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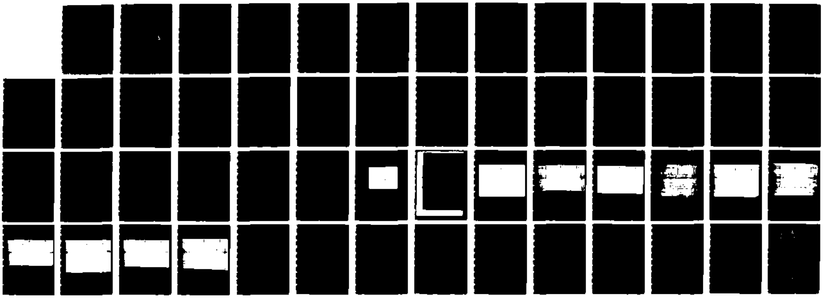

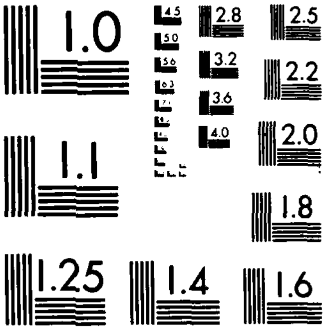

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STUDIES OF THE PROCESSING OF SINGLE WORDS USING POSITRON TOMOGRAPHIC MEASURES OF CEREBRAL BLOOD FLOW CHANGE

Steven E. Petersen, Peter T. Fox, Michael I. Posner, Marcus Raichle

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STUDIES OF THE PROCESSING OF SINGLE WORDS USING AVERAGED POSITRON EMISSION TOMOGRAPHIC MEASUREMENTS OF CEREBRAL BLOOD FLOW CHANGE

Steven E. Petersen, Peter T. Fox, Michael I. Posner, Marcus E. Raichle

INTRODUCTION

Language is an essential characteristic of the human species, and as such has been a focal point for study in disciplines ranging from philosophy to neurology. The totality of language is amazingly complex and includes the study of syntax, semantics and pragmatics. Cognitive and neurological investigations of language often narrow the focus of study to the processing of individual words (lexical items). Lexical processing involves a network of several levels of internal coding that can be isolated by experiment (LaBerge & Samuels, 1974; Rumelhart & McClelland, 1982, 1986). Examples of some of these separate codes include a visual image of the form of a spoken word (visual code), pronunciation of the word (phonological code) or the association of related words (semantic codes). Studies of the time course of activation of these internal codes of words and the roles they play in performance has been a central topic in the cognitive psychology of reading and listening (Carr & Pollatsek, 1985; Posner, 1978 and Rumelhart & McClelland, 1986 for examples). Behavioral neurologists have been concerned as well with issues in lexical processing, but the focus has been in correlating the internal stages of processing with different brain regions (Geschwind, 1979).

Recent advances in activation techniques and data analysis strategies using positron emission tomographic (PET) measurements of blood flow (BF) change have made it possible to address concerns relevant to both cognitive science and behavioral neurology. These techniques have been used to make precise anatomical-functional correlations in the primary and secondary sensory and motor areas of the human brain (e.g., the mapping of the visual field onto primary visual cortex, Fox, et al, 1987) by comparing several test and control conditions within a single session. In this paper, we take advantage of these techniques to study the neural mechanisms underlying the processing and production of single words in normal subjects. Our results indicate that the processing of single lexical items during simple sensory, word repetition, and word generation tasks activates a small number of discrete areas. These findings suggest a framework for the processing of single words that is quite different from the standard clinical neurological account based on cortical lesions (Geschwind, 1965;1979), but is consistent with recent results from cognitive science (Coltheart, 1985; Carr & Pollatsek, 1985).

METHODS

PET techniques common to all studies

Tracer strategy Changes in neural activity induce changes in local BF (Fox & Raichle, 1986). We used 015-labeled water injected as an intravenous

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bolus to measure BF in normal subjects. The short half life of 015 (120 s) allowed a short interscan interval of 10 minutes (5 half lives) and acquisition of 8-10 40 sec scans per subject. This in turn allowed comparisons of several different task conditions within single subjects, who remain in the same position with respect to the scanner throughout the session.

Image subtraction Side-by-side visual inspection of the blood flow measurements in two conditions gives some information about the presence of focal blood flow changes (Fig 1A and B, page 10), but to attain quantitative information about the location and magnitude of differences between the scans, subtraction of the activity in one image from another (activated - control condition) were performed. When a direct pixel-by-pixel subtraction is made, the resultant image was of foci of change between the two primary images (Fig 1C). The subtractions were made after linear normalization that negated the effects of global BF fluctuation. The global brain blood flow was calculated using a standardized mean regional method (Perlmutter, et al, 1985). Each scan was normalized by multiplying every pixel of each scan by a correction factor, calculated as the mean normal global BF of this laboratory [50 ml/(100 gm * min)] divided by the scan global BF, before computing subtraction images.

Anatomical standardization Because the precise alignment and position of the seven PET slices vary from subject to subject, foci of change in subtraction images are in coordinates unique to the individual being scanned. To anatomically identify areas of change, each individual's scan information must be converted to a standardized reference space. To achieve this standardization, the seven slice information on each individual is first subjected to an interslice interpolation to fill an array of uniform pixel size (about 2 mm). These arrays were then standardized to a single anatomical coordinate space using information from a lateral skull X-ray taken while the subject was in position, and slice length and width information from the scans themselves. This anatomical standardization made it possible for the investigator to "look up" the anatomical location of the areas of change in a standard atlas (Fox, Perlmutter & Raichle, 1985).

Image averaging The anatomical standardization of subtraction scans to an individual anatomical standard gives a second advantage: subtraction images during the same condition from different individuals can be summed and averaged. The rationale behind image averaging is that areas of activation that are consistent across individuals will sum and those that are not consistent will be random and cancel one another out. This simple signal averaging technique greatly enhances the detection and localization of the subtle activations that are produced during cognitive manipulations (Mintun, Fox,and Raichle).

Automated response detection The subtraction images from single individuals and averaged subtraction images across individuals show many foci of change. A computer search routine was designed to find all local peaks of activity change within an image, and record their location and magnitude. This routine was used for objective localization of areas of change in activated pair subtractions (Fox, et al, 1986).

Statistical Analysis As the local-maximum search routine allowed all independent local changes to be identified within any subtraction image, significance testing was based upon analysis of this entire population. During the averaging process spatially nonrandom changes (i.e., stimulus-related responses) gained in magnitude relative to random changes (i.e., noise), lying progressively further (more standard deviations) from the mean. That is, consistent responses became "outliers" in the population. This prompted the application of tests for outlier detection as a means of identifying significant responses (Snedecor and Corcoran, 1980). Our statistical analysis was two-tiered, first using omnibus tests (g^1 and g^2 statistics) to determine whether a data set (a population of regional differences) contained significant outlier responses, then applying post-hoc analysis (Z-score) to determine the significance levels of specific responses within the population (see tables I-VII). All responses with Z scores giving a P-value less than .03 are reported.

Stimulus presentation Visual stimuli were presented on a color monitor suspended about 12 inches in front of the subject perpendicular to the line of sight. Auditory stimulation was generated through small speakers placed in the ear of the subject. The speakers were driven by a digital tape recorder on which appropriate stimuli have been recorded. All stimuli were single common nouns (e.g., cake, radio, etc.), and were presented at 1 Hz. The visual stimuli were presented for 150 ms with an 850 ms interword interval. The auditory stimuli varied in presentation time with the length of the word.

Subjects The subjects were medical students, medical residents, psychology graduate students and represented a high normal group for intelligence and reading skills. All were native English speakers and were right-handed as assessed with the Edinburgh handedness inventory.

Paradigm design The paradigms were designed to address two interrelated issues. 1) To utilize our battery of data analysis techniques, it is important to design runs in activated-control subtraction pairs. In these experiments, a stepwise design was used so that the stimulated member of one pair became the control for the next pair. 2) To make the images of change interpretable, an attempt must be made to hold all but a small number of task components in the two runs constant so that the changes in blood flow may be attributed to a small number of specific functions.

The lexical processing experiments presented here represent a first attempt to address some basic issues in the processing and production of single words (11). There were four basic tasks that the subjects were asked to perform; each task was performed twice, once with visual input and once with auditory input.

The core tasks were: 1) to fixate on a small crosshair with no other stimulation (fixation point); 2) passive nouns presented visually or auditorily through the speakers while the person fixates the crosshair (passive words); 3) repeating aloud the visually or auditorily presented nouns (repeat words); 4) generating aloud an appropriate verb or use for the presented noun, for example, to say the word "eat" if the presented word was "cake" (generate uses).

The core tasks then were organized into three stepwise subtractions. In the first level substraction, activity during the fixation point condition was subtracted from the passive words condition (sensory subtraction). The second level was the subtraction of passive words condition from the repeat words condition (motor subtraction). The third level subtraction was of the repeat words condition from the generate uses condition (cognitive subtraction). Some other subtractions, spanning more than one level were performed to assess questions about our subtractive assumptions.

We recognize the difficulty of designing two tasks that are the same except for the addition of a single new operation (Sternberg, 1969). Indeed, the activations in our tasks are often due to more than one type of operation. It is also possible that subjects alter their basic strategy when confronted with a new task. However, by appropriate subtractions one can check up on whether strategies for more complex tasks still involve activation of those areas comprising simpler tasks. Some secondary experiments were also performed to aid in the interpretations of the results, and will be explained where appropriate.

RESULTS

Sensory Subtraction

A comparison of the resting task and the passive nouns task (sensory subtraction) showed modality specific activation in those areas that are related to the basic sensory information contained in the words, namely primary visual and auditory cortices. In addition, higher order, but modality specific areas were identified that appear to be specific to higher level, possibly lexical processing. There are no regions that are activated by the passive presentation of both auditory and visual words.

Visual (Passive visual words - fixation point) (PVW)

As would be expected, the most responsive foci of activation in the visual sensory subtraction are found in the occipital lobe. There is a bilateral response in buried calcarine striate cortex (primary visual cortex, foci 1, 2; Table 1). There are also extrastriate regions of response (Fig. 3): one region is represented bilaterally (Foci 3,4) with about 30% greater activation on the left, and a region still further anterior and inferior in right occipital cortex (Focus 5). This is also a left lateralized area of activation in the basal ganglia, probably in the putamen (Focus 6).

The occipital pole has long been associated with visual function so that occipital activation here is hardly surprising. However, in a recent PET activation studies, simple visual checkerboard (Fox, et al, 1986) or random dot stimuli (unpublished observations) did not produce consistent responses in lateral occipital cortex anterior to striate cortex, areas that are clearly activated during the presentation of visual words. The lateral occipital activation may well represent activation reflecting lexical or letter level processing (see discussion).

Auditory (Passive auditory words - fixation point) (PAW)

The presentation of auditory words activates several regions in and near the posterior temporal lobe. From animal and human studies, primary auditory cortex is presumed to be located in the posterior third of the temporal sylvian cortex (Geschwind & Levitsky, 1968; Imig, et al, 1977). We find a clear bilateral activation in this region (Fig. 4, Foci 7,8; Table II). There is also a second focus of activation, in the left hemisphere, anterior and inferior to the primary activation (Fig. 3, Focus 9, Table II), and this focus may represent one of the secondary auditory areas that have been described extensively in other species, for example, by Imig et al (1977). There is an active focus in inferior anterior cingulate cortex (Fig. 4, Focus 12, Table II). Finally, activation can also be found in the supramarginal gyrus (SMG, Fig. 4, Focus 10) in the left hemisphere. The SMG is the only activation focus in any of our tasks that is in the Wernicke's-angular gyrus region that is commonly associated with language processing. Since neither the inferior temporal (Focus 9) or supramarginal gyrus has been shown to be active for simple auditory stimuli, including tones, clicks, or rapidly-presented synthetic syllables (Lauter, et al, 1984, and unpublished observations), these foci could be considered as candidates for regions performing word-level processing.

Motor Subtraction

When the repeat task is compared to the passive task (motor subtraction), areas related to overt reading, the generation of an articulatory code, motor programming, and the generation of the movements themselves are activated. Since we are focusing on the output, which is similar across the two input modalities, and subtracting the different sensory specific responses, we would expect that the structures that would be activated would be similar for the auditory and visual presentations and our results confirm this expectation.

Visual (Repeat visual words - passive visual words) (RVW)

One area of activation in the repeat conditions, Rolandic cortex (Fig. 5, Foci 13, 14; Table III), represents primary motor cortical activation that would be expected to be present in the repeat condition. Rolandic cortex has been associated with somatosensory and motor function, primary somatosensory cortex located posteriorly and primary motor cortex located anteriorly in this region. Both of these representations are laid out somatotopically so that adjacent parts of the body are represented in adjacent parts of the cortex. Recent studies using vibrotactile stimulation have identified the locations in our stereotactic space of toes, hand and lips somatosensory representation (Fox, Burton & Raichle, 1987). The area identified as Rolandic mouth cortex is just anterior and superior to the somatosensory lips representation.

