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I am submitting herewith a dissertation written by Renée-Michelle Culver entitled "Operant Modulation of Amygdaloid 40 Hz Spindle Density and the Concomitant Effects on Behavior in the Rat." I recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Psychology.

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OPERANT MODULATION OF AMYGDALOID 40 Hz SPINDLE DENSITY AND THE CONCOMITANT EFFECTS ON BEHAVIOR IN THE RAT

A Dissertation

Presented for the

Doctor of Philosophy

Degree

The University of Tennessee, Knoxville

Renée-Michelle Culver

August 1977

1382611

I dedicate this study to the mentors in my life, past and present. You have given me those things that are most valuable to me; things that can never be taken away.

To Joel L. who has taught me about those things professional and much, much more.

To Debra K. who has taught me the finest things about personhood.

To Michael M. who has shown me peace, morality, integrity and love.

To Tom L. who gave me my science and taught me of kindness.

To Tom P. who taught me about feelings.

To Ann R. who has shown me the wonders of enduring friendship.

To Jeff W. who taught me an appreciation of quality in my work.

To Ethel E. who has taught about where I'd like to be in our brief encounters.

To Konrad R. who teaches me about teaching.

Thank you.

ABSTRACT

The purpose of this study was to investigate the effects of operant facilitation of 40 hz EEG spindles in the amygdala of the rat. After demonstrating 40 hz spindle densities were increased behavioral observations were made to determine if there was an effect on emotionality and reactivity.

Five male hooded rats (Blue Spruce Farms) were used as subjects. Electrodes were aimed bilaterally at the corticomedial amygdala. Histological evaluation after the experiment showed that the majority of the hits were in the medial nucleus (N=5, 50%) and the central nucleus (N=3, 30%).

The experiment employed a within subjects pretest-test-posttest design. The three part experiment included habituation (10 days), acquisition (40 days) and extinction (20 days) periods. At the end of these periods behavioral observations were made. Reactivity to handling and aversive stimulation (shock) were measured in addition to open field behavior and attack behavior toward a pencil presented at the snout.

During the course of the experiment the animals were maintained on 23 hr water deprivation. Preexperimental training included water dipper training and a bar pressing period to demonstrate the effectiveness of water as a behavioral reinforcer. At this time the animals also learned the significance of simultaneously presented visual and auditory stimuli as secondary reinforcers.

The only parameter changed across the three conditions was the contingency of the reinforcement. During habituation and extinction, reinforcement was presented randomly. Reinforcement was made contingent upon the production of 38-42 hz amygdaloid spindles during acquisition.

The paradigm in which this was accomplished lasted 40 minutes per day for six days a week. Conditioning was accomplished unilaterally at any given time but the contingent or rewarded hemisphere was alternated, with both hemispheres receiving 15 minutes or a total of 30 minutes of conditioning per day. The remaining time was spent acquiring baseline data for one of the two hemispheres. Baseline data, taken during a period in which no reinforcement was available, was accumulated for a given hemisphere on alternating days.

The execution of the daily paradigm was completely automated. The EEG frequency discrimination was a hybrid method using a combination of analog preprocessing with broad bandpass filters and "instantaneous" frequency discrimination. Individual instances of 40 hz activity above 5 uv activity was monitored by a digital burst detector which enabled the establishment of quantitative and temporal criteria for defining a burst.

Conditioning was unequivocably demonstrated in all subjects in both hemispheres. Assymptoting during acquisition was marred by some equipment problems but recovery was seen after repairs were effected. The reliability of the conditioning phenomena and the monotonicity of the acquisition were indicators that the associated physiological states concomitant with the 40 hz activity were highly discriminable to the animal.

There was considerable behavioral variability seen across the subjects. Animals showing low levels of pretest activation showed increases in activation. There was no evidence of "superactivated" open field behavior. At no times were there changes in reactivity to shock. There were however noticeable changes in reactivity to handling the animals. After 40 hz aquisition the animals became more reactive to handling. Some animals became more aggressive toward a pencil presentation to the snout. All of the changes seen in the animals disappeared after extinction.

One animal's behavior was completely anomalous. This animal showed overwhelming increases in reactivity to handling and vocalization. During conditioning the animal showed what was the beginning of an unpredictable series of "quiet attacks" on the investigator. The animal also made reliable and prompt attacks on a pencil when inserted into its cage. These changes disappeared after extinction.

It is suggested that behavioral changes seen in these experiments were due firstly to the locus of the recording electrode. There was a correlation between the conditioning electrode site and the degree of affective change seen in the animal. The animals having central nucleus recording sites showed more changes than did the animals having medial nucleus implants. It is further suggested that the observed changes are related to modulation of mesencephalic activity which in turn effects arousal.

The results warrant further investigation as it is anticipated that these avenues of investigation could potentially add much to the existing picture of amygdaloid function.

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CHAPTER I

INTRODUCTION

The amygdala is a phylogenetically old subcortical nuclear system embedded anterolaterally in the temporal pole of each cerebral hemisphere. Part of the limbic system, the amygdala has intimate connections with the olfactory bulbs, hypothalamus, septum, and periamygdaloid and prepiriform cortices.

Functional discussions on this nuclear group must be wide in scope as there is input to the amygdala from all of the sensory systems. However, amydalopetal pathways are indirect and circuitous, passing through several relay nuclei or sensory cortex. Due to the high degree of information preprocessing the amygdala receives a highly abstracted representation of environmental occurrences. Amygdaloid receptor mechanisms monitor internal states with highly specialized endocrine, gonadal steroid and metabolic receptors (Stumpf and Roth, 1966) influencing cyclic reproductive and sexual behaviors. Structures have been identified for the regulation of internal homeostases (Hayward, 1972), neurotransmitters and neurohumors (Zolovick, 1969). There is an extensive body of literature functionally mapping the amygdala and implicating it in such diverse processes as hyperkinesis, epilepsy, emotionality, cardiovascular regulation, hormone regulation, defense reactions, learning territoriality, rage, sleep, awakening, aggression and many other behaviors. Simultaneously there is much controversy

among investigators concerning the proper interpretation of these observed behaviors.

