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ON SKILLED MOTOR FUNCTIONS IN CATS.

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INFLUENCE OF n. VENTRALIS LATERALIS ON SKILLED MOTOR FUNCTIONS IN CATS

by

FREDERICK M. KRUGER

A dissertation submitted to the
Graduate Faculty in Psychology in partial
fulfillment of the requirements for the
degree of Doctor of Philosophy,
The City University of New York.

1969

To my beloved wife, Barbara,
who, with her constant aid
in every phase of these
investigations, has taught
me the true meaning of
love and devotion.

This manuscript has been read and accepted for the Graduate Faculty in Psychology in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

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TABLE OF CONTENTS

CHAPTER I. LITERATURE REVIEW

CHAPTER II. THE PRESENT STUDY

Results of Experiments #2 and #3

Experiment #4--Results

LIST OF TABLES

LIST OF FIGURES

Acute and chronic animal preparations were used in this multiphasic study. In phase I, conditioning shocks to n. Ventralis Lateralis (VL) were found to produce decreases in latency and increases in amplitude of the contralateral forelimb flexion elicited by test shocks to the motor cortex (MC). In phase II, other cats were trained either to press buttons in serial order, or to run a narrow elevated ramp, or both, for food reinforcement (Friskies). Unilateral VL lesions were then made in these animals at the electrode locus yielding maximum augmentation of the shock-elicited response in MC. Postoperatively, these cats showed marked deficits in the forelimb contralateral to the VL lesion on both performance tests. This behavioral deficit was accompanied by a persistent absence of contact placing in the same limb. In these same animals, terminal acute experiments showed that longer latency, smaller amplitude forelimb flexions elicited by MC stimulation on the side of the VL lesion were observed when compared to the effects of contralateral (control) stimulation. In additional cats, control lesions in n. Medialis Dorsalis (MD) did not produce the same behavioral or electrophysiological effects. These results indicate that the integrity of the VL complex is essential for normal coordinated movement and suggest that it operates via afferent-efferent connections to the motor cortex and periphery.

In the neurobehavioral literature of recent years, considerable research energy has been devoted to the problem of describing the mode of operation of some major thalamic nuclei in relation to skilled movement. The research reported in this dissertation was undertaken in an attempt to clarify the possible role of one thalamic nucleus, Ventralis Lateralis, on coordinated motor activity. The details of the research will be presented after a preliminary discussion of the relevant neurophysiological, clinico-pathological, and behavioral literature.

Physiological and Anatomical Background

Since Sherrington's original description of decerebrate rigidity following midbrain transection, the classical formulation of the neural processes mediating motor movement has been expressed in terms of the interaction between two functional systems (1947). One system, the pyramidal, consists of long descending fibers originating mainly in the primary motor area of the cortex and terminating upon the ventral horn cells in the spinal cord. The other system, the extrapyramidal, arises from more diffuse origins (cerebellum, midbrain tegmentum, basal ganglia, etc.) and also descends to finally terminate upon the spinal motoneuron (the final common pathway). In classical theory, the pyramidal system controls motor power, while the extrapyramidal system "modulates" it to make smooth coordinated movements possible (Jung & Hassler, 1960). Examination of animals or patients with lesions of the pyramidal system reveals a noticeable deficit in motor power (paresis) (Berman, Kruger, & Fulton, 1954; Travis, 1955; Hamuy, 1956; Kruger & Porter, 1958; and Woolsey, 1958), while cases of extrapyramidal lesions show deficits primarily of coordinated movements, i.e., Parkinsonism (Jung & Hassler, 1960; Patton & Amassian, 1960).

With the advent of sophisticated stimulation and recording techniques, considerable interest has centered around the functional relationships between the "specific" somatosensory and motor (pyramidal) systems and the more "diffuse" systems arising in the brainstem or cerebellum. Thus, for example, Magoun and Rhines (1948) showed that stimulation of the mesencephalic reticular formation could result in either inhibition or facilitation of the spinal reflex depending upon the locus of the stimulating electrodes. Along these lines, the observations of Moruzzi (1950) indicated that the effect of cerebellar stimulation upon the motor response could be either facilitory or inhibitory in nature (see also, Li & Tew, 1966). Similarly, studies of the effects of stimuli applied to various parts of the basal ganglia have demonstrated both facilitation and inhibition of ongoing motor activity depending upon stimulus parameters and locus (Morison, et.al., 1941; Mettler & Zimmerman, 1943; Forman & Ward, 1957; Glees, 1961). Stimulus parameters are important in the specific system as well. Gellhorn (1953) showed that cortically elicited movements (i.e., from the stimulation of the motor cortex) were dependent upon not only the stimulus frequency, amplitude, and pulse width, but also upon the proprioceptive "feedback" from the moving body parts. He suggested, therefore, that interactions must occur at both peripheral and central levels between the pyramidal and more diffuse systems.

In more recent years, considerable interest has centered upon the functional significance of the nucleus Ventralis Lateralis (VL according to the terminology of Walker--p.184, 1938). This nucleus derives its most important afferent supply from the rostral end of the red nucleus (RN) and more directly from the cerebellum by crossed fibers in the brachium conjunctivum (Carpenter & Stevens, 1957; Blum, et.al., 1968) and has direct projections to the motor cortex (Walker, 1938). Anatomically, therefore, it could function as a convergent focus for interactions between the specific (pyramidal) motor system, the more diffuse elements of the extrapyramidal system, and the classical sensory systems[1].

It is significant that electrophysiological studies have shown that stimulation of medial-thalamic (non-specific) nuclei yielded frequency specific inhibitory effects in VL. Cohen, et.al. (1962), for example, showed that low frequency medial-thalamic stimulation produced early facilitation and long latency inhibition of brachium

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[1] Buser (1966) has recorded sensory responses at the level of VL which are compatable in their latencies and shape with the hypothesis that they represent the activity of an ascending sensory pathway to the motor cortex (see discussion about ascending fibers later).

conjunctivum evoked activity in VL. Similar stimuli applied to the brachium conjunctivum elicited short latency (1 msec) activity in VL and specific responses in motor cortex. These responses were associated with 3-4 msec. latency relayed discharges in the pyramidal tract. Further, it has been demonstrated that a single stimulus applied to the head of the caudate nucleus or to the midline thalamus elicits a response in the region of VL and Ventralis Anterior (VA)[2] (Buchwald, et.al., 1961; Heuser, et.al., 1961; Purpura, 1962; Buser, 1966). Collectively, these observations support the anatomical evidence that connections exist between both structures and the ventral thalamus, while a functional blockage of VL-VA (by coagulation) suppresses recruiting responses[3] on the motor cortex (Buser, 1966). Other studies have shown that stimulation of VL inhibits the activity of cortical interneurons (Li, 1956 & 1958; Patton & Amassian, 1960; Amassian, 1966), which in turn prevent re-excitation of pyramidal neurons (Branch & Martin, 1958; Li, 1958) by

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[2] Anatomical data regarding VA indicate that it also projects to the frontal cortex, although the extent of these projections is not so clearly delimited as for VL (Hassler, 1949; Scheibel & Scheibel, 1966). Electrophysiological findings have emphasized the role of VA as a site of passage or as a relay station for impulses from the non-specific thalamus that project to the anterior cortex (Jasper, 1960).

[3] Stimulation of non-specific thalamic nuclei at pulse rates of 5-10/sec. can trigger wave discharges which are recorded bilaterally over widespread cortical regions. These waves are surface negative. With successive discharges, the waves increase in size due to the recruitment of more neurons into the group giving rise to the discharge. These incrementing waves are referred to as <u>recruiting responses</u>.

polarizing the pyramidal cell membrane so as to affect subsequent activity (Purpura & Shofer, 1964). Clearly, then, anatomical (Waller, 1940) and electrophysiological (Brookhart, et.al., 1958; Brookhart & Zanchetti, 1956; Branch & Martin, 1958; Purpura, Shofer & Musgrave, 1964; Hanberry & Jasper, 1963; Schlag & Balvin, 1964) studies confirm that VL projects to the motor cortex. For example, a low frequency (5-10/sec.) gated stimulus burst (i.e., more than three impulses) to VL elicits an augmenting response[4] in the pericruciate area in cats (Dempsey & Morison, 1942a,b,c; Morison, et.al., 1941; Morison & Dempsey, 1942; Brookhart & Zanchetti, 1956; Jasper, 1960 & 1961; Spencer & Brookhart, 1961; Spuler, et.al., 1962; Purpura & Shofer, 1964; Purpura, et.al., 1964) and in the lateral motor area in humans (Houspian & Purpura, 1963 and Yoshida, et.al., 1964).[5] The stimulation of VL also alters peripheral activity, such as the rate of muscle spindle discharge (Granit & Kaada, 1952; Eldred, et.al., 1953; Stern & Ward, 1960) and the frequency of discharge of the gamma motoneurons (Stern & Ward, 1960; Buchwald & Eldred, 1961; Shimazu, et.al., 1962; Yanagisawa, et.al., 1963; Langfitt, et.al., 1963). For example, Yanagisawa, et.al., (1963)

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[4] A negative-positive potential complex with initial short latency positivity and of localized unilateral distribution.

[5] In addition, VL and part of VA serve as an intrinsic relay nucleus for the cerebello-cortical pathway originating from cerebellar nuclei (Combs, 1959; Dennery & Combs, 1961; Scheibel & Scheibel, 1966; Purpura, et.al., 1966).

showed non-reciprocal facilitation of the gamma motor system by the repetitive stimulation of VL in cats under light pentobarbital anesthesia.[6] They suggest that the diffuse suppression of muscle spindle activity produced by low frequency stimulation of VL might be similar to the suppression, reported by Hongo, et.al. (1963), resulting from stimulation of various thalamic nuclei and basal ganglia. In agreement, Ohye, et.al. (1964), in human surgery, also observed non-reciprocal increases in muscle tone in the contralateral forelimb muscles when VL was stimulated by high frequencies.

Interest has focused upon pyramidal tract (PT) neurons because they provide an opportunity to sample an important outflow from the cerebral cortex to lower motor centers. Early bulbar PT responses to thalamic stimulation can occur without the artificial enhancement of a "convulsant" anesthetic such as Chloralose. Specifically, Brookhart & Zanchetti (1956), Purpura (1958), Cohen, et.al. (1962), and Schlag & Balvin (1964) demonstrated bulbar PT responses with overall latencies of 2-4 msec. following stimulation of several thalamic nuclei including VL and VA. Stimulation of the thalamus yields short latency responses which may not be

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[6] The gamma efferent system has gained importance recently in neurophysiological investigations of muscle innervation via segmental and intrasegmental reflexes and supraspinal mechanisms (Gellhorn, 1953). Gamma motor fibers are small ventral root fibers with an average diameter of 5μ and conduction velocities of 20-44 meters/second. They innervate the muscular portion of the muscle spindle. Changes in the gamma efferent innervation thus affect spindle discharge.

due to synaptic activation, but rather, the direct activation of collaterals of PT axons in the ventrolateral nucleus (Clare, et.al., 1964). The low threshold and short latency of PT responses resulting from stimulation of the anterior part of VL and the lateral part of VA suggest that the afferent projection originates in these nuclei. These findings, however, do not exclude the possibility that responses to stimulation of the lateral part of VA are mediated by axons of passage from VL.

In so far as sensory inputs to the ventrolateral complex of the thalamus are concerned, much discussion has dealt with <u>direct</u> sensory and ascending pyramidal inputs. Brodal and Walberg (1952), for example, traced degeneration from lesions in the cord and nuclei of the dorsal funiculi in adult cats and found a significant number of fibers projecting to the sensory cortex. They suggest that the new pathways demonstrated might be of importance for the coordination of differentiated movement and further, might be concerned in certain reflexes having their center in the cerebral cortex, such as placing and hopping reactions in animals and the plantar reflex in man (see also: Woolsey & Bard, 1936). Brodal and Kaada (1953) used evoked potential techniques to confirm the existence of the anatomically demonstrated ascending fibers in the pyramid. They observed that there was a greater pyramidal response to foreleg stimulation and that the response was greater from the more distal parts of the limbs. Patton and Amassian (1955) disagreed, while Landau (1956) felt that the problem was a lack of precise anatomical control. Cohen (1955), however, again confirmed the existence of ascending pathways to the thalamus. In further support for the presence of somatic afferents in the thalamus, Kruger and Albe-Fessard (1960) found non-tactile responses of longer latency with reasonable consistency in the VL complex and red nucleus as well as in other thalamic and subthalamic nuclei. Subsequently, Batsel (1963) speculated that the ascending pyramidal fibers sent collaterals into some part of the "cephalic activating system" at levels rostral to the pons and Clare, et.al. (1964) presented substantial electrophysiological evidence for the pyramidal tract collateral pathway. They stimulated VL in cats, recorded evoked potentials in sensorimotor cortex and the pyramidal tract, and evaluated the results in terms of isolation of the stimuli and the time courses of the responses.

Finally, it has been shown that the neocerebello-cortical pathway can act upon the excitability of the pyramidal system (Casey & Towe, 1961; Buser, 1966; Schalg, 1966; Marco, et.al., 1967) so as to modify the outflow to the periphery.

In summary, present electrophysiological evidence suggests that the ventrolateral nucleus of the thalamus may be a primary area for the sensory activation of the cortical neurons (Buser, 1966), or may influence the sensorimotor integration at the spinal level, or may have both actions

(Granit, 1955; Jung & Hassler, 1960; Stern & Ward, 1960; Hofmann, 1962b; Sugczynski, et.al., 1963; Yanagisawa, et.al., 1963; Ohye, et.al., 1964; Denny-Brown, 1965; Buser, 1966; Purpura, et.al., 1966). These data would further suggest that destruction of this nucleus would produce disorders in mobility. On this issue some clinical information is available.

Clinico-pathological Background of Problem

Stereotaxic destruction of VL is presently the most commonly used surgical procedure for relieving rigidity, hypokinesia, and tremor in patients with Parkinsonism (Cooper, 1956; Jung & Hassler, 1960; Spiegel & Wycis, 1958; Stern & Ward, 1960; Dierssen, et.al., 1962). During such procedures, the localization of electrodes within VL has been carried out using radiographic controls alone or, infrequently, in conjunction with electrophysiological techniques. Specifically, high frequency stimulation of VL has been found to produce a change in muscle tone and/or tremor in the patient[7] (Adey, et.al., 1959; Ohye, et.al., 1964), and low frequency stimulation has elicited an augmenting response from the motor cortex which resembles that found in the experimental animal (Brookhart & Zanchetti, 1956; Brookhart, et.al., 1958; Yoshida, 1964). For this reason, it has been suggested that Parkinsonian symptoms might be the result of an abnormality in the supranuclear control of the gamma motoneurons (Hofmann, 1962a,b; Langfitt, et.al., 1963; Yanagisawa, et.al., 1963; Yoshida, et.al., 1964). Along these lines, Jung and Hassler (1960) have suggested that Parkinsonian rigidity is due, at least to some extent, to insufficient gamma motoneuron excitation.

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[7] An unpublished study by the author and A.J. Berman has confirmed these observations in humans. Stimulation of VL with 100/sec. pulses was found to inhibit tremor of the contralateral forelimb, while 10/sec. stimulation was found to increase the amplitude of the tremor.

In agreement, Stern and Ward (1960) suggested that lesions in VL might relieve rigidity by eliminating an inhibitory input to the gamma motoneurons. Thus, the electrophysiological data indicate that VL, either directly or indirectly, through cerebral or peripheral pathways, or both, can have significant influences on the integrative activities between the somatosensory and motor cortical regions and the muscles involved in movement (Andersen & Eccles, 1962; Brookhart, et.al., 1958; Jung & Hassler, 1960; Ohye, et.al., 1964; Schlag & Balvin, 1964; Stern & Ward, 1960; Yanagisawa, et.al., 1963). There is available, in brief, considerable information about the various components of the complex systems that may be involved in Parkinsonism, but no data can be found on the role of VL in normal complex motor behavior.

VL integrity is necessary for normal coordinated motor movement. Observations of pathological cases suggest that VL somehow modifies, controls, or changes motor activity. Such observations, however, of necessity, have been limited to patients with preexisting disorders of the extrapyramidal system. A therapeutic lesion in VL is beneficial to the parkinsonian patient because it reduces or eliminates the disabling symptoms. The question is raised, however, as to what would be the effects of VL lesions in organisms in which the rest of the brain was normal---i.e., the effects of experimentally induced lesions.

In view of the wealth of electrophysiological, anatomical, and clinico-pathological data, it is indeed surprising that, so far, no such experimental studies have been conducted. It would seem important, therefore, to investigate this problem by examining the final output (the motor behavior), since it would be affected by all preceding activity and interaction between VL, cortex, spinal cord, etc., and would have significance for all of the studies cited above.

Effects of Experimentally Induced Lesions in VL

As noted above, studies of the behavioral functions mediated by VL, for the most part, have been primarily electrophysiological or clinical. If clinical, the observations have been made on patients during or subsequent to surgical ablation of VL in the attempt to alleviate some of the motor symptoms of Parkinson's Disease (Dierssen, et.al., 1962). Cohen, et.al. (1962), have suggested the possible existence of excitatory and inhibitory interactions involving the medial thalamic (non-specific) and VL nuclei. These electrophysiological interactions operate upon relay elements in the cerebello-cortical projection so as to affect cortico-spinal neurons. In partial support, the behavioral study of Tarnecki (1962) on instrumentally conditioned responses demonstrated that cats with bilateral lesions within the VL complex showed performance deficits similar to those seen in animals with motor cortex lesions (Berman, et.al., 1954; Travis, 1955; Kruger & Porter, 1958; Forward, et.al., 1962). Hofmann's (1962a,b) study of patients with parkinsonian rigidity provides some evidence which suggests that the rigidity may be associated with <u>defective bias</u> on muscle length sensors due to changes in the nature of VL rhythms, etc. Buser (1966) believes that the level of the VL complex may be of particular importance in its exerting a "gating" effect on the ascending pathway to the motor cortex; i.e., that, at this level, both sensory and cerebellar controls of the pyramidal system may be influenced by a number of mechanisms.

With the above information in mind, it is clear that a trained response using instrumental techniques would seem to be of great value as a behavioral indicator for use in assessing the functional effects of lateral thalamic lesions.

There have been other studies, outside of VL and motor cortex, in which motor activity has been evaluated. It might be worthwhile to briefly review several of them to gain some idea of techniques used. For example, Schreiner and Kling (1953) studied manipulatory behavior in cats after lesions were made in the rhinencephalon and Beach, et.al. (1955) even found that destruction of the frontal lobes reduced the frequency of intromission by male cats in mating tests. Yet, there is only one known study[8] (Tarnecki, 1962) of the behavioral effects of lesions in VL, and this study only required a simple hind-limb scratch reflex response by the animal. Unfortunately, the task observed was neither comparable to human motor patterns, nor of sufficient complexity to reveal possible long term effects. No evaluation was made of the animals' ability to use its forelimbs in a complex coordinated manner. The author did observe, however, that the effect of the lesion was a difficulty with the performance of the movement itself, and not with postural adjustments. It is evident, therefore, that if one

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[8] After an exhaustive search of the literature, this was the only study found which attempted to relate chronic VL lesions to observed behavioral deficits.

is to take advantage of the enormous body of published anatomical and electrophysiological research data studying various aspects of the ventrolateral nucleus, in cats, it is necessary to devise much more complex behavior tasks which will be sensitive to the smallest of possible deficits resulting from surgical lesions in the VL complex.

Introduction to the Present Study

The present study is concerned primarily with the post-operative retention of the ability to perform learned complex coordinated motor tasks following chronic lesions in VL and the evaluation of any observed decrements in the measured performance. It also evaluates, electrophysiologically, interactions between VL and motor cortex elicited movements.

To demonstrate that lesions elsewhere in the thalamus would not result in the same effects as those in VL, control lesions were made in n. Medialis Dorsalis (MD). This nucleus was selected since its projections to the frontal area of the cortex have already been demonstrated both electrophysiologically and anatomically (Hanberry & Jasper, 1963). Unlike VL, however, stimuli applied to MD elicit recruiting responses which can be recorded over most of the anterior cortex. In addition, some possible effects upon motor ability have been stated by Schreiner, et.al., (1953).

It would appear necessary, therefore, to compare these two thalamic sites in order to specify that any effects obtained were specific to VL and not to some effects related to anterior thalamic activity in general.

With these thoughts in mind, the present study was designed in terms of four specific experiments as described below.

Experiment #1

Method

Subjects.—Twenty-four male adult cats (1.9-3.3 kgs.) of unknown age were used in various aspects of this acute study.

Apparatus.—Almost all cats were initially anesthetized with intraperitoneal injections of Nembutal[9] (25mg./kg.) and received intermittent I.P. supplementations (0.5 to 2.0 mg.) as required to maintain a relatively constant anesthesia level as indicated by the EEG activity recorded from the motor cortex (MC) (Goldring & O'Leary, 1951; King, 1956; and Faulconer & Bickford, 1960). The EEG was sampled before and after each excitability series was run (Fig. 1). The animals were placed in a stereotaxic instrument (Kopf), contact points and skin margins were infiltrated with Propiticaine[10] and normal body temperature was maintained with a heat blanket. A left unilateral exposure of the cortex was made extending from the frontal sinus (entire cruciate gyrus exposed) posterior about 3 cm. and lateral from the midline about 2 cm. (Fig. 2). After the bipolar depth and surface electrodes were in place, a plastic barrier was constructed to keep the cortex moist throughout the experiment. A linear accelerometer[11] was attached to

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[9] Abbott--Sodium pentobarbital.

[10] Astra--Xylocaine derivative.

[11] Devised by the author--See Appendix D.

Fig. 1. Sample of successive EEG recordings from MC during electrophysiological interaction studies. (Bipolar ball tipped electrodes--Scope: Vertical-200 uV/cm.; Horizontal-200 msec./cm..

