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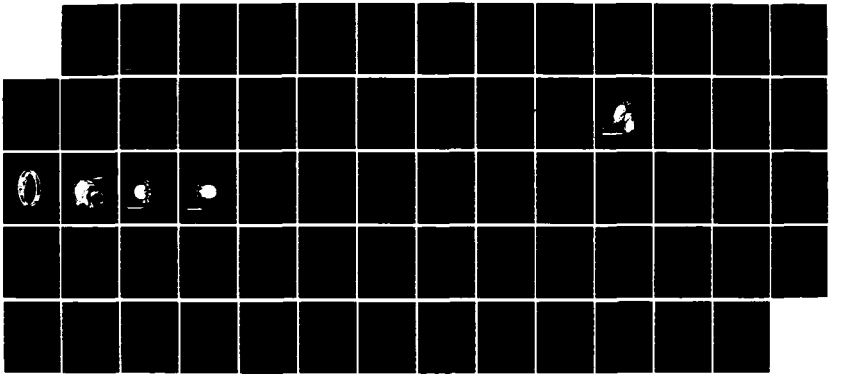

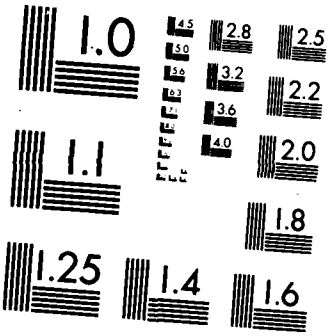

NEUROPHYSIOLOGICAL BASES OF EVENT-RELATED POTENTIALS

Annual Report No. 4

August 8, 1986

By: Charles S. Rebert
SRI International

Prepared for:

AIR FORCE OFFICE OF SCIENTIFIC RESEARCH
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In order to more fully understand the physiological and psychological significance of event-related brain potentials, cortical and subcortical recordings were obtained from monkeys performing an operant conditioning task (cued reaction time). During the past year three cynomolgus monkeys were studied following the administration of MPTP, a drug that selectively destroys nigra-striatal dopaminergic neurons in the pars compacta of the substantia nigra. This manipulation indicated the critical role of the nigra-striatal dopamine for task performance and generation of certain electrophysiological responses. A goal of relevance to performance enhancement would be to determine if increasing nigra-striatal dopaminergic activity would enhance performance and electrophysiological responsivity.

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INTRODUCTION AND BACKGROUND

Man-Machine Systems

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

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

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

Event-Related Brain Potentials

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

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

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

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

Basic Research in Animals

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

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

Choices of Experimental Paradigm

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

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

Importance of Brain Slow Potentials

Study of slow-potential (SP) changes is important for several reasons in addition to those mentioned above. Recently, there has been increasing recognition that interneuronal information can be transmitted in ways other than classical synaptic transmission, which involves a specific chemical transmitter that induces a rapid and brief de- or 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 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 dendro-

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

Experimental Issues

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

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

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

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

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

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

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

GENERAL METHODS

Test Paradigm

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

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

The general procedure used to bring the monkeys up to a good level of performance entails, first, training them to press the bar reliably for juice reward, contingent on the presence of the IS. The monkeys can be trained to emit relatively short-latency responses to the IS by having the IS (and the availability of reinforcement) terminate after 500 to 3000 msec if the bar has not been struck by that time. The strictest requirement is usually not used, and the limit is relaxed if experimental treatments might prolong reaction time. This training is followed by the introduction of the WS or the WS and NS on different trials.

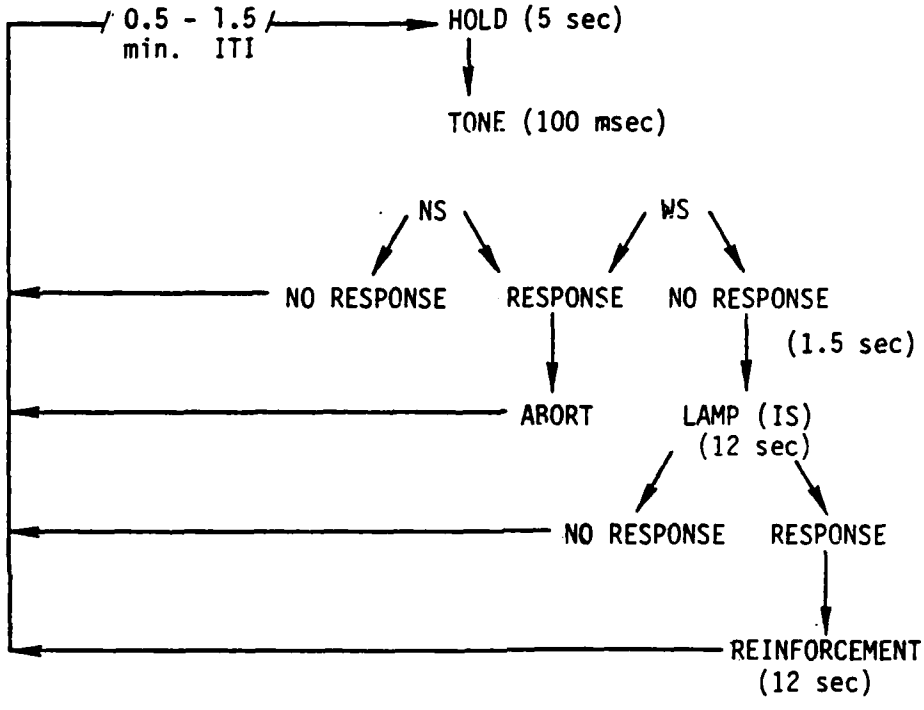

Figure 1 Schematic illustrating technique used to establish a cued discriminative reaction time task in the monkey

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

Instrumentation

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

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

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

Surgical Preparation

In preparation for surgery, the monkey is given a 15-mg/kg intramuscular (im) dose of ketamine hydrochloride, a rapid and short-acting anesthetic. The scalp and the posterior aspect of the legs are shaved and

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

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

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

RESULTS AND DISCUSSION

Histological Analyses

Histological analyses have been completed for three male cynomolgus monkeys and four female stump-tailed macaques. Of the original six cynomolgi, two are still being tested. One never performed adequately and so was sacrificed, and another died from drug-induced Parkinsonism (this brain has not yet been sectioned). The electrode implants of the other two were becoming loose (after 3.5 years), so these monkeys were also sacrificed and the brains were sectioned. Of the six original female stump-tailed monkeys, two are still being tested. One dislodged her headplug several weeks after surgery by banging her head on the cage, and another died, apparently from meningitis three months after surgery. Another began having convulsions 7 months post-surgery, and the last dislodged her headplug 7 months post-surgery.

The technique of photographic enlarging and printing of frozen sections, described by Guzman 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 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 too posterior as well 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 1. 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 1. 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.

Nuclear Magnetic Resonance Imaging to Improve Electrode Placements

There were several sources of error in the placement of the electrodes discussed above, including one miscalculated coordinate and one bumped electrode, but a major source of error 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 also introduces 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

Table 1

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.

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), so 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 determining 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 2, 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. Saggital, 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 3. The simpler, two-dimensional case is shown in Figure 4. The upper figure is of a monkey with a shallow suborbital ridge. The triangle E-F-G, involving the subcortical structure of

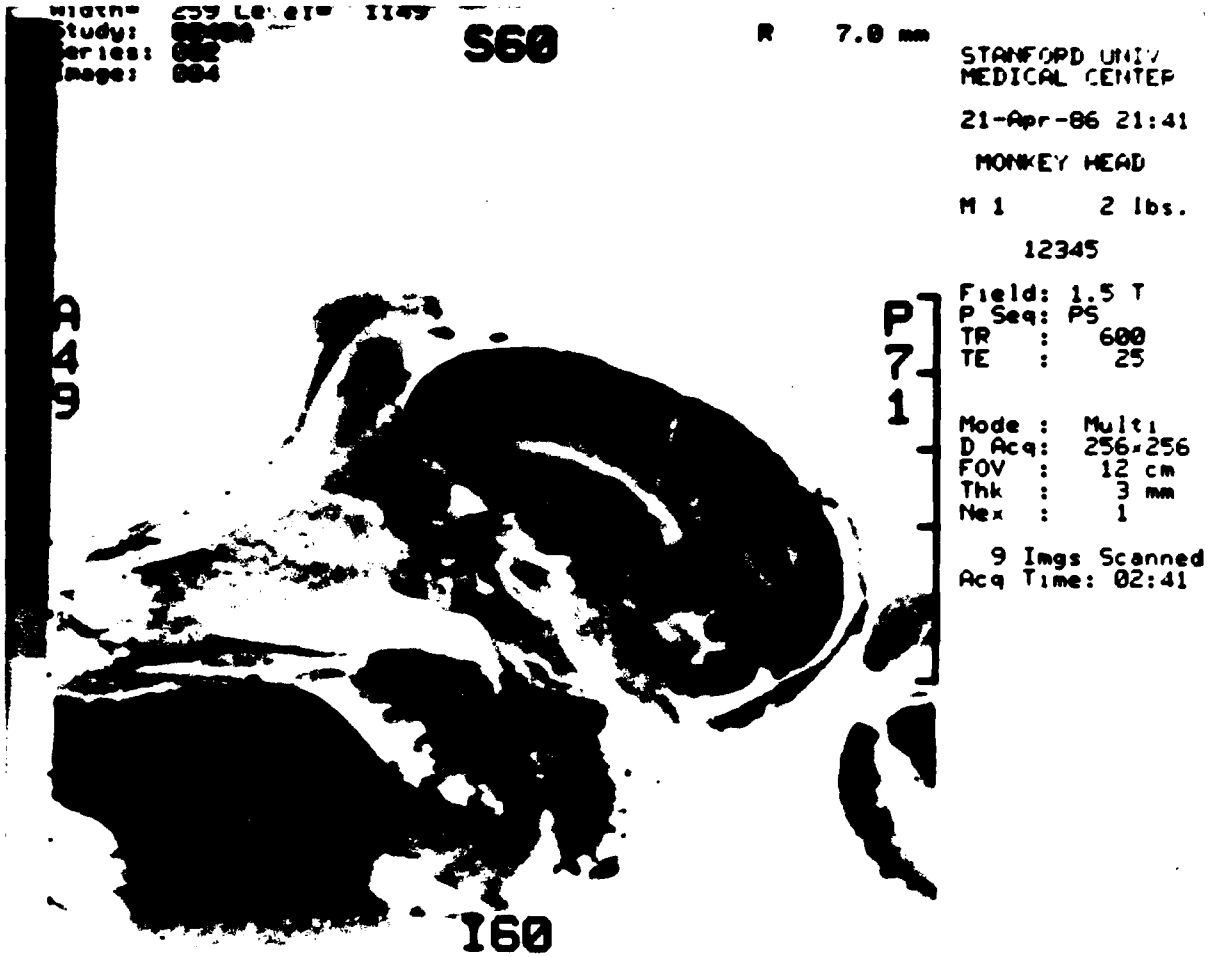

FIGURE 2 Saggital magnetic resonance image of a monkey's head, showing anatomical structures and electrode tracks

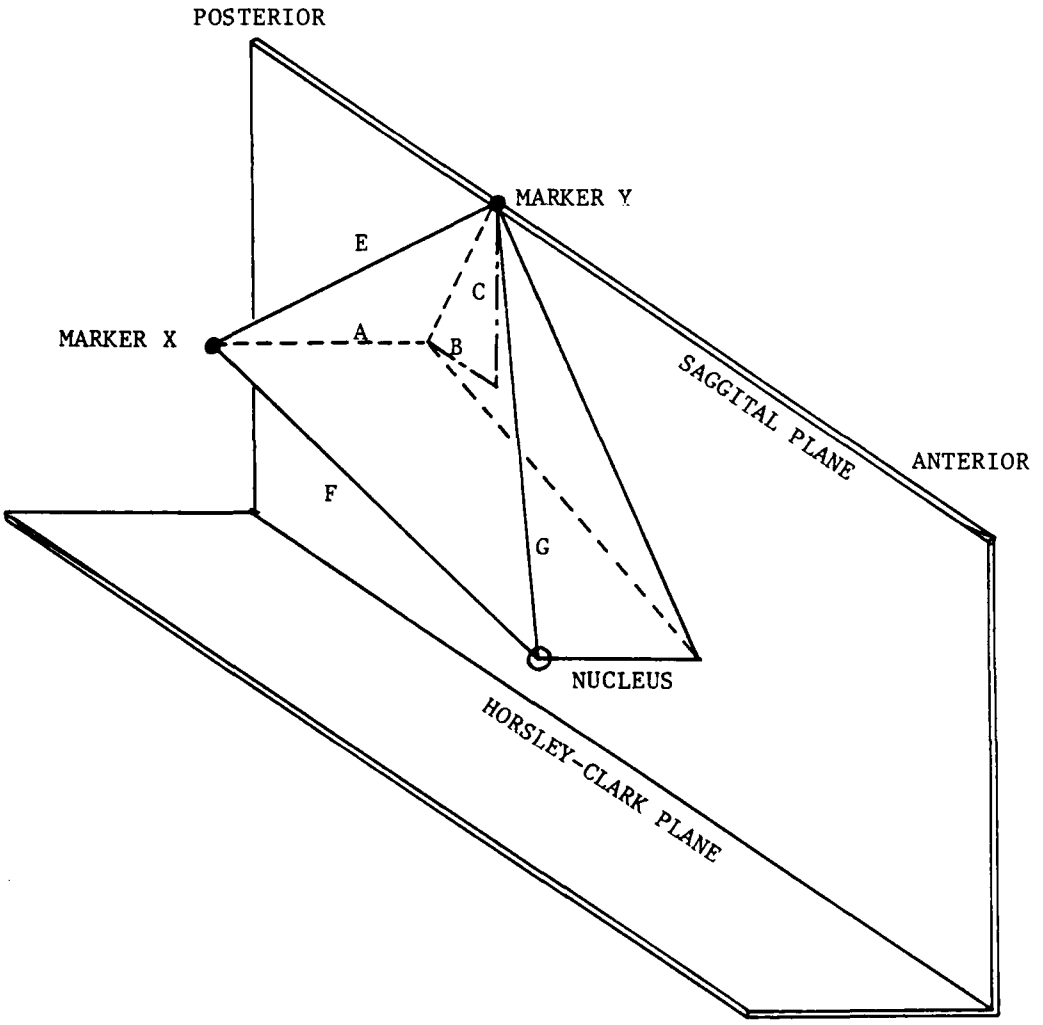

FIGURE 3 Three-dimensional representation of an intracerebral site and the geometric extrapolation required for stereotaxic implantation.