A second area activated in the repeat condition is superior, anterior cerebellum (Foci 19,20; Table III). The cerebellum has also been associated with aspects of motor coordination, and cerebellar activation during the speech output is expected. Other studies, where subjects performed hand and eye movements, have shown activation in a similar location (Fox, Thach & Raichle, 1987).

Speech production also bilaterally activated a region of the inferior frontal operculum anterior to the Rolandic strip (Fig. 6, Foci 15,16). The left site of activation is in a location often defined as Broca's area. Damage to Broca's area in the left hemisphere is often thought to be associated with speed production deficits and agrammatism. In our paradigms, however, the activation is bilateral, and while this area could be related to some specifically linguistic functions. Simple tongue movement (Fig. 7) and hand movement (Fox, Pardo, Petersen and Raichle, 1987) both cause activation in a similar location. Given these observations, it seems most plausible at this time to associate this region with some aspect of motor programming, or praxis, than with specifically linguistic or speech function.

A region of medial frontal cortex, in a location often identified as the supplementary motor area (SMA), is activated in the repeat visually presented words task (Fig. 8, Focus 18, Table III). A covert task which required a subject to monitor and count pairs of associated targets with no overt output during the task also activated this region (Petersen, et al, 1986, Soc. Neurosci.).

Finally, there an activation focus (17, Table III) which lies anterior and inferior to the Rolandic mouth representation, that is left lateralized, and a focus of activation in the colliculus (Focus 21; Table III).

Auditory (Repeat auditory words - passive auditory words) (RAW)

The most startling aspect of the results from the RAW subtraction is the degree of similarity between the results from auditory and visual presentation. With only a small number of exceptions, foci activated when repeating auditorily presented words were also activated when repeating visually presented words, when the passive sensory activation is subtracted away.

The area in RAW overlapping RVW includes bilateral rolandic mouth representation (Foci 22,23; Table IV), left buried "Broca" cortex (Focus 24, Table V), right lateral "Broca's" cortex (Focus 25; Table IV), SMA (Focus 27, Table IV), and left premotor cortex (Focus 66, Table IV).

For most of these foci, the anatomical location between input modalities is within .5 cm. In the case of the left premotor area, however, the slightly larger difference between locations may well represent a modality specific specialization of adjacent zones having similar functions.

There are a small set of activation foci not shared across modalities including the superior, anterior cerebellum and colliculus (Foci 19,20, 21; Table III) for RPW.

Cognitive Subtraction

Our final comparison is the most subtle, and should represent activation related to purely cognitive processes, since the sensory input is identical in the stimulated and control condition, and the motor output is very similar. Again, since similar operations are called for in the performance of the task for auditory or visual presentations, there were similar areas activated in the input conditions.

Visual (Generate visual words - Repeat visual words) (GVW)

Inferior and anterior to the SMA is a region activated in the generate uses tasks (Fig. 9, Focus 31, Table V). This area is located in the anterior cingulate cortex (ACC). Inferior and anterior to this midline activation is a second focus of anterior cingulate activation (Focus 32, Table V).

Left lateralized anterior inferior cortex in and around areas 45, 46,and 47 shows several active foci only during the generation task (Fig. 10, Foci 28,29,30; Table V). Our choice of a verb (use) associate to a noun confounds grammatical and semantic transformations. The lesion literature shows effects that appear to be related to verb association, and agrammatism associated with lesions in these regions (McCarthy & Warrington, 1985). Subjects with Broca's aphasia have deficits on semantic priming tasks (Milberg & Blumstein, 1981; Milberg, Blumstein & Dworetzky, 1987). So, in a converging experiment, a semantic monitoring task (monitoring strings of nouns for members of a semantic category), an inferior frontal region near focus 35 was activated (see Fig. 11). Since one task involves monitoring for semantic association of nouns in a string of presented nouns, and the other involves the generation of a semantically- associated verb, it seems likely that some common computation involved in semantic association takes place in the anterior inferior frontal lobe. It remains to be seen whether syntactic operations, will also involve these foci.

There is also a striking focus of activation in right inferior lateral cerebellum (Fig. 12, Focus 36, Table V). The lateralization to the right cerebellar hemisphere is consistent with observations that a cerebellar hemisphere is anatomically and functionally related to the contralateral (in this case left language dominant) cerebral hemisphere. It seems unlikely that this represents motor activation since in the generate subtraction the activation related to the motor output associated with words has been subtracted away, and this activation is anatomically distinct from the foci found in the motor subtractions.

There are also two other foci of activation in the inferior cerebellum, one along the midline anteriorly (Focus 35, Table V) and one located more posteriorly and bilaterally (Foci 33, 34, Table V).

Auditory (Generate auditory words - Repeat Auditory Words GAW)

In the generate subtractions (GVW, GAW), as in the repeat subtractions (RVW, RAW), there is overlap in the areas activated across modalities. For generation of uses using auditory input, there are regions similar to those activated by generation of uses from visual input in inferior prefrontal cortex (Fig. 10, Focus 37; Table VI), anterior and inferior anterior cingulate (Foci 38,39; Table VI), and anterior (Focus 11) and inferior lateral (Fig. 12, Focus 40, Table VI) cerebellum.

For the prefrontal (Foci 37) and inferior anterior cingulate (Focus 39) responses, there are anatomical dissimilarities with their counterpart foci from GVW visual subtraction that may represent a modality specific but similar computation taking place in adjacent anatomical locations.

The small number of foci that are present for only one modality of presentation include the more superior prefrontal activations (foci 28,29; Table V), and the right posterior cerebellum (Focus 39, Table V) for GVW.

DISCUSSION

The results reported here represent our first attempt to extend the PET activation techniques of image subtraction and image averaging to "higher brain function", in particular to issues in lexical processing. The results have implications on several fronts. First, there is the information that can be obtained about how lexical information processing is represented in the brain. We believe our results agree quite well with multiple route models of lexical processing advanced by cognitive science (Coltheart, 1981; 1985; Marshall & Newcombe, 1973), and disagree substantially with the serial models (e.g. Geschwind, 1965, 1979). A second issue is the broader utility of PET activation studies in the neurobiology of human cognition and behavior. It seems reasonable that the techniques employed in these lexical studies could be extended to other cognitive questions as well. In order to assess the applicability of this technology to other human neurobiological and cognitive questions, questions about resolution, localization, and sensitivity of the techniques will be addressed. A third important topic is the applicability of the PET activation technology to clinical questions.

The representation of lexical processing in the brain

To assess the implications of our results for the representation of lexical processing in the brain, a two stage discussion of the results will be follow. First, we will focus on individual regions that are activated in our tasks and come up with reasonable hypotheses about the specific type of processing that might be taking place within that region. Next we will then attempt to arrange these functional regions into a framework that is consistent with our data and some of the other information extant on lexical processing.

Regions of activation

The regions in the occipital region activated in the passive visual words subtraction represent stages of visual processing. The activation of striate cortex is to be expected; the activation of the extrastriate regions is more interesting. The lack of activation in the extrastriate regions activated by visual words when other types of visual stimuli such as counterphase-flickered checkerboards, or dynamic random dot displays give preliminary evidence that this extrastriate activation is quite specific.

Some models of word processing, (LaBerge & Samuels, 1974, McClelland & Rumelhart, 1982) postulate levels of feature, letter, and word form analysis. In connectionist models (Rumelhart, 1986) these levels are reciprocally connected in a parallel distributed fashion. The existence of multiple areas of activation in the occipital lobe is consistent with such a multi-level processing network, with the end level representing activation at a visual word form level of analysis. Further evidence that visual word form codes might be present in anterior occipital areas is that lesions of this area in the dominant hemisphere sometimes cause pure alexia, that is, the inability to read words (although letter by letter reading may still occur) without other language deficits (Damasio & Damasio, 1983; Henderson, 1986). Letter by letter reading has been attributed to a deficit in the visual word form (Warrington & Shallice, 1980) but could also involve earlier stages of the network (Shallice & Saffran, 1986). Our overall results are certainly consistent with an important role of the occipital temporal junction in processing words either passively or actively. However, the PET results do not reflect the degree of lateral asymmetry found in lesions.

In audition as in vision, there appears to be activation in the primary sensory receiving zone, and also in secondary regions (SMG, inferior temporal cortex) that are not activated by simple stimuli, such as clicks, tones, or noise bursts. It is tempting to hypothesize that these secondary regions of activation may represent a phonological level of encoding. Lesions of the supramarginal gyrus have been shown to produce a phonological agraphia in which patients can write words from dictation but not nonwords (Roeltgen, Sevush & Heilman, 1983; Shallice, 1981). This result has identified the left supramarginal gyrus with phonological as distinct from auditory processing. The activation of the left SMG during passive auditory word presentation (but in unpublished work from this laboratory not for auditory clicks or tones) makes the SMG a good candidate for phonological encoding of words at least from auditory input.

Several foci are activated when subjects repeat words presented either visually or auditorily. Activation in motor cortex and cerebellum would be expected in any motor task, and is present for verbal output. Several other areas are activated as well, areas that have been implicated in some aspect of motor coding or programming including the SMA, bilateral activation inferior premotor "Broca's" cortex, and a left lateralized premotor region superior to the Broca's activation.

While Broca's area has been implicated in language-specific deficits, a review by Mohr et al, (1978) has shown that lesions that are confined to this region produce only motor and praxis deficits, without specific language involvement, and that to produce the full-blown syndrome of Broca's aphasia requires larger lesions that extend more anteriorly. Our results showing that simple tongue movement also activates this region is consistent with this view. Recent studies showing that actual and imagined hand movement activate cortex at or near this site make it likely that the "Broca's" activation plays a role in higher level motor coding or production.

SMA is activated in conditions similar to that of our inferior premotor region. It is activated during verbal output and silent counting of associated pairs. This area has been hypothesized to act as a stage in programming of complex movements (Roland, Larson, Lassen & Skinhoj, 1980) or as a stage in a medial motor system related to lower motor process (Goldberg, 1985). The activations in our lexical processing tasks are not inconsistent with these hypotheses. However, SMA is also activated during simple hand movements, and during visual imagination of simple hand movements (Fox, et al, 1987) While all of the tasks include at least an implied output (silent counting, verbalization, or imagined or actual hand movement), neither an actual movement, nor complex programming appears to be necessary to activate this region.

Potential explanations for activation in the generate task include semantic association, grammatical association, spontaneous generation from internal representation (since this task is not directly input driven), and possible non-specific arousal (since this task is the most difficult). The areas activated by the generate use stage include cingulate cortex, left inferior frontal cortex.

Some literature has implicated cingulate cortex with emotion, or autonomic response (Burns & Wyss, 1985), so it is possible that the activation there is related to the nonspecific arousal from task difficulty. A more intriguing possibility is that the ACC activation is related to spontaneous generation, that is, to the initiation or production of a response that does not represent a simple sensory to motor translation. Large midline lesions including SMA & ACC often produce akinetic mutism, a syndrome in which spontaneous speech is extremely rare (Masdau, Schoene, Funkenstein, 1978; Barris & Schuman, 1953; Nielsen & Jacobs, 1951). This deficit is consistent with ACC activation in the generate task, since our generate task demands a spontaneous associated response.

Mohr's (et al, 1978) study of inferior frontal lesions showed that large lesions that extended anteriorly to Broca's area were needed to produce full-blown Broca's aphasia. Studies by Goldman-Rakic (1987) have implicated similar areas in monkeys as being involved in higher order transformations or representations of information. An animal with lesions to this area has difficulty in withholding a preponent, direct response to the stimulus when the animal is asked to hold and transform the information and act on that transformed representation. Goldman also hypothesizes that different subregions of dorsolateral prefrontal cortex may perform similar transformations on different input information, and the adjacent but slightly different localizations for auditory and visual presentations would be consistent with this hypothesis. Since there is convergence of activation on two semantic association tasks, the inferior anterior prefrontal activation in the generate and semantic monitoring task is a candidate for computation related to semantic association.

The activation in right lateral inferior cerebellum is anatomically distinct from activation found with the repeat words and other motor tasks. The different response locale from cerebellar motor activation and the presence of the activation in the generate use subtractions argue for cognitive rather than sensory or motor computation being related to this activation. A role for the cerebellum in cognition has been advanced in recent papers (e.g. Leiner, Leiner & Dow, 1987), but there appears to be no specific candidate set of computations required by our generate task that might be related to cerebellar activation.

