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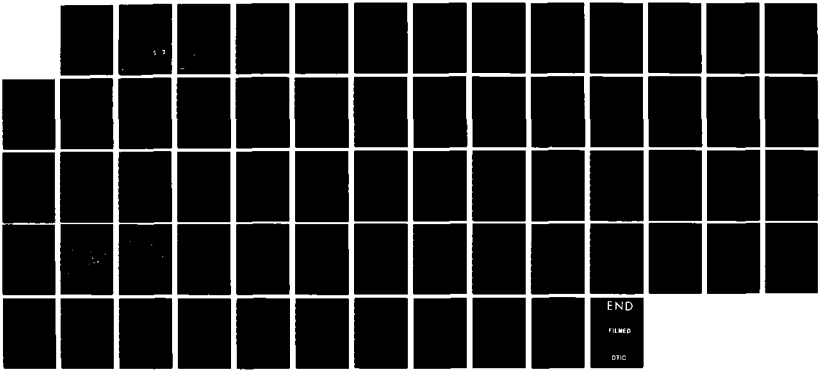

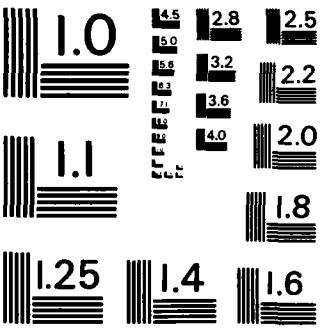


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# NEUROPHYSIOLOGICAL BASES OF EVENT-RELATED POTENTIALS

Annual Report No. 3

June 1985

By: Charles S. Rebert
SRI International

Prepared for:

AIR FORCE OFFICE OF SCIENTIFIC RESEARCH
Life Sciences Directorate
Bolling AFB, D.C. 20332

Attention: Dr. Alfred R. Fregly
Program Manager

AFOSR Contract No. F49620-82-K-0016

SRI Project LSU-4373

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Approved by:

Gordon T. Pryor, Director
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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

In order to more fully understand the physiological and psychological significance of event-related potentials, cortical and subcortical recordings are being obtained from monkeys performing in operant-conditioning tasks. Five cynomolgus monkeys were successfully trained in the cued-reaction time task at SRI International and recordings were obtained in several experimental conditions--tone discrimination, variation of interstimulus interval (ISI) and stimulus proportionality, and administration of atropine. Under some

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20. ABSTRACT (Concluded)

conditions stimulus salience was enhanced, as evidenced by enlarged evoked potentials, when the ISI and stimulus proportionality were altered. The effects of the anticholinergic drug atropine could be attributed to its peripheral effects. Preliminary examination of dynamic intracerebral interactions in one monkey was carried out in collaboration with A. Gevins at the EEG Systems Laboratory, and studies of two monkeys were continued at Stanford in order to study the P300 wave. Five female stump-tailed macaque monkeys were purchased, trained, and implanted and are ready for tone-light pairing and recording.

CONTENTS

## ACKNOWLEDGMENTS

The author thanks Dr. Gordon T. Pryor for improving several programs written for the LSI-11/23 computer and for implementing training and testing routines on the VIC-20 computer. Appreciation is extended to Mr. James Diehl for his thorough, consistent, and dedicated technical help in all aspects of these experiments; to Edward E. Davis for help in the surgical preparation of the monkeys; to Ms. Rosie McCormick for her outstanding clerical contributions; and to Dr. Samuel Jackson for his veterinary help.

FIGURES

TABLES

# INTRODUCTION AND BACKGROUND

## Man-Machine Systems

The modern fighter pilot is primarily an "executive"--an information-processing and decision-making element of a complex man-machine system. The almost overwhelming amount of information to be processed from displays related to flight-systems status, navigation, communications, weapons-threat warning, radar, imaging sensory systems, and situational displays has precipitated the need for improvements in the engineering of cockpit displays and in the understanding of the human operator's information-processing characteristics (Reising, 1980; Furness, 1980) and workload parameters (Moray, 1978). Although the human operator is generally regarded as the weakest link in man-machine systems, the human element is critical if systems are to retain the capability to react intelligently and imaginatively to unanticipated conditions (Gomer et al., 1979).

Because pilot workload is now primarily "mental," the concepts and procedures of cognitive psychology are particularly relevant to the solution of workload problems and man-machine interfacing. Cognitive psychology has undergone a striking revolution within the last quarter century, involving greater emphasis on concepts such as information-processing (Simon, 1980) and intention (Jung, 1981; O'Connor, 1981). Early behaviorists generally considered "cognitions" such as thoughts, feelings, evaluations, and expectancies as epiphenomena that had no relevance to the mechanics of actual behavior, which was conceived to flow from particular stimulus events. However, as recently emphasized by O'Connor (1981), Jung (1981), and Donchin (1980), intentions and goals precede and precipitate (rather than result from) perceptual, attentional, and behavioral strategies.

Although the information-processing revolution has led to a synthesis of several dimensions of psychological research, there remains a large gap in explanations of cognition in that little is known about its neural substrates. A complete understanding of human thinking will probably not be possible until the neural processes underlying symbol manipulations can be specified (Simon, 1980). Obviously, the more complete our knowledge of cognitive processes, the more thorough will be the solution of problems relating to the efficiency of man-machine systems.

## Event-Related Brain Potentials

The only direct indications of brain function routinely available to the psychophysiologist are electric fields accompanying "spontaneous" and event-related intracerebral activity. The slow-wave (1-20 Hz) electroencephalogram (EEG) provides a very general index of the patterning of "activation" across the cerebral mantle. Such measures can be useful in assessing the extent to which various cortical regions--for example, the left and right hemispheres--are differentially involved in various types of tasks (Rebert, 1980a).

Event-related potentials (ERPs) are patterns of electric change associated with the occurrence of fairly discrete external or internal events--a flash of light, a decision. Various components of ERPs reflect activity in different regions of the brain and different information-processing functions, but--with few exceptions--the exact source of the potentials and their precise relationships to cognition, effort, motivation, and overt behavior are unknown. These potentials range from the very specific click-evoked, high-frequency burst of waves generated in brainstem auditory structures (volume-conducted to scalp electrodes) to long-lasting direct-current (DC) potentials of the cortex related to anticipatory processes. Although ERPs are composite reflections of a myriad of intracerebral transactions and their true form is distorted by tissues between the cortex- and scalp-recording electrodes, they are extremely useful tools for assessing the functional integrity of the nervous system (Regan, 1972; Aminoff, 1980; Rebert, 1980b). ERPs have been the focus of interest of many psychophysiologists interested in the neural correlates of cognitive processes (e.g., Donchin, 1969; Kornhuber and Deecke, 1980). Picton and Stuss (1980) have thoroughly summarized the component structure of the known ERPs, their sensitivities to various types of experimental manipulations, and their presumed relationships to psychological processes. The component structure of ERPs varies as a function of stimulus modality, recording location, task parameters, and subject state, among many other factors. In a situation requiring the detection of a rare event, a prominent positive wave (P300) occurs, with latency of about 300 msec. This may represent the response to disconfirmation of expectancy and is influenced by other subjective factors such as decision confidence (Hillyard et al., 1978).

In the cued reaction-time (RT) task, one stimulus acts as a warning that a second stimulus, which has significance for the subject, will subsequently appear. During the few seconds of the interstimulus interval, there appears a slow negative potential shift, called the contingent negative variation (CNV). This event is probably a nonspecific sign of localized cortical activation (Rebert, 1980c). A slow potential shift, the Bereitschaftspotential (BP), which is morphologically similar to the

late portion of the CNV, occurs when a S prepares, in the absence of any preparatory or imperative cues, to carry out a behavioral act.

## Basic Research in Animals

Although studies of human electrocortical activities demonstrate the validity of the "biocybernetic" concept (Donchin, 1980; Rebert, 1980a), a complete knowledge of ERPs using just those procedures is precluded by a number of limitations in human scalp-recording methods. For example, scalp potentials are not precise reflections of the underlying cerebral activity because of distortions produced by intervening tissues, many cortical events are not apparent in scalp recordings, and ERP components recorded from the scalp are unlikely to be due to discrete generators, but probably reflect overlapping sources of potentials.

The foregoing considerations point clearly to the need for studies of ERPs in animals. The advantages of using animal subjects lie, of course, in the wide variety of procedures and experimental manipulations that can be carried out--e.g., intracerebral recording and stimulating (either electrically or pharmacologically), disruption of known neural pathways, histological evaluations, long-term study of a subject, systemic injection of a variety of pharmacological agents, direct manipulation of biological drive states by deprivation, and rigorous control over the experimental experiences of the subjects.

## Choices of Experimental Paradigm

A host of experimental paradigms can be employed with animals to study ERPs. The one selected should cognitively engage the animal and closely approximate paradigms used in human research. Most preferred is a paradigm that is sufficiently general to include a variety of psychological processes and ERP components, is rigorous in terms of good control over the behavioral sequences and psychological sets induced in the animal, and is flexible in terms of the ability to manipulate a variety of experimental variables while not altering the basic logical structure of the task. In addition, because homology between animal and human ERPs is important, advantages should accrue from the use of a behavioral paradigm for which there already exist data indicating a close homology of ERPs elicited by the situation (Rebert, 1972).

The cued RT task meets the foregoing criteria and was considered to be the most promising one to use in early studies of the electrogenesis of ERPs in animals.

## Importance of Brain Slow Potentials

Study of slow-potential (SP) changes is important for several reasons in addition to those mentioned above. Recently, there has been increasing recognition that interneuronal information can be transmitted in ways other than classical synaptic transmission, which involves a specific chemical transmitter that induces a rapid and brief de- or hyper-polarization of the postsynaptic membrane. These developments involve both electrotonic and molecular mechanisms. They have been reviewed by Schmitt et al. (1976) and Dismukes (1979) and elaborately treated by numerous authors in the NRP Fourth Study Program (Schmitt and Worden, 1979). Eccles and McGeer (1979) distinguished the classical synaptic system (the ionotropic system, which depends on the opening of ionic gates in nerve membranes for its effects) from what they termed metabotropic systems, which act on neurons by way of intracellular metabolic alterations--so-called second messenger systems like cyclic adenosine monophosphate. The basic thrust of these new concepts is that there are communication systems that act more slowly, for longer periods of time, and less discretely than do the classical synaptic systems. Communication involves modulation of activity in the classical systems as well as direct influences on neural activity. For example, dopamine released from terminals ascending from the substantia nigra to the caudate nucleus alters the responsiveness of the caudate to sensory stimulation (York and Lynch, 1976).

Both the modes of cellular action and the anatomical configuration of metabotropic systems are incompatible with discrete and highly localized activity. For example, the raphe system, which contains almost all of the brain's serotonin-containing cell bodies, is extremely small; yet its processes ramify to innervate almost all areas of the brain (Eccles and McGeer, 1979). Chemical modulator substances are not necessarily released at specific synaptic sites, but may diffuse to multiple distant targets through the extracellular space. Transmission of slowly varying or tonic information is suggested by these arrangements (Dismukes, 1979), and such activities have been suggested as the mechanisms that may underlie many behavioral/psychological processes such as attention, affective state (Dismukes, 1979), and other cognitive functions (Schmitt et al., 1976)--concepts that are quite in line with the newer views of cognitive psychology.

Of specific relevance to the work reported here is that the metabotropic functions are manifested at the cellular level by very slow membrane potentials (Libet, 1978) that could underlie slow field potentials such as the CNV (Rebert, 1978; 1980b). The concept of local neuronal circuits (Rakic, 1976) is also relevant to studies of SPs. These complex neuronal circuits are composed primarily of short-axon Golgi type

II neurons that interact in unconventional ways, such as through dendrodendritic, somatodendritic, dendrosomatic, somatoaxonic, and axoaxonic synapses and through gap junctions that allow direct electrotronic coupling. Thus, many neurons have only local synaptic connections, in contrast to long "through" neurons, and an enormous amount of bioelectric information is processed locally by dendritic networks, primarily through graded (slow) potentials rather than regenerative spikes. The number and proportion of local circuit neurons increase phylogenetically and these neurons constitute a pool of modifiable cells with highly complex dendritic processes (Schmitt et al., 1976). The dendritic processes of stellate cells in the superficial region of the cortex are more complex than those of deeper neurons, and it has been suggested (Caspers et al., 1980) that they are a major source of surface-recorded SPs. Thus, as has been indicated before (Rebert, 1978), it appears that the study of SP phenomena provides an increasingly important method for relating complex psychological processes to neural events.

## Experimental Issues

A host of specific issues concerning the electrogenesis of ERPs, especially the SPs, remain unresolved. These include the following:

- Distribution in the brain. In what regions and layers of the cortex do specific ERP components occur? In what subcortical nuclei do they appear, and how are they distributed within a given nucleus or region? Does the distribution of an ERP component like the CNV reveal anything about general cerebral systems that mediate behavior in a task?

- Relationship to neuronal activity. Do ERPs occur in close relationship to neuronal spiking? Is this a necessary relationship, or might dendritically mediated SPs appear in the absence of spikes? How do positive and negative SPs relate to neuronal discharge? Is that relationship the same throughout the brain? What is the best way to study the relationship--by single or massed unit analysis? How do SP and unit activities respond to the manipulation of psychologically relevant variables--i.e., do both measures reflect the same neural processes, or do they reflect two functional compartments that might mediate different psychological processes?

- Relationship to nonneuronal activity. To what extent do SPs reflect the activity of glial cells, and what implication might such findings have for interpreting the significance of SPs? Can this relationship be studied by measuring extracellular potassium concentrations?

- Neurochemical substrates. What neurotransmitter and neuromodulatory systems underlie the production of ERPs? For example, does the dopamine pathway from the substantia nigra play a role in producing or modulating the positive SP in the caudate nucleus that accompanies the CNV? Are fast and slow components of ERPs mediated separately by ionotropic and metabotropic systems? Can systemic injection of pharmacological agents provide meaningful data concerning these issues, or is localized intracerebral perfusion of such agents necessary?

- Intracerebral dynamics. How do ERPs in different brain regions correlate over the course of trials? Can such relationships reveal dynamic interactions among intracerebral nuclei or general systems--for example, are the limbic and nonspecific reticular activating systems reciprocally interactive?