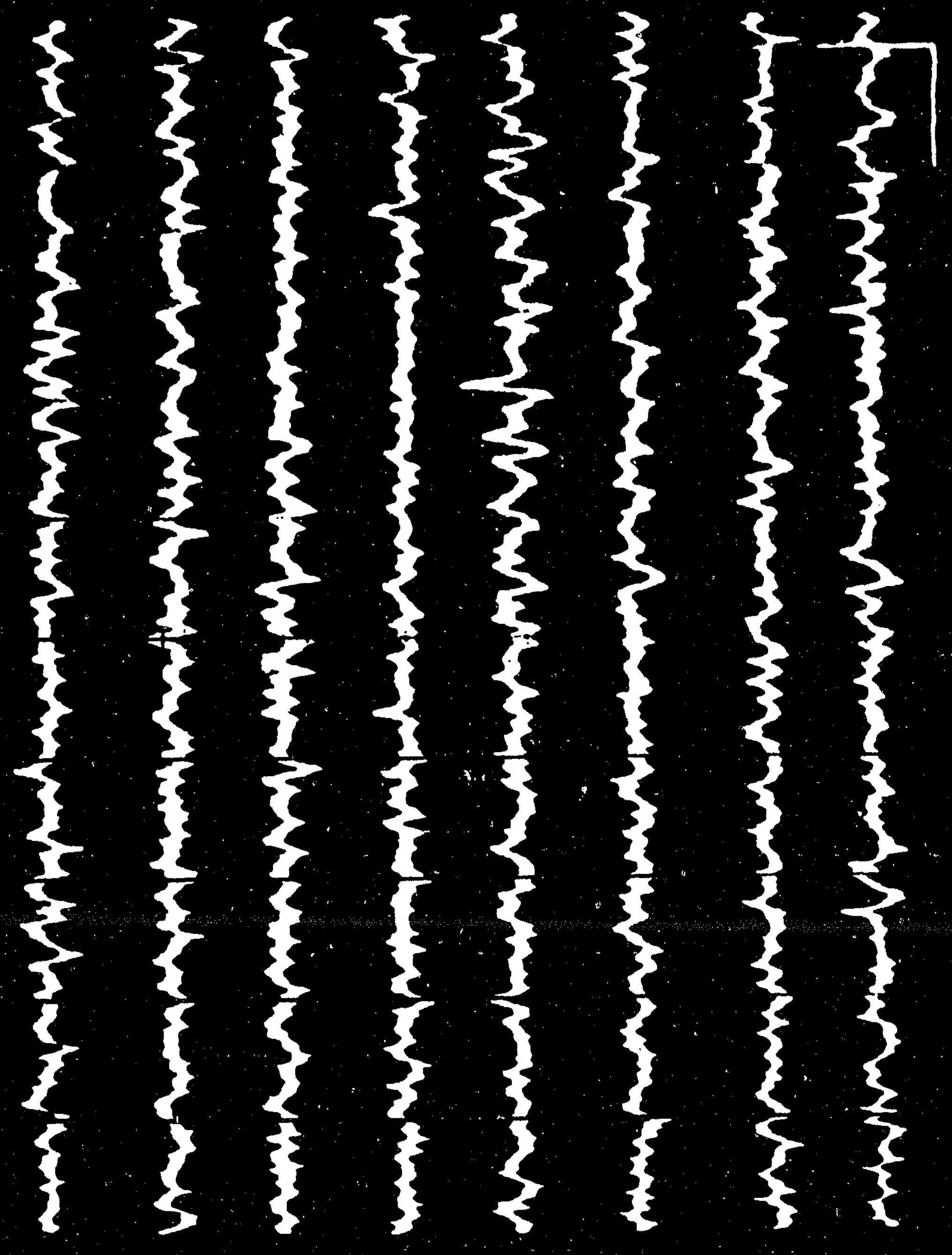
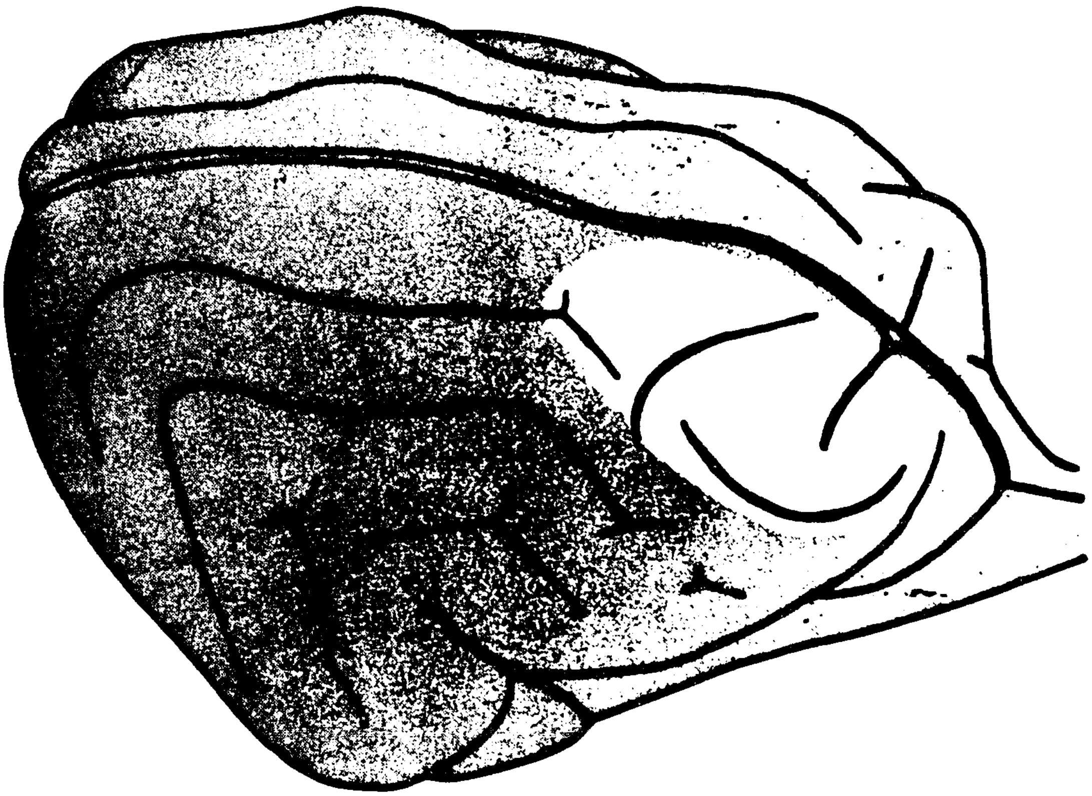


Fig. 2. Illustration of surgical exposure of cortex for all unilateral operative procedures. (Right hemisphere exposure shown.).



the right foreleg such that flexion or extension of the limb yields a voltage output porportional to the acceleration of the limb.

In all the experiments, bipolar stimulation was applied to the thalamus (VL) and to the surface of the pericruciate gyrus (MC). The bipolar depth electrode was made from two 5 mil. tungsten wires, insulated with Formvar except for the flush cut tips, which were set 0.25 to 0.50 mm. apart. The interelectrode impedence in normal saline was between 20 and 70 thousand ohms. The bipolar cortical electrode was made of two stainless steel wires with 0.5 mm. balled tips placed 2 to 3 mm. apart on the pial surface. The bipolar surface electrode was first positioned over MC for maximum foreleg flexion response to stimulation. The bipolar depth electrode was then directed at VL, by stereotaxic coordinates (F=11, L=4, H=+2). It was moved, if necessary, until an augmenting response of the proper characteristics (Fig. 3) could be recorded at the cortical electrodes.[12] The stimuli applied to the depth electrode during the placement, were monophasic square waves at 10 cps., 200 msec. train (3 impulses), with an amplitude of 2 to 12 volts,[13] a pulse width of 0.5 msec., and a recycling rate

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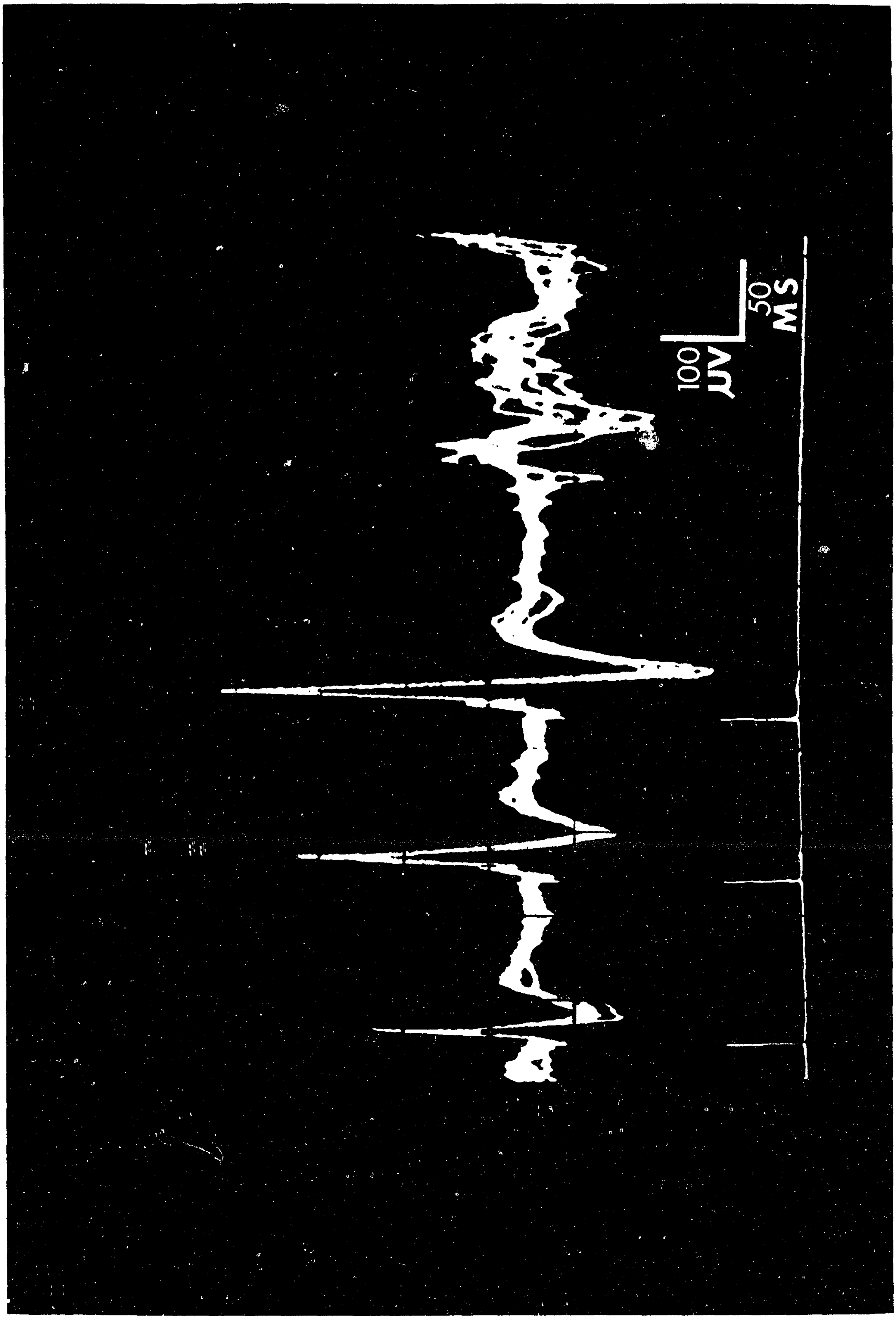
[12] Augmenting response--negative-positive potential comples with initial short latency positivity and of sharply localized distribution in the pericruciate area which increments in amplitude over the first several responses.

[13] The stimulus amplitude required to elicit an adequate response varied with the particular animal and with the exact electrode placement.

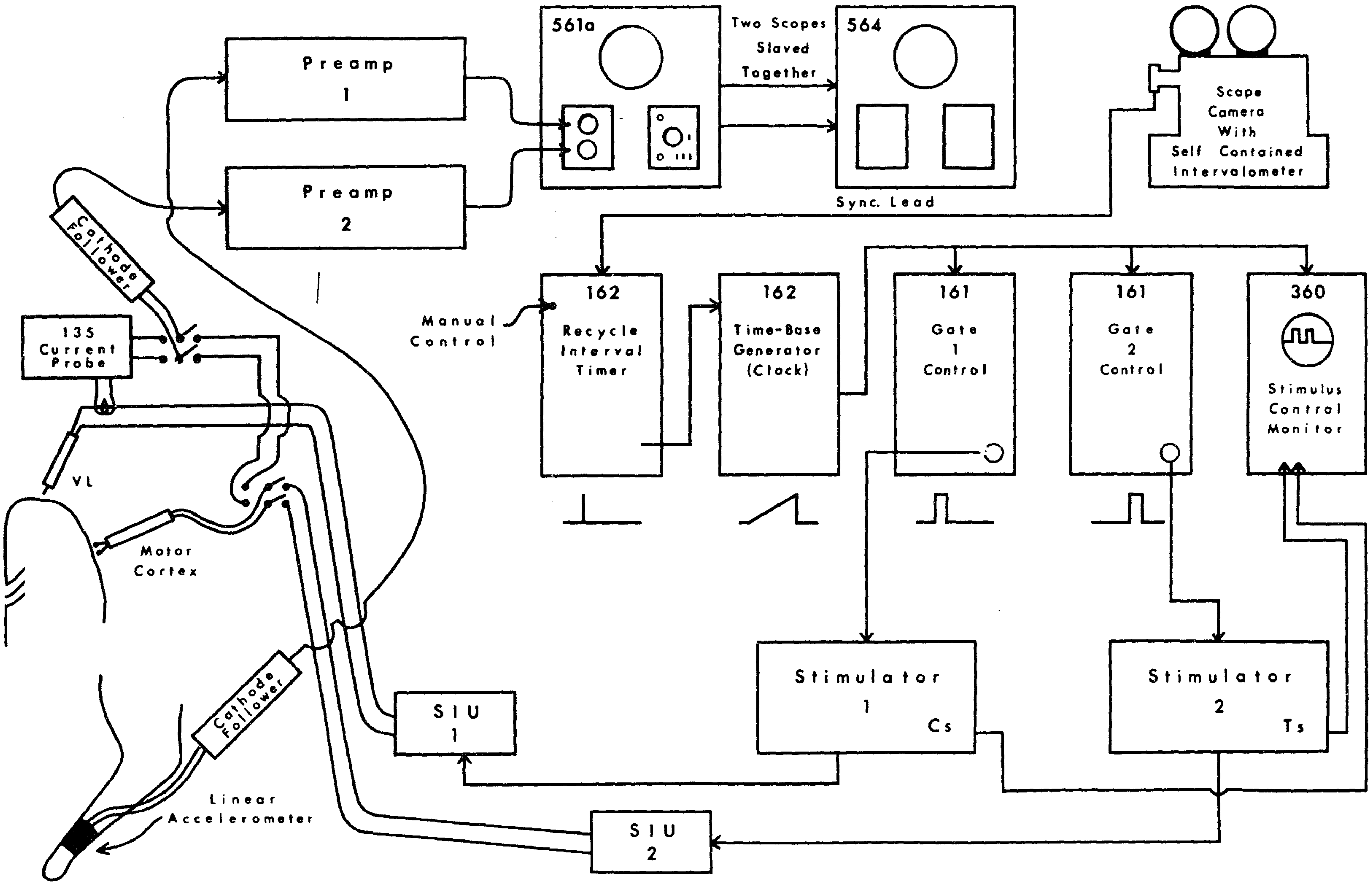
Fig. 3. Illustration of an augmenting response recorded at MC with VL stimulation. (3 pulses at 10 per sec. rate, 5 volts, 0.5 msec. pulse width--10 superimposed sweeps; 100 uV/cm., 50 msec./cm..).


100 µV
50 MS

of one in ten seconds. The surface electrode was then moved, if necessary, for the best compromise between maximum limb flexion and high amplitude augmenting responses from VL stimulation. In practice, the movement of the electrode was a few mm. at most.

Stimulus relationships and overall timing were controlled by a combination of Tektronix Waveform (Model 162) and Pulse (Model 161) generators which programmed a pair of Grass S-4 stimulators with R. F. isolation units. The delay circuit on the Tektronix pulse generator units were used to vary intervals between conditioning and test shock trains, while the pulse width controls determined the train duration (Fig. 4). With infrequent exceptions, all excitability cycle studies were determined with the thalamus and pial surface stimulated with three to five monophasic square wave pulses at a 1 kcps. rate. Pulse width was 0.25 msec. and amplitude was within the range of 2 to 10 volts. When both conditioning and test stimuli were applied, the delay interval between VL and MC stimulation was varied from 0 to 500 msec. in order to determine the excitability cycle for the effects of the VL stimulation on the motor responses elicited by cortical stimulation. After the excitability series was run at the initial depth setting, the depth electrode was lowered in 1 mm. steps, the excitability series rerun, and the process repeated until an augmenting response could no longer be elicited by VL stimulation.

Fig. 4. Assembly and interconnection of electrophysiological stimulating and recording system.


Preamp 1
Preamp 2
561a
Two Scopes Slaved Together
564
Scope Camera With Self Contained Intervalometer
Sync. Lead
Cathode Follower
135 Current Probe
VL
Motor Cortex
Cathode Follower
Linear Accelerometer
Manual Control
162 Recycle Interval Timer
162 Time-Base Generator (Clock)
161 Gate 1 Control
161 Gate 2 Control
360 Stimulus Control Monitor
Stimulator 1 Cs
Stimulator 2 Ts
SIU 1
SIU 2

The recording system consisted of Grass cathode follower and differential A. C. preamplifiers (x1000 gain), followed by Tektronix Model 561a and 564 oscilloscopes. Images were successively accumulated on the 564 storage scope and summations of five or ten trials at each delay interval were then photographed. All records were photographically enlarged (4x) for the measurement of the amplitude and time course of the recorded response. The movement response is defined by the change in electrical output (deviation from zero) of the linear accelerometer, during the interval from stimulus (MC) onset to the first two amplitude maxima as displayed on the oscilloscope.

At the completion of each experiment, the depth electrode was placed at the position (H or depth plane) of the best augmenting response and a small lesion was made by passing a D. C. current of 0.5 ma. between one pole of the depth electrode and the ear bars for 30 seconds. (The electrode was anodal.) The animal was then killed, decapitated, and the head placed in a 10% buffered formalin solution. The brains were subsequently removed, sliced in the stereotaxic coronal plane and prepared for histologic verification of the electrode tracts.[14]

Analysis of the data was made in terms of the median amplitude of deflections from the accelerometer at each

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[14] Please refer to Appendix C, for details on the blocking of the brain in the proper stereotaxic orientation and the histologic procedures.

delay interval and penetration level. That is baseline amplitude was considered as zero deflection and the maximum median deflection of the trace in the excitability study was taken as the 100% level (Figs. 5 & 6, for example). Thus, the relative deviation of a recorded movement response is evaluated in terms of percentage change from zero deflection (Table 1).

Results of Experiment #1

The results of the excitability experiments on cats show that there was a definite enhancement of the cortically elicited motor response when it was preceded in time by VL stimulation (Fig. 7 and Table 1). This enhancement of the amplitude of the response was dependent upon the delay interval between conditioning and test stimulation and, in general, seemed to be of a two component nature. There was a rapid enhancement effect between 0 and 10 msec. delay and a slower, longer lasting enhancement becoming clear at about 100 msec. delay and sometimes continuing beyond 500 msec.[15] (Fig. 6, for example). On several occassions, it was noted that stimulation of VL alone resulted in limb movement, although this was not the usual case.

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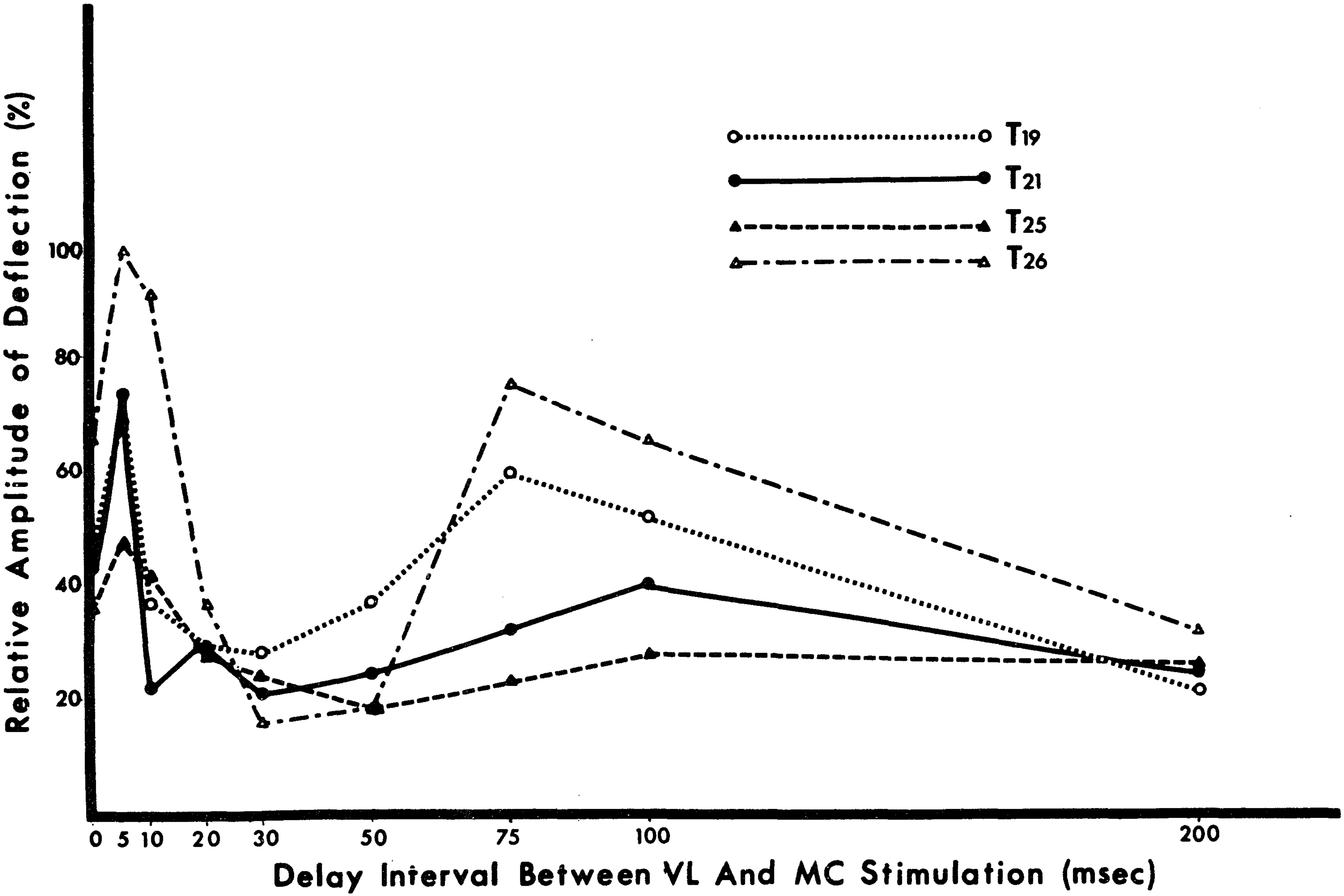
[15] The primary enhancement observed was quite stable in all cats. In a few cats, the secondary response was not observed. This may have been due to changes in anesthesia level.

Fig. 5. Graph of effect of conditioning stimuli applied to VL on cortically elicited limb movements. Delay interval in msec. between conditioning shock and test shock. Sample interaction recordings from four animals.



Relative Amplitude of Deflection (%)
100
80
60
40
20
0
5
10
20
30
50
75
100
200
Delay Interval Between VL And MC Stimulation (msec)
T19
T21
T25
T26

Fig. 6. Graph of effect of conditioning stimuli applied to VL on cortically elicited limb movements. Delay interval in msec. between conditioning shock and test shock. Average of interaction recordings shown in Fig. 5.