Using information obtained at the time of surgery (ABC) and from NMRI (EFG), the position of the nucleus orthogonal to the stereotaxic planes and markers can be calculated.

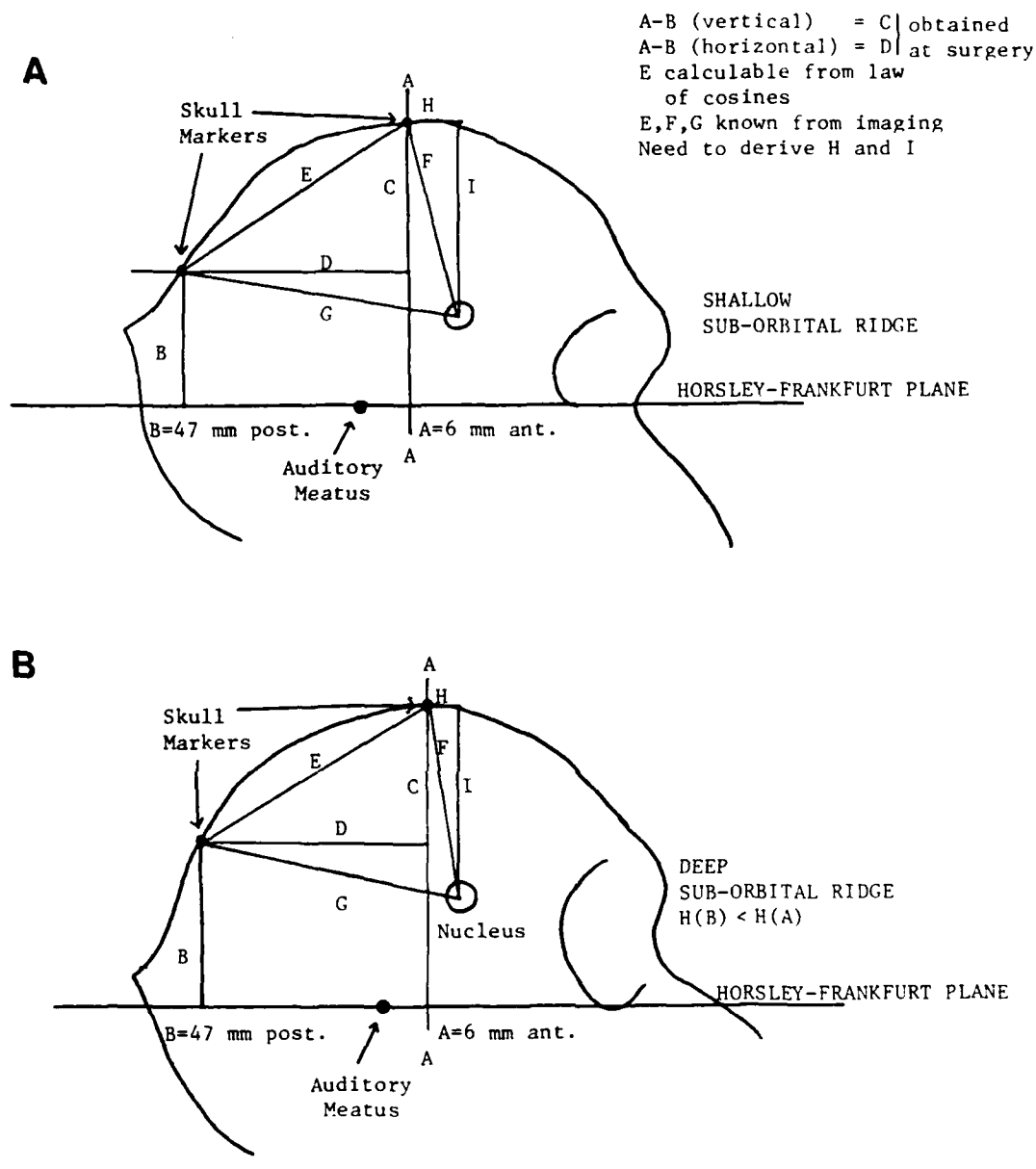

FIGURE 4A Two-dimensional representation of the geometric extrapolation required from MRI to stereotaxic situation

4B Effect of head rotation due to altered skull morphology on the determination of stereotaxic coordinates

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 4. 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 manipulation at the time of surgery (Brown et al., 1980), we are taking a simpler approach initially.

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 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 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), and two others 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 (Figure 5).

On the day of imaging the monkeys were immobilized with 15 mg/kg of ketamine im and anesthetized with 8 mg/kg sodium pentobarbital iv 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. Saggital, coronal, and axial planes were imaged. Examples of these images from one monkey are shown in Figures 6, 7, and 8. The marker beads are seen exceptionally well in the saggital view (Figure 6). Unfortunately, the other views did not reproduce well photographically but general outlines of white matter and the caudate nuclei can be seen.

Figure 9 compares outlines of midline saggital 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,

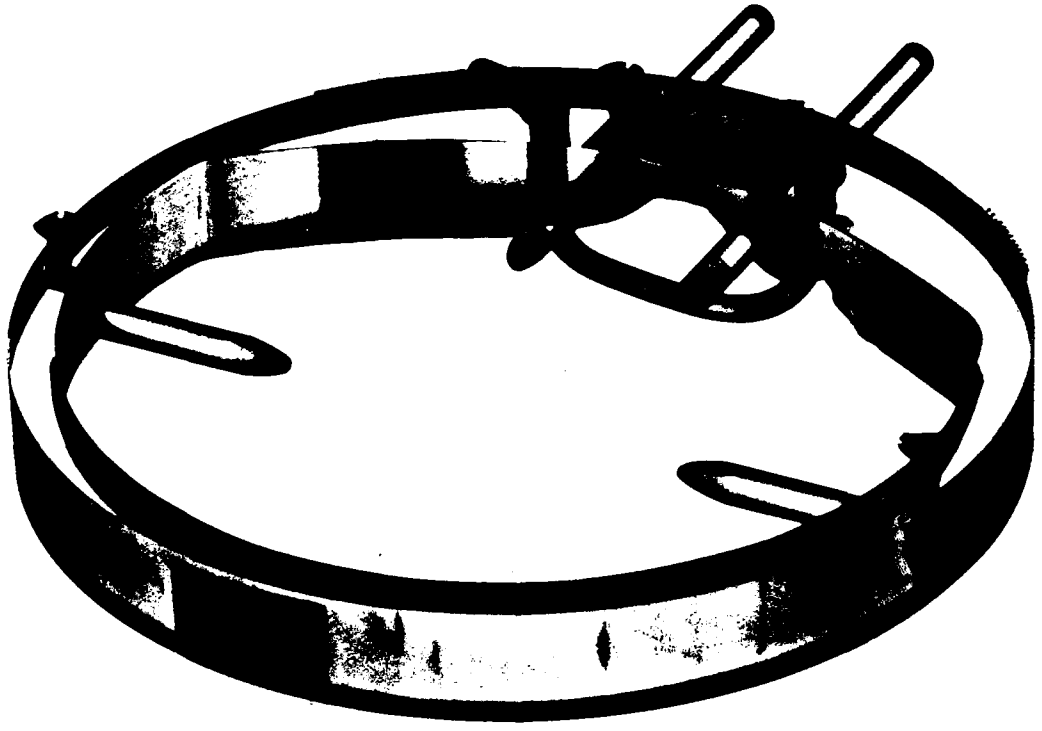

FIGURE 5 Plastic stereotaxic ring for maintaining a monkey's head-positioning during MRI

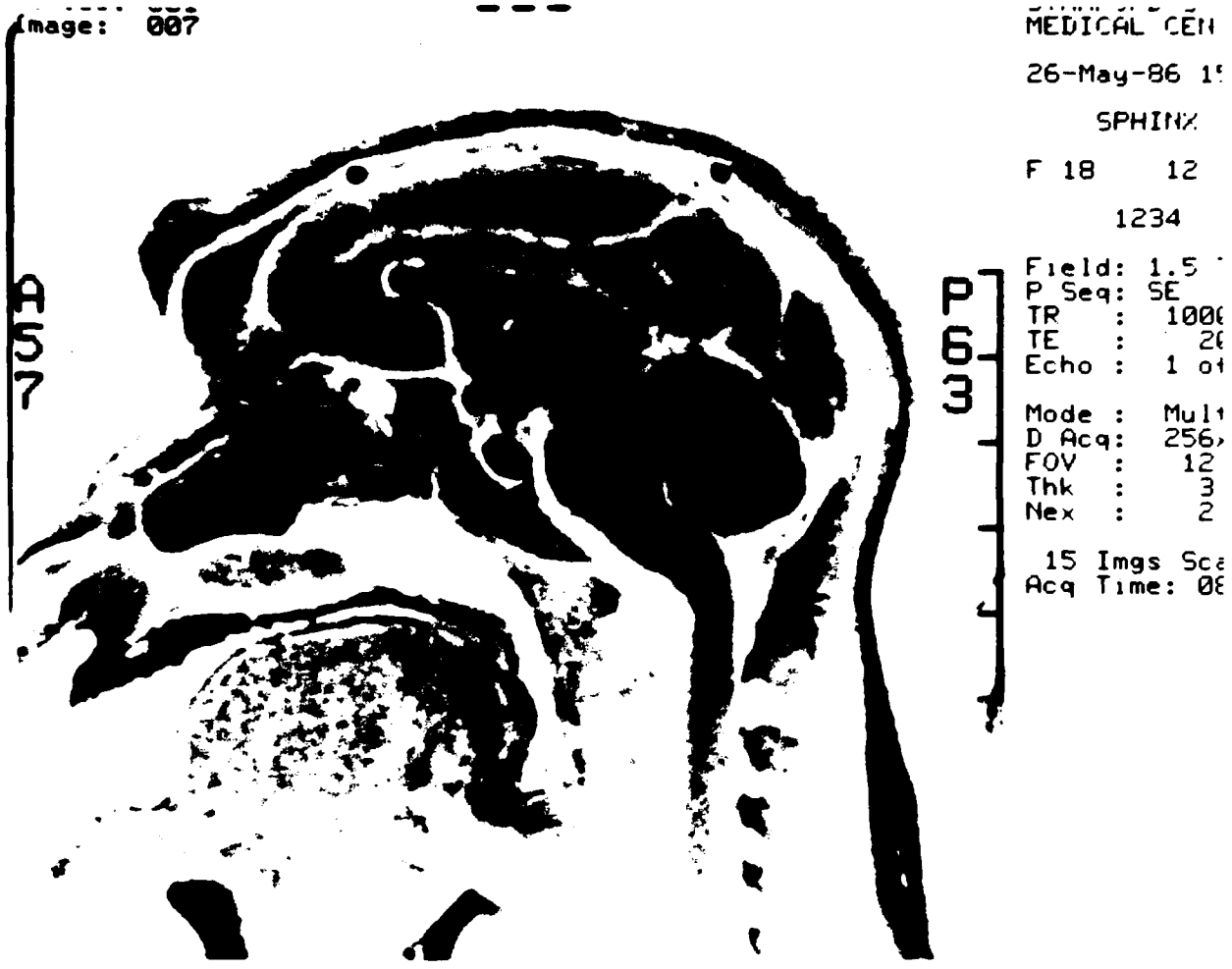

FIGURE 6 Saggital MRI showing midline neuroanatomical structures and marker beads implanted in the skull