Models of lexical processing

The study of lexical processing has taken two relatively independent courses. There have been studies from a neurological orientation with a focus of correlating specific brain regions with particular subcomponents of language processing (See Henderson 1986 for a recent review). These studies have tended to focus on observations and tests on individuals with brain injuries that affect aspects of their language processing or speech production. The most influential synthesis of these studies is in the disconnection models of Geschwind (1965, 1979). His interpretations of these results, while not substantially different from other accounts that had been offered in the late 1800s (See Henderson 1986) were so compelling that they have become the standard neurological model. This model is essentially serial in its analysis of aphasias, and related problems. For example, to read aloud a printed word, the visual information must first be processed in the visual cortex. This visual information is then sent to the angular gyrus where the visual word forms organize the letters, and transform the organized form to an auditory form. Wernicke's area holds a concomitant auditory word memory and directs associations so that an analysis of the word meaning takes place. This code is then sent to Broca's area, where the articulation of the word is prepared, and then to primary motor cortex for output. When this serial neurological model was advanced in the middle 1960's, serial models were in vogue in other areas of neuroscience as well. This was the era when the simple to complex to hypercomplex model of visual information processing (Hubel & Wiesel, 1962, 1965) was having a great impact. Also, in the absence of information to the contrary, a serial model would reasonably be considered a best first guess.

Over the past twenty years, cognitive studies of word processing have focused on different aspects of the problem (See Coltheart, 1985). Cognitive scientists have been more interested in the elementary cognitive operations that make up language than in the anatomical substrates underlying these operations (Mehler, Morton & Jusczyk, 1984). As such, their experiments have been directed toward dissociations of the different aspects of lexical processing. Many experiments take the form of reaction time studies of normals, but lesion behavior studies have been performed as well. In the lesion-behavior studies, the focus has also been to define mental operations that are dissociated from one another by brain injury rather than on associating the loss of a particular cognitive operation with a particular lesion. For example, can a brain-injured individual be found who can pronounce a familiar visually presented word, such as colonel, while being unable to translate a simple pronounceable nonword such as "caik" into a phonological representation that could then be said aloud? Such a dissociation between a visual word form, and phonological encoding of simple pronounceable visual nonword form can be shown to exist, and is strong evidence against a single pathway serial model (Coltheart, 1981; 1985, Humphreys & Evett, 1985).

Recent cognitive models for lexical processing have tended to focus on a variations of a dual route approach for reading of visual words (Coltheart, 1985; Humphreys & Evett, 1985; Carr & Pollatsek, 1985). In these models, visual information has relatively independent access to phonological information about the word (phonological codes), and information about the meaning of the word (semantic codes). In other words, separate phonological and semantic pathways are postulated to arise from visual information about the word.

Our first impetus for investigating the multiple route models were our early results from the PET visual word processing experiments. In the visual task conditions that we employed, there was never any evidence of activation in Wernicke's area or angular gyrus in any of the conditions. When reading a word aloud, the serial neurological model would have predicted activation in both of these regions (Geschwind, 1979). One potential explanation for this result could be that our PET activation techniques were not sensitive enough to see activation in these areas, perhaps because of a particularly high degree of anatomical variability in these regions that subverted the image averaging process. This explanation seems unlikely in that we find clear activation near this region during auditory word presentation (SMG activation). The other explanation is that a strictly serial model for word processing is insufficient. The evidence for independent pathways from cognitive literature argues that this is the case, and our results confirm that there is more than one pathway for the processing of visual words. We will now review some of the evidence for separate routes to word processing in light of cognitive studies, lesion studies, and our PET activation findings, and attempt to find a tentative framework that is consistent with many of these results.

To build up this framework, we will focus on several issues of dissociation that make it likely that there are separate processing routes for the different types of information. These dissociations include independent pathways for the generation of word codes for visual and phonological information, independence of phonological input and articulatory output codes, and independence of semantic association and articulatory codes. In this context, independence between codes is defined as the ability for information used to generate one code not obligatorily activating or generating the other code. We will assess this independence in several ways. From cognitive literature, we will use information from dual task performance and other tests that attempt to define independent processing modules. The logic of dual task interference studies is that when performing two tasks, the amount of deficit that the performance of the second task adds to the first is a measure of the dependence on shared pathways of information processing between the two tasks. From lesion-behavior studies, we will attempt to find behavioral dissociations such that a lesion affects one type of behavior, while leaving another type of behavior relatively intact. From our PET results we will assess the conditions that do or do not activate a region in an attempt to correlate an area with processing demands of the activity tasks.

Our first evidence from the PET studies came during the visual studies in the lack of activation in angular gyrus-Wernicke's region during any of the visual reading tasks. This made it seem reasonable that the visual information, perhaps in the form of a visual word code generated in the lateral occipital extrastriate cortex, had relatively direct access to articulatory output. This made it unlikely that a phonological input-type recoding of the word had to take place for output to occur.

There is considerable evidence on the independence of visual from phonological codes in the cognitive literature of visual word reading (See Carr & Pollatsek, 1985 for a review). According to these studies, visual word forms have direct access to semantic and articulatory codes using a lexical route as well as access to phonological codes. Once source of evidence is the ability of subject to pronounce irregular words (e.g. pint and colonel) rapidly (Baron & Strawson, 1976). A second line of research shows that visual factors rather than phonological ones, influence the time to determine if a letter string is a lawful English word (Coltheart, Davelaar, Jonasson & Besner, 1977) and whether a word string (e.g. tie the not) is meaningful (Baron, 1973). Finally, dual tasks in which subjects are required to process visual words while also processing auditory information show that the secondary auditory tasks affect rhyming judgments but often do not affect meaning judgments (Kleiman, 1975; Rollins & Hendricks, 1980). These data have usually been interpreted as suggesting that in the skilled reader visual word forms have direct access to areas for articulation and semantics.

Studies of individuals with brain injuries also suggest the existence of somewhat separate routes. There are reported brain injury cases in which individuals correctly pronounce regular words and nonsense syllables but who mispronounce irregular words such as "pint" and "colonel" in accordance with the rules for English. These people have difficulty with the direct route from visual word form to articulation. Other patients correctly pronounce these irregular words, but have difficulty with constructions such as "caik", even though they sound like a real word that they can readily pronounce (Coltheart, 1981; 1985).

The PET results, the cognitive studies of normals and the studies of dissociations in dyslexia provide support for a direct route from visual word forms to semantic and articulatory codes.

There also seems to be independence in the phonological input and output codes. It has been postulated that a single representation of the sound of a word could suffice for decoding auditory input and for encoding word output. The PET results would argue against this. While there appears to be a common region activated for word output for both visual and auditory presentation near classically defined Broca's area, this area is not activated by auditory word input. Dual task studies by Shallice, McLeod & Lewis (1985) confirm the necessity of separate representations for phonological input and articulatory output. In these studies, a load was placed on the output system by having people read aloud visually presented words. When this was combined with a task where people were to monitor for a target word in a stream of words presented auditorily, there was very little dual task interference. This not only argues for separate speech input and output codes, but is also confirmatory evidence again that visual reading does not require (interfere with) phonological encoding. Many lesion studies as well confirm that auditory processing of words (comprehension) can be impaired while leaving articulation relatively intact, and articulation be affected while leaving processing of auditory words intact (Broca's vs. Wernicke's Aphasia, Geschwind, 1965).

It is evident that we can pronounce words or letter strings the meaning of which we do not know. Our PET results agree that it is possible to process and articulate words without measurable activation of regions related to semantic association. The inferior frontal area that is activated in semantic association tasks, is not activated during the repeat condition.

Lesions that produce a syndrome called isolation aphasia confirm that a pathway that allows pronunciation without semantic processing might exist. In isolation aphasia, repetition is relatively spared while comprehension is deficient. Often, a syndrome known as echolalia can result, in which the individual parrots whatever is heard without apparent comprehension. James (1890) addressed this point to the effect that "it is more difficult to ascend to the meaning of a word than to pass from one word to another; or to put it otherwise, it is harder to be a thinker than to be a rhetorician, and on the whole nothing is commoner than trains of words not understood."

Given these associations, a tentative cognitive-anatomical framework is presented in Fig. 3. This represents a best guess arrangement of cognitive operations and their associated anatomical region from the evidence described above. While we do not attempt a complete breakdown of the cognitive components in lexical processing, it provides a guiding framework for further experiments is provided.

Application of PET to studies of higher function

We believe that these and related studies using similar techniques can answer questions often raised about the use of PET for structure-function correlation. The questions involve matters of resolution, localization and sensitivity.

The resolution of the reconstructed images using PETT VI is 1.8 cm. The resolution is the distance between two simultaneously presented sources of radiation at which the two become resolvable as independent sources. More directly relevant to activation studies like those presented here is not the resolution of the image, but the localization of single point sources. In a study of the mapping of the retina onto striate cortex, changes in the location of sequentially imaged point sources of less than .5 cm. were consistently obtained (Fox, et al, 1986 Nature). Localization on this order seems appropriate for the studies that we have performed. The fact that we can find consistent localization across overlapping groups of subjects between modalities for regions such as rolandic motor mouth cortex or lateral cerebellum, confirms the reliability of the localization techniques that we employ.

The question of sensitivity presents a more complex problem. Our results indicate that consistent activation attributable to strictly cognitive operations is obtainable; in other words, our techniques have a level of sensitivity that produces consistent results. Both in the generate - repeat, and the converging covert monitoring tasks, areas are active that are very likely related to some level of semantic processing. The use of convergent paradigms to assess the association of an elementary cognitive operation with a particular anatomical region seems to us to be a fruitful way to proceed with the study of localization of function using PET activation techniques. On the other hand, studies from cognitive psychology argue that activation of associated words occur automatically even when the subject is unable to identify the word (Marcel, 1987). Priming studies show that presentation of an associate (e.g. doctor) will speed pronunciation or word-nonword judgments for a related word (e.g. nurse). In our passive conditions we see no activation that is easily attributable to semantic level coding, yet with 150 msec unmasked presentation there is little doubt that semantic priming would occur. The best interpretation would suggest that our PET method in measuring the activation of areas related to higher function is sensitive to information that is coded and used by the person in deliberately performing the task. Representation passively activated by input but not used in the execution of the task may be below the threshold of our PET method.

Another important issue in the application of our PET methodology involves the subtractive assumptions. Cognitive psychologists often object to the subtraction of two different tasks on the grounds that subjects may adopt entirely different strategies for the two tasks. Our PET methodology provides a means of checking up on this idea. Consider the comparison called generate - repeat. If generate involves all the processes involved in repeat plus some additional ones, subtracting fixation from generate should produce a pattern of activation like that found in the passive - fixation condition plus repeat - passive condition plus the additional areas in the generate - repeat condition. In fact, when we make such a subtraction, we find activation in several additional areas not found in generate - repeat. These include the cerebellum, SMA and areas around and Broca's area, and SMG and auditory receiving areas (Table VII). To a first approximation, our subtractive assumptions appear to be true for this set of tasks.

Clinical Implications

Can the view outlined in Figure 13 be reconciled with the lesion data that has supported the Geschwind model? For example, it is known that lesions of the angular gyrus produce alexia with agraphia. Our PET method only shows the activation of nuclear areas and not of white matter tracts. There has been a long unresolved discussion (see Henderson, 1986) in clinical neurology whether angular gyrus lesions have effects on the cortex or on fibers passing under the gyrus. If the routes from the visual system to frontal areas pass under the gyrus one would expect alexias if these fiber tracts are compromised. In addition, many readers do use phonological codes for individual words and readers generally require such codes in storing information during processing of passages.

Another discrepancy between our results and many clinical views is in the location of semantic association. It is well known that patients with lesions in Wernicke's area produce speech which is fluent but empty of semantic content. This suggests that Wernicke's area is involved in semantic processing. Recent evidence from studies of semantic priming has suggested however, that patients with anterior lesions and not posterior lesions have difficulty in access to semantic codes of individual items (Milberg & Blumstein, 1981; Milberg, Blumstein & Dwoetzky, 1987). It seems quite possible that the problems of Wernicke's aphasics involve the integration of semantic codes during the processing of word strings, possibly using phonological information, a level of processing not addressed in our tasks.

The current direct clinical utility of PET activation techniques is limited, but the ability to determine the anatomical location of areas related to specified functions could have clinical implications in the future. For example, our findings of lateralized foci in certain of the lexical processing tasks could be the basis for a method for determining language dominance that is less invasive than the Wada hemispheric dominance test. Preliminary tests using these tasks to assess language dominance have been encouraging (Pardo, Fox, Goldring, Raichle, 1987).

In general, PET activation studies can be used to confirm and extend the catalogue of anatomical-functional relationships. This information can then be used in behavioral neurological diagnosis and would allow neurosurgeons to operate with greater confidence knowing the precise location of vital areas in relation to various surgical procedures.