The goal of this study is to investigate the effects of operant modification of specific EEG (electroenecephalographic) components. In the experimental section a very detailed description of how the conditioning occurs will be offered followed by a description of resulting behavioral changes. The geneses of these EEG components are anatomically related to the olfactory bulbs which have extensive primary and secondary projections to many of the amygdaloid nuclei. Very little research has been conducted in the conditioning of amygdaloid EEG. In view of the functional complexities of amygdaloid and olfactory structures a comprehensive discussion is offered herein including associated anatomical data related to these systems. Studies relating EEG and behavior follow.

Amygdaloid Anatomical Considerations

The behavioral diversity demonstrated by stimulation and ablation studies indicate that the amygdala is by no means a unitary structure. The amygdaloid complex, viewed historically is a descriptive anatomical concept rather than ahighly differentiated system of nuclei. It serves as the subcortical grisea for the basal aspect of the caudal telencephalon which is the piriform lobe (Lammers, 1972). The organization is that of a system of interconnected nuclei and subnuclei, the number and classification of which is still debated because of interspecies variations and characteristically subtle and diffuse

cytoarchitectonic transitions (Kaada, 1972). Earlier investigators relied upon relatively poor discriminative staining techniques for normal and experimentally treated materials such as the Marchi technique. Newer methods have aided in mapping nuclear boundaries but determinations are still arbitrary. For example, it is still acknowledged that the lateral nucleus shows cytoarchitectonic continuity with the putamen (Humphrey, 1972) yet the two nuclei are treated very differently. Classification of the nuclear systems is complicated by the fact that the Nissl and Golgi staining methods reveal very different cell groupings (Hall, 1972).

Early taxonomies were achieved through embryological (Holmgren, 1923) and comparative methods (Johnston, 1923). From the latter criteria, the amygdala can be roughly subdivided into two nuclear groupings: an older corticomedial group whose afferents include significant direct or primary olfactory input (Cowan et al., 1965; Koikegami, 1955; LeGros Clark and Meyer, 1947) and the phylogenetically younger basolateral group which is rich in reciprocating hypothalmic projections.

Johnston's (1923) initial divisions of the corticomedial group included the central and medial nuclei and the nucleus of the lateral olfactory tract. The cortical nucleus is included in this group by many investigators (Gloor, 1960; Kaada et al., 1954; Pribram and Kurger, 1954). This is a convention of convenience however, as cogent arguments can be made to the effect that the cortical nucleus is not an amygladoid nucleus based on its structure and function. On the other

hand it should be included when one considers the relations and pathways of its afferents and efferents (Kaada, 1972). Goddard (1964) advocated leaving the nucleus unclassified until further data is gathered.

The second nuclear system is the basolateral component which is the phylogenetically newer group. This group is composed of the basal and lateral nuclei and the less well defined anterior amygdaloid area, first identified and distinguished from the central nucleus by Gurdjian (1928). These regions characteristically lack primary olfactory input. The central nucleus is dorsal to the amygdala. Its boundaries laterally are the putamen and superior is the globus pallidus. The basal nucleus is superior to the central nucleus and lies between the lateral and medial nuclei. The cortical nucleus is superficial to the basal nucleus and extends from the medial nucleus to the amygdaloid fissure (Hall, 1972).

The main projection pathway of the basolateral group is the ventral amygdalofugal pathway (VAF). The pathway originates primarily in the periamygdaloid cortex with contributions from the basal and lateral nuclei. The extent of these contributions are species dependent with increasing basolateral involvement with phylogenetic advancement (Nauta, 1961; Valverde, 1965; Egger, 1972). Previously it was thought that the VAF fibers were entirely efferent (Fox, 1943), but recent investigations have demonstrated the existence of amygdalopetal (afferent) fibers originating in the lateral preoptic area and rostral hypothalamus. Such findings demonstrate an important reciprocity or exchange of information between the basolateral complex and diencephalon.

Telencephalic connections were demonstrated by De Olmos (1972) using cupric silver techniques with the rat. After placing discrete lesions in the piriform cortex and the basal and lateral nuclei, cellular degeneration was found in the entorhinal cortex, amygdalo-transition area, prepiriform area, ventral external capsule and claustrum. Earlier studies in the cat have demonstrated orbital gyrus projections from the anterior orbital area to the lateral amygdala and from the orbitosylvian area to medial regions. Powell (1965) however, reports finding no such cortical projections for the rat. There is the suggestion of two organizational processes here. First, there seems to be the beginning of a phylogenetically related tendency for fibers of orbito-cortical origin to project to lateral nuclear structures and for ecto-sylvian fibers to project to the central nuclear structures. A second consideration is that these systematic changes may reflect a corresponding change in the role of the amygdala, from the primary function of being an olfactory projection area, to becoming more of an association area or cortical relay with the corresponding increase in encephalization (Lammers, 1972).

Some supporting comparative observations have been made, relating changes in deficits from amygdaloid lesions to phylogenecity. In the rat, bilateral electrolytic lesions produce aphagia and adipsia. No change in pituitary function, glucose metabolism or stress related ACTH (adrenal corticotropic hormone) were seen. Affect was left unchanged.

In the agouti, the same surgery produced a taming effect while food intake was left unaffected.

In adult domestic cats, anorexia and hypersexuality were seen. Docility also resulted. The response in the lynx is seen with less stupor than was observed in the domestic cat. Inappropriate oral exploration of objects in the environment also appeared.

Similar effects were seen in both juvenile and adult rhesus monkeys. Modifications of oral explorations became most pronounced. Increases in sexual arousal and autoeroticism were also augmented. Changes in fear responses and docility toward humans were also seen (Kling, 1966).

These results support Lammers' (1972) assertions on the changing structure and role of the amygdala with phylogenetic development. Modification of food intake seen in the rat is evidence of predominating amygdaloid control at diencephalic and mesencephalic levels. Modification of oral and sexual patterns seen in the more advanced monkey indicates that the amygdala is involved in influencing or relaying information to cortical and telencephalic levels. Kling (1966) states that these trends are reflections of two different systems which shift in relative adaptive importance with phylogenetic development.