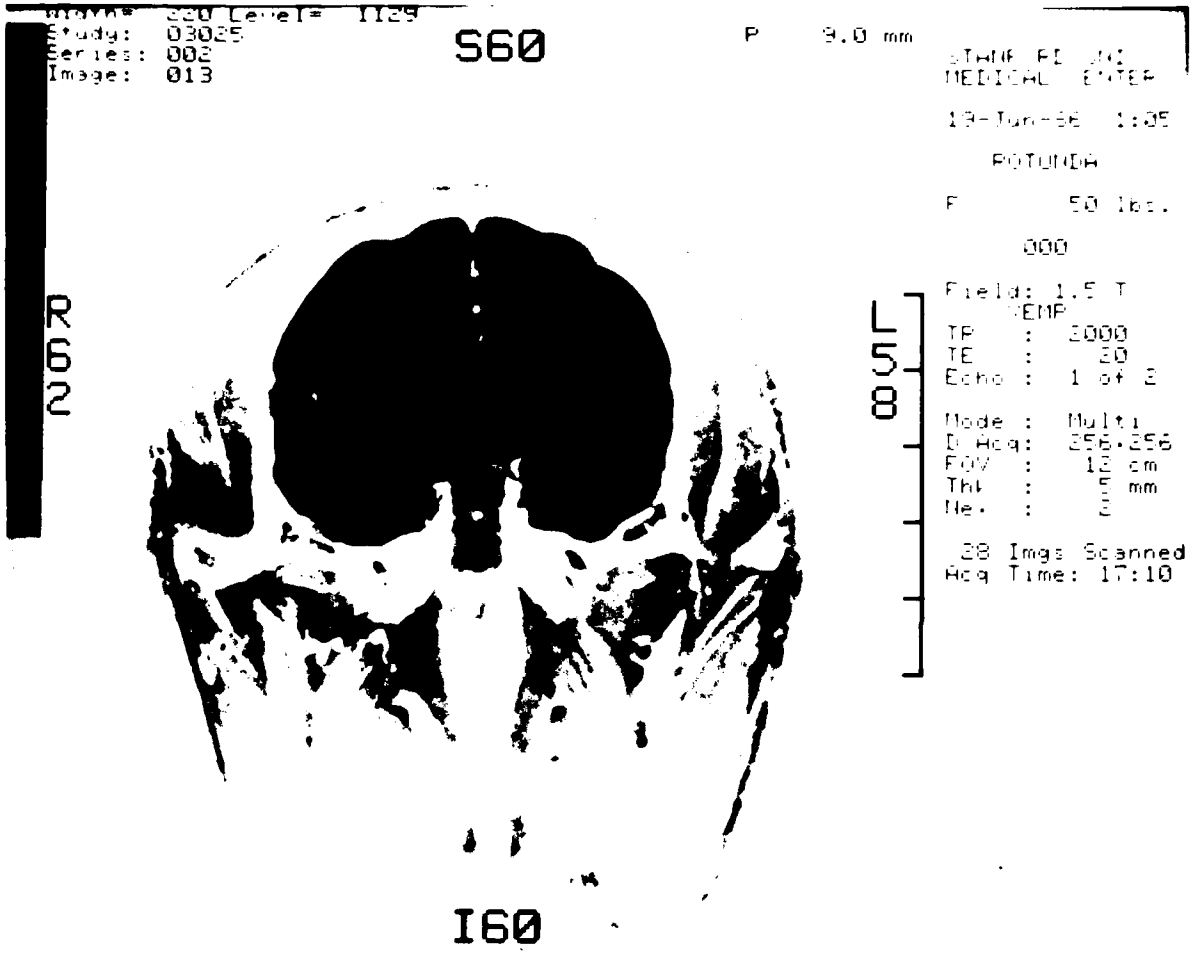

FIGURE 7 Coronal MRI

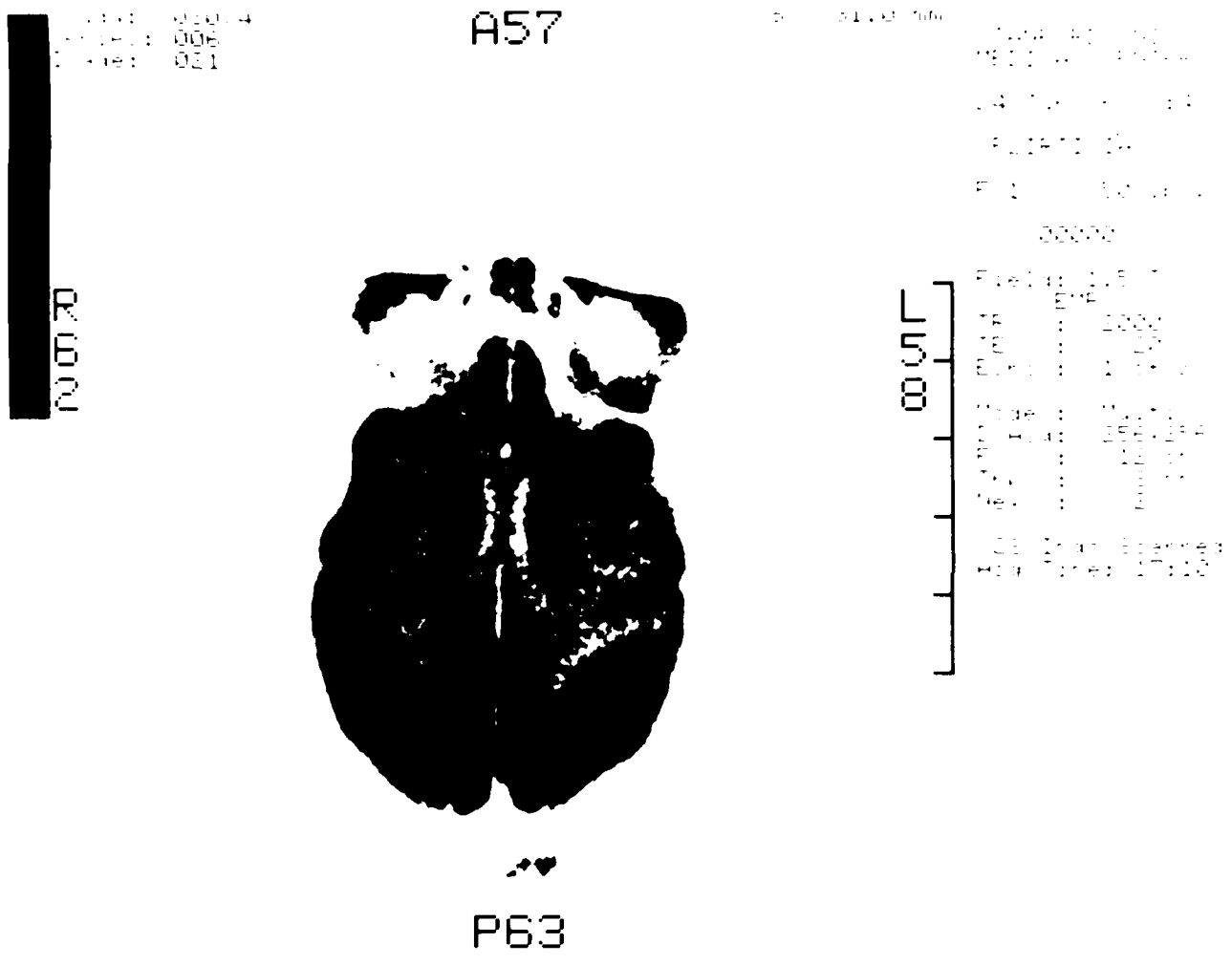

FIGURE 8 Axial MRI

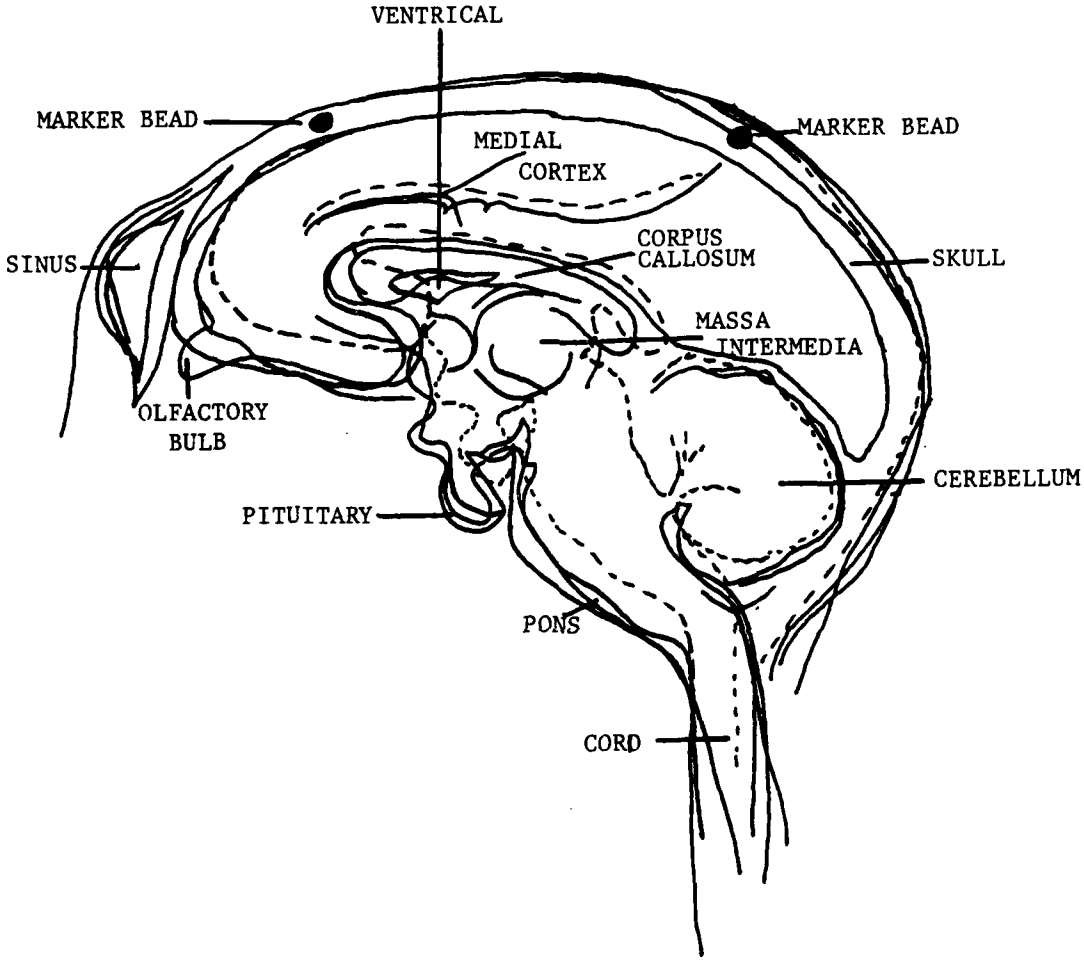

FIGURE 9 Comparison of skull-brain relationships in four female rhesus monkeys.

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

and in three of them the brains were similar as well. 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 so far is that the machine employed had a large coil designed for human clinical imaging, resulting in a disadvantageous tradeoff between in-plane resolution and slice thickness. In-plane resolution 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 have been made to study this problem further at the General Electric facility in Fremont, California, using an experimental machine that should provide good in-plane resolution with 1-mm slices.

Critical Role of Nigra-Striatal Dopamine in Preparatory Set: Effects of MPTP-Induced Pars Compacta Lesions on Behavior and Event-Related Brain Potentials in Macaque Monkeys

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., 1986), 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—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 slow potential (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 reaction time (RT) task (Rebert, 1985), and conjectures about the role of nigra-striatal 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-tetrahydopyrine) to induce the lesion.

The pars compacta is the major nigra-striatal dopaminergic pathway and is 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 caused reaction time to increase, 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, two of these monkeys are still being studied, and none of these brains have yet been histologically analyzed. To avoid severe symptoms we gave small intravenous 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 carbidopa). 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 in the figures below.

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 over all items for each day of observation to obtain a general clinical score. The results of these observations are shown in Figures 10, 11, and 12 for monkeys ET, Grey, and Smacker, respectively.

As shown in Figure 10, 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. At 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

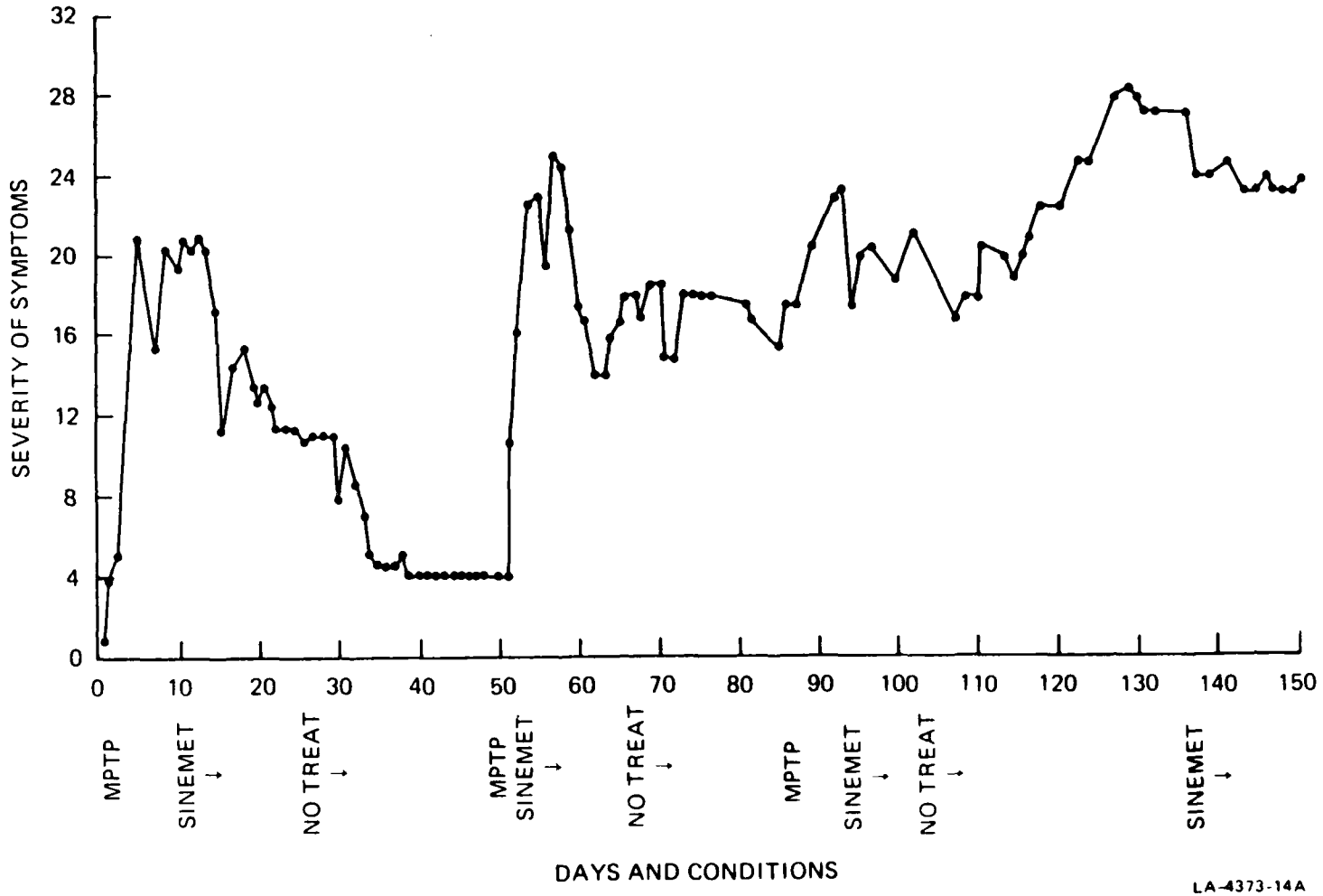

FIGURE 10 Changes in clinical symptoms associated with MPTP injections: monkey ET

be improving by a second observer, and some improvement in the ratings appeared through day 150.

Grey's results are shown in Figure 11. 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 12 shows, Smacker'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 therapy. 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 13, 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 14). Grey's reaction time decreased slightly during the midportion of the experiment but increased precipitously after the fourth injection (Figure 15-left), as did his clinical signs. As with ET, Grey's increased reaction time was due to a slowing of movement (Figure 15-middle). Smacker's reaction time also increased in association with the development of clinical signs and decreased toward normal when clinical signs abated (Figure 16). As shown in Figure 17, changes in both initiation time 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 15,18, and 19).

