These annihilation photons are then recorded by detectors arrayed around the head in a circular fashion. Simultaneous measurements of more than one tomographic slice may be obtained from several rings of detectors. When two photons are recorded simultaneously, the conclusion is made that the

annihilation reaction occurred somewhere along the line connecting the detectors. These events are recorded from different angles (sinogram) the distribution (activity image) is calculated by tomographic reconstruction procedures (Budinger, Derenzo, Huesman, Jagust, & Valk, 1989; Jacobson, 1988; Raichle, 1987; G. Smith, personal communication, 1992; Sorenson & Phelps, 1987).

Similar to MRI images, the digital PET images consist of a grid or matrix of picture elements, or pixels. Each pixel can be located by x,y coordinates and has a pixel value representing the quantity of activity (or amount of energy emitted by a particular piece of tissue) associated with that pixel (Sorenson & Phelps, 1987; G. Smith, personal communication, 1991). The values for the particular PET scanner used in this study are represented as ECAT counts per pixel per second, henceforth referred to as ECAT counts. These pixel values can be represented by different color codes in the image according the amount of activity in the pixel. The PET studies were done on a Siemens ECAT Scanner, 931-08012 series, also housed at the UTMCK Department of Radiology.

Procedures

Magnetic Resonance Imaging Procedures

The subjects were scanned according to the protocol of the Department of Radiology, UTMCK (S. McClain, personal communication, 1992). Prior to entering the MRI area, the subjects were requested to remove metal objects such as watches and rings in order to avoid exposing ferromagnetic materials to the magnet. The MRI technician explained the procedures to each subject. The subjects were informed that they were to lie still on the scanning table during the scans. They would experience noise during the scans, but would be given head phones to diminish the noise and through which they could listen to their choice of music. The subjects were informed that during the approximately forty minute procedure they could communicate at any time

with the MRI technologist. They were also advised that should they experience any adverse feelings, in particular related to being in a confined space, that they could stop the procedure at any time if they so chose.

The pulsing sequence for the T1 MRI images was: TR (time to repeat) = 450 ms and TE (time to echo) = 13.0 ms. Fifteen transaxial slices 5 mm thick and 2 mm apart parallel to the canthomeatal line were made for each subject. The inplane resolution is 0.5 mm and the out of plane resolution is 5 mm. The canthomeatal line lies from a point located at the outside corner of the eye to a point at the external auditory meatus. In brain imaging, the canthomeatal line is a conventional deliminator for the transaxial planes of the brain because of the identifiable external body landmarks.

Positron Emission Tomography Procedures

Explanation of Procedures by a Radiologist

Prior to the day of the PET procedure, each subject met with a radiologist in the PET Center to discuss the risks and benefits of exposure to radiation and to determine whether a pregnancy test was necessary. Two subjects had pregnancy tests on the day before the procedure. The results were negative. The third subject was determined not to need the test because she had undergone a tubal ligation two years previously.

Positioning of the Subject in the Scanner

On the day of the PET procedure, several steps were undertaken prior to the actual PET scans. In preparation for the scans, the subject lay on the scanner bed and adjustments were made with pillows to make her as comfortable as possible. The subject's head was positioned in the foam cushioned headholder of the scanner.

Before the PET scan procedure, a face mask/head holder was made for each subject. This device was intended to help the subject maintain a head position during a possible two hour experimental session. An

occupational therapist from the UTMCK assisted in the fabrication of the face mask. The mask was constructed of plastic material, a type used in the Occupational Therapy Department for splints (e.g. Ezeform, Smith & Nephew Rollyan, Inc.). It fit over the subject's upper face from the forehead to the tip of the nose, with open holes over the eye areas. An individual template for the mask was made for each subject and the basic mask was constructed prior to the day of the PET scan. The final fitting of the mask was done just prior to the scan to ensure a correct fit. This involved softening the material in warm water to a temperature that was comfortable to the subject. The material was then molded to the subject's face and allowed to cool and harden for approximately two minutes. Velcro straps were attached to the mask which would then be attached to the head holder of the PET scanner. A more detailed description of the procedure is contained in Appendix E. While the subject was lying on the scanner bed, the final adjustments were made to the face mask. The nuclear medicine technologist in charge of the procedure adjusted the mask and the position of the head in the holder according to specifications of the UTMCK PET Scanning Protocol (Appendix F).

Placement of Insert Earphones

For presentation of the stimuli E.A.RTONE 3A Insert earphones were connected to a Sony APR - 2003 reel to reel tape recorder. The intensity level of the stimuli was calibrated with a Bruel and Kjaer (B & K) Sound Level Meter, model 2209. For calibration, the tubing of the earphone was connected to a 2 cc coupler attached to the Sound Level Meter. The signal was played from the tape recorder, through the earphones, and measured with the Sound Level Meter. The intensity of the signal was adjusted with the monitor volume control knob of the tape recorder. A difference of approximately 2 dB was found in the presentation level for the first subject between the initial calibration and the first presentation of the stimuli. Most likely, this was due to

the tape recorder's being moved around during the preparation of the subject after the initial calibration was completed. Therefore, the levels were recalibrated for each condition to ensure that the stimuli were presented at the same level in both conditions. In one other instance the levels changed between the initial calibration and the presentation of the stimuli. The difference was not greater than 2 dB and was corrected at the time.

For the study, the insert earphone was placed in the subject's right ear and connected to the tape recorder. The left ear was occluded with a soft foam earplug (E.A.R Group Noise Filter, Cabot Corporation). To establish the comfortable listening levels, each subject listened to an audio tape recording of a list of all the stimuli presented to the right ear. The levels had been established originally to be approximately 70 dB SPL which was acceptable to Subject 1 and 3. Subject 2 requested that the level be increased by 2 dB. Equipment noise within the gantry of the PET scanner where the subjects heads would lie during the procedure was determined to be approximately 65 dB SPL (B & K Sound Level Meter, Model 2209). The design of the earphone and earplug, however, provided an excess of 30 dB attenuation of background noise in the speech frequencies, according to the manufacturer's specifications. Therefore, the attenuation of the background noise was assumed to be sufficient for the study because each subject had established her own comfortable listening level, with her ears occluded against the background noise, while listening to the stimuli. In addition, to assure that each of the stimuli was identifiable to the subject in the presence of the gantry noise, Subjects 1 and 3 silently read a printed list of the stimuli during the presentation of the calibration tape. The subjects reported that the stimuli were easily recognizable. This list was not available for Subject 2 because the investigator inadvertently neglected to bring it to the session. Nevertheless, Subject 2 reported that the stimuli were

easily recognizable without the printed list. The visual list was not presented to the subjects during the actual stimulation conditions.

Establishment of the Intravenous Line

An intravenous line was established by a nurse for each subject to allow for the injection of the radioisotope, in the right arm for Subjects 1 and 3 and the left for Subject 2. Subject 2 reported that her right arm was sore from having blood drawn the previous day for the pregnancy test and requested the IV be placed in her left arm. After the preparations were completed, the subject's eyes were closed and covered with a cloth and the room was quiet and darkened.

Instructions to the Subjects

Before the scanning procedures began, the subjects were instructed to remain alert, relaxed, and cautioned not to move during the transmission scan and the subsequent cerebral blood flow studies. Further responses were not requested of the subjects in order to avoid confounding the effects of the stimuli with effects of specific mental or behavioral activity. The subjects were requested, however, to maintain their head positions and to limit talking or any other physical movement between the scans. The subjects were informed they would be alerted a minute or two before a scan was to start by a pat on the leg as a reminder to cease movement and that they would be told when the scan was completed. Between the actual scans, the investigator did talk briefly with each subject, informing her about the amount of time until the next scan and inquiring about the subject's comfort. In general, the subjects' responses were short one or two word replies. The subjects indicated being sufficiently comfortable to continue with the study. No further interaction was expected to occur, nor did occur, between the investigator and the subjects during the procedure. Instructions to the subject are contained in Appendix G.

Scanning Procedures

Transmission scan. An initial 15 minute transmission scan for individual attenuation correction was performed with a ring source activity containing ^{68}Ge. This procedure corrects for the number of photons in the PET scan that are deflected or absorbed as they pass through the structures of the head and is necessary for the reconstruction of the PET images for each subject in order to avoid image distortions (Sorenson & Phelps, 1987).

PET scans. Dynamic PET scans were performed for each subject. Data were recorded simultaneously for 15 tomographic slices, parallel to the canthomeatal line, with a separation of 7 mm and an in plane resolution of 6.5 mm. The scans were begun at the time of an intravenous bolus injection of saline containing 60-70 mCi of ^{15}O water. The estimated radiation dose was to be no more than 0.1 rads per study with a cumulative dose of 0.5 rads which is comparable to less than two and a half times the natural background radiation in the Knoxville/Oak Ridge area. These radiation doses are well within the limits permitted by the National Council of Radiation Protection (NCRP) and were approved by the Isotope Committee of UTMCK. Dosimetry is the measurement of the amount of radiation to which a person has been exposed. Dosimetry constraints prohibited exposure of the subjects to a greater amount of radioactivity for this serial study.

Images were acquired over a 120 s time period. Previous investigations in which CBF has been studies with ^{15}O have used a 40 s data collection time. In those studies, however, either the amount of radioactivity per injections was greater (e.g. 55-80 mCi, Lauter et al., 1985) than that of this study or the activity of several subjects was averaged together to increase the signal to noise ratio (Petersen et. al, 1988; Perlmutter, Herscovitch, Powers, Fox, & Raichle, 1985). A two minute time frame has been suggested, however, for data collection on single subjects as a way to attain an optimal signal-to-noise (S/N)

ratio (Kanno, Iida, Muira, and Murakami, 1991). Kanno et al. reported that the gain in S/N of a 120 s over 40 s scan time corresponds to an 80% increase in the number of trials to reach the same S/N ratio.

As originally proposed, each subject was to undergo five cerebral blood flow studies: an initial resting baseline scan with no stimulation, an activation scan with auditory stimulation, another baseline scan, a second activation scan with auditory stimulation, and a final baseline scan, all with a 10-15 minute inter-scan interval. Only Subject 1 received all five PET scans, however. In a preliminary analysis of the results of Subject 1's scans, the overall activation of the second baseline was greater than that of the second activation scan. Therefore, the decision was made to increase the time between the first activation and the second baseline scan to 30 minutes to allow more time for the effects of the activation to diminish before the second activation scan. In order to increase the time between scans and not increase the overall time of the experiment, the final baseline scan for the subsequent subjects was omitted.

During the stimulation conditions, the presentation of the auditory stimuli was initiated 1 min prior to administration of the isotope and continued throughout the 2 min scan. The stimuli were presented before the injection to ensure that the scan would capture ongoing activity in the brain. At end of the scan the presentation was terminated. As previously described, the stimuli were presented at the rate of one per 1.6 s at a comfortable listening level, in the right ear, through insertion earphones connected to an audio recorder.

The order of presentation of the stimuli was counterbalanced in an effort to control for an order effect. To avoid confounding the results of the study by any effects of presenting the stimuli in the same order, Subjects 1 and 2 received meaningless auditory stimuli in the initial activation scan and meaningful auditory stimuli in the second activation

scan. The order was reversed for the Subject 3. The subjects were not told in which order the stimuli would be presented.

The PET scanning procedure was anticipated to take approximately 2-1/2 h for each subject, including 30-40 min for preparation and 1-3/4 h on the scanner bed. The first subject's time on the scanner bed was increased by about 1/2 h due to technical difficulties with the scanner. The procedures for the other two subjects were accomplished within the expected time frame.

The subjects were interviewed after the scans regarding the nature of any discomfort they might have experienced. Although no subject reported experiencing enough discomfort to necessitate terminating the scanning procedure, each subject indicated some discomfort from the site of the I.V.; Subject 1 and 2 reported bladder discomfort; and Subject 3 reported that her back had bothered her during the entire procedure.

Image Preparation Procedures

The data for the 2 min acquisition time of each dynamic PET scan were reconstructed by the Siemens ECAT software into images consisting of 12, 10 s time frames for each of the 15 transaxial planes scanned. Each time frame represented the integrated activity for that 10 s period.

Creation of Summed Images

The levels of activity in the blood fluctuated during the acquisition time according to the rate of injection of the radioisotope and the amount of radioactivity present in the injection. Although each subject was to receive 60 mCi of ^{15}O for each scan, the actual counts varied slightly for each injection. Subject 1 received five 70 mCi injections, whereas Subjects 2 and 3 received four 60 mCi injections. In order to determine the patterns of activity of each scan, time/activity curves (the amount of activity over the 120 s period) were plotted for the blood pools of each study. These curves represented the activity detected for an ROI traced around the carotid artery area, on

the side of the injection, for all the frames of each of the four scans. The ROI corresponding to the carotid artery was identified by a radiologist in the PET Center in frame 2, plane 14 of the first baseline dynamic PET scan for each subject.

To determine the reliability of the time activity curves for the blood pool data, averaged blood pool time/activity curves were generated. For Subject 1 the averaged activity in left and right carotid artery ROIs in two adjacent planes was plotted over time. For Subjects 2 and 3, the activity in three adjacent left and right carotid ROIs were averaged and plotted over time. Both sets of time/activity curves for each subject are contained in Figure 2 a, b, c. From visual comparison of the two time activity curves for each subject, it appears that both sets of curves are sufficiently similar to consider the first set to be a reliable measure of the blood pool activity for each subject.

The amount, the slopes, and the time of the peak activity of each curve varied among the scans for each subject. The concern, therefore, was to avoid attributing changes in brain activation to the stimulation conditions which instead were due to variations related to the injection of the radioisotope. For each subject, five consecutive 10 s time frames that represented relatively flat portions of the 120 s time/activity curves for each scan were selected for data analysis. A composite image of these five frames of the 15 planes were summed by the ImageCalc program of Imagetool (CTI, Knoxville, TN). The resultant images consisted of a single summed frame, representing integrated activity over 50 s, for each of the 15 brain planes. Table 10 contains a summary for each subject of the selected frames for analysis.

Selection of Regions of Interest

The ROIs to be analyzed were based on 1) the results of studies of localization of response to auditory stimuli with PET, SPECT and nontomographic rCBF and 2) the results of studies of the effects of

brain damage on language comprehension. As noted in the literature review, the areas identified with increased rCBF or metabolism in response to auditory stimulation in many of the brain imaging studies were not clearly identifiable because of the confounding effects of the complexity of the experimental designs. The overall results of these investigations, however, indicate greater left than right hemisphere activation in the temporoparietal regions for meaningful auditory stimuli (Knopman et al., 1980; Maximillian, 1982; Nishizawa et al., 1982; Bartlett et al., 1987; Petersen, et al., 1988). Discrete meaningless auditory stimuli have been shown to activate the primary auditory cortex (Lauter et al., 1985). With increased acoustical complexity, cerebral activity widens (Knopman, et al., 1980; Lauter et al., 1988). In some studies, greater right than left activation occurred for meaningless auditory stimulation (Roland et al., 1981; Mazziotta et al., 1982). Some changes in cerebral activation were attributed to the nature of the task rather than to the stimuli (Knopman et al., 1982; Mazziotta et al., 1982). Frontal and right hemisphere activation was attributed to attention factors (Walker-Batson et al., 1988; Lechevalier et al., 1989).

The subcortical structures associated with auditory processing which could be expected to be identified with PET include the inferior colliculus (IC) at the level of the midbrain, and the medial geniculate body (MGB) and the pulvinar in the thalamus (DeArmond, Fusco, & Dewey, 1989; Harrison & Hunter-Duvar, 1989). Lauter et al. (1988) identified subcortical activation with PET in the IC and a combination of the MGB and pulvinar in response to passive listening to synthetic CV syllables.

The cortical areas of the left hemisphere associated with comprehension of speech and language have been identified from the results of studies correlating the effects of cerebral lesions and speech and language deficits (Naeser & Hayward, 1978; Basso, Lecours, Moraschini, & Vanier, 1985; Gelbert, Bergvall, Salamon, Sobel, Jiddane,

Corbaz, & Morel, 1986). Lesions in the temporoparietal areas, also known as the perisylvian region, have been implicated in disorders of comprehension. Typically, Wernicke aphasia is the aphasia syndrome most likely characterized by deficits in auditory comprehension, with paraphasia and paragrammatism in spontaneous speech, as well. For this disorder, lesions have been identified in the dominant posterior temporal region which involve parts of Brodman's area 22, located posterior to the primary auditory cortices (areas 41 and 42). Lesions also may extend into the angular gyrus (area 39) and the supramarginal gyrus (area 40). In some cases the lesions remain solely in the temporal lobe itself including areas 20, 21, and the lateral surface of area 37 (Naeser & Hayward, 1978; Damasio, 1989). Kirschner, Casey, Henson, & Heinrich (1989) identified severe auditory comprehension deficits in Wernicke aphasia subjects associated with large infarcts of the superior temporal gyrus that extended into adjacent areas of either or both the frontal and parietal lobes with considerable extension in the temporal lobe, as well. Lesions in subcortical areas associated with comprehension deficits have involved posterior structures and pathways such as the thalamus, temporal isthmus, and corpus callosum (Metter, Wasterlain, Kuhl, Hanson, & Phelps, 1981; Graff-Radford & Damasio, 1984; Alexander & Naeser, 1988).

Based on these findings of previous brain imaging studies and investigations of the comprehension deficits of aphasic patients, the ROIs to be studied were located in the perisylvian areas of both hemispheres and included the primary auditory cortex (PAC), the superior temporal lobe (STC), the angular gyrus (AG), and the supramarginal gyrus (SMG). Posterior subcortical midbrain and thalamic ROIs included the inferior colliculus (IC), medial geniculate body (MGB), and the pulvinar (PUL). Additional bilateral ROIs to evaluate were the superior frontal gyrus (SFG), the inferior frontal areas (Broca's area, BA), the anterior cingulate cortex (ACC), the occipital lobes (OCC), the middle temporal

cortex (MTC), and the inferior temporal cortex (ITC) of the left hemisphere (sometimes involved in aphasic comprehension deficits). A single ROI was created for the cerebellum (CER), reported activated in some imaging studies. The ROIs are contained in Table 11. The ROIs are represented in Figure 3 a,b,c. Figure 3.a shows the ROIs that can be located on the lateral view of the brain. Figure 3.b shows a transverse section of the brain parallel to the canthomeatal line where the anterior cingulate gyrus can be located. Figure 3.c shows the dorsal view of the brainstem and the subcortical ROIs for this study.

Procedures for Localization of Regions of Interest

As stated earlier, identification of ROIs based on the PET scans alone is problematic due to the spatial resolution of PET. A localization protocol was developed at the PET Center of UTMCK. According to this protocol, each subject had MRI scans to provide anatomical images of the brain. A visual registration between the MRI and PET images would then be performed to locate the regions to be studied in the PET scans. The necessary steps to achieve this goal will be described more fully in the following sections. Briefly, the first task was to zoom and interpolate the MRI and PET images for each subject to the same dimensions so that they could be overlaid. The interpolated transaxial images were then rotated to align with an anterior-posterior axis and the interpolated sagittal images were rotated to align with an axis through the internal capsule. A new set of transaxial MRI and PET images were then created for these interpolated and rotated sets of MRI and PET images. The offset between MRI and PET images was corrected by a radiologist in the PET Center. A neuroradiologist identified the selected ROIs on the new MRI images. These ROIs were then transferred to the PET images and the activity, in ECAT counts, was computed for each ROI with the Imagetool (CTI, Knoxville, TN) software.

Interpolation of the MRI and PET images. A protocol for modification of the PET and MRI images so that they could be overlaid

was established and implemented in the Image Processing Lab of the PET Center at the UTMCK (H. Bond, personal communication, 1991). Initially, the MRI and PET images had different pixel sizes, plane widths, and distances between the planes. In a series of steps that are described in Appendix H, the MRI images were converted to the same format as the PET images and the PET images, in turn, were modified to be consistent with the modified MRI images. The resultant images could be reconstructed as transaxial, sagittal, or coronal views.

The following description is a synopsis of the protocol for the modification of the MRI and PET images contained in Appendix H. Basically, the MRI images were converted to the same format as the PET images to be compatible with the CTI software. The original MRI images consisted of 15 transaxial images, in a 256 x 256 pixel matrix with a pixel size of 0.94 mm. The planes were 5 mm thick with a 2 mm gap between the planes. The images were zoomed to a pixel size of 1 mm, resulting in images of 240 x 240 pixels. Images then were expanded to their original 256 x 256 matrix by padding (the addition of null bytes at the edges). The zoomed images were then interpolated to 78 planes with a 1 mm separation between adjacent planes giving cubic volume elements, or voxels.

The original PET images consisted of a 128 x 128 pixel matrix with a pixel size of 2.35 mm. The frame of images held 15 planes with a distance between planes of 6.75 mm. These images were zoomed to a pixel size of 1 mm, resulting in an image size of 300 x 300 pixels. The images were cropped to a 256 x 256 matrix by removing strips of pixels from all four edges of the image. These zoomed images were interpolated to 100 slices with a 1 mm separation between adjacent planes, also yielding cubic voxels.

Correction of the orientation of the images. The PET and MRI scans were done with the subject's head in approximately the same position in both sets of scans, with the transaxial images parallel to

the canthomeatal line. The resulting images, however, had slightly different orientations because of the difficulty in positioning the head in exactly the same position for both scanning situations. Therefore, the images had to be reoriented so that the planes could be matched. This was accomplished with the Neurotool software program (CTI, Knoxville, TN). First, the interpolated transaxial MRI and PET images were aligned to an anterior-posterior midline axis. A line was drawn with the computer software along the midline of the transaxial image, corresponding to the longitudinal cerebral fissure, from the frontal lobes to the occipital lobes. The computer software program then rotated the midline of the transaxial image to the midline of the viewing box of the computer. In this way all the transaxial images were aligned to the same midline. Next, the sagittal images of the scans were aligned to an anterior-posterior axis identified as crossing midway through the lateral ventricles. This landmark was identified by a radiologist in the PET Center. Figures 4.a and 4.b show simulated and completed transaxial and sagittal rotations of the MRI images. Figures 5.a and 5.b show the simulated and completed rotations for the PET images. A new set of images were then created for the corrected interpolated PET and MRI scans with the Neurotool software.

Correction of the offset of the PET and MRI images. The interpolated PET and MRI images had the same pixel matrix size and plane thickness but had a different number of interpolated planes. Because of differences in thickness and interplane distances in the original images, the PET images were interpolated to 100 planes and the MRI images to 78 planes. Therefore, it was necessary to correct for the offset of the images, to determine which planes of the MRI scan corresponded to comparable planes of the PET scans. A radiologist in the PET Center corrected the offset for each subject by visually matching the cerebral and cerebellar contours between the PET and MRI images. No attempt was made to match the images statistically. For

Subject 1 the MRI planes were five planes higher than the PET planes; for example, the superior frontal gyrus ROI was located on plane #15 of the MRI scan and on plane #10 on the PET scan. For Subject 2 the MRI planes were 8 planes higher than the PET plane. For Subject 3 the MRI planes were 10 planes higher than the PET planes. As an example, Figure 6 shows the alignment of MRI planes 51 through 54 with PET planes 41 through 44 for Subject 3.

Identification of regions of interest. A neuroradiologist from the Department of Radiology, UTMCK, located the ROIs on the 78 newly configured transaxial MRI images. Two atlases of the brain were selected as references for ROI identifications, An Atlas of the Human Brain for Computerized Tomography (Matsui & Hirano, 1978) and Structure of the Human Brain: A Photographic Atlas, Third Edition (DeArmond, Fusco, & Dewey, 1989). The atlas of Matsui and Hirano depicted brain sections at various angles from the canthomeatal line. The MRI images for this study appeared to align best with the 0 degree sections, or parallel to the canthomeatal line, as had been intended at the times of the scans.

Because the neuroradiologist was unfamiliar with the software that was being used to analyze the data, he found drawing the ROIs with the computer mouse somewhat cumbersome. Therefore, hard copies from the transaxial computer images were made on x-ray film of the 78 planes of each subject's MRI images so the ROI boundaries could be drawn with a marking pen. The MRI images were then viewed at a light box for ROI identification. Using the atlases as reference, the neuroradiologist selected planes that he identified as containing a good exemplar of the ROI. In most cases the ROI could be found in several consecutive planes. He then drew a boundary around the ROI with a marking pen.

Transfer of the ROIs to the MRI computer images. The investigator copied each ROI from the hard copy to the MRI computer image, using the Imagetool program and the computer mouse to redraw the boundaries. The

computer images were enlarged to twice their size so that the anatomic landmarks could be more easily identified.

To test the reproducibility of the process of copying the ROIs from one MRI image to another, the investigator created ten ROIs of different sizes and shapes on one MRI plane and then redrew the ROIs with the computer mouse to another MRI plane. The differences in total pixel counts and the percent error was computed for each set of ROIs. The percent error was computed by dividing the difference in the number of pixels between the two ROIs by the sum of the number of pixels in each ROI and multiplying that number by 100 ((x-y)/(x+y)*100). Table 12 contains the pixel differences and the percent error between the first ROIs to the redrawn ROIs. The percent error range was from 3.3% to 15.7%. Because the procedures were developed for this study, no previous reproducibility data are available for comparison.

Transfer of the ROIs to the PET images. Next, the investigator transferred the ROIs from the MRI images to the transaxial images on the comparable PET planes which had also been enlarged to twice their original size. Although every effort had been made to match MRI and PET planes, some discrepancies existed. In some cases, because the MRI and PET planes were not located in exactly the same x,y coordinates, a one to one transfer of MRI ROIs to the PET images was not feasible. Therefore, to accomplish the transfer, a trace ROI that also included the selected ROI was made around the entire transaxial MRI image. This transaxial trace ROI, which included all the smaller ROIs located in that plane, was saved in the computer and then transferred to the appropriate transaxial PET plane. The trace ROI acted as a template for locating the smaller ROIs in the PET image. The edges of the MRI trace ROI were matched to the edges of the PET image within which the small ROIs then could be moved. The procedure was done for each plane containing ROIs of the four PET studies for each subject. This process is depicted in Figures 7 a,b and 8 a,b. Figure 7a shows four ROIs (the

larger bilateral superior temporal gyrus and the smaller primary auditory cortex) drawn on the MRI. Figure 7b shows the trace ROI drawn around the edges of the image and the four ROIs. Figure 8a shows the trace ROI and the four ROIs transferred and adjusted to the edges of the PET image. Lastly, Figure 8b shows the four ROIs located on the PET image. the ROIs.

To test the reproducibility of the process of transferring ROIs from the MRI to the PET images, the investigator copied 15 ROIs from the MRI to the PET images and calculated the percent error, as previously described, in total pixel counts from the original placement of the ROI to the second placement of the ROI. (Table 13). The percent error range was from 0.0% to 2.2%. As noted above, because the procedures were developed for this study, no previous reproducibility data are available for comparison.

Acquisition of the Data

The ECAT counts per pixel per second were generated from the ROI entries and computed by the Imagetool software for each subject's PET scans. The data for each subject, including the number of pixels, ROI average, and percent standard deviation, are contained in Table 14. This table also contains the corrected data described in the next section.

Normalization of the Data

For each subject, the global level of CBF varied for the four conditions, resting baseline, first activation, second baseline, and second activation. Therefore, before analysis of the data was possible, the data were normalized for each subject so that changes in activity in the selected ROIs of the four scans could be compared. The overall ^{15}O activity for all planes, obtained by taking the mean ECAT counts of the transaxial images in the planes in which the selected ROIs were located, are contained in Table 15. The ROIs for Subject 1 and 3 were located in 10 planes, for those for Subject 2 in 11 planes. As can be seen in this

table, the overall ^{15}O activity differed among the scans for each subject.

The two activation scans and the second baseline scan were normalized to the initial baseline scan for each subject according to the following procedure. An example of the procedure will then be presented. First, a ROI in the shape of an ellipse was placed around the transaxial image in any planes of the initial baseline study in which one or more of the ROIs to be studied were located (e.g. for Subject 1, the ROI identified as superior frontal gyrus was located in Plane #10). The shape of the ellipse could be adjusted to approximate closely the shape of the transaxial image. The activity was then computed for the transaxial ROIs in the selected planes of the baseline scan and those located in comparable planes in the subsequent three scans for each subject. Next, the factors to correct the activity in the second, third, and fourth scan to the initial baseline were computed. These correction factors were derived by dividing the total activity in the selected transaxial ROIs for these three scans by the activity from the comparable transaxial ROI in the baseline scan. The values for the transaxial ROIs and the correction factors for the normalization to baseline are contained in Table 16 a,b,c. Finally, the correction factors for each transaxial ROI were applied to the individual ROIs that were located in that plane by dividing the computed activity in the ROI by the correction factor of that plane. For example, to normalize the activity for the ROI identified as the superior frontal gyrus (SFG) of Subject 1, first an elliptical ROI was adjusted around the transaxial image in Plane #10 of the baseline scan. The computed activity in this ROI for Plane #10, in ECAT counts, for the first baseline, the first activation, the second baseline, and the second activation was 1.05, 1.09, 1.04, and 0.99, respectively. The correction factors for Plane #10 were computed by dividing the ECAT counts of first activation (1.09), the second baseline (1.04), and

second activation (0.99) by the ECAT count of the first baseline (1.05). Thus, the correction factors for ROIs located on Plane #10 for Subject 1 were 1.04, 0.99, and 0.94 for the first activation, the second baseline, and the second activation, respectively. Finally, the counts for the SFG ROIs in the first activation, the second baseline, and the second activation were normalized to the first baseline condition; the left and right SFG ROIs in the first activation were divided by 1.04, in the second baseline by 0.99, and in the second activation by 0.94. The normalized data for each subject for the fourteen ROIs, for the right and left hemispheres, in each condition are presented, as mean ECAT counts, in the Table 17 a,b,c for Subject 1, Subject 2, and Subject 3, respectively.

CHAPTER III. RESULTS

Analysis of the Data

As originally stated, the purpose of this study was to determine whether there was a significant difference in the amount of regional cerebral blood flow (rCBF) as measured by PET for specific intra- and inter-hemispheric regions of interest (ROIs) during the presentation of meaningless and meaningful auditory stimuli matched for acoustic parameters. Because of the small number of subjects, this study was considered as a series of single subject experiments. Each subject acted as her own control.

Before the data were analyzed it was necessary to determine whether the stimuli were adequate to activate changes in CBF. These procedures will be described in the following section.

Determination of Stimuli Adequacy

Prior to any statistical analysis of the data, the activity in the subcortical and primary auditory cortex ROIs was examined to determine whether the acoustic properties of the CVC stimuli, irrespective of their meaningfulness or meaninglessness, were sufficient to produce detectable changes in CBF in the auditory system (J. Lauter, personal communication, 1992). The right ear presentation of the complex auditory signal was expected to elicit a shift in any asymmetry of resting baseline CBF to the direction of the left hemisphere in these structures (Lauter et al., 1988). To this end, percent differences were calculated between the left and right ROIS for the inferior colliculus, medial geniculate body, pulvinar, and primary auditory cortex in all conditions. The percent differences were obtained in the following way: the activation in the right ROI was subtracted from that in the left; this was divided by the sum of the activation in the left ROI plus that in the right; the result was then multiplied by 100 [(x-y)/(x+y)*100] (Lauter et al., 1990). For the inferior colliculus, the pulvinar, and the medial geniculate body no clear pattern of shift of symmetry was

demonstrated among the subjects. For the primary auditory cortex ROIs, however, a clear shift was noted towards the left from baseline to the first activation, irrespective of the meaningless or meaningful content of the stimuli, in all three subjects. Figure 9 represents the shifts in symmetry noted in the primary auditory cortex for the three subjects. Although the shift in symmetry was less robust for Subject 2, the initial response to auditory stimulation at the level of the primary auditory cortex was taken to mean that the CVC stimuli were adequate to activate the auditory system.

The ambiguous results for the subcortical ROIs may be related to the following two factors. These small ROIs were difficult to identify in the MRI and, therefore, may not have been transferred accurately to the PET scans. The total pixel counts for these areas were notably smaller than for most other ROIs. In addition, located well within the transaxial image, these subcortical areas were associated with less easily identifiable landmarks, such as sulci and image edges, than were most of the other ROIs. For these reasons, the subcortical ROIs were eliminated from the statistical analysis. An additional factor to note was the necessity to eliminate two other areas from the analysis. When the PET images were rotated for registration with the MRI images, the areas identified as the supramarginal gyrus and the angular gyrus on the MRI scans were partially cut out of the PET images. Because the entire ROI was not available, the remainder was considered to be insufficient for analysis. Therefore, analysis was performed on nine of the original 14 ROIs for each subject in each condition.

Statistical Analysis

Correlated t-Tests (for related measures) were done for each subject to determine whether there were significant inter- and intra-hemispheric differences in CBF between any of the conditions in the study: the first resting baseline, the first activation, the second resting baseline, and the second activation. The data for the analyses

consisted of the mean ECAT counts of the nine ROIs for each condition. The reader is asked to recall that with PET the radioisotope activity detected in each ROI is represented by the mean ECAT counts per pixel per second, referred to as ECAT counts in this study.

The small number of subjects (n = 3) in the study precluded statistical analysis of the individual ROIs. The contribution of individual ROIs was addressed in a descriptive post hoc analysis, however.

The order of presentation of the stimuli was counterbalanced in an attempt to control for an order effect. The order of presentation of the meaningless and meaningful stimuli was as follows: for Subject 1 and Subject 2, the meaningless stimuli were presented in the first activation and the meaningful stimuli in the second activation; for Subject 3 the order was reversed so that the meaningful stimuli were presented in the first activation and the meaningless stimuli were presented in the second activation.

Four sets of analyses were done for each subject's data sets. The first analyses were made for the baseline data to determine the activity of the baseline conditions before examining the results of the activation conditions. The second set of analyses compared the activation conditions to the preceding baseline conditions to determine whether the auditory stimuli effected any detectable changes in mean baseline activity. Finally, the third and fourth sets of analyses were done to answer the questions posed in the study, whether there were significant differences in the amount of CBF for specific intra- and inter-hemispheric ROIs during the presentation of meaningless and meaningful auditory stimuli matched for acoustic parameters.

Differences Between Baselines

For all subjects the results of the following t-Tests revealed that there were no significant differences in mean ECAT counts of the ROIs among the baselines themselves. The following sections contain the

results for the intra- and inter-hemisphere comparisons.

Intra-hemispheric comparisons. In the left hemisphere, no significant differences were found between the mean ECAT counts of the ROIs in the first resting baselines and the second resting baselines of all the subjects (Subject 1, $t = 0.38$, $df = 8$, $p>0.05$; Subject 2, $t = 0.57$, $df = 8$, $p>0.05$; Subject 3, $t = 0.16$, $df = 8$, $p>0.05$). Similarly, for the right hemisphere no significant differences were found in mean ECAT counts of the ROIs between the first and second resting baselines of the subjects (Subject 1, $t = 0.44$, $df = 8$, $p>0.05$; Subject 2, $t = 0.82$, $df = 8$, $p>0.05$; Subject 3, $t = 2.12$, $df = 8$, $p>0.05$).

Inter-hemisphere comparisons. No significant differences in the mean ECAT counts of the ROIs were found between the left and right hemispheres in the first resting baselines of all the subjects (Subject 1, $t = 0.83$, $df = 8$, $p>0.05$; Subject 2, $t = 1.04$, $df = 8$, $p>0.05$; Subject 3, $t = 1.75$, $df = 8$, $p>0.05$) or in the mean ECAT counts of the ROIs between the left and right hemisphere in the second resting baselines of all the subjects (Subject 1, $t = 1.18$, $df = 8$, $p>0.05$; Subject 2, $t = 1.45$, $df = 8$, $p>0.05$; Subject 3, $t = 1.13$, $df = 8$, $p>0.05$).

Differences Between Activation and Baseline Conditions

Comparisons were made between the mean ECAT counts in the ROIs between the activation conditions and the baseline conditions for each subject. For each subject intra-hemisphere comparisons were made between the meaningless auditory stimuli condition and the preceding baseline condition and between the meaningful auditory stimuli condition and its preceding baseline condition. Recall that the order of presentation of the stimuli was counterbalanced between the subjects. The meaningless auditory stimuli were presented in the first activation for Subjects 1 and 2 and in the second activation for Subject 3. The meaningful auditory stimuli were presented in the second activation

condition for Subjects 1 and 2 and in the first activation condition for Subject 3.

Meaningless activation condition and resting baseline. For left hemisphere comparisons, for all three subjects there were no significant differences between the meaningless auditory stimuli conditions and in the resting baselines (Subject 1, $t = 0.88$, $df = 8$, $p>0.05$; Subject 2, $t = 0.22$, $df = 8$, $p>0.05$; Subject 3, $t = 0.32$, $df = 8$, $p>0.05$).

For the right hemisphere comparisons, no significant differences were found between the meaningless auditory stimuli conditions and the resting baseline conditions for Subject 1 ($t = 0.03$, $df = 8$, $p>0.05$) or Subject 2 ($t = 2.15$, $df = 8$, $p>0.05$). For Subject 3, however, the meaningless auditory stimuli, presented in the second activation condition, elicited significantly greater activity than was present in the second baseline condition ($t = 3.15$, $df = 8$, $p<0.05$).

Meaningful activation condition and baseline. For the left hemisphere, for all three subjects, no significant differences were found between the meaningful auditory stimuli conditions and the baseline conditions (Subject 1, $t = 1.06$, $df = 8$, $p>0.05$; Subject 2, $t = 0.48$, $df = 8$, $p>0.05$; Subject 3, $t = 0.25$, $df = 8$, $p>0.05$).

In the right hemisphere, no significant differences were found between the meaningful auditory stimuli conditions and the baseline conditions for Subject 1 ($t = 1.60$, $df = 8$, $p>0.05$) or Subject 2 ($t = 0.19$, $df = 8$, $p>0.05$). For Subject 3, however, the mean of the ECAT counts in the initial baseline condition was significantly greater than that in the meaningful auditory stimuli condition, presented in the first activation condition, ($t = 2.63$, $df = 8$, $p<0.05$).

Intra-Hemisphere Differences Between Meaningless and Meaningful Stimuli

The effects of meaningless and meaningful auditory stimuli were examined in both the left and right hemisphere for each subject. The results are described in the following section.

Left hemisphere. The effects of meaningless and meaningful

auditory stimulation conditions were compared in the left hemisphere of each subject. No significant differences in mean ECAT counts were found between the effects of meaningless or meaningful auditory stimuli in the left hemisphere for any of the three subjects (Subject 1, $t = 0.44$, $df = 8$, $p>0.05$; Subject 2, $t = 0.29$, $df = 8$, $p>0.05$; Subject 3, $t = 0.13$, $df = 8$, $p>0.05$).

Right hemisphere. A similar comparison was made for the right hemisphere between the effects of the meaningless and meaningful auditory stimuli. No significant differences in mean ECAT counts were found between these conditions for Subject 1 ($t = 1.45$, $df = 8$, $p>0.05$) or Subject 2 ($t = 1.52$, $df = 8$, $p>0.05$). For Subject 3, the mean activity elicited by meaningless auditory stimuli was found to be significantly greater than the mean activity elicited by meaningful auditory stimuli ($t = 4.22$, $df = 8$, $p<0.01$). For this subject the meaningless auditory stimuli were presented in the second activation condition and the meaningful auditory stimuli were presented in the first activation condition. The order of presentation was reversed for Subjects 1 and 2.

Inter-Hemisphere Differences for Meaningless and Meaningful Stimuli

Possible hemispheric asymmetries in mean ECAT counts for the ROIs were examined for both the meaningless and for meaningful auditory stimuli. The results of the t-Tests revealed that no statistical inter-hemisphere differences were found for the meaningless auditory stimuli or for the meaningful auditory stimuli. The results of these analyses are in the following sections.

Meaningless auditory stimuli. For each subject, the mean activity in the ROIs was compared between the right and left hemispheres for the condition in which meaningless auditory stimuli were presented. No significant differences were found for all three subjects (Subject 1, $t = 2.29$, $df = 8$, $p>0.05$; Subject 2, $t = 0.59$, $df = 8$, $p>0.05$; Subject 3, $t = 0.96$, $df = 8$, $p>0.05$).

Meaningful auditory stimuli. For each subject, the mean activity in the ROIs was compared between the right and left hemispheres for the condition in which meaningful auditory stimuli were presented. No significant differences were found for all three subjects (Subject 1, $t = 1.90$, $df = 8$, $p>0.05$; Subject 2, $t = 0.23$, $df = 8$, $p>0.05$; Subject 3, $t = 0.84$, $df = 8$, $p>0.05$).

Post hoc Analyses

Analysis of ROIs. The data for Subject 3 were examined to determine which ROIs contributed to the three instances of significant differences found in the t-Tests: 1) the meaningless auditory stimuli elicited significantly greater activity than the preceding baseline condition in the right hemisphere; 2) the activity in the initial resting baseline was significantly greater than that elicited by the meaningful auditory stimuli in the first activation condition in the right hemisphere; 3) the meaningless auditory stimuli elicited significantly greater activity than the meaningful auditory stimuli in the right hemisphere.

In all three cases, although not statistically significant, the differences between the conditions appeared to be related to greater activity in the primary auditory cortex and the anterior cingulate gyrus ROIs, in which the differences in ECAT counts were twenty counts or greater. The standard deviations of raw data for all individual ROIs were examined. In only two instances for these comparisons, however, did the data points for the ROIs fall outside a range greater than one standard deviation of the other. The mean activity, in ECAT counts, of the primary auditory cortex ROI for the right hemisphere initial resting baseline (mean = 1.65, SD = 0.13) was one standard deviation greater than the same ROI in the first activation condition, for meaningful auditory stimuli (mean = 1.39, SD = 0.10). The mean activity of the primary auditory cortex ROI for the right hemisphere second activation condition, for meaningless auditory stimuli, (mean = 1.61, SD = 0.20)

was one standard deviation greater than the same ROI in the second resting baseline condition (mean = 1.21, SD = 0.20). Therefore, it appeared that the cumulative effect of the differences in CBF in the ROIs contributed to the significant differences between the conditions, and in only these two instances were there differences between specific ROIs themselves.

Analysis of original summed images to determine possible ROIs based on activity. Results of electrophysiological studies involving electrical stimulation of the cortex of the brain have underscored the difficulties in predicting human brain physiology based on human brain anatomy (Ojemann, 1983; Ojemann & Whitaker, 1979; Mateer, 1983; Mateer, Rappaport, & Polly, 1990; Penfield & Rasmussen, 1950). Whereas overall the areas related to language functions may be relatively uniform, studies have shown considerable variability among individual subjects (Mateer et al., 1990). As Mateer and her colleagues point out (1990), this may be related the individual differences in gross morphology (Rubens, Mahowald, & Hutton, 1976) and cytoarhitectonic patterns (Galabruda, Sanides, & Geshwind, 1978) of the human cortex. Additional factors such as gender, intelligence (Mateer et al., 1990), verbal ability (Ojemann & Whitaker, 1978), and prior experience (Ojemann, 1983) have been suggested as contributing to the individual differences found in the electrical stimulation studies.

In this investigation, the selection of ROIs was based on 1) the results of previous rCBF and metabolic brain imaging studies and 2) the results of studies of the effect of brain damage on auditory comprehension. The selected ROIs were first identified on the subject's MRI and then transferred to the PET images. The statistical analyses were performed on the activity computed for these ROIs.

The original PET images were re-examined in consideration of the the possible effects of individual variability on the accuracy of ROI identification. Several steps were attempted, therefore, to identify

visually ROIs based on activity patterns for each subject. First, the original dynamic images were examined by a neuroradiologist for possible increased activity in the perisylvian regions of the scans. These images proved to be insufficiently clear, due to background noise, for visual identification of areas of increased activity. Similarly, differences could not be determined visually between activity in the baseline and stimulation conditions from the 50 s summed images used in the study. An attempt was made to reduce the noise in the baseline images. For each subject, the original Baseline 1 and Baseline 2 images were summed and averaged, creating a new Averaged Baseline image. Subtraction images were then generated to determine whether areas of increased activity could be identified. The new Averaged Baseline was subtracted from each of the stimulation conditions and the stimulation conditions were subtracted from each other. From visual inspection of these images, no areas appeared to stand out markedly as having differences. Therefore, no new ROIs based on activity differences between the scans were developed. Examples of these processes are depicted in Figure 10. The first row shows the averaged baselines for planes 5 through 12. The second and third rows show the effects of stimulation with meaningless and meaningful CVCs, respectively, for these planes. The fourth and fifth rows show the subtraction images. Row four shows the results of subtraction of the averaged baseline from the meaningless condition. Row five shows the results of subtraction of the averaged baseline from the meaningful condition. The sixth row shows the results of subtraction of the meaningful condition from the meaningless condition.

Summary

In summary, a significant intra-hemisphere difference in CBF was found for one subject between the meaningless and meaningful auditory stimuli conditions. For Subject 3 the meaningless auditory stimuli elicited greater mean right hemisphere CBF than did the meaningful

auditory stimuli in that hemisphere. In addition, also for this subject, significantly greater mean right hemisphere CBF was found for the first resting baseline than for the meaningless auditory stimuli condition, and significantly greater mean right hemisphere CBF was found for the meaningless auditory stimuli condition than for the second resting baseline.

Two post hoc analyses were done. In the first, the post hoc examination of the data, although not statistically significant, revealed that in each of these instances the primary auditory cortex and the anterior cingulate gyrus ROIs in the right hemisphere appeared to contribute the most to these differences. No other significant intra- or inter-hemispheric differences were found between the meaningless or meaningful stimuli activation conditions, between the baselines themselves, or between the baseline conditions and the activation conditions for the three subjects. The second post hoc analysis was a visual analysis of the scans and the creation of subtraction images. This analysis failed to reveal additional ROIs based on activity patterns for any subject.

CHAPTER IV. DISCUSSION

Discussion of Results

Whereas previous investigators have reported differential responses in cerebral blood flow or cerebral metabolism to meaningless and meaningful auditory stimuli, the complexity of the research designs, and in particular the varying complexities of the auditory stimuli themselves, make direct comparison of the effects of meaningless and meaningful auditory stimuli problematic. The meaningful auditory stimuli in previous studies were not controlled for acoustic complexity; effects considered to be related to the meaning of the stimuli instead might have been related to the varying acoustic complexity of the stimuli. In addition, in studies directly comparing the effects of meaningless or meaningful auditory stimuli, investigators used entirely different stimuli (e.g., comparison of the effects tone patterns and discourse, Mazziotta et al., 1982). Therefore, in the present study, the meaningless and meaningful auditory stimuli were matched as closely as possible for acoustic parameters (overall duration, fundamental frequency contours, and overall intensity), phonemic content (consonant vowel consonant combinations of voiced and voiceless plosive consonants and acoustically related vowels), and a balance between the number of meaningless and the number of meaningful auditory stimuli presented to the subjects. To avoid any additional confounding effects related to task complexity (e.g., motor or cognitive responses), this study was designed as a passive listening task, in which no response was required of the subject. Therefore, direct comparison of the results of this study to those of other investigators must be tempered by consideration of the possible confounding factors of stimuli and task complexities of the previous investigations.

The research question asked in this study was whether there is a significant difference in the amount of cerebral blood flow as measured by PET for specific intra- and inter-hemispheric regions of interest

during the presentation of meaningless and meaningful auditory stimuli matched for acoustic parameters. To address this question, comparisons were made for each subject to determine whether there were: 1) intra-hemispheric differences between meaningless and meaningful auditory stimuli; 2) inter-hemispheric differences between meaningless and meaningful auditory stimuli; 3) intra- and inter-hemispheric differences between the baselines; and 4) intra-hemispheric differences between the activation and baseline conditions. A discussion and interpretation of the results of the t-Test for related measures of these comparisons are contained in the following sections. Unless otherwise noted all significance levels were at the 0.05 level of confidence.

Differences Between Baselines

As a precursor to analysis of the effects of the stimuli, the baseline data were examined to see if, in the resting conditions, any differences in mean ECAT counts of the ROIs would be found among the baselines themselves. Comparisons were made between the first and second baseline conditions in the left hemisphere and between the first and second baseline conditions in the right hemisphere (intra-hemisphere comparisons) and between the left and right hemispheres in the first resting baseline and between the left and right hemispheres in the second resting baseline condition (inter-hemisphere comparisons). No significant differences were found in any of these comparisons for any subjects.