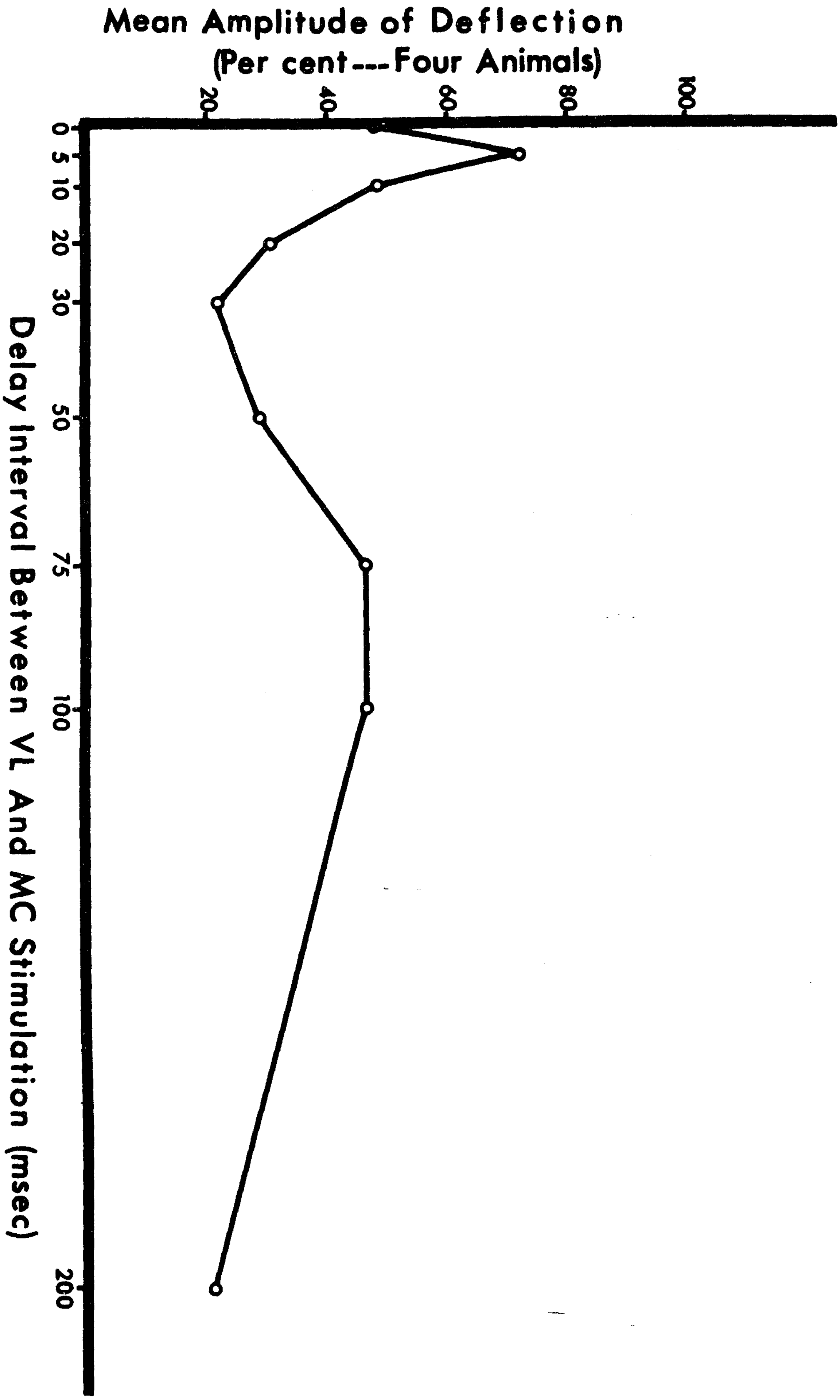
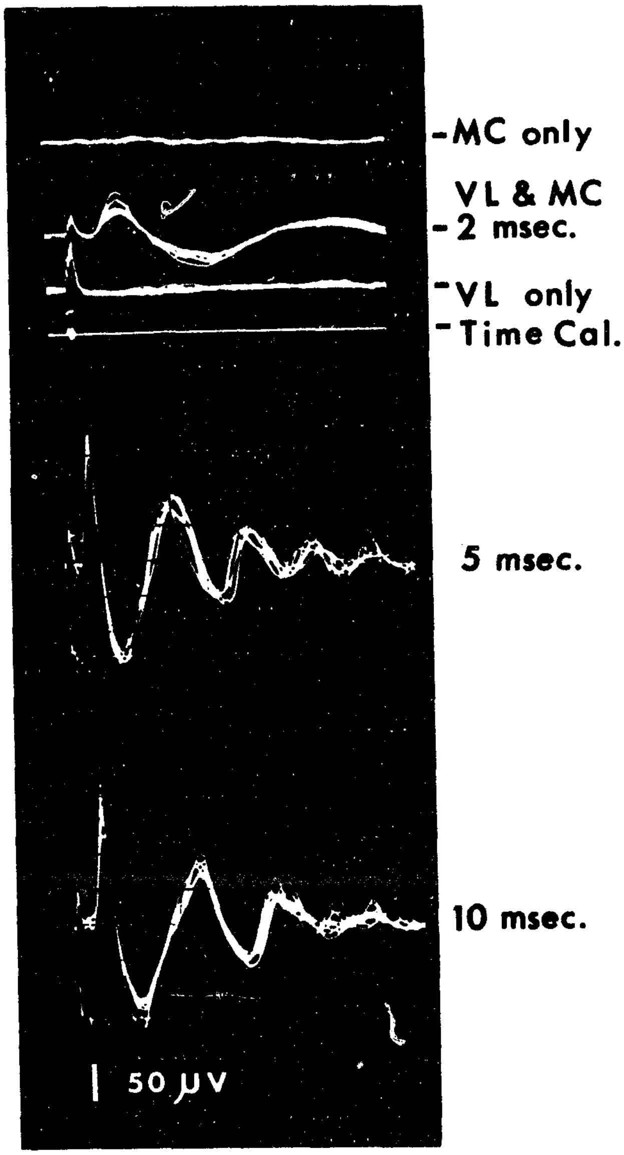

Mean Amplitude of Deflection
(Per cent---Four Animals)
20
40
60
80
100
0
5
10
20
30
50
75
100
200
Delay Interval Between VL And MC Stimulation (msec)

Fig. 7. Photographs of electrical analogs of observed **limb flexion** responses to interacting stimuli applied to VL and MC. (2, 5, 10, 20, 30, 50, 100, 200 msec.) All photographs are of 10 superimposed sweeps each.


-MC only
VL & MC
-2 msec.
-VL only
-Time Cal.
5 msec.
10 msec.
50 μV

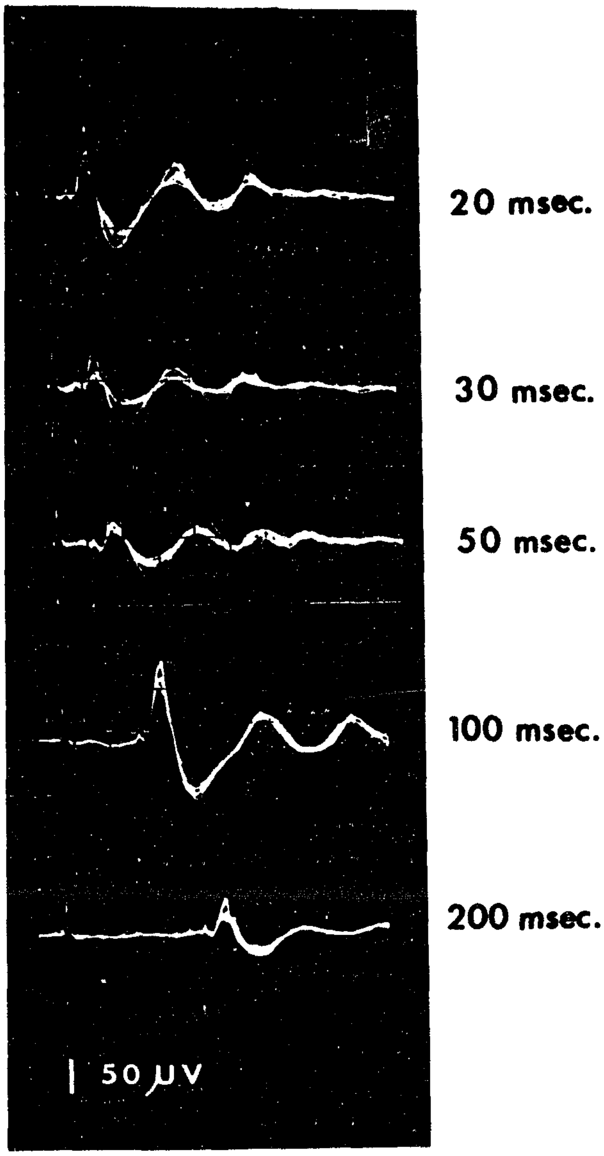

20 msec.
30 msec.
50 msec.
100 msec.
200 msec.
50 μV

Table 1. Summary of electrophysiological interaction data on four representative cats. Effects of conditioning stimuli applied to VL on cortically elicited limb movements. Delay interval in msec. between conditioning shock and test shock.

Delay Interval (msec.)	% Maximum Amplitude				
	Cat				Mean Values
	T19	T21	T25	T26	
0	48	44	37	65	48
5	69	74	48	100	73
10	37	23	42	92	49
20	29	29	28	37	31
30	28	21	24	16	22
50	37	44	18	18	29
75	60	32	23	76	47
100	52	40	28	66	47
200	21	24	26	31	26

Introduction to Experiments #2 and #3

Since the foregoing experiment has demonstrated the functional connection between VL and MC elicited responses, subsequent experiments (#2 & #3) were designed to evaluate its possible behavioral significance. To this end, cats were trained to make rapid sequential movements and were subjected to neurological examinations (see below) several times a week post-operatively.

Specifically, cats were trained to perform a serial motor tracking-task at maximum speed (push button task) and/or to run a 3/4 inch wide bar at maximum speed (tightrope walking task) to get food reinforcement.[16] After training to criterion, lesions were made unilaterally in VL. After a minimum recovery period of 24 to 72 hours (according to the animal's post-operative condition and responsiveness) the animals were tested for their ability to perform the learned task(s) to the pre-operative criterion levels. Details of these procedures are given below:

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[16] It was decided to use the above mentioned tasks since available clinical evidence (Jung & Hassler, 1960; Purpura, et.al., 1966; for example) indicated that the influence of VL on motor function is more probably in terms of coordination rather than motor power. Specifically, the Parkinson's patient has difficulty in rapid directed movements of their hands and in tandem walking (standard tests in neurological examination). The present tasks were thought, by the author, to best sample the possible effects of the experimental lesions.

Experiment #2

Method

Subjects.—The subjects were four littermate cats raised in the laboratory since birth. Training was begun when the cats were 10 months old.

Apparatus.—Training was done in a conditioning box 8" wide, 24" deep, and 16" high; having two arcs of three illuminated push buttons each placed on the floor at the front of the box such that each of the cat's forelegs was at the center of curvature of a given arc (Fig. 8). Between the two sets of push buttons was an opaque barrier which reduced the possibilities of S's trying to press buttons on the opposite side once a trial had begun. Food pellet reinforcement was delivered to a clear plastic cup mounted upon the median barrier such that it was just below the level of S's mouth (Fig. 8). The inside of the box was colored a light blue and was dimly illuminated. The front end of the box was made of transparent plastic. Stimulus control, programming, and response analysis was by a digital device designed and constructed by the author (Fig. 9).

Procedure.—The subjects were trained to press each push button, using a VR (variable ratio of reinforcement) schedule to establish good response rates, and were then taught to chain their responses to each push button as it was illuminated in the sequence: 1,2,3,1,2,3,1,2,3.

To initiate a trial, the start button on the digital

Fig. 8. Front view of push button conditioning box. Food cup is in center, supported by opaque divider.

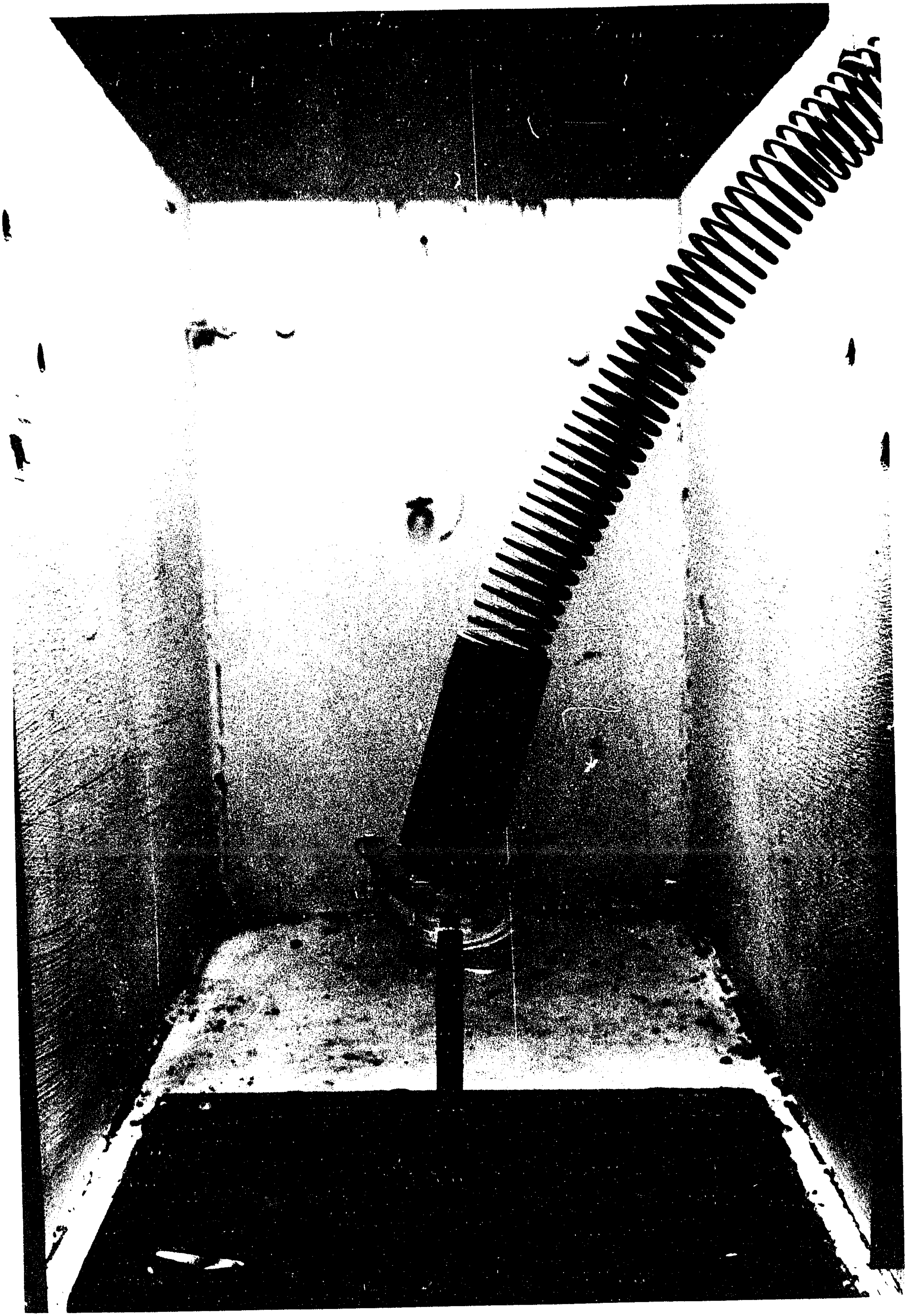
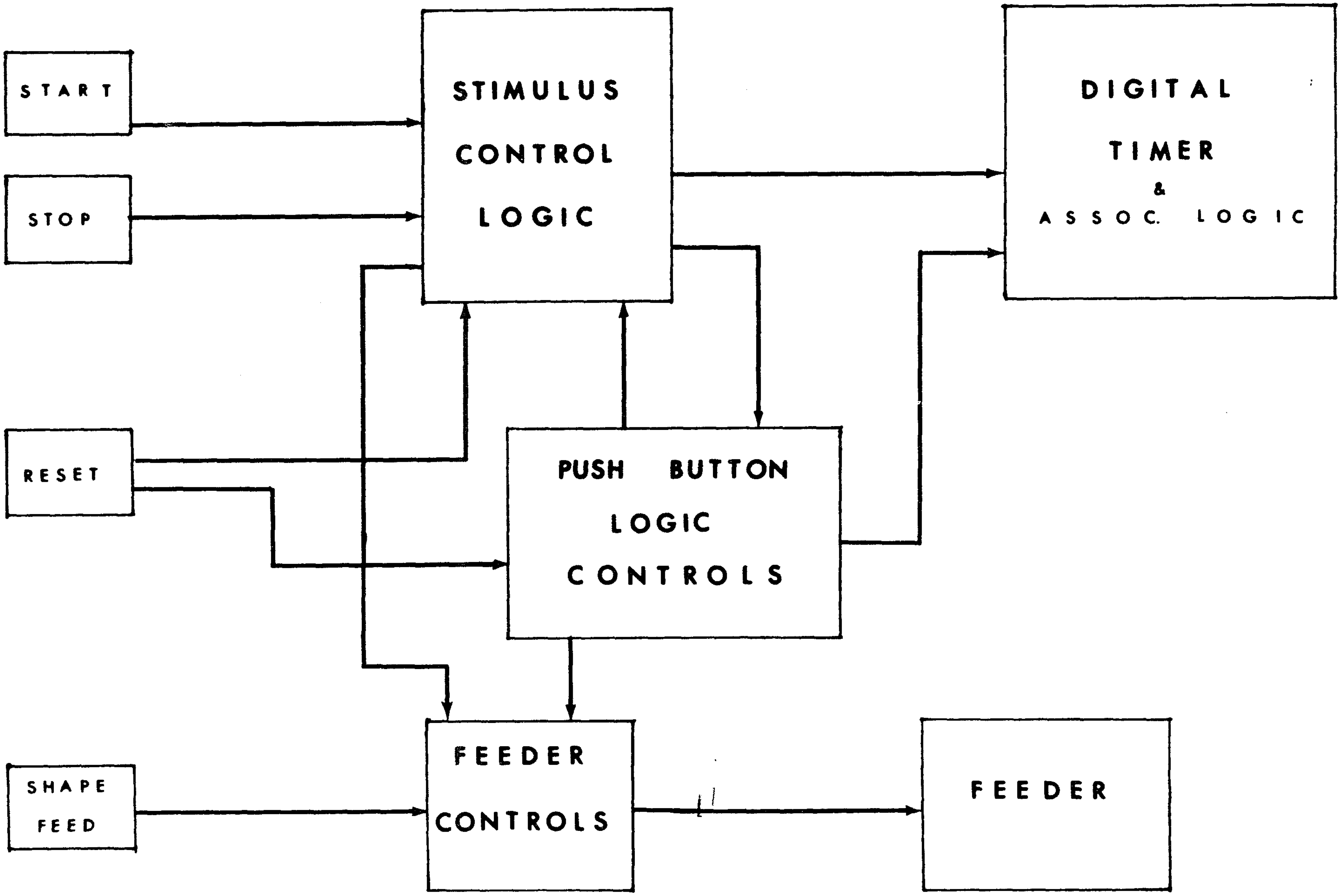


Fig. 9. Digital programmer--Logic flow diagram.


START
STOP
RESET
SHAPE FEED
STIMULUS CONTROL LOGIC
DIGITAL TIMER & ASSOC. LOGIC
PUSH BUTTON LOGIC CONTROLS
FEEDER CONTROLS
FEEDER

programmer was pressed. This illuminated the first of the push buttons on the preselected side and also made the push buttons responsive to S's pressing. When S pressed the first illuminated push button, it was immediately extinguished and the next button in the sequence was illuminated. When S pressed this button (#2), it was extinguished and button #3 was illuminated. When push button #3 was pressed by S, it was extinguished and #1 was again illuminated. This sequence continued until S pressed button #3 for the third time in the correct sequence (Fig. 10). At that point, push button #3 was extinguished and a food pellet was dispensed. Simultaneous with the pressing of push button #1 for the first time in a given trial by S, an electronic digital counter began to count tenths of a second. When S pressed button #3 for the third time, the counter stopped. The time for the trial was read to the nearest tenth of a second and recorded.

If at any time during the trial S pressed the same push button twice, or skipped a button, or did not complete the sequence within one minute, the trial was automatically terminated and an error of the observed type was recorded. The trial was also terminated by E, if S attempted to use the wrong leg to press the push button.

Initial training procedures.—Ss were familiarized with the food pellets used (Friskies). Ss were then trained to take the dispensed food pellets from the food cup. They were then deprived of food for 24 hours (or more if

Fig. 10. Photograph of cat pressing buttons in the push button tracking task.

if necessary) and returned to the test box where pressing of any illuminated button resulted in immediate reinforcement. Shaping continued with variable ratio reinforcement until each S pressed any of the illuminated buttons at fairly stable rates. The cats were required to press two, or three, or more buttons, as they learned the task, until they reliably pressed any button or combination of buttons, as they were illuminated, for food pellets. At this point, the Ss were trained to press a sequence of nine push buttons as they were illuminated, for a single food pellet. Training was continued with this chaining procedure and time and error scores were recorded (see Appendix E for sample data sheets). Each S received an average of 55 trials per day for each leg (a total of 110 trials per day).

Criterion performance.—The criterion level of performance was reached when S no longer showed a significant change in his maximal rate of responding (i.e., all trials within ±0.4 seconds of the mean time for the days testing session) on any trial for four consecutive testing sessions. Also, S's error score had to be below a total of 10 for each session. A retention period of several days followed. Each S was then retested and, if still at criterion level, was scheduled for training on experiment #3. Throughout training on experiment #3, S was aperiodically tested on the push button task to be sure that performance was maintained at the criterion level.

With one exception, Ss met their criterion levels with both legs. Desdemona pressed buttons with her left foreleg to the normal criterion of nine responses for one reinforcement. Criterion performance for her right foreleg was set at three responses per reinforcement since she refused to respond beyond this level.[17] All four of the Ss were subsequently trained successfully on experiment #3.

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[17] It was decided that, at surgery, the lesion would be placed in the right hemisphere so that any resultant changes in left foreleg performance (nine button presses) could be compared to the other animals.

Experiment #3

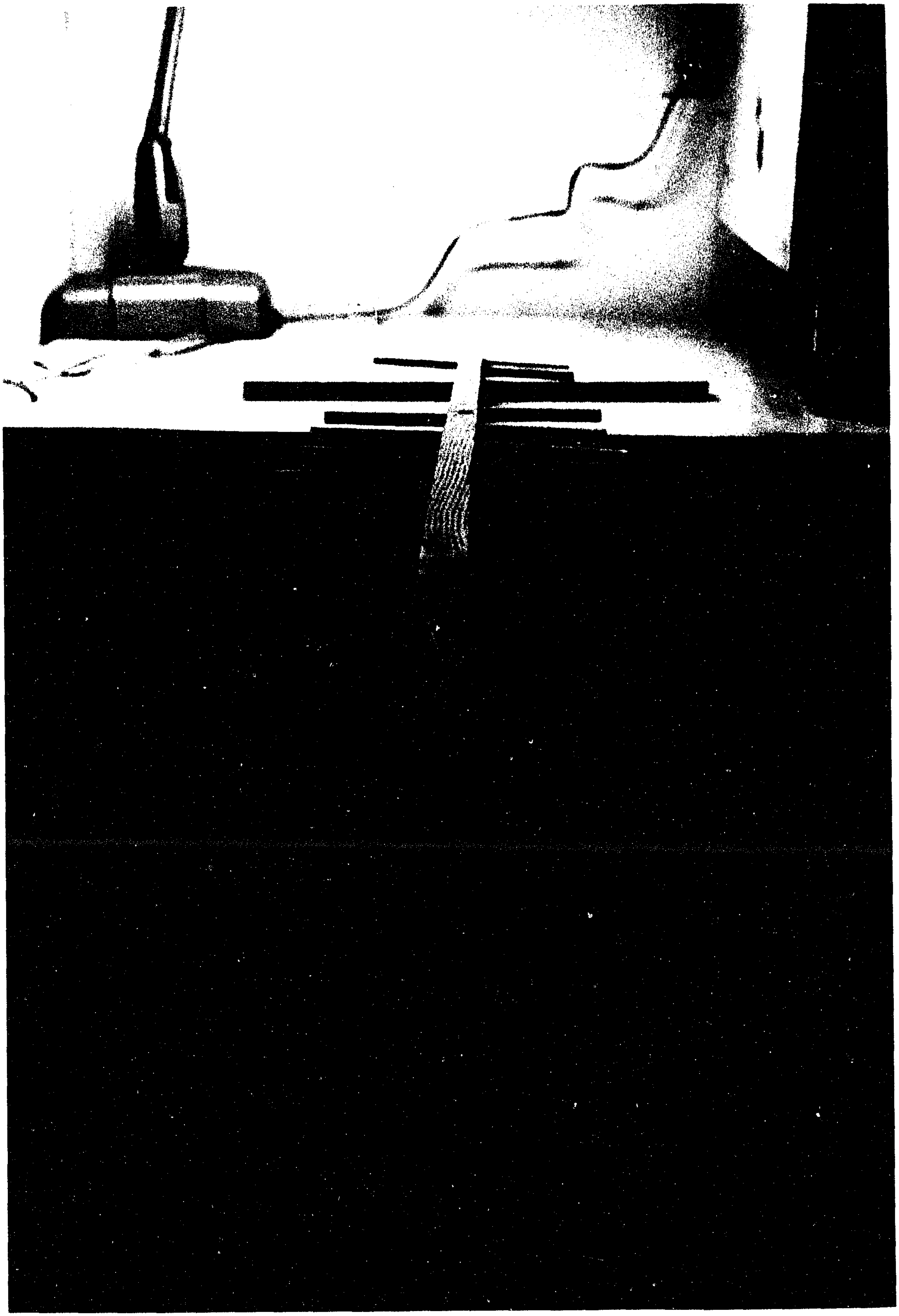
Method

Subjects.—The four trained animals from experiment #2 and four additional (experimentally naive) animals were used for a total of eight animals.