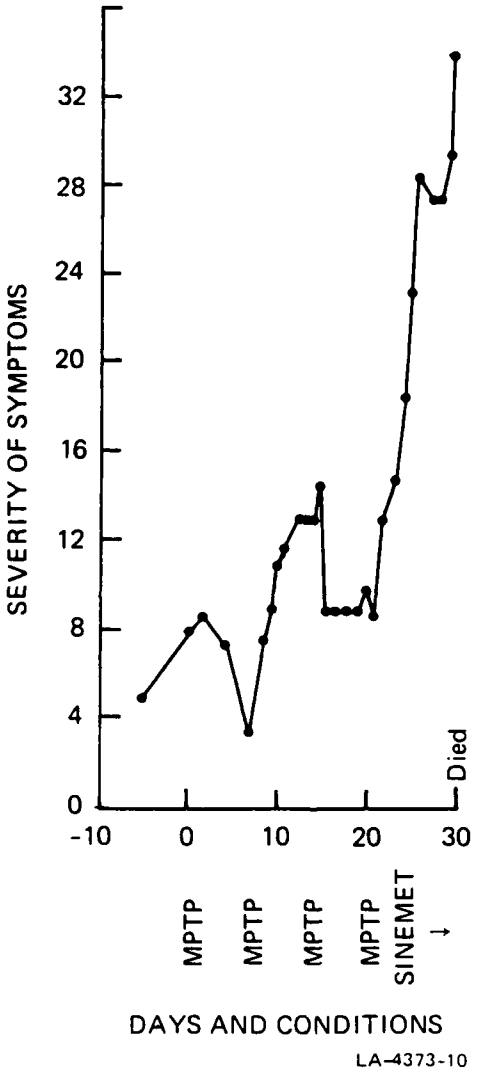

FIGURE 11 Changes in clinical symptoms associated with MPTP injections: monkey GR

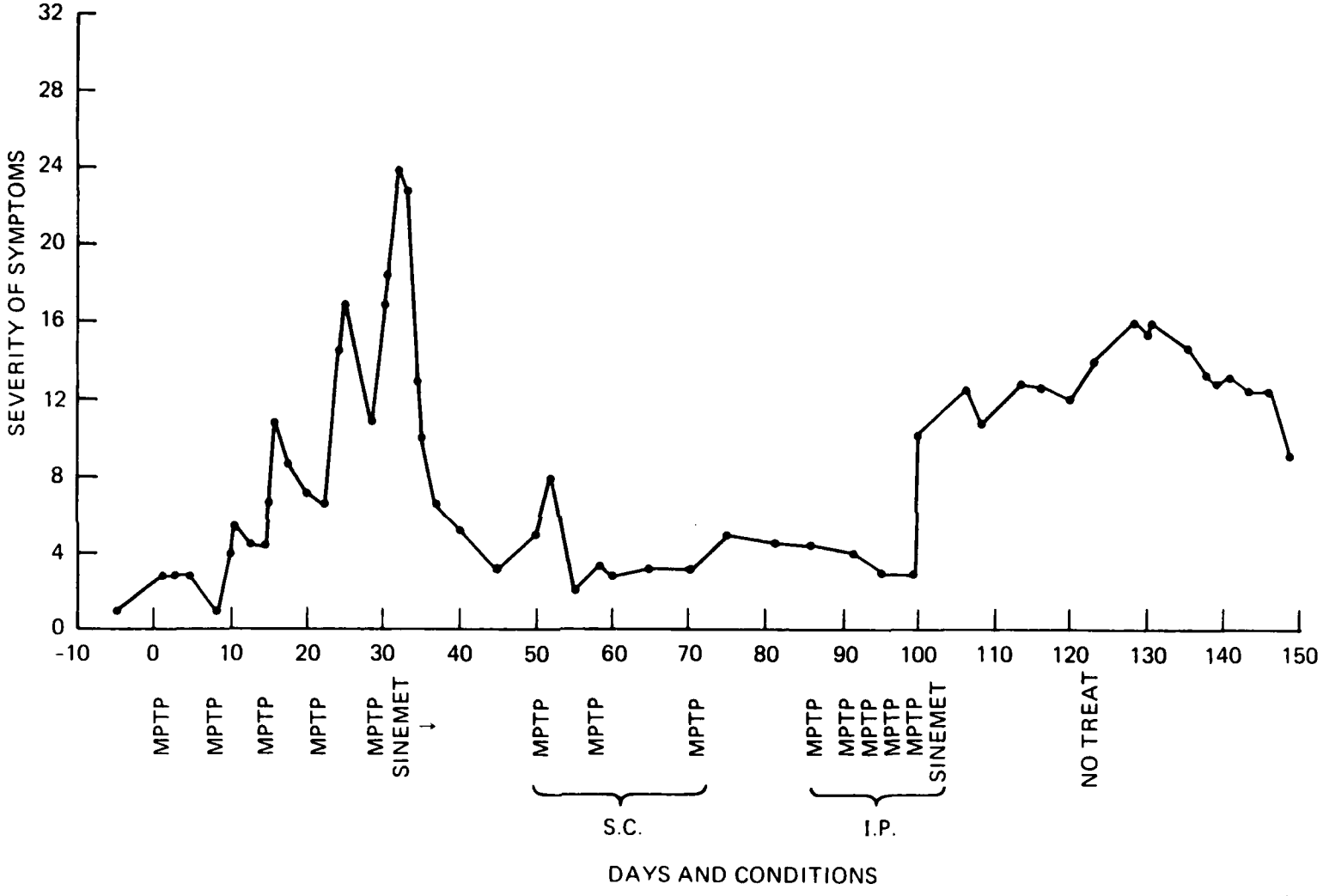

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FIGURE 12 Changes in clinical symptoms associated with MPTP injections: monkey SM

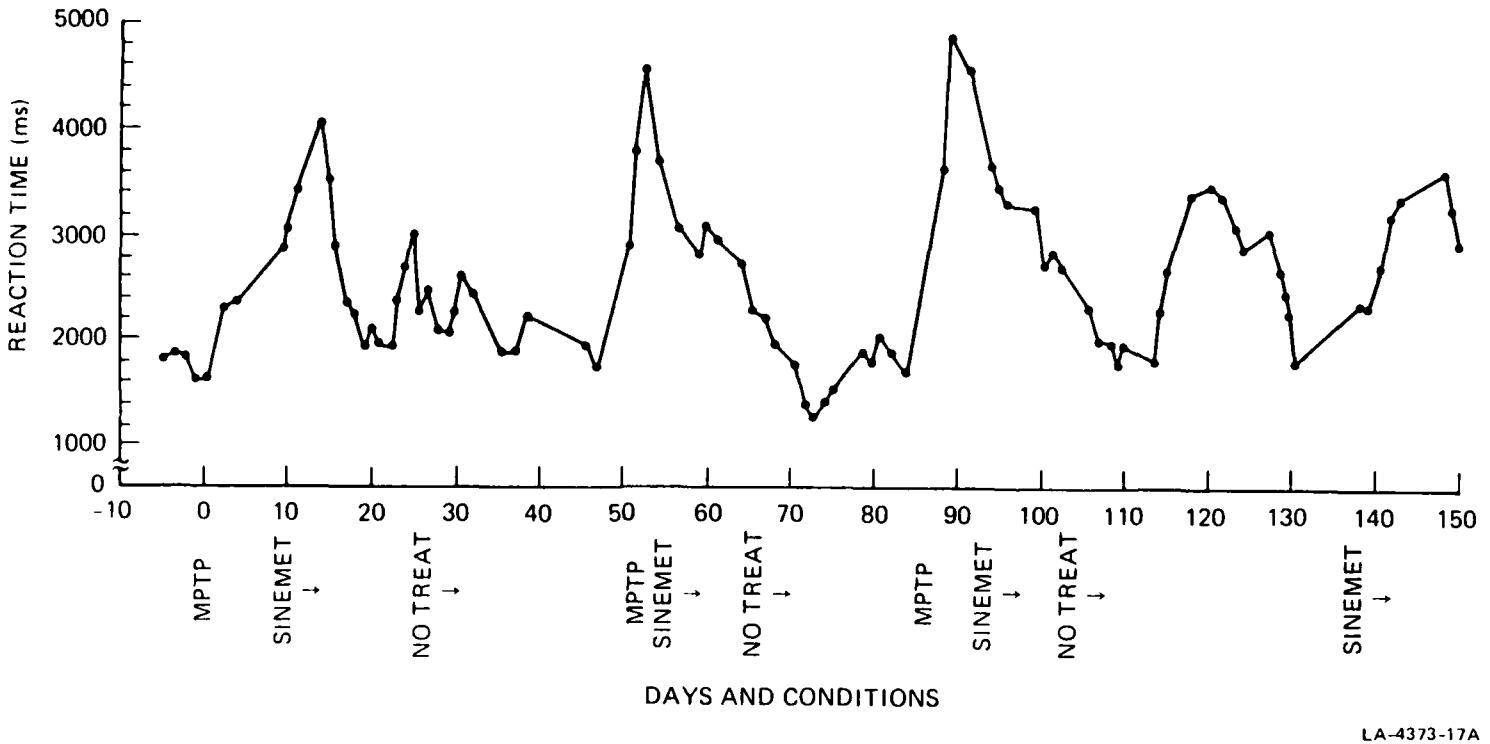

FIGURE 13 Changes in ET's reaction time associated with MPTP injections

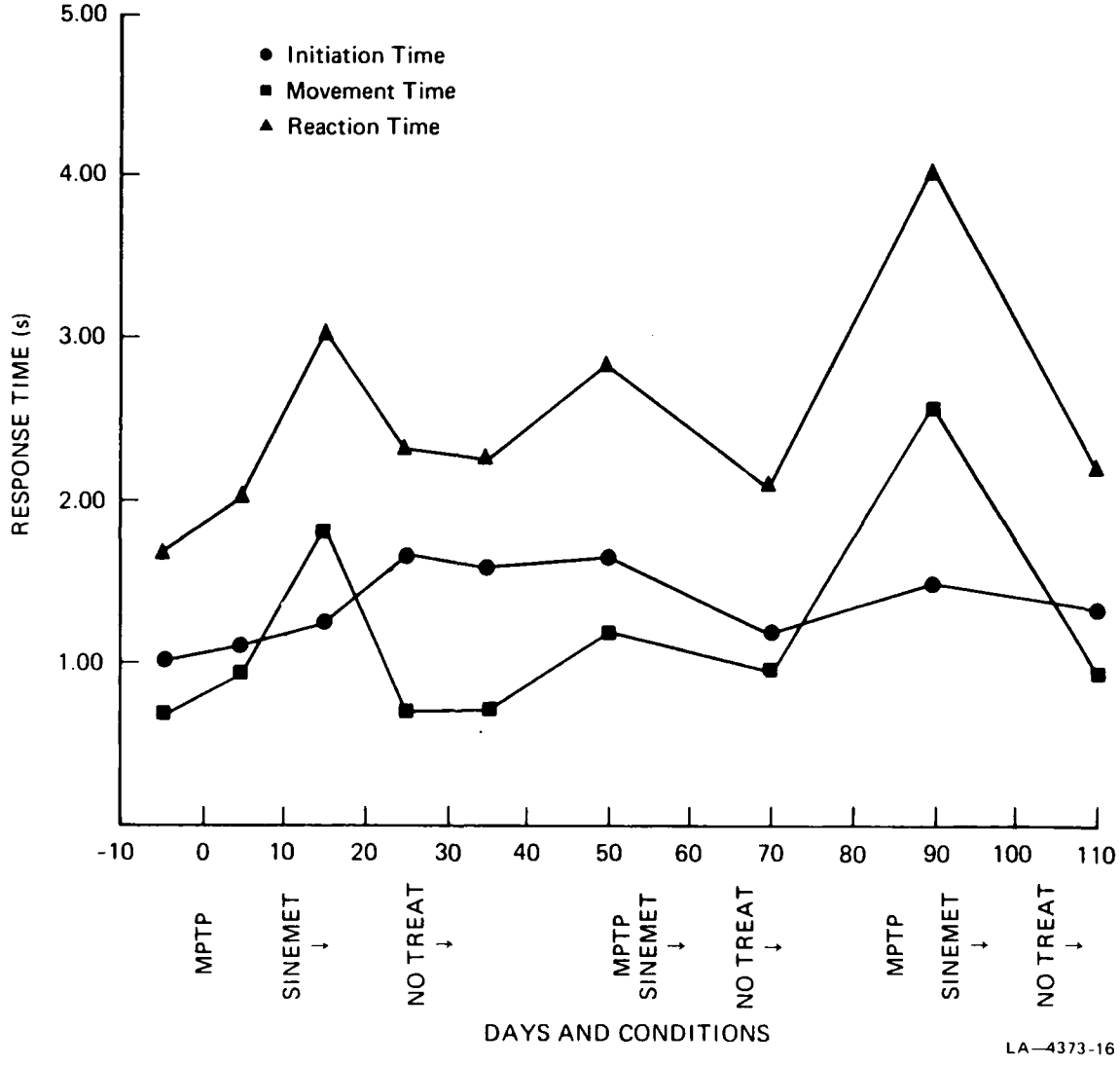

FIGURE 14 Initiation time, reaction time, and movement time in monkey ET

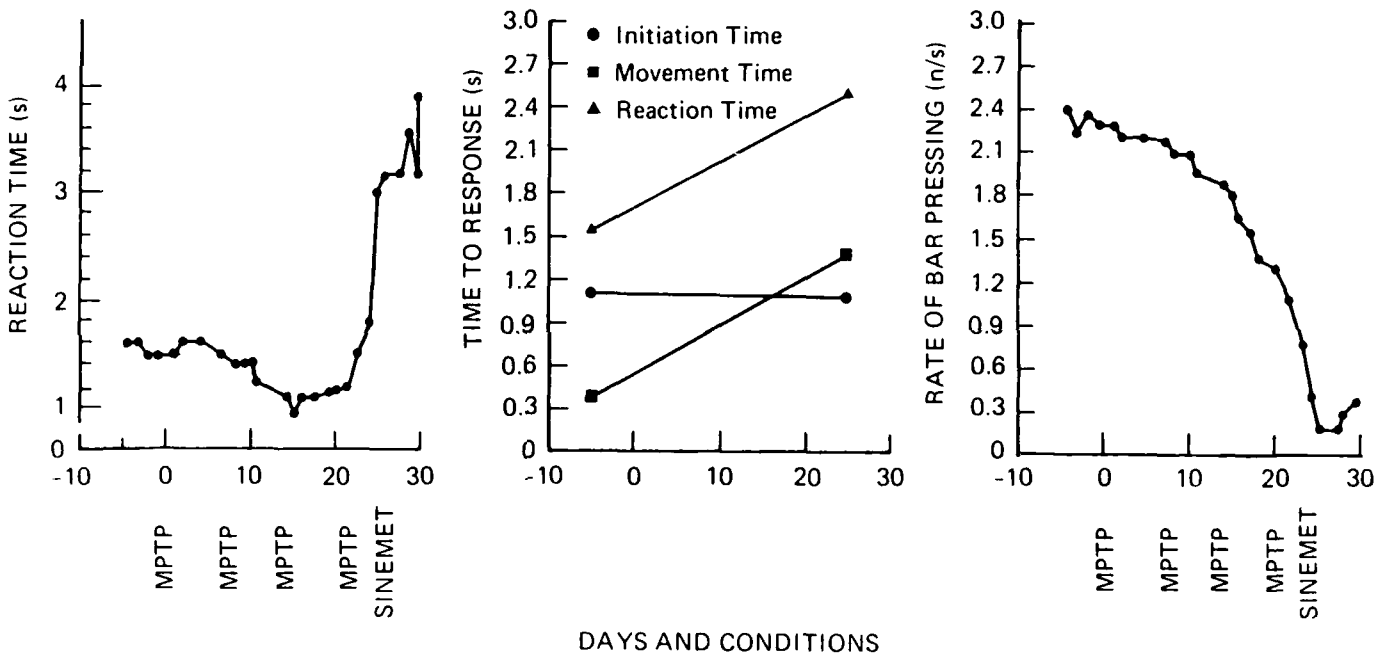

FIGURE 15 Changes in behavioral parameters of monkey GR associated with MPTP injections