- Homology across species. Do ERPs react to experimental variations in animals in the same manner as they do in humans? Do potentials of similar configuration occur in the same brain regions in animals and humans?

## GENERAL METHODS

### Test Paradigm

A schematic representation of the logic of the cued RT task is shown in Figure 1. A trial can be initiated if the animal has maintained a specified hand posture (resting its hand on and depressing a paddle attached to the primate chair for at least 5 sec). After a period of training, the position is usually maintained throughout the intertrial interval (ITI). This contingency assures a greater homogeneity of RT because the instrumental response is always made from the same starting position. Tone bursts (1000 or 3000 Hz) of 100-msec duration constitute warning or neutral stimuli (WS and NS, respectively). The WS is followed by an imperative stimulus (IS), a light, which indicates to the monkey that it can obtain reinforcement by making the appropriate operant response (a bar-press in this case). The interstimulus interval is typically 1.5 sec, but can be manipulated for experimental reasons. If the monkey releases the "hold" position any time before onset of the IS, the trial is aborted and no reward is available. Correct performance allows the monkey to receive 0.6 cc of an orange-flavored drink (Tang®) for each bar-press made during the 12 sec that the IS remains on (usually 15-20 cc during each trial).

The NS occurs in isolation--i.e., it is not paired with any other cue—and provides a comparison for assessing ERP components related to the associative responses elicited by the WS. Typically, CNVs are evoked by both the WS and NS early in the training period, but later only by the WS. Thus, this paradigm permits assessment of the development of associative and discriminative events in several regions of the brain (Rebert, 1977).

The general procedures used to bring the monkeys up to a good level of performance entails, first, training them to press the bar reliably for juice reward, contingent on the presence of the IS. The monkeys can be trained to emit relatively short-latency responses to the IS by having the IS (and the availability of reinforcement) terminate after 500 msec if the bar has not been struck by that time. This training is followed by the introduction of the WS or the WS and NS on different trials.

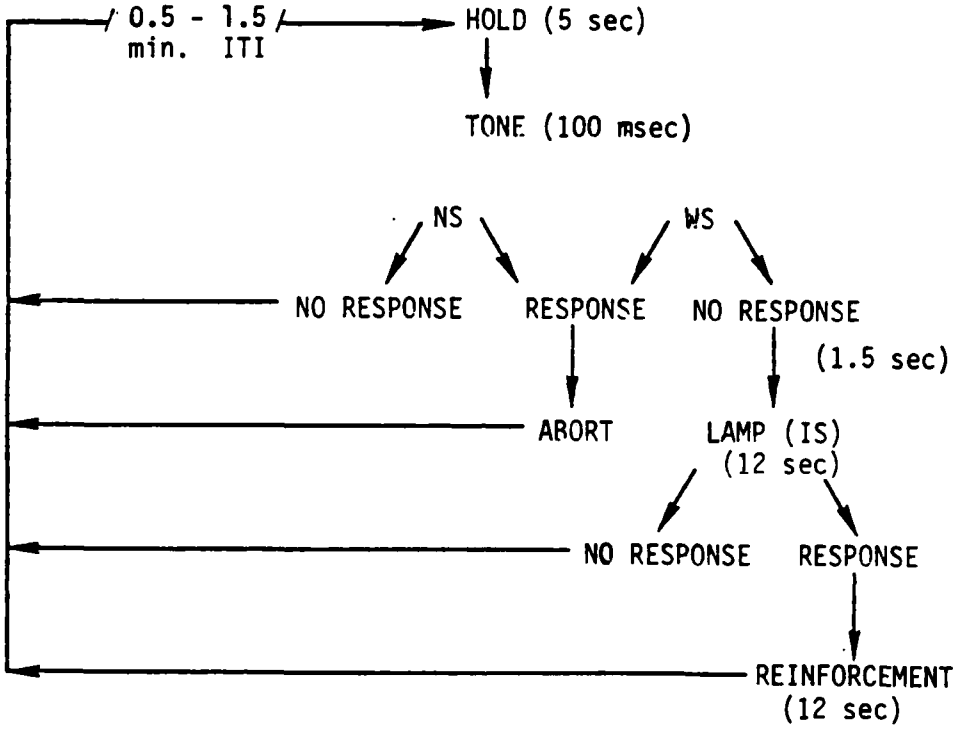


Figure 1 Schematic illustrating technique used to establish a cued discriminative reaction time task in the monkey

NS = neutral stimulus; WS = warning stimulus; IS = imperative stimulus

## Instrumentation

During testing sessions, an animal is placed in a Plexiglas primate chair that is housed in an electrically shielded, sound-attenuating chamber. Pressure on the response bar activates a metering pump through which the liquid reinforcement is delivered to a drinking tube placed in front of the monkey's mouth. A lamp in front of the monkey constitutes the IS when lit. Head restraint is accomplished by placing an inverted U-shaped tube over the monkey's snout. Vertical eye movements are recorded through an electrode above one eye. These recordings are primarily precautionary because it appears that eye movement artifacts are not picked up by intracerebral electrodes when an intracerebral reference is used. That possibility was alluded to by Low (1969) and was shown in a demonstration of human intracerebral recording at the Burden Neurological Institute in 1973. Our recordings from anesthetized monkeys indicate that when the eyeball is mechanically rotated, an artifact appears between intracerebral electrodes and a scalp reference, but it does not appear with intracerebral references in anterior or posterior white matter.

During a previous contract period, an LSI-11/23 computer system was installed and software was written to implement the CNV paradigm. The configuration of this system is schematized in Figure 2. It consists of an LSI-11/23 processor with extended memory (256 KB), clock board, analog-to-digital converter and associated direct memory access board, a digital-to-analog converter, contact closure detector, latched open-collector board for operating external devices, a 30-MB Winchester disk with associated 1-MB floppy, a 9-track digital tape recorder, and VT640 graphics terminal. Associated devices include solid-state tone generators under computer control, a circuit interface between the computer and liquid delivery system (A Valcor 5P94R-7 metering pump), a gain and DC-offset control panel, indicator panel, H-P model 7034A X-Y plotter, and TTY Model 43 printer.

The Winchester disk is used to store programs and, temporarily, single-trial data during testing. At the end of the test session, the single-trial data are transferred to digital tape. The floppy disks are used to store waveform averages and summary statistics of behavioral data for the session. The summary statistics are printed on the TTY-43 printer at the end of the session, and waveform averages are plotted on the HP plotter.

## Surgical Preparation

In preparation for surgery, the monkey is given a 15-mg/kg intramuscular (im) dose of ketamine hydrochloride, a rapid and short-acting

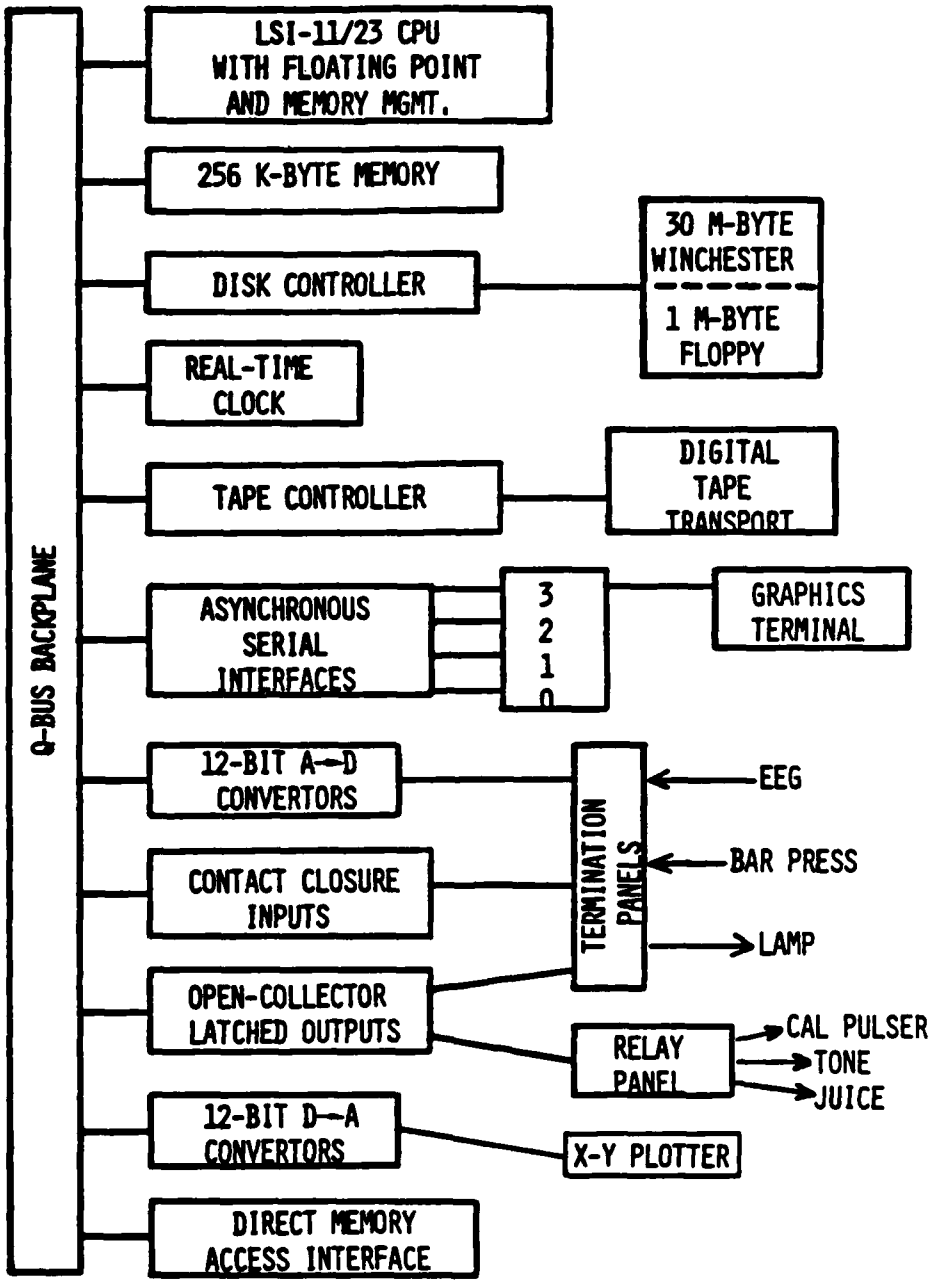


FIGURE 2 SCHEMATIC OF COMPUTER SYSTEM

The central processing unit is a digital equipment corporation Model LSI-11/23 with extended memory and floating point enhancement. It's Q-Bus backplane holds an array of special-purpose hardware boards to operate peripheral devices.

anesthetic. The scalp and the posterior aspect of the legs are shaved and cleaned. An intravenous catheter is inserted into the saphenous vein and a drip of lactated Ringer's solution with glucose is begun. Sodium pentobarbital (65 mg/ml) is infused via the saphenous catheter to maintain the anesthetic state.

After the monkey has been placed in a stereotaxic device, the scalp is reflected, the skull is thoroughly cleaned, and the sites for burr holes (to be drilled for insertion of electrodes) are marked. Holes are drilled in accordance with coordinates determined from an appropriate stereotaxic atlas. Depth electrodes consist of 0.7-mm O.D. glass pipettes attached to a larger glass cell containing a sintered Ag-AgCl pellet, as described by Rebert and Irwin (1973). After the glass pipette electrodes are lowered to the proper depth and cemented to the skull, they are cut approximately 5 mm above the surface of the skull and the electrode cell is attached and cemented in place. Epidural electrodes are placed into small saline-filled wells of acrylic built up around the burr holes and are cemented into place by floating a thin layer of acrylic on top of the saline. Following attachment of electrode wires to a self-locking multi-pin connector, the whole assembly is encased in an acrylic plug. A wide-spectrum antibiotic is administered postoperatively, and triple antibiotic salve is placed on the skin around the acrylic head plug.

In cynomolgus monkeys, electrodes were placed over the left premotor area (LPM), right premotor area (RPM), left motor cortex (LMC), right motor cortex (RMC), left parietal cortex (LPC), right parietal cortex (RPC), and in the caudate n. (CAN), substantia nigra (SUN), n. ventralis anterior of the thalamus (VAN), hippocampus (HPC), midbrain reticular formation (MRF), and the bony orbit to measure the electrooculogram (EOG).

## EXPERIMENTAL MANIPULATIONS AND RESULTS

### Introduction of the Neutral Stimulus

Previous reports for this contract described potentials recorded in cynomolgus monkeys when only the WS was included in the experimental paradigm. To provide a control condition to discriminate evoked potential (EP) components related to the tone per se, in contrast to those related to anticipatory aspects of the task, we added the neutral stimulus (NS) (Figure 1) to the experimental paradigm. This was a tone of 1 KHz or 3 KHz that occurred by itself (i.e., not paired with the imperative stimulus) on a proportion of trials during each test session. The NS tone frequency for a monkey was that not being used as the warning stimulus (WS). On the basis of previous work (Rebert, 1972), we expected that anticipatory responses would be observed following the WS but not the NS.

There were three phases to this experiment: 1) testing with 50% of the trials WS and 50% NS; 2) testing with approximately 20% WS trials; and 3) a phase in which the proportion of WS trials was maintained at 20% but the interstimulus interval (ISI) was varied so that each animal was tested for 2 days at each of 3 ISIs--1000 msec, 1500 msec (normal), and 2000 msec. The three phases represented successive attempts to improve the discrimination (in terms of brain potentials) between the WS and NS. We reasoned that if WS trials were rare events and NS trials were common, larger potentials would be generated to the former and, as a result of habituation, smaller potentials would be generated in response to the latter. In Phase 3 we varied the ISI to ensure that the monkeys used the WS as a cue but were not responding on the basis of exactly timing the interval.

Results from four monkeys trained with the NS are shown in Figure 3. Recordings were from six placements, as indicated in the figure, and represented effects on the ninth day of training in this paradigm. In some cases there were transient EP components elicited by the tone and light but little, if any, anticipatory slow potential (SP) change. For monkey SM this was true of all placements but the MRF.

