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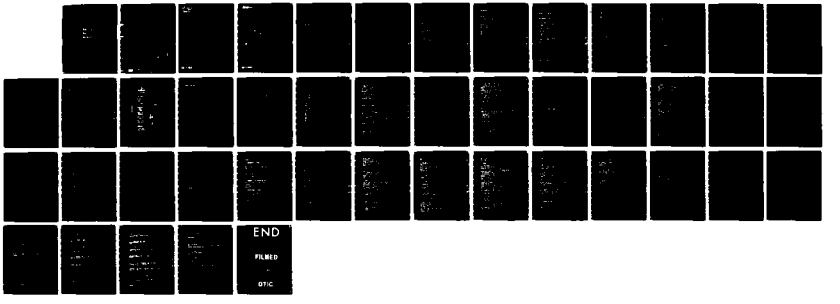

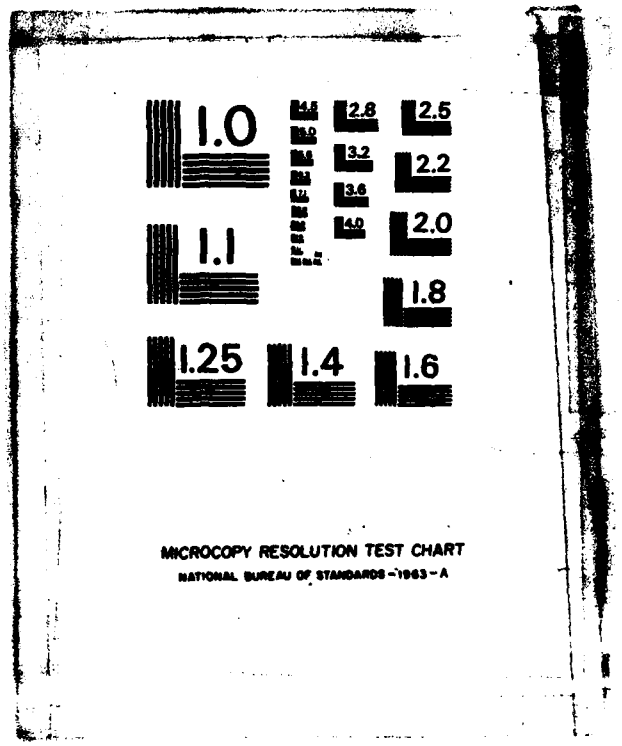
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NEUROPHYSIOLOGICAL BASES OF EVENT-RELATED POTENTIALS

Annual Report No. 2

June 1984

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By: Charles S. Rebert and Michael B. Hennessy
SRI International

and

Karl H. Pribram and Merle M. Prim
Stanford University

Prepared for:

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

Attention: Dr. Alfred R. Fregly
Program Manager

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Approved by:

Gordon T. Pryor, Director
Psychobiology Department

W. A. Skinner
Vice President
Life Sciences Division

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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. Six animals were trained on the cued reaction-time task at SRI International and were subsequently implanted with electrodes capable of recording transient and sustained evoked potentials and massed-unit activity. Two monkeys were trained on an "oddball" task at Stanford University, and electrodes were implanted so that the subcortical generators of the P300 wave could be assessed. At SRI,

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19. KEY WORDS (Continued)

20 ABSTRACT (Continued)

Slow potential changes were observed in a variety of cortical and subcortical regions and were observed to change as a function of discrimination, proportionality of stimuli, the interstimulus interval, and dose of an anticholinergic drug.

CONTENTS

FIGURES

TABLE

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 corter- 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 non-specific 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 [illegible], 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?

METHODS

General 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 (holding on to a round knob 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 discriminative stimuli (WS and DS, 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 1 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).

The DS 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 DS 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 DS on different trials.

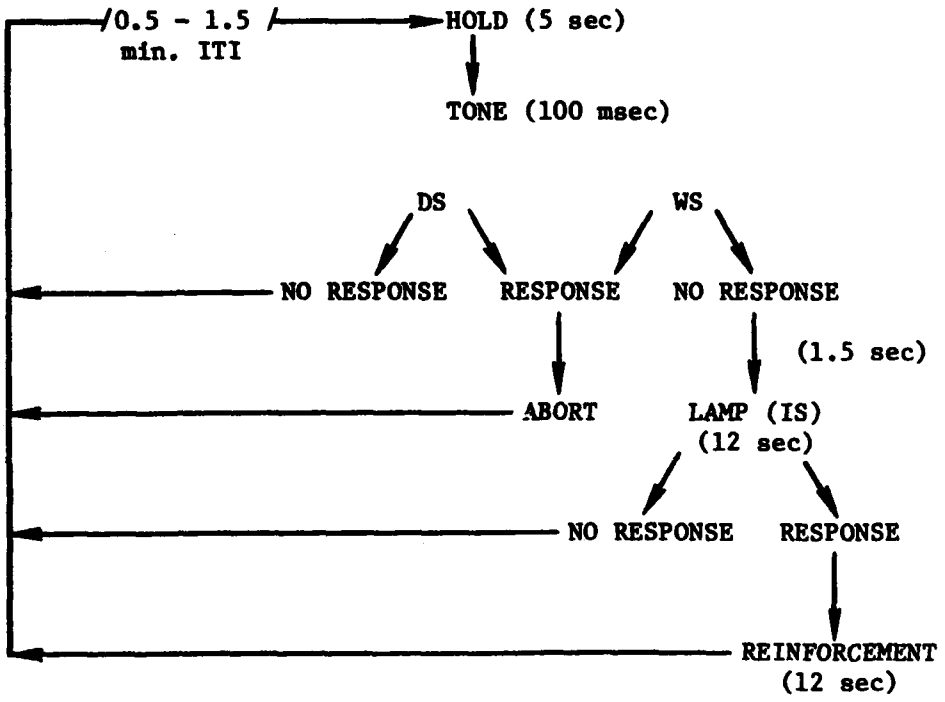

FIGURE 1 Schematic illustrating techniques used to establish a cued discriminative reaction time task in the monkey.

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 a small bar mounted on the front of the chair 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 the 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.

