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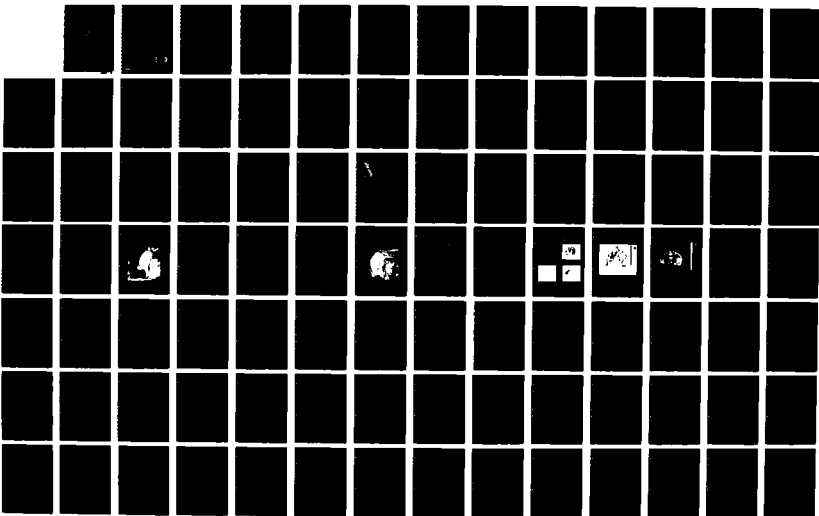
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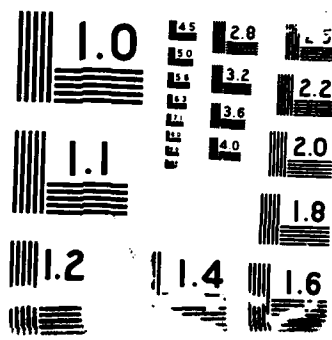
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NEUROPHYSIOLOGICAL BASES OF EVENT-RELATED POTENTIALS

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By: Charles S. Rebert
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Attention: Dr. Alfred R. Fregly
Program Manager

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Approved by:

Gordon T. Pryor, Director
Psychobiology Department

Masato Tanabe
Acting Executive Director
Life Sciences Division

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In order to more fully understand the physiological and psychological significance of event-related brain potentials (ERPs), cortical and subcortical recordings were obtained from monkeys performing an operant conditioning task (cued reaction time). Five groups of 3-to-5 monkeys each were studied over a period of five years to examine several important issues—distribution of ERPs in the brain, neurochemical mediators of ERPs, homology of ERPs across species, relationship of ERPs to associative conditioning, and the effects of varying signal and non-signal proportionalities. The region of the substantia nigra generated large and consistent transient and steady potentials and exhibited cue discriminations, in terms of amplitude, when other brain regions did not. Other subcortical areas, including the reticular formation, n. basalis of Meynert, and red nucleus exhibited waveforms similar to the nigra. ERPs from some placements, especially the nigra, in some monkeys increased in amplitude.					
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when the warning stimulus was made a rare event. It seems clear that a complex intracerebral system mediates the generation of scalp-recorded ERPs. Chemical (MPTP) inhibition or destruction of the pars compacta region of substantia nigra in three monkeys produced Parkinsonism and a lengthening of movement time with less effect on initiation time, and decreased the amplitudes of ERPs in the nigral region and the N2 component of premotor cortex. The nigra-striatal dopaminergic pathway is involved in preparatory set. Behavior was disrupted by cholinergic antagonism whether or not the drug crossed the blood-brain barrier, suggesting caution in the interpretation of the effects of systemically administered drugs on ERPs. There are several similarities between ERPs in monkeys and humans, but a variety of differences as well--preparatory set may be a more encephalized process in humans than in monkeys.



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INTRODUCTION AND BACKGROUND

A. 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 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.

B. Event-Related Brain Potentials

The only direct indications of brain function routinely available to the psychophysiolgologist 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 psychophysiolgologists 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.

C. 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.

D. 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.

E. 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 hyperpolarization 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 (SPs) 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 electrotonic 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.

F. 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?
- Development of ERP changes during associative conditioning. Do ERPs change systematically as an organism acquires information? Are rates of development the same in all areas of the brain? Can ERPs be used to study the differential involvement of different brain structures in associative conditioning?
- 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?

In this report we have addressed several of these issues. Recordings were made from a variety of brain structures to determine which structures are involved in the cued RT task. Cholinergic synapses were manipulated by the administration of atropine and of the nigra-striatal dopaminergic projection by neurotoxic (MPTP) lesion of the pars compacta region of the substantia nigra. Preliminary examination of intracerebral dynamics was made by the application of Neurocognitive Pattern Analysis (Gevins et al., 1985), and experimental manipulations (e.g., amount of muscular effort required to respond) were carried out to determine whether the monkey's CNV would react like the human's. In addition we examined SP acquisition functions and carried out a preliminary study of SPs (Bereitschafts/readiness potential) related to self-paced voluntary responding.

G. General Rationale for Electrode Placements

1. Epidural Electrodes

The cued RT task, which was the main focus of interest in this work, is logically similar to delayed response paradigms that have been extensively used in the study of higher brain functions and that are performed poorly by monkeys with lesions in the frontal areas of the cerebral cortex (Warren and Akert, 1964; Pribram, 1975; Divac, 1972; Fuster, 1980). The frontal mediation of such tasks naturally dictates an interest in recording ERPs from the frontal lobes in the cued RT task. This interest is supported by data on the scalp distribution of CNVs in humans indicating a frontal focus (see Tecce, 1972, for review) and direct recordings from monkeys that reinforce findings from human studies (Low et al., 1966; Borda, 1970; Donchin et al., 1971; Rebert, 1972; McSherry and Borda, 1973; Hablitz, 1973; Stamm and Rosen, 1969). Because the frontal lobes do not, obviously, function in isolation from many subcortical structures, recordings from those subcortical regions most intrinsically related to the frontal lobes must also be obtained to meaningfully evaluate ERPs associated with performance of the RT task.

Although many studies of the human CNV using scalp-recording techniques imply that the potential is generated primarily in regions anterior to the central sulcus and that there may be several major generators (Jarvilehto and Fruhstorfer, 1970), such investigations are greatly limited in their usefulness for making topographical distinctions because of the gross distortions and confounding of cerebral potentials by skull and overlying tissues. On the basis of intracerebral recordings from human patients, Walter (1968) suggested that CNVs occur patchily in the frontal cortex and may sweep from anterior to posterior regions of the area.

In macaque monkeys performing the cued RT task, CNV-like slow potentials have been recorded from the motor strip, premotor cortex, and prefrontal cortex (e.g., Borda, 1970) but not in postcentral areas (Borda, 1970; Donchin et al., 1971), although postcentral CNVs have been recorded in the squirrel monkey (Boyd et al., 1979). The data from macaques are consistent with the notion that there are at least two independent generators localized in the motor strip and premotor cortex. McSherry and Borda (1973) have suggested that the region of the arcuate gyrus is also a particularly robust generator of CNVs. Stamm and Rosen (1969) recorded slow negative potentials in the prefrontal cortex of monkeys performing a delayed-response task. These several investigations of CNVs in monkeys used a relatively small number of electrodes, and each study involved electrode placements different from those in the other studies; hence it is difficult to draw definite conclusions from them about the relative strengths and numbers of CNV generators in the frontal lobes. In our studies we investigated the premotor, motor, and supplementary motor areas.

2. Depth Electrodes

Major subcortical afferent connections of the prefrontal lobes (Fuster, 1980) include the medial dorsal nucleus (MDN) of the thalamus (the primary thalamic projection), the ventral anterior thalamic nucleus, and nonspecific midline thalamic nuclei. The MDN, in turn, receives major inputs from the reticular formation, amygdala, prepyriform cortex, and inferior temporal cortex. There are three major divisions of the MDN that project to different parts of the frontal lobes--pars paramellaris to the arcuate region, pars parvocellularis to the dorsal convexity, and pars magnocellularis to the orbital cortex. Interruption of the pathways that interconnect thalamus and prefrontal cortex (anterior thalamic radiation and inferior thalamic peduncle) interferes with the generation of cortical SPs in cats (Skinner, 1978). Prefrontal efferents project primarily to the amygdala (orbitofrontal origin), hippocampus (dorsolateral origin), and basal ganglia (especially to the caudate nucleus). Orbital and dorsolateral cortices project to ventrolateral and anterodorsal portions of the caudate, respectively.

The primary thalamic relay to the premotor cortex arises from the ventral anterior nucleus, and to the motor cortex from the ventral lateral nucleus. Efferents from the premotor area extend to the cingulate gyrus, substantia nigra, putamen, globus pallidus, and red nucleus. Motor cortex efferents are primarily to spinal motoneurons and cranial nerve nuclei.

In previous work on the cued RT task we have observed SPs in a variety of subcortical nuclei of monkeys (Rebert, 1972, 1976a, 1977), and other investigators have recorded them from human patients (see Rebert, 1976b, 1977, and 1980b for summaries). The areas from which recordings have been obtained include the midbrain reticular formation, caudate nucleus, specific and nonspecific thalamic relay nuclei, amygdala, hippocampus, and hypothalamus. Of considerable interest with respect to homologies between animals and humans is the fact that the waveshapes, polarities, and intracerebral distributions of "CNVs" were nearly identical in monkeys (Rebert, 1972) and the human patients studied by McCallum et al. (1973).

That the SPs recorded from the thalamus are probably causally related to those appearing in the cortex is supported by the fact that SPs did not occur in the pulvinar of three monkeys with placements in that nucleus (Rebert, 1972), which projects to the postcentral cortex, where CNVs are minimal or absent in monkeys.

Because of their intrinsic relationships to cortical regions and demonstrated ability to generate ERPs in the CNV paradigm, the thalamic nuclei are of special interest for study to determine to what extent the

thalamic and cortical waveforms co-vary and whether they are affected similarly by various experimental manipulations.

Cortical relationships to the caudate nucleus, the caudate's involvement in a variety of motoric, motivational, and cognitive functions, (Divac, 1972) and appearance of SPs there in both man and monkey (McCallum et al., 1973; Rebert, 1972; Tsubokawa and Moriyasu, 1978) indicated that structure as one of primary interest. A major subcortical structure influencing the caudate is the substantia nigra, which projects both dopaminergic and cholinergic fibers to the caudate, the former of which appears to exert an inhibitory effect on the caudate. Because the caudate also exerts an inhibitory influence on the cortex (Buchwald et al., 1967) and exhibits a positive SP in the cued RT task [which probably represents inhibition of the caudate itself (Rebert, 1973a)], we have conjectured previously (Rebert, 1972) that the decline of caudate activity might be causally related to generation of the cortical CNV by way of disinhibition of the cortex. The substantia nigra was expected to play a role in that process and we expected to observe negative SPs there in association with increased neural activity.

Because of the patterning of positive and negative SPs observed in previous studies (Rebert, 1972, 1977), we also conjectured, in line with Routtenberg's (1968) notion of a two-arousal system (nonspecific reticulothalamic and limbic), that the two systems were reciprocally active in the cued RT task (Rebert, 1977). Therefore, some limbic structures were also of interest to us--e.g., the hippocampus, amygdala, anterior thalamus and septum. The hippocampus was especially interesting because of recent suggestions that it may be a major site of generation of the P300 (Wood et al., 1986; Halgren et al., 1980). These observations of P300-like waves in the hippocampal region and amygdala raise a question concerning the extent to which the surface-recorded P300 is actually a volume-conducted reflection of activity in deep structures.

Many types of experimental manipulations suggest that the CNV reflects a general state of activation, presumably mediated by activity in the non-specific reticulothalamic "arousal" system (e.g., Tecce, 1972). However, whereas we have recorded large SPs in such areas from the monkey, there are several dissociations of those responses from the cortical potentials, thus complicating the interpretation of the role of the reticular formation in causing or modulating cortical SPs (Rebert, 1977). Because of this consideration and the very general role that the midbrain reticular formation (MRF) plays in brain function, we felt that it must be further studied in the cued RT task.

The specific regions of the brain from which we recorded are described later for the various groups of monkeys examined.

H. Summary of Groups

Five groups of monkeys were used on this project. The first was composed of six male cynomolgus monkeys, one of which proved intractably vicious and impossible to train. Some of these monkeys were studied over the course of three years and three of those were used in a terminal study of MPTP-induced nigral lesions. The second group comprised six female stump-tailed macaques. One of these dislodged her head plug two months after surgery so no data were obtained from her. Another developed an infection beneath the acrylic head plug and was sacrificed. The remaining four were studied for seven months and sacrificed. Group 3 consisted of four female rhesus monkeys. Three of these received electrode implants; one did not in order to continue studies of magnetic resonance imaging (MRI) with that monkey. Group 4 comprised three male rhesus monkeys that were to be used to examine the effects of cerebellar manipulation on ERPs, but this study was not completed and the monkeys were assigned to another project. The fifth group was composed of five male rhesus monkeys prepared with electrodes for a long-term drug study. They were used on this project before exposure to the drug in order to obtain additional information about electrophysiological changes related to associative conditioning.

PREPARATION OF FACILITIES AND EQUIPMENT

A. General Stages of Preparation

The SRI laboratory facility used for this research was developed in two stages. First, equipment previously used for similar purposes, including an Iconix Logic unit and Linc-8 computers, was configured so that preliminary training of six monkeys could be undertaken early in the project period. Subsequently, a DEC LSI-11/23 computer system, purchased by SRI for use on this project, was installed, and software and hardware elements were configured to provide more automatic and comprehensive experimental control, data acquisition, and analysis than were available with the older equipment.

B. Iconix Logic Unit for Preliminary Training of Monkeys

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 (1 kHz or 3 kHz), 100 msec and 72 dB (re: 20 $\mu\text{N}/\text{m}^2$), 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 1 ml of an orange-flavored drink (Tang®) for each bar-press made during the 12 sec that the IS remains on (usually a total of 15-20 ml).

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).

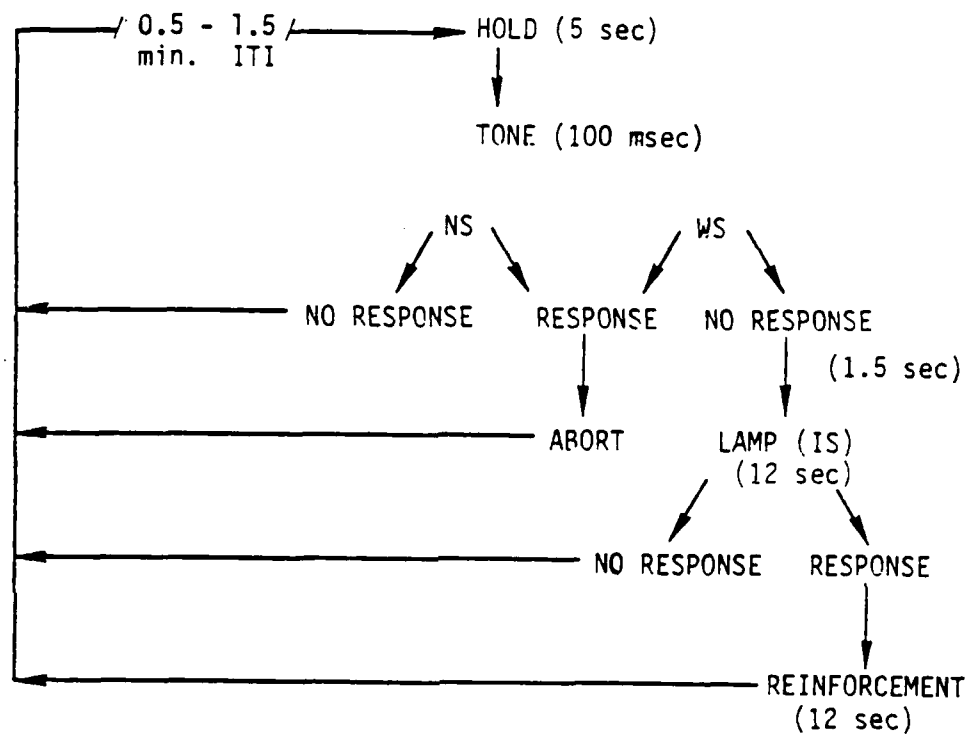


Figure 1 Schematic illustrating technique used to establish a cued discriminative reaction time task in the monkey

NS = neutral stimulus; WS = warning stimulus;

IS = imperative stimulus

ITI = intertrial interval

The many contingencies in this paradigm required an elaborate and fairly time-consuming programming of the Iconix unit. For example, trials are not initiated unless the animal has maintained a fixed position of the right hand for at least 5 sec, the availability of reinforcement is contingent on the presence of the IS, trials are aborted if a premature response occurs, and the IS terminates if a response is not made quickly enough. The logical configuration of this system is presented in Appendix A.

Associated with the Iconix unit were three counters that measured reaction time and counted the total number of bar presses and reinforcements. Liquid was delivered through a solenoid, which gated a gravity or pressurized flow system so that 1 ml of juice was delivered with each bar press.

Several limitations of this preliminary system mandated an upgrading of the facility. These limitations included the following:

- A hard-wired system is inherently inflexible; therefore, new wiring configurations have to be done to implement even trivial experimental changes.
- The logical control system was only indirectly tied to the electrophysiologic data-acquisition system; automatic tagging of data, automatic sorting, and selective averaging could not be accomplished.
- Behavioral data had to be tabulated manually.
- Tone frequencies had to be changed manually, requiring a manual system for keeping track of WS and NS trials.
- Summary statistics of behavioral data could not be obtained immediately after a test session.
- The gravity and pressure flow systems were cumbersome and messy.
- Obsolete Linc-8 computers were inadequate for modern requirements of data analysis.

Consequently, SRI purchased the LSI-11/23 computer system described below for use on this project.

C. LSI-11/23 Computer and Related Components

1. Hardware Configuration

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 was used to store programs and, temporarily, single-trial data during testing. At the end of the test session, the single-trial data were transferred to digital tape. The floppy discs were used to store waveform averages and summary statistics of behavioral data for the session. The summary statistics were printed on the TTY-43 printer at the end of the session, and waveform averages were plotted on the HP plotter. Listings for the programs developed for this system are provided in Appendix B.

2. Software Development

a. CNV Paradigm

A program was written to implement the logical paradigm shown in Figure 1. The program was designed to provide all record-keeping and summary statistics of behavioral data and to execute the paradigm while obtaining the ERP data. Thus, the parameters of stimulation and recording, sampling rates, artifact-reject criteria, experimenter remarks, ratios of WS and NS trials, date, experimental conditions, and so on are stored with each set of waveforms so that manual notations and paper records are minimal.

Program "CNV" implements a cued RT paradigm by controlling the sequence of stimulus events, acquiring data from each of up to 8 electrode input channels, monitoring responses by the subject (S) and input from the experimenter (E), and labeling and storing all results on Winchester and floppy disks.

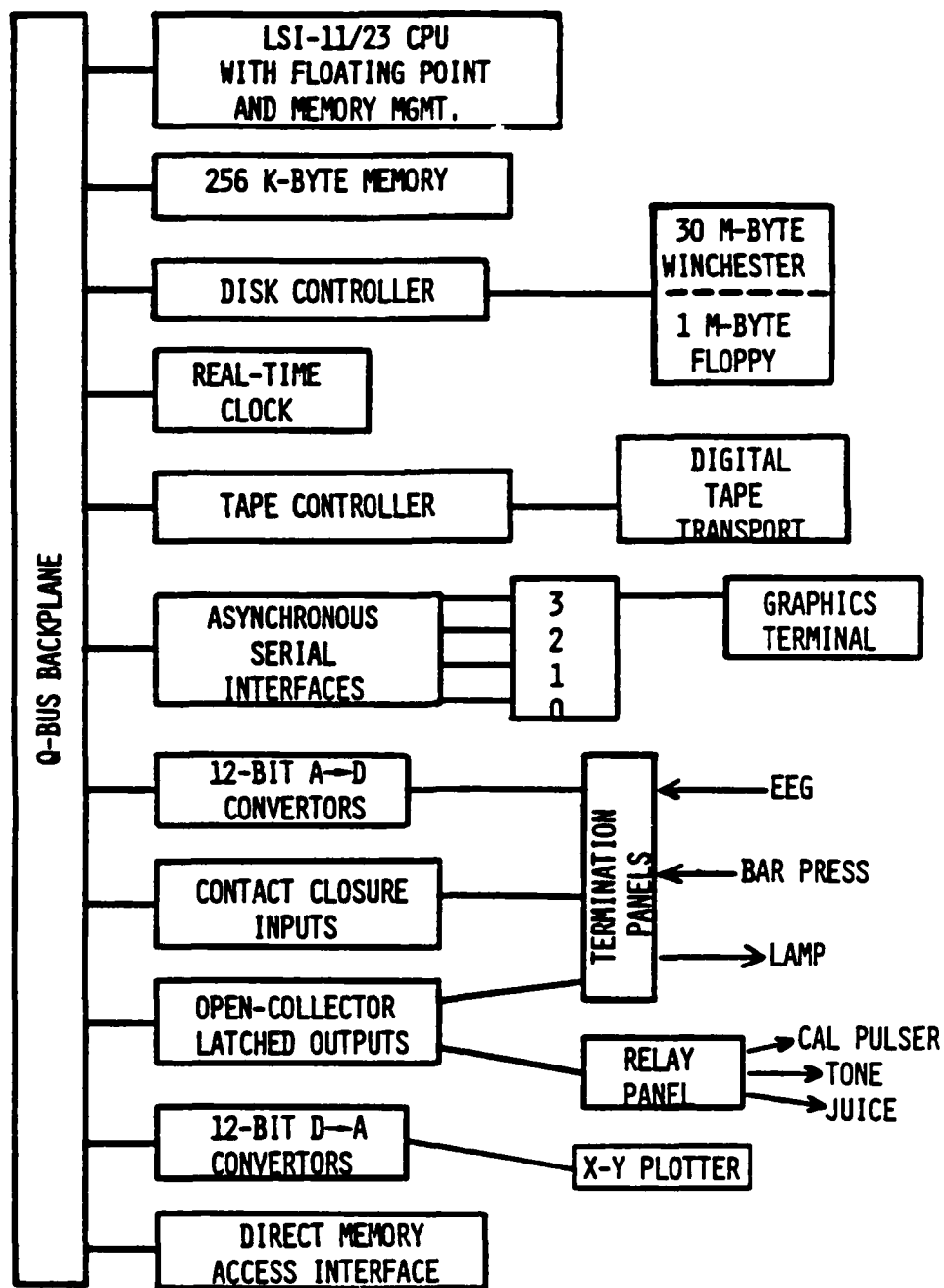


FIGURE 2 SCHEMATIC OF COMPUTER SYSTEM

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.

Input parameters at the beginning of the program are:

- Name of the subject
- Date
- Experimental condition and day within the condition
- Channels that are to be sampled.
- Probability that each trial will have a WS rather than a NS tone
- Longest RT following light (IS) onset that will still be rewarded
- Smallest voltage that will be considered an "artifact"
- Channel to be automatically displayed at the end of each trial
- Amplitude of the calibration pulse for each channel
- Interval between tone onset and light onset
- Duration of the IS light
- Speed mode--i.e., whether optional intertrial (ITI) activities are conducted.

Trial-by-trial results are reported on the terminal screen, including the number of bar presses by S, reaction time, duration of ITI, and number of ITI responses. The program logic considers each trial to consist of seven consecutive "phases," demarcated by experimental events: onset and offset of a tone, onset of the IS light, termination of sampling, etc. To time both the sampling (one set of A-D conversions every 12 msec; 400 consecutive sets per trial) and the stimulus events, a clock is set to overflow once per millisecond. Every 12th overflow, sampling is executed and the obtained values are stored in a buffer. Between samples, a contact closure register is polled to see whether any bar presses have occurred. If S presses the response bar while the IS is on, then the metering pump is operated to provide a juice reward to S. Bar presses at earlier times during a trial are tabulated according to the trial phase in which they occur; also, they cancel the IS and the opportunity to earn juice. If there is a contact closure--on a separate circuit--due to E rather than S, an ongoing trial is aborted.

On WS trials, unless S has bar-pressed prematurely, the IS appears during Phase 6 and the reaction time to bar press is recorded. (On NS trials, although no IS is presented, responses are nevertheless recorded for all seven phases of the trial.) If a bar press happens within a 3000-msec, "limited-hold" interval after IS onset, the IS remains on for a total of 12 sec and each subsequent bar press is rewarded. If no bar press is made in time, the IS ends and the ITI begins. At the end of each trial, E has a chance to insert a comment that will be stored with the data of the previous trial.

To detect bar presses during the ITI, the contact-closure register is set so that all bar presses are noted (including when they occur), meanwhile enabling the system to perform other tasks. Data from the foregoing trial are screened for artifacts, and their maxima, minima, and DC levels are computed. All this information, along with E's comments, settings of all parameters, and the waveform data, is written--as a single record--into the session's file on disk.

Waveform data are added into an averaging buffer; separate buffers are used for data from WS and NS trials. However, if there were too many artifacts or if the trial was aborted (due to premature bar press, too slow RT, or E's intervention), then the data are not added to these buffers. Unless E has opted for "high-speed" mode (short ITIs), waveform data from one of the channels is displayed on the graphics terminal. E can opt to review single-trial data from any channel or cumulative averages for WS or NS on any channel. When the sample sizes for WS and NS trials are adequate (e.g., $n \geq 15$), the session's data are saved as a file on the Winchester disk and a summary is prepared of the statistics and parameters for the session, including:

- . Total number of trials
- . Sample sizes for WS and NS trials
- . Number of trials aborted for each possible reason
- . Mean RT
- . RT standard deviation
- . Mean number of reinforcements
- . Total number of bar presses
- . Number of bar presses during ITIs
- . Number of artifact-rejected trials
- . Mean number of artifact-rejected trials
- . Mean number of deviant data per artifact-rejected waveform per channel.

The WS and NS averages, along with the session's parameters and statistics, are stored as a file on floppy disk. Finally, a session summary and a listing of E's comments are output on a line printer.

b. P300 paradigm

A program was written to carry out preliminary studies of the P300 evoked by tones of different frequencies in a "passive" paradigm--i.e., no behavioral responses are required. However, when the program was used with

human Ss, the Ss were asked to count the rare tones because we were primarily interested in verifying the adequacy of the program.

Program "P300" implements a P300 paradigm in which 100-msec tone pips are presented at a fixed rate (e.g., once per second). Differently pitched tones are included in each series; "common" tones occur more often than "rare" tones. No overt response by S is required.

Four channels of the A-D converter are used to sample potentials from various electrode sites. Each "trial" consists of an epoch of 1000 msec during which 400 samples per channel (four channels) are acquired, one set of samples every 2.5 msec.

Input parameters for this program are:

- . Percentage of common tones
- . Minimum value that will be considered an "artifact"
- . Amplitude of each channel's calibration pulse
- . Duration of recording epoch
- . Interepoch interval
- . Speed mode--i.e., whether optional activities occur between epochs
- . Number of the upcoming tone series
- . Pitch of the rare and common tones
- . Number of trials per average.

If the waveforms for some rare tone epochs are artifact-rejected, the series is continued until the sample size for the rare tone is adequate.

Following the completion of each tone series, there are a variety of options: to add more trials and extend the tone series; to write the data--along with parameter information--as a record in the session's file; to begin the next tone series; to list the current parameter values; to display either the common or rare tone averages (or the most recent single-trial data) for any of the four channels; to plot any of these waveforms on an X-Y recorder; to get a status report on the just-completed tone series; or to end the session.

As each set of data is written to disk, a summary of the experimental conditions is printed out. It includes items such as:

- . Date and name of subject
- . Number of preceding tone series

- Name of data file on floppy disk
- Amplitudes of calibration pulses on each channel
- Common vs. rare tone sample sizes
- Total number of trials
- Numbers of common vs. rare tones presented
- Smallest voltage value to be deemed an "artifact"
- Number of samples artifact-rejected
- Time between samples
- Time between epochs.

c. Other Programs

Data analysis software was developed that enabled us to reopen any data file written during a CNV, P300, or other class of experiment, recall what conditions were employed, review the data obtained, and sort or analyze the waveforms as needed. Currently, we are able to display waveforms off-line on our graphics terminal and "score" the voltage values at any point along the waveform. Initially, we operated an analog X-Y plotter with our D-A converter to plot waveforms recorded during experiments and a line printer was used to print out textual information. With a graphics printer slaved to the terminal, we are now able to obtain hard copies of anything (text, graphs, bar charts, or waveforms) that can be displayed on the terminal.

"Averag" is a software system obtained from Neuroscience Systems (Dr. Robert Norman) that provides a series of programmable macro software routines that facilitate data collection and display on the LSI-11/23 (Exhibit 1). This system was used in our study of readiness potentials (see below) and for off-line summarization of data collected earlier on this project.

D. Verification of System Performance

Electrodes somewhat different from those used previously for recording subcortical slow potentials (SPs) from monkeys were employed (see General Methods Section B). Briefly, the pipettes were sharpened so that multiple units as well as SPs could be obtained, and the low-frequency filters on the EEG amplifiers (Grass Model 7P511) were modified to 0.01 Hz to allow measurement of SPs. Therefore, recordings were made from the lateral geniculate of one acutely prepared cat to check these items. Because of the fairly high electrode impedance, a major purpose of the check was to ensure that recordings without excessive noise could be obtained.

[illegible]

Change Level (F) PF1	1	(C) PF2	8	(M) PF3	9	(S) PF4	—
	7					(F)	
	4		5		6	(E)	9
	1		2		3	ENTER	
	0					(M)	

Change Level	Q1 PF1	Q1 PF2	Q1 PF3	Q1 PF4
7	8	9	0	1
Cursor Left	Cursor Stop	Cursor Right	ENTER	2
4	5	6	3	4
1	2	3	4	5
0	1	2	3	4

(010) 989-3968
5650 Columbus Ave.
Van Nuys, CA 91411

AVERAGE COMMANDS:

Any numeric expression
A channel number
Offset in a channel
A list string bounded by delimiters
List "x" or "x/y" or "x/y/z" or "x/y/z/w"
Bracketed arguments are optional
An RT-11 file name
See WISAP for complex argument list

CHANNEL DATA MANIPULATION:

ADD [c]	Add channel(s) to sum
ADN [c]	Add channel(s) (single precision)
ADI [c]	Add channel(s) selected ADI buffer
CDI [c]	Clear channel(s)
CSL [c]	Clear selected SUI buffer
CSS [c]	Clear selected SUI buffer
MNO [e]	Move one channel to another
PVS [e]	Put value into channel as offset
RIN [e]	Return average to DATA buffer
RES [e]	Reset from extended memory
SUB [c]	Subtract from sum
SER [e]	Serialize contents of two channels.

FILTERS/TRANSFORMATIONS

[illegible]

FFT AND SPECTRA

PARAMETER SPECIFICATION

Allocated buffer space	Alloc
Set number of active channels and ports	CHANS
Set sample timing parameters	TIME
Read timing table from file	TIME
Set sample rate in Hz	RATE

DATA ACQUISITION

DATA ACQUISITION	
AV n	Set up for average of n sweeps
CSM	Do continuous sample
SAM(c)	Sample one sweep at trigger
SM[c]	Immediate sample one sweep
STW v ...	Set up stimulus table
MM n	Set averaging resolution window

FILE NO

Close the N file	Close the S file	Close the X file	Close the Y file	Get next record	Get sum data from special file	Get sum record from X file	Get next record from Y file	Open the N file	Open the S file	Open the X file	Open the Y file	Save data N file with heading	Save sum buffer in special file	Save data X file	Save data Y file
closeN	closeS	closeX	closeY	getNextRecord	getSumDataFromSpecialFile	getSumRecordFromXFile	getNextRecordFromYFile	openN	openS	openX	openY	saveDataNFileWithHeading	saveSumBufferInSpecialFile	saveDataXFile	saveDataYFile

PLOT COMMANDS

Initial plot hard copy with options
Set up hidden line drawing
O topographic map
O landscape map
Set up various plot styles (Plot
Plot circle at CP with radius r
F4 viewport with color
Set text size
Turn on cursor
Draw to new location
Draw relative to 'CP'
Change pen color value
Change pen width value
Plot data in viewport
Set line type
Move to new location
Move relative to new location
Plot densely mapped vectors
Put text on graph
Set viewport location and size
Set PCB layout table
Set title block table
Restore viewport image
Save viewport image

DISPLAY COMMANDS

Command	Parameter	Description
Set display/prior channel(s) bias table	Set display 1st	Set display/prior scale value as 2 ⁿ
Set dynamic display heading	Set display/prior scale value as 2 ⁿ	Set display/prior scale value as 2 ⁿ
Send display cursor to the left	Send display cursor to the left	Send display cursor to the left
Send display movement of display cursor	Send display movement of display cursor	Send display movement of display cursor
Send display movement of display cursor	Send display movement of display cursor	Send display movement of display cursor
Increase display/prior scale value	Increase display/prior scale value	Increase display/prior scale value
Decrease display/prior scale value	Decrease display/prior scale value	Decrease display/prior scale value

RUN-TIME MODULES

LOAD THE RUN TIME MODULES

Load a run-time module
Run the loaded module and pick up arguments. Each module defines the argument(s) that it will use

PROGRAM CONTROL

DO	DO WHILE	DO UNTIL	DO WHILE	DO UNTIL
Branch on Equal	Branch on Not Equal	Branch on Equal	Branch on Not Equal	Branch on Not Equal
Branch on Greater Than	Branch on Less Than	Branch on Greater Than	Branch on Less Than	Branch on Less Than
Branch on Greater Than or Equal	Branch on Less Than or Equal	Branch on Greater Than or Equal	Branch on Less Than or Equal	Branch on Less Than or Equal
Branch on Not Greater Than	Branch on Not Less Than	Branch on Not Greater Than	Branch on Not Less Than	Branch on Not Less Than
Branch on Not Greater Than or Equal	Branch on Not Less Than or Equal	Branch on Not Greater Than or Equal	Branch on Not Less Than or Equal	Branch on Not Less Than or Equal
Branch on Plus	Branch on Minus	Branch on Plus	Branch on Minus	Branch on Minus
Branch on Unconditional	Branch on Unconditional	Branch on Unconditional	Branch on Unconditional	Branch on Unconditional

CC · statements · ELS · statements · END

If the condition is true then execute the first group of statements, otherwise execute the second group. The ELS and END are both optional since the end of the command line will terminate the clause.

II EQUATION

IF	Greater than or equal	IF	Greater than or equal
GT		GT	
IF	Greater than	IF	Greater than
GT		GT	
IF	Less than or equal	IF	Less than or equal
LT		LT	
IF	Less than or equal	IF	Less than or equal
LT		LT	
IF	Minus	IF	Minus
MINUS		MINUS	
IF	Not equal	IF	Not equal
NE		NE	
IF	Plus	IF	Plus
PLUS		PLUS	
IF	Divides IF ELSE clause (optional)	IF	Divides IF ELSE clause (optional)
ELSE		ELSE	
IF	Matches and IF clause (optional)	IF	Matches and IF clause (optional)
AND		AND	

JACROS

DEF name [v]	"test"
SET name [v]	"test"
TEXT name [v]	"test"
ED name	
ERASE name	Erase definitions at (or above) level
ERA name	Erase named definition
IS [v]	List definitions on terminal
IS [v]	Print definition(s) to current print file
PDF [v]	Trace error
TBT	Delete an RT, if any
DEL file	Do structure on RT, if device
NUR file	
NO-OLD	

COMMAND FILES

Use terminal as obyr agent
Take commands from a file
Return from an obyr file
Abort command file with error
NO "message"

UTILITY

Set a clock delay in 1/64th seconds	Turn on display	Used when testing
Turn on display	Enable copy/calc	Used when testing
Turn on display	Exit from Average and chain to 146	
Set terminal to immediate mode	Quit immediate mode	
Quit immediate mode	Stop process I/O	
Stop process I/O	Turn on V1 display	
Turn on V1 display	Decrement variable	
Decrement variable	Set variable to value	
Set variable to value	Set variable to value	
Set variable to value	SET the n	

TYPE/PRINT

PRINT	Print test string
PRINT "test"	Print test with newlines
PRINT	Type a test string and numbers
PRINT	Type out with newlines (TYP)
PRINT	Type (formatted) without newlines
PRINT	Close the print file
PRINT	Open a print file

AVERAGE FUNCTIONS

CHANNEL REFERENCES:

- Channel number
- Offset in channel (Optional - defaults to 1)
- Sample points (Optional - defaults to number remaining)

FUNCTION:

[illegible]

The cat was anesthetized with sodium pentobarbital (42 mg/kg, i.p.) and placed in a stereotaxic instrument. An incision was made in the scalp, and fascia was cleared from the skull. A small hole was drilled in the skull at coordinates appropriate for approaching the lateral geniculate nucleus (LGN), and a saline-filled pipette with a 100- μ tip was lowered into the LGN while flashes from a Grass PS-2 photostimulator were being presented.

We could not conveniently average the ERPs at this time, but multiple-unit activity comparable to that observed in earlier studies (Rebert, 1973b) was obtained and slow potential ERPs could be observed sufficiently frequently in the raw records to confirm the adequacy of the amplifier low-frequency modification. Thus, both slow and massed-unit responses were obtained through the same electrode and amplifier with adequate resolution, except that the 60-cycle filter had to be used for ERP recording.

Several human Ss were tested in both the CNV and P300 paradigms to evaluate the computer program performance as well as the amplifiers. Beckman Ag-AgCl discs were placed on the mastoids for reference and above and below the left eye for recording the vertical electrooculogram (EOG). A stretchable cap containing a conductive gel-filled tube attached to another Ag-AgCl disc was used to obtain vertex records. The forehead was grounded via another Ag-AgCl disc. The warning and neutral tones, the imperative stimulus (light), and the response manipulandum to be used with the monkeys were also employed to test the human Ss. The same tones were used in the P300 paradigm, and Ss were instructed to count the rare tone.

Figure 3 shows CNVs from two Ss; the first was tested with an inter-stimulus interval (ISI) of 1500 msec and the second with an ISI of 2500 msec. Recording was with one of the Grass 7P511 amplifiers modified to have a low-frequency cutoff of 0.01 Hz. These are very typical CNVs. The CNV in the long ISI exhibits some decay consistent with the amplifier time-constant shown in the lower part of the figure. We determined that this time-constant was consistent across the eight channels to be used with the monkeys. Examples from one S of P300 responses associated with several proportions of rare tones are shown in Figure 4. The inset shows a typical decline in N200-P300 amplitude as the proportion of rare tones increases.

After recordings from monkeys were instituted, it was necessary to construct a high input impedance preamplifier (Fox and Rosenfeld, 1972) to reduce 60-Hz line noise.

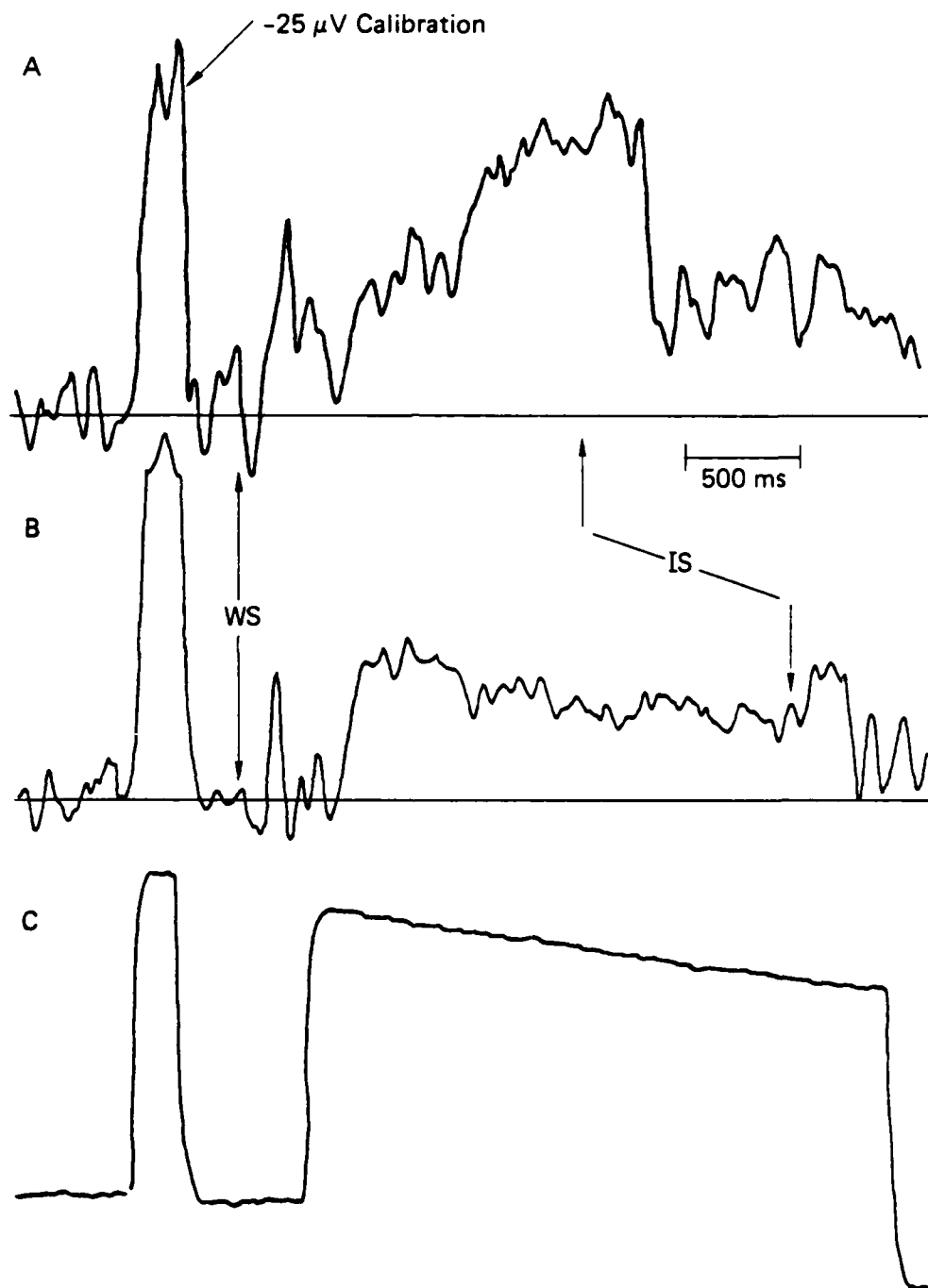


FIGURE 3 CNV AND SQUARE WAVE RECORDINGS WITH 0.01 to 100 Hz BANDPASS

A. CNV from one S with 1500 ms interstimulus interval. B. CNV from another S with 2500 ms interstimulus interval. C. Square wave showing time-constant of the recording system.

% RARE TONE

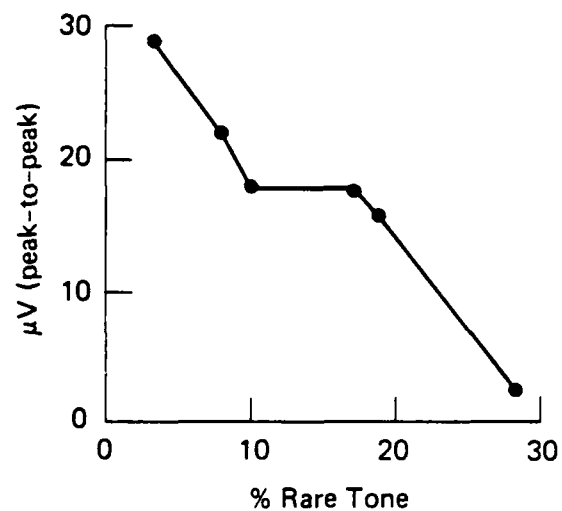
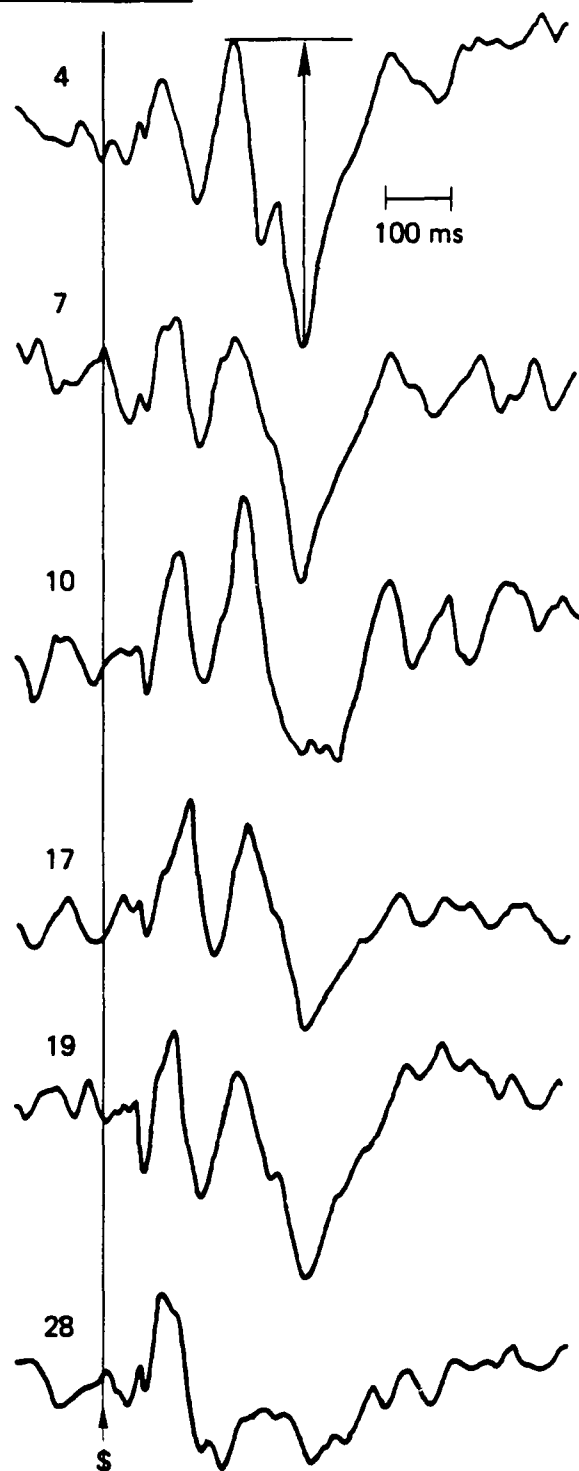


FIGURE 4 EXAMPLES FROM ONE S OF VERTEX POTENTIALS EVOKED BY RARE TONES IN AN "ODDBALL" TASK, AND THE PEAK-TO-PEAK P300 AMPLITUDE AS A FUNCTION OF THE PERCENTAGE OCCURRENCE OF RARE TONES

GENERAL METHODS

A. Animal Housing and Care

Monkeys were employed in these studies for both conceptual and practical reasons. First, the nature of the studies precluded their systematic pursuit in humans, yet the results have the most basic and clinical relevance if obtained from an organism with a brain like that of the human. The monkey was the most practical species to use, although its brain is less like the human than are those of the great apes. The recording and manipulative procedures, involving multiple glass pipettes and intracerebral cannulae, dictated the study of as large a brain as practicable to minimize the proportion of tissue disturbed by the implants.

The monkeys received high-quality care--for both humane and scientific reasons; healthy and highly motivated animals were required in order to obtain meaningful results. Their diet was certified monkey chow supplemented with fruit and fruit juice. The monkeys were housed in standard primate cages in a clean environment that was automatically kept at an appropriate temperature. Cages were rinsed daily and sanitized weekly. Appropriate anesthetics and analgesics were used during surgery or minor therapeutic maneuvers, aseptic procedures were followed during electrode implantation, and the monkeys were given the postsurgical care consonant with their needs. During training and testing a standard type of primate chair was used to hold the monkey, usually for periods of 15 to 90 min each day. The testing situation was not aversive, as evidenced by cooperation of the monkeys in working on manipulanda to receive positive reinforcement.

The animal care facilities occupy approximately 40,000 square feet, including 84 animal rooms and outdoor facilities. The areas for the laboratory animals are separated and self-sufficient and have individual air-conditioning systems, cage and bottle washers, autoclaves, and secluded storage and garbage rooms. Additional support units include feed-mixing and diet-preparation rooms, separate laboratories, incinerator, and a health support complex including separate quarantine areas. Our surgical suite for aseptic surgery consists of three rooms--one for sterilization of surgical instruments and surgeon scrubbing, a second for preparation of the monkey (e.g., presurgical scrubbing, placement of the saphenous catheter), and the surgery room itself.

Individual animal rooms are approximately 200 square feet each; they are air-conditioned at 21° to 24°C, with humidity of about 45%. Fresh-filtered, temperature-controlled air is supplied to each room via ceiling ducts at a rate of 10 to 15 room volumes per hour. Each room is individually light-controlled by a time clock; the light cycle in the room is 12 hours on and 12 hours off. The rooms have cement, epoxy-finished floors. Each room has a sink and recessed electric receptacles, and fluorescent light fixtures are suspended from the ceiling. An automatic water-supply system is provided for the animals. The walls and ceiling are surfaced with epoxy coatings and are resistant to cleaning chemicals.

Maintenance of and research practices with laboratory animals were in accordance with the requirements of the Public Health Service Policy on the Humane Care and Use of Laboratory Animals by Awardee Institutions, the Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training, and the Guide for the Care and Use of Laboratory Animals. SRI adheres to the Animal Welfare Act, as amended, and the regulations of the U.S. Department of Agriculture and state and local governments concerning animals used in research. SRI's animal facilities have been accredited by AAALAC since 1974, and are registered with the Department of Agriculture (Research Facility Registration No. 93-26). SRI also files assurance with the U.S. Public Health Service Office of Protection from Research Risks. SRI has a State of California Certificate of Approval to Keep and Use Laboratory Animals (#534), issued by the Department of Public Health. Each person who comes in contact with monkeys used at SRI has received appropriate training in the care, handling, and treatment of nonhuman primates and is involved in an Institutional Health and Safety Program requiring periodic examination for tuberculosis. The research described in this report was approved by SRI's Animal Care and Use Committee, the operation of which has been evaluated and approved by the NIH Department of Research Resources, Office of Protection from Research Risks.

B. Electrodes

Electrodes capable of simultaneously recording DC potentials, transient ERPs, and massed-unit activities were constructed of glass pipettes and cells housing commercially available sintered Ag-AgCl pellets. These were like the electrodes described by Rebert and Irwin (1973). The tips were sharpened to 100 μ by pulling 0.7-mm O.D. pipettes to very small tips and then, under a microscope, chipping away the tip to the 100- μ size. This was facilitated by first etching a 100- μ diameter platinum wire to a gradual taper and inserting it into the pipette. The wire provided a means of determining when the tip diameter was the right size. A short piece of shrink tubing was applied to the upper shank of the pipette to prevent its

slippage in the stereotaxic electrode carrier during surgery. The pipettes were then filled and sterilized by boiling in normal saline.

Electrode cells, which are placed over the top of the pipette during surgery, were constructed of 1-cm lengths of 4-mm O.D. glass tubing. One end of each tube was fire-polished to an inside diameter of 1 mm (just large enough to slip over the pipette). These tubes were half-filled with Agar-saline followed by normal saline when the agar had set. A Ag-AgCl pellet was then placed in the tube, resting on the agar, and the upper opening was closed with dental acrylic. These cells were stored in a refrigerator until used.

C. Surgical Procedures

Because no stereotaxic atlas was available for the size of cynomolgus monkey (Macaca fascicularis) being used, placements were estimated from atlases for M. fuscata (7.4 kg) and small M. fascicularis (3.5 kg) and from sections of M. arctoides from a previous study. These last sections were critical to a determination of placement depths because other atlases do not show the cortical surface, and the dura must be used for M. fascicularis because of extreme interanimal variability of brain placement with respect to the stereotaxic landmarks--auditory meatus and inferior orbit (Dubach and Bowden, unpublished manuscript).

Monkeys were deprived of food the night before surgery. Ketamine hydrochloride, a fast-acting nonbarbiturate anesthetic, was administered intramuscularly (i.m.) at a dose of 14 mg/kg, which was sufficient to heavily tranquilize the monkey for preparatory activities. A dose of atropine sulfate (0.05 mg/kg) was administered i.m. and the head and calves were shaved and cleansed. A catheter was placed in the saphenous vein, through which sterile saline was dripped at a rate of 16 drops/min--sufficient to keep the catheter clear and provide some hydration during the 4-5 hr of surgery. The monkey was then placed in the stereotaxic apparatus. The electrocardiogram and the electromyogram (EMG) of the right triceps were recorded. The EMG was used to monitor state of alertness, and 0.2 to 0.3 ml of sodium pentobarbital (65 mg/ml) was administered through the catheter as required. Typically, an infusion was required each half-hour. Rectal temperature was also monitored.

Muscle and fascia were cleared from the skull and the small blood vessels were cauterized. Then, stereotaxic coordinates for the anterior-posterior and lateral planes were marked on the skull. Four 6-32 stainless-steel bolts were threaded into burr holes, and bone primer and a layer of dental acrylic were applied. The EOG electrode was inserted into a burr-hole in the frontal bone, then the remaining holes were drilled. After the

stereotaxic reading for the dura was obtained, the electrodes were lowered into the brain. The electrode cells were then attached and wired to a 14-pin plug. The assembly was encased in acrylic, the wounds were sutured, and 0.5 ml of penicillin-G in dihydrostreptomycin sulfate was administered i.m. Furacin (nitrofurazone) antibiotic salve was applied around the headplug.

Antibiotic was given for 2 to 5 days postsurgically. Each day, the head was washed, and the wound was infiltrated with Liquimast (oxytetracycline HCl).

D. Proton Magnetic Resonance Imaging

A major source of error in stereotaxic work is variability among monkeys in the sizes and shapes of their skulls and relationships of brain to the skull. A difference in the relationship of the lower orbit to the meatus, for example, alters the tilt of the head and compromises the placements considerably. The shape and accessibility of the meatus can also introduce error. These types of error are well known, and corrective techniques--involving the intraventricular introduction of a radiologically opaque substance and X-ray at the time of surgery--have been attempted (Pickering, 1971). The aim of this technique is to visualize the anterior and posterior commissures during surgery and adjust electrode coordinates as appropriate. We X-rayed five rhesus monkeys in the stereotaxic instrument and observed large deviations of skull landmarks with respect to the instrument. At the time of electrode placement in two monkeys, a cannula aimed at the lateral ventricle was also implanted. Several weeks post-surgery the animals were anesthetized and placed in the stereotaxic instrument, and the head was X-rayed after metrisamide was injected into the ventricle. The ventricle was visualized in only one monkey, and poorly in that one--only the massa intermedia could be partially localized. Therefore, this approach was not pursued for several reasons: (1) It would take considerable time to adequately develop the technique, (2) the time to adequately localize and perfuse the ventricle plus the time to make images would, in light of the already 6-hr surgical procedure, make the operation prohibitively long, (3) we were not in possession of the necessary portable X-ray machine, and (4) only corrections to coordinates based on a particular intracerebral structure could have been obtained because most structures could not be visualized.

The procedure of choice for solving this problem is nuclear magnetic resonance imaging (MRI). In 1986 arrangements were made with Drs. Dieter Enzmann and Robert De La Paz of the Stanford Imaging Center to determine the feasibility of facilitating electrode implants by using MRI to determine coordinates prior to surgery, by MRI. It was first necessary to develop an appropriate marker for the skull as a basis for coordinate referencing.

Paraffin was not satisfactory, so we had SRI's glassblower construct 3 mm-diameter, thin-walled glass bubbles with a small hole in them. These were then filled with 0.05 M copper sulfate, which is well imaged, and capped with acrylic and epoxy glue.

To determine whether the MRI resolution would be satisfactory, the head of a previously sacrificed monkey was imaged with the normal electromagnetic coil or one designed for imaging knee injuries. The latter gave better resolution. As shown in Figure 5, the tracks of 0.7 mm-O.D. glass tube electrodes can be seen, along with the general outline of the corpus callosum, medial cortical sulci, thalamus, and cerebellum. These details are seen more clearly in the original images, and the practiced clinician can discern relatively small structures. Sagittal, coronal, and horizontal planes can be produced. The in-plane resolution is about 0.5 mm, but plane thickness is 3 to 5 mm.

At least two general methods of translating the MRI coordinate system to the surgical setting can be described. The first is as follows. From measurements of skull markers placed during surgery, the subcortical position of interest and the appropriate stereotaxic approach are mathematically extrapolated. The general three-dimensional extrapolation required is shown in Figure 6. The simpler, two-dimensional case is shown in Figure 7. The upper figure is of a monkey with a shallow suborbital ridge. The triangle E-F-G, involving the subcortical structure of interest, is known from MRI and the triangle C-D-E is known from measurements and calculations made during surgery. Because our electrodes require vertical entry, it is necessary to calculate H and I. The effect of head rotation about the plane of the auditory meatus (because of a deeper suborbital ridge) on the geometric relationships is shown in the lower panel of Figure 7. All the relationships are altered because the markers are placed at fixed anterior-posterior distances from the meatus, which the rotation changes. Since this method would involve the development or modification of complex computer routines and data entry and would necessitate manipulation at the time of surgery (Brown et al., 1980), we took a simpler approach.

The second method involves using skull markers to establish a horizontal plane in the anterior-posterior dimension that is used to calculate placements orthogonal to it during MRI, and then stereotaxically orienting the monkey during surgery so that the marker plane is parallel to the Horsely-Frankfurt plane. The animal must also be placed so that the coronal midline is orthogonal to the plane of the ear bars. This is checked by including lateral skull marker beads, but is usually less of a problem than anterior-posterior tilt and general relationship of the brain to the meatus and suborbital ridge. In preparation for examination of this procedure, four monkeys were implanted with copper sulfate-filled glass beads. Two beads were placed in the skull on the midline 11 mm posterior and 34 mm



FIGURE 5 SAGGITAL MAGNETIC RESONANCE IMAGE OF A MONKEY'S HEAD, SHOWING ANATOMICAL STRUCTURES WITH MARGINAL CLARITY, AND ELECTRODE TRACKS

anterior to the auditory meatus; the 45-mm span was chosen to include fifteen 3-mm slices in the coronal plane that would show both beads. Two other beads were placed 10 mm left and right of the anterior midline bead.

We also constructed a Plexiglas® stereotaxic-like device to provide restraint and consistent orientation of the monkey in the magnetic coil.

On the day of imaging the monkeys were immobilized with 15 mg/kg of ketamine i.m. and anesthetized with 8 mg/kg sodium pentobarbital i.v. following placement of a catheter in the saphenous vein. The plastic stereotax was mounted on the head and the monkey was transported to the imaging center. Figure 8 shows a midsagittal image with the marker beads in the skull.

Figure 9 compares outlines of midline sagittal brain images from four female rhesus monkeys of similar ages and weight. Tracings of skull and brain were justified with respect to the skull to evaluate brain variability. Exterior aspects of the skull were very similar in these monkeys, and in three of them the brains were also similar. The fourth monkey's brain was smaller in the dorsal-ventral dimension. Overall lengths of the brains were 71.25, 75.00, 76.50, and 77.25 mm. Lengths of the corpus callosi were 33.00, 34.50, 35.25, and 37.50 mm. These are significant differences considering the required accuracy of ± 1.0 mm in some cases. Such variability is undoubtedly greater in a less homogeneous set of monkeys.

A problem with the data collected at Stanford was that the machine employed had a large coil designed for human clinical imaging, resulting in a disadvantageous tradeoff between in-plane contrast and slice thickness. Adequate in-plane contrast of coronal grey and white matter required use of a 5-mm slice, thereby compromising resolution in the anterior-posterior dimension. In light of this problem, arrangements were made to continue these studies at the General Electric Advanced Imaging Center in Fremont, California. All imaging at GE has been provided as a courtesy of Dr. Ralph Hurd.

At GE we used an experimental system with a 2T magnet and 33-cm coil to improve various aspects of the imaging. Some software changes were implemented to improve the signal-to-noise ratio, contrast, resolution, and efficiency of obtaining images for our purposes. After the monkey was placed in the coil, a rapid T1-weighted image was obtained to determine if the longitudinal fissure was parallel to one axis of the scan plane; adjustments were made until this was achieved. A similar midline sagittal image was obtained to verify the position of the marker beads implanted in the skull. This was followed by a high-resolution set of four 2-mm-thick sagittal sections (including the midline), using a multislice inversion-recovery procedure. Sets of coronal sections, guided by midsagittal

Image: 007

MEDICAL CENTER

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SPHINX

F 18 12

1234

Field: 1.5

P Seq: SE

TP : 1000

TE : 24

Echo : 1 04

Mode : Multi

D Acq: 256

FOV : 13

Thk : 3

Nex : 2

15 Imgs Scanned

Acq Time: 08

P 63



FIGURE 8 SAGGITAL MRI SHOWING MIDLINE NEUROANATOMICAL STRUCTURES AND MARKER BEADS (DARK CIRCLES) IMPLANTED IN THE SKULL

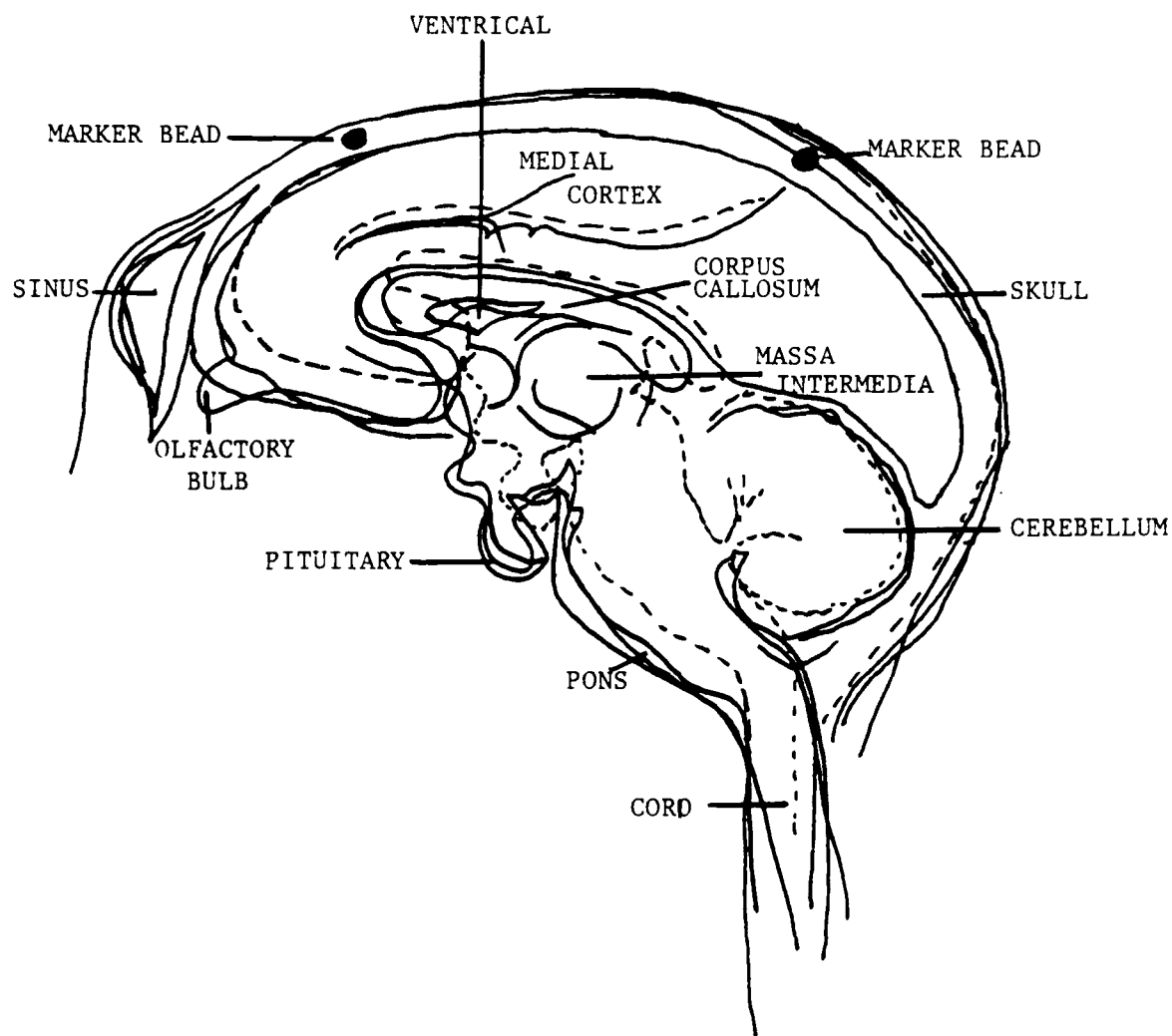


FIGURE 9 Comparison of skull-brain relationships in four female rhesus monkeys.