Apparatus.—The Ss were trained to run down a 3/4 inch wide wood (White pine) bar approximately six feet long. At one end was a start platform and at the other end was a large platform supporting the food cup. Three-eighth inch diameter holes were drilled through the sides of the bar one half inch below the walking surface and spaced on three inch centers. During early training, 4" wood dowels (3/8" diameter) were inserted in the holes on alternate sides (Fig. 11). Each S was required to run the entire length of the bar to get food. Runway time was recorded to the nearest one-half second for each of the 25 daily trials. The number of times each S fell off the bar was also recorded.

Initial training procedures.—As in the previous experiment, each S was first familiarized with the experimental situation, the food cup, and the food pellets. In the earlier training procedures, the four inch pegs were inserted in every hole over the length of the bar. Successive dowels were placed so as to protrude from alternate sides of the bar. The Ss were coaxed over the entire length of the bar with food reinforcements given aperiodically.

Fig. 11. Photograph of tight-rope walking apparatus.



After an S ran the entire length of the bar at a reasonable rate, several of the pegs were removed and training was continued. Finally, all of the pegs were removed and each S was required to run down the 3/4" bar without the side pegs. Times were recorded for all trials. For the later training procedures (2 cats), S was simply food deprived until he would walk along the narrow bar (without side pegs) to the food dish. During the period of food deprivation, the Ss were placed in the test situation <u>every</u> six hours. It required as much as fifty hours of food deprivation to get one cat (Hamlet) to traverse the bar properly, but the end result was that the training time was reduced from 12-14 days to no more than two test days after the deprivation period.

<u>Criterion performance</u>.—When an S consistently ran the entire length of the bar without stopping and with less than 0.4 seconds mean variation in time, criterion level was reached. At this point, the animals were running with less than one second variation over all trials for at least four consecutive test sessions (100 trials).

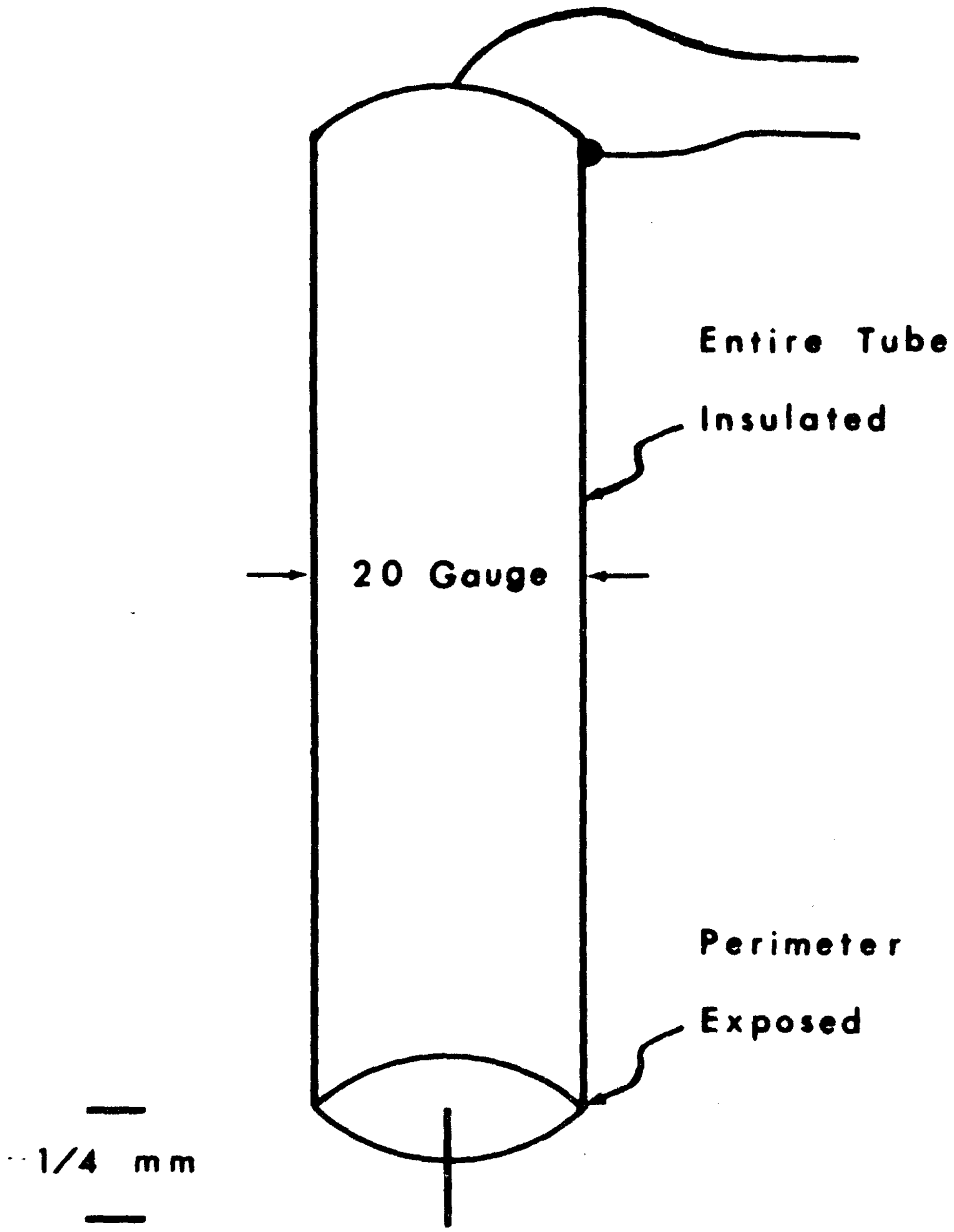
Surgery

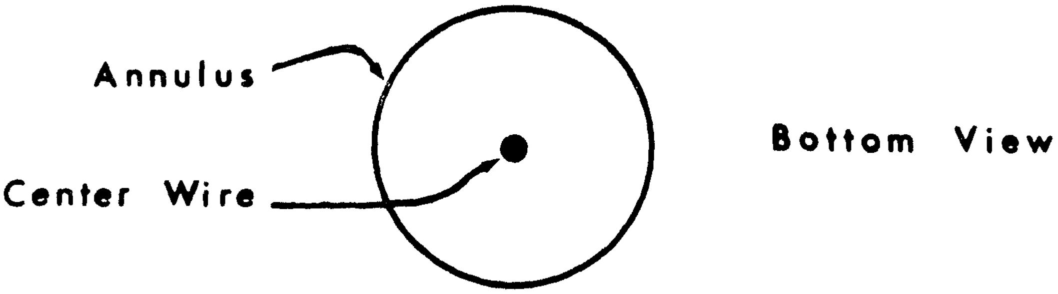
The surgical procedure was the same as previously described (refer to experiment #1 for a detailed description). At the time of surgery, an electrolytic lesion was placed in either the right or left ventrolateral region. The hemisphere selected for surgery was determined by the side of better performance in experiment #2. That is, if S performed the required task faster and with less variability with the right foreleg, the left hemisphere was selected for the lesion. Included in the group receiving unilateral VL lesions were two animals trained only in experiment #3. The two remaining animals trained only on the tight-rope task (experiemtn #3) received unilateral lesions in MD. Similar surgical exposures of the cortex for approximately equal amounts of time were required for both procedures.

Before any VL lesion was made, the electrode was stereotaxically placed under electrophysiological control as discussed by Brookhart, et.al., (1958), Hanberry and Jasper, (1963) and Yoshida, et.al., (1964). The initial placement was made based upon the atlas coordinates; AP=+11.0, L=+4.0, and H=+2.0 (Jasper & Ajmone-Marsan, 1954). An augmenting response had to be recorded at the motor cortex when several impulses at a 10 per second rate were presented to VL (see experiment #1).

All lesions were made using a coaxial electrode consisting of a 20 gauge stainless steel tube insulated except for its flush-cut bottom end and a central insulated 5 mil. tungsten wire. While all stimulation was made between the 1/4 mm. exposed tip of the 5 mil. wire and the annulus formed by the uninsulated edge of the tube (Fig. 12), electric current was passed between the annulus (anode) and the frame of the stereotaxic instrument

Fig. 12. Illustration of coaxial (concentric) depth electrode used to make chronic lesions.


Entire Tube
Insulated
20 Gauge
Perimeter
Exposed
1/4 mm


Annulus
Center Wire
Bottom View

(cathode)--the indifferent, to produce the lesions. This was accomplished by passing 5 milliamperes of direct current through the annulus of the electrode for 45 seconds. Two lesions were made, one above the other, with one millimeter spacing between the lesions. After the lesions were made, the electrode was removed and the cortical surface was irrigated with Bacitracin solution. All membranes were removed from the exposed frontal sinus and the open nasal passage was sealed with electrocoagulation and bone wax. Then, a piece of sterile Gel-Film was placed over the exposed cortex and the cut edges of the dura were sutured over it. Cut muscles were sutured together and the scalp incision was closed with subcutaneous sutures. No bone replacement was made. All animals were given an intramuscular injection of penicillin (500,000 units) postoperatively.

Post-operative Procedure

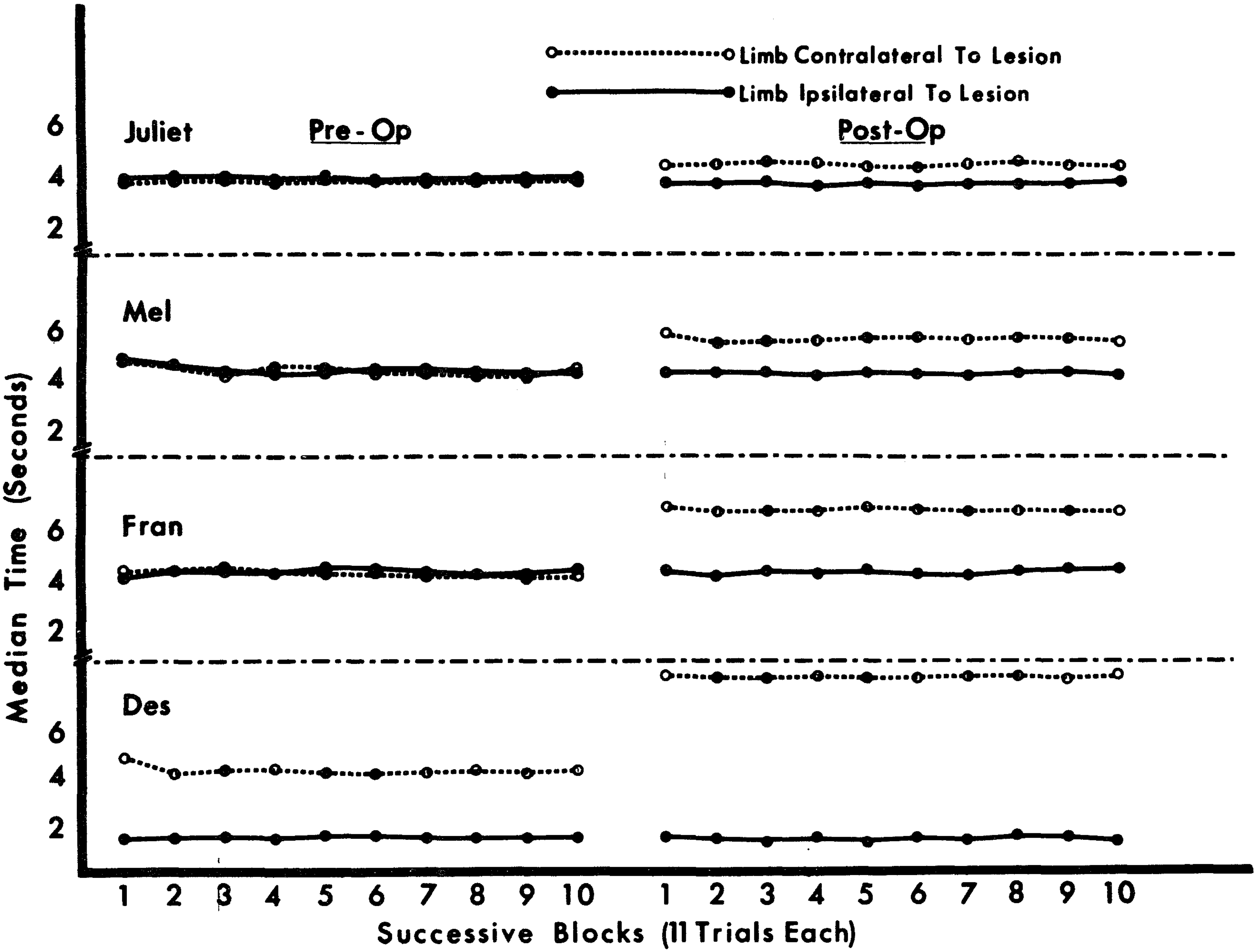
Post-operatively, all testing procedures were identical with those used pre-operatively. Reinforcement was given where appropriate. The subjects' general condition and behavior was observed in the free situation several times a week as well as in the actual testing sessions. During each observation session, clinical neurological evaluations were made using a 0,1,2,3,4 rating scale (fail, poor, questionable, fair, normal) to evaluate ability and behavior as detailed on the examination sheet (Appendix E). Formal testing was begun as soon as the animal was willing to work--sometimes within 24 hours after surgery, but more often after 36 hours.

Results of Experiments #2 and #3

Effects of VL lesion on push button tracking performance (Experiment 2)

The results obtained for each animal are presented in Fig. 13, in terms of median time (11 trials/data point) for nine successive button presses along the ordinate, and successive blocks (11 trials/block), for the last ten blocks prior to surgery and prior to sacrifice on the abscissae. The data are plotted separately for each of the four animals. The solid lines represents the performance of the limb ipsilateral to the lesion, while the broken lines represent the performance of the limb contralateral to the lesion (i.e., the affected side). As can be seen in Table 2, "t" tests of the data for each of the four animals show that there was a significant ($p < 0.001$) increase in the time required to press nine buttons in sequence for the foreleg contralateral to the lesion. These data show that there are no significant effects of the surgery in the limb contralateral to the normal hemisphere, while the average performance times with the affected limb is one and a half times slower than it was pre-operatively (mean time of 6.29 sec. vs. 4.20 sec.). Three of the animals had similar performance times with the unaffected limb prior to surgery. The fourth, Desdemona, showed no significant changes with

Fig. 13. Summary of data on push button task in terms of pre- and post-operative terminal performance. Graph of median time to press nine buttons in a trial vs. successive blocks of trials (11 trials/block).


Limb Contralateral To Lesion
Limb Ipsilateral To Lesion
Juliet
Pre-Op
Post-Op
Mel
Fran
Des
Median Time (Seconds)
6
4
2
1 2 3 4 5 6 7 8 9 10
Successive Blocks (11 Trials Each)

her right (normal) leg. The low mean performance times (as discussed previously) are due to the fact that she was required to press only three push buttons with this leg. The "t" values calculated (range 10.9 to 52.6) indicate the reliability of the surgical affect on forelimb performance.

In one cat involved in experiment #2, Juliet, there was a slight post-operative decrement in the push button performance of the foreleg on the unaffected side. The response times were greater than those of the other animals, but within a week performance on this side was at the pre-operative level. Performance of the foreleg on the side affected by the lesion, however, remained significantly poorer.

Each animal served as its own post-operative control for statistical evaluation, with the right and left performance times compared pre- and post-operatively. Table 3, lists the total number of errors made by each animal on each of the last five days prior to surgery and prior to sacrifice. It is clear that more errors were made by the limb affected by the surgery.

Effects of VL and MD lesions on tight-rope running performance (Experiment 3)

The influences of VL or control MD lesions in altering tight-rope performance can best be analyzed by considering the individual performance curves obtained during experiment #3. Fig. 14, presents these data, for each animal, in terms of mean running times (mean of 5 trials) along the ordinate

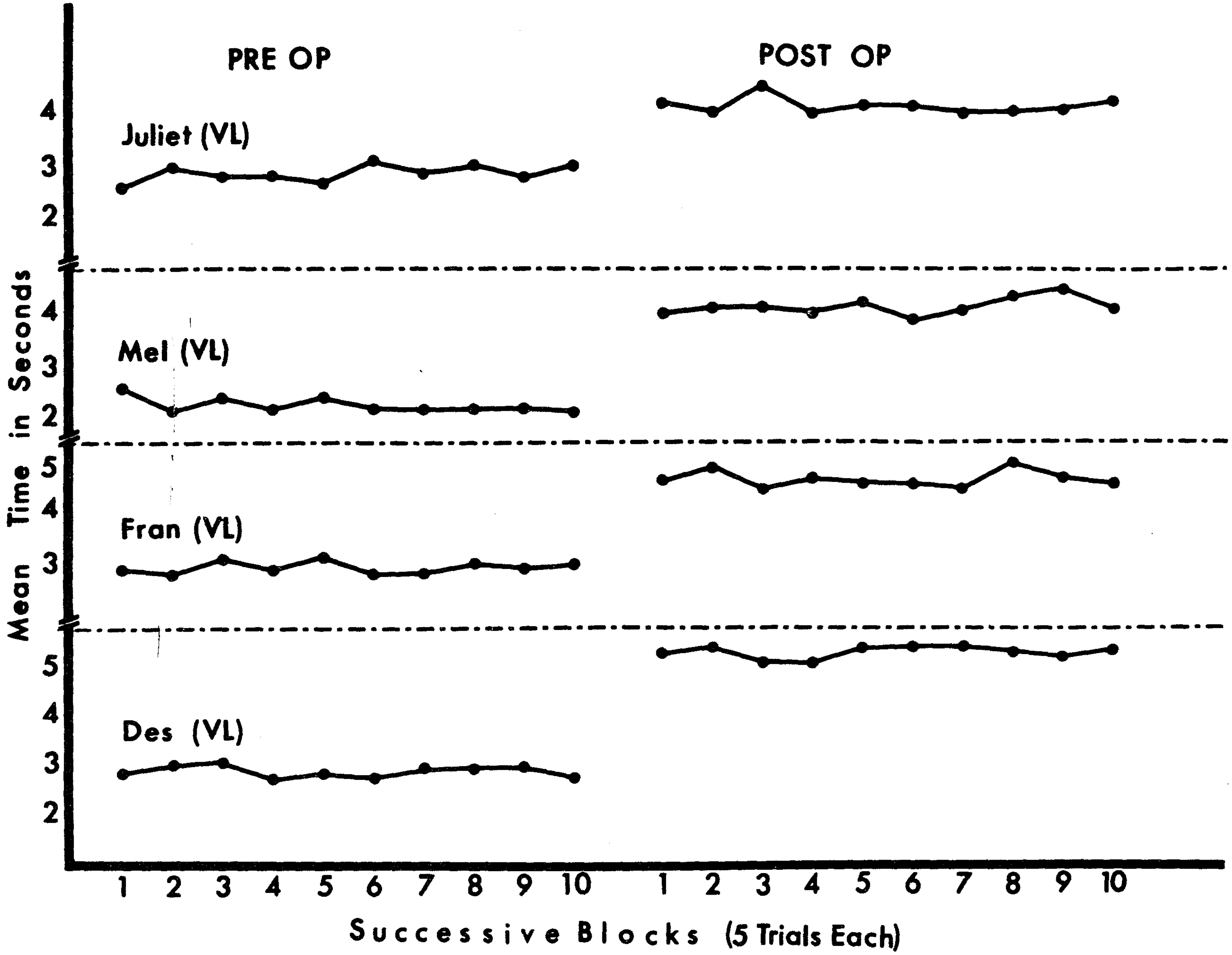
Table 2. Push button performance summary. The last 10 blocks pre-operative and the last 10 blocks post-operative. Each block is mean performance time in seconds. (11 trials/block)

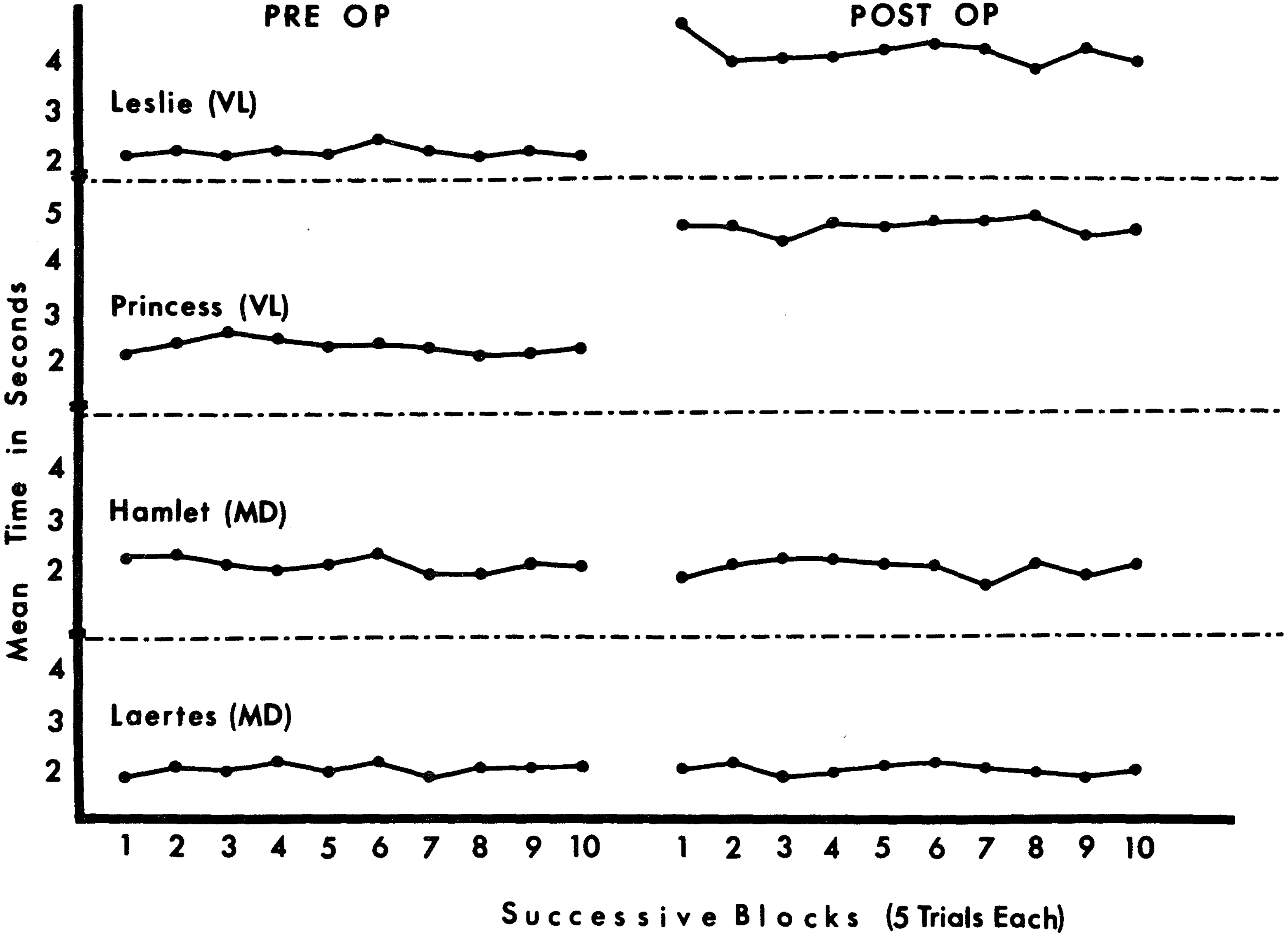
Cat	Lesion	Leg	Pre-operative Mean of last 110 trials	Post-operative Mean of last 110 trials	Difference	t	p
Jul	VL	right	3.87	3.80	-0.07	1.2	not sig
		left (op)	3.74	4.59	+0.85	10.9	<.001
Mel	VL	right (op)	4.27	5.68	+1.41	27.6	<.001
		left	4.43	4.38	-0.05	1.04	not sig
Fran	VL	right	4.32	4.29	-0.03	0.5	not sig
		left (op)	4.27	6.75	+2.48	52.8	<.001
Des	VL	right	1.80	1.79	-0.01	0.36	not sig
		left (op)	4.48	8.14	+3.66	44.8	<.001

Table 3. The total number of skip, omission, wrong leg and repeat errors of each of the last five testing sessions (Pre-operative and post-operative comparisons for each animal.).