Consistent with these findings, previous investigators also have reported no differences in overall hemispheric means in the resting state studies (Bartlett et al., 1987; Knopman et al., 1980; Knopman et al., 1982; Lassen and Roland, 1983; Lechevalier et al., 1987; Maximillian, 1982; Mazziotta et al., 1982; Nishizawa et al., 1982; Roland et al., 1981; Walker-Batson et al., 1988). A resting asymmetry to the right, however, was reported by Goldenberg et al. (1987) and

other investigators have reported resting asymmetries to the right for specific regions, in particular the prefrontal and temporal regions (Knopman et al., 1982; Lassen and Roland, 1983; Reivich et al., 1984).

Additionally, investigators have also reported bilateral increases in CBF during the resting state in the prefrontal and frontal areas (Knopman et al., 1980; Knopman et al., 1982; Lassen and Roland, 1983; Maximillian, 1982; Nishizawa et al., 1982). The inter- and intra-hemisphere differences reported in the literature were generally attributed to attention factors even in the absence of specific stimulation. In this study the small number of subjects precluded statistical analysis of possible asymmetries of the specific ROIs.

Differences Between Baseline and Activation Conditions

Intra-hemisphere comparisons of the activation conditions and the preceding resting baselines were done to determine whether the auditory stimuli effected any change in CBF over the baseline conditions. The reader is asked to recall that the order of stimuli presentation was counterbalanced. For Subjects 1 and 2 the meaningless auditory stimuli were presented in the first activation condition and the meaningful auditory stimuli were presented in the second activation condition; for Subject 3 the presentation order was reversed.

In the left hemisphere, for all three subjects no significant differences were found between the meaningless auditory stimuli and their preceding baselines or the meaningful auditory stimuli and their preceding baselines. In the right hemisphere, as well, for Subjects 1 and 2, no significant differences were found between the meaningless auditory stimuli and their preceding baselines or the meaningful auditory stimuli and their preceding baselines. In findings similar to those in the present study, Walker-Batson et al. (1988) reported in their SPECT study that no differences were found between the stimulated and nonstimulated conditions. They attributed this finding to intrasubject variability.

For Subject 3, however, in two instances significant right hemisphere differences were found between the activation and baseline conditions: 1) the activity in the initial resting baseline was significantly greater than the activity in the initial activation condition with meaningful auditory stimuli ($p<0.05$); 2) the activity in the second activation condition with meaningless auditory stimuli was significantly greater than for the second resting baseline ($p<.05$).

Factors Accounting for Results of Comparison of Activity in the Initial Resting Baseline and the First Activation Condition

A combination of three factors may account for the greater right hemisphere activity found in the initial resting baseline than the first activation condition for Subject 3 (with meaningful auditory stimuli) that was not found for the other two subjects (with meaningless auditory stimuli). One factor may be related to the effects of attention in the right hemisphere, the second to the order of presentation of the stimuli, and the third to reported hemispheric asymmetries for processing meaningful auditory stimuli and meaningless auditory stimuli.

Effects of attention. As noted previously in this chapter, investigators have reported resting right hemisphere asymmetry, particularly in the frontal and temporal areas due to attention to the environment even in the absence of auditory stimulation (Goldenberg et al., 1987; Knopman et al., 1982; Lassen and Roland, 1983; Reivich et al., 1984). For Subject 3, a post hoc examination of the data revealed that activity contributing the greatest toward the differences appeared to be located in the right frontal lobe, in an ROI identified as the right anterior cingulate gyrus, and the right temporal lobe, in an ROI identified as the primary auditory cortex. In the present study, whereas every effort was made to limit any noise, talking, or physical activity in the test room both between scans and during scans, a certain increase in room activity was unavoidable during the actual administration of the radioisotope. For this subject, perhaps the

increase in room activity during her first PET study elicited an increase in attention, thus causing the right hemisphere increase in CBF. Habituation to the test conditions has been reported (Roland and Lassen, 1983). For this subject, habituation to these conditions during subsequent scans may account for the lack of similar increase during the second baseline.

Effects of presentation order and hemispheric asymmetries. The reasons for Subject 3's and not the other subjects' greater right hemisphere activity in the initial resting baseline than for the meaningful auditory stimulation condition may be related, at least in part, to order of the presentation of the stimuli and to hemispheric asymmetries for processing meaningful and meaningless auditory stimuli. Previous investigators have reported greater left than right hemisphere activation for meaningful auditory stimuli (Bartlett et al., 1987; Lechevalier et al, 1989; Maximillian, 1982; Nishizawa et al., 1982; Petersen et al., 1988; Wood et al., 1980) and greater right than left hemisphere activation for meaningless auditory stimuli (Mazziotta et al., 1982; Reivich et al., 1984; Roland et al., 1981). For Subject 3 meaningful auditory stimuli were presented first and according to these studies would not necessarily be expected to elicit a right hemisphere response. Therefore, for her, the significant difference could be related to increased right hemisphere activity due to attention in the resting scan and lack of activation in the right hemisphere from the meaningful auditory stimuli.

For Subjects 1 and 2 the results might be related to the following interaction. Given the premises of 1) greater right hemisphere activation for attention to the environment and 2) greater right hemisphere activation for meaningless auditory stimuli, then any increase in right hemisphere activation due to attentional factors in the resting condition and any increase in right hemisphere activation due to the meaningless auditory stimuli could have "canceled" the other

due to the meaningless auditory stimuli could have "canceled" the other so that no differences were found.

Factors Accounting for the Results of Comparison of Activity in the Second Resting Baseline and the Second Activation Condition

For Subject 3, the right hemisphere activity elicited with the meaningless auditory stimuli, presented in the second activation condition, was significantly greater than for the second resting baseline. Again, this difference might be related to the combined effects of the order of presentation and to asymmetry in processing meaningful and meaningless auditory stimuli. For Subject 3, the meaningless auditory stimuli were presented in the second activation condition. According to the previously described investigations, right hemisphere activation has been found for meaningless auditory stimuli (Mazziotta et al., 1982; Reivich et al., 1984; Roland et al., 1981). In addition, Roland and Lassen (1983) reported a decrease in CBF during subsequent baseline studies. Therefore, for this subject any right hemisphere attention effects, found in the initial resting baseline, may have decreased in the second baseline. As a result any increase in right hemisphere activity over the second resting baseline condition in response to meaningless auditory stimuli might be more evident.

For Subjects 1 and 2, the meaningful stimuli were presented in the second activation condition. According to the above mentioned theories of hemispheric asymmetry in processing meaningless and meaningful auditory stimuli, the meaningful stimuli might be less likely to elicit a right hemisphere effect.

Intra-Hemisphere Differences Between Meaningless and Meaningful Stimuli

The main purpose of the study was to determine whether meaningless and meaningful auditory stimuli elicited different patterns of cerebral activity. For all three subjects, no differences were found in the left hemisphere between the effects of meaningless and meaningful auditory

stimuli. For Subjects 1 and 2, as well, no differences were found in the right hemisphere between the effects of meaningless and meaningful auditory stimuli. For Subject 3, however, in the right hemisphere the effect of meaningless auditory stimuli was significantly greater than the effect of meaningful auditory stimuli ($p<0.01$).

Explanation for Left Hemisphere Results

An explanation for the left hemisphere results, in which no differences were found between the meaningless and meaningful stimuli for all the subjects, is not clearly obtained from a review of the literature. Whereas none of the other investigators used the type of stimuli in this study, comparisons with other studies are limited. One study (Knopman et al., 1980) reported that meaningful auditory stimuli (listening for word meaning) elicited a wider left hemisphere response than did meaningless auditory stimuli (discriminating differences in noise burst intensities). The differences in task complexity and stimuli composition between that study and this study, make comparison difficult.

Explanation for Right Hemisphere Results

A possible explanation for the right hemisphere results, in which only Subject 3 demonstrated a significantly greater right effect for meaningless auditory stimuli than for meaningful auditory stimuli, may be related to an interaction between 1) subject characteristics and 2) reported hemispheric asymmetries for processing meaningless auditory stimuli and the effect of listener's "analysis strategy" (Mazziotta et al., 1982, p. 921).

Subject characteristics. Regarding subject characteristics, Subjects 1 and 2 shared a background in speech-language pathology. Subject 3's professional training was in a related health care field, but did not include education in speech science. This variable was not considered at the time of subject selection.

Listener's "strategy." Whereas meaningless auditory stimuli have been shown to elicit a right hemisphere effect (Mazziotta et al., 1982; Reivich et al., 1984; Roland et al., 1981), Mazziotta et al. (1982) reported in their study of "musically naive" (p. 921) and trained musicians' responses to tone patterns that the musically naive listeners processed the meaningless stimuli in the right hemisphere and the trained listeners ("musically sophisticated" p. 921) in the left. Mazziotta et al. (1982) concluded that the "analysis strategy" (p. 921) of the listener played an important part in the response to auditory stimulation. Although neither overt nor covert response was required of the subjects in the present study, it may be that the subjects listened differentially to the stimuli. Perhaps the subjects with a speech science background listened more "analytically" to the meaningless CVCs than the subject without such a background, therefore producing a less pronounced right hemisphere effect. Indeed, one of the speech-language pathologist subjects (Subject 2) mentioned that the meaningless CVCs while easily identifiable were more "difficult" to listen to. She reported mentally identifying the segments of the meaningless CVCs but not the meaningful CVCs. In addition, this subject also reported that she perceived the intensities and durations of the meaningless stimuli as being different from each other, but not for the meaningful stimuli. Without this background, Subject 3 may have processed the meaningless auditory stimuli more as meaningless sound with less analysis of the composition of the stimuli, thus eliciting greater right hemisphere CBF.

Inter-Hemisphere Differences for Meaningless and Meaningful Auditory Stimuli

When the effects of meaningless auditory stimuli were compared between the left and right hemispheres, no significant differences were found for any subject. Similarly, no significant differences were found for the effects of meaningful auditory stimuli between the left and right hemispheres for the subjects. Whereas within hemisphere

differences were found for one subject in the right hemisphere for the meaningless auditory stimuli, as previously described, no inter-hemisphere asymmetries were found for the two types of stimuli. In other studies of meaningless and meaningful auditory stimuli, asymmetries were reported. Knopman et al. (1982) did report, however, no hemispheric differences for processing single meaningful words.

According to a review of the literature by Gur et al. (1982), females show less lateralization behaviorally than males to auditory and visual spatial stimulation. In their study of sex and handedness differences during rest and cognitive activity, however, they found that females showed greater lateralized rCBF than males for both auditory (left hemisphere) and visual spatial (right hemisphere) tasks. Perhaps in this study the lack of hemispheric rCBF differences between the meaningful auditory stimuli and the meaningless auditory stimuli could be related to increased blood flow for both types of stimuli in the left and right hemisphere, respectively. The result might be no detectable inter-hemispheric differences between the two conditions.

The task and stimuli differences between this study and the previous studies make comparison difficult. The explanation for the symmetrical response for the stimuli may await further research with similar stimuli and task demands.

Limitations of this Study

Other factors may have contributed to the lack of significant difference between most of the comparisons in this study. In the following section consideration will be given to 1) stimulus adequacy, 2) small number of subjects, 3) habituation, 4) task and stimuli characteristics, 5) image manipulation, and 6) the effect of error intrinsic to the procedures.

Stimulus Adequacy

Earlier, in Chapter I, mention was made of the importance of controlling stimuli complexity, in particular acoustic complexity.

Whereas in other studies in which meaningful auditory stimuli were used this was not the case (Bartlett et al., 1987; Goldenberg et al., 1987; Knopman et al., 1980; Knopman et al., 1982; Lechevalier et al., 1989; Maximillian, 1982; Mazziotta et al., 1982; Mazziotta et al., 1984; Petersen et al., 1988; Reivich et al., 1984; Wood et al., 1980), considerable effort was made to ensure that the stimuli in this study met a number of criteria.

According to several measures described in earlier sections of Chapter II, the stimuli presented in this study were judged to be adequate to meet the criteria of the study. The stimuli were considered to be adequate acoustically. Acoustic analyses determined that there were no differences between the meaningless and meaningful groups in overall duration, fundamental frequency contours, or overall intensities. In the perceptual realm, the stimuli were judged to be 100% identifiable. The stimuli were judged as meaningful or meaningless with 100% agreement among the subjects. The stimuli were sufficient to elicit increased CBF at the auditory cortex. According to percent difference calculations, the stimuli elicited an expected left hemisphere shift in CBF in the area of the primary cortex for all subjects. Indeed, one might assume that with "perception" and recognition of the stimuli as meaningless or meaningful, that some sort of cortical processing has occurred in each subject. The stimuli, therefore, appeared to meet all the criteria for the purposes of this study. There may have been other factors that limited the results of this study, however. They will be discussed in the following sections.

Small Number of Subjects

Because of the cost of the study, the number of subjects was limited to three. At the outset of the study, three was considered the minimal number to show any trends if they existed. As it turned out, the two subjects who were presented the stimuli in the same order and who, coincidentally, shared the same professional background in

speech-language pathology also shared similar results. The third subject's greater right hemisphere response to meaningless auditory stimuli than the other subjects' is intriguing in terms of order of stimulus presentation and possible listening "strategy." This evidence of intersubject variability underscores the need for a larger number of subjects for examining patterns of response to stimulation. A larger number of subjects would have permitted statistical analysis of the activity in the individual ROIs in the different conditions.

Habituation

The effects of habituation to the scanning situation have been described by previous investigators (Roland & Lassen, 1983; Warach et al., 1987). Roland and Lassen (1983) report that they and others have recorded a 5% decrease in CBF when a repeated rest measurement is made at a 20-40 min interval. Whereas Roland and Lassen (1983) factored in this decrease in subsequent activation studies, this was not attempted in the present study.

Warach et al. (1987) reported greater habituation in females than males. Detectable effects of habituation might be expected, therefore, in this group of female subjects. Only Subject 3, however, demonstrated reduced CBF in the second condition (for meaningful auditory stimuli in the right hemisphere). The effects of habituation may have contributed to this decrease. Other factors, such as task order and type of stimuli must also be considered, especially because this effect was present in only one hemisphere for one subject.

Another habituation issue involves the number of stimulus presentations for each condition. In a study of electrophysiological response to meaningful and nonmeaningful sentences, Hume (1984) noted that for her subjects, the peaks of the waveforms were generally reduced during the second presentation of the stimulus, thus suggesting an habituation effect. In this study, the randomized stimuli were presented 1 min prior to scanning and during the 2 min scan time. In

all, the 22 stimuli were presented five times and three of the stimuli were presented six times during the three minute period. In addition, as preparation for the PET scans, each subject had listened to a sample of each stimulus to calibrate comfortable loudness levels and to ensure that the stimuli were identifiable in the presence of the gantry noise. Although this presentation was at least 45 min before the beginning of the first activation condition for each subject, its contribution to any possible habituation effect is unknown. The effects of the presentation should have equalled itself out between the subjects, however.

To avoid confounding the data with the effects of variations in the radioisotope injections in the blood pool, as described in the previous chapter, the data to be analyzed for each scan were taken from the portions of the time/activity curves that were relatively flat. For each scan, the data for analysis came from 50 s summed images taken from the second minute of stimulation.

Therefore, the data represented activation from stimuli which had been presented five to six times. An habituation effect may well have contributed to the lack of differences noted in the most of the inter- and intra-hemispheric comparisons.

Stimuli and Task Characteristics

This study was designed specifically to present meaningless and meaningful auditory stimuli which differed minimally in acoustic characteristics to the subjects with no task requirements beyond passive listening. The essence of the study was to determine whether the addition of meaning to an acoustically similar auditory stimulus would elicit detectable changes in rCBF with PET. The study was designed as a passive listening task to limit possible confounding effects of mental or behavioral activity.

Previous electrophysiological studies (Hume, 1984; Molfese, 1979) did find differences between meaningless and meaningful auditory stimuli. In these studies, however, attention and a response were

required of the subjects which may have made the evoked response more measurable. In brain imaging studies, researchers have shown that changes in blood flow and metabolism may be more related to the task than the stimuli (Knopman et al., 1982; Mazziotta et al., 1982). Wise et al. (1991) found no difference between passive listening and category judgment tasks with meaningless and meaningful auditory stimuli. Variation in the results, therefore, are more likely related to the task than the stimulus. It may be that the minimal differences in the stimuli and the lack of requirements for attention and response from the subjects in this study, elicited responses which were too subtle to be detected by PET.

Image Manipulation

Another possible influence on the results of this study relates to the procedures for image preparation. In order to overlay the MRI and PET images for ROI identification, a number of steps were taken, the first of which was to interpolate the MRI and PET images from 15 planes to 78 and 100 planes, respectively. The interpolated images were then rotated around transaxial and sagittal axes so that the MRI and PET images for each subject were in approximately the same position. The offset between the MRI and PET images was determined for each subject so that the planes would be at the same level.

These procedures were somewhat problematic. One major concern was that the Neurotool program was in an initial production and lacked a way to assign coordinates to the images during the rotations. It was not possible, therefore, to replicate any of the rotations exactly. All work was done with visual alignments. Although every effort was made to match the orientations of the PET scans to each other and to the MRI scans, it was not possible to verify that this had occurred.

In fact, the Image Processing Lab at UTMCK has been in the process of redesigning the procedure for identifying PET ROIs. The new procedure involves rotating and translating the edges of the MRI or CT

images to the edges of the PET scan and eliminates the cumbersome and nonreproducable Neurotool program (G. Smith, personal communication, 1992).

Another concern was related to the interpolated PET images. The original set of images consisted of 15 planes, with a separation of 6.75 mm; the interpolated images consisted of 100 planes with a separation of 1 mm. Although each ROI could be located on more than one plane, the ROIs for analysis were identified on single 1 mm planes. That is, no attempt was made to determine whether the selected plane represented the greatest activity for that ROI. In a previous study of hand activation which also used interpolated images (Lauter et al., 1990), the ROIs were identified by taking a "core" sample, which had been identified from visual examination, through several planes to determine where the greatest activity occurred. Because the ROIs in this study were identified on the MRI scans, this step did not seem indicated. In retrospect, however, such a core might have ensured that the selected plane contained the "best" exemplar of the ROI.

Effects of Error

Whereas "all measurements are subject to measurement error" (Sorenson & Phelps, 1987, p. 115), the types of error that may influence interpretation of the data in this PET study must be considered. For the purposes of this study, the effects of error inherent to the PET techniques and those attributable to the procedures developed for this study will be addressed.

Error inherent in PET

A number of factors have been identified as having possible confounding effects on the interpretation of PET data (cf. Mazziotta & Koslow, 1987). Inherent in PET is approximately 5% variation in spatial resolution (Sorenson & Phelps, 1987). Two additional possible sources of error that might apply to the results of this study are partial-volume effect and background noise.

Partial-volume effect. Partial-volume effect refers to the phenomenon that occurs when the size of an object is smaller than the "characteristic 'resolution volume'" (Sorenson & Phelps, 1987, p. 406) of the PET system, or 1.0 full width half maximum (FWHM) (Hoffman, Huang, & Phelps, 1979). (Collimator resolution is defined as the FWHM of the radiation profile from a point or line source of radiation projected by the collimator onto the detector, according to Sorenson and Phelps, 1987, p. 335). The size of the viewed object determines the recovery of counts from the object. It must have dimensions that are twice as great as the resolution of the PET system at FWHM (Frackowiak, Lenzi, Jones, & Heather, 1980). The result of the effect is that small objects near the resolution limits of the system may appear to be larger than they are with smaller than actual concentrations of activity. A correction factor can be applied to objects with known sizes but is less easily applied to "in vivo objects (which) usually are too poorly defined for this method to be useful" (Sorenson and Phelps, 1987, p. 407).

In the present study, it well may be that some of the ROIs were below the 6.5 mm resolution limits of the ECAT system and, therefore, were inaccurately measured. For the primary auditory cortex, however, volume measurements made by Galabruda and Sanides (1980) demonstrate that the cytoarchitectonic volumes of this area far exceed the resolution limitations imposed by PET. They reported volumes of areas associated with the primary auditory cortex for a 32-year-old female to be 1780 mm^3 in the left hemisphere and 1840 mm^3 in the right hemisphere. Further analyses of the data would be necessary to determine the volumes of the ROIs and the partial-volume effect on individual ROIS.

Noise. PET images may also contain noise that can mask the presence of a signal. Image noise is usually considered in relationship to the signal and thus is expressed as a signal-to-noise ratio (S/N) (Sorenson & Phelps, 1987). Image noise can be related to radioactive

scatter, statistical fluctuations of the activity (standard deviation), and to the half-life of the radiotracer. Regarding the radiotracer, a trade-off is made between spatial and temporal resolution depending on the choice of the tracer, a tracer with a longer half-life (e.g., ^{18}F, half-life = 109 min) versus a tracer with a shorter half-life (e.g., ^{15}O, half-life = 124 s). The images made with longer lasting radiotracers have better image S/N and better image contrast. On the other hand, data collection time is longer (40 min with ^{18}F fluorodeoxyglucose (FDG)) than with ^{15}O (as short as 40 s). Factors such as habituation to the stimuli and extraneous mental activity, which are difficult to control in any event, can further confound the results of studies with long data collection times.

Signal-to-noise ratio has been statistically improved in 40 s, ^{15}O studies using intersubject averaging (Fox, Mintun, Reiman, & Raichle, 1988). A concern with averaging, however, is that subject variability can be masked in the process (Wise et al., 1991). In the present single subject study, the data were collected over 120 s which has been found to improve the S/N ratio in single subject studies (Kanno et al., 1991). Even so, it may be that activity in response to some stimulation was less than the background noise and thus was not detectable. For example, Wise et al. (1991) reported no differences in the results of a rCBF PET study using meaningful and meaningless auditory stimuli with both passive listening and category judgment tasks. They addressed this lack of difference in terms of two possibilities: 1) that there was an overlap of neural networks involving different levels of auditory processing and 2) that the signal was "below the sensitivity of the technique to distinguish signal for background noise..."(p. 221). They made an analogy of the signal to noise relationship as viewing a range of mountains beyond a forest and concluded that the "forest ... is the noise inherent in the technique of PET, we shall always stand behind a forest that partially obscures our view" (p. 227).

It must be noted, however, that even with the inherent errors in PET, this technique has been shown to be sufficiently sensitive to determine blood flow differences of 5-10% in cerebral vascular disease in stroke patients (Hubner, 1990). Therefore, it should be able to determine differences in blood flow changes in response to physiological stimulation.

Error inherent to the procedures for this study

In addition to the 5% variability inherent to PET and the factors of partial-volume effect and noise, a number of sources of possible measurement error where introduced with the procedures developed for this particular study. Examples of sources of error include: 1) the acoustic measurement of the stimuli, 2) the orientation of the MRI and PET images on Neurotool, 3) the correction of offset of the MRI and PET images, 4) the identification of ROIs on the MRI scans, 3) the transfer of the ROIs to the computer MRI image, 5) the transfer of the ROIs from the MRI to the PET images. Of these, reliability measures were obtained for the acoustic measurements and reproducibility measures were obtained for the transfer of ROIs to the computer MRI image and the transfer of ROIs to the PET images.

For the acoustic measurements, the percent error between the first and second measurements of duration and fundamental frequency was 0.8 and 1.01%, respectively. For the reproducibility of the transfer of ROIs to the computer MRI images, the mean percent error was 7.5%. For the reproducibility of the transfer of the ROIs to the PET images, the mean percent error was 0.9%. Because of the limitations of Neurotool, no reproducibility measurements could be taken for orientation of the MRI and PET images. Neither intra- nor inter-examiner reliability measures were taken for correction of the offset for MRI and PET images or for ROI identification.

These multiple sources of error, whether measurable or not, must be considered in the final interpretation of the data. Statistical

significance was achieved in three instances in this study. The actual percent difference between the means of these conditions was 5% or less in each case. For Subject 3, the right hemisphere difference between the initial resting baseline and the first activation with meaningful stimuli was significant at the 0.05 level of confidence, with the percent difference between the conditions of 2.8%. For Subject 3, the right hemisphere difference between the second resting baseline and the second activation condition with meaningless auditory stimuli was also significant at the 0.05 level of confidence, with a percent difference of 4.2%. For Subject 3, the right hemisphere differences between the meaningless and meaningful activation conditions was significant at the 0.01 level of confidence, with a percent difference of 4.9%. It should be noted that these differrences fall below the 5-10% blood flow differences that were acceptable in studies of patients with cerebral vascular disease (Hubner, 1990). The concern is whether these differences would remain significant, or conversely whether more differences would emerge, if all the sources of error could be factored into the final results.

Suggestions for Further Research

The results of this study provide an indication that differential responses in CBF to meaningless and meaningful auditory stimuli may be detected with PET given some refinements in the research protocol. Further studies might involve a greater number of subjects, analysis of the data looking first at areas of increased activity and then matching them to ROIs, more careful control of the subjects' mental activity during the stimulation conditions, examining the effects of the stimuli with other techniques such as cortical evoked potentials or transcranial doppler studies of cerebral blood flow. In the future, investigation of attention factors will be included in the design of the experimental task. These efforts may ultimately provide useful data against which to compare neurologically impaired persons.

Summary

In summary, a number of factors may account for the differences or lack thereof found for the comparisons in this study. Variables discussed in this chapter included subject characteristics, specifically subject's listening "strategies", order of presentation of stimuli, and hemispheric asymmetries in processing of meaningless and meaningful auditory stimuli. In many instances the findings of this study could be supported by previous investigators, e.g. Mazziotta et al. (1982) reported that processing of some types of meaningless auditory stimuli depended on the listener's strategy. In other cases, differences in stimuli composition and task demands of this study compared to others precluded direct comparison of these results to the results of other studies. For this reason some of the findings, such as the lack of difference in the effects of meaningful and meaningless stimuli in the left hemisphere in all subjects, await further investigation in similar studies. Limitations of the study included the small number of subjects, possible habituation effects, task and stimuli characteristics, the complexities of image manipulation, and the effect of measurement error. The results of the study do indicate that differential responses to meaningful and meaningless auditory stimuli may be detected with PET given some refinements in the research protocol.

CHAPTER V. SUMMARY AND CONCLUSIONS

Responses to various types of auditory stimulation have been mapped in the normal-human brain by the measurement of regional cerebral blood flow (rCBF) and cerebral metabolism with brain imaging techniques of nontomographic regional cerebral blood flow (rCBF), single photon emission tomography (SPECT), and positron emission tomography (PET). These techniques are based on the closely coupled relationship of neuronal activity and rCBF and cerebral metabolism (Yarowsky & Ingvar, 1981). Of the techniques, PET has the shortest data collection time and superior spatial and temporal resolution for the study of acoustic events and, therefore, was the technique of choice for this study.

The variety of auditory stimuli used in brain mapping studies can be categorized as either carrying linguistic meaning or as being linguistically meaningless acoustic signals. In previous studies in which the effects of meaningless and meaningful stimuli were compared, the stimuli varied considerably in linguistic and acoustic composition. Whereas the meaningless stimuli in these studies were well defined acoustically, the lack of definition of the acoustic parameters of the meaningful stimuli leaves open the question of whether the responses are due to the meaningfulness of the stimuli or to the acoustical complexity of the stimuli. Therefore, a clear interpretation of results of previous studies was difficult. There had yet to be a systematic study of the changes that occur in rCBF or cerebral metabolism when meaning is added to an acoustic signal. The purpose of this study was to determine whether there is a difference in localization and amount of cerebral blood flow (CBF) in specific regions of interest (ROIs), as measured by PET, in response to meaningless and meaningful auditory stimuli that have been matched for acoustic parameters.

Three native American English speaking females, ages 33 to 39 years, with no history of speech, language, hearing, or neurological disorders were subjects. The stimuli were 44 naturally produced

consonant vowel consonant (CVC) combinations. Twenty-two CVCs were classified as meaningless and 22 CVCs as meaningful. For each subject, PET scans, using ^{15}O labelled water, were made in the following four conditions: during an initial resting baseline condition; during stimulation with either the set of meaningless CVCS or the set of meaningful CVCs; a second resting baseline; and stimulation with the set of CVCs not presented in the first activation condition. Data were collected over 120 s.

The cortical and subcortical ROIs to be examined were selected prior to the PET studies based on the results of previous rCBFR, SPECT, and PET studies and the results of studies of the effects of brain damage. A series of steps were undertaken to identify the ROIs on the PET scans. Each subject had a magnetic resonance imaging (MRI) scan which depicts brain anatomy. Procedures were developed in the UTMCK Department of Radiology for matching MRI and PET images. The ROIs were identified on the MRI scans and transferred to the PET scans. The activity, in ECAT counts per pixel per s, was computed for each ROI to determine changes in rCBF that occurred during each condition.

This study was a series of single subject experiments. Correlated t-Tests (for related measures) were done for each subject to determine whether there were significant differences in rCBF between 1) the baselines, 2) the baselines and the activation conditions, 3) the meaningful and meaningless stimuli within the same cerebral hemisphere (intra-hemisphere), and 4) the meaningless and meaningful stimuli between the cerebral hemispheres (inter-hemisphere). Significant intra-hemisphere differences, all in the right hemisphere, were found for one subject in three instances. The meaningless auditory stimuli elicited greater mean CBF than the meaningful auditory stimuli. The mean CBF in the first resting baseline was greater than in the first activation with meaningful auditory stimuli. The mean CBF in the second activation with meaningless auditory stimuli was greater than the second resting baseline.

Two post hoc analyses were done. In the first, the post hoc examination of the data, although not statistically significant, revealed that in each of these instances the primary auditory cortex and the anterior cingulate gyrus ROIs in the right hemisphere appeared to contribute the most to these differences. No other significant intra- or inter-hemispheric differences were found between the meaningless or meaningful stimuli activation conditions, between the baselines themselves, or between the baseline conditions and the activation conditions for the three subjects. The second post hoc analysis was a visual analysis of the scans and the creation of subtraction images. This analysis failed to reveal additional ROIs based on activity patterns for any subject.

These significant findings as well as the lack of significant differences among the other comparisons were discussed in relation to attention factors, presentation order, hemispheric asymmetries for processing meaningless and meaningful auditory stimuli, subject characteristics, and listener strategy. Possible limitations of the study were examined. Whereas the stimuli were determined to be adequate for the purposes of this study, other potentially limiting factors included: habituation, task and stimuli characteristics, image manipulation, and the effect of error intrinsic to the measurement procedures.

The results of this study do indicate that differential responses in CBF to meaningless and meaningful auditory stimuli may be detected with PET, given some refinements in the research protocol. These results support the notion that in the field of speech language pathology PET holds great promise for the study of normal language processing. There is also potential for PET as a clinical tool for the study of how these processes are disrupted and recover after neurological disease and trauma. To these ends, however, it is

important to recognize that PET procedures may yet lack the sensitivity for the study of some subtle language processes.

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APPENDIXES

APPENDIX A.

TABLES

Table 1. Summary of brain imaging studies comparing meaningless and meaningful stimuli.

Study Category	Study Information
Author:	Knopman et al., 1980
Type of study:	nontomographic rCBF
Purpose:	To determine if there is a difference between rCBF patterns elicited by 1) meaningless and 2) meaningful auditory stimuli
Stimuli:	1) noise bursts 2) single words from Thorndike Lorge word list
Task:	1) intensity discrimination 2) identify "something to eat"
Response:	Press button with right index finger
Results:	Both types of stimuli produced greater rCBF in left than right posterior Sylvian region. Meaningful activation produced wider distribution than meaningless.
Author:	Roland et al., 1981
Type of study:	nontomographic rCBF
Purpose:	To determine effects of tone rhythm discrimination task on rCBF
Stimuli:	tone rhythms (Seashore test)
Task:	discriminate between same and different rhythms
Response:	no overt motor or verbal response
Results:	Increase in rCBF bilaterally in the auditory area, Broca area, frontal eye fields, frontal polar regions, superior frontal regions. Greater right than left activation in temporal and parietal lobes and right posterior frontal areas.

TABLE 1. Continued.

Study Category	Study Information
Author:	Nishizawa et al., 1982
Type of study:	nontomographic rCBF
Purpose:	To determine the effect on rCBF of listening to words passively
Stimuli:	onomotopoetic words
Task:	listen passively
Response:	none
Results:	Small bilateral increase in temporal and frontal regions. Greater left than right activation in superior temporal regions and anterior superior temporal regions with spread to inferior parietal regions.
Author:	Mazziotta et al., 1982
Type of study:	PET-FDG
Purpose:	To study cerebral metabolic responses to verbal and nonverbal auditory stimuli
Stimuli:	1. tone sequence pairs with different frequencies 2. single chords with identical or different harmonic composition 3. spoken discourse - Sherlock Holmes story
Task:	1. discriminate differences in tone sequences 2. discriminate differences in chord pairs 3. listen to story during scan and answer questions after scan.
Response:	1. press switch with finger 2. press switch with finger
Results:	1. Monaural stimulation with tone sequence pairs produced asymmetries depending on subject's listening strategy. Musically naive had right greater than left frontotemporal asymmetries; musicians had left greater than right asymmetries. 2. Monaural stimulation with chords produced bilateral parietotemporal activation with right greater than left frontotemporal asymmetries. 3. Binaural presentation of a story and music produced diffuse activations of frontal and temporal cortex.

TABLE 1. Continued.

Study Category	Study Information
Author:	Mazziotta et al., 1984
Type of study:	Same as above
Purpose:	To determine subcortical response to auditory stimuli
Stimuli:	Same as above
Task:	Same as above
Response:	Same as above
Results:	1. Bilateral activation of the thalamus in the story condition 2. Head of the left caudate nucleus activated when discriminating tone pairs while using visual imagery.
Author:	Wise et al., 1991
Type of study:	PET - rCBF, ^{15}O labelled water
Purpose:	To determine the distribution of cortical neural networks in word comprehension
Stimuli:	1. Words played backwards 2. Non-words (words with no meaning, but normal phonological structure) 3. Pairs of real words
Task:	1. Passive listening 2. Passive listening 3. Category judgments (mental)
Response:	1. No response 2. No response 3. Mental judgments (no overt behavioral response)
Results:	No difference in activation was found between these conditions.

Table 2. Summary of brain imaging studies involving meaningless stimuli only.

Study Category	Study Information
Author:	Lauter et al., 1985
Type of study:	PET - rCBF, ^{15}O labelled water
Purpose:	To determine tonotopic organization of the human auditory cortex
Stimuli:	pure tones: 500 Hz and 4000 Hz
Task:	passive listening
Response:	none
Results:	Activation in two different regions of the left superior temporal plane depending on the frequency of the stimulus.
Author:	Lauter et al., 1988
Type of study:	PET - rCBF, ^{15}O labelled water
Purpose:	To determine location of activation due to consonant vowel (CV) stimuli
Stimuli:	CV syllables: /pa,ta,ka,ba,da,ga/
Task:	passive listening
Response:	none
Results:	Activation of area of angular gyrus. Increased rCBF with increases in rate and level of stimuli. With changes in ear of presentation predominance of contralateral response with suggestion of asymmetrical response.

Table 3. Summary of brain imaging studies involving meaningful stimuli only.

Study Category	Study Information
Author:	Wood et al., 1980
Type of study:	nontomographic rCBF
Puropose:	To determine differences in rCBF with recognition and semantic memory
Stimuli:	40 common words varying in "concreteness"
Task:	1. listen for word presented previously 2. listen for words representing a concrete object
Response:	lift left index finger
Results:	Semantic classification produced greater left hemisphere activation than recognition memory task. Inverse relationship between accuracy of recognition memory and blood flow in occipital and angular gyrus regions of left hemisphere.

Table 3. Continued

Study Category	Study Information
Author:	Knopman et al., 1982
Type of study:	nontomographic rCBF
Purpose:	To determine the effect of handedness and rCBf correlates of phonological processing on meaningful auditory stimuli
Stimuli:	1. single words - target: something to eat 2. noise bursts 3. single words - target: words that rhyme with words ending in "-ate" 4. "pan" and "tan"
Task:	1. Identify types of food (meaning condition) 2. intensity discrimination (loudness condition) 3. identify rhyming words (rhyme condition) 4. identify "tan"
Response:	press button with left index finger
Results:	Hemispheric means differed only in rhyme condition which produced greater left than right rCBF in 9/10 subjects. Baseline condition showed greater frontal activity. In the meaning condition an increase in rCBF occurred in right posterior Sylvian region. In the loudness condition the increase occurred in the left Sylvian region. In the rhyme condition increases occurred in the left Sylvian and right temporal region. No changes occurred in the "pan-tan" condition. Conclusions: 1) changes were due to tasks, not stimuli; 2) processing for sound occurs in the left posterior Sylvian region; 3) processing for meaning may be bilateral; 4) auditory short term memory involves the left posterior Sylvian region.

TABLE 3. Continued.

Study Category	Study Information
Author:	Maximillian, 1982
Type of study:	nontomographic rCBF
Purpose:	To determine whether lateralized verbal input affected differently ipsi- versus contralateral hemisphere activity in dichotic listening.
Stimuli:	two syllable meaningful Swedish words (native language of listeners)
Task:	identify least common Swedish plural endings
Response:	affirmative response (nonspecified)
Results:	No asymmetry in resting state. Greater left temporoparietal activation irrespective of ear of stimulation.
Author:	Reivich et al., 1984
Type of study:	PET - FDG
Purpose:	To examine the factors of attention, vigilance and anxiety affecting cerebral response in perceptual tasks.
Stimuli:	1. Factual story 2. Hungarian discourse (unfamiliar language)
Task:	1. Passive listening 2. Indentification of the word "vonat" in the discourse
Response:	1. Recall information after the scan 2. Press bar with both hands
Results:	1. Elevated metabolic rates in temporal cortex contralateral to ear of stimulation 2. Activation in right inferior parietal lobe

TABLE 3. Continued.

Study Category	Study Information
Author:	Bartlett, et al., 1987
Type of study:	PET - (11C)-deoxyglucose
Purpose:	To determine the difference in patterns of correlation of glucose cerebral metabolic rates at rest and during language stimulation
Stimuli:	monosyllabic English words spoken by a female
Task:	to identify words starting with a /b/ or /s/
Response:	foot movement
Results:	1. Pattern of cross hemispheric symmetry at rest 2. Assymetry during stimulation. Within hemisphere correlations in the left hemisphere not right, in left inferior frontal, left superior temporal, and left temporal regions. Also correlation between the left regions and the right superior temporal region.
Author:	Goldenberg et al., 1987
Type of study:	SPECT - rCBF
Purpose:	To investigate the effect on rCBF of memorization of high and low imagery words, whether there is an anatomically distinct "imagery system" for concrete nouns.
Stimuli:	1. concrete and abstract meaningful words (in German, native language of listeners) 2. meaningless words, "phonotactically correct"
Task:	Memorization of words with and without visual imagery. Listen to list and identify whether word was in previous list.
Response:	flash lamp in left hand
Results:	1. At rest there was greater right than left blood flow. 2. All memory tasks activated hippocampal and inferior temporal regions of both hemispheres. Occipital lobe was activated with concrete nouns; with imagery the left occipital lobe increased for some subjects. Imagery instruction also lead to bilateral superior frontal and left middle frontal activation. Without imagery right hemisphere activation was greater than left. Overall correlational structures indicate that in memorization activation occurs primarily in the - left hemisphere.

TABLE 3. Continued.

Study Category	Study Information
Author:	Petersen et al., 1988
Type of study:	PET - rCBF, O-15 labelled water
Purpose:	To measure activity related changes in rCBF in three levels of single word processing
Stimuli:	frequent English words
Task:	1. passive listening [not reviewed in this study: 2. repetition 3. production of semantic associations]
Response:	none
Results:	Bilateral activation in auditory cortex, lateralized to the left temporoparietal cortex, anterior superior temporal cortex, and inferior cingulate cortex.
Author:	Walker-Batson et al., 1988
Type of study:	SPECT - rCBF
Purpose:	To assess rCBF during resting, passive listening, and phoneme detection conditions
Stimuli:	CV syllables: /pa,ta,da,ka,ga,ba/
Task:	1. passive listening 2. detection of the phoneme /b/
Response:	1. none 2. lift left index finger
Results:	No difference noted in total hemispheric uptake in either group. Subjects demonstrated intrasubject variability. Some subjects demonstrated as much activation in passive listening from resting state as phoneme detection in language related areas. In the phoneme detection task activation occurred in the mesial frontal region. Authors unable to separate linguistic and attentional factors.

TABLE 3. Continued.

Study Category	Study Information
Author:	Lechevalier, et al., 1989
Type of study:	nontomographic rCBF
Purpose:	To determine effects on rCBF from comprehension of spoken discourse and production of speech.
Stimuli:	1. Dialogue between female and male speaker 2. 17 nouns and 8 transitive verbs
Task:	1. listen passively 2. listen to words
Response:	1. after scan select pictures related to text 2. define or use words in a context
Results:	1. Right hemisphere activation greater than left in comprehension task. Both inferior parietal areas showed increased activation with left greater than right. Increases occurred in left prerolandic, midrolandic, superior rolandic and posterior parietal areas. Increased right hemisphere rCBF may have been related to emotional context and attentional factors. 2. Speech task produced diffuse bilateral hemispheric increase in rCBF with regional increases in both inferior parietal, left opercular, and right upper motor and premotor areas.

TABLE 4. Summary of subject data.

Subject Number	Age (years/months)	Gender	Handedness	Hearing Threshold (dB) Frequency (kHz) Right Ear 0.25	0.50	1.00	2.00	4.00	8.00	Left Ear 0.25	0.50	1.00	2.00	4.00	8.00
1*	39/0	F	R	0	5	10	5	10	5	5	5	5	10	15	5
2*	39/10	F	R	0	5	10	0	5	20	0	0	5	5	5	15
3**	32/8	F	R	10	15	15	15	15	15	10	15	10	10	5	20

Occupation: * Speech-Language Pathologist
** Certified Occupational Therapist Assistant

Note: Audiometric testing was done for subjects 1 and 2 in a sound treated room. Subject 3 was tested in a hospital treatment room in the presence of air conditioner noise.

TABLE 5. Possible CVC syllables to be used as stimuli

/C ɛ C/ as in "pep"

p ɛ p	p ɛ t	p ɛ k	p ɛ b	p ɛ d	p ɛ g
t ɛ p	t ɛ t	t ɛ k	t ɛ b	t ɛ d	t ɛ g
k ɛ p	k ɛ t	k ɛ k	k ɛ b	k ɛ d	k ɛ g
b ɛ p	b ɛ t	b ɛ k	b ɛ b	b ɛ d	b ɛ g
d ɛ p	d ɛ t	d ɛ k	d ɛ b	d ɛ d	d ɛ g
g ɛ p	g ɛ t	g ɛ k	g ɛ b	g ɛ d	g ɛ g

/C ʌ C/ as in "pup"

p ʌ p	p ʌ t	p ʌ k	p ʌ b	p ʌ d	p ʌ g
t ʌ p	t ʌ t	t ʌ k	t ʌ b	t ʌ d	t ʌ g
k ʌ p	k ʌ t	k ʌ k	k ʌ b	k ʌ d	k ʌ g
b ʌ p	b ʌ t	b ʌ k	b ʌ b	b ʌ d	b ʌ g
d ʌ p	d ʌ t	d ʌ k	d ʌ b	d ʌ d	d ʌ g
g ʌ p	g ʌ t	g ʌ k	g ʌ b	g ʌ d	g ʌ g

/C æ C/ as in "pap"

p æ p	p æ t	p æ k	p æ b	p æ d	p æ g
t æ p	t æ t	t æ k	t æ b	t æ d	t æ g
k æ p	k æ t	k æ k	k æ b	k æ d	k æ g
b æ p	b æ t	b æ k	b æ b	b æ d	b æ g
d æ p	d æ t	d æ k	d æ b	d æ d	d æ g
g æ p	g æ t	g æ k	g æ b	g æ d	g æ g

/C ɑ C/ as in "pop"

p ɑ p	p ɑ t	p ɑ k	p ɑ b	p ɑ d	p ɑ g
t ɑ p	t ɑ t	t ɑ k	t ɑ b	t ɑ d	t ɑ g
k ɑ p	k ɑ t	k ɑ k	k ɑ b	k ɑ d	k ɑ g
b ɑ p	b ɑ t	b ɑ k	b ɑ b	b ɑ d	b ɑ g
d ɑ p	d ɑ t	d ɑ k	d ɑ b	d ɑ d	d ɑ g
g ɑ p	g ɑ t	g ɑ k	g ɑ b	g ɑ d	g ɑ g

TABLE 6. CVC stimuli selected according to criteria related to meaning and phonemic composition.

TABLE 6.a. CVC stimuli selected according to criteria related to meaning and phonemic composition:

CVC Composition						
					Meaning	
Group	C1	Vo	C2		+	-
I	V	S	VL	=	5	5
II	V	L	VL	=	3	3
III	VL	S	VL	=	1	1
IV	VL	L	VL	=	1	1
V	V	S	V	=	2	2
VI	V	L	V	=	2	2
VII	VL	S	V	=	4	4
VIII	VL	L	V	=	4	4
					22	22

C1 = initial consonant
C2 = final consonant
Vo = vowel
V = Voiced consonant
VL = voiceless consonant
S = Short vowel
L = Long vowel
+ = meaningful
- = meaningless

TABLE 6.b. CVC stimuli selected according to criteria related to meaning and phonemic composition:

	Semantic Composition	
	Meaningful CVCs	Meaningless CVCs
Group I. V-S-VL	b ɛ t	b ɛ p
	b ʌ k	b ʌ p
	d ʌ k	d ʌ t
	g ɛ t	g ɛ k
	g ʌ t	g ʌ p
Group II. V-L-VL	b æ t	b æ p
	d ɑ k	d æ p
	g æ p	g ɑ k
Group III. V-S-VL	t ʌ k	t ʌ p
Group IV. VL-L-VL	k æ t	k ɑ k
Group V. V-S-V	b ɛ d	b ɛ b
	d ɛ d	d ɛ g
Group VI. V-L-V	d ɑ g	d æ g
	g æ g	g ɑ g
Group VII. VL-S-V	p ɛ g	p ɛ b
	t ʌ b	t ʌ d
	k ɛ g	k ɛ b
	k ʌ b	k ʌ g
Group VIII. VL-L-V	p æ d	p æ b
	p ɑ d	p æ g
	t æ g	t ɑ b
	k æ b	k æ g

C1 = initial consonant
C2 = final consonant
Vo = vowel
V = Voiced consonant
VL = voiceless consonant
S = Short vowel
L = Long vowel
\+ = meaningful
\- = meaningless

TABLE 6.c. CVC stimuli selected according to criteria related to meaningful and phonemic composition:

Phonological Composition

	Meaningful CVCs					Meaningless CVCs				
Initial consonants (C1):										
	III	IV	VII	VII		III	IV	VII	VIII	
/p/	0	0	1	2	= 3	0	0	1	2	= 3
/t/	1	0	1	1	= 3	1	0	1	1	= 3
/k/	0	1	2	1	= 4	0	1	2	1	= 4
					10					10
	I	II	V	VI		I	II	V	VI	
/b/	2	1	1	0	= 4	2	1	1	0	= 4
/d/	1	1	1	1	= 4	1	1	1	1	= 4
/g/	2	1	0	1	= 4	2	1	0	1	= 4
					12					12
Vowels (Vo)										
Short Vowels										
	I	III	V	VII		I	III	V	VII	
/ɛ/	2	0	2	2	= 6	2	0	2	2	= 6
/ʌ/	3	1	0	2	= 6	3	1	0	2	= 6
					12					12
Long Vowels										
	II	IV	VI	VIII		II	IV	VI	VIII	
/æ/	2	1	1	3	= 7	2	1	1	3	= 7
/ɑ/	1	0	1	1	= 3	1	0	1	1	= 3
					10					10

TABLE 6.c. Continued.