The brain of one monkey, shown in dashed lines, was small in the dorsal-ventral dimension.

landmarks, were subsequently obtained. The new procedures provided exceptional images if all parameters of the experiment were right. Figure 10 shows a coronal and two midsagittal scans with a spin-echo sequence using T1- or T2-weighting to emphasize different aspects of the anatomy (e.g., the cerebellar white matter is seen better in the T2-weighted image). The use of inversion recovery provided much clearer midsagittal images (Figure 11) and clear contrast of not only neural grey and white matter, but cerebral spinal fluid (dark) as well, as shown in Figure 12.

E. Training and Operant Conditioning Procedures

Initial training and recording sessions were carried out with a chaired monkey placed in a 6' x 6' sound-attenuated chamber. Subsequent to movement of the laboratory, tests were carried out in a 29 x 37 in. sound-attenuated wooden chamber that was placed inside an 8' x 11' shielded room.

During training sessions a monkey was placed in a primate chair with some special features. A drinking tube was mounted so that it was readily accessible to the monkey, and an inverted, metal U-bolt covered with tygon tubing arched over the monkey's snout and prevented turning of the head. A Plexiglas partition to the left of midline of the belly plate kept the arms separated and encouraged the pressing of the response bar with the right hand. The bar--a 5-cm wide piece of stainless steel--protruded 5 cm from the Plexiglas plate on the front of the chair, 27 cm from the monkey's stomach. A ball mounted on the midline of the belly plate 12 cm from the monkey's stomach provided a place for the monkey to put its right hand prior to a trial in order to stabilize reaction times. A light box (4.5 x 4.5 cm square) with a white plastic front was mounted on the chair 27 cm away from the monkey's brow and 10 cm above eye level. Intensity of the light, which constituted the IS, was 400 ft-lamberts. Two video cameras and monitors were used to obtain (1) a wide-angle view of the monkey and (2) a close-up of the ball so that trial initiation by E could be made contingent on a proper placement of the monkey's hand.

A number of changes were eventually made to improve several aspects of these procedures. Because it was very difficult to train the monkeys to find the small operant bar and to place their right hand on the ball, these items were replaced by an upper "response bar" and lower "hold paddle" constructed of 12-cm-wide pieces of Plexiglas. The lower "paddle" was 5 mm above the belly plate of the primate chair; a microswitch was activated when the monkey rested its hand on the paddle. The response "bar," a shorter piece of Plexiglas, was mounted 8 cm above the paddle. Being longer and wider than the previous devices, these manipulanda made it much easier for the monkeys to perform the task. In addition, this change allowed us to automate detection of the hold time and to measure initiation time (time to

Proton images of normal monkey

Images were collected using the GE CSI imaging spectroscopy system with automated spin echo sequence

Image parameters for the coronal view (Fig. 1) were: TR = 2500 msec, TE = 28 msec, FOV = 9 cm, slice = 2 mm, NA = 2, matrix = 256 x 256

Image parameters for the sagittal T1 weighted image (Fig. 2a) were: TR = 400 msec, TE = 15 msec, FOV = 15 cm, slice = 2 mm, NA = 2, matrix = 256 x 256

The T2 weighted sagittal image (Fig. 2b) parameters were: TR = 2500 msec, TE = 28 msec, FOV = 15 cm, slice = 2 mm, NA = 2, matrix = 256 x 256

Acknowledgment

Ralph E. Hurd, Ph.D. GE NMR Instruments

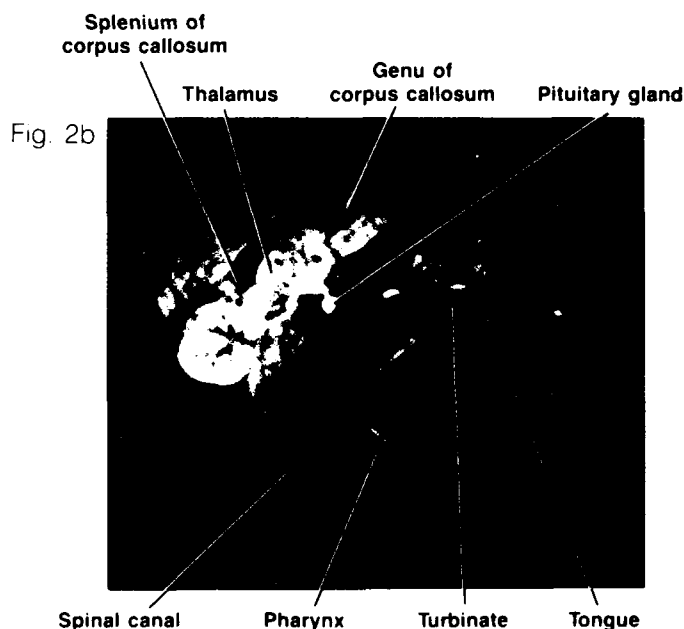
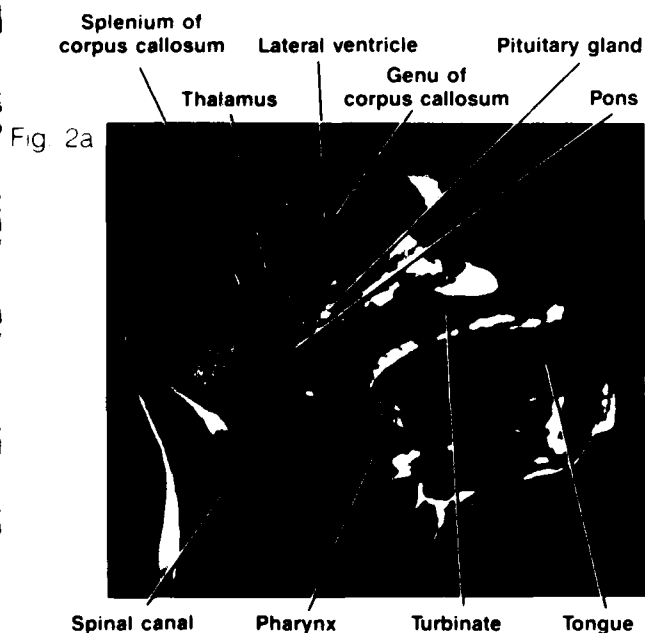
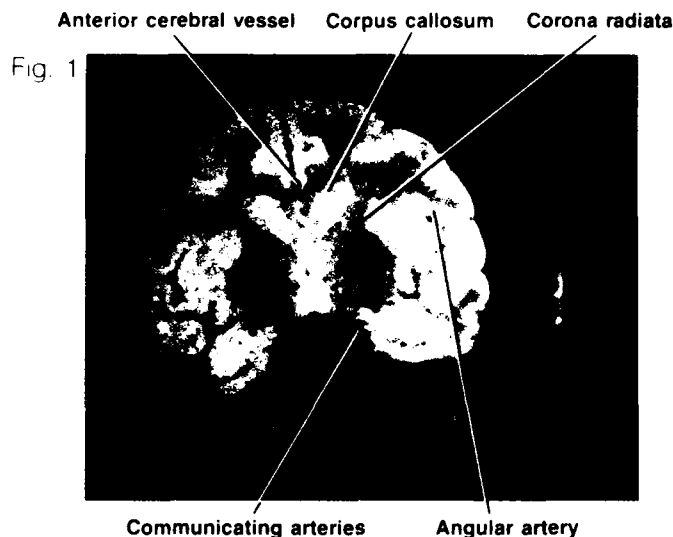


FIGURE 10 IMAGES OF A MONKEY'S BRAIN USING A GE 2-TESTLA INSTRUMENT

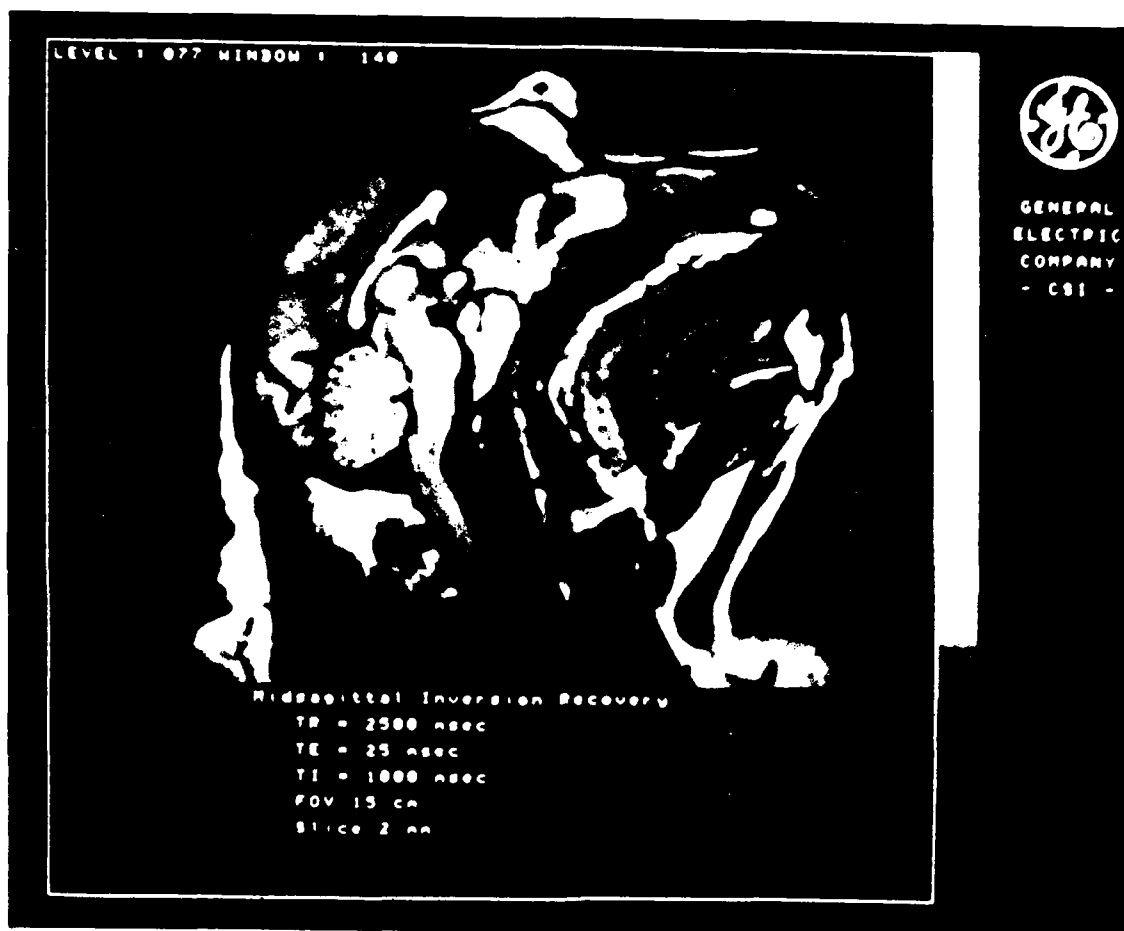


FIGURE 11 MIDSAGGITAL IMAGE OF A RHESUS MONKEY BRAIN USING AN INVERSION RECOVERY PROCEDURE. THE FORNIX, ANTERIOR COMMISSURE, OPTIC CHIASM, PITUITARY GLAND, THALAMUS, COLLICULI, AND PONS ARE CLEARLY DELINEATED.



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FIGURE 12 CORONAL MRI AT THE LEVEL OF THE ANTERIOR COMMISSURE OBTAINED WITH AN INVERSION RECOVERY SEQUENCE. THIS RESULTED IN DISCRIMINATION OF NEURAL GRAY AND WHITE MATTER AS WELL AS CEREBRAL SPINAL FLUID (BLACK).

release of the hold paddle), response time (time to press the response bar), and movement time (response time minus initiation time).

To increase the attentional demands of the task and minimize eye movements, the IS was changed to a 2-cm-diameter aperture of light (30 ft-lamberts) mounted 30° above eye level, 22 inches in front of the monkey. A red LED was mounted in the center of the aperture to provide a point of focus. In some cases this was lighted only when the paddle was pressed to provide feedback to the monkeys about operation of the paddle (some monkeys would press too lightly to activate it).

Training proceeded in three phases: (1) bar-pressing for reward, (2) light-contingency, and (3) pretrial placement of the hand. During Phase 1 successive approximations of the bar-press response were reinforced until the bar was consistently pressed. In Phase 2 the delivery of reward was made contingent on presence of the IS. This involved extinguishing responses during dark periods and training the monkeys to tolerate widely varying inter-stimulus intervals so that they would be responding to the IS rather than in a temporal pattern. Phase 3 was initiated during early stages of Phase 2--when the monkeys indicated some awareness of the meaning of the light. This phase involved using the IS as a secondary reinforcer to reward placing the right hand on the ball. Later in this phase, RTs were recorded and a limited-hold contingency was included so that slow RTs resulted in extinguishing of the IS and unavailability of reward. This procedure was included so that, if necessary, the RT could be pushed to the point where use of the warning signal (WS) is necessary in order to have a RT sufficiently short to obtain reward (there is nothing else in this paradigm that requires the monkeys to pay attention to--or utilize--the WS, although they do so). On the last day of preliminary testing, mean RTs of individual monkeys over trials ranged from 894 msec (SD = 164) to 1812 msec (SD = 950). The rate of bar-pressing ranged from 1.0/sec (SD = 0.1) to 1.7/sec (SD = 0.2). For the five monkeys consistently responding (all except Samurai), mean RT was 1389 msec (SD = 342, SEM = 153) and the mean rate of pressing was 1.4/sec (SD = 0.3, SEM = 0.1).

These procedures were eventually automated to a greater degree. Instead of "shaping" performance on the paddle, the onset of the IS was made automatically contingent on press of the paddle by the monkey. Once the monkeys learned to make the IS reappear by holding down the paddle, the hold-time requirement was added, starting with 1 sec and increasing eventually to 5 sec as the monkeys learned to wait. Premature release of the paddle recycled the hold period. Finally, a variable intertrial interval was included, ranging from 30 to 90 sec. Thus, the monkeys were simultaneously learning cue significance (IS) and the paddle-hold response. These improvements greatly facilitated training.

F. Verification of Electrode Placements

To verify electrode placements the monkeys were anesthetized with ketamine (15 mg/kg) and sodium pentobarbital (40 mg/kg) and perfused through the heart with normal saline and formalin. Blocks of brain were cut into 50- μ -thick sections using a freezing microtome. The sections were placed in a photographic enlarger and prints were made as described by Guzman-Flores et al. (1958).

RESULTS

A. Development of Event-Related Potentials During Associative Conditioning

1. Introduction

The training procedures used in our experiments allow the study of electrophysiologic concomitants of associative conditioning. Preliminary training consists of the light-contingency and paddle-holding performance described before. At this stage the monkeys hold the paddle down almost continuously, waiting for the light cue to initiate pressing on the reward bar. After stabilization of this performance, the introduction of the WS and NS tones leads to the development of electrophysiologic events in the interstimulus interval indicating that the monkeys utilize the WS as a preparatory cue. That utilization may also be evidenced by a decrease in response time. Initially, similar electrophysiological responses may be elicited by the NS because the monkey has not yet developed a discrimination between the meanings of the two stimuli. Eventually, such responses may extinguish (Rebert, 1972).

In a previous study (Rebert, 1972) we observed that the development of preparatory ERPs does not occur simultaneously in all parts of the brain. Since this may indicate the utility of these recordings for mapping brain regions most intimately involved in associative learning, we were interested in undertaking similar studies on this project.

2. Cynomolgus Monkeys

a. Performance

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.

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.

Table 1 presents a summary of several performance parameters for five monkeys (one monkey was an excessively erratic performer) under two training conditions. Scores obtained when only the light cue--the imperative stimulus--was presented are in the upper portion of the table. Those obtained during tone-light pairing are in the lower part of the table. The latter scores are those for a period 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 of the IS. 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, 945 msec after tone-light pairing. This shortened RT indicates that the monkeys learned to associate the tone and light. The 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.

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.

b. Electrode Placements and Spontaneous EEG

Structures at which electrodes were aimed in these monkeys are described below. Recordings were with reference to an electrode aimed at white matter below parietal cortex.

Left motor and premotor cortices (LMC, LPMC). Epidural electrodes were placed here to study potentials related to specific (motor cortex) and non-specific (premotor cortex) aspects of the behavior mediated via the right arm and hand. We previously observed (Rebert, 1972) that potentials were typically larger in premotor than in motor cortex. The premotor electrode was aimed at the arcuate gyrus, a region suggested by McSherry and Borda (1973) as being a robust generator of ERPs.

Table 1

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

Condition	Monkey (I.D.)	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)
Light only	Conan (CO)	289 (138)	269 (130)	7 (3.4)	1.2 (0.1)	1340 (164)	24 (11)
	Mickey (MI)	261 (90)	222 (76)	14 (42)	1.6 (0.3)	1521 (154)	30 (14)
	E.T. (ET)	240 (57)	218 (52)	9 (3.1)	0.7 (0.1)	1563 (251)	22 (11)
	Smacker (SM)	282 (102)	240 (76)	14 (6.5)	1.7 (0.2)	1579 (210)	28 (10)
	Grey (GR)	401 (95)	339 (76)	15 (3.6)	1.6 (0.2)	1084 (178)	21 (6)
	Mean	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
Tone- light pairing	Conan	356 (114)	329 (111)	8 (3.2)	1.1 (0.3)	1082 (167)	26 (19)
	Mickey	322 (72)	290 (64)	9 (2.2)	2.1 (0.2)	919 (221)	32 (11)
	E.T.	216 (54)	192 (47)	9 (6.3)	0.9 (0.1)	1118 (272)	35 (12)
	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)
	Mean	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

Hippocampus (HPC). Marczyński (1978) proposed a model of brain function implying a role of hippocampus in preparatory set, and the hippocampus has been suggested as a site that is important to the generation of scalp-recorded event-related potentials.

Caudate nucleus (CAN). An electrode was aimed at this structure because it appears to be involved in motor activity, it is intimately interconnected with the frontal lobes, and we had previously recorded positive slow potentials from the caudate.

Substantia nigra (pars compacta--SUN). This structure projects inhibitory dopaminergic fibers to the caudate nucleus. Since we interpret the caudate positive potential as being reflective of neuronal inhibition we predicted that negative slow potentials would be observed in the substantia nigra.

Midbrain reticular formation (MRF). This complex of structures is involved in the control of wakefulness, attention, motor outflow, and a variety of other "nonspecific" functions, and we previously observed very robust activity there associated with preparatory set.

N. ventralis anterior, thalamus (NVA). This nucleus is the main thalamic relay to the premotor cortex.

Superior orbital bone (electrooculogram--EOG). Recordings above one eye were obtained to determine the extent to which eye movements contributed to recordings from other sites.

Figure 13 shows a period of spontaneous EEG recordings from an (extra) reference electrode aimed at anterior white matter, the MRF, and right parietal cortex in association with the EOG. Whereas the EOG exhibits large changes in potential associated with blinks and eye movements, those events are not reflected in the other recording sites.

c. Averaged Event-Related Potentials

Examples of averaged responses obtained from one monkey (ET) after several weeks of testing are shown in Figure 14. 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

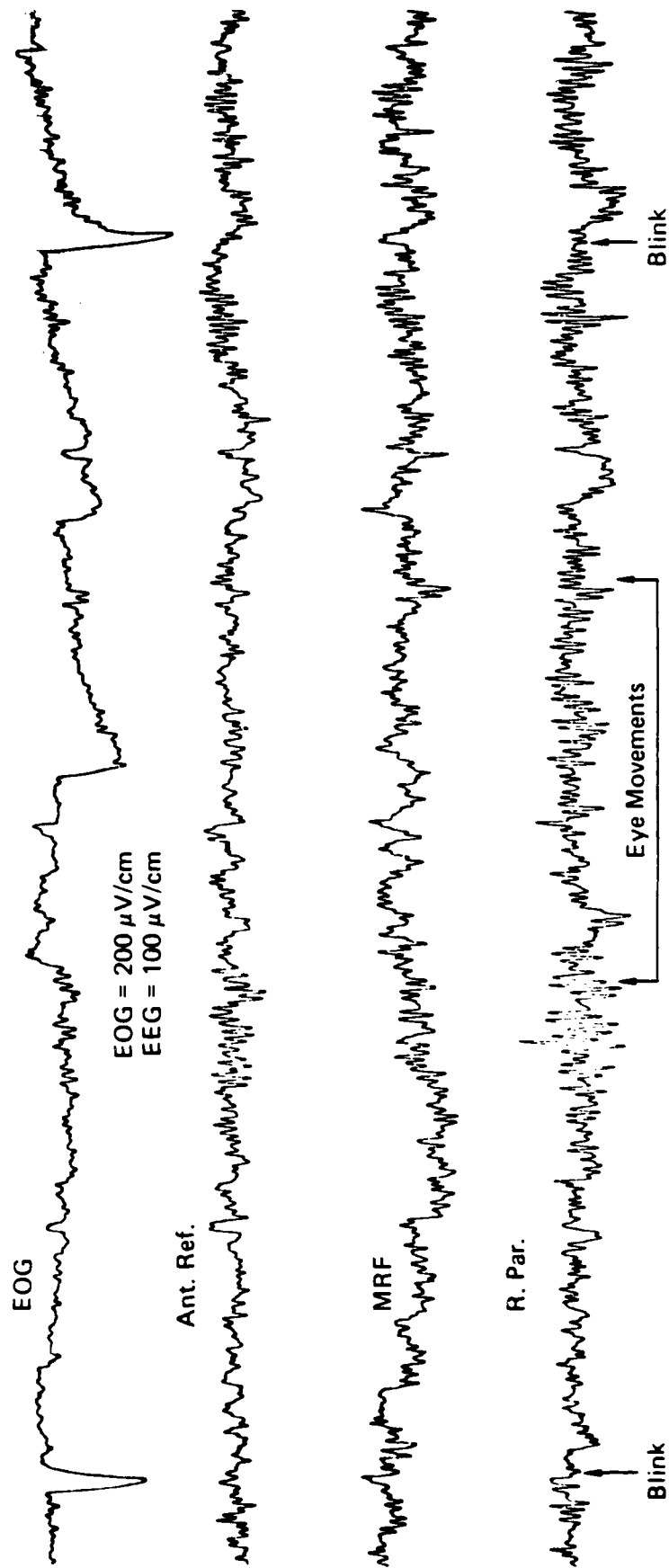
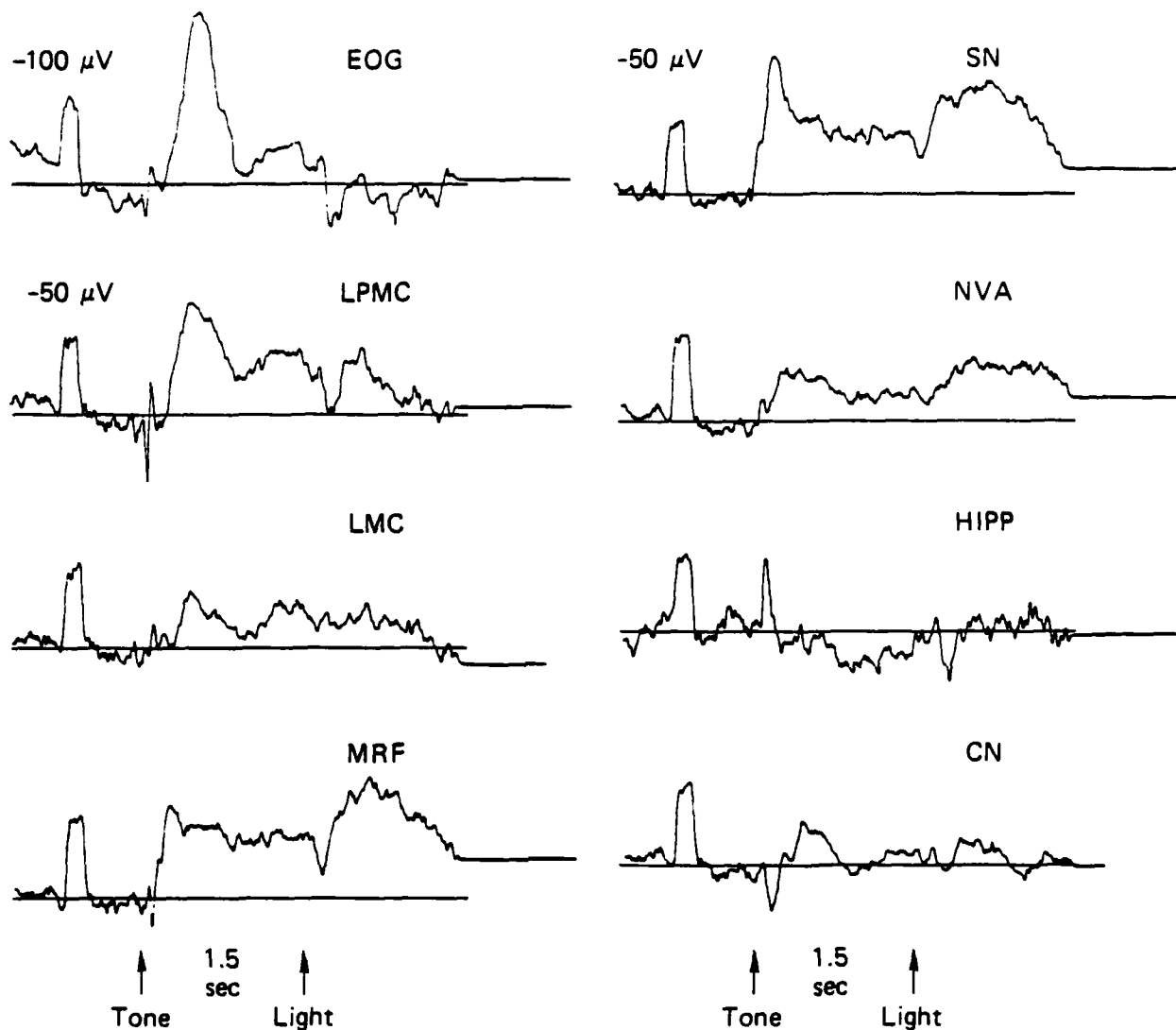


FIGURE 13 EEG RECORDS FROM ONE MONKEY SHOWING MINIMAL EFFECTS OF BLINKS AND EYE MOVEMENTS ON CORTICAL AND SUBCORTICAL RECORDINGS

EOG = electrooculogram; Ant. Ref. = reference in anterior white matter; MRF = midbrain reticular formation; R. Par. = right parietal cortex. All recordings, including the EOG, were made with respect to the reference electrode in posterior white matter.



LA-4373-1

FIGURE 14 EXAMPLES OF EVENT-RELATED POTENTIALS RECORDED FROM SEVERAL BRAIN REGIONS OF MONKEY NUMBER 3 (ET)

EOG = Electrooculogram, LPMC = 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.

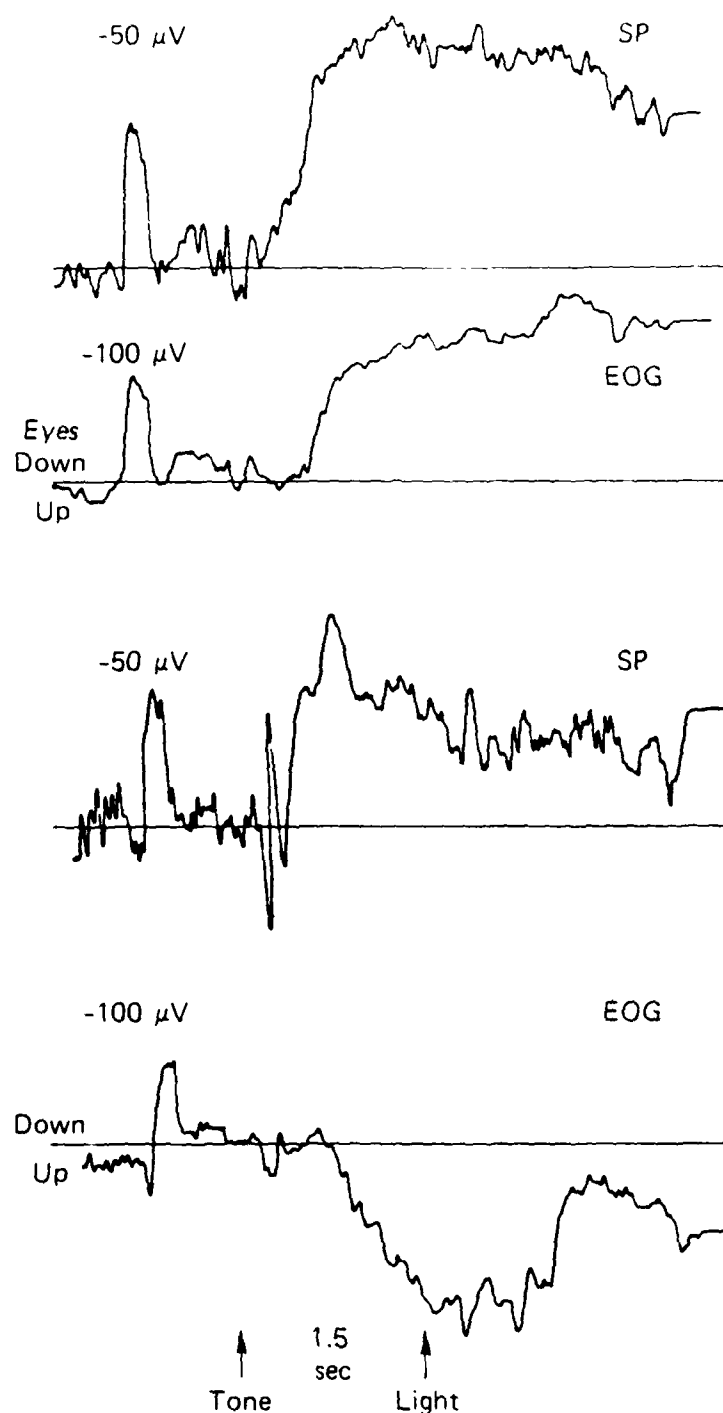
from regions anterior and lateral to the arcuate sulcus would help clarify this issue. Although the left motor cortex (LMC) waveform was also similar to the EOG record, the initial negative peak was comparatively small and occurred later in time than the blink, and the slow negative shift in LMC persisted throughout the recording epoch while the EOG returned to baseline.

A rapid change occurred in the midbrain reticular formation (MRF) after onset of the WS. A 50- μ V 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 from the EOG and could not be considered an artifact of eye movements or blinks. An almost identical response was obtained from the substantia nigra (SUN). 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 (CAN) of this monkey without any definite SP occurring during the interstimulus interval in this recording session. On the average, however, this monkey exhibited a small negative shift in the CAN.

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 15), 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 (SA) 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 (SM), the LMC response was sometimes absent or even positive rather than negative. The variety of waveshapes obtained from the LMC is exemplified in Figure 16. All five monkeys exhibited negative SPs in the MRF, and four of the responses (except that of SM) started with a fast-rising negativity like that shown in Figure 14. The same consistency was true of responses in the SUN, with all but one response (from SM) starting with a fast negativity. In three of the four monkeys with good SUN responses, amplitudes were about 50 μ V. In one monkey (MI), however, the response reached 100 μ V during the interstimulus interval and 150 μ V shortly after the light appeared.

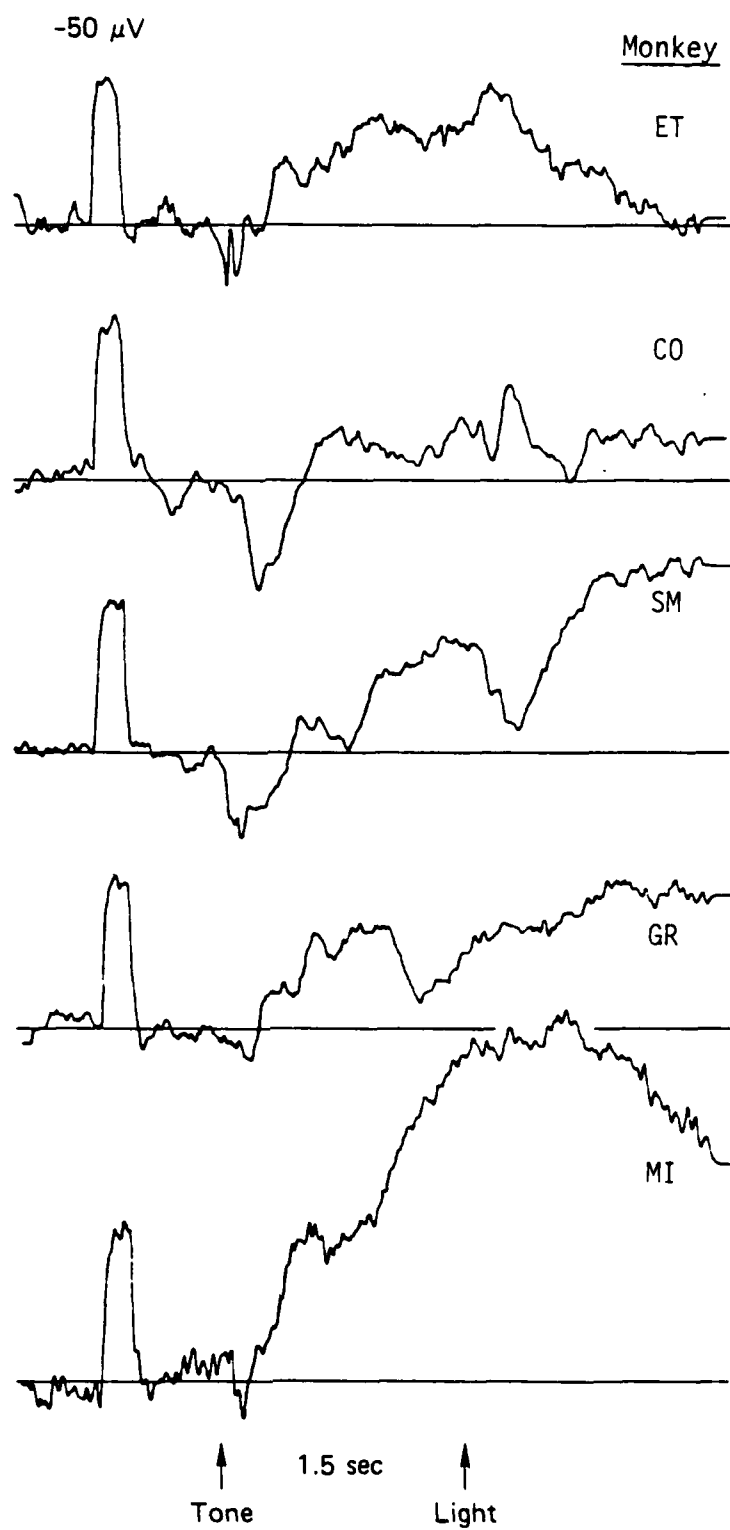
Inconsistent waveforms were obtained from the NVA. A negative shift with a fast rise, and about 30 μ V, was seen in three monkeys, and the other two showed little or no response. In contrast, small positive SPs, with amplitudes of about 12 μ V, occurred in the hippocampus of five monkeys.



LA-4373-2

FIGURE 15 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 polarity 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 14, without drug.



LA-4373-3

FIGURE 16 LEFT MOTOR CORTEX RECORDINGS FROM FIVE MONKEYS

Slow-rising negative shifts of 10 to 40 μ V, preceded by a brief positive component, were observed in the caudate nucleus in four of the five monkeys.

d. Acquisition of Slow Potentials with Tone-Light Pairing

The rate of development of SPs over the course of initial tone-light pairing varied, depending on the monkey and electrode placement. Examples of such development are shown in Figures 17 and 18. Figure 17 shows daily waveform plots of the ventralis anterior electrode of monkey GR. Except for the EP complex elicited by the IS, there was little systematic activity evident in association with the WS until the fifth day of tone-light pairing, when a small negative shift became evident. The shift became more pronounced as training continued (shown through day 12). Figure 18 shows a similar development for selected days for the substantia nigra electrode of monkey ET.

Plots of SP amplitude over the course of training are shown for several monkeys and placements in Figure 19. These are based on a 3-point smoothing procedure to reduce day-to-day variability, thus showing the trends more clearly. In some cases (e.g., ET-SUN) the SP developed within three days, whereas in other cases--e.g., CO-MRF, the negative shift typical of the placement did not begin to develop before 7 days. Different placements within an animal also exhibited different patterns of development. For example, the NVA and SUN placements in monkey ET developed SPs at different rates, as did the MRF and LMC placements in monkey SM.

e. Introduction of the Neutral Stimulus (NS)

Because of the difficulty that we had in training these monkeys, the NS was not included during the initial phases of tone-light pairing. After stabilization of the SPs following acquisition training, the NS was introduced for four of the monkeys. The NS occurred pseudorandomly on half of the trials with the restriction that no more than three WS or NS could occur in succession. We expected that anticipatory responses would be observed following the WS but not the NS. Results after 16 to 23 days of testing in this paradigm are shown in Figure 20. For most placements there was little difference in the waveforms associated with WS and NS trials, but the SUN was larger during the foreperiod on WS than on NS trials in three of the monkeys and the MRF showed the same effect in two of the monkeys. These results are in considerable contrast to results obtained before (Rebert, 1972), where clear discrimination developed in female stump-tailed macaques. It is possible that the results reflect the general consensus of opinion regarding the low intelligence of cynomolgus monkeys. It is of interest, however, that the SUN exhibited a discrimination whereas most regions did not. To determine whether the extent of discrimination could be improved, the proportions of WS and NS trials were varied, as described later.

DAY

1

2

3

4

5

6

WS

IS

DAY

7

8

9

10

11

12

WS

IS

FIGURE 17 ACQUISITION FUNCTION OF SLOW POTENTIALS
IN THE N. VENTRALIS ANTERIOR OF MONKEY GR

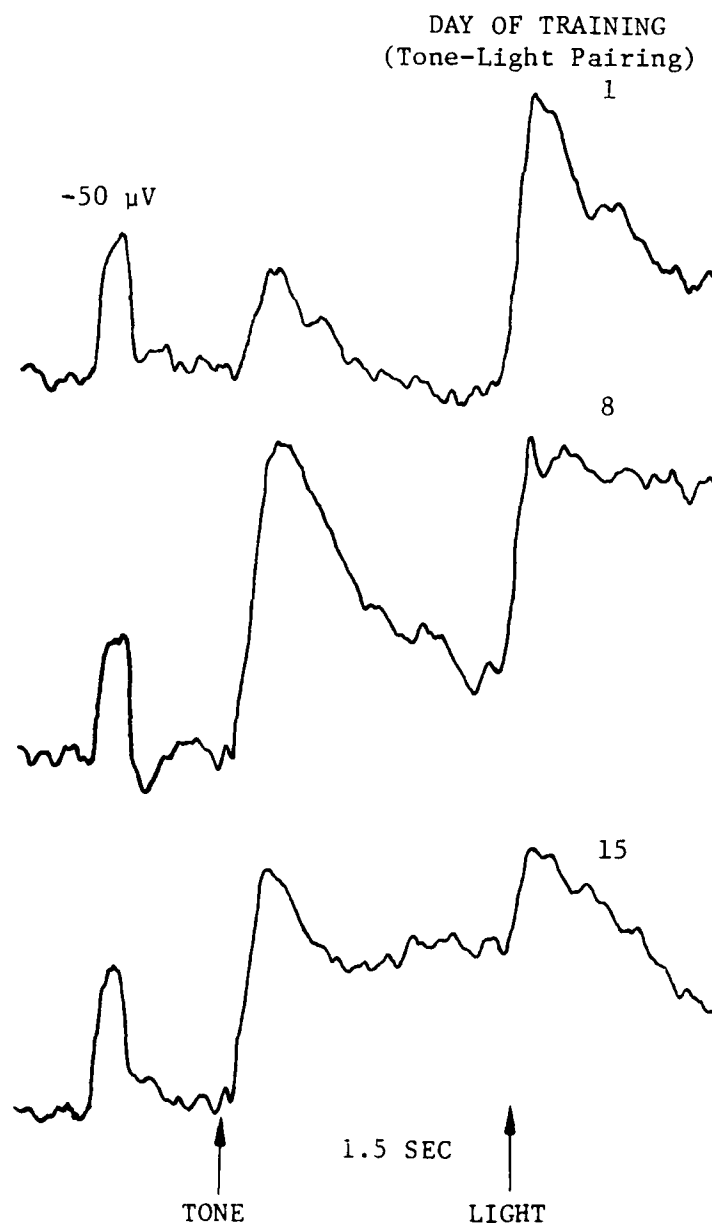


FIGURE 18 CHANGES OF TRANSIENT AND STEADY POTENTIALS IN
SUBSTANTIA NIGRA OF ONE MONKEY (ET) AS A FUNCTION
OF NUMBER OF DAYS OF TONE-LIGHT PAIRING

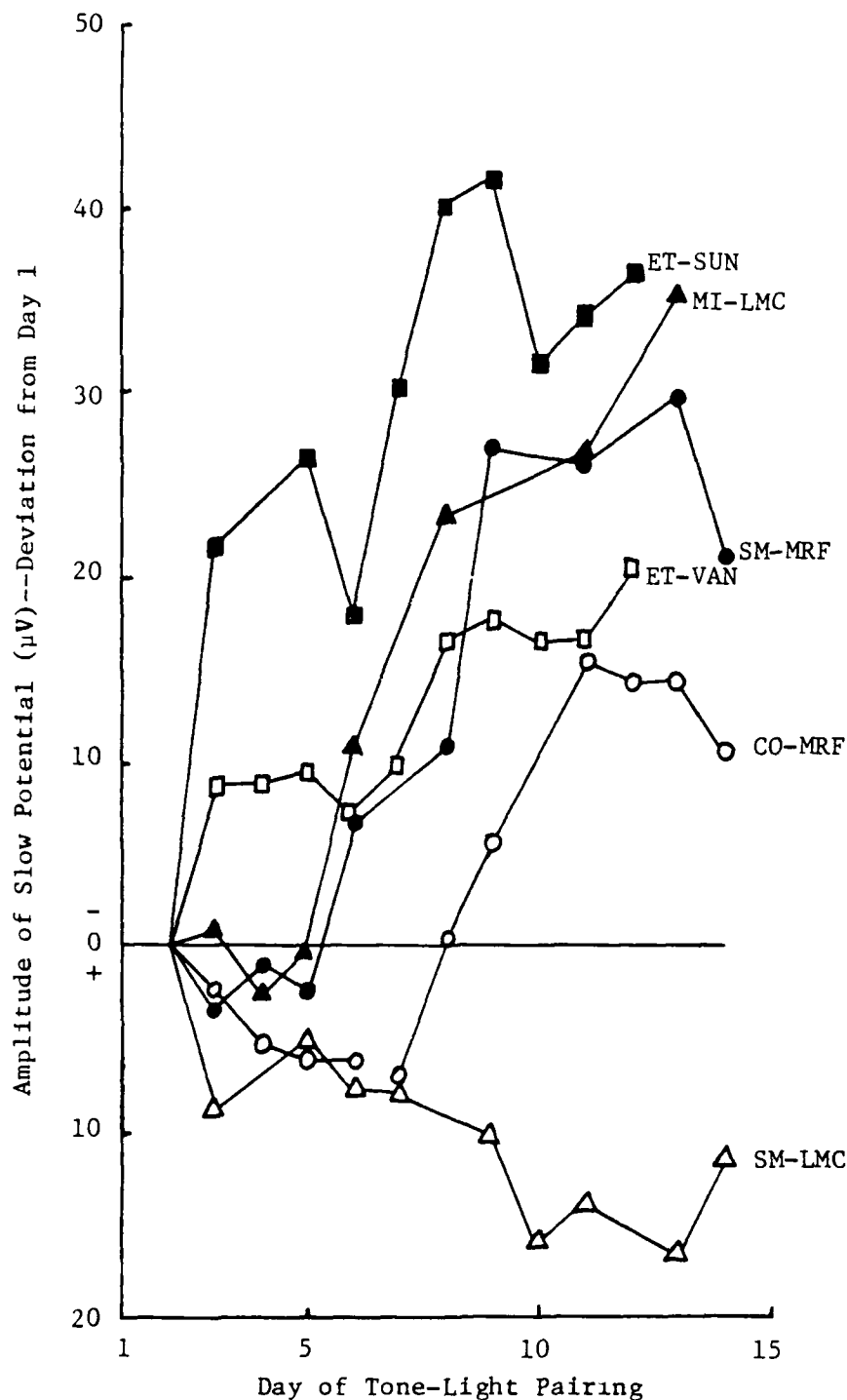


FIGURE 19 ACQUISITION FUNCTIONS FOR SEVERAL MONKEYS AND PLACEMENTS

Day-to-day variation was reduced by use of a 3-point smoothing procedure (thus, the start on Day 2). The first value was subtracted from subsequent points to emphasize relative trends.

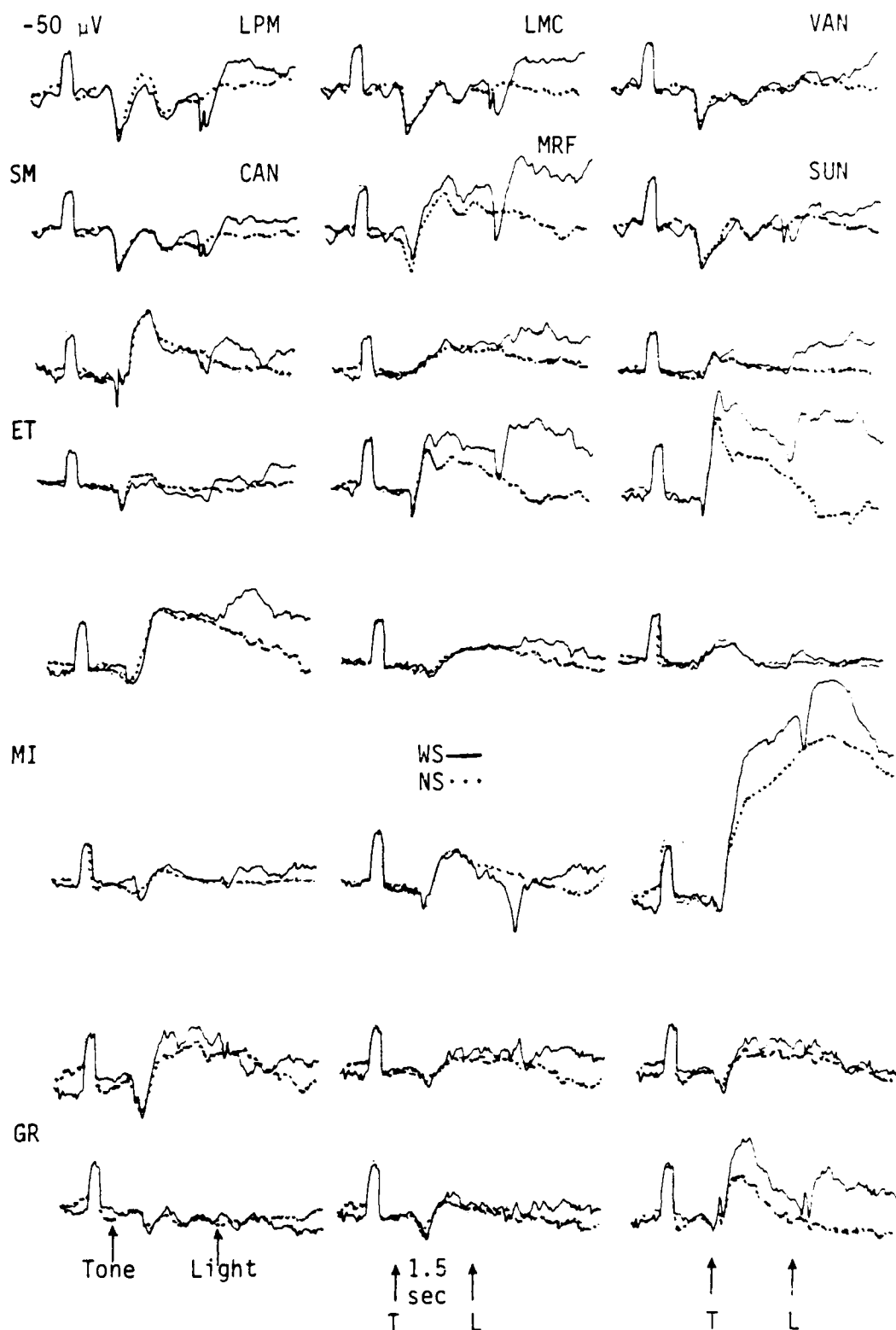


Figure 20 Averaged waveforms from electrodes aimed at left premotor cortex (LPM), left motor cortex (LMC), n. ventralis anterior of the thalamus (NVA), caudate n. (CAN), midbrain reticular formation (MRF), and substantia nigra (SUN) in four monkeys--elicited by the warning (WS) or neutral (NS) stimuli.

f. Recording with Respect to Different References

Reference electrodes were placed in white matter 10-12 mm below the dura. One was in the left hemisphere 22 mm anterior to the meatus and 7.5 mm left of midline. The other was 5 mm anterior to the meatus, 10 mm to the right of midline. Thus, the references were widely spaced and in completely different spatial relationships to the other electrodes. As shown in Figure 21, recordings were qualitatively identical when the different references were used and the recordings from different sites retained their unique waveforms. The responses obtained by recording between the references exhibited some small transient EPs, but nothing comparable to the waveforms typically recorded--except perhaps from the caudate. These results suggest that potentials recorded at the active sites are generated by neurons in the vicinity of the electrode tips.

3. Female Stump-Tailed Macaques

Six female stump-tailed macaques were purchased, quarantined, and trained on the behavioral task. Their training was interrupted for about two weeks to install a new chamber. This consisted of a sound-attenuated wooden chamber just large enough to hold the primate chair. It was placed inside the larger shielded chamber. These changes provided greater isolation from laboratory noises and a smaller and visually less complicated environment. 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.

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 Bereitschaftspotential 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--Rebert, 1972-- 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 (the locus 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 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).

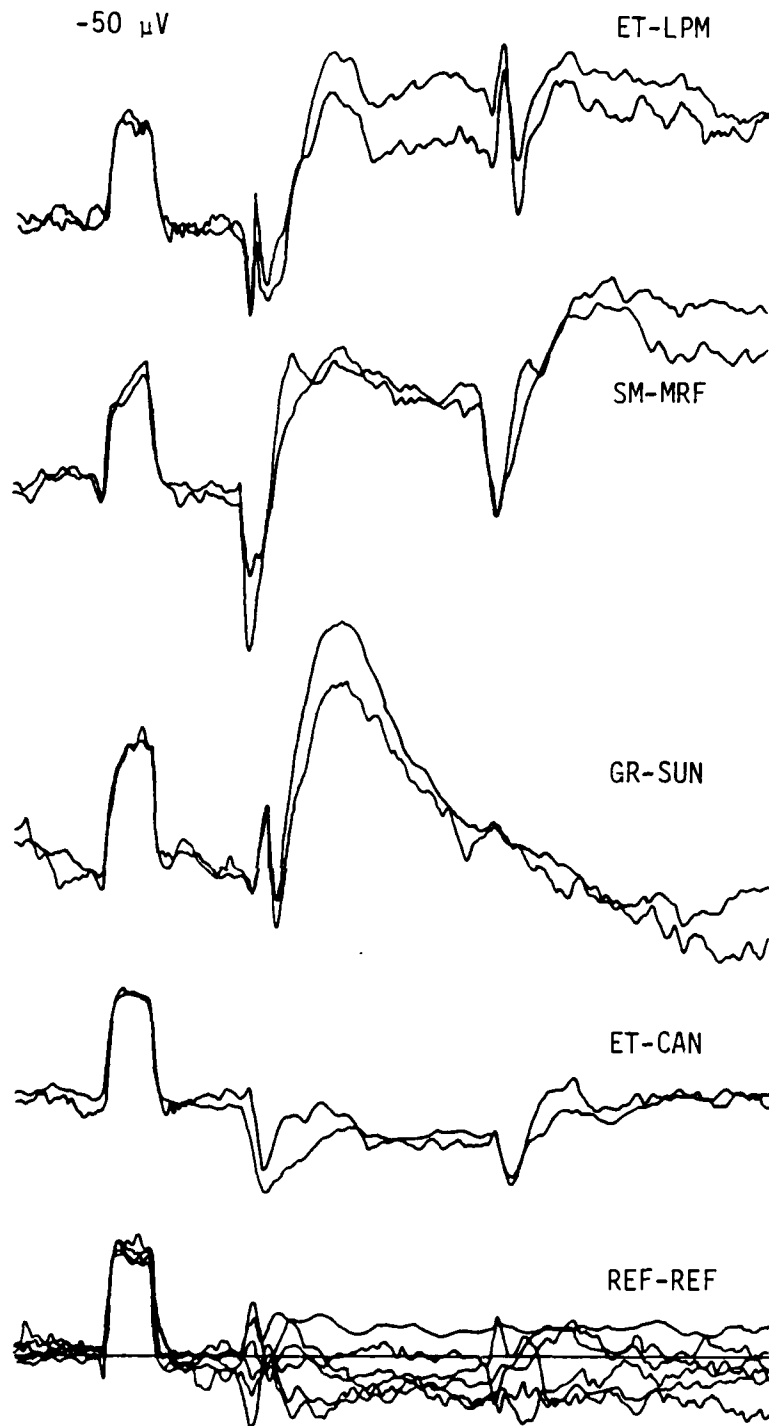


FIGURE 21 EVENT-RELATED POTENTIALS RECORDED WITH RESPECT TO ANTERIOR OR POSTERIOR REFERENCE ELECTRODES
Lower tracings are recordings between the references.

One monkey dislodged her headplug several weeks after surgery and another developed an infection and was sacrificed, so only four of these monkeys were available for testing. In contrast to the procedure used with the cynomolgus monkeys, the WS and NS were both included in the paradigm from the first day of introducing the tones. The WS was a 500-Hz tone and the NS a 3-KHz tone. Mean RT during the 5 days preceding tone-light pairing was 1450 ($\pm$ 365) msec. It declined slightly over the course of the next month, being 1304 ($\pm$ 12a), 1303 ($\pm$ 144), 1285 ($\pm$ 110), and 1262 ($\pm$ 182) msec for sequential blocks of 5 weekdays.

Because of erratic performance by these monkeys and the need to retrain them after initiation of tone-light pairing, clear ERP acquisition functions could not be obtained. Also, we discovered that the reference electrode was active and so the parietal cortex electrode, which appeared to be relatively inactive, was used as the reference.

Examples of the waveforms observed in the electrodes aimed at the N. basalis of Meynert (NBM) are shown in Figure 22. They are quite similar to the responses from other deep structures, such as the MRF and SUN observed in the cynomolgus monkeys. The response from the SUN in three monkeys was typical of that placement. Although not as consistent from monkey to monkey as the NBM, a similar waveform was observed in the electrode aimed at the raphe nucleus. Although the NBM is the major source of cholinergic input to the cortex and would be expected to be exerting significant control over cortical activities, the waveform elicited from motor cortices [Figure 23--supplementary motor area (SMA)] was quite different from that from NBM. Except for the very small slow potentials observed in motor cortices of these monkeys compared with our earlier study (Rebert, 1972) and several of the cynomolgus monkeys, the general waveform was very similar to that observed before--i.e., a slow wave preceded by a W-shaped EP complex elicited by the tone.

There is considerable interest in the relationships among the major divisions of frontal cortex involved in the control of movement--i.e., motor cortex, premotor cortex, and the supplementary motor area (SMA). It has been suggested that the SMA is the main source of the Bereitschaftspotential associated with uncued voluntary movement (Deecke, 1985), and it might also, therefore, be involved in generating potentials associated with the cued RT task. Although none of the motor placements exhibited robust negative SPs, the SMA tended to be slightly more negative on the average than were the other placements (Table 2, SP). More consistent differences were observed among the transient components associated with the WS and IS; in each monkey those were larger in PMC than LMC and largest in the SMA (Table 2). This greater responsiveness to sensory input is consistent with conjectures that the SMA is more involved with sensorimotor integration than are the other motor areas (Weinrich and Wise, 1982; Wise, 1985).

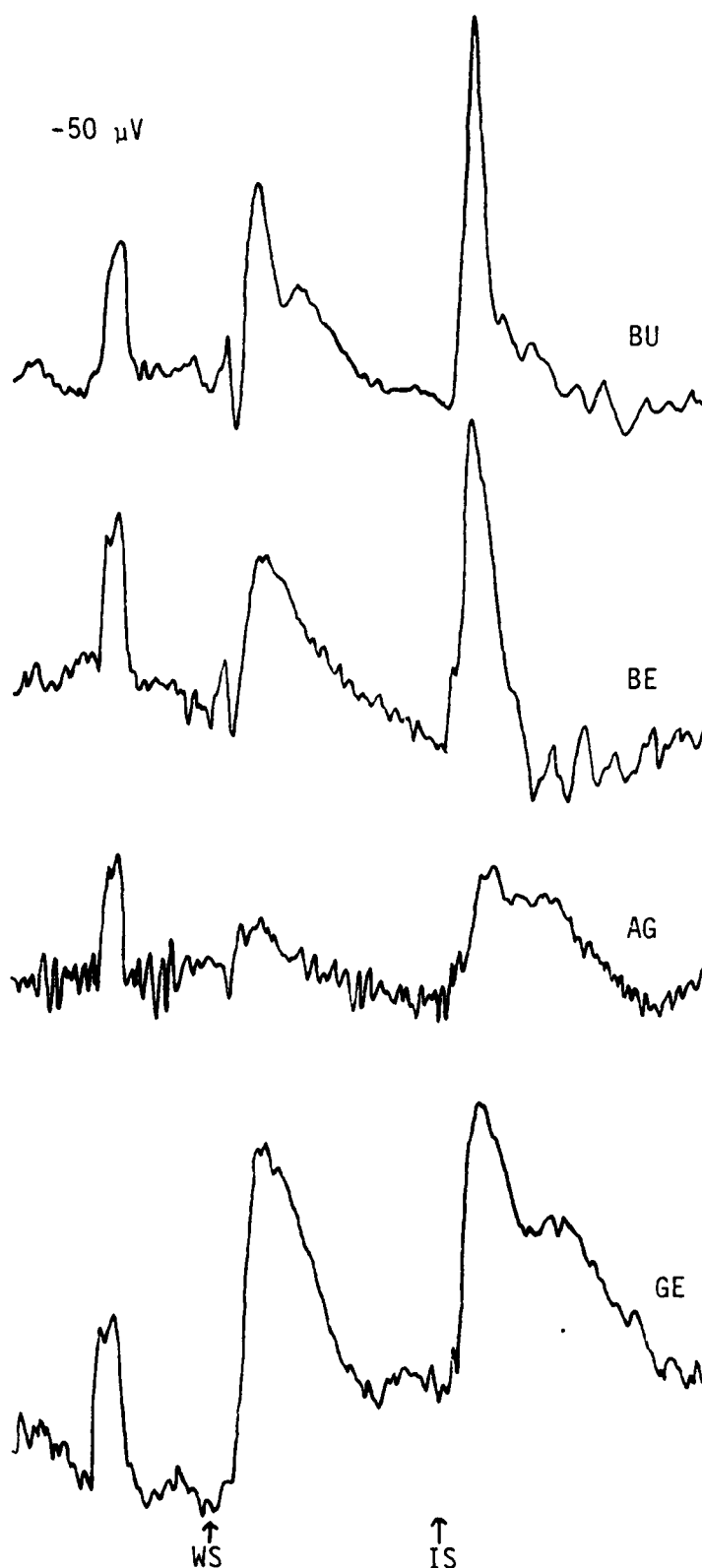


FIGURE 22 RESPONSES FROM ELECTRODES AIMED AT THE N. BASALIS OF MEYNERT RECORDED FROM FOUR STUMP-TAILED MACAQUE MONKEYS

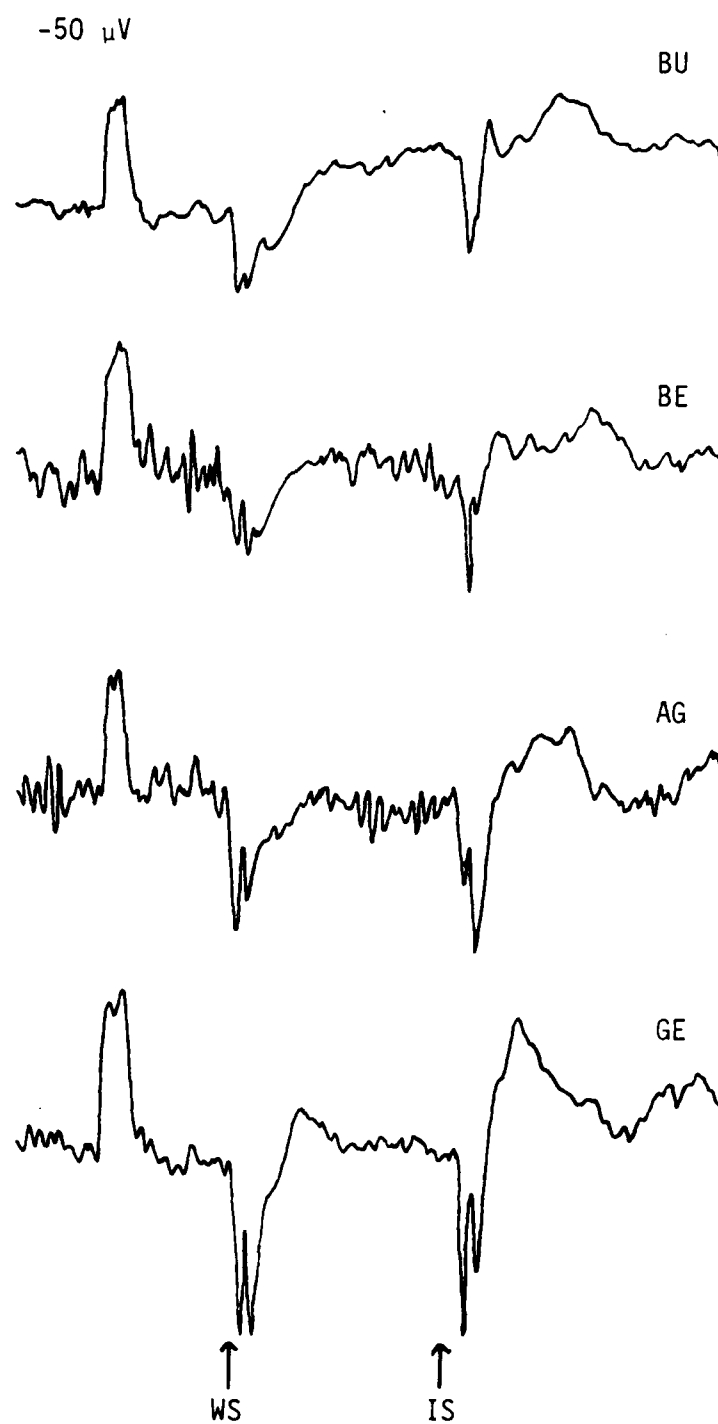


FIGURE 23 RESPONSES FROM ELECTRODES AIMED AT THE SUPPLEMENTARY MOTOR AREA RECORDED FROM FOUR STUMP-TAILED MACAQUE MONKEYS

Table 2

DIFFERENCES IN THE AMPLITUDES (μV) OF TRANSIENT
AND SUSTAINED POTENTIALS IN MOTOR CORTICES
[$\bar{X}$ (SD)]

Component	Placement		
	LMC	LPMC	SMA
N1-P1	25.9 (5.9)	38.1 (13.0)	47.7 (14.9)
% of LMC		146%	184%
SP	-0.8 (7.6)	+1.3 (10.0)	-6.2 (15.4)
N2-P2	33.6 (6.0)	47.9 (10.4)	56.9 (12.8)
% of LMC		142%	169%
P2-N3	51.7 (8.3)	65.1 (10.7)	82.4 (19.4)
% of LMC		126%	159%

4. Female Rhesus

a. Baseline and Acquisition

Four elderly female rhesus monkeys were obtained because of difficulties experienced with the stump-tailed macaques. Only three of them received electrode implants because one was used intermittently to try different magnetic resonance imaging techniques. The mean composite performance score based on the algorithm $[(\text{total trials}) + (\% \text{ correct}) + (\text{press}/5) + (\text{rate of pressing}) - (\text{RT} \cdot 2)]$ for presurgical training is shown in Figure 24. After early improvement and intermediate decline, the monkeys' performances improved dramatically, so surgeries were completed. After post-surgery and retraining the performance scores reached a mean of 206 (optimum performance would score 278).