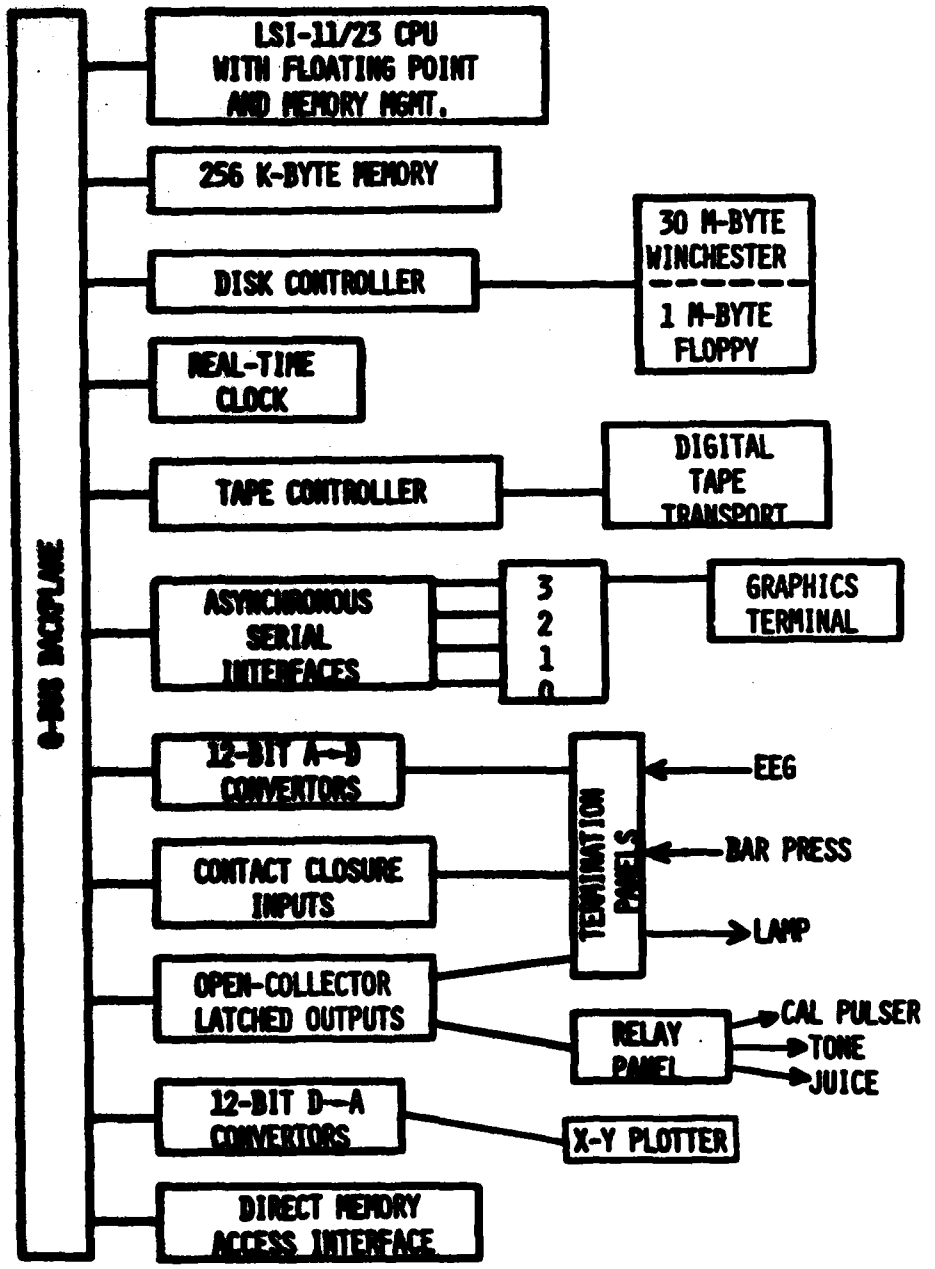

FIGURE 2 SCHEMATIC OF COMPUTER SYSTEM

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.

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 anesthetic. The animal is then placed in a stereotaxic device; the scalp is shaved and cleansed. Halothane gas is used as necessary to maintain anesthesia after metabolism of the ketamine. A small dose of atropine is given to control mucous membrane secretions. Aseptic surgical procedures are used throughout.

After the scalp has been 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. 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. Depth electrodes consist of sharpened 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). These can be used to simultaneously record SP and massed-unit responses (Rebert, 1973a, 1973b). 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 multipin 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.

RESULTS

Preliminary Results

Six adult male cynomolgus monkeys (Macaca fascicularis) were implanted with electrodes following an extensive period of training to bar-press only during the presence of a light and to hold onto a ball prior to onset of the light (Rebert et al., 1983). Electrodes were placed bilaterally over premotor (arcuate region), motor, and parietal cortices, in the CA1 region of the hippocampus, and in the caudate nucleus, substantia nigra, midbrain reticular formation, and nucleus ventralis anterior of the thalamus. Reference electrodes were placed in anterior and posterior white matter. An electrode was also implanted in the superior bony orbit to record the electrooculogram (EOG).

These monkeys were more difficult to train than the stump-tailed macaques used in previous work (Rebert, 1972, 1977). They were very persistent in making anticipatory movements and reluctant to maintain a fixed hand position during the intertrial intervals. In addition, they were very difficult to motivate, requiring a consistent regimen of testing and receipt of their total daily fluid intake during testing in order to maintain performance. Currently, the monkeys are being trained under a more rigorous and automated procedure for detecting anticipatory responses. This training is important because premature movement from the resting position changes the nature of the task; i.e., the tone becomes a cue to respond rather than a cue to "wait" (Donchin et al., 1971).

Several performance parameters are summarized for five monkeys (one monkey, No. 6, was an excessively erratic performer) in Table 1 for two training conditions. Scores obtained when only the light cue--the imperative stimulus--was presented are in the upper portion of the table. Scores obtained during tone-light pairing are in the lower part of the table. The latter scores are those for the period of 23 September through 19 October 1983 following one month of tone-light training.

The monkeys would work for 250 to 300 ml of juice each day. The percentage of bar-presses made during ITIs was low, averaging about 10, which reflects the previous training to respond only during the presence

Table 1

PERFORMANCE SUMMARY FOR FIVE MONKEYS
DURING LIGHT ONLY AND TONE-LIGHT PAIRING

Conditions	Monkey (No.)	Total Bar-Press $\bar{X}$ (SD)	Total Reinf. $\bar{X}$ (SD)	% ITI Bar Press $\bar{X}$ (SD)	Rate(n/sec) Bar Press $\bar{X}$ (SD)	Reaction Time (ms) $\bar{X}$ (SD)	% Abort $\bar{X}$ (SD)
	Conan (1)	289(138)	269(130)	7(3.4)	1.2(0.1)	1340(164)	24(11)
Light	Mickey (2)	261(90)	222(76)	14(42)	1.6(0.3)	1521(154)	30(14)
only	E.T. (3)	240(57)	218(52)	9(3.1)	0.7(0.1)	1563(251)	22(11)
	Smacker (4)	282(102)	240(76)	14(6.5)	1.7(0.2)	1579(210)	28(10)
	Grey (5)	401(95)	339(76)	15(3.6)	1.6(0.2)	1084(178)	21(6)
	$\bar{X}$	295.0	258.0	11.8	1.4	1417.0	25.0
	SD	62.5	49.8	3.6	0.4	209.3	3.9
	SE	28.0	22.3	1.6	0.2	93.6	1.7
	Conan	356(114)	329(111)	8(3.2)	1.1(0.3)	1082(167)	26(19)
Tone-	Mickey	322(72)	290(64)	9(2.2)	2.1(0.2)	919(221)	32(11)
light	E.T.	216(54)	192(47)	9(6.3)	0.9(0.1)	1118(272)	35(12)
pairing	Smacker	280(47)	257(45)	8(3.0)	1.8(0.2)	1290(267)	23(11)
	Grey	437(87)	381(71)	9(2.2)	2.5(0.5)	318(224)	37(15)
	$\bar{X}$	322.0	290.0	8.6	1.7	945.0	31.0
	SD	82.7	71.6	0.6	0.7	374.7	5.9
	SE	37.0	32.0	0.2	0.3	167.6	2.7

of the ISI. Most of the intertrial responses reflected the continuation of responding after the light terminated (usually two or three responses). The rate of pressing by the several monkeys varied from 0.7 to 2.5/sec and was characteristic of a monkey's performance, being stable over the course of training. Reaction time averaged 1417 msec when no tone cue was present and 945 msec after tone-light pairing. This shortened RT indicates that the monkeys learned to associate the tone and light. The current average RT value is, however, contaminated by premature responses because automatic detection of such responses had not yet been implemented during these tests. The percentage of trials aborted reflects several factors--excessively slow RTs, experimenter aborts, and--especially--premature responses. Trial rejects due to electrophysiological artifacts can also be included in this score, but that procedure has not been employed to date.

In general, performance was brought to a stable point under two conditions, and the main factors affected by introducing the tonal warning cue were the number of anticipatory responses and the RT. The tendency to make premature movements was more prevalent in some monkeys than in others, but RT was shorter in all cases when the tone cue was present than when it was not.

Electrophysiological recordings were obtained from the left premotor and motor cortical placements, all of the subcortical electrodes, and the superior orbit. Examples of responses obtained from one monkey (No. 3) are shown in Figure 3. The EOG indicated the occurrence of a blink shortly after tone onset, with a downward excursion of the eyes reflected by elevation of the DC level during the interstimulus interval. A waveform similar in shape to the EOG was recorded from the arcuate gyrus in the left premotor cortex (LPMC). Correspondence between these two records was sufficient to suggest that the arcuate recording was primarily a passive reflection of the EOG. However, because the arcuate region is intimately involved in the control of eye movement (Akert, 1964), the premotor response might still be generated in the cortex. Recordings from regions anterior and lateral to the arcuate sulcus would help clarify this issue. In addition, once software is completed, we plan to capture epochs time-locked to spontaneous blinks to more thoroughly determine the effects of blinks and eye movements on brain recordings. Although the left motor cortex (LMC) waveform was also similar to the EOG record, the initial negative peak was comparatively small and occurred later in time than the blink, and the slow negative shift in LMC persisted throughout the recording epoch while the EOG returned to baseline.