Cat	Pre-operative			Post-operative		
	Dates	Left	Right	Dates	Left	Right
Jul	12-31-68	0	0	5-14-68	23	0
	1- 3-68	0	0	5-27-68	22	0
	1-10-68	0	1	6- 4-68	26	1
	1-14-68	0	0	6-19-68	24	0
	2- 1-68	0	0	6-30-68	30	0
Mel	1- 3-68	5	4	6- 3-68	5	26
	1- 6-68	5	3	6-10-68	6	22
	2- 8-68	3	4	6-19-68	2	35
	2-19-68	7	2	6-27-68	4	22
	2-25-68	4	1	7- 4-68	1	26
Fran	2- 6-68	2	0	6-10-68	34	1
	2-12-68	0	1	6-14-68	31	1
	2-18-68	2	1	6-20-68	35	0
	2-28-68	2	2	6-25-68	24	1
	3- 3-68	0	0	6-30-68	30	0
Des	1-10-68	2	3	6- 7-68	38	1
	2- 6-68	3	1	6-13-68	46	1
	2- 8-68	3	4	6-20-68	39	3
	3- 9-68	3	2	6-27-68	36	1
	3-12-68	1	2	7- 2-68	30	1

Fig. 14. Summary of data on tight-rope task in terms of pre- and post-operative terminal performance. Mean running time vs. successive blocks of trials (5 trials/ block).


PRE OP
POST OP
Juliet (VL)
Mel (VL)
Fran (VL)
Des (VL)
Mean Time in Seconds
4
3
2
4
3
2
5
4
3
5
4
3
2
1 2 3 4 5 6 7 8 9 10
1 2 3 4 5 6 7 8 9 10
Successive Blocks (5 Trials Each)


PRE OP
POST OP
Leslie (VL)
Princess (VL)
Hamlet (MD)
Laertes (MD)
Mean Time in Seconds
4
3
2
5
4
3
2
4
3
2
4
3
2
1 2 3 4 5 6 7 8 9 10
1 2 3 4 5 6 7 8 9 10
Successive Blocks (5 Trials Each)

and the last ten blocks (5 trials each) prior to surgery and prior to sacrifice on the abscissae. These plots show that the six animals receiving VL lesions had significantly longer running times than pre-operatively ("t" test: $p < 0.001$), while the two animals with MD lesions showed no significant changes in running rate subsequent to surgery. Throughout the observation period--which lasted, in some cases, as long as six months--no animal with a VL lesion ever approached his pre-operative level of performance. This indicates that the VL lesion had produced a serious effect upon the animals' ability to tandem walk (i.e., run) down the tight-rope. Table 4, presents a summary of the tight-rope performance in terms of pre- and post-operative running times for each animal. It shows that "t" tests of the differences in performance of all animals with VL lesions are significant at better than p 0.001. The animals with MD lesions showed no significant changes in performance as a result of surgery. Further, Table 5 shows that no animals with MD lesions fell from the tight-rope bar, while those animals with VL lesions fell frequently--<u>always</u> to the side contralateral to the lesion!

The behavior of the animals with medial dorsal thalamic lesions demonstrated that this surgical procedure did not significantly ($p > 0.65$) affect their running speed on the tight-rope tandem running task in contrast to the animals having ventrolateral thalamic lesions. As previously mentioned, in all animals with VL lesions there were some

Table 4. Tight-rope performance summary. The last 10 blocks pre-operative and the last 10 blocks post-operative. Each block is mean running time in seconds (5 trials/block).

Cat	Lesion	Pre-operative Mean of last 50 trials	Post-operative Mean of last 50 trials	Difference	t	p
Juliet	**VL**	2.77	4.10	1.48	5.5	<.001
Mel	**VL**	2.17	4.11	1.94	16.2	<.001
Fran	**VL**	2.93	4.78	1.85	6.4	<.001
Des	**VL**	2.84	5.19	2.35	9.8	<.001
Princess	**VL**	2.33	4.69	2.36	19.7	<.001
Leslie	**VL**	2.17	4.12	1.95	12.2	<.001
Laertes	**MD**	2.06	2.05	1.09	0.1	not sig
Hamlet	**MD**	2.09	2.04	1.05	0.4	not sig

Table 5. The total number of falls off the tight-rope for each animal, pre- and post-operatively.

Cat	Lesion	Falls	
		Pre-op	Post-op
Juliet	VL	0	16
Mel	VL	0	38
Fran	VL	0	19
Des	VL	0	47
Leslie	VL	2	43
Princess	VL	1	24
Hamlet	MD	0	0
Laertes	MD	0	0

neurologic deficits, which were quite apparent during the clinical neurological examination (see Table 6 for a summary of these data). Most significant, there was always a consistent absence of contact placing in the limb contralateral to the side of the lesion, which persisted until sacrifice in every animal.[18]

Effects of lesions as determined by clinical neurological examinations

Post-operative testing for all animals was begun within 48 hours after surgery. There were some individual variations in appetite and spontaneous behavior, but all animals were alert and performed in the testing situations. All of the animals with VL lesions showed defects in contact-placing with the forelimb contralateral to the lesion. After a three day recovery period, approximately normal placing behavior was observed <u>when vision was permitted</u>. When the experimenter blocked the animals' vision by covering the entire face with one hand, normal contact-placing was no longer observed. With the exception of Fran, who made some very sluggish partial responses just before sacrifice, no animals showed normal contact-placing at any time post-operatively when vision was blocked. In all animals there was immediate and brisk withdrawal of <u>any</u> limb when it was pricked by a pin.

In summary, behavioral assay methods have clearly

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[18] Refer to Appendix B for individual neurological summaries.

Table 6. Summary of neurological examination results at one week post-operative and at time of sacrifice.

Key:
0 = Absence of response
1 = Poor (very sluggish and/or low amplitude
2 = Questionable (possible true resp. - not clear
3 = Fair
4 = Normal

1 Week Postoperative														
Cat	Pin Prick		Spont. Behav.	Placing (Fore-leg)		Right. Resp.	Crossed Extensor	Gross Coord.	Resp. to Grav.	Muscle Tone Passive Stretch	Visual Fields	Orient. to Sounds	Eat & Drink	Spin
	L	R												
	F/R	F/R		L	R									
Jul	4/4	4/4	3	0	4	3	3 - 4	3+	4	3+	4	4	4	3
Mel	4/4	4/4	4	4	0	4	4	3+	4	4	4	4	4	4
Fran	4/4	4/4	3	0	4	3	4	3+	4	4	4	4	4	4
Des	4/4	4/4	3	0	4	3	4	3+	4	3+	4	4	4	4
Prin	4/4	4/4	4	4	0	3	4	3	4	4	4	4	4	4
Les	4/4	4/4	3	4	0	3	3	3	4	3	4	4	3	3
Ham	4/4	4/4	4	4	4	4	4	4	4	4	4	4	3	3
Laer	4/4	4/4	4	4	4	4	4	4	4	4	4	4	3 - 4	4
At Sacrifice														
Jul	4/4	4/4	4	0	4	4	4	4	4	4	4	4	4	4
Mel	4/4	4/4	4	4	0	4	4	4	4	4	4	4	4	4
Fran	4/4	4/4	4	0	4	4	4	4	4	4	4	4	4	4
Des	4/4	4/4	4	0	4	4	4	4	4	4	4	4	4	4
Prin	4/4	4/4	4	4	0	4	4	4	4	4	4	4	4	4
Les	4/4	4/4	4	4	0	4	4	4	4	4	4	4	4	4
Ham	4/4	4/4	4	4	4	4	4	4	4	4	4	4	4	4
Laer	4/4	4/4	4	4	4	4	4	4	4	4	4	4	4	4

demonstrated that a unilateral lesion in VL produces reliable decrements in performance on tasks requiring complex coordinated motor responses. Additionally, neurological examinations demonstrated consistent defects in contact-placing in the same limb affected by such lesions. In contrast, lesions in MD caused no observable changes in motor ability: either within the formal testing situation, or in the clinical examination.

Introduction to Experiment #4

The purpose of this phase of the investigation was to determine whether the experimental lesions had, in some way, caused a change in the nature of the cortically elicited motor responses as compared to the unoperated side.

Experiment #4

Method

Subjects.--All of the animals used in the behavioral experiments were subjects in this experiment.

Apparatus.--The apparatus was the same as was used in experiment #1.

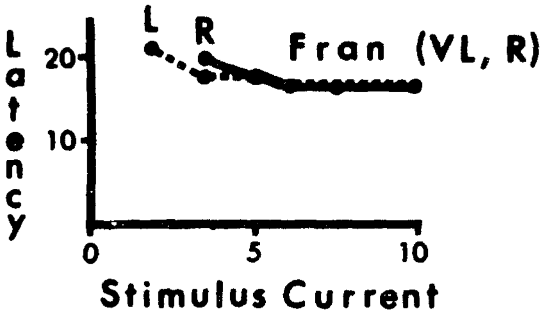
Procedure.--After post-operative behavioral testing, all animals were prepared surgically, as in experiment #1, except that the frontal cortical area was exposed bilaterally. Identical accelerometers were placed on each foreleg. Both precruciate gyri were stimulated--one at a time--in alternating order, The stimulus amplitudes (ma.) and response latencies (msec.) of the contralateral forelimb were recorded.

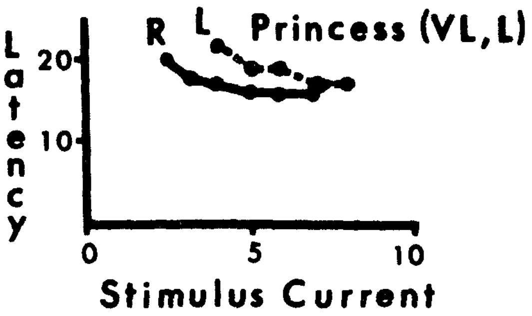
Results

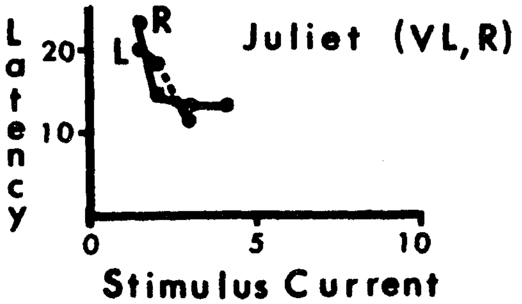
Effects of VL or MD lesions on latency and threshold of cortically elicited limb flexions

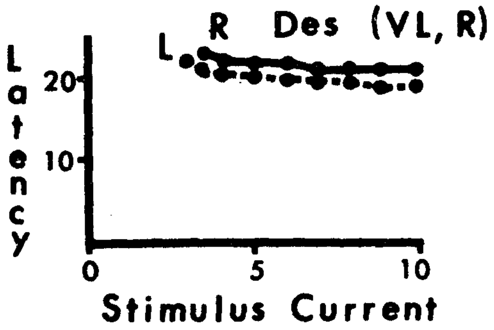
The results, as presented graphically in Fig. 15, show that the threshold and latency differences between legs for any animal are not very great. There are consistent trends, however, in that with the stimulus intensity constant, shorter latencies were observed from the normal side in five out of six animals. There were no effects seen in the animals with MD lesions. The graph for each animal is labeled separately for right (R) and left (L) hemispheric

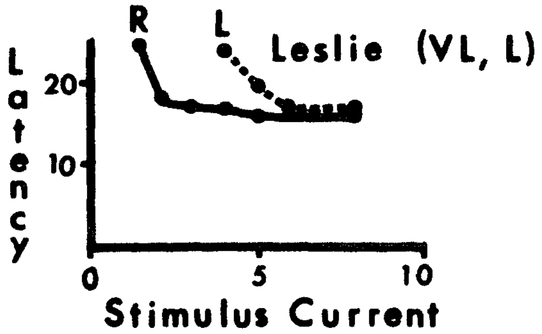
Fig. 15. Graph of data from Experiment #4. Stimulus amplitude and response latencies for each animal (R=right hemisphere, L=left hemisphere).

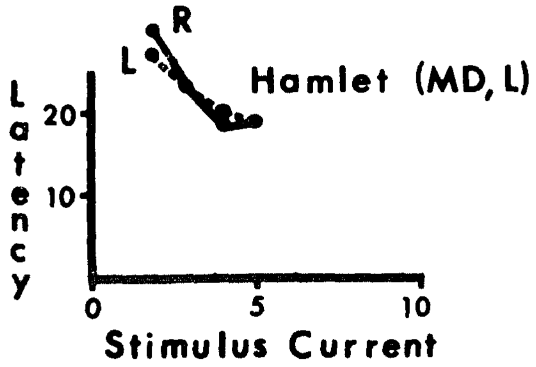

Fran (VL, R)
L
R
Latency
20
10
0
5
10
Stimulus Current

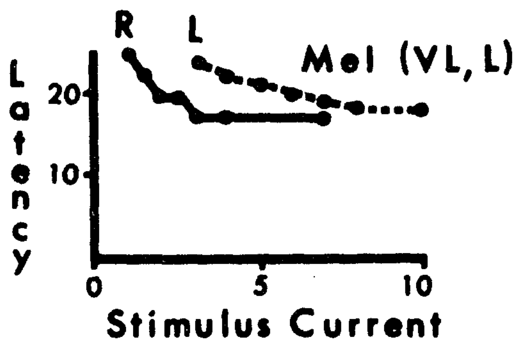

Princess (VL, L)
R
L
Latency
20
10
0
5
10
Stimulus Current

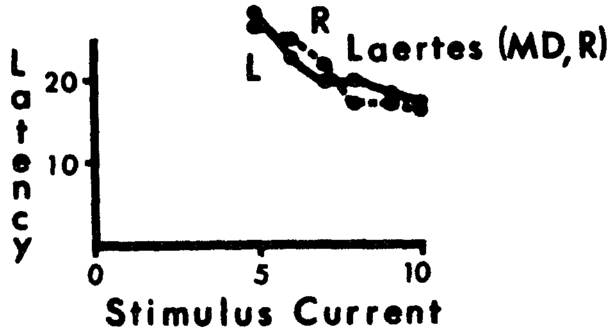

Juliet (VL, R)
L
R
Latency
20
10
0
5
10
Stimulus Current


Des (VL, R)
L
R
Latency
20
10
0
5
10
Stimulus Current


Leslie (VL, L)
R
L
Latency
20
10
0
5
10
Stimulus Current


Hamlet (MD, L)
L
R
Latency
20
10
0
5
10
Stimulus Current


Mel (VL, L)
R
L
Latency
20
10
0
5
10
Stimulus Current


Laertes (MD, R)
R
L
Latency
20
10
0
5
10
Stimulus Current

stimulation. Table 7 summarizes the minimum latencies recorded and the stimulus levels required to elicit these responses. The large differences in stimulus amplitudes listed are probably due to changes in anesthesia level during testing.[19] The results indicate that the VL lesions, in addition to any other effects, apparently increase the threshold for cortically elicited motor responses and/or increase motor response latencies. More complex possibilities are discussed below.

Characteristics of VL and MD lesions as determined by histological evaluation

All histology was done with frozen sections. The brains were sliced at 40u intervals, and every fifth one was stained by the Kluver technique for fibers and cell bodies. It was found that all lesions were placed in either VL or MD as planned (Table 8). All of the VL lesions were in the anterior (rostral) portion with some showing slight intrusion into VA. The MD lesions were of similar size and were well placed. All lesions were approximately the shape of an oblate spheroid with its long axis vertical and the bottom end of larger radius than the top.

Specifically, the following observations were noted:

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[19] Upon initial inspection, the current levels listed in Table 7 may appear a little high in absolute magnitude (ma.), although they probably weren't physiologically. It must be recalled that the electrodes had ball tips which were placed on the pial surface in the pericruciate area and, probably, much of the current spread over its surface with relatively little actually exciting the cortical motoneurons.

Table 7. Experiment #4 data summary--Comparison of effects of MC stimulation on normal and operated hemispheres. Stimulus thresholds and response latencies recorded from linear accelerometers on each foreleg.

Cat	Lesion	Hemisphere Stimulated	Minimum Latency (msec.)	Stimulus Amplitude At Minimum Latency (ma.)
Juliet	Right VL	Left	12	3
		Right	13	3
Mel	Left VL	Left	18	8
		Right	17	3
Fran	Right VL	Left	18	3
		Right	17	6
Desdemona	Right VL	Left	20	9
		Right	22	9 - 10
Princess	Left VL	Left	17	7
		Right	16	5
Leslie	Left VL	Left	17	6
		Right	16	5
Laertes	Right MD	Left	17	10
		Right	16	10
Hamlet	Left MD	Left	19	5
		Right	19	4

Table 8. Histological summary for all cats showing coordinates of each lesion according to the Atlas of Jasper and Ajmone-Marsan (1954).

Cat	Lesion	A - P Plane	Height Vertical	Lateral Plane
Juliet	VL	+9.8 - +11.3	+1.0 - +3.7	3.0 - 4.0
Mel	VL	+9.9 - +11.3	+0.7 - +3.5	3.0 - 4.25
Fran	VL	+9.7 - +11.3	+0.7 - +3.3	3.3 - 4.5
Desdemona	VL	+10.2 - +11.5	+0.3 - +3.0	3.5 - 4.6
Princess	VL	+10.5 - +12.0	+0.5 - +3.3	3.5 - 4.7
Leslie	VL	+10.3 - +11.4	+1.0 - +3.5	3.5 - 4.5
Laertes	MD	+8.7 - +10.1	+3.0 - +5.0	0.5 - 2.1
Hamlet	MD	+8.8 - +10.0	+3.0 - +4.9	0.8 - 2.0

Juliet had a lesion which was about 1 mm. higher than the other VL lesions. It was well placed with destruction extending approximately from anterior +9.8 to +11.5 mm. and laterally from 3 to 4 mm.[20] The lesion extended vertically from +1.0 to +3.7 mm. The anterior part of the lesion may have encroached upon VA slightly. Princess's lesion extended from anterior +10.5 to +12.0 mm. and did enter VA for about 1/2 mm. The lesion extended in height from +0.5 to +3.3 mm. and was centered in VL laterally from +3.5 to +4.7 mm. Desdemona had a lesion which also had a slight intrusion into the region of VA. Her lesion extended from anterior +10.2 to +11.5 mm. Laterally it extended from +3.5 to +4.5 mm., while its vertical range was from +0.3 to +3.0. Mel's lesion was slightly narrower than the others, but was centered in almost the same place as Juliet's. It extended from anterior +9.9 to +11.3 mm., had a lateral span from 3.0 to 4.3 mm. and extended vertically from +0.7 to +3.5 mm. A slightly narrower lesion was found in Leslie's brain. It extended from anterior +10.3 to +11.4 mm. and from 3.5 to 4.5 mm. in the lateral plane. The vertical range was from approximately +1.0 to +3.5 mm. Some intrusion into VA is apparent. Finally, Fran had a well centered lesion, totally within the confines of VL. It extended in the A-P plane from +9.7 to +11.3 mm., laterally from 3.3 to 4.5 mm., and vertically from +0.7 to +3.3 mm.

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[20] All coordinates are presented according to the system and atlas of Jasper and Ajmone-Marsan (1954).

With respect to the MD lesions, it was found that both of the control animals has lesions well placed in the nucleus. Hamlet had a lesion extending in the A-P plane from +8.8 to +10.0 mm., in the lateral plane from 0.8 to 2.0 mm. and vertically from +3.0 to +4.9 mm. Laertes has a slightly larger lesion which showed a slanted path, being about 1/2 mm. more medial at the top of the lesion. The extent of the lesion was from anterior +8.7 to 10.1 mm., in the lateral plane from 0.5 to 2.1 mm. (slight slant) and vertically from +3.0 to +5.0 mm.

In summary, all lesions were properly placed in either VL or MD. Two of the VL lesions--those of Desdemona and Princess--definitely included small parts of posterior VA, while Juliet and Leslie may have had some damage to the VL-VA border region. In all cases, much more than 90% of the lesion was contained in the anterior portion of VL. From all indications, the electrode path was through the anterior-medial part of n. Anterior Ventralis. No other thalamic nucleus appears to be directly affected by the lesions.

The major extent of each MD lesion is in the anterior part of MD, slightly medial of the center of the nucleus. In both animals, there is some damage to adjacent midline nuclei, including n. Periventricularis Anterior, n. Parataenialis, and Stria medullaris. This was in part due to the passage of the electrode to MD.

Figure 24 is a photomicrograph of a section from

Juliet's brain. The size and extent of this typical VL lesion can be seen clearly. Figure 25 is a photomicrograph of a section from Hamlet's brain. It can be seen that the lesion is well placed in MD. Adjacent damage can also be seen. Diagrammatic representations of the extent of all lesions can be found in Appendix C. For each animal, a coronal and sagittal drawing is presented. All lesions are presented as though they were made in the left hemisphere. That is, the left hemisphere lesions were drawn in normally, while those brain sections having lesions in the right hemisphere were turned over and traced on the left hemisphere diagram.

An attempt to relate the loci of the VL lesions to observed differences in behavior was not successful. No pattern could be found to relate observed behavioral differences to the locus of the lesion. This suggests at least two possibilities: first, the behavioral differences were not very great on either task, or clinically; and second, all of the VL lesions were within one area of VL--the anterior third of the nucleus. Since the locus of the lesions was determined electrophysiologically, and the resultant behavioral effects were consistent, it is conceivable that the exact physical position of the lesion within the described region of VL is not as critical as is the electrically determined locus.

Discussion

When three successive electrical impulses were applied to VL (at a 10/sec. rate) an augmenting response was reliably elicited from motor cortex in all animals. The conclusion that the shape of the observed electrical response is unique to stimuli applied to VL and observed at MC is supported by the data of Brookhart, et.al., (1958), and by Yoshida, et.al., (1964), as well as by other investigators who have reported that the thalamic area which produces rhythmic negative-positive incrementing potentials with initial short latency positivity in the pericruciate area (augmenting) was indeed the ventrolateral nucleus. At these loci, some motor responses to VL stimulation alone were observed. It is possible that this was due to non-reciprocal adjustments in flexor muscle tone of the forelimb during the period of stimulation (under light barbiturate anesthesia). This suggestion is in agreement with Yanagisawa, et.al., (1963). They report that VL stimulation exerts a nonreciprocal facilitory influence on spindle discharges from antagonistic muscles under light pentobarbital anesthesia and a reciprocal influence (i.e., facilitory to the flexor and inhibitory to the extensor spindles) under moderate or deep anesthesia. The resultant enhancement of the movement during the trials in which MC, as well as VL, is stimulated could then be due to changes in the cortical motor system associated with the VL stimulation.

Support for this hypothesis is also found in the data of Ohye, et.al., (1964), who report that "stimulation within the VL nucleus results in nonreciprocal increase in muscle tone on the contralateral forelimb muscles."