One issue addressed with these monkeys was the localization of generator sources of the potentials usually recorded with respect to a remote reference (generally subcortical white matter). Although the preferred method for undertaking localization studies is current-density analysis, that process requires a large number of closely spaced electrodes. However, this was not feasible because of the three-dimensional sampling required and the nature of our electrodes. Therefore, we aimed several reference electrodes at white matter near structures of interest. Active placements were left premotor cortex (PMC), right arcuate gyrus (ARC), substantia nigra (SUN), red nucleus (RUB), pulvinar (PUL), caudate n. (CAN), and midbrain reticular formation (MRF). Reference electrodes were aimed at white matter below cortical electrodes, and at white matter as closely adjacent to active placements as possible (e.g., the pyramidal tract lateral to SUN). General references were also placed on the midline approximately 15 mm posterior to the auditory meatus and in parietal white matter. The former was considered an appropriate reference because event-related SPs like the CNV have not been observed in that region of monkey cortex (Donchin et al., 1971).

Recordings were obtained first (using the posterior midline reference) when only the light was presented in order to study responses to the light irrespective of interactions that might occur during tone-light pairing. The light was a significant cue for responding as the monkeys were already trained on the light-dark discrimination. It would be useful some time to implant animals prior to discrimination training to determine the changes that might occur as the light develops cue significance. Examples of ERPs from each monkey are shown in Figures 25-27.

Responses evoked in the premotor areas (PMC and ARC) were quite different in different monkeys but similar to one another within a monkey. Waveforms generated from electrodes aimed at the SUN and MRF were typical of those observed during tone-light pairing in other monkeys, consisting of a

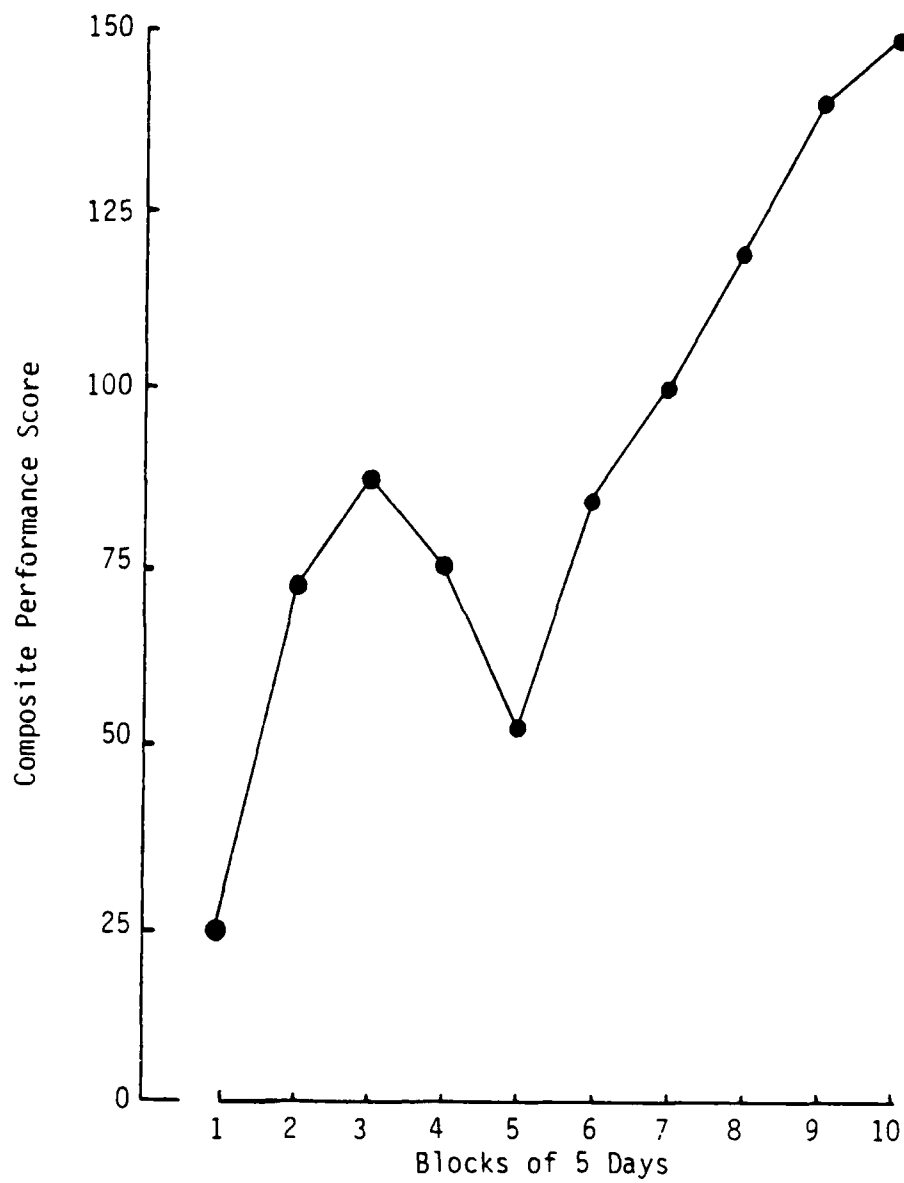


FIGURE 24 COMPOSITE PERFORMANCE SCORE OF
FOUR FEMALE RHESUS MONKEYS AS
A FUNCTION OF TIME OF TRAINING

very fast-rising large negative potential that was sustained during the rest of the recording epoch. A similar response was obtained from the electrodes aimed at the red nucleus in two monkeys, and probably the third, although the electrode was not functioning properly in that monkey (MS). Smaller and more transient potentials were obtained in monkeys FL and RO from electrodes aimed at the CAN and PUL, but large sustained potentials were generated at these electrodes in monkey MS. EOG recordings varied considerably from monkey to monkey. There was little response in monkey FL, a large but relatively slowly-rising and transient response from RO, and a peak- and slow-wave type of waveform from MS. These different patterns and great differences in waveforms among placements in a given monkey clearly indicate that eye movements contribute little to the potentials recorded from the brain. Also, because the large negative shifts elicited by the IS were not observed in all of the placements, apparently they were not due to activity at the posterior reference. Mean reaction time over the three days of these recordings was 1364 ($\pm$ 166) msec.

Potentials elicited by the unpaired tones are shown in Figures 25-30. Responses in the motor areas were rapid transients with little or no post-response negative shifts. In subcortical areas transient spikes were generally followed by a negative shift that was sustained for various lengths of time depending on electrode and monkey. Except for transient spikes, tones elicited no significant responses from the EOG electrodes.

With a few exceptions, these monkeys did not exhibit well-developed responses in the foreperiod. Potentials obtained from the three monkeys are shown in Figures 31A-D. Monkey FL (Figure 31A) generated enhanced responses after 8 days of tone-light pairing (right column) compared to the first day of training (left column) in the SUN, MRF, RUB, PUL, and CAN. This was true also, but to a lesser extent (Figure 31B), for the SUN, MRF, PUL, and CAN of monkey RO (primarily enhancement of the early slow negative wave and increased positivities in PUL and CAN). Only the CAN positivity and late SUN negativity were enhanced by training in monkey MT (Figure 31C). Some enhancement appears as early as the first day of training. Responses of the SUN to tone only and on the first and twelfth days of training are shown in Figure 31D. In each case there was an increase in the amplitude and/or duration of the early tone-evoked slow wave, and in monkeys FL and MS the SP level just prior to onset of the IS was also elevated. This latter change was further augmented with further training in those two monkeys, but not in RO. In all three monkeys, the response to the neutral stimulus on the twelfth day of training was like that observed when the tones were presented alone--i.e., the SUN exhibited a differentiation on WS and NS trials. Over the first three days of tone-light pairing mean RT was 1277.2 ($\pm$ 88.2) msec and over the last three days (days 10-12) it was 1207 ($\pm$ 71.7)--i.e., all

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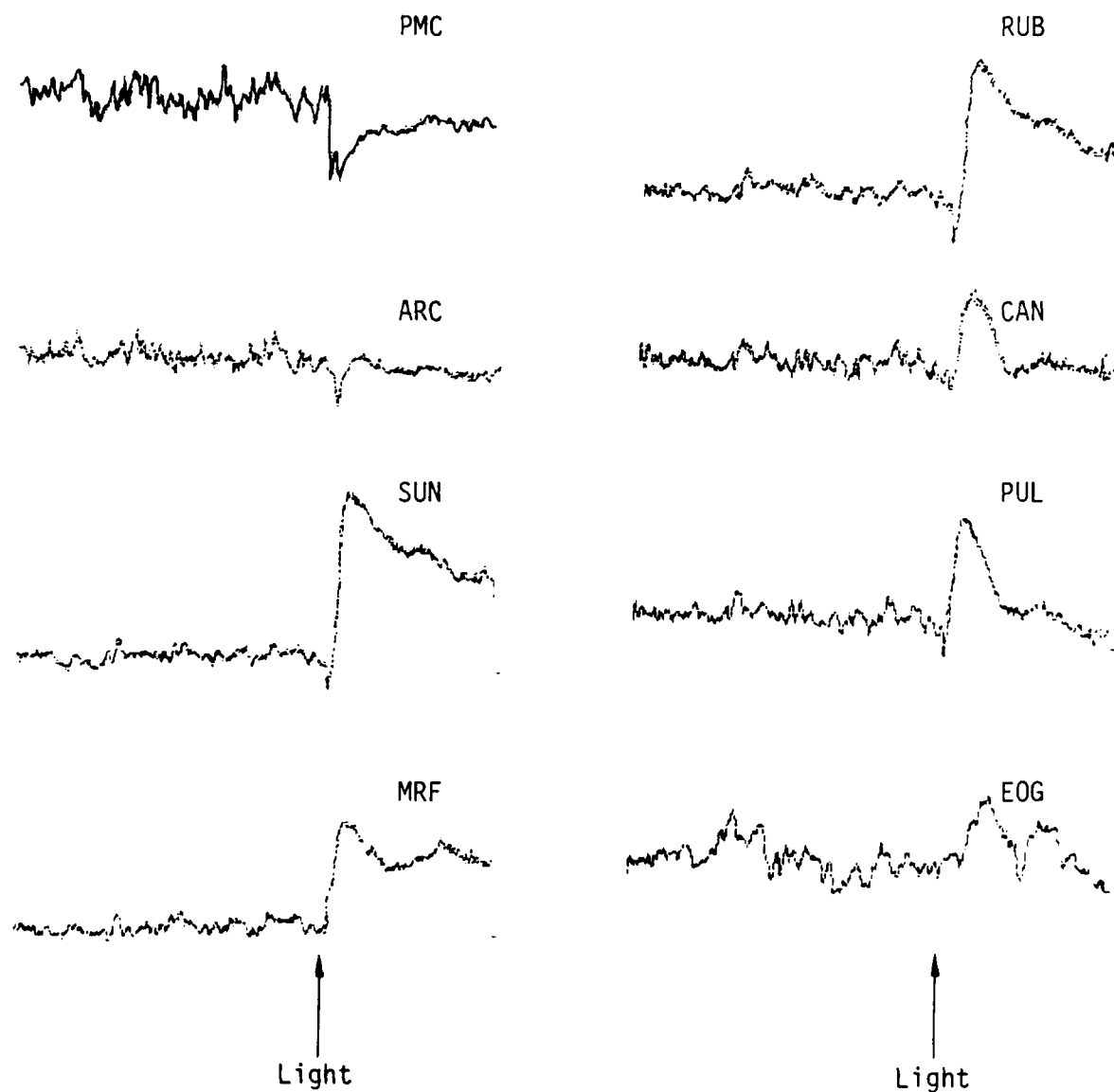


FIGURE 25 POTENTIALS ELICITED BY THE IMPERATIVE STIMULUS (LIGHT) FROM CORTICAL AND SUBCORTICAL PLACEMENTS RECORDED WITH REFERENCE TO POSTERIOR SKULL

ROTUNDA

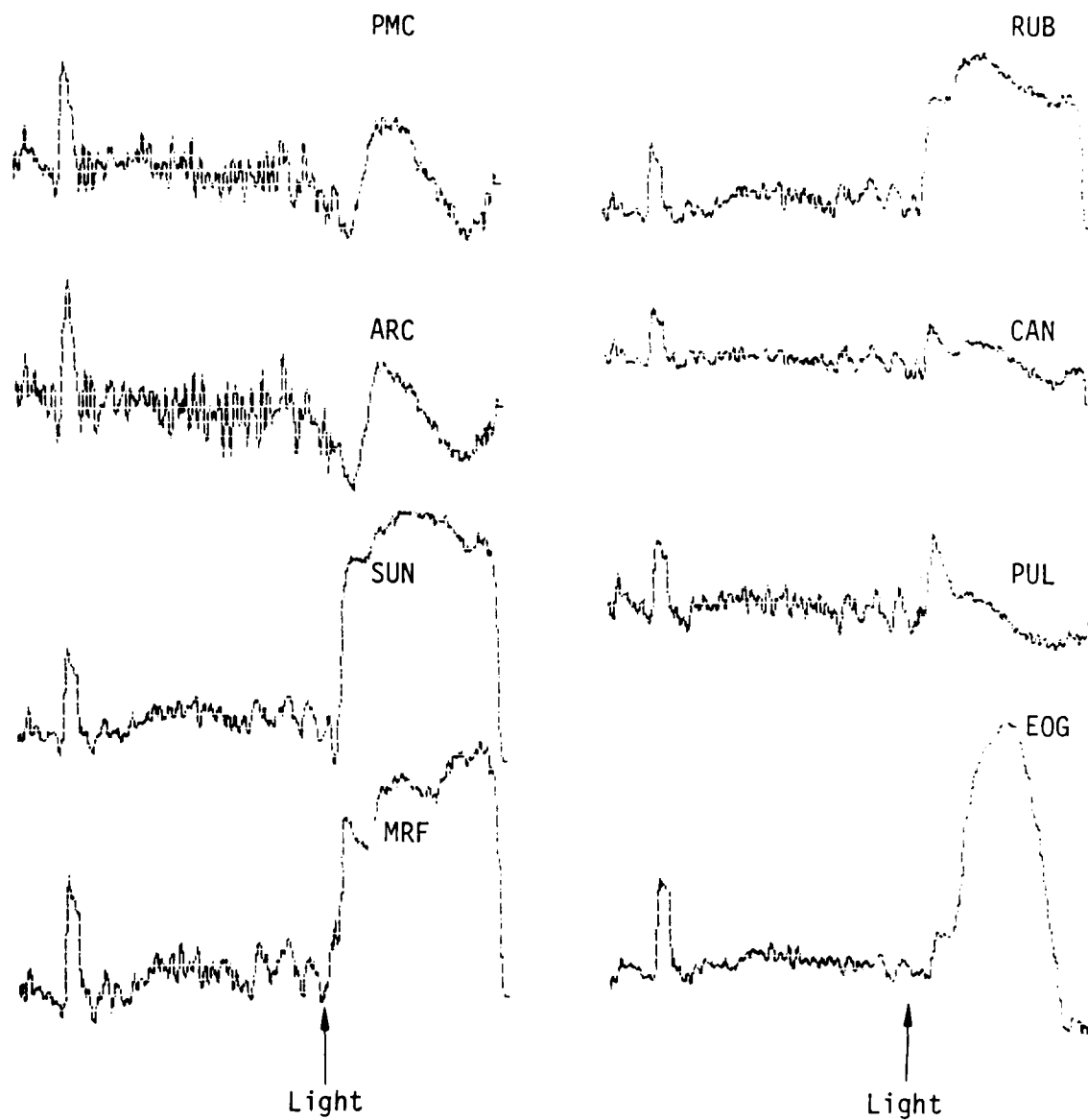


FIGURE 26 POTENTIALS ELICITED BY THE IMPERATIVE STIMULUS (LIGHT) FROM CORTICAL AND SUBCORTICAL PLACEMENTS RECORDED WITH REFERENCE TO POSTERIOR SKULL

MS TUBS

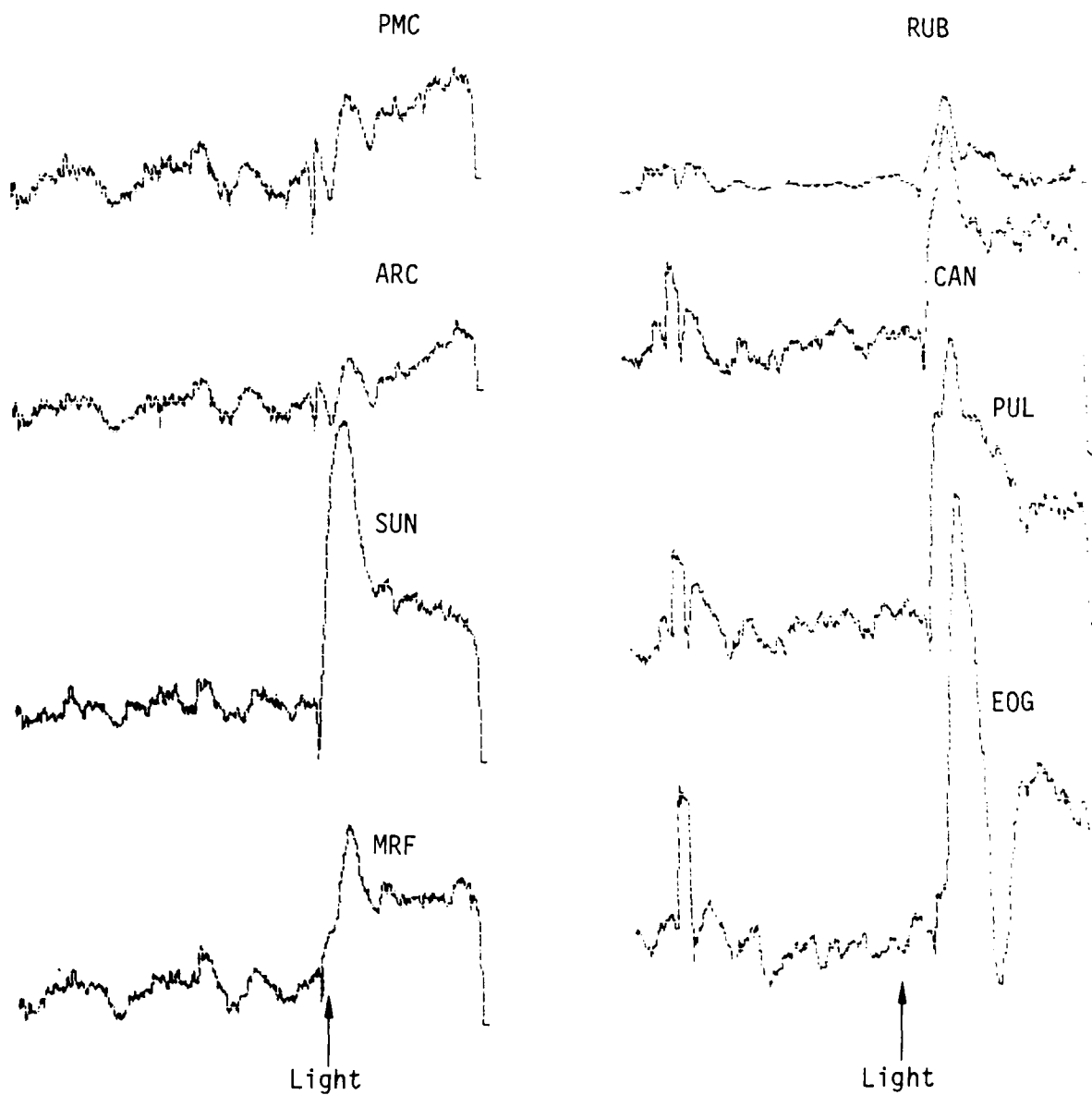


FIGURE 27 POTENTIALS ELICITED BY THE IMPERATIVE STIMULUS (LIGHT) FROM CORTICAL AND SUBCORTICAL PLACEMENTS WITH REFERENCE TO POSTERIOR SKULL

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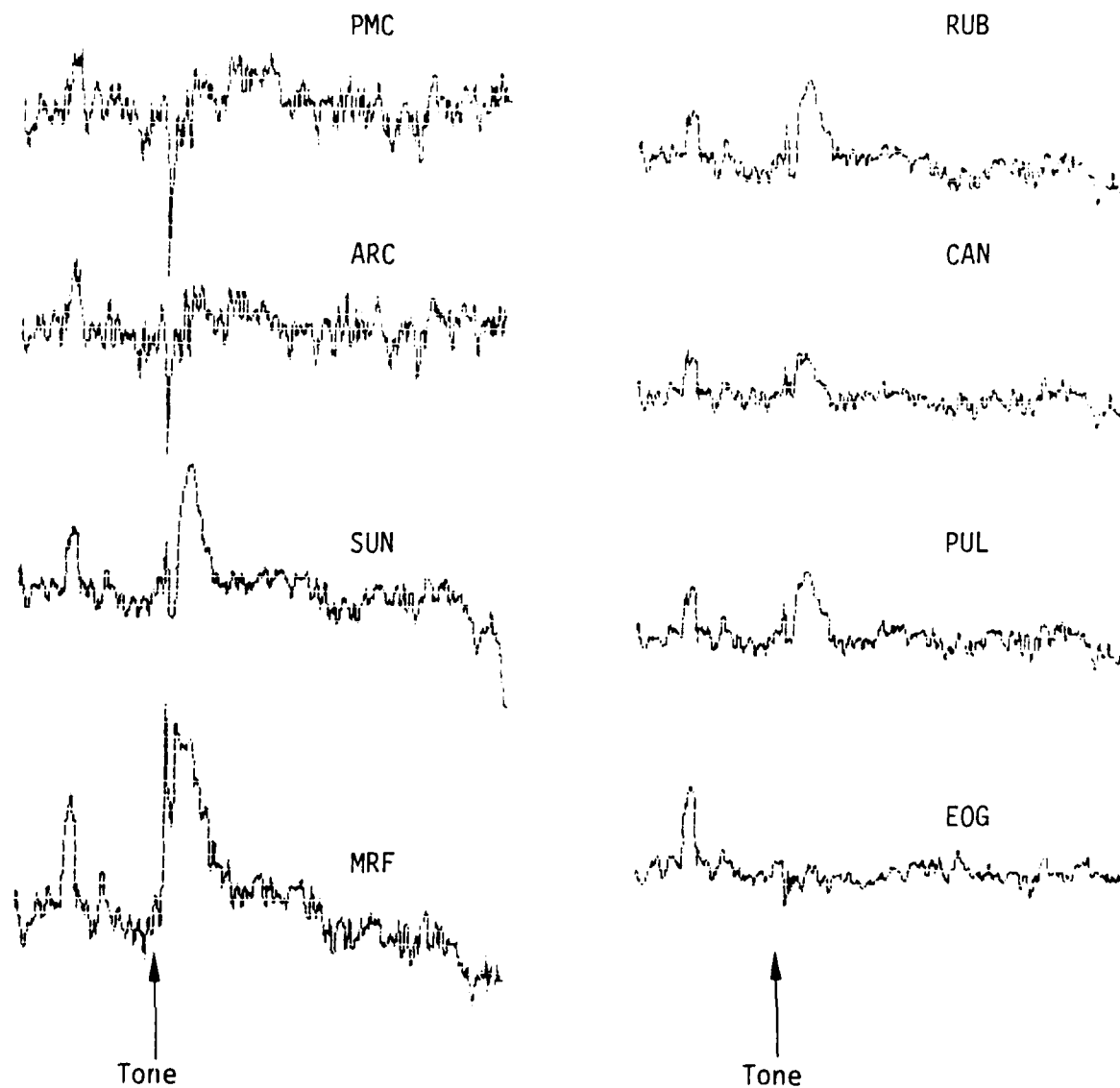


FIGURE 28 POTENTIALS ELICITED BY TONES FROM CORTICAL AND SUBCORTICAL PLACEMENTS RECORDED WITH REFERENCE TO POSTERIOR SKULL

ROTUNDA

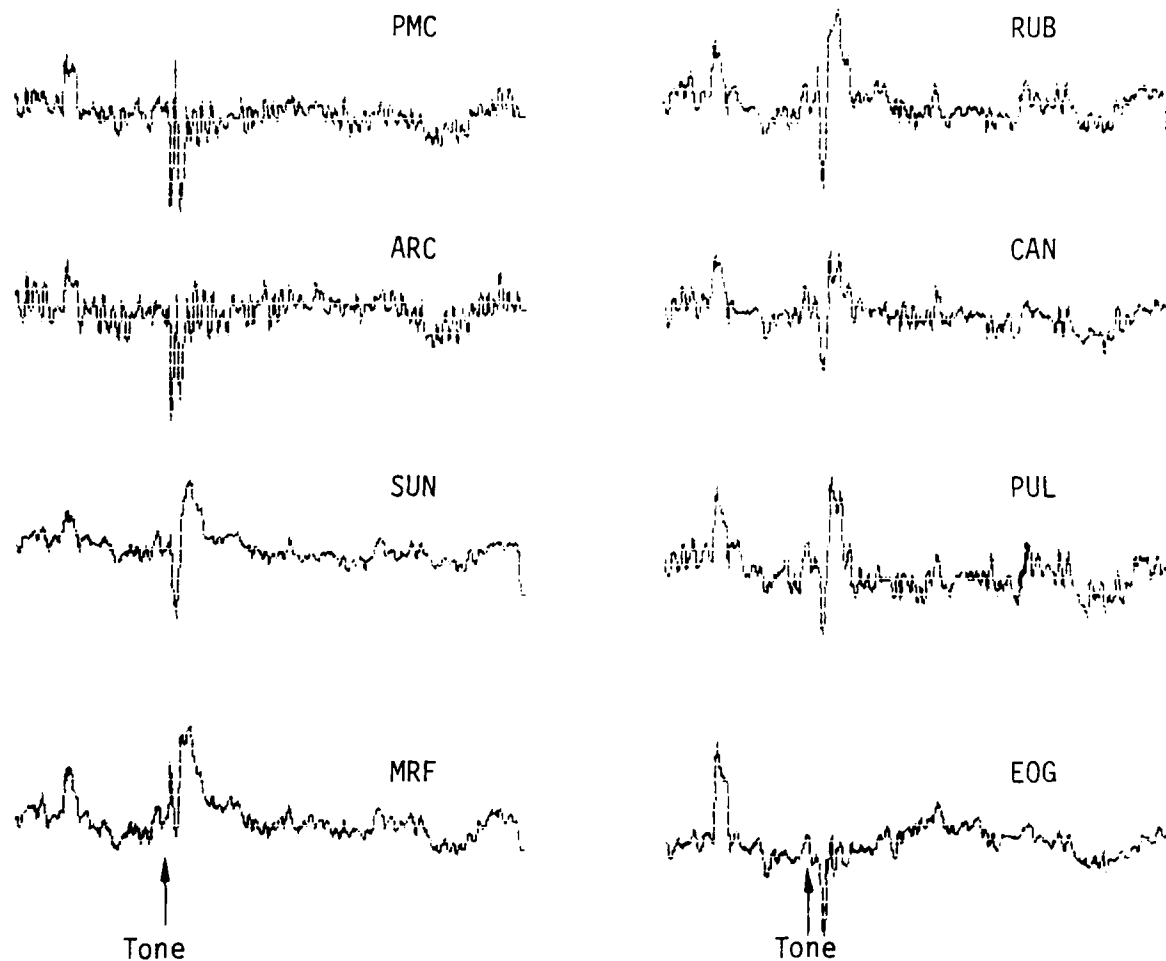


FIGURE 29 POTENTIALS ELICITED BY TONES FROM CORTICAL AND SUBCORTICAL PLACEMENTS RECORDED WITH REFERENCE TO POSTERIOR SKULL

MS TUBS

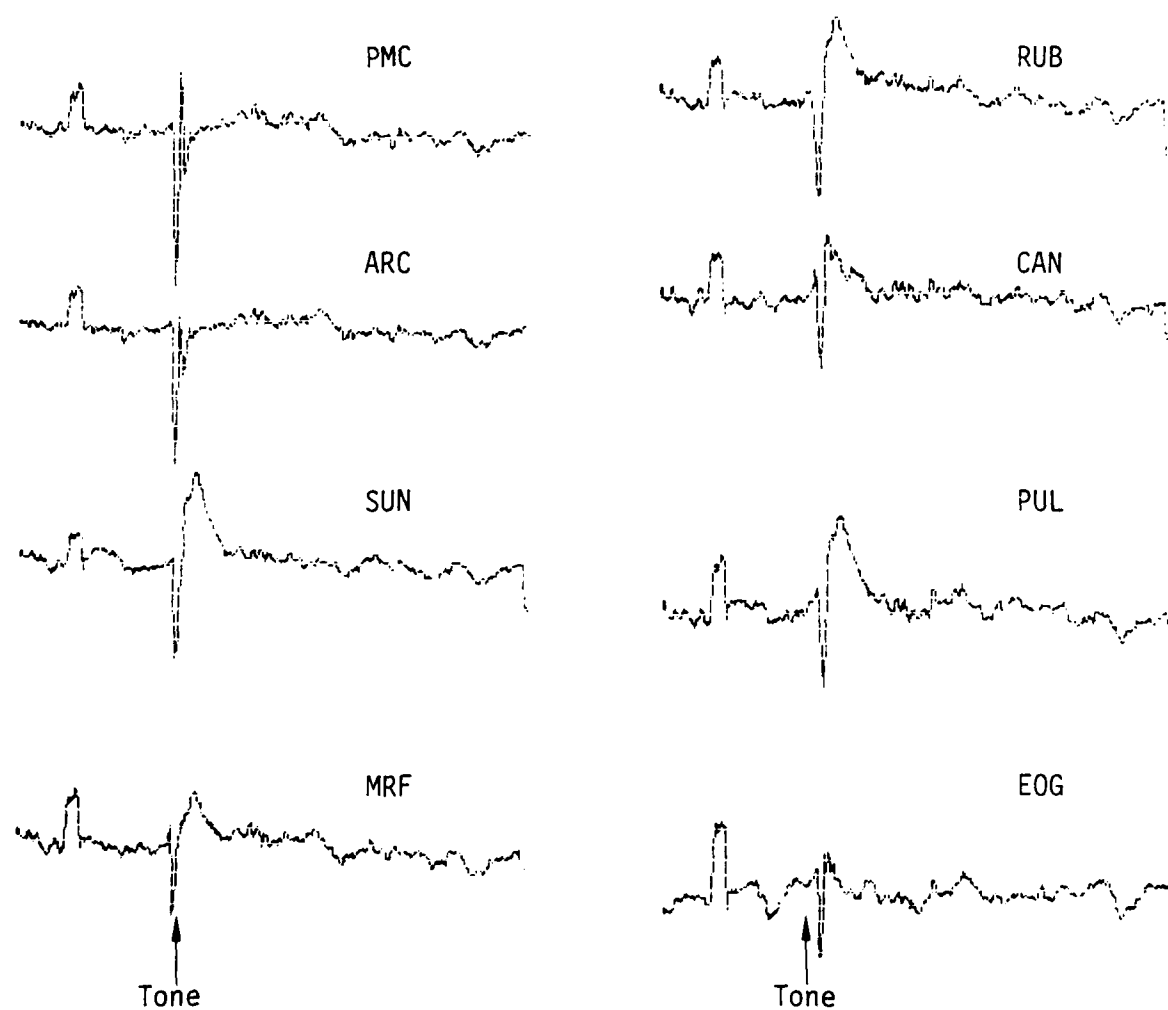


FIGURE 30 POTENTIALS ELICITED BY TONES FROM CORTICAL AND SUBCORTICAL PLACEMENTS RECORDED WITH REFERENCE TO POSTERIOR SKULL

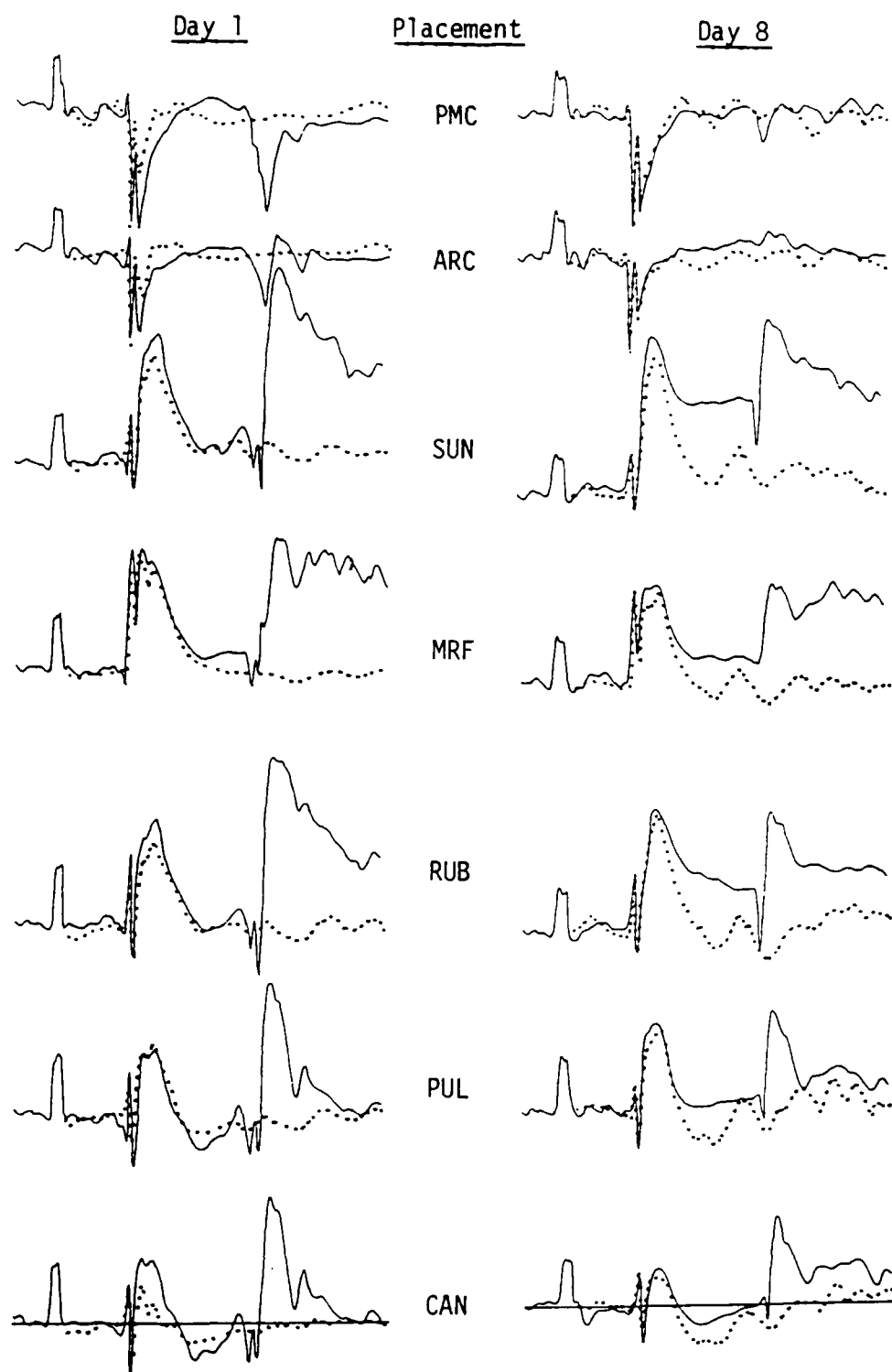


FIGURE 31A EVENT-RELATED POTENTIALS ELICITED ON WS (SOLID) AND NS (DOTTED) TRIALS ON THE FIRST (LEFT) AND EIGHTH (RIGHT) DAYS OF TONE-LIGHT PAIRING. FEMALE RHESUS FL.

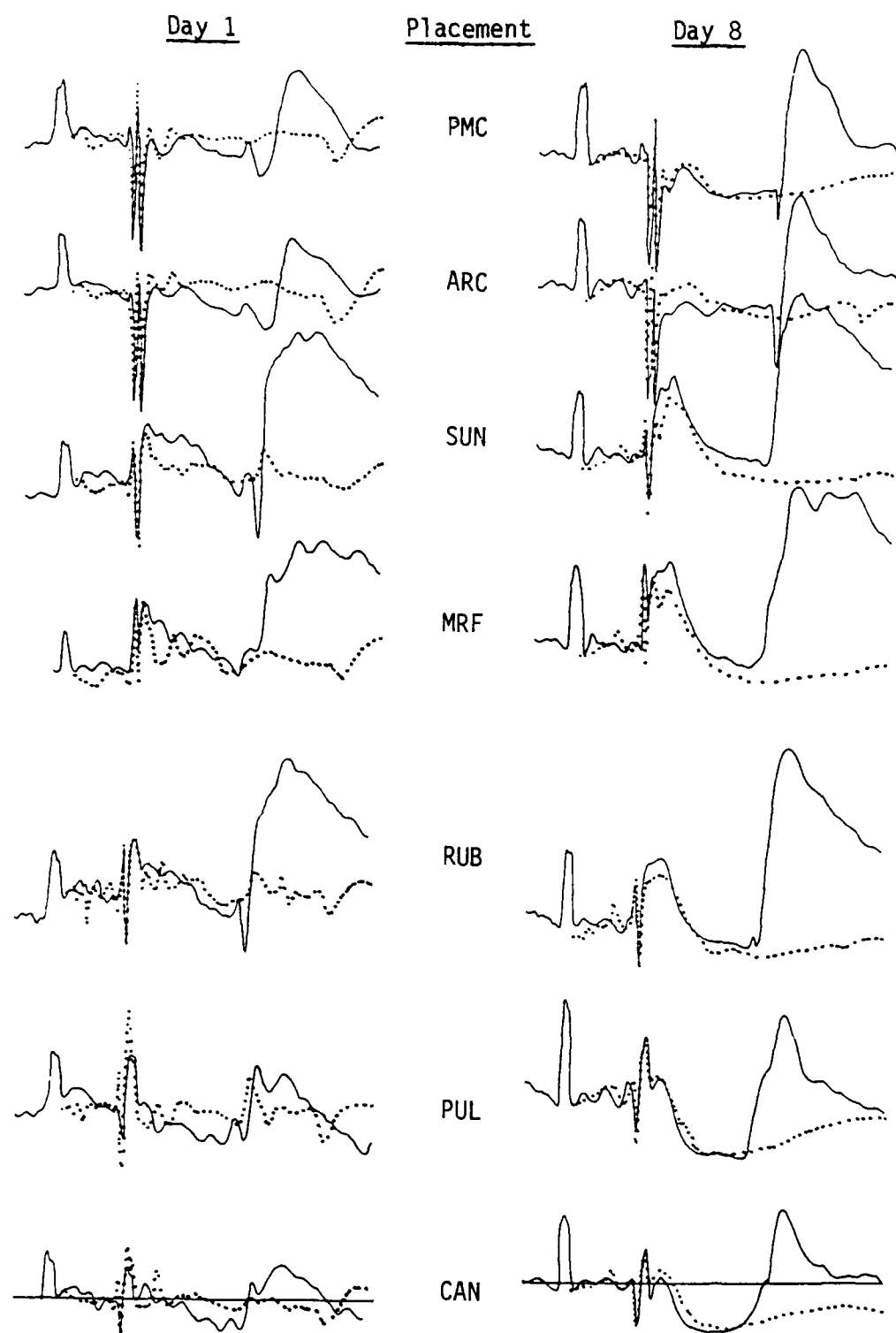


FIGURE 31B EVENT-RELATED POTENTIALS ELICITED ON WS (SOLID) AND NS (DOTTED) TRIALS ON THE FIRST (LEFT) AND EIGHTH (RIGHT) DAYS OF TONE-LIGHT PAIRING. FEMALE RHESUS RO.

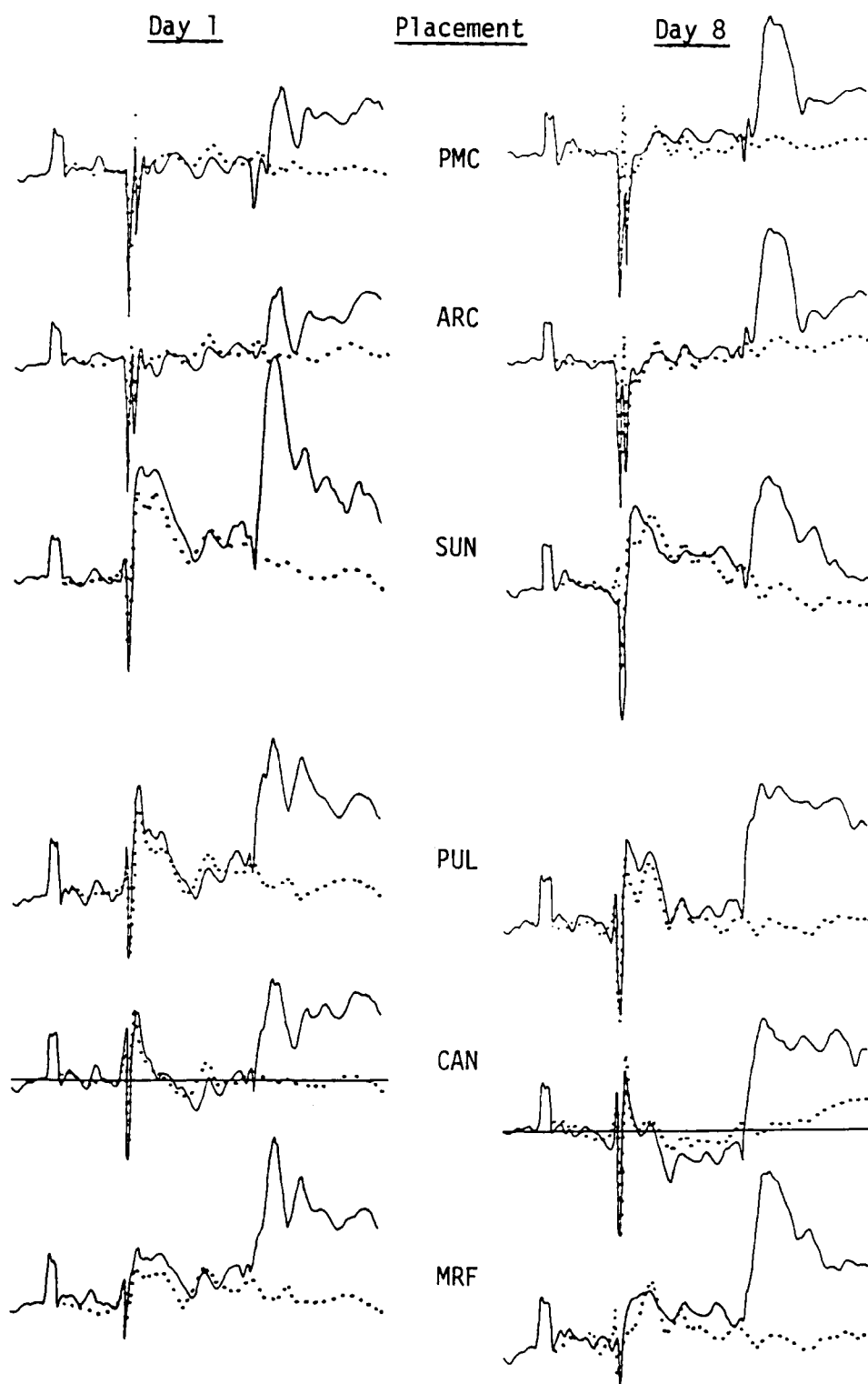


FIGURE 31C EVENT-RELATED POTENTIALS ELICITED ON WS (SOLID) AND NS (DOTTED) TRIALS ON THE FIRST (LEFT) AND EIGHTH (RIGHT) DAYS OF TONE-LIGHT PAIRING. FEMALE RHESUS MT.

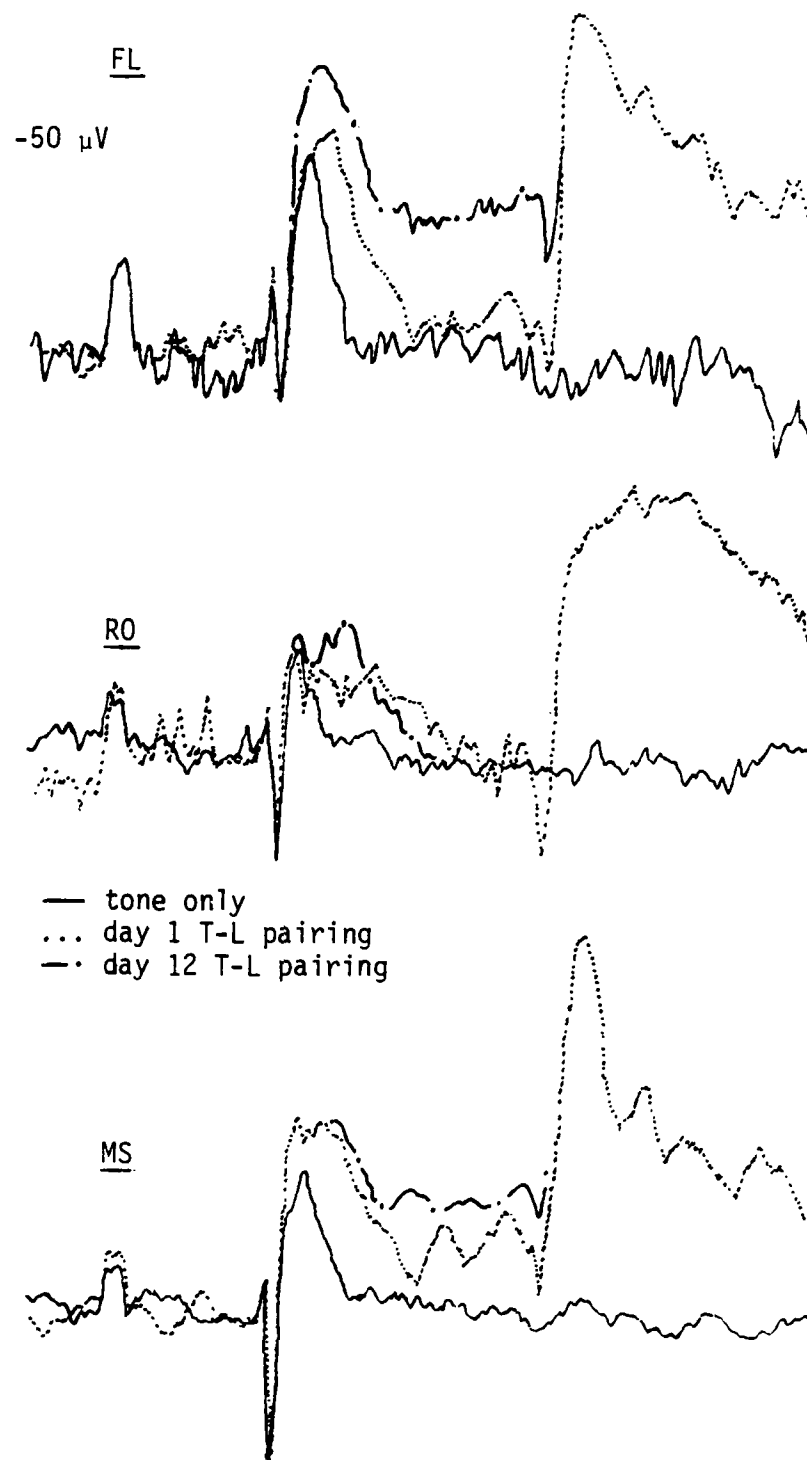


FIGURE 31D POTENTIALS FROM ELECTRODES AIMED AT THE SUBSTANTIA NIGRA BEFORE AND DURING TONE-LIGHT PAIRING IN THREE FEMALE RHESUS MONKEYS

three monkeys exhibited improvement in RT when the WS was included in the paradigm.

b. Use of Local References

A typical waveform elicited from frontal cortices in the cued RT task consists of an early W-shaped wave followed sometimes by a CNV-like slow potential. The W-wave in PMC and ARC was observed in both MS and RO, and a large negative SP was elicited by the light (Figure 32). When recorded transcortically (surface to depth) the W-wave was apparent, but was shifted overall in the negative direction in MS, although it remained essentially the same in RO. In both monkeys, however, the response of the reference just below the cortex was inverted in polarity when recorded with respect to a general white matter reference (aimed 11 mm anterior to the meatus, 13 mm lateral to midline, and 9 mm below the dura). This suggests that the W-wave either is generated in the lower layers of cortex or represents a response in white matter itself. The post-IS slow potential was reduced in amplitude with transcortical recording and was not evident when the transcortical references for PMC and ARC were recorded against the general white matter reference. This suggests that the post-IS slow potential was generated in superficial regions of the motor areas.

Characteristics of the response from the electrodes aimed at the SUN were altered by recording with respect to the nearby reference (Figure 32). In MS the waveform decreased in amplitude overall, especially the post-IS slow wave. In RO the main effect was on the post-IS slow wave. Since fairly typical responses were still evident in the SUN-local reference recordings, they were probably generated in the vicinity of the active electrode. Their reduced sizes with bipolar recording suggests either a contribution from the routinely used reference (midline posterior cortex) or a widespread generator that includes the local reference (thus reducing the differential bipolar response). The latter is supported by the recording with respect to the general white matter reference, which evidenced both foreperiod and (in RO) post-IS negativity. The absence of post-IS negativity in either bipolar or referential (white matter) records of MS suggests a remote generator--perhaps the midline posterior bone reference.

In both monkeys a dramatic change occurred in the post-IS MRF slow potential with bipolar recording--it reversed in polarity, increased in amplitude, and decreased in duration (Figure 32). The inverted response did not appear in reference-to-reference recording or in the pulvinar. It appears to be generated in the griseum centrale, since the active and reference electrodes were in opposite hemispheres and the recording spanned the griseum and pulvinar.

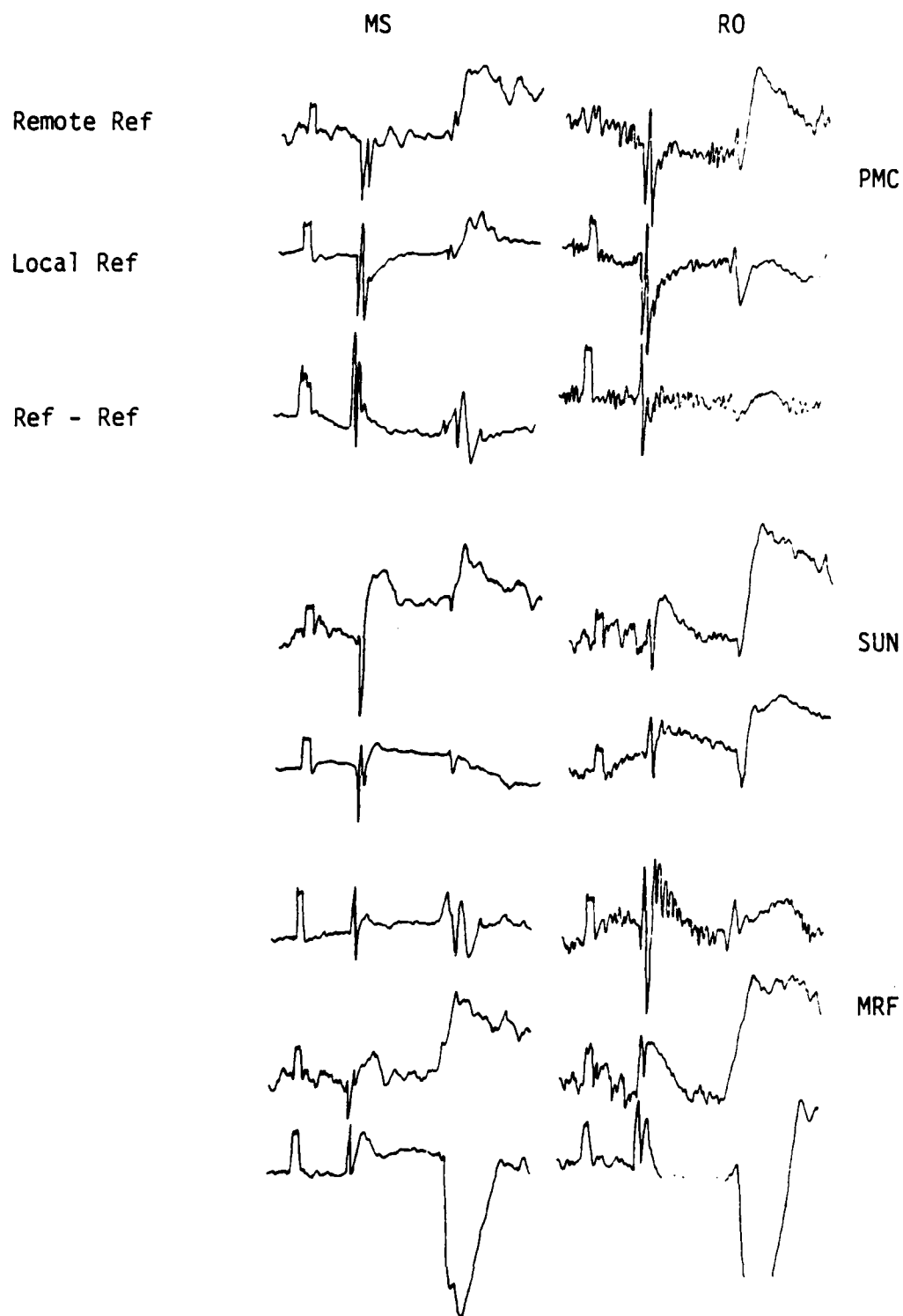


FIGURE 32 RECORDINGS FROM SUBCORTICAL STRUCTURES WITH RESPECT TO DIFFERENT REFERENCES

5. Male Rhesus

Five male juvenile rhesus monkeys obtained for a drug study were used initially on this project to further study acquisition of ERPs during tone-light pairing in the cued RT task. These monkeys had previously been trained to have short RTs. During four days of pseudoconditioning in which tones and lights were randomly intermixed, mean RT was 785 (± 84) msec. For sequential 5-day blocks of tone-light pairing, mean RTs were 720 (± 39), 760 (± 94), 687 (± 61), and 706 (± 116.3) msec. Thus, provision of the WS facilitated the performance of these monkeys. During tone-light pairing both the WS and NS were included.

Recordings of main interest in these monkeys were from electrodes aimed at the premotor cortex (PMC), basolateral amygdala (AMG), midportion of the hippocampus (HPC), substantia nigra (SUN), cerebellar fastigial n. (FAS), cerebellar dentate n. (DEN), pulvinar (PUL), and midbrain reticular formation (MRF). Recording was referential to midline posterior bone, 15 mm posterior to the auditory meatus.

Potentials that developed consequent to the associative conditioning--obtained on the 18th day of training--are shown in Figure 33. Three monkeys (BU, MA, JE) developed robust anticipatory SPs in PMC, one (DU) exhibited a small negative SP, but the fifth (MI) showed only a small early slow wave and a subsequent small positive SP. In the MRF, transient positive spikes were a feature of the response of every monkey to the WS and IS, but only BU and JE generated SPs in the foreperiod. Responses from the PUL were similar in the three monkeys (MI, BU, JE) with that recording--i.e., there was a large fast-rising slow wave elicited by the WS, with subsequent fast return to baseline or positive overshoot (JE). In two monkeys (DU, MA) waveforms recorded from electrodes aimed at the CAN were almost exactly like those obtained from PMC. Only one monkey (JE) exhibited a response from the SUN that was typical of other groups of monkeys with electrodes aimed at that nucleus. In the DEN there was a tendency toward development of positive SPs in four monkeys (except JE) with a large sustained response generated by MA. Responses from the AMG were variable and generally nondescript except for a relatively robust response from JE. The electrode aimed at the FAS in monkey MI exhibited a large positive SP in the foreperiod, whereas responses characterized by large early slow waves with a rapid decline and positive overshoot at the end of the foreperiod were observed in BU and JE. In one monkey (MA) the response from an electrode aimed at the cingulate gyrus was like the PMC response, whereas in the other monkey with this placement the response was similar to responses observed in the AMG and DEN.

Although many of the placements studied here did not exhibit sustained activity in the foreperiod indicative of preparatory set, there was, typically, a considerable difference in the early part of the responses to the

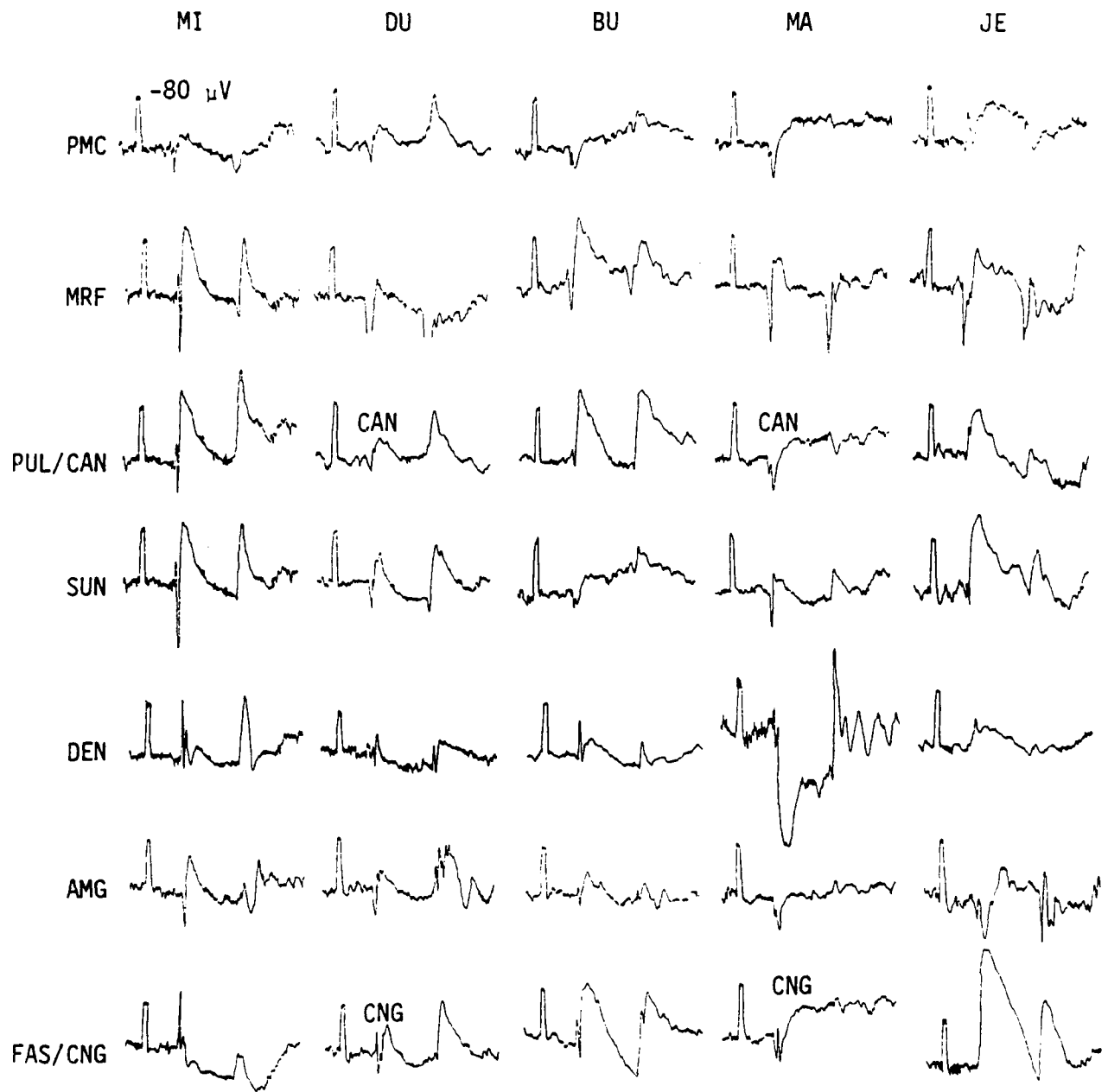


FIGURE 33 EVENT-RELATED POTENTIALS FROM CORTICAL AND SUBCORTICAL ELECTRODES IN MALE RHESUS MONKEYS

WS obtained during pseudoconditioning (wherein the tones had no cue significance) and after tone-light pairing. These changes were evident to a small extent in many cases on the first day of tone-light (T-L) pairing. Examples of these are shown in Figures 34-37. The appearance of a change of this time in one placement was not always associated with a change in other placements, suggesting differential involvement of various nuclei in associative conditioning.