General Discussion

Rather than an endpoint, we view these studies as a preliminary example of the utility of combining state of the art PET techniques with paradigms designed to address specific cognitive questions. The results lead us to tantalizing hypotheses about the representation of different aspects of lexical processing in the brain. Further experiments can be designed that directly address these hypotheses. For example, if a person must make a phonological (rhyme) judgment about visual word input, is our candidate region for phonological word coding, the supramarginal gyrus, activated?

Successful experiments along these lines could generate significant information about the neural mechanisms related to the processing of single words.

The methods employed here also represent a set of techniques that can be used in the study of the neural mechanisms underlying other higher functions such as attention, perception, and motor control. The results from PET activation studies can be used to complement and extend results using other techniques in both humans and other animals. As a result, the techniques can function in an integrated approach to basic neurobiological questions about higher processes.

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Table legend

For all of the tables in this paper the following conventions are used: the region is given a mnemonic anatomical name associated with the coordinates. The coordinates and magnitudes of response are determined using a three dimensional search algorithm on the averaged subtraction image. The coordinates are in mm. from a 0,0,0 point that is at the level of a line drawn between the anterior and posterior commissures (z=0), at the midline of the brain (x=0), and located anterior posteriorly halfway between the commissures (y=0). The magnitudes are the change in blood flow in gm/100ml/min, and the statistical significance of the points are assessed with a two stage testing procedure. The distribution of the magnitudes of local BF change is tested for outliers using an omnibus gamma2 test. For all averaged images presented here, there are statistically significant outliers. The foci with the largest magnitude of BF change are then given a z-score with respect to the population of all local changes within an image. All foci of change with a p-value < .03 are reported in the tables. *--p < .03, **--p < .01.

There is also a column in which other subtractions with anatomically similar significant foci of change are listed. +-- there is a region in a location near to the activation focus listed, but may be anatomically distinct.

For table 7, the 15 foci with the greatest magnitude of change are reported irrespective of their statistical significance since this table is for comparison purposes. #--p > .03

In general, the passive presentation subtractions identify modality specific foci of activation, while the higher level subtraction generally activate similar regions across modalities. Table VII shows that to a first approximation our subtractive assumptions are correct, since this cross level subtraction contains regions which are the sum of the three subtraction levels within it (see discussion).

Table I

Subtraction Conditions Passive Visual Words - Fixation Point (PVW)

N = 7; omnibus test, $p < .01$

Region		COORDINATES (mm)			Magnitude	Other conditions w/similar activation foci
		Z	X	Y		
1. Striate Cortex	(L)	10	6	-72	2.28*	---
2.	(R)	10	-12	-72	2.66*	---
3. Extrastriate Cortex	(L)	2	24	-58	3.82**	---
4.	(R)	6	-26	-66	2.95**	---
5. Inferior Lateral Occipital Cortex	(R)	-4	-34	-46	3.38**	---
6. Putamen	(L)	4	22	24	3.32**	---

Table II

Subtraction Conditions Passive Auditory Words - Fixation Point (PAW)

N = 8; omnibus test, $p < .05$

Region		COORDINATES (mm) Z	X	Y	Magnitude	Other conditions w/similar activation foc
7. Posterior Superior Temporal Cortex	(L)	14	46	-10	2.46*	---
8.	(R)	12	-42	-16	2.76**	---
9. Inferior Temporal Cortex	(L)	-2	42	10	3.02**	---
10. Supramarginal Gyrus	(L)	14	54	-30	2.88**	---
11. Lateral "Broca" Cortex	(R)	8	-62	-12	3.30**	RVW,RAW
12. Inferior Anterior Cingulate Cortex	(L)	18	12	44	2.34*	---

Table III

Subtraction Conditions Repeat Visual Words - Passive Visual Words (RVW)

N = 11; omnibus test, $p < .01$

Region		COORDINATES (mm)			Magnitude	Other conditions
		Z	X	Y		w/similar activation foc
13. Mouth Region, Rolandic Cortex	(L)	40	46	0	4.34**	RAW
14.	(R)	32	-52	6	3.46**	RAW
15. Buried "Broca" Cortex	(L)	14	31	6	3.04*	RAW
16. Lateral "Broca" Cortex	(R)	8	-63	-4	2.96*	RAW,PAW
17. Premotor Cortex	(L)	18	48	14	2.98*	RAW^{+}
18. SMA		50	-2	10	3.36*	RAW
19. Superior Anterior Cerebellum	(L)	-8	6	-42	4.62**	---
20.	(R)	-9	-16	-44	4.47**	---
21. Colliculus		-6	0	-24	3.04	GAW

Table IV

Subtraction Conditions Repeat Auditory Words - Passive Auditory Words (RAW)

N = 10; omnibus test, p < .05

Region		COORDINATES (mm) Z	X	Y	Magnitude	Other conditions w/similar activation fo
22. Mouth Region, Rolandic Cortex	(L)	42	46	-2	3.64**	RVW
23.	(R)	40	-56	2	3.78**	RVW
24. Buried "Broca" Cortex	(L)	14	34	10	3.17*	RVW
25. Lateral "Broca" Cortex	(R)	12	-62	-7	3.22**	RVW,PAW
26. Premotor Cortex	(L)	26	52	2	3.06*	RVW+
27. SMA		52	2	14	2.80*	RVW

Table V

Subtraction Conditions Generate Visual Words - Repeat Visual Words (GVW)

$N = 12, p < .01$

Region		COORDINATES (mm)			Magnitude	Other conditions w/similar activation fo
		Z	X	Y		
28. Dorsolateral Prefrontal Cortex	(L)	20	44	36	2.98**	GAW$^+$
29. Lateral Prefrontal Cortex	(L)	8	38	36	2.96**	GAW$^+$
30. Inferior Prefrontal Cortex	(L)	-6	-28	50	2.26*	GAW$^+$
31. Anterior Cingulate		38	-6	24	3.12**	GAW
32. Inferior Anterior Cingulate		28	-2	34	2.76**	GAW$^+$
33. Posterior Cerebellum	(L)	-22	16	-64	2.26*	---
34.	(R)	-18	-10	-58	2.62**	---
35. Anterior Cerebellum/ Colliculus	(L)	-16	0	-36	2.70**	GAW
36. Inferior Lateral Cerebellum	(R)	-22	-38	-48	3.34**	GAW

Table VI

Subtraction Conditions Generate Auditory Words - Repeat Auditory Words (GAW)

N = 7; omnibus test, $p < .01$

Region	COORDINATES (mm)			Magnitude	Other conditions
	Z	X	Y		w/similar activation fo
37. Inferior Prefrontal Cortex (L)	-6	33	43	3.10**	GVW^{+}
38. Anterior Cingulate	38	7	28	3.28**	GVW
39. Inferior Anterior Cingulate	28	11	31	3.04**	GVW^{+}
40. Inferior Lateral Cerebellum (R)	-22	-37	-47	2.52**	GVW
41. Anterior Cerebellum/ Colliculus	-6	2	-30	3.00**	GVW

Table VII

Subtraction Conditions Generate Auditory Words - Fixation Point

N = 8, p < .01

Region		COORDINATES (mm)			Magnitude	Other conditions
		Z	X	Y		w/similar activation foc
Posterior Superior Temporal Cortex	(L)	14	42	-16	2.76*	PAW
Supramarginal Gyrus	(L)	14	54	-30	2.32#	PAW
Lateral "Broca" Cortex	(R)	11	-63	-18	3.60**	PAW,RAW,RVW
Inferior Anterior Cingulate Cortex	(L)	22	14	48	2.40#	PAW
Mouth Region, Rolandic Cortex	(L)	37	47	4	3.02**	RAW,RVW
	(R)	32	-54	4	2.52#	RAW,RVW
Buried "Broca" Cortex	(L)	14	42	10	4.44**	RAW,RVW
SMA		45	-2	16	4.66**	RAW,RVW
Superior Anterior Cerebellum	(L)	-12	22	-42	4.04**	RVW
	(R)	-12	-12	-34	3.04**	RVW
Anterior Cerebellum/ Colliculus		-16	0	-30	3.40**	GAW,GVW
Anterior Cingulate		38	0	19	4.66**	GAW,GVW
Dorsolateral Prefrontal Cortex	(L)	27	32	46	2.20#	GAW,GVW^{+}
Lateral Prefrontal Cortex	(L)	16	48	29	2.58#	GAW^{+},GVW
Inferior Prefrontal Cortex		2	42	38	2.20#	GAW,GVW^{+}
Inferior Lateral Cerebellum		-19	-26	-44	3.22**	GAW,GVW
Putamen		4	23	27	2.70#	

Figure 1. A. Primary image of brain blood flow (BF) while viewing fixation point only (control state). Each of the seven slices is a horizontal slice from top (1) to bottom (7), with anterior at the top and left left on the slice representing the left brain.
B. Primary BF image acquired during peripheral field stimulation (5.5 to 15.5 degrees eccentricity).
C. Subtraction image of the change in BF induced by peripheral visual stimulation, created by subtracting image A from image B. Peak response is on slices 3 and 4. All images are from a single subject.

Figure 2. Schematic lateral surface view of the brain. Anterior is to the right. The horizontal lines mark two reference planes of section in the standardized stereotactic space. The 0.0 line runs through the anterior and posterior commissures (AC-PC line). The 4.2 line is parallel to the AC-PC line and 4.2 cm above it.

Figure 3. Auditory vs. visual comparison. A horizontal slice through averaged subtraction image represents BF change when BF fixation is subtracted from BF present during presentation of word stimuli at 1 Hz (sensory subtraction). Slice is taken .2 cm below AC-PC line. Foci of activity present at this level includes inferior temporal non-primary auditory cortex in the left hemisphere (A) for auditorily-presented words, and extrastriate inferior occipital responses (B) for visually-presented words.

Figure 4. Same condition as Fig. 3. Slice in Fig. 4 is taken 1.6 cm above AC-PC line. Foci of activity present at this level include supramarginal gyrus (SMG) (A), bilateral superior posterior temporal cortex (B), and inferior anterior cingulate (C) for auditory presentation, and some occipital cortical activation (D) for visual presentation. Note the non overlapping distributions of activity in Figs. 3 and 4 during passive presentation.

Figure 5. Auditory vs. visual comparison. A horizontal slice through an averaged subtraction image representing blood flow (BF) change when blood flow during passive presentation of words is subtracted from blood flow during vocal repetition of presented words (motor subtraction). Slice is taken 4.0 cm. above AC-PC line. The foci present for both auditory and visual presentation are located on rolandic cortex, just anterior and superior to regions activated by somatosensory stimulation of the lips (Fox, , 1987) and likely represent the mouth representation of primary motor cortex.

Figure 6. Same conditions as Fig. 5. Slice is taken 1.2 cm. above AC-PC line. Foci for both auditory and visual presentation are located on the frontal cortex (F3) buried in the sylvian sulcus. The left site of activation is similar in location to Broca's area, but our activation is clearly bilateral.

Figure 7. Comparison of activation for repetition of words and simple tongue movement. The repeat words slice is taken from Fig. 6 (visual presentation of words); the tongue movement slice represents a subtraction of blood flow during an eyes closed resting state from simple side-to-side movements of the tongue throughout the scan. Similar activation is present in the two conditions, and also for actual and imagined hand movement (Fox, Pardo, ,1987).

Figure 8. Same conditions as Figure 5. Foci for both auditory and visual representations occur near the midline on frontal cortex (F1). This region is commonly referred to as the supplementary motor area (SMA). This area appears to be active for all tasks that require motor programming (Fox, Pardo, 1987, Roland, , Goldberg, 1985).

Figure 9. Auditory vs. visual comparison. A horizontal slice through an averaged subtraction image representing BF change when BF during repetition of presented words is subtracted from BF during vocalization of an appropriate use for the presented word (e.g. presentation of "cake"...output might be "eat") (cognitive subtraction). Slice is taken 3.4 cm. above AC-PC line. Foci for both auditory and visual presentation are in the anterior cingulate cortex.

Figure 10. Conditions same as Fig. 9. Slice is taken .8 cm. below AC-PC line. Foci for both presentation modalities occur in inferior anterior frontal cortex, probably area 47 of Brodmann. Those areas of activation are strongly left lateralized.

Figure 11. Comparison of activation in two semantic tasks. The slice on the right is the same as Fig. 9, visual presentation; the slice on the left represents the BF change when the BF during passive presentation of words at 2.5 Hz is subtracted from BF during a condition where the subject is asked to monitor this string of words for members of a specific semantic category. In the semantic monitoring task, there is no motor output during the scan. Subjects are asked after the scan for a gross estimate of the percentage of target words. The similar foci of activation in these two different semantic tasks implicate this region in some level of semantic processing.

Figure 12. Conditions the same as Fig. 9. Slice taken 2.2 cm. below AC-PC line. Foci in both slices are strongly lateralized to the right and are located in the lateral cerebellum. The right lateralization (and its implied relationship to the left cerebral hemisphere) implicate the cerebellum in some higher cognitive function.