In monkeys ET, MI, and GR, anticipatory SPs were evident in almost all placements except the CAN. In agreement with previous findings (Rebert, 1972; Borda, 1970; Hablitz, 1973), the response in the premotor cortex (PMC) of these three monkeys was more robust than that recorded

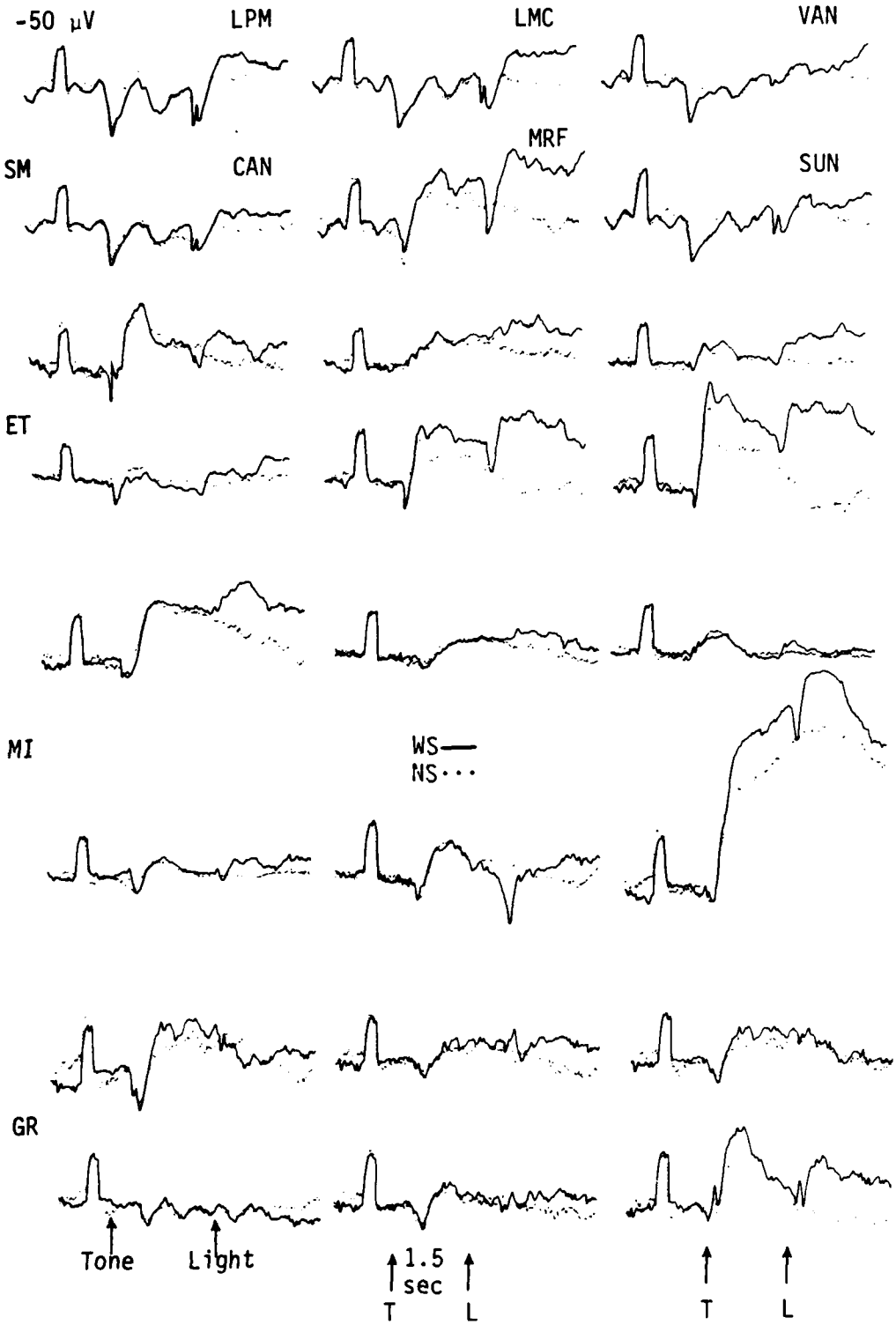


Figure 3 Averaged waveforms from electrodes aimed at left premotor cortex (LPM), left motor cortex (LMC), n. ventralis anterior of the thalamus (VAN), caudate n. (CAN), midbrain reticular formation (MRF), and substantia nigra (SUN) in four monkeys--elicited by the warning (WS) or neutral (NS) stimuli.

from the motor cortex (MC), especially in terms of the early slow component occurring about 300 msec after the tone. This component was greater than 50 μV in PMC, but only approximately 25 μV in MC. The differences evident in the shape of the responses in these two regions--a more complex early transient EP and faster rise-time of the early SP--indicate that the response in MC is not simply a volume-conducted reflection of PMC activity. This is also consistent with our earlier suggestion that there are at least two separate generators of the CNV in monkey cerebral cortex. Responses to the WS and NS during the ISI were the same in both of these areas.

Responses from electrodes aimed at VAN varied considerably from monkey to monkey. Two monkeys (SM and GR) exhibited an initial positive wave following the tone(s). Four of the five monkeys (see Figure 4 for responses of monkey CO, which was not trained with the NS at this time) showed a transient negative SP after the tone regardless of whether a preceding positivity occurred. This SP peaked at 300 to 400 msec, then usually declined to baseline level during the remainder of the ISI. Because VAN is the major thalamic projection to premotor cortex, we thought that if that projection was the dominant source of cortical activity, then the VAN waveform would correspond closely to that recorded cortically. However, that was not the case--responses to the WS and NS were the same.

Contrary to expectation, the CAN did not exhibit the large positive SPs previously observed in female stump-tailed macaques. However, after several manipulations designed to increase the salience of the WS (e.g., variation of WS-NS proportion), the behaviorally most adept monkey (ET) eventually developed small SPs in the CAN (see below, Figures 8 and 9).

Negative SPs occurred in the MRF of all five monkeys (see Figure 4 for data from CO). Except in GR, MRF responses were typified by a small positive transient EP followed by a fast-rising negative shift of 40 to 75 μV that often remained throughout the ISI (e.g., SM and ET) or declined slowly after peaking (e.g., MI). The response from GR was atypical in its small size and general morphology. Typically, the MRF exhibited a positive transient EP following onset of the light--reminiscent of CNV "resolution" seen in human cortex--followed by another negative shift, presumably related to behavioral responding and ingesting of reinforcement. In SM and ET the MRF exhibited some differentiation of interstimulus responses to the WS and NS--the latter being of lower amplitude than the former, as would be expected.

In all but one monkey (SM), large responses, ranging from 50 to 150 μV, were observed in the SUN. The general morphology of this response was similar to that observed in the MRF--with a sharp-rising initial

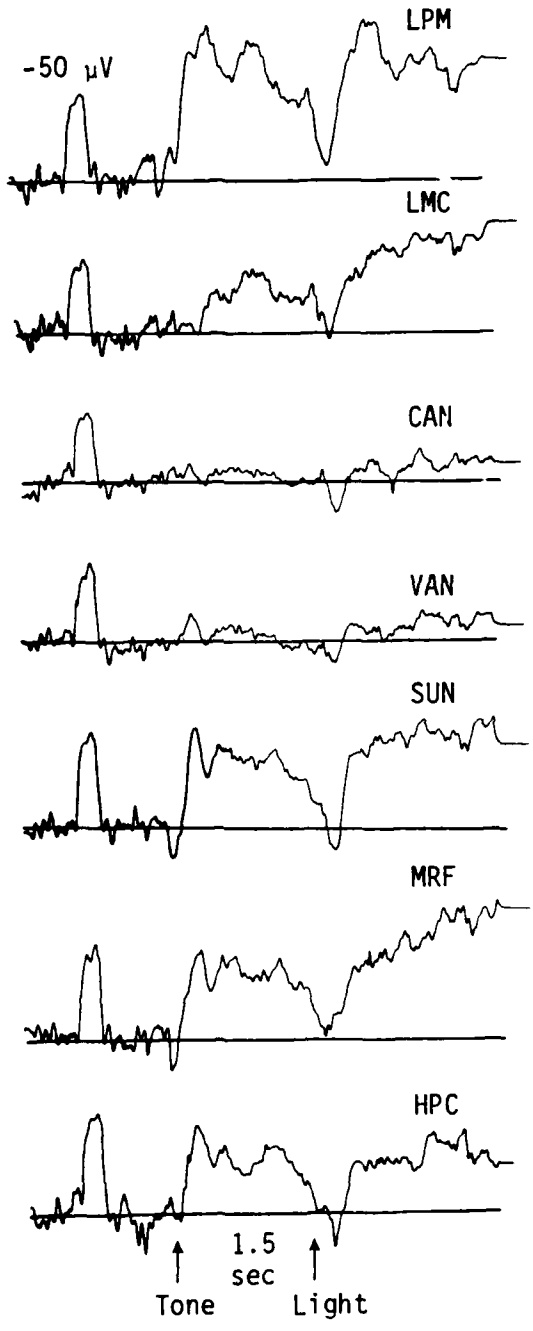


Figure 4 Averaged ERPs from monkey CO elicited by the WS.

negativity and large negative SP associated with light onset. In some cases the response was sustained throughout the interstimulus interval, or declined gradually. The response from one monkey (MI) was especially pronounced, and it will be interesting to determine whether this relates to the exact placement of electrodes. Tips were aimed at the pars compacta area of the substantia nigra. The similarity of waveforms in MRF and SUN implies a strong functional linkage of these regions, suggesting the application of cross-trial correlational analyses of such relationships. The NS response was smaller than the WS response in three of these four monkeys.

Variation of Stimulus Proportionality (WS = 20%)

Testing was carried out for about 4 weeks with the WS occurring on 20% of the trials. Because of the low percentage of reward, monkeys GR and MI began responding erratically, and at this time there were also mechanical problems with the juice delivery system. Therefore, only nine days of this testing were available with complete records.

The expected effect--enhancement of the differentiation between responses to WS and NS--occurred robustly in only one monkey, ET. He exhibited enhanced discrimination of the WS and NS in the LPM, LMC, SUN, and MRF (Figure 5, first four tracings). A clear differentiation also occurred in SM's MRF (Figure 5, bottom tracing). For ET, the altered proportion not only resulted in general extinction of responses to the NS in the 20% WS condition, but enhanced late SP responses to the WS, particularly in the LMC and MRF. Proportional increases from the 50% WS condition were: LPM = 82%, LMC = 162%, MRF = 97%, SUN = 115%. The size of the response in SM's MRF increased by 30% when the proportion of WS trials was reduced to 20%. Proportional reductions in the size of the late SP response to the NS in ET were: LPM = 77%, LMC = 83%, MRF = 100%, SUN = 100%.

The early negative peak in SUN, with latency of 350 msec, was also dramatically affected in ET, increasing in size when the WS was the rare stimulus. This is potentially interesting with respect to the P300 wave, because that response appears to be due to a deep negative generator that is reflected at the scalp as a positive potential (Halgren et al., 1980). Although contribution from anterior limbic structures (amygdala, hippocampus) have been suggested (Okada et al., 1983) others have questioned this conclusion (Yingling and Hosobuchi, 1984; R. Johnson, Jr., NIMH, personal communication). We suggest that the SUN and probably related ventral tegmental nuclei are components of the intracerebral system related to genesis of the P300.

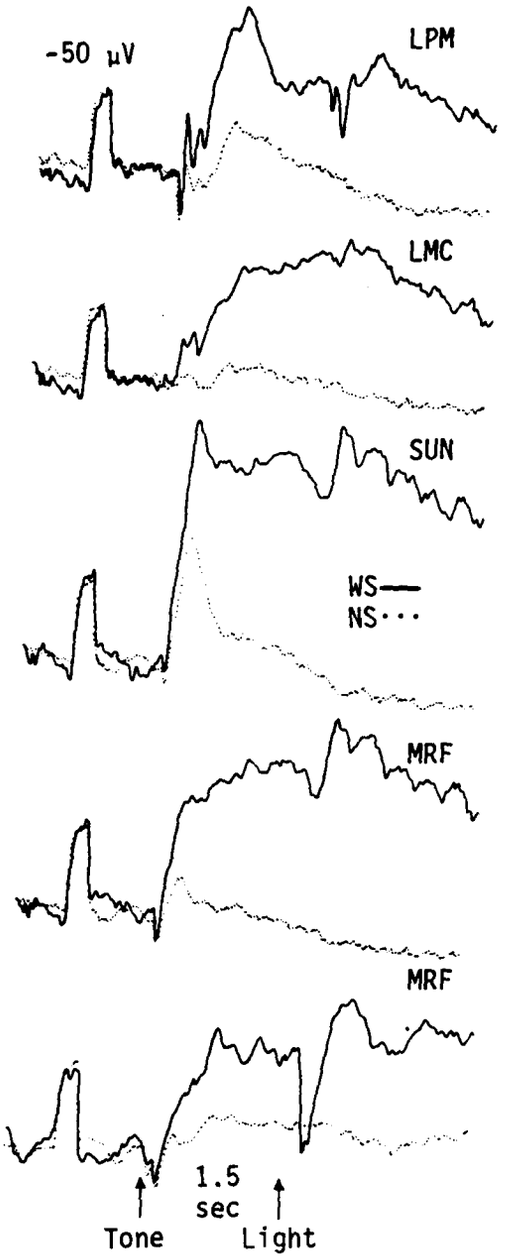


Figure 5 Averaged ERPs from several placements in monkey ET and the MRF of monkey SM (bottom tracing) when the WS occurred on only 20% of the trials. The discrimination of WS and NS tones was enhanced compared to earlier tests when the WS and NS each occurred 50% of the time.

## Variation of Interstimulus Interval

Because these monkeys had been trained for a long period of time with the same interstimulus interval, it seemed likely that some adaptation to the situation might have developed--e.g., ability to exactly time the interval, thus reducing anticipatory arousal. Therefore, the interval was varied from day to day at 1000, 1500, and 2000 msec. This continued for one to three weeks, depending on the monkey. During this time the proportion of WS trials remained at 20%. Week 1 of this procedure was considered to be a time of familiarization with the new paradigm, as the performance of two monkeys was disrupted; consequently, we considered only the data for later days when performance had stabilized and a sufficient number of WS trials had been run.