In general, these monkeys showed fair to good discrimination between responses to the WS and NS when a robust response was evoked by the WS (e.g., Figures 34-37). Of 23 good responses (on one day late in T-L pairing--e.g., day 18) only 3 cases of poor discrimination occurred (i.e., responses in these cases were elicited by the NS as well as the WS). Some placements exhibited very systematic acquisition functions (e.g., Figures 34-37), and during development of the ERPs to the WS there was generally a concomitant, but transient, enhancement of responses elicited by the NS. Although the responses to the NS were attenuated later in training than were the responses to the WS, they remained larger than the response obtained during pseudoconditioning. This is probably because the monkeys continued to "evaluate" both tones in the process of discriminating them. Examples of plots of quantitated SP amplitude measured at the end of the foreperiod are shown in Figures 38 and 39.

B. Variation of Proportions of Warning and Neutral Stimuli

1. 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 one 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. (1986) 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

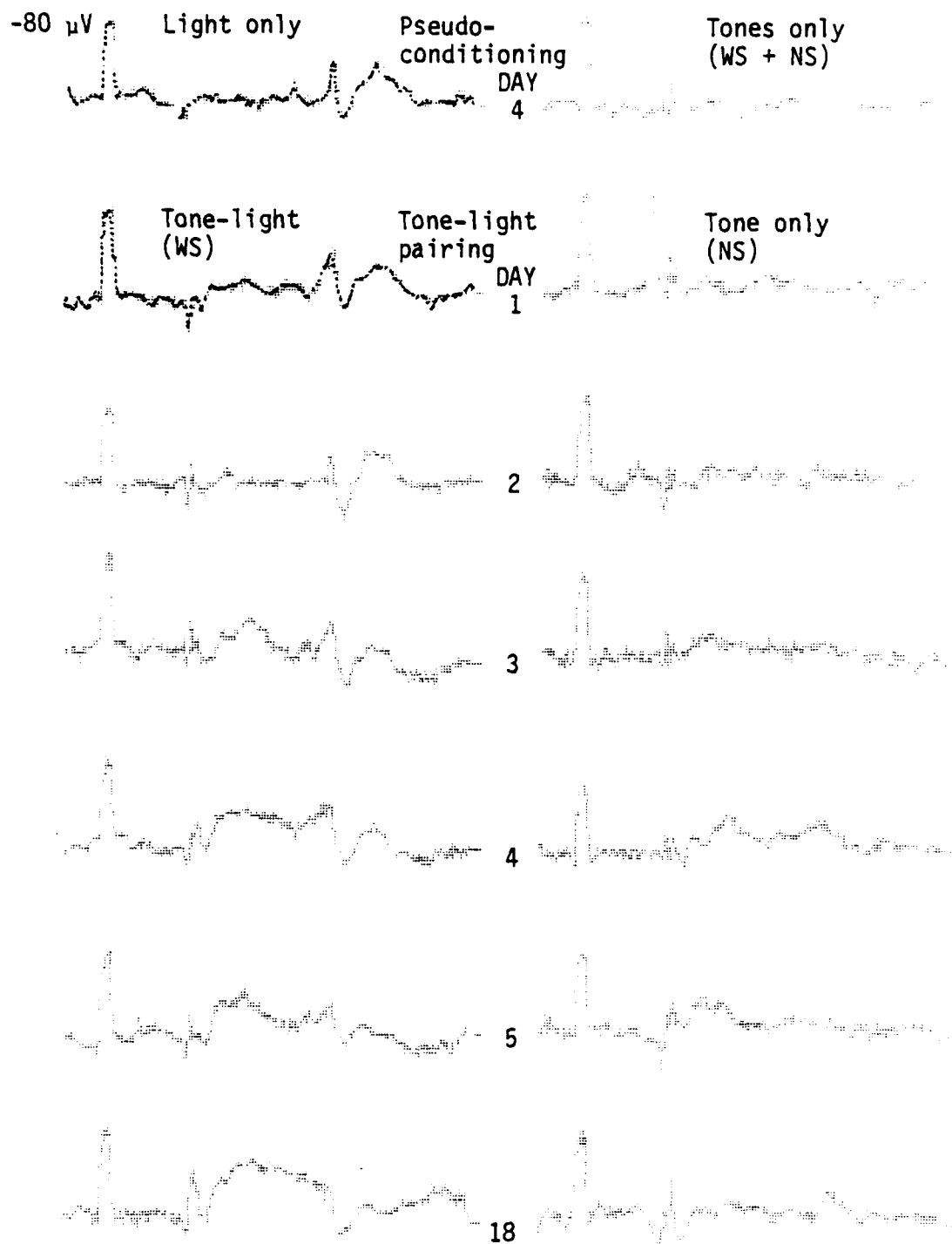


FIGURE 34 EVENT-RELATED POTENTIALS FROM JE-PMC DURING PSEUDOCONDITIONING AND TONE-LIGHT PAIRING. EPOCH = 4800 MSEC.

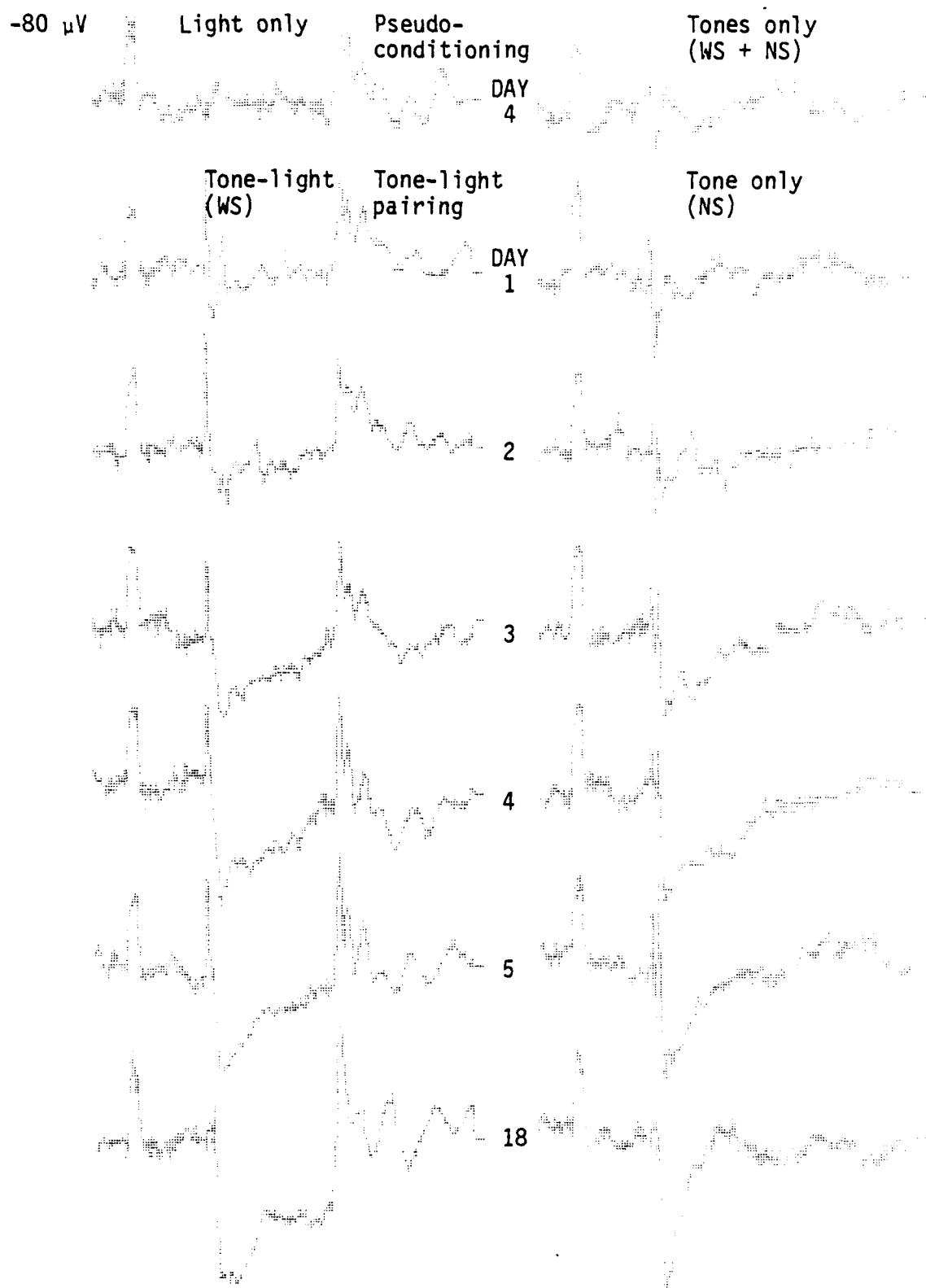


FIGURE 37 EVENT-RELATED POTENTIALS FROM MA-DEN DURING PSEUDOCONDITIONING AND TONE-LIGHT PAIRING. EPOCH = 4800 MSEC.

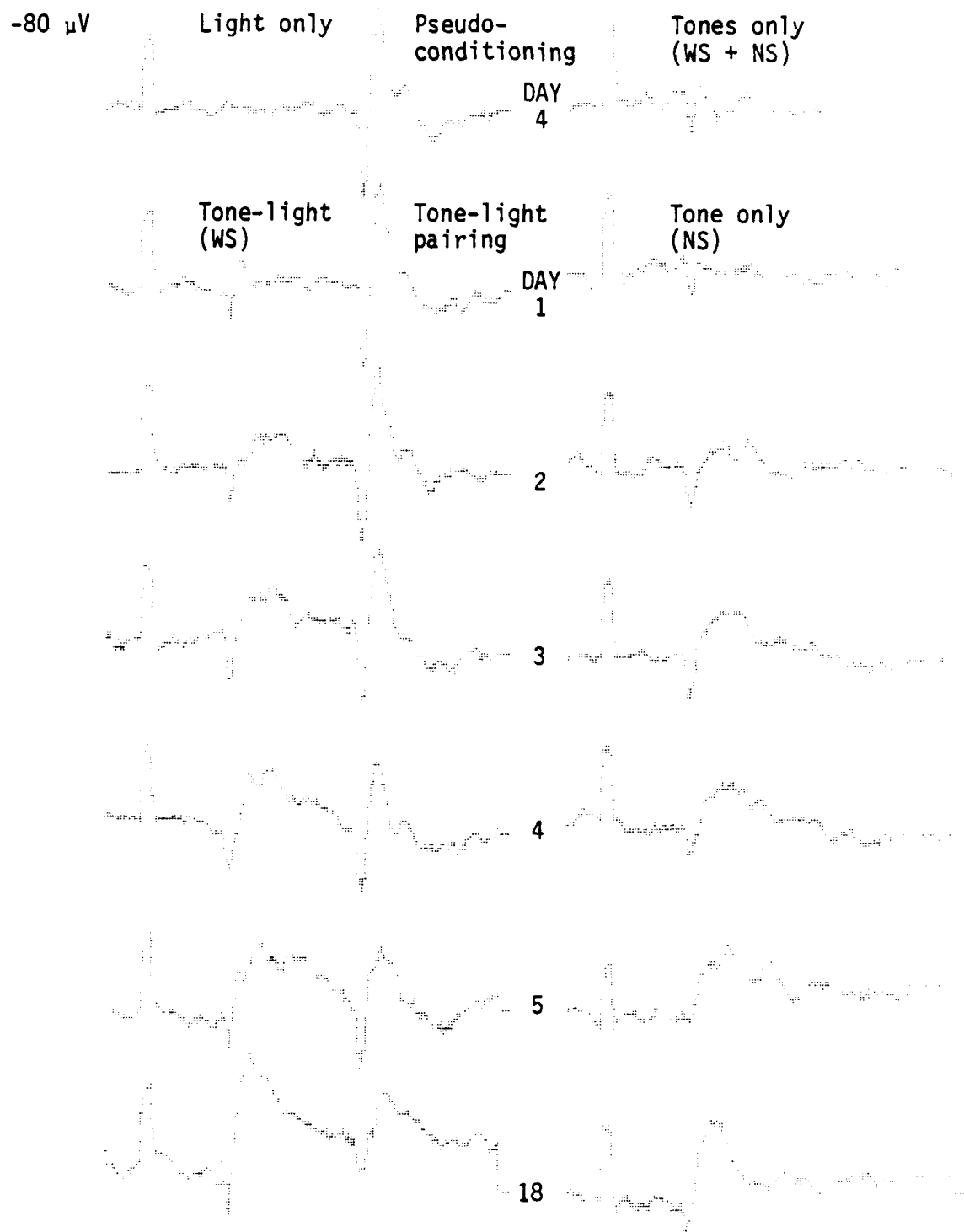


FIGURE 36 EVENT-RELATED POTENTIALS FROM BU-MRF DURING PSEUDOCONDITIONING AND TONE-LIGHT PAIRING. EPOCH = 4800 MSEC.

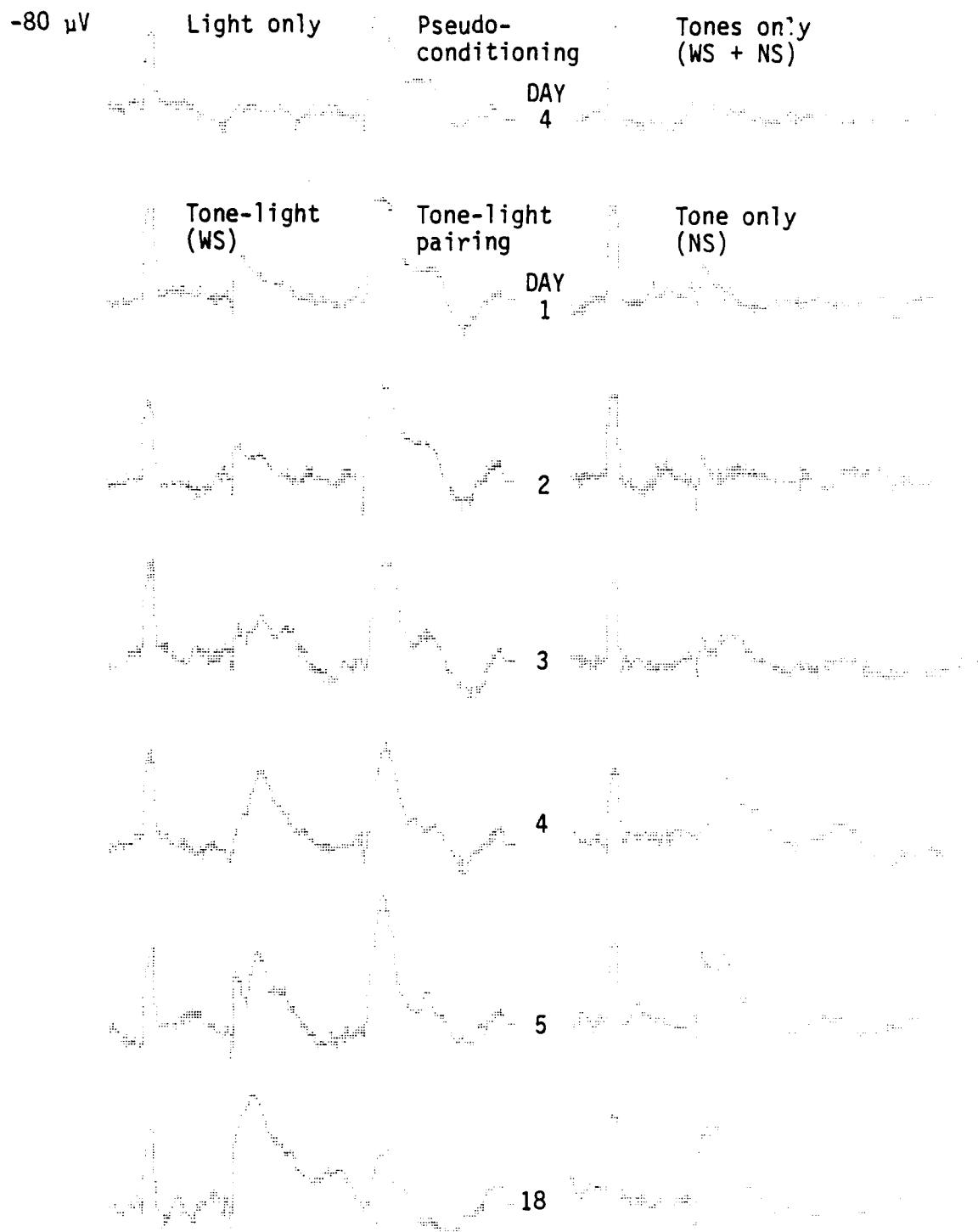


FIGURE 35 · EVENT-RELATED POTENTIALS FROM JE-SUN DURING PSEUDOCONDITIONING AND TONE-LIGHT PAIRING. EPOCH = 4800 MSEC.

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NEUROPHYSIOLOGICAL BASES OF EVENT-RELATED POTENTIALS

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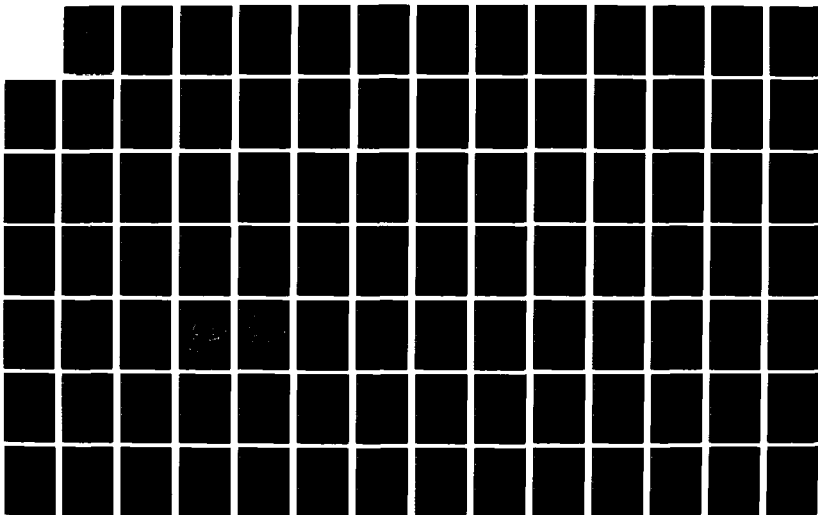
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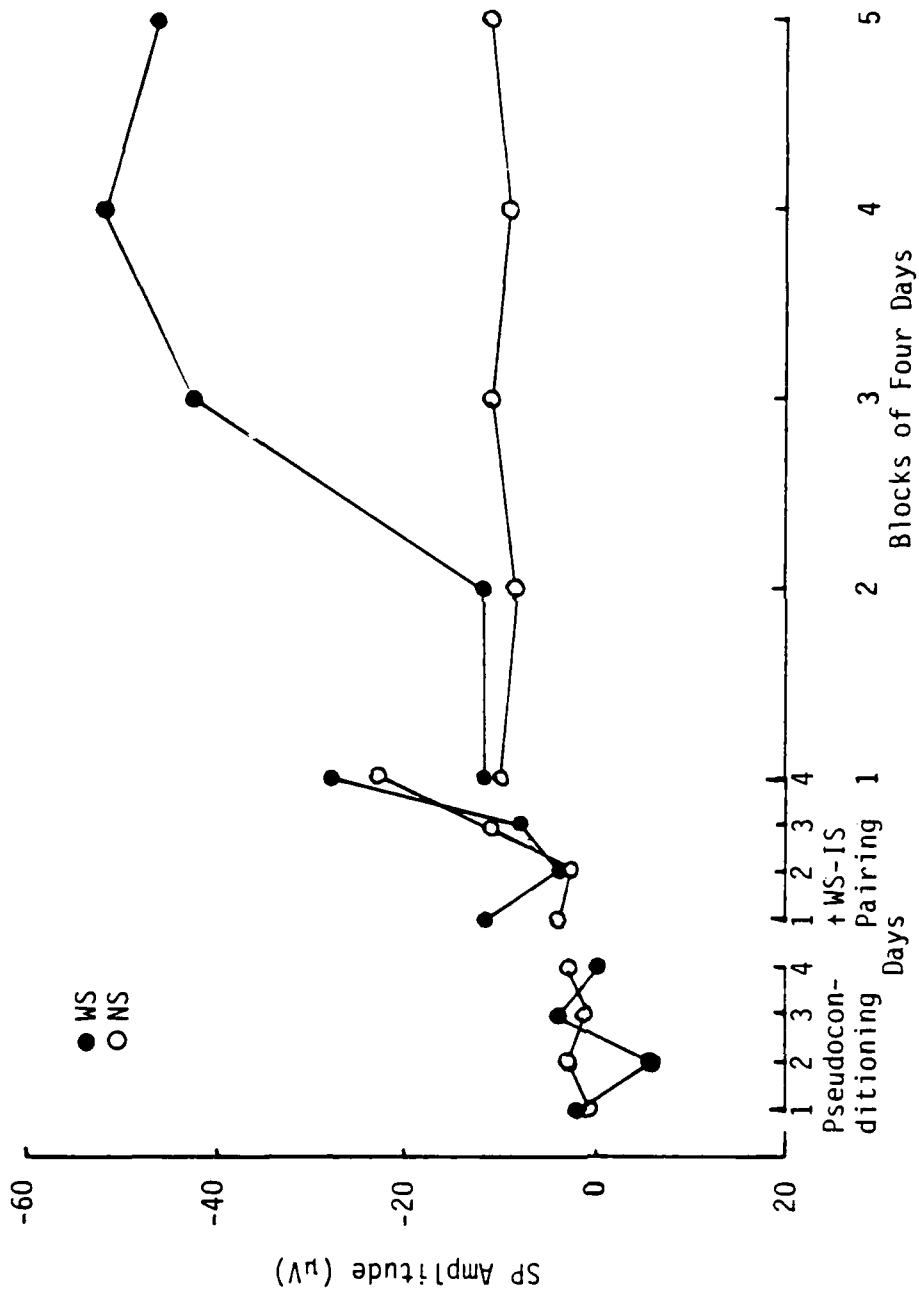


FIGURE 38 CHANGE IN SP AMPLITUDE IN JE'S PMC AS A FUNCTION OF TRAINING AND CUE VALUE OF TONES

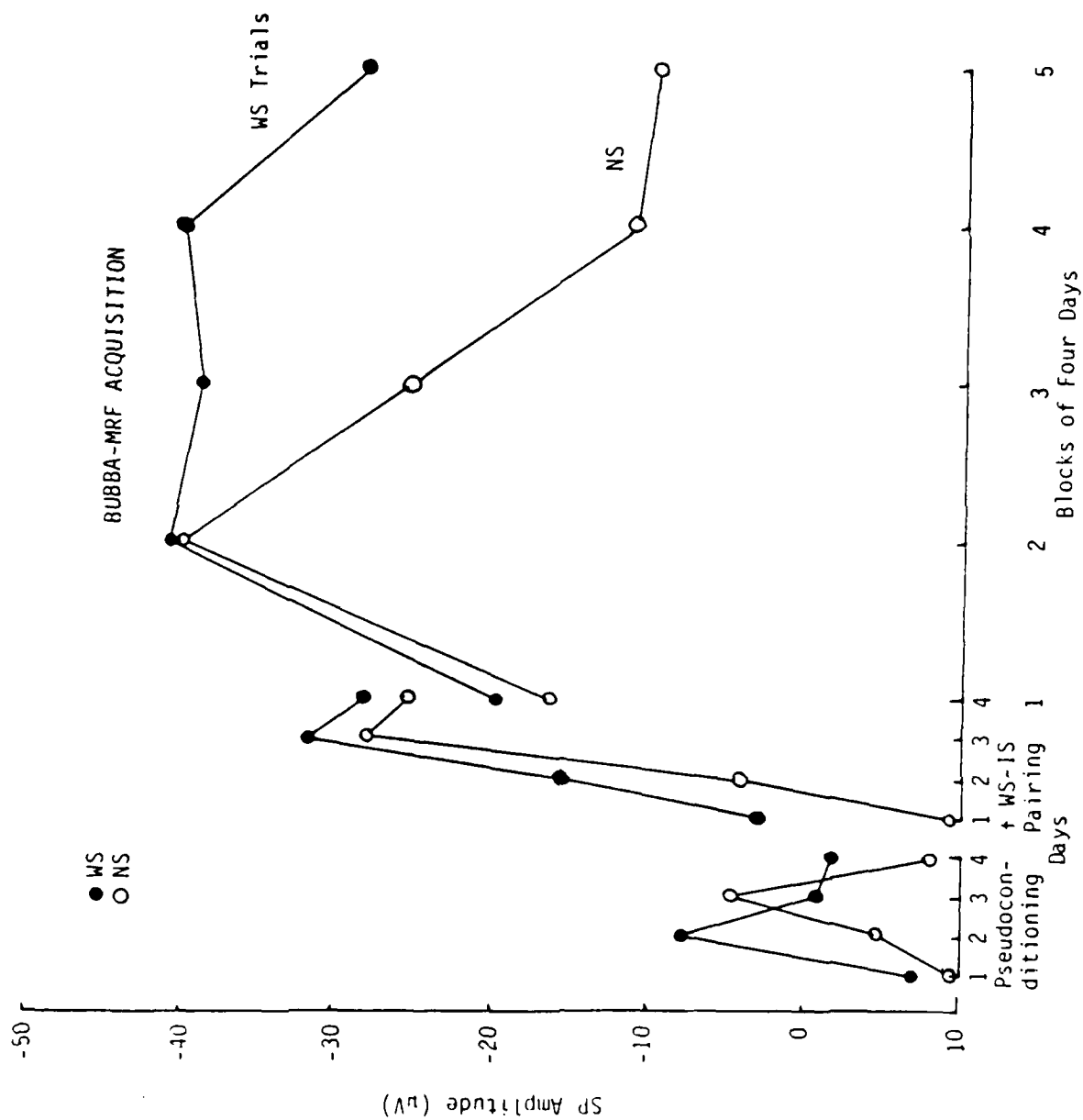


FIGURE 39 CHANGE IN SP AMPLITUDE IN BU'S MRF AS A FUNCTION OF TRAINING AND CUE VALUE OF TONES

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.

Results of several studies suggest that potentials with characteristics like the human P300--e.g., sensitivity to changing proportions of target and nontarget stimuli--can be observed in animals (e.g., Pineda et al., 1987; Arthur and Starr, 1984; Glover et al., 1986; Gabriel et al., 1983). With the exception of the study by Gabriel et al., who reported P300-like potentials in the rabbit's thalamus, all animal studies have involved recordings only from the cortex, providing little information about the involvement of subcortical structures in the processes related to the P300.

P300-like potentials have been observed in animals when a classical conditioning paradigm has been used to establish cue significance (e.g., Glover et al., 1986). The cued-RT task is similar to the classical paradigm, but differs in that the animal must withhold an overt response until the imperative stimulus appears, rather than respond to the conditioned stimuli. Nevertheless, the WS and NS tones in our paradigm are analogous to the significant and nonsignificant cues used in the other studies, and they elicit different responses as shown above. Because the variation of proportions of significant and nonsignificant cues is a fundamentally defining condition of the P300, we varied the proportions of WS and NS trials of the cued-RT task.

Another reason for our examination of this manipulation was to determine whether we could promote a more robust discrimination of ERPs on WS and NS trials. We conjectured that having NS trials occur more frequently than normal (50%) would lead to extinction of responses to the NS--and, perhaps because of a contrast effect, to larger responses on WS trials. Because the manipulation of stimulus proportions has never been carried out in a CNV paradigm, we were also interested in determining whether the late SPs would respond to the manipulation.

2. Cynomolgus Monkeys

In the first examination of the manipulation of WS-NS proportions (using the cynomolgus monkeys described above) 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, complete records were available for only nine days of this testing. The effect we expected to see was enhancement of the differentiation of responses on WS and NS trials in the 20% condition compared

with the condition involving 50% WS trials. That result occurred robustly in only one monkey (ET) and in the MRF electrode in another (SM). ET exhibited enhanced discrimination in the LPM, LMC, SUN, MRF, and NVA placements. Figure 40 shows responses from monkey ET on WS and NS trials during the last day of this procedure for the 20% and 50% conditions.

There was no component that looked like a P300 wave, but in all cases there was enhancement of most components of the waveforms on WS trials and diminution of the responses on NS trials when the WS occurred only 20% of the time. Of particular interest may be the sharp-rising negativity in the SUN (and MRF) that peaks around 350 msec. Halgren et al., 1980 suggest that the P300 may be due to a deep negative generator that is reflected at the scalp as a positive potential. Although contributions 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). Also, we have not generally observed robust responses from the hippocampus and low WS proportion had only a small effect in this structure in monkey ET. We suggest that the SUN, MRF, and related deep structures are components of the intracerebral system related to genesis of the P300.

Our results also indicate that processes other than those specifically related to the P300 are sensitive to the manipulation of the proportions of significant and insignificant cues. The altered proportions probably cause extinction of responses to neutral stimuli and, through a contrast effect, enhance responses to significant stimuli. This affects both stimulus evaluation (reflected in early and middle components) and preparatory processes (reflected in late SPs).

Factors that control the appearance of the proportionality effect were not known or controlled sufficiently to elicit it in all monkeys. Therefore, additional tests were carried out with the percentage of WS trials varied from 10% to 90% (10, 30, 50, 70, 90%). The proportion was varied from day to day. Figure 41 shows superimposed waveforms for the WS and NS trials at 10 and 50% presentations of the WS. The placements shown are those that exhibited good responses during previous testing, plus the CAN which began to show small positive shifts. Only the MRF was examined in monkey SM (not shown) because other electrodes seemed dysfunctional (all showing nearly identical waveforms).

In Figure 41 the records are arranged from top to bottom in terms of the degree (least to most) to which the SUN waveforms differed in response to WS and NS tones. The ERPs in WS and NS trials in monkey CO differed slightly in the SUN and MRF but not in other placements. In the other monkeys, the WS-NS differentiation in the 50% WS condition was greater than observed in the previous experiment, due probably to the additional

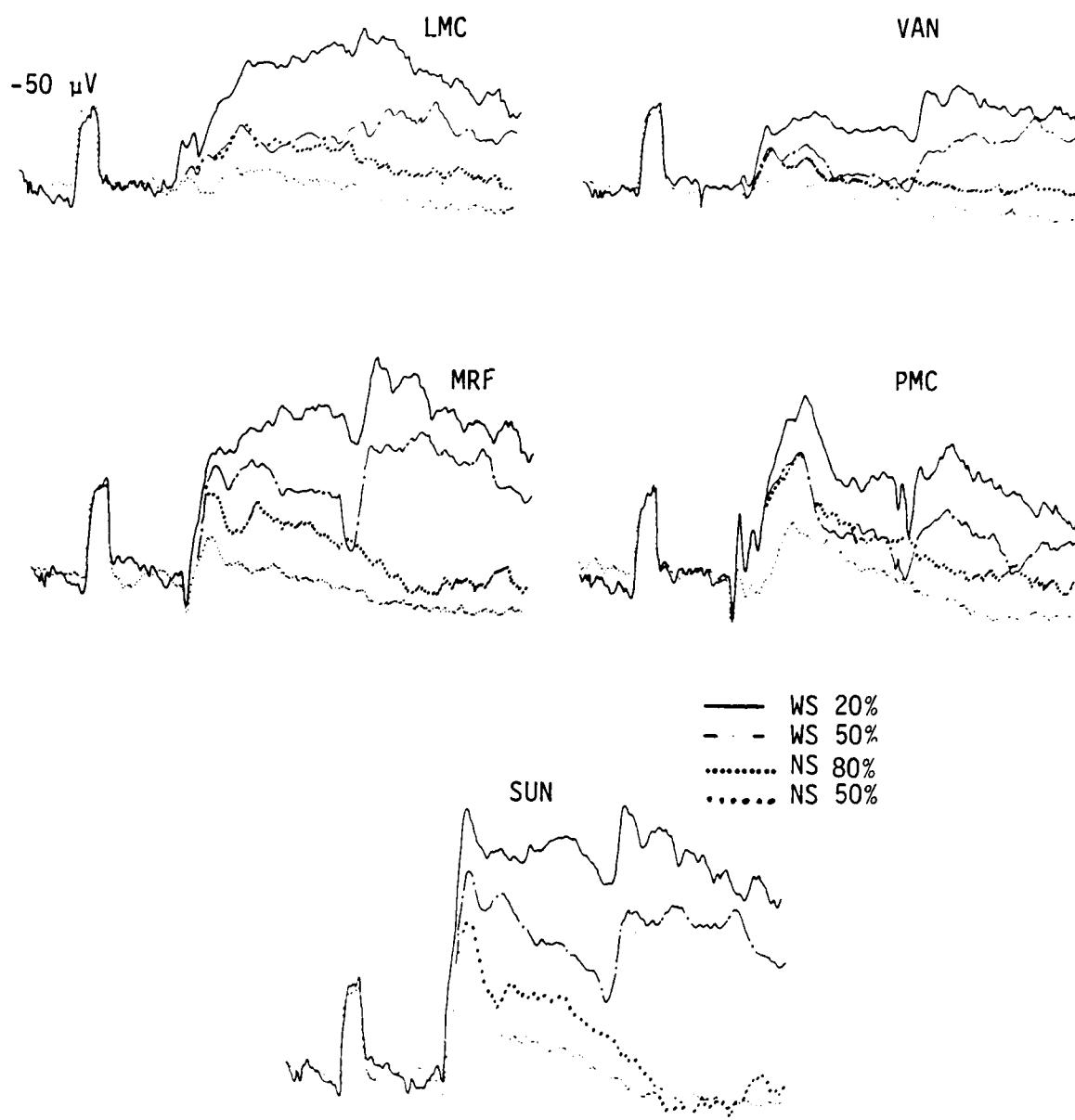


FIGURE 40 COMPARISON OF ERPS IN SEVERAL BRAIN REGIONS OF MONKEY ET ELICITED ON WS AND NS TRIALS WHEN THE WS OCCURRED ON EITHER 20% OR 50% OF THE TRIALS. EPOCH = 4800 MSEC.

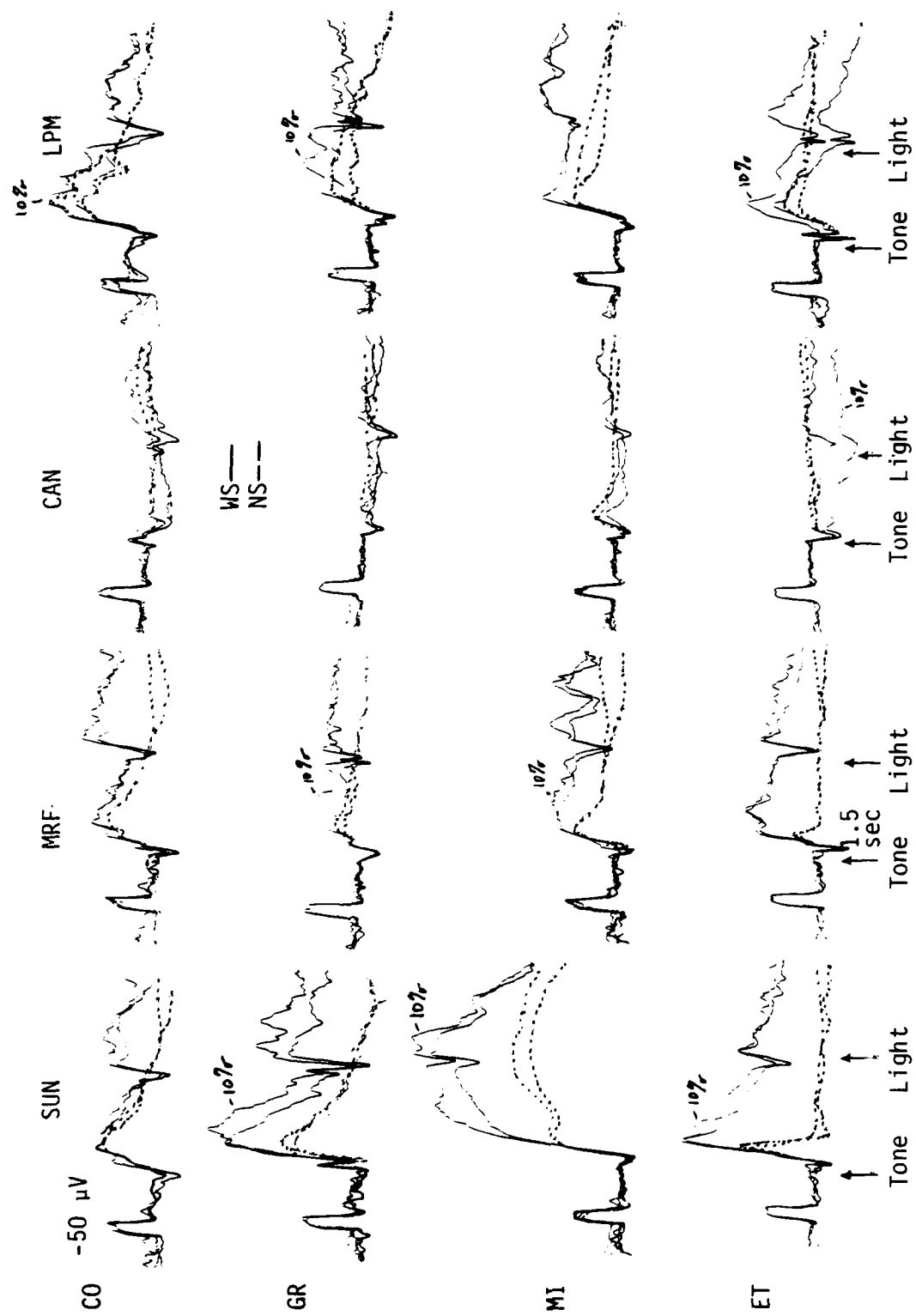


FIGURE 41 Averaged ERPs from several placements in four monkeys when the WS occurred on 10 or 50% of the trials.

training. Enhancement of the WS-NS differentiation by lowering the WS proportion to 10% occurred most consistently (3 of 4 monkeys) in the SUN. The effect was also evident in the MRF and PMC of GR, the MRF, CAN, and PMC of MI, and the CAN and PMC of ET. In CO, positivity in the CAN and negativity in the PMC were enhanced in the 10% WS condition even though no change in WS-NS differentiation occurred (i.e., responses to the NS were also enhanced).

When the range of proportions used was considered, the most systematic relationship between SP amplitude and WS proportions occurred in either the SUN or MRF, depending on the monkey. Results were most systematic when the ratio of SP amplitude on WS trials to SP amplitude on NS trials was computed, emphasizing the extent of discrimination occurring. As shown in Figure 42 for the late SP this relationship was extremely pronounced for monkey ET (SUN), but it also occurred in varying degrees for the other monkeys.

To determine whether increasing the discriminability of the tones would enhance differentiation of responses on WS and NS trials (proportion = 0.5), the WS tone was decreased from 1 kHz to 500 Hz (the NS remained at 3 kHz). These tones were presented for 7 days but recordings were obtained only on the last 5 days (the first two days were considered as a period of acclimatization). This manipulation did not increase ERP differences; in fact, responses on WS and NS trials were nearly identical, even in ET. Thus, the general intractability of these monkeys with respect to differential responses to significant and nonsignificant cues was probably not the result of poor sound discrimination. Introduction of the new stimulus probably caused a dishabituation of responses to the NS as ET had previously shown good discrimination in the 50% condition.

3. Female Stump-tailed Macaques

Two female stump-tailed macaques (GE and AG) were also studied when the WS occurred on 20% or 50% of the trials. Following the acquisition phase of their training, at the end of which there was no consistent differentiation of responses on WS and NS trials, an alternating series of 20% and 50% WS trials was carried out (WS = 20% for ten days, 50% for 4 days, 20% for 5 days, and 50% for 5 days). All daily records for like conditions were averaged together. The training with 20% WS trials resulted in clear WS-NS differentiation for several placements in both monkeys. This was true for the SMA--but not the PMC--CAN, SUN (very slight effect), and raphe nucleus in GE (Figure 43), and for all placements in AG (Figure 44). This differentiation carried over to the 50% WS condition as well, and in GE this effect was as pronounced in the 50% condition as it was with 20% WS trials. In AG, however, responses on WS trials were larger in the 20% condition than in the 50%.

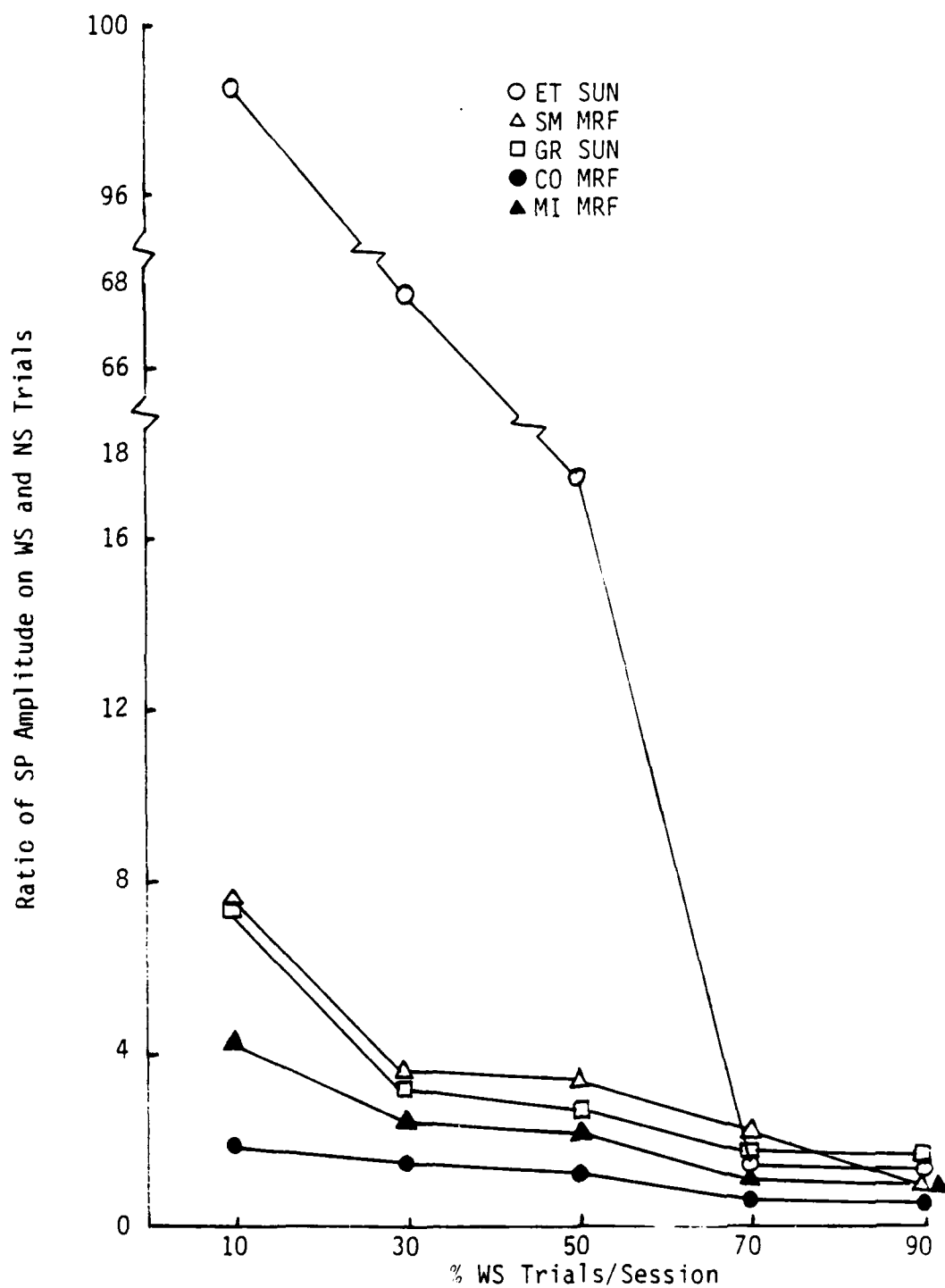


FIGURE 42 RATIO OF SP AMPLITUDES ON WS AND NS TRIALS AS A FUNCTION OF THE PERCENTAGE OF WS TRIALS FOR ELECTRODES AIMED AT THE SUN OR MRF IN MALE CYNOMOLGUS MONKEYS

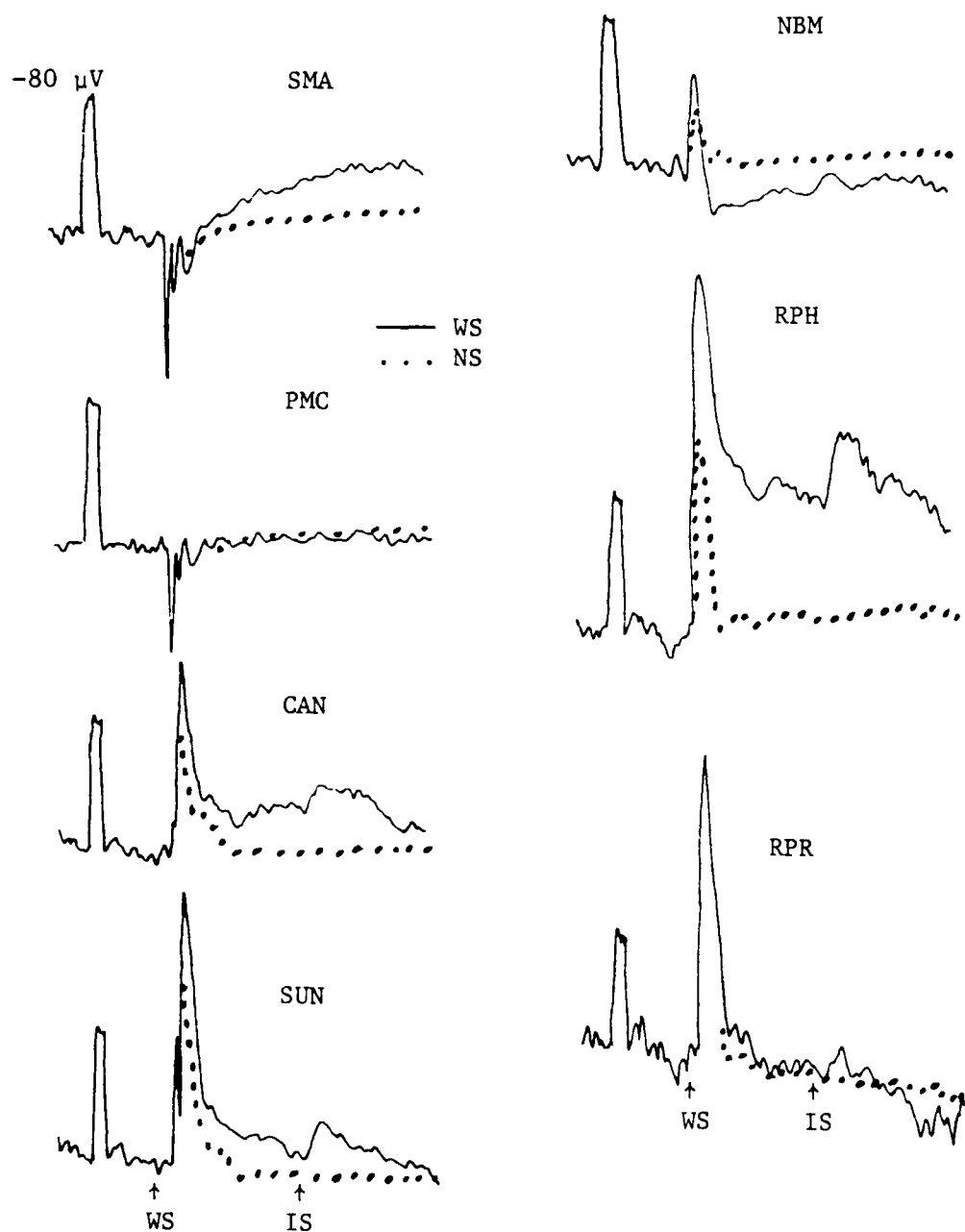


FIGURE 43 EVENT-RELATED POTENTIALS FROM SEVERAL ELECTRODE PLACEMENTS IN MONKEY GE EXHIBITING DIFFERENT RESPONSES ON WS AND NS TRIALS WHEN THE WS OCCURRED ON 20% OF THE TRIALS

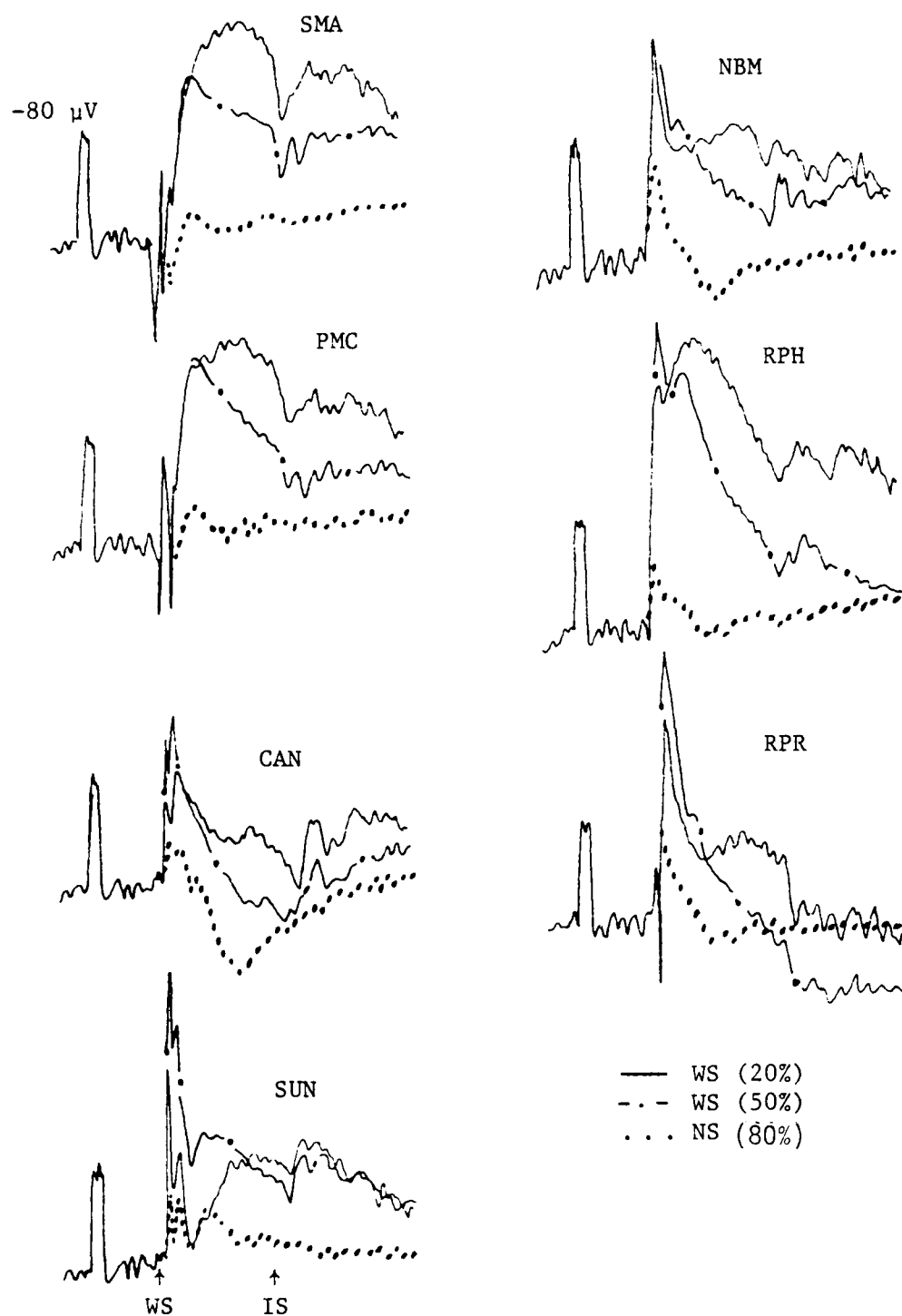


FIGURE 44 EVENT-RELATED POTENTIALS FROM SEVERAL ELECTRODE PLACEMENTS IN MONKEY AG EXHIBITING DIFFERENT RESPONSES ON WS AND NS TRIALS WHEN THE WS OCCURRED ON 20% OF THE TRIALS

4. Male Rhesus

After completion of acquisition training on tone-light pairing of the five male rhesus monkeys discussed earlier, they were tested for two days with the percentage of WS trials at 20. Additional testing in this paradigm was precluded by their schedule for the drug study. These monkeys already exhibited relatively good discrimination of responses on WS and NS trials with small ERPs being elicited by the NS (Figures 34-37). Reducing the proportion of WS trials for two days had minor effects. One monkey (BU) exhibited some enhancement of responses to the WS in the 20% condition relative to the 50% condition (Figure 45). The greatest differences were from electrodes aimed at the pulvinar and fastigial nuclei. Another monkey (JE) also showed the same effect, but to a lesser degree, in the FAS.

C. Effort Required for Operant Response

Rebert et al. (1967) demonstrated that in humans, CNVs are enhanced when the muscular effort required in responding to the IS is increased, which was confirmed by Low and McSherry (1968). We conducted the following experiments to examine the effect of increasing the effort required to respond to the IS on the CNVs of monkeys. The amount of effort required to respond was varied by suspending weights (ranging from 0.3 to over 3000 grams) from the response bar.

We first studied three male cynomolgus monkeys over a period of one month. The weights were 250, 1000, and 1500 g. Each weight was used for 5 to 10 days and all the sessions at each weight were averaged together. There was no clear change in the CNVs of these monkeys due to this experimental manipulation. Only the early slow-wave component of the NVA and MRF placements in monkey ET were enhanced.

Two female stump-tailed monkeys were also studied with variation of effort. Weight on the bar was increased daily by 100 g from 100 to 2500 g. We averaged ERPs over 500-g weight ranges (i.e., 100-500, 600-1000, etc.). The electrodes implanted in these monkeys were approximately two years old, precluding use of many of the placements. Two of AG's placements exhibited changes with increasing bar weights--the raphe (RPH) and CAN. The negative SP of the RPH increased by 28.9 μ V and the positive SP of the CAN decreased by 67.0 μ V from the low- to the high-effort requirement (Figure 46). Subsequently, the weight required for these monkeys to press was varied between 3 g and a high weight which was increased every other day (i.e., 3 g, 2000 g, 3 g, 2500 g, 3 g, etc.). Three placements exhibited especially good results, but two others (AG-PMC and GE-RPH) from which recordings could be obtained did not change. The SP recorded from the RPH of monkey GE showed

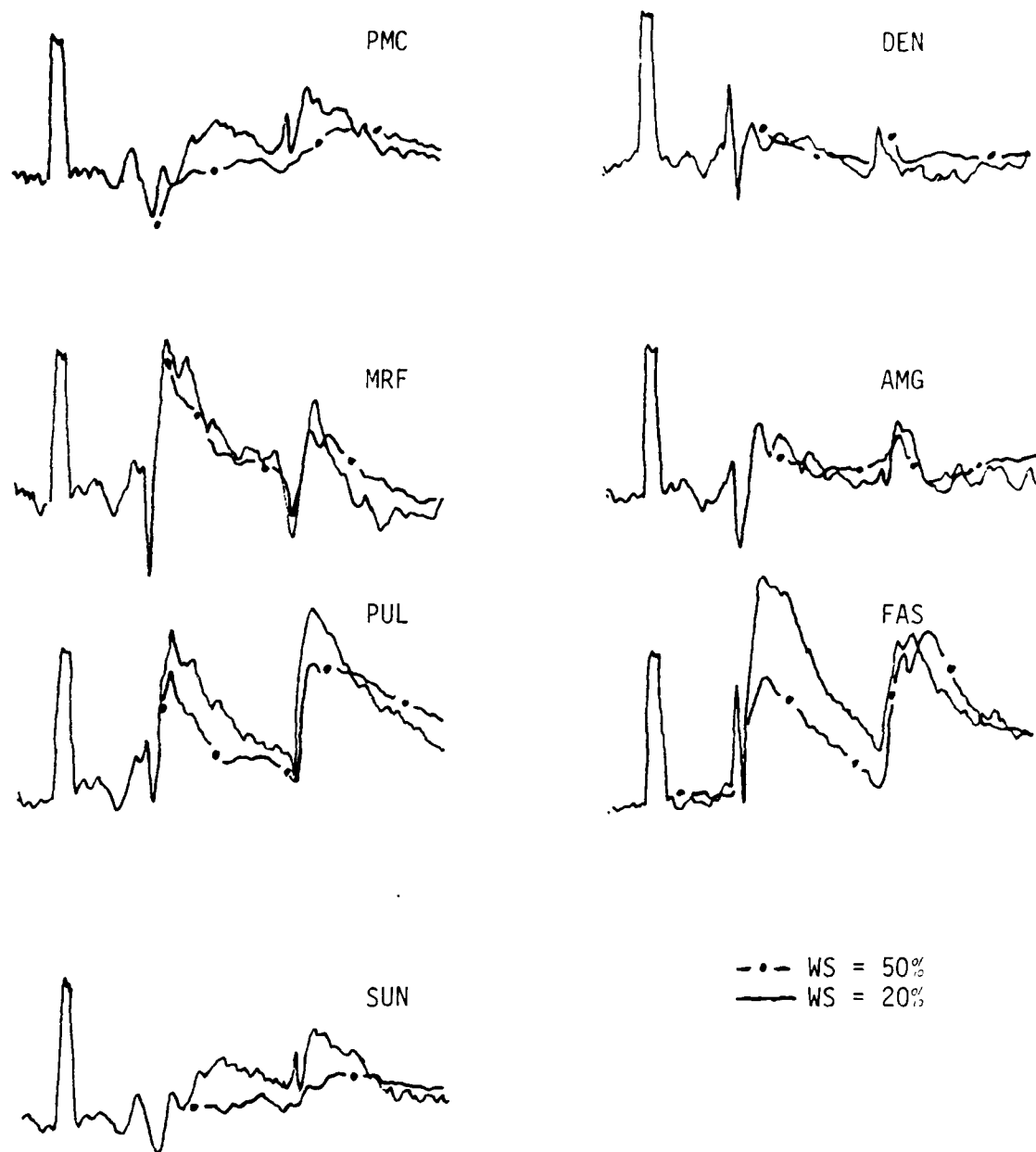


FIGURE 45 ENHANCEMENT OF ERPS IN SOME PLACEMENTS IN MONKEY BU ASSOCIATED WITH REDUCING THE PERCENTAGE OF WS TRIALS FROM 50 TO 20

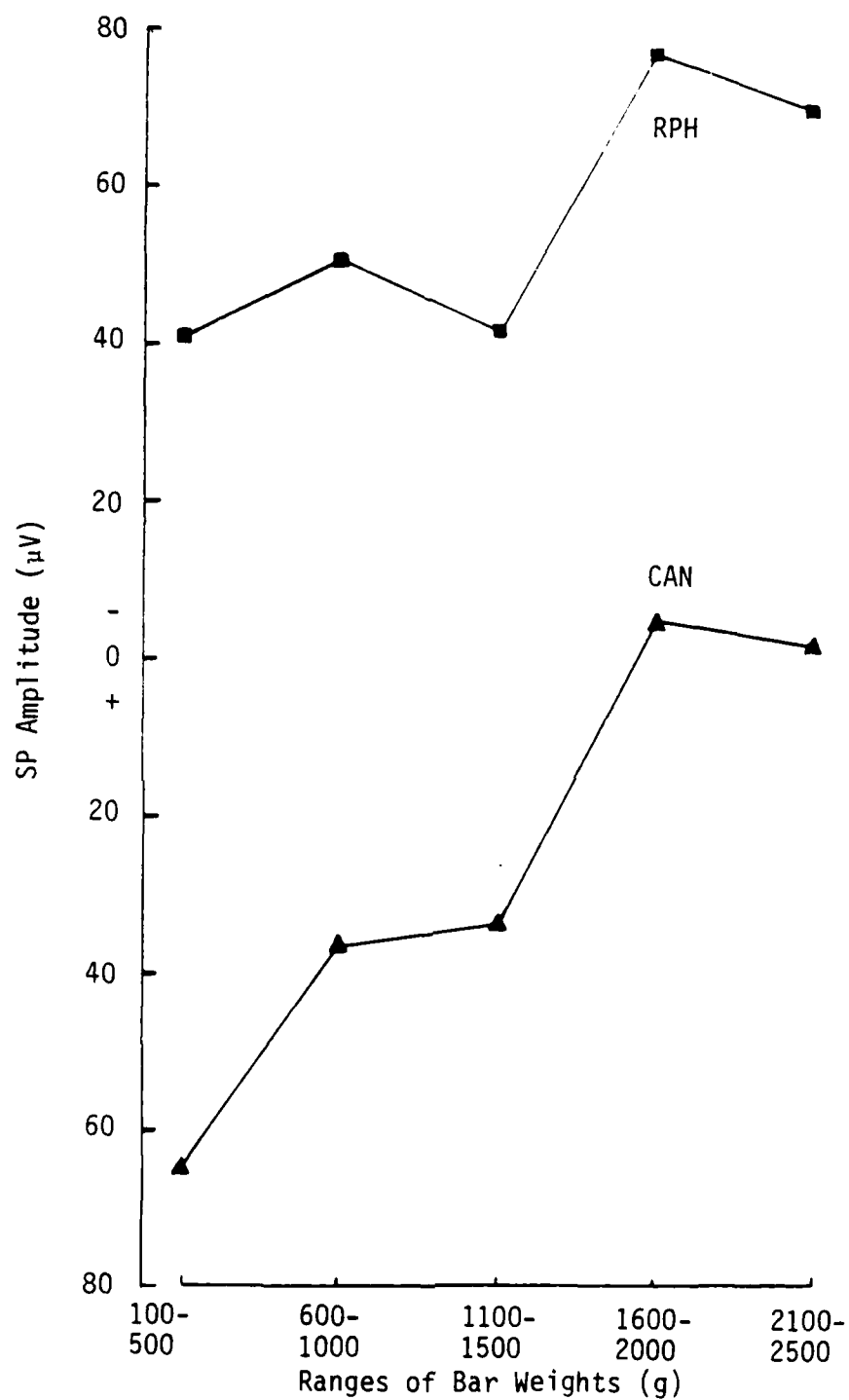


FIGURE 46 CHANGES OF SP AMPLITUDE IN TWO PLACEMENTS IN MONKEY AG AS A FUNCTION OF INCREASING BAR WEIGHTS

an enhancement during the high-effort phases of the test over the low-effort conditions (Figure 47). The SMA and CAN of monkey AG exhibited a similar effect.