Returning to neuroanatomical details, the lateral and basal nuclei have piriform projections via the VAF. Reciprocal projections between these two nuclei are established via short axoned (Golgi II) association fibers, part of the amygdala's intrinsic relay system (De Olmos, 1972).

The lateral nucleus has one additional efferent, a diffuse pathway extending medially and joining the medial forebrain bundle (MFB). Experimental transection of these fibers has resulted in terminal degeneration seen in the whole extent of the lateral hypothalamus

dorsomedial and ventromedial thalamus and lateral habenula (De Olmos, 1972). Additionally, basal nuclear fibers projecting from the optic area have been described in the cat (Nauta, 1958).

The main projection pathway for the remaining corticomedial amygdala is the stria terminalis. The stria terminalis is divided into three components (Fox, 1940; 1943). The first is the precommissural component projecting to the medial preoptic area and anterior hypothalamus, continuing to the VMH and ventral premammilary body in the rat (Heimer and Nauta, 1969).

The second is the commissural component and links the two cortical nuclei. "Commissural component" is in reality a misnomer in that the fibers are actually a decussation. The post-commissural or supra-commissural component terminates in the bed nucleus of the stria terminalis and the anterior hypothalamus, and is the projection field of the medial and basolateral nuclei. These projections have been identified in the rat, mouse and hamster (Leonard and Scott, 1971; De Olmos, 1972; Van der Sprinkle, 1926).

The nucleus of the lateral olfactory tract is another taxonomically enigmatic area. It is clearly distinct from the piriform cortex (Valverde, 1965) and can be considered part of the amygdala primarily on the basis of its afferent and efferent relationship with the stria terminalis. It receives direct input from the olfactory bulbs as it is the target relay nucleus of the olfactory tract.

The cortical nucleus is the amygdaloid nucleus having the fewest VAF efferents, having instead profuse projections to almost every other

amygdaloid nucleus. The cortical nucleus has rich projections to the basolateral complex and receives extensive projections from the basal medial nucleus. It is a second quasi-amygdaloid nucleus receiving primary olfactory input from the olfactory bulb to its antero-lateral division. In addition to receiving primary input from the main bulb, the posteromedial section of the cortical nucleus receives projections to the accessory olfactory bulb (Winans and Scalia, 1970).

The anterior amygdala area contains the bed nucleus of the medial forebrain bundle and thusly effects fibers that project to the preoptic area, lateral hypothalamus, dorsomedial thalamus and midline thalamic nuclei (Lammers, 1972). The anterior amygdaloid area receives projections from the preoptic area via the MFB. The area is a most important intermediary for the reciprocal interrelationships between the cortical amygdalo-piriform complex and the diencephalic structures listed above (Lammers, 1972).

The medial nucleus lacks projections from the anterior amygdaloid area and the lateral nucleus. The primary medial nuclear afferentation is from the periamygdaloid cortex and from the cortical nucleus. Several investigators have demonstrated primary olfactory input to the anterior medial nucleus (Nauta, 1958; Scalia, 1966; De Olmos, 1972).

The central nucleus has projections to the lateral preoptic area and to the anterior amygdaloid area (Valverde, 1965; Nauta, 1958). Neocortical afferents from the temporal cortex have also been demonstrated (Hall, 1972). Discrete lesions placed in the central nucleus will cause terminal degeneration all along the VAF and in the lateral hypothalamus.

Intercommunication between the associated amygdaloid nuclei are made possible through a complex network of short axoned fibers composing the amygdala's intrinsic relay system. The intrinsic relay system is the source of the amygdla's piriform and periamygdaloid interconnections. In addition, the organization of intrinsic fibers interconnect the dorsal and ventral areas of the complex (Valverde, 1965).

To review, the amygdala has two major projection fields in addition to its own intrinsic relay system. The primary field is characterized by short latency monosynaptic pathways and consists of projections to the basal septal region, caudate nucleus, preoptic area, anterior and ventromedial hypothalamus, contralateral amygdala, piriform cortex, anterior temporal and insular cortex. Longer latency, multisynaptic pathways are characteristic of the secondary fields projecting to the remainder of the hypothalamus, subthalamus, entopeduncular nucleus, mesencephalic tegmentum, hippocampus, diffuse thalamic projection system and eventually, most of the neocortex (Gloor, 1960). There are projections to the nuclei medialis dorsalis and lateralis posteriori which are the thalamic nuclei having associative cortical projections (Fox, 1949; Pribram, 1960). It can be seen that the amygdala has ample opportunity to exert a strong influence on the limbic system mediating a wide variety of emotional, survival related, internal vegetative homeostatic processes.

Amygdaloid afferents and efferents having a "multisensory" influence not unlike the diffuse mesencephalic reticular activating system (Adey, 1958) have been identified. Figures 1, 2, and 3 are pictorial representations of the amygdaloid connections.

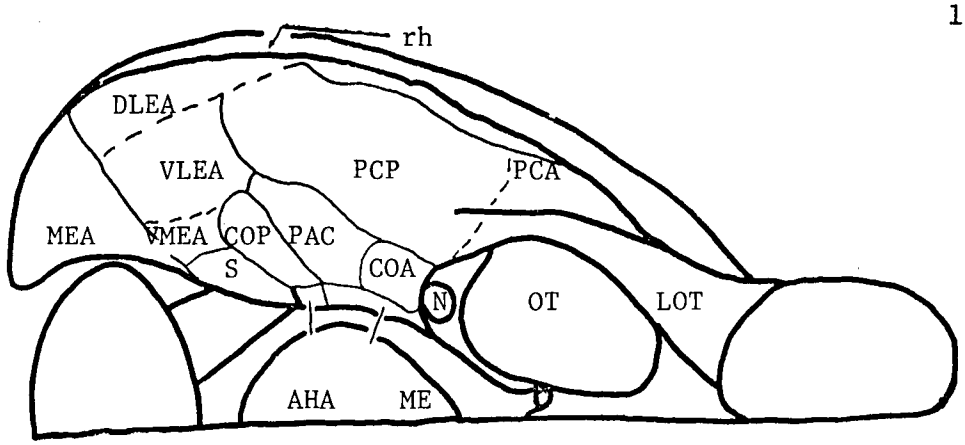


Figure 1a. Schematic diagram of the main cytoarchitectonic subdivisions of the cerebral cortical areas to receiving amygdaloid projections.