	Meaningful CVCs					Meaningless CVCs				
Final consonants (C2)										
	I	II	III	IV		I	II	III	IV	
/p/	0	1	0	0	= 1	3	2	1	0	= 6
/t/	3	1	0	1	= 5	1	0	0	0	= 1
/k/	2	1	1	0	= 4	1	1	0	1	= 3
					--					--
					10					10
	V	VI	VII	VIII		V	VI	VII	VIII	
/b/	0	0	2	1	= 3	1	0	2	2	= 5
/d/	2	2	0	2	= 6	0	2	1	0	= 3
/g/	0	0	2	1	= 3	1	0	1	2	= 4
					--					--
					12					12

C1 = initial consonant
C2 = final consonant
Vo = vowel
V = Voiced consonant
VL = voiceless consonant
S = Short vowel
L = Long vowel
+ = meaningful
- = meaningless

TABLE 7. Parameters of the CVC stimuli grouped according to vowel duration and voicing of final consonant.

Meaningful Stimuli				Meaningless Stimuli			
Short Vowels - Voiceless Final Consonants							
	FO (Hz)	Duration (ms)	Intensity (relative dB)		FO (Hz)	Duration (ms)	Intensity (relative dB)
I. V-S-VL							
bɛt	115	529	42.2	bɛp	97	499	42.0
gɛt	111	547	42.4	gɛk	101	538	42.5
bʌk	107	529	42.2	bʌp	110	546	42.4
dʌk	114	552	42.4	dʌt	123	536	42.3
gʌt	106	529	42.2	gʌp	100	832	42.3
III. VL-S-VL							
tʌk	89	553	42.4	tʌp	108	552	42.4
	---	---	-----		---	---	-----
$\bar{X}$ =	107.0	539.8	42.3		106.5	533.8	42.3
SD =	9.5	12.0	0.1		9.5	18.5	9.1
Range =	89-115	529-553	42.2-42.4		97-123	449-552	42.0-42.4
Difference =	26	29	0.2		26	53	0.4
n =	6	6	6		6	6	6

TABLE 7. Continued.

	Meaningful Stimuli				Meaningless Stimuli		
Short Vowels - Voiced Final Consonants							
	FO (Hz)	Duration (ms)	Intensity (relative dB)		FO (Hz)	Duration (ms)	Intensity (relative dB)
V. V-S-V							
bɛd	96	511	42.1	bɛb	115	520	42.2
dɛd	102	508	42.2	dɛg	89	512	42.1
VII. VL-S-V							
pɛg	95	559	42.5	pɛb	117	538	42.6
kɛg	100	557	42.5	kɛb	93	552	42.3
tʌb	111	528	42.2	tʌd	106	524	42.2
kʌb	101	523	42.2	kʌg	106	526	42.2
	---	---	-----		---	---	-----
$\bar{X}$ =	100.8	531.0	42.3		104.3	528.6	42.2
SD =	5.7	22.2	0.2		11.3	14.2	0.1
Range =	95-111	508-559	42.1-42.5		89-117	512-538	42.1-42.3
Diffrerence =	16	51	0.4		28	26	0.3
n =	6	6	6		6	6	6

TABLE 7. Continued.

	Meaningful Stimuli				Meaningless Stimuli		
Long Vowels - Voiceless Final Consonants							
	FO (Hz)	Duration (ms)	Intensity (relative dB)		FO (Hz)	Duration (ms)	Intensity (relative dB)
II. V-L-VL							
bæt	104	656	43.2	bæp	120	625	43.0
gæp	115	630	43.0	dæp	85	607	42.8
dɑk	117	631	43.0	gɑk	99	629	43.0
IV. VL-L-VL							
kæt	128	629	42.9	kæk	124	623	42.9
	---	---	-----		---	---	-----
$\bar{X}$ =	116.0	634.0	43.0		107.0	621.0	42.9
SD =	9.8	15.6	0.1		18.3	9.7	0.1
Range =	104-128	619-656	42.9-43.2		85-124	607-629	42.8-43.0
Difference =	24	37	0.3		39	22	0.2
n =	4	4	4		4	4	4

TABLE 7. Continued.

	Meaningful Stimuli				Meaningless Stimuli		
Long Vowels - Voiced Final Consonants							
	FO (Hz)	Duration (ms)	Intensity (relative dB)		FO (Hz)	Duration (ms)	Intensity (relative dB)
VI. V-L-V							
gæg	78	638	42.1	dæg	94	639	43.1
dɑg	75	637	53.0	gɑg	82	642	43.1
VII. VL-L-V							
pæd	109	674	43.2	pæb	83	668	43.3
kæb	100	691	43.4	pæg	99	678	43.3
tæg	113	699	43.5	kæg	98	700	43.5
pɑd	109	661	43.2	tɑb	124	682	43.3
	---	---	-----		---	---	-----
$\bar{X}$ =	97.3	666.7	43.1		96.7	668.2	46.6
SD =	16.7	26.2	0.5		15.3	23.8	0.2
Range =	75-113	637-699	42.1-43.6		82-124	639-700	42.1-43.5
Difference =	38	62	1.4		42	61	0.4
n =	6	6	6		6	6	6

FO = Fundamental Frequency (Hz)
V = Voiced Consonant
VL = Voiceless Consonant
S = Short Vowel
L = Long Vowel

TABLE 8. Overall durations, fundamental frequency contours, and intensities for the four groups.

	S-VL	S-V	L-VL	L-V
Duration (ms)				
$\bar{X}$ =	538.5	529.8	627.5	667.4
SD =	14.73	17.01	13.00	22.86
Range =	499-553	508-559	607-656	75-124
Difference =	54	51	49	63
n =	12	12	8	12
Fundamental Frequency Contours (Hz)				
$\bar{X}$ =	106.75	102.67	111.5	97.0
SD =	8.68	8.38	13.50	14.61
Range =	89-123	89-117	85-128	75-124
Difference =	34	28	43	49
n =	12	12	8	12
Intensity (relative dB)				
$\bar{X}$ =	42.30	42.23	42.97	43.16
SD =	0.12	0.13	0.09	0.36
Range =	41.98-42.44	42.06-42.47	42.83-43.17	42.05-43.45
Difference =	0.46	0.41	0.34	0.14
n =	12	12	8	12

S = Short Vowel (/ɛ/ or /ʌ/)
L = Long Vowel (/æ/ or /ɑ/)
VL = Voiceless Final Consonant
V = Voiced Final Consonant

TABLE 9. Reliability of acoustic measurements with CSRE (10% of 44 stimuli).

	Original Measurements		Repeated Measurements	
	Duration (ms)	FO (Hz)	Duration (ms)	FO (Hz)
1. /pæd/	674	109	673	111
2. /gɛt/	547	111	546	112
3. /pæg/	678	99	676	96
4. /dʌt/	536	123	535	129
5. /bɛd/	511	96	510	101
Mean =	589.2	107.6	588.0	109.8
SD =	71.8	9.6	71.6	11.3

TABLE 10. Frames selected for summed images.

	Frame Numbers		
Study	Subject 1	Subject 2	Subject 3
Baseline 1	8 - 12	8 - 12	8 - 12
Activation 1	6 - 10	7 - 11	8 - 12
Baseline 2	6 - 10	7 - 11	8 - 12
Activation 2	7 - 11	8 - 12	8 - 12

TABLE 11. Regions of interest (ROIs) to be identified on the transaxial magnetic resonance imaging (MRI) images of each subject.

- Subcortical Areas:
  - Midbrain
    - Inferior Colliculus (IC)
  - Thalmus
    - Medial Geniculate Body (MGB)
    - Pulvinar (PUL)
- Cortical Areas:
  - Temporal Lobe
    - Primary Auditory Cortex (PAC)
    - Superior Temporal Cortex (STC)
    - Medial Temporal Cortex (MTC)
    - Inferior Temporal Cortex (ITC)
  - Parietal Lobe
    - Supramarginal Gyrus (SMG)
    - Angular Gyrus (AG)
  - Frontal Lobe
    - Anterior Cingulate Cortex (ACC)
    - Broca's Area (BA)
    - Superior Frontal Gyrus (SFG)
  - Occipital Lobe (OCC)
  - Cerebellum (CER)

TABLE 12. Reproducibility of magnetic resonance imaging (MRI) drawings.

Region of Interest (ROI)	Number of Pixels Different	Percent Difference
1a + 1b	90	8.2
2a + 2b	66	9.0
3a + 3b	75	6.1
4a + 4b	42	3.3
5a + 5b	44	3.3
6a + 6b	35	4.1
7a + 7b	62	6.1
8a + 8b	79	11.3
9a + 9b	42	15.7
10a + 10b	25	7.8

TABLE 13. Reposition of ROIs on PET scans

$\bar{X}$ ECAT Count Position 1	Position 2	Percent Difference
1.3	1.4	1.1
1.4	1.4	0.7
1.3	1.3	1.5
1.4	1.4	0.4
1.1	1.1	1.3
1.6	1.6	2.2
1.7	1.6	1.9
1.5	1.5	1.0
1.5	1.5	0.7
1.3	1.3	1.1
1.5	1.5	0.3
1.6	1.6	0.0
1.4	1.4	0.4
1.3	1.3	0.4
1.4	1.4	0.7

TABLE 14. ECAT data for all subjects, all conditions.

ROI = Region of interest
# Pix = Number of pixels
ROI Ave = ROI average ECAT count
% SD = Percent standard deviation
SD = Standard deviation
CF = Correction factor
Cor Data = Corrected data

TABLE 14.a. Data for Subject 1 - Baseline 1.

ROI	# Pix	ROI Ave	% SD	SD
SFG-L	1555	1.21	14.1	0.17
SFG-R	1367	1.17	15.6	0.18
SMG-L	2279	1.05	15.5	0.16
SMG-R	2452	1.10	13.7	0.15
AG-L	2148	0.93	15.2	0.14
AG-R	1357	1.13	24.7	0.28
ACC-L	367	1.24	20.7	0.30
ACC-R	367	1.18	19.1	0.23
BA-L	1168	1.29	11.2	0.14
BA-R	1163	1.37	12.3	0.20
MTC-L	2349	1.23	13.1	0.16
MTC-R	2407	1.24	9.6	0.12
OCC-L	4319	1.18	15.4	0.18
OCC-R	3581	1.18	16.4	0.20
PAC-L	726	1.32	19.2	0.25
PAC-R	726	0.83	21.2	0.20
STC-L	2136	1.26	9.7	0.12
STC-R	2703	1.24	14.2	0.20
PUL-L	481	1.08	26.4	0.30
PUL-R	481	0.80	20.5	0.18
ITC-L	1416	1.06	13.5	0.14
ITC-R	1126	1.16	12.8	0.15
MGB-L	133	1.28	7.2	0.10
MGB-R	133	1.08	5.0	0.05
CER	1928	1.14	14.7	0.20
IC-L	302	1.36	11.9	0.16
IC-R	302	1.25	7.5	0.10

SFG = Superior Frontal Gyrus
SMG = Supramarginal Gyrus
AG = Angular Gyrus
ACC = Anterior Cingulate Cortex
BA = Broca's Area
MTC = Medial Temporal Cortex
OCC = Occipital Lobe
PAC = Primary Auditory Cortex
STC = Superior Temporal Cortex
PUL = Pulvinar
ITC = Inferior Temporal Cortex
MGB = Medial Geniculate Body
CER = Cerebellum
IC = Inferior Colliculus

TABLE 14.b. Data for Subject 1 - Activation 1.

ROI	# Pix	ROI Ave	CF	Cor Data	% SD	SD
SFG-L	1555	1.33	1.04	1.29	10.2	0.13
SFG-R	1367	1.09	1.04	1.05	13.3	0.14
SMG-L	2279	1.05	1.06	0.99	9.0	0.10
SMG-R	2452	1.16	1.06	1.09	15.7	0.20
AG-L	2148	1.06	1.06	1.00	14.5	0.15
AG-R	1357	1.26	1.06	1.19	20.6	0.25
ACC-L	367	1.47	1.05	1.40	21.2	0.30
ACC-R	367	1.37	1.05	1.30	14.8	0.20
BA-L	1168	1.43	1.05	1.36	13.1	0.20
BA-R	1163	1.36	1.05	1.30	15.0	0.20
MTC-L	2349	1.27	1.05	1.21	14.1	0.20
MTC-R	2407	1.26	1.05	1.20	12.0	0.15
OCC-L	4319	1.16	1.05	1.10	13.1	0.14
OCC-R	3581	1.15	1.05	1.10	16.1	0.20
PAC-L	726	1.25	1.02	1.23	21.2	0.30
PAC-R	726	1.04	1.02	1.02	14.8	0.15
STC-L	2136	1.39	1.02	1.36	9.7	0.13
STC-R	2703	1.28	1.02	1.25	13.3	0.20
PUL-L	481	1.32	1.06	1.25	12.8	0.16
PUL-R	481	1.00	1.06	0.94	15.8	0.15
ITC-L	1416	1.21	1.06	1.14	16.8	0.20
ITC-R	1126	1.27	1.06	1.19	10.8	0.13
MGB-L	133	1.35	1.05	1.29	4.4	0.10
MGB-R	133	1.34	1.05	1.28	4.0	0.10
CER	1928	1.14	1.06	1.08	11.2	0.12
IC-L	302	1.20	1.06	1.13	3.3	0.04
IC-R	302	1.36	1.06	1.28	10.3	0.13

SFG = Superior Frontal Gyrus
SMG = Supramarginal Gyrus
AG = Angular Gyrus
ACC = Anterior Cingulate Cortex
BA = Broca's Area
MTC = Medial Temporal Cortex
OCC = Occipital Lobe
PAC = Primary Auditory Cortex
STC = Superior Temporal Cortex
PUL = Pulvinar
ITC = Inferior Temporal Cortex
MGB = Medial Geniculate Body
CER = Cerebellum
IC = Inferior Colliculus

TABLE 14.c. Data for Subject 1 - Baseline 2.

ROI	# Pix	ROI Ave	CF	Cor Data	% SD	SD
SFG-L	1555	1.29	0.99	1.30	13.1	0.17
SFG-R	1367	1.11	0.99	1.12	13.1	0.15
SMG-L	2279	1.01	1.00	1.01	11.6	0.12
SMG-R	2452	1.05	1.00	1.05	12.8	0.13
AG-L	2148	1.00	1.00	1.00	16.5	0.20
AG-R	1357	1.18	1.00	1.18	19.6	0.23
ACC-L	367	1.30	1.00	1.30	16.0	0.21
ACC-R	367	1.32	1.00	1.32	19.9	0.26
BA-L	1168	1.31	1.00	1.31	14.6	0.19
BA-R	1163	1.34	1.00	1.34	15.2	0.20
MTC-L	2349	1.29	1.00	1.29	12.8	0.17
MTC-R	2407	1.20	1.00	1.20	11.0	0.13
OCC-L	4319	1.14	1.00	1.14	16.7	0.19
OCC-R	3581	1.13	1.00	1.13	15.7	0.18
PAC-L	726	1.17	1.01	1.16	17.3	0.20
PAC-R	726	0.87	1.01	0.86	18.2	0.20
STC-L	2136	1.29	1.01	1.28	8.9	0.11
STC-R	2703	1.32	1.01	1.31	15.5	0.20
PUL-L	481	1.14	1.02	1.12	14.8	0.20
PUL-R	481	0.96	1.02	0.94	20.0	0.20
ITC-L	1416	1.16	1.02	1.14	12.8	0.15
ITC-R	1126	1.23	1.02	1.21	19.5	0.24
MGB-L	133	1.27	1.01	1.26	11.4	0.14
MGB-R	133	1.04	1.01	1.03	8.9	0.10
CER	1928	1.11	1.01	1.10	16.6	0.20
IC-L	302	1.28	1.01	1.27	12.9	0.20
IC-R	302	1.33	1.01	1.32	18.4	0.24

SFG = Superior Frontal Gyrus
SMG = Supramarginal Gyrus
AG = Angular Gyrus
ACC = Anterior Cingulate Cortex
BA = Broca's Area
MTC = Medial Temporal Cortex
OCC = Occipital Lobe
PAC = Primary Auditory Cortex
STC = Superior Temporal Cortex
PUL = Pulvinar
ITC = Inferior Temporal Cortex
MGB = Medial Geniculate Body
CER = Cerebellum
IC = Inferior Colliculus

TABLE 14.d. Data for Subject 1 - Activation 2.

ROI	# Pix	ROI Ave	CF	Cor Data	% SD	SD
SFG-L	1555	1.22	0.94	1.30	16.0	0.21
SFG-R	1367	0.83	0.94	0.88	24.1	0.21
SMG-L	2279	0.93	0.95	0.98	19.0	0.20
SMG-R	2452	1.04	0.95	1.09	14.9	0.20
AG-L	2148	1.00	0.95	1.05	18.7	0.20
AG-R	1357	1.09	0.95	1.15	2504	0.30
ACC-L	367	1.35	0.97	1.39	17.7	0.25
ACC-R	367	1.17	0.97	1.21	15.8	0.20
BA-L	1168	1.25	0.96	1.30	9.0	0.12
BA-R	1163	1.25	0.96	1.30	6.7	0.10
MTC-L	2349	1.23	0.96	1.28	17.0	0.22
MTC-R	2407	1.17	0.96	1.22	11.5	0.14
OCC-L	4319	1.07	0.96	1.11	14.5	0.20
OCC-R	3581	1.07	0.96	1.11	19.9	0.22
PAC-L	726	1.31	0.97	1.35	12.3	0.20
PAC-R	726	0.88	0.97	0.91	16.3	0.15
STC-L	2136	1.25	0.97	1.29	12.2	0.20
STC-R	2703	1.24	0.97	1.28	13.0	0.20
PUL-L	481	1.14	0.98	1.16	9.2	0.11
PUL-R	481	0.96	0.98	0.98	24.0	0.24
ITC-L	1416	1.15	0.98	1.17	14.6	0.20
ITC-R	1126	1.19	0.98	1.21	10.2	0.12
MGB-L	133	1.02	0.97	1.05	8.6	0.09
MGB-R	133	0.95	0.97	0.98	5.7	0.05
CER	1928	1.03	0.97	1.06	18.4	0.20
IC-L	302	1.35	0.96	1.41	10.4	0.17
IC-R	302	1.26	0.96	1.31	9.8	0.17

SFG = Superior Frontal Gyrus
SMG = Supramarginal Gyrus
AG = Angular Gyrus
ACC = Anterior Cingulate Cortex
BA = Broca's Area
MTC = Medial Temporal Cortex
OCC = Occipital Lobe
PAC = Primary Auditory Cortex
STC = Superior Temporal Cortex
PUL = Pulvinar
ITC = Inferior Temporal Cortex
MGB = Medial Geniculate Body
CER = Cerebellum
IC = Inferior Colliculus

TABLE 14.e. Data for Subject 2 - Baseline 1.

ROI	# Pix	ROI Ave	% SD	SD
SFG-L	1498	1.44	12.7	0.18
SFG-R	1368	1.35	17.2	0.23
SMG-L	1897	1.31	15.8	0.21
SMG-R	2007	1.34	19.5	0.26
AG-L	634	1.08	27.8	0.30
AG-R	980	1.37	11.7	0.16
ACC-L	367	1.58	11.5	0.18
ACC-R	367	1.41	10.4	0.15
BA-L	1815	1.25	14.1	0.18
BA-R	2087	1.38	14.4	0.20
MTC-L	1865	1.41	14.6	0.21
MTC-R	1972	1.40	16.3	0.23
OCC-L	5205	1.43	17.3	0.25
OCC-R	4866	1.43	19.3	0.30
PAC-L	765	1.55	7.6	0.12
PAC-R	706	1.35	14.3	0.20
STC-L	2690	1.43	15.7	0.22
STC-R	2455	1.45	15.9	0.23
PUL-L	481	0.98	23.3	0.23
PUL-R	481	0.93	15.0	0.14
ITC-L	2109	1.39	11.6	0.16
ITC-R	1840	1.41	17.3	0.24
MGB-L	106	1.61	3.7	0.06
MGB-R	106	1.72	6.2	0.11
CER	660	1.33	15.9	0.21
IC-L	260	1.50	8.8	0.13
IC-R	260	1.30	16.9	0.22

SFG = Superior Frontal Gyrus
SMG = Supramarginal Gyrus
AG = Angular Gyrus
ACC = Anterior Cingulate Cortex
BA = Broca's Area
MTC = Medial Temporal Cortex
OCC = Occipital Lobe
PAC = Primary Auditory Cortex
STC = Superior Temporal Cortex
PUL = Pulvinar
ITC = Inferior Temporal Cortex
MGB = Medial Geniculate Body
CER = Cerebellum
IC = Inferior Colliculus

TABLE 14.f. Data for Subject 2 - Activation 1.

ROI	# Pix	ROI Ave	CF	Cor Data	% SD	SD
SFG-L	1498	1.47	1.02	1.44	11.6	0.17
SFG-R	1368	1.45	1.02	1.42	16.8	0.24
SMG-L	1897	1.30	1.00	1.30	17.8	0.23
SMG-R	2007	1.37	1.00	1.37	14.6	0.20
AG-L	634	1.12	1.00	1.12	17.0	0.11
AG-R	980	1.34	1.00	1.34	14.0	0.19
ACC-L	367	1.37	1.04	1.32	12.9	0.17
ACC-R	367	1.69	1.04	1.63	9.0	1.15
BA-L	1815	1.36	1.34	1.32	11.1	0.15
BA-R	2087	1.41	1.03	1.36	12.6	0.17
MTC-L	1865	1.60	1.03	1.55	11.9	0.18
MTC-R	1972	1.46	1.03	1.42	15.8	0.22
OCC-L	5205	1.42	1.03	1.38	17.5	0.24
OCC-R	4866	1.51	1.03	1.47	16.3	0.24
PAC-L	765	1.69	1.02	1.66	6.9	0.11
PAC-R	706	1.40	1.02	1.37	16.6	0.23
STC-L	2690	1.43	1.03	1.39	20.5	0.28
STC-R	2455	1.48	1.03	1.44	14.6	0.21
PUL-L	481	1.26	1.03	1.22	18.4	0.22
PUL-R	481	1.00	1.03	0.97	19.3	0.19
ITC-L	2109	1.49	1.03	1.45	12.9	0.19
ITC-R	1840	1.44	1.03	1.40	16.4	0.23
MGB-L	106	1.70	1.03	1.65	3.4	0.06
MGB-R	106	1.73	1.03	1.68	4.7	0.08
CER	660	1.42	1.01	1.41	13.0	0.18
IC-L	260	1.51	1.01	1.50	7.7	0.12
IC-R	260	1.27	1.01	1.26	8.6	0.11

SFG = Superior Frontal Gyrus
SMG = Supramarginal Gyrus
AG = Angular Gyrus
ACC = Anterior Cingulate Cortex
BA = Broca's Area
MTC = Medial Temporal Cortex
OCC = Occipital Lobe
PAC = Primary Auditory Cortex
STC = Superior Temporal Cortex
PUL = Pulvinar
ITC = Inferior Temporal Cortex
MGB = Medial Geniculate Body
CER = Cerebellum
IC = Inferior Colliculus

TABLE 14.g. Data for Subject 2 - Baseline 2.

ROI	# Pix	ROI Ave	CF	Cor Data	% SD	SD
SFG-L	1498	1.41	0.95	1.48	14.1	0.21
SFG-R	1368	1.37	0.95	1.44	15.8	0.23
SMG-L	1897	1.19	1.92	1.29	15.2	0.20
SMG-R	2007	1.20	0.92	1.30	18.3	0.24
AG-L	634	0.99	0.92	1.08	10.4	0.11
AG-R	980	1.20	0.92	1.30	10.1	0.13
ACC-L	367	1.32	0.97	1.37	10.5	0.14
ACC-R	367	1.44	0.97	1.47	4.7	0.07
BA-L	1815	1.30	0.95	1.37	16.7	0.23
BA-R	2087	1.33	0.95	1.40	13.8	0.20
MTC-L	1865	1.49	0.95	1.57	11.4	0.18
MTC-R	1972	1.28	0.95	1.35	16.6	0.22
OCC-L	5205	1.34	0.95	1.41	15.7	0.22
OCC-R	4866	1.39	0.95	1.46	16.5	0.24
PAC-L	765	1.41	0.93	1.52	8.4	0.13
PAC-R	706	1.25	0.93	1.34	14.7	0.20
STC-L	2690	1.30	0.95	1.37	18.4	0.25
STC-R	2455	1.32	0.95	1.39	11.6	0.16
PUL-L	481	1.19	0.94	1.27	10.9	0.14
PUL-R	481	1.00	0.94	1.06	18.4	0.20
ITC-L	2109	1.34	0.94	1.43	13.1	0.20
ITC-R	1840	1.29	0.94	1.37	20.5	0.30
MGB-L	106	1.77	0.94	1.88	4.7	0.10
MGB-R	106	1.77	0.94	1.88	5.1	0.10
CER	660	1.32	0.92	1.43	5.9	0.10
IC-L	260	1.00	0.92	1.08	13.8	0.15
IC-R	260	1.30	0.92	1.41	4.3	0.06

SFG = Superior Frontal Gyrus
SMG = Supramarginal Gyrus
AG = Angular Gyrus
ACC = Anterior Cingulate Cortex
BA = Broca's Area
MTC = Medial Temporal Cortex
OCC = Occipital Lobe
PAC = Primary Auditory Cortex
STC = Superior Temporal Cortex
PUL = Pulvinar
ITC = Inferior Temporal Cortex
MGB = Medial Geniculate Body
CER = Cerebellum
IC = Inferior Colliculus

TABLE 14.h. Data for Subject 2 - Activation 2.

ROI	# Pix	ROI Ave	CF	Cor Data	% SD	SD
SFG-L	1498	1.30	0.94	1.38	20.7	0.29
SFG-R	1368	1.29	0.94	1.37	21.7	0.30
SMG-L	1897	1.17	0.92	1.27	16.7	0.21
SMG-R	2007	1.19	0.92	1.29	21.5	0.23
AG-L	634	0.93	0.92	1.01	12.2	0.12
AG-R	980	1.27	0.92	1.38	8.4	0.12
ACC-L	367	1.41	0.95	1.48	13.0	0.19
ACC-R	367	1.50	0.95	1.58	6.3	0.10
BA-L	1815	1.28	0.95	1.35	17.0	0.23
BA-R	2087	1.38	0.95	1.45	16.2	0.23
MTC-L	1865	1.45	0.95	1.53	12.0	0.18
MTC-R	1972	1.38	0.95	1.45	17.2	0.25
OCC-L	5205	1.31	0.95	1.38	17.1	0.24
OCC-R	4866	1.30	0.95	1.37	17.3	0.23
PAC-L	765	1.65	0.94	1.76	6.4	0.11
PAC-R	706	1.37	0.94	1.46	15.3	0.22
STC-L	2690	1.36	0.95	1.43	18.2	0.26
STC-R	2455	1.37	0.95	1.44	16.0	0.23
PUL-L	481	1.09	0.94	1.16	22.7	0.26
PUL-R	481	1.03	0.94	1.11	29.4	0.36
ITC-L	2109	1.38	0.94	1.47	11.3	0.17
ITC-R	1840	1.34	0.94	1.43	16.8	0.24
MGB-L	106	1.54	0.94	1.64	3.3	0.05
MGB-R	106	1.92	0.94	2.04	3.7	0.08
CER	660	1.10	0.93	1.18	12.3	0.15
IC-L	260	1.48	0.93	1.59	11.2	0.18
IC-R	260	1.09	0.93	1.17	13.1	0.15

SFG = Superior Frontal Gyrus
SMG = Supramarginal Gyrus
AG = Angular Gyrus
ACC = Anterior Cingulate Cortex
BA = Broca's Area
MTC = Medial Temporal Cortex
OCC = Occipital Lobe
PAC = Primary Auditory Cortex
STC = Superior Temporal Cortex
PUL = Pulvinar
ITC = Inferior Temporal Cortex
MGB = Medial Geniculate Body
CER = Cerebellum
IC = Inferior Colliculus

TABLE 14.i. Data for Subject 3 - Baseline 1.

ROI	# Pix	ROI Ave	% SD	SD
SFG-L	1498	1.13	12.5	0.20
SFG-R	1368	1.49	12.3	0.20
SMG-L	1897	1.28	14.2	0.20
SMG-R	2007	1.27	14.4	0.20
AG-L	634	1.35	13.8	0.20
AG-R	980	1.42	25.7	0.40
ACC-L	367	1.37	11.1	0.15
ACC-R	367	1.49	8.0	0.12
BA-L	1815	1.50	10.0	0.15
BA-R	2087	1.56	16.9	0.30
MTC-L	1865	1.43	11.0	0.20
MTC-R	1972	1.35	13.8	0.20
OCC-L	5205	1.33	17.7	0.24
OCC-R	4866	1.38	14.8	0.20
PAC-L	765	1.55	5.5	0.10
PAC-R	706	1.65	7.8	0.13
STC-L	2690	1.46	12.0	0.20
STC-R	2455	1.45	12.3	0.20
PUL-L	481	1.19	10.6	0.13
PUL-R	481	1.06	16.6	0.20
ITC-L	2109	1.32	10.5	0.14
ITC-R	1840	1.34	9.5	0.13
MGB-L	116	1.27	4.2	0.05
MGB-R	116	1.55	9.0	0.14
CER	660	1.40	8.9	0.12
IC-L	260	1.54	5.2	0.10
IC-R	260	1.57	9.4	0.15

SFG = Superior Frontal Gyrus
SMG = Supramarginal Gyrus
AG = Angular Gyrus
ACC = Anterior Cingulate Cortex
BA = Broca's Area
MTC = Medial Temporal Cortex
OCC = Occipital Lobe
PAC = Primary Auditory Cortex
STC = Superior Temporal Cortex
PUL = Pulvinar
ITC = Inferior Temporal Cortex
MGB = Medial Geniculate Body
CER = Cerebellum
IC = Inferior Colliculus

TABLE 14.j. Data for Subject 3 - Activation 1.

ROI	# Pix	ROI Ave	CF	Cor Data	% SD	SD
SFG-L	1498	1.30	0.94	1.38	14.1	0.20
SFG-R	1368	1.35	0.94	1.44	12.6	0.20
SMG-L	1897	1.25	0.97	1.29	10.4	0.13
SMG-R	2007	1.23	0.97	1.27	10.5	0.13
AG-L	634	1.19	0.97	1.23	24.8	0.31
AG-R	980	1.25	0.97	1.29	35.0	0.50
ACC-L	367	1.57	0.96	1.64	6.8	0.11
ACC-R	367	1.21	0.96	1.26	13.5	0.20
BA-L	1815	1.41	0.96	1.47	9.9	0.15
BA-R	2087	1.53	0.96	1.59	15.0	0.24
MTC-L	1865	1.45	0.96	1.51	7.3	0.11
MTC-R	1972	1.35	0.96	1.41	11.5	0.20
OCC-L	5205	1.26	0.96	1.31	14.7	0.20
OCC-R	4866	1.32	0.96	1.38	13.5	0.20
PAC-L	765	1.60	0.96	1.67	5.9	0.10
PAC-R	706	1.33	0.96	1.39	6.8	0.10
STC-L	2690	1.45	0.96	1.51	12.1	0.20
STC-R	2455	1.40	0.96	1.46	11.2	0.20
PUL-L	481	1.15	0.95	1.21	11.6	0.13
PUL-R	481	1.04	0.95	1.10	14.0	0.15
ITC-L	2109	1.24	0.95	1.31	14.1	0.20
ITC-R	1840	1.19	0.95	1.25	13.2	0.20
MGB-L	116	1.16	0.96	1.21	5.7	0.07
MGB-R	116	1.09	0.96	1.14	10.3	0.18
CER	660	1.42	0.97	1.46	13.3	0.20
IC-L	260	1.64	0.98	1.67	7.6	0.13
IC-R	260	1.38	0.98	1.41	7.7	0.11

SFG = Superior Frontal Gyrus
SMG = Supramarginal Gyrus
AG = Angular Gyrus
ACC = Anterior Cingulate Cortex
BA = Broca's Area
MTC = Medial Temporal Cortex
OCC = Occipital Lobe
PAC = Primary Auditory Cortex
STC = Superior Temporal Cortex
PUL = Pulvinar
ITC = Inferior Temporal Cortex
MGB = Medial Geniculate Body
CER = Cerebellum
IC = Inferior Colliculus

TABLE 14.k. Data for Subject 3 - Baseline 2.

		Ave Ave	CF CF	Data Data	SD SD	SD SD
SFG-L	1498	1.15	0.89	1.29	15.8	0.20
SFG-R	1368	1.25	0.89	1.40	13.8	0.30
SMG-L	1897	1.13	0.87	1.30	17.6	0.23
SMG-R	2007	1.16	0.87	1.33	14.1	0.20
AG-L	634	1.21	0.87	1.39	12.4	0.20
AG-R	980	1.17	0.87	1.34	36.0	0.50
ACC-L	367	1.51	0.92	1.64	8.3	0.14
ACC-R	367	1.15	0.92	1.25	13.8	0.20
BA-L	1815	1.33	0.91	1.46	11.6	0.20
BA-R	2087	1.39	0.91	1.53	7.4	0.11
MTC-L	1865	1.25	0.91	1.37	11.4	0.20
MTC-R	1972	1.19	0.91	1.31	14.1	0.20
OCC-L	5205	1.19	0.91	1.31	16.9	0.22
OCC-R	4866	1.26	0.91	1.38	16.5	0.23
PAC-L	765	1.33	0.89	1.49	3.5	0.05
PAC-R	706	1.08	0.89	1.21	16.1	0.20
STC-L	2690	1.26	0.89	1.42	9.6	0.14
STC-R	2455	1.25	0.89	1.40	17.4	0.24
PUL-L	481	1.07	0.88	1.22	16.7	0.20
PUL-R	481	1.02	0.88	1.16	13.3	0.20
ITC-L	2109	1.19	0.86	1.38	12.4	0.20
ITC-R	1840	1.13	0.86	1.31	7.1	0.10
MGB-L	116	1.08	0.87	1.24	11.6	0.14
MGB-R	116	1.42	0.87	1.63	5.6	0.10
CER	660	1.20	0.88	1.36	8.9	0.12
IC-L	260	1.44	0.87	1.66	8.6	0.14
IC-R	260	1.37	0.87	1.57	5.6	0.10

SFG = Superior Frontal Gyrus
SMG = Supramarginal Gyrus
AG = Angular Gyrus
ACC = Anterior Cingulate Cortex
BA = Broca's Area
MTC = Medial Temporal Cortex
OCC = Occipital Lobe
PAC = Primary Auditory Cortex
STC = Superior Temporal Cortex
PUL = Pulvinar
ITC = Inferior Temporal Cortex
MGB = Medial Geniculate Body
CER = Cerebellum
IC = Inferior Colliculus

TABLE 14.1. Data for Subject 3 - Activation 2.

		Ave Ave	CF CF	Data Data	SD SD	SD SD
SFG-L	1498	1.04	0.87	1.20	21.3	0.30
SFG-R	1368	1.36	0.87	1.56	16.0	0.25
SMG-L	1897	1.12	0.85	1.32	10.2	0.13
SMG-R	2007	1.08	0.85	1.27	18.0	0.23
AG-L	634	1.10	0.85	1.29	13.0	0.20
AG-R	980	1.20	0.85	1.41	25.3	0.40
ACC-L	367	1.15	0.86	1.34	22.3	0.30
ACC-R	367	1.32	0.86	1.53	21.9	0.34
BA-L	1815	1.33	0.87	1.53	14.7	0.22
BA-R	2087	1.41	0.87	1.62	16.7	0.30
MTC-L	1865	1.33	0.87	1.53	13.1	0.20
MTC-R	1972	1.15	0.87	1.32	10.6	0.14
OCC-L	5205	1.06	0.87	1.22	24.1	0.30
OCC-R	4866	1.20	0.87	1.38	20.7	0.30
PAC-L	765	1.34	0.87	1.54	7.1	0.11
PAC-R	706	1.40	0.87	1.61	11.4	0.20
STC-L	2690	1.42	0.87	1.63	13.5	0.22
STC-R	2455	1.30	0.87	1.49	19.0	0.30
PUL-L	481	1.17	0.87	1.15	14.9	0.17
PUL-R	481	0.94	0.87	1.08	22.9	0.25
ITC-L	2109	1.24	0.87	1.43	15.0	0.21
ITC-R	1840	1.23	0.87	1.41	16.8	0.24
MGB-L	116	1.14	0.86	1.33	3.3	0.04
MGB-R	116	1.24	0.86	1.44	7.2	0.10
CER	660	1.26	0.87	1.45	11.5	0.20
IC-L	260	1.26	0.86	1.47	3.4	0.05
IC-R	260	1.22	0.86	1.42	13.3	0.19

SFG = Superior Frontal Gyrus
SMG = Supramarginal Gyrus
AG = Angular Gyrus
ACC = Anterior Cingulate Cortex
BA = Broca's Area
MTC = Medial Temporal Cortex
OCC = Occipital Lobe
PAC = Primary Auditory Cortex
STC = Superior Temporal Cortex
PUL = Pulvinar
ITC = Inferior Temporal Cortex
MGB = Medial Geniculate Body
CER = Cerebellum
IC = Inferior Colliculus

TABLE 15. Overall CBF for all planes in mean ECAT counts for each subject and condition.

Condition	Subject 1	Subject 2	Subject 3
B1	1.07	1.20	1.26
A1	1.12	1.24	1.20
B2	1.07	1.13	1.11
A2	1.03	1.14	1.09

B1 = Baseline 1
A1 = Activation 1
B2 = Baseline 2
A2 = Activation 2

TABLE 16. Correction factors for all three subjects.

	Mean ECAT Counts/Plane				Correction Factors (CF)		
Subject 1							
Plane No.	**scan 1**	**scan 2**	**scan 3**	**scan 4**	**CF-2**	**CF-3**	**CF-4**
10	1.05	1.09	1.04	1.77	1.0381	0.9905	1.6857
18	1.00	1.05	0.99	1.78	1.0553	0.9958	1.7889
41	1.03	1.08	1.03	1.70	1.0485	1.0000	1.6505
46	1.11	1.16	1.52	1.63	1.0450	1.3694	1.4685
48	1.06	1.08	1.50	1.62	1.0170	1.4151	1.5283
51	1.09	1.15	1.55	1.68	1.0550	1.4220	1.5413
53	1.11	1.18	1.61	1.75	1.0631	1.4505	1.5766
56	1.10	1.16	1.65	1.77	1.0545	1.5000	1.6091
66	1.06	1.12	1.95	2.10	10.566	1.8396	1.9802
68	1.07	1.13	1.98	2.12	1.0561	1.8505	1.9813
Subject 2							
Plane No.	**scan 1**	**scan 2**	**scan 3**	**scan 4**	**CF-2**	**CF-3**	**CF-4**
7	1.21	1.24	1.15	1.14	1.0248	0.9504	0.9421
15	1.16	1.17	1.07	1.07	1.0046	0.9187	0.9187
38	1.16	1.21	1.13	1.10	1.0431	0.9741	0.9483
42	1.18	1.21	1.12	1.12	1.0254	0.9482	0.9492
43	1.20	1.24	1.14	1.14	1.0333	0.9500	0.9500
46	1.28	1.30	1.19	1.20	1.0156	0.9297	0.9375
49	1.24	1.28	1.16	1.17	1.0323	0.9355	0.9435
51	1.24	1.28	1.16	1.17	1.0323	0.9355	0.9435
53	1.23	1.27	1.15	1.16	1.0325	0.9350	0.9431
63	1.21	1.22	1.11	1.13	1.0083	0.9174	0.9339
64	1.16	1.17	1.07	1.08	1.0086	0.9224	0.9310
Subject 3							
Plane No.	**scan 1**	**scan 2**	**scan 3**	**scan 4**	**CF-2**	**CF-3**	**CF-4**
5	1.23	1.16	1.08	1.07	0.9431	0.8780	0.8699
13	1.20	1.16	1.04	1.02	0.9703	0.8699	0.8532
36	1.18	1.13	1.08	1.02	0.9576	0.9153	0.8644
41	1.26	1.21	1.14	1.10	0.9641	0.9084	0.8741
44	1.30	1.24	1.16	1.13	0.9553	0.8937	0.8706
47	1.28	1.22	1.13	1.11	0.9531	0.8828	0.8672
48	1.28	1.22	1.12	1.11	0.9531	0.8750	0.8672
51	1.31	1.26	1.15	1.13	0.9583	0.8747	0.8594
61	1.27	1.23	1.12	1.10	0.9685	0.8819	0.8661
63	1.24	1.21	1.08	1.07	0.9758	0.8710	0.8629

TABLE 17. Normalized ECAT counts for all ROIs.

TABLE 17.a. Normalized ECAT counts for all ROIs - Subject 1.

Subject 1

ROI	B1-L	B1-R	A1-L	A1-R	B2-L	B2-R	A2-L	A2-R
IC	1.36	1.25	1.13	1.28	1.27	1.32	1.41	1.31
MGB	1.29	1.08	1.29	1.28	1.26	1.03	1.05	0.98
PUL	1.08	0.88	1.25	0.94	1.12	0.94	1.16	0.98
PAC	1.32	0.83	1.23	1.02	1.16	0.86	1.35	0.91
STC	1.26	1.24	1.36	1.25	1.28	1.31	1.29	1.28
MTC	1.23	1.24	1.21	1.20	1.29	1.20	1.28	1.22
ITC	1.06	1.15	1.14	1.19	1.14	1.21	1.17	1.21
SMG	1.05	1.10	0.99	1.09	1.01	1.05	0.98	1.09
AG	0.93	1.13	1.00	1.19	1.00	1.18	1.05	1.15
ACC	1.24	1.18	1.40	1.30	1.30	1.32	1.39	1.21
BA	1.29	1.37	1.36	1.30	1.31	1.34	1.30	1.30
SFG	1.21	1.17	1.29	1.05	1.30	1.12	1.30	0.88
OCC	1.18	1.18	1.10	1.10	1.14	1.13	1011	1.11
CER	1.14	1.14	1.08	1.08	1.10	1.10	1.06	1.06

B1 = Baseline 1
A1 = Activation 1
L = Left Hemisphere

B2 = Baseline 2
A2 = Activation 2
R = Right Hemisphere

IC = Inferior Colliculus
MGB = Medial Geniculate Body
PUL = Pulvinar
PAC = Primary Auditory Cortex
STC = Superior Temporal Cortex
MTC = Medial Temporal Cortex
ITC = Inferior Temporal Cortex

SMG = Supramarginal Gyrus
AG = Angular Gyrus
ACC = Anterior Cingulate Cortex
BA = Broca's Area
SFG = Superior Frontal Gyrus
OCC = Occipital Lobe
CER = Cerebellum

TABLE 17.b. Normalized ECAT counts for all ROIs - Subject 2.

Subject 2

ROI	B1-L	B1-R	A1-L	A1-R	B2-L	B2-R	A2-L	A2-R
IC	1.50	1.30	1.50	1.26	1.08	1.41	1.59	1.17
MGB	1.61	1.72	1.65	1.68	1.88	1.88	1.64	2.04
PUL	0.98	0.92	1.22	0.97	1.27	1.06	1.16	1.11
PAC	1.55	1.35	1.66	1.37	1.52	1.34	1.76	1.46
STC	1.43	1.45	1.39	1.44	1.37	1.39	1.43	1.44
MTC	1.41	1.40	1.55	1.42	1.57	1.35	1.53	1.45
ITC	1.39	1.41	1.45	1.40	1.43	1.37	1.47	1.43
SMG	1.31	1.34	1.30	1.37	1.29	1.30	1.27	1.29
AG	1.08	1.38	1.12	1.34	1.08	1.30	1.01	1.38
ACC	1.58	1.41	1.32	1.63	1.36	1.48	1.48	1.58
BA	1.25	1.38	1.32	1.36	1.37	1.40	1.35	1.45
SFG	1.47	1.35	1.44	1.42	1.48	1.44	1.38	1.37
OCC	1.43	1.43	1.38	1.47	1.41	1.46	1.38	1.37
CER	1.33	1.33	1.41	1.41	1.43	1.43	1.18	1.18

B1 = Baseline 1
A1 = Activation 1
L = Left Hemisphere
B2 = Baseline 2
A2 = Activation 2
R = Right Hemisphere

IC = Inferior Colliculus
MGB = Medial Geniculate Body
PUL = Pulvinar
PAC = Primary Auditory Cortex
STC = Superior Temporal Cortex
MTC = Medial Temporal Cortex
ITC = Inferior Temporal Cortex
SMG = Supramarginal Gyrus
AG = Angular Gyrus
ACC = Anterior Cingulate Cortex
BA = Broca's Area
SFG = Superior Frontal Gyrus
OCC = Occipital Lobe
CER = Cerebellum

TABLE 17.c. Normalized ECAT counts for all ROIs - Subject 3.

Subject 3

ROI	B1-L	B1-R	A1-L	A1-R	B2-L	B2-R	A2-L	A2-R
IC	1.54	1.54	1.67	1.41	1.66	1.57	1.47	1.42
MGB	1.27	1.55	1.21	1.14	1.24	1.63	1.33	1.44
PUL	1.19	1.06	1.21	1.10	1.22	1.16	1.15	1.08
PAC	1.55	1.65	1.67	1.39	1.49	1.21	1.54	1.61
STC	1.46	1.45	1.51	1.46	1.42	1.40	1.63	1.49
MTC	1.43	1.35	1.51	1.11	1.37	1.31	1.53	1.32
ITC	1.32	1.34	1.31	1.25	1.38	1.31	1.43	1.41
SMG	1.28	1.27	1.29	1.27	1.30	1.33	1.32	1.27
AG	1.35	1.42	1.23	1.29	1.39	1.34	1.29	1.41
ACC	1.37	1.49	1.64	1.26	1.64	1.25	1.34	1.53
BA	1.50	1.56	1.47	1.59	1.46	1.53	1.53	1.62
SFG	1.31	1.49	1.38	1.44	1.29	1.40	1.20	1.56
OCC	1.33	1.35	1.31	1.38	1.31	1.38	1.22	1.38
CER	1.40	1.40	1.46	1.46	1.36	1.36	1.45	1.45

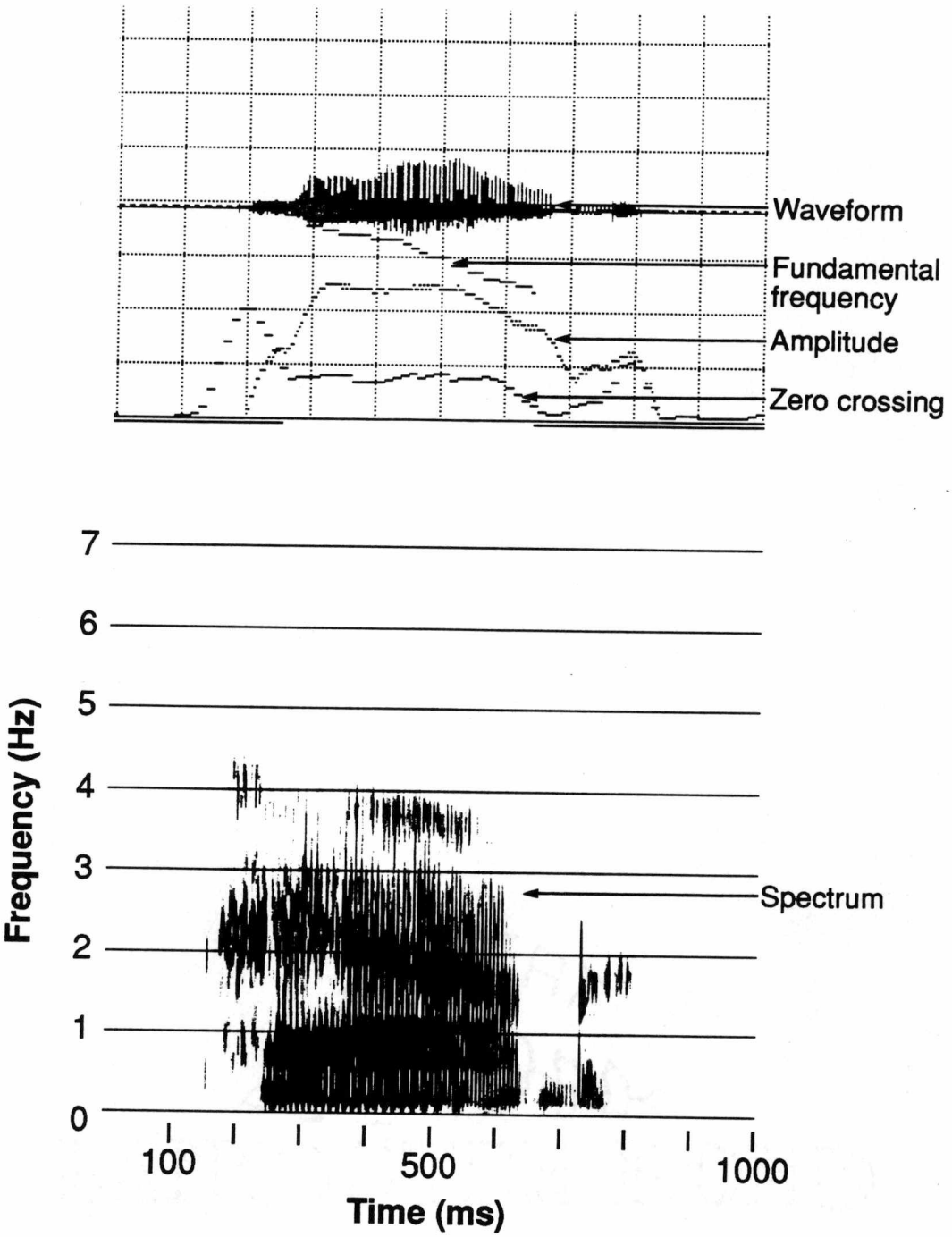
B1 = Baseline 1
A1 = Activation 1
L = Left Hemisphere
B2 = Baseline 2
A2 = Activation 2
R = Right Hemisphere

IC = Inferior Colliculus
MGB = Medial Geniculate Body
PUL = Pulvinar
PAC = Primary Auditory Cortex
STC = Superior Temporal Cortex
MTC = Medial Temporal Cortex
ITC = Inferior Temporal Cortex
SMG = Supramarginal Gyrus
AG = Angular Gyrus
ACC = Anterior Cingulate Cortex
BA = Broca's Area
SFG = Superior Frontal Gyrus
OCC = Occipital Lobe
CER = Cerebellum

APPENDIX B.