A final examination of effort was made in two female rhesus monkeys. This experiment was run like the one with the stump-tailed macaques--i.e., the weight was increased daily by 100-200 g, from 100 g to 3100 g. ERP averages were constituted from data obtained in 500-g weight ranges (100-500, 600-1000, etc.). Systematic changes were observed primarily in the electrode aimed at the MRF. In general, the negative amplitudes increased with increasing effort (Figure 48).

D. Variation of Interstimulus Interval

In an early study of the CNV in humans (McAdam et al., 1969), we showed that lengthening the interstimulus interval (ISI) between the warning and imperative stimuli from the usual duration of about 1 sec to 4.8 sec dramatically altered the form of the CNV. A typical result was that an early rise in negativity following the WS subsided in the midportion of the long ISI and was followed by another increase that became progressively larger prior to the occurrence of the IS. Later studies (e.g., Loveless and Sanford, 1974) indicated that the early and late negative SPs were differently affected by changes in the intensity of WS and IS, probably reflecting the operation of distinct psychological processes--"orienting" and response-preparation, respectively.

The cynomolgus monkeys had been trained for a long period of time with the same ISI. 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 49). 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 μ V for the 1-, 1.5-, and 2-sec ISIs, respectively. This effect was

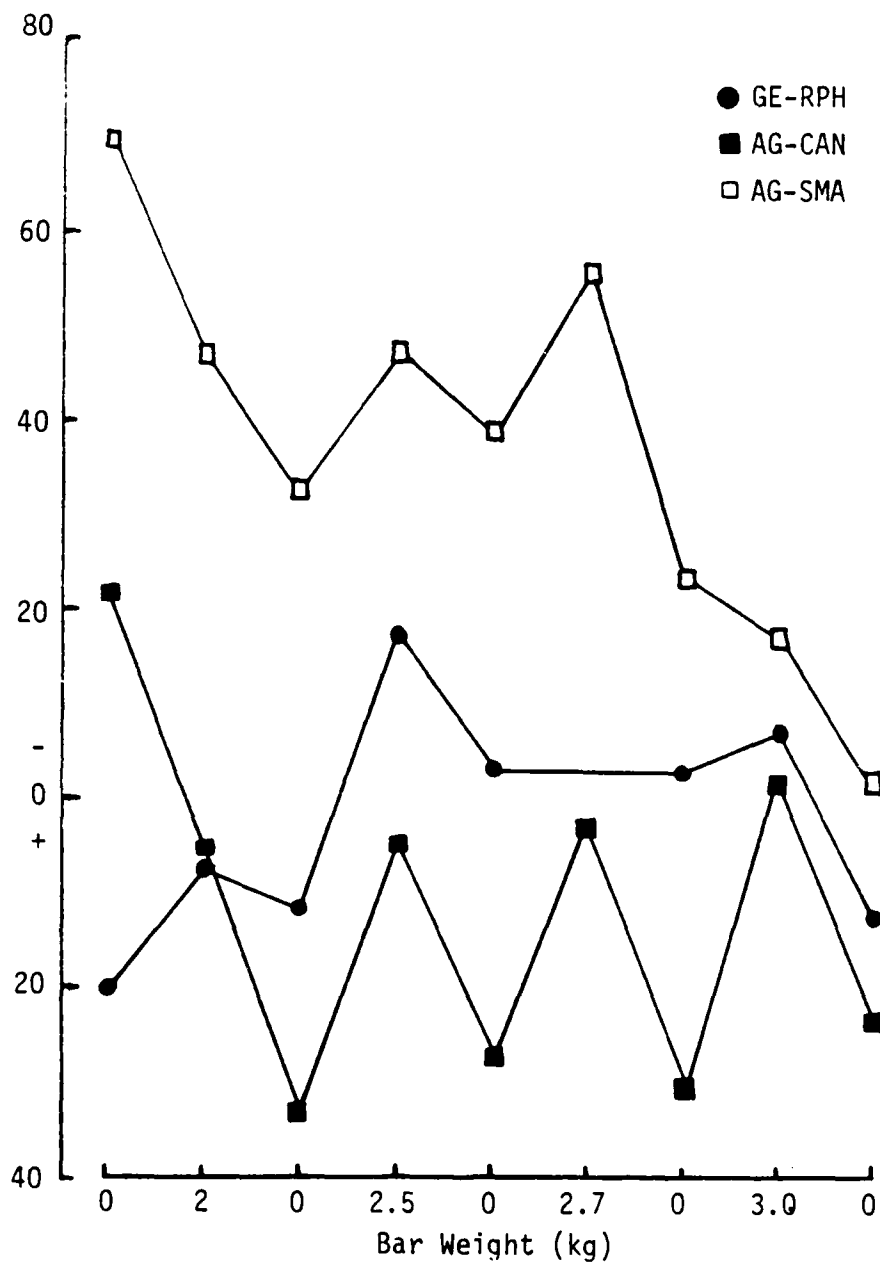


FIGURE 47 EFFECTS OF CYCLING LOW AND HIGH WEIGHT DEMANDS ON SPs IN SOME ELECTRODE PLACEMENTS IN STUMP-TAILED MONKEYS AG AND GE

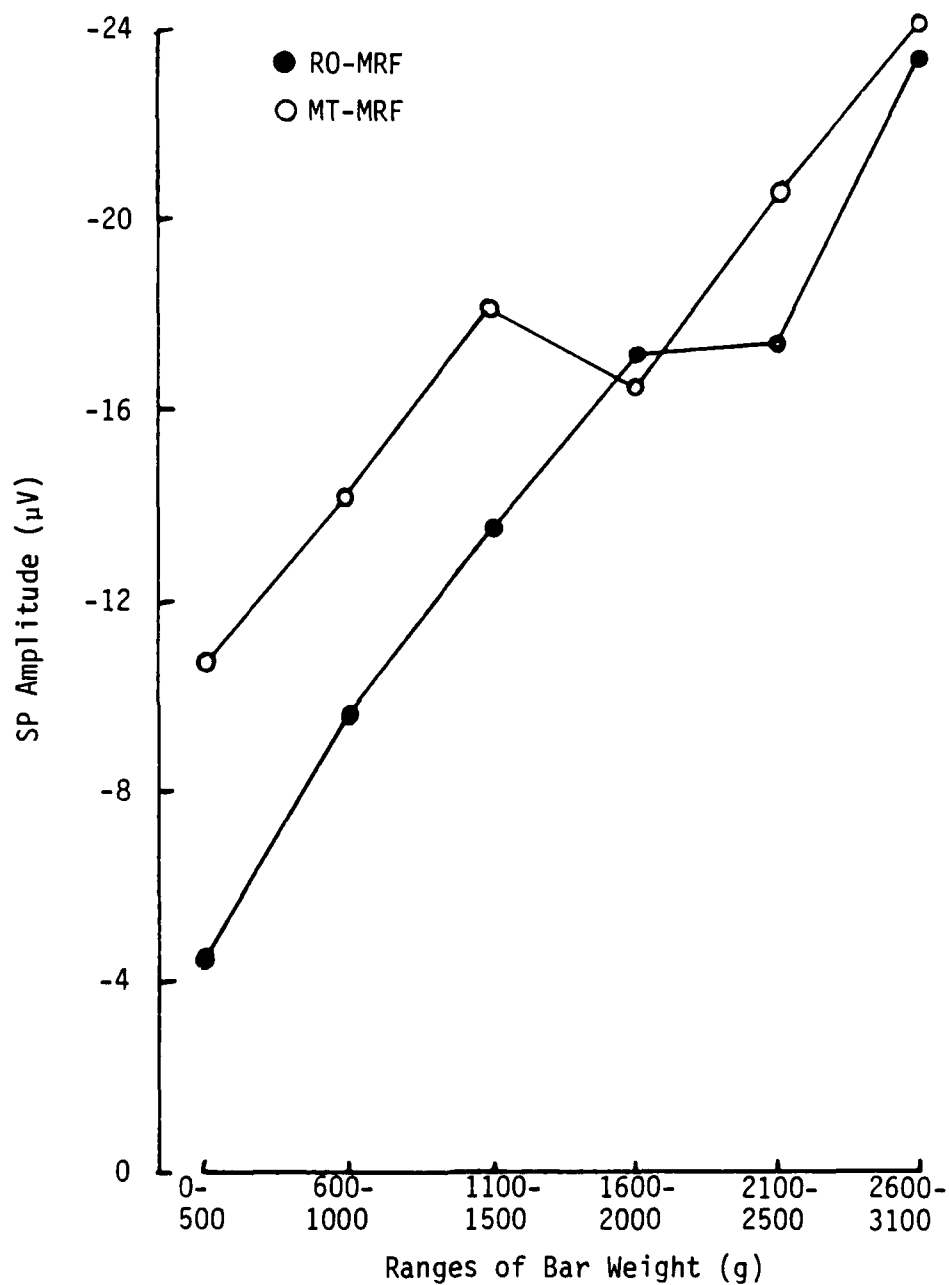


FIGURE 48 INCREASING AMPLITUDE OF THE SP FROM ELECTRODES AIMED AT THE MRF IN TWO FEMALE RHESUS MONKEYS AS A FUNCTION OF INCREASING BAR WEIGHT

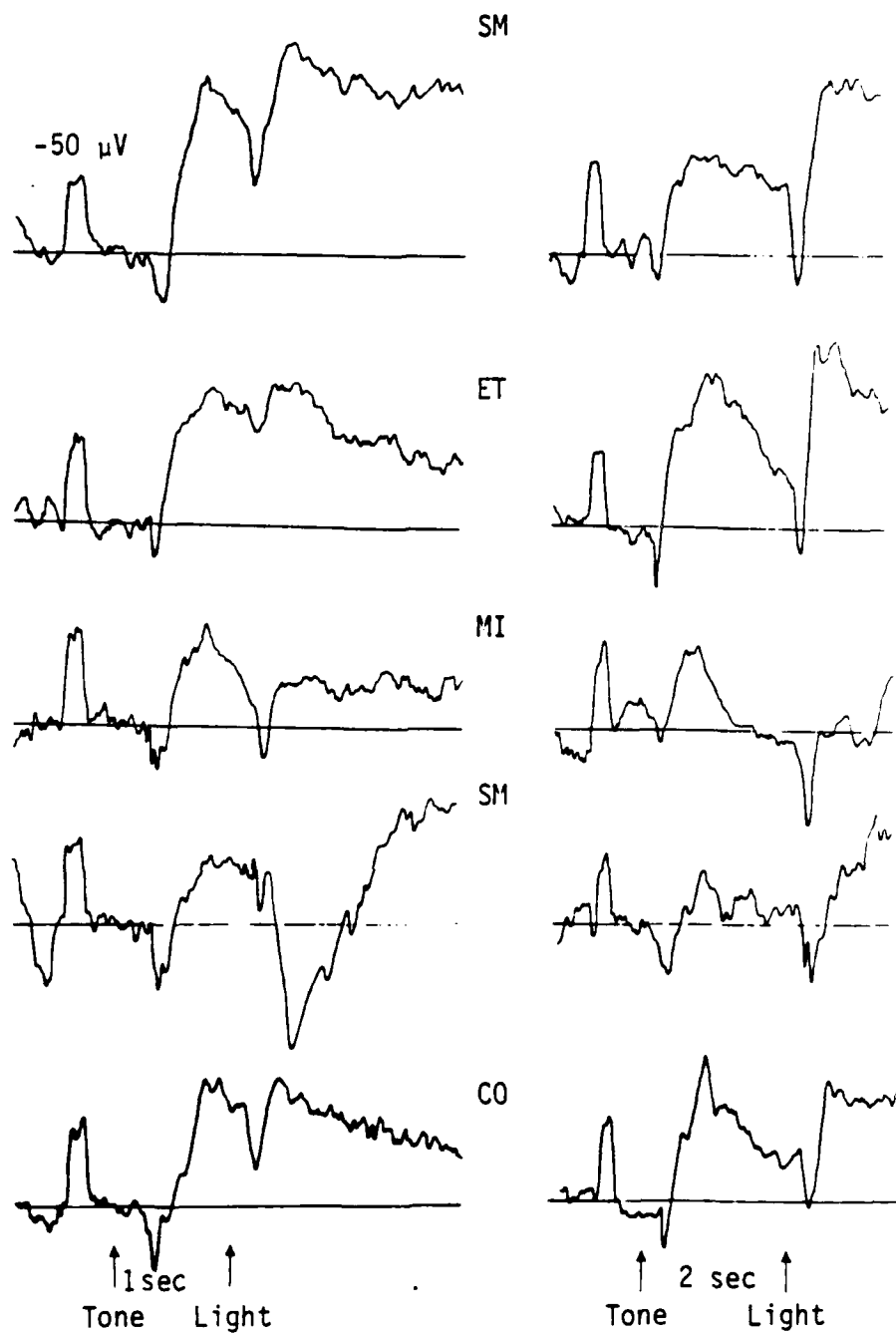


FIGURE 49 AVERAGED ERPs FROM THE MRF OF 5 CYNOMOLGUS MONKEYS WHEN THE INTERSTIMULUS INTERVAL (ISI) WAS 1.0 OR 2.0 SEC, SHOWING DECREASE IN SP AMPLITUDE DURING LATER PARTS OF THE LONGER ISI.

not due to amplifier time constant; that would account for only a 12.5% decrease in terminal SP amplitude (just prior to the IS) 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, because 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.

E. Manipulation of Cholinergic Synapses: Atropine

Although specification of anatomical factors associated with intracerebral ERPs is critical to a full description of ERPs and to an understanding of cerebral systems mediating particular behaviors, such specifications are incomplete because there are neurochemical subsystems imbedded within structurally defined neural pathways. Shute and Lewis (1967) and Lewis and Schute (1967), for example, defined two major cerebral cholinergic subsystems related to the ascending reticular activating system and another related to the limbic system. Similarly, other neurochemical systems involving dopamine, norepinephrine, and serotonin have been described. These systems consist of pathways from the substantia nigra, locus coeruleus, and raphe nuclei, traversing mainly the nigra-striatal and medial forebrain bundle systems (e.g., Fuxe et al., 1970).

Given the chemical basis of synaptic transmission, it is axiomatic that manipulation of the chemical milieu of the brain should have profound behavioral and psychological consequences, thus providing a powerful tool for unraveling the neural systems involved in various psychological and behavioral processes. This kind of work is now one of the main pursuits of neuroscientists, and the psychopharmacological literature is vast. The basis of such work is that a variety of substances can antagonize or facilitate synaptic neurotransmission in a variety of ways, leading to inferences about the role of particular transmitters in specific behaviors. For example, Carlton (1963) suggested that the cholinergic system mediates the effects of habituation and nonreward on behavior, and Stein (1967) suggested that the cholinergic and adrenergic systems act in a complementary way to mediate punishment and reward, respectively. Such global categorizations of neurochemical functions are obvious oversimplifications, and more meaningful information is obtained in studies wherein the criterion of responsivity is more precisely defined--for example, in terms of ERP components. Pirch (1977a, 1977b) reported that systemically administered d-amphetamine, a catecholamine agonist and a neurotransmitter re-uptake blocker, depressed the amplitude of conditioned cortical SPs in rats. He also found that chlorpromazine, a dopamine antagonist and re-uptake blocker, at doses of 0.5 to 1.0 mg/kg, increased the amplitude of the same cortical SPs. In another study,

Pirch (1980) reported that d-amphetamine affected conditioned SPs in frontal but not posterior cortical areas in rats, suggesting that the genesis of SPs associated with "expectancy" in different brain regions may be dependent on different arrangements of neurochemical mediators.

In a study on human CNV, Thompson et al. (1978) systemically administered atropine (an acetylcholine muscarinic antagonist), thymoxamine (a norepinephrine antagonist), and metoclopramide (a dopamine antagonist). Their rationale was that if any of the neurotransmitters for which these substances were antagonists were involved in the genesis of the CNV, their administration should be reflected in an alteration of the CNV. They reported that atropine and metoclopramide significantly reduced CNV amplitude, but that the effect of thymoxamine on the CNV was not significantly different from that of an injection of physiological saline.

Thus, systemic application of pharmacological agents has been effectively used to study the neurophysiological responses of awake, behaving organisms. Although this route of administration of drugs and other chemicals does not provide detailed information about the specific sites and mechanisms of action, it has heuristic value in that it does provide a "first estimate" of the effects of a chemical on the nervous system. Insofar as some of the pharmacological substances are used clinically and experimentally, this approach permits the comparison of observations of the effects of these agents on humans with similar observations in animal subjects. This is important in establishing the validity of an animal model of human cognitive processes. With the addition of multiple cortical and subcortical electrodes, the systemic administration of neuropharmacological substances might lead to specific intracerebral patterns of effects on ERP components, thereby adding significantly to our information on the details of mechanisms underlying the generation of ERPs associated with cognitive efforts.

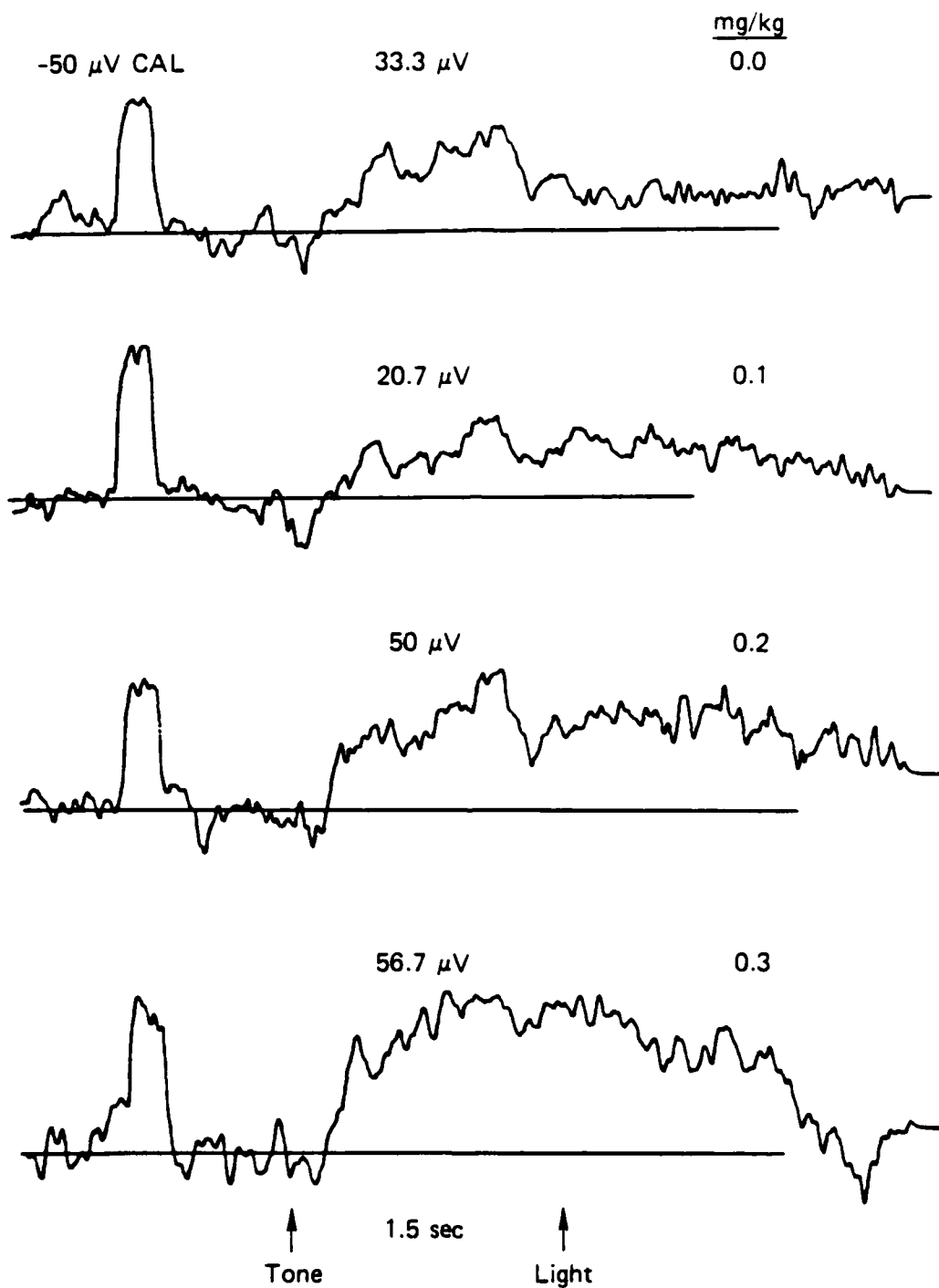
Several authors have suggested that cortical SPs are generated by cholinergic neurons (Pirch et al., 1986a; Marczyński, 1986). Although manipulations of transmitter systems by systemic administration of drugs are difficult to interpret (Rebert, 1980b), there is considerable interest in such manipulations in the study of human ERPs (Thompson et al., 1986). Therefore, we carried out a pilot study of the cholinergic blocking agent atropine in our monkeys. Our first effort was primarily to determine an appropriate dose to use in later, more systematic studies. The drug was administered im in doses of 0.1, 0.2, and 0.3 mg/kg. Because the appropriate dose was unknown, drugs were given once per day for three days during one week, starting with the lowest dose. Dilation of the pupils was apparent at 0.3 mg/kg and--to a lesser extent--at 0.2 mg/kg. No dilation was noted at 0.1 mg/kg.

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; the effect was not dose-related. 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, 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 similar for the three doses. The number of reinforcements was 290 and 141 per session in the baseline and drug conditions, respectively.

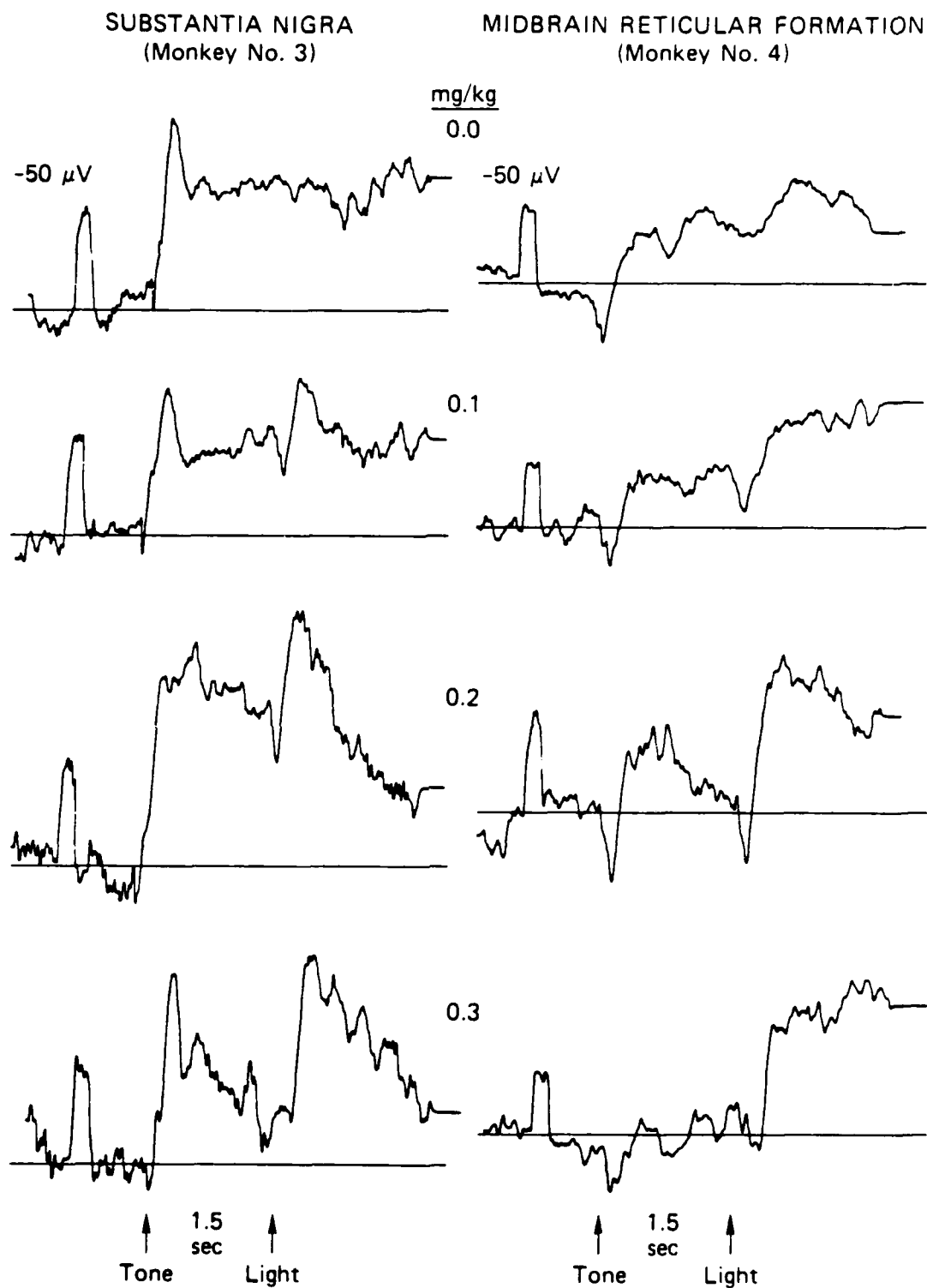
Four of the five monkeys exhibited unusual behavior during testing on days of drug administration, particularly at higher doses. This consisted of seemingly nondirected waving of the limbs, especially the arms. Movements were usually rapid and "jerky." The monkeys appeared to be agitated and would grab 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 fifth monkey at the high dose. In this fifth monkey 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. One monkey exhibited a clear dose-response function, shown in Figure 50). 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 51.



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FIGURE 50 DOSE-RELATED EFFECTS OF ATROPINE ON SLOW POTENTIALS
IN MOTOR CORTEX OF ONE MONKEY



LA-4373-7

FIGURE 51 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.

The potentials evoked by the light and those developing in the inter-stimulus interval in both the SUN and MRF appear to be independent. In general the post-imperative response is well developed before the inter-stimulus potential becomes sustained, and appears to be "covered up" by the interstimulus SP. In contrast, as shown in Figure 51, atropine appears to "uncover" the post-imperative response by attenuating the interstimulus negativity. No consistent effects of atropine were evident in recordings from the NVA or on the EOG. In one monkey, however (ET--normal records shown in Figure 14), 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 15).

The foregoing preliminary study of atropine sulfate suggested that it either increased or decreased the amplitude of several EP components. The following describes a more systematic evaluation of that possibility.

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 23 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.

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 i.m. in the leg 15 min prior to testing. The 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 two 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 week-end 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 injected 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 0.2 mg/kg and one day's data 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 3 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, 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.

Table 3

EFFECT OF ATROPINE SULFATE AND ATROPINE METHYL NITRATE ON BEHAVIORAL PARAMETERS

	<u>Reaction Time (msec)</u>	<u>No. of Reinf.</u>	<u>Rate of Pressing (No./sec)</u>	<u>Percent Abort</u>	<u>Total Presses</u>
<u>Atropine Sulfate</u>					
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
<u>Atropine Methyl Nitrate</u>					
Saline	853	307	1.6	3.8	321
0.3 mg/kg	856	126	1.1	40.4	134

Table 4

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

<u>Drug</u>	<u>Dose (mg/kg)</u>	<u>Electrode Site</u>					
		<u>CAN</u>	<u>SUN</u>	<u>VAN</u>	<u>MRF</u>	<u>LMC</u>	<u>LPM</u>
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 effects on slow potentials were mixed, depending on the site, but were comparable for the two drugs (Table 4). Small positive potentials (averaging 5.5 μ V) evident in the caudate nucleus were enhanced slightly by the 0.3-mg/kg dose (to a mean of 12 μ V by atropine sulfate and 15 μ V by methyl atropine). Negative shifts in the SUN, NVA, and MRF were decreased, and the effect was dose-related in SUN (-34 and -37%) and NVA (-41 and -53%). The potentials in SUN, NVA, 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 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.

F. Manipulation of the Nigrostriatal Dopamine Pathway:
Effects of MPTP-Induced Pars Compacta Lesions

One experimental issue important to an eventual understanding of ERPs concerns the neurochemical systems involved in their generation. This issue was considered in detail in a recent symposium presentation (Rebert et al., 1986a), wherein the relevant literature was reviewed. A major concern with most pharmacological approaches involving systemic administration of drugs is that few concrete conclusions can be drawn about where in the brain the injected substance acts (Rebert, 1980b; Pirch et al., 1986a). However, in a series of experiments, Pirch and his colleagues (e.g., Pirch et al., 1986b) directly manipulated the n. basalis of Meynert in the rat and showed an influence of this nucleus on cortical slow ERPs, thus implicating that cholinergic projection in the genesis of the CNV and showing the efficacy of direct manipulation of the tissue.

In view of our earlier findings of positive SP changes in the caudate nucleus associated with preparatory set, recent indications that the substantia nigra and related brainstem nuclei exhibit large negative SPs in the cued RT task (Rebert et al., 1986b), and conjectures about the role of nigrastriatal systems in preparatory set (Evarts et al., 1984), we explored the effect of producing discrete lesions of the pars compacta of the substantia nigra on behavior and ERPs in monkeys. We used the chemical MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine) to induce the lesion.

The pars compacta is the major nigrastriatal dopaminergic pathway and the major region of dysfunction in Parkinson's disease. In young drug addicts accidentally exposed to MPTP, a Parkinsonian condition has been observed, and subsequent investigations with macaque (Burns et al., 1983) and squirrel monkeys (Langston et al., 1984) indicated that the pars compacta was uniquely sensitive to the drug and was apparently the only region permanently damaged (although there is currently some controversy about this localization). This experimental lesion appears at this time to be much more discrete than is the case in Parkinson's disease and provides the best means of studying the effects of blocking dopaminergic output in that specific pathway. Schultz et al. (1985) found that MPTP treatment of monkeys increased reaction time, delayed onset of muscle activity, and prolonged movement time in a forelimb-reaching task.

We used three cynomolgus monkeys in this study. They had extensive experience in the cued RT task and had been implanted with an electrode array, including one aimed at the pars compacta of the substantia nigra. However, none of these brains have yet been histologically analyzed. To avoid severe symptoms we gave small i.v. or i.p. doses on an intermittent schedule, depending on the monkey's response. If no severe acute reactions occurred, we planned to dose once per week with 0.4 mg/kg. When symptoms of Parkinson's disease were evident, the monkeys were treated with Sinemet (L-dopa and carbi-dopa). The planned schedule of treatments was initially used for two monkeys, but the third required more time between injections. The schedules of treatment for each animal are shown on the following figures.

An observational checklist was used to rate clinical symptoms. It included the following items: immobility, increased muscle tone, fixed stare, decreased blinking, drooling, tremor, flexed posture, hypokinesia (decreased movement), bradykinesia (slowness of movements), decreased oral intake, awkward positions, and hypophonia. Severity was rated from 0 to 5, the latter being most severe. The ratings were quantified by summing all items for each day of observation to obtain a general clinical score. The results of these observations are shown in Figures 52, 53, and 54 for monkeys ET, GR, and SM, respectively.

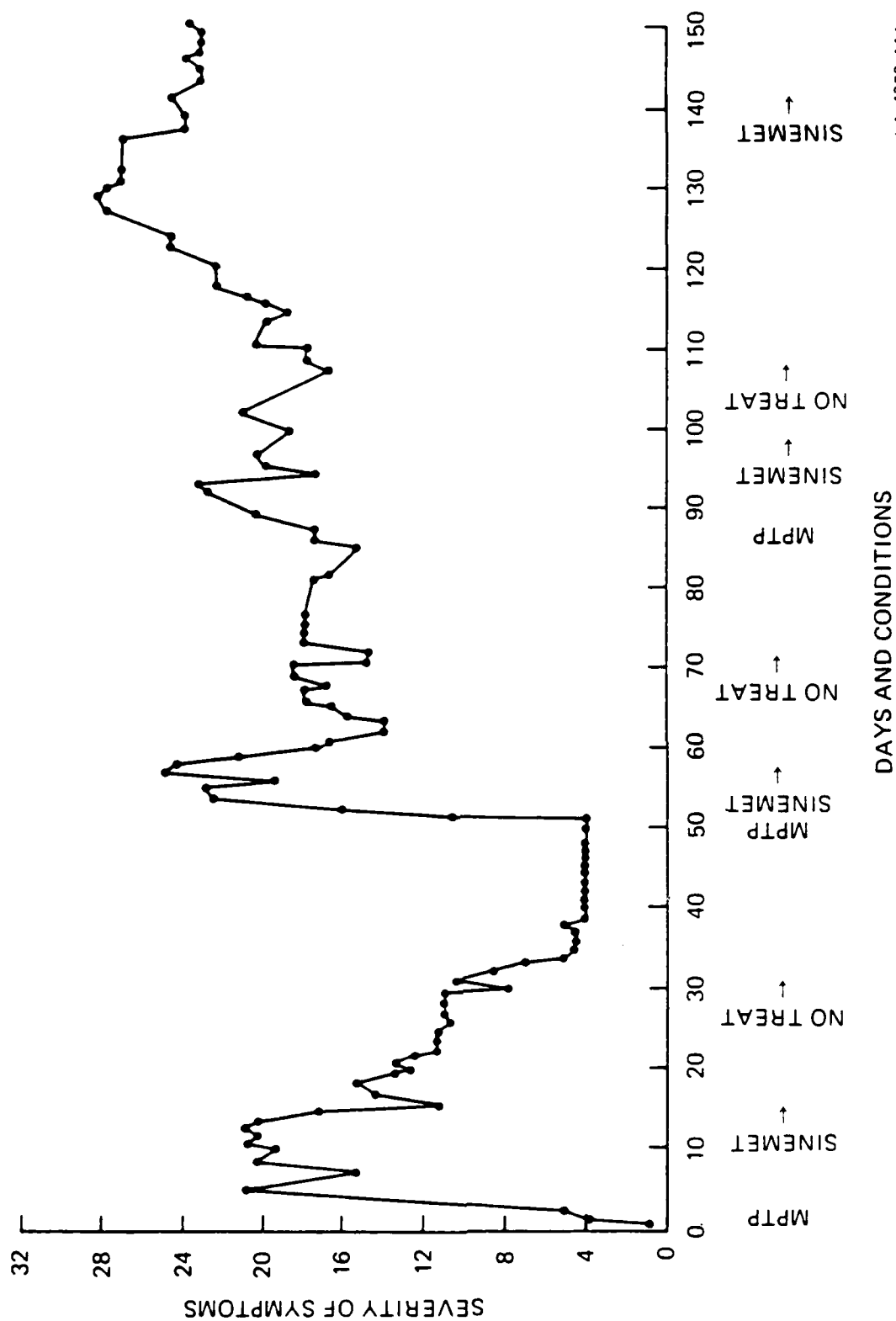
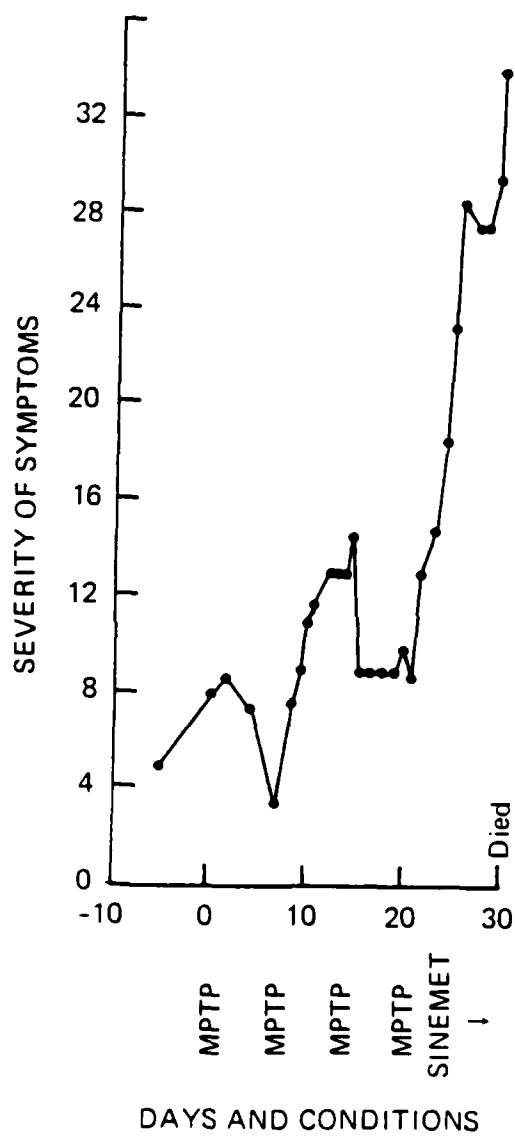
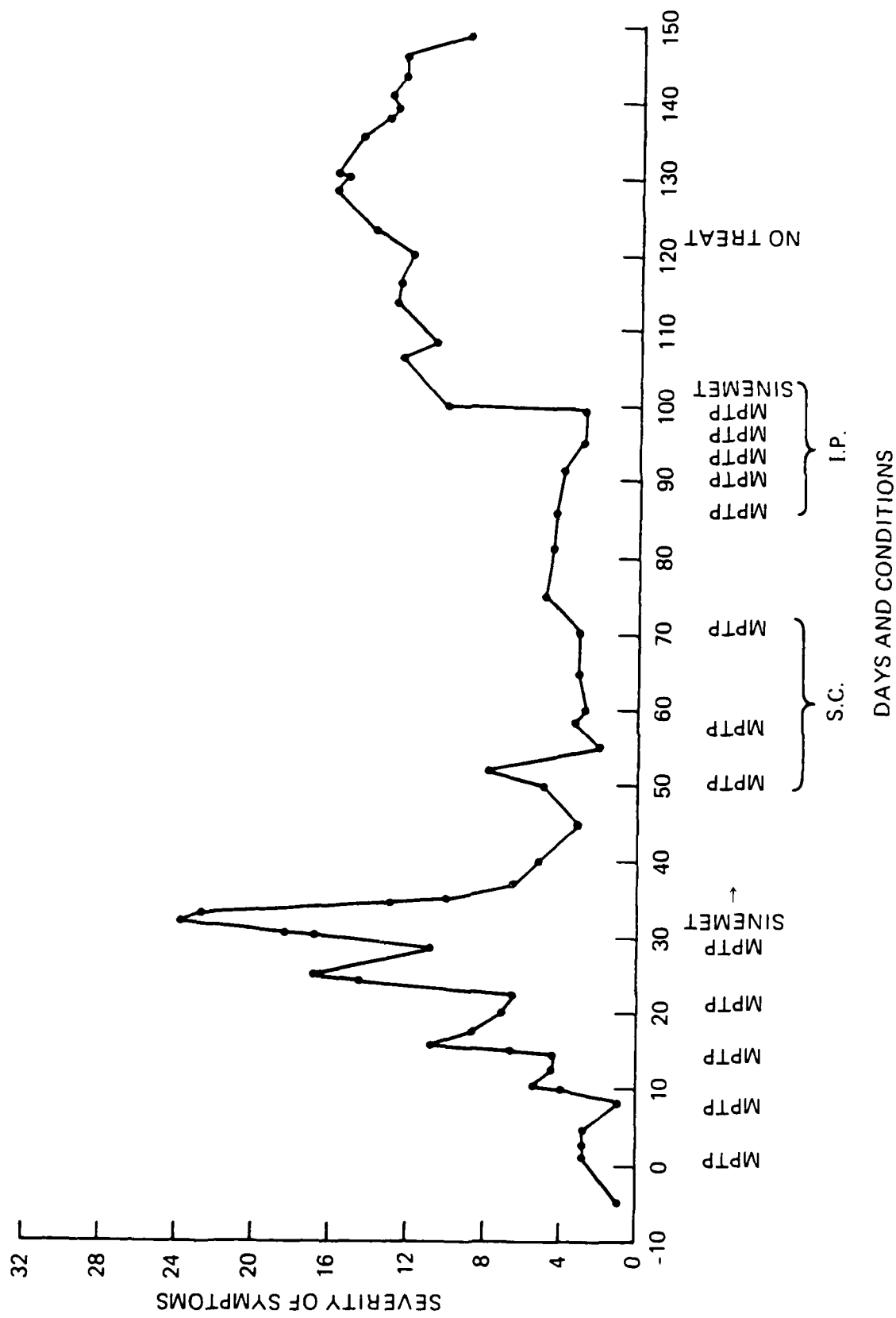


FIGURE 52 CHANGES IN CLINICAL SYMPTOMS ASSOCIATED WITH MPTP INJECTIONS: MONKEY ET



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FIGURE 53 CHANGES IN CLINICAL SYMPTOMS ASSOCIATED WITH MPTP INJECTIONS: MONKEY GR



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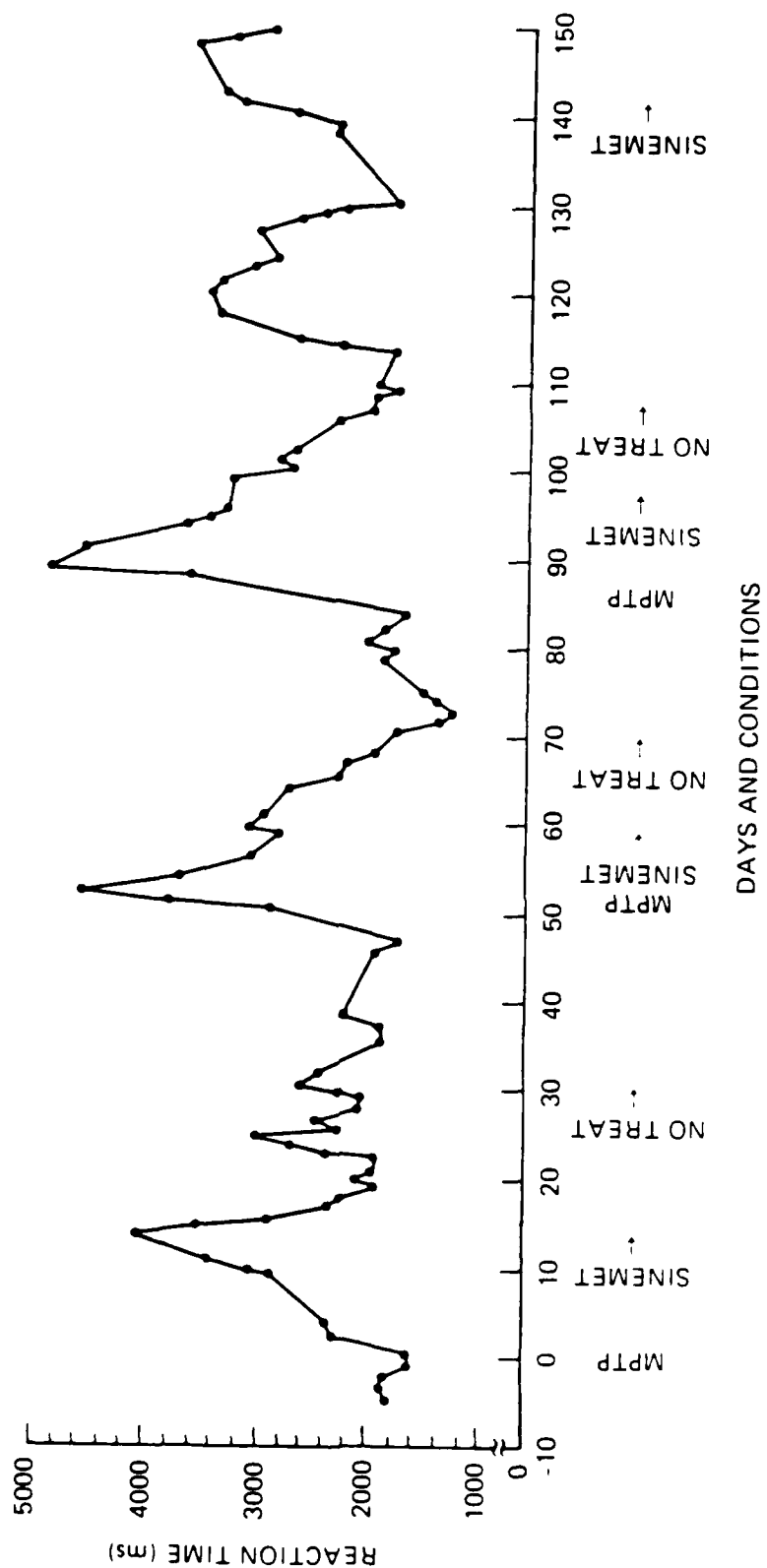
FIGURE 54 CHANGES IN CLINICAL SYMPTOMS ASSOCIATED WITH MPTP INJECTIONS: MONKEY SM

As shown in Figure 52, ET exhibited a rapid and pronounced response to a single injection of MPTP, and therapeutic treatment with Sinemet was initiated after ten days. However, the symptoms ameliorated even with cessation of therapy. Another two series of treatment and therapy were subsequently carried out. Symptoms were greatly exacerbated by the second dose of MPTP and remained abnormal thereafter, worsening after day 100 of the experiment when therapy was discontinued. On day 137 therapy was reinstituted, unknown to the clinical rater, to obtain an indication of the validity of these observations. The monkey's condition was noted to be improving by a second observer, and some improvement in the ratings appeared through day 150.

GR's results are shown in Figure 53. There was little effect of the first three injections on this monkey, but after the fourth dose his condition deteriorated rapidly and he died despite the administration of Sinemet. However, prior to his death he continued to perform the cued RT task, at varying levels of proficiency, throughout this time period.

As Figure 54 shows, SM's clinical signs increased after each injection of MPTP, but decreased shortly afterward. Nevertheless, there was a cumulative increase in clinical deterioration over the first 30 days, then a return to near normal values with the introduction of L-dopa therapy (Sinemet). Three subsequent doses of MPTP, which were subcutaneously administered, were without effect. Following five additional doses given intraperitoneally, clinical signs reappeared and the monkey would no longer perform the cued-RT task despite drug therapy. Adding bromocriptine (a cholinergic agonist) to the therapeutic regimen did not improve his performance.

Measures of performance in the cued RT task included initiation time (time to first lift of the hand from the "hold" paddle), reaction time (time to first depression of the reward paddle), movement time (reaction time minus initiation time), and rate of bar-pressing. ET's reaction time, shown in Figure 55, increased following each MPTP treatment and decreased to near control levels between these doses. This change peaked about 14 days after the first injection and within 5 days with subsequent doses. The declines to baseline occurred in approximately 20 days. After day 100 reaction time again increased when treatment was discontinued, and oscillated again through day 150. In this monkey, the slowed reaction time was due primarily to slowed movement time: initiation time remained relatively constant over the course of the experiment (Figure 56). GR's reaction time decreased slightly during the midportion of the experiment but increased precipitously after the fourth injection (Figure 57-left), as did his clinical signs. As with ET, GR's increased reaction time was due to a slowing of movement (Figure 57-middle). SM's reaction time also increased in association with the development of clinical signs and decreased toward normal when clinical signs abated (Figure 58). As shown in Figure 59, changes in both initiation time



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FIGURE 55 CHANGES IN ET'S REACTION TIME ASSOCIATED WITH MPTP INJECTIONS

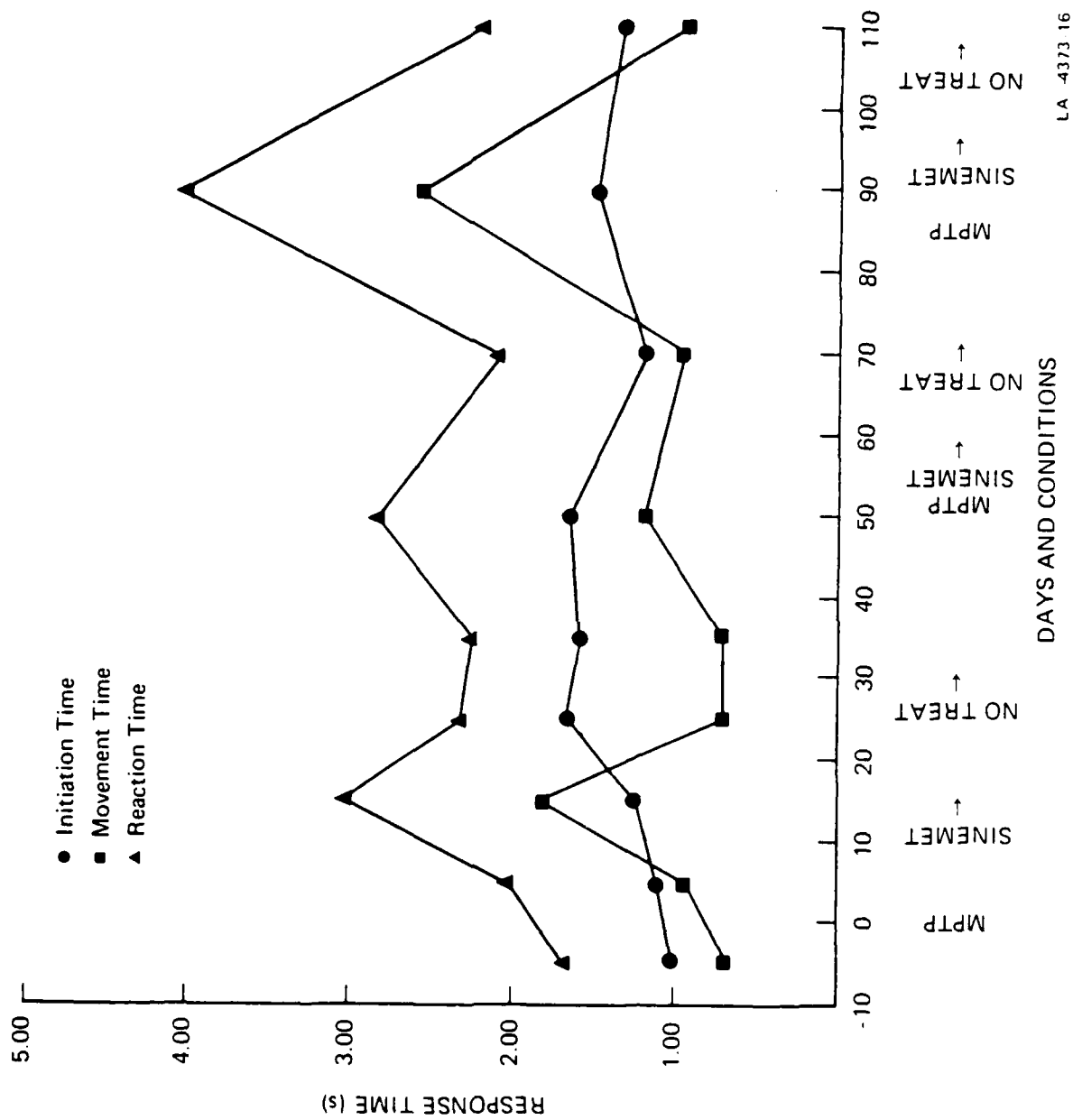
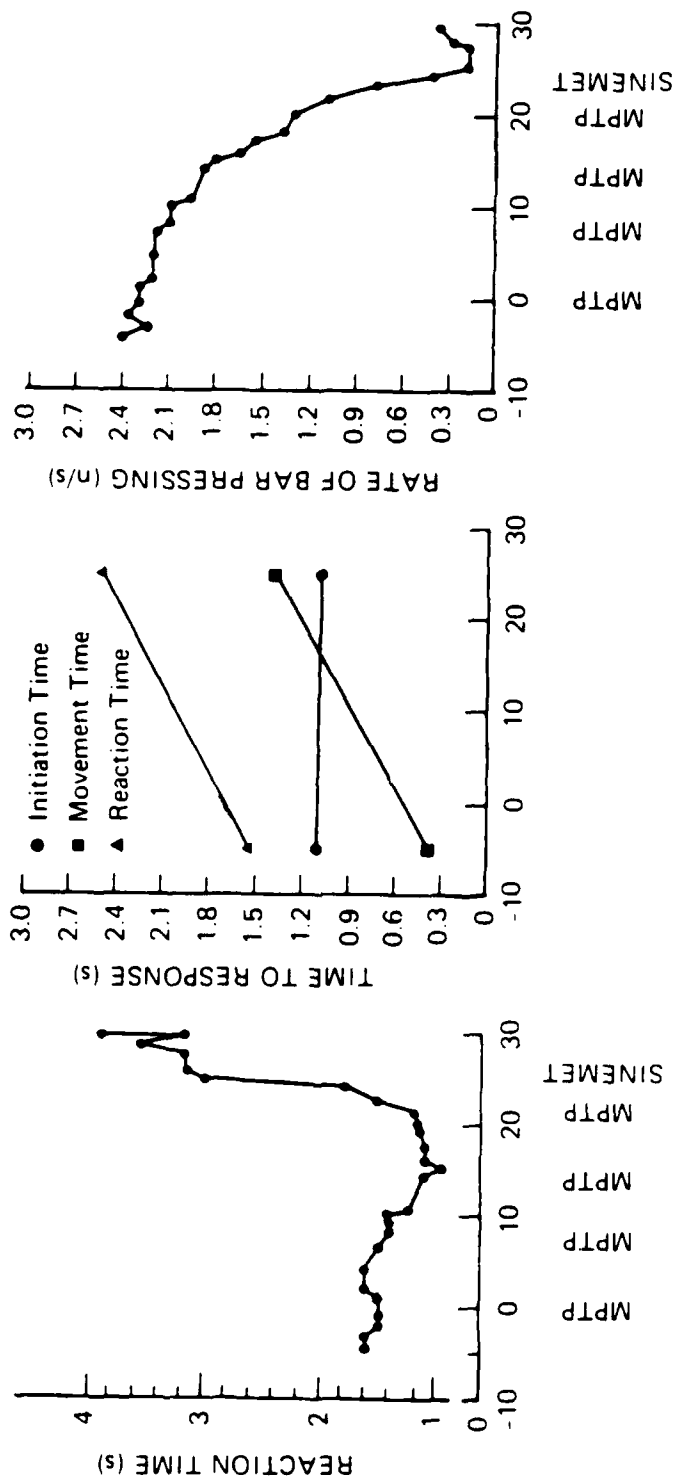


FIGURE 56 INITIATION TIME, REACTION TIME, AND MOVEMENT TIME IN MONKEY ET

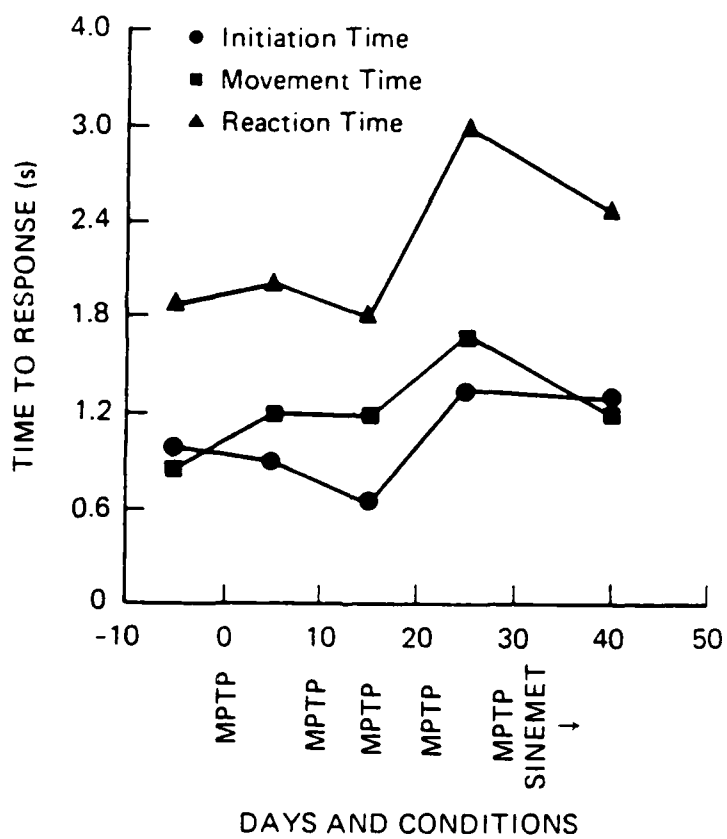
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FIGURE 57 CHANGES IN BEHAVIORAL PARAMETERS OF MONKEY GR ASSOCIATED WITH MPTP INJECTIONS

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FIGURE 59 INITIATION TIME, REACTION TIME, AND MOVEMENT TIME IN MONKEY SM

and movement time contributed to the increase in reaction time in this monkey.

Bar-pressing rates declined following injections and changed over the course of the experiment in a way similar to reaction time. However, bar-pressing was affected somewhat earlier than reaction time in all three monkeys (Figures 57, 60, and 61).

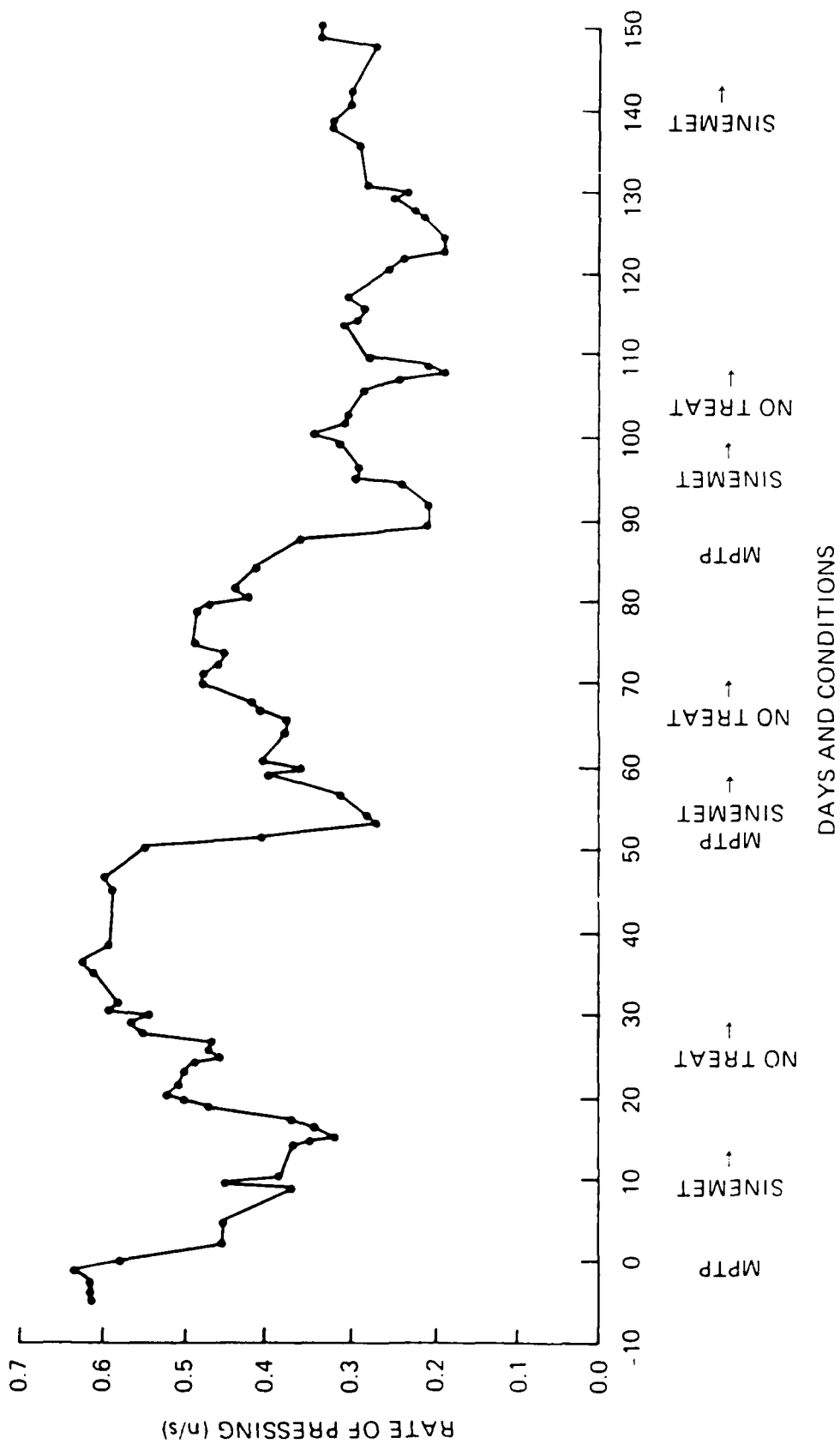
Electrophysiological responses from the premotor cortex and substantia nigra were evaluated. Examples of pretreatment and treatment responses from the PMC of each monkey are shown in Figure 62.

Average responses from trials with the warning (WS) and neutral (NS) stimuli are shown together in each set of tracings; examples from pretreatment and treatment phases of the experiment are included. In all three monkeys there was a fairly substantial response to the NS, an irrelevant stimulus, with which the monkeys had considerable experience. In two monkeys (GR and ET) the late negative and slow potential responses on trials with the WS were larger than when the NS was presented, but they were equivalent in monkey SM (except during the period following the light--imperative stimulus). The treatment waveforms, associated with a period of decreased behavioral performance (SM on day 25; GR on day 22; ET on day 14), are shown in the right column. In all cases the N2 and SP components were reduced, and in SM the tone-evoked transient EP complex was also reduced as well.

Sequential changes in the various components of the PMC over the course of the experiment, for WS trials only, are shown in Figures 63-67.

The N1-P2 peak-to-peak and SP amplitudes for ET (Figure 63) varied considerably from day to day but did not exhibit alterations clearly associated with variations in clinical signs or the behavioral changes. This was also true for the amplitude of P1 (measured with respect to the pre-stimulus baseline--Figure 64). In contrast, the N2 component (Figure 65) did decrease in amplitude in association with reaction time during the first two treatment cycles, but not during the third. The decrease was in phase with reaction time around day 130, but at this time clinical signs were worse. In general, these data suggest that the N2 component is more closely associated with the nigralstriatal dopamine system than are the other components in premotor cortex.