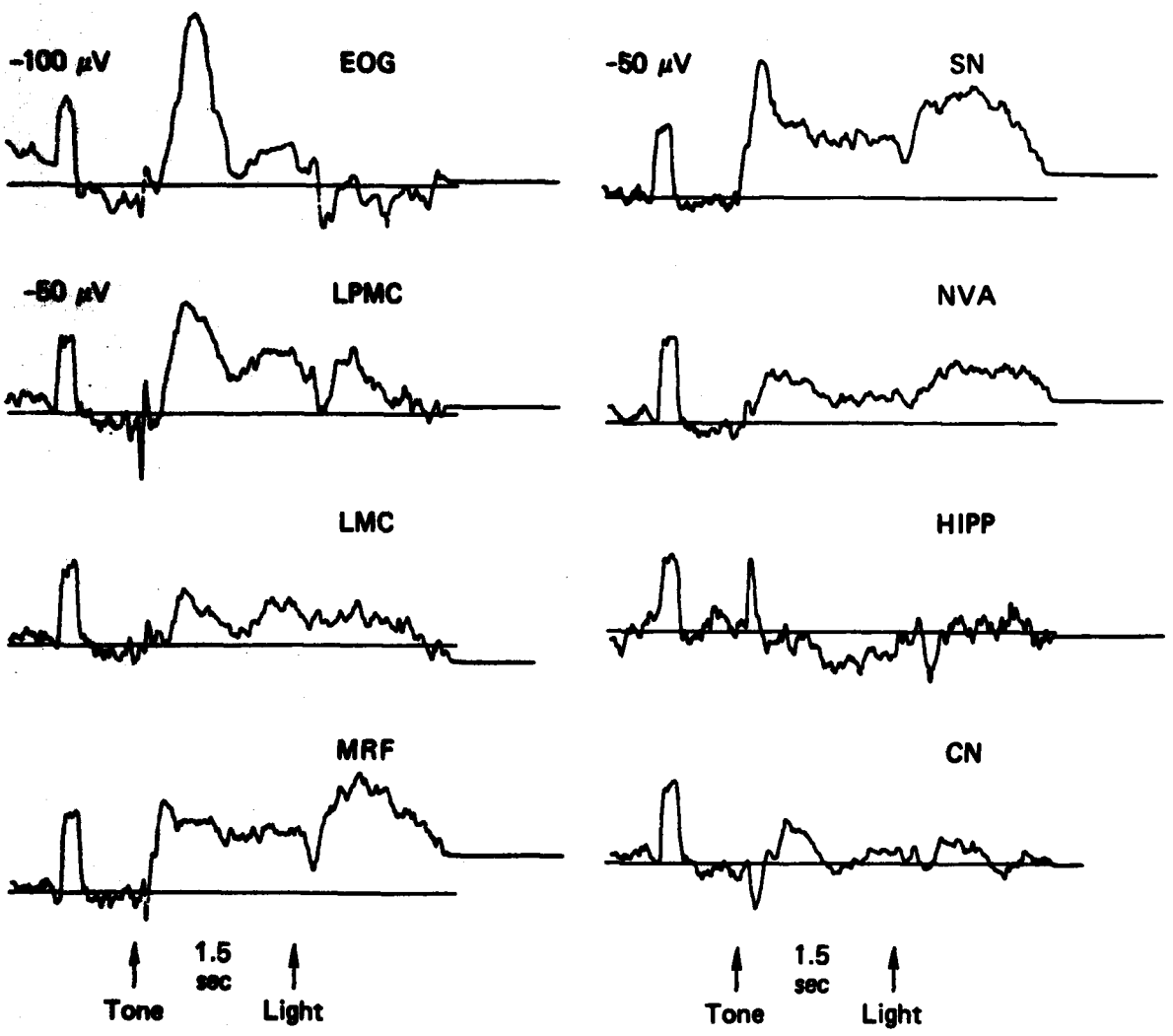

FIGURE 3 EXAMPLES OF EVENT-RELATED POTENTIALS RECORDED FROM SEVERAL BRAIN REGIONS OF MONKEY NUMBER 3

EOG = Electrooculogram, LMPC = Left Premotor Cortex (arcuate gyrus), LMC = Left Motor Cortex, MRF = Midbrain Reticular Formation, SN = Substantia Nigra, NVA = Nucleus Ventralis Anterior (thalamus), HIPP = hippocampus, (CA1 region), CN = Caudate Nucleus. In this and other figures, averaged waveforms are usually based on fifteen trials and 0.01 to 40 Hz recording bandpass.

A rapid change occurred in the midbrain reticular formation (MRF) after onset of the US. A 50-μV negative shift, peaking with a latency of about 200 msec, persisted throughout the interstimulus interval and increased in amplitude after onset of the light. This pattern was very different than the EOG and could not be considered an artifact of eye movements or blinks. An almost identical response was obtained from the substantia nigra (SN). A similarly shaped, but smaller, change occurred in the nucleus ventralis anterior (NVA). A slight positive shift occurred in the hippocampus following a brief, transient negative potential. A transient positive-negative component appeared in the caudate nucleus (CN) of this monkey without any definite SP occurring during the interstimulus interval on this recording session. On the average, however, this monkey exhibited a small negative shift in the CN.

The close correspondence of the EOG and arcuate gyrus waveforms was evident in other monkeys as well, but there were a sufficient number of differences in waveforms, in both latencies and polarity (e.g., Figure 4), to require caution in attributing the arcuate response exclusively to ocular activity.

Evoked-potential waveforms from other regions varied moderately among the monkeys [records from the behaviorally erratic monkey (No. 6) are not considered]. Negative SPs were obtained from the LMC, and this response was invariably smaller than that observed in the LPMC. In one monkey (No. 4), the LMC response was sometimes absent or even positive rather than negative. The variety of waveshapes obtained from the LMC is exemplified in Figure 5. All five monkeys exhibited negative SPs in the MRF, and four of the responses (except from No. 4) started with a fast-rising negativity like that shown in Figure 3. The same consistency was true of responses in the SN, with all but one response (from No. 4) starting with a fast negativity. In three of the four monkeys with good SN responses, amplitudes were about 50 μV. In one monkey (No. 2), however, the response reached 100 μV during the interstimulus interval and 150 μV shortly after the light appeared.

Inconsistent waveforms were obtained from the NVA. A negative shift with a fast rise, and about 30 μV, was seen in three monkeys, and the other two showed little or no response. In contrast, small positive SPs, with amplitudes of about 12 μV, occurred in the hippocampus of five monkeys. Slow-rising negative shifts of 10 to 40 μV, preceded by a brief positive component, were observed in the caudate nucleus in four of the five monkeys.

Fully developed SPs were rarely observed in the interstimulus interval when the tone was first paired with the light. An example of