If one adopts Hofmann's (1962b) concept of interacting excitatory and/or inhibitory effects on certain nuclei and muscle groups as a result of VL stimulation, the enhancement of the elicited motor responses could then be the result of the conditioning stimulus (VL) predisposing the limb for a more rapid, higher amplitude response to the motor signal. These effects could be due to direct alterations at the periphery, or through alterations of the excitability of neurons in the motor cortex.

The observed short latency enhancement of the cortically elicited movements in the early part of the present report is supported by the results of Schlag (1966). He observed that the VL conditioning stimulus, through possible disinhibition of cortical cells, increased the responsiveness of pyramidal tract cells with a minimum delay of about 6 msec. It is more difficult, however, to explain the secondary enhancement which was observed with conditioning--test shock intervals upward of 75 msec. If it represents the time consumed in conduction, quite a large circuit would have to be postulated. A possible explanation is that, subsequent to discharge, the recovery of the thalamic units imposed a periodicity of about 80 to 120 msec.

In fact, long standing evidence attributes a thalamic origin to the 8 - 12 per second cycles recorded over most of the cortex (Dempsey & Morison, 1942c; Andersen & Rudjord, 1964). This oversimplified view does not even consider the various feedback pathways known to exist between the thalamus, the cortex, and other loci, but it seems to point in the correct direction (Schlag & Balvin, 1964; Stephanis & Jasper, 1964).

The results of the behavioral aspects of the present study show that unilateral lesions in the ventrolateral complex of the cat result in a loss of contact (tactile) placing reactions and impairment of coordinated voluntary motor ability. The inability to perform the skilled coordination tasks with the affected forepaw persisted throughout the post-operative observation period. On the push button task, the operated animals were unable to reach their own pre-operative criterion performance levels. The decrement in performance is clearly the result of the surgical procedure since the unoperated side was not affected at all. Similar conclusions are easily drawn about the performance comparisons on the running task. Although it is not possible to completely quantify the performance decrements, qualitatively the effects of the unilateral lesions are quite clear. During testing, the animals only fell to the side contralateral to the lesion. Additional justification for the correlation of runway performance deficits with the surgical procedures can be found in the fact that four of the six animals used in this experiment (VL lesions) also showed the clear unilateral push button deficits described above. Further, all of the animals with VL lesions showed long lasting contact-placing deficits contralateral to the side of the lesion. Classically, this defect in motor performance has been attributed to lesions of the primary motor cortex (Pribram, et.al.--p.441, 1955). This observation strongly suggests that this deficit is more likely due to some damage in one or more of the "loop" pathways operating between VL and MC, or to fibers passing through the ventrolateral complex on the way to, or from, the motor cortex.[21]

As indicated in Table 3, the performance decrement was more than simply an increase in the time required to press buttons to the criterion level. It involved many more errors and aborted attempts. The cat would begin to press and then skip buttons, or hesitate, stroking the tops of buttons but not pressing, or press the same button repetitively, rather than pressing the proper sequence of nine push buttons. When using the defective limb, the cats appeared more visually attentive to the illuminated push buttons than previously, to the extent that the performance was clearly slowed down while the animals "looked" for the illuminated push button. Previously, the animal immediately

[21] This finding of a VL-lesion-induced defect in placing has recently been confirmed by V. Amassian, personal communication; Dec. 1968.

began to respond when the first button was illuminated and the rest of the sequence was a smooth flow from one button to the next.

When these animals trained on the push button task, as well as the other two with VL lesions, were tested on the running task, they occassionally fell off the bar--falling to the side of the impaired leg. Even before the trials began, however, the cats did not behave normally. Most of them would sit in a fairly normal manner, or stand still on the start platform with the normal foreleg supporting the weight of the anterior part of the body. The other foreleg was alternately placed on the top of the bar or against its side, and lifted off, in an almost stroking-like manner. When a trial was initiated, this leg sometimes fell, or slipped off of the bar. In all cases, this was the limb contralateral to the lesion. As the post-operative testing continued, it became evident that the animals tended to "favor" their defective limb as they crossed the bar. That is, they appeared to do most of the walking with three legs, using the fourth only for balance rather than for full support. The animals appeared to look much more carefully before they moved that limb. They appeared to be incapable of making discrete, temporally integrated extension movements at the wrist and elbow and the normal pattern of stepping--one foot in front of the other ("indian walking")--seemed to be disrupted. These types of defects in patterned, coordinated movements are also seen during the examination of human patients with neurological defects.

During some of the post-operative push button test sessions, several of the animals attempted to perform the tracking task presented to the impaired leg with the normal leg. This behavior was not much of a problem, however, since the experimenter immediately terminated these trials and withheld reinforcement.

The above observations agree with, and extend, the early findings of Tarnecki (1962) that, after lesions were made in VL, the animals had difficulty with trained responses: behaving in an atypical fashion, and emitting less adequate responses. He further described the deficits as being similar to those which are seen after ablation of the motor cortex (Discussions of the effects of motor cortical ablations can be found in the reports of Berman, et.al., (1954) and Kruger and Porter (1958), for example.). After the VL lesions, the motor activity was preserved from the very beginning, but the coordination was much impaired. In the present study, the results are similar, but are more quantitative and show that defects can be obtained with unilateral VL lesions.

It is unfortunate that Tarnecki's study made use of a conditioned scratch reflex rather than a more complicated instrumental response since direct comparisons can not be made with the present study. The fact that his animals recovered much of their abilities quite rapidly, in spite of bilateral VL lesions, serves to substantiate the conviction that the task selected in the study was probably not sufficiently sensitive to demonstrate the long lasting deficits reported in this paper. The tasks selected for the present investigation required much more complex responses and were evaluated as continuous functions. This is in contrast to Tarnecki's observations in which a rather gross response was either present or absent. It is possible that an additional factor accounting for the observed differences in post-operative performance is the exact locus of the lesions. Precise anatomical information about the lesions in Tarnecki's animals is not available, but it is conceivable that they, unlike the lesions in the present study, spared the anterior part of VL adjacent to VA, and this could be a factor to be considered in evaluating the differences in long term post-operative performance.

Since there are no other reported behavioral studies involving the study of complex coordinated motor responses in the presence of chronic lesions in VL, with which to make comparisons, it is impossible to critically compare and further evaluate the observed behavioral motor deficits.

The tasks used in the present study required very discrete control of movements at all levels of the forelimb as well as appropriate coordinated shifting of body weight, etc., in addition to requiring coordinated interactions between vision and limb movement. The decrements in performance level, as well as the absence of normal contact (tactile) placing persisted until the time of sacrifice--as long as six months.

The observations related to the MD lesions are totally different. The two animals with these (control) lesions showed no observable deficits either in performance or upon clinical examination. Exactly what these negative findings mean, with respect to the role of MD is not clear. It is possible, however, as Chow (1953) suggests, that the lack of behavioral effects was due to the incompleteness of the lesions. With total bilateral destructions of MD, some behavioral symptoms might occur. In any event, it is evident that the small unilateral lesions in MD, in the control animals, did not have the same or similar effects on coordinated motor performance as did the small unilateral lesions in VL.

Clearly, VL has some important involvement in the integration of coordinated movement. This has been substantiated by Branch and Martin (1958), Kruger and Albe-Fessard (1960), Purpura (1962), Buser (1966), Marco, et.al., (1967); and many others with electrophysiological findings. Support is also given by Stern and Ward (1960), Dennery and Combs (1961), Yanagisawa, et.al., (1963), Yoshida, et.al., (1964), and many others in their studies of the role of VL in the integration of motor activity.

As a result of the present study as well as a thorough review of the relevant literature, the conceptualization of VL as a primary sensorimotor integrative center becomes quite acceptable. It has been established that VL has direct projections to and from the primary motor cortex (Jung & Hassler, 1960), is activated by somatic afferents (Kruger & Albe-Fessard, 1960), receives direct and red nucleus relayed fibers from the dentate nucleus of the cerebellum (Carrea & Mettler, 1954; Carpenter & Stevens, 1957; Combs, 1959; Cohen, et.al., 1962; Marco, et.al., 1967), receives collateral fibers from the pyramidal tract (Clare, et.al., 1964) and is supplied by ascending fibers in the pyramidal tract (Brodal & Walberg, 1952; Brodal & Kaada, 1953). Blum and associates (1968) have shown that stimulation of VL simultaneously excites fibers in both corticofugal projections and thalamocortical relay cells which project directly to both pre- and post-cruciate cortex. Also, the direct control of muscle spindle discharge by VL by way of the gamma efferents has been clearly demonstrated (Stern & Ward, 1960; Langfitt, 1963; Yanagisawa, et.al., 1963; and Yoshida, et.al., 1964). In addition, the role of VL in Parkinsonism has been studied by many of the above investigators as well as by Hofmann (1962a,b). Kruger and Albe-Fessard (1960) report that the region of VL activated by somatic afferent stimuli is predominently its caudal portion, which is also the area known to receive fibers from the brachium conjunctivum, while the rostral portion is the area in which few tactile evoked responses were recorded consistently.

In other words, VL could easily serve to exert fine control over complex motor functions. Through its multiple input-output connections, as well as its many "loop" circuits, it can act to bias the threshold level of cortical or pyramidal tract fibers for smooth action and/or sharpen projections to sensorimotor cortex to discretely delimit and define outgoing information for fine control in the periphery.

Alternatively, or in addition to this role as a modulatory influence, VL could act as an integrative nucleus for the control of central feedback circuits ("loops") which could plan and control the expression of coordinated peripheral motor acts, even in the absence of peripheral proprioceptive feedback. This might explain, in part, why totally deafferented monkeys have been observed to be capable of some coordinated movements (Knapp, Taub, & Berman, 1963).

It was the fine control of movement that was absent in the post-operative observations reported in this study. Also, the absence of normal contact placing correlates well with the above hypothesis since it has already been shown that tactile evoked responses can be recorded from parts of VL, adjacent to VA. Thus, the lesions, although small and not fully destroying the entire nucleus, as delimited anatomically, were placed in precisely that locus (VL-VA) where they would predictably have significant effect. The similarity of the observed effects to those resulting from lesions in the motor cortex is understandable, since it has been known for some time that the motor cortex is not purely an efferent system (Pribram, et.al., 1955), but has interactions with a number of systems basic to motor function, such as VL, for example (Jung & Hassler, 1960)!

At this point, however, much caution must be exercised because it might well be that the lesions damaged fibers passing through this area of the VL complex--on their way to and/or from the cortex--as well as specific cells of this nucleus. It was this precise region, though, from which the augmenting responses recorded at the motor cortex were elicited. This increases the probability that most of the observed effect is due to damage to the nucleus. More thorough investigations of this point must be made before any definite conclusions can be drawn.

In the present study, one major problem was that there was no provision for experimentally determining whether the deficits observed were due to coordination deficits, slight motor weaknesses, or both. Also, the running task did not clearly show the laterality of the deficit in quantitative terms (except for the fact that the subjects fell to one side) even though the overall performance decrements, as discussed above, were quite clear. With respect to the electrophysiological experiments, very short time intervals and latencies were involved. Yet, the level of accuracy of the several timing devices and readouts used was not great enough to give absolute reliability to the time intervals reported.

It is suggested that a future study of the effects of unilateral VL lesions on motor coordination be carried out using two groups of illuminated levers which the cat could be trained to press with either foreleg. The cat would be trained to press each lever, in sequence, with a certain pressure, in order to be rewarded. Alternatively, the cats could be presented with one lever in front of each foreleg and be required to press the lever with a specified amount of force and to hold it for some finite interval. The tolerance limits for an "adequate" response could then be reduced in steps to determine the animals' ability to perform fine pressure discriminations, while the steadiness of the response and the rapidity with which the criterion was attained might be used as an indicator of the cats' coordination ability. If a signal panel were placed in front of the animal and illuminated while an adequate response was being made, shaping probably would not take too long. In addition, subsequent to the studies involving the effects of VL lesions, these and other, intact, animals could be subjected to partial or total dorsal root sections and the subsequent responses studied in the absence of what are generally acknowledged to be the primary proprioceptive pathways. The illuminated panel would permit an evaluation of the animals' ability to integrate visual sensory feedback with the fine motor responses required.

SUMMARY

Acute and chronic animal preparations were used in this multiphasic study. In phase I, conditioning shocks to n. Ventralis Lateralis (VL) were found to produce decreases in latency and increases in amplitude of the contralateral forelimb flexion elicited by test shocks to the motor cortex (MC). In phase II, other cats were trained either to press buttons in serial order, or to run a narrow elevated ramp, or both, for food reinforcement (Friskies). Unilateral VL lesions were then made in these animals at the electrode locus yielding maximum augmentation of the shock-elicited response in MC. Post-operatively, these cats showed marked deficits in the forelimb contralateral to the VL lesion on both performance tests. This behavioral deficit was accompanied by a persistent absence of contact placing in the same limb. In these animals, terminal acute experiments showed that longer latency, smaller amplitude forelimb flexions elicited by MC stimulation on the side of the VL lesion were observed when compared to the effects of contralateral (control) stimulation. In additional cats, control lesions in n. Medialis Dorsalis (MD) did not produce the same behavioral or electrophysiological effects. These results indicate that the integrity of the VL complex is essential for normal coordinated movement and suggest that it operates via afferent-efferent connections to the motor cortex and periphery.

APPENDIX A

Performance Data

Table 9. Push button tracking. Total number of trials for each animal--both legs--pre- and post-operatively.

Cat	Foreleg Trained	Total Trials	
		Pre-op	Post-op
Juliet	Left	2343	5115
	Right	2398	5115
Mel	Left	2387	2992
	Right	2508	3113
Fran	Left	3047	3795
	Right	2937	3685
Des	Left	1936	2398
	Right	1771	2233

Table 10. Tight-rope running. Total number of trials for each animal, pre- and post-operatively.

Cat	Lesion	Total Trials	
		Pre-op	Post-op
Juliet	VL	375	680
Mel	VL	500	425
Fran	VL	575	525
Des	VL	550	325
Leslie	VL	350	900
Princess	VL	350	800
Hamlet	MD	325	125
Laertes	MD	300	100

Table 11. Chronological history of each animal.

Cats	Date Training Began (Shaping)	Date Push button Training Began	Running Task Began	Date Operation #1	Date of Operation #2 and Sacrifice
Jul	2- 4-67	3-27-67	12-23-67	2- 2-68	7- 9-68
Mel	2- 3-67	3-22-67	12-23-67	2-28-68	7-19-68
Fran	2- 3-67	3-24-67	12-23-67	3- 6-68	7- 3-68
Des	2- 3-67	5-25-67	12-23-67	3-13-68	7-18-68
Prin	12-23-67	——	12-23-67	1-26-68	7-17-68
Les	12-23-67	——	12-23-67	1-23-68	7-12-68
Ham	3- 8-68	——	3- 8-68	6-18-68	7-24-68
Laer	3-30-68	——	3-30-68	6-24-68	7-26-68

APPENDIX B

Neurological Data

Figs. 16 - 23. Individual summaries of the clinical neurological examinations.

Cat: Juliet
Date of operation: 2/2/68
Locus: Right hemi. VL lesion

Twenty-four hours post-operatively, it was observed that Juliet was quite responsive. Her appetite was good. She oriented perfectly to visual and auditory stimuli presented from all directions, was slower than normal in responding to her environment, but appeared to be in good condition. Muscle tone was good. A gross defect in contact placing was immediately noticable on the left side--particularly in the left foreleg. Righting responses were good, but walking was somewhat sluggish. There was a brisk withdrawal when any leg was pricked with a pin. Balance on the spin table was good.

Within two weeks, motor behavior appeared almost normal when observed with the cat moving freely about, but there was still a persistent contact placing deficit which was still apparent at the time of sacrifice.

Cat: Mel
Date of operation: 2/28/68
Locus: Left hemi. VL lesion

It was about 36 hours after surgery before Mel clearly responded to auditory and visual stimuli. His appetite was fair, There was a good withdrawal to pin prick in all four extremities. Righting responses and spontaneous behavior were fair and good muscle tone was observed in all extremities. No contact placing could be elicited with the right foreleg (eyes covered). Balance on the spin table was good.

After about two weeks, Mel responded almost normally to all environmental stimuli. His appetite was good and he walked and righted well. His balance on the spin table was good. There was normal contact placing with the left foreleg, but no response with the right foreleg when the eyes were covered. At the time of sacrifice, contact placing was fairly good <u>with vision</u>, but totally absent when the eyes were covered.

Cat: Fran
Date of operation: 3/6/68
Locus: Right hemi. VL lesion

Fran walked spontaneously with a slight tilt to the left less than 24 hours after surgery. Her righting response started well, but sometimes the rear of her body rolled to the left (this roll was not observed two days later). She oriented and responded well to auditory and visual stimuli even in the first observation session. There was a brisk withdrawal response to pin prick in all four extremities. With her eyes covered, there was no contast placing with her left foreleg. Fairly good balance on the spin table was observed from three days post-operatively.

After two weeks, all gross motor and sensory responses appeared normal, with the exception that contact placing was absent from the left foreleg when vision was occluded. Fran's appetite had returned to normal. She walked and righted fairly well and balanced well on the spin table. At the time of sacrifice, contact placing with the left foreleg was still absent. All other responses, except as noted experimentally, were normal.

Cat: Desdemona
Date of operation: 3/13/68
Locus: Right hemi. VL lesion

The animal was very sluggish and only slightly responsive to stimuli for about 36 hours after surgery. She showed slow, but good orientation to auditory and visual stimuli. The righting responses were almost normal after three days. There was a brisk withdrawal response to pin prick in all four legs. Contact placing was normal in the right foreleg, while there were sluggish responses in the left foreleg with vision and no response when vision was occluded. Her muscle tone was fairly good one day after surgery and almost normal after three days, while walking was quite sluggish for the first few days. When dropped from a height, she rotated her trunk normally but, for the first ten days or so, fell over when she contacted the ground. Her balance was good.

Within 3 weeks, her walking was again normal. All gross motor and sensory responses appeared normal with the exception of an absence of contact placing in the left foreleg with vision occluded. Her appetite was normal. Righting responses appeared normal as did her balance on the spin table.

Cat: Princess
Date of operation: 1/26/68
Locus: Left hemi. VL lesion

Twenty-four hours after surgery, the animal was still quite sluggish. A great deal of coaxing was required in order to get the cat to respond. She did, however, orient to auditory and visual stimuli presented from various directions. She showed little desire to eat although she did drink a little milk. Muscle tone was fair on the left side, but quite poor--almost non-existent--on the right, but it improved quite rapidly. Walking was quite poor and righting responses were not good. There was almost no spontaneous movement. No contact placing was observed with the right foreleg, while placing with the left foreleg was just about normal. Behavior was fair on the spin table. The response to pin prick was normal in all four legs at all times.

Three weeks after operation, gross recovery was almost complete, with good tone in all extremities, fairly good righting responses and good responses to spin. There was no contact placing with the right foreleg. This absence of placing was still observed at time of sacrifice.

Cat: Leslie
Date of operation: 1/23/68
Locus: Left hemi. VL lesion

Leslie was fairly responsive 24 hours after surgery. There was good orientation to sounds and visual stimuli. A slight tilt to the right side when walking was seen for one day. There was normal withdrawal to pin prick in all four legs. His appetite was poor, but righting responses and spontaneous behavior was fair. There was good tone in all extremities. No contact placing with the right foreleg was observed--with eyes covered. Balance on the spin table was good.

After about three weeks, fairly good responses were seen to dropping and spinning. Contact placing remained absent in the right foreleg with vision occluded.

Cat: Hamlet
Date of operation: 6/18/68
Locus: Left hemi. MD lesion

Spontaneous walking was observed within 24 hours after surgery. His appetite was fair but improved rapidly and he appeared to eat normally after another 12 hours. There were no apparent neurological defects. Contact placing was normal bilaterally, with and without vision. Balance on the spin table was good. Brisk responses to pin prick were observed in all four extremities. He oriented well to sound and visual stimuli. Muscle tone was normal and righting responses were excellent.

Hamlet's behavior was normal during the entire time he was observed and tested, before sacrifice.

Cat: Laertes
Date of operation: 6/24/68
Locus: Right hemi. MD lesion

Laertes was alert within 12 hours after surgery, but was unwilling to walk or eat for another 24 hours. He then began to drink milk and eat. There were no apparent neurologic deficits. Contact placing was normal under all testing conditions. Auditory and visual responses were normal and balance was good on the spin table. Brisk responses to pin prick were observed in all extremities. Muscle tone and righting responses were normal.

Laertes' behavior was normal during the entire time he was observed and tested before sacrifice.

APPENDIX C

Histological Data

Table 12. Details of blocking of brain section in preparation for histology.

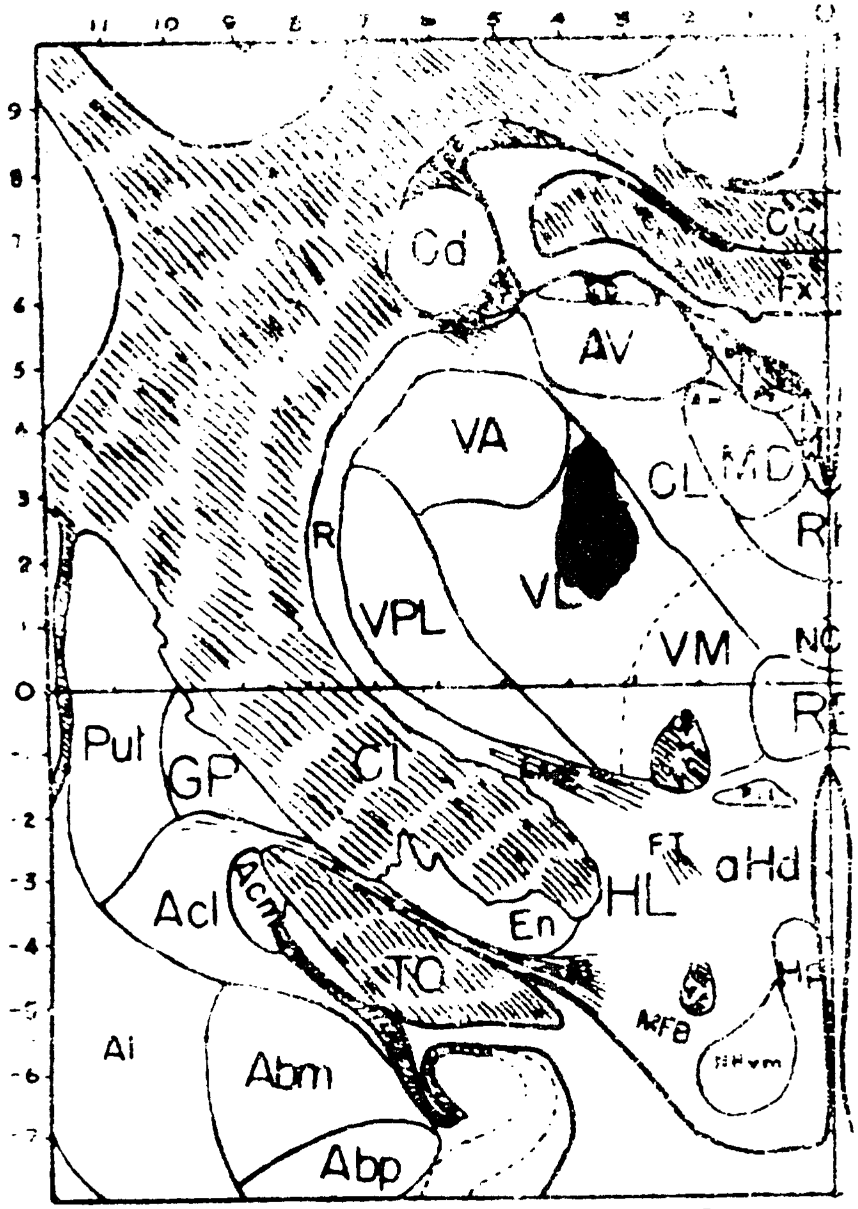
After the cat was sacrificed, the top of the skull was removed and the dura cut away so as to expose maximum cortical area while still retaining enough skull to subsequently replace the head in the stereotaxic frame. The head was then removed and placed in a formalin solution for about 14 days. It was then replaced in the stereotaxic frame and aligned with the reference axes.