In general, the effects of this manipulation were minor. The main consequence was a decrease in the late SP amplitude in the 2-sec ISI, dependent on monkey and recording site. This effect occurred most consistently in the MRF. In every case, the response was smaller with the 2-sec than with the 1-sec interval (Figure 6). In four of the five monkeys, the 2-sec amplitude was also smaller than that at 1.5 sec. Average amplitudes were 63.7, 49.1, and 25.7 $\mu$V for the 1, 1.5, and 2-sec ISIs, respectively. This effect was not due to amplifier time constant; that would account for only a 12.5% decrease in terminal SP amplitude (just prior to the imperative stimulus) from the 1- to the 2-sec interval, and the SP decrease was actually 59.7%. It is not obvious why this effect occurred consistently only in the MRF in these monkeys, when the cortical CNV in humans shows effects of this manipulation (e.g., McAdam et al., 1969). It might be useful to maintain a given interval for several consecutive days to determine the effect of the interval *per se* rather than the effects of its variation from day to day.

## Administration of Atropine

Our preliminary study of atropine sulfate (Rebert et al., 1984) suggested that it decreased the amplitude of several EP components. The current study represented a more systematic evaluation of that possibility. This was of interest because of suggestions that the CNV is, in part, due to cholinergic activity (e.g., Pirch et al., 1985).

Only the WS was used in this study (1000 Hz for two subjects and 3000 Hz for the other three). The WS occurred 1.5 sec prior to IS onset. The animals were tested on week days only and were deprived of liquid for about 24 hr prior to each test session. Water was available *ad lib* from after testing on Friday until the beginning of deprivation for Monday's session.

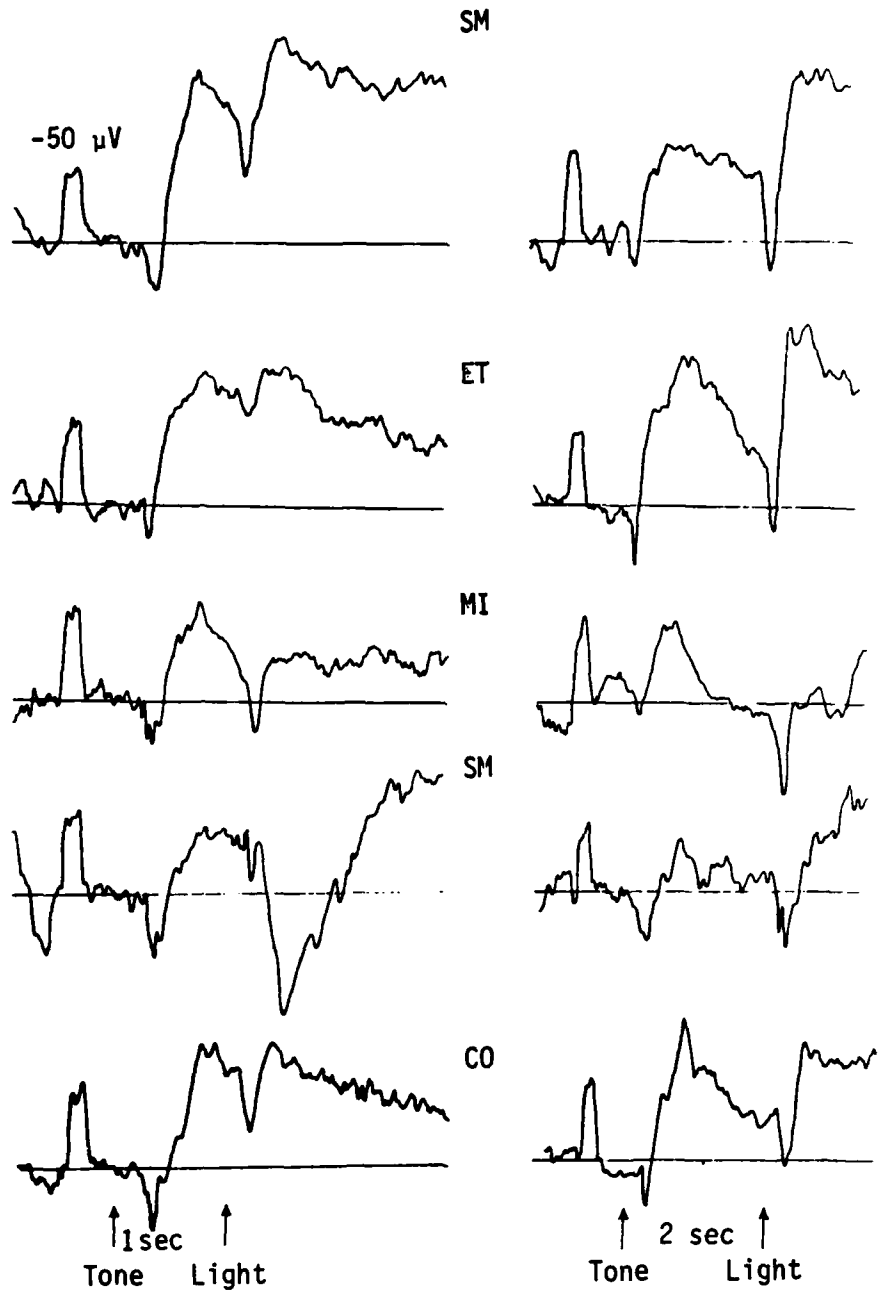


Figure 6 Averaged ERPs from the MRF of 5 monkeys when the interstimulus interval (ISI) was 1.0 or 2.0 sec, showing decrease in SP amplitude during later parts of the longer ISI.

For those trials on which bar-pressing occurred, the length of time that the IS was illuminated (and hence that reinforcement was available) was adjusted individually for each animal so that it could obtain a sufficient amount of liquid in a session of 15 reinforced trials. These individual adjustments were based on the monkey's bar-pressing speed and the amount of liquid that it would consume in sessions with unlimited numbers of trials. Supplementary liquid was given when a monkey drank an unusually small amount of water during a test session. The monkeys were fed standard monkey chow ad lib and were given fruit after testing on Fridays.

The experiment was run in a 3-week period. In the first 2 weeks, each monkey was tested with atropine sulfate at doses of 0, 0.2, and 0.3 mg/kg body weight. The drug was injected im in the leg 15 min prior to testing. A preliminary pilot study conducted several months earlier with the same animals indicated that 0.2 and 0.3 mg/kg atropine sulfate injected 15 min before testing dilated the subjects' eyes, impaired their performance, and possibly altered brain potentials in our test situation. The atropine sulfate was dissolved in water; the total volume injected into monkeys on test days ranged from 0.06 to 0.14 ml. On the days that the 0 dose level was administered, the monkeys were injected with physiological saline at the same volume used for the 0.3-mg/kg dose.

For each of the initial 2 weeks, all five monkeys were tested with 0 mg/kg on Thursdays and with 0.2 and 0.3 mg/kg on Tuesdays and Fridays in an ABBA sequence. On the first Tuesday, two monkeys were tested with 0.2 mg/kg and three with 0.3 mg/kg. On Mondays and Wednesdays, the animals were not injected but were run in the test paradigm (except for the second Wednesday, when animals were not run but were given supplementary water). This schedule allowed animals to recover for at least 48 hr after being tested with atropine before they were run in the experiment again. It also gave the animals one day of "pretraining" in the test situation after each weekend hiatus before being tested again with the drug.

In the third week of the experiment, the monkeys were tested with atropine methyl nitrate. Because atropine sulfate, but not atropine methyl nitrate, can cross the blood-brain barrier, we were able to assess which effects of atropine were peripherally rather than centrally mediated. Each animal was injected im with 0.3 mg/kg atropine methyl nitrate in saline on Tuesday and Friday, and was with the same volume of plain physiological saline on Thursday. Other experimental details were the same as described above for the first two weeks of the experiment.

Our earlier pilot data indicated that animals often would not respond for the full 15 trials after administration of atropine. Therefore, we established a criterion that a session would be terminated if the monkey did not respond on three consecutive trials.

For atropine sulfate and separately for atropine methyl nitrate, we combined the data collected on the two days at each dose level for analysis. This was done because the animals typically terminated a test session prematurely when injected with either of these drugs. By combining the two sessions at a single dose level for the same drug, a better estimate of each animal's performance could be achieved. For one animal, one day's data on atropine sulfate at the 0.2 mg/kg and one day's at 0.3 mg/kg were lost due to mechanical problems. However, because this animal responded for nearly the entire session on each remaining day at each of these doses, analysis of atropine sulfate data was based on the remaining individual days.

Both forms of atropine disrupted behavioral performance. Table 1 shows effects of the drugs on several behavioral parameters. Both drugs reduced the rate of bar-pressing, which was reflected in the number of reinforcements received and total presses, as well as the rate of pressing. These measures and the percentage of trials aborted (premature responses or too slow reaction time) were altered by atropine sulfate in a dose-related manner. Atropine sulfate, but not methyl atropine, also slowed reaction time, although this effect was about the same for the two doses.

Drug effects on slow potentials were mixed--depending on the site--but were comparable for the two drugs (Table 2). Small positive potentials (averaging 5.5 μV) now evident in the caudate nucleus were enhanced slightly by the 0.3-mg/kg dose (to a mean of 12 μV by atropine sulfate and 15 μV by methyl atropine). Negative shifts in the SUN, VAN, and MRF were decreased, and the effect was dose-related in SUN (-34 and -37%) and VAN (-41 and -53%). The potentials in SUN, VAN, and MRF were reduced by atropine sulfate, on the average, by 37, 53, and 15%, respectively, from the saline to the 0.3 mg/kg condition. Slow potentials in LMC and LPM were virtually unaffected by atropine sulfate (2 and 3% decreases), but methyl atropine caused a 32% decrease in those areas.

Because methyl atropine (which does not cross the blood-brain barrier) had essentially the same effects on behavior and the evoked potentials as did atropine sulfate, the effects cannot be attributed to actions at cholinergic sites in the brain. Apparently, the peripheral anticholinergic effects are sufficient to produce distracting--or other--sensations that disrupt performance. We believe that the effects are due partly to a change in the taste of the juice, because we had previously observed that monkeys given atropine exhibit unusual smacking and grimacing on drinking. This outcome reinforces a point made before about the utility of systemic administration of drugs to study event-related potentials. Rebert (1980b) pointed out that the approach does not allow an unequivocal interpretation of the site of intracerebral action of the

Table 1

EFFECT OF ATROPINE SULFATE AND ATROPINE METHYL NITRATE ON BEHAVIORAL PARAMETERS

| | Reaction Time (msec) | No. of Reinf. | Rate of Pressing (No./sec) | Percent Abort | Total Presses |
|---|---|---|---|---|---|
| | | | Atropine Sulfate | | |
| Saline | 733 | 348 | 1.8 | 7.6 | 369 |
| 0.2 mg/kg | 964 | 179 | 1.4 | 36.5 | 155 |
| 0.3 mg/kg | 919 | 92 | 1.0 | 41.4 | 100 |
| | | | Atropine Methyl Nitrate | | |
| Saline | 853 | 307 | 1.6 | 3.8 | 321 |
| 0.3 mg/kg | 856 | 126 | 1.1 | 40.4 | 134 |

Table 2

EFFECTS OF ATROPINE SULFATE AND ATROPINE METHYL NITRATE ON AMPLITUDE (μV) OF EVOKED SLOW POTENTIALS

| Drug | Dose (mg/kg) | Electrode Site CAN | SUN | VAN | MRF | LMC | LPM |
|---|---|---|---|---|---|---|---|
| Saline | | + 5.5 | -75.6 | -15.2 | -43.1 | -36.2 | -50.2 |
| Atropine sulfate | 0.2 | +11.7 | -50.1 | -9.0 | -31.8 | -36.3 | -52.2 |
| Atropine methyl nitrate | 0.3 | +12.4 | -47.9 | -7.2 | -36.6 | -35.3 | -48.6 |
| | 0.3 | +15.2 | -36.2 | -6.6 | -21.4 | -24.2 | -34.3 |

drug. As shown here, the situation is even more critical in that ERPs can be indirectly modified because of the peripheral action of drugs. It is clear that local intracerebral perfusion techniques (Myers, 1974) are necessary. This requirement and the desire to be able to simultaneously record from and perfuse a site led us to develop the cannula and electrode device shown in Figure 7. However, we have not yet had the opportunity to test this chemitrode. We plan to do so by recording from the lateral geniculate nucleus of a cat during stimulation with flashes, which induce large evoked DC potentials in the geniculate (Rebert, 1973b).

## Additional Analysis of Stimulus Proportionality

Because most of the monkeys showed little effect of the previous manipulation of the proportion of WS and NS trials, additional tests were carried out with the proportion of WS trials varied from 10% to 90% (10, 30, 50, 70, 80%). The proportion was varied from day to day. Only data from the 10 and 50% conditions have been evaluated so far.

Figure 8 shows superimposed waveforms for the WS and NS at 10 and 50% proportions of the WS. The placements shown are those that exhibited good responses during previous testing and the CAN, which began to show small positive shifts. Only the MRF was studied in monkey SM because other electrodes seem dysfunctional in that they all exhibited nearly identical form, suggesting dominance by the reference.

In Figure 8 the monkey records are arranged from top to bottom in terms of the degree (least to most) to which the SUN waveforms differed in response to the WS and NS tones. The ERPs in monkey CO (upper left) were the same in all conditions. In the other monkeys the responses to the NS were smaller than responses to the WS. This was most evident with respect to the SP recorded from monkey ET, which exhibited only a brief NS-evoked transient EP in the SUN, which quickly returned to baseline. Previously (e.g., Figure 3) the response returned only gradually to baseline in the interstimulus interval, the more rapid decline indicating effects of the additional training. The relative ranking of monkeys in the SUN with respect to WS-NS discrimination in the SUN carried across other placements as well.