FIGURES

Figure 1. A sample spectrogram. Waveform, fundamental frequency contours, amplitude, and frequency spectrum for a CVC are displayed.

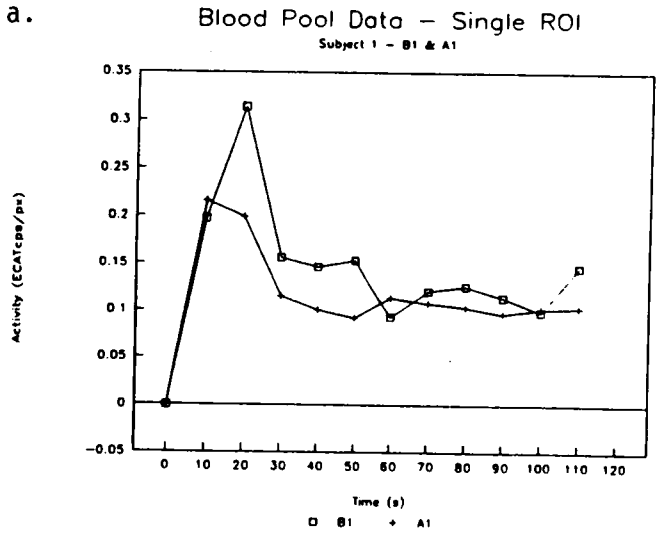

Waveform
Fundamental frequency
Amplitude
Zero crossing
7
6
5
4
3
2
1
0
Frequency (Hz)
Spectrum
100
500
1000
Time (ms)

/pæb/

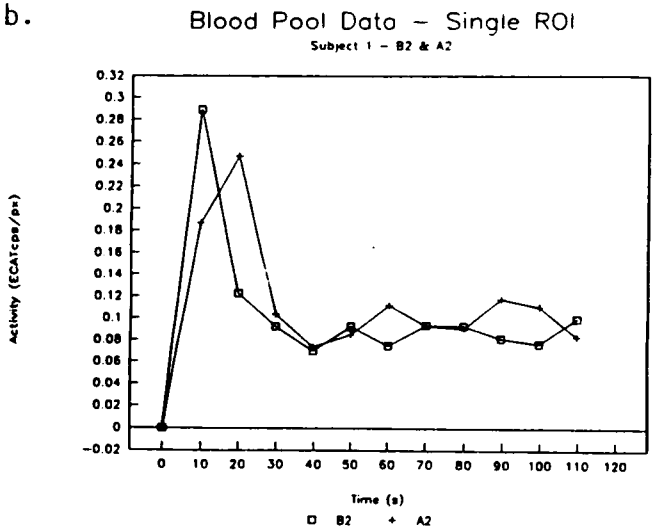
Figure 2. Blood Pool Data.

Figure 2.a. Blood pool data - Subject 1. A = obtained from single carotid ROI for Baseline 1 (B1) and Activation 1 (A1); B = obtained from single carotid ROI for Baseline 2 (B2) and Activation 2 (A@); C = obtained from averaged carotid ROIs for Baseline 1 (B1) and Activation 1 (A1); D = obtained from averaged carotid ROIs for Baseline 2 (B2) and Activation 2 (A2).

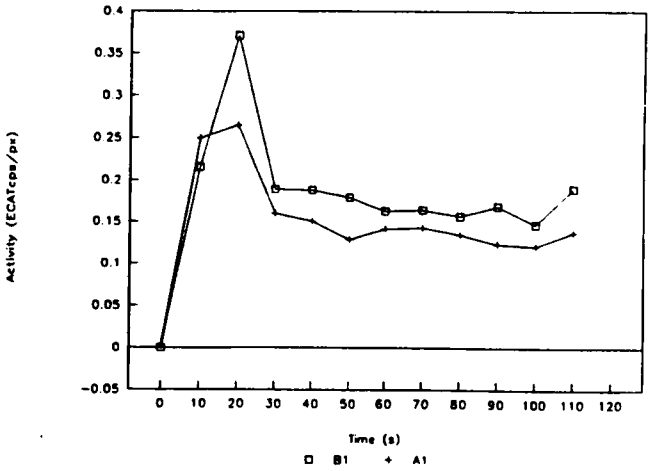
a.


Blood Pool Data – Single ROI
Subject 1 – B1 & A1
Activity (ECATcps/px)
Time (s)
B1
A1

b.


Blood Pool Data – Single ROI
Subject 1 – B2 & A2
Activity (ECATcps/px)
Time (s)
B2
A2

c.


Blood Pool Data – Averaged
Subject 1 – B1 & A1
Activity (ECATcps/px)
Time (s)
B1
A1

d.

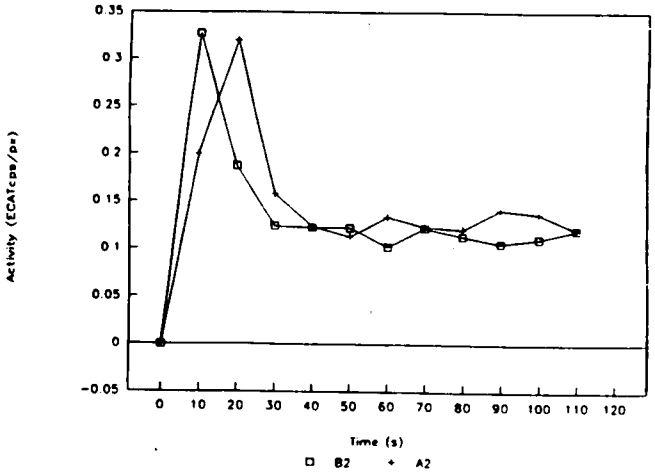
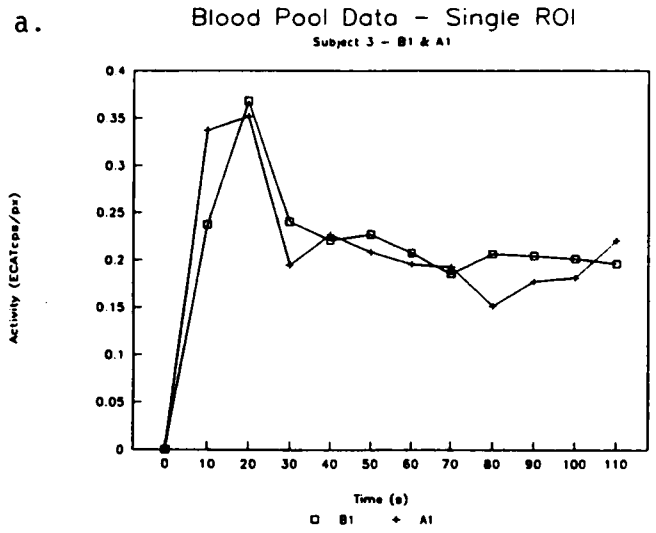
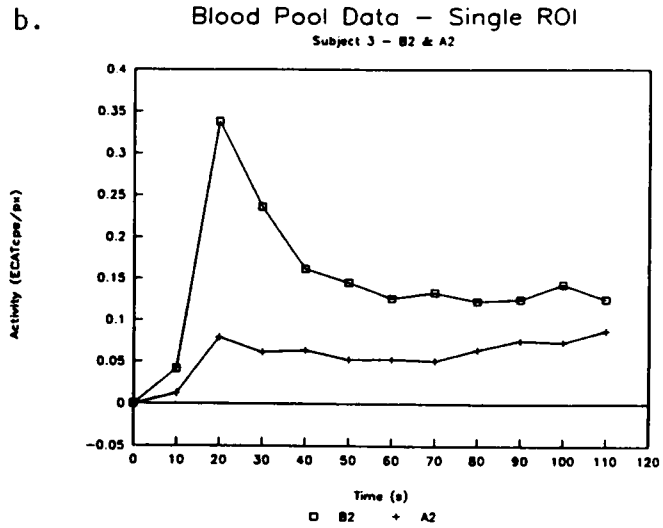

Blood Pool Data – Averaged
Subject 1 – B2 & A2
Activity (ECATcps/px)
Time (s)
B2
A2

Figure 2.b. Blood pool data - Subject 2. A = obtained from single carotid ROI for Baseline 1 (B1) and Activation 1 (A1); B = obtained from single carotid ROI for Baseline 2 (B2) and Activation 2 (A2); C = obtained from averaged carotid ROIs for Baseline 1 (B1) and Activation 1 (A1); D = obtained from averaged carotid ROIs for Baseline 2 (B2) and Activation 2 (A2).

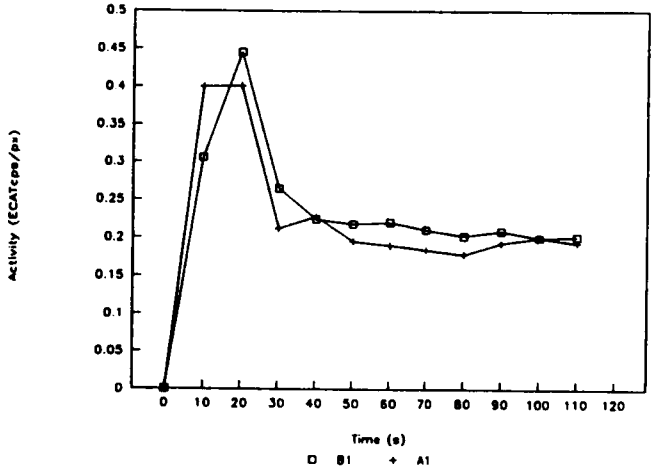
a.


Blood Pool Data – Single ROI
Subject 3 – B1 & A1
Activity (ECATcps/px)
Time (s)
B1
A1

b.


Blood Pool Data – Single ROI
Subject 3 – B2 & A2
Activity (ECATcps/px)
Time (s)
B2
A2

c.


Blood Pool Data – Averaged
Subject 3 – B1 & A1
Activity (ECATcps/px)
Time (s)
B1
A1

d.

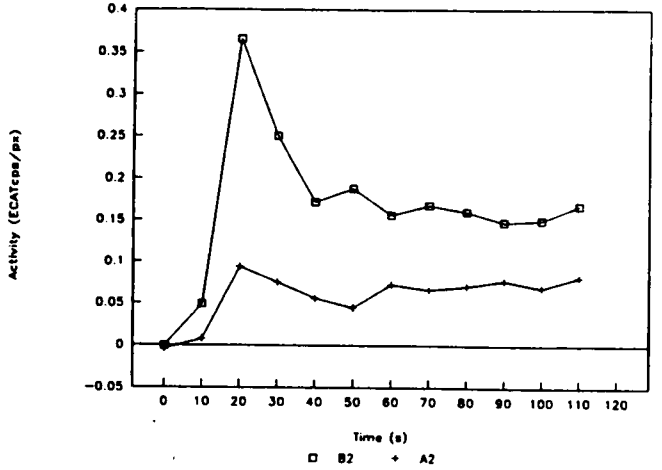
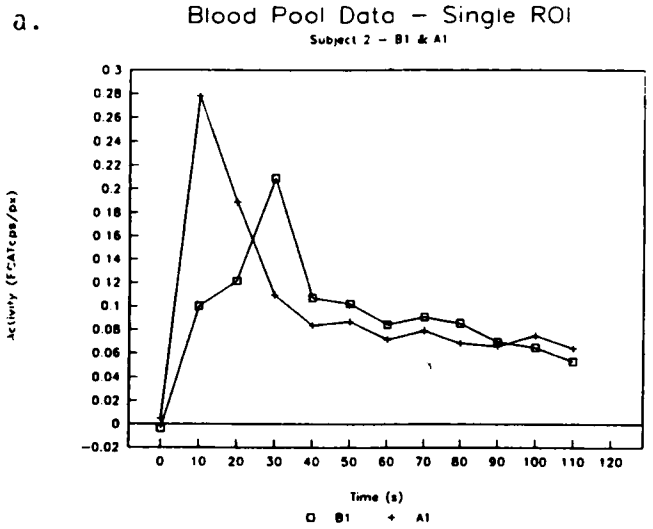
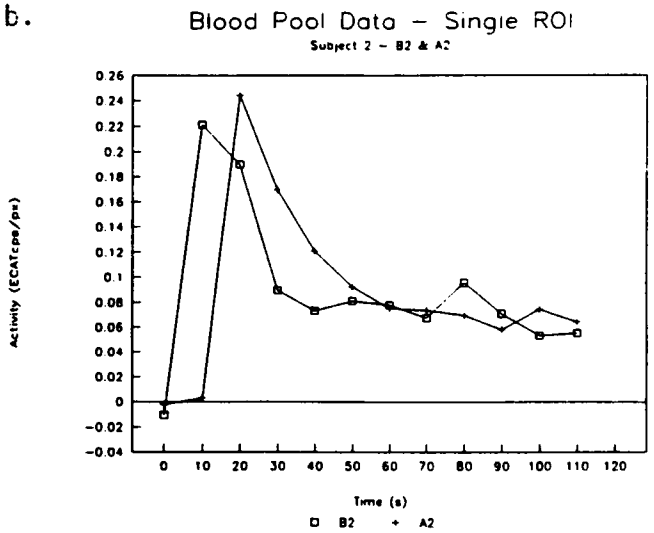

Blood Pool Data – Averaged
Subject 3 – B2 & A2
Activity (ECATcps/px)
Time (s)
B2
A2

Figure 2.c. Blood pool data - Subject 3. A = obtained from single carotid ROI for Baseline 1 (B1) and Activation 1 (A1); B = obtained from single carotid ROI for Baseline 2 (B2) and Activation 2 (A2); C = obtained from averaged carotid ROIs for Baseline 1 (B1) and Activation 1 (A1); D = obtained from averaged carotid ROIs for Baseline 2 (B2) and Activation 2 (A2).

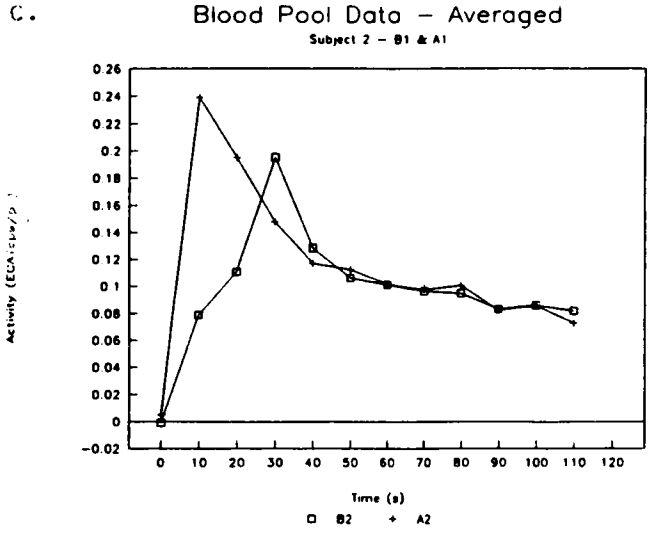
a.


Blood Pool Data – Single ROI
Subject 2 – B1 & A1
Time (s)
B1
A1

b.


Blood Pool Data – Single ROI
Subject 2 – B2 & A2
Time (s)
B2
A2

c.


Blood Pool Data – Averaged
Subject 2 – B1 & A1
Time (s)
B2
A2

d.

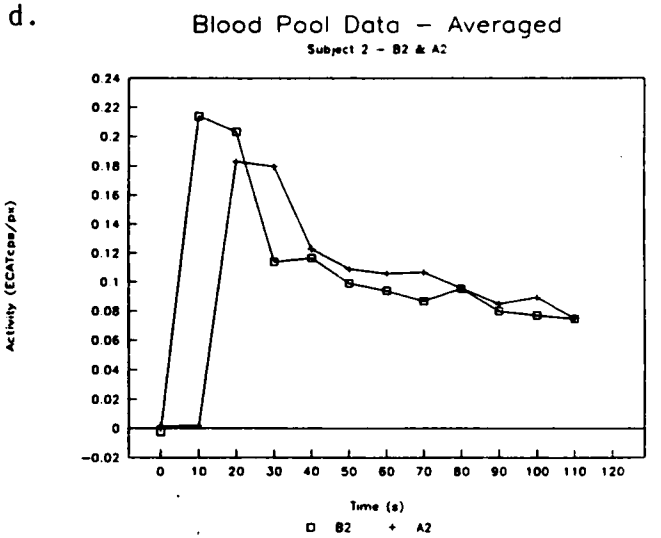

Blood Pool Data – Averaged
Subject 2 – B2 & A2
Time (s)
B2
A2

Figure 3. Anatomical representations of the regions of interest (ROIs).

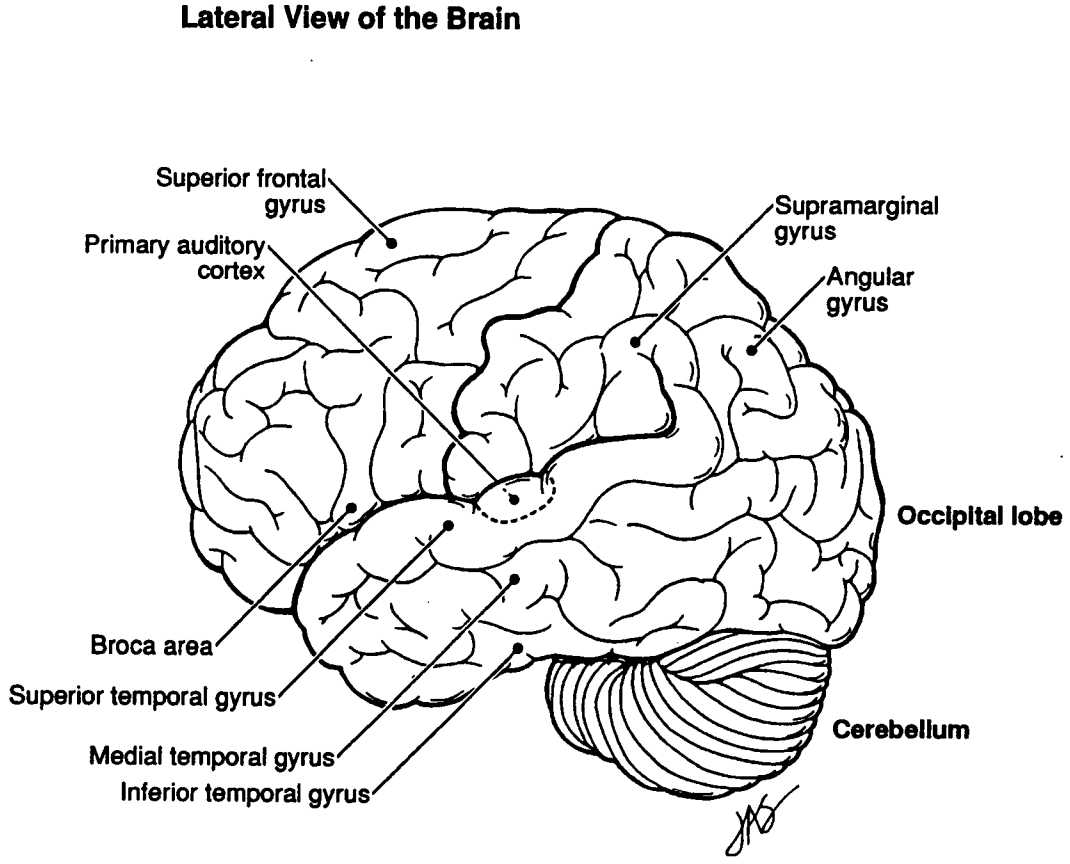


Figure 3.a. Lateral view of the brain depicting locations of the following: Superior frontal gyrus, Broca's Area, Superior temporal gyrus, Medial Temporal Gyrus, Inferior Temporal gyrus, Supramarginal gyrus, Angular Gyrus, Occipital Lobe, and Cerebellum.

Transverse Section of the Cerebrum Approximately Parallel to the Canthomeatal Line

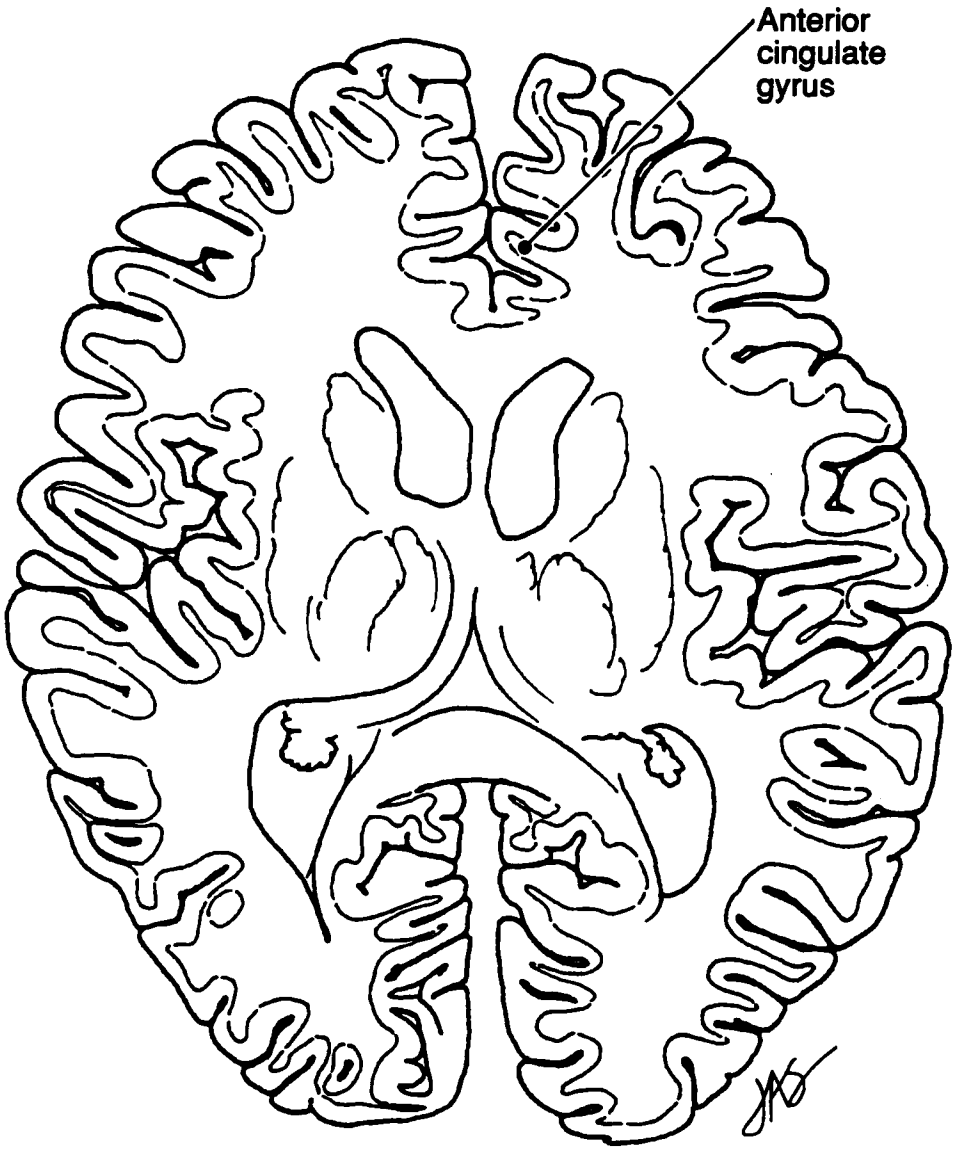


Figure 3.b. Transverse section of the cerebrum approximately parallel to the canthomeatal line depicting the following: Anterior cingulate gyrus.

Dorsal View of the Brain Stem

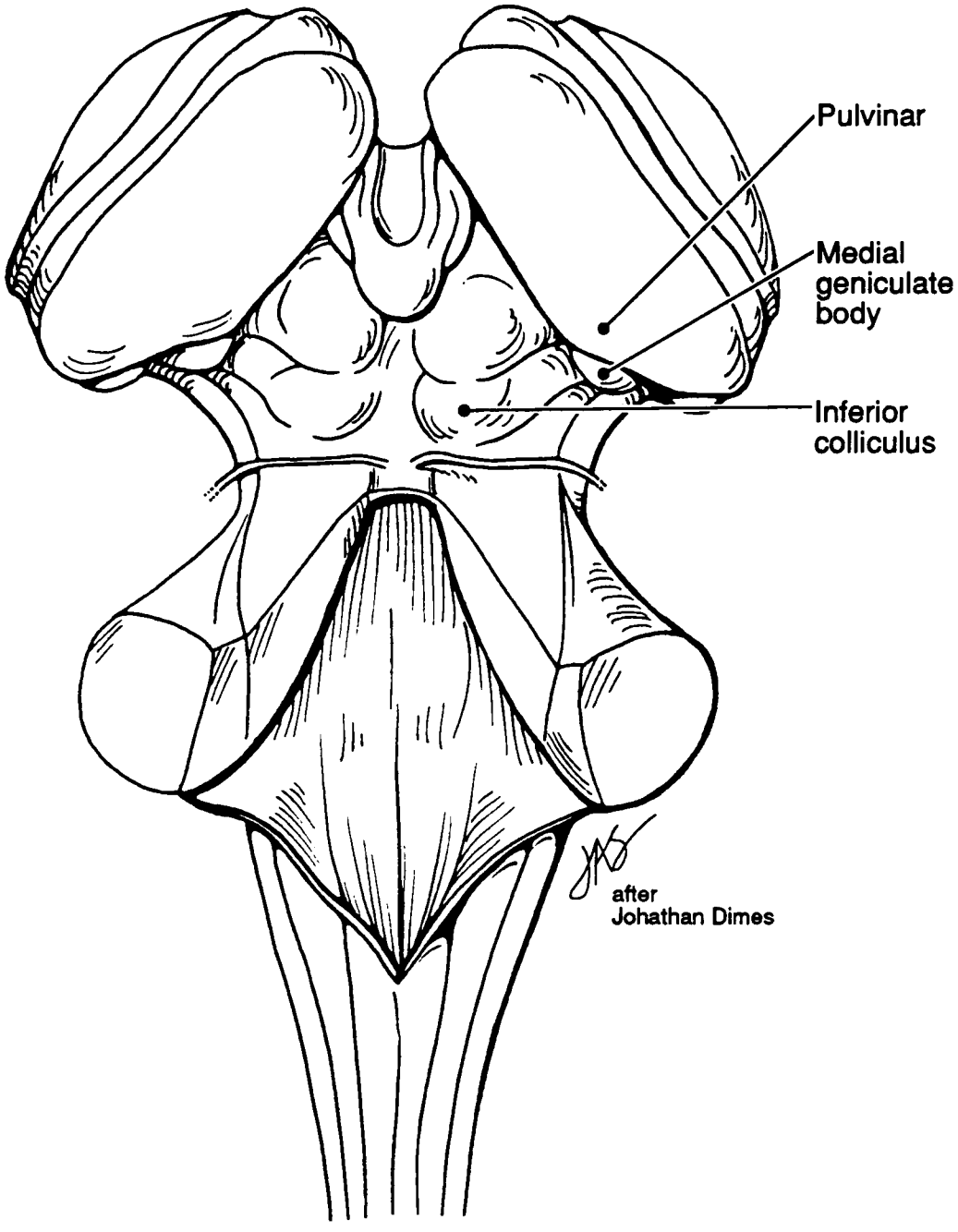
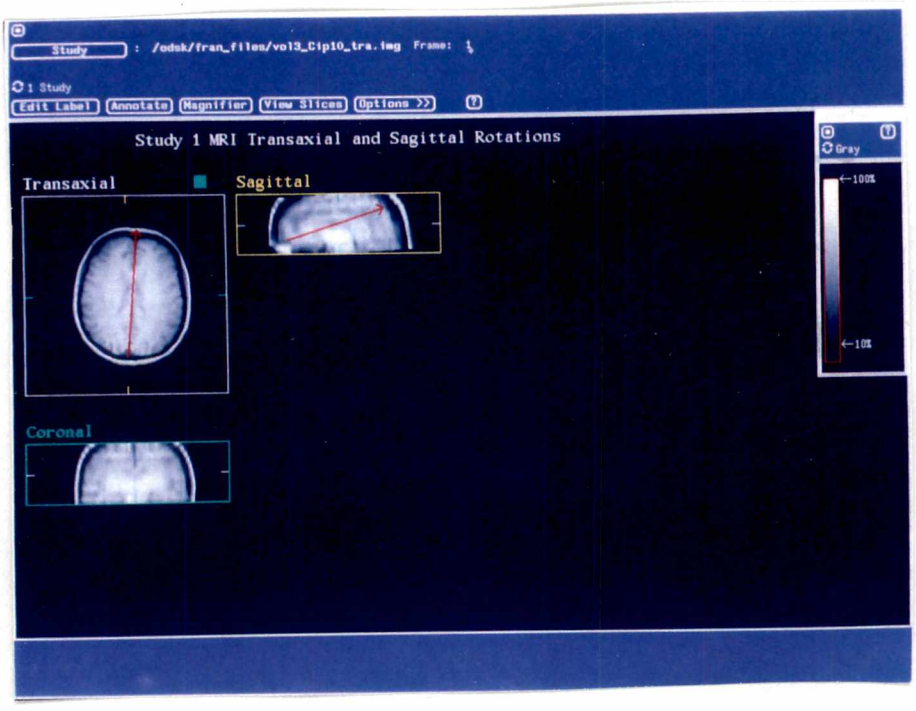


Figure 3.c. Dorsal view of the brain stem depicting the following: Pulvinar, Medial geniculate body, Inferior colluculus.

Figure 4. Transaxial and sagittal rotations of a MRI scan. Figure 4.a. Simulated transaxial and sagittal rotations. Figure 4.b. Completed rotations of a MRI scan.

a.

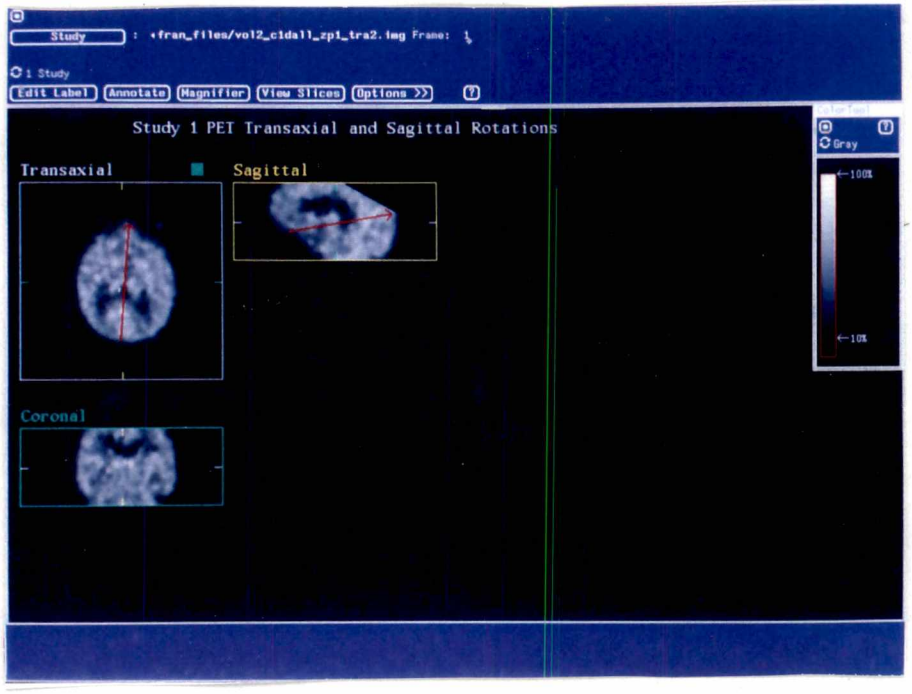

Study
: /odsk/fran_files/vol3_Cip10_tra.img Frame: 1
1 Study
Edit Label
Annotate
Magnifier
View Slices
Options >>
Study 1 MRI Transaxial and Sagittal Rotations
Transaxial
Sagittal
Coronal
Gray
100%
10%

b.


Study
: /odsk/fran_files/vol3_Cip10_tra.img Frame: 1
1 Study
Edit Label
Annotate
Magnifier
View Slices
Options >>
Study 1 MRI Rotation Completed
Transaxial
Sagittal
Coronal
Gray
100%
10%

Figure 5. Transaxial and sagittal rotations of a PET Scan. Figure 5.a. Simulated transaxial and sagittal rotations of a PET scan. Figure 5.b. Completed rotations of a PET scan.

a.


Study
: ‹fran_files/vol2_c1dall_zp1_tra2.img Frame: 1
1 Study
Edit Label
Annotate
Magnifier
View Slices
Options >>
Study 1 PET Transaxial and Sagittal Rotations
Transaxial
Sagittal
Coronal
Gray
100%
10%

b.

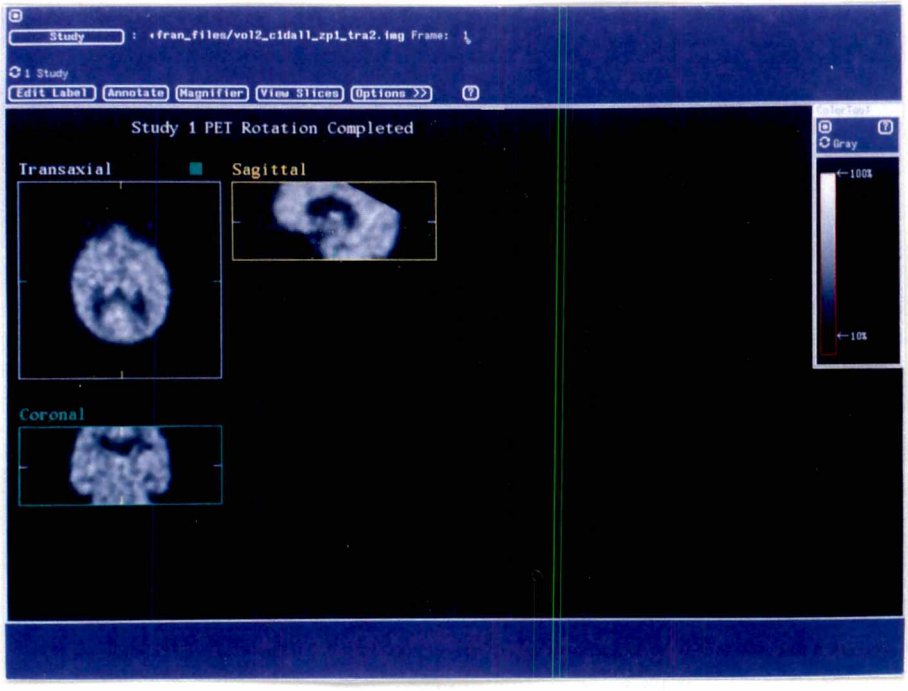

Study
: ‹fran_files/vol2_c1dall_zp1_tra2.img Frame: 1
1 Study
Edit Label
Annotate
Magnifier
View Slices
Options >>
Study 1 PET Rotation Completed
Transaxial
Sagittal
Coronal
Gray
100%
10%

Figure 6. Example of the corrected offset for a set of MRI and PET scans.

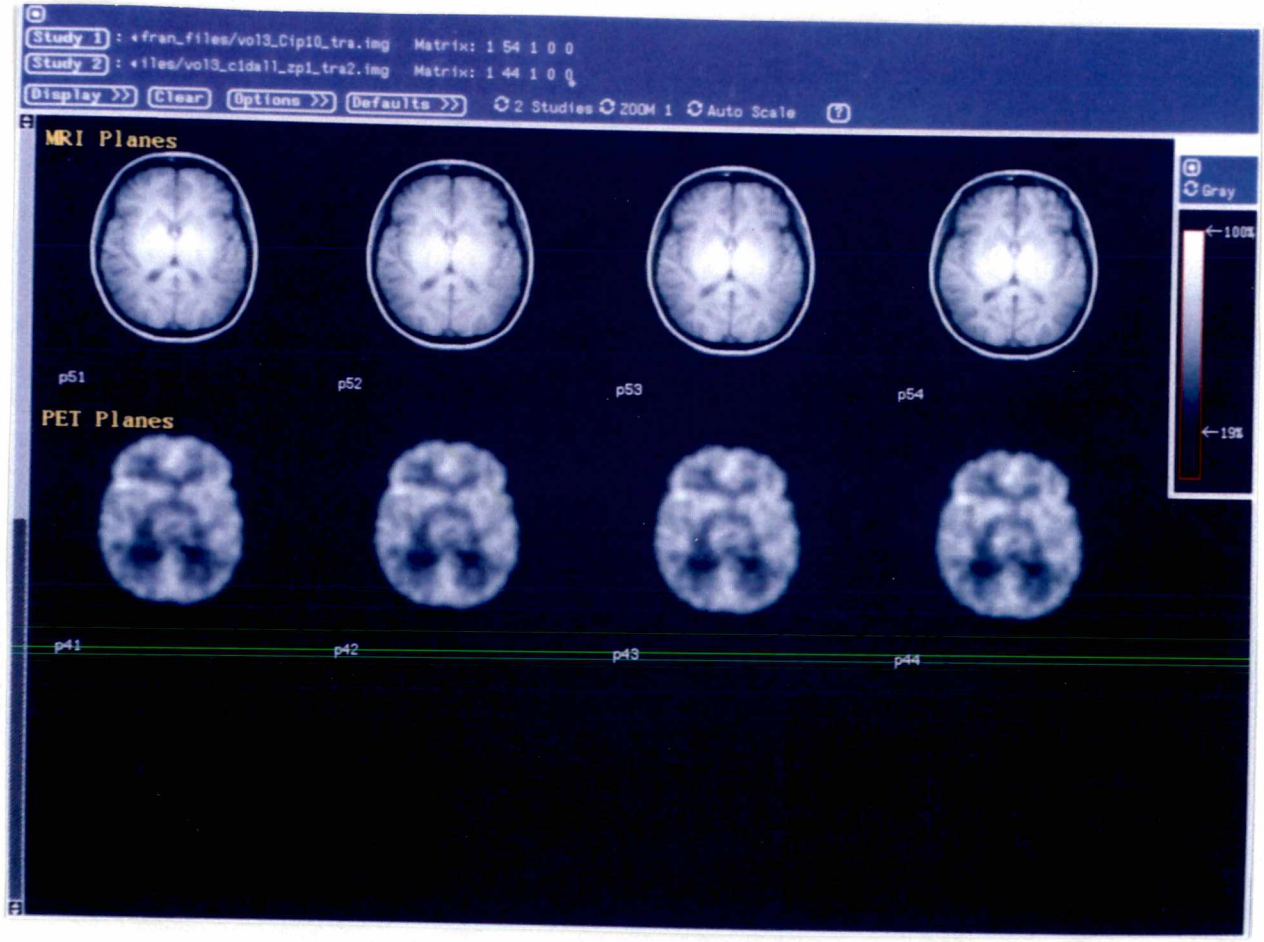
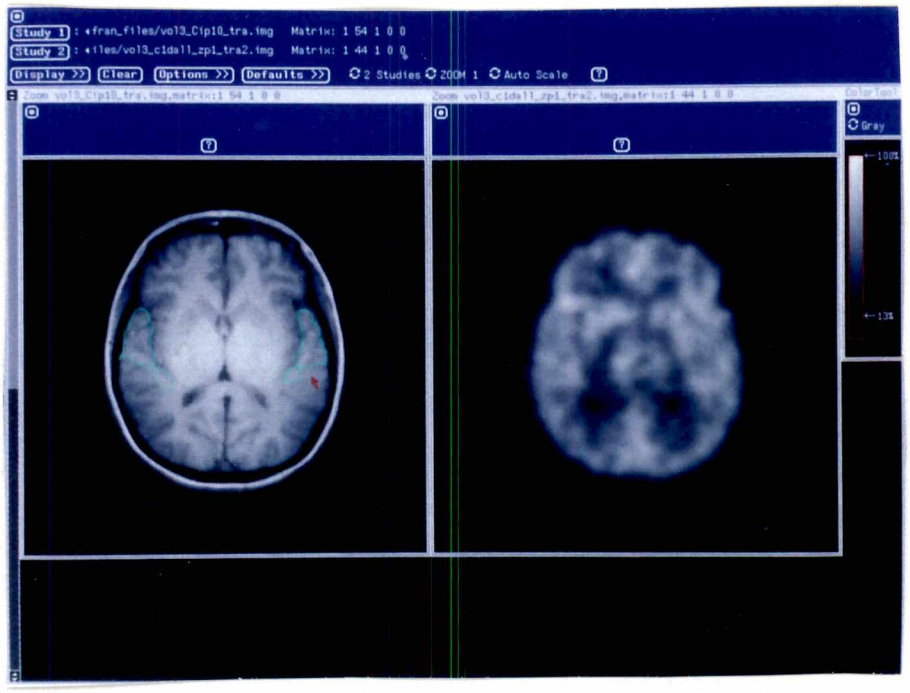

Study 1 : ◂fran_files/vol3_CipI0_tra.img Matrix: 1 54 1 0 0
Study 2 : ◂iles/vol3_cidall_zpl_tra2.img Matrix: 1 44 1 0 0
Display >> Clear Options >> Defaults >> 2 Studies ZOOM 1 Auto Scale
MRI Planes
p51
p52
p53
p54
PET Planes
p41
p42
p43
p44
Gray
100%
19%

Figure 7. Location of ROIs on a MRI Image.
a. ROI located on MRI image (top, left).
b. Trace ROI drawn around ROI and edges of MRI image (bottom, left).

a.


Study 1 : ◂fran_files/vol3_Cip10_tra.img Matrix: 1 54 1 0 0
Study 2 : ◂iles/vol3_c1dall_zp1_tra2.img Matrix: 1 44 1 0 0
Display >> Clear Options >> Defaults >> 2 Studies ZOOM 1 Auto Scale
Gray
100%
13%

b.

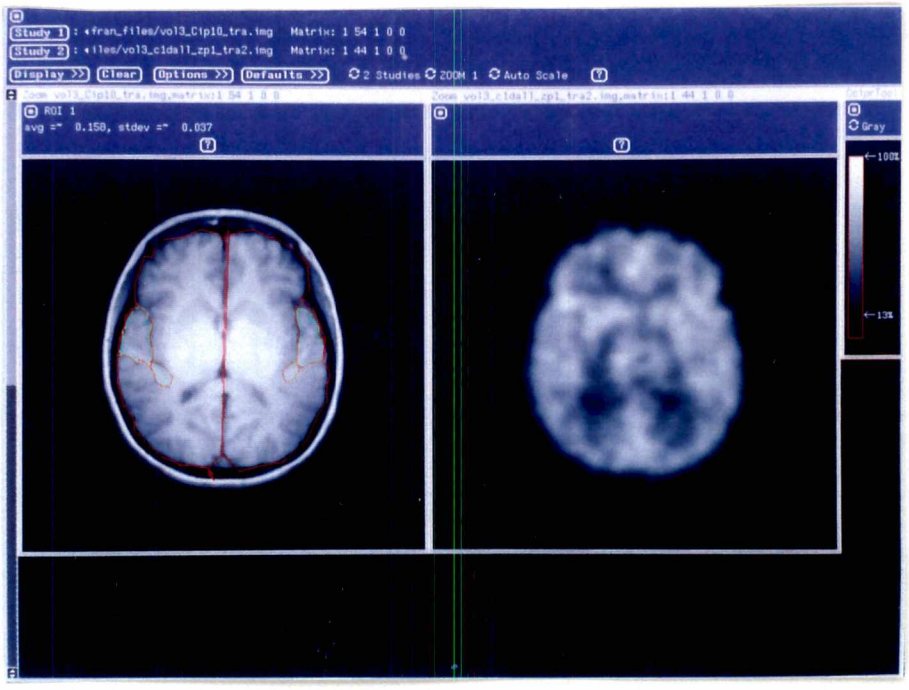
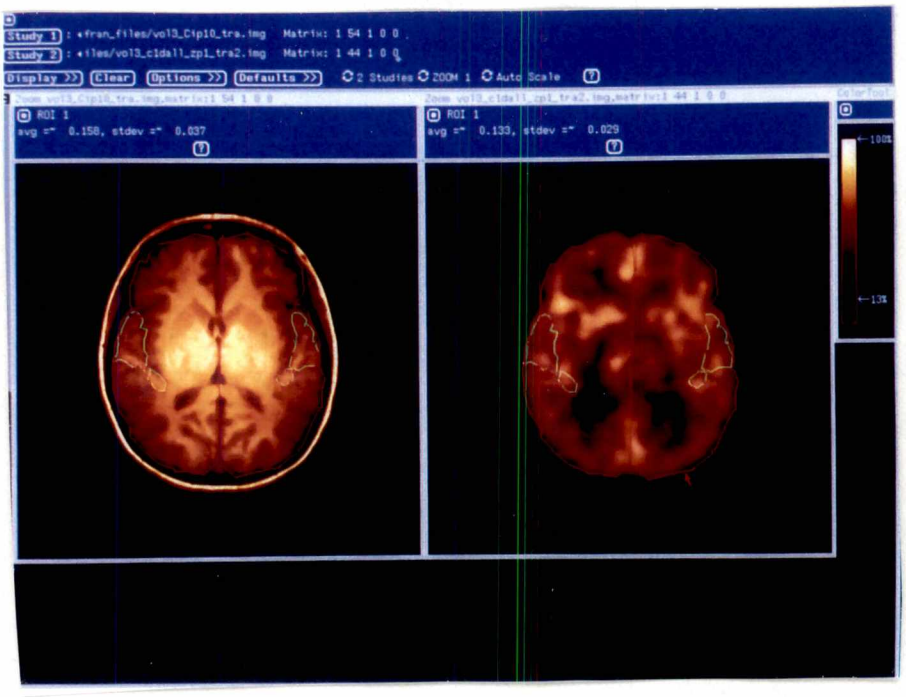

Study 1 : ◂fran_files/vol3_Cip10_tra.img Matrix: 1 54 1 0 0
Study 2 : ◂iles/vol3_c1dall_zp1_tra2.img Matrix: 1 44 1 0 0
Display >> Clear Options >> Defaults >> 2 Studies ZOOM 1 Auto Scale
ROI 1
avg =" 0.158, stdev =" 0.037
Gray
100%
13%

Figure 8. Location of ROIs on PET Image.
a. Trace ROI transferred to PET image (top, right).
b. ROI located on PET image (bottom, right).

a.