The most severely affected monkey (GR) exhibited changes in all components of the PMC waveform (Figure 66). A general decline in P1 amplitude began around day 20; this was also true of the N1-P2 component following an earlier period of increasing amplitude. In contrast, the N2 and SP components decreased over the whole course of the experiment, including a



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FIGURE 60 BAR-PRESSING RATES FOR MONKEY ET ASSOCIATED WITH MPTP INJECTIONS

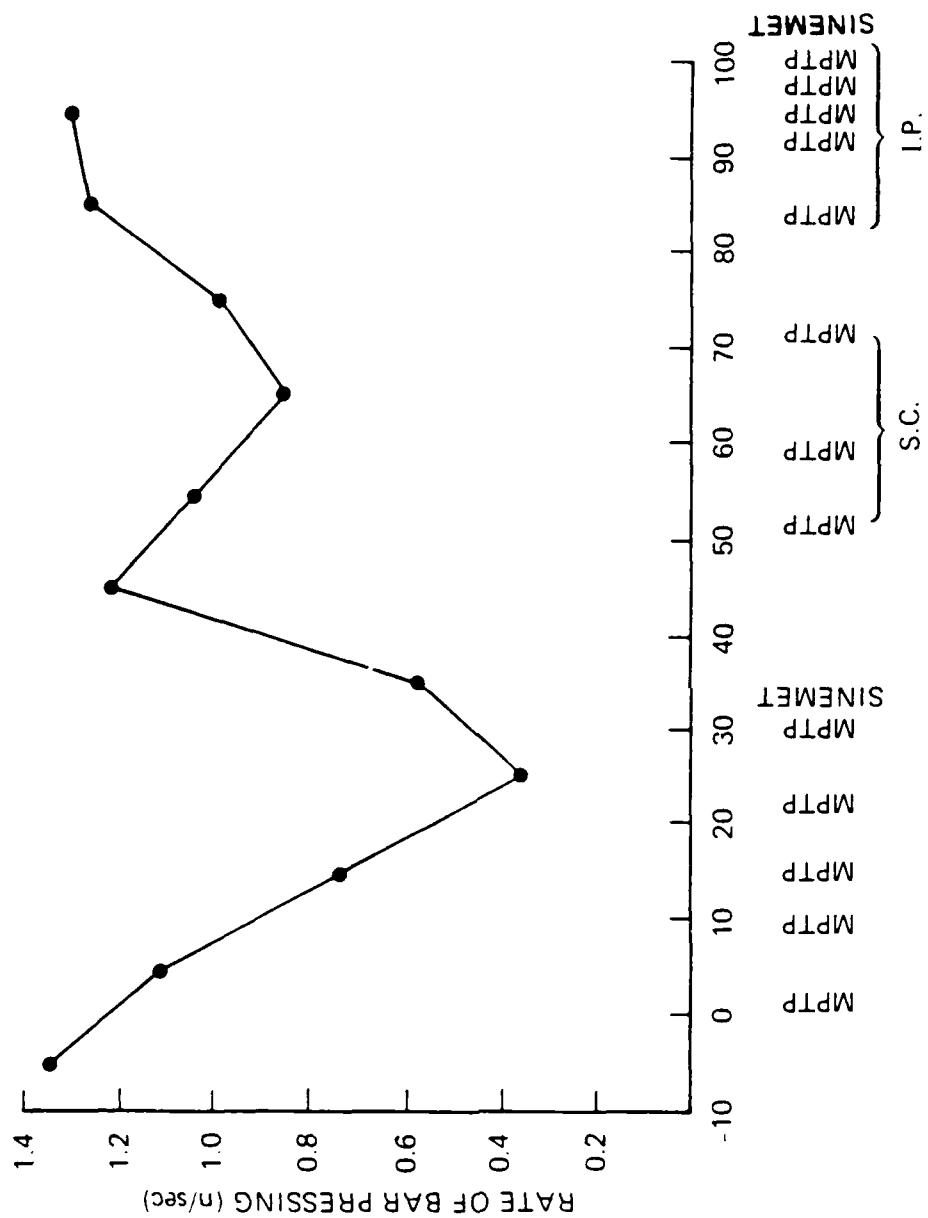
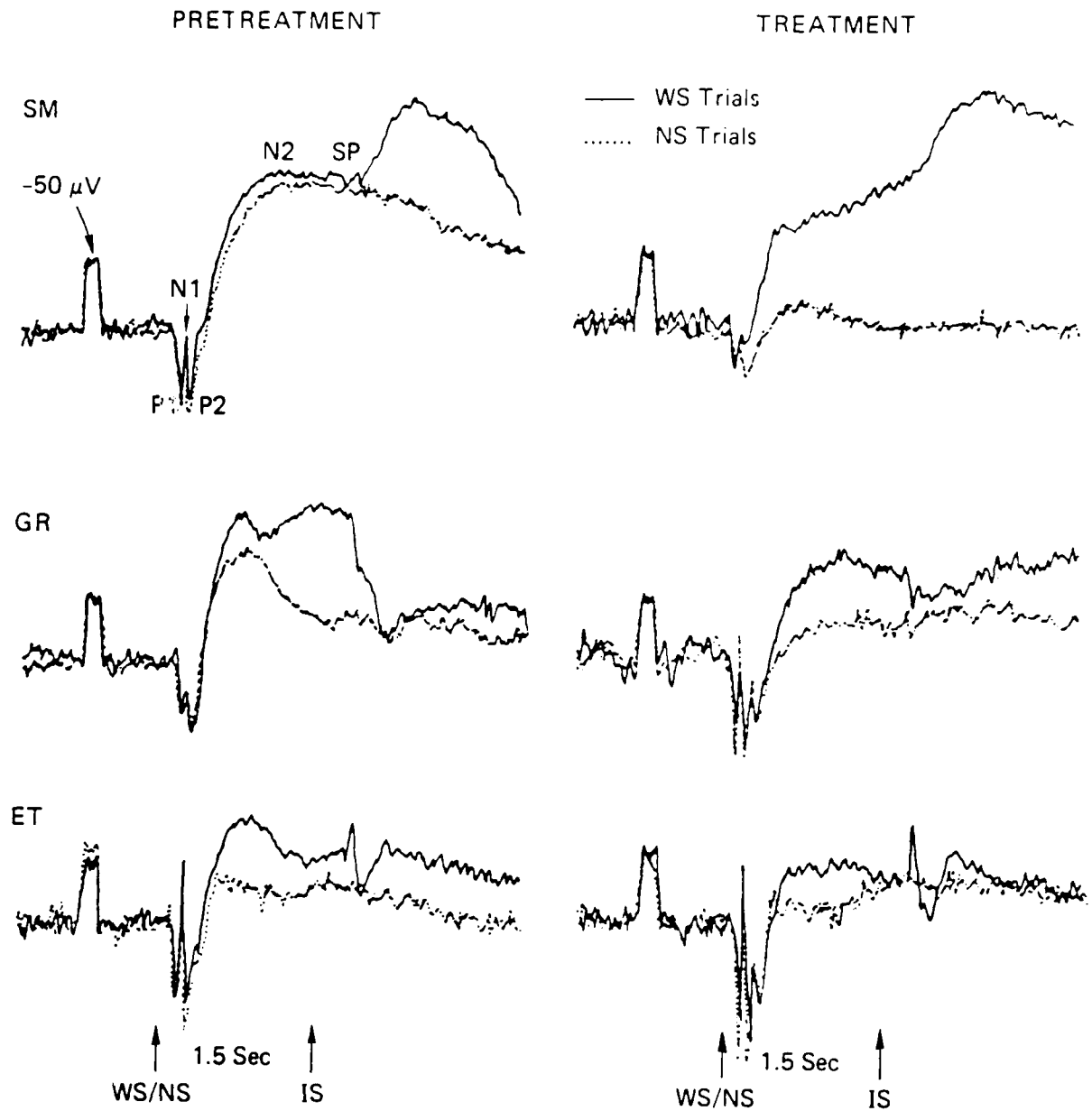


FIGURE 61 BAR-PRESSING RATES FOR MONKEY SM ASSOCIATED WITH MPTP INJECTIONS

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PREMOTOR CORTEX



LA-4373-8A

FIGURE 62 EXAMPLES OF EVENT-RELATED POTENTIALS IN THE PREMOTOR CORTEX DURING PRETREATMENT AND POST-MPTP PHASES OF THE EXPERIMENT

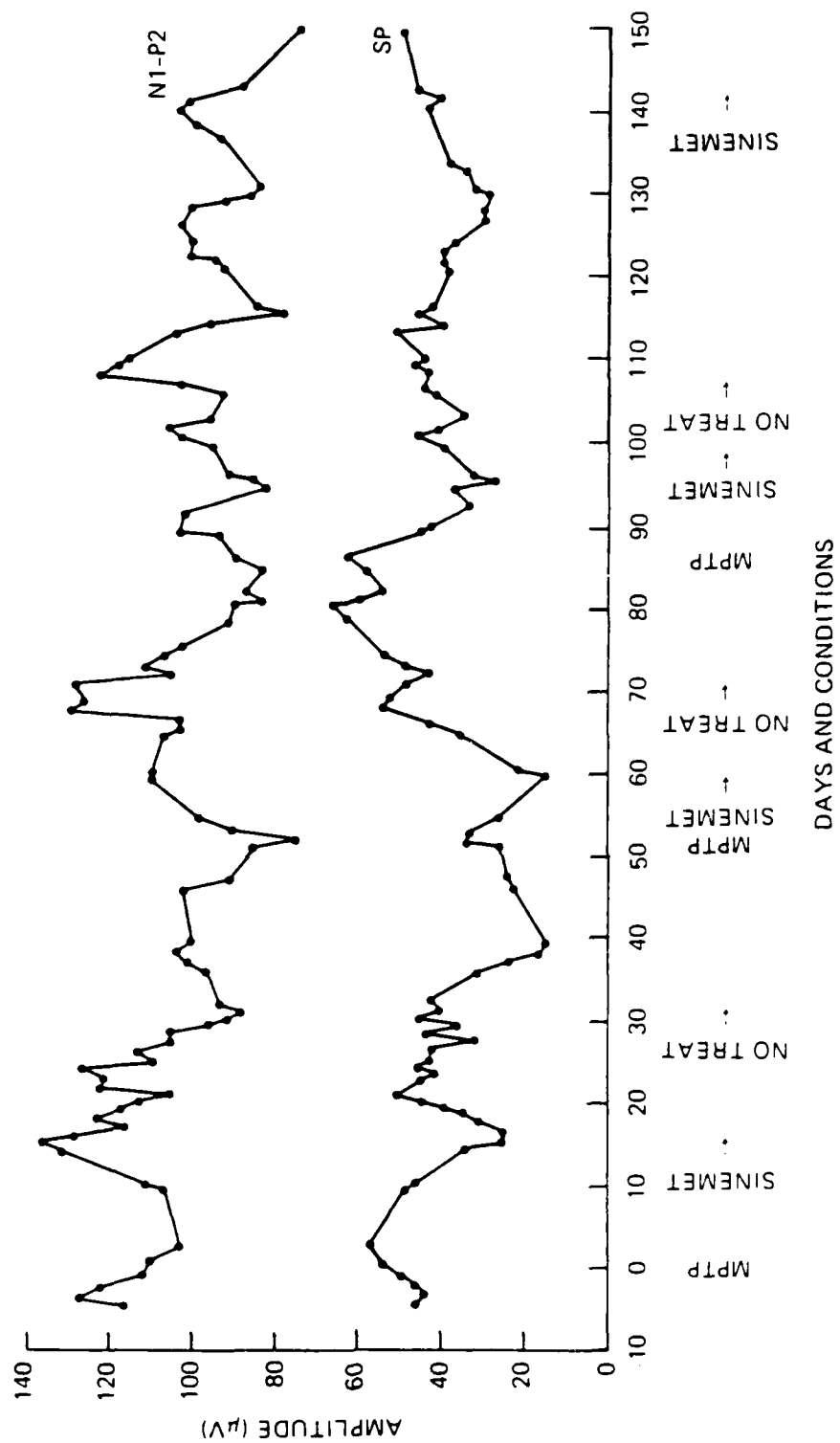
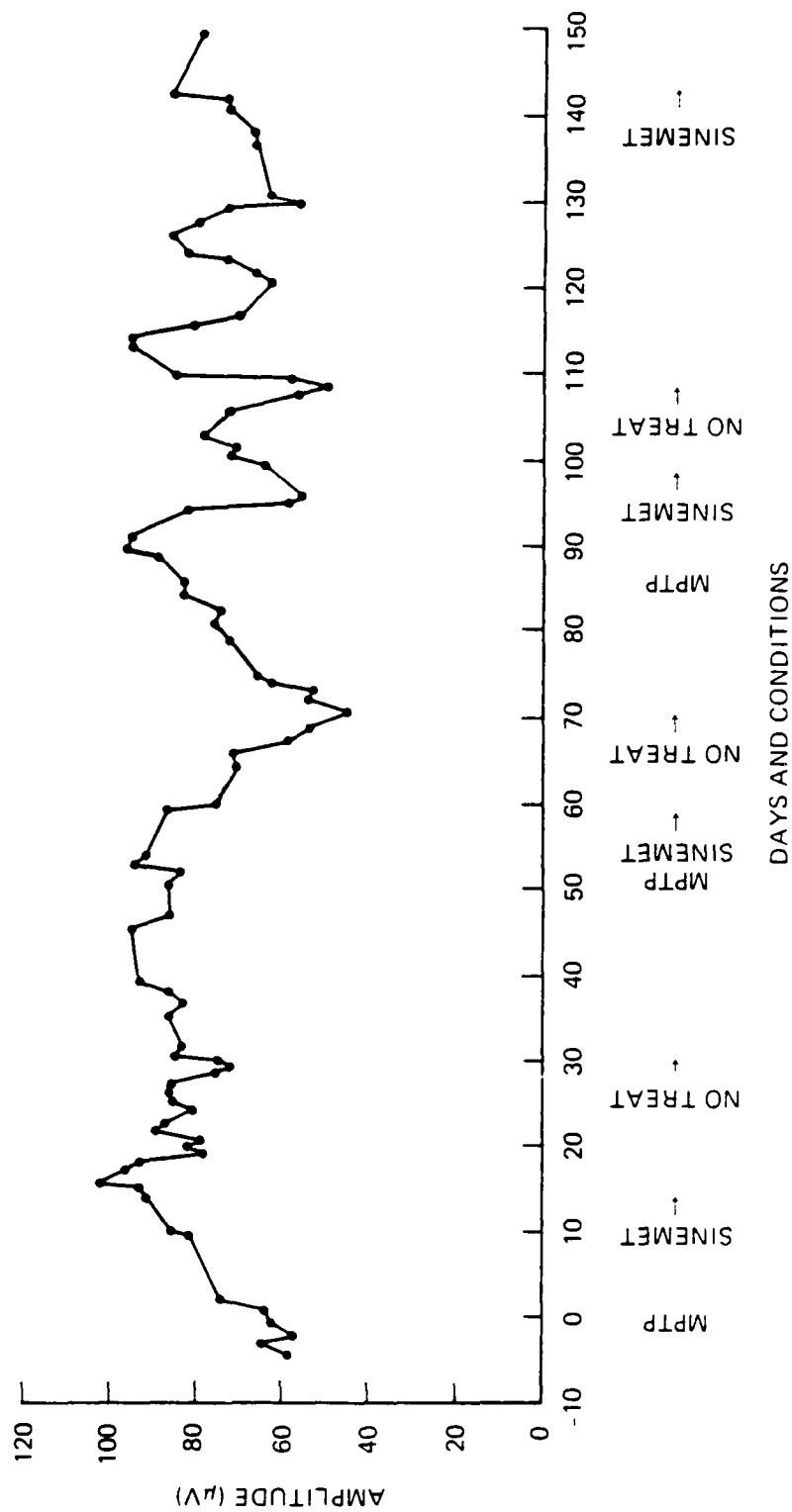


FIGURE 63 CHANGES IN THE N1-P2 AND SP COMPONENTS IN ET'S
PREMOTOR CORTEX ASSOCIATED WITH MPTP INJECTIONS

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FIGURE 64 CHANGES IN THE P1 COMPONENT IN ET'S PREMOTOR
CORTX ASSOCIATED WITH MPTP INJECTIONS

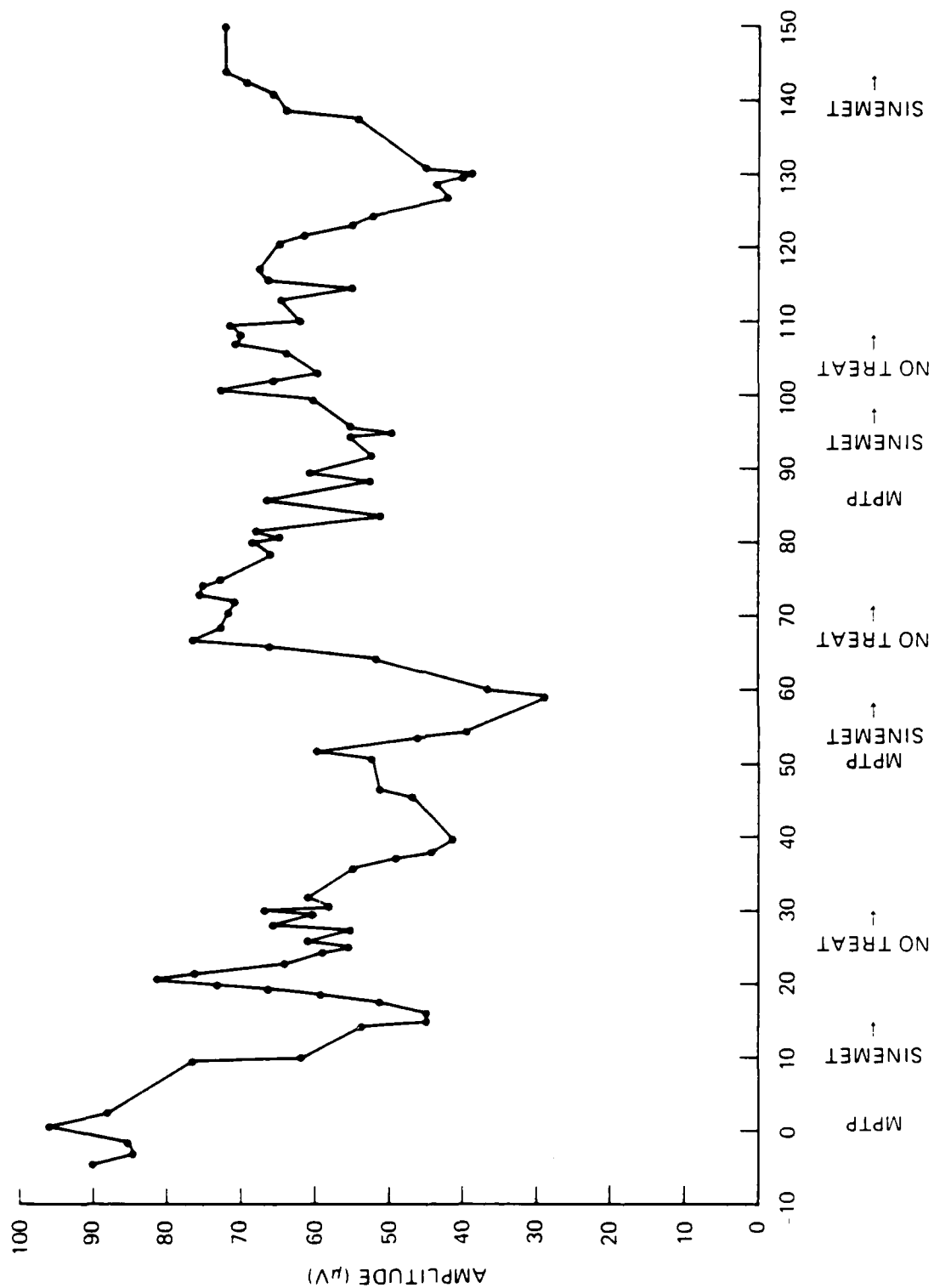
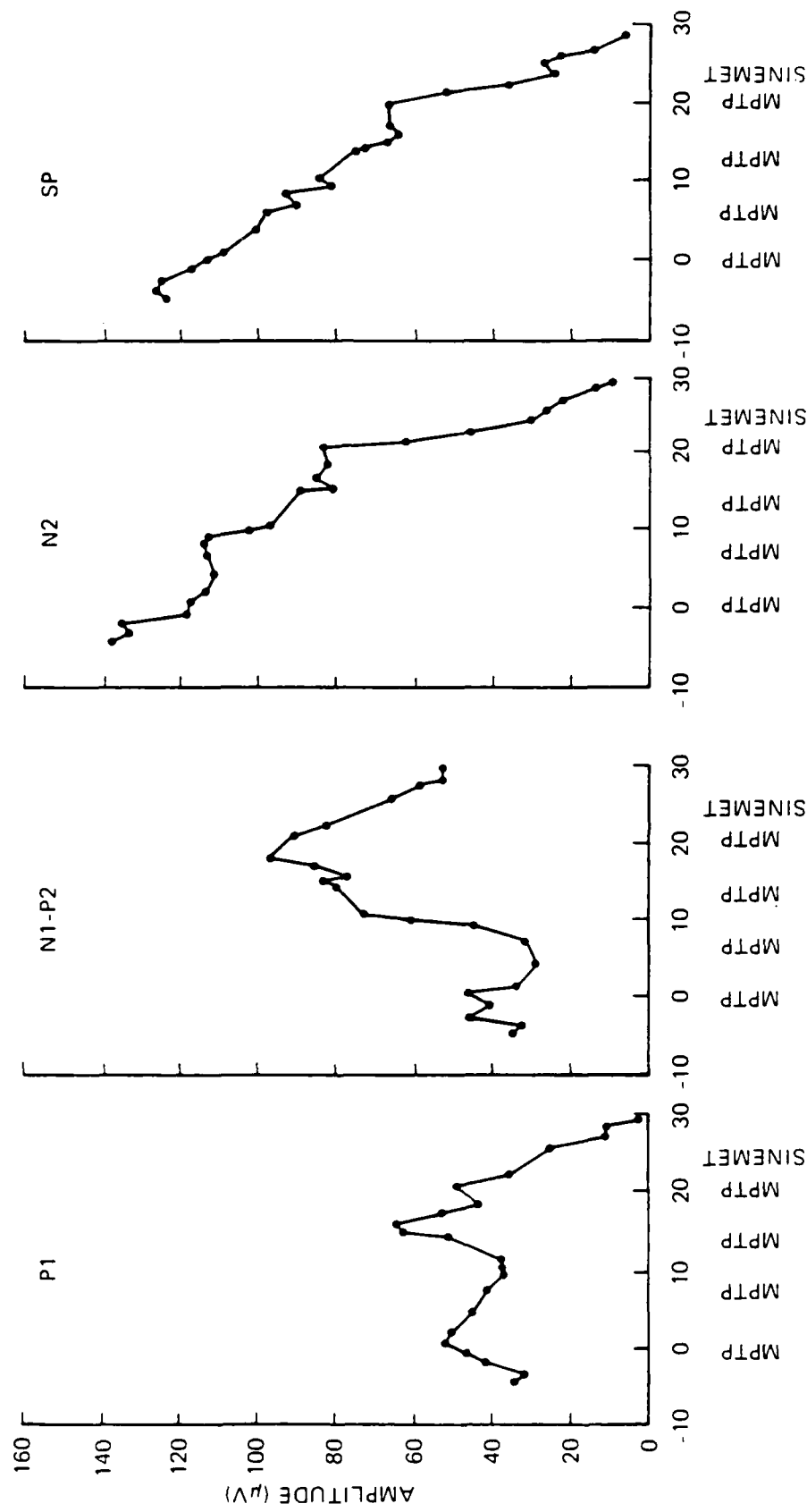


FIGURE 65 CHANGES IN THE N2 COMPONENT IN ET'S PREMOTOR
CORTEX ASSOCIATED WITH MPTP INJECTIONS

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FIGURE 66 CHANGES IN SEVERAL EVOKED POTENTIAL COMPONENTS IN GR'S PREMOTOR CORTEX ASSOCIATED WITH MPTP INJECTIONS

decrease on the day prior to the beginning of MPTP administration for which we cannot account. For both components, however, the rate of change increased following the last dose of MPTP, at the same time that the clinical signs and task performance rapidly deteriorated. Perhaps this rapid deterioration could have been prevented had we more closely monitored the electrophysiological changes (N2 and SP) and determined the dosing schedule on that basis rather than on the basis of behavior.

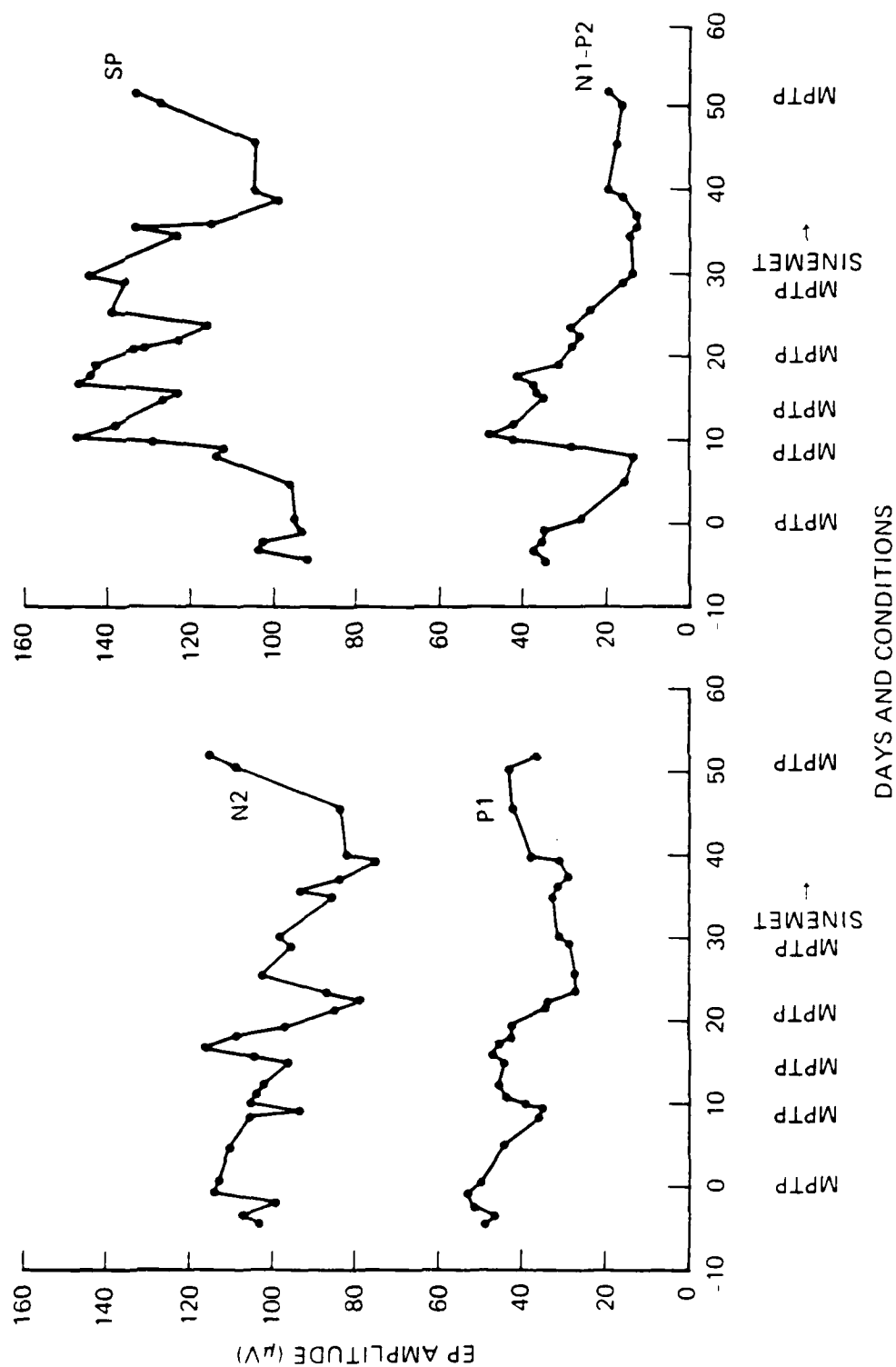
Alterations of PMC components in monkey SM are shown in Figure 67. Only the N2 component exhibited a decrease in amplitude clearly associated with the time of RT increase, and this occurred two days before the RT was most affected. The SP was generally larger during treatments than during the baseline phase. There was a slight decline in the N1-P2 amplitude after day 20.

Figure 68 shows event-related potentials in the substantia nigra. These waveforms differed from those in the PMC in that (1) the initial transient complex was less consistent across monkeys, in two cases (SM and ET) comprising fewer components than the PMC did, (2) the rise to the major initial negative component of the SP (N2) was steeper, and (3) there was a much clearer discrimination between the WS- and NS-evoked waveforms (in two cases there was essentially no SP following the NS). As with the PMC, amplitudes were reduced following MPTP treatments; in monkey SM this effect was more pronounced on the NS-evoked waveform than on the WS-evoked waveform.

Sequential changes over the course of the experiment are shown in Figures 69 through 71. In contrast to the PMC, several components of the SUN were altered in close temporal correspondence to the RT deficits. This was true for the N2 and SP components of monkey ET, shown in Figure 69. The N2 component, especially, decreased in amplitude, clearly in association with the first three episodes of increased reaction time and less clearly thereafter when clinical signs remained substantially abnormal and the RT deficit was not as sharply defined temporally. In addition, amplitude of N2 decreased gradually over the course of the experiment.

The SP exhibited decreases in amplitude that were time-locked to RT changes, but these were proportionally less than those of the N2 component. Also, SP amplitude, overall, remained relatively constant across the experiment after the first dose of MPTP. Presumably, the gradual decline of the SUN N2 component was due to the loss of cells in the nigra.

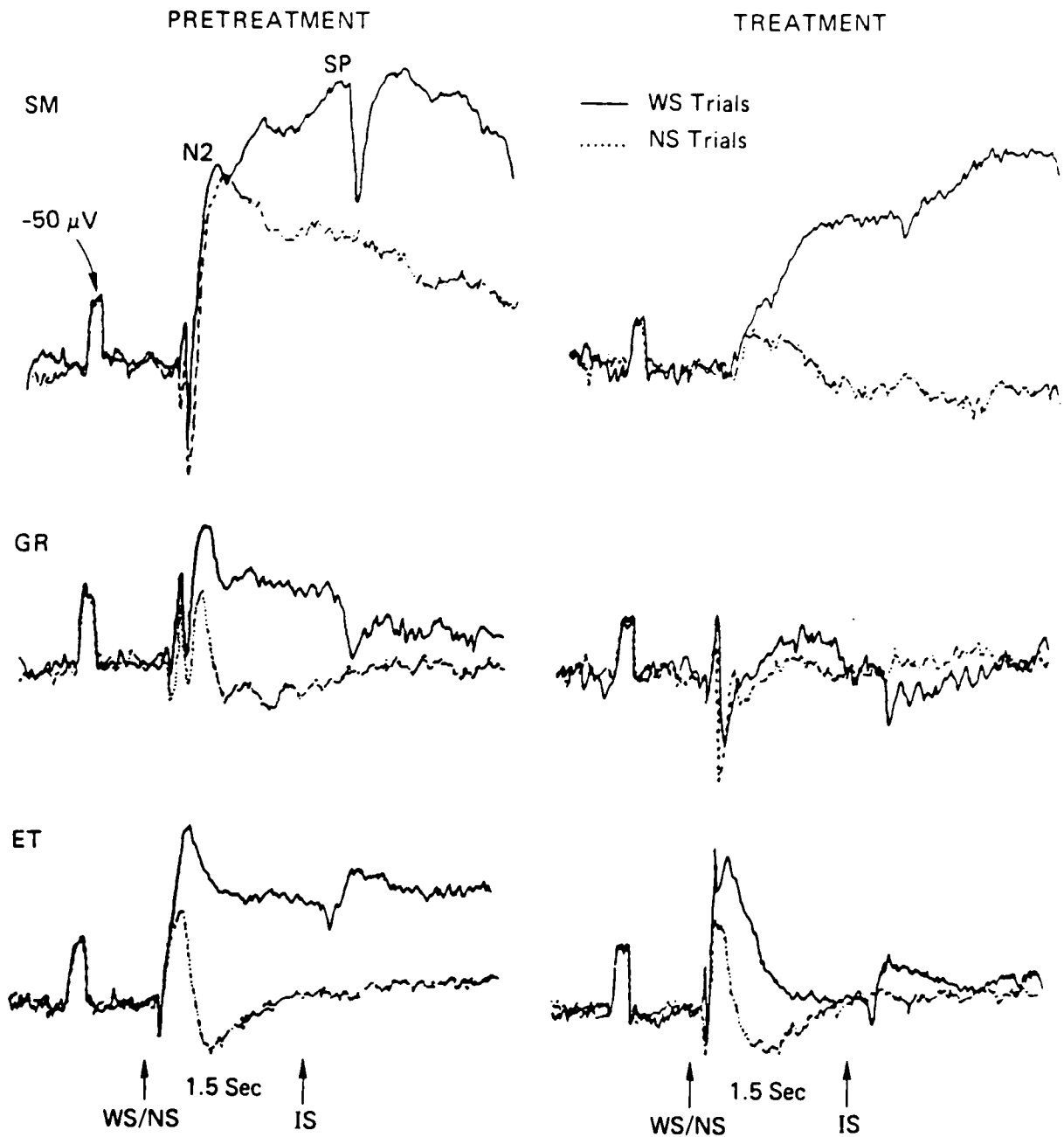
Figure 70 shows precipitous decreases in the amplitudes of the fast transient N1 and slower N2 and SP components of the SUN in the severely affected monkey GR, associated with his clinical and behavioral decline. Change in the N2 component preceded the rapid change in reaction time (which occurred after day 20). Onset of the N2 decline appeared to be associated



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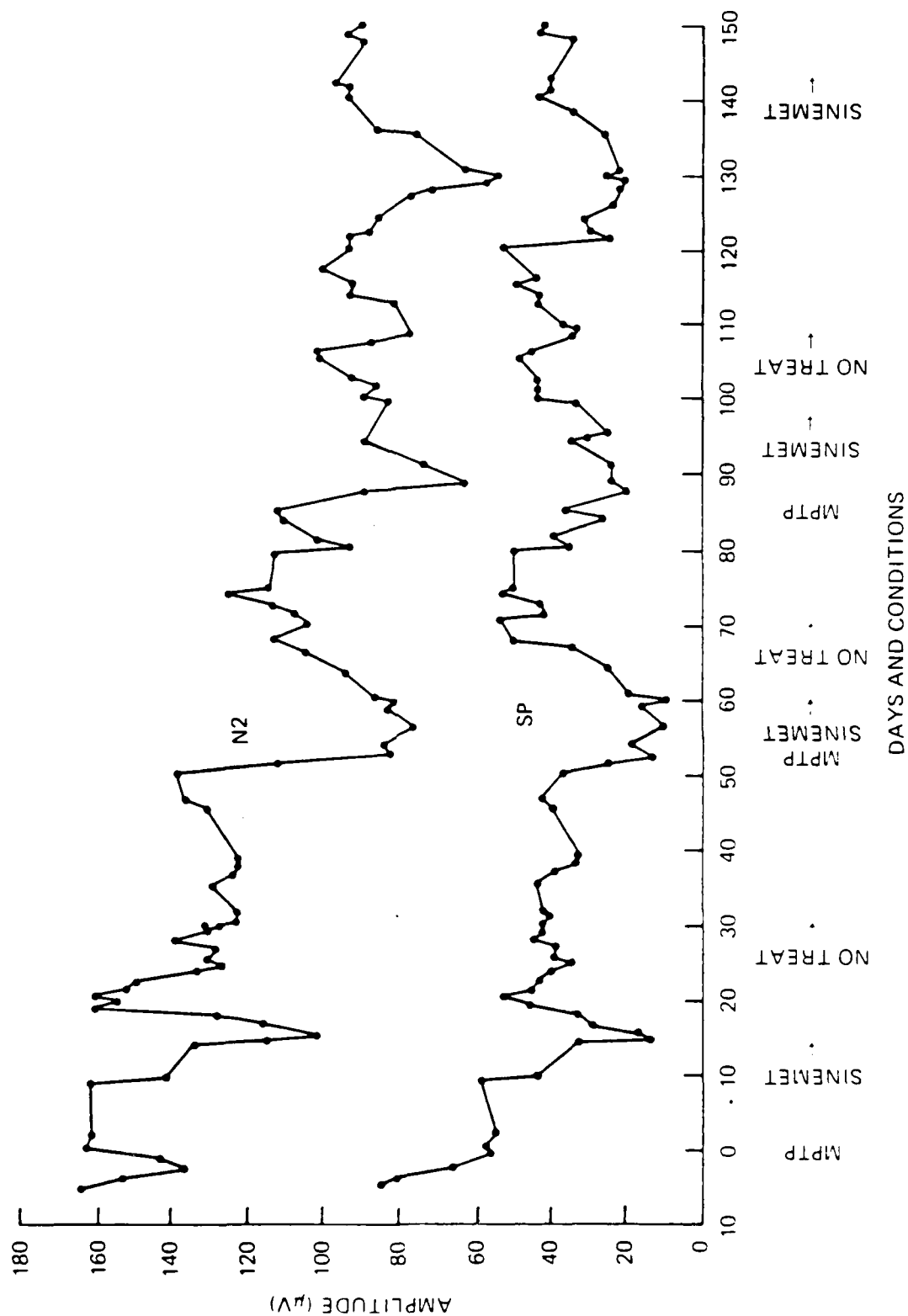
FIGURE 67 CHANGES IN SEVERAL EVOKED POTENTIAL COMPONENTS OF SM'S
PREMOTOR CORTEX ASSOCIATED WITH MPTP INJECTIONS

SUBSTANTIA NIGRA



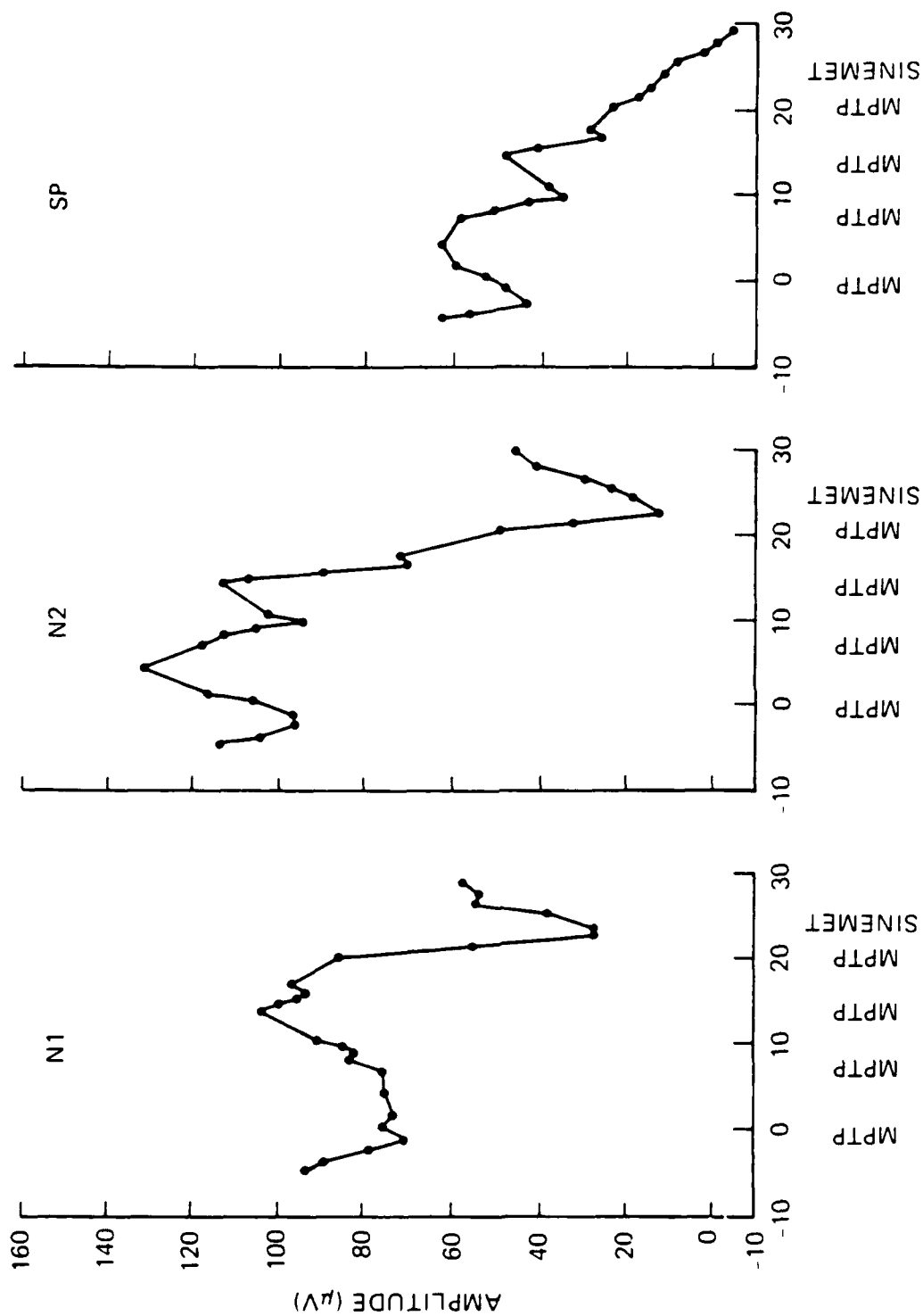
LA-4373-9A

FIGURE 68 EXAMPLES OF EVENT-RELATED POTENTIALS IN THE VICINITY OF THE SUBSTANTIA NIGRA DURING PRE-TREATMENT AND POST-MPTP PHASES OF THE EXPERIMENT



LA-4373-19A

FIGURE 69 CHANGES IN THE N2 AND SP COMPONENTS OF ET'S
SUBSTANTIA NIGRA ASSOCIATED WITH MPTP INJECTIONS



DAYS AND CONDITIONS

LA-4373-12

FIGURE 70 CHANGES IN SEVERAL EVOKED POTENTIAL COMPONENTS IN GR'S SUBSTANTIA NIGRA ASSOCIATED WITH MPTP INJECTIONS

with the first peak in clinical signs on day 15. In this monkey, changes in the PMC were as substantial as those in the SUN, presumably because of the swift and severe decline of the monkey.

Reaction time in monkey SM peaked at day 25 (Figure 58). All measured components of the SUN potential exhibited peak decreases in amplitude at about that same time (Figure 71). The onset of amplitude declines for the N1-P2 transient wave and the SP occurred slightly earlier (day 18) than the early changes in reaction time (about day 22). The N2 component, in contrast, decreased in amplitude on day 10, substantially preceding the RT change, but corresponding to the first clear increase in clinical signs and decrease in rate of bar-pressing (Figures 54 and 61).

Patients with Parkinson's disease have neurological abnormalities in regions other than the pars compacta of the substantia nigra, and there continues to be controversy about the extent to which particular clinical abnormalities depend on particular underlying neural deficits (Langston, 1985). Clearly, compromise of the nigrostriatal dopamine system produces a host of motor and cognitive deficits in monkeys, altering both behavioral and electrophysiological measures of performance in the cued RT task. The "lesion" resulted in some specificities of effect in both classes of measures as well. Clinical ratings and rate of bar-pressing were altered before reaction time; movement time was changed in two cases whereas initiation time was not; and reaction time changed in more restricted time bands than did clinical signs or rate of bar-pressing. Electrophysiologically, the SUN region exhibited changes that were generally more closely associated with behavioral signs than were changes in the PMC. Within the PMC, however, there appeared to be a greater correspondence with behavior of the N2 component than with other components. Perhaps the N2 generator neurons are more intimately related to the SUN than are other neurons in that region.

The fact that behavioral measures recover from the MPTP injections (except when reactions were severe, as in the case of GR) leads to uncertainty about the mechanisms of these effects. MPTP and its metabolites may persist in the organism for several weeks (Ian Irwin, Santa Clara Valley Medical Center, personal communication), so effects might be due to pharmacological rather than neurotoxicological actions of the compounds. However, the slow accumulation of behavioral effects over several days is not compatible with such an interpretation because the compounds would be diminishing rather than increasing in concentration. Alternatively, the rate of onset of deficiencies might relate to the rate of conversion of MPTP to MPP⁺ (the major ion active in the nigra). However, according to Irwin and Langston (1985), that conversion is completed in about one hour. Another possibility is that the compounds undergo a redistribution in the brain and migrate to the SUN. Such a redistribution has been noted by Irwin and Langston (1985), although the time course of this has not been precisely determined.

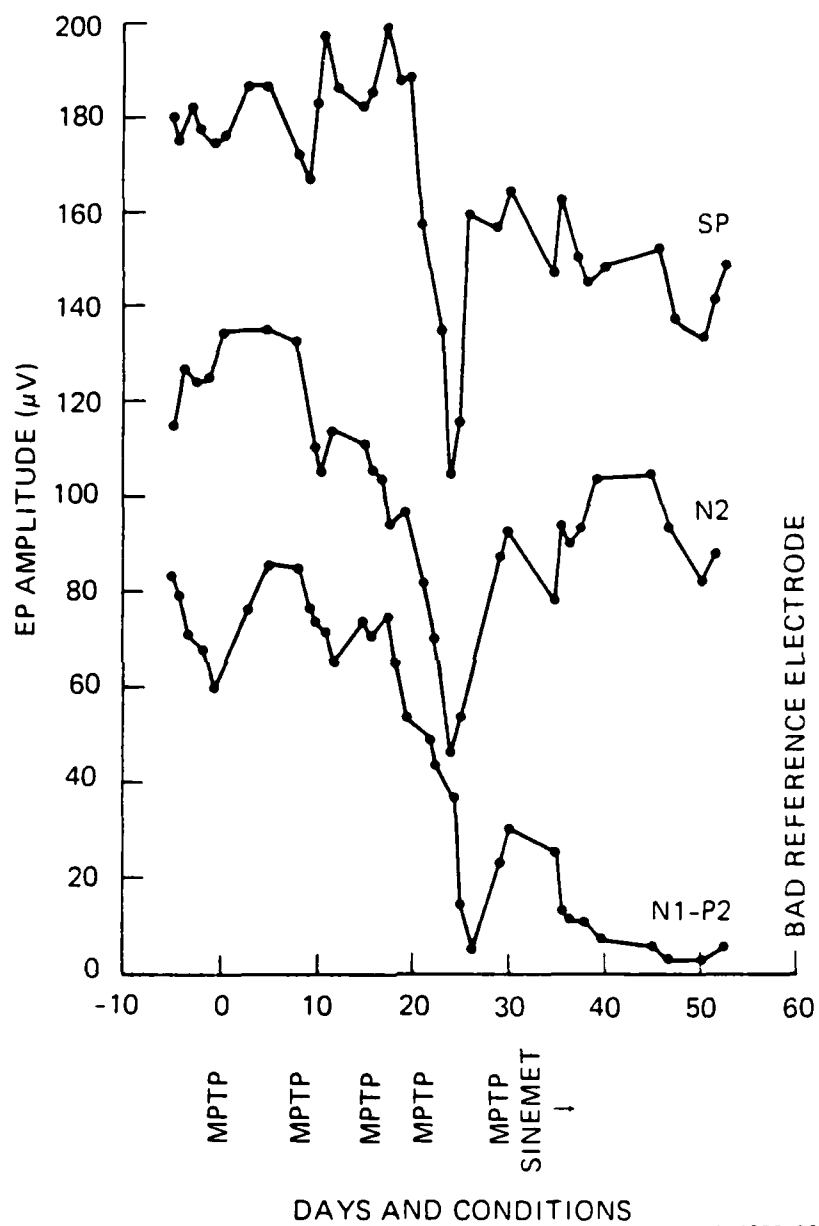


FIGURE 71 CHANGES IN SEVERAL EVOKED POTENTIAL COMPONENTS OF SM'S SUBSTANTIA NIGRA ASSOCIATED WITH MPTP INJECTIONS

Finally, the worsening deficits could relate to the rate of release from MPTP binding to melanin in the nigra.

Recovery of behavioral function could be due to slowly diminishing pharmacological consequences of the foregoing actions or, if there actually is cell damage, to reactions of undamaged neurons, including increased rate of conversion of L-dopa to dopamine or proliferation of terminals in the caudate nucleus (Ian Irwin, Santa Clara Valley Medical Center, personal communication).

These data indicate that the nigrastriatal dopamine pathway is a critical substrate for performance of the cued RT task and for generation of event-related potentials, especially those generated in the vicinity of the substantia nigra. The N2 component of the potentials generated in the premotor cortex was also affected in association with behavioral decrements and might be particularly associated with the nigrastriatal system.

G. Interactions Among Recording Sites: Neurocognitive Pattern Analysis

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, 1976b), 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, 1973b) rather than by specific local generators of ERP components.

To pursue evaluation of intracerebral interactions more rigorously, we instituted collaboration with Alan Gevins and colleagues 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 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 72): they were left premotor cortex (LPM), hippocampus (HPC), ventro-anterior thalamic nucleus (VAN), substantia nigra (SUN), and midbrain reticular formation (MRF). Figure 73 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 5). 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. This procedure permits trios of time series that are correlated pairwise can be analyzed with this measure to ensure that the

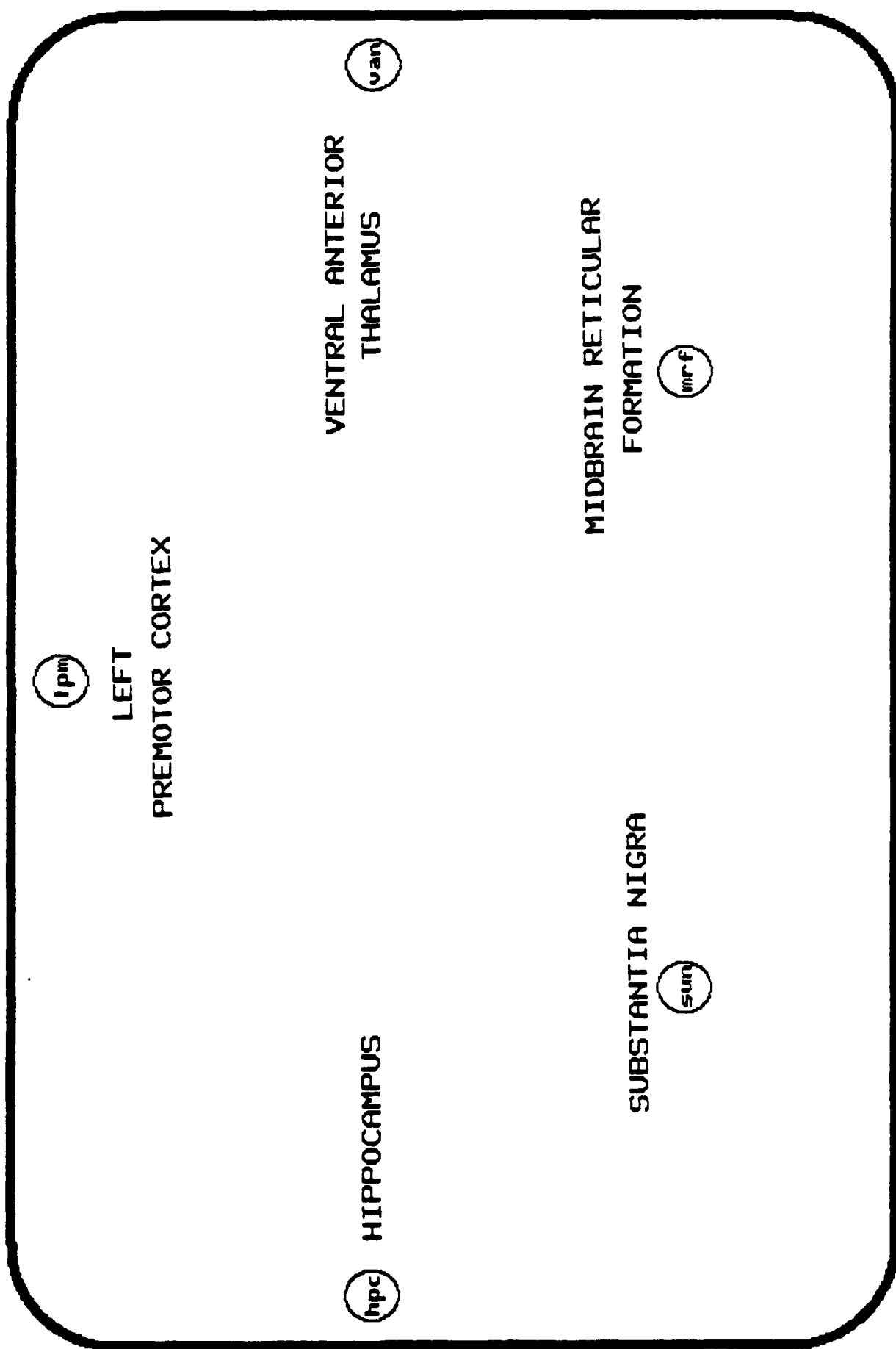


FIGURE 72 REFERENCE MAP OF PLACEMENTS FOR INTERPRETING DATA IN FIGURES 74a and 74b.

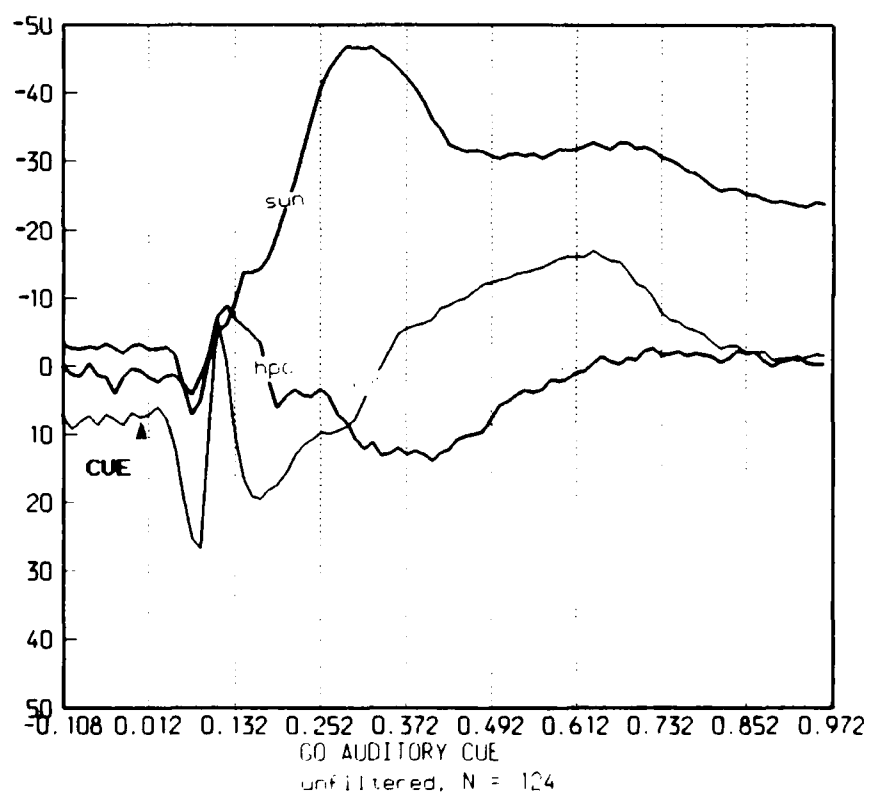
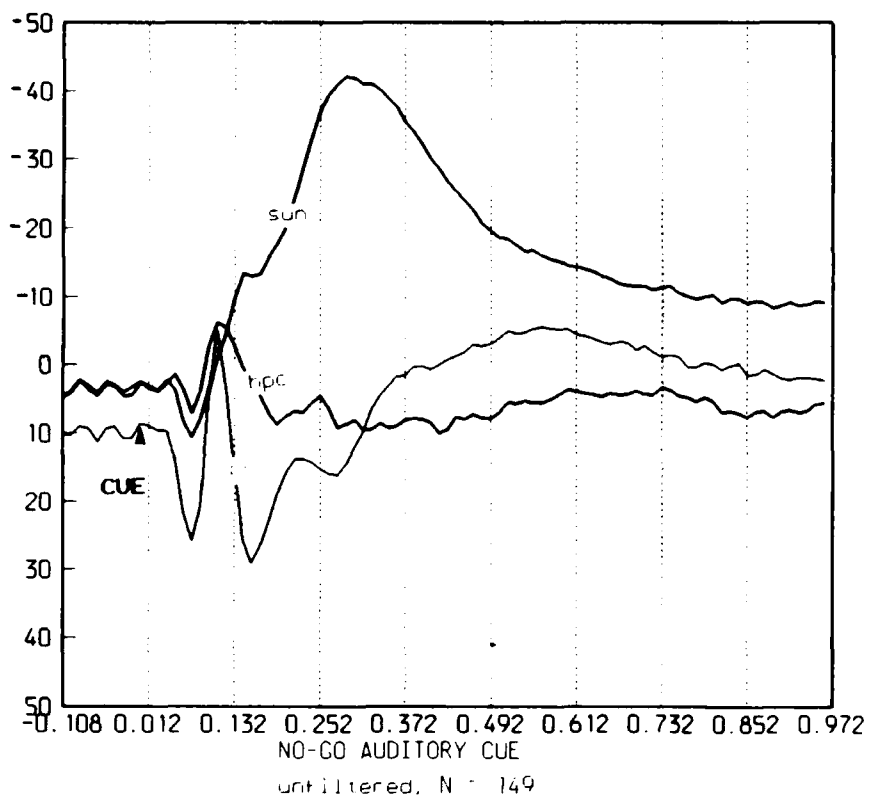


FIGURE 73 AVERAGED ERPs FROM MONKEY ET, USING EEGSL'S PROCEDURES, SHOWING SIMILARITY TO ERPs PREVIOUSLY OBTAINED AT SRI

Table 5

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

measured correlations are not due merely to the similarities between contributions from a third channel. The partial correlation is computed as:

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

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 ρ_{xy} , ρ_{xz} , and ρ_{yz} are the correlations between x and y, x and z, and y and z, respectively.

The results of this analysis are presented in Figures 74a and 74b. 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 74a, "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.

The second row of Figure 74a 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 74a, 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 74a, 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 74b. 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. 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

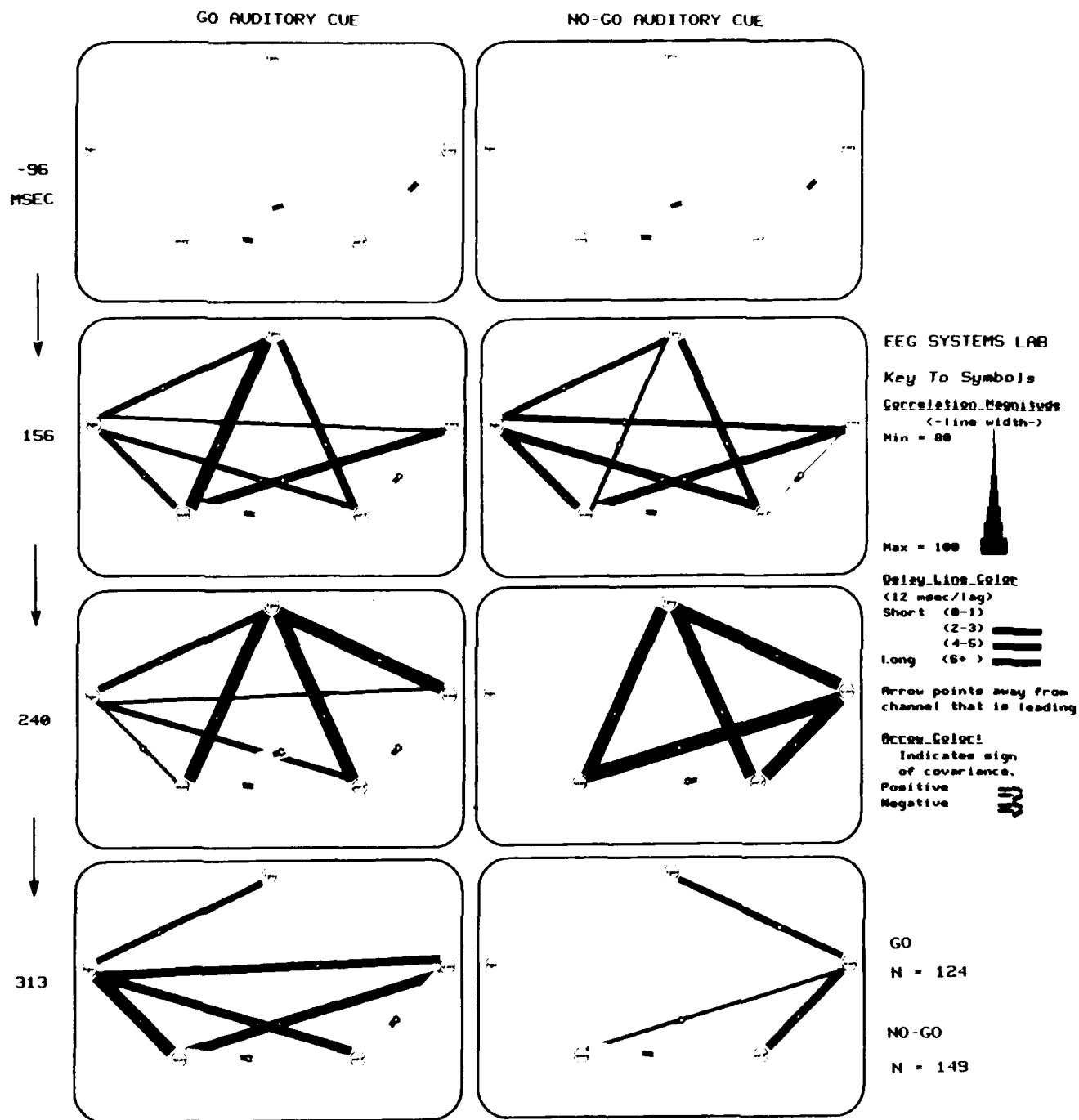


FIGURE 74a INTRACEREBRAL PATTERNS OF "DIRECTED MUTUAL INFORMATION FLOW" AMONG FIVE RECORDING SITES IN MONKEY ET ASSOCIATED WITH THE WS (GO) AND NS (NO-GO) TONES DURING TIME EPOCHS OF -96 TO 313 MSEC PRE- AND POST-STIMULUS

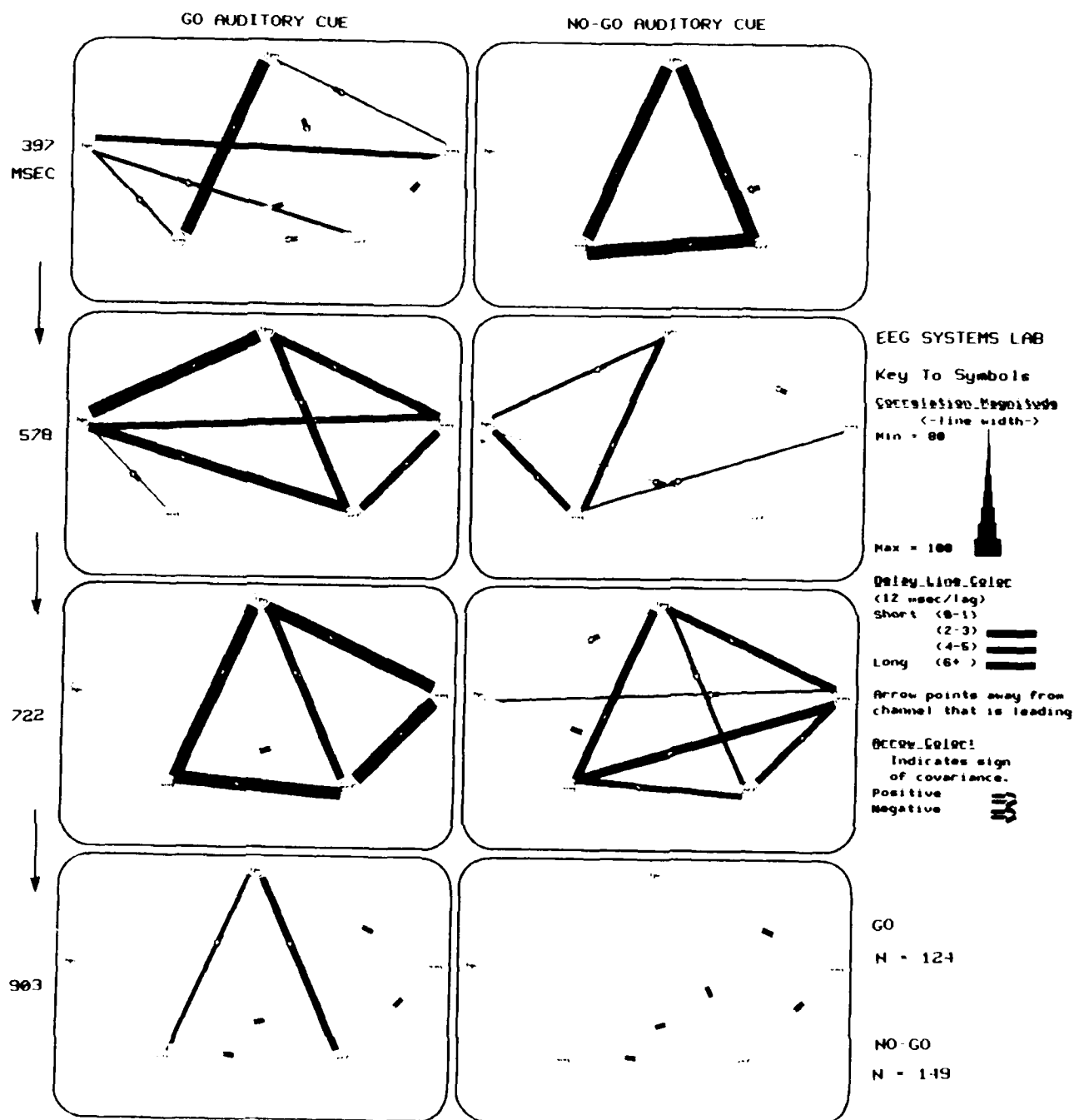


FIGURE 74b INTRACEREBRAL PATTERNS OF "DIRECTED MUTUAL INFORMATION FLOW" AMONG FIVE RECORDING SITES IN MONKEY ET ASSOCIATED WITH THE WS (GO) AND NS (NO-GO) TONES DURING TIME EPOCHS OF 397 TO 903 MSEC POST-STIMULUS

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 msec, width = 276 msec) (Figure 74b, second row), the magnitude of the LPM correlations that 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 74b, 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 74b, 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 74 suggest 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-LPM (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, the patterns continue to diverge for both 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 may depend 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 patterns of activity for "go" and "no-go" appear to be the same before the cue onset and continue so into the 156-msec interval, in which 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.