Another factor of interest in this experiment was the difference between the 10 and 50% conditions. Larger ERPs would be expected in the WS-10% condition due to habituation to the NS and increased salience of the WS due to its rarity. This occurred only occasionally—it appeared most consistently (3 of 4 monkeys) in the SUN. A slight effect was also evident in the MRF, CAN, and LPM of monkey MI and in the CAN and LPM of

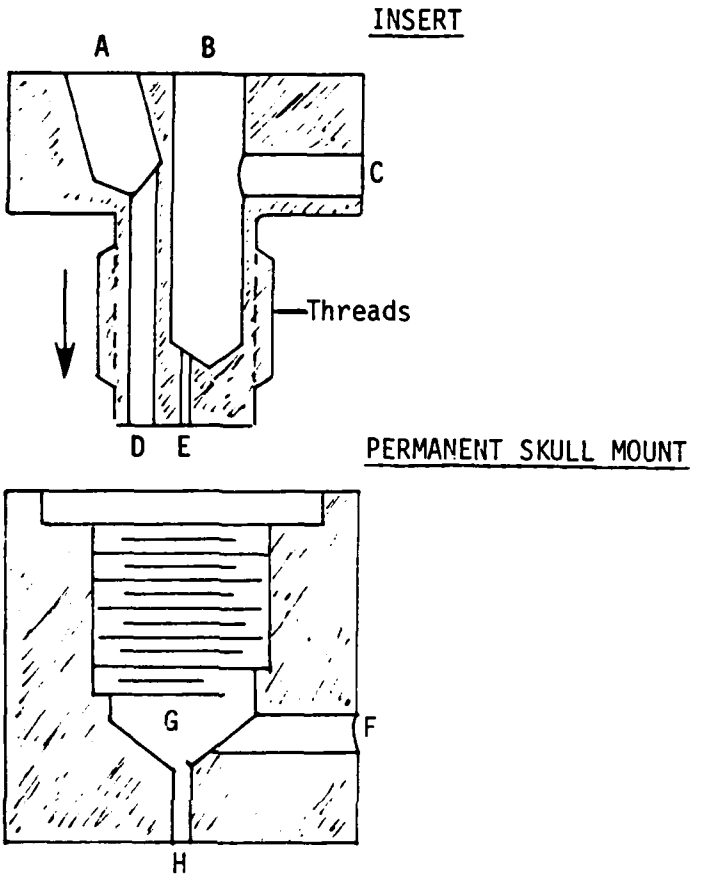


Figure 7 Concentric push-pull cannula with capability for recording bipolar or referential transient and DC potentials during perfusion.

A. Opening for connector to outer (pull) cannula.
B. Opening for connector to inner (push) cannula.
C. Opening for insertion of Ag-AgCl recording pellet: inner cannula.
D. Fluid return path from outer cannula.
E. Fluid entering path through inner cannula. Inner cannula is cemented into place in this channel.
F. Opening for insertion of Ag-AgCl recording pellet: outer cannula.
G. Fluid well and flow path for outer cannula: flow is over the Ag-AgCl pellet.
H. Channel into which outer cannula is cemented.

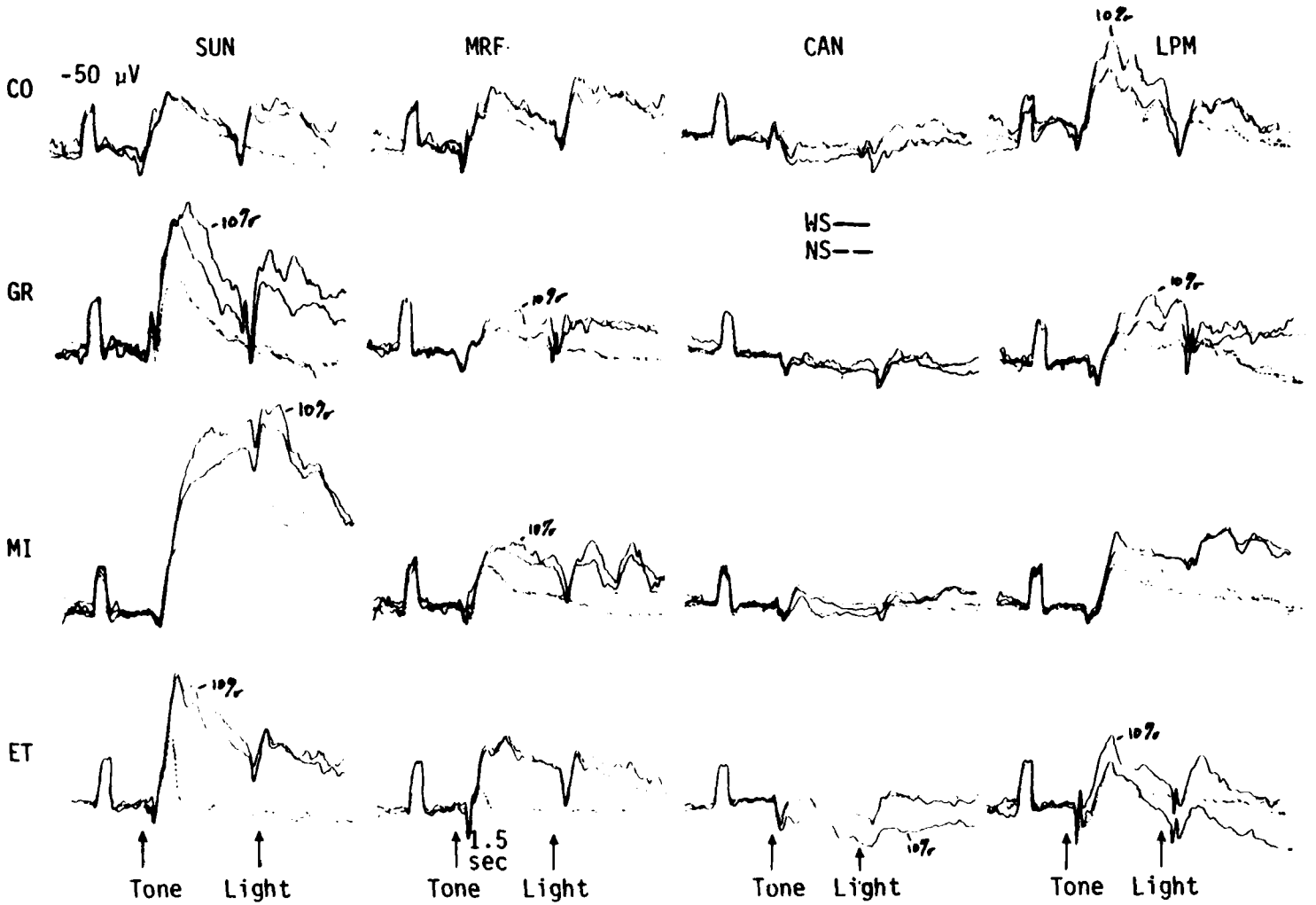


Figure 8 Averaged ERPs from several placements in four monkeys when the WS occurred on 10 or 50% of the trials.

monkey ET. This result in ET was in contrast to the clear enhancement of EPs by rare events observed in the first examination of proportionality.

The minor effect of the manipulation might have been due to the day-to-day alteration of the proportions, which prevented the monkeys from becoming clearly aware of the situation. To evaluate this possibility, one monkey (ET) was tested on proportions of 10 and 50% for five consecutive days for each proportion. As can be seen by comparing Figures 8 and 9, this increased the proportionality effect in the SUN and MRF. The differences in LPM and CAN were about the same as before. In addition, the HPC placement showed an enhanced negative wave in the 10% condition (in previous runs this placement had exhibited little activity). We plan to use the procedure of presenting a given WS proportion several days in a row with the remaining monkeys as well.

## Correlational Analyses of Intracerebral Interactions

### Background

Slow potentials previously recorded from stump-tailed macaque monkeys (Rebert, 1972) were sufficiently clear for scoring of single trial events from polygraph tracings (Rebert, 1976), allowing a rough determination of how various cortical and subcortical areas covaried over the course of a training session (Rebert, 1977). Such a determination of interactions among intracerebral nuclei was consistent with the notion that the static evaluation of scalp-recorded ERP components was insufficient for unraveling the electrophysiologic correlates of cognition, and that psychological processes must be reflected electrophysiologically by interactions among elements of a "general cerebral system" (Rebert, 1973a) rather than by specific local generators of ERP components.

To pursue evaluation of intracerebral interactions more rigorously, we instituted collaboration with Alan Gevins and collegues at the EEG Systems Laboratory (EEGSL), San Francisco. They have developed a Neurocognitive Pattern Analysis (NCPA) for assessing interrelations among arrays of electrodes attached to the human scalp (Gevins et al., 1985). The method was applied to a set of data from monkey ET.

A major aspect of the method, called nonstationary directed mutual information flow, yields an estimate at each time sample of the direction and timing of "information flow" between two nonstationary time series. The mutual information between two sets of data at a single time point is a measure of how well one can be predicted from the other. The sum of the mutual information between each of a number of past points in one time series and the "present" point in the second time series is called the

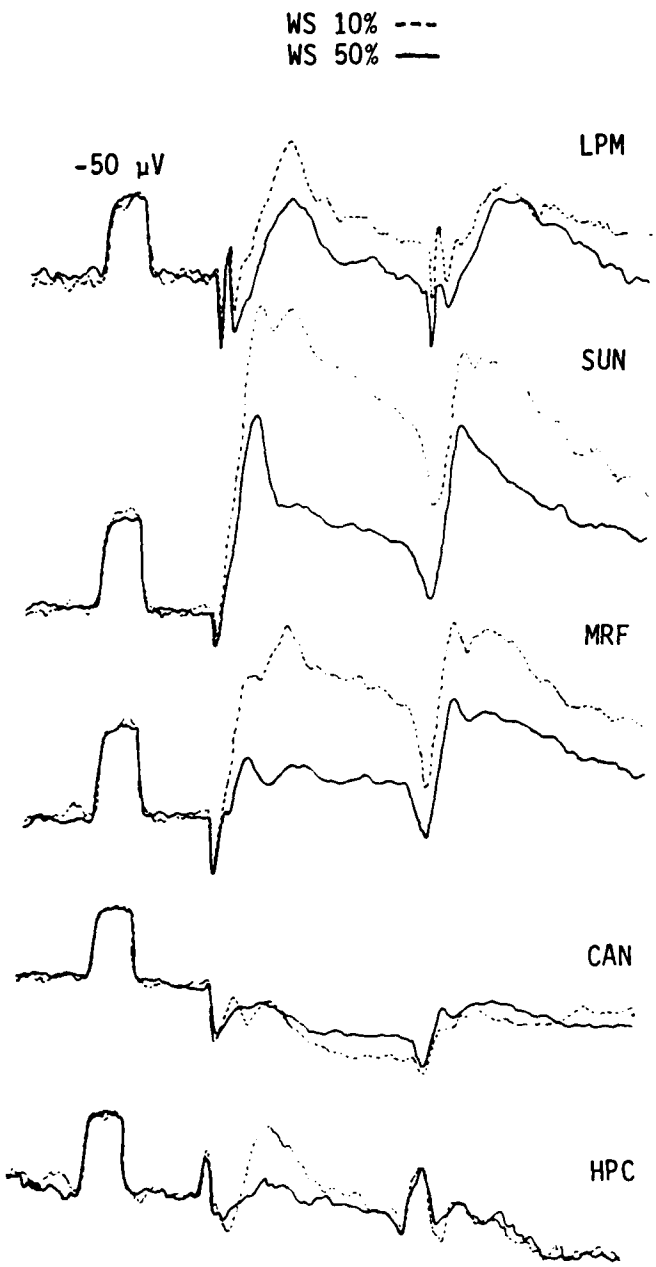


Figure 9 Enhanced proportionality effect (WS = 10 or 50%) in monkey ET when conditions of proportionality were each tested for 5 consecutive days, compared to previous run shown in Figure 8.

directed mutual information. It can be interpreted as the total information about the current time point of the second time series that is found in the past time points in the first time series.

Results and Discussion (A. Gevins and S. Bressler)

Single-trial records written onto digital tape by the LSI-11/23 computer at SRI were transferred to disk files at the EEGSL and converted into standard ADIEEG system data format on the PDP11-60 computer. A set of randomized reference baseline data was constructed and pattern recognition analysis was performed to select those trials that, in the interval of interest, were significantly different from the randomized reference baseline set, i.e., trials that contained a significant event-related signal. "Purified" averaged ERPs were constructed from the selected trials for five placements (Figure 10): they were left premotor cortex (LPM), hippocampus (HPC), ventro-anterior thalamic nucleus (VAN), substantia nigra (SUN), and midbrain reticular formation (MRF). Figure 11 shows averaged ERPs of LPM, HPC, and SUN. The "go" (WS) averaged ERP was formed from 124 selected trials, and the "no-go" (NS) from 149 selected trials. The averaged ERPs from selected trials were then transferred to the EEGSL's MASSCOMP computer for spatial interdependency analysis.

The center points and widths of the major peaks of the purified averaged ERPs were determined and used to form intervals for interdependency analysis (Table 3). For each pair of channels, a cross-correlation function was computed over the designated interval. The magnitude of that value was represented on a diagram by the thickness of a line extending between circles representing the two channels. The lag number corresponding to the maximum absolute value of the cross-correlation function represented the "time delay" between the averaged ERPs of the two channels. Time delay was displayed by the color of the line between the two channels. Each line on the diagram had an arrow superimposed, pointing away from the leading channel of the pair. The color of the arrow indicated the sign of the correlation. Only those correlations that exceeded 0.80 were included on the diagram. These were significant at the $p < 0.01$ level.