An electrode carrier with a #22 scalpel blade in its holder was then placed on the frame and lateral cuts were slowly made from one side to the other until the slice had been made through the entire depth of the brain. Two such cuts were made, 6 - 8 mm. anterior and posterior to the position of the electrode tract. The remainder of the skull above the inter-aural plane was then ronjoured away and the block of brain tissue containing the tract and lesion was placed in a fresh formalin solution and prepared for subsequent sectioning.

Fig. 24. Photomicrograph of a section of Juliet's brain (VL lesion).

Fig. 25. Photomicrograph of a section of Hamlet's brain (MD lesion).

Figs. 26 - 33. Histological reconstructions of each cat's brain lesion. (Jasper & Ajmone-Marsan Atlas, 1954.)



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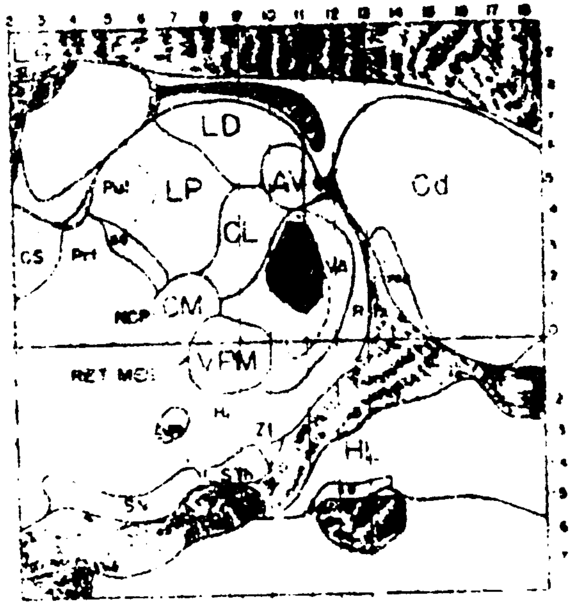

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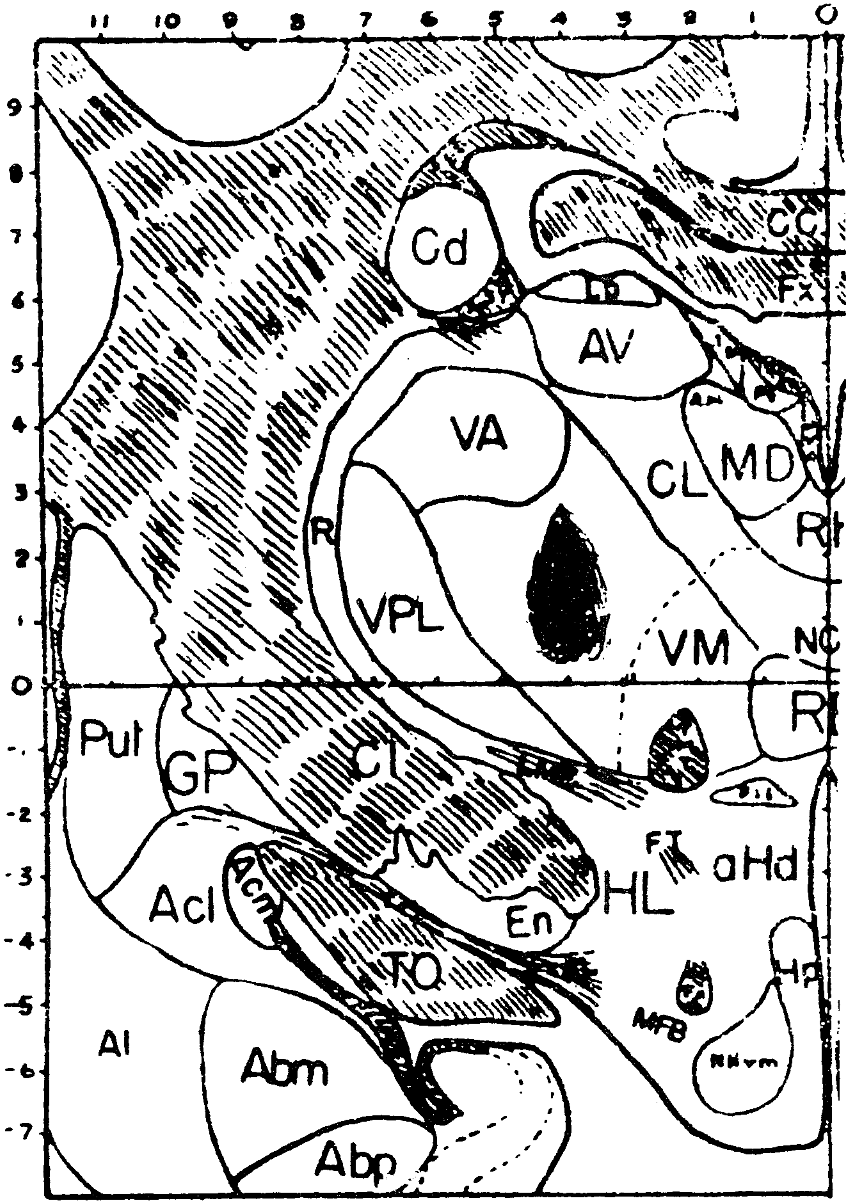
Juliet



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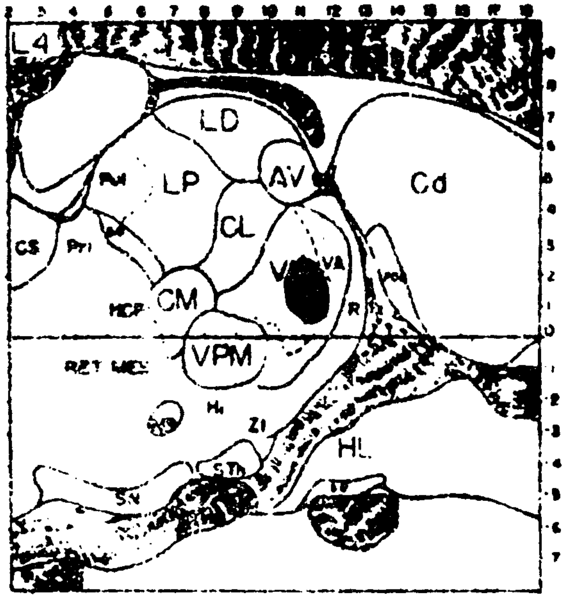

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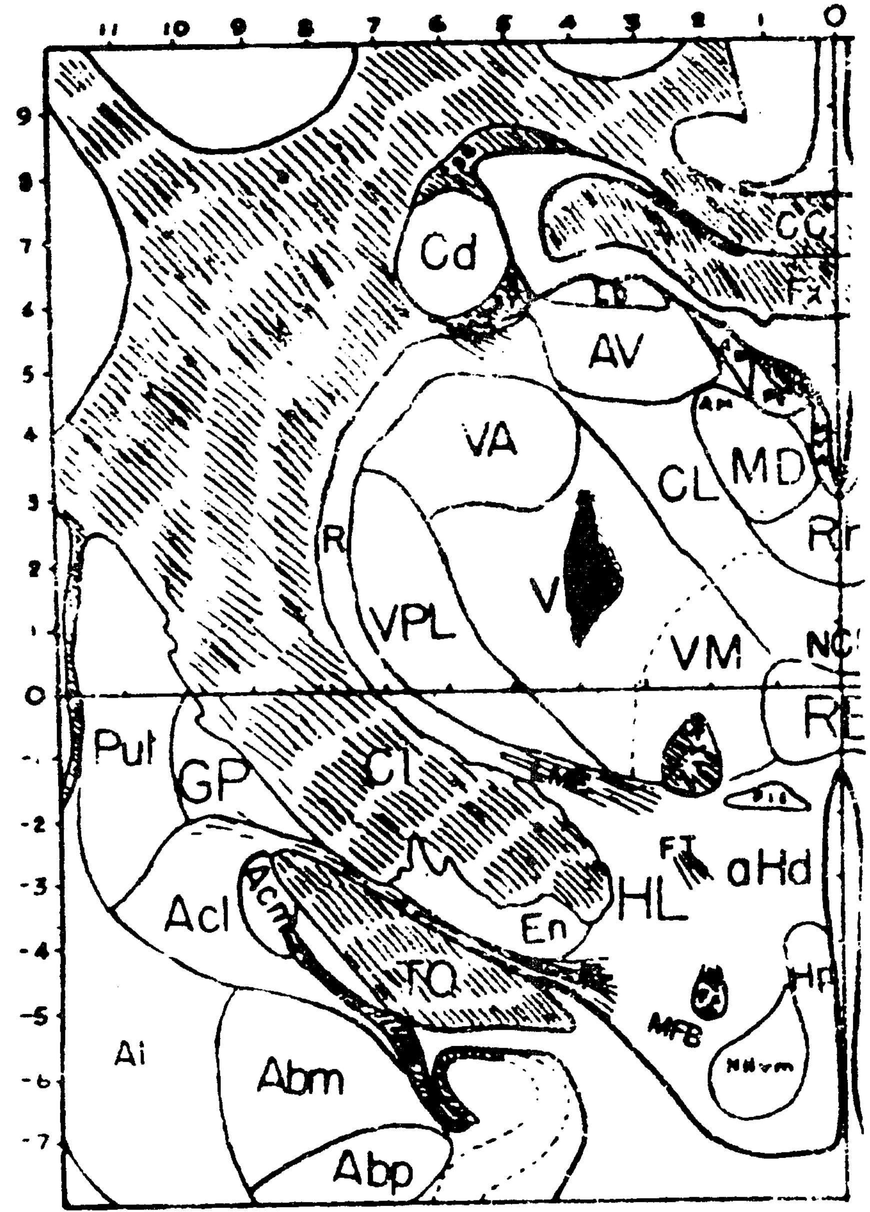
Desdemona



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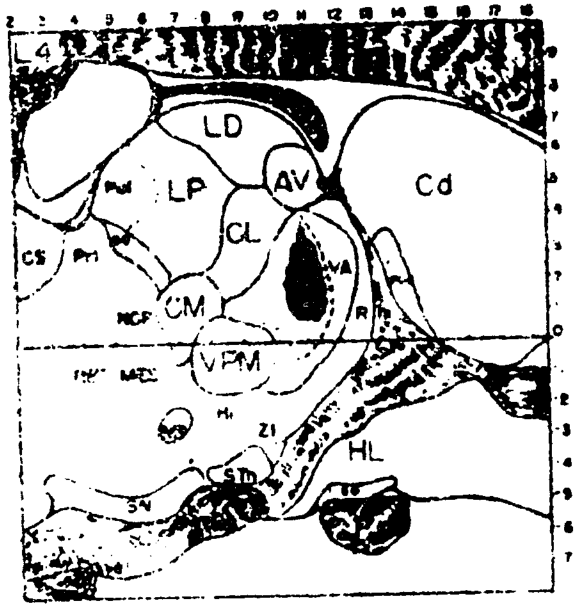

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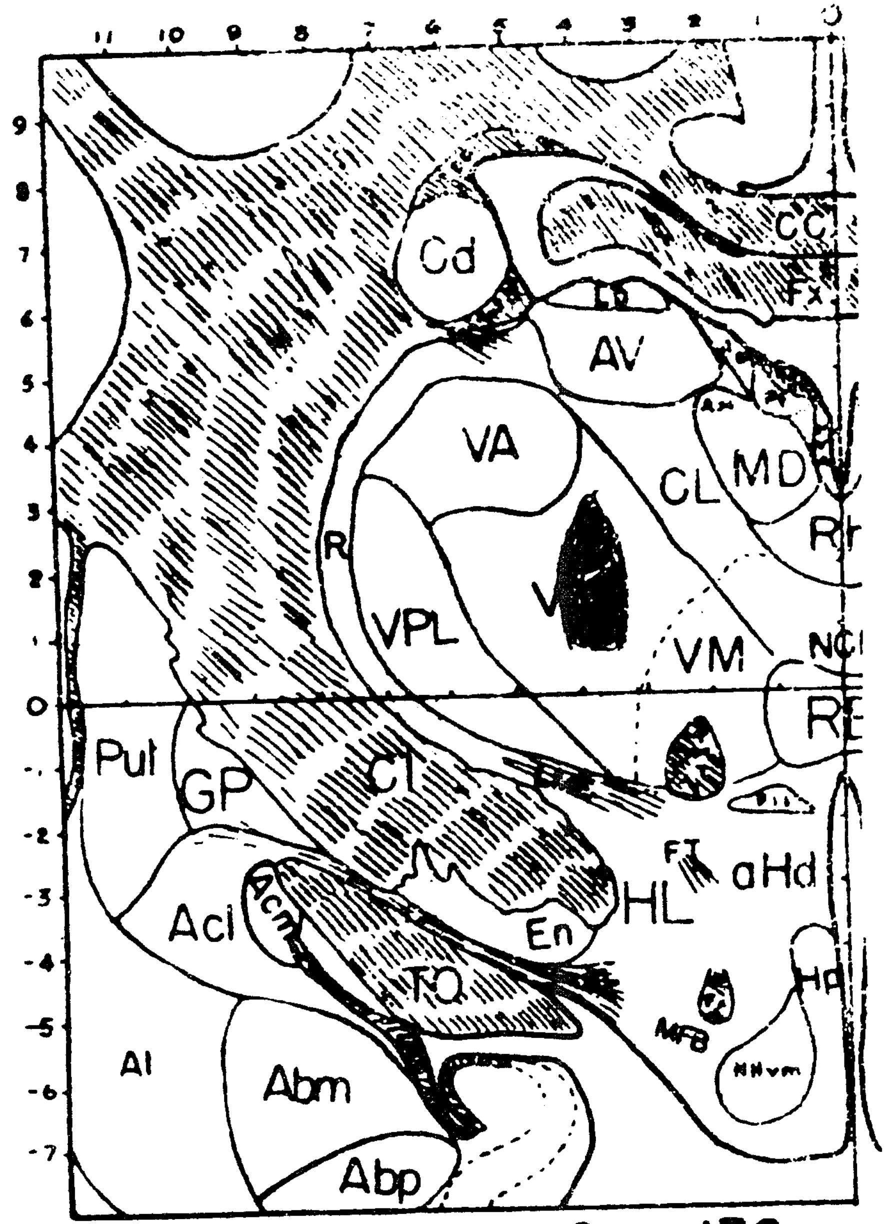

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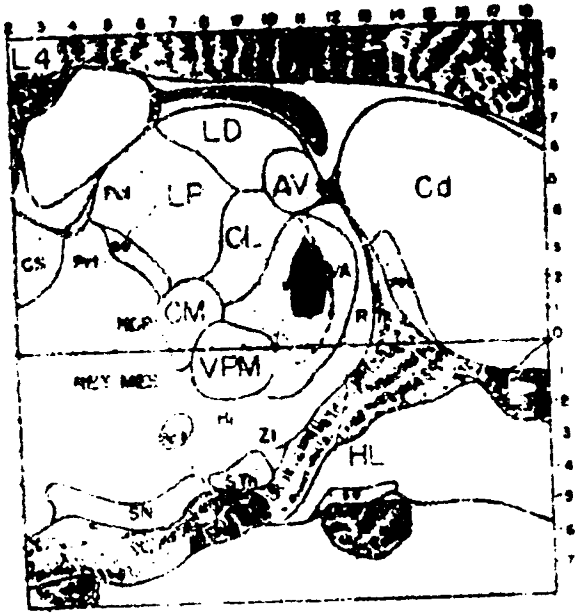

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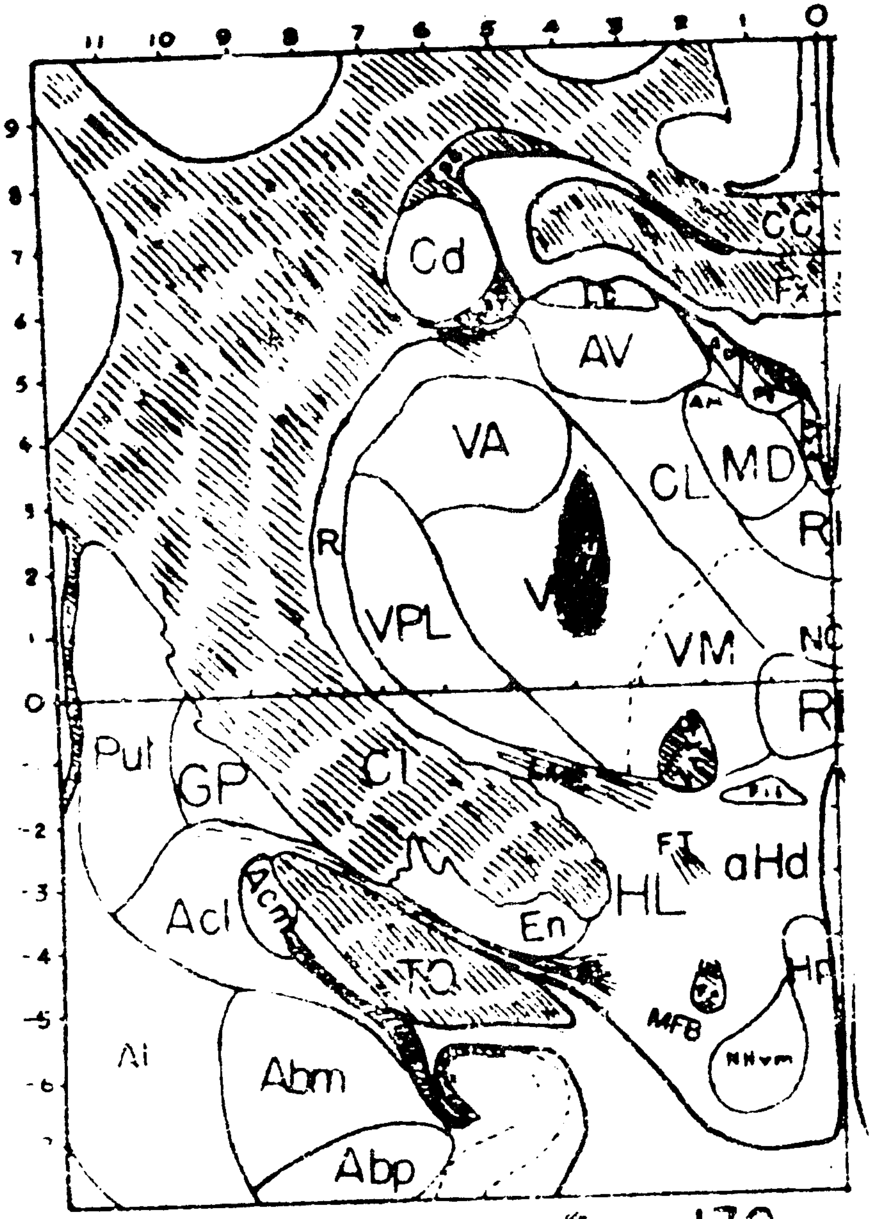

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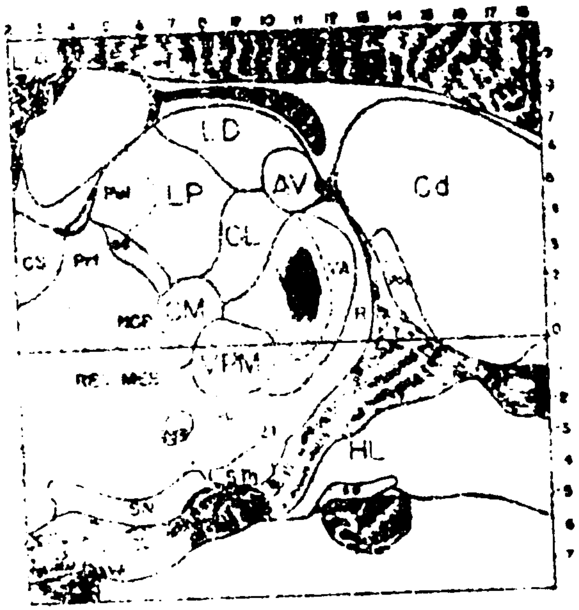

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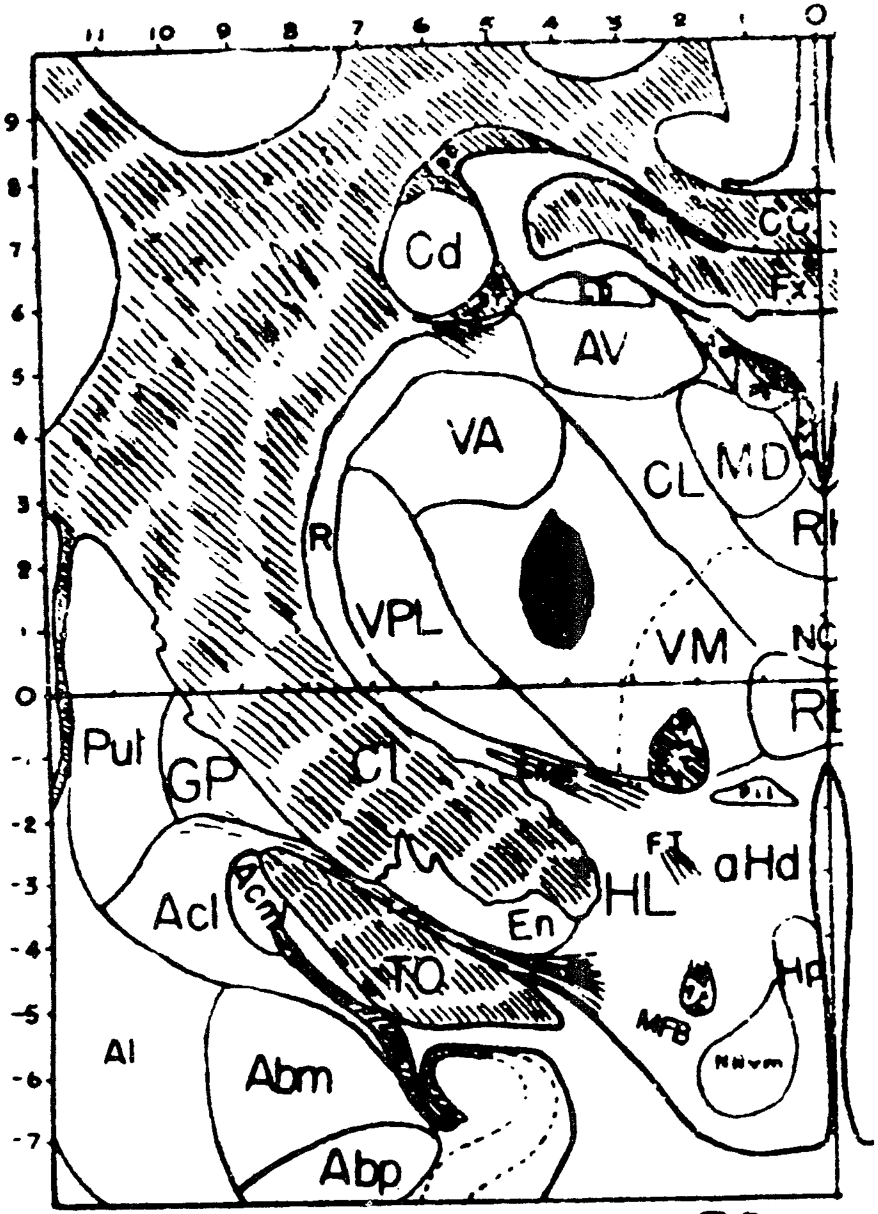
Leslie