Figure 13. A general network relating some of the areas of activation in this study to the different levels of lexical processing. There are many alternative networks consistent with the conditions under which the areas are activated, but this arrangement represents a simple design consistent with our results, and some convergent experiments from other types of studies.

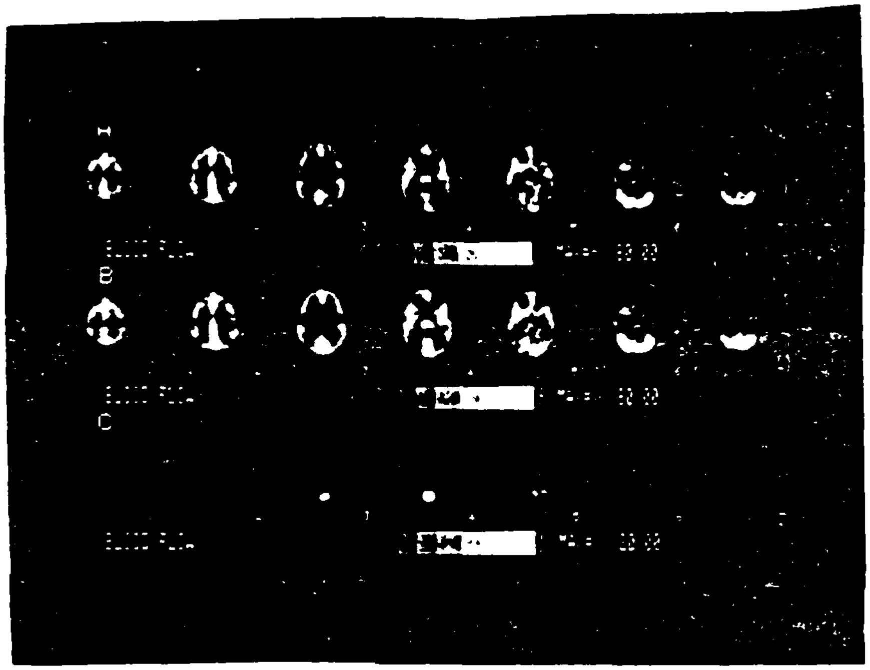


FIGURE 1

A. Primary image of cerebral blood flow (CBF) while viewing fixation point only (control state).

B. Primary CBF image acquired during peripheral field visual stimulation (5.5 to 15.5 degrees eccentricity)

C. Subtraction image of the absolute change in CBF induced by peripheral stimulation, created by subtracting image A from image B. Peak response is on slices 3 and 4. All images are from scanning a single subject.

FIGURE 2

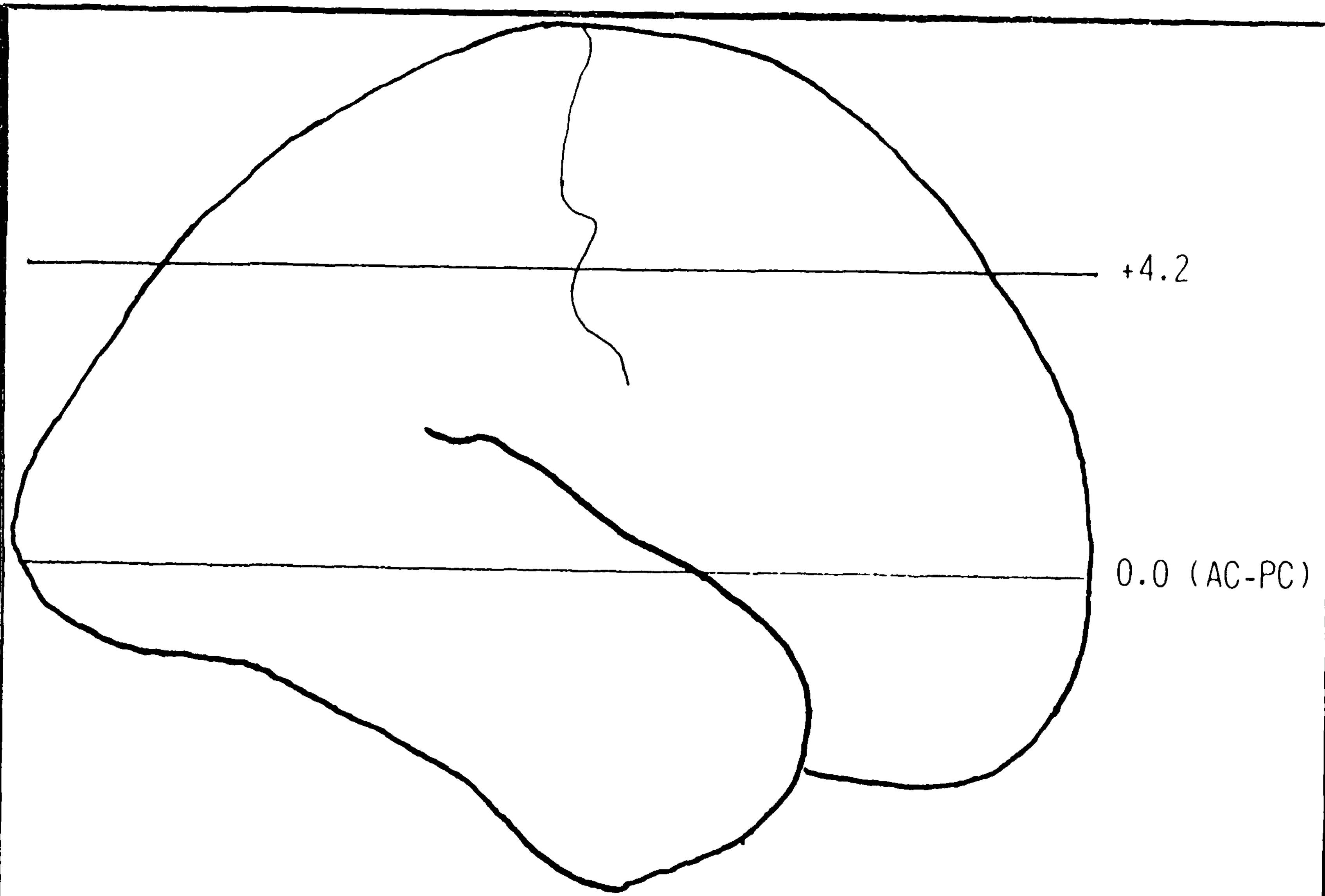
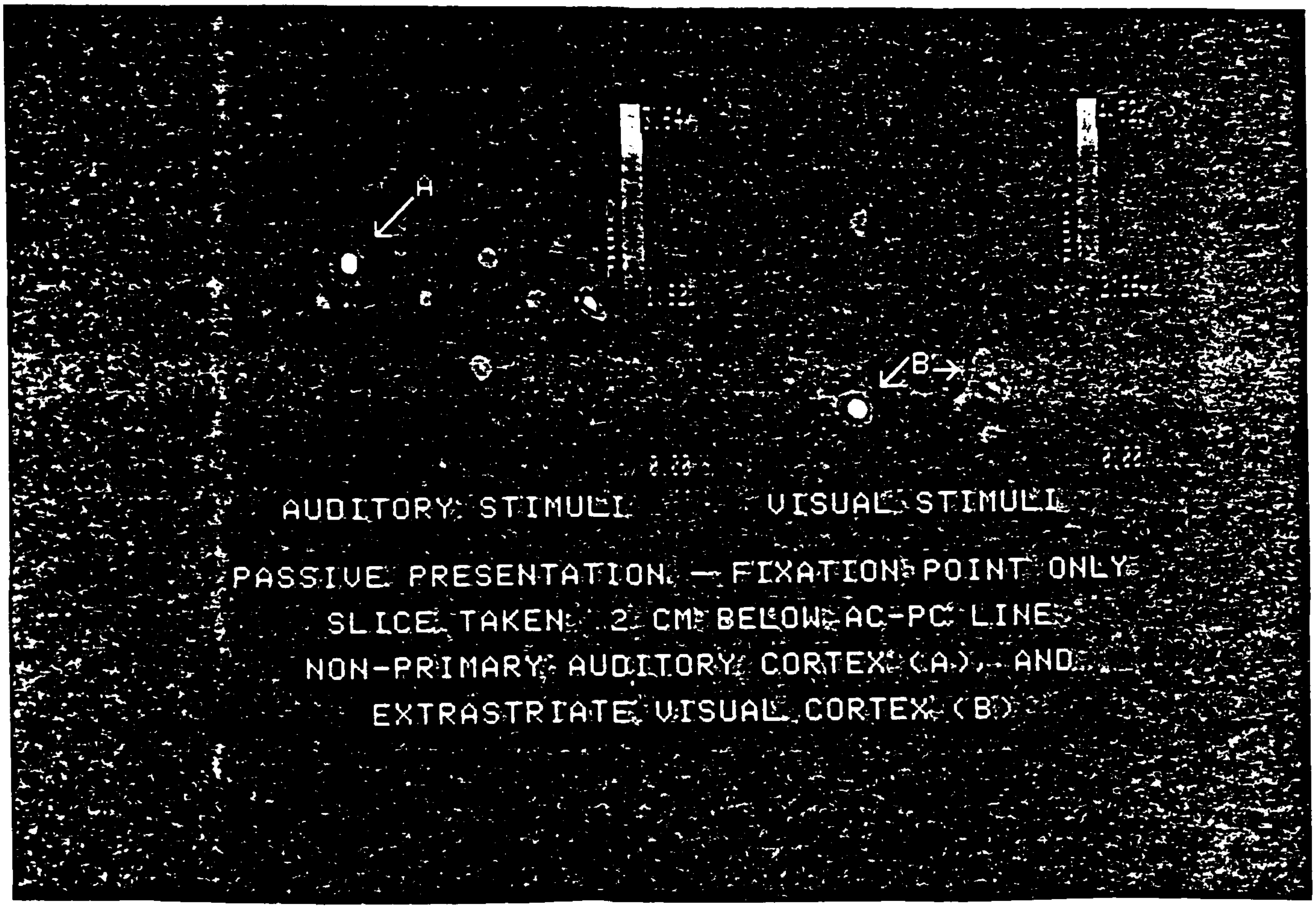


FIGURE 3



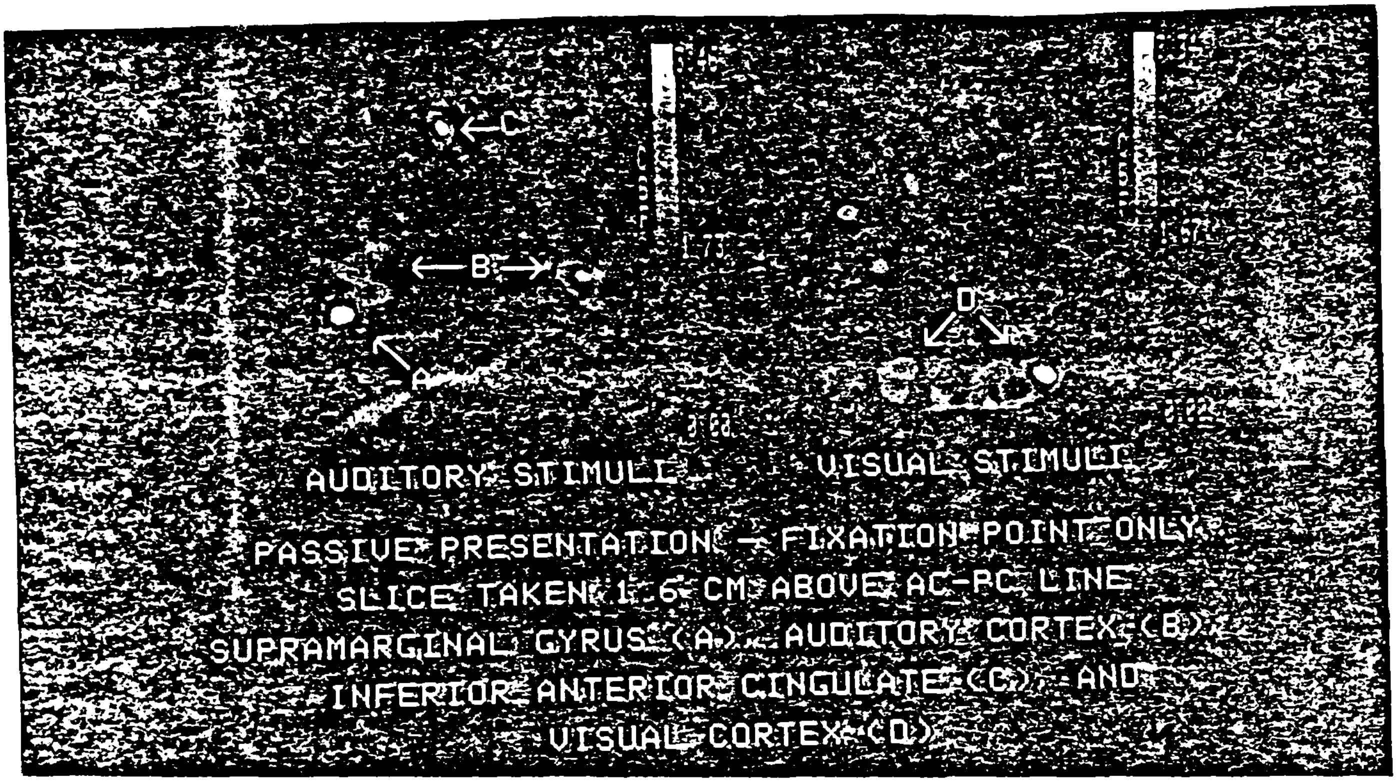
PASSIVE PRESENTATION — FIXATION POINT ONLY