Study 1 : «fran_files/vol3_C1p10_tra.img Matrix: 1 54 1 0 0
Study 2 : «iles/vol3_c1dall_zp1_tra2.img Matrix: 1 44 1 0 0
Display >> Clear Options >> Defaults >> 2 Studies ZOOM 1 Auto Scale
ROI 1
avg =* 0.158, stdev =* 0.037
ROI 1
avg =* 0.133, stdev =* 0.029
100%
13%

b.

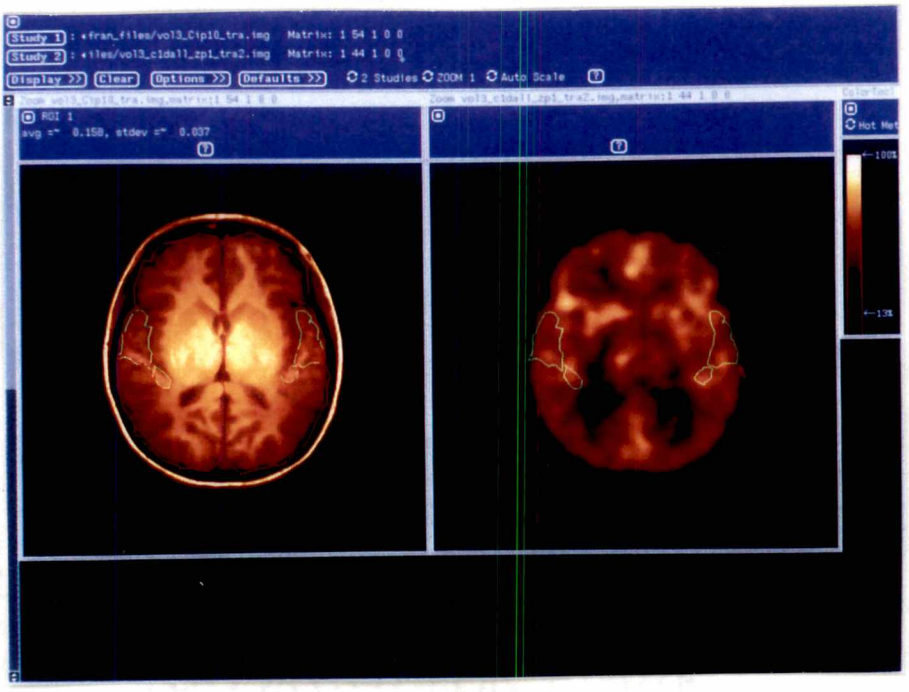
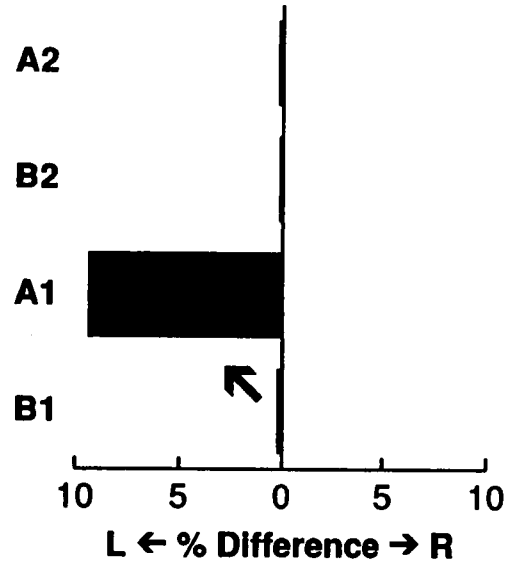
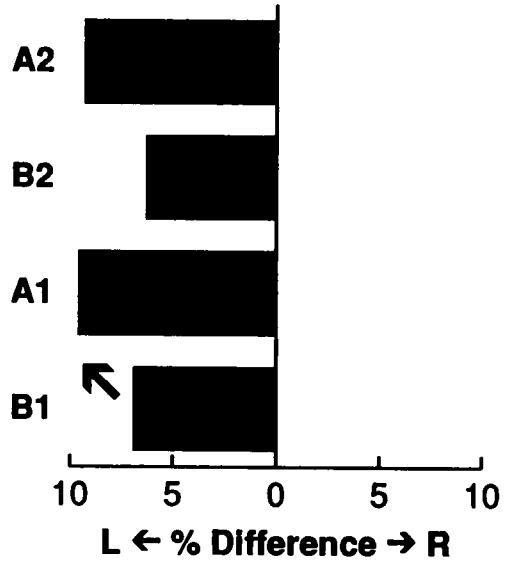

Study 1 : «fran_files/vol3_C1p10_tra.img Matrix: 1 54 1 0 0
Study 2 : «iles/vol3_c1dall_zp1_tra2.img Matrix: 1 44 1 0 0
Display >> Clear Options >> Defaults >> 2 Studies ZOOM 1 Auto Scale
ROI 1
avg =* 0.158, stdev =* 0.037
Hot Met
100%
13%

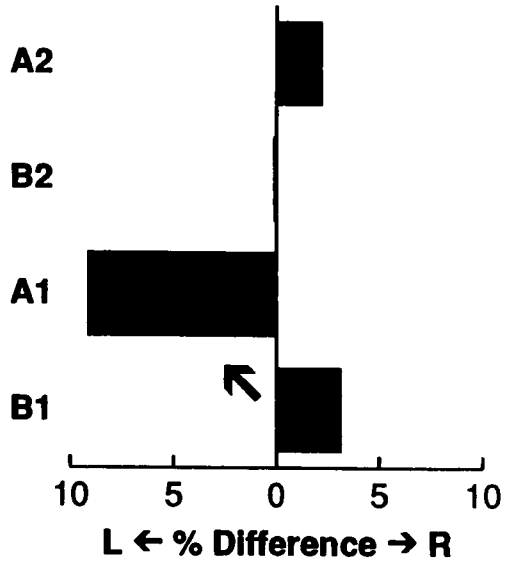
Figure 9. Shifts in Symmetry. Arrow indicates shifts in symmetry (percent difference to the left primary auditory cortex, from the first resting baseline (B1) to the first activation (A1) condition with auditory stimulation for the three subjects. Shifts were inconsistent for the second baseline (B2) to the second activation (A2) for the subjects.



Subject 1

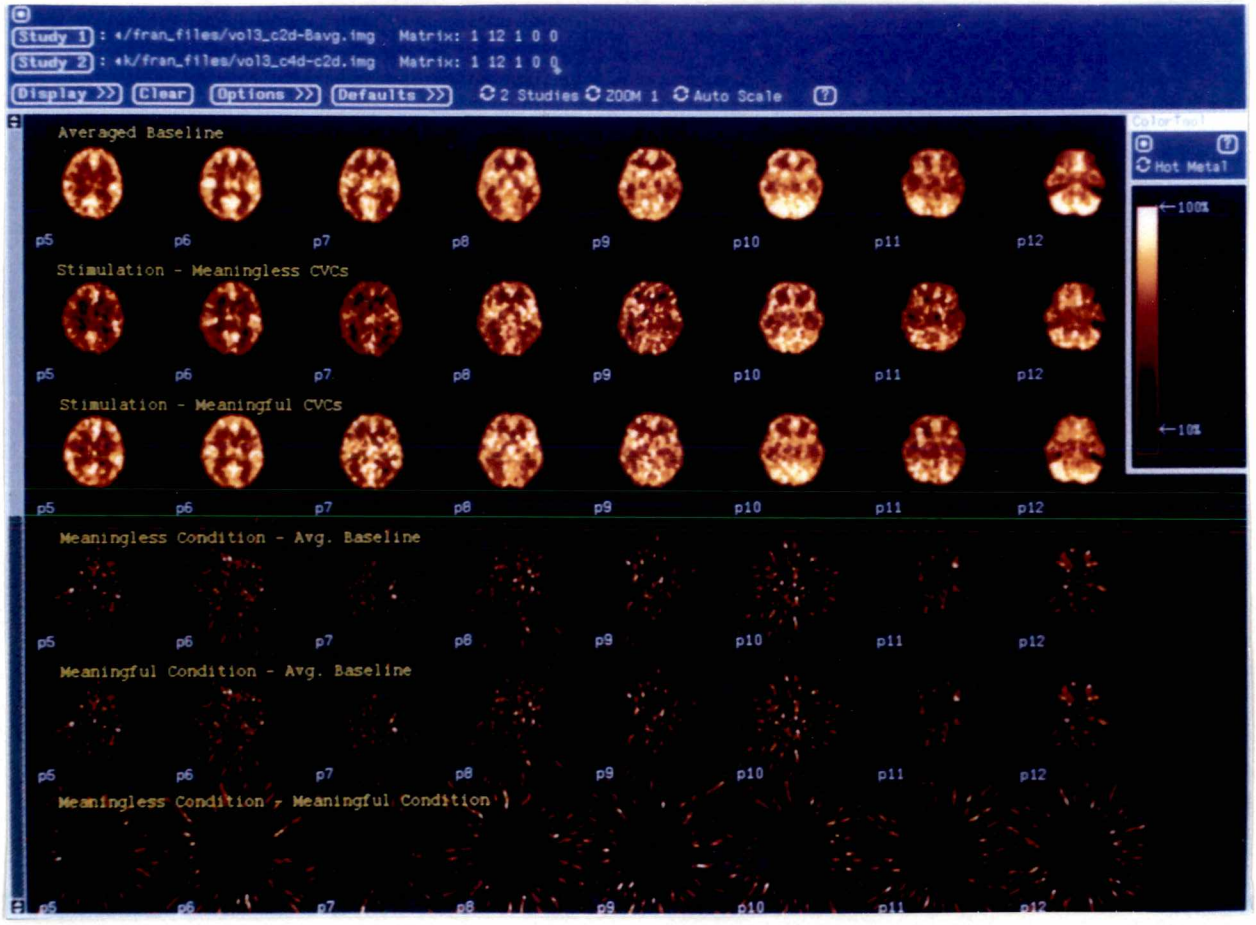


Subject 2



Subject 3

Figure 10. Example of PET Subtraction Analyses. Averaged baseline (top row), stimulation with meaningless CVCs (second row); stimulation with meaningful CVCs (third row); subtraction of the averaged baseline from the meaningless condition (fourth row); subtraction of the averaged baseline from the meaningful condition (fifth row); subtraction of the meaningful condition from the meaningless condition (sixth row).


Study 1 : ~/fran_files/vol3_c2d-Bavg.img Matrix: 1 12 1 0 0
Study 2 : ~k/fran_files/vol3_c4d-c2d.img Matrix: 1 12 1 0 0
Display >> Clear Options >> Defaults >> 2 Studies ZOOM 1 Auto Scale
Averaged Baseline
Stimulation - Meaningless CVCs
Stimulation - Meaningful CVCs
p5 p6 p7 p8 p9 p10 p11 p12
ColorTool
Hot Metal
←100%
←10%
Meaningless Condition - Avg. Baseline
Meaningful Condition - Avg. Baseline
Meaningless Condition - Meaningful Condition

APPENDIX C. Informed consent form.

THE UNIVERSITY OF TENNESSEE KNOXVILLE

Research Investigation of
Positron Emission Tomography (PET) Techniques

STATEMENT OF INFORMED CONSENT

I authorize the performance upon _____ (name of volunteer) of a $H_2{}^{15}O$ water PET scan of the brain. I understand that this test is part of a research project in PET scanning. The nature and purpose of the test, the risks involved, and the possibilities of complications have been explained to me as follows:

1. The purpose of the test is to get biochemical information concerning the processing of sounds in the normal human brain.

2. $H_2{}^{15}O$ is a radioactively labeled water that can be used to examine blood flow in various organs.

3. I will undergo $H_2{}^{15}O$ cerebral blood flow scans. Small earphones will be used to deliver the auditory stimuli. The loudness of the sounds will be no greater than those in a hearing test or conversational speech and as such pose no risk. My eyes will be covered and my head will be positioned with a holder to avoid movement.

4. I will undergo magnetic resonance imaging (MRI) either before or after the PET scans to provide anatomical images of my brain. Providing that care is taken to avoid exposing ferromagnetic materials to the magnet by removing metal objects such as watches and rings, MRI poses no risk. MRI involves being in a confined space for approximately 40 minutes which has been known to cause discomfort in some individuals. I am free to stop the procedure any time, if I so choose.

5. Prior to the PET scan, I will receive a hearing test from a certified speech language pathologist and a brief neurological examination from a neurologist. Each procedure should take no more than thirty minutes.

6. Side effects and/or toxic effects such as discomfort from the injection or a febrile reaction (development of a fever) are remotely possible. The chance of such a reaction is approximately 1/10,000. A physician and nurse will be present to assist if necessary. Throughout the studies, I.V. access will be maintained to allow for the injection of the radiotracer and to maintain an open line in the event that some treatment is necessary. No other potential risks are anticipated with these procedures. Vital signs will be recorded.

Date: _____

Research Subject initial here _____

Witness initial here _____

7. Because $H_2{}^{15}O$ is radioactive, I will receive a radiation dose. I will receive five doses of $H_2{}^{15}O$ during the study session. The estimated radiation dose from $H_2{}^{15}O$ will be no more than 0.1 rads per study for a cumulative dose of 0.5 rads which is comparable to less than two and one half times the natural background radiation in the Knoxville/Oak Ridge area. These radiation doses are well within the limits permitted by the National Council of Radiation Protection (NCRP) and have been approved by the Isotope Committee of the University of Tennessee Medical Center.

8. I understand that female subjects will be tested for pregnancy by the Standard Pregnancy Test (UTMCK Pathology Laboratory). I state that to the best of my knowledge I am not pregnant nor do I plan to become pregnant within the next month; I understand that radioactive material con be harmful to the unborn child. Pregnancy or suspected pregnancy would exclude me from this study. If I am breast feeding, I should skip the two consecutive feedings immediately following the PET scan.

9. Scans will be made with an ECAT scanner. I understand that this examination will require approximately 3 hours for completion during which time I will lie quietly on a comfortable bed in a relaxed position.

10. Every effort will be made to keep all medical records confidential. The data about the study will be stored in data bases at the University of Tennessee Medical Center and in a locked file cabinet in room 574-1 So. Stadium Hall at the University of Tennessee. In any report or publication of the results of this study, I will be referred to only by subject number and any possible identifying information will be disguised or omitted. There may be, however, occasions when my identity must be made known to state and federal agencies, such as the Food and Drug Administration, which regulates medical research, including this study, and to the sponsor of this study when they require such disclosure for audit purposes. However, agencies and sponsors are also required to keep information regarding participant identity confidential. Otherwise, access to my records will be limited to the principal investigators (Ms. Fran Tucker, Dr. Gloriajean Wallace, or Dr. Karl Hubner) or their assistants, such as those individuals in the Department of Radiology who configure the computer data in preparation of the PET images and assist the investigators in running the computer programs during data analysis. Names will be provided to the UTMCK Internal Review Board and to the University Committee of Research Participation at a later time when those people who helped with the study are specified.

Date: _____

Research Subject initial here _____

Witness initial here _____

11. I understand that the total time requirement for participation in this study will be approximately 5 hours, including the time for the PET and MRI scans and the hearing and neurological screenings and the pregnancy test (for female subjects).

12. If I wish to discuss any concerns regarding the PET or MRI scan, I may contact either Dr. Karl F. Hubner, Department of Radiology, University of Tennessee Medical Center, Knoxville (615-544-9662); Fran Tucker (615-974-5019), Department of Audiology and Speech Pathology, University of Tennessee, Knoxville; Dr. Gloriajean Wallace, Department of Audiology and Speech Pathology, University of Tennessee, Knoxville (615-974- 5019), or Dr. Edward Buonocore, Chair of the Department of Radiology, University of Tennessee Medical Center, Knoxville (615-544-9663).

13. I understand that the examiner may terminate the study at any time and that I am free to refuse participation at any time without prejudice to current or future medical care for _____ (name of volunteer) at the UT Medical Center

or speech, language, or hearing services at the University of Tennessee Hearing and Speech Center.

I have read and understood this consent form and agree to have this examination performed on _____ (myself) and acknowledge that all my questions have been answered. A copy of this form has been provided to me.

I understand that in the event of injury resulting from the research procedures, financial compensation is not available and medical treatment is not provided free of charge.

I understand that I am not waiving any legal rights or releasing the hospital or its agents from liability for negligence.

_____ _____

Signature of Volunteer Date

_____ _____

Signature of Investigator Date

_____ _____

Signature of Witness Date

APPENDIX D. Response form.

Subject: Date:

IDENTIFICATION OF CVCs WITH MEANING - RESPONSE FORM

Instructions:

The purpose of this task is to determine which consonant-vowel-consonant (CVC) combinations have meaning to you. You will listen to the combinations said aloud. Please indicate all CVCs that sound like a recogizable English word, even if it is a slang or obscure word. Also, please indicate any CVC that has meaning idiosyncratic to you (e.g. a family nickname, name of a pet, or a family "made up" word).

Stimuli:

bat	bap	beb	bed	bep	bet
buk	bup	dad	dag	dak	ded
deg	dep	dek	det	dob	dok
dog	dop	dot	duk	dup	dut
gag	gak	gap	ged	gek	gep
get	god	gog	gok	gop	got
gub	gud	gug	gup	gut	kab
kag	kak	kat	keg	kep	kek
ket	kub	kud	kug	kuk	kup
pab	pad	pag	peb	peg	pob
pod	pog	pub	pud	pop	pog
pob	pot	tag	teb	teg	tep
tob	tub	tuk	tud	tug	tup
dap	keb				

Note: Vowels are represented orthographically: a = /æ/, e = /ɛ/, o = /ɑ/, and u = /ʌ/.

APPENDIX E. Face mask instructions.

Instructions for making face mask

Materials:

Splinting material - (e.g. Ezeform) sufficiently long and wide to cover the top half of the face; purchasable in a case of four 16"x24" sheets at @$172 (O.T. supplied me with scraps remaining from their splints)

Velcro strips - purchasable at fabric store, Walmart, etc.

Carpet knife and cutting board

Scissors

Electric frying pan

2 Paper towels

Cloth towel

Ball point pen or mechanical pencil

Instructions:

A. To Be Done Ahead

1. Make a template for the final mask by laying a paper towel over the subject's face and tracing a mask to cover approximately the forehead, bridge of the nose and cheekbones of subject, marking eye holes - like a Lone Ranger mask. Cut this out including eye holes.

2. If approximate size splinting material is not available, use the carpet knife and cutting board to cut a piece from a larger piece of the material which would fit the template.

3. Lay the paper mask on the splinting material and trace with a pen or pencil that is indelible in water.

4. Heat sufficient water in electric frying pan to cover mask. Lay a paper towel on the bottom of the frying pan to keep the material from sticking to the pan. Heat water to boiling then reduce to simmer.

5. Place the material in the frying pan and leave it until it loses stiffness. Remove with tongs or scissors and place on the cloth towel. Pat dry, then pick up the piece and gently toss on your hands until it is cool enough to handle easily.

6. Cut out mask and eye holes from the pattern with the scissors. Gently roll the edges around eyes outward so the no edges are sticking into the eye holes. Trim edges around the mask so that no sharp points remain.

7. At this point, mask can be left to finish on the day of the scan.

B. On the day of the scan (It is important to finish the mask at the time of the scan so it fits the subject's face as it is at that time):

1. Heat water in the frying pan as above. Place paper towel. Lay the mask in the water and leave until softened. Remove and cool as above.

2. Have subject lie down on the scanner bed with head in the head rest.

3. When the material is sufficiently cool - both by your judgment and that of the subject - place the mask on the subject's face and gently mold around the features.

   - check eye holes, whether large enough
   - check for rough edges
   - check that part over nose is short enough that it does not cover tip nor in anyway impede breathing

4. Pay particular attention that the mask fits snugly over the bridge of the nose and against the sides of the face.

5. Make necessary adjustments by removing mask from the subject's face and cutting the mask with scissors while material is still warm. Material may be reheated two-three times without its losing its molding character.

6. When mask has mostly cooled on the face and the subject agrees to the fit, remove the mask and run it under cold water to set.

7. Attach Velcro (hook side) to the mask, two on each side, above and below the eye holes, and one up and down in the middle of the forehead. Replace on the subject's face.

8. Attach strips of Velcro to the Velcro on the mask to secure the head in the headrest. Adjust according to the needs for scanning.

   Note: This procedure will not keep the head entirely immobilized without the subject's cooperation, but should assist in limiting movement as much as possible and give the subject a point of reference against movement, especially over the bridge of the nose.

APPENDIX F. Protocol for PET scans at UTMCK

UTMCK PET CENTER SCANNING PROTOCOL

O-15 WATER BRAIN SCANS -- BASELINE AND AUDITORY STIMULATION

Radiopharmaceutical:	O-15 water
t1/2:	2 minutes
dose:	63 mCi
start scan:	immediately post injection
scan mode:	dynamic scan, 12 10-second frames (2 min. total)

Patient Prep

1. Informed consent signed

2. IV (250ml normal saline, 18g needle)

3. Face mask in place (prior measurements by investigator)

4. Ear phones in place (by investigator). Stimuli presented in the right ear, EAR plug in left ear.

Methods

1. Position patient in the gantry. The first slice is parallel to and begins at the canthomeatal line. Reduce external stimulation - use eye covers and keep the room quiet and darkened.

2. Transmission scan for 15-20 minutes (10-30M counts per direct plane, 220-660M counts total). Give the pharmacist and physician a 10 minute before-injection notice.

3. A series of five injections of 63 mCi O-15 water doses will be given for acquisition of data in the following sequence: baseline #1, auditory stimuli #1, baseline #2, auditory stimuli #2, and baseline #3.

4. Set up a dynamic acquisition for 12 10-second frames (2 minute total). Start ECAT at the time of injection for each of the baseline data acquisitions.

5. After completion of baseline #1 and baseline #2 acquisitions, the auditory stimuli will be started (by the investigator) one minute prior to a the injection of 63 mCi O-15 water dose using an identical acquisition protocol.

6. Reconstruct data with optimal zoom factor and filter.

Processing

1. Create numeric data on ROIs dividing the brain into four quadrants.

2. Create numeric data on ROIs dividing the brain into right and left hemispheres.

3. Create time:activity curves of all numeric data

4. Archive all data.

APPENDIX G. Instructions to PET subjects.

INSTRUCTIONS TO PET SUBJECTS

The purpose of this study is to determine whether there is a difference in cerebral blood flow, as measured by positron emission tomography (PET), in response to auditory stimulation with meaningless and meaningful consonant vowel consonant (CVC) combinations.

Prior to the PET scan

1. Before the day of the PET scan, as a participant in this study you will receive:

   a. a pure tone hearing test
   b. a brief neurological screening
   c. a magnetic resonace imaging (MRI) scan

Arrangements will be made for your hearing test at the University, for the neurological screening with Andrew Zimmerman, M.D., and the MRI at the University of Tennessee Medical Center at Knoxville (UTMCK).

2. You will be asked to answer a brief questionnaire related to any history of speech, language, hearing and neurological disorders.

3. You will listen to a group of consonant-vowel-consonant syllables (CVCs) and asked to judge which have meaning to you.

4. A face mask will be fashioned for you in the Occupational Therapy Dept at UTMCK. Prior to the day of the PET scan, you will be asked to go to the OT Dept. to have a pattern of the mask made for you. The actual mask will be made on the day of the scan.

5. You will be given and asked to sign a Statement of Informed Consent.

Procedure for the PET scan

1. You will lie on the scanner couch. Wear comfortable, warm clothing, including warm socks!

2. The face mask will be applied and your head positioned for the scan.

3. A small insertion earphone will be placed in your right ear and your left ear will be occluded with a small ear plug.

4. Your eyes will be covered with a cloth.

5. The nurse will start an I.V. in your hand which contains a saline solution into which the $H_2{}^{15}O$ will be injected.

6. The room will be quiet and darkened.

7. You will receive an initial transmission scan for individual attenuation correction, and five $H_2{}^{15}O$ cerebral blood flow (CBF) scans. During the transmission scan,the first, third and fifth CBF scan, no stimuli will be presented. In the second and fourth CBF scans, you will listen to either meaningless of meaningful CVCs.

The transmission scan will be about 20 minutes. Each of the CBF studies will be two minutes.

8. During each scan, please lie quietly and remain alert and relaxed. Do not talk or make any movements during the scans.

9. Between scans please refrain from extensive talking or movement. After each scan, you will be informed how long it will be until the next scanning procedure. There will be a period of about 10-15 minutes between the transmission and the first scan and between the first and second scan. There will be a thirty minute interval between the second and third scan.

THANK YOU FOR YOUR PARTICIPATION IN THIS STUDY !

APPENDIX H.

Image Preparation for Processing with Neurotool.

Developed by Hedley Bond, Ph.D., Department of Radiology, University of Tennessee Medical Center, Knoxville.

IMAGE PREPARATION FOR PROCESSING WITH NEUROTOOL

1. Acquire MR images.

Logon to the Unix host and change to the appropriate directory for storing the MR files, e.g. */anlz/mri1*. Images are transferred from the research (or northern) machine using *ftp*. .Each image is stored in a separate file on the PDP11. Filenames have the form - G<*MR_study_number*><*image_number*><*image_designation*>.IMG
The MR_study_number field is in hexadecimal and comprises 4 characters; the image_number field is also in hex. and comprises 2 characters; the image_designation comprises two characters and has the form 1A, 1B, etc. Coronal, sagittal, and axial views are assigned different study numbers. For example, the 22 images for study number 24424 are named G5F68*.IMG; actual filenames are G5F68011A.IMG - G5F68161A.IMG. The images can be copied to the working directory of the Unix host with ***mget *.IMG***.

2. Rename MR images, strip headers and concatenate.

The images after copying will be in RSX format in which the high order (or more significant) byte of a short integer pair of bytes is at a higher address. To convert to Sun format, the pair of bytes specifying a pixel value must be swapped. The filenames should also be changed. MR images contain 256 x 256 pixels, usually with a field of view of 24 cm. Each pixel is specified by 10 bits so that image data occupies 131,072 bytes per image. To convert to a general image format, the Elscint header information that precedes the image data must be removed, bytes must be swapped and, optionally, data compressed to 8 bits per pixel. This conversion is done with a locally written C program (*mstrip*). *Mstrip* takes a list of filenames for input and one filename for output. To get a list of input files, enter - ***ls G5F68*.IMG > flist***
Be sure that ls is unaliased, otherwise asterisks may appear after executable image files.
Run mstrip with - ***mstrip flist dummy1091AX.img 1***
Here flist refers to a list of files, all images are to be concatenated in one file (*dummy1091AX.img*) and 1 indicates that several files are to be converted to 1 file. The user is prompted for the number of 1K bytes to strip (headers), whether to compress to 1 byte per pixel or not, and, if so, how to compress (generally by dividing by 4).

3. Convert MR images to CTI format.

Get the section width (FOV), slice width and slice gap for the MR study from the MR logbook or the films. Occasionally one or more images at either end are blurry or outside the region of interest. These images can be deleted with the Unix utility *dd*. Remove images 1 and 14 from dummy1091AX.hdr with -

dd if=dummy1091AX.img of=dmyAX1091AXd.img bs=65536 skip=1 count=12

Note: the letter d in the output filename indicates that one or more of the original images have been removed. Zoom the images to a specified pixel size, generally 1 mm/pixel, with a program developed in the IPL - *zoom_img*. To zoom *jone1091AXd.img* to 1mm/pixel enter: ***zoom_img dmy1091AXd.img dmy1091AXdz.img***
Zoom_img reads the Analyze header (if it exists) to determine input file details; if no header exists, you will be prompted for the details.

The input MR images all have the same basic paramters - 14 transaxial images, each 256 x 256 with a pixel size of 0.9375 mm. The sections are 5 mm thick with a 2 mm slice gap. Zooming to a pixel size of 1mm results in images of 240 x 240 pixels. The zoomed MR images are interpolated to achieve a 1 mm separation between adjacent sections. Run ***interp*** with input and output filenames as parameters. Interpolate *dmy1091AXdz.img* with - ***interp dmy1091AXdz.img dmyAXdzi.img***

You will be prompted for input and output file parameters and told the number of new slices. Assuming *dmy1091AXdz.img* to have 12 sections, each 5 mm thick with a 2mm gap, 76 interpolated sections 1mm apart are produced giving 78 sections in all. Each image is 240 x 240 (1 byte/pixel) so the total size of *dmyAXdzi.img* is 4,492,800 bytes or 4.28 Mb. Currently a maximum of 93 images in one file (that is, three CTI directory blocks) can be converted to CTI format. If the number of images exceeds the conversion limit, split the interpolated file into 2 with *dd*. *Zoom_img* can now be run with the interpolated image files with CTI format requested for output and using the same image size for output (240 x 240). That is, the images are copied, not zoomed, CTI headers and directory blocks are setup and bytes are swapped. Convert *dmyAXdzi.img* with -

zoom_img dmyAXdzib.img dmyCip10.img

The user will be prompted as to whether the images should be "padded" to 256 x 256 by adding 0's around the edges of the 240 x 240 matrix; each pixel still occupies 1 mm. Images sized in this way will display better with CTI software.

4. MR Image Specifics

Each study consisted of 14 transverse (axial) sections 5mm thick with a 2mm gap. All images were 256 x 256 with a 24 cm FOV. The 14 images were concatenated to 1 file (8 bit pixels). Two images were deleted; the remaining 12 were zoomed to 1 mm/pixel, interpolated, padded to 256 x 256 and converted to CTI format for use with neurotool.

a. Subject 1 - Sep. 18, 1991.
Sections = *vola0991ax01.img - vola0991ax14.img*. Images 1 & 14 discarded, remaining 12 images zoomed, interpolated, padded and converted to CTI format.
Final images - *volaCip10.img* - 78 images @ 256*256

b. Subject 2 - Aug. 28, 1991.
Sections = *volb0891ax01.img - volb0891ax14.img* Images 13 & 14 discarded (dd), remaining 12 images zoomed, interpolated, padded and converted to CTI format.
Final images - *volbCip10.img* - 78 images @ 256*256

c. Subject 3 - Aug. 29, 1991.
Sections = *volc0891ax01.img - volc0891ax14.img*. Images 13 & 14 discarded, remaining 12 images zoomed, interpolated, padded and converted to CTI format.
Final images - *volcCip10.img* - 78 images @ 256*256

E. Resize Pet Images

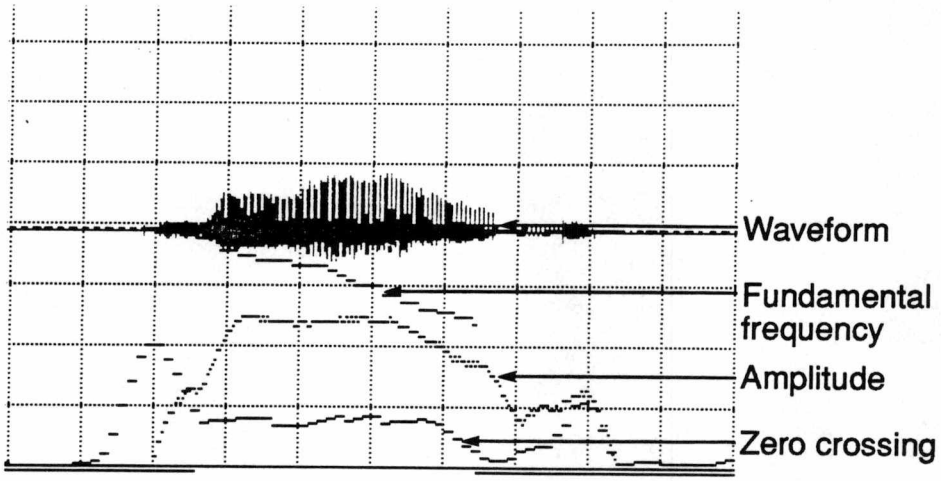
The composite PET images (*volac1dall.img, volac2dall.img*, etc.) have to be zoomed to the same pixel size (1mm) as the processed MR images. The PET images before processing have 128 x 128 pixels with each pixel covering 2.347 mm. A frame of images holds 15 planes with the distance between planes being 6.75 mm. Using *zoom_img*, the PET images are -

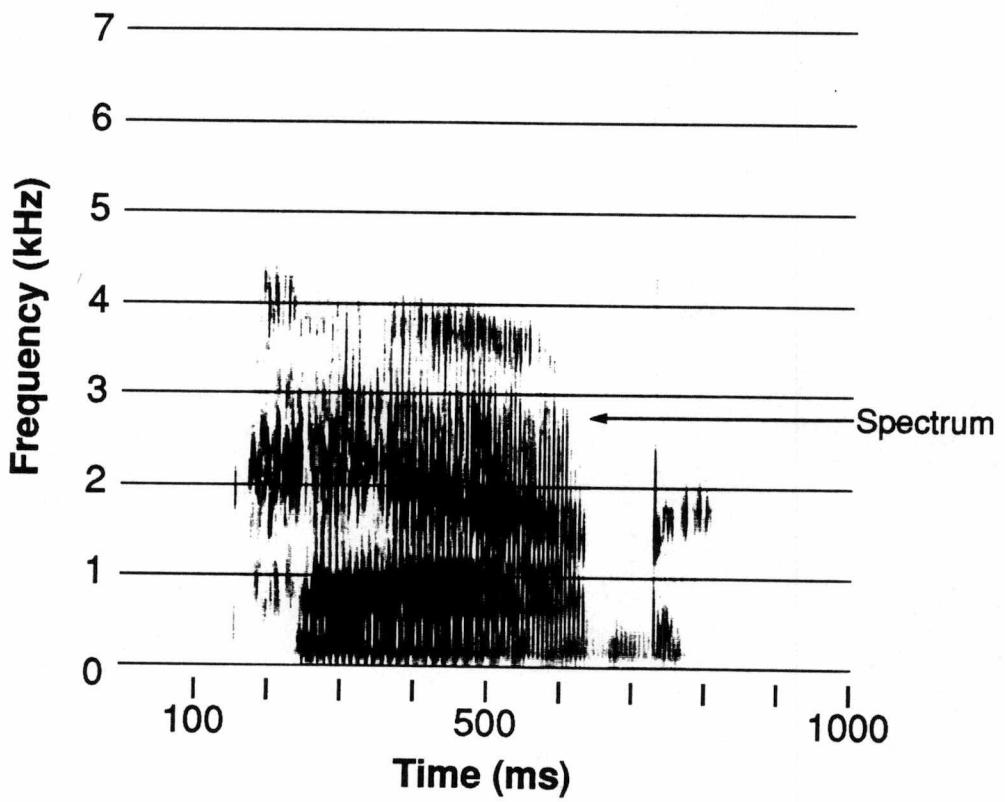
- zoomed to a pixel size of 1 mm, giving an image size of 300 x 300,
- cropped to an image size of 256 x 256 (In cropping, strips of zero pixels are removed from all four sides of the image.), and
- written out in CTI format with new header data.

Thus, the PET image file *volcc1dall.img* (15 images - 500,224 bytes) after zooming and cropping is saved as the file *volcc1dall_zp1.img* (zp1 = Zoomed to pixel size of 1mm.) containing 15 images each 256 x 256 pixels (1,974,784 bytes). Other PET images were treated similarly.

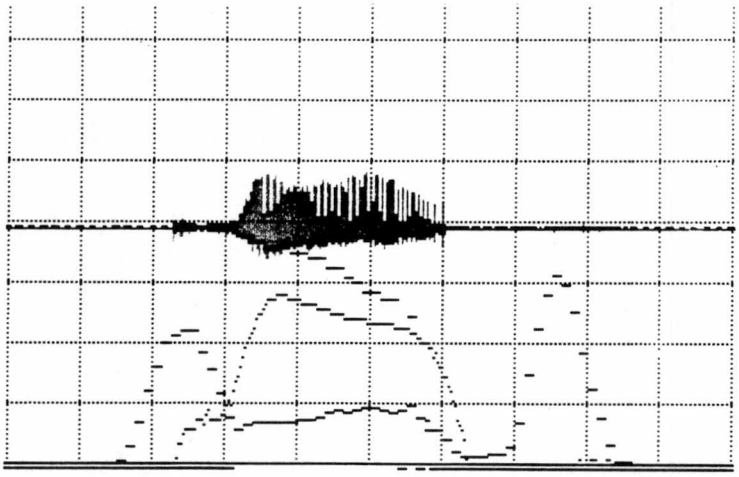
APPENDIX I.

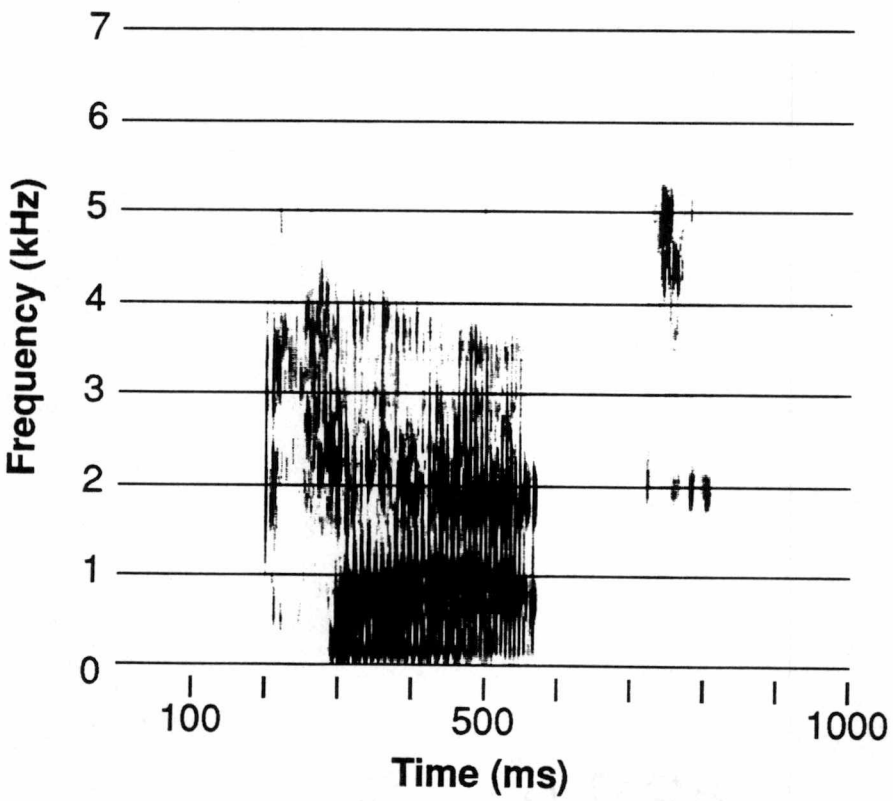
Spectrograms


Waveform
Fundamental frequency
Amplitude
Zero crossing

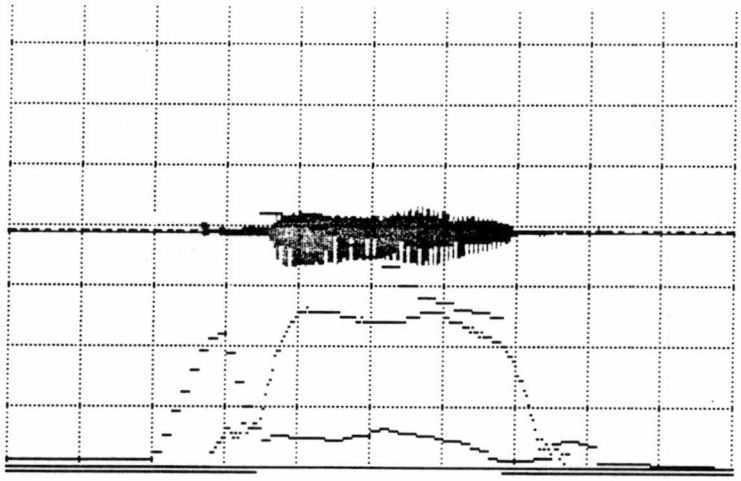

7
6
5
4
3
2
1
0
Frequency (kHz)
Spectrum
100
500
1000
Time (ms)

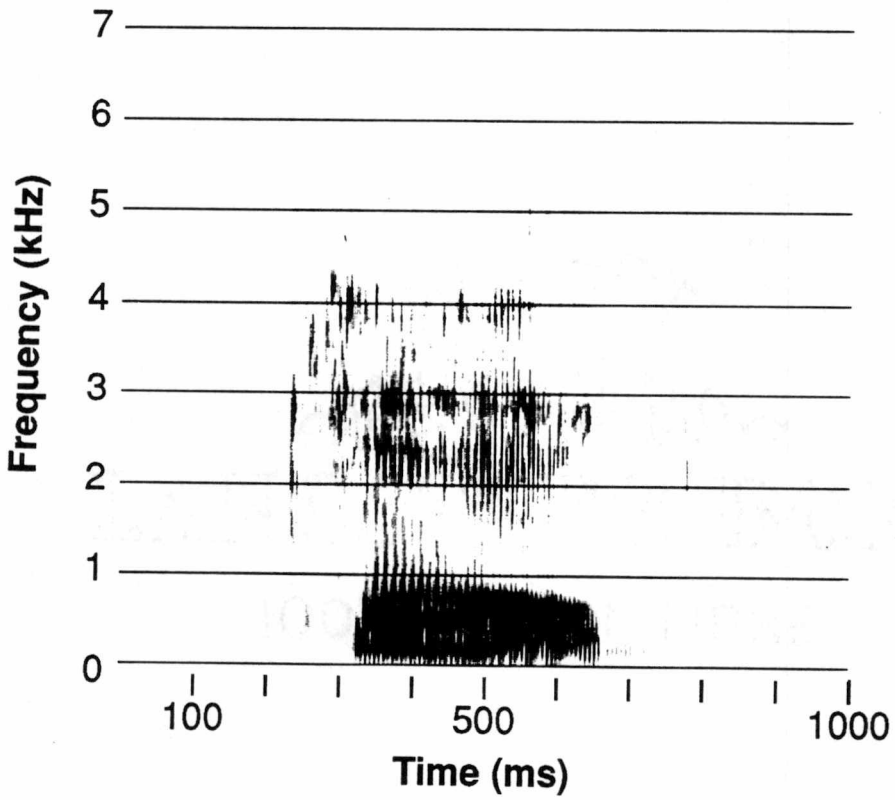
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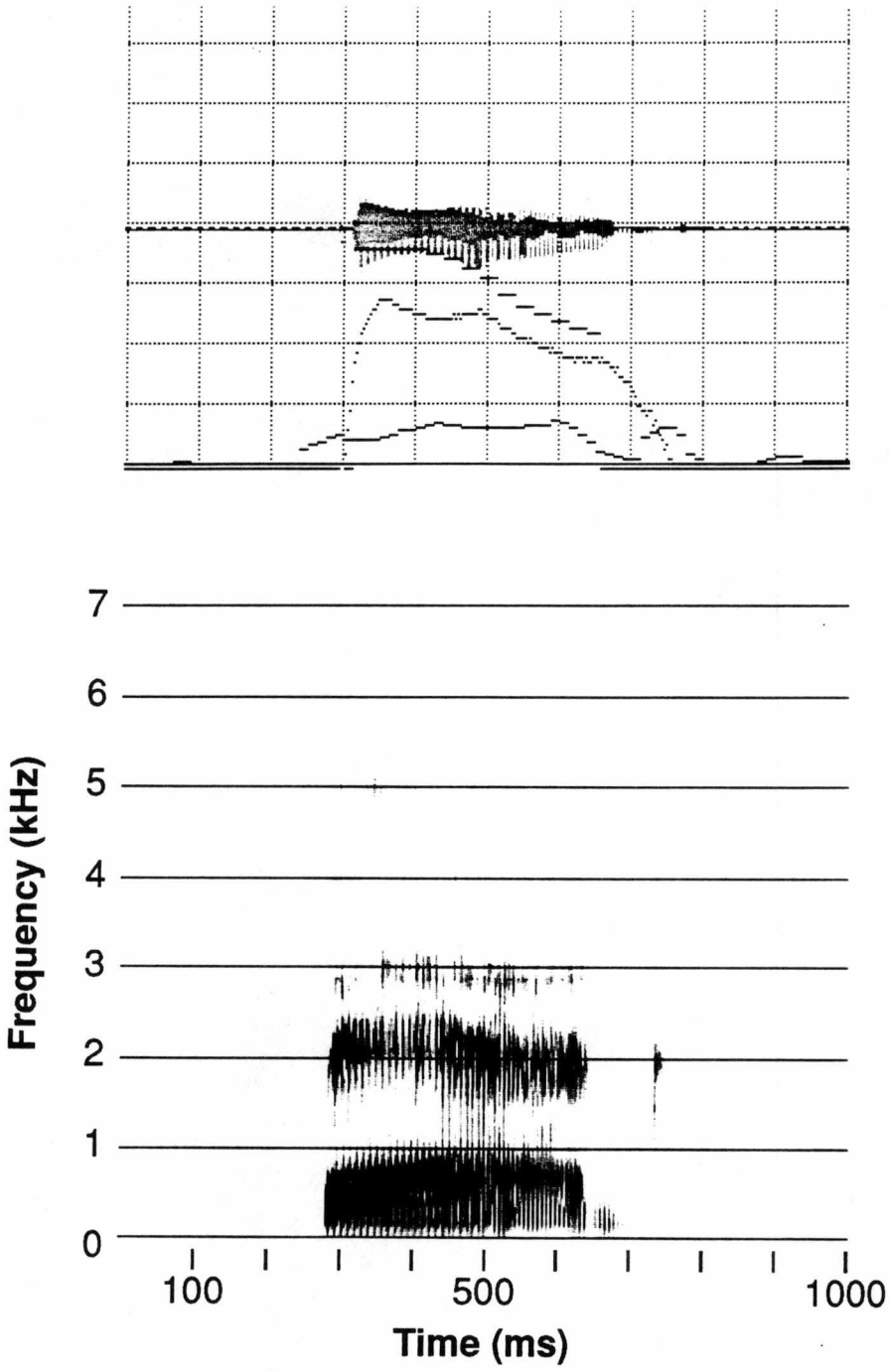


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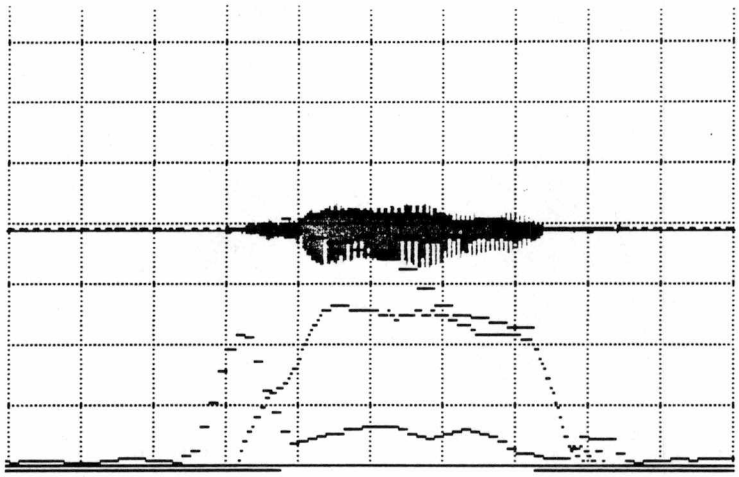