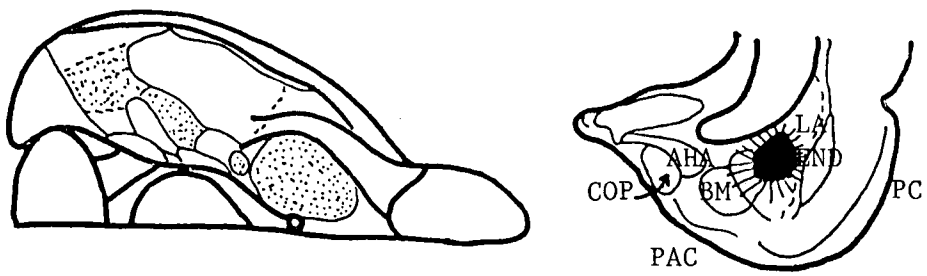


Figure 1b. The cortical projection of the lateral amygdaloid nucleus as shown by the transport of tritiated amino acids (leucine or proline).

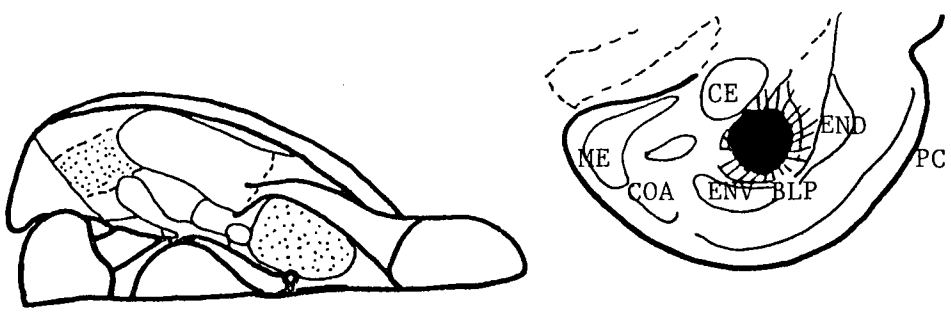


Figure 1c. An injection of tritiated proline into the anterior and posterior divisions of the basolateral nucleus. The axoplasmically transported silver grains are concentrated in the ventral part of the lateral entorhinal area, the parasubiculum and the subiculum.

Figure 1. Schematic diagrams of the main connections of the amygdaloid complex with cortical and subcortical structures as revealed by anterograde transport and degeneration studies in the rat, drawn from Kretteck and Price (1977a and 1977b). The site of injection within the amygdaloid complex is shown in black, and the radiating lines nearby represent areas which may or may not be involved in the cortical projections but which contain silver deposits in a photoemulsion responding to tritium sufficiently above background to be considered a possible cortical projection. The brain is viewed from its ventral surface, and the rostral pole (olfactory bulbs) are to the reader's right. Abbreviations are on page 12.

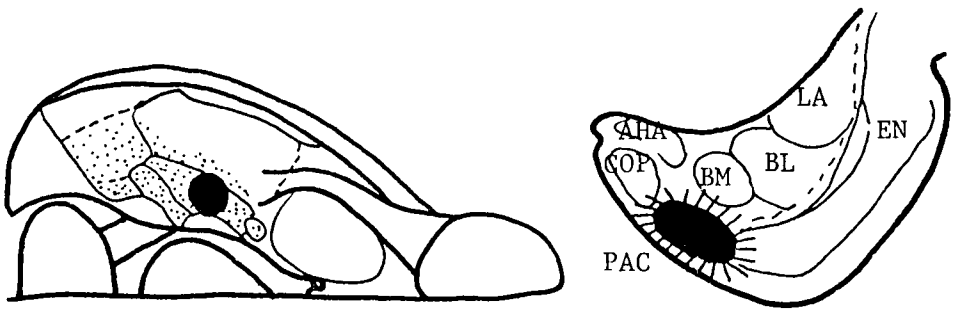


Figure 2a. An injection of tritiated amino acid into the periamydaloid cortex and anterior cortical nucleus. Silver grains are found deposited in the in areas corresponding to the adjacent ventromedial and ventral parts of the lateral entorhinal area and the subiculum.

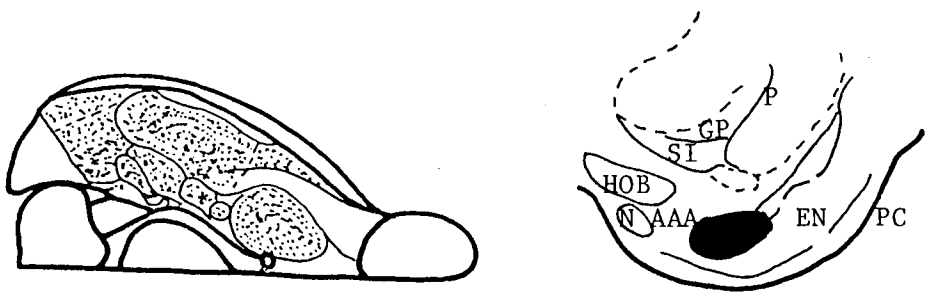


Figure 2b. An injection into the ventral part of the endopiriform nucleus and the lateral part of the anterior amygdaloid area. Silver deposits are found in the lateral entorhinal area and in the ventral two-thirds of the subiculum.

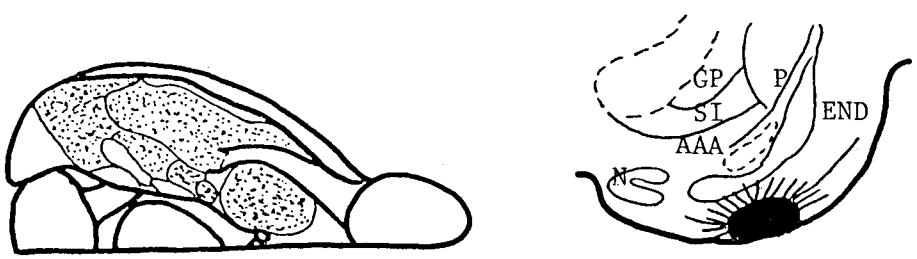


Figure 2c An injection into the prepiriform cortex and the resulting distribution of silver grains in the entorhinal cortex.