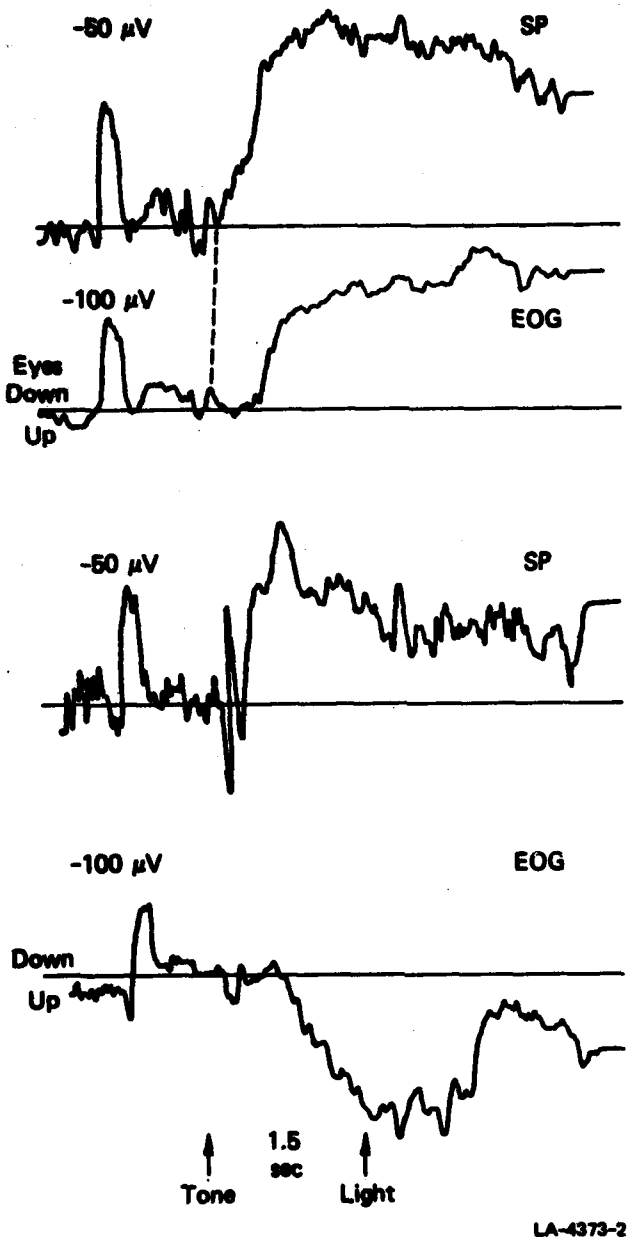

FIGURE 4 DISSOCIATIONS BETWEEN SLOW POTENTIALS (SPS) IN PREMOTOR CORTEX AND THE EOG

Upper two traces from monkey 2 showing earlier development of SP than EOG. Lower two traces from monkey 3 show normal potarity SP but reversed polarity of EOG after atropine administration. The last two tracings compare with the EOG and premotor recordings, which are alike in Figure 3, without drug.

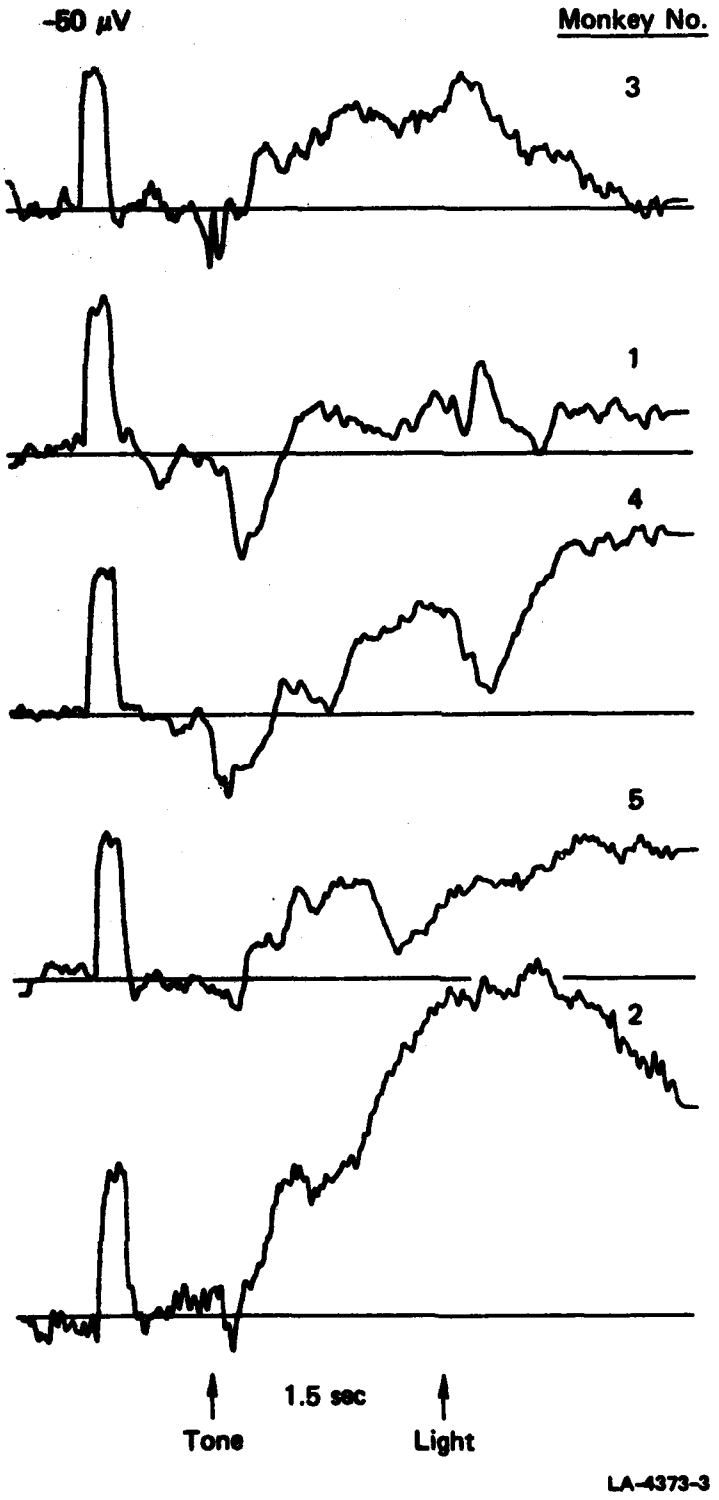

FIGURE 5 LEFT MOTOR CORTEX RECORDINGS FROM FIVE MONKEYS

[redacted] is shown in Figure 6. On the first day of [redacted] a large negative shift was observed in the SN at [redacted] a small, but similar, response occurred to the [redacted] day of tone-light pairing. There was not, however, a [redacted] at that time. On the eighth day of pairing, the early [redacted] was much larger and more persistent. By Day 15 the SP [redacted] throughout the preparatory interval.

[redacted] the relationship between the SPs and neuronal [redacted] the recordings were filtered, with bandpass settings of 300 Hz [redacted] and integrated with a Ballantine 320A RMS meter. The [redacted] (IMU) activity was digitized and averaged on-line [redacted] the corresponding SP. To date, only the MRF, SN, and CN have [redacted] in this way. IMU changes were evident only in the SN of [redacted]. Activity increased in association with the negative SPs, [redacted] in Figure 7. In most cases the IMU changes were small with [redacted] to background noise, but were large in monkey No. 2. It is [redacted] that the electrode was placed exactly in that monkey, but not in [redacted]. The fact that IMU potentials decrease in amplitude more [redacted] as a function of distance from the neuronal generators than do [redacted] potentials (Vaughan, 1981) accounts for the occurrence of SPs with [redacted] no discernible IMU activity. This possibility will be checked histo-[redacted] at the end of the experiments. In the other areas, the cells [redacted] the SP response may have been too small to have an impact on [redacted], or the SPs may have reflected either glial depolariza-[redacted] or synaptic dendritic changes not associated with neuronal firing. [redacted] single- or multiple-unit measures of neuronal activity, rather [redacted] gross-unit recording, will probably be required to adequately [redacted] the [redacted] relationships in the areas of interest in these studies. [redacted], the SPN response was very adequate for studies of the lateral [redacted] nucleus of cats (Rebert, 1973a).

Several authors have suggested that cortical SPs are generated by [redacted] neurons (Pirch et al., 1983; Marczynski, 1983). Although [redacted] of transmitter systems by systemic administration of drugs [redacted] difficult to interpret (Rebert, 1980b), there is considerable [redacted] in such manipulations in the study of human ERPs (Thompson et [redacted], 1983). Therefore, we carried out a pilot study of the cholinergic [redacted] agent atropine in our monkeys. Our first effort was primarily [redacted] to determine an appropriate dose to use in later, more systematic [redacted]. The drug was administered im in doses of 0.1, 0.2, and 0.3 mg/kg. Each dose has been tested only once so far. Because the [redacted] dose was unknown, drugs were given once per day for three [redacted] during one week, starting with the lowest dose. Dilation of the [redacted] was apparent at 0.3 mg/kg and--to a lesser extent--at 0.2 [redacted]. No dilation was noted at 0.1 mg/kg.