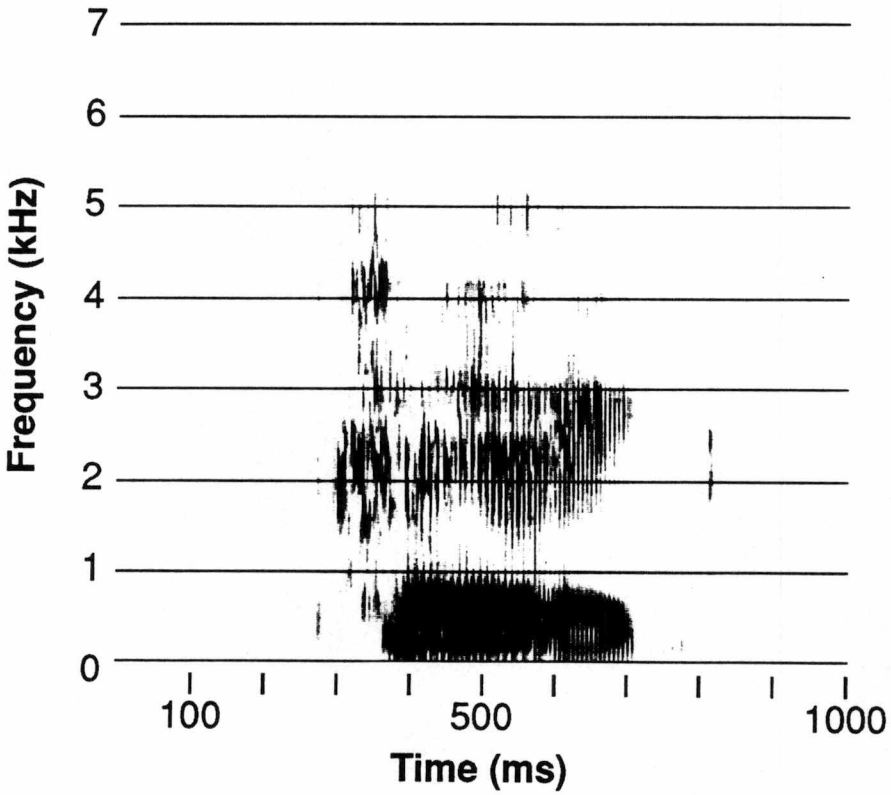


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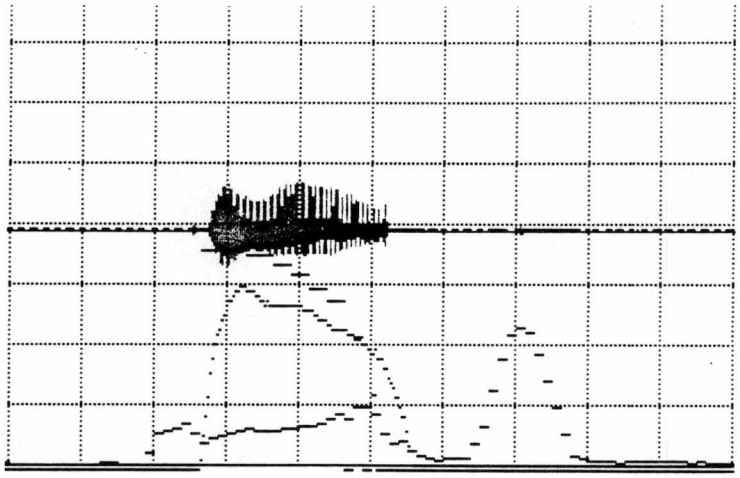


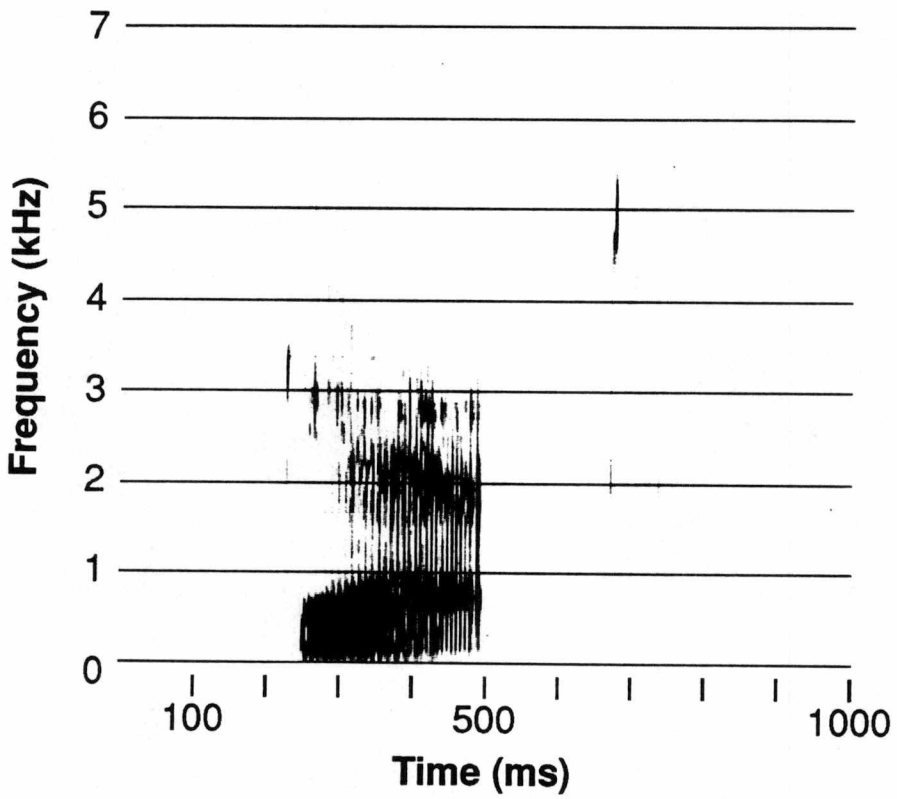
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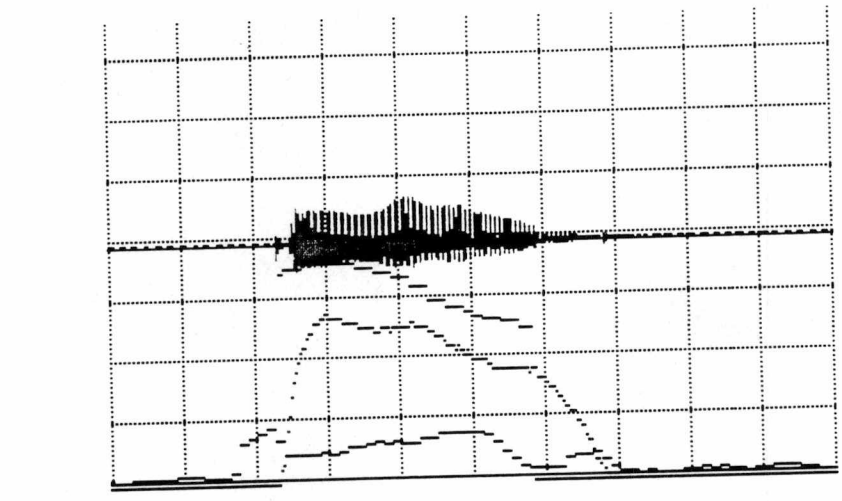


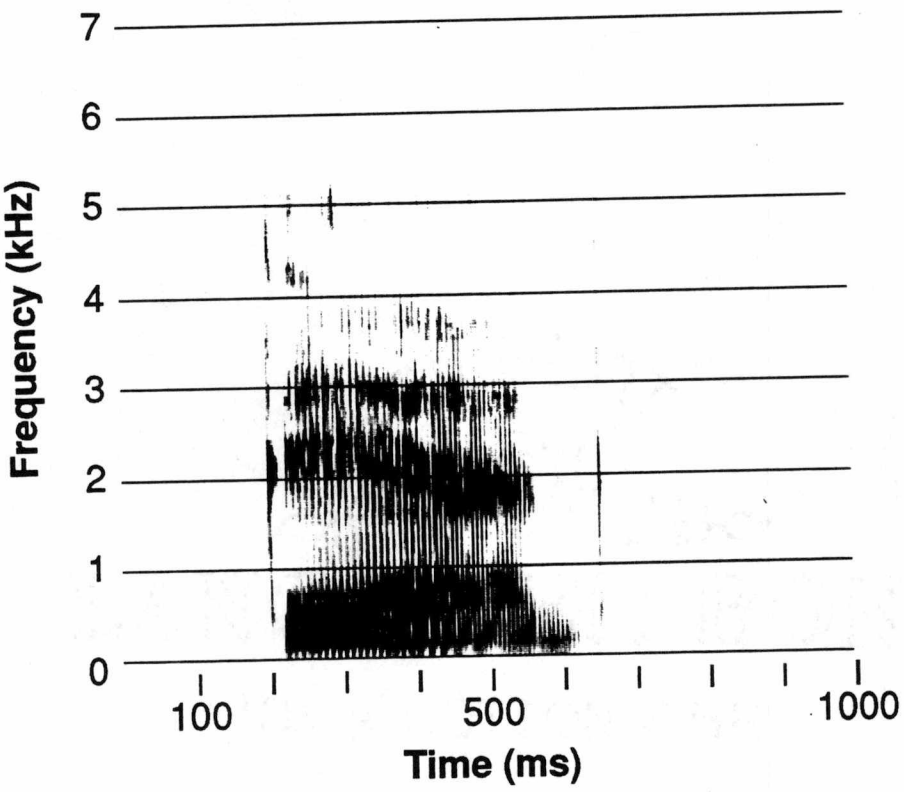
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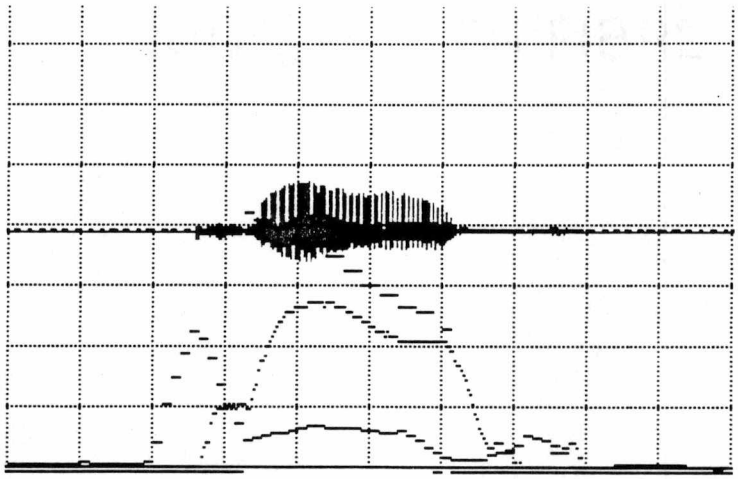


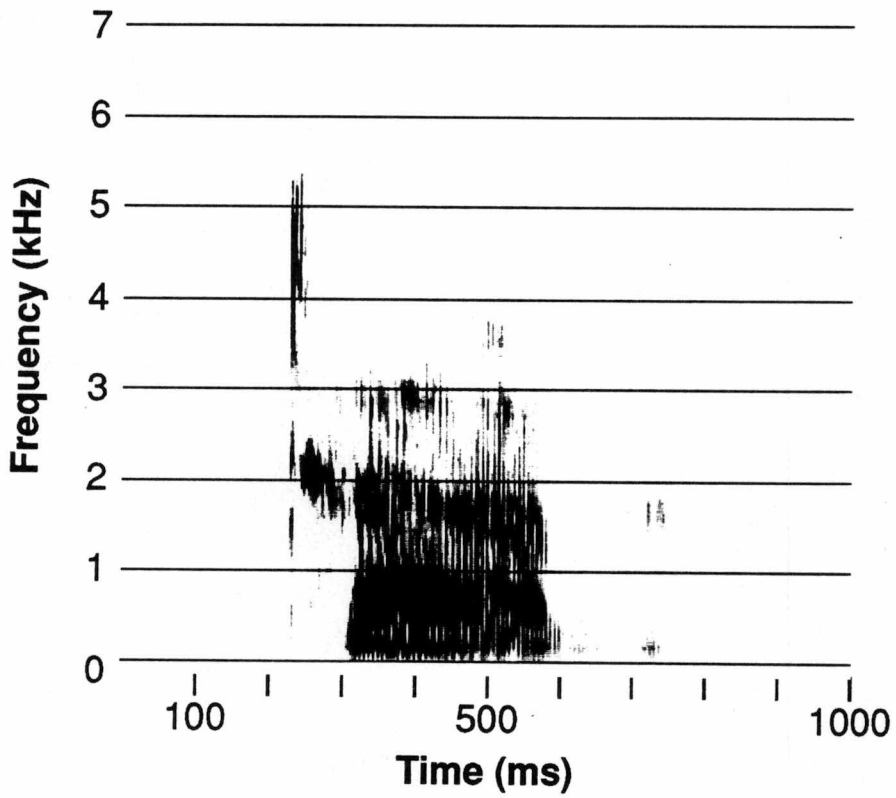
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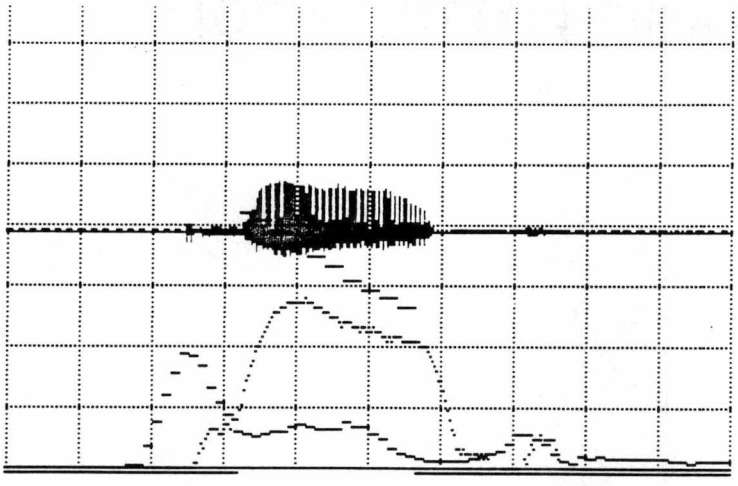


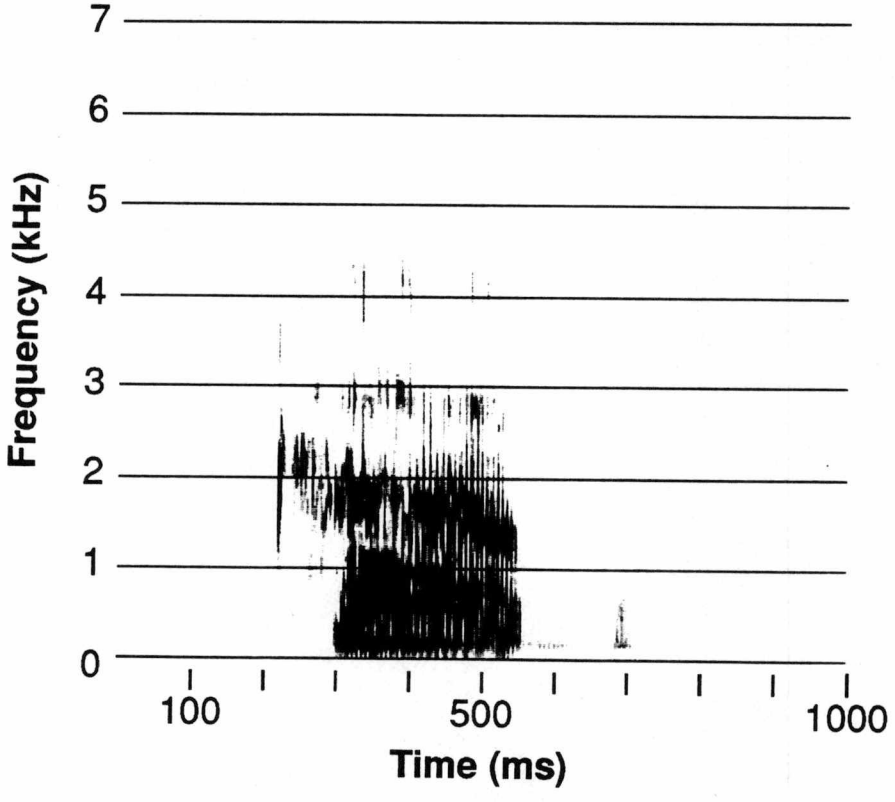
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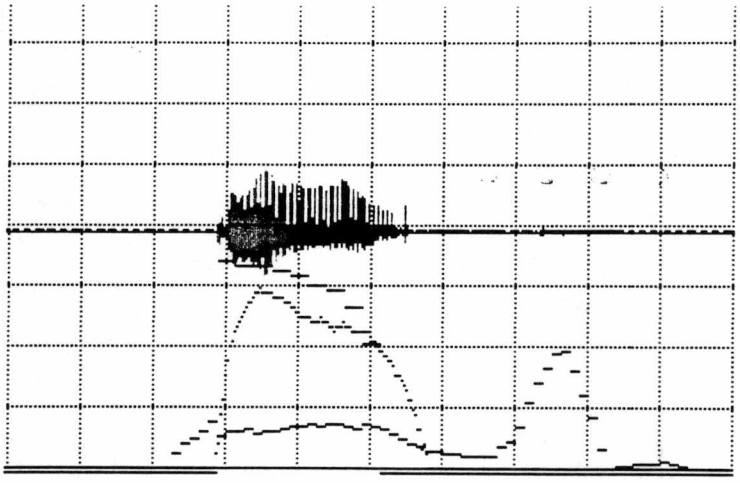


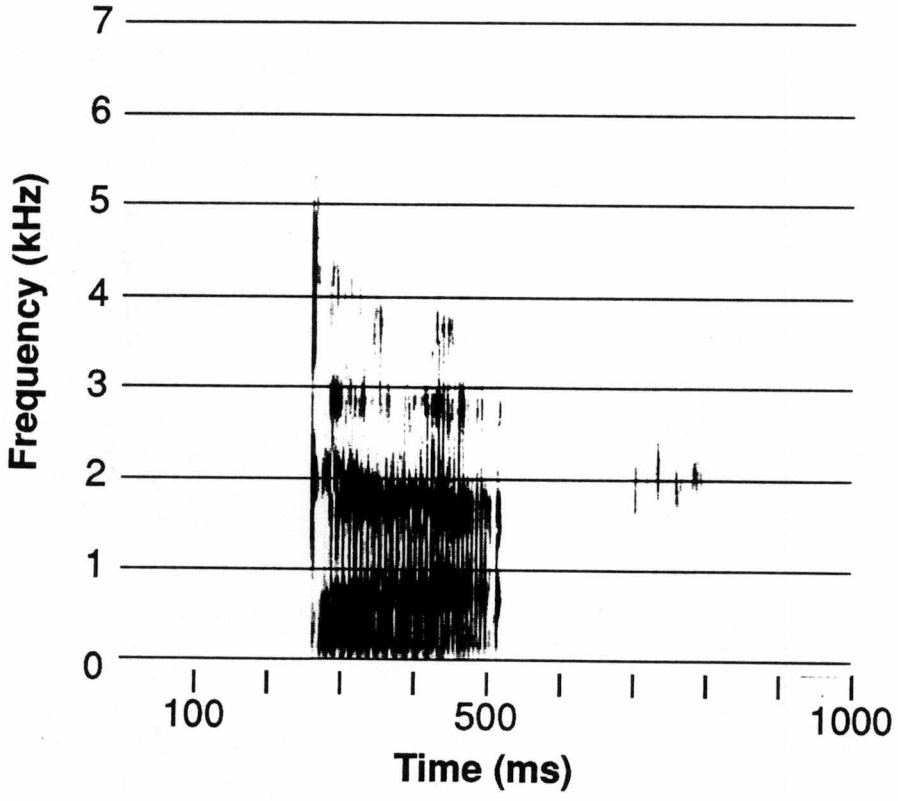
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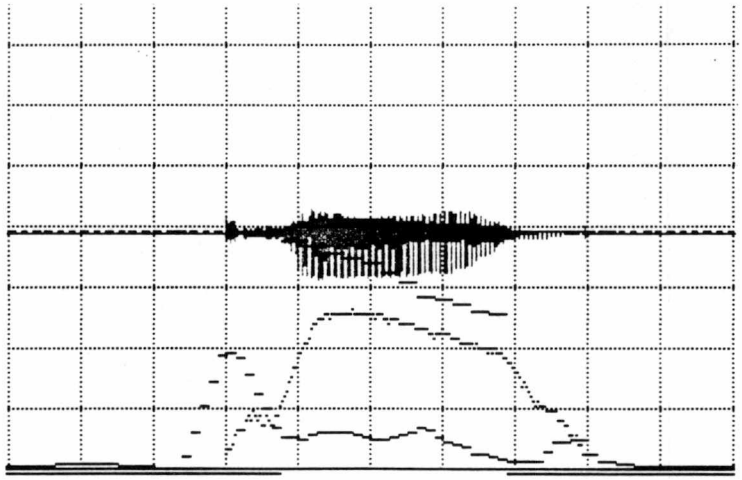


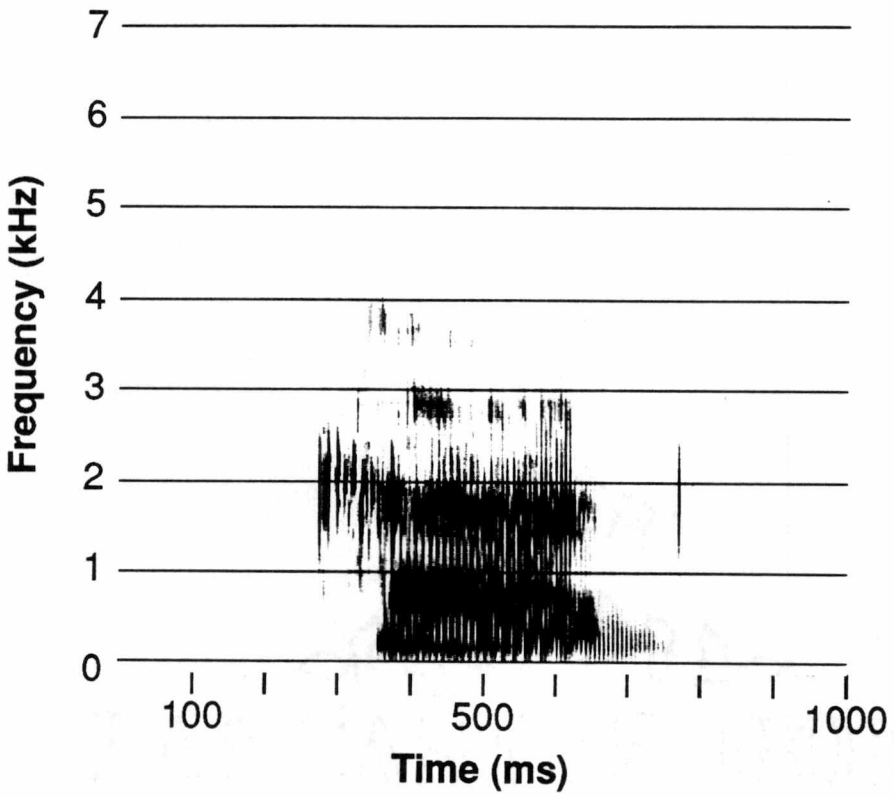
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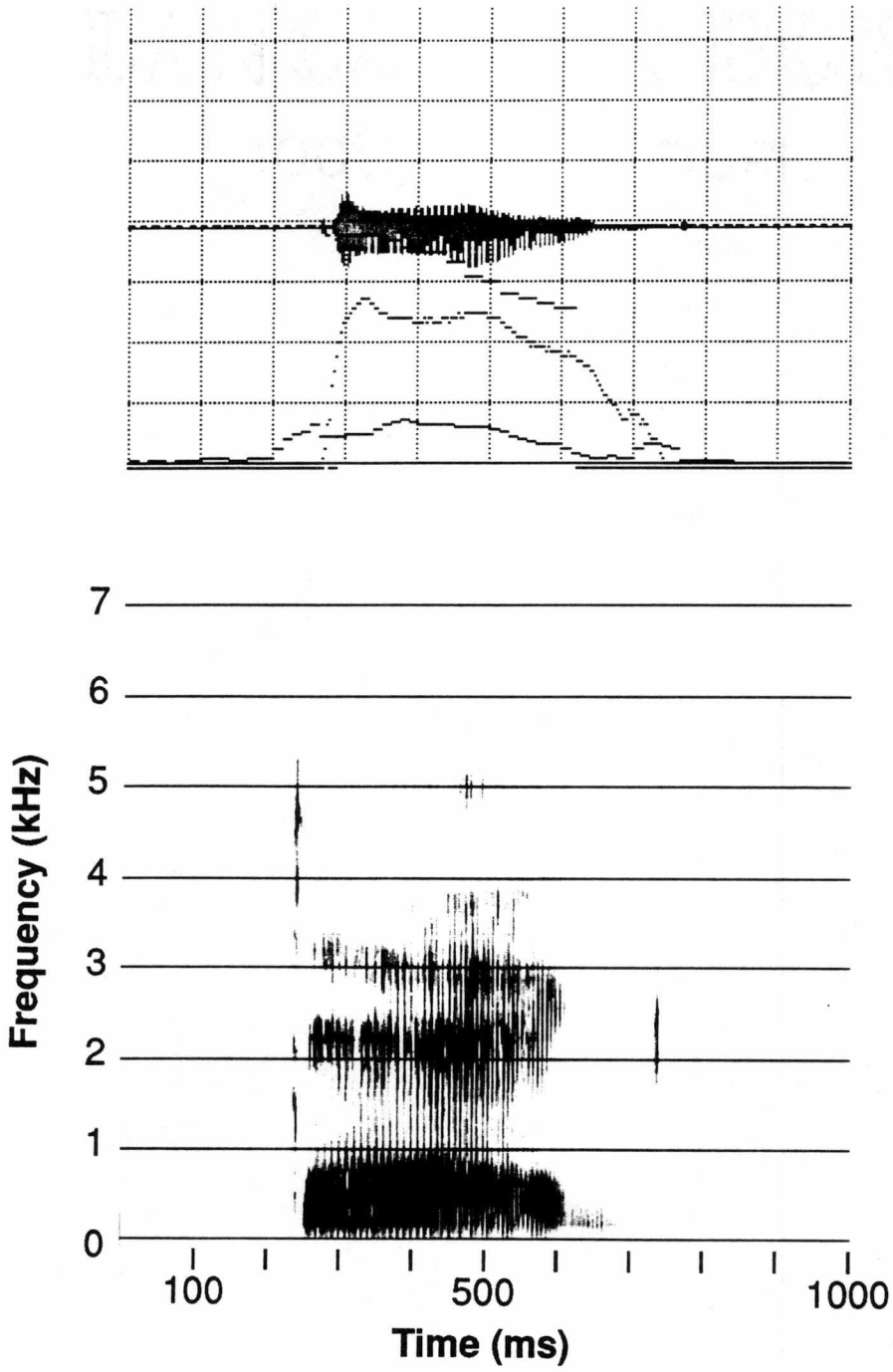


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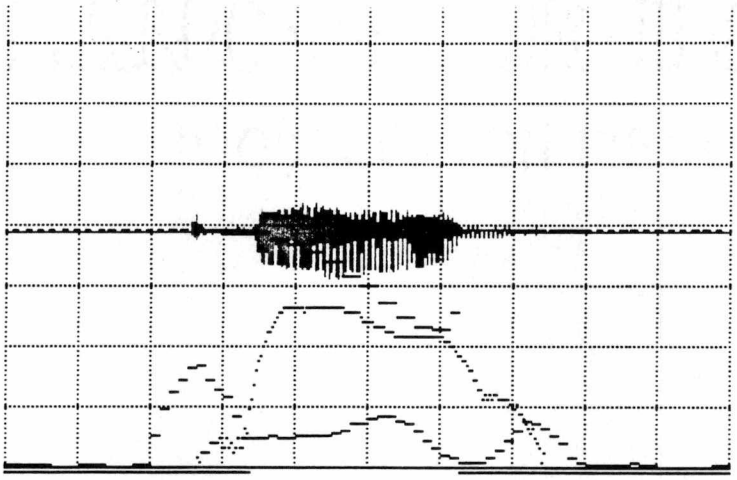


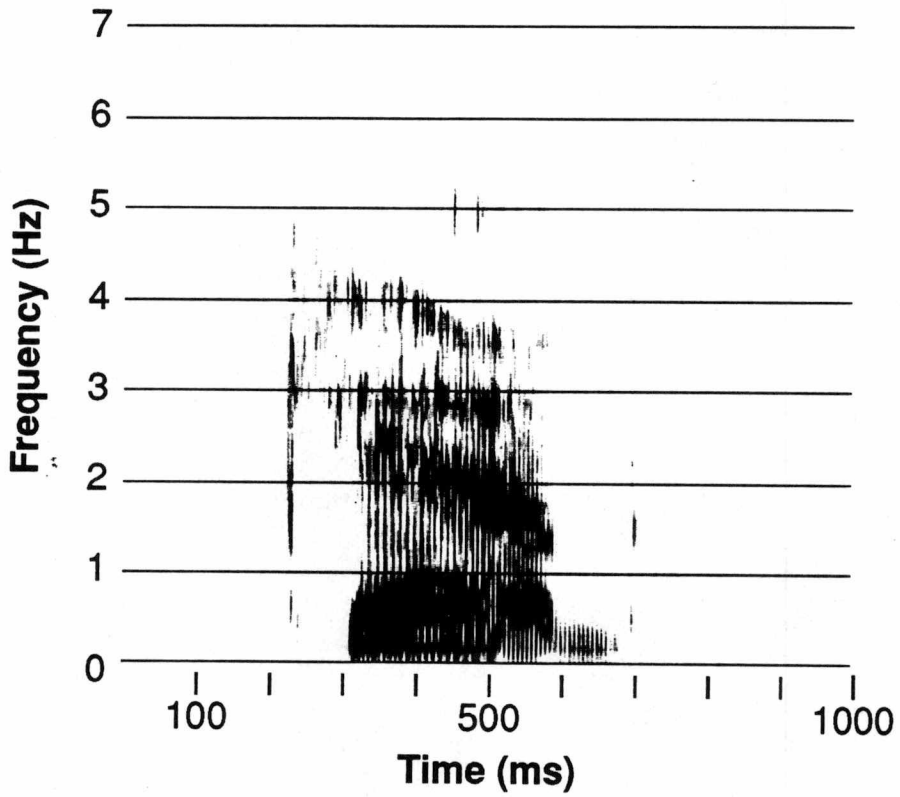


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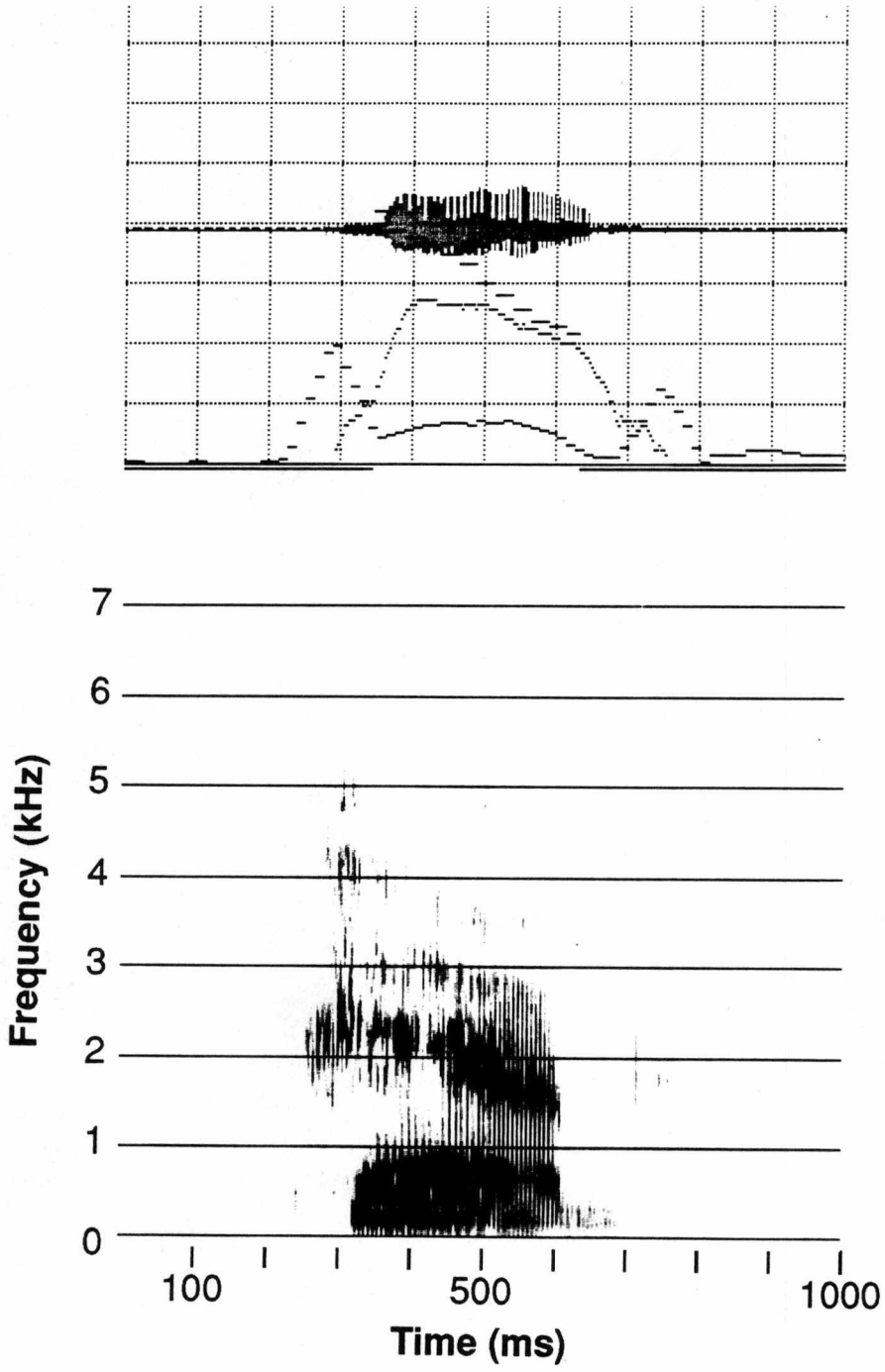


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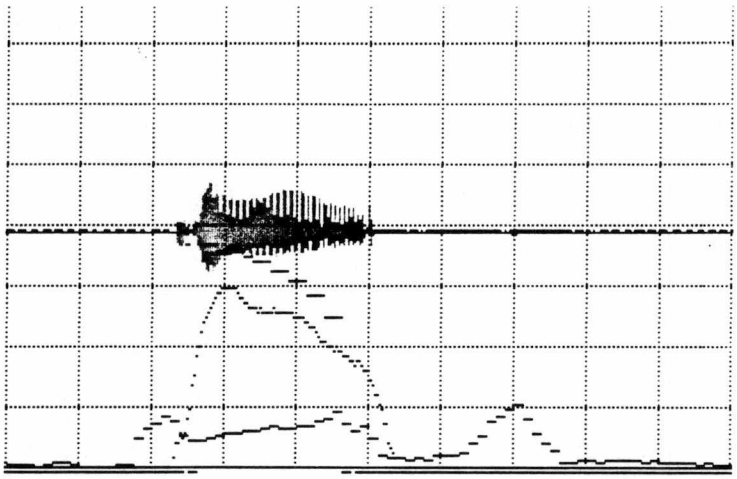


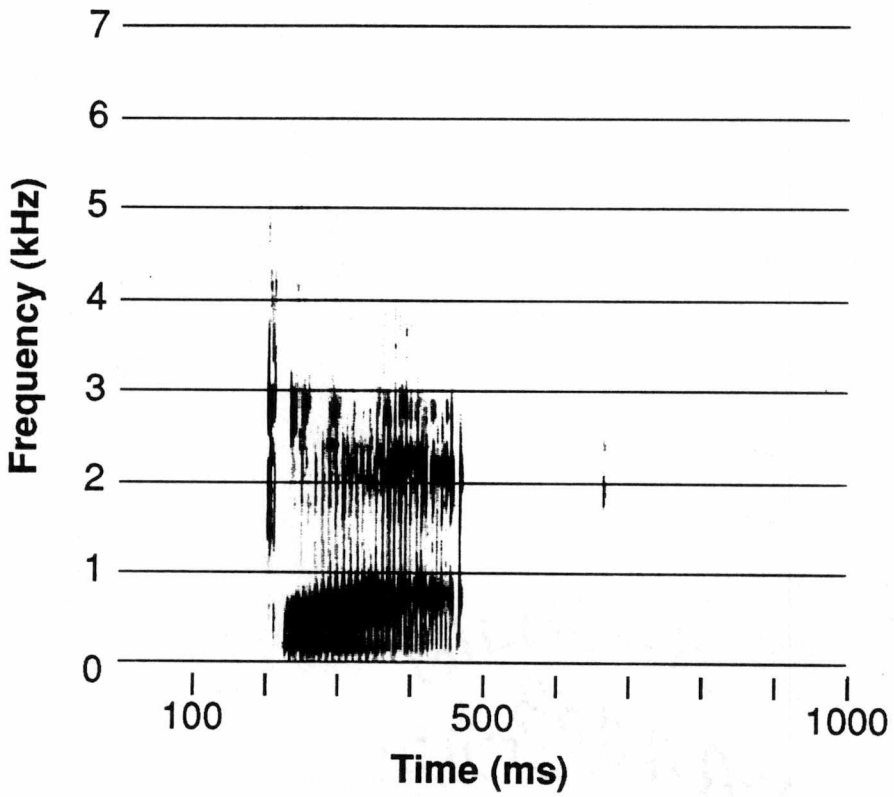


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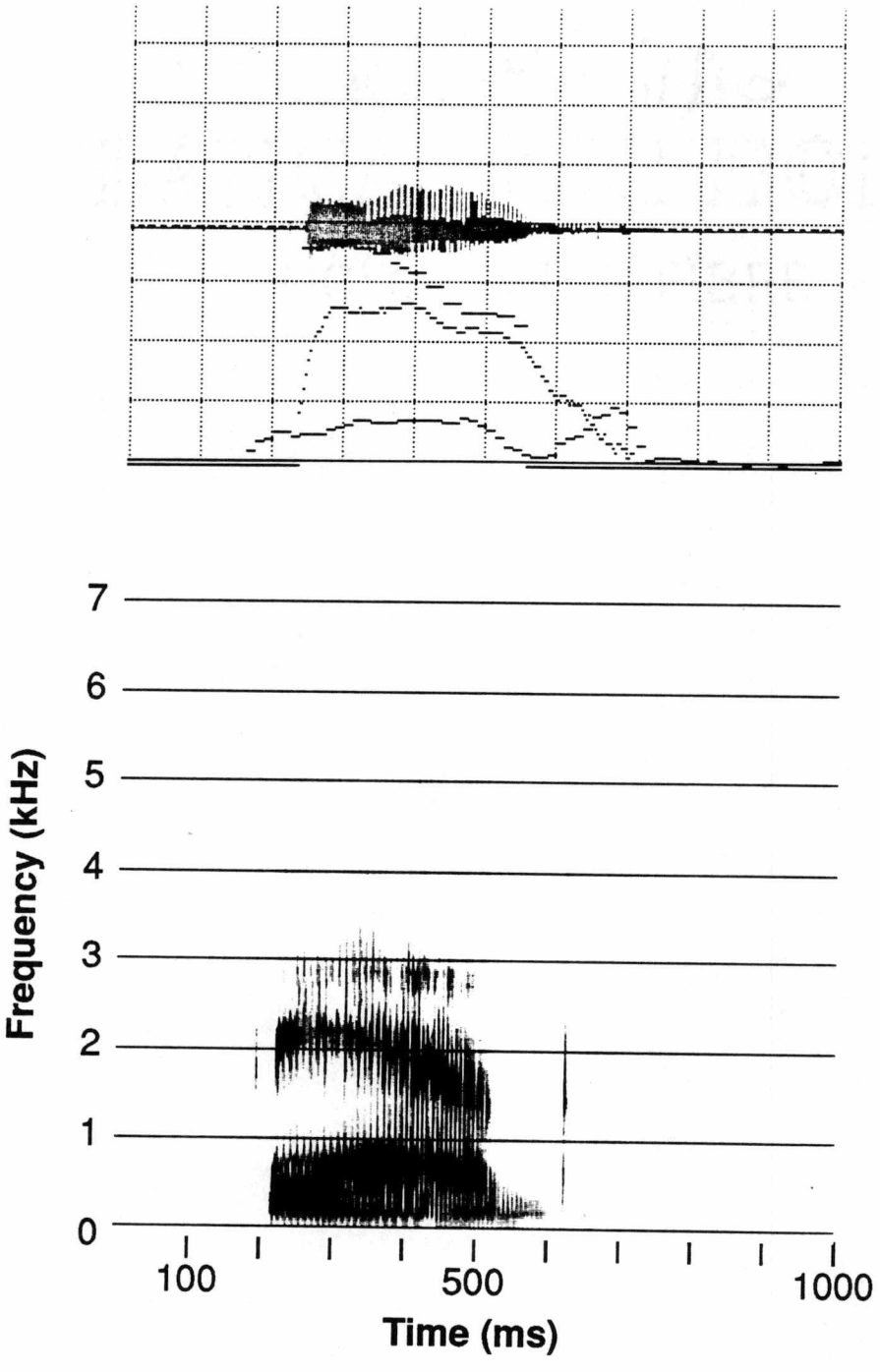


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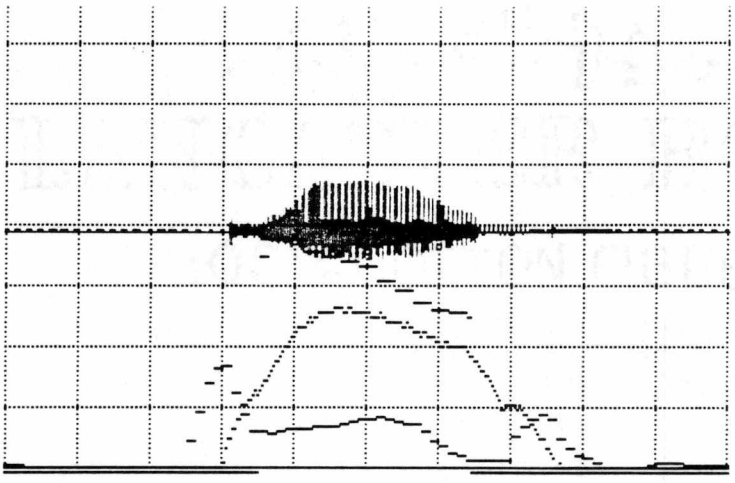


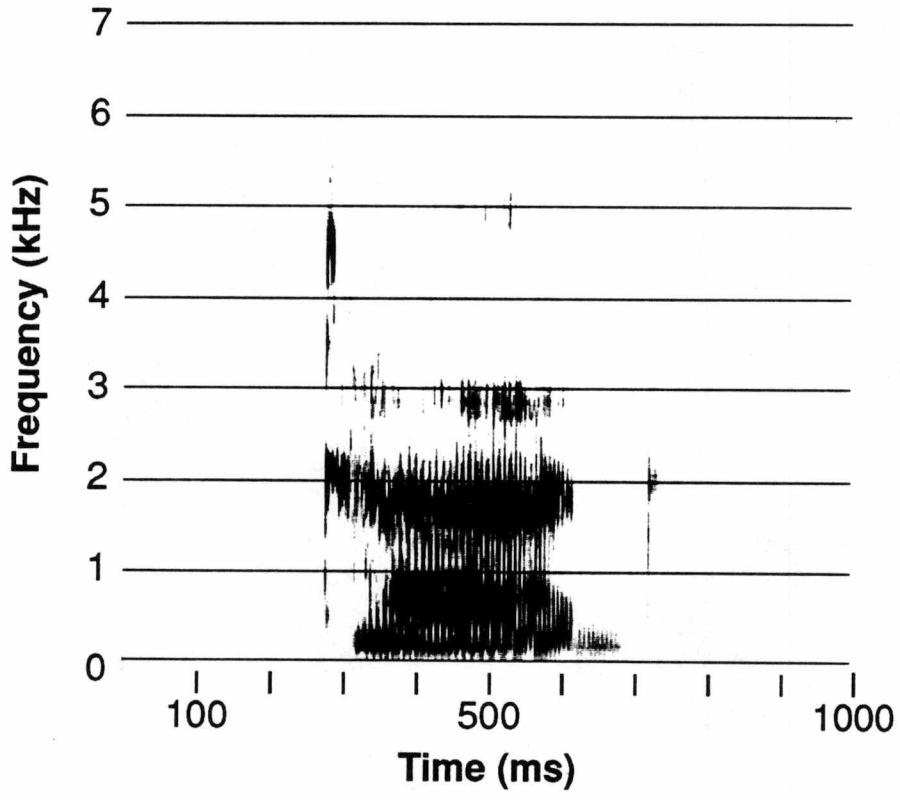


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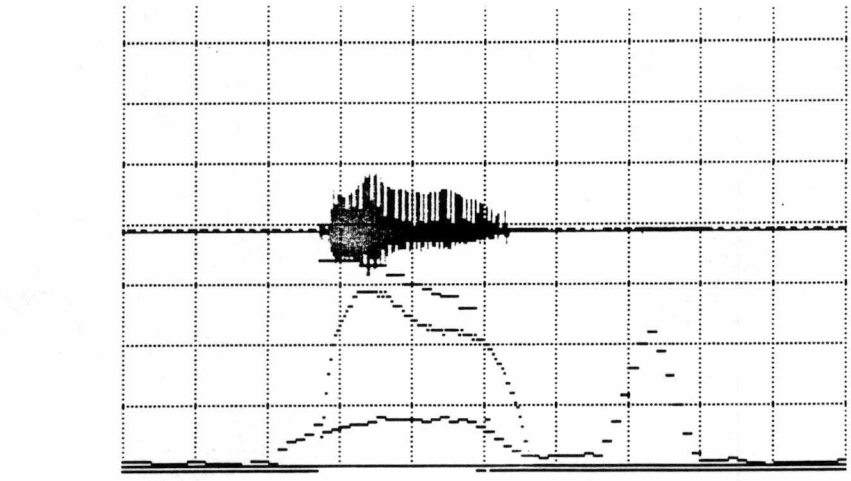


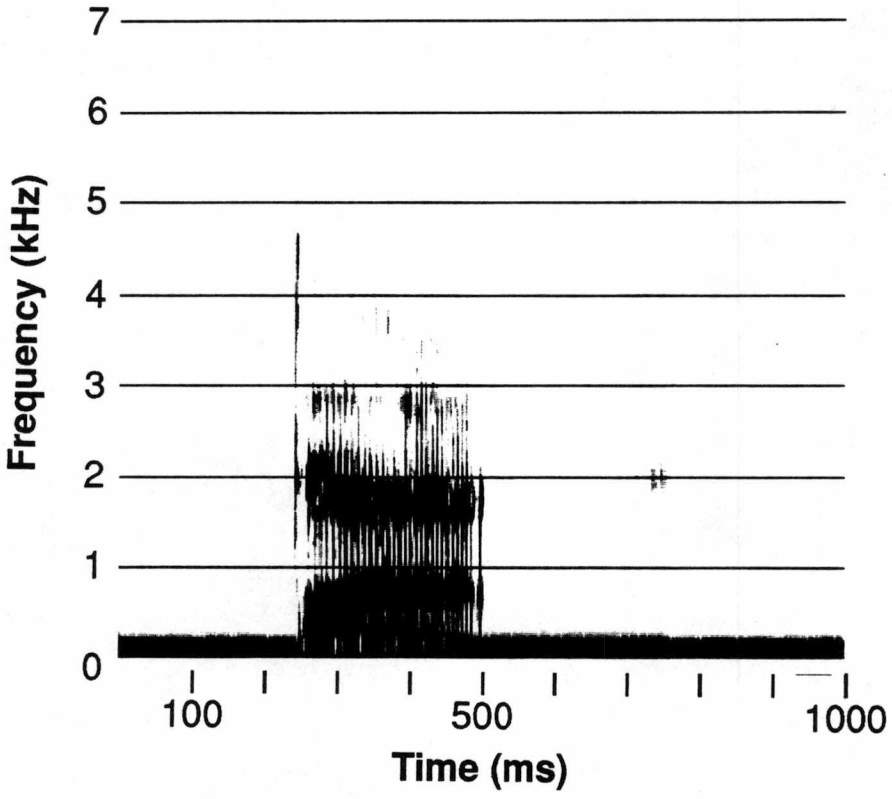
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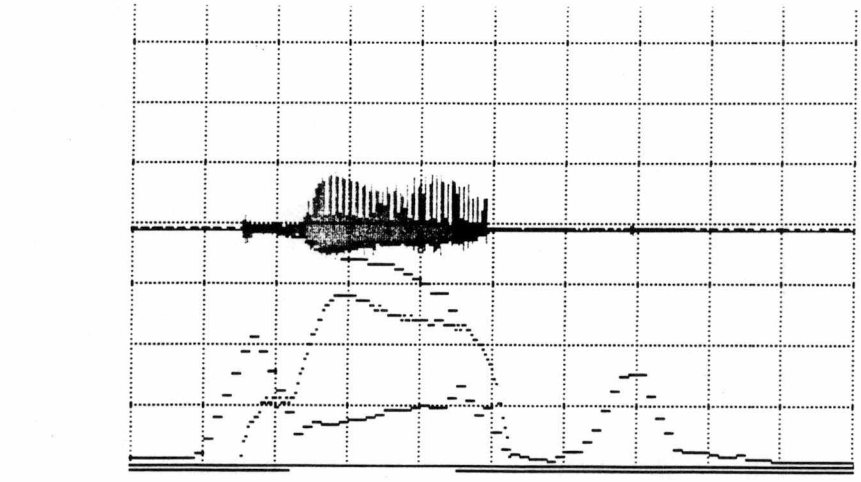