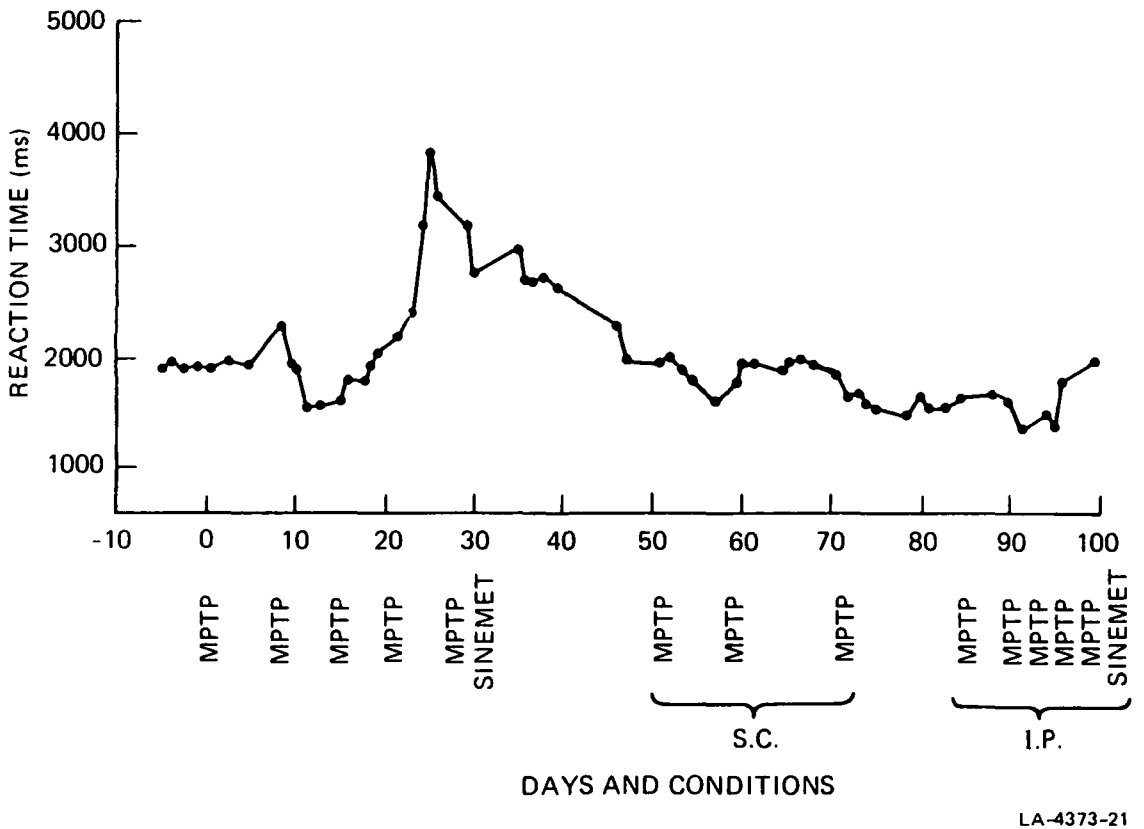

FIGURE 16 Changes in SM's reaction time associated with MPTP injections

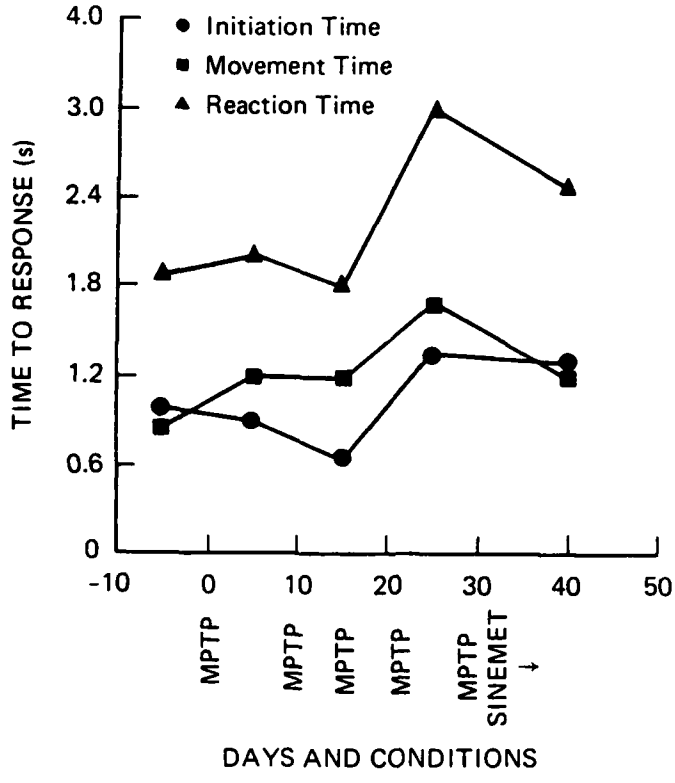

FIGURE 17 Initiation time, reaction time, and movement time in monkey SM

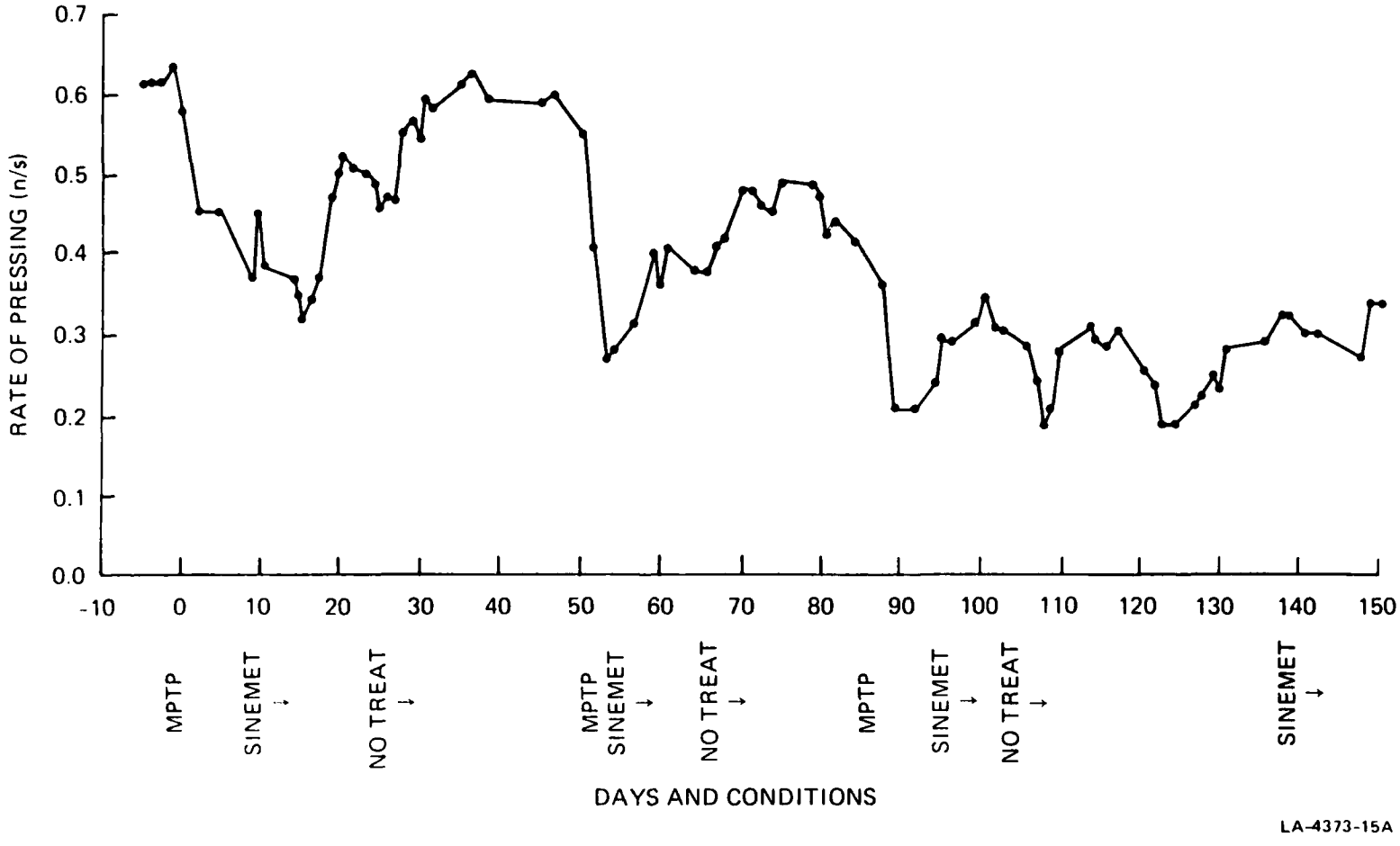

FIGURE 18 Bar-pressing rates for monkey ET

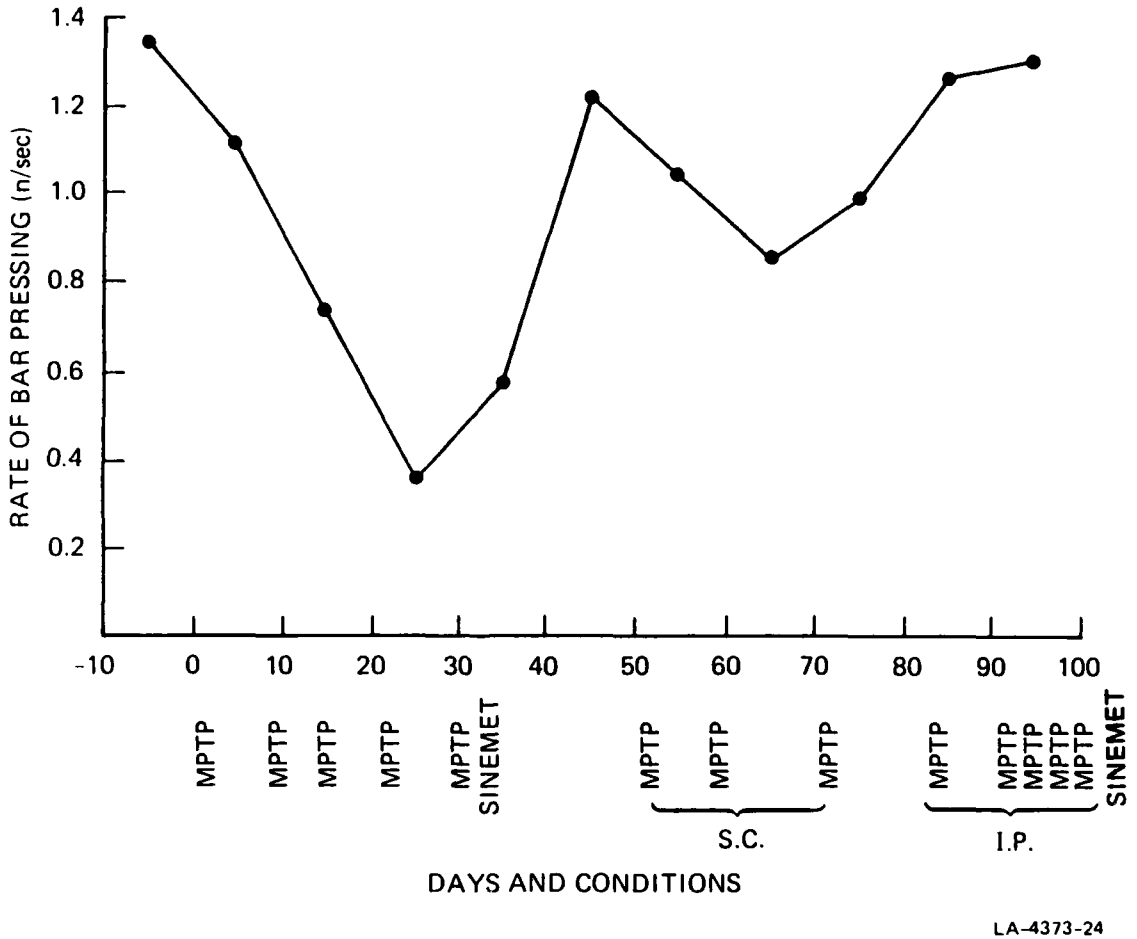

FIGURE 19 Bar-pressing rates for monkey SM

Electrophysiological responses from the premotor cortex and substantia nigra were evaluated. Examples of pretreatment and treatment responses from the premotor cortex (PMC) of each monkey are shown in Figure 20.

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, which is 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 = day 25; GR = day 22; ET = day 14), are shown in the right column. In all cases the N_2 and SP components were reduced, and in Smacker the tone-evoked transient EP complex was 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 21-25.

The N1-P2 peak-to-peak and SP amplitudes for ET (Figure 21) 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 prestimulus baseline--Figure 22). In contrast, the N2 component (Figure 23) 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 nigral-striatal 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 24). 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 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.