Figure 2. Further schematic diagrams of amygdaloid cortical projections demonstrated by autoradiography, drawn from Krettek and Price (1977a and 1977b). Orientation of the brain remains the same as in Figure 1. Abbreviations are on page 12.

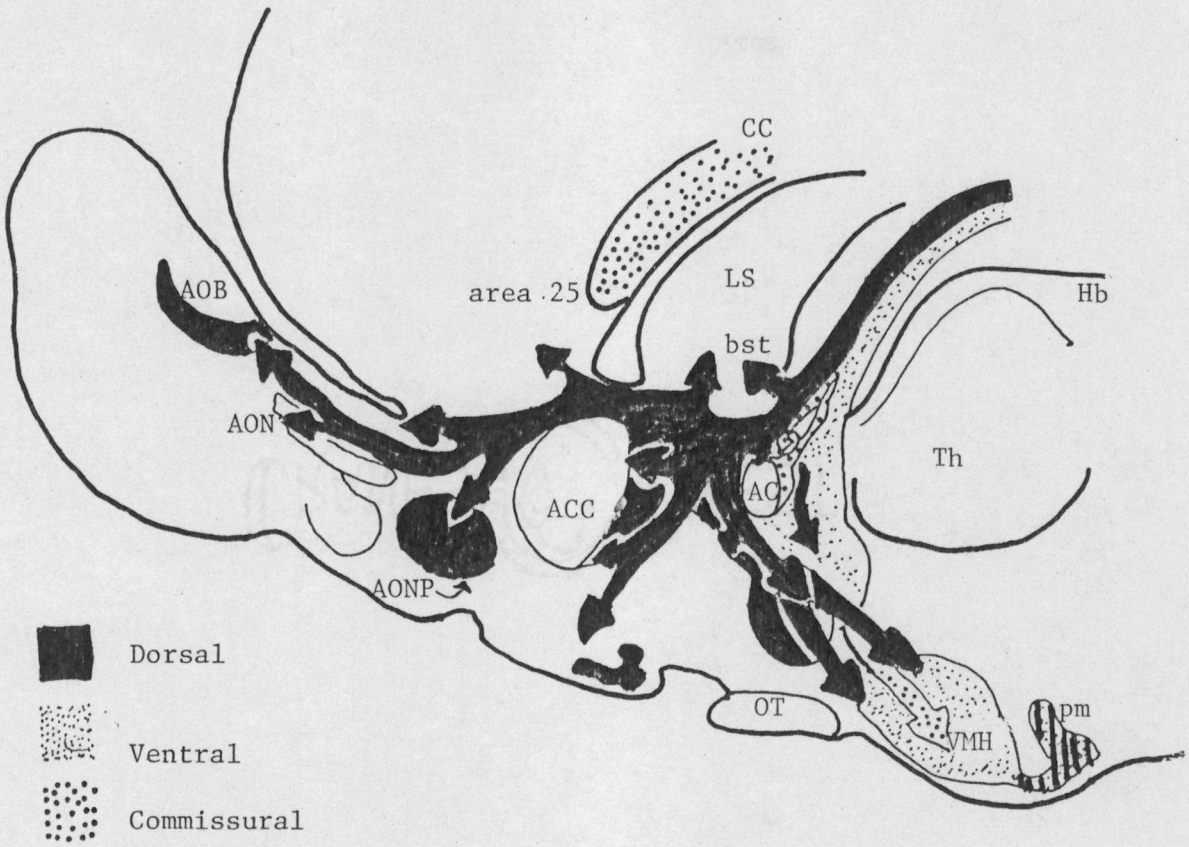


Figure 3. A schematic diagram of the three amygdaloid pathways of the stria terminalis as revealed by anterograde degeneration studies. The three components of this pathway are, the dorsal, ventral and commissural parts. This figure is a composite of several para-sagittal sections on which the several pathways are outlined as they ascend through the basal telencephalon. The figure is drawn from (De Olmos, 1972). Abbreviations for Figures 1, 2, and 3 are: AAA: anterior amygdaloid area; AC: anterior commisure; AHA: amygdalo-hippocampal area; AOB: accessory olfactory bulb; AON: accessory olfactory nucleus; AONP: accessory olfactory nucleus posterior; area 25: area praegenualis, cortical area 25; BLA: basolateral amygdaloid nucleus anterior; BL: basolateral amygdala; bst: bed nucleus of stria terminalis; CC: corpus callosum; ACE: central nucleus of the amygdala; COA: anterior cortical nucleus; COP: posterior cortical nucleus; DLEA: dorsal lateral entorhinal area; EN, END: endopirform cortex; GP: Globus Palidus; Ha: Habenula; HDB: nucleus of the diagonal band of Broca; LA: lateral nucleus; LS: lateral septum; ME: medial nucleus; medial olfactory tubercle; NAS: nucleus acumbens septi; N: nucleus of the lateral olfactory tract; OT: olfactory tubercle; P: putamen; PAC: periamydaloid cortex; PC: piriform cortex; PCA: anterior piriform cortex; PCP: posterior piriform cortex; pm: premammillary area; rh: rhinal sulcus; S: subiculum; Th: thalamus; TO: optic tract; VLEA: ventral lateral entorhinal area; VMEA: ventromedial lateral entorhinal area; VMH: ventromedial hypothalamic area.

Anatomy of the Olfactory System

The olfactory system is of special interest to comparative neuro-anatomists since its morphology is relatively constant across all vertebrates. In this wide range of species from cyclostomes to mammals, the olfactory bulb and associated nuclear systems are relatively unchanging while simultaneously there is prodigious telencephalic development (Allison, 1953b). Olfaction is one of the most primitive sensory modalities appearing very early in vertebrates. A strong point of interest is that the rest of the forebrain structures developed after olfaction and perhaps from the olfactory substrata themselves. Recognition of these interrelationships suggested that the key to understanding forebrain evolution is through the olfactory system and its interaction with the rest of the brain (Allison, 1953a). Interactions with the environment based on olfactory sensory impingement is heavily relied upon by all vertebrates and is not diminished appreciably with phylogenetic development, until the human who has a relatively poorly differentiated olfactory system (Crosby and Humphrey, 1936b). Olfaction as a sensory modality is extremely important in the ungulate, feline and canine species and is especially important in the macrosmatic rodent (Lauer, 1963; Thomas, 1973; Sieck, 1973).