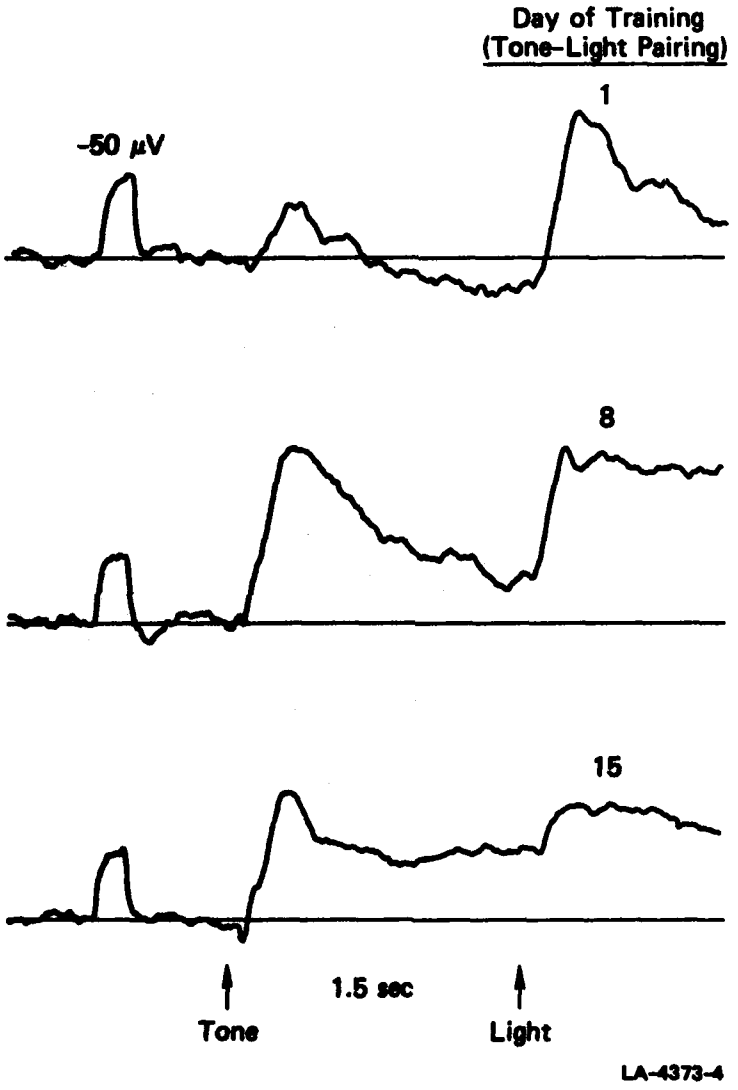

FIGURE 6 CHANGES IN SUBSTANTIA NIGRA OF ONE MONKEY AS A FUNCTION OF DAYS OF TRAINING

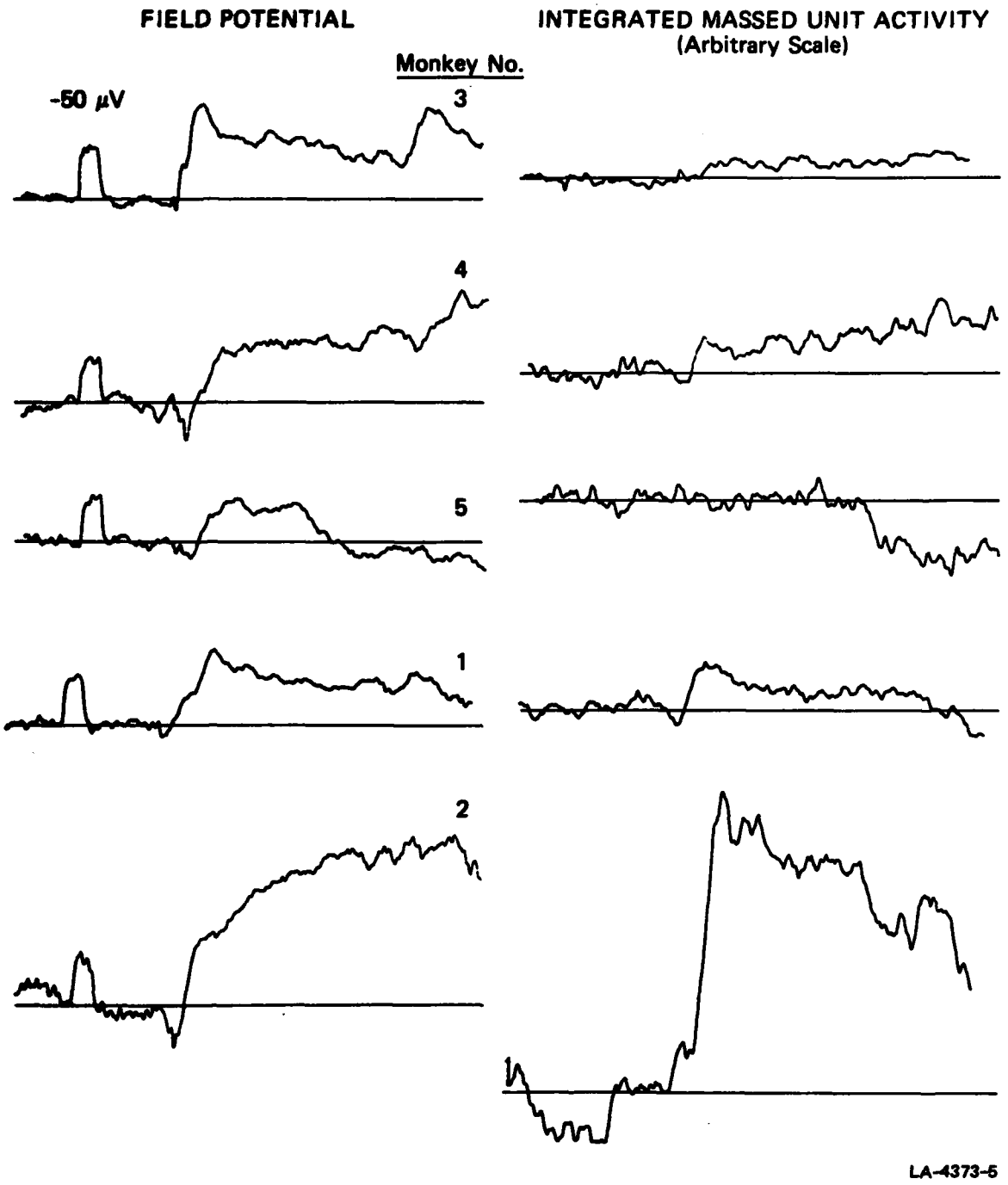

FIGURE 7 SLOW FIELD POTENTIALS AND MASSED UNIT ACTIVITY IN THE SUBSTANTIA NIGRA

Following atropine administration, behavioral performance deteriorated. This effect was clearest in terms of the number of acceptable trials per testing session. On days during which no drug was administered, the subject almost always met criteria for an acceptable trial (no anticipatory responses, RT below cutoff criterion, etc.) on at least 15 trials per session. In contrast, during drug tests, 15 acceptable trials were recorded for only 2 of 15 sessions (5 monkeys x 3 dose levels). Overall, the mean number of acceptable trials per session for drug trials was 9.3. There was no effect of dose level on this measure. In addition, during some of the drug trials judged acceptable, the subjects would cease responding prior to offset of the imperative stimulus. This was particularly true of one monkey (No. 5), who stopped responding prematurely on 11 of 15 acceptable trials at the 0.3-mg/kg dose.

The percentage of bar-presses during the ITI increased from a predrug mean of 8.6 to an average of 16.5 over all drug doses, being largest (19.6) in the high-dose condition. Reaction time was not clearly affected. The percentage of trials aborted increased from the predrug level of 31 to an average of 62 during atropine treatment, the effect being comparable for the three doses. The number of reinforcements was 290 and 141 per session in the baseline and drug conditions, respectively.

Four of the five monkeys exhibited unusual behavior during testing on days of drug administration, particularly at higher doses. This consisted of seemingly nondirected waving of the limbs, especially the arms. Movements were usually rapid and "jerky." The monkeys appeared to be agitated and would grab the loose end of their restraining collar and swing it rapidly back and forth, or push outward against the chair. Subjectively, this gave the impression that there had been some release of behavior from normal inhibitory control following atropine administration, which was consistent with the increased number of intertrial responses and aborted trials.