For each diagram, the partial correlation was computed for each significantly correlated channel pair in which each channel of the pair was also significantly correlated with a common third channel. The partial correlation between two time series is the correlation with the influence of a third time series removed. Trios of time series that are correlated pairwise can be analyzed with this measure to ensure that the measured correlations are not due merely to the similarities between

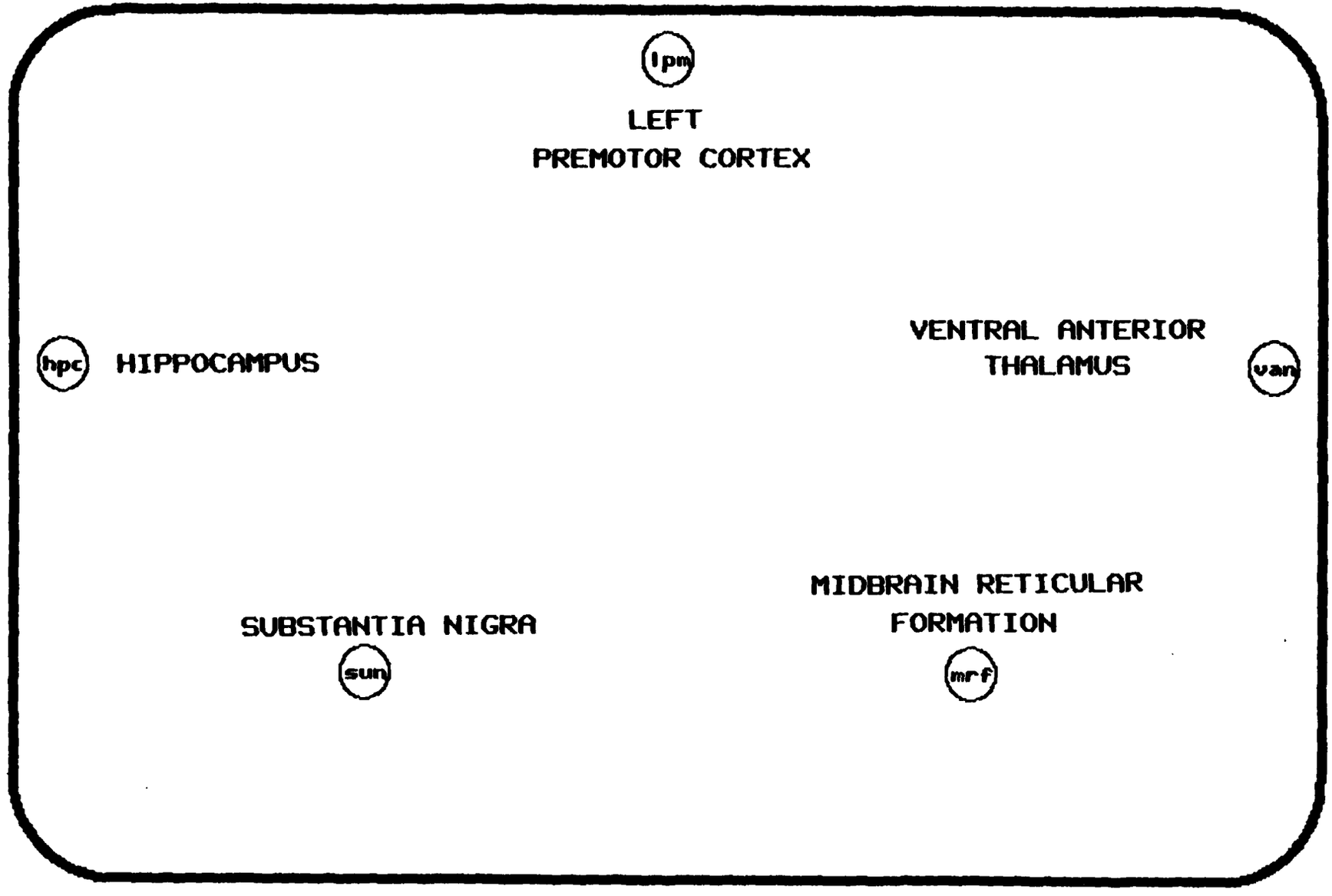


Figure 10 Reference map of placements for interpreting data in Figures 12a and 12b.

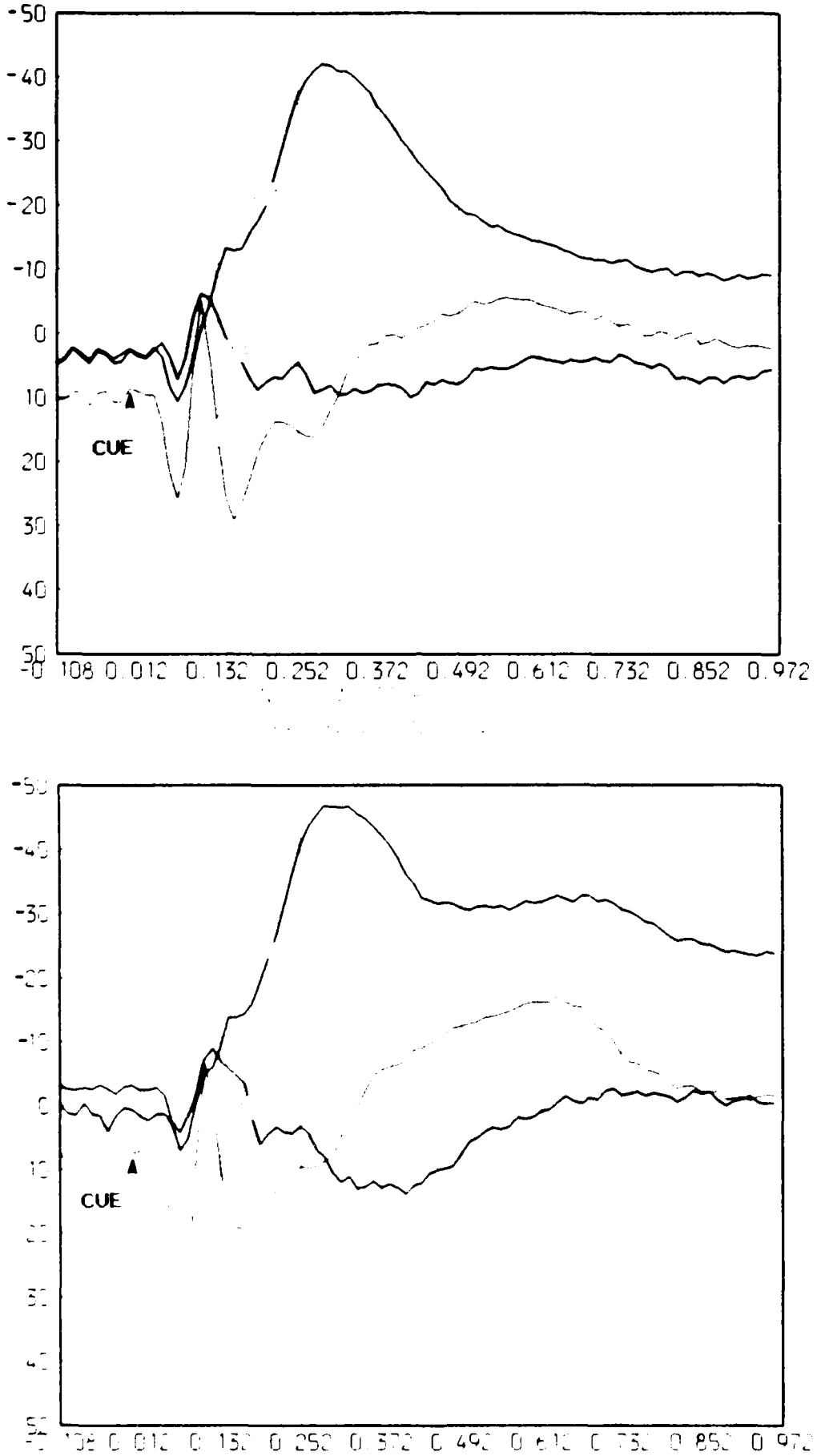


Figure 11 Averaged ERPs from monkey ET, using EEG System's procedures, showing similarity to ERPs previously obtained at SRI.

Table 3

CENTERPOINTS AND WIDTHS FOR
SPATIAL INTERDEPENDENCY ANALYSIS

| Interval | Center (msec) | Width (msec) |
|---|---|---|
| 1 | -96 | 204 |
| 2 | 156 | 144 |
| 3 | 240 | 144 |
| 4 | 313 | 240 |
| 5 | 397 | 240 |
| 6 | 578 | 276 |
| 7 | 722 | 240 |
| 8 | 903 | 240 |

contributions from a third channel. The partial correlation is computed as:

$$\rho_{xy/z} = \frac{\rho_{xy} - \rho_{xz}\rho_{yz}}{\sqrt{(1-\rho_{xz}^2)(1-\rho_{yz}^2)}}$$

where x and y represent the correlated channels to be tested, z represents the third channel whose influence is to be removed, $\rho_{xy/z}$ is the partial correlation of x and y, conditional on z, and $\rho_{xy}$, $\rho_{xz}$, and $\rho_{yz}$ are the correlations between x and y, x and z, and y and z, respectively.

The results of this analysis are presented in Figure 12a and 12b. The first interval analyzed is centered at 96 msec before the onset of the auditory cue. The interval width is 204 msec. The diagrams for this interval are shown in the top row of Figure 12a, "go" (WS tone) and "no-go" (NS tone) in the first and second columns, respectively. Both the "go" and "no-go" conditions show highly similar patterns of correlation. ERPs from SUN, VAN, and MRF are all correlated with one another during this interval. They are all in phase since the maximum correlation is positive and is at 0 lags. None of the other channel pairs has correlations above the threshold level. The similarity of the two conditions suggests that the monkey had no expectation as to which tone would be presented prior to tone onset.

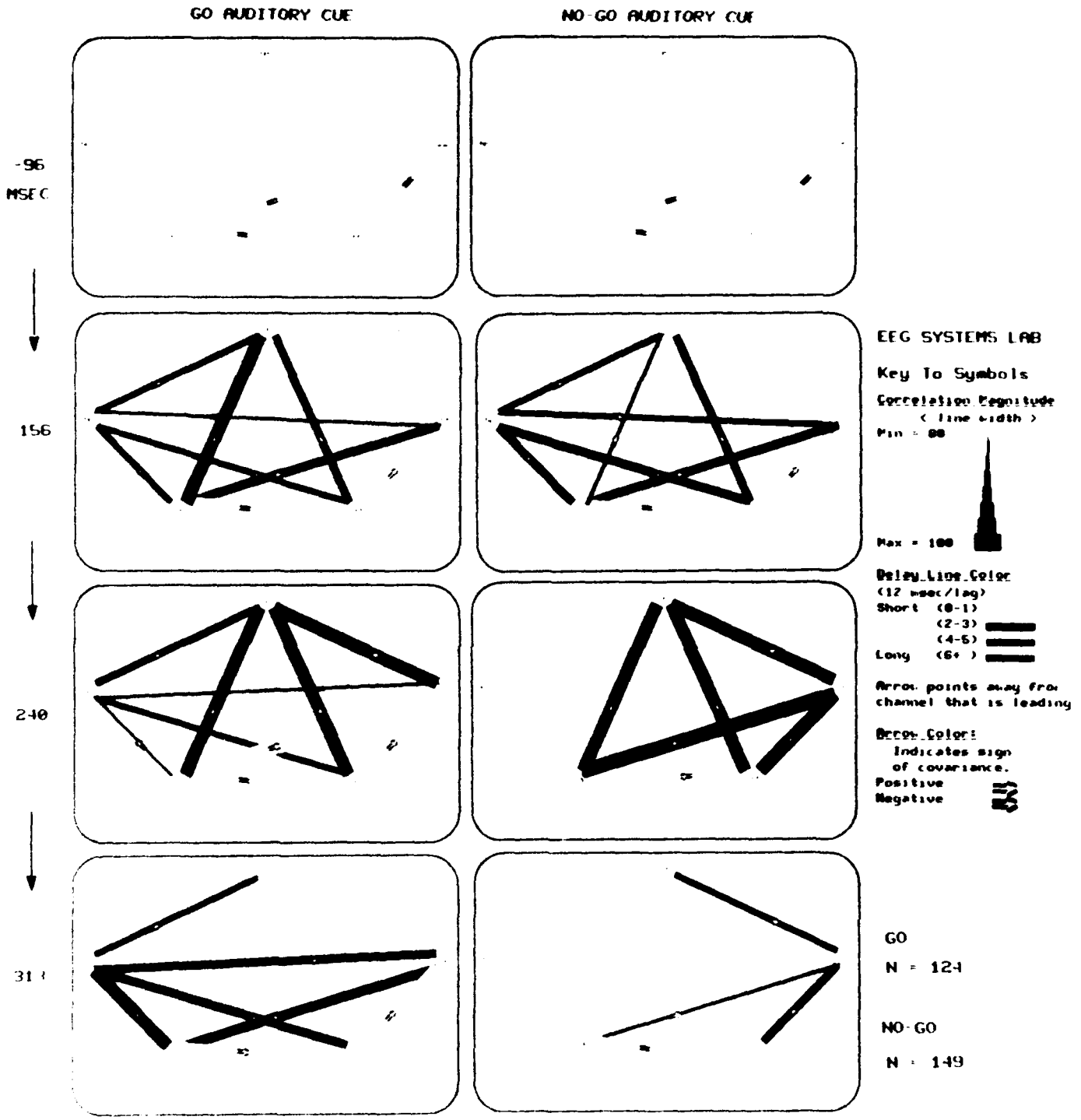


Figure 12a Intracerebral patterns of "directed mutual information flow" among five recording sites in monkey ET associated with the WS (go) and NS (no-go) tones during time epochs of -96 to 313 msec pre- and post-stimulus.