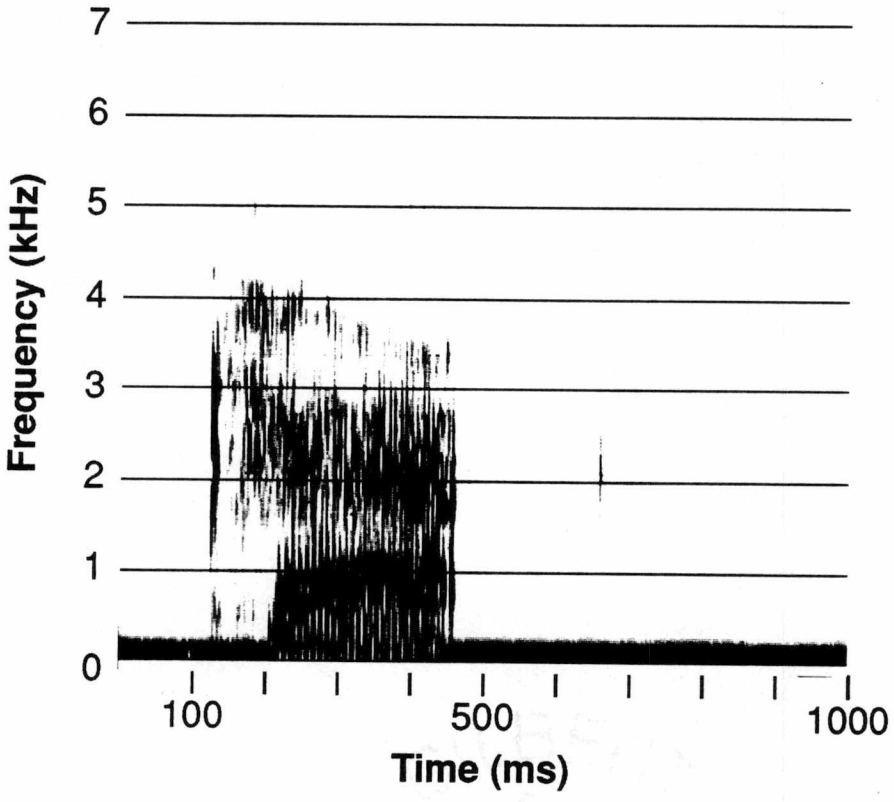
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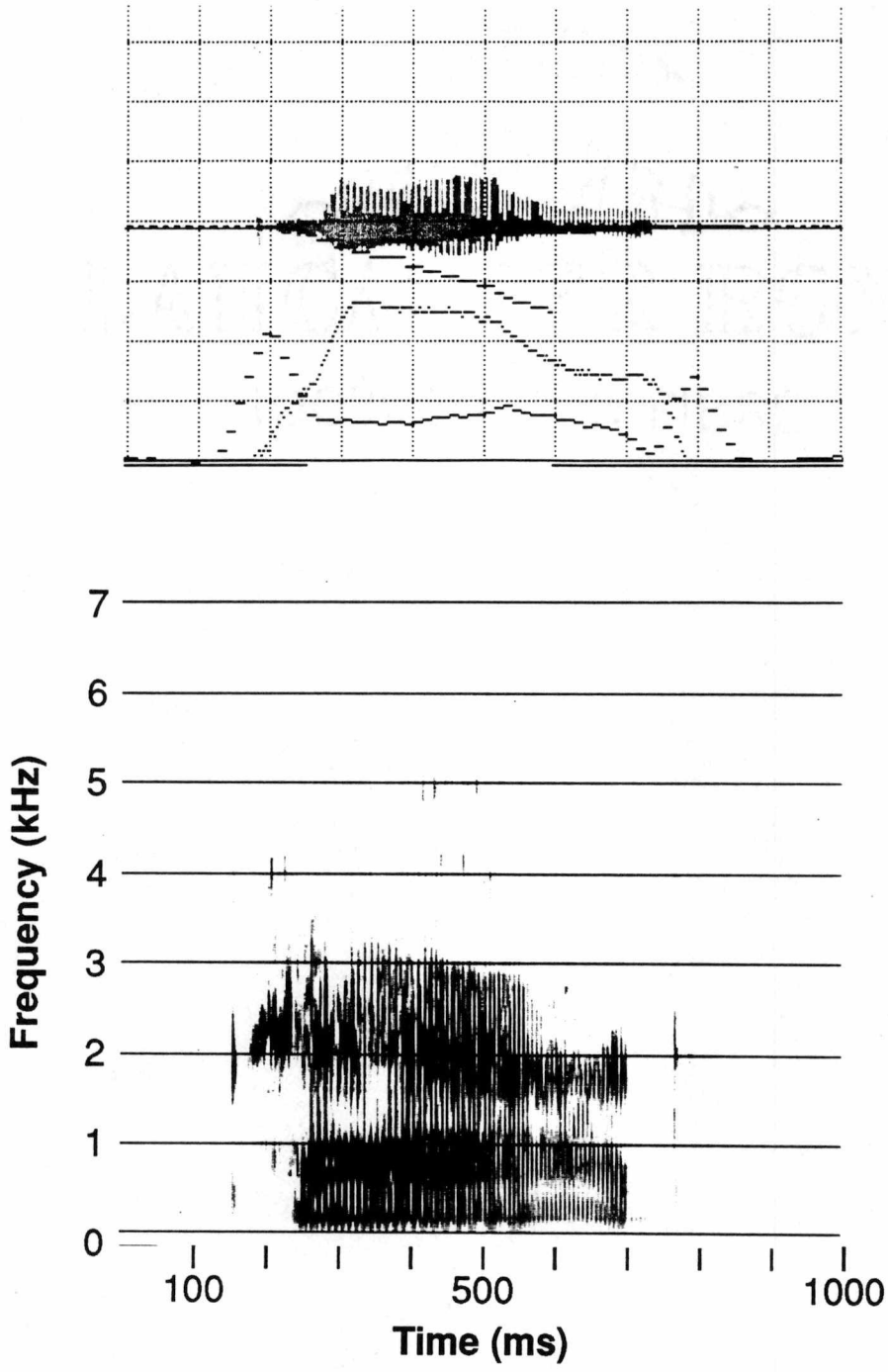


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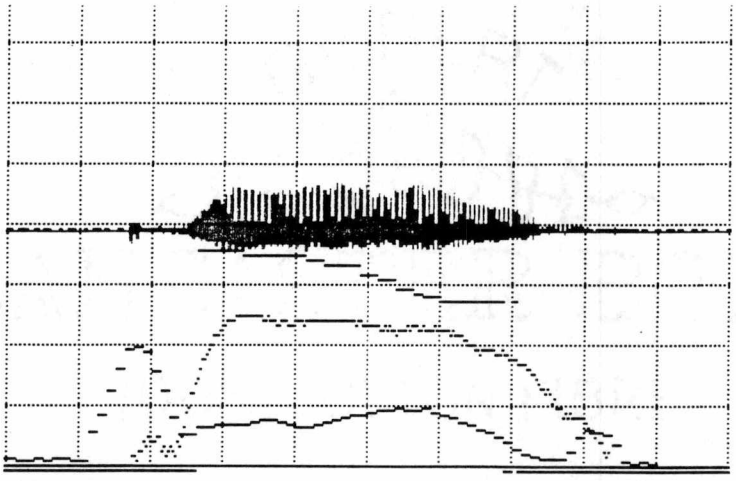


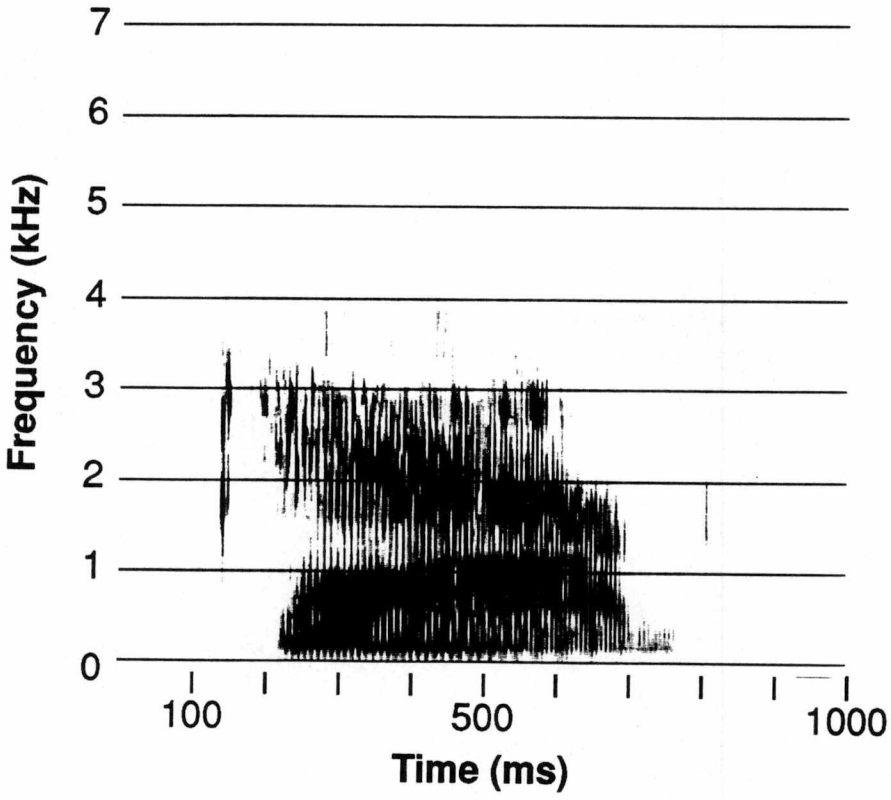


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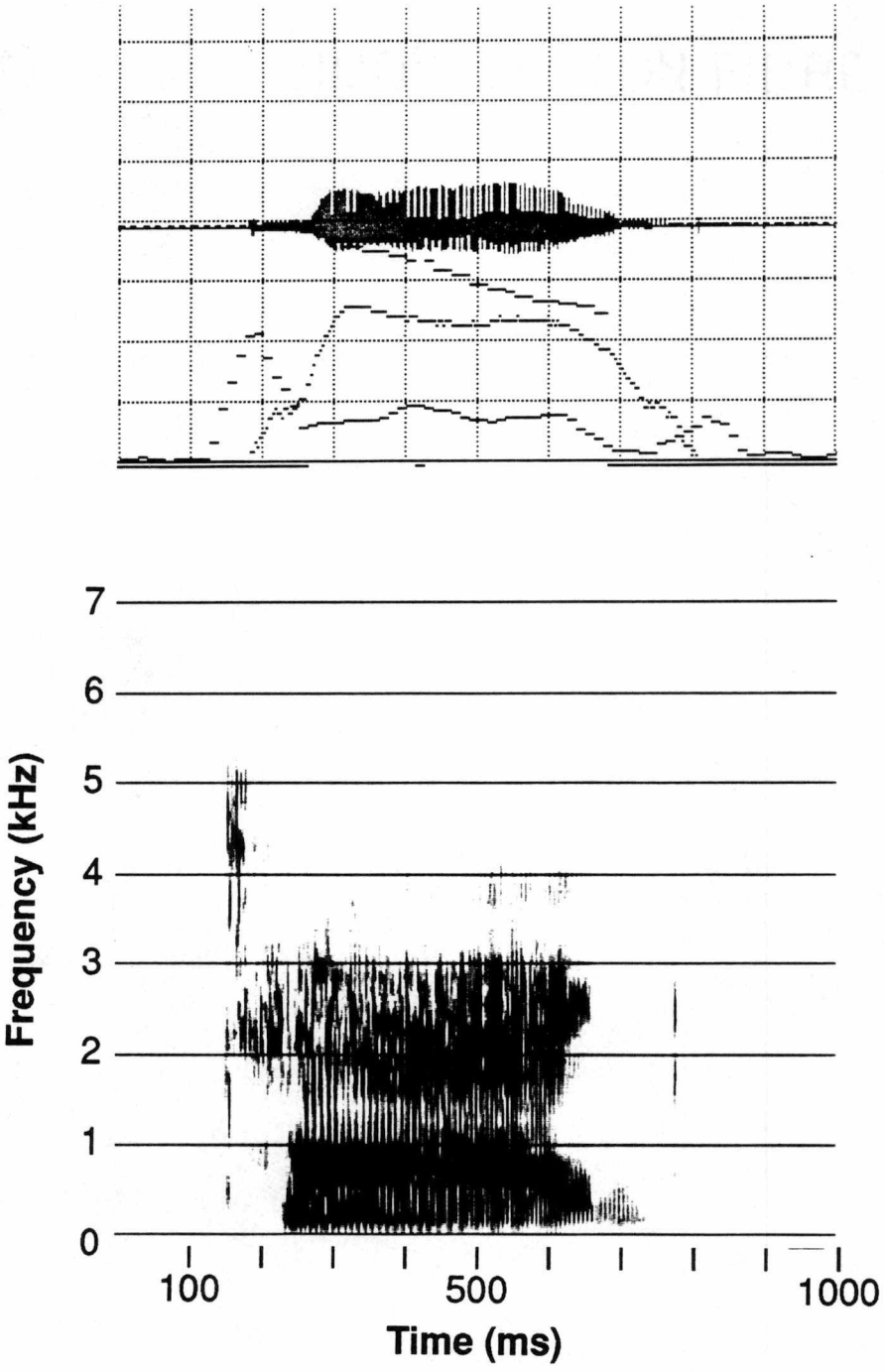


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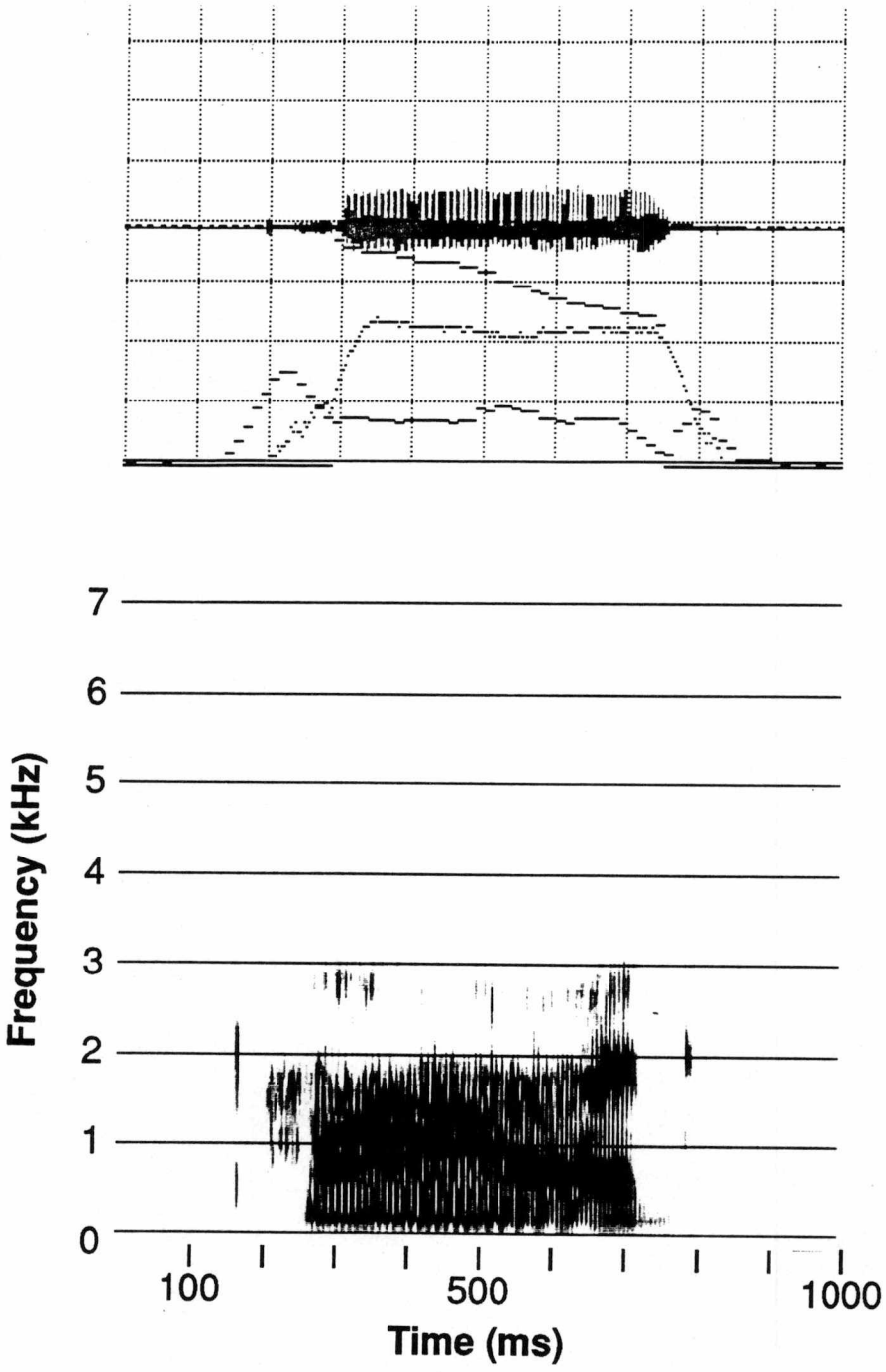




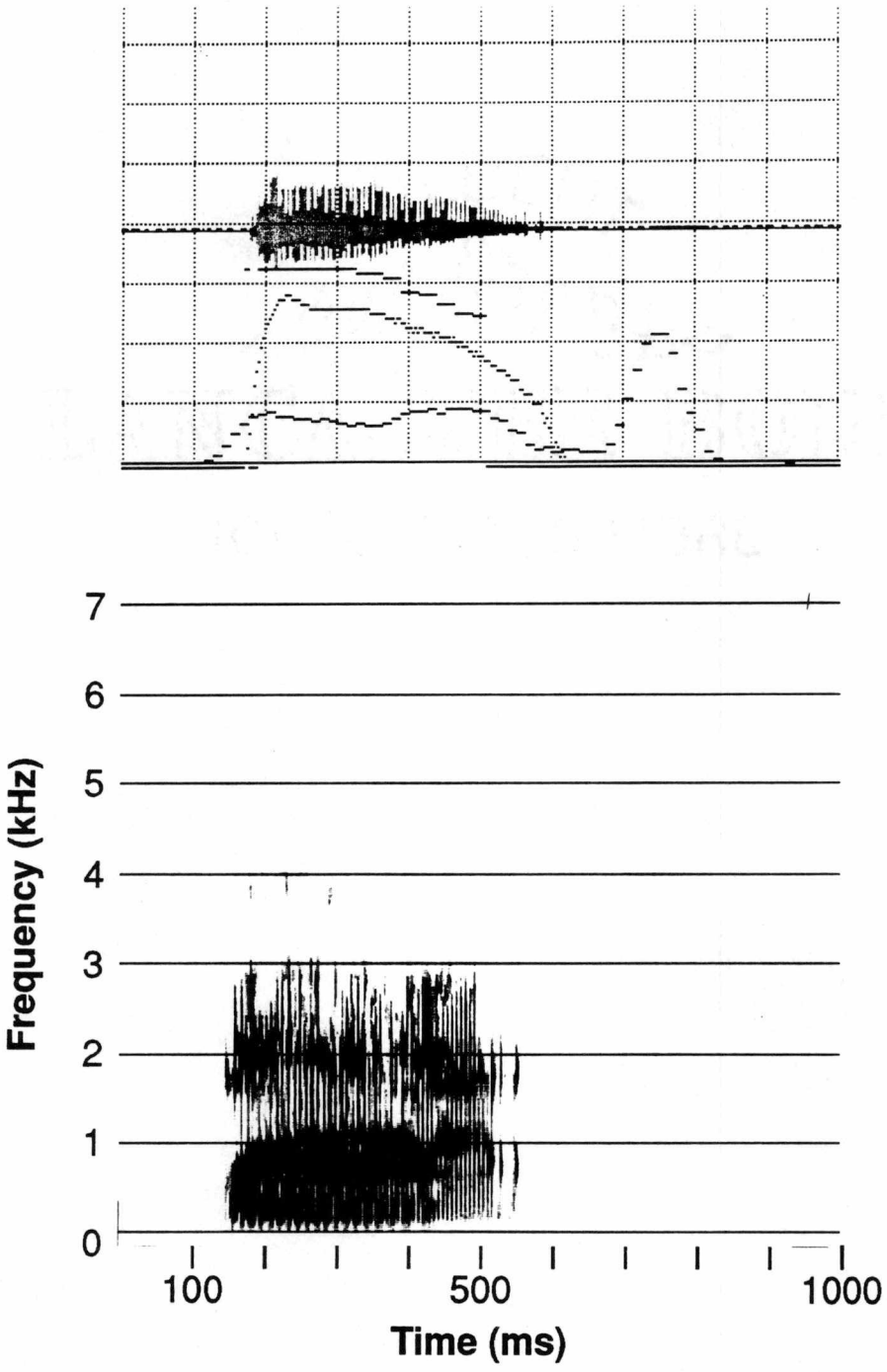
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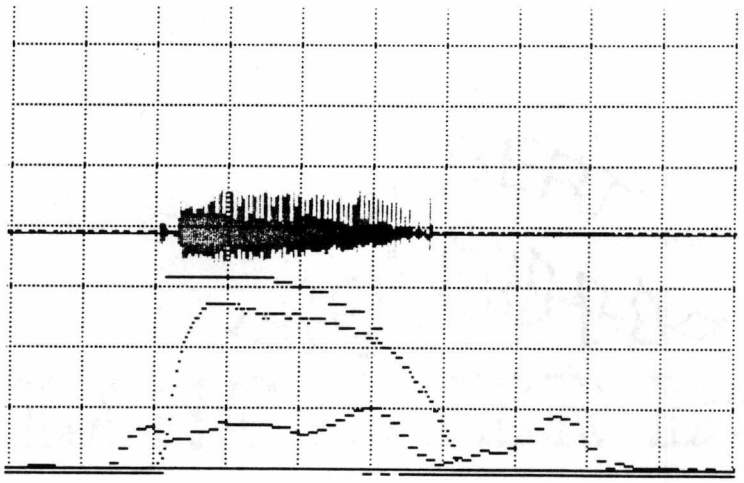
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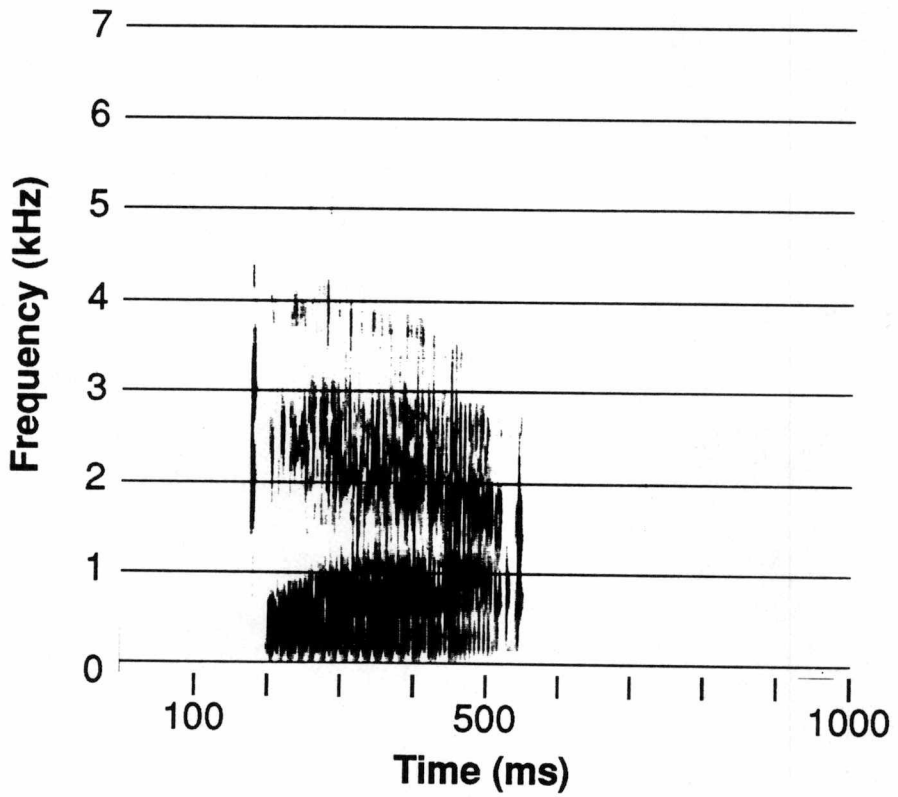


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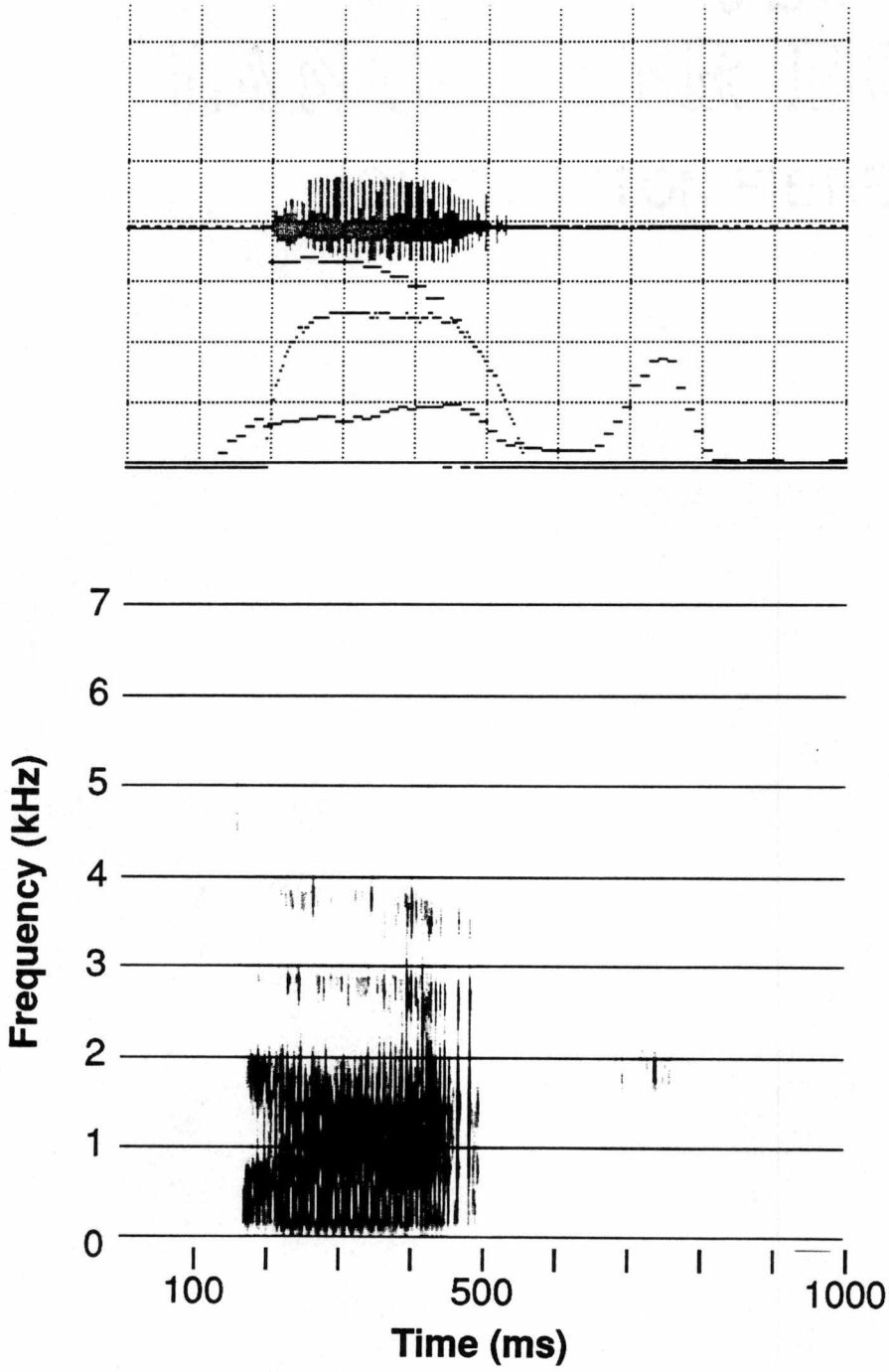


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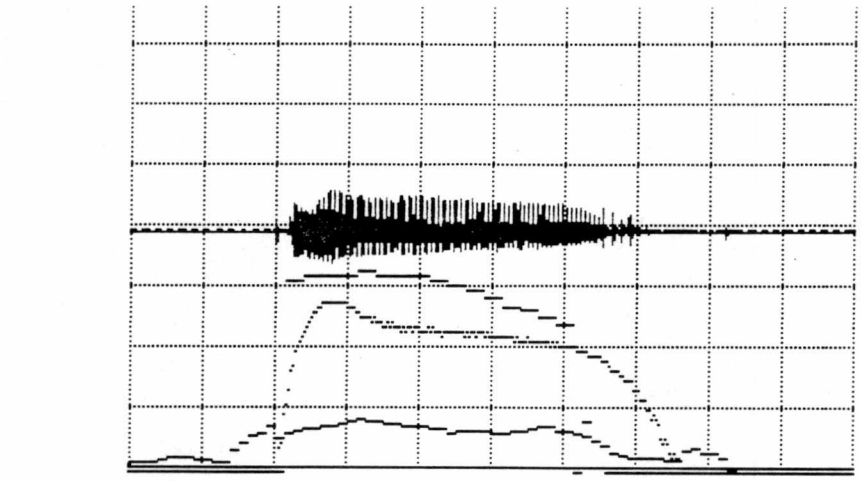


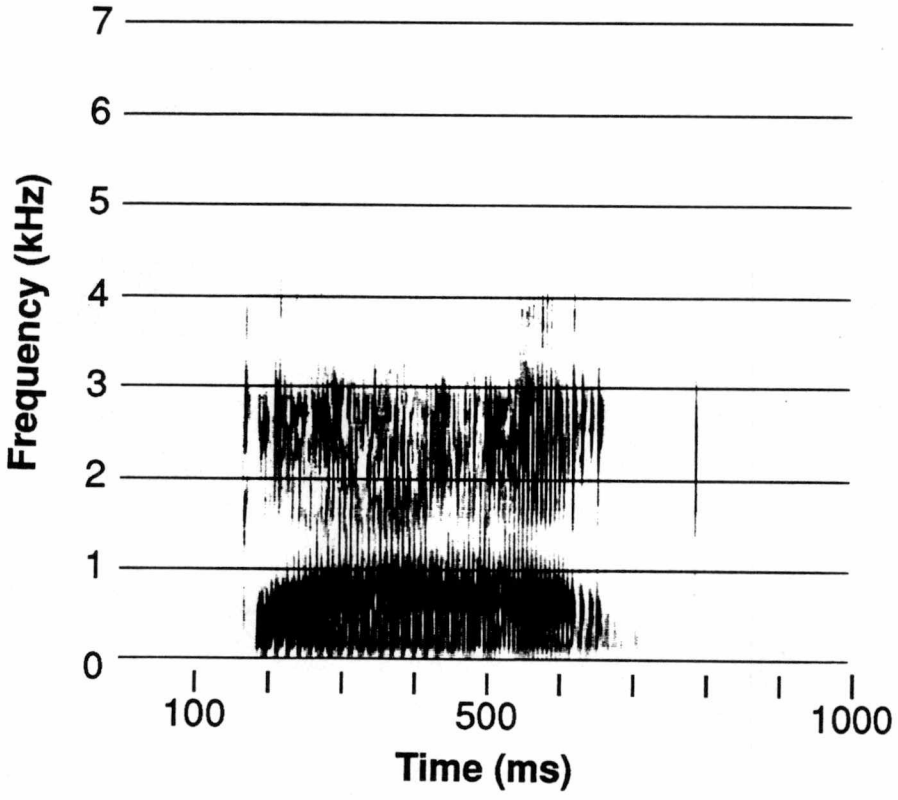


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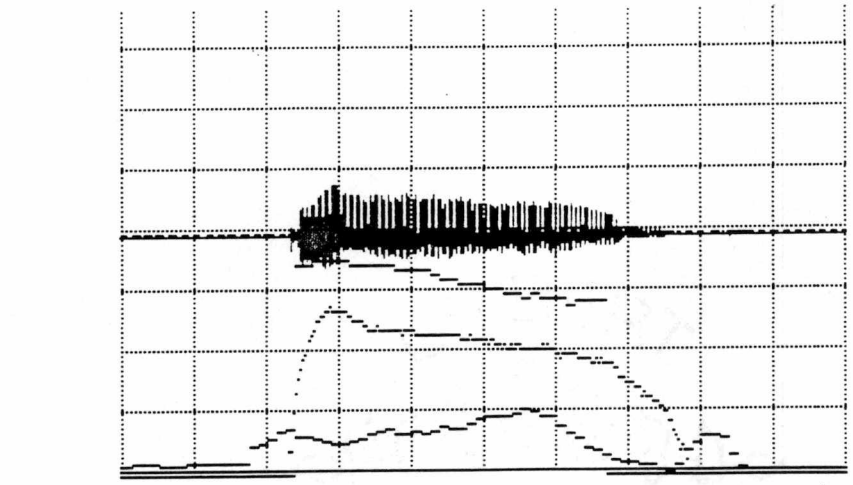


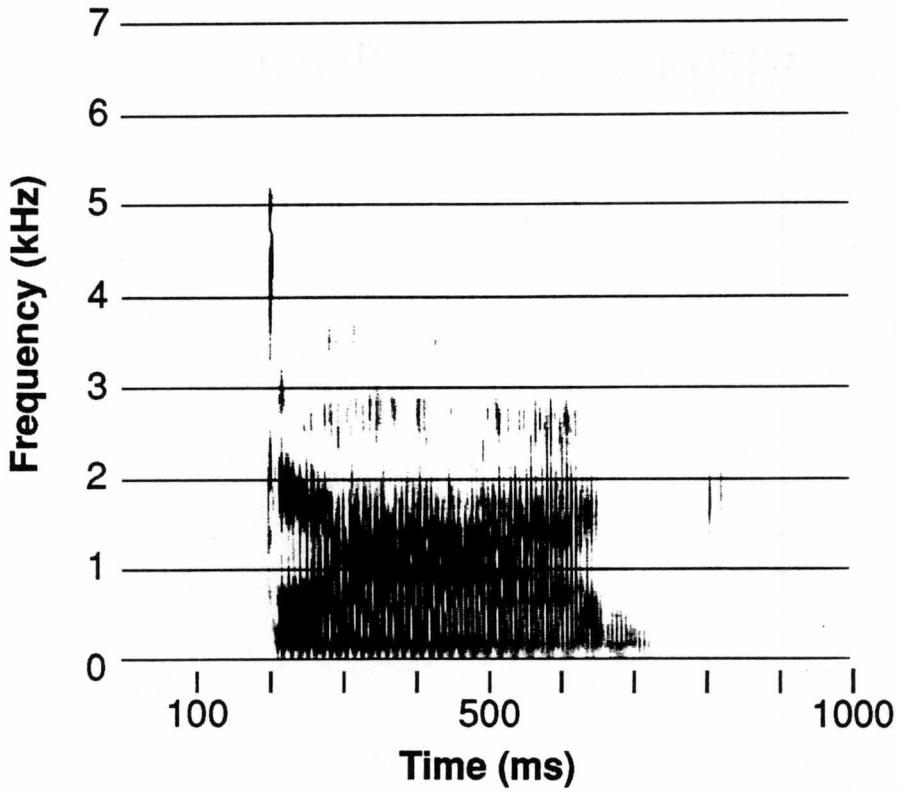
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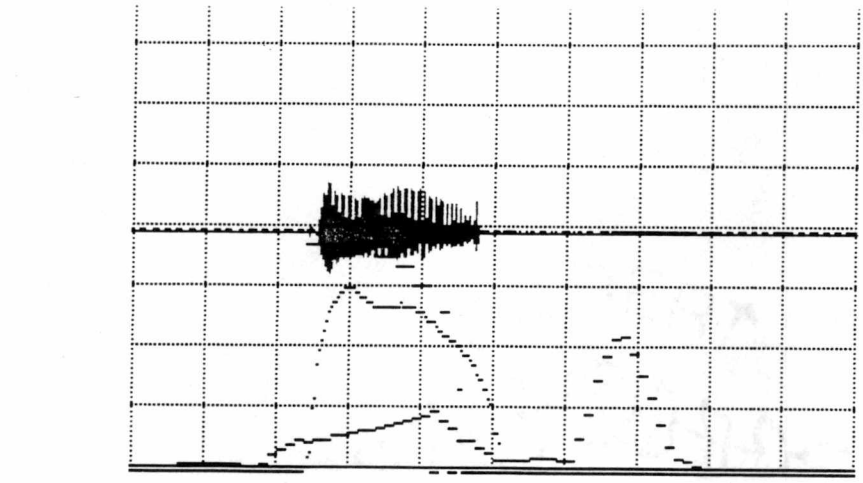


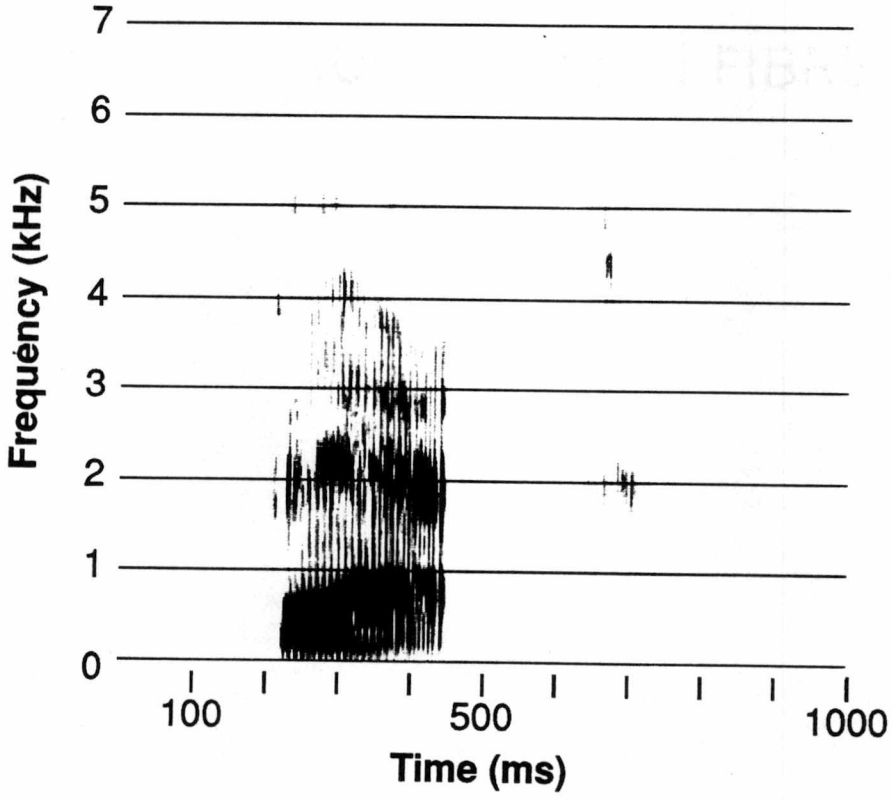
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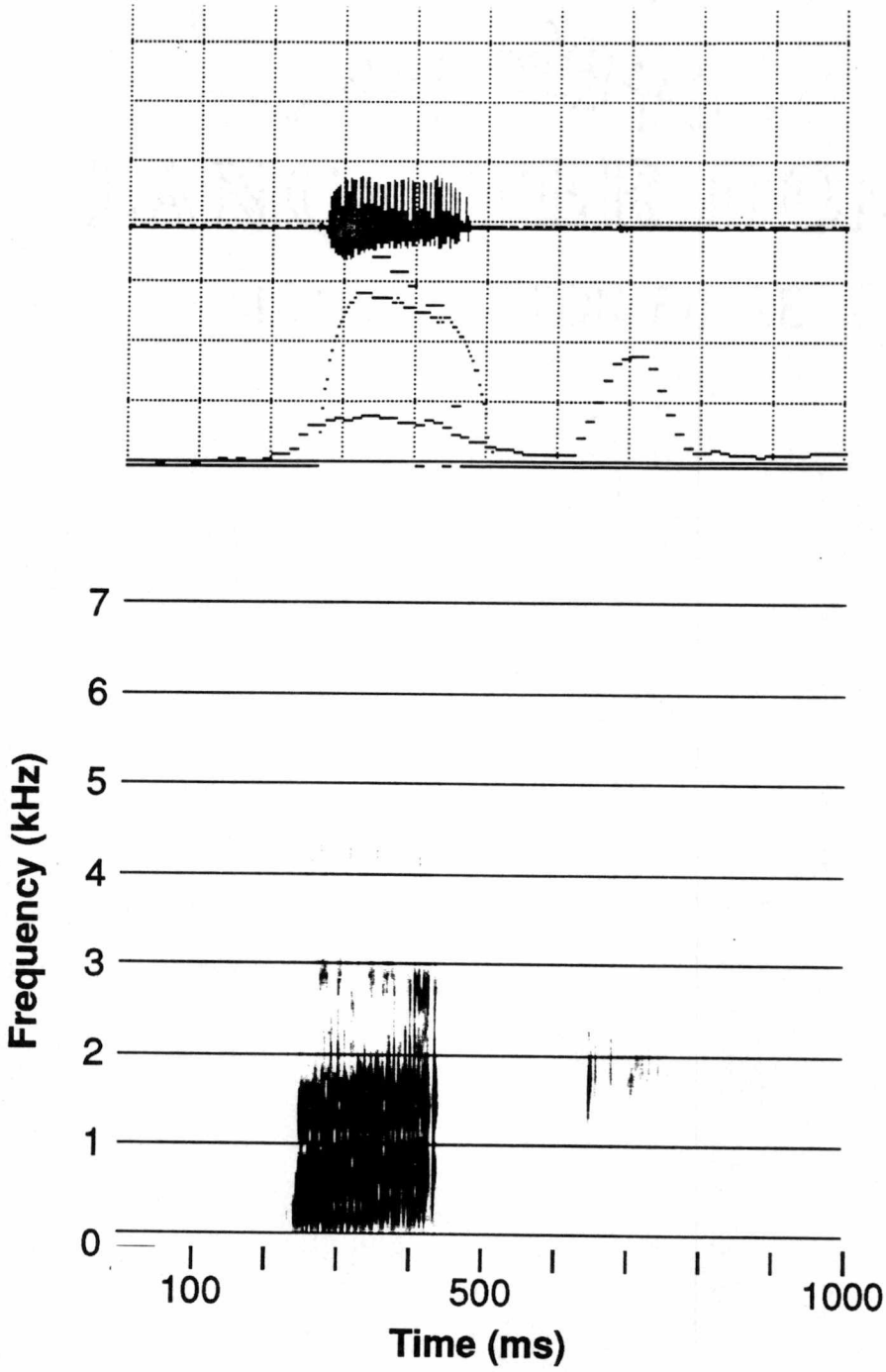


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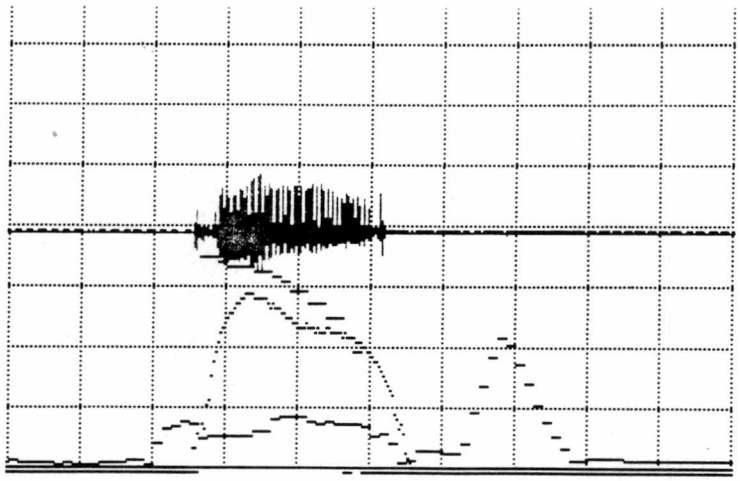


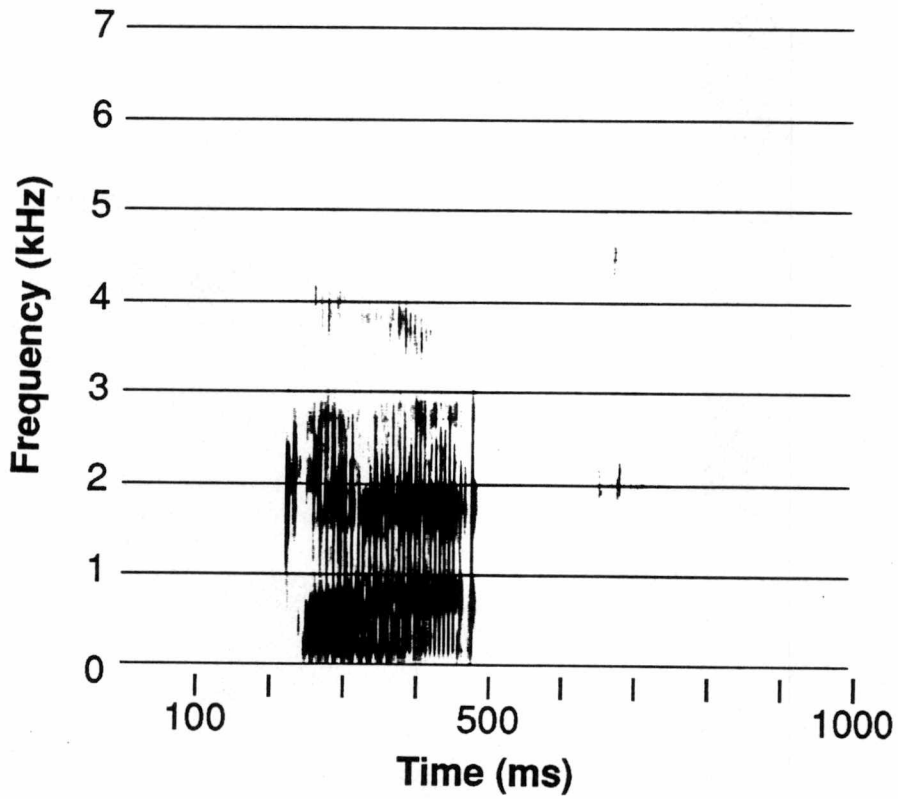


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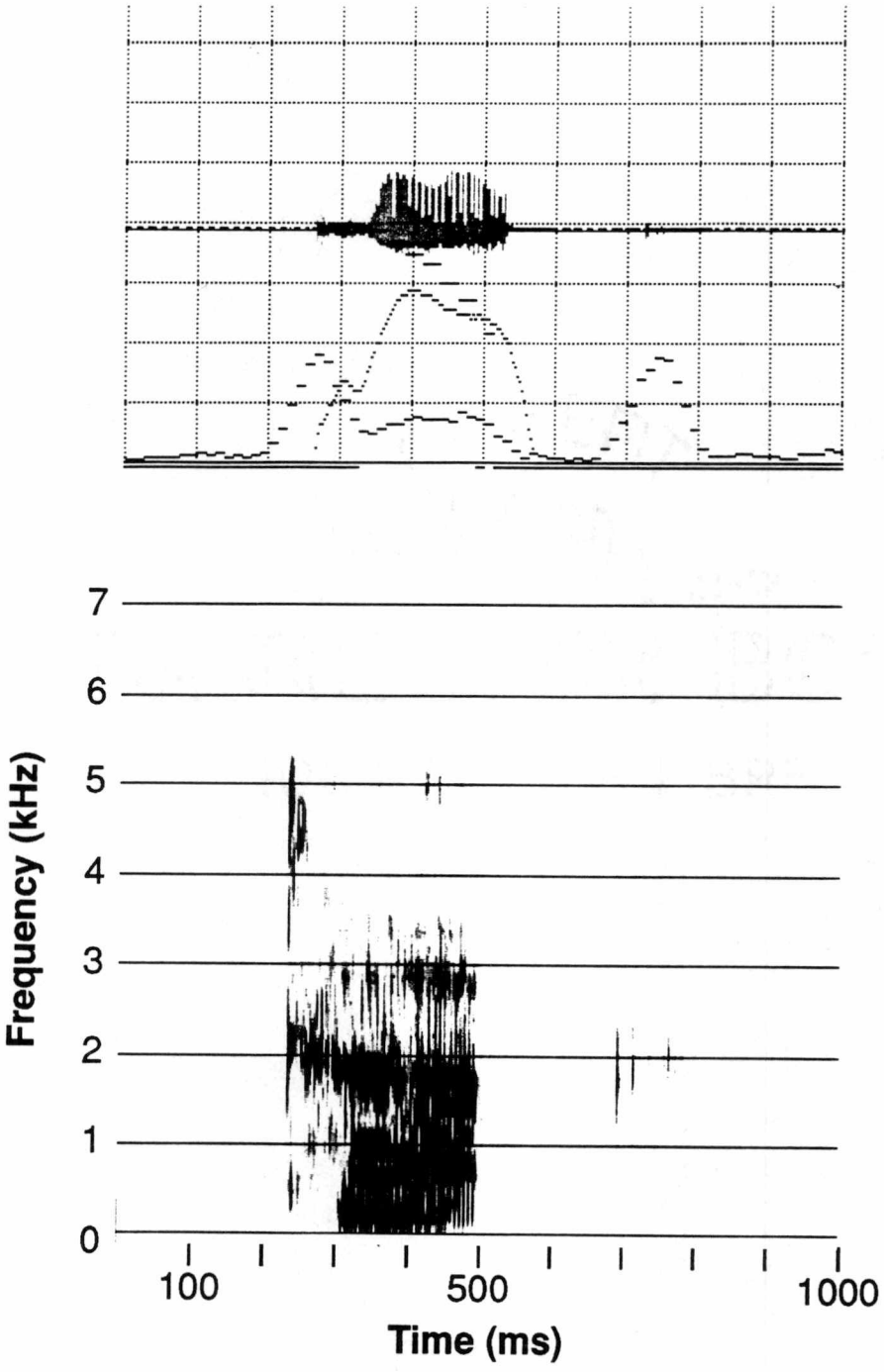