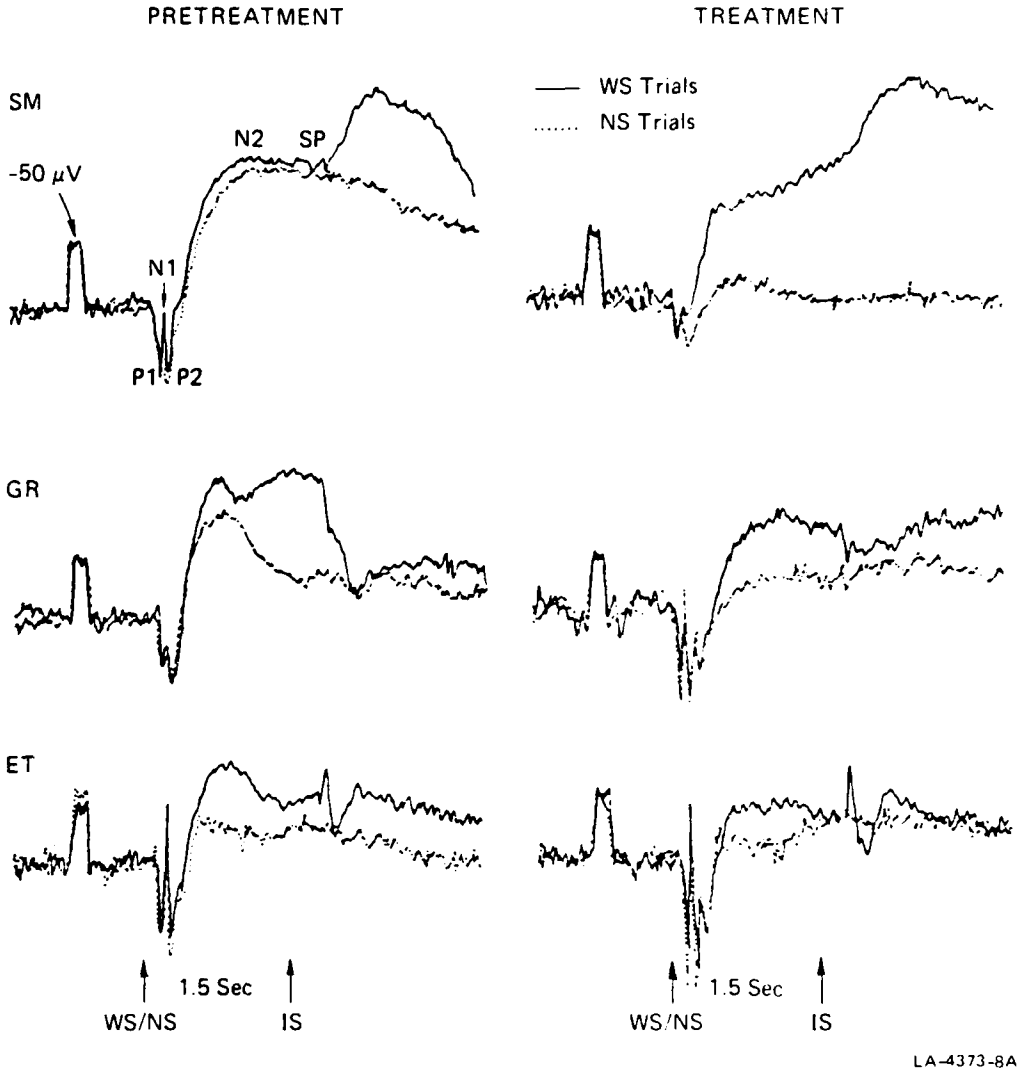

FIGURE 20 Examples of event-related potentials in the premotor cortex during pretreatment and post-MPTP phases of the experiment

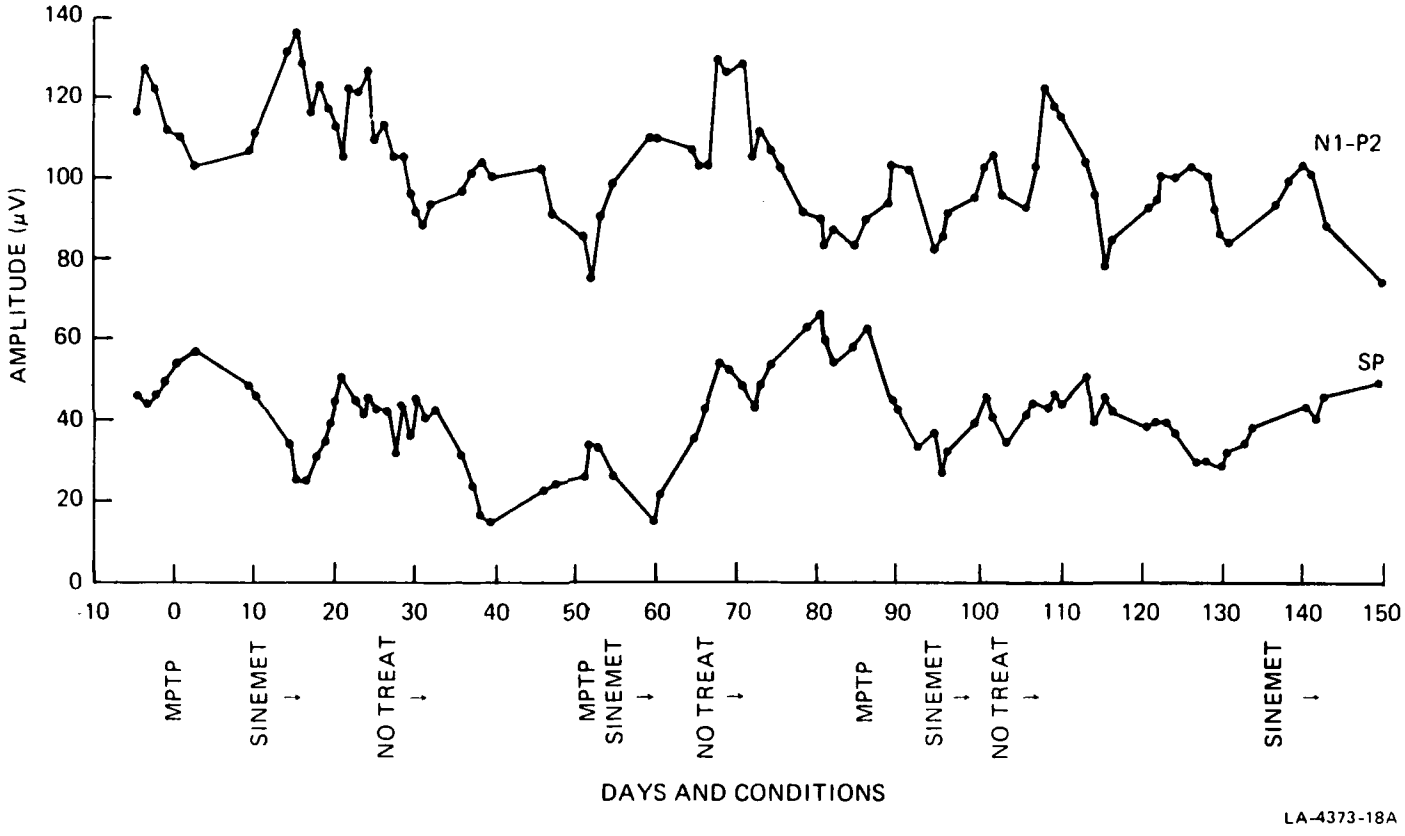

FIGURE 21 Changes in the N1-P2 and SP components in ET's premotor cortex associated with MPTP injections

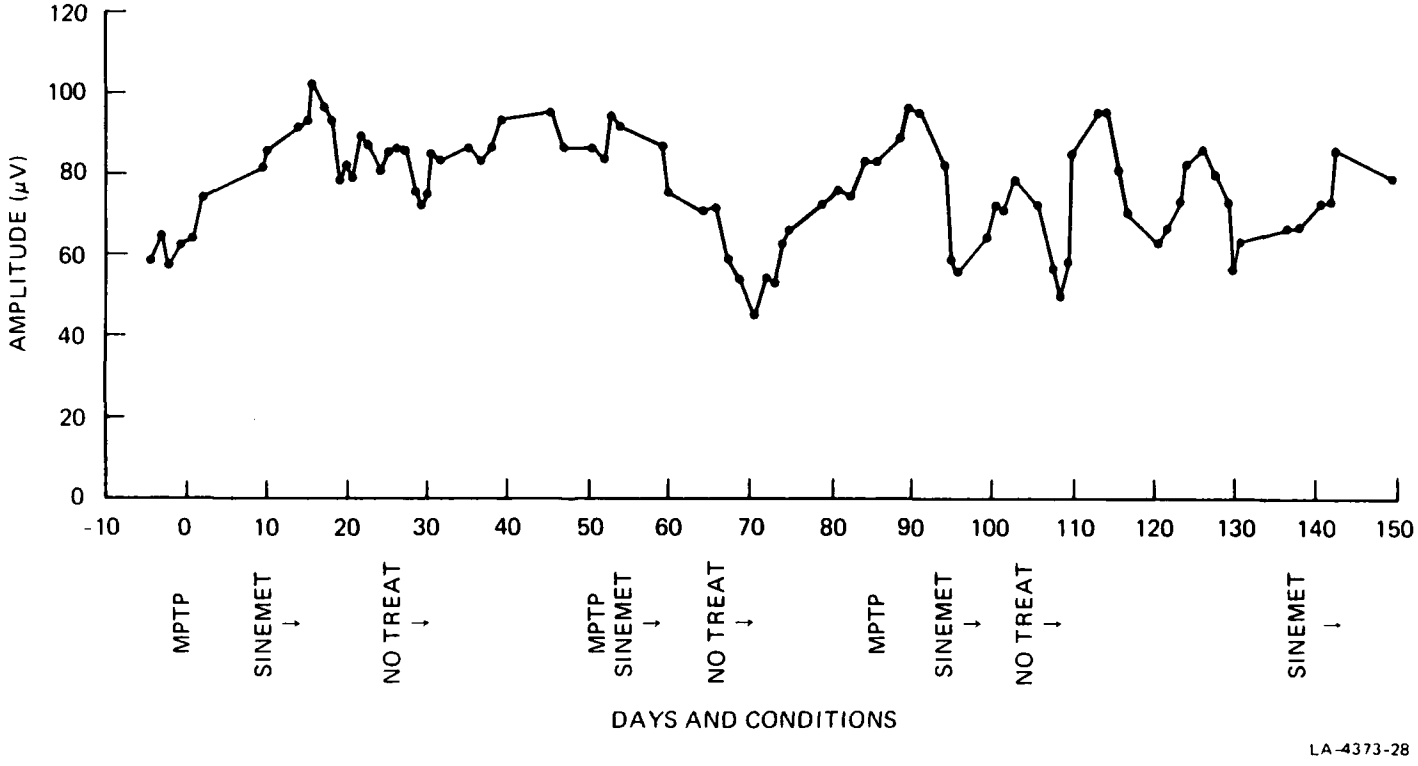

FIGURE 22 Changes in the P1 component in ET's premotor cortex associated with MPTP injections

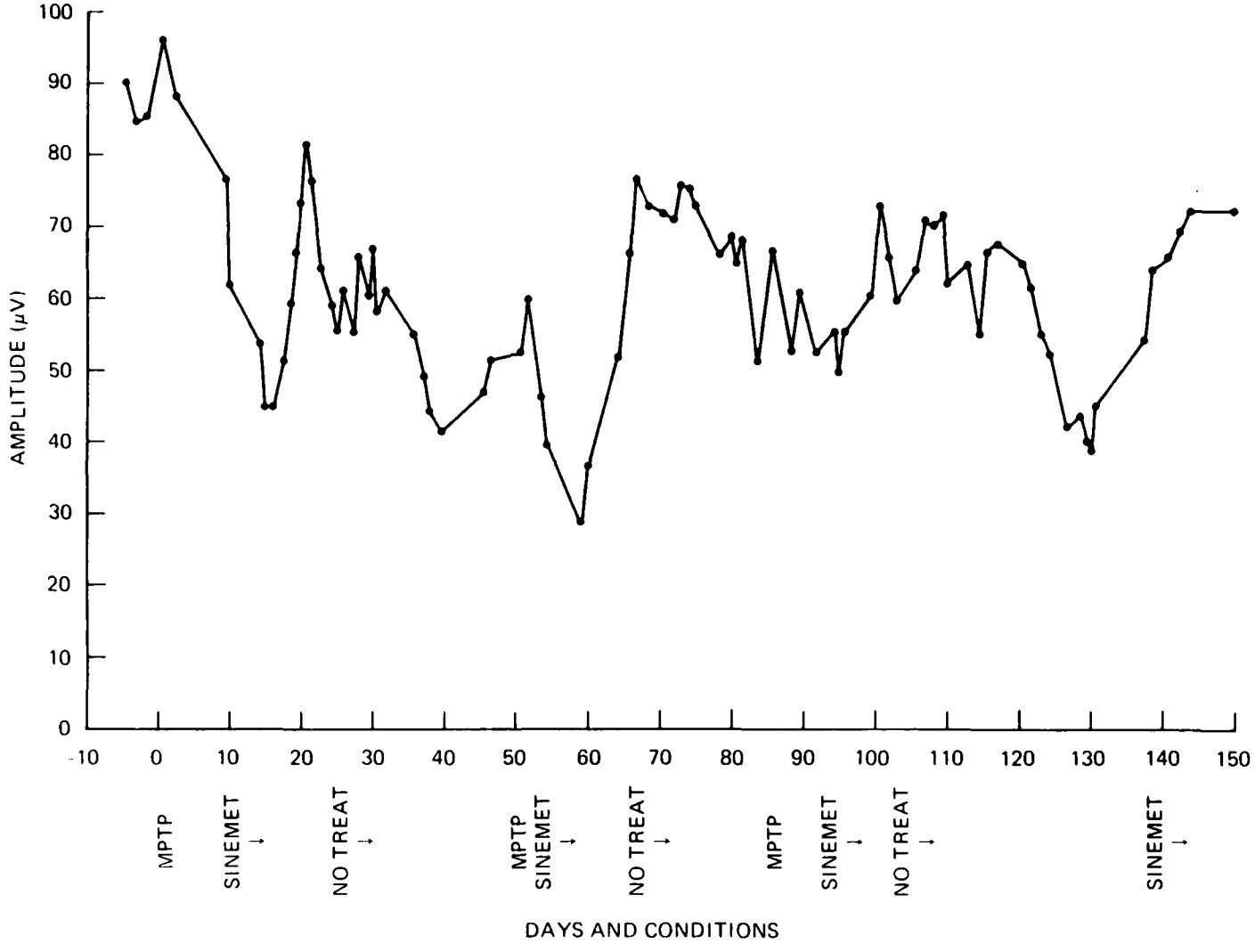

FIGURE 23 Changes in the N2 component in ET's premotor cortex associated with MPTP injections