SLICE TAKEN 2 CM BELOW AC-PC LINE

NON-PRIMARY AUDITORY CORTEX (A), AND

EXTRASTRIATE VISUAL CORTEX (B)

FIGURE 4



AUDITORY STIMULI

VISUAL STIMULI

PASSIVE PRESENTATION — FIXATION POINT ONLY

SLICE TAKEN 1.6 CM ABOVE AC-PC LINE

SUPRAMARGINAL GYRUS (A), AUDITORY CORTEX (B), INFERIOR ANTERIOR CINGULATE (C), AND VISUAL CORTEX (D)

FIGURE 5

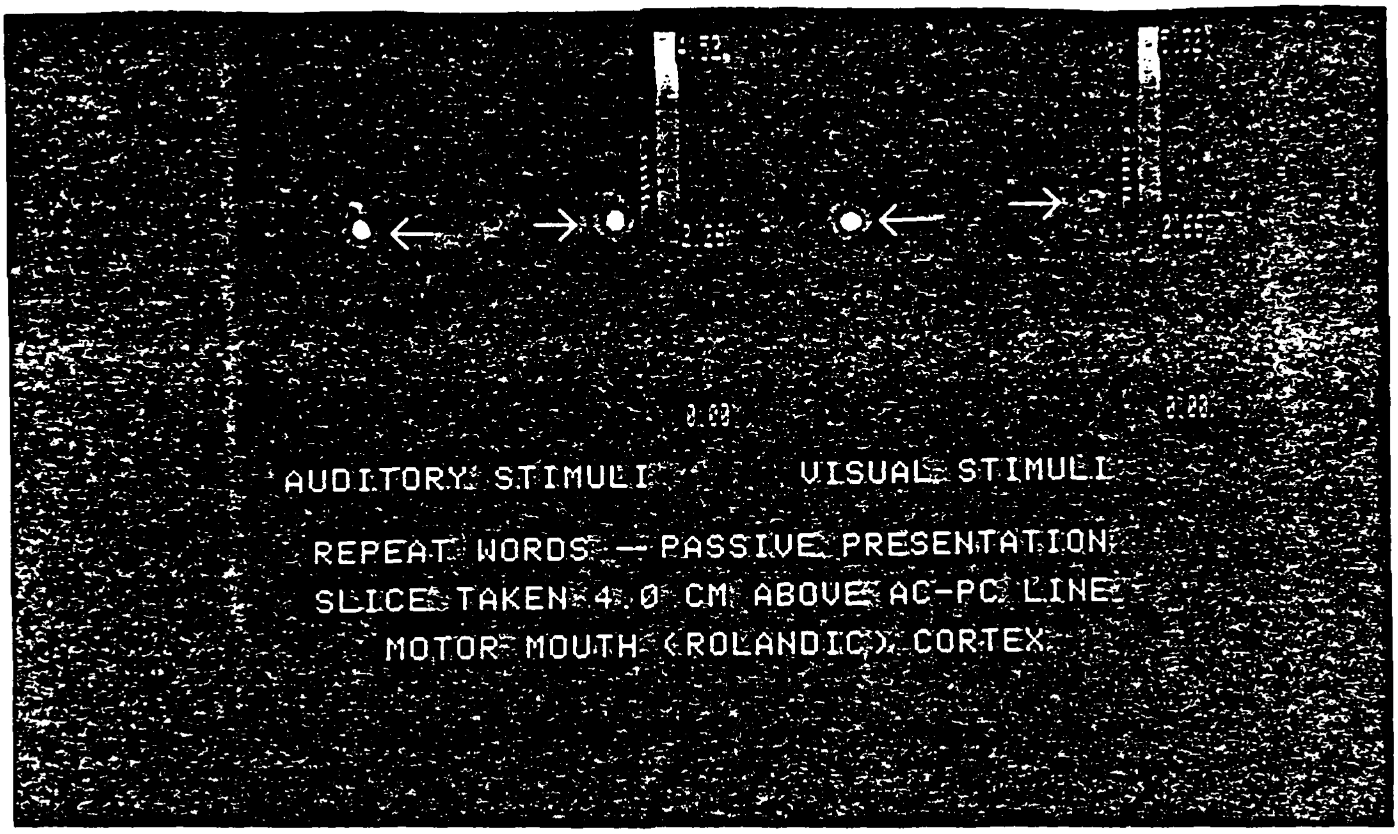

AUDITORY STIMULI
VISUAL STIMULI
REPEAT WORDS — PASSIVE PRESENTATION
SLICE TAKEN 4.0 CM ABOVE AC-PC LINE
MOTOR MOUTH (ROLANDIC) CORTEX

FIGURE 6

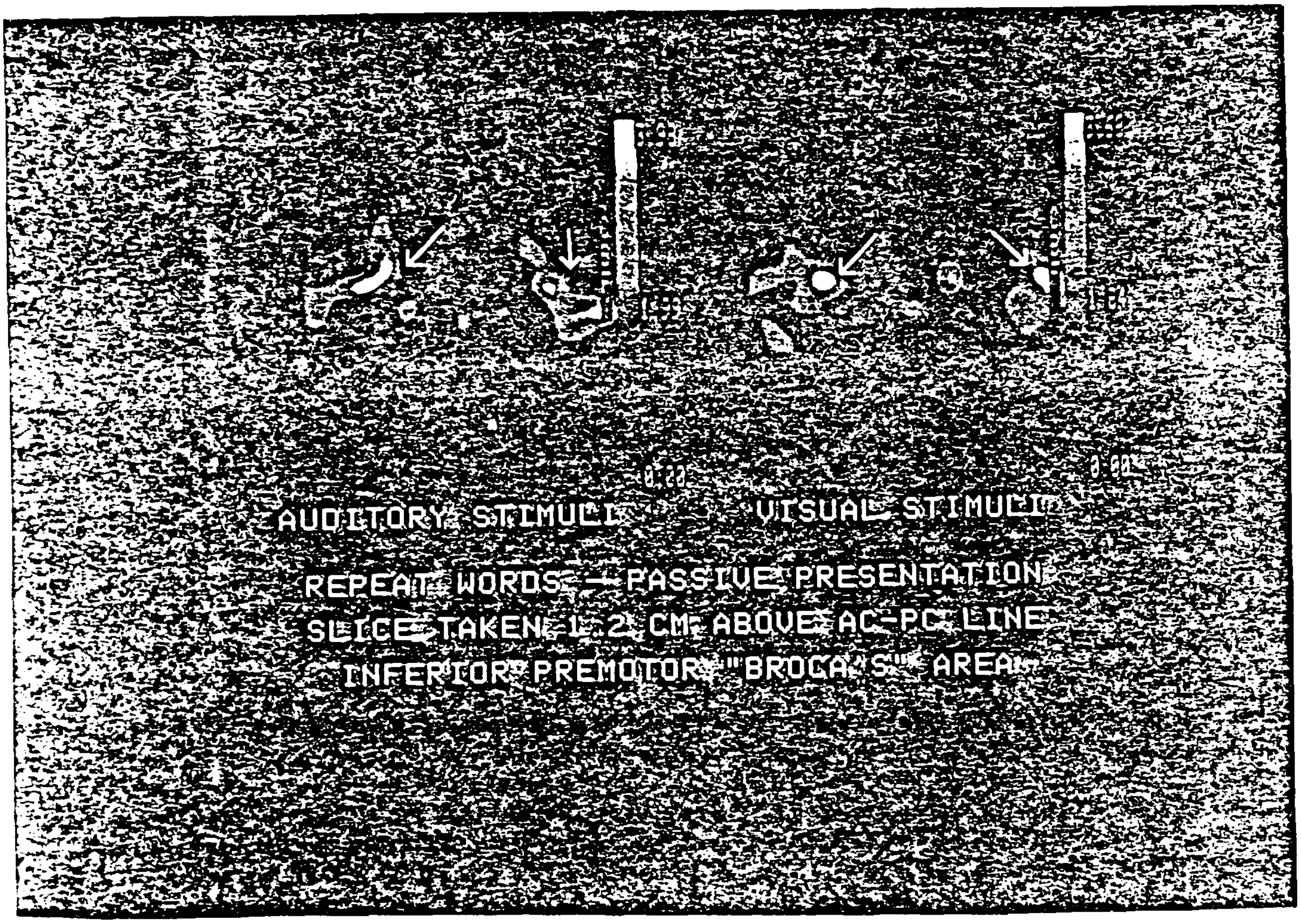
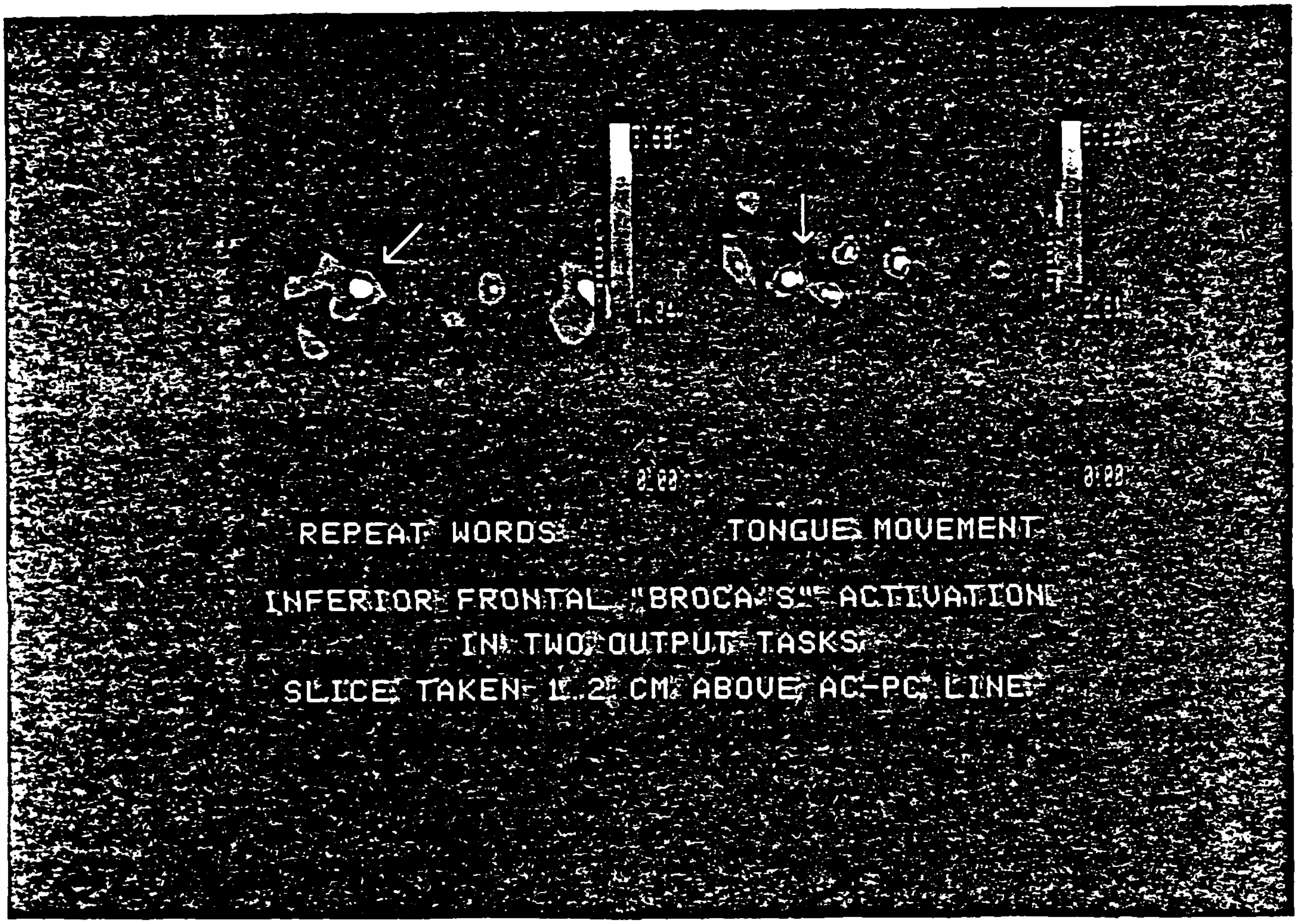