H. Slow Potentials Related to Self-Paced Voluntary Responding

The Bereitschaftspotential (readiness potential--RP) is a slowly increasing negative shift of the EEG baseline that begins 800-1500 msec prior to the execution of a self-initiated discrete motor act (Kornhuber and Deecke, 1965; Libet, 1985). Its discovery generated great interest as it appeared to be an ideal tool for studying human volition, giving rise to speculations about cortical and subcortical mechanisms underlying voluntary acts (Kornhuber, 1971). However, there is little information about subcortical potentials associated with the cortical RP, and the available data were obtained from patients with diseased motor systems (Knapp et al., 1980; Straschill and Takahashi, 1980; Haider et al., 1968, 1981).

Although the RP has been observed in monkeys (Johnson, 1980; Pieper et al., 1980; Gamba et al., 1979), these studies involved only recordings from the cortical surface.

We retrained three monkeys to perform in a self-paced manner by eliminating the tones and light from the cued RT task and rewarding the monkey on the first spontaneous bar press after the hold paddle was depressed for at least 6 sec. Eventually, the monkeys were making only one or two presses before returning their hand to the hold paddle, and they responded with intervals varying from 6 to 30 sec. An EEG sampling procedure using the AVERAG software was developed so that EEG epochs included a 3-sec period preceding and a 1-sec period following release of the hold paddle (mid-signal trigger). The recording epoch could be averaged with respect to either release of the hold paddle (initiation time) or the bar press (reaction time) (usually the former as it was the initial part of the movement). Inclusion of an EEG sample in the average was also contingent on a minimum movement time (reaction time minus initiation time) of 1 sec.

These data are being analyzed by Dr. Bauer in Vienna. Preliminary averaging indicated the presence of RPs in several regions of the brain, but prominently in electrodes aimed at the SUN and MRF. Examples from one female rhesus monkey are shown in Figure 75. There was little activity in the arcuate gyrus or at the electrode below that gyrus, but positive shifts, beginning about 500 msec before the response, appeared in PMC and the response was larger in the subcortical PMC reference electrode (producing a relative surface negativity). These responses from PMC attained maximum amplitude at--or a little later than--the time of the response. The subcortical response peaked slightly sooner. Responses from the SUN and MRF were very similar negative-going potentials that, in contrast to surface PMC, peaked slightly before the response. Similar premovement activity was observed in the electrode placed lateral to the SUN as a possible reference (SUN-R), but the postmovement potential was not sustained as long at this site as were those in SUN and MRF. The electrode aimed at the red n. exhibited activity most like the human RP in appearing a second or more before the behavioral response.

Extensive analyses of eye movements and blinks indicated little influence of blinks on any of the recordings. Eye movements had a small effect on recordings from frontal cortex but no effects on recordings from subcortical nuclei.

I. Cerebellar Dentate Manipulation Using Push-Pull Perfusion

The cerebellum is generally conceived to be a motor coordination organ (Bullock, 1977; Ito, 1984). The paleo- and neocortical portions of the cerebellum are most involved in voluntary movements (Bullock et al., 1977; Ito, 1984). Beaubaton et al. (1984) showed that dentate dysfunction, induced by cooling, increased reaction time. Our system is uniquely suited to study the DEN and to determine the effect of its manipulation on behavior and electrophysiological interrelationships noted in the cued RT task.

This task involves three general types of elicited brain processes--those associated with the reception and evaluation of information in the WS, those associated with preparatory set (late portion of CNV), and those associated with stimulus (IS)-initiated behavioral responding. We planned to use push-pull cannulae placed bilaterally in the dentate to pharmacologically modify these nuclei. This procedure is superior to lesioning or cooling methods in allowing greater synaptic specificity of effects, avoiding alteration of fibers of passage, and allowing bidirectional influence (excitation or inhibition) of the nuclei, using appropriate pharmacologic agonists and antagonists. Of interest here is the influence that such manipulations might have on the relationships among the several cortical and

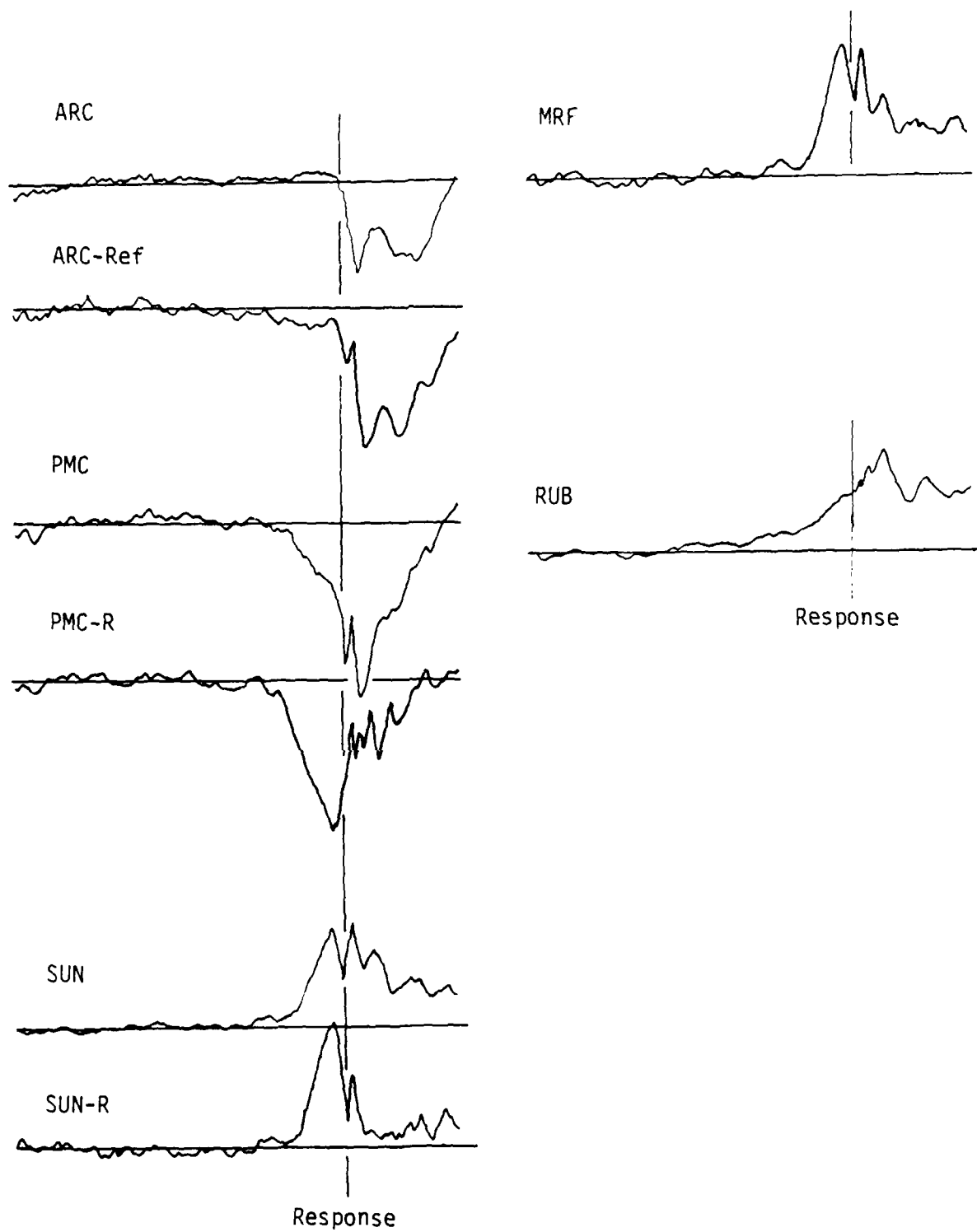


FIGURE 75 READINESS POTENTIALS IN SEVERAL
BRAIN REGIONS OF MONKEY MS.
EPOCH = 4 SEC.

subcortical structures from which the transient and slow potentials can be recorded.

After attempting to develop a push-pull cannula capable of also recording DC slow potential changes, we decided to employ a smaller device and record transient, evoked potentials rather than CNV from the site of manipulation. The push-pull cannulae were constructed of 24- and 32-gauge needle stock by the method of Dluzen and Ramirez (1986). The 24-gauge outer cannula was coated with Epoxylite electrode insulator, with 0.5 mm of the tip exposed for recording massed-unit activity. Four cannulae were built and tested in air, using a four-channel Harvard Apparatus reciprocating perfusion pump. A relatively stable bubble of fluid (1.0-1.5 mm diameter) developed at the tip, with flow rates from 3 to 15 μ l/min.

Three male rhesus monkeys were trained in the preliminary aspects of the cued reaction task--i.e., to bar-press only in the presence of the IS-- and then were aseptically implanted with marker beads for magnetic resonance imaging. After the scanning, we intended to implant electrodes in several sites known to be active in the cued RT task and/or related to the cerebellum (e.g., substantia nigra, red nucleus, ventrolateral thalamus), in addition to the bilaterally placed dentate push-pull cannulae. We did not pursue these activities further because there was insufficient time and resources to carry out both this study and our evaluation of readiness potentials.

J. Electrode Placements

The technique of photographic enlarging and printing of frozen sections, described by Guzman-Flores et al. (1958), was used to obtain information about electrode placements. Normally, the monkey was perfused with the electrodes in place, which results in the tissue hardening around them, leaving a clear track upon their removal. Before sectioning, a gross map of the dorsal brain surface is made and electrode insertion points and epidural electrode locations are marked. The brains were cut into large blocks and then sectioned at 40- μ thickness in a plane angled slightly with respect to the electrode track to prevent tissue separation along the track. Sections were saved in 0.9% saline. Subsequently, the sections near electrode tips were individually slid onto glass, placed in a photographic enlarger, projected onto photosensitive paper, and developed as a glossy print. Locations of the electrodes were then determined by matching the prints with sections in a stereotaxic atlas.

The brain of the nonperforming (and extremely aggressive) cynomolgus monkey was considerably deformed and since no electrophysiological data were collected, histological results on him are not discussed. His sections were collected to provide practice with the sectioning procedure. In the two

other sectioned cynomolgi, the references, hippocampal, and midbrain reticular formation (MRF) electrodes were in the appropriate structures, although the MRF placement in one monkey was more superficial than intended and was on the borderline of the griseum centrale and MRF, very near the oculomotor nerve in the medial longitudinal fasciculus. Both caudate placements were too high, on the border of the corpus callosum and caudate--they did not penetrate the nucleus. One electrode was correctly placed in the n. ventralis anterior, but in the other monkey it was in dorsomedial or central lateral nucleus. The electrodes aimed at the substantia nigra were both too superficial, one being also too posterior in the MRF and the other too medial just above the nigra in the lower region of the red nucleus.

Results for the four stump-tailed macaques are summarized in Table 6. Electrodes in these monkeys were aimed at the caudate, globus pallidus, amygdala, hippocampus, dorsal raphe, substantia nigra, and n. basalis of Meynert. Many placements were not accurate in these monkeys. As in the cynomolgi, the caudate placements were too high--either in the corpus callosum or on the border of the caudate and callosum. The globus pallidus electrodes were usually in or on the border of the internal capsule, but in one case the tip bordered the caudate and pallidus. Electrodes aimed at the amygdala were too posterior, except in one case, and were as noted in Table 6. Two of the hippocampal placements were correct: of the other two, one was in the globus pallidus, one in the internal capsule. Electrodes aimed at the MRF were in the MRF or griseum centrale. Nigral placements were usually too superficial, as were those aimed at the n. basalis.

The failure to place electrodes in the caudate explains our inability to record the positive SPs observed in that nucleus in a previous set of monkeys (Rebert, 1972). Lack of SP changes in the corpus callosum supports the contention that the SP records reflect activity in the vicinity of the electrode tips.

K. P300 (K. Pribram and M. Prim, Stanford University)

The evoked-potential technique is being used to determine which fore-brain 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 poststimulus or prereponse 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

Table 6

ELECTRODE PLACEMENTS IN FEMALE
STUMP-TAILED MACAQUE MONKEYS

Monkey	CAN*	GLP	AMG	HIP	RPH	SUN	NBM	REF
MONA	corpus callosum	border of GLP and IC	AMG	globus pallidus	grisea centralis	red n.	border of GLP and int. capsule	L = grey R = border
BERTHA	border of lower CAN	internal capsule	just above HIP, OT	internal capsule	MRF + inf. coll.	MRF	dorsal hypothal.	L = border R = WM
BUELA	corpus callosum	border of CAN and GLP	substantia innominata	HIP	MRF	zona incerta	n. stria terminalis	L = border R = WM
MELISSA	border CC and CAN	internal capsule	optic tract	HIP	griseum centralis	SUN or above	CAN or CC	L = WM R = grey

*CAN = caudate n., GLP = globus pallidus, AMG = amygdala, HIP = hippocampus, RPH = raphe n., SUN = substantia nigra, NBM = n. basalis of Meynert, REF = reference, L = left, R = right, WM = white matter, IC = internal capsule, OT = optic tract, MRF = midbrain reticular formation, CC = corpus callosum.

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. From the standpoint of the results obtained in our laboratory, the "oddball" task as usually given confounds 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 resection 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.

A behavioral testing system used extensively in a variety of neuro-behavioral studies of monkeys at Stanford University (Kimble et al., 1965; Bagshaw et al., 1965; Grandstaff and Pribram, 1971; Pribram et al., 1980) was employed in this investigation. The system hardware consists of PDP-11/34 and Apple computers implementing a "discrimination apparatus for discrete trial analysis - sixth version" (DADTA-VI--Cutcumb et al., 1981). Nine translucent panels in front of a color television set, controlled by the Apple II microprocessor, serve as both stimulus display and response panels. The PDP-11/34 controls the Apple II and records panel press position, reaction time, error scores, and electrical brain activity during task performance. During testing, a monkey is restrained in a primate chair housed in a modified refrigerator. Correct responses result in the delivery of liquid reinforcement.

Five 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 relationships 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.

Four 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 (chloramphenicol, 50 mg/kg) was given the monkey for a 10-day period after surgery.

All four monkeys completed training 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. These 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 recorded from either eight cortical or eight subcortical electrodes on tests during any one day. The subcortical recordings were 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 in which 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.

A difference in a P300-like wave was produced when a truly novel stimulus appeared least often. When the green stimulus, to which the animals had been trained, was used as the "odd ball," no clear-cut difference emerged. The P300 differences were obtained from the far frontal and amygdala leads and a somewhat later difference was obtained from the posterior leads. Basal ganglia and hippocampus showed little difference and the medial thalamic recordings were equivocal.

These results could be interpreted as showing that the truly novel stimulus presentation is reflected in a waveform difference in the recordings from amygdala and farfrontal cortex and that perhaps this waveform corresponds to P3A in humans. The difference in waveforms obtained from the posterior cortex (especially parietal) could possibly be the equivalent of a P3B. Statistical analysis of these results is limited by the fact that we had really good recordings on only two animals. One animal died before the experiment was completed and the other one showed the effects described above, but not as clearly.

DISCUSSION

In the introduction several issues concerning ERPs were delineated. The work described in this report addressed several of those--distribution in the brain, development during associative conditioning, neurochemical mediators, intracerebral dynamics, and homology across species.

Distribution in the brain. In this work we confirmed observations made earlier about the occurrence of SPs related to preparatory set in the cortex and midbrain reticular formation. As in previous studies (Rebert, 1972), cortical SPs were not as consistent and robust as those generated in certain subcortical areas such as the MRF, and responses in motor cortex were typically smaller than in premotor cortex. We did not find the arcuate gyrus to be a particularly robust generator of CNVs as had been suggested by McSherry and Borda (1973), but we did observe that the SMA generated larger transient and slow potentials than MC or PMC when compared in four female stump-tailed macaque monkeys. The greater responsiveness of the SMA to sensory input than the other motor areas is consistent with conjectures that the SMA is more involved with sensorimotor integration than are the other regions (Weinrich and Wise, 1982; Wise, 1985). As in previous work we also observed that the cortical SPs exhibited less differentiation of responses on WS and NS trials than several subcortical areas, but, in general, such differentiation was much less robust on the whole than observed before (Rebert, 1972).

The MRF waveform was usually like that previously observed, consisting of a sharp-rising negativity that was sustained for at least part of the foreperiod. Similar potentials were elicited from several placements not previously examined in this way. These included responses from electrodes aimed at the substantia nigra, n. basalis of Meynert, red n., and raphe n. The nigral region was studied in all of the monkeys and exhibited relatively consistent responses across monkeys. Of considerable importance is that the latency of the major negative peak of these responses occurs at about 350 msec and exhibits some characteristics of the P300 phenomenon (e.g., in some cases its size was related to the proportions of warning and neutral stimuli). We believe that many deep nuclei are involved in a widespread system related to the genesis of scalp-recorded CNVs and P300 waves (Rebert, 1973b).

In earlier work we observed robust positive SPs in the caudate n., but that was not true in the current studies. When tested in the normal routine with 50% WS, the cynomolgus monkeys, with one exception, exhibited small

negative shifts in the CAN. However, when the proportion of WS trials was reduced to enhance WS/NS differentiation, four monkeys (CO, GR, MI, ET) produced small positive shifts in the CAN. Similarly, electrodes aimed at the CAN in the female stump-tailed macaques also exhibited small and inconsistently positive and negative SPs or little response at all. However, during the experiment on changing bar pressure, prominent positive SPs were observed in monkey AG during the low effort conditions. The SPs may, then, depend on the general context of the testing as well as the specifics of any given test session. Histologic analyses of two cynomolgus monkeys and the stump-tailed macaques indicated that the electrodes were generally too high, in the corpus callosum (except in one female the electrode was exceedingly deep in the internal capsule), perhaps accounting for the lack of SPs in these placements. In contrast to most of the monkeys we have currently studied to date, all three of the female rhesus monkeys showed positive SPs of the electrode aimed at the caudate, and the potential was enhanced by training in all three of them. Perhaps because those electrode implants were guided by MRI, the placements were more accurate (this is yet to be determined).

It is difficult to draw definitive conclusions about the generator sources of subcortically recorded potentials. With referential recording the recorded potential may be generated at many sites that could influence either electrode. However, several considerations lend support to the contention that some of the records reflect activity in the vicinity of the active electrode. First, we observed essentially identical records when two very differently placed reference electrodes were used in the cynomolgus monkeys. Second, bipolar recording near the SUN exhibited a waveform similar to the referentially recorded response, albeit of reduced amplitude, indicating activity in that region. On the other hand, the response to the light in the MRF of monkeys MS and RO appeared to be generated at some other site, as it changed when the reference was changed.

Bipolar recording between closely spaced electrodes is likely to be counterproductive in the case of slow potentials, as they appear to occur widely within and among subcortical nuclei. Thus, these potentials would not be observed because of similar activity at each electrode. Since many areas are active, spacing the electrodes more widely would lead to uncertainty about the amount of electrical activity at the two electrodes. It seems as if resolution of these problems would require a mm x mm mapping of the brain's interior and the application of current source density analysis in three dimensions--a formidable task, indeed.

Another approach would be to pharmacologically inactivate the local region around an electrode and determine the extent to which the potential is altered so that the local contribution could be estimated. Also, as Legatt et al. (1980) have suggested, massed unit (MU) recording in

association with EP recording (e.g., Rebert, 1972; Rowland and Dines, 1973) can help localize electrical events since the MU response has a much smaller space constant than does the EP. More recently, Rowland (1987) has suggested that bipolar recording between a stainless steel and Ag-AgCl electrode pair allows localization of slow potential generators. However, this seems questionable since the Ag-AgCl electrode may still be influenced by remote generators via volume conduction.

Despite these difficulties, it remains the case that there are considerable difference in waveshapes and amplitudes among recording sites and the various sites respond differently to experimental manipulations, and exhibit different extents and patterns of development with training. All of these facts indicate that these procedures reflect, at least grossly, differentiable intracerebral activities.

Development of ERPs during associative conditioning. Although highly variable from placement to placement and among monkeys, there were strong indications from all sets of monkeys that one can experimentally follow the acquisition of ERP changes as the monkeys learn that the WS has cue significance. This involved alterations in the early slow wave and late slow potential. In these current studies the enhancement with learning was clearer for the early slow wave than for the SP in most placements, but the SUN was particularly consistent in developing SP enhancement as well. Changes in that nucleus occurred quite often when there was little, if any, change in epidural leads. Thus, it seems clear that scalp recordings in humans are not capable of adequately revealing the preparatory states of Ss--i.e., lack of a cortical CNV does not necessarily indicate that processes related to preparatory set are not active. This may account for the lack of correlation between parameters of the human CNV and reaction time (Rebert and Tecce, 1972).

Of particular interest were the clear indications of differential acquisition and exhibition of CNV-like events in different parts of the brain, including various degrees of discrimination between WS and NS trials. These results are consistent with earlier suggestions concerning the important role of relatively "nonspecific" subcortical regions in learning (Buchwald and Brown, 1973; Olds et al., 1973).

Neurochemical mediators. The systemic administration of cholinergic antagonists degraded behavioral performance and altered ERPs whether or not the agent crossed the blood-brain barrier. Thus, peripheral actions of drugs can induce distracting or other sensations that indirectly influence central processes. Obviously, it is difficult to determine the role of various neurotransmitters in the genesis of ERPs given this situation. Local intracerebral administration of drugs would seem necessary. However, another approach--selective destruction of sources of certain transmitters--

would also seem useful. We interfered with the nigra-striatal dopamine pathway by selective destruction (or inhibition) of the pars compacta area of the substantia nigra. This induced typical symptoms of Parkinson's disease and interfered with performance of the cued RT task--but differentially affected initiation and movement times. In monkey ET the N2 component of the PMC response was reduced in relation to behavioral changes more so than were other components, suggesting a functional connection of the generator of that component and the nigra. In general, changes in the nigra were more pronounced than in the PMC in terms of the number of components affected and the degree to which these alterations were clearly associated with behavioral changes--as might be expected since the nigra was the target of the chemical modification.

Schultz et al. (1985) also found MPTP to induce delayed responses in two monkeys performing a reaction time task, but in both of their monkeys initiation time as well as movement time was affected. However, in their paradigm the monkeys did not receive a warning cue. Thus prewarning, as used in our study, appears to allow sufficient preparation to overcome the deficits in response initiation, even though movement remains slow.

Results concerning slow potential changes in human Parkinsonian patients are mixed. Deecke and Kornhuber (1978) and Shibasaki et al. (1978) reported that the readiness potential was smaller in patients than in controls, but normal responses were found in patients by Barrett et al. (1986). The last authors considered the positive findings to be the result of inadequate techniques or failure to control for age effects. These studies were focused in the readiness potential, but our results suggest that more consistent results might be obtained by studying Parkinsonian patients in the cued RT task, focusing on the early "orienting" wave that may be comparable to the N2 component in our monkeys. In the one study of CNVs in Parkinsonian patients of which we are aware (Amabile et al., 1986) the CNV was about 40% larger when patients were medicated with L-dopa and bromocryptine than during drug-washout periods. These results are consistent with ours, and with Marczyński's (1978) conjecture that dopaminergic pathways are involved in CNV genesis.

Intracerebral dynamics. Statistical procedures describing time-dependent intercorrelations among recording sites (Neurocognitive Pattern Analysis) were carried out in one monkey in order to determine whether systematic patterns of relationship among the sites could be delineated. As discussed earlier, the extent of correlated activity and temporal leads and lags among regions varied as a function of trial events. Onset of the WS or NS caused a synchronization of activity in several regions, but this was replaced subsequently by different organizational patterns on WS and NS trials, reflecting the monkey's discrimination of the meaning of the two tones. These procedures seem capable of extracting information from these recordings not evident in routine analyses--for example, they suggest a more

substantial role of hippocampus in preparatory activity than is suggested by the routine recordings. This role would be compatible with Marczyński's (1986) model of hippocampal function in motor control and attention. The major limitation in this experiment is the lack of verification of the conclusions that are suggested. Validation of the procedures by direct manipulation of intracerebral structures would be valuable.

Homology across species. The monkey's CNVs are like humans in several respects. They occur predominantly in the frontal cortex, the SP component in cortex is preceded by a complex set of transients and an "orienting" type of wave, and the SP varies as a function of motivational influences (e.g., hunger--Borda, 1970; and to some extent response effort--this report). During uncued, self-paced responding the monkey also exhibits an SP similar to the human readiness potential (Gemba et al., 1979; this report). It also appears that when the proportions of WS and NS trials are varied in the cued-RT task, human CNVs are enhanced when the proportion of WS trials is low, similar to our results with several monkeys (Bauer et al., 1988, University of Vienna, personal communication). Subcortical CNVs recorded from humans are also similar to those recorded from monkeys--the caudate n. generates positive SPs, and the MRF exhibits a simple sharp-rising negativity (McCallum et al., 1973). It is quite likely, therefore, that conclusions reached about the electrogenesis and pharmacologic substrates of CNVs in monkeys would be generalizable to the human.

Some functional aspects of CNVs differ between monkey and human. Although there are indications from the work reported here that monkeys appreciate the significance of the WS to some extent within one session of tone-light pairing, the CNVs do not fully develop for several days. In contrast, the CNV of human Ss not verbally informed about the WS-IS contingency develops fully within a few trials. Our current work also indicates that the monkey is less likely than the human to exhibit clearly different responses on WS and NS trials.

Readiness potential. Although the RP has been studied extensively in the human (scalp-recording), and has been recorded under a variety of conditions from the cortex of monkeys (e.g., Johnson, 1980; Pieper et al., 1980; Gemba et al., 1979), to our knowledge it has not been recorded in subcortical regions of monkeys. This is a significant development as there has been considerable conjecture about the mechanisms of volitional behavior and "free-will" (Libet, 1985) with focus on structures related to the cerebellum (Kornhuber, 1971). Our findings suggest that the red nucleus becomes active earlier than other structures preceding self-initiated responses in the monkey. However, we also observed preparatory activity in the substantia nigra, reticular formation, cortex, and other structures, indicating a widespread system related to this process as well.

General conclusions. This work indicates that it is possible to study event-related potentials in monkeys that are similar to those recorded from the human scalp, and that some subcortically generated potentials have considerably different characteristics than the cortical potentials (e.g., they are often more robust). It is possible that the functions manifested by CNV-like potentials are more encephalized in human than in monkey. It is extremely more difficult to study these processes in monkeys than in man for several reasons: the process of "instructing" the monkey about experimental conditions involves lengthy training procedures; it appears that it is necessary to maintain a particular condition (e.g., stimulus proportions) for a period of time before the monkeys "appreciate" what the condition is; the motivational status of monkeys is critical to performance and it appears to vary for unknown reasons; and there are extremely large individual differences in apparent intelligence and motivation among monkeys. Nevertheless, to the extent that human-like ERPs can be studied in the monkey, the opportunity is provided to eventually understand the distribution, functional significance, and mechanisms of ERP electrogenesis. Electrical signals from the brain are becoming ever more useful in a variety of practical settings, but their full utilization depends on a complete understanding of their sources and significance. Thus, the development of animal models expressing these events is of increasing importance.

PUBLICATIONS AND PRESENTATIONS

- Rebert, C. S., Hennessy, M. B., and Donovan, W. J. Slow potentials in substantia nigra and other regions of monkey brain during a cued-reaction time task. In: W. C. McCallum, R. Zappoli, and F. Denoth (Eds.). *Cerebral Psychophysiology: Studies on Event-Related Potentials*. Amsterdam, Elsevier, 1986, pp. 558-560.
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- Rebert, C. S. Cortical and subcortical evoked potentials related to expectancy. AFOSR Seminar, Bolling AFB, December 1984.
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- Rebert, C. S., Diehl, J. J., and Matteucci, M. J. Critical role of nigrostriatal dopamine in preparatory set. Presented at the Eighth Evoked Potential International Congress, Palo Alto, California, July 1986 and Second World Congress of Neuroscience, Budapest, August 1987.

Manuscripts planned:

- Rebert, C. S., Donovan, W. J., Hennessy, M. B., Diehl, J. J., and Matteucci, M. J. Cerebral physiology of preparatory set.
- Rebert, C. S., Diehl, J. J., and Matteucci, M. J. Critical role of nigrostriatal dopamine in preparatory set: Effects of MPTP-induced pars compacta lesions on behavior and event-related brain potentials in macaque monkeys.
- Gevins, A. S., Bressler, S., Matteucci, M. J., and Rebert, C. S. Interdependency analysis of intracerebral brain potentials of macaque monkeys performing the cued reaction time task.

Bauer, H. and Rebert, C. S. Readiness potentials in subcortical structures of monkeys performing a self-paced voluntary limb movement.

Rebert, C. S., Matteucci, M. J., and Diehl, J. J. Changes in subcortical event-related potentials in monkeys associated with varying proportions of significant and nonsignificant auditory stimuli in a cued reaction time task.

LIST OF PROFESSIONAL PERSONNEL

Charles S. Rebert, SRI International
Michael B. Hennessy, SRI International
Gordon T. Pryor, SRI International
Edward E. Davis, SRI International
Karl H. Pribram, Stanford University
Merle M. Prim, Stanford University
Alan S. Gevins, EEG Systems Laboratory
Steve Bressler, EEG Systems Laboratory
William J. Donovan, SRI International
Herbert Bauer, University of Vienna
Samuel J. Jackson, SRI International

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NEUROPHYSIOLOGICAL BASES OF EVENT-RELATED POTENTIALS

3/1

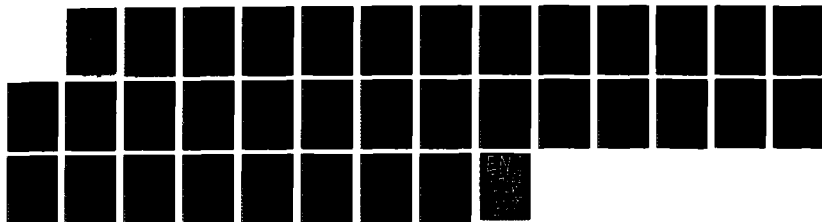
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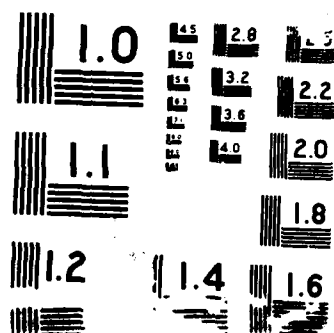
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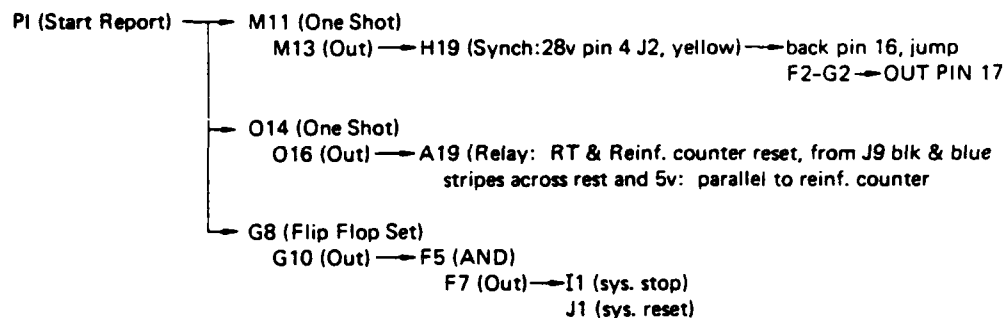
Appendix A
ICONIX LOGIC SCHEMATIC

ICONIX CNV PROGRAM

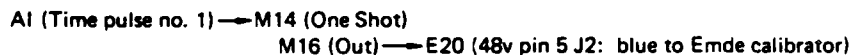
TIMER OUTPUTS

START Report Synch	1 CAL	2 WS	3 ABORT OFF	4 IS ON	5 IS TIMEOUT	6 IS OFF
TIME (MS) 00000	00100	00700	02690	02700	04700	14700

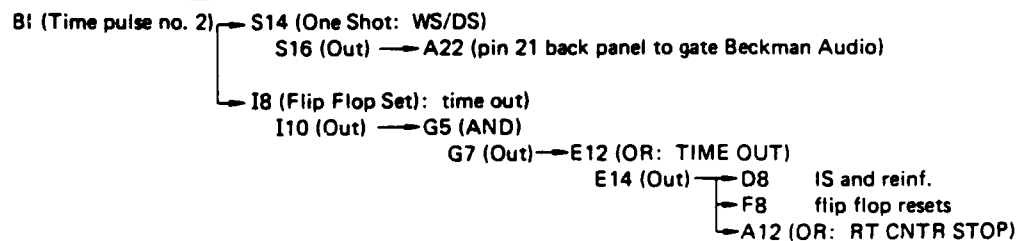
SYNCH



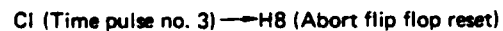
CAL



WS/DS & Time Out Set

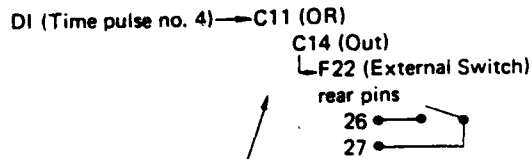


ABORT OFF

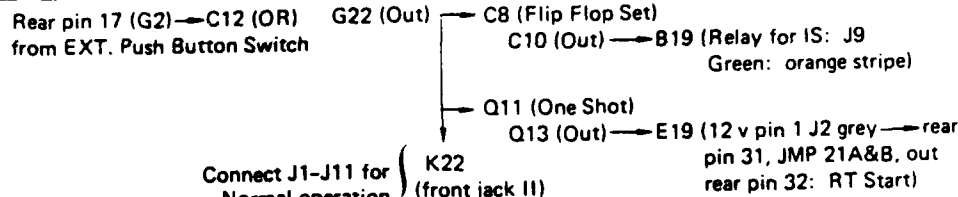


ICONIX CNV PROGRAM (Continued)

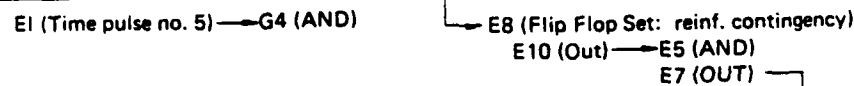
IS ON/RT START



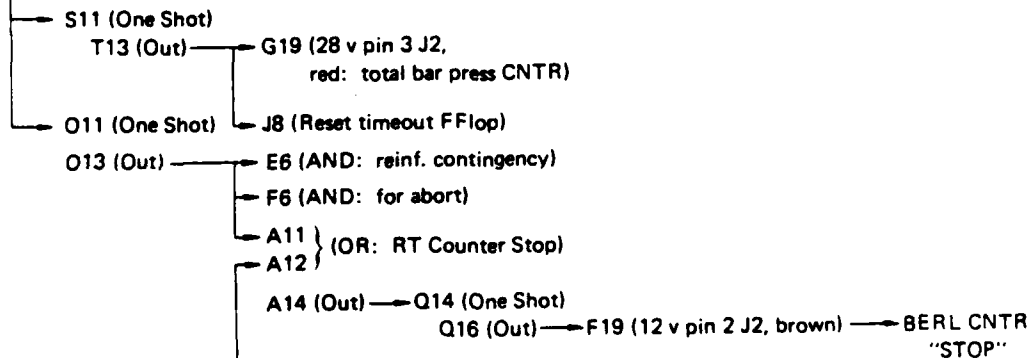
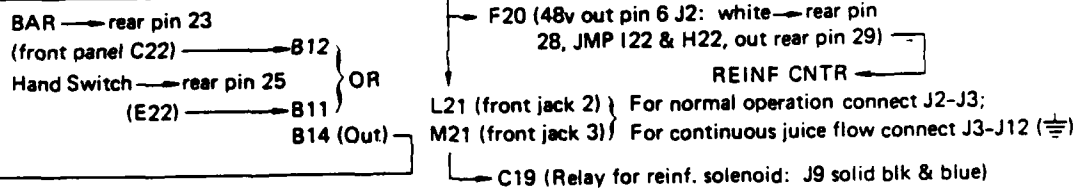
REMOTE IS ON



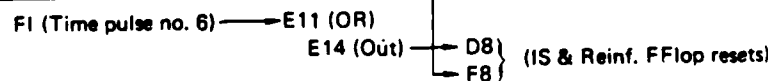
IS TIME OUT



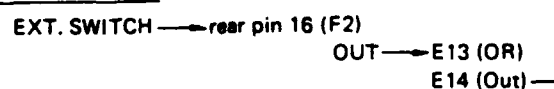
RESPONSE BAR



IS OFF



REMOTE IS OFF



Appendix B

LSI-11/23 PROGRAM LISTINGS

- CNV
- P300
- PLTCNV

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C      PROGRAM CNV2 IS THE MASTER PROGRAM FOR RUNNING
C      THE CUED REACTION TIME STUDY, SAMPLING EIGHT
C      CHANNELS OF EITHER EVENT RELATED POTENTIALS OR
C      MULTIPLE UNIT ACTIVITY, AND ALL RELATED DATA
C      MANIPULATION AND STORAGE, VIA MENU SELECTION.
C      SOFTWARE TRIGGER INITIATES SAMPLING EVERY 10 MSEC.
C      DIGITIZED WAVEFORMS STORED IN MATRIX AS INTEGERS,
C      PRIOR TO DISPLAYING AND WRITING TO WINCHESTER DISK.
C      AT END OF SESSION, AVERAGES WRITTEN TO FLOPPY DISK; USER
C      TRANSFERS SINGLE-TRIAL DATA FROM WINCHDISK TO MAGTAPE.
      PROGRAM CNV2
      EXTERNAL WATCH, ITISUM
      COMMON /BLOCK1/MSNEU, ISI/BLOCK2/ITIRSP/BLOCK3/IDIS/BLOCK4/MSROFF
      VIRTUAL USAVG(8,400), DSAVG(8,400), YVAL(400), XVAL(400)
      VIRTUAL MATRIX(8,400), TAGS(68)
      REAL*8 FNAME(2)
      REAL YVAL, XVAL, RLSTAT(14), USAVG, DSAVG, PREADJ, ADDEND, USCNT, DSCNT
      REAL SORTOT, TOTMS
      LOGICAL*1 YESNO, TASK(3), GONOW, IDMONK(8), TYPE, EXTMSG(34), COMENT(60)
      LOGICAL*1 FSTRNG(14), TONE(3), NUFIL(14)
      LOGICAL*1 FSPEC1(4), FSPEC2(7), FSPEC3(4), FSPECA(10), FSPECB(13), ERR1
      INTEGER*2 MSOLD, MSNEU, ISI, NRESP(7), MSECRT, IDIS, CALUV(8)
      INTEGER*2 MATRIX, ISTAT, IBUFF(8), IBFCNT, ICHAN, TAGS, INSTAT(30)
      INTEGER*2 MONTH(12), WINCHD, LCH(8), LIMAX(8), LIMIN(8), KLIPT(8)
      INTEGER*4 ITIME
      DATA WINCHD/3RDL1/, FNAME(1)/12RDL1FTN3  DAT/, RLSTAT/14*0.0/
      DATA IBUFF/8*0/, NRESP/7*0/, INSTAT/30*0/
      DATA MONTH/31,28,31,30,31,30,31,31,30,31,30,31/
      DATA FSPEC1/'D','L','1',0/, FSPEC3/'D','A','T',0/
      ITRIAL=0                ! Counter for # of trial
      LIMIT=3770              ! Artifact window size(+ or -)
      NDAYS=0
      ITIRSP=0
      ITISEC=0
      LOOK=0                  ! Automatically displayed channel
      INTGR1=0
      INTGR2=0
      DSCNT=0                 ! Zero out DS sample size
      USCNT=0                 ! Zero out US sample size
      ISPEED=0
4      TYPE 8
8      FORMAT(' NAME OF MONKEY IS: ',*)
      CALL GETSTR(5, IDMONK, 7, ERR1)    ! Input up to 7 letters of name
      IF(ERR1) GOTO 4
D      CALL SCOPY(IDMONK, IDMONK, 2)    ! Store initial 2 letters only
      CALL SCOPY('DY:XTABL.DAT', FSTRNG) ! Initialize filename
      CALL INSERT(IDMONK, FSTRNG, 4, 2)  ! Insert 1st 2 letters of name
      CALL IDATE(MON, IDAY, IYEAR)      ! Access date entered upon boot
      TYPE 12, MON, IDAY, IYEAR
12     FORMAT(' IS TODAY'S DATE: ', I3, '/', I3, '/', I3, ' (Y or N)? ', *)
      ACCEPT 16, YESNO
16     FORMAT(A1)
      IF(YESNO .EQ. 'Y') GOTO 24        ! If date OK, proceed
      TYPE 20
20     FORMAT(' YOU FORGOT TO ENTER DATE; START ALL OVER ', /)
      GO TO 832

```

```

24 OPEN(UNIT=2,NAME=FSTRNG,TYPE='OLD',DISPOSE='SAVE')
   READ (2,*) MONKEY,LMON,LDAY,LYEAR,KONDTN,KONDAY,LIMHLD,
   9ISTINI,ISDURA,KPCTWS,CALUV
   REWIND 2
   CLOSE(UNIT=2,DISPOSE='SAVE')
   TYPE 28,LMON,LDAY,LYEAR
28  FORMAT(/,' LAST SESSION WAS ON:',I3,'/',I3,'/',I3,/)
   LMON=MON           ! UPDATE DATE OF MOST RECENT SESSION
   LDAY=IDAY
   LYEAR=IYEAR
   KONDAY=KONDAY+1    ! UPDATE THE N OF DAYS WITHIN THIS CONDITION
   TYPE 32,KONDAY,KONDTN
32  FORMAT(/,' THIS WILL BE DAY N',I3,' OF CONDITION N',I3,' ;CHANGE? ',%)
   ACCEPT 36,YESNO
36  FORMAT(A1)
   IF(YESNO .NE. 'Y') GOTO 500
   TYPE 40
40  FORMAT(/,3X,'M1---IS-RT TESTING',/,3X,'M2---PSEUDOCONDITIONING',/,3X,
   9'M3---MS-DS TESTING',/, ' WHICH N FOR NEXT CONDITION? WHAT N DAY?',
   9'(e.g.,4,1): ',%)
   ACCEPT 44,KONDTN,KONDAY
44  FORMAT(I3,I3)
   GO TO 500
48  CALL PUTSTR(7,' ENTER CHANNELS IN ASCENDING ORDER',%)
52  DO 56 I=1,8
   LCH(I)=0           ! Zero out channel pointers
56  CONTINUE
   NCHS=0
   TYPE 60
60  FORMAT(' WHICH CHANNELS ARE TO BE SAMPLED(1,2,...,8/):',%)
   ACCEPT *,LCH(1),LCH(2),LCH(3),LCH(4),LCH(5),LCH(6),LCH(7),LCH(8)
   LHIGH=LCH(1)       ! Initialize high channel pointer to 1st channel
   DO 68 M=1,8
   IF(LCH(M) .EQ. 0) GOTO 72      ! Stop at empty pointer
   IF(LCH(M) .LT. LHIGH) GOTO 48  ! Only ascending order OK
   LHIGH=LCH(M)
   NCHS=NCHS+1
   TYPE 64,LCH(M)
64  FORMAT(10X,'CHANNEL',I2)
68  CONTINUE
72  TYPE 76
76  FORMAT(' IS THIS LIST CORRECT ? (Y or N):',%)
   ACCEPT 80,YESNO
80  FORMAT(A1)
   IF(YESNO .NE. 'Y') GOTO 52
   IF(MOD(IYEAR,4) .EQ. 0) MONTH(2)=29      ! If leap yr, Feb has 29
   NYEAR=MOD(IYEAR,10)                     ! Which year of the decade
   DO 84 JMON=1,MON
   NDAYS=NDAYS+MONTH(JMON)
84  CONTINUE
   NDAYS=NDAYS+IDAY-MONTH(MON)              ! Which day of the year
   IPART=(NDAYS-MOD(NDAYS,100))/100
   JPART=(MOD(NDAYS,100)-MOD(NDAYS,10))/10
   KPART=MOD(NDAYS,10)

```

```

      FSPEC2(1)=IDMONK(1)
      FSPEC2(2)=IDMONK(2)
      ENCODE (4,88,FSPEC2(3)) IPART,JPART,KPART,NYEAR
88      FORMAT(4I1)
      FSPEC2(7)=0
      CALL CONCAT(FSPEC1,FSPEC2,FSPECA,9)
      CALL CONCAT(FSPECA,FSPEC3,FSPECB,12)
      CALL IRAD50(12,FSPECB,FNAME(2))          ! Store file name
      CALL SCOPY('DL1:XXXXXX.DAT',NUFILE)
      CALL INSERT(FSPEC2,NUFILE,5,6)
      DO 96 L=1,400
      DO 92 K=1,8
      MATRIX(K,L)=0          ! Zero out single-trial matrix
      USAVG(K,L)=0           ! Zero out US average matrix
      DSAVG(K,L)=0           ! Zero out DS average matrix
92      CONTINUE
      YVAL(L)=0              ! Zero out display matrix
      XVAL(L)=0
96      CONTINUE
      DO 100 M=1,NDAYS+5
      USORDS=RAN(INTGR1,INTGR2)          ! Start RAN subrtn at new point
100     CONTINUE
      NMSRUN=0
      NDSRUN=0
      ID0="0"
      ID1="4000"
      ID2="44"
      ID3="10000"
      ID5="400"

      PAUSE 'HIT RETURN TO GO'
      CALL DEVICE(-1,ID0,"164000")
      CALL IPOKE("170420","0")          ! Turn off clock
108     OPEN(UNIT=3,NAME='DL1:FTN3.DAT',FORM='UNFORMATTED',INITIALSIZE=500)
      ITRIAL=ITRIAL+1          ! Set next trial #
      TYPE 112,ITRIAL
112     FORMAT(/,' NEXT TRIAL IS #',I3)
      IF(KPCTWS .LT. 100) GOTO 116      ! If not all US trials, skip ahead
      GO TO 124
116     IF(KPCTWS .EQ. 0) GOTO 132
      USORDS=RAN(INTGR1,INTGR2)
      CUTOFF=FLOAT(KPCTWS)/100.
      IF(USORDS .GT. CUTOFF) GO TO 128   ! If true, DS tone next
120     NDSRUN=0                      ! Otherwise, US tone next
      NMSRUN=NMSRUN+1
      IF(NMSRUN .GT. ((KPCTWS/10)+3)) GOTO 128! 3 too many US tones ?
124     CALL SCOPY('US',TONE)
      IF(MONKEY .GT. 1024) GOTO 140     ! Counterbalance
      GO TO 136
128     NMSRUN=0
      NDSRUN=NDSRUN+1
      IF(NDSRUN .GT. 3) GOTO 120        ! Already had 3 DS tones ?
132     CALL SCOPY('DS',TONE)
      IF(MONKEY .GT. 1024) GOTO 136     ! Counterbalance
      GO TO 140

```

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136     ID4="100010
      GO TO 144
140     ID4="20002
144     TYPE 148,TONE
148     FORMAT(' Next trial:',3A1,'tone')
C      HERE REPORT, THEN INITIALIZE OTHER STARTING VALUES
      IF(ITRIAL .EQ. 1) GOTO 168
      TYPE 152
152     FORMAT(/,' BAR-PRESSES FOR LAST TRIAL BY PHASE : ')
      DO 160 J=1,7          ! Zero out counters for bar-presses
      TYPE 156, J,NRESP(J)
156     FORMAT(' DURING PHASE',12,' : ',13,' RESPONSES')
      NRESP(J)=0
160     CONTINUE
      MSECRT=MSECRT-2500
      TYPE 164,MSECRT
164     FORMAT(/,' REACTION TIME FOR LAST TRIAL WAS ',15,' MSEC')
168     MSECRT=17500          ! Default for when no response
      JPHASE=1              ! Reset trial phase indicator
      JDATUM=0              ! Reset pointer for storing data
      MSOLD=0               ! Counter for every msec in trial
      MSNEW=0               ! Updated msec counter
      ISI=0                 ! Counter for every 10 msec
      ISYNOT=0              ! Initialize reject reason code
      MSROFF=20000          ! Initialize reinforcement timer
      IDIS="40000
      CALL DEVICE(-1,ID1,"164000)
      IF(ITRIAL .EQ. 1) GOTO 180
      CALL CCSETI(0)        ! Disable ITI response counter
      CALL GTIM(ITIME)
      CALL CUTTIM(ITIME,IHRS,IMIN,ISEC,ITCK)
      JTIRSP=ITIRSP         ! Store # of responses in last ITI
      ITISEC=(3600*IHRS)+(60*IMIN)+(ISEC)-ITISEC      ! Msec since
      TYPE 176,ITISEC,ITIRSP ! last trial
176     FORMAT(' LAST ITI OF',14,' SEC INCLUDED',14,' BAR-PRESSES',/)
      ITIRSP=0              ! Reset ITI response tally
      NOW=0
D      CLOCK WILL RUN AT 10 KHz, OVERFLOW EACH 1 MSEC
C      CLOCK INTERRUPT WILL ONLY BE USED TO UPDATE MSNEW AND ISI
C
180     CALL CCREAD(MBPRSS,MYET,MSTILL,"164010)
      IF((MBPRSS+MYET+MSTILL).GT.0) GOTO 180
      CALL CLOCKU(1,3,-10,,WATCH,"170420,"440)      ! Start clock
184     IF(MSNEW .LE. MSOLD) GOTO 184      ! Wait for next clock overflow
      MSOLD=MSNEW              ! Resynch msec counters
      IF(ISI .LT. 10) GOTO 208          ! Sample or check for bar-presses
      ISI=0
      JDATUM=JDATUM+1
      CALL AREADP(ISTAT,IBUFF,8,-7)      ! Sample channel(s)
      CALL EXTSL2(IBUFF,8)
188     IF(ISTAT .EQ. 0) GOTO 188          ! Wait until sampling all done
      IF(ISTAT .EQ. 1) GOTO 196          ! Without any errors ?
      TYPE 192
192     FORMAT(' ERROR IN DATA COLLECTION ',/)
      CALL IPOKE("170420,"0)      ! Turn off clock, then abort trial

```

```

ITRIAL=ITRIAL-1
GO TO 448      ! Terminate trial
196 DO 200 K=1,8
MATRIX(K,JDATUM)=IBUFF(K)      ! Transfer data to full matrix
200 CONTINUE
IF(MSNEW .GE. MSROFF) CALL ROFF
GO TO 184

204 ISYNOT=3      ! Experimenter opts to abort
GO TO (216,220,224,228,232,236), JPHASE ! Continue aborted trial
208 CALL CCREAD(MBPRSS,MYET,MSTILL,"164010) ! Any contact closures?
IF(MYET .GE. 4096) GOTO 204      ! Chan 13-16;Experimenter aborted
IF(MBPRSS .EQ. 0) GOTO 212      ! If none, time for next event ?
NRESP(JPHASE)=NRESP(JPHASE)+1 ! Bar-press
IF(IDIS .NE. "40200) GOTO 212 ! If DS, or abort, or phase<6
CALL REINF
IF(MSECRT .EQ. 17500) MSECRT=MSNEW      ! Note reaction time

C TRANSITION TO NEXT PHASE OF TRIAL YET ?
212 GO TO (216,220,224,228,232,236), JPHASE
216 IF(MSNEW .GT. 400) GOTO 240      ! Begin CAL trigger pulse
GO TO 184
220 IF(MSNEW .GT. 450) GOTO 244      ! End CAL trigger pulse
GO TO 184
224 IF(MSNEW .GT. 1000) GOTO 248      ! Begin tone
GO TO 184
228 IF(MSNEW .GT. 1200) GOTO 252      ! End tone
GO TO 184
232 IF(MSNEW .GT. ISON) GOTO 256      ! Turn on light
GO TO 184
236 IF(MSNEW .GT. 4000) GOTO 264      ! Stop sampling
GO TO 184
240 JPHASE=2
CALL DEVICE(-1,ID2,"164000)      ! CAL pulse ON
GO TO 184
244 JPHASE=3
CALL DEVICE(-1,ID3,"164000)      ! CAL pulse OFF
GO TO 184
248 JPHASE=4
CALL DEVICE(-1,ID4,"164000)      ! Tone ON
GO TO 184
252 JPHASE=5
CALL DEVICE(-1,ID5,"164000)      ! Tone OFF
GO TO 184
256 JPHASE=6
IF((NRESP(1)+NRESP(2)+NRESP(3)+NRESP(4)+NRESP(5)) .EQ. 0) GOTO 260
ISYNOT=2      ! Premature bar-press
260 IF(ISYNOT .GT. 0) GOTO 184
IF(SCOMP('WS',TONE) .NE. 0) GOTO 262      ! If DS trial, no IS
IDIS="40200
262 CALL DEVICE(-1,IDIS,"164000)      ! Phase 6 events begin
GO TO 184

```

```

264 JPHASE=7 ! No more sampling but trial not over yet
IF(ISYNOT .GT. 0) GOTO 296
IF(IDIS .EQ. "40000") GOTO 293 ! If DS trial, skip ahead
IDWSOK=IDIS-16384+512 ! Switch indicator lights: 6th to 7th
CALL DEVICE(-1,IDWSOK,"164000") ! Without altering ongoing reinf
IDIS="1200
IF(NRESP(6) .EQ. 0) GOTO 268 ! If no 1st bar-press yet, skip ahead
266 IF(MSROFF .EQ. 20000) GOTO 280
GO TO 276
268 CALL CCREAD(MBPRSS,MYET,MSTILL,"164010)
IF(MYET .GT. MSTILL) GOTO 272 ! Was there a contact closure?
IF(MSNEW .LT. LIMRT) GOTO 268 ! More time left ?
ISYNOT=1 ! Too slow reaction time
GO TO 296
272 MSECRT=MSNEW ! Record reaction time to 1st bar-press
CALL REINF
NRESP(7)=1
276 IF(MSNEW .LT. MSROFF) GOTO 276 ! Wait for reinforcement delivery
CALL ROFF
GO TO 280
278 IF(IDIS .NE. "1200") GOTO 278
280 CALL CCREAD(MBPRSS,MYET,MSTILL,"164010)
IF(MBPRSS .EQ. 0) GO TO 284 ! If no bar-press, skip ahead
NRESP(7)=NRESP(7)+1
CALL REINF
IF(MSROFF .EQ. 20000) GOTO 292
288 IF(MSNEW .LE. MSROFF) GOTO 288 ! Wait for reinf relay offset
CALL ROFF
292 IF(MSNEW .GE. ISOFF) GOTO 296 ! End of trial yet ?
GO TO 280

293 IDIS="1000
CALL DEVICE(-1,IDIS,"164000") ! Phase #7 light on
294 CALL CCREAD(MBPRSS,MYET,MSTILL,"164010)
IF(MBPRSS .EQ. 0) GOTO 295
NRESP(7)=NRESP(7)+1
295 IF(MSNEW .LT. ISOFF) GOTO 294

296 CALL DEVICE(-1,ID0,"164000") ! Light OFF, end reinf
CALL IPOKE("170420","0") ! Turn off clock during ITI
CALL GTIM(ITIME)
CALL CVTTIM(ITIME,IHRS,IMIN,ISEC,ITCK)
ITISEC=(3600*IHRS)+(60*IMIN)+(ISEC)
NOW=ITISEC ! Store time at end of this trial
C BEGIN INTER-TRIAL INTERVAL RESPONSE-COUNTING,
C THEN REVIEW DATA FOR ARTIFACTS, THEN STORE RAW DATA
C TEMPORARILY ON WINCH DISK AS A SINGLE RECORD PER TRIAL.
CALL CCSETI(ITISUM,"164010","270") ! Count # ITI bar-presses
CALL WINDOW(MATRIX,LHIGH,LIMIT,LCH,LIMAX,LIMIN,KLIPT)
TYPE 300
300 FORMAT(/,' ENTER COMMENT(up to 59 chars) FOR THIS TRIAL:',/)
CALL GETSTR(5,COMENT,59)
CALL STRPAD(COMENT,59)

```

```

TAGS(1)=MONKEY
TAGS(2)=MON
TAGS(3)=IDAY
TAGS(4)=IYEAR
TAGS(5)=KONDTN
TAGS(6)=KONDAY
TAGS(7)=KPCTWS
TAGS(8)=LIMHLD
TAGS(9)=ISTIMI
TAGS(10)=ISDURA
TAGS(11)=LIMIT
TAGS(12)=MCHS
DO 304 I=13,20
TAGS(I)=LCH(I-12)
304 CONTINUE
TAGS(21)=USCNT
TAGS(22)=DSCNT
TAGS(23)=MSECR-2500
TAGS(24)=ID4
TAGS(25)=JTIRSP
TAGS(26)=NOW
TAGS(27)=ITRIAL
TAGS(28)=ISYNOT
DO 308 I=29,35
TAGS(I)=MRESP(I-28)
308 CONTINUE
DO 312 J=36,43
TAGS(J)=LIMAX(J-35)
TAGS(J+8)=LININ(J-43)
TAGS(J+16)=KLIPT(J-51)
TAGS(J+24)=CALUV(J-59)
312 CONTINUE
WRITE (3) TONE,TAGS,((MATRIX(LCH(M),K),K=1,400),M=1,MCHS),COMENT
IF(ISYNOT .GT. 0) GOTO 324
DO 320 I=1,8
IF(KLIPT(LCH(I)) .GT. 5) ISYNOT=4      ! More than 5 artifacts?
IF(LCH(I) .EQ. LHIGH) GOTO 324
320 CONTINUE
324 GO TO (328,364,372,380,388),(ISYNOT+1)

328 IF(SCOMP('DS',TONE) .EQ. 0) GOTO 348      ! If DS trial,update DSAVG
DO 340 L=1,8
MCH=LCH(L)
DO 332 N=1,400
PREADJ=USAVG(MCH,N)
ADDEND=MATRIX(MCH,N)
USAVG(MCH,N)=(PREADJ*USCNT+ADDEND)/(USCNT+1.0)
332 CONTINUE
336 IF(MCH .EQ. LHIGH) GOTO 344
340 CONTINUE
344 USCNT=USCNT+1.0
GO TO 396

```

```

348      DO 356 L=1,8
          MCH=LCH(L)
          DO 352 N=1,400
              PREADJ=DSAVG(MCH,N)
              ADDEND=MATRIX(MCH,N)
              DSAVG(MCH,N)=(PREADJ*DSCNT+ADDEND)/(DSCNT+1.0)
352      CONTINUE
          IF(MCH.EQ. LHIGH) GOTO 360
356      CONTINUE
360      DSCNT=DSCNT+1.0
          GO TO 396

364      TYPE 368
368      FORMAT(/,' TOO SLOW REACTION TIME; DATA NOT ADDED TO AVERAGE')
          PAUSE 'HIT RETURN'
          GO TO 396
372      TYPE 376
376      FORMAT(/,' PREMATURE BAR-PRESS; DATA NOT ADDED TO AVERAGE')
          PAUSE 'HIT RETURN'
          GO TO 396
380      TYPE 384
384      FORMAT(/,' EXPERIMENTER INTERVENED; DATA NOT ADDED TO AVERAGE')
          PAUSE 'HIT RETURN'
          GO TO 396
388      TYPE 392
392      FORMAT(/,' TOO MANY ARTIFACTS; DATA NOT ADDED TO AVERAGE')
          PAUSE 'HIT RETURN'

396      IF(ISPEED.EQ. 1) GOTO 448
          IDCH=LOOK
400      DO 404 N=1,400
          YVAL(N)=MATRIX(IDCH+1,N)+380
          XVAL(N)=N+150+N
404      CONTINUE
408      CALL GINIT(1)           ! Set default parameters
          CALL GEND             ! Go to transparent mode
          CALL STXOX
          CALL STOTU(7)         ! Graphic output on console
          CALL STERR(2)         ! Print error and warning messages
          TYPE 412
412      FORMAT(25(/))         ! Clear screen
          DO 416 M=1,400
          CALL POINT(XVAL(M),YVAL(M)) ! Plot values
416      CONTINUE
          CALL GEND             ! Go to transparent mode
          CALL HOLD             ! Wait for carriage return
          CALL ERASE            ! Clear screen
          CALL GEND             ! Go to transparent mode
          TYPE 420
420      FORMAT(' VIEW MORE SINGLE-TRIAL DATA (Y or N) ? ',*)
          ACCEPT 424,YESNO
424      FORMAT(A1)
          IF(YESNO.EQ. 'Y') GOTO 464