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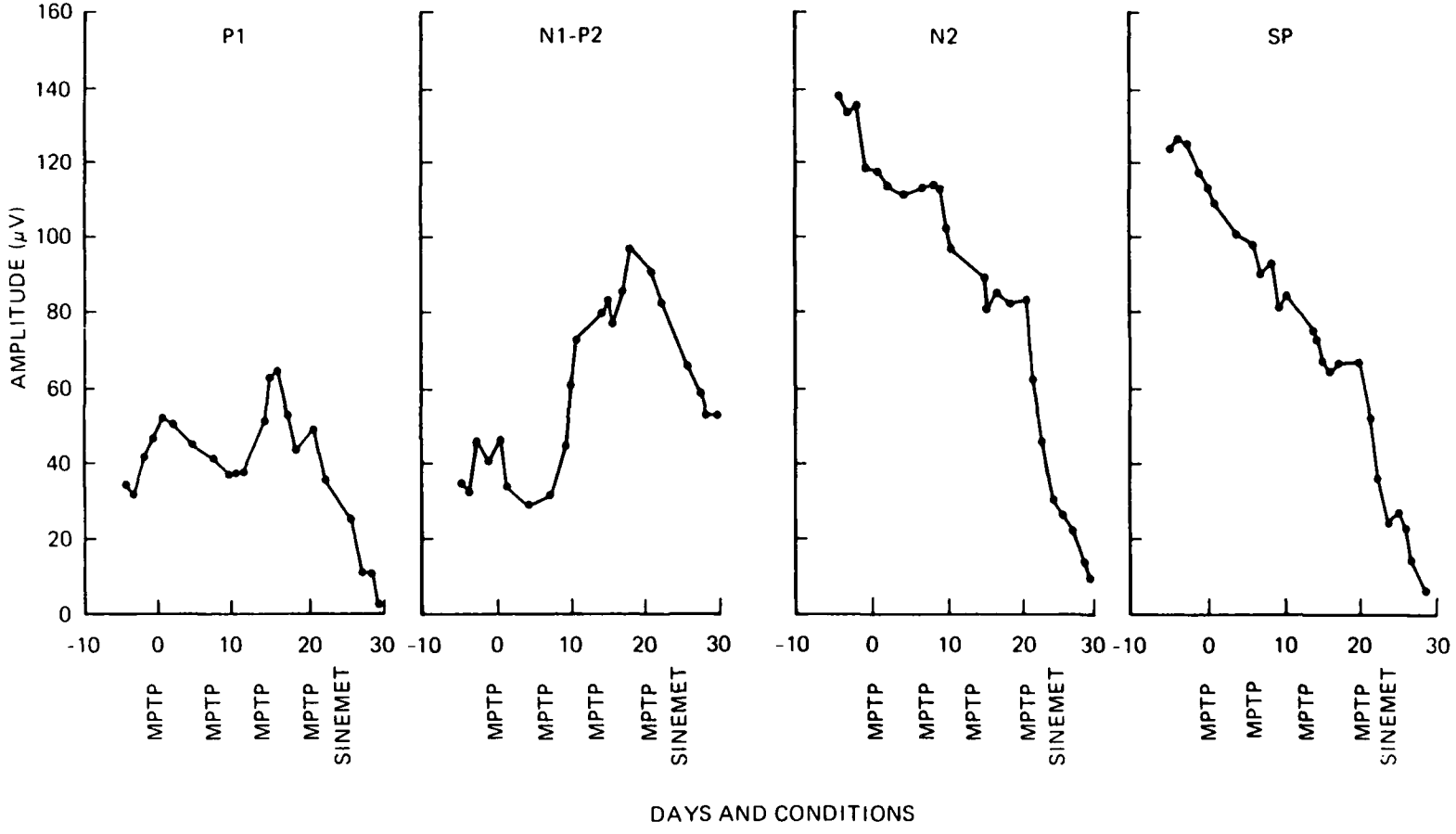

FIGURE 24 Changes in several evoked potential components in GR's premotor cortex associated with MPTP injections

Alterations of PMC components in monkey SM are shown in Figure 25. 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 26 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--this effect was more pronounced on the NS-evoked waveform in monkey SM than on the WS-evoked waveform.

Sequential changes over the course of the experiment are shown in Figures 27 through 29. 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 27. 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 28 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, particularly, preceded the rapid change in reaction time (which occurred after day 20). Onset of the N2 decline appeared to be associated 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.

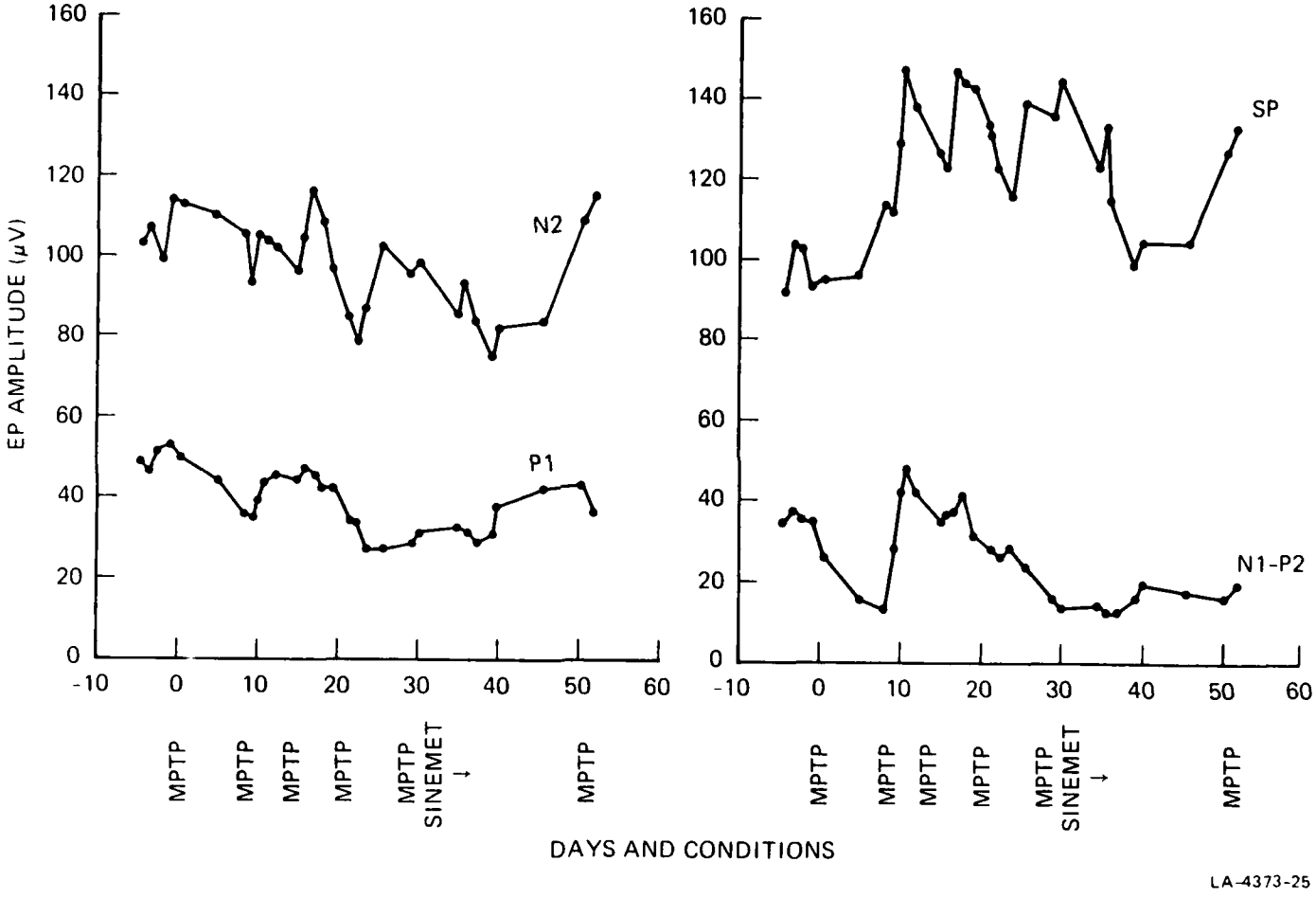

FIGURE 25 Changes in several evoked potential components of SM's premotor cortex associated with MPTP injections

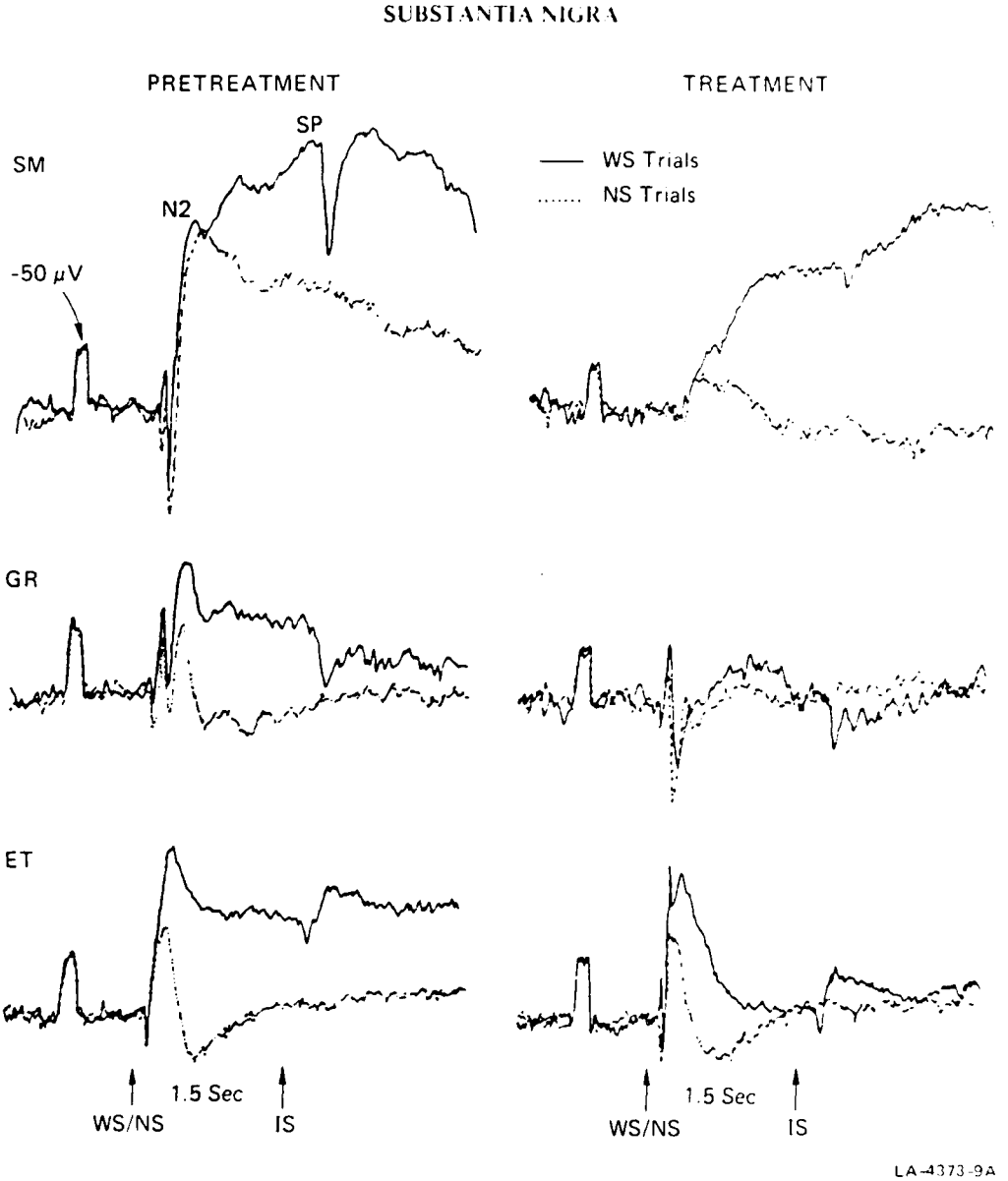

FIGURE 26 Examples of event-related potentials in the vicinity of the substantia nigra during pretreatment and post-MPTP phases of the experiment

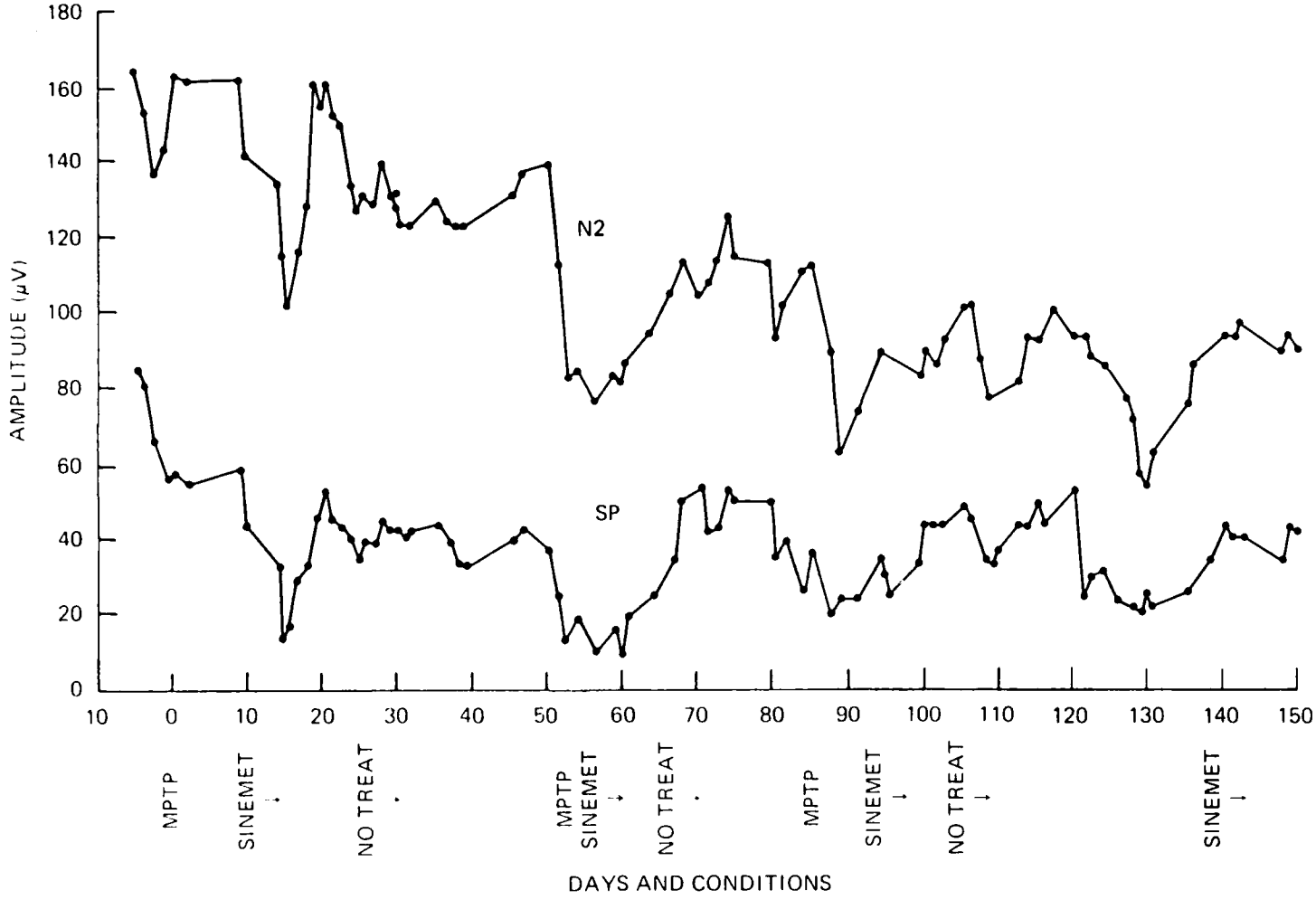

FIGURE 27 Changes in the N2 and SP components of ET's substantia nigra associated with MPTP injections