The olfactory bulbs comprise the anterior most pole of the brain and are separated from the frontal aspects of the brain by the rhinal fissure. The receptor cells for olfaction are embedded in a mucous membrane, the olfactory epithelium , and are modified hair cells, typically bipolar neurons lying in the middle third of the epithelium.

This mucous membrane is the antero-dorsal portion of the olfactory bulb, joined to the main portion of the bulb by the olfactory fasiculi. Receptor cell degeneration resulting from bulbar extirpation demonstrates that the olfactory fasiculi, consists of the efferent processes of the bipolar receptor lying in the olfactory mucosa (Le Gros Clark and Warwick, 1946). The olfactory fasiculi are interwoven in a complex fashion as they enter the cavity through the ethmoid bone terminate on the olfactory glomeruli of the bulbs which are spherical masses of neural tissue. Here the olfactory nerve fibers have intimate synaptic contact with the mitral and tufted cells which appears to be the main connective style and function of the bulb with other kinds of connections being accessory. The relatively large mitral and tufted cells have processes that are projections of the olfactory bulbs to telencephalic secondary olfactory projection areas. Within the main bulb there are intrinsic connections between the glomeruli provided by short-axoned granular and periglomerular cells providing a large number of inter-neuronal chains. Such chains are believed to be the origin of spontaneous electrical activity seen in the bulb, which was first described by Adrian (1942).

The dorsal and medial aspects of the posterior main bulb are occupied by the accessory olfactory apparatus (Gurdjian, 1925). In species such as reptiles the olfactory organ is divided into two separate sensory mechanisms. The first is the main olfactory mechanism described previously. The second is the Jacobson's organ or the vomernasal organ. In animals having the organ anatomical and functional

overlap occur between the olfactory and vomeronasal sense which frequently make the two difficult to distinguish (Burghardt, 1970). Vomernasal organs have been identified in turtles, all snakes, lizards (Burghardt, 1970) and amphibians (Herrick, 1923). The overlap seen in olfactory and vomeronasal morphology is not repeated in the resulting central neural projections. Winans and Scalia (1970) have demonstrated clearly identifiable projections to the antero-lateral cortical nucleus of the amygdala via the vomeronasal nerve in the rabbit.

Burghardt and Hess (1968) assert that the vomeronasal sense is used in snakes for the recognition and tracking of prey. In mammals it has been suggested (Winans and Scalia, 1970) that both sexual and feeding functions are served. The vomeronasal organ is maximally sensitive to nonvolatile macromolecular compounds where the olfactory senses respond to volatile compounds.

Nonprimate land mammals are generally macrosmatic (Allison, 1953b) and have highly differentiated olfactory apparati while the accessory structure begins to disappear in primates "until it is a mass so small that it is of more theoretical than practical importance in the adult" human (Crosby and Humphrey, 1939a).

Anatomically, the organization of the sensory projections to the bulb differs from the primary structure in that the glomeruli show much less differentiation and are much smaller. Tufted cells are completely absent and mitral cells are scattered throughout the outer plexiform layer of epithelium. Mitral cells also have more dendrites than do their primary analogs. Finally there seems to be a dimunition of the

of the internuncial cells and a lessening of branching accessory dendrites. There are also fewer periglomerular cells (Allison, 1953b). Such an organizational scheme would definitely effect electrical behaviors and sensory capabilities of the accessory bulb when contrasted to the main bulb.

There is a high degree of convergence of sensory information between the first order and second order cells. Allison and Warwick (1949) demonstrated in the rabbit that on the average 26,000 olfactory receptors project to glomeruli containing 24 mitral cells and 68 tufted cells. This is the basic organizational scheme which allows spatial summations of the cell potential, a structural architecture seen in all sensory systems designed to achieve very low sensory thresholds. At the time there is no mixing of these fibers until the glomerular level which suggests that the capability for making acute sensory discriminations is maintained.

Vertebrate olfactory projections in the telencephalon are divided between the lateral olfactory tracts and the intermediate and medial tracts, or join the anterior limb of the anterior commissure. The olfactory tract and commisural component are quite distinct and almost entirely separate in mammals. There are strong indications that there is a consistent relationship between the fiber tract and the originating cell type in the olfactory bulb. Mitral processes gather to form the lateral olfactory tract while axons from tufted cells compose the commisural component (Allison, 1953b).

Olfactory projections to the forebrain show little variation across species and therefore mammilian data obtained from carnivores, rodents

and primates are validly applicable even to humans (Allison, 1953b). The two secondary olfactory pathways are visible macroscopically. Projections of the lateral olfactory tract have a wide distribution. A small number collateral fibers and end in the dorsal anterior olfactory nucleus. A second projection is to the plexiform layer of the temporal prepiriform cortex where axo-dendritic connections are formed with the pyramidal cells in this layer. Additionally, some of the fibers from this group will pass back into the amygdala where axo-somatic connections are made with cells of the nucleus of the lateral olfactory tract and dendrites of cells in the cortical nucleus.

The commissural tract, consisting of very fine fibers has a portion of uncrossed fibers projecting to the full extent of the nucleus of the stria terminalis. The majority of the remaining fibers decussate and have similar projections to the contralateral nucleus of the stria terminalis. The last significant component establishes connections with deep portions of the contralateral bulb (Allison, 1953b).