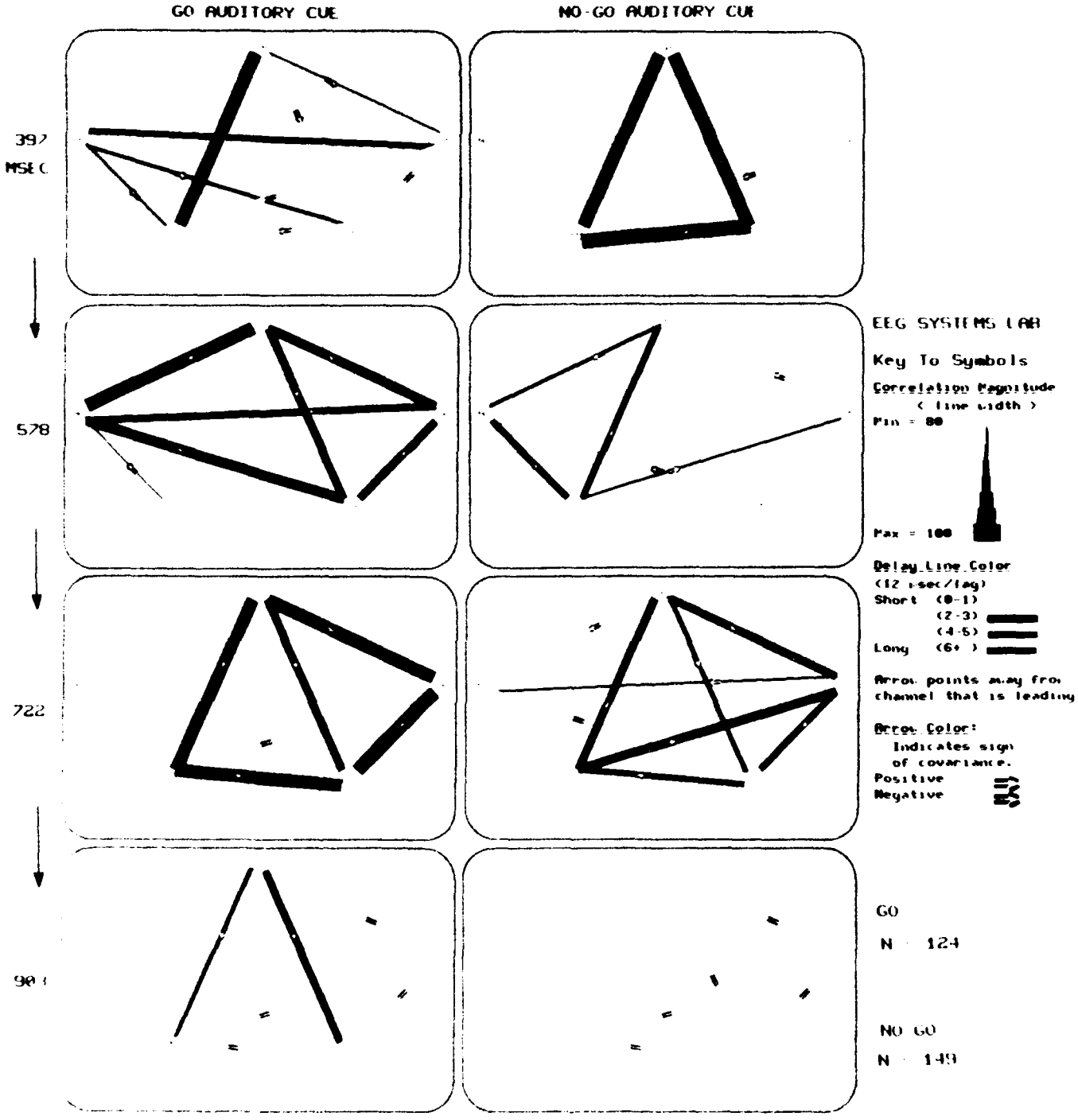


Figure 12b Intracerebral patterns of "directed mutual information flow" among five recording sites in monkey ET associated with the WS (go) and NS (no-go) tones during time epochs of 397 to 903 msec post-stimulus.

The second row of Figure 12a contains the diagrams for the "go" and "no-go" conditions for an interval centered at 156 msec after cue onset, with an interval width of 144 msec. The patterns for the two conditions are again highly similar. The only differences are that HPC leads SUN by 84 msec for "no-go" but lags by 48 msec for "go," that HPC leads VAN by 24 msec more for "no-go" than for "go," and that the correlation between SUN and LPM is 0.08 less for "no-go" than for "go." For both conditions, all correlations are positive except for those of HPC, which is out of phase with the other four channels. The striking overall similarity of the patterns from the two conditions suggests that by this interval the areas displayed still have not registered any difference in reaction to the two tones.

By the next interval, centered at 240 msec post-cue and 144 msec wide, the patterns of correlation have diverged for the two conditions (Figure 12a, third row). The correlations of the hippocampus are strikingly different between "go" and "no-go." There are no significant correlations of HPC to any other channel for "no-go," whereas there are significant correlations with every other channel for "go." In the "go" condition, HPC leads SUN, MRF, and VAN by 4-5 lags (48-60 msec) and it lags LPM by 36 msec. As in the previous interval, the HPC-averaged ERP is changing in the opposite direction from those of the other channels, causing its correlations to be negative. The other channel pairs show very similar results for "go" and "no-go" conditions. The correlations of LPM with SUN, MRF, and VAN are the same in the two conditions. The correlations among SUN, MRF, and VAN are alike except that their delays are 1-2 lags (12-24 msec) longer for "no-go."

The next interval is centered at 313 msec post-cue and is 240 msec wide (Figure 12a, bottom row). Here the "go" and "no-go" conditions continue to diverge. HPC continues to lack significant correlation with any other area for "no-go" and maintains the same timing relations for "go" as in the previous interval, except that LPM increases its lead on HPC by an additional 12 msec. The magnitude of the HPC correlations also increases over the previous interval. LPM is not significantly correlated with SUN, MRF, or VAN for "go" and is only significantly correlated with VAN for "no-go." The correlations among SUN, MRF, and VAN are similar for "go" and "no-go" except that SUN and MRF both lead VAN by a larger delay for "no-go."

The sequence of intervals continues with Figure 12b. The top row shows diagrams from an interval centered at 397 msec, of 240 msec width. HPC continues to lack any significant correlation with other channels for "no-go." For the "go" condition, HPC is no longer correlated with LPM but has now become positively correlated with MRF and VAN, leading them by 84 and 96 msec, respectively. A new pattern involving LPM emerges in this

interval involving LPM. In the "go" condition, LPM is now negatively correlated with SUN, MRF, and VAN, leading all three. For "no-go," LPM is negatively correlated with SUN and MRF, but unlike "go," it lags these channels. The lack of correlation between LPM and VAN in the previous interval for "go" has changed to correlation with LPM leading, whereas the previous correlation of LPM and VAN for "no-go" no longer appears. The previous interval showed MRF leading VAN in both conditions, whereas now they are in phase for "go" and not significantly correlated for "no-go."

In the following interval (center = 578, width = 276) (Figure 12b, second row), the magnitude of the LPM correlations, which emerged in the previous interval, continues to increase in the "go" condition, but diminishes for "no-go." For "go," LPM is positively correlated with HPC, MRF, and VAN, leading all three. HPC and VAN, in turn, are positively correlated with and lead MRF. VAN is positively correlated with and leads HPC. SUN is relatively unimportant in this picture, having only a small negative correlation with HPC. For "no-go," the picture is quite different. SUN shows prominent negative correlations with HPC and LPM and a positive correlation with VAN. In each case, SUN leads the other channel. As in the "go" condition, LPM is positively correlated with HPC, leading it by 84 msec. In fact, this is the first of these pictures in the "no-go" condition to show involvement of HPC. HPC is correlated with and lags LPM, SUN, and MRF.

The next interval (center = 722 msec, width = 240 msec) (Figure 12b, third row) shows an important difference from previous intervals. This is the first post-cue interval not to show involvement of HPC in the "go" condition. The interdependency pattern of LPM, VAN, and MRF is very similar to that in the previous interval. Now, however, SUN--rather than HPC--is positively correlated with LPM and MRF, lagging the former and leading the latter. There is also a strong correlation without delay between SUN and VAN. The "no-go" picture is complex in this interval. SUN is positively correlated with and leads LPM, VAN, and MRF, with long delays. LPM, although lagging SUN, leads MRF and VAN, with shorter delays. VAN lags both SUN and LPM and leads MRF. HPC is weakly correlated with LPM, VAN, and MRF.

During the last interval (center = 903 msec, width = 240 msec) (Figure 12b, bottom row), the averaged ERPs are in the process of flattening out, although not at their pre-cue levels, with the SUN channel showing the most prominent offset. In both conditions, SUN, MRF, and VAN return to their pre-cue pattern of zero-lag positive correlations. In Addition, in both conditions, LPM and VAN are positively correlated, with no lag. In the "go" condition, there remains the pattern of LPM correlated with and leading SUN and MRF; however, the correlations have diminished in magnitude and the delays have decreased into the 2-3 lag

range. In the "no-go" condition, LPM is correlated with MRF but with no delay. As in the pre-cue interval, HPC is not significantly correlated with any other channel in either condition.

Interpretation of these preliminary results must be approached with caution. First, these data came from only one monkey. Second, histological verification of the electrode placements has not yet been performed, so the assignment of anatomical locations to the positions of electrode tips is now tentative. Third, the number of electrode placements analyzed in this preliminary study is very small compared to the number of potentially interacting brain structures.

Beyond these limitations lies the question of the meaning of the correlation of two averaged waveforms, particularly when they are correlated, with delays of up to 100 msec. A positive- or negative-going peak in a structure's averaged event-related potential is taken to mean that the structure is undergoing "activation" during that time. The active state is not likely to be simply excitatory or simply inhibitory but, rather, is more likely to be a complex combination of both. Two peaks in different structures that are temporally correlated are interdependent, but the basis for the interdependence is currently unknown.

There are well known anatomical connections between many of the areas analyzed in this study. Direct fiber projections exist from HPC to MRF, from MRF to VAN, from VAN and SUN to PMC, and from PMC back to VAN. However, because of the high degree of convergence of multiple inputs from diverse structures and the multiple pathways between two areas, it is impossible to conclude that there is a direct influence of one brain region on another based on their correlation and timing. Correlation of waveforms from two regions might be due to functional interaction of their neural populations, imposed synchronization from a third area, or a combination of both. The use of partial correlation analysis takes into account the possibility of driving from those structures involved in this analysis, but does not eliminate the possibility of driving by other structures. With the addition of more channels in forthcoming recordings and the use of multiple partial correlation, it will be possible to consider the interactions of more brain regions.

For now, we can say that two channels that are significantly correlated in one condition of the experiment after partial correlation analysis, but not in the other condition, are functionally interdependent in the first condition and that the interdependence is not explained by any other analyzed channel. Confirmation of functional interdependencies within the context of other lines of evidence, such as lesion and stimulation studies, holds the promise of a new tool in analysis of brain function. Because many brain locations may be simultaneously sampled from a

chronically implanted animal performing trained behaviors, this technique may prove to be a valuable supplement to single-unit analysis.

Partial correlation analysis confirmed that most correlations were not explainable by the influence of a third channel. The exceptions were as follows. In the interval centered at 156 msec, the correlation between VAN and HPC in both conditions became insignificant when the influence of MRF was removed. In the intervals centered at 240 and 313 msec in the "no-go" condition, the correlation between MRF and VAN could be explained by their correlations with SUN. At 903 msec in the "no-go" condition, the correlation between LPM and MRF could be explained by the influence of VAN and the correlation between VAN and SUN could be explained by the influence of MRF.

The series of diagrams in Figure 12 suggests certain features of brain dynamics associated with the performance of the delayed reaction task. The interval centered at -96 msec reveals a pre-cue pattern of zero-lag correlation among SUN, MRF, and VAN common to both "go" and "no-go" conditions. There is a striking transformation of this pattern following the onset of the auditory cue, as evidenced by the picture of multiple correlations with delay in the interval centered at 156 msec. That the patterns for the two conditions appear to be very similar except for the correlation between HPC and SUN is a sign that by this interval, the five areas of this analysis are only beginning to discriminate between the two tones. (We have no indication of what is taking place in other brain areas.) That there is a high level of correlation between all pairs, except VAN-LMP (and VAN-HPC, which drops out with partial correlation analysis), suggests that information about the cue is being widely distributed in this interval. Since LPM and VAN lag the other channels with which they are correlated, their activities appear to be dependent on those other areas.

In the interval centered at 240 msec there is a substantial between-condition difference in that HPC is highly correlated with the other four channels in the "go" condition but is not significantly correlated in the "no-go" condition. Activity in HPC is intermediate between the subcortical channels and the cortical channel, lagging the former and leading the latter. Perhaps HPC involvement is necessary for motor preparation and stimulus expectation. In both conditions, LPM is highly correlated with VAN, SUN, and MRF with long delay. In this interval, activation of LPM seems to depend on these three areas regardless of condition.

In the next interval, however, the correlations of LPM are dramatically changed. At 313 msec, except for the strong correlations of SUN with MRF and VAN which have persisted since before the cue onset, this interval shows the continued divergence of the patterns for the two

conditions. While HPC continues to be involved for the "go" condition and uninvolved for "no-go," LPM is now correlated only with HPC in "go," and correlated only with VAN in "no-go." Since LPM lags in both conditions, it is possible that LPM activation at this stage depends on activation in HPC for "go" and on activation in VAN for "no-go."

By the 397-msec interval, the timing relations of LPM for "go" have reversed. Instead of lagging as it did in the previous three intervals, LPM now leads. SUN, MRF, and VAN are still correlated with one another, and their activity is predictable from both LPM and HPC, but LPM and HPC are uncorrelated with each other. For "no-go," VAN is no longer significantly correlated with MRF and only slightly so with SUN. This is a departure from the strong correlations among all three areas that have persisted since before the cue. Unlike "go," LPM still lags the channels with which it is correlated (SUN and MRF in this interval), as it has in every interval since the cue. This contrast between conditions suggests that a motor set is developing for "go" that involves an influence from LPM and HPC on motor nuclei in MRF.

The correlations of SUN distinguish the conditions in the next two intervals. For "go," SUN is intermediate in timing between LPM and MRF. LPM continues to lead the other areas with which it is correlated. HPC falls out by the 722-msec interval. For "no-go," SUN now has the leading role, being correlated with LPM, VAN, and HPC at 578 msec and with LPM, VAN, and MRF at 722 msec. HPC is correlated for the first time in this condition but, unlike "go," it is in a following rather than a leading position.

By the 903-msec interval, SUN, MRF, and VAN have returned to their pre-cue zero-lag correlations with one another in both conditions. For "no-go," however, partial correlation analysis showed that the correlation between SUN and VAN could be explained by the influence of MRF. For "no-go," LPM is still involved with VAN but at zero lag (the LPM-MRF correlation drops out by partial correlation). For "go," LPM also has a zero-lag correlation with VAN but still has a small leading correlation with SUN and MRF.

These results suggest certain conclusions concerning the differential "activation" of brain regions during the two conditions of this task. The pattern of activity for "go" and "no-go" appear to be the same before the cue onset and continue so into the 156-msec interval, where there is only a small sign of divergence, involving SUN and HPC. By 240 msec there are clear signs that discrimination of the two tones has been made. The involvement of HPC in motor preparation is indicated, and activity in LPM is predictable from activity in HPC. By 397 msec, LPM reverses the direction of its relations and appears to exert an influence on

subcortical channels for the remaining intervals. In the 578- and 722-msec intervals, SUN appears to be involved in movement inhibition in the "no-go" condition. Involvement of substantia nigra in movement inhibition is consistent with the hyperkinetic features of rigidity and tremor characteristic of parkinsonism, which is known to result from a deficiency in dopaminergic neurons of the substantia nigra.