AUDITORY STIMULI
VISUAL STIMULI
REPEAT WORDS — PASSIVE PRESENTATION
SLICE TAKEN 1.2 CM ABOVE AC-PC LINE
INFERIOR PREMOTOR "BROCA'S" AREA

FIGURE 7



REPEAT WORDS TONGUE MOVEMENT

INFERIOR FRONTAL "BROCA'S" ACTIVATION
IN TWO OUTPUT TASKS
SLICE TAKEN 1.2 CM ABOVE AC-PC LINE

FIGURE 8

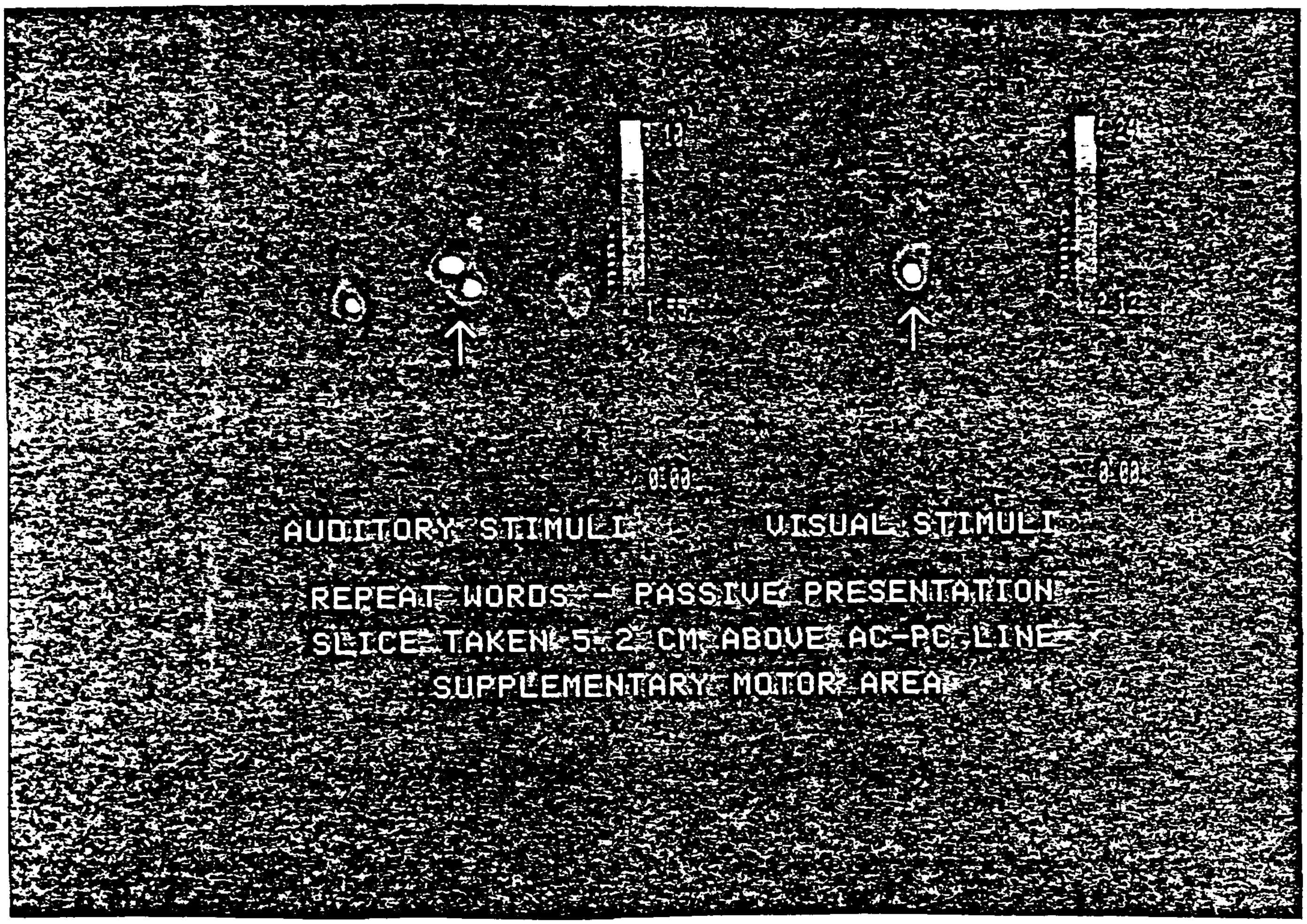

1.55
0.00
0.00
AUDITORY STIMULI
VISUAL STIMULI
REPEAT WORDS - PASSIVE PRESENTATION
SLICE TAKEN 5.2 CM ABOVE AC-PC LINE
SUPPLEMENTARY MOTOR AREA

FIGURE 9

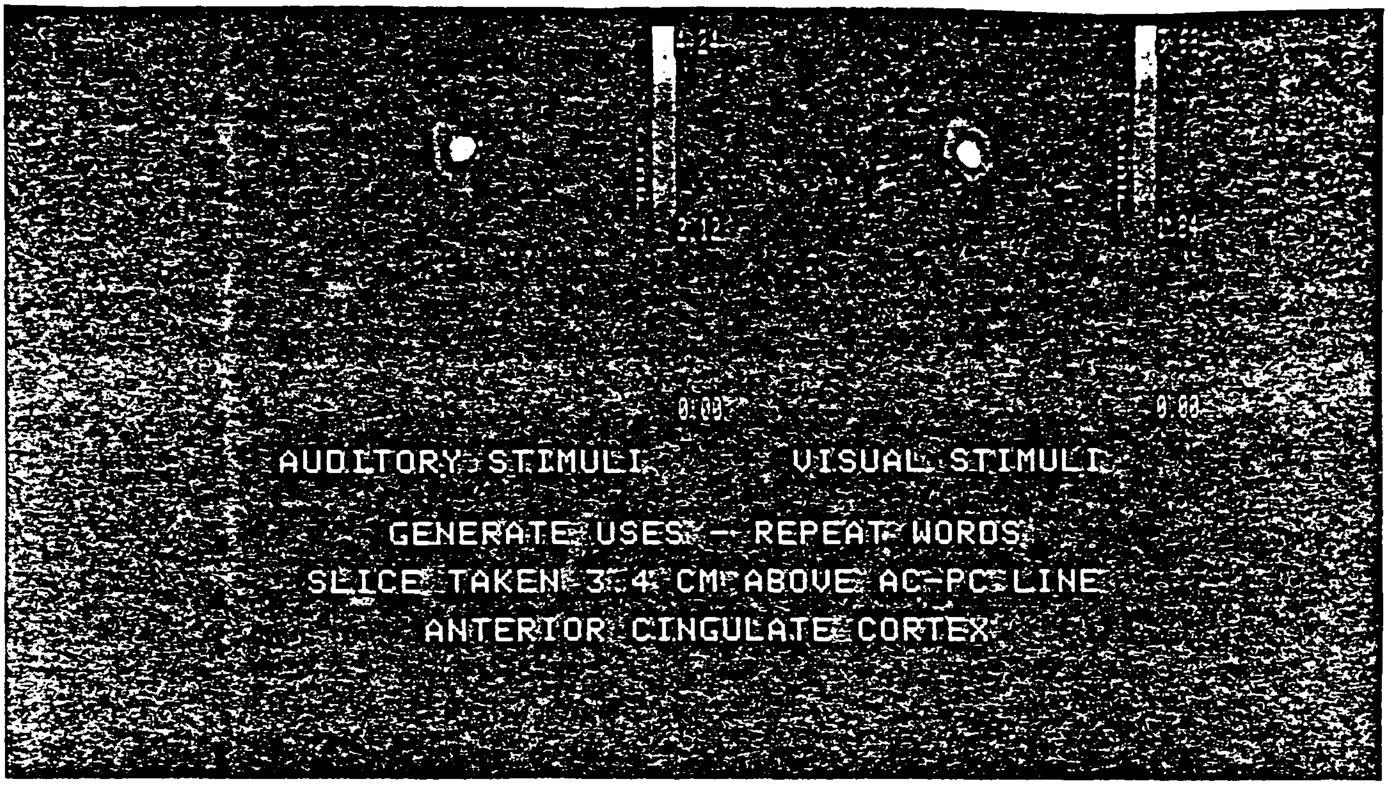

2.12
0.00
0.00
AUDITORY STIMULI
VISUAL STIMULI
GENERATE USES -- REPEAT WORDS
SLICE TAKEN 3.4 CM ABOVE AC-PC LINE
ANTERIOR CINGULATE CORTEX

FIGURE 10

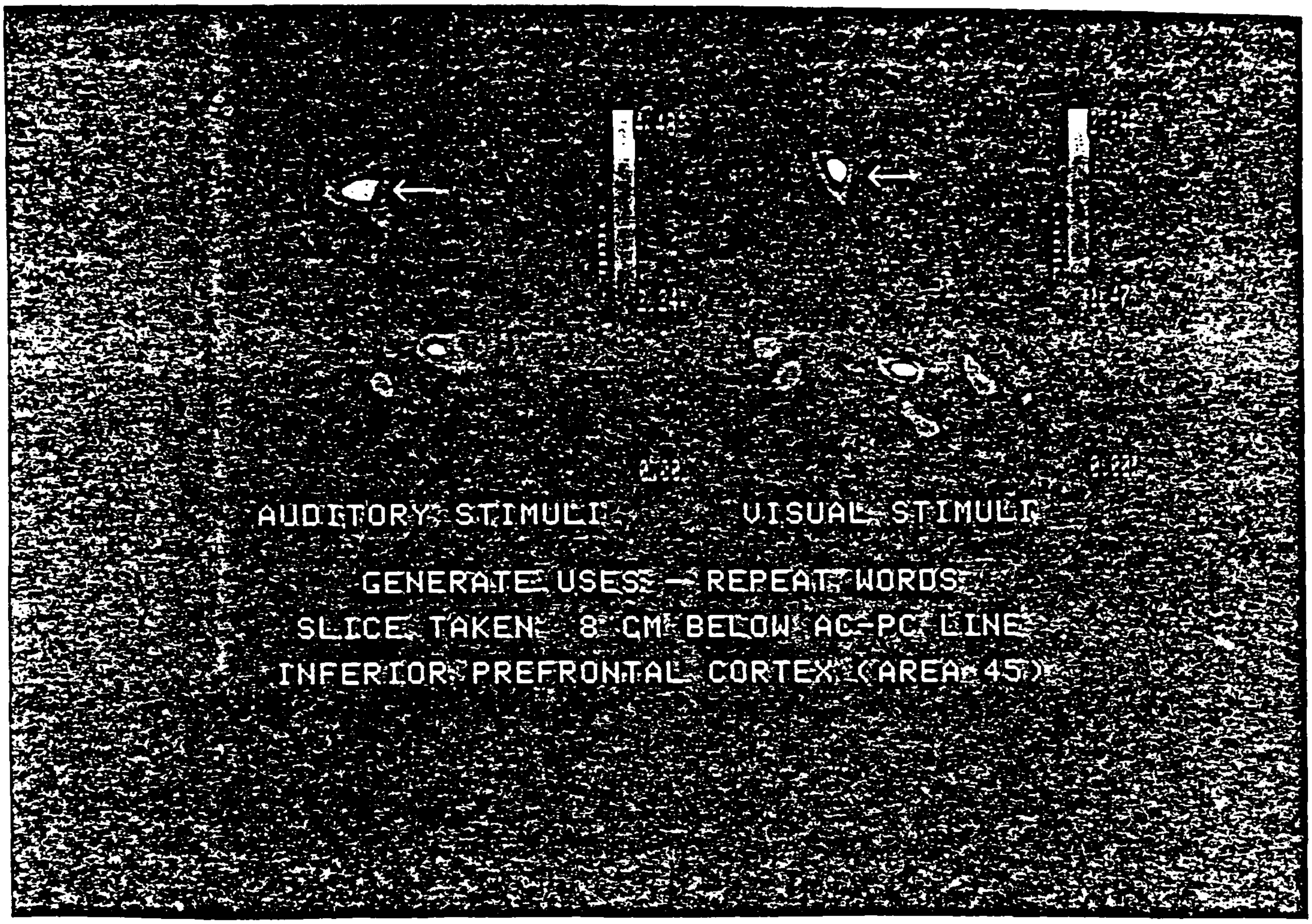

AUDITORY STIMULI
VISUAL STIMULI
GENERATE USES — REPEAT WORDS
SLICE TAKEN 8 CM BELOW AC-PC LINE
INFERIOR PREFRONTAL CORTEX (AREA 45)