The electrophysiological effects of atropine were highly variable, depending on dose, placement, and monkey. Because of the very preliminary nature of these results (this was basically a dose-finding study), only qualitative descriptions of the effects are given. Atropine caused a slight increase in the premotor-cortex SP of three monkeys at the medium and high doses, had no effect in one animal, and produced a moderate decrease in the SP of the fifth monkey at the high dose. In this same monkey (No. 3), the medium dose enhanced the SP in the motor cortex. SPs in motor cortex were also slightly enhanced in three additional monkeys, with no effect in the fifth (No. 1). Monkey No. 5

exhibited a clear dose-response function, shown in Figure 8. One effect of atropine on the substantia nigra and reticular formation was to increase the size of the response to light onset. This occurred clearly in three monkeys. Examples are shown in Figure 9.

The potentials evoked by the light and those developing in the interstimulus interval in both the SN and MRF appear to be independent. In Figure 6 the post-imperative response is well developed before the interstimulus potential becomes sustained, and appears to be "covered up" by the interstimulus SP. In contrast, as shown in Figure 9, atropine appears to "uncover" the post-imperative response by attenuating the interstimulus negativity. No consistent effects of atropine were evident in recordings from the MVA or on the EOG. In one monkey, however (No. 3—normal records shown in Figure 3), the EOG pattern was reversed from downward to upward movements by the high dose of atropine, but the premotor recording remained essentially normal--a dissociation indicating independence of the cortical recording from eye movements (see Figure 4).

In the above described work we have developed an almost fully automated system for studying event-related potentials in monkeys, performed surgery on and trained six monkeys over the course of about 18 months, and recorded anticipatory SPs and related transient responses. Very preliminary attempts were also made to record massed-unit activity and to study the effects of the cholinergic blocking agent atropine. Some outcomes were similar to, and some different from, those obtained in earlier related research. For example, the waveform elicited from the MRF--a fast-rising response—was like that observed previously (Rebert, 1972). In contrast, the positive SPs expected in the caudate nucleus were not observed. The prediction (Rebert, 1980b) that negative SPs would be recorded from the substantia nigra was confirmed. In general, as was observed before, SPs in the premotor cortex were larger than those in the motor cortex. However, in the present monkeys, there was not a sharp decline in the response upon occurrence of the imperative stimulus. This might be related to general deficiency in inhibitory capability—perhaps similar to the perseverative tendencies of human schizophrenics, who also exhibit prolonged SP changes following the imperative stimulus (Timsit-Berthier et al., 1976).

Other Experimental Manipulations

During the last part of Year 2 and the initial month of Year 3 of this contract, several experimental manipulations were undertaken to determine their effects on the potentials being recorded in the standard