Electrical Behaviors of the Olfactory Bulbs and the Amygdala Related to Their Morphologies

Classical physiology has explained sensory perception as a process of cortical selection and integration of a variety of afferent signals received from passive end organs and was thought to be accomplished in the absence of any central influence exerted peripherally at the receptor. These views were challenged in the fifties as a result of the work of Hernandez-Peon (1955), who demonstrated centrifugal control of visual (Hernandez-Peon et al., 1956a), auditory (Hernandez-Peon et

al., 1956b), and somatic (Hernandez-Peon et al., 1956c) receptor systems. Work on the fine anatomy of the olfactory bulb by Allison (1950; 1953a; 1953b) renewed interest in the possibility of such mechanisms in the olfactory bulbs. Electrographic studies in the olfactory bulbs (Lavin et al., 1959) indicated the presence of such influences in the cat. These effects were manifested as bursts of 40 hz electrical activity as a result of the presentation of nonspecific, arousing stimuli (other than olfactory) to the awake and unrestrained animal. Conversely, centrally administered anesthesia or mesencephalic lesions adequate to render the animal unconscious eliminated the 40 hz spindling. The question of mechanism is answered in both those pathways efferent to the bulb and its internal fine structure.

A cortical system is one in which there is neuronal differentiation into several distinct types, having cells bodies and axonal processes organized in several nonrepeating layers. There is generally a large output neuron spanning most of the layers and eventually projecting to other parts of the CNS. Cortical systems are generally associated with a free surface. Defined in this light the olfactory bulb itself comprises a cortical system having a much simpler laminar structure than does the neocortex (Shepard, 1970).

In the earlier bulbar anatomical discussion it was shown that the bulbar fine structure consisted of interconnected networks of excitatory cells, specifically the tufted cells in the external plexiform layer whose axons pass through the mitral cell layer and on into the deep layers of the bulb where they form the anterior limb of the anterior

commissure. These axons have recurrent collaterals which pass back out to the external plexiform layer and synapse on accessory dendrites of the mitral and tufted cells (Kerr and Hagbarth, 1955). Such structures are positive feedback loops which are inherently unstable and consequently have oscillating outputs. In order for the oscillatory "arousal activity" such as that described by Adrian (1942, 1950) and Lavin et al. (1959) to occur there must be the additional component of recurrent inhibition (Stephanis, 1962; Jasper and Stephanis, 1965; Andersen et al., 1963, Eccles, 1965; Granit, 1963, Andersen and Anderson, 1968). Recurrent inhibition is analogous to negative feedback and is generally capable of simultaneously inhibiting large populations of cells such as the tufted cells having the recurrent collateral processes. In the Andersen and Anderson model for spindling there are afferent volleys from excitatory cells, projecting to other parts of the CNS and those cells comprising the recurrent inhibitory network. These cells, in turn, act on the exciting cells turning them off. Differences in the number of synapses in the loops will determine the characteristic oscillatory frequency of the resulting electrical sinusoid or spindle. Once again we can see a physiological process paralleling well known physical models where the length of a mechanically resonant entity is a primary determinant of its oscillatory frequency. The mechanism for the recurrent inhibitory network has been elegantly described by Rall and Shepard (1968) and Shepard (1970). They have described a dendro-dendritic pathway formed by the axonless granule cell which exerts itself only on the prehillock portions of the mitral and tufted cells.

Precise analogs for this circuitry has been found in amacrine interactions with the optic ganglion cells (Shepard, 1970).

Bulbar 40 hz activity is strongest in the rhinencephalon where it is the predominant form of spindle. Bulbar 40 hz was initially observed by Adrian in the hedgehog (1942, 1950). It has been observed in the bulbs of vertebrate species from catfish to the human (Sheer and Grandstaff, 1970). During Adrian's initial investigations of bulbar behaviors he referred to the 40 hz spindling or arousal behavior as being intrinsic to the bulb. The later findings of Lavin et al. (1959) indicated central influences controlled the spindling, generating the inevitable questions of anatomical substrates and how these influences might exert themselves. Later investigators questioned Lavin's conclusion in view of the data collected and the degree of control exerted through his design. A central issue was the relationship between respiration and the appearance of the 40 hz spindle, autonomy between the two would indicate that 40 hz had more than a completely mechanical relationship to airflow over the olfactory mucosa. Adrian's early studies showed no such dissociation and based on these observations he concluded that the spindling resulted from receptor discharges due to air passage over the membrane. Later findings on amygdaloid 40 hz spindles (MacLean and Delgado, 1953) supported the earlier studies by Adrian, failing to find any dissociation in respiration and 40 hz spindling in monkeys (Maccaca Mulatta). The primate olfactory and amygdaloid spindle was observed to be more sinusoidal than in nonprimates.

These investigators were unsuccessful in their attempt to find 40 hz pace makers in the amygdala. They also noted the disappearance of

the spindle with occlusion or with the insertion of a tracheal cannula which bypasses the airflow from the olfactory apparatus. Later studies using dogs and monkeys (Maccaca Mulatta) repeated the respiratory experiments which indicate that airflow in the nostril is a requisite for much of the visible rhinecephalic 40 hz activity. This study supported Adrian's original conclusions relating arousal as a component of the 40 hz appearance. The sleeping monkey shows a significant dimunition of 40 hz activity during sleep than does the awake and active monkey and the awake and active animal shows a much higher density of spindle activity than does the placid animal. There is a high correlation between the appearance of the 40 hz activity and EEG arousal which manifests itself in the form of generalized cortical desynchronization meaning that cortical activity shows an abrupt shift away from synchronous high voltage low frequency sinusoids to high frequency low voltage activity patterns.

Canine rhinencephalic behavior is similar to that found in primates with the exception that 40 hz spindling occurs with both inspiration and expiration. There were two predominating patterns of electrical behavior seen in the canine rhinecephalon. The most prominent was the 40 to 46 hz activity, however, every second cycle was enhanced at the rate of 20 to 23 hz. These individual and augmented cycles correlated precisely with amygdaloid 20 to 23 hz spindles. It is safe to assume that unitary volleys driving the EEG in the bulbs are being physiologically transmitted to the amygdala and subsequently driving the EEG there. Investigators reported finding respiration related 40 hz activity in the

piriform and prepiriform cortices as well as in the posterior hypothalamus. It is significant that they found that the activity could be abolished with the application of a local anesthetic to the olfactory mucosa.