```

```

428      TYPE 428
      FORMAT(' VIEW MORE AVERAGE DATA (Y or N) ? ',%)
      ACCEPT 432,YESNO
432      FORMAT(A1)
      IF(YESNO .EQ. 'Y') GOTO 476
D       GO TO 448
D436     TYPE 440
D440     FORMAT(/,' Enter "G" to start next trial, "M" for menu',%)
D       ACCEPT 444,YESNO
D444     FORMAT(A1)
D       IF(YESNO .EQ. 'G') GOTO 108

448      TYPE 450
450      FORMAT(/,' HIT RETURN FOR NEXT TRIAL, OR:')
      TYPE 452
452      FORMAT(' PICK FROM MENU : ??,QT,EX,DS,DA,CP,PL,...',%)
      ACCEPT 456, TASK(1),TASK(2)
456      FORMAT(2A1)
      IF(SCOMP('??',TASK) .EQ. 0) GOTO 458      ! Display menu
      IF(SCOMP('QT',TASK) .EQ. 0) GOTO 456      ! Quit session
      IF(SCOMP('EX',TASK) .EQ. 0) GOTO 460      ! Exit session
      IF(SCOMP('DS',TASK) .EQ. 0) GOTO 464      ! Display data
      IF(SCOMP('DA',TASK) .EQ. 0) GOTO 476      ! Display average
      IF(SCOMP('CP',TASK) .EQ. 0) GOTO 500      ! Change parameters
      IF(SCOMP('PL',TASK) .EQ. 0) GOTO 648      ! Plot data
      GO TO 108
458      TYPE 460
460      FORMAT(' MENU IS AS FOLLOWS: ??---EXPLAIN MENU',/,23X,
7'QT---QUIT SESSION(DELETE DATAFILES)',/,23X,'EX---EXIT ',
7'FROM SESSION(SAVE DATAFILES)',/,23X,'DS---DISPLAY SINGLE
7'TRIAL DATA',/,23X,'DA---DISPLAY AVERAGES',/,23X,
7'CP---CHANGE PARAMETERS',/,23X,'PL---PLOT DATA',/,/)
      GO TO 448

464      TYPE 468
468      FORMAT(' VIEW DATA FROM WHICH CHANNEL (1-8) ? ',%)
      ACCEPT 472,IDCH
472      FORMAT(I3)
      IDCH=IDCH-1
      IF(IDCH .LT. 0 .OR. IDCH .GT. 7) GOTO 464
      GO TO 400

476      TYPE 480
480      FORMAT(' US OR DS ? WHICH CHANNEL ? (e.g. U4 or U8 or D1)',%)
      ACCEPT 484,TYPE,NUMCH
484      FORMAT(A1,I1)
      IF(TYPE.NE.'U' .AND. TYPE.NE.'D') GOTO 476
      IF(NUMCH.LT.1 .OR. NUMCH.GT.8) GOTO 476
      IF(TYPE .EQ. 'D') GOTO 492
      DO 488 K=1,400
      YVAL(K)=USAVG(NUMCH,K)+380.
      XVAL(K)=K+150+K
488      CONTINUE
      GO TO 408

```

```

492      DO 496 K=1,400
        YVAL(K)=DSAVG(NUMCH,K)+380.
        XVAL(K)=K+150+K
496      CONTINUE
        GO TO 408
500      TYPE 504,KPCTWS,LIMHLD,LIMIT,(LOOK+1)
504      FORMAT(/,' PARAMETERS ARE AS FOLLOWS: ',/, ' 1) % OF US TRIALS= ',I4,
          9/, ' 2) LIMITED HOLD(msec)= ',I5,/, ' 3) ARTIFACT LIMIT= +/- ',I6,/,
          9/ ' 4) CHANNEL DISPLAYED AT END OF EACH TRIAL= ',I2,/, ' 5) CAL PULSES: ')
        DO 512 M=1,8
          TYPE 508,M,CALUV(M)
508      FORMAT(3X,'CH',I2,' : ',I5,'uV')
512      CONTINUE
          TYPE 516,ISTIMI,ISDURA,ISPEED
516      FORMAT(/,' 6) INTER-STIMULUS INTERVAL(210-2990 msec)= ',I5,/,
          9/ ' 7) IS DURATION(>2800 msec)= ',I6,/, ' 8) SPEED(0=slow;1=fast)= ',I2)
          TYPE 520
520      FORMAT(' ENTER NUMBER OF ITEM TO BE CHANGED, OR 0 IF NONE : ',*)
          ACCEPT 524,NPARAM
524      FORMAT(I2)
          GO TO (644,528,540,552,564,596,608,620,632), (NPARAM+1)

528      TYPE 532
532      FORMAT(' WHAT % (0-100) TRIALS SHOULD BE US ? ',*)
          ACCEPT 536,KPCTWS
536      FORMAT(I4)
          GO TO 500
540      TYPE 544
544      FORMAT(' HOW MANY MSEC FOR LIMITED HOLD ? ',*)
          ACCEPT 548,LIMHLD
548      FORMAT(I5)
          GO TO 500
552      TYPE 556
556      FORMAT(' NEW WINDOW LIMIT= ',*)
          ACCEPT 560,LIMIT
560      FORMAT(I6)
          GO TO 500
564      TYPE 568
568      FORMAT(' CHANNEL TO LOOK AT FIRST(1-8) = ',*)
          ACCEPT 572,LOOK
572      FORMAT(I2)
          LOOK=LOOK-1
          GO TO 500
576      DO 584 J=1,8
          TYPE 580,J,CALUV(J)
580      FORMAT(3X,'CH ',I1,' CAL= ',I5,'uV')
584      CONTINUE
          TYPE 588
588      FORMAT(/,' CHANGE CAL uV VALUES ? ',*)
          ACCEPT 592,YESNO
592      FORMAT(A1)
          IF(YESNO .NE. 'Y') GOTO 500
596      TYPE 600
600      FORMAT(' ENTER CHANNEL #, THEN NEW uV CALIBRATION, e.g. 5,75 : ',*)

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        ACCEPT 604,K,CALUV(K)
604      FORMAT(I2,I4)
        GO TO 576
608      TYPE 612
612      FORMAT(/, ' ENTER NEW INTER-STIMULUS INTERVAL(210-2990 msec): ',%)
        ACCEPT 616,ISTIMI
616      FORMAT(I5)
        IF(MOD(ISTIMI,10) .EQ. 0) GOTO 500
        CALL PUTSTR(7, ' MULTIPLES OF 10 ONLY', ' ')
        GO TO 608
620      TYPE 624
624      FORMAT(/, ' ENTER NEW IS DURATION(>2800 msec): ',%)
        ACCEPT 628,ISDURA
628      FORMAT(I6)
        IF(MOD(ISDURA,10) .EQ. 0) GOTO 500
        CALL PUTSTR(7, ' MULTIPLES OF 10 ONLY', ' ')
        GO TO 620
632      TYPE 636
636      FORMAT(/, ' Enter "1" for fast, or "0" for slow mode: ',%)
        ACCEPT 640,ISPEED
640      FORMAT(I2)
        GO TO 448
644      ISON=ISTIMI+1000      ! Compute when to turn light on
        ISOFF=ISON+ISDURA    ! Compute when to shut light off
        LIMRT=ISON+LIMHLD     ! Compute limited hold cutoff(msec)
        IF(ITRIAL .EQ. 0) GOTO 52
        GO TO 448

648      TYPE 652
652      FORMAT(' THIS OPTION NOT YET AVAILABLE ',/)
        GO TO 448
656      CLOSE(UNIT=3,DISPOSE='DELETE')
        CALL IPOKE("170420,"0)      ! Shut off clock
        CALL CCSETI(0)
        GO TO 832
660      TYPE 664
664      FORMAT(' OK TO END THIS SESSION (Y or N): ?',%)
        ACCEPT 668,YESNO
668      FORMAT(A1)
        IF(YESNO .NE. 'Y') GOTO 448
        CLOSE(UNIT=3,DISPOSE='SAVE') ! Save single-trial data
        ICHANL=IGETC()
        IF(ICHANL .LT. 0) STOP 'NO CHANNEL'
        IF(IFETCH(WINCHD) .NE. 0) STOP 'FATAL ERROR FETCHING HANDLER'
        CALL IRENAME(ICHANL,FNAME)
        CALL ICLOSE(ICHANL)
        CALL IFREED(ICHANL)
        CALL IPOKE("170420,"0)      ! Shut off clock
        CALL CCSETI(0)              ! Ignore contact closures
C      An "ok" trial: neither aborted, nor rejected due to artifacts
        TOTMS=0      ! Sum RTs for ok WS trials
        SQRTOT=0      ! Sum squared RTs
        NREINF=0      ! Total # reinforcements
        DO 672 J=1,8
        KLIPT(J)=0    ! Total # artifacts on art.-rej. WS trials
672      CONTINUE

```

```

D      PAUSE / UPDATE TABLE/
      OPEN(UNIT=2,NAME=FSTRNG,TYPE='OLD',DISPOSE='SAVE')
      WRITE(2,*) MONKEY,LMON,LDAY,LYEAR,KONDTN,KONDAY,LIMHLD,
      9ISTIMI,ISDURA,KPCTWS,CALUV
      CLOSE(UNIT=2,DISPOSE='SAVE')

D      PAUSE / NOW REOPEN RENAMED FILE/
D      OPEN(UNIT=3,ERR=725,NAME=NUFILE,FORM='UNFORMATTED',TYPE='OLD')
      OPEN(UNIT=3,ERR=725,NAME=NUFILE,READONLY,TYPE='OLD',
      7FORM='UNFORMATTED',DISPOSE='SAVE')
D      PAUSE / NOW REVIEW RECORDS/
      DO 724 NREC=1,ITRIAL
      READ(3) TONE,TAGS,((MATRIX(M,K),K=1,400),M=1,NCHS),COMENT
      NBP5=0 / N of bar-presses in phases 1-5
      IF(TAGS(27).GT.1) GOTO 684
      DO 680 I=1,20
      INSTAT(I)=TAGS(I) / Session-wide parameters
680      CONTINUE
      INSTAT(21)=USCNT
      INSTAT(22)=DSCNT
684      INSTAT(23)=INSTAT(23)+1 / N of trials
      INSTAT(30)=INSTAT(30)+TAGS(25) / N III bar-presses
      DO 688 L=29,33
      NBP5=NBP5+TAGS(L) / N phase 1-5 bar-presses
688      CONTINUE
      NBPIS=TAGS(34)+TAGS(35) / N IS bar-presses
      INSTAT(29)=INSTAT(29)+NBP5+NBPIS+TAGS(25) / All bar-presses
      IF(SCOMP('DS',TONE).EQ.0) GOTO 716 / If DS, skip ahead
      INSTAT(24)=INSTAT(24)+1 / N of US trials
      IF(TAGS(28).GT.0) GOTO 692 / If not ok trial skip ahead
      TOTMS=TOTMS+TAGS(23) / RT tally for ok US trials
      SQRTOT=SQRTOT+FLOAT(TAGS(23))*2 / RT squared tally
      NREINF=NREINF+NBPIS / Reinforcement tally

692      GO TO (724,696,700,704,708),(TAGS(28)+1) / ISYNOT value?
696      INSTAT(25)=INSTAT(25)+1 / US reject--too slow RT
      GO TO 724
700      INSTAT(26)=INSTAT(26)+1 / US reject--premature bar-press
      GO TO 724
704      INSTAT(27)=INSTAT(27)+1 / US reject--E opted to abort
      GO TO 724
708      INSTAT(28)=INSTAT(28)+1 / US reject--too many artifacts
      DO 712 J=1,8
      KLIPT(J)=KLIPT(J)+TAGS(J+51) / Artifact tally:US reject;not aborted
712      CONTINUE
      GO TO 724
716      IF(ISYNOT.GT.1) GOTO 724 / Skip DS trials with problems
720      RLSTAT(6)=RLSTAT(6)+NBPIS / DS trial bar-presses:phases 6+7
      GO TO 724
724      CONTINUE
      CLOSE(UNIT=3,DISPOSE='SAVE')
      GO TO 727
725      TYPE 726
726      FORMAT(' ERROR REOPENING FILE ON DL1 ')
      GO TO 832

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D      PAUSE      ' COMMENT HEADER'
727    PRINT 728
728    FORMAT(5(//),15X,'LISTING OF SESSION COMMENTS: ',/)
D      PAUSE      ' REOPEN DL1 FILE'
      OPEN(UNIT=3,NAME=NUFILE,FORM='UNFORMATTED',TYPE='OLD')
732    READ(3,END=740) TONE,TAGS,((MATRIX(LCH(M),K),K=1,400),M=1,NCH5),COMENT
      PRINT 736,TAGS(27),(COMENT(K),K=1,LEN(COMENT))
736    FORMAT(' TRIAL N',I3,' : ',59(A1))
      GO TO 732
740    CLOSE(UNIT=3,DISPOSE='SAVE')
D      PAUSE      ' COMPUTE STATS'
      X1=INSTAT(24)                ! Total N of WS trials
      X2=INSTAT(25)                ! N of WS aborts due to slow RT
      X3=INSTAT(26)                ! "   due to premature response
      X4=INSTAT(27)                ! "   due to E intervention
      X5=INSTAT(28)                ! N of WS rejects due to artifacts
      X6=X1-X2-X3-X4-X5           ! X6 (=WSCNT) : N of ok WS trials
      IF(X1 .LE. 0) GOTO 752
      RLSTAT(1)=((X2+X3+X4)/X1)*100. ! % of WS trials aborted
      RLSTAT(2)=(X5/X1)*100.        ! % of WS trials artifact-rejected
      IF(X6 .LE. 0.) GOTO 744       ! If no WS trials OK, skip ahead
      RLSTAT(3)=TOTMS/X6           ! Mean RT for ok WS trials
      RLSTAT(4)=SQRT(SQRTOT/X6-(RLSTAT(3)**2)) ! Stand. dev.
      RLSTAT(5)=FLOAT(NREINF)/X6   ! Avg N of reinf per ok WS trial
744    IF(X5 .LE. 0.) GOTO 752     ! If no WS artifact-rejects, skip ahead
      DO 748 I=1,8
      RLSTAT(I+6)=FLOAT(KLIPT(I))/X5 ! Avg N artifacts per WS reject
748    CONTINUE
752    IF(DSCNT .LE. 0.) GOTO 756
      RLSTAT(6)=RLSTAT(6)/DSCNT    ! Avg N resp(phases 6+7)for ok DS
D      PAUSE      ' PRINT STATS'
756    PRINT 760
760    FORMAT(5(//))
      CALL PUTSTR(6,IDHONK,' ')
      PRINT 764,(INSTAT(I),I=1,4)
764    FORMAT(/,' Monkey N',I5,5X,' Date:',I3,'/',I3,'/',I3)
      PRINT 768,(INSTAT(J),J=5,7)
768    FORMAT(/,' Condition N',I2,' ; Day N',I3,' ; % WS trials=',I3)
      PRINT 772,(INSTAT(K),K=8,10)
772    FORMAT(/,' Limited hold(ms)=',I5,/, ' Inter-stimulus interval(ms)=',
      9I5,/, ' IS duration(ms)=',I6)
      PRINT 776,(INSTAT(L),L=11,(INSTAT(12)+12))
776    FORMAT(/,' Artifact limit= +/-',I6,/,/, ' Sampled the following',I2,
      9' channels:',8(IX,I2))
      PRINT 780,INSTAT(21),INSTAT(22)
780    FORMAT(/,' Sample size for WS average=',I3,' ; for DS average=',I3)
      PRINT 784,INSTAT(23),INSTAT(24)
784    FORMAT(/,' Total N trials=',I3,/, ' N of WS trials=',I3)
      PRINT 788,(INSTAT(M),M=25,28)
788    FORMAT(/,' N aborts due to slow RT=',I3,/, ' N aborts due to premature
      9 bar-pressing=',I3,/, ' N aborts due to E opting to abort=',I3,/,
      9' N rejects due to artifacts=',I3)
      PRINT 792,INSTAT(29),INSTAT(30)
792    FORMAT(/,' Total N bar-presses=',I5,/, ' All bar-presses during
      9 ITIs=',I5)

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796 PRINT 796,RLSTAT(1),RLSTAT(2)
    FORMAT(/,' Z US trials aborted=',F4.0,/, ' Z of US trials rejected
9 due to artifacts=',F4.0)
    PRINT 800,RLSTAT(3),RLSTAT(4)
800 FORMAT(/,' Mean RT(ms) for "ok" US trials=',F7.1,/,
9' Standard deviation for these RTs=',F10.4)
    PRINT 804,RLSTAT(5),RLSTAT(6)
804 FORMAT(/,' For ok US trials,mean # reinforcements=',F6.3,/,
9' For ok DS trials,mean # bar-presses(in phases 6+7)=',F6.3)
    PRINT 808,(RLSTAT(K),K=7,14)
808 FORMAT(/,' For artifact-rejected US trials,mean # deviant points:',
9/,2X,'Chan 1',2X,'Chan 2',2X,'Chan 3',2X,'Chan 4',2X,'Chan 5',
92X,'Chan 6',2X,'Chan 7',2X,'Chan 8',/,8(2X,F6.3))

D PAUSE ' CREATE BY FILE'
    CALL INSERT(FSPEC2,FSTRNG,4,6)
    OPEN(UNIT=2,NAME=FSTRNG,TYPE='NEW',FORM='UNFORMATTED',DISPOSE='SAVE')
    WRITE (2) (INSTAT(N),N=1,30),(RLSTAT(N),N=1,14)
    DO 816 I=1,NCHS
    DO 812 J=1,400
        YVAL(J)=USAUG(LCH(I),J) ! MULT BY USCNT?
812 CONTINUE
    WRITE (2) (YVAL(N),N=1,400)
816 CONTINUE
    DO 824 K=1,NCHS
    DO 820 L=1,400
        YVAL(L)=DSAVG(LCH(K),L) ! MULT BY DSCNT?
820 CONTINUE
    WRITE (2) (YVAL(N),N=1,400)
824 CONTINUE
    CLOSE(UNIT=2,DISPOSE='SAVE')

    TYPE 828
828 FORMAT(/,' SESSION IS OVER; PUT NEW FILE ON MAGTAPE BY TYPING:',/)
    CALL SCOPY('COPY DL1:XXXXXX.DAT MT:XXXXXX.DAT ',EXTMSG)
    CALL INSERT(FSPEC2,EXTMSG,10,6)
    CALL INSERT(FSPEC2,EXTMSG,24,6)
    CALL PUTSTR(7,EXTMSG,' ')
832 CALL EXIT
    END

SUBROUTINE WATCH
COMMON /BLOCK1/MSNEW,ISI
MSNEW=MSNEW+1 ! Update msec counter
ISI=ISI+1 ! Update inter-sample interval timer
CALL IPOKE("170420,"133) ! Clear overflow flag
RETURN
END

```

```

SUBROUTINE ITISUM
COMMON /BLOCK2/ITIRSP
836 CALL CCREAD(MBPRSS,MYET,MSTILL,"164010)
IF(MSTILL .GT. 0) GOTO 836
ITIRSP=ITIRSP+1      ! Update # of ITI bar-presses
CALL IPOKE("164010,"100)
RETURN
END

SUBROUTINE WINDOW(MATRIX,LHIGH,LIMIT,LCH,LIMAX,LIMIN,KLIPT)
VIRTUAL MATRIX(8,400)
INTEGER*2 MATRIX,LCH(8),LIMAX(8),LIMIN(8),KLIPT(8)
DO 844 L=1,8
IF(LCH(L) .EQ. 0) GOTO 848      ! End at 1st null pointer
NX=LCH(L)      ! Point to next channel with data
LINTOP=MATRIX(NX,1)      ! Initial max value
LIMBOT=MATRIX(NX,1)      ! Initial min value
KLIPT(NX)=0      ! Reset artifact counter
DO 840 M=1,400
IF(IABS(MATRIX(NX,M)) .GT. LIMIT) KLIPT(NX)=KLIPT(NX)+1
LINTOP=MAX0(MATRIX(NX,M),LINTOP)
LIMBOT=MINO(MATRIX(NX,M),LIMBOT)
840 CONTINUE
LIMAX(NX)=LINTOP      ! Store highest datum for Chan n
LIMIN(NX)=LIMBOT      ! Store lowest datum for Chan n
844 CONTINUE
848 RETURN
END

SUBROUTINE REINF
COMMON/BLOCK1/MSNEW,ISI/BLOCK3/IDIS/BLOCK4/MSROFF
INTEGER*2 IDIS
IDTANG=IDIS+1024      ! Set bit #10 of HCO register
CALL DEVICE(-1,IDTANG,"164000)
MSROFF=MSNEW + 50      ! Set relay operation time
RETURN
END

SUBROUTINE ROFF
COMMON/BLOCK3/IDIS/BLOCK4/MSROFF
INTEGER*2 IDIS
CALL DEVICE(-1,IDIS,"164000)      ! Clear bit #10 of HCO register
MSROFF=20000
RETURN
END

```

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C      PROGRAM P300 IS THE MASTER PROGRAM FOR RUNNING
C      THE UNCUED TONE PROTOCOL, SAMPLING FOUR
C      CHANNELS OF EITHER EVENT RELATED POTENTIALS OR
C      MULTIPLE UNIT ACTIVITY, AND ALL RELATED DATA
C      MANIPULATION AND STORAGE, VIA MENU SELECTION.
C      SOFTWARE TRIGGER INITIATES SAMPLING EVERY X MSEC.
C      DIGITIZED WAVEFORMS STORED IN MATRIX AS INTEGERS,
C      ARTIFACT-REJECTED AND, OPTIONALLY, DISPLAYED.
C      AT END OF EACH SET, AVERAGES WRITTEN TO FLOPPY DISK.
C      *****C=common ; Higher probability*****
C      *****R=rare ; Lower probability*****

PROGRAM P300
EXTERNAL WATCH
COMMON /BLOCK1/MATRIX,JDATUM,IBUFF
VIRTUAL HISUM(4,400),LOSUM(4,400),YVAL(400),XVAL(400)
REAL YVAL,XVAL,HISUM,LOSUM,HICNT,LOCNT
LOGICAL*1 YESNO,TASK(3),IDSUBJ(8),TYPE,ICHAR
LOGICAL*1 FSTRNG(14),TONE(4),FSPEC(7),ERR1,ERR2,IDHIHZ
INTEGER*2 ISTAT,IBUFF(4),IBFCNT,ICHAN,INSTAT(30),CALUV(4)
INTEGER*2 MONTH(12),LEVEL(4),KLIPT(4),MATRIX(4,400)
INTEGER*4 ITIME
DATA IBUFF/4*0/,INSTAT/30*0/,CALUV/4*25/
DATA MONTH/31,28,31,30,31,30,31,31,30,31,30,31/
DATA LEVEL/4*0/,KLIPT/4*0/

LIMIT=4000          ! Artifact window size(+ or -)
NDAYS=0
ITISEC=0
LOOK=0              ! Automatically displayed channel
INTGR1=0
INTGR2=0
ISPEED=1            ! Skip single-trial display
IEPOKI=0             ! 0 sec between epochs
NTIX=25              ! Sample every 2.5 msec
IEPOCH=1000          ! Epoch lasting 1000 msec
ITIX=-25             ! Clock overflow every 2.5 msec
NTRIAL=1              ! Total N trials
ID0="0"              ! Bit pattern during ITI
ID1="4000"            ! " " " phase 1
ID2="44"              ! " " " " 2
ID3="10000"           ! " " " " 3
ID5="400"             ! " " " " 5
NSET=0               ! Initialize counter for data sets
KNIPCT=80            ! Initialize Z of common tones

4      TYPE 8
8      FORMAT(' NAME OF SUBJECT IS: ',8)
      CALL GETSTR(5,IDSUBJ,7,ERR1) ! Input up to 7 letters of name
      IF(ERR1) GOTO 4
      CALL SCOPY('DY:XXXXXX.DAT',FSTRNG) ! Initialize filename

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```

CALL IDATE(MON,IDAY,IYEAR)      ! Access date entered upon boot
TYPE 12,MON,IDAY,IYEAR
12  FORMAT(' IS TODAY'S DATE: ',I3,'/',I3,'/',I3, '(Y or N)? ',%)
ACCEPT 16,YESNO
16  FORMAT(A1)
IF(YESNO .EQ. 'Y') GOTO 22      ! If date OK, proceed
TYPE 20
20  FORMAT(' YOU FORGOT TO ENTER DATE; START ALL OVER ',/)
GO TO 832

22  TYPE 24
24  FORMAT(/,' ENTER NEW FILE NAME (up to 6 letters/numbers) : ',%)
CALL GETSTR(5,FSPEC,6,ERR2)
IF(ERR2) GOTO 22
FSPEC(7)=0
TYPE 26,(FSPEC(J),J=1,6)
26  FORMAT(/,2X,6A1,'.DAT WILL BE WRITTEN ONTO FLOPPY DISK )

NCHS=4
TYPE 38
38  FORMAT(/,' FOUR CHANNELS ARE TO BE SAMPLED: 1,2,3, and 4')

IF(MOD(IYEAR,4) .EQ. 0) MONTH(2)=29      ! If leap yr, Feb has 29
NYEAR=MOD(IYEAR,10)                      ! Which year of the decade?
DO 40 JMON=1,MON
NDAYS=NDAYS+MONTH(JMON)
40  CONTINUE
NDAYS=NDAYS+IDAY-MONTH(MON)              ! Which day of the year

DO 44 M=1,NDAYS+5
RANUM=RAN(INTGR1,INTGR2)                 ! Start RAN subrtn at new point
44  CONTINUE

C *****OPEN DATA FILE FOR THIS SESSION*****
CALL INSERT(FSPEC,FSTRNG,4,6)             ! Open session's data file
OPEN(UNIT=2,NAME=FSTRNG,TYPE='NEW',FORM='UNFORMATTED',DISPOSE=SAVE)

C *****RESET PARAMETERS*****
50  NSET=NSET+1
51  TYPE 52,KHIPCT,LIMIT,(LOOK+1)
52  FORMAT(/,' PARAMETERS ARE AS FOLLOWS: ',/, ' 1) % OF COMMON TONES
9 = ',I4,/, ' 2)ARTIFACT LIMIT= +/- ',I6,/,
9' 3)CHANNEL DISPLAYED AT END OF EACH TRIAL= ',I2,/, ' 4)CAL PULSES: )
DO 54 M=1,4
TYPE 53,M,CALUV(M)
53  FORMAT(3X,'CH',I2,': ',I5,'uV')
54  CONTINUE
TYPE 55,(NTIX+40),IEPOKI,ISPEED,NSET
55  FORMAT(/,' 5)EPOCH DURATION = ',I5,' msec',/, ' 6)Inter-
9epoch interval = ',I6,' sec',/, ' 7)SPEED(0=slow;1=fast)= ',I2,
9/, ' 8) # OF NEXT DATA SET = ',I4)
TYPE 56
56  FORMAT(' ENTER NUMBER OF ITEM TO BE CHANGED, OR 0 IF NONE : ',%)
ACCEPT 57,NPARAM
57  FORMAT(I2)

```

```

58      GO TO (90,58,61,64,67,75,78,81,86), (NPARAM+1)
59      TYPE 59
60      FORMAT(' WHAT % OF OCCURRENCE (50< % <100) FOR COMMON TONES ? ',%)
        ACCEPT 60,KHIPCT
        FORMAT(I4)
        IF(KHIPCT .LT. 50) GOTO 58
        GO TO 51

61      TYPE 62
62      FORMAT(' NEW WINDOW LIMIT= ',%)
        ACCEPT 63,LIMIT
        FORMAT(I6)
        GO TO 51

64      TYPE 65
65      FORMAT(' CHANNEL TO LOOK AT FIRST(1-4) = ',%)
        ACCEPT 66,LOOK
        FORMAT(I2)
        LOOK=LOOK-1
        GO TO 51

67      DO 69 J=1,4
        TYPE 68,J,CALUV(J)
68      FORMAT(3X,'CH ',I1,' CAL= ',I5,'UV')
69      CONTINUE
        TYPE 70
70      FORMAT(/,' CHANGE CAL UV VALUES ? ',%)
        ACCEPT 71,YESNO
71      FORMAT(A1)
        IF(YESNO .NE. 'Y') GOTO 51

72      TYPE 73
73      FORMAT(' ENTER CHANNEL #, THEN NEW UV CALIBRATION, e.g. 3,75 : ',%)
        ACCEPT 74,K,CALUV(K)
74      FORMAT(I2,I4)
        GO TO 67

75      TYPE 76
76      FORMAT(/,' ENTER NEW EPOCH DURATION (msec): ',%)
        ACCEPT 77,IEPOCH
77      FORMAT(I5)
        NTIX=IEPOCH/(40)
        ITIX=-1+NTIX
        GO TO 51

78      TYPE 79
79      FORMAT(/,' ENTER NEW INTER-EPOCH INTERVAL (sec): ',%)
        ACCEPT 80,IEPOKI
80      FORMAT(I6)
        GO TO 51

81      TYPE 82
82      FORMAT(/,' Enter "1" for fast, or "0" for slow mode: ',%)
        ACCEPT 84,ISPEED
84      FORMAT(I2)
        GO TO 51

```

```

86      TYPE 87
87      FORMAT(/, ' WHAT IS THE N FOR THE NEXT SET OF AVERAGES? ',%)
      ACCEPT 88,NSET
88      FORMAT(I4)
      GO TO 51
90      TYPE 91
91      FORMAT(/, ' MAKE HIGHER-PITCHED TONE COMMON(C) OR RARE(R)? : ',%)
      ACCEPT 92,IDH1HZ      ! Identify C or R for high-pitch tone
92      FORMAT(A1)

      IEPOCH=40*NTIX      ! Reentry point after setting parameters
      NCTONE=0             ! # of common tones presented
      NRTONE=0             ! # of rare tones presented
      NRSAMP=0             ! # of rare samples needed
      HICNT=0              ! Zero out common sample size
      LOCNT=0              ! Zero out rare sample size
      ITRIAL=0             ! Counter for # of trial

      DO 94 I=1,4
      LEVEL(I)=0           ! Estimator of waveform DC level
94      CONTINUE
      DO 96 L=1,400
      DO 95 K=1,4
      MATRIX(K,L)=0        ! Zero out single-trial matrix
      HISUM(K,L)=0         ! Zero out common summing matrix
      LOSUM(K,L)=0         ! Zero out rare summing matrix
95      CONTINUE
      YVAL(L)=0            ! Zero out display matrix
      XVAL(L)=2*L+150      ! Initialize abscissa values
96      CONTINUE
      ITIX=-1*NTIX         ! Update N ticks before clock overflow
97      TYPE 98
98      FORMAT(/, ' HOW MANY TRIALS ? (e.g., 35): ',%)
      ACCEPT 99,NTRIAL
99      FORMAT(I3)
      NRSAMP=NTRIAL-(NTRIAL*KHIPCT)/100
      PAUSE 'HIT RETURN TO GO'

      CALL DEVICE(-1,ID0,"164000)      ! Turn off all devices
      CALL IPOKE("170420,"0)          ! Turn off clock

C      *****EACH TRIAL BEGINS HERE*****
108     IF(LOCNT .GE. NRSAMP) GOTO 382  ! Already have enough R samples?
      ITRIAL=ITRIAL+1                ! Set next trial N
      RANUM=RAN(INTGR1,INTGR2)
      CUTOFF=FLOAT(KHIPCT)/100.
      IF(RANUM .GT. CUTOFF) GO TO 128      ! If true, R tone next
      CALL SCOPY('COMM',TONE)
      NCTONE=NCTONE+1                    ! Count N of common tones presented
      IF(IDH1HZ .EQ. 'R') GOTO 140
      GO TO 136
128     CALL SCOPY('RARE',TONE)
      NRTONE=NRTONE+1                    ! Count N of rare tones presented
      IF(IDH1HZ .EQ. 'R') GOTO 136
      GO TO 140

```

```

136      ID4="20002
      GO TO 144
140      ID4="100010
144      TYPE 148,ITRIAL,TONE
148      FORMAT(/, Trial N ,I3, : ,4A1)

C      HERE, INITIALIZE OTHER STARTING VALUES
      JDATUM=0          ! Reset pointer for storing data
      ISYNOT=0          ! Initialize reject reason code
      IF(IEPOKI .EQ. 0) GOTO 185

      IF(ITRIAL .EQ. 1) GOTO 180
160      CALL GTIM(ITIME)
      CALL CUTTIM(ITIME,IHRS,IMIN,ISEC,ITCK)
      ITISEC=(3600*IHRS)+(60*IMIN)+(ISEC)-NOW ! Sec since last epoch
      IF(ITISEC .LE. IEPOKI) GOTO 160

180      NOW=0
185      CALL DEVICE(-1,ID1,"164000)      ! Turn on phase #1 indicator light

C      *****CLOCK WILL RUN AT 10 KHz, OVERFLOW EACH 1 MSEC*****
C      *****CLOCK INTERRUPT WILL ONLY BE USED TO UPDATE MSNEW AND ISI*****
      CALL CLOCKW(1,3,ITIX,,WATCH,"170420,"440)      ! Start clock

214      IF(JDATUM .LT. 1) GOTO 214          ! Begin CAL trigger pulse ?
      CALL DEVICE(-1,ID2,"164000)          ! CAL pulse ON
218      IF(JDATUM .LT. 25) GOTO 218          ! End CAL trigger pulse ?
      CALL DEVICE(-1,ID3,"164000)          ! CAL pulse OFF
222      IF(JDATUM .LT. 100) GOTO 222          ! Begin tone ?
      CALL DEVICE(-1,ID4,"164000)          ! Tone ON
226      IF(JDATUM .LT. 150) GOTO 226          ! End tone ?
      CALL DEVICE(-1,ID5,"164000)          ! Tone OFF
230      IF(JDATUM .LT. 400) GOTO 230          ! End trial; Stop sampling ?

      CALL IPOKE("170420,"0)      ! Turn off clock between epochs
      CALL DEVICE(-1,ID0,"164000)      ! Turn off all devices
      IF(IEPOKI .EQ. 0) GOTO 300
      CALL GTIM(ITIME)
      CALL CUTTIM(ITIME,IHRS,IMIN,ISEC,ITCK)
      ITISEC=(3600*IHRS)+(60*IMIN)+(ISEC)
      NOW=ITISEC          ! Store time at end of this trial
C      *****BEGIN INTER-TRIAL INTERVAL ACTIVITIES:*****
C      *****REVIEW DATA FOR ARTIFACTS*****
300      CALL WINDOW(MATRIX,LIMIT,LEVEL,KLIPT)
      TYPE 310,(LEVEL(N),N=1,4)
310      FORMAT(/, ' DC LEVELS: ',3X,I4,10X,I4,10X,I4,10X,I4)

      DO 320 I=1,4
      IF(KLIPT(I) .GT. 5) ISYNOT=4          ! More than 5 artifacts?
320      CONTINUE
      IF(ISYNOT .EQ. 4) GOTO 370

```

```

328      IF(SCOMP('RARE',TONE) .EQ. 0) GOTO 348      ! If R trial,update LOSUM
      DO 340 L=1,4
      DO 332 N=1,400
      HISUM(L,N)=HISUM(L,N)+MATRIX(L,N)              ! Might need to convert
332      CONTINUE                                     ! integer-to-real
340      CONTINUE
344      HICNT=HICNT+1.0
      GO TO 380

348      DO 356 L=1,4
      DO 352 N=1,400
      LOSUM(L,N)=LOSUM(L,N)+MATRIX(L,N)              ! Might need to convert
352      CONTINUE                                     ! integer-to-real
356      CONTINUE
360      LOCNT=LOCNT+1.0
      GO TO 380

370      DO 374 I=1,4
      DO 372 J=1,400
      MATRIX(I,J)=MATRIX(I,J)                      ! Keep time between tones equal
372      CONTINUE                                     ! to when data are added to average
374      CONTINUE
      TYPE 376
376      FORMAT(/,' TOO MANY ARTIFACTS; DATA NOT ADDED TO AVERAGE ')

380      TYPE 381,IFIX(HICNT),IFIX(LOCNT)
381      FORMAT(' SO FAR: C =',I4,5X,'R = ',I4)
      IF(ISPEED .EQ. 0) GOTO 395
      ICHAR=ITINR()                                ! Last ASCII character entered on TI
      IF(ICHR .GT. "100) GOTO 382                    ! If LETTER there, then quit speedmode
      IF(LOCNT .LT. NRSAMP) GOTO 108                 ! Not enough rare tone samples ?
382      TYPE 383,NCTONE,NRTONE,IFIX(HICNT),IFIX(LOCNT)
383      FORMAT(/,' # Presented : C=',I4,5X,' ; R=',I4,/,
      7 ' # Averaged : C=',I4,5X,' ; R=',I4)
      TYPE 385
385      FORMAT(/,' HOW MANY MORE TRIALS ? (0 if averages final) : ',%)
      ACCEPT 387,NMORE
387      FORMAT(I3)
      NTRIAL=NTRIAL+NMORE                            ! Set new max # of trials
      NRSAMP=(NTRIAL*KHIPCT)/100                     ! Adjust rare-sample size criterion
      IF(NMORE .GT. 0) GOTO 448                      ! Continue with current averages
      TYPE 388
388      FORMAT(/,' PUT CURRENT AVERAGES ON FLOPPY? ',%)
      ACCEPT 389,YESNO
389      FORMAT(A1)
      IF(YESNO .EQ. 'Y') GOTO 670
      TYPE 390
390      FORMAT(/,' BEGIN NEW SET OF AVERAGES ? ',%)
      ACCEPT 391,YESNO
391      FORMAT(A1)
      IF(YESNO .EQ. 'Y') GOTO 50
      GO TO 448

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395     IDCH=LOOK
400     DO 404 N=1,400
        YVAL(N)=MATRIX(IDCH+1,N)+390.
404     CONTINUE
408     CALL GINIT(1)           ! Set default parameters
        CALL GEND              ! Go to transparent mode
        CALL STXOX
        CALL STOTU(7)          ! Graphic output on console
        CALL STERR(2)          ! Print error and warning messages
        TYPE 412
412     FORMAT(25(/))          ! Clear screen
        DO 416 M=1,400
        CALL POINT(XVAL(M),YVAL(M)) ! Plot values
416     CONTINUE
        CALL GEND              ! Go to transparent mode
        CALL HOLD              ! Wait for carriage return
        CALL ERASE              ! Clear screen
        CALL GEND              ! Go to transparent mode
        IF(SCOMP('DS',TASK) .EQ. 0) GOTO 464
        IF(SCOMP('DA',TASK) .EQ. 0) GOTO 476

448     TYPE 450
450     FORMAT(/, ' HIT RETURN FOR NEXT TRIAL, OR: ')
        TYPE 452
452     FORMAT(' PICK FROM MENU : ??,QT,EX,WT,NU,DS,DA,LP,UD,PL,... ,')
        ACCEPT 456, TASK(1),TASK(2)
456     FORMAT(2A1)
        IF(SCOMP('??',TASK) .EQ. 0) GOTO 458 ! Display menu
        IF(SCOMP('QT',TASK) .EQ. 0) GOTO 456 ! Quit session
        IF(SCOMP('EX',TASK) .EQ. 0) GOTO 660 ! Exit session
        IF(SCOMP('WT',TASK) .EQ. 0) GOTO 382 ! Trial # status
        IF(SCOMP('NU',TASK) .EQ. 0) GOTO 50 ! Begin new set
        IF(SCOMP('DS',TASK) .EQ. 0) GOTO 464 ! Display data
        IF(SCOMP('DA',TASK) .EQ. 0) GOTO 476 ! Display average
        IF(SCOMP('LP',TASK) .EQ. 0) GOTO 600 ! List parameters
        IF(SCOMP('UD',TASK) .EQ. 0) GOTO 670 ! Write data to disk
        IF(SCOMP('PL',TASK) .EQ. 0) GOTO 648 ! Plot data
        GO TO 108

458     TYPE 460
460     FORMAT(' MENU IS AS FOLLOWS: ??---EXPLAIN MENU',/,23X, 'QT---
7 QUIT SESSION (DELETE DATAFILES)',/,23X, 'EX---EXIT FROM SESSION
7 (SAVE DATAFILES)',/,23X, 'WT---# EACH TONE TYPE SO FAR',/,23X,
7 'NU---START NEW DATA SET',/,23X, 'DS---DISPLAY SINGLE TRIAL DATA',
7/,23X, 'DA---DISPLAY AVERAGES',/,23X, 'LP---LIST PARAMETERS',/,23X,
7 'UD---WRITE DATA TO DISK',/,23X, 'PL---PLOT DATA')
        GO TO 448

464     TYPE 468
468     FORMAT(' VIEW DATA FROM WHICH CHANNEL (1-4) ? ',)
        ACCEPT 472,IDCH
472     FORMAT(I3)
        IDCH=IDCH-1
        IF(IDCH .LT. 0 .OR. IDCH .GT. 3) GOTO 448
        GO TO 400

```

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476     TYPE 480
480     FORMAT(' C OR R ? WHICH CHANNEL W ? (e.g. C2 or C3 or R1)',%)
ACCEPT 484,TYPE,NUMCH
484     FORMAT(A1,I1)
IF(TYPE.NE.'C'.AND..TYPE.NE.'R') GOTO 448
IF(NUMCH.LT.1 .OR. NUMCH.GT.4) GOTO 476
IF(TYPE.EQ.'R') GOTO 492
DO 488 K=1,400
YVAL(K)=HISUM(NUMCH,K)/HICNT+390.          ! Display C average
488     CONTINUE
GO TO 408
492     DO 496 K=1,400
YVAL(K)=LOSUM(NUMCH,K)/LOCNT+390.          ! Display R average
496     CONTINUE
GO TO 408
600     TYPE 602,KHIFCT,LIMIT,(LOOK+1)
602     FORMAT(/,' PARAMETERS ARE AS FOLLOWS:',/, ' 1) Z OF C TONES= ',I4,
9/, ' 2) ARTIFACT LIMIT= +/- ',I6,/, ' 3) CHANNEL DISPLAYED AT END
9 OF EACH TRIAL= ',I2,/, ' 4) CAL PULSES:')
DO 606 M=1,4
TYPE 604,M,CALUV(M)
604     FORMAT(3X,'CH',I2, ': ',I5,'uV')
606     CONTINUE
TYPE 608,(NTIX+40),IEPOKI,ISPEED
608     FORMAT(/,' 5) EPOCH DURATION= ',I5,' msec',/, ' 6) INTER-EPOCH
9 INTERVAL = ',I6,' sec',/, ' 7) SPEED (0=slow;1=fast) = ',I2)
TYPE 610,IDH1HZ
610     FORMAT(/,' THE HIGHER-PITCH TONE IS THE ',A1,' TONE')
GO TO 448

648     TYPE 652
652     FORMAT(' THIS OPTION NOT YET AVAILABLE ',/)
GO TO 448

656     CALL IPOKE("170420,"0)          ! Shut off clock
CLOSE(UNIT=2,DISPOSE='DELETE')        ! Delete datafile from DYdisk
GO TO 832

660     TYPE 664
664     FORMAT(' OK TO END THIS SESSION (Y or N): ?',%)
ACCEPT 668,YESNO
668     FORMAT(A1)
IF(YESNO.NE.'Y') GOTO 448
CALL IPOKE("170420,"0)          ! Shut off clock
GO TO 828

C     *****GENERATE LABELS FOR CURRENT DATA SET*****
670     INSTAT(1)=300          ! This was a P300 session
INSTAT(2)=MON
INSTAT(3)=IDAY
INSTAT(4)=IYEAR
DO 672 J=1,6
INSTAT(J+4)=FSPEC(J)
672     CONTINUE

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DO 673 M=1,5
  INSTAT(M+10)=IDSUBJ(M)
673  CONTINUE
  DO 675 K=1,4
    INSTAT(K+15)=CALUV(K)
675  CONTINUE
    INSTAT(20)=HICNT      ! Common tone sample size
    INSTAT(21)=LOCNT      ! Rare tone sample size
    INSTAT(22)=NTRIAL     ! Total N of trials
    INSTAT(23)=NCTONE     ! Total N common tone trials
    INSTAT(24)=NRTONE     ! Total N rare tone trials
    INSTAT(25)=NSET       ! Which N set of averages is this?
    INSTAT(26)=LIMIT      ! Artifact window size
    INSTAT(27)=NTRIAL-IFIX(HICNT+LOCNT) ! N rejects
    INSTAT(28)=NTIX       ! Tenths of msec per sample
    INSTAT(29)=IEPOKI     ! Inter-epoch interval
    INSTAT(30)=NCHS       ! N of sampled channels

D    GO TO 800
756  PRINT 760
760  FORMAT(3(/))
    CALL PUTSTR(6,IDSUBJ,' ')
    PRINT 764,(INSTAT(I),I=1,4)
764  FORMAT(/,' P',I3,5X,'Date:',I3,'/',I3,'/',I3)
    PRINT 768,INSTAT(23),INSTAT(24)
768  FORMAT(/,' N of common tones=',I3,' ; N of rare tones= ',I3)
    PRINT 772,INSTAT(28),INSTAT(29)
772  FORMAT(/,' Tenths of msec per sample(ms)=',I5,'/,' ; Inter-epoch
    9 interval (sec) = ',I6)
    PRINT 776,INSTAT(26)
776  FORMAT(/,' Artifact limit= +/-',I6,'/',I6,' Sampled the first four
    9 channels only')
    PRINT 780,INSTAT(20),INSTAT(21)
780  FORMAT(/,' Sample size for C average=',I3,' ; for R average= ',I3)
    PRINT 784,INSTAT(22)
784  FORMAT(/,' Total N trials=',I3)
    PRINT 788,INSTAT(27)
788  FORMAT(/,' Total N rejects due to artifacts=',I3)
    PRINT 796,INSTAT(16),INSTAT(17),INSTAT(18),INSTAT(19)
796  FORMAT(/,' For each channel, CAL signal amplitude :',
    9/,6X,'Chan 1',6X,'Chan 2',6X,'Chan 3',6X,'Chan 4',/,4(6X,I6))
    PRINT 798,INSTAT(25)
798  FORMAT(/,' THAT WAS THE N',I4,' SET OF AVERAGES')

C    *****WRITE DATA RECORD TO DY FILE*****
800  WRITE (2) (INSTAT(M),M=1,30)
    DO 816 I=1,4
      DO 812 J=1,400
        YVAL(J)=HISUM(I,J)/HICNT      ! Divide sum by sample size
812  CONTINUE
      WRITE (2) (YVAL(N),N=1,400)
816  CONTINUE

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      DO 824 K=1,4
      DO 820 L=1,400
      YVAL(L)=LOSUM(K,L)/LOCNT           ! Divide sum by sample size
820   CONTINUE
      WRITE (2) (YVAL(N),N=1,400)
824   CONTINUE

      TYPE 825
825   FORMAT(/,' BEGIN NEW SET OF AVERAGES ? ',*)
      ACCEPT 826,YESNO
826   FORMAT(A1)
      IF (YESNO .NE. 'Y') GOTO 448
      GO TO 50                          ! Go start next set of averages
828   CLOSE(UNIT=2,DISPOSE='SAVE')     ! End this session

832   CALL EXIT
      END

      SUBROUTINE WATCH
      COMMON /BLOCK1/MATRIX,JDATUM,IBUFF
      INTEGER*2 MATRIX(4,400),IBUFF(4)
      CALL AREADP(ISTAT,IBUFF,4,-3)
      CALL EXTS12(IBUFF,4)
      JDATUM=JDATUM+1
      MATRIX(1,JDATUM)=IBUFF(1)
      MATRIX(2,JDATUM)=IBUFF(2)
      MATRIX(3,JDATUM)=IBUFF(3)
      MATRIX(4,JDATUM)=IBUFF(4)
      CALL IPOKE("170420","133")       ! Clear overflow flag
      RETURN
      END

      SUBROUTINE WINDOW(MATRIX,LIMIT,LEVEL,KLIPT)
      INTEGER*2 MATRIX(4,400),LIMIT,LEVEL(4),KLIPT(4)
      DO 844 L=1,4
      KLIPT(L)=0                        ! Reset artifact counter
      LEVEL(L)=0                       ! Reset DC level estimator
      DO 840 M=1,400
      IF (IABS(MATRIX(L,M)) .GT. LIMIT) KLIPT(L)=KLIPT(L)+1
      LEVEL(L)=LEVEL(L)+MATRIX(L,M)
840   CONTINUE
      LEVEL(L)=LEVEL(L)/400            ! Calculate mean integer value
844   CONTINUE
848   RETURN
      END

```

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PROGRAM PLTCNV
C   PLTCNV EMPLOYS VERTICAL CURSOR ONLY
C   Y VALUES ARE FROM ORIGINAL DATA, NOT INTERPOLATED
EXTERNAL WATCH
COMMON /BLOCK1/JDATUM
VIRTUAL USAVG(8,400),DSAVG(8,400)
REAL RLSTAT(14),USAVG,DSAVG,USCNT,DSCNT,PARAM(6)
REAL XTABL(10),YTABL(10),XVAL(400),YVAL(400)
LOGICAL*1 YESNO,TYPE,ICHAR,FSTRNG(14),LFILE(6),LABELX(13),LABELY(10)
LOGICAL*1 STROFF(4),STRON(4)
INTEGER*2 INSTAT(30),LCH(8),NUMCH
DATA RLSTAT/14*0.0/,INSTAT/30*0/
CALL SCOPY('Milliseconds',LABELX)      ! Abscissa label
CALL SCOPY('Microvolts',LABELY) ! Ordinate label
CALL SCOPY('DY:MIXXXX.DAT',FSTRNG)    ! Initialize filename
STROFF(1)="033
STROFF(2)="057
STROFF(3)="061
STROFF(4)="144
STRON(1)="033
STRON(2)="057
STRON(3)="060
STRON(4)="144

1   TYPE 5
5   FORMAT(' Enter 6-character file code, e.g. "MI0553" : ',*)
ACCEPT 10,(LFILE(N),N=1,6)
10  FORMAT(6A1)
CALL INSERT(LFILE,FSTRNG,4,6)

DO 20 L=1,400
DO 15 K=1,8
USAVG(K,L)=0      ! Zero out US average matrix
DSAVG(K,L)=0      ! Zero out DS average matrix
15  CONTINUE
YVAL(L)=0         ! Zero out display matrix
XVAL(L)=0
20  CONTINUE

PARAM(1)=460.     ! XMAX
PARAM(2)=0.       ! XMIN
PARAM(3)=0.       ! YGRDLO
PARAM(4)=500.     ! YMAX
PARAM(5)=-500.    ! YMIN
PARAM(6)=-500.    ! XGRDLO
MMFLG=1

OPEN(UNIT=2,NAME=FSTRNG,FORM='UNFORMATTED',TYPE='OLD',DISPOSE='SAVE')

READ (2) (INSTAT(M),M=1,30),(RLSTAT(N),N=1,14)
NCHS=INSTAT(12)
DO 35 K=1,8
LCH(K)=INSTAT(K+12)
35  CONTINUE

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DO 45 I=1,NCHS
READ (2) (YVAL(N),N=1,400)
DO 40 J=1,400
USAVG(LCH(I),J)=YVAL(J)
40 CONTINUE
45 CONTINUE

DO 60 K=1,NCHS
READ (2) (YVAL(N),N=1,400)
DO 55 L=1,400
DSAVG(LCH(K),L)=YVAL(L)
55 CONTINUE
60 CONTINUE

USCNT=INSTAT(21)
DSCNT=INSTAT(22)

TYPE 63
63 FORMAT(/,' Print out session info + stats ? Y or N : ',8)
ACCEPT 65,YESNO
65 FORMAT(A1)
IF(YESNO .NE. 'Y') GOTO 145

PRINT 70,(INSTAT(1),I=1,4)
70 FORMAT(/,' Monkey W',I5,5X,'Date:',I3,'/',I3,'/',I3)
PRINT 75,(INSTAT(J),J=5,7)
75 FORMAT(/,' Condition W',I2,' ; Day W',I3,' ; Z US trials=',I3)
PRINT 80,(INSTAT(K),K=8,10)
80 FORMAT(/,' Limited hold(ms)=',I5,/, ' Inter-stimulus interval(ms)=',
9I5,/, ' IS duration(ms)=',I6)
PRINT 85,(INSTAT(L),L=11,(INSTAT(12)+12))
85 FORMAT(/,' Artifact limit= +/-',I6,/,/, ' Sampled the following',I2,
9' channels:',8(IX,I2))
PRINT 90,INSTAT(21),INSTAT(22)
90 FORMAT(/,' Sample size for US average=',I3,' ; for DS average=',I3)
PRINT 95,INSTAT(23),INSTAT(24)
95 FORMAT(/,' Total W trials=',I3,/, ' W of US trials=',I3)
PRINT 100,(INSTAT(M),M=25,28)
100 FORMAT(/,' W aborts due to slow RT=',I3,/, ' W aborts due to premature
9 bar-pressing=',I3,/, ' W aborts due to E opting to abort=',I3,/,
9' W rejects due to artifacts=',I3)
PRINT 105,INSTAT(29),INSTAT(30)
105 FORMAT(/,' Total W bar-presses=',I5,/, ' All bar-presses during
9 ITIs=',I5)
PRINT 110,RLSTAT(1),RLSTAT(2)
110 FORMAT(/,' Z US trials aborted=',F4.0,/, ' Z of US trials rejected
9 due to artifacts=',F4.0)
PRINT 120,RLSTAT(3),RLSTAT(4)
120 FORMAT(/,' Mean RT(ms) for "ok" US trials=',F7.1,/,
9' Standard deviation for these RTs=',F10.4)
PRINT 125,RLSTAT(5),RLSTAT(6)
125 FORMAT(/,' For ok US trials,mean W reinforcements=',F6.3,/,
9' For ok DS trials,mean W bar-presses'in phases 6+7)='F6.3)
PRINT 130,(RLSTAT(K),K=7,14)
130 FORMAT(/,' For artifact-rejected US trials,mean W deviant points:',
9/,2X,'Chan 1',2X,'Chan 2',2X,'Chan 3',2X,'Chan 4',2X,'Chan 5',
92X,'Chan 6',2X,'Chan 7',2X,'Chan 8',/,8(2X,F6.3))

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      PRINT 140
140   FORMAT(5(/))
145   TYPE 150
150   FORMAT(' Display WS or DS ? Channel M ? (e.g. W4 or W8 or D1) ',%)
      ACCEPT 160,TYPE,NUMCH
160   FORMAT(A1,I1)
      IF (TYPE.NE.'W' .AND. TYPE.NE.'D') GOTO 145
      IF (NUMCH.LT.1 .OR. NUMCH.GT.8) GOTO 145
      IF (TYPE .EQ. 'D') GOTO 175

      DO 170 K=1,400
        YVAL(K)=WSAVG(NUMCH,K)
        XVAL(K)=K
170   CONTINUE
      GO TO 185

175   DO 180 K=1,400
        YVAL(K)=DSAVG(NUMCH,K)
        XVAL(K)=K
180   CONTINUE

185   TYPE 190,(PARAM(L),L=1,6)
190   FORMAT(/,' Display parameters are:',/,5X,'1)XMAX= ',F9.2,/,5X,
        2'2)XMIN= ',F9.2,/,5X,'3)YGRDLO= ',F9.2,/,5X,'4)YMAX= ',F9.2,/,5X,
        5'5)YMIN= ',F9.2,/,5X,'6)XGRDLO= ',F9.2)
200   TYPE 202
202   FORMAT(/,' Change display parameters ? Y or N : ',%)
      ACCEPT 203,YESNO
203   FORMAT(A1)
      IF (YESNO .NE. 'Y') GOTO 210
      TYPE 207
207   FORMAT(/,' Enter parameter M and new value, e.g. "6,5385.7": ',%)
      ACCEPT 209,NPAR,REVALU
209   FORMAT(I2,F9.2)
      PARAM(NPAR)=REVALU
      GO TO 185

210   DO 213 L=1,10
        XTABL(L)=0
        YTABL(L)=0
213   CONTINUE
        XMAX=PARAM(1)
        XMIN=PARAM(2)
        YGRDLO=PARAM(3)
        YMAX=PARAM(4)
        YMIN=PARAM(5)
        XGRDLO=PARAM(6)
        YZERO=0.

      TYPE 214
214   FORMAT(/,' "Z" to zero baseline, Ws to score points, "Q" to quit')
      PAUSE 'HIT RETURN'
      TYPE 215
215   FORMAT(25(/))

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CALL BELL(1)
CALL ERASE
CALL GRID(LABELX,XMAX,XMIN,YGRDLO,LABELY,YMAX,YMIN,XGRDLO,MMFLG)
CALL POINT(400,XVAL,YVAL)
CALL HTEXT('X data',405.,YMAX)
CALL HTEXT('Y data',405.,-10.)
220 CALL BELL(1)
CALL VCURSR(ICHAR,XCOORD,YCOORD)
IF(ICHAR.EQ.'Q') GOTO 270
IF(ICHAR.EQ.'E') GOTO 260
IF(ICHAR.NE.'Z') GOTO 225
YZERO=YCOORD
GO TO 220
225 DECODE (1,227,ICHAR) NDATUM
227 FORMAT(I1)
IF(NDATUM.EQ.0) NDATUM=10
230 XCOORD=AINT(XCOORD+0.5) ! Reconstruct original x value
NPOS=IFIX(XCOORD)
CALL POINT(1,XVAL(NPOS),YVAL(NPOS)) ! Intensify scored point
XTABL(NDATUM)=XCOORD ! Enter x value into table
XPOS=XCOORD-3. ! Where to affix tag
CALL PLTSYM(1,XPOS,150.,ICHAR) ! Mark tag up top
VERT1=150.-10.*FLOAT(NDATUM)
VERT2=-20.-10.*FLOAT(NDATUM)
CALL HTEXT(ICHAR,405.,VERT1)
CALL FLTXT(XTABL(NDATUM),425.,VERT1) ! Display X table entry
YTABL(NDATUM)=YVAL(NPOS)-YZERO ! Non-interpolated y value
CALL HTEXT(ICHAR,405.,VERT2)
YDISP=AINT(YTABL(NDATUM)*100.)/100.
CALL FLTXT(YDISP,415.,VERT2) ! Display Y table entry
GO TO 220
260 CALL VCURSR(JCHAR,XNEW,YNEW)
DECODE (1,265,JCHAR) NDATUM
265 FORMAT(I1)
IF(NDATUM.EQ.0) NDATUM=10
CALL MVCUR(XTABL(NDATUM),YTABL(NDATUM))
XPOS=XTABL(NDATUM)-3.
YDISP=AINT(YTABL(NDATUM)*100.)/100.
VERT1=150.-10.*FLOAT(NDATUM)
VERT2=-20.-10.*FLOAT(NDATUM)
CALL PUTSTR(7,STROFF,' ') ! Data level = 1
CALL PLTSYM(1,XPOS,150.,JCHAR)
CALL FLTXT(XTABL(NDATUM),425.,VERT1)
CALL FLTXT(YDISP,415.,VERT2)
CALL PUTSTR(7,STRON,' ') ! Data level = 0
ICHAR=JCHAR
XCOORD=XNEW
YCOORD=YNEW
GO TO 230 ! Go enter new values
270 CALL ERASE
275 IF(ITTOUR("030").NE.0) GO TO 275 ! Enter transparent mode

TYPE 280
280 FORMAT(/,12X,'Datum M',8X,'X-coordinate',8X,'Y-coordinate')
DO 290 M=1,10 ! REPLACE NDATUM
TYPE 285,M,XTABL(M),YTABL(M)
285 FORMAT(12X,I3,10X,F10.3,10X,F10.3)
290 CONTINUE

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295      TYPE 295
      FORMAT(/, ' Now plot data ? : ', $)
      ACCEPT 299, YESNO
299      FORMAT(A1)
      IF (YESNO .NE. 'Y') GOTO 399
300      TYPE 305
305      FORMAT(/, ' ENTER GAIN AND OFFSET INTEGERS : ', $)
      ACCEPT 310, IGAIN, ILEVEL
310      FORMAT(I5, I5)
      JOLD=0
      JDATUM=0
      INIVAL=(YVAL(1)*IGAIN)-(ILEVEL*IGAIN)+2047
      CALL DAOUTP(1, INIVAL, "170440")
      PAUSE 'SET PLOTTER; HIT RTN'
      IPEN=1
      CALL DEVICE(-1, IPEN, "164000")
      CALL CLOCKW(1, 3, -500, WATCH, "170420, "440")
315      IF (JDATUM .LE. JOLD) GOTO 315
      JOLD=JDATUM
      IF (JDATUM .NE. 2) GOTO 317
      IPEN=0
      CALL DEVICE(-1, IPEN, "164000")
317      IF (JDATUM .GT. 400) GOTO 320
      IVAL=(YVAL(JDATUM)*IGAIN)-(ILEVEL*IGAIN)+2047
      CALL DAOUTP(1, IVAL, "170440")
      GOTO 315
320      CALL IPOKE("170420, "0)          ! Turn off clock
      TYPE 325
325      FORMAT(/, ' REPLOT DATA ? : ', $)
      ACCEPT 330, YESNO
330      FORMAT(A1)
      IF (YESNO .EQ. 'Y') GOTO 300

399      TYPE 400
400      FORMAT(/, ' View more average data (Y or N) ? ', $)
      ACCEPT 410, YESNO
410      FORMAT(A1)
      IF (YESNO .EQ. 'Y') GOTO 145

      CLOSE(UNIT=2, DISPOSE='SAVE')
      TYPE 430
430      FORMAT(/, ' OPEN NEW DATAFILE ? : ', $)
      ACCEPT 435, YESNO
435      FORMAT(A1)
      IF (YESNO .EQ. 'Y') GOTO 1

      CALL EXIT
      END

      SUBROUTINE WATCH
      COMMON /BLOCK1/ JDATUM
      JDATUM=JDATUM+1
      CALL IPOKE("170420, "133)
      RETURN
      END

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END

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