In these pictures we have intuitively appealing patterns that differ in time and between conditions. Following the cue onset, the patterns are highly similar in both conditions, suggesting sensory integration. The hippocampus is differentially "involved" following the "go" cue. This involvement may be important in orienting the monkey in its environment with respect to expectation of the visual stimulus while preparing to extend its arm. Premotor cortex seems to be functionally dependent on subcortical areas before the 397-msec interval, and then, differentially in the "go" condition, the subcortical areas appear to depend on premotor cortex in successive intervals. The involvement of the midbrain reticular formation in later intervals may represent a "priming" of motor nuclei in preparation for movement. The strong differential influence of substantia nigra in later intervals for "no-go" may represent a role in motor inhibition.

Although tantalizing, these interpretations are preliminary and conjectural and await confirmation in more subjects.

## FACILITIES AND PROCEDURAL ENHANCEMENTS

Because of the difficulty of training the cynomolgous monkeys, compared to stump-tailed macaques, and the general desirability of improving the rigor of our methods, several hardware and procedural enhancements were made.

- A small, sound-attenuated chamber was placed inside the larger chamber to reduce distraction from laboratory noises and generally to provide a smaller and visually less complicated environment.

- An improved tone generator interface to the LSI-11/23 computer was constructed to eliminate distortion of the WS and NS cues.

- The manipulanda were modified to provide a larger "paddle" for the monkey to hold down as the pretrial stabilizing response and a larger "bar" to facilitate learning of the bar-press response. Left and right paddles and bars were also incorporated to allow testing of more complex behavioral tasks.

- Measurement of the time from light onset to release of the paddle (initiation time) and the difference between reaction time (time to bar-press) and initiation time (RT - IT = movement time) have been included to provide more detailed descriptions of the behavioral parameters.

- An automated training routine was written for the LSI-11 to reduce experimenter involvement in monkey training and improve consistency of procedures from one monkey to the next.

- A separate, complete behavioral training facility was constructed in conjunction with another project. It will allow training of additional monkeys prior to surgical implant and maintenance of performance when EEG recordings are not obtained. This facility consists of (1) a chamber identical to the one in which EEG recordings are obtained; (2) a VIC-20 computer for controlling all the stimlus, response, and reinforcement contingencies; and (3) an interface between the VIC-20, manipulanda, and stimulus devices.

- Software routines were developed for the LSI-11 system to allow our single-trial records to be analyzed by Dr. Alan Gevins at the EEG Systems Laboratory in San Francisco.

## INITIATION OF STUDIES WITH FEMALE STUMP-TAILED MACQUES AND RHESUS MONKEYS

Six female stump-tailed macaques were purchased, quarantined, and trained on the behavioral task. Their training was interrupted for about two weeks to install the new chamber. We attempted to develop a discrimination task, using left (green) and right (red) lamps to cue left- or right-hand bar presses. We were able to train the monkeys to hold both paddles during the intertrial interval and to respond to either the left or right bar during any given session, but did not complete the discrimination training because it was proving to be too time-consuming. The monkeys received electrode implants and subsequent retraining with just the right bar and right paddle. One monkey dislodged the headplug and had to be sacrificed, and another became ill and may not be testable.

Electrode placements in the stump-tailed macaques were left motor cortex (related to execution of the right-handed response), right supplementary motor area (the hypothesized generator of the Bereitschafts-potential and an area thought to be involved in programming motor sequences), caudate nucleus (a region that is intimately interconnected with the frontal lobe and that previously showed large positive shifts in the cued-RT task), n. basalis of Meynert (the main source of cholinergic input to cortex), globus pallidus (the major output region of the basal ganglia), amygdala and hippocampus (possible sites of P300 genesis), raphe nucleus (a major source of serotonin neurons), substantia nigra (a key component of cerebellar-basal ganglia circuitry and the source of large negative slow potentials in the cued RT task, as recently observed in our cynomolgus monkeys), parietal cortex area 7 (a region thought to be involved in directing movements in relation to spatial aspects of the environment), and superior orbit (to record the electrooculogram). All recordings are to be carried out with respect to a reference electrode aimed at white matter below the parietal cortex.

Because of problems with the two stump-tailed macaques, four female rhesus have also been purchased and are now in quarantine.

## STUDIES AT STANFORD UNIVERSITY
(Karl H. Pribam and Merle M. Prim)

The evoked-potential technique is being used to determine which forebrain structures are involved in cognitive processing. The purpose of such experiments is to locate the structures that constitute the possible spatial code by which forebrain systems communicate with the circuits involved in conditioning and learning. To accomplish this we need to relate the work we have done with monkeys to the components of the event-related brain electrical activity in humans. The analyses in our earlier studies have been centered on the differences that appeared in an entire 500-msec post-stimulus or pre-response period. Analyses of human event-related brain electrical activity have focused on differences that appear in various portions of that record: the first 100, second 100, third 100, and late components. This approach has yielded a rich harvest of data and interpretation. Briefly, the early components reflect the stimulus input and the later components, beginning somewhere around 300 msec, reflect "psychological" processes initiated in reaction to the stimulus. The intermediate components, centering around 200 msec, reflect intermediate types of activity—attentional factors related to processing the stimulus display.

It is the components beginning around 300 msec that have captured our interest because there is so little agreement as to just what cognitive operations are reflected in these late components of the waveform. the task that has been most useful in delineating the nature of the components around 300 msec is the "oddball" task in which the subject is trained or instructed to perform a discrimination and an "oddball" cue is presented unexpectedly while the discrimination is being performed. As indicated in our initial application, from the standpoint of the results obtained in our laboratory, the "oddball" task as usually given confounds these very different cognitive operations: discrimination (among cues that are differentiated by a consistent history of reinforcement), differential response (as in a go/no-go task), and reaction to novelty (which is dependent on reactions to trial-unique types of procedures). We have shown that these processes depend on the integrity of different brain systems: discrimination is interfered with by resections within the posterior cortex associated with specific sensory systems; differential responses and reaction to novelty, by contrast, are interfered with by resections of structures within the frontolimbic forebrain.

The unconfounding of these types of cognitive operations is important to our analyses of the components of the event-related brain potentials. Analysis can take two forms. The usual one is to pursue the type of work done with humans, which tries to relate variations in the problem situation to changes in the event-related potential. Our approach has been to track the locus of the generators of the waveform, and when we find these, to infer--from knowledge of the anatomy and function of these loci--something about the cognitive operation that is under way. But for either type of analysis it is imperative that the task variables (in this case discrimination, differential response, and orienting to novelty) be unconfounded.

One clue has come from the results with humans, which have separated two components in the positive deflection that occurs around 300 msec: P300a and P300b. Experiments by Duncan-Johnson and Donchin (1982); Roth et al. (1975), and Squires and Donchin (1976) have provided evidence that the amplitude of the earlier occurring P300a is linearly related to the intensity of an unexpected response. The later P300b, on the other hand, appears to reflect the degree of expectancy set up by the precise probabilities of the task.

In the light of these results, we have trained four monkeys and have implanted each with approximately 50 electrodes in a variety of cortical and subcortical locations. Because we are using a visual version of the "oddball" task, the electrodes have been placed in the striate, prestriate, and inferotemporal cortex as well as the far frontal and pre- and post-central areas. Deep electrodes are located in the head of the caudate nucleus, the amygdala, hippocampus, and in the medial thalamus at the level of the centromedian nucleus.

Baseline recordings were taken prior to the initiation of training on the "oddball" task. For these recordings, the monkeys had simply to press the panel behind which the green square appeared. As in all our tasks, the monkey is shaped to press the center panel displaying a small circle when the computer has set up the trial. This press initiates the trial, during which the circle disappears and the green square appears in one of the nine possible locations (including the center panel), as determined by a modified Gellerman sequence. The monkey has been trained to wait for a limited time (which varies from 250 to 1500 msec) before responding to the green square. Electrical recording from eight of the implanted sites commences at the time of the center panel press, which initiates the trial, and continues to 500 msec after the completion of the next panel press, which, if correct (i.e., if he presses the panel behind which the green square is displayed) causes a squirt of Tang is delivered by tube to the monkey.

All four monkeys have completed the initial training regimen in the Discrimination Apparatus for Discrete Trial Analysis (DADTA). This apparatus consists of a response panel having a 3 x 3 clear plastic panel array amenable to back-projection of visual stimuli. The monkeys are placed in a primate chair daily for testing while under a 23-hour water deprivation regimen, which consists of access to water after completion of the run and ad libitum food. Visual stimuli are back-projected via a standard RCA television set under the control of the color graphics of an Apple microprocessor. Visual stimuli are programmed onto the TV tube face in such a way that discrete squares of color can be centered in each of the clear plastic panels of the response board. Reward consists of 1 cc of liquid Tang delivered when the monkey makes a correct response. Each monkey is considered shaped when it can generate 85%+ response over ten consecutive days. All four monkeys have reached this criterion.

On meeting the criterion, the monkeys were placed in the experimental program, which presents the stimuli in much the same manner, only under the joint control of a PDP11 computer and the Apple microprocessor so that brain electrical activity, as well as the position, latency, and reinforcement information regarding the monkey's responses on each trial, can be collected by the PDP11 computer.

As in the case of the training regimen, the location of the stimulus is distributed according to a Gellerman series, which is sufficiently long so that the monkey cannot learn the sequence. The Gellerman series is changed daily. Variable interstimulus and intertrial intervals are presented to ensure that the monkey does not learn to expect when a stimulus and trial are to be presented. For each trial, brain electrical activity is recorded over an epoch starting 250 msec before the stimulus appears and lasting through 4 sec. Eight Grass amplifiers take the output from eight instrumentation preamplifiers, each differentially connected to two electrodes. The brain electrical activity recording during this epoch is subjected to A/D conversion and held within the computer for a printout of averaged waveforms and for further analysis. Behavior is simultaneously recorded on a trial-by-trial basis and is recovered in printed form after the end of the session. Data collection calls for three consecutive days at over 85% correct on a daily run, which consists of a sufficient number of trials to assure that 100 correct responses have been completed.

We record from either eight cortical or eight subcortical electrodes on tests during any one day. The subcortical recordings are made bipolarly across an entire nucleus: e.g., from the bottom to the top of the amygdala. Once we have differential results, we can focus on adjacent electrode sites within a nucleus.

So far, we have recorded runs in which the green square was changed to red on 10% of the trials and in another condition where the green square was changed to red on 20% of the trials. Each of these conditions was run for 100 correct trials.

In addition, the monkeys have finished a modified equivalent of the standard "oddball" task. The task consists of training the monkey to make a differential response in the presence of a condition in which any of the nine panels are illuminated by a green or red square. In the green square condition, the monkey is to press the green square. In the red square condition, all the panels except the center panel are red and the monkey has to press the center, unlit panel (a modified no-go response). The red square ("oddball") condition was presented pseudorandomly on 10% of the trials in one run of 100 trials and on 20% of the trials in another run of 100 trials.

Next we are proceeding with a red-green discrimination, which will be followed by the more standard "oddball" procedure in which one of the discriminanda (the rewarded one) is changed to yellow for 10% and then for 20% of the trial runs.

This experimental approach has the advantage of maximizing the chance of finding the locations where the waveforms related to the stimulus discrimination, differential response, and novel stimulus occur.

To confirm that the computer was recording the brain electrical activity properly, a trial-by-trial comparison was made on runs in which some notable characteristics in the waveform could be identified.

Data analysis has not as yet begun. However, the data on the runs completed thus far are in the proper form and ready to be taken to the laboratory of Alan Gevins, where sophisticated time-course-by-location procedures will be performed. The results obtained from such an analysis promise to shed considerable light on the issue of which parts of the brain are involved in processing the "oddball" tasks and in what order.

## PLANS FOR THE COMING YEAR

During the new contract period we plan to begin recordings from the stump-tailed macaques. In this case, in contrast to the procedure used with the cynomolgus, we will immediately introduce both the WS and NS tones once tone-light pairing begins so that the learning and discrimination curve of SP amplitudes can be tracked. A general methodological change during initial training stages and between experimental manipulations will be to routinely vary the interstimulus interval (1.0, 1.5, and 2.0 sec) from day to day to help prevent adaptation to the situation. We plan to vary the proportions of stimuli with the stump-tailed macaques to further evaluate P300-like events, as was done with the cynomolgus. In this case we will maintain a given proportion for 5 consecutive days. Because several of the structures from which we will be recording are involved in motor activity, we also plan to vary the effort required to make the operant response by spring-loading the bar to various activating pressures.

Because one of our major interests is in the relationships among various recording sites, these manipulations and variation of ERP parameters from session to session will provide clues as to the co-variation among sites. For example, it was noted previously (Rebert, 1977) that the MRF and PMC were dissociated in several respects, especially in that the MRF exhibited a much clearer WS-NS discrimination than did the PMC. Differential discrimination at various loci was also observed in the cynomolgus monkeys. If the recordings from our new stump-tailed macaques are as clear and robust as those obtained before (Rebert, 1972), intersite correlations of ERP parameters derived from single-trial waveforms will be calculated. To the extent possible, depending on the availability of funds, we will also expand our collaboration with the EEG Systems Laboratory to more rigorously evaluate interarea relationships.

The remaining four cynomolgus monkeys are being retrained in the new chamber. If their performance is improved by this situation, we will continue working with them, studying the same parameters evaluated in the stump-tailed macaques.

Four female rhesus monkeys have also been purchased. Following quarantine they will be trained on a VIC-20 system and subsequently evaluated electrophysiologically with our LSI-11 system. The VIC-20 system allows us to continue behavioral training and testing of monkeys

with intermittent electrophysiological evaluations, increasing the number of monkeys that can be studied.

Because the effects of atropine were due, apparently, exclusively to peripheral actions, and this could also be a problem with other pharmacologic agents, our intention to use intracerebral push-pull methods to evaluate neurochemical mediators of ERPs has been strengthened. To this end we plan to use the cannula shown in Figure 7 on at least one monkey to evaluate its usefulness in modifying flash-evoked potentials in the lateral geniculate nucleus.

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