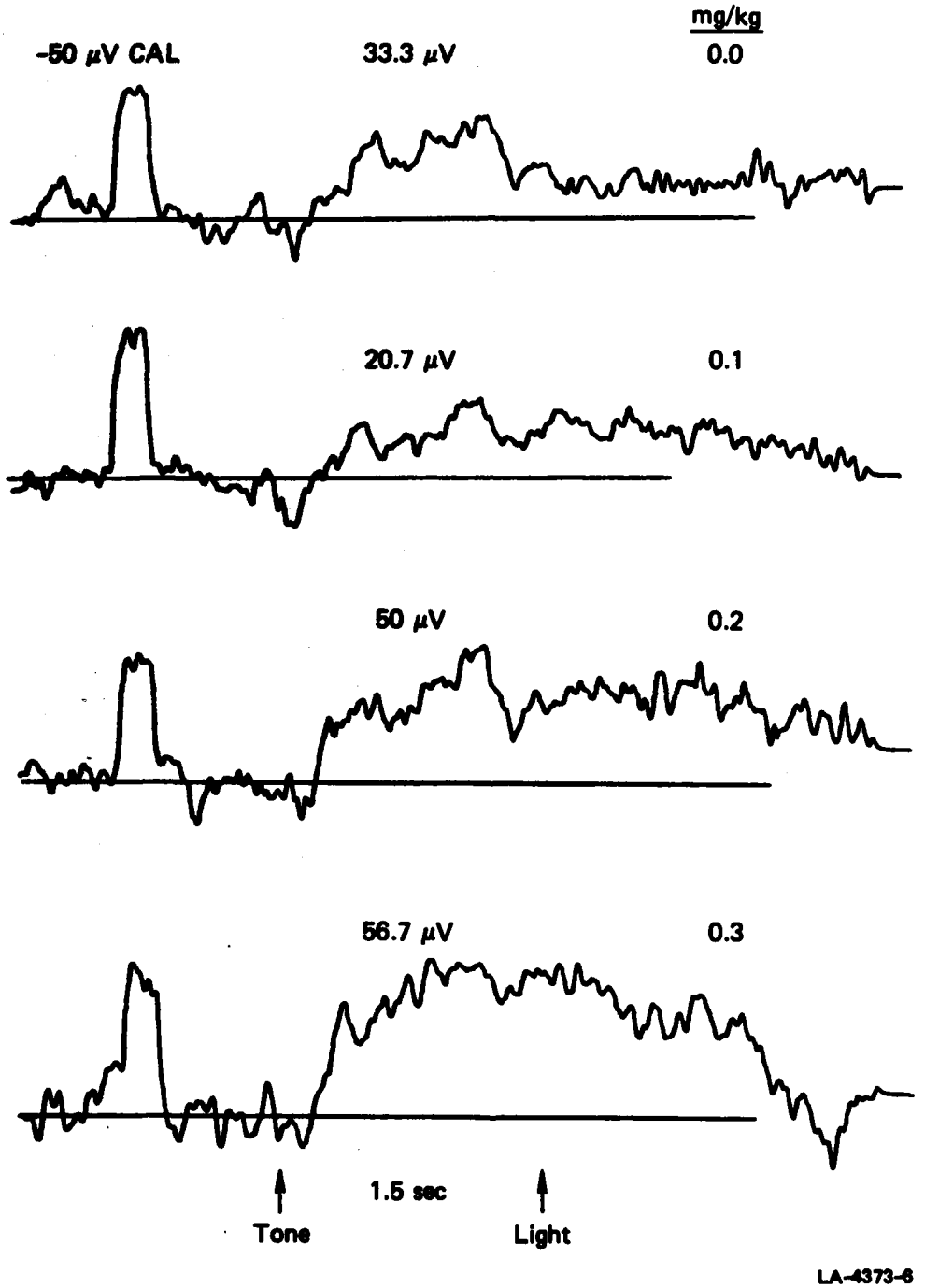

FIGURE 8 DOSE-RELATED EFFECTS OF ATROPINE ON SLOW POTENTIALS IN MOTOR CORTEX OF ONE MONKEY

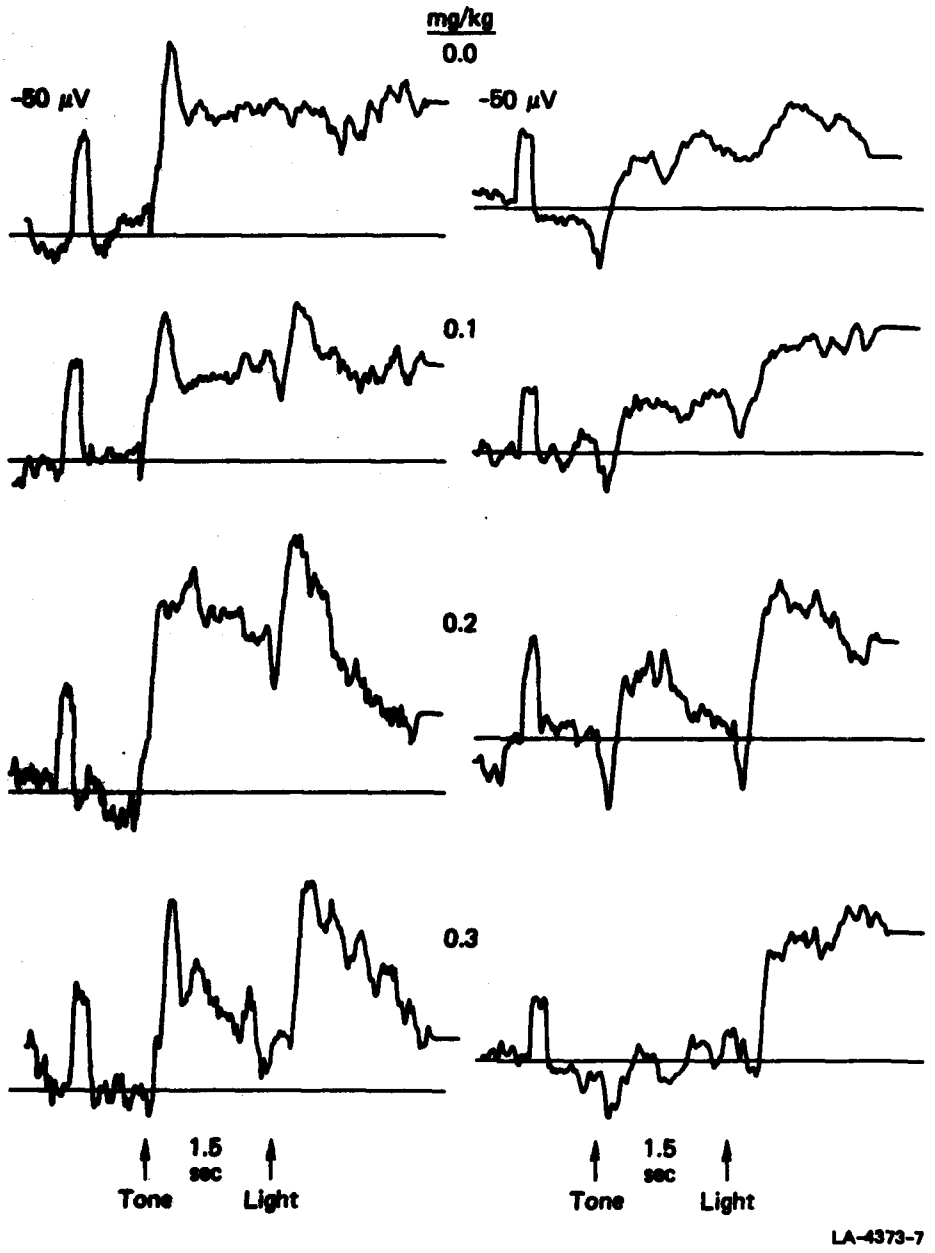

FIGURE 9 EFFECTS OF ATROPINE ON SUBSTANTIA NIGRA AND RETICULAR FORMATION RESPONSES DURING THE INTERSTIMULUS INTERVAL AND TO ONSET OF THE IMPERATIVE STIMULUS

The interstimulus slow potential was reduced and the post-imperative peak-to-peak amplitude was enhanced as a function of the dose of atropine.

paradigm. Only a summary is provided here as the data have not yet been systematically evaluated.

Discrimination training. The neutral or discriminative stimulus (DS) was added to the paradigm. We expected to observe SP responses to this tone during a few days of testing, with subsequent extinction because the stimulus is not paired with the light that indicates availability of reward. Our bright monkey exhibited this distinction almost immediately, whereas the others showed only minor or no discrimination. To facilitate this development, the proportion of the DS was increased to 80%, which eventually led to the development of discrimination in the other monkeys. The discrimination appears to have occurred first in the subcortical structures, as was observed in a previous experiment (Rebert, 1972). This paradigm, with varying proportions of stimuli, is similar to the oddball task, and we plan to compare the waveforms obtained with the 50% vs 80% DS conditions, with the aim of identifying a P300 analogue.

Variation of the interstimulus interval. Because the monkeys had been trained for a long time on the same interstimulus interval, it was changed from 1500 msec to 1000 and 2000 msec on alternate days (all three intervals were used). This added uncertainty about the temporal relationship between stimuli appeared to enhance the SP responses, but quantification of the responses will be required to confirm this impression.

Administration of atropine. Because the cholinergic projection from the n. basalis to cortex has been implicated in the genesis of cortical potentials (Pirch et al., 1983), the cholinergic antagonist atropine sulfate was injected in at 0.2 or 0.3 mg/kg on Tuesday and Friday for two weeks. Saline was administered on Thursday. Monday was considered a retraining day following the weekend, and Wednesday a post-drug recovery session. Recordings were obtained on all weekdays. Because atropine severely disrupted behavioral performance, there were few trials on which to base evoked-potential averages, so we are in the process of developing a program to average across test sessions. In addition, methyl atropine, which does not readily cross the blood-brain barrier, is now being administered to determine the extent to which the behavioral disruption was some consequence of peripheral mechanisms (e.g., alteration of the taste of the reinforcement).

STUDIES AT STANFORD UNIVERSITY

This section is divided into two parts. The first part deals with studies that were in progress at Stanford University (SU) when Air Force Contract F49620-82-K-0016 to SRI became effective, studies that could be completed because of funds provided to SU from that contract. The second part describes new studies undertaken with the aid of the SRI contract in conjunction with subsequent funding to SU from the Office of Naval Research. Both parts describe experiments undertaken as an aid in understanding brain function in cognition by analyzing the electrical potentials evoked in monkeys while they are solving problems.

Part I: Automatic vs. Controlled Processing

Four monkeys were trained to respond in a variety of cognitive tasks in a computerized testing device, the Discrimination Apparatus for Discrete Trial Analysis (DADTA). Various forms of this device have been successfully used since 1960 to train monkeys to solve problems (e.g., Cutcomb et al., 1971). The current version consists of an Apple II color graphics microprocessor-controlled television display fronted by nine individual translucent panels and a liquid-reinforcement delivery system. This version allows the recording, by a PDP 11/34, of event-related brain electrical potentials to be collated with the recording of presses of a panel and with the presence or absence of a reinforcing event.

Three different displays were presented to the monkeys. One display consisted of a green square appearing in pseudorandomized positions among eight red diamonds. Rewarding the presses of the panel on which the green square appears constitutes a simple task readily learned by the monkeys. This display (matched for identical luminance and contour among cues) is "disjunctive" because none of the features that differentiate correct from incorrect cues are present in the incorrect cues. Problem solution appears to be independent of the number of background cues, suggesting that solution proceeds by virtue of parallel processing in a fairly automatic fashion.

A second display consisted of a green square appearing in pseudorandomized positions among green and red diamonds and red

squares. Again, the displays were matched for luminance and contour. Now, however, the features that distinguish the correct cue are also present in the incorrect cues. Reward is determined by the "conjoining" of both greenness and squareness in the green square. Solution of this problem is sensitive to the number of background cues and is more difficult than in the disjunctive task. Reaction times are longer, suggesting that serial search of the display occurs.

The monkeys were tested daily with a trial-to-trial mix of the disjunctive and conjunctive displays. Each monkey had implanted some twelve bipolar electrodes, which recorded the electrical activity evoked by the displays and the monkeys' responses to those displays. Electrode sites were: primary visual cortex, prestriate cortex, posterior inferotemporal cortex, anterior inferotemporal cortex, parietal cortex, precentral motor cortex, and far frontal cortex. Recordings were bipolar from surface to depth (approximately 2 mm).

Because the variables "disjunctive" and "conjunctive" were confounded with task difficulty, a third display set was devised in which the number of features defining the background cues was increased without, however, replicating the features that defined the correct cue, which remained the green square. Thus, the background cues consisted of white circles, red diamonds, and blue triangles. The task consisting of this disjunctive display did prove to be more difficult than the original disjunctive task and the difficulty, as measured by number of trials to learn, was approximately the same as that of the conjunctive task.

On some days, the more difficult disjunctive task was presented to the monkeys in a mix with the easier disjunctive task, and on other days in a mix of trials with the conjunctive task. Brain electrical recordings were again made and collated with the record of the behavioral data.

A preliminary analysis of the data was based on dividing the recorded epoch of one second into 4-msec bins and performing an analysis of variance for repeated measures with latency bin and cortical location as the independent variables.

This preliminary analysis showed that when the features that characterize the displays are matched for color, luminance, and contour, no differences are obtained between the disjunctive and conjunctive task performances in the potentials evoked in the primary visual cortex. Differences are recorded, however, in both inferotemporal and far

frontal locations and these differences appear in the later (300 to 500 msec) portions of the recorded potential changes.

The analysis also showed that increases in the difficulty of the task produced by increases in the number of features in the display resulted in differences in the potentials evoked in the primary visual cortex as well as those recorded from the inferotemporal and the far frontal cortex. Thus, the preliminary pass through the data suggest that the number of features being processed is reflected in the electrical activity of the primary visual cortex, whereas processing of tasks more difficult involves the inferotemporal and far frontal intrinsic portions of the brain.