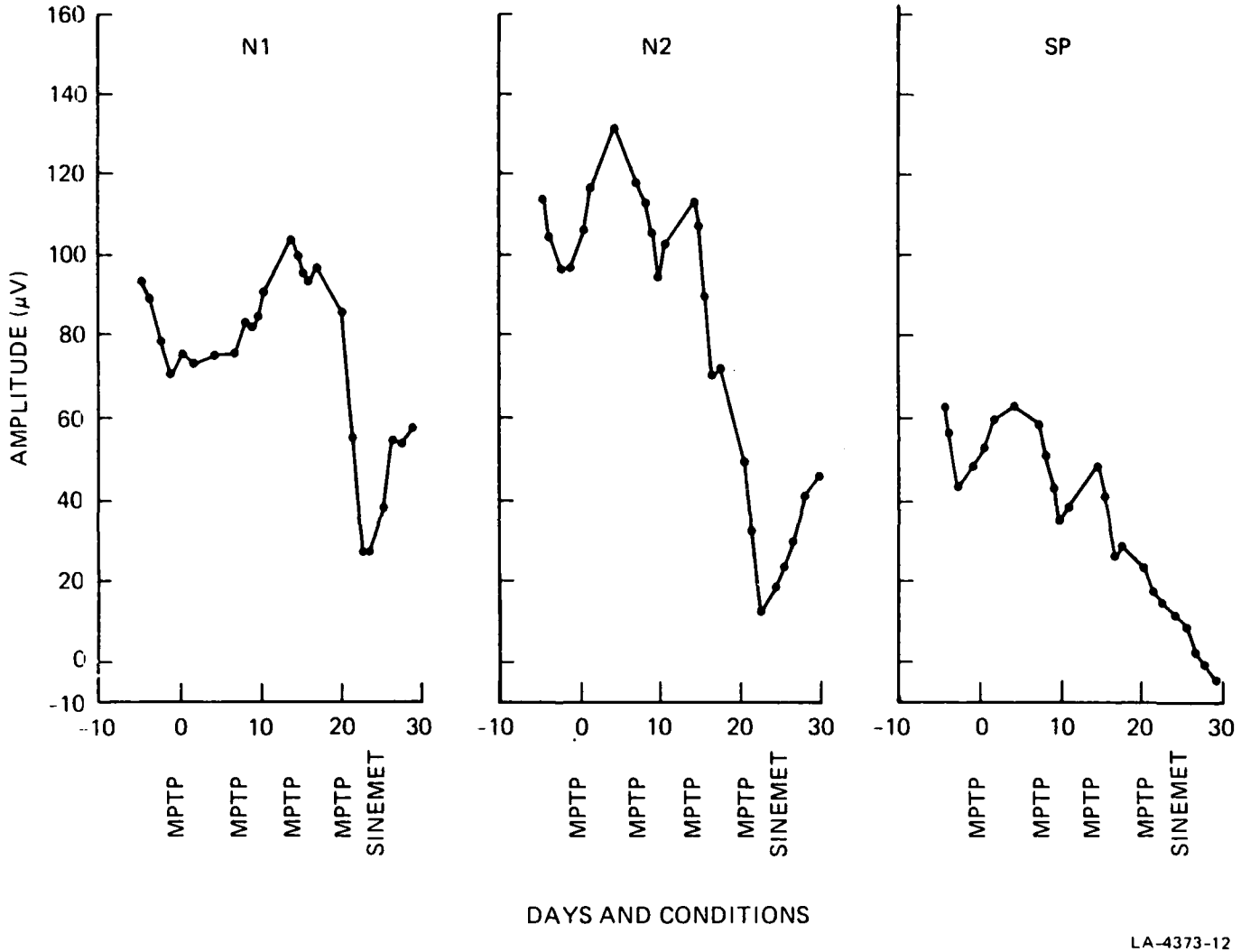

FIGURE 28 Changes in several evoked potential components in GR's substantia nigra associated with MPTP injections

Reaction time in monkey SM peaked at day 25 (Figure 16). All measured components of the SUN potential exhibited peak decreases in amplitude at about that same time (Figure 29). 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 12 and 19).

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

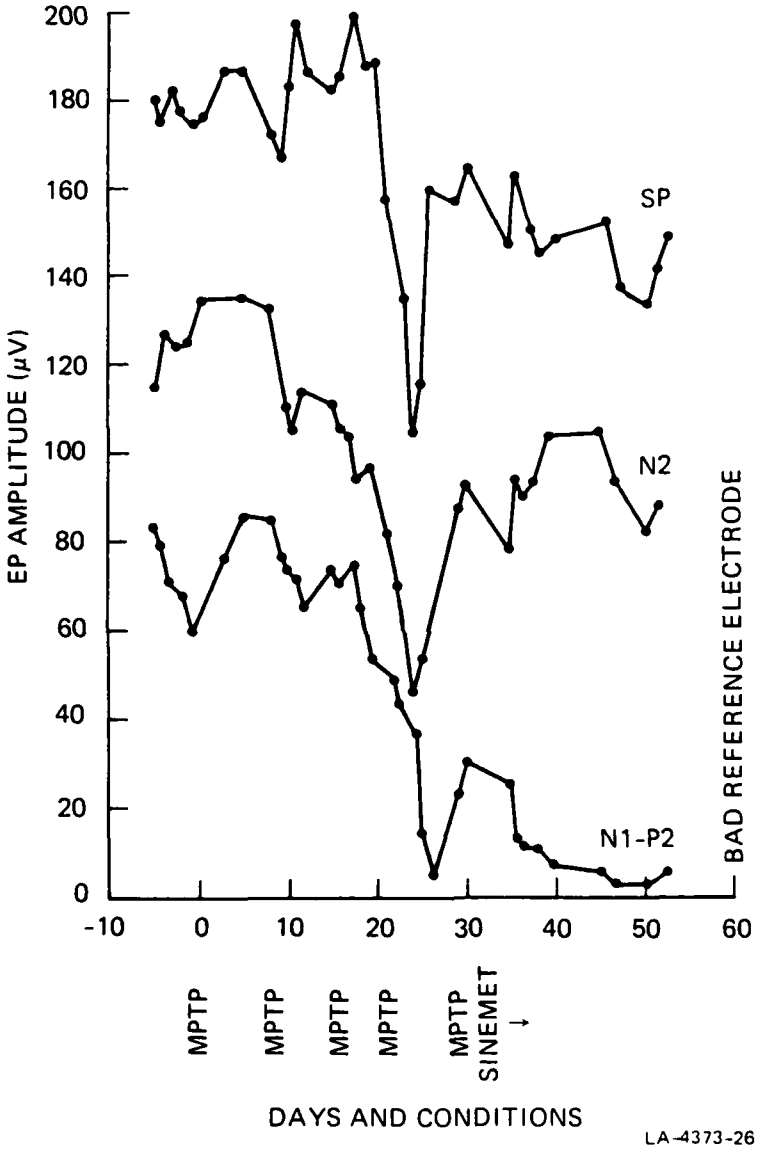

FIGURE 29 Changes in several evoked potential components of SM's substantia nigra associated with MPTP injections

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 nigra-striatal 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 nigra-striatal system.

Other Activities

Other activities that were undertaken this year and that will be discussed in the Final Report include (1) the recording of event-related potentials from ten male rhesus monkeys and transfer of those data to the EEG Systems Laboratory in San Francisco for analysis of interrelationships among recording sites, (2) study of transient and steady-state evoked potentials in the cynomolgus monkeys exposed to MPTP, and (3) evaluation of event-related potentials in female stump-tailed macaques, including tests of the effects of changing stimulus probability in two monkeys.

PLANS FOR THE COMING YEAR

During the new contract period we will continue the study of CNVs in two stump-tailed macaque monkeys, examining the effect of varying the proportions of neutral and warning trials. Histological analyses of the brains of MPTP-treated monkeys will be completed. Additional evaluation of MRI will be carried out in one female rhesus monkey. Electrodes will be implanted in three female rhesus. Electrodes will be implanted in accordance with coordinates derived from MRI, and the issue of localization of potential sources will be addressed by recording from several closely spaced electrodes, transcortically, and with respect to reference electrodes placed in the mastoid bones. Analyses of data from male rhesus monkeys, using the facilities and procedures of the EEG Systems Laboratory in San Francisco will continue.

PUBLICATIONS AND PRESENTATIONS

Three manuscripts are planned:

C. S. Rebert, W. J. Donovan, M. B. Hennessy, J. J. Diehl, and M. J. Matteucci. Cerebral physiology of preparatory set (Exp. Brain Res.).

C. S. Rebert, J. J. Diehl, and M. J. Matteucci. Critical role of nigra-striatal dopamine in preparatory set: Effects of MPTP-induced pars compacta lesions on behavior and event-related brain potentials in macaque monkeys (Life Sciences).

A. S. Gevins, S. Bressler, M. J. Matteucci, and C. S. Rebert. Interdependency analysis of intracerebral brain potentials of macaque monkeys performing the cued reaction time task (Electroencephalogr. Clin. Neurophysiol.).

The following was presented:

C. S. Rebert, J. J. Diehl, and M. J. Matteucci. Critical role of nigra-striatal dopamine in preparatory set. Presented at the Eighth Evoked Potential International Congress, Palo Alto, California, July 1986.

LIST OF PROFESSIONAL PERSONNEL

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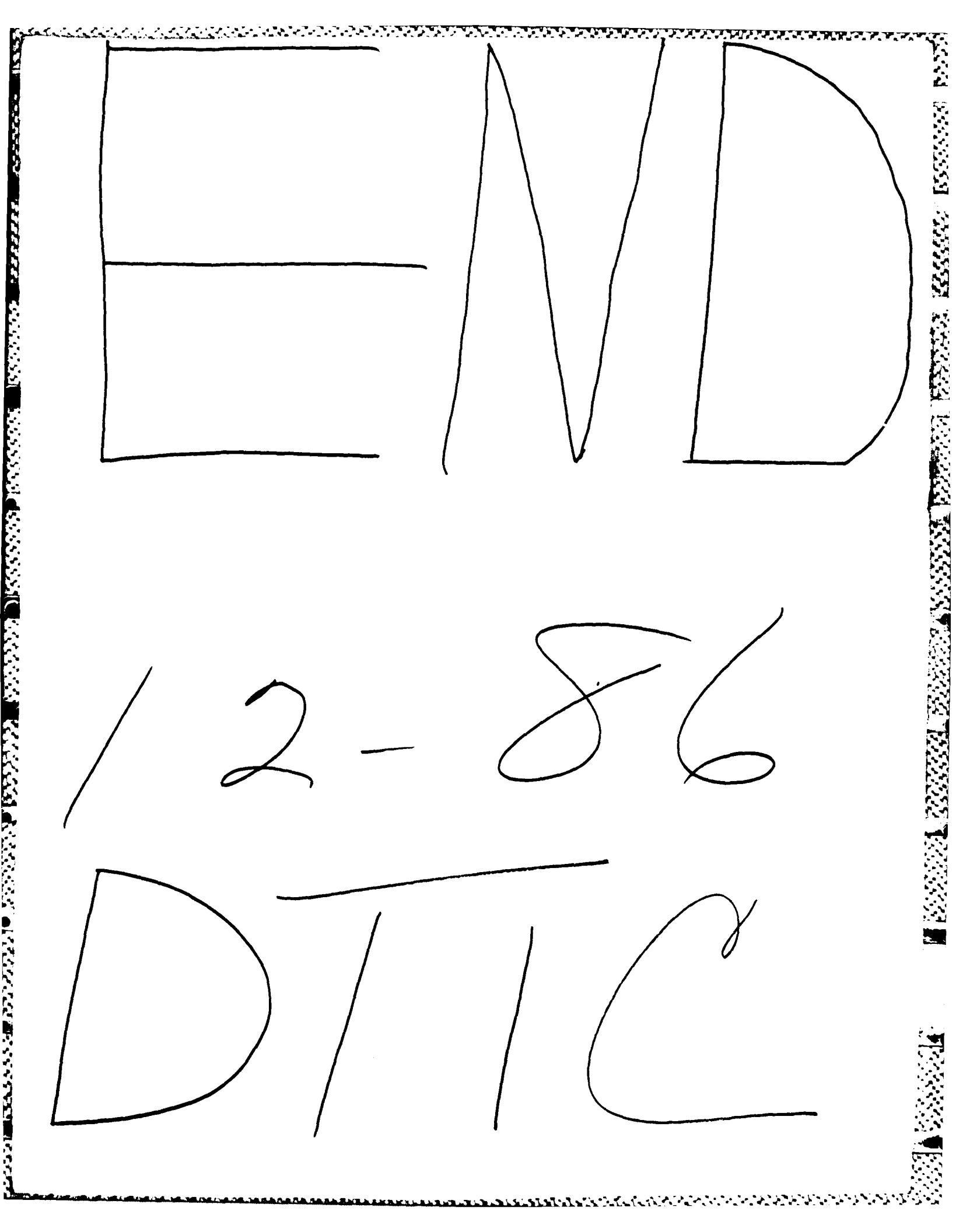
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