FIGURE 11

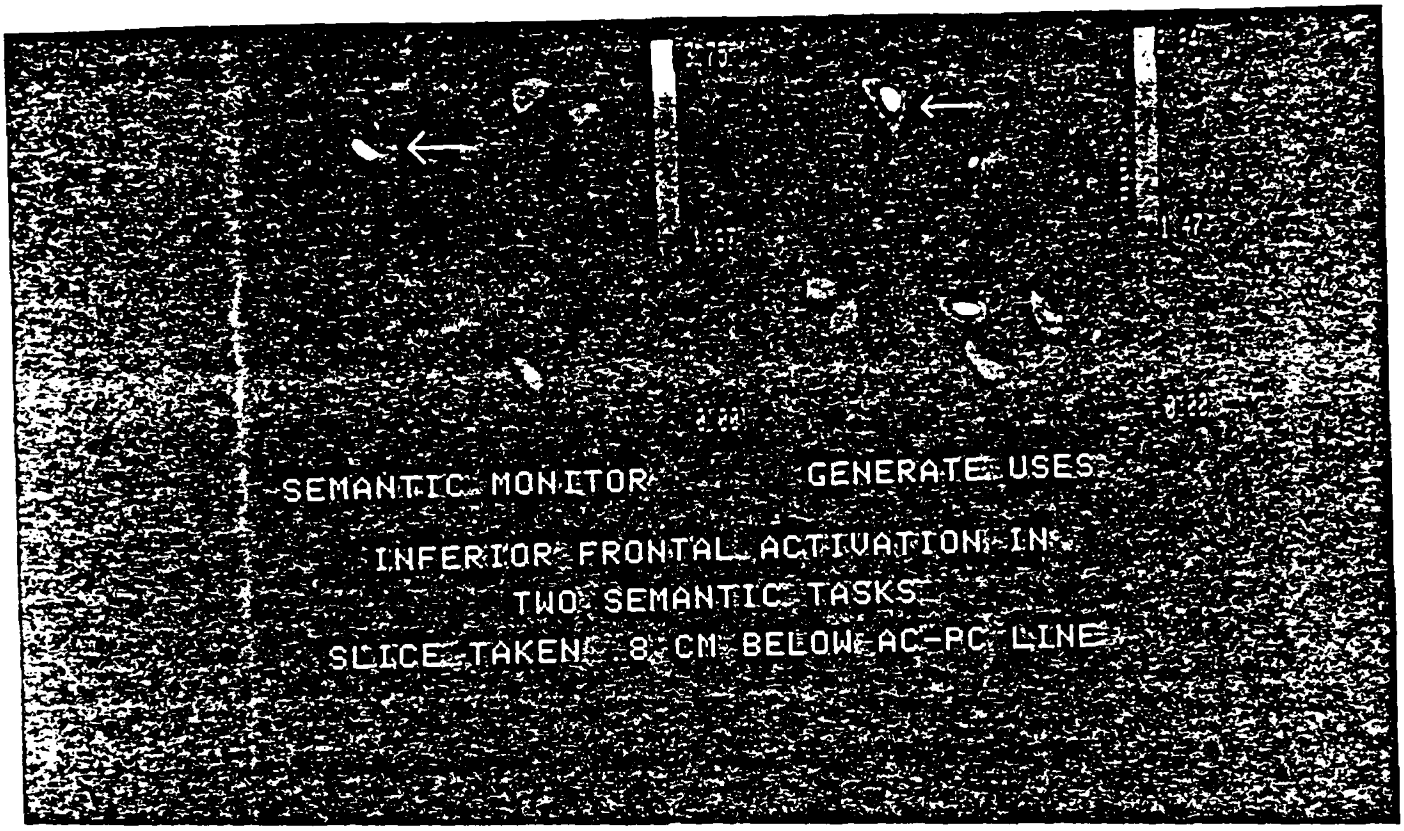

SEMANTIC MONITOR
GENERATE USES
INFERIOR FRONTAL ACTIVATION IN
TWO SEMANTIC TASKS
SLICE TAKEN .8 CM BELOW AC-PC LINE

FIGURE 12

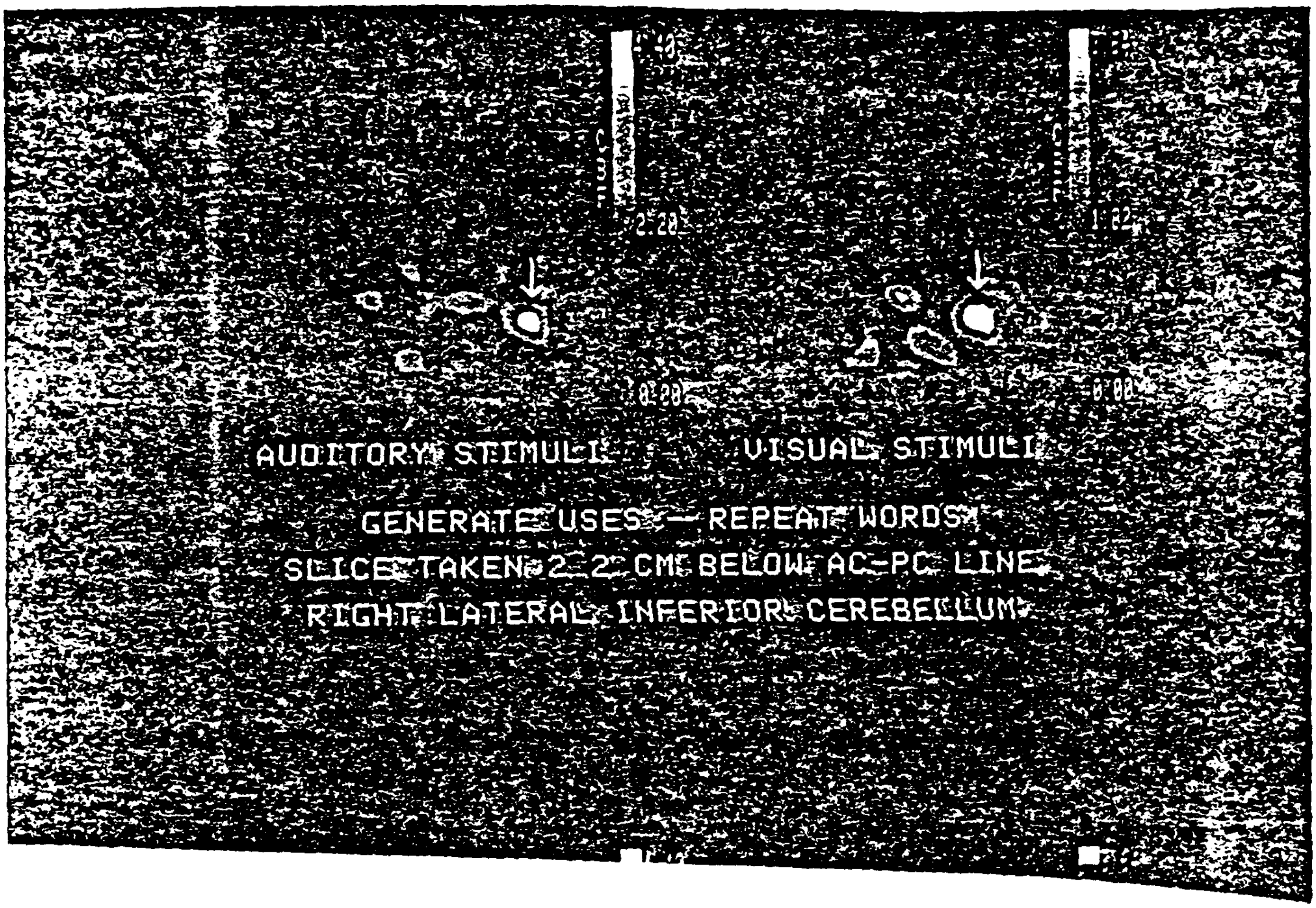
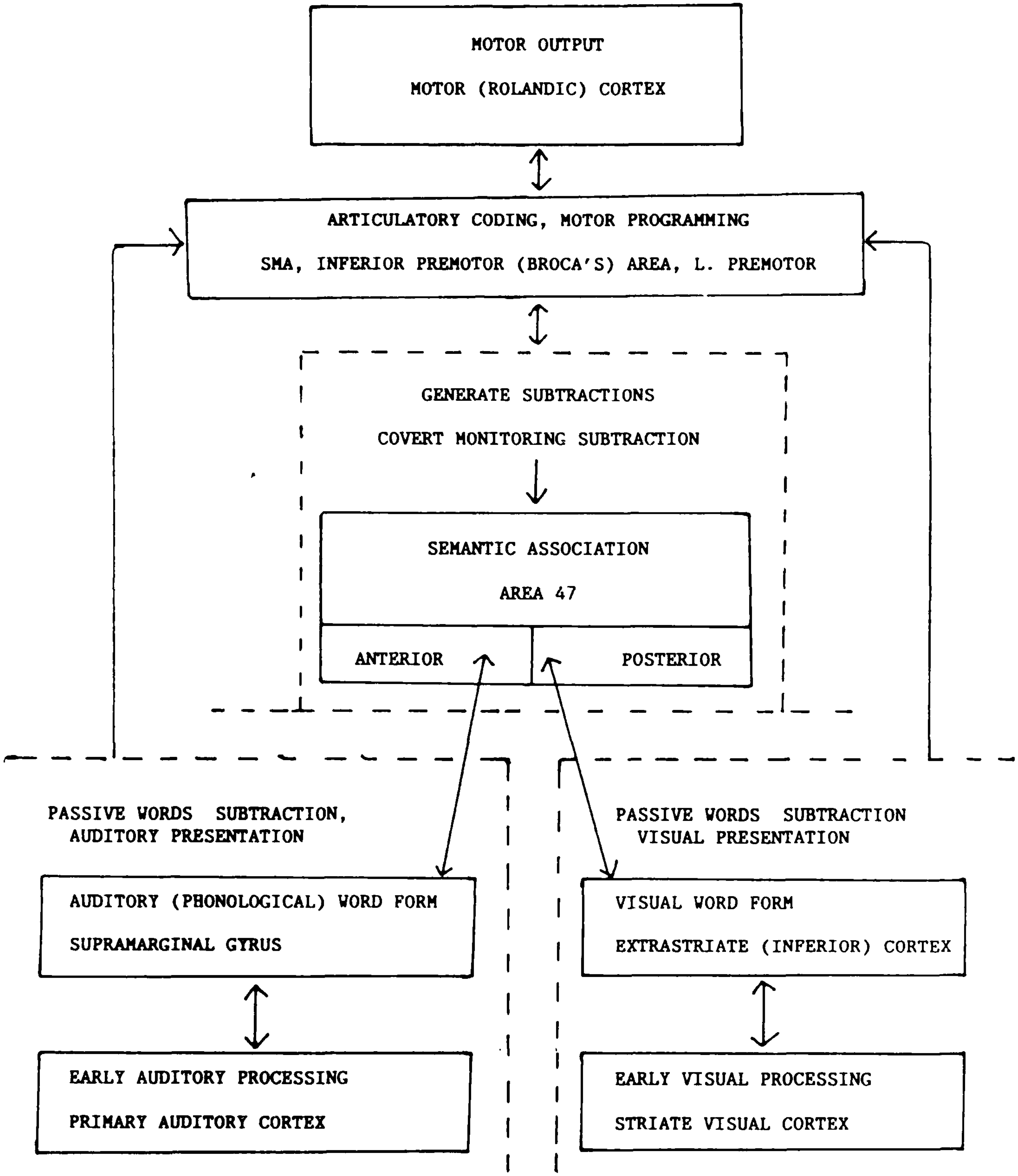

2.20
0.00
0.00
AUDITORY STIMULI
VISUAL STIMULI
GENERATE USES — REPEAT WORDS
SLICE TAKEN 2.2 CM BELOW AC-PC LINE
RIGHT LATERAL INFERIOR CEREBELLUM

FIGURE 13


MOTOR OUTPUT
MOTOR (ROLANDIC) CORTEX
ARTICULATORY CODING, MOTOR PROGRAMMING
SMA, INFERIOR PREMOTOR (BROCA'S) AREA, L. PREMOTOR
GENERATE SUBTRACTIONS
COVERT MONITORING SUBTRACTION
SEMANTIC ASSOCIATION
AREA 47
ANTERIOR
POSTERIOR
PASSIVE WORDS SUBTRACTION, AUDITORY PRESENTATION
PASSIVE WORDS SUBTRACTION VISUAL PRESENTATION
AUDITORY (PHONOLOGICAL) WORD FORM
SUPRAMARGINAL GYRUS
VISUAL WORD FORM
EXTRASTRIATE (INFERIOR) CORTEX
EARLY AUDITORY PROCESSING
PRIMARY AUDITORY CORTEX
EARLY VISUAL PROCESSING
STRIATE VISUAL CORTEX

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