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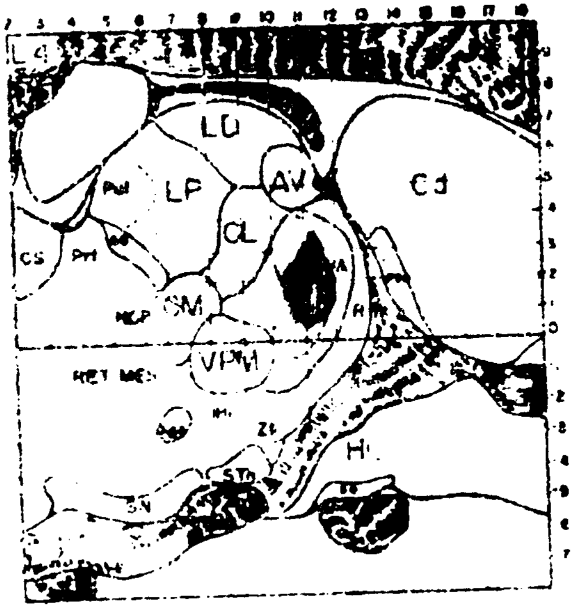

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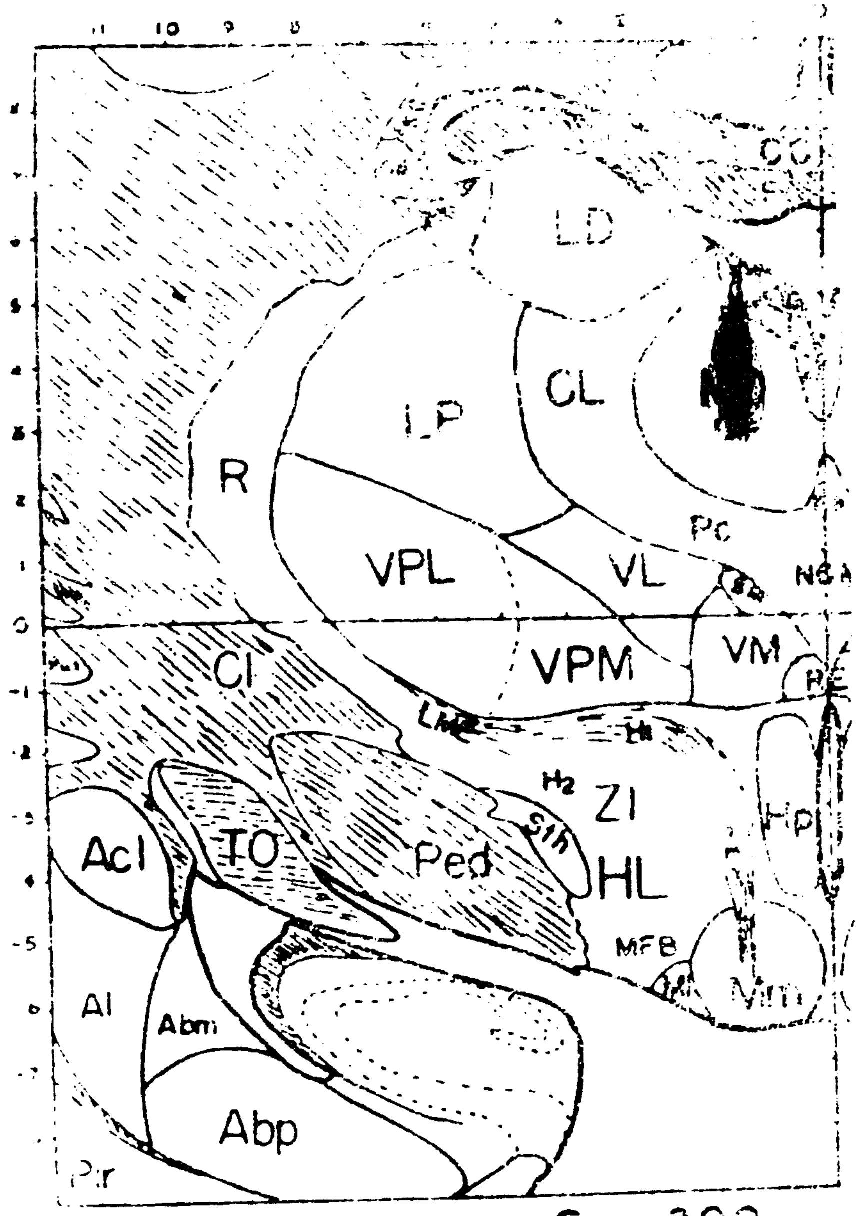
Princess



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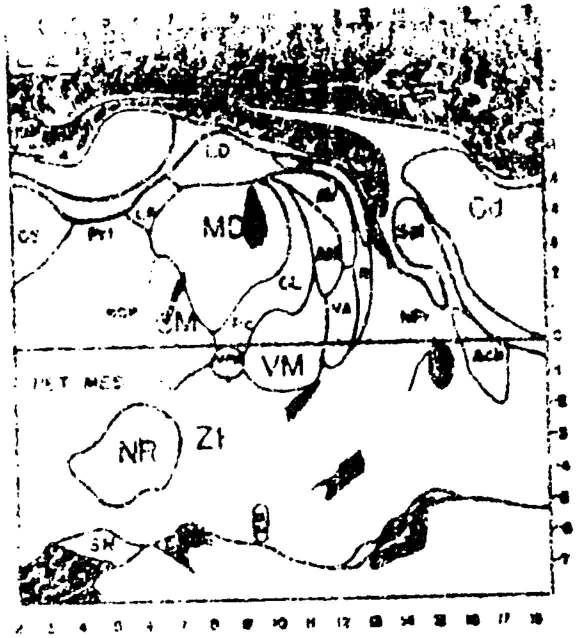
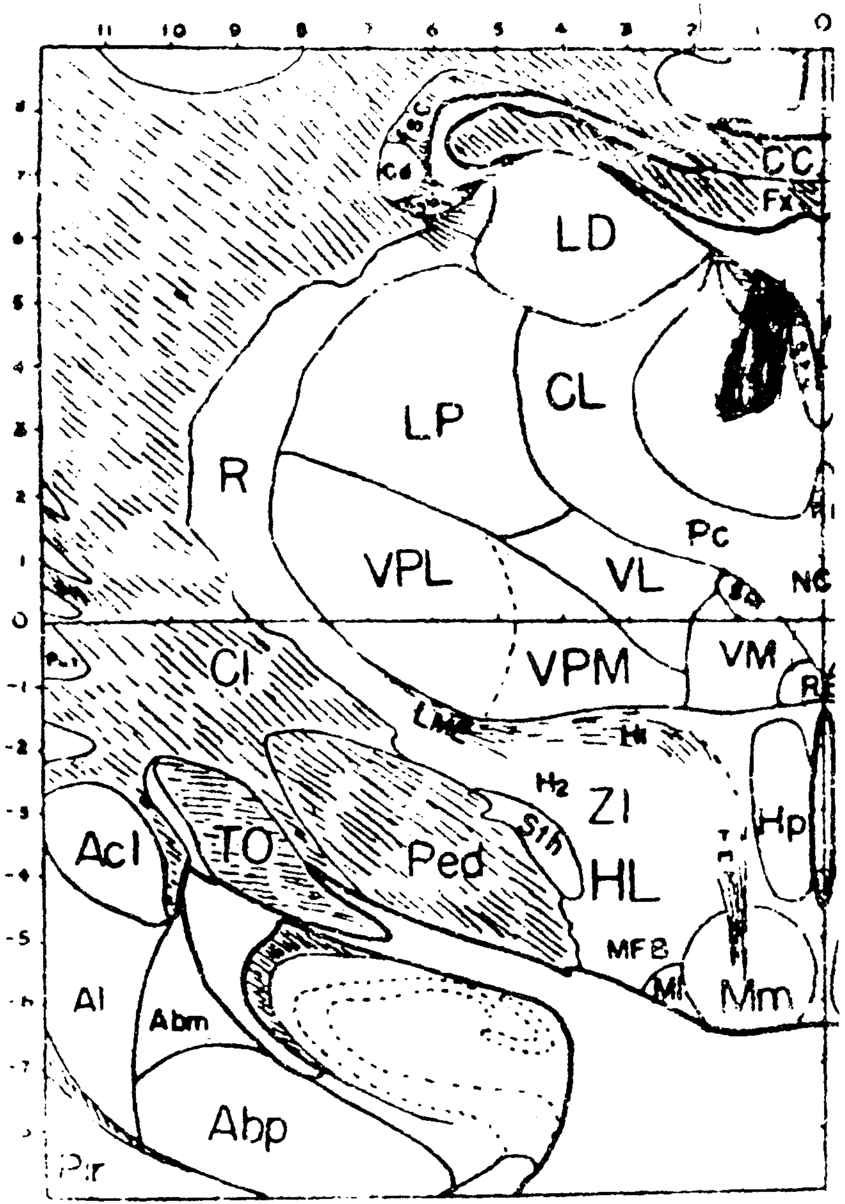


Fr. 9 5

Hamlet



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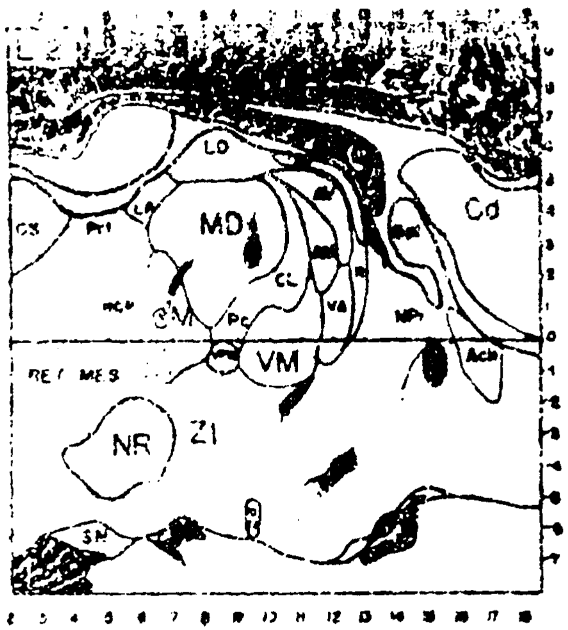


Fr. 95

Laertes

APPENDIX D

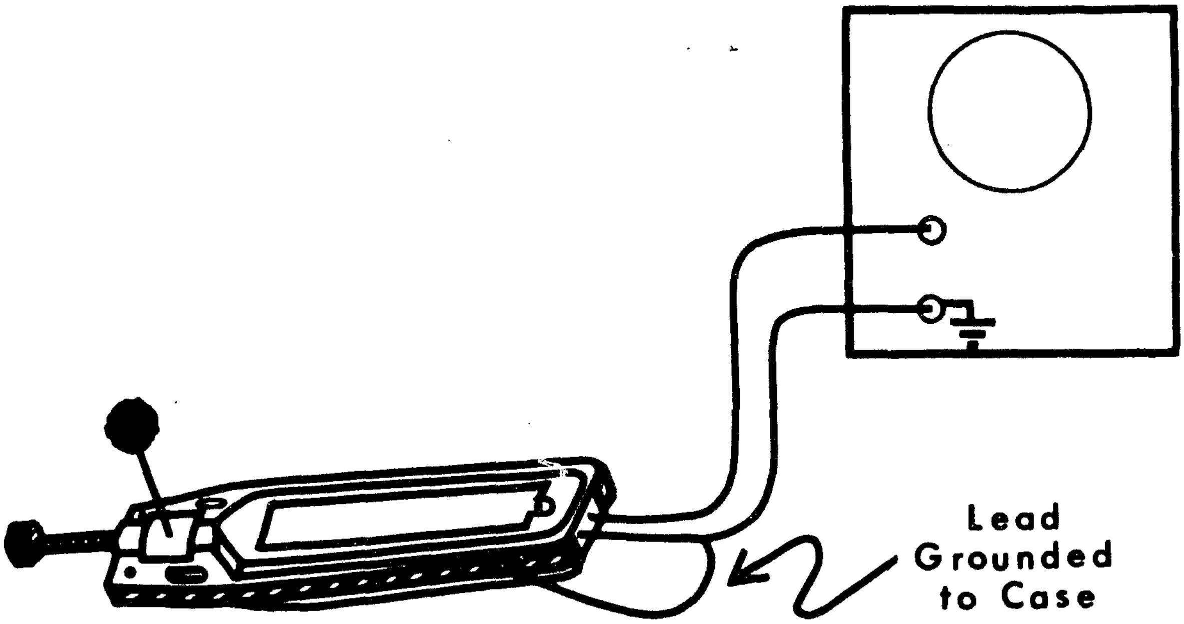
Apparatus

Table 13. Details of linear accelerometer. Used in experiments #1 and #4.

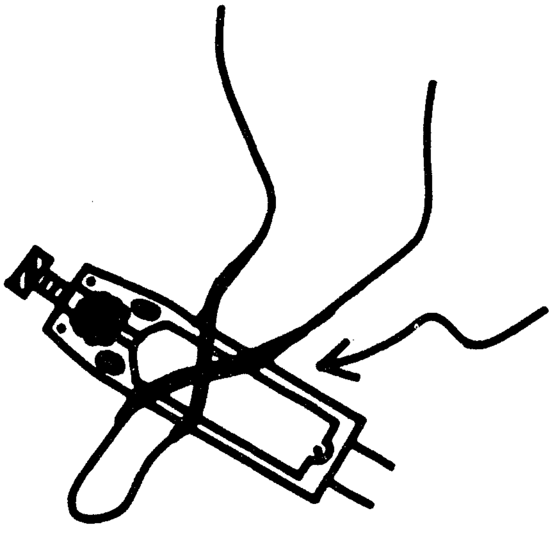
The linear accelerometer used in experiments #1 and #4 was devised by the author. It consisted of a piezoelectric phonograph cartridge of high output design, with a screw clamp needle chuck. The needle was removed and a 1/2 inch long, number 20 gauge steel wire was clamped in the needle-chuck. A 12 gram ball of lead was melted onto the distal end of the wire shaft. Shielded wire was attached to the output of the cartridge and was connected directly to the scope input. Several identical units were made and were matched for equal amplitude output for equal accelerations. Accelerometers were matched two at a time. They were mounted, one at a time, on a pivot arm of known length and were then pulled, against a spring, for a distance of 3 inches and then released. The resultant output from the unit was stored on a Tektronix 564 storage scope. Other units were then sampled in the same manner until several were found which indicated the same output under the controlled calibration conditions.

When an accelerometer was mounted on an animal's leg as shown in Fig. 34, flexion of the limb resulted in an indication on the scope. The amplitude of the scope deflection was proportional to the acceleration of the limb. Latency measurements were made from the stimulus onset to the first major point of inflection. That is, to the point in the curve where the rising curve begins to fall.

Fig. 34. Drawing of the linear accelerometer and its attachment to the cat's leg.

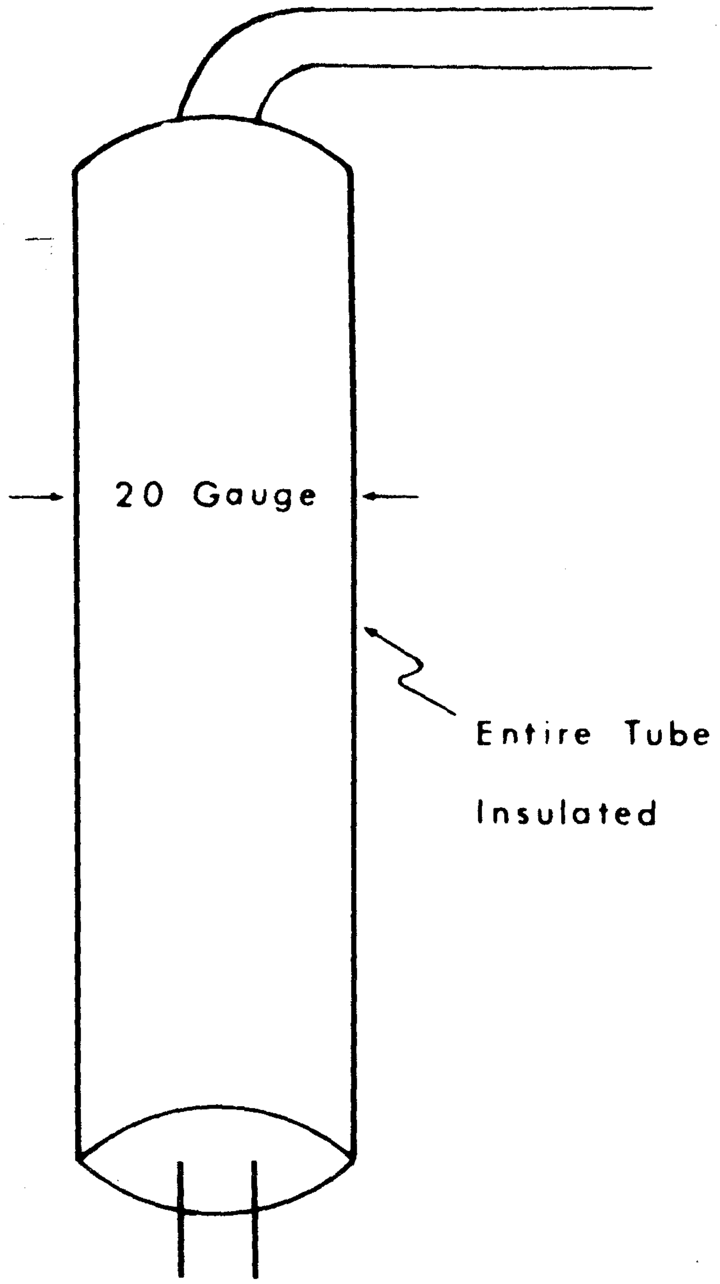


Lead
Grounded
to Case



Taped to Foot
of Foreleg

Fig. 35. Illustration of bipolar stimulating and recording depth electrode used in experiment #1.


20 Gauge
Entire Tube Insulated

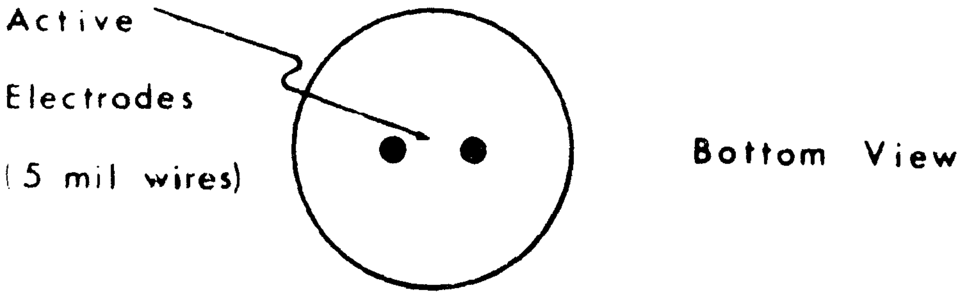
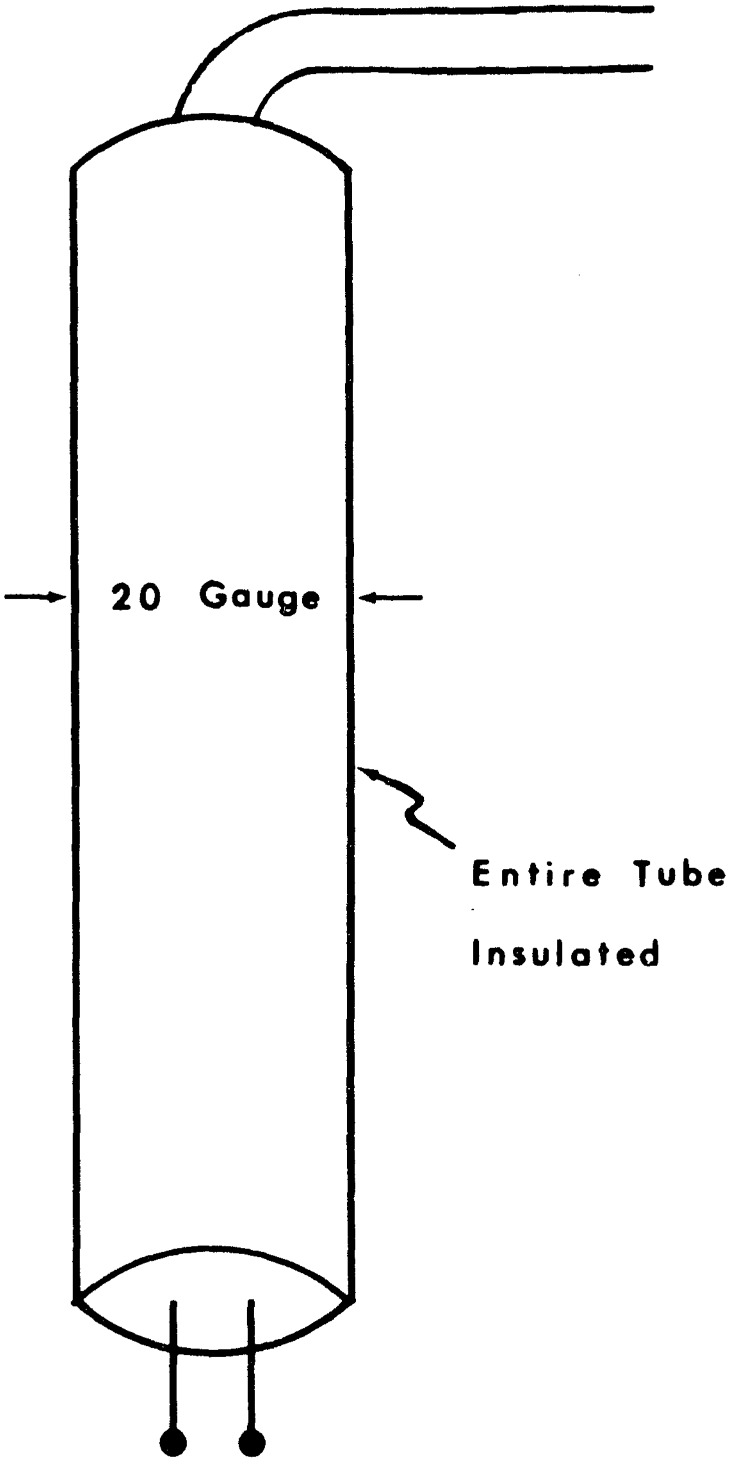

Active Electrodes (5 mil wires)
Bottom View

Fig. 36. Illustration of bipolar stimulating and recording ball tipped surface electrode used in experiment #1, Chronic surgery, and experiment #4.


20 Gauge
Entire Tube
Insulated

APPENDIX E

Sample Data Sheets

Fig. 30. Sample clinical neurological examination data sheet.

CAT: ____________

DATE OF OPER: ________

LOCUS OF LESION: ____________

0 = ABSENCE OF RESPONSE
1 = POOR (VERY SLUGGISH AND/OR LOW AMPLITUDE)
2 = QUESTIONABLE (POSSIBLE TRUE RESP. - NOT CLEAR)
3 = FAIR
4 = NORMAL

DATE	PIN-PRICK L	PIN-PRICK R	SPONT. [illegible]	PLACING (TACTILE)		RIGHTING REACTIONS	CROSSED EXTENSOR	GROSS LOCOMO.	RESP. TO GRAVITY	[illegible] ([illegible])	VISUAL FIELDS	ORIENTS TO SOUNDS	EAT + DRINK	COMMENTS
	1/2	1/2		L	R									

Fig. 38. Sample error summary sheet.

1

	LEFT LEG			RIGHT LEG		
CAT/DATE	SKIP	OMIT OR WRONG LEG	REPEAT	SKIP	OMIT OR WRONG LEG	REPEAT

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