More sophisticated analyses were not possible at the conclusion of these experiments because of limited funds and facilities. On the basis of these preliminary results, however, support for further research was obtained from the Office of Naval Research.

Part II: Subcortical Events Related to P300

Background

Of the several transient potentials of the brain associated with the perception and processing of environmental events, the P300 "component" (a complex of late positive waves) is the most clearly associated with cognitive events. This "component" seems to reflect only the general-information properties of stimuli and is uninfluenced by informationally irrelevant physical characteristics or by specific behavioral response requirements (Pritchard, 1981). These characteristics have made the P300 complex particularly relevant to the evaluation of workload, to the general field of biocybernetics (e.g., Donchin et al., 1982), and to clinical research on cognitive disorders (Hillyard and Kutas, 1983). Consequently, an interest in obtaining a more complete understanding of the intracerebral sources of the P300 complex has developed (Galambos and Hillyard, 1981). However, to date the results of research provide only hints about the electrogenesis of the P300. For example, Halgren et al. (1980) recorded P300-like activity in amygdala and hippocampal gyrus, Wood et al. (1980) noted the lack of polarity reversals of P300-like events in depth recordings above the hippocampus, and Okada et al. (1983) concluded from magnetic field recordings that the P300 is generated in anterior hippocampus. On the other hand, Johnson (NIMH, personal communication) has recorded the P300 complex from human patients with hippocampal lesions, and Yingling and Hosobuchi (1984) presented evidence for a dorsal thalamic generator.

Clearly, there is little concrete evidence localizing the sources of the P300 phenomenon, and invasive studies in animals are necessary to clarify this issue.

Surgery

Three monkeys were subjected to surgical procedures for this study. One monkey was used to explore the use of Bowden's technique (unpublished manuscript) to improve the accuracy of placing deep electrodes. Two monkeys were implanted with an array of electrodes without using Bowden's corrections. In Macaca fascicularis the relationship between internal brain nuclei and the bony structures used in the stereotaxic coordinate system are highly variable. Internal brain structures can deviate as much as 1/2 cm from the locations presented in an atlas. Bowden noted that the accuracy of electrode placements could be greatly improved by injecting an X-ray opaque dye into the lateral ventricle and visualizing the anterior and posterior commissures. Coordinates could then be derived for each animal.

This procedure was attempted in one monkey. The monkey was given ketamine HCl (15 mg/kg) as a preanesthetic; the head was shaved and cleaned and placed in the stereotaxic frame. Halothane was given to effect. The skin was incised and retracted. The underlying fascia was incised and retracted to expose the top of the skull. The periosteum over the area to be drilled was removed, anterior 17.0 mm from Horsley-Clark 0. At this location a small hole was drilled through the bone, 1.5 mm lateral to the midline. The dura was exposed and incised and a small cannula was introduced through this hole into the brain. At 16 mm into the brain, cerebral spinal fluid was seen to flow from the cannula with slight negative pressure. A portable X-ray machine was positioned 30 inches from the monkey. Matrizamide, a water-soluble X-ray dye, was injected into the ventricles through the implanted cannula and the X-ray shots were taken as the dye was being injected.

The resultant X-ray film clearly outlined the lateral and third ventricles. The anterior commissure was visible as a protrusion near the base of the third ventricle, anterior and dorsal to the pituitary stalk. The posterior commissure was much harder to visualize. The contrast outlining the skull was not sharp, demonstrating some movement of the X-ray gun. A better system of fixing the X-ray source will have to be found. An X-ray exposure 30 inches from source to film gives a skull magnification of 1.2. A slightly higher magnification of the skull can be gained by moving the source of the X-ray further from the skull. This might help to increase the visibility of the posterior commissure. An exposure time of 1/2 second longer would also help to

visualize this structure. This is especially true for small monkeys (3 kg or less). However, this emphasizes the need for a better arrangement of holding the X-ray source. A ruled grating should be placed between the film and the skull such that the X-ray film would have imposed on the exposure an accurate grating to measure distance of the nuclei from the cannula and the anterior commissure. A pair of proportional dividers would then allow an accurate representation of the scale of the film to the sections in Samantha and Bourne's atlas. More pilot work was deemed necessary for use of this technique, which was not used as a guide for implanting electrodes in the two monkeys currently in the program.

Two monkeys were prepared for implantation of a bilateral symmetrical array of electrodes in deep structures of the brain across the cortical surface. Each animal was prepared for sterile surgery with a preanesthetic dose of ketamine hydrochloride (15 mg/kg); the head was shaved and cleaned, and the monkey was intubated. Halothane was given to effect, and the monkey was placed in a Kopf stereotaxic frame. Transcortical electrodes were placed in the prefrontal, premotor, temporal, parietal, and occipital areas. A vertical bundle of four electrodes each was placed in the head of the caudate, amygdala, lateral thalamus, and hippocampus. The electrodes were cemented in place with dental cement. On hardening of the cement, the electrodes were crimped to a 30-pin connector (one connector for each hemisphere). Two of the vertical electrode arrays, in amygdala and hippocampus, surrounded a central cannula, and these cannulas were brought out to small metal holders cemented to the skull. (These chemodes are used to infuse pharmacologic agents.) The electrode connectors and chemode holders were then embedded in dental cement. When the dental cement was dry, the scalp wound was freshened and dental debris was removed. The wound was cleaned and a topical bactericide was applied. Where necessary, two sutures were placed to close portions of the skin wound. The monkey was then returned to its cage for recovery. A regimen of antibiotic (chloramphenacol, 50 mg/kg) was given the monkey for a 10-day period after surgery.

Procedures and Results

Four monkeys have been placed in a training regimen. All monkeys will accomplish a two-part program--a pretraining or shaping phase and an experimental phase. Two monkeys have been trained in the general shaping phase and have proceeded to the general experimental phase. The other two are nearing the completion of the general shaping phase and should be ready for surgery during July 1984. Each monkey is considered shaped when the monkey can generate 85% correct responses over ten consecutive days.The monkeys respond to a green square, which changes

positions randomly. During a "passive" oddball paradigm, the square will be red on various proportions of the trials. Subsequently, an active discrimination task will be implemented. The monkey is under a 24-hr water-deprivation regimen. The monkey receives 1 ml of liquid Tang® per correct response and is given one hour of water after completion of the experiment and food ad lib. Behavioral parameters are printed after the end of the session.

The two monkeys that have had surgery are currently being run in the standard experimental program, which calls for the monkey to make 100 correct responses over a day's run. The location of the stimulus is under a Gellerman series and is sufficiently long that the monkey cannot learn the sequence. The Gellerman series is changed daily. A variable intertrial interval is used to ensure that the monkey cannot anticipate presentation of a trial. A 4-second EEG epoch is obtained; each trial starts 250 msec before the stimulus appears and lasts through the 4 seconds.

Significant difficulty was encountered in the amount of 60-cycle noise present in the EEG signal, and it is likely that a set of high-impedance amplifiers will be required as interface between the animal and Grass amplifiers.

PLANS FOR THE COMING YEAR

The five male cynomolgus monkeys now being studied will be further evaluated with respect to the effects of other pharmacologic agents—(e.g., dopamine agonists and antagonists) to determine whether we can elicit the caudate positive slow potential previously observed.

The female stump-tailed macaques now in quarantine will also be studied. To facilitate their training while the other monkeys are being tested, a Commodore VIC-20 microcomputer is being programmed to present stimuli and record behavioral responses. Because of problems encountered with the use of sharpened pipettes for electrodes, we plan to use the original unsharpened design in the stump-tailed macaques to insure that all conditions are comparable to earlier studies wherein extremely robust slow potentials were observed, including large responses in the caudate. Our impression, supported by the opinions of several veterinarians, is that the cynomolgus monkey is not as intelligent as other varieties of macaques. We expect to observe the caudate response in our stump-tailed macaques, and this replication might imply that the possible species (or sex) difference in performance/intelligence is related to activity in the striatal system.

LIST OF PROFESSIONAL PERSONNEL

Charles S. Rebert, SRI International

Michael B. Hennessy, SRI International

Karl H. Pribram, Stanford University

Merle M. Prim, Stanford University

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