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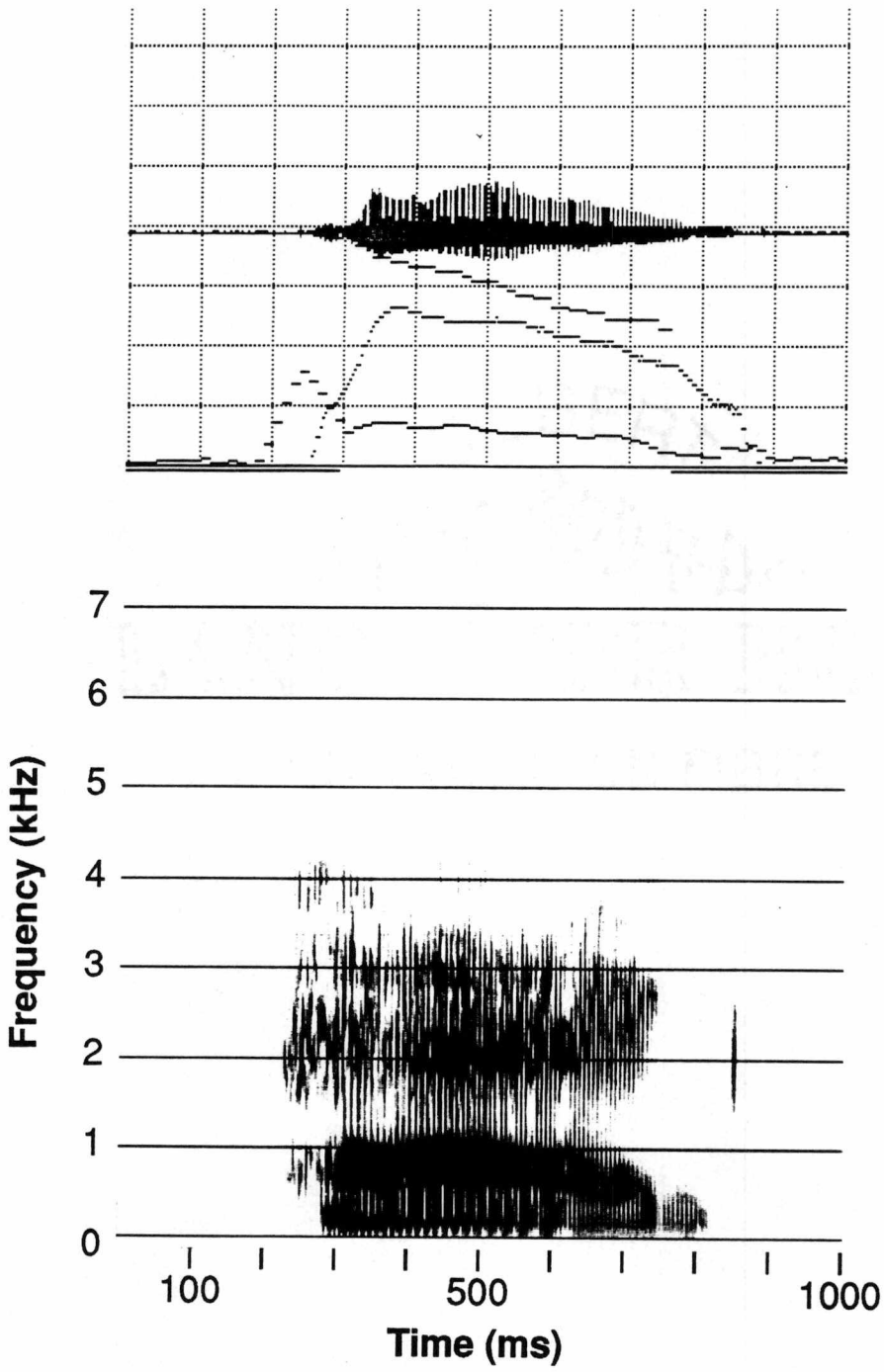




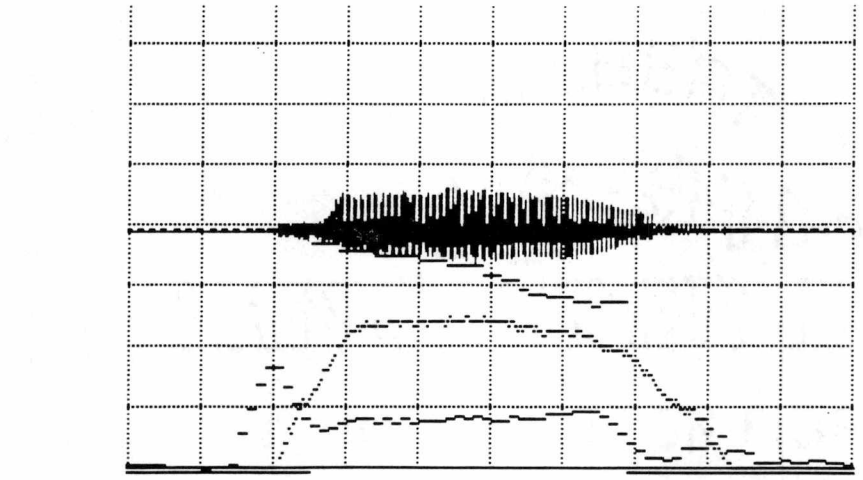
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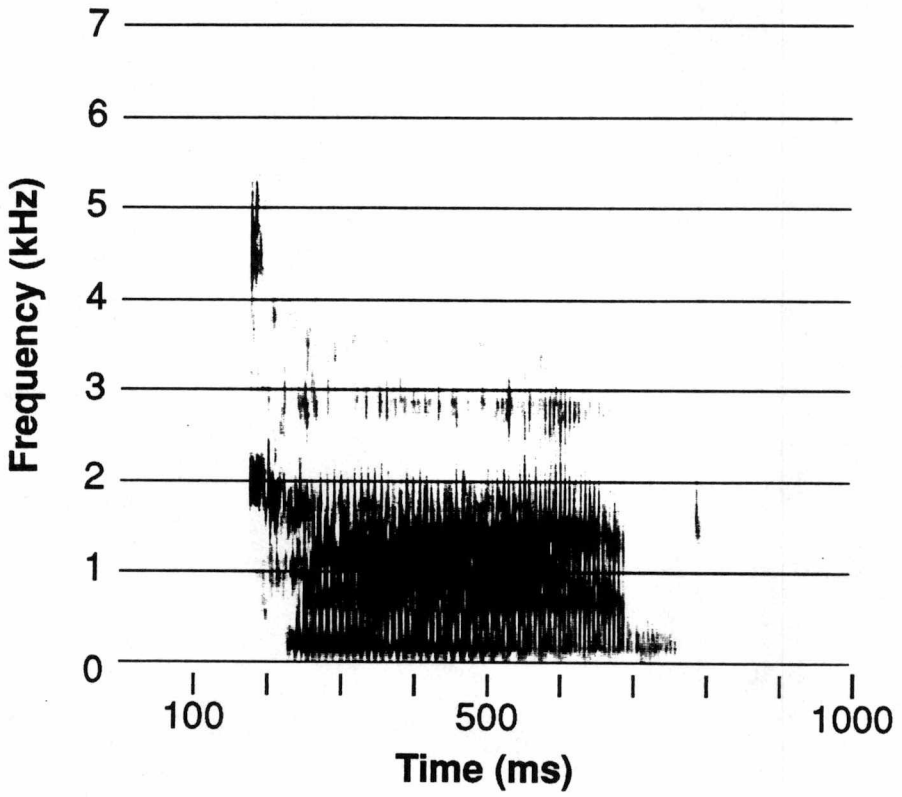


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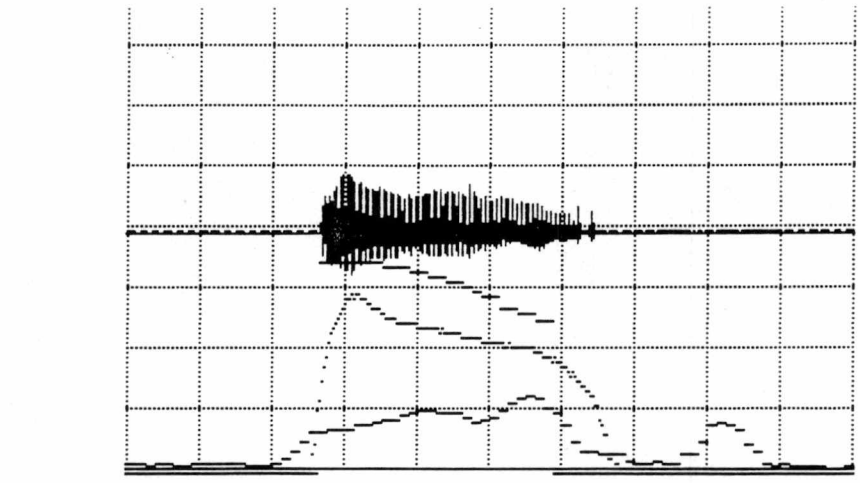


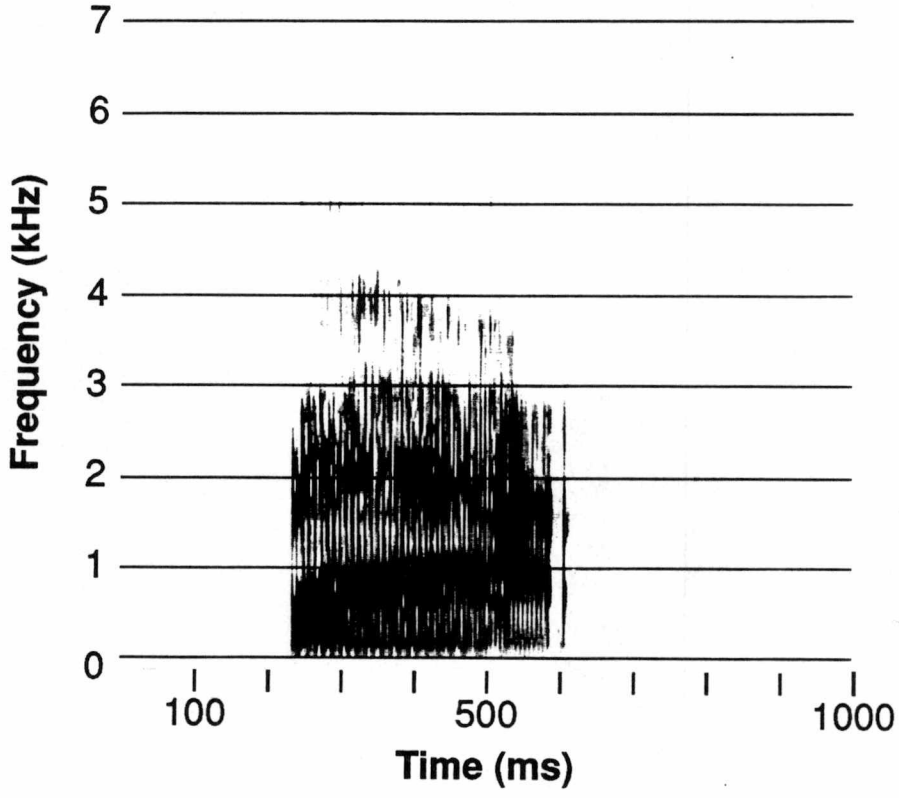
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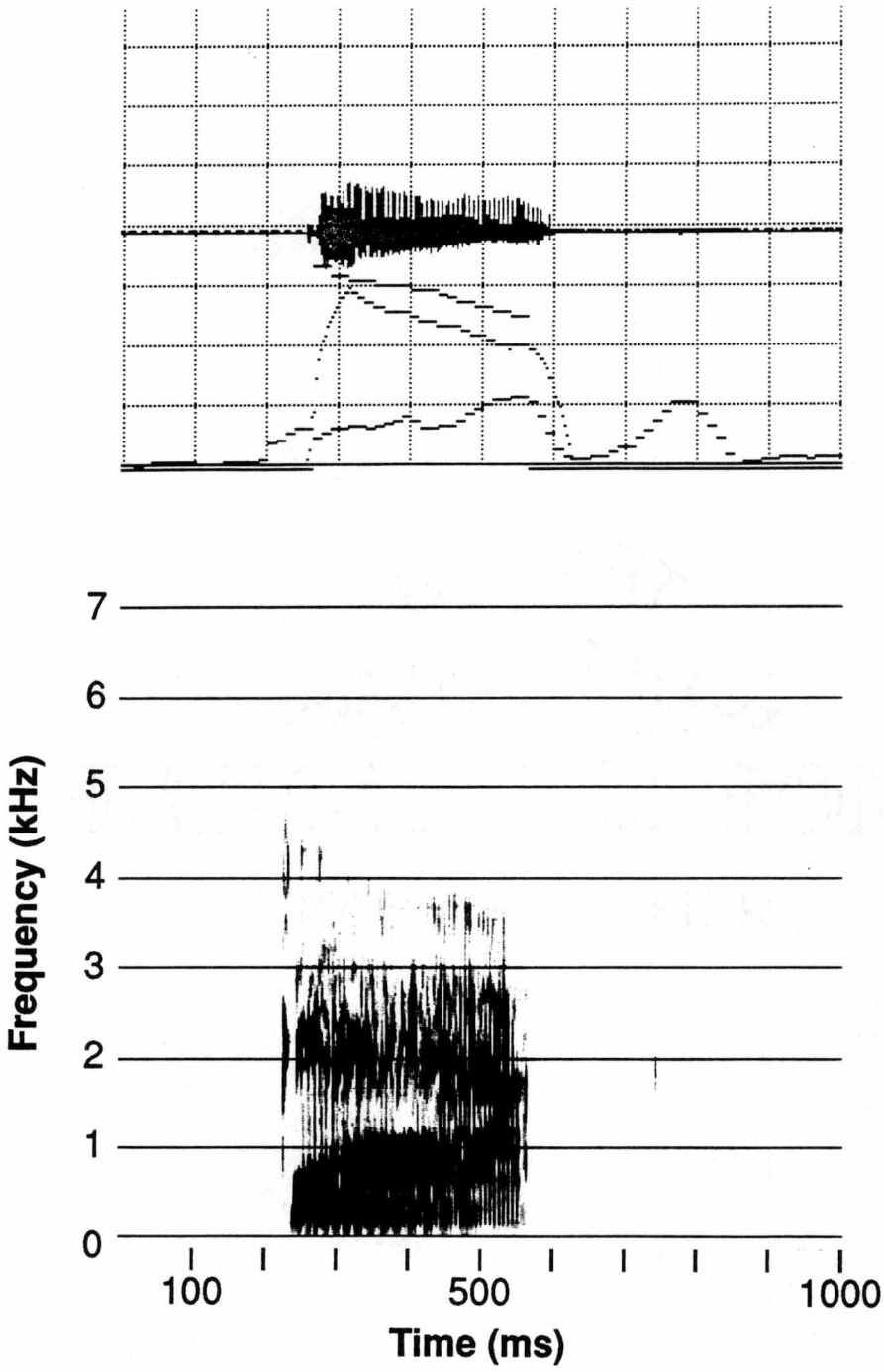


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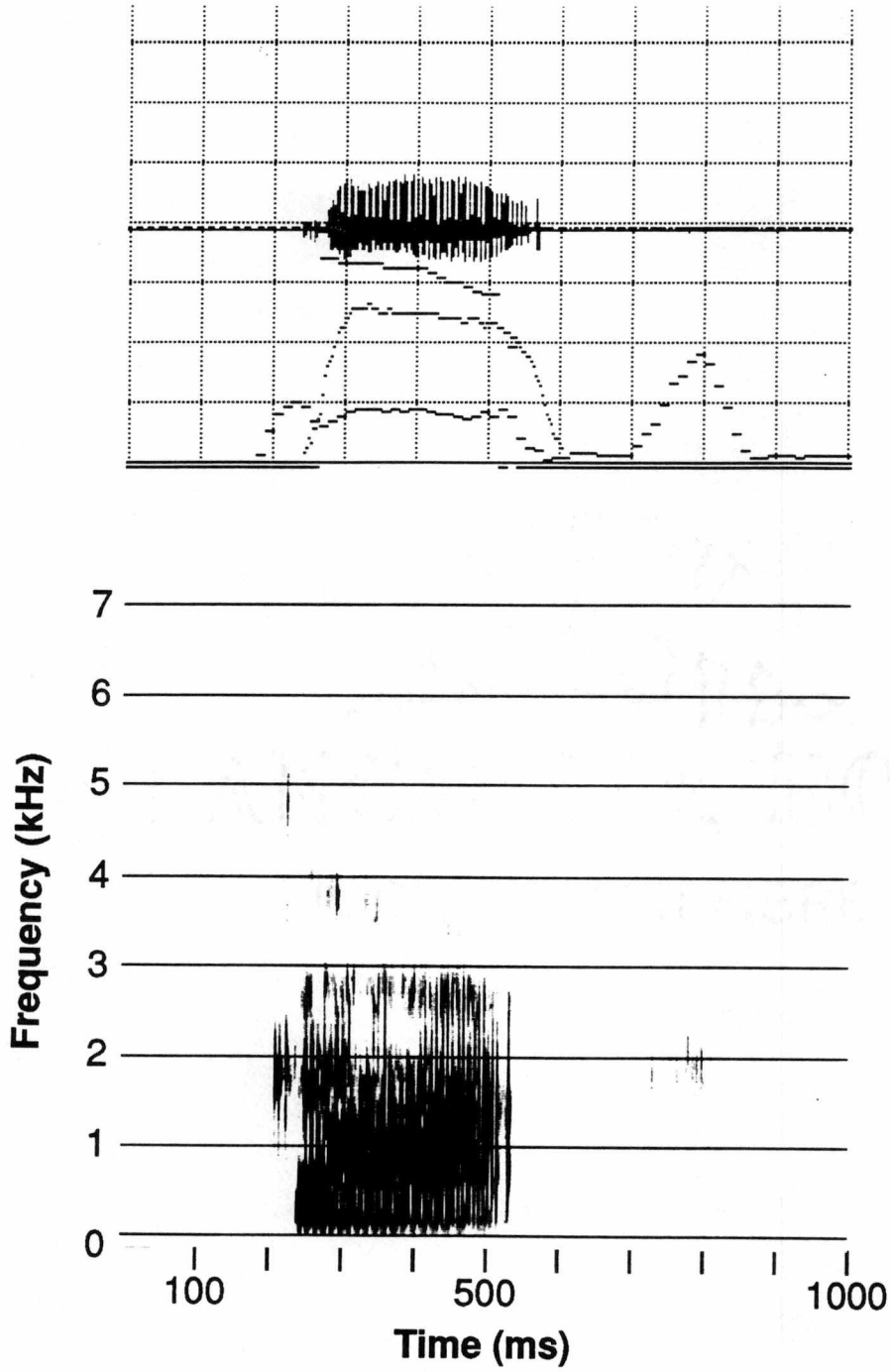




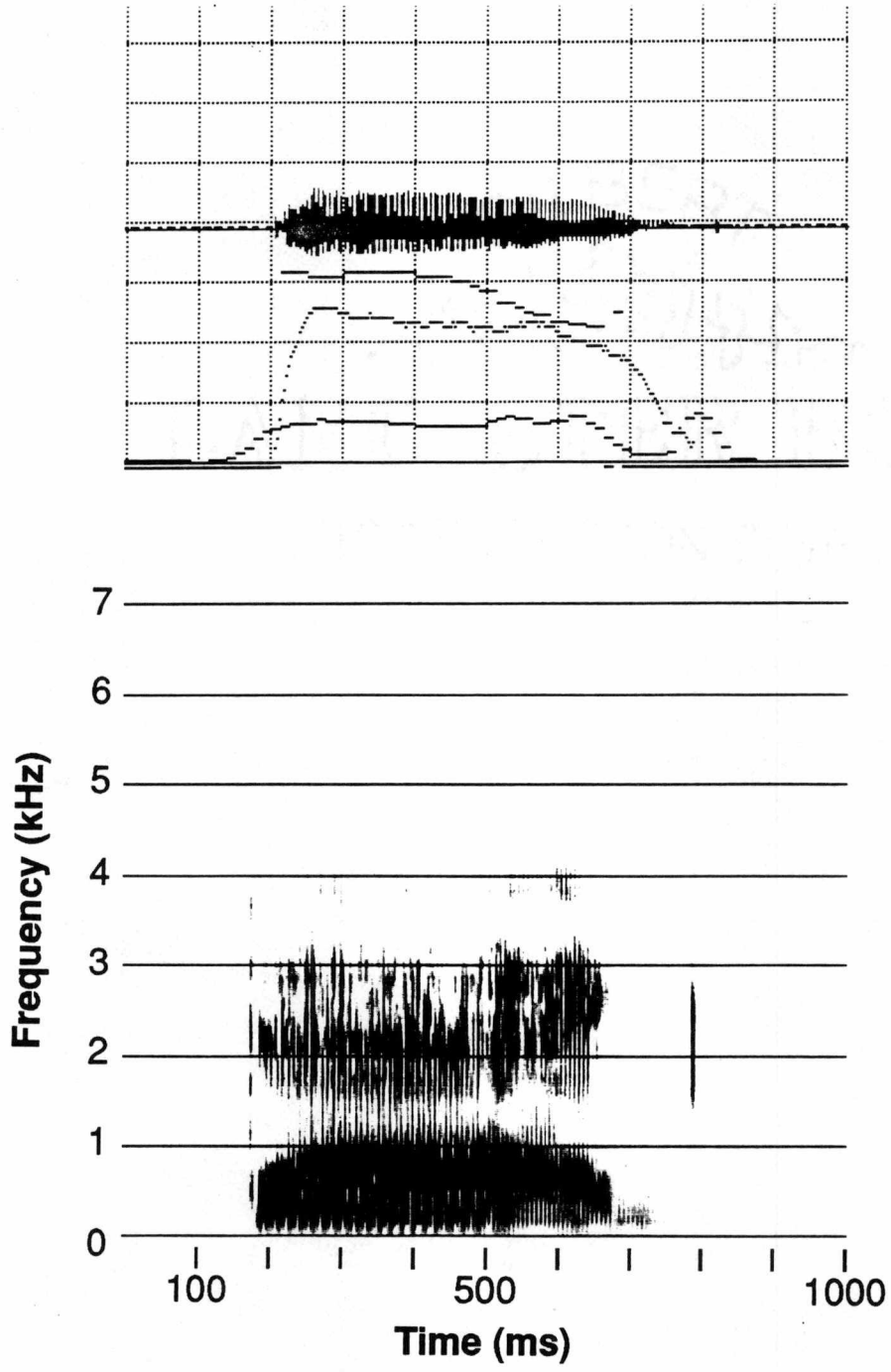
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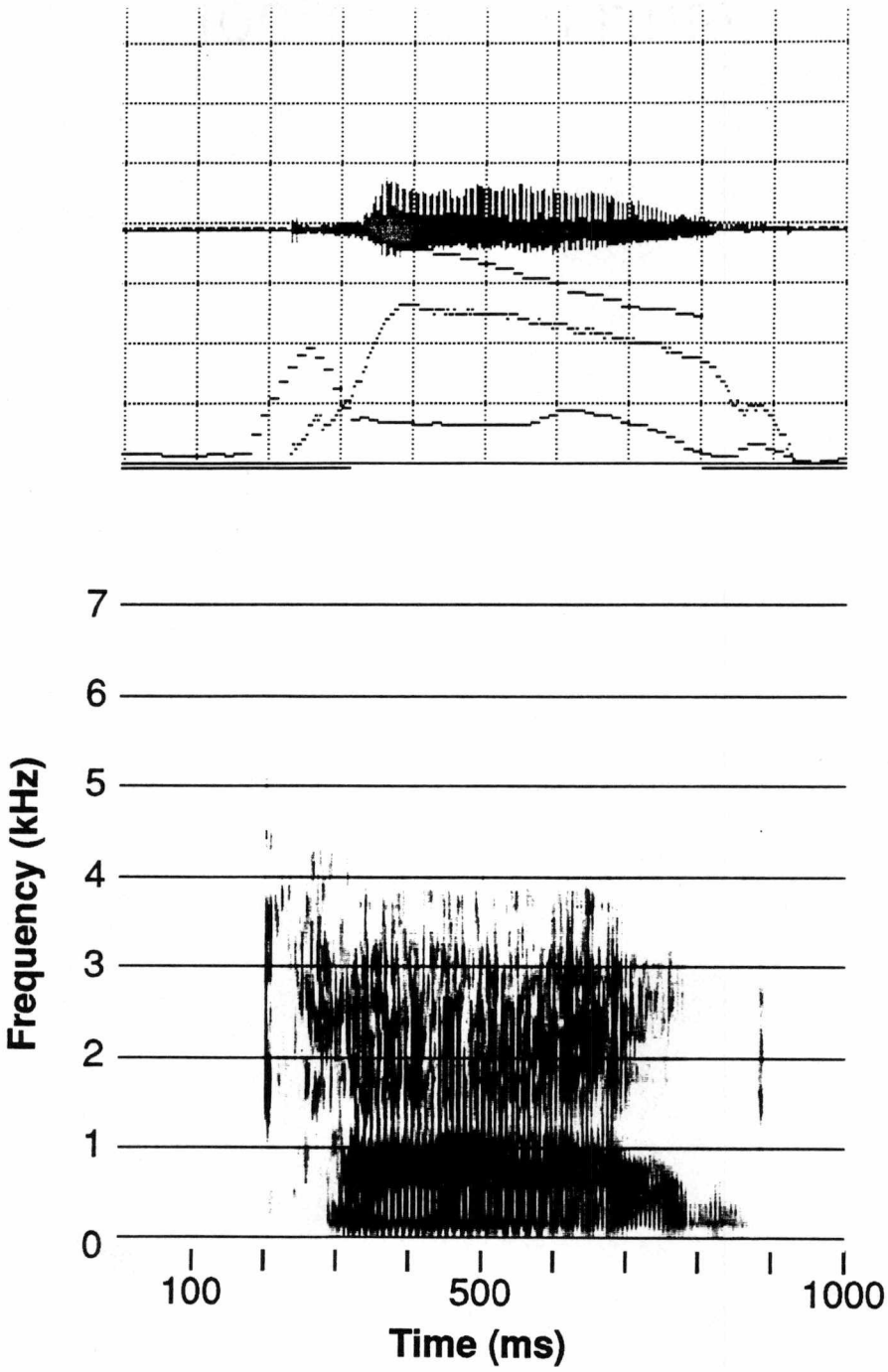
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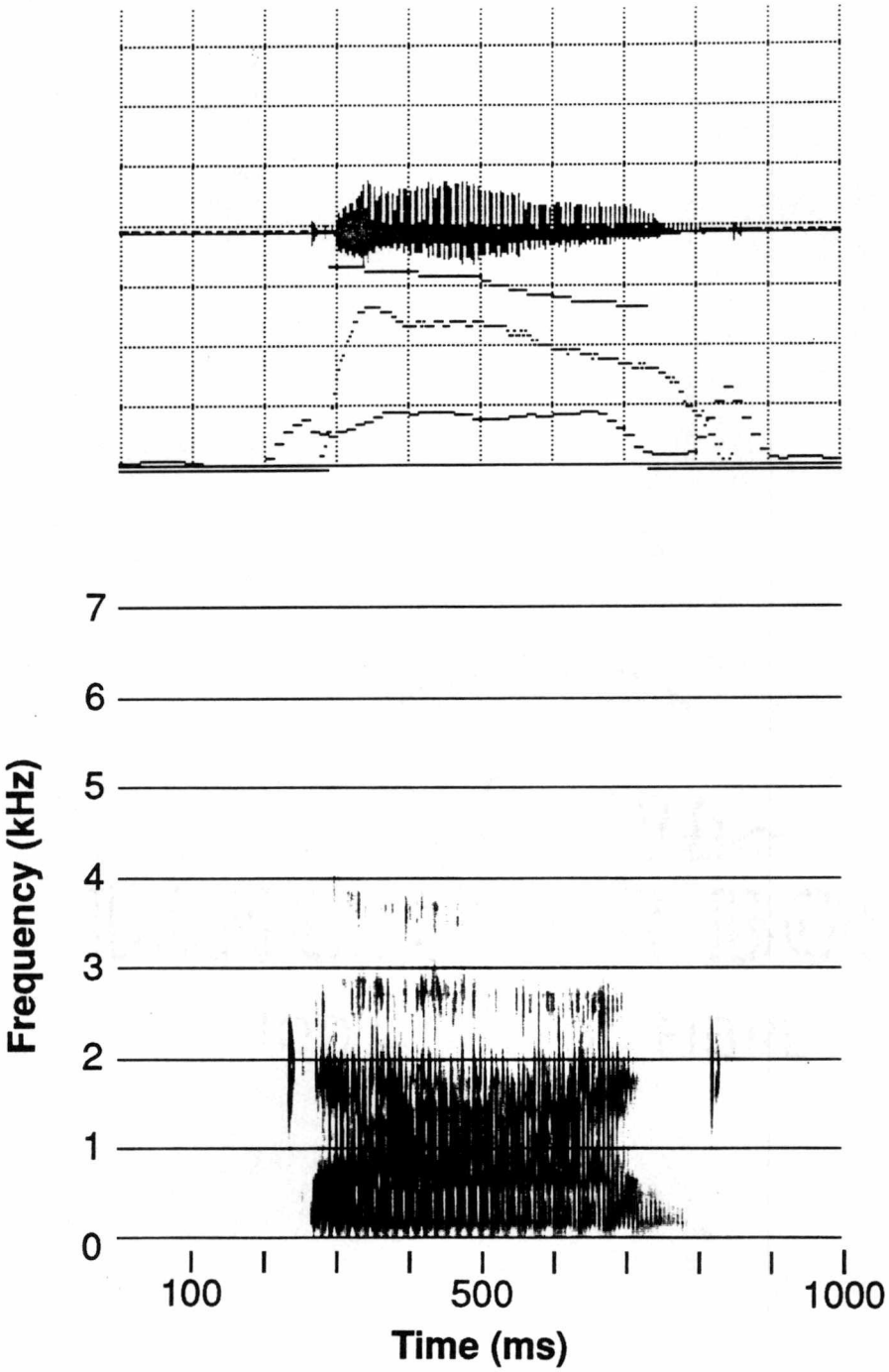
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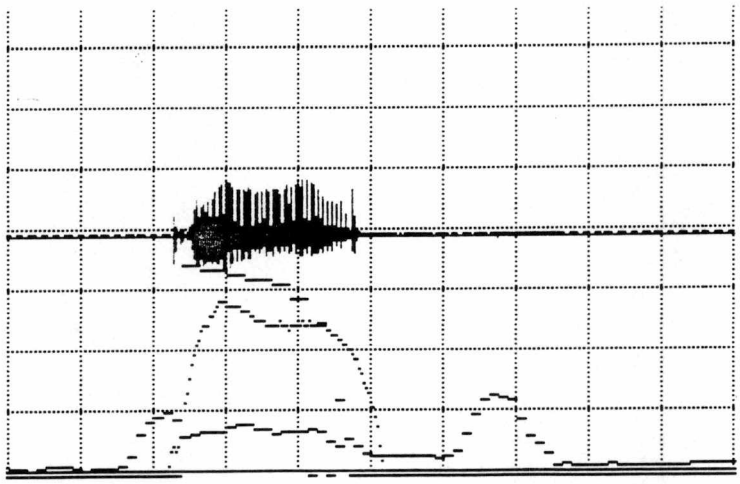
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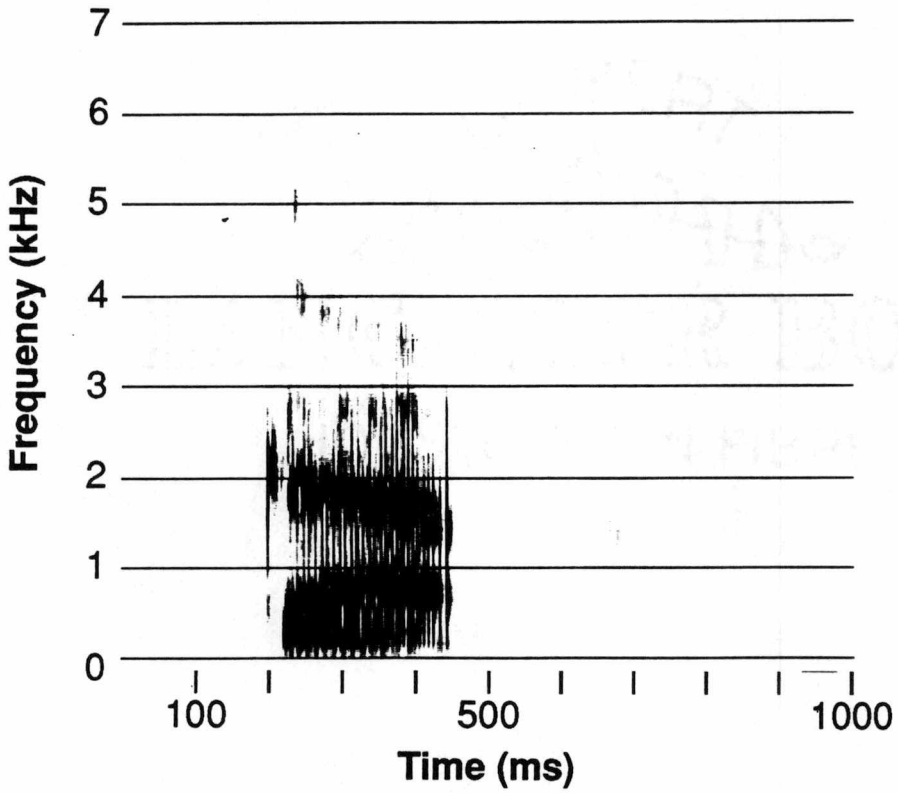


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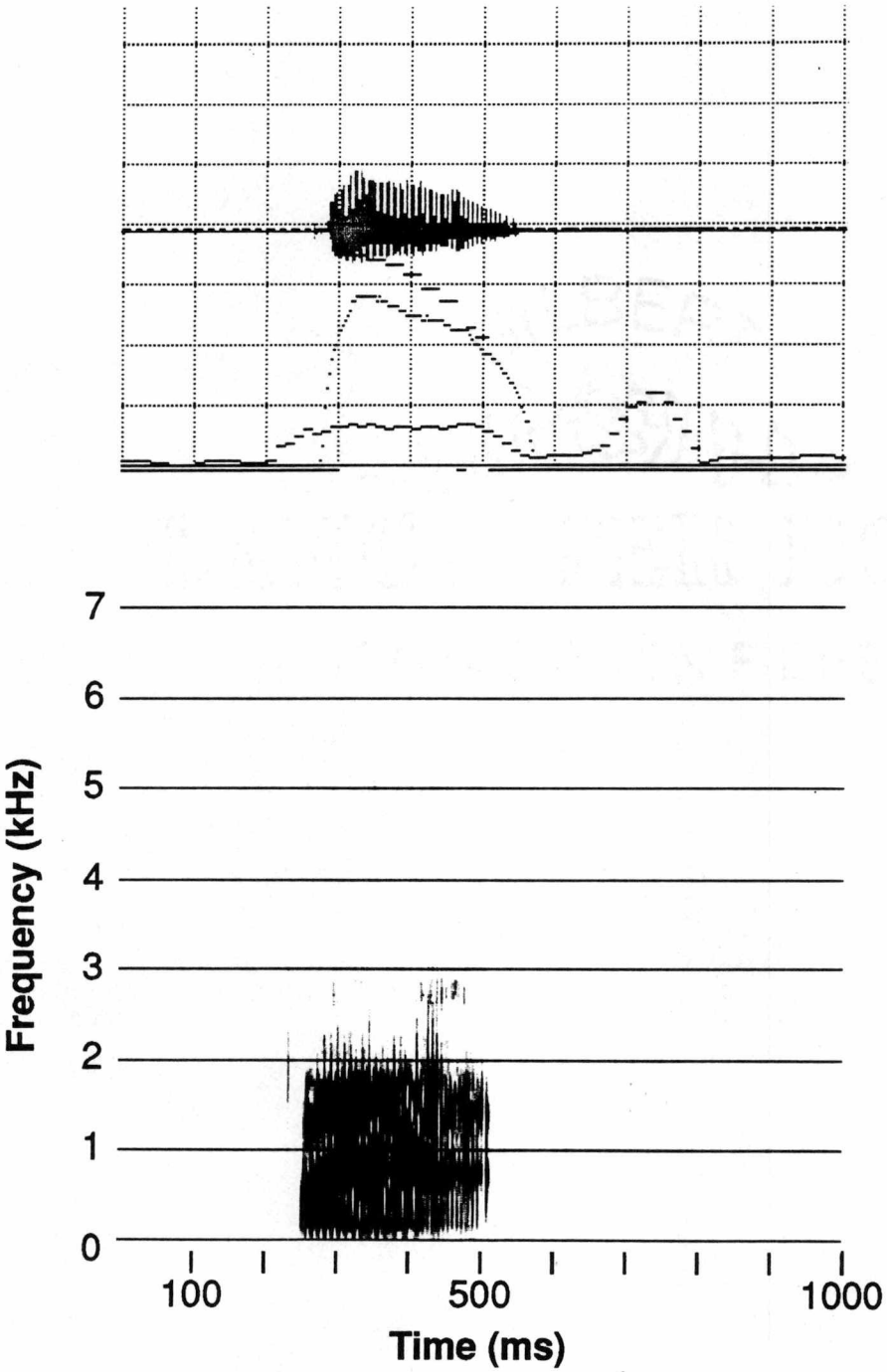


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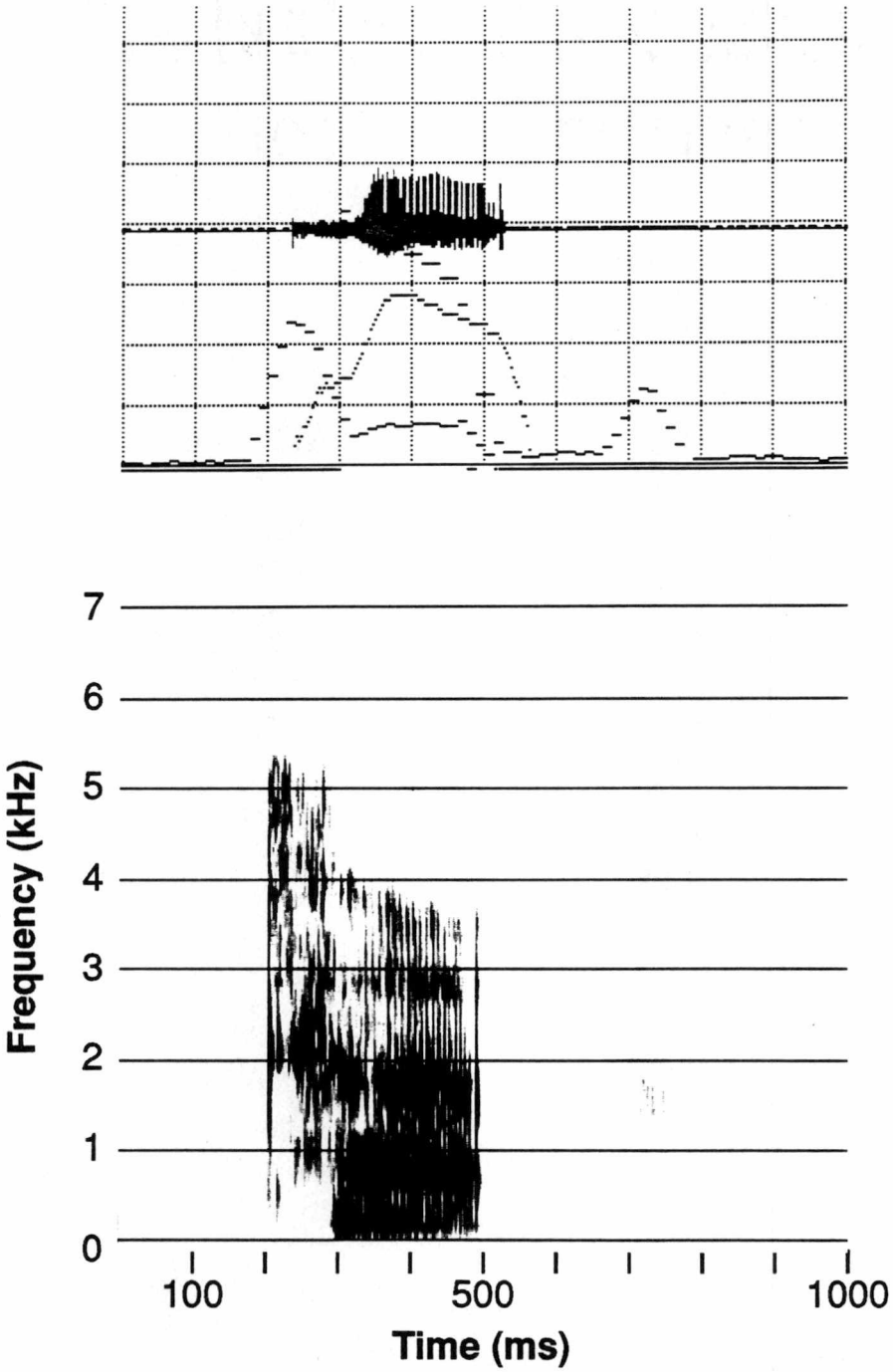




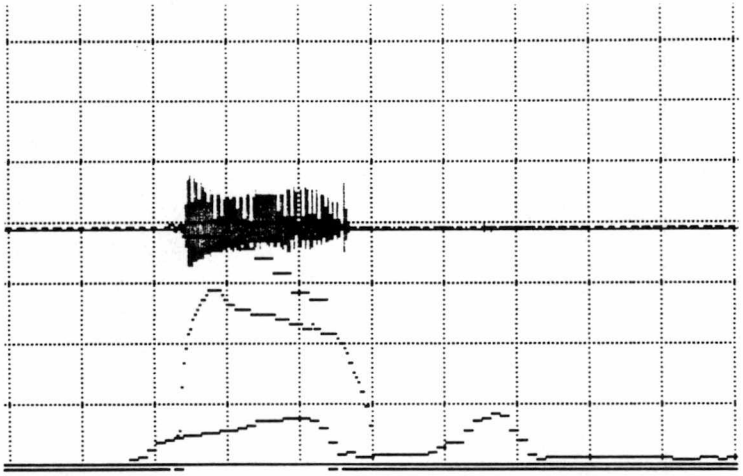
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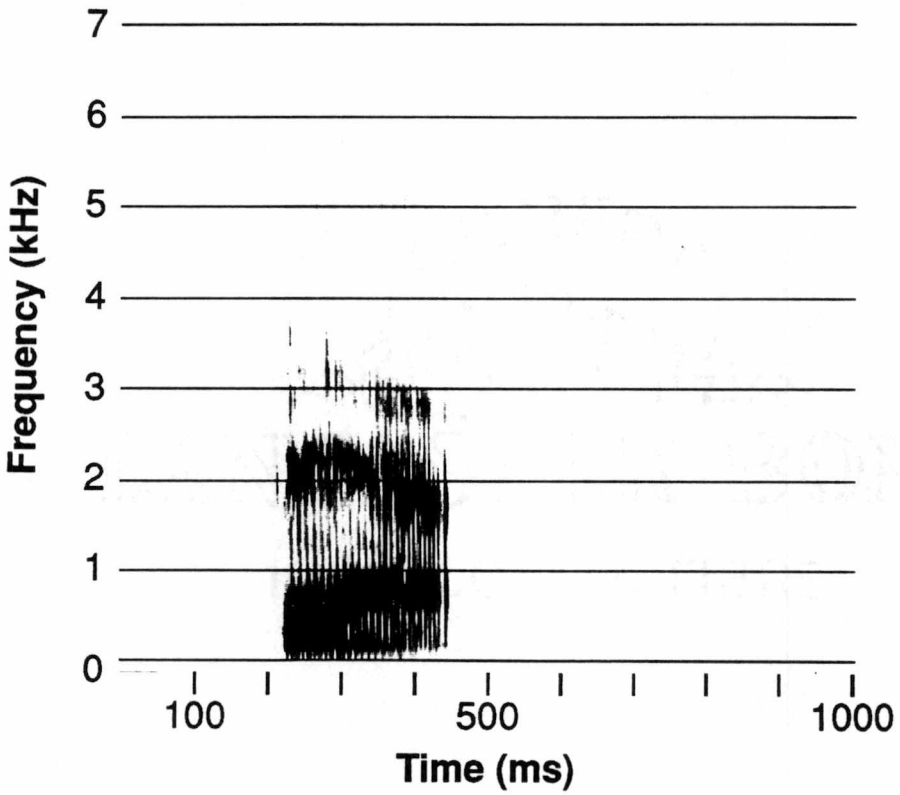


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VITA

Frances Martin Tucker was born in Chicago, Illinois on October 8, 1944. She attended elementary school in Piedmont, California and graduated from the Dominican Convent Upper School in San Rafael, California in 1962. Her Bachelor of Arts degree was in Speech from the University of California at Santa Barbara in 1966. She received a Master of Arts degree in Communication Disorders from San Francisco State University in 1968. After working in Berkeley and Oakland, California as a speech-language pathologist in medical settings, she was appointed as an Instructor in the Department of Communication Sciences and Disorders at the University of Montana in 1977. In 1984, she began her doctoral studies at the University of Tennessee, Knoxville and received a Doctor of Philosophy degree in Hearing and Speech Science in 1992.

She is currently employed at Saint Louis University, Saint Louis, Missouri, in the Department of Communication Disorders.