The Lavin et al. (1959) findings directly contradicted the previous findings. They reported definite dissociation between the 40 hz spindles and respiration in the cat bulb. The dissociation was related to arousal and specific environmental stimuli occurring in sensory modalities other than the olfactory bulb. Multisensory elicitation of the arousal response (the 40 hz spindling) in the bulb was indicative of a central component efferent to the bulbs. The study included application of 50 hz stimulation (2 to 3 seconds in duration) to the mesencephalic reticular system which elicited the arousal pattern in the olfactory bulb. Lesions in this system sufficient to render the animal unconscious or central anesthesia eliminated the bulbar arousal response. In a study of the cat prepiriform cortex, the primary cortex for olfaction, Freeman (1960) resported activity with two predominating components. The first was a slow wave corresponding exactly with thoracic respiration. Riding on the slow wave were high amplitude 40 hz spindles, comprising a second component. Freeman observed that at times the respiratory wave occurred without the 40 hz wave but the 40 hz wave never occurred in the absence of the respiratory component, and in this respect it is phased locked to it. These findings, and those of Lesse (1957) support Lavin's conclusion that centrifugal influences are important in the production of 40 hz spindles in the bulb in as far as

they show that rhinencephalic dissociation is possible in a restricted sense and therefore are not related in a purely automatic or mechanical manner. These findings were augmented by a study by Gault and Leaton (1962) who investigated the nature of olfactory slow potentials reported by Ottoson (1954) in Rana Pipens. Ottoson reported finding a stimulus bound slow potential in the bulb itself which is elicited by odor laden air. He concluded that the responses are transmitted neurophysiologically rather than propagating electrotonically because the polarity found at the receptors is reversed when recorded in the bulb. They found that slow potentials correlated exactly with respiration disappearing in the ipsilateral nostril when occluded. Furthermore, they found that 40 hz activity did not occur in the absence of the slow potential, concluding that it is essential in the genesis of the spindle. They further asserted that mere arousal was insufficient to elicit a bulbar 40 hz spindle but that respiration capacity or volume automatically increases upon presentation of a novel stimulus in a microsmat augments the spindling in the same way humans open their eyes wider to take in more information.

The relation between the appearance of 40 hz is different in the amygdala than it is in either the prepiriform cortex or the bulb. Gault and Leaton observed a significant degree of dissociation between 40 hz spindling in the amygdala and the bulb, noting that there is a marked increase in the correlation of spindle occurrence during periods of arousal. In their final analysis they were unable to determine the extent to which centrifugal arousal is a requisite for bulbar spindling,

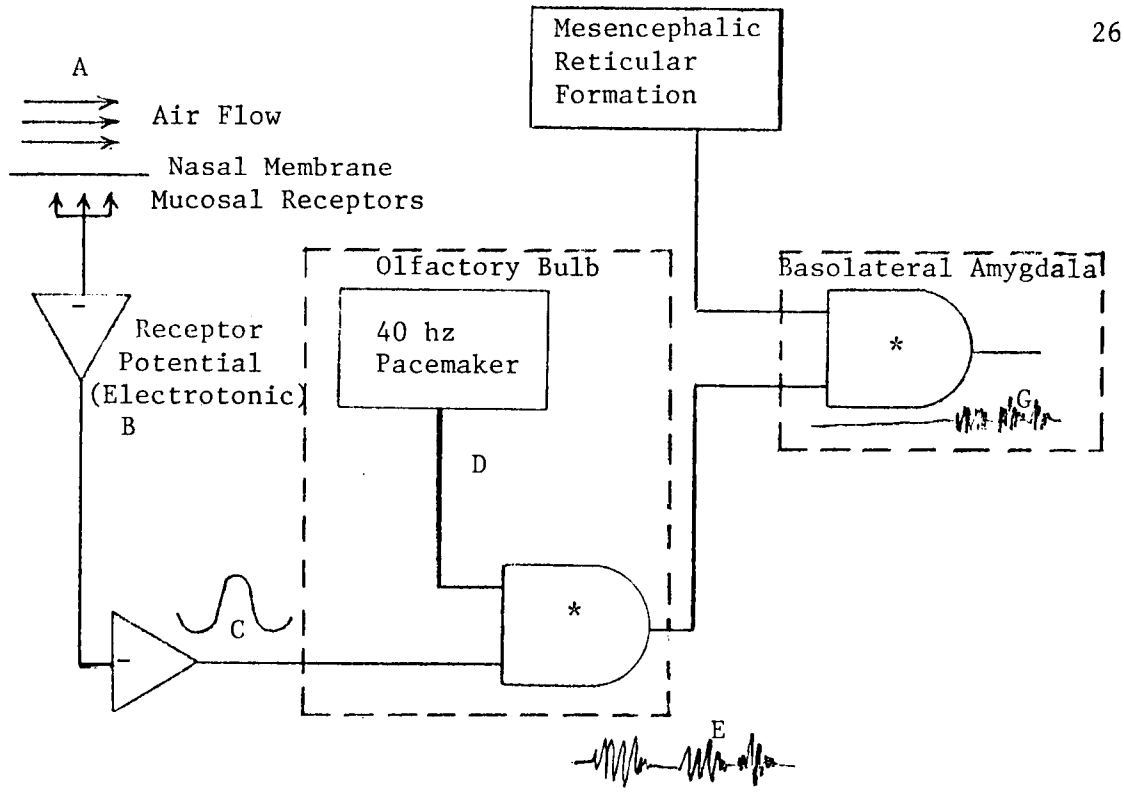
but left no doubt that both airflow and central arousal is required for the appearance of 40 hz amygdaloid spindling. Using special nasal and tracheal tubing for regulating sources of airflow in acute and chronic cats, Gault and Leaton (1964) concluded that the arousal component of the olfactory bulb is actually mediated by changes in airflow related to thoracic respiration concomittant with changing emotional states. In a later study Pagano and Gault (1963) conducted studies in the cat amygdala and incorporated rather precise scales for measuring behavioral arousal as they recorded basolateral amygdaloid EEG. They demonstrated a very high positive correlation between behavioral arousal and amygdaloid 40 hz spindling density. There was a simultaneous high negative correlation with cortical low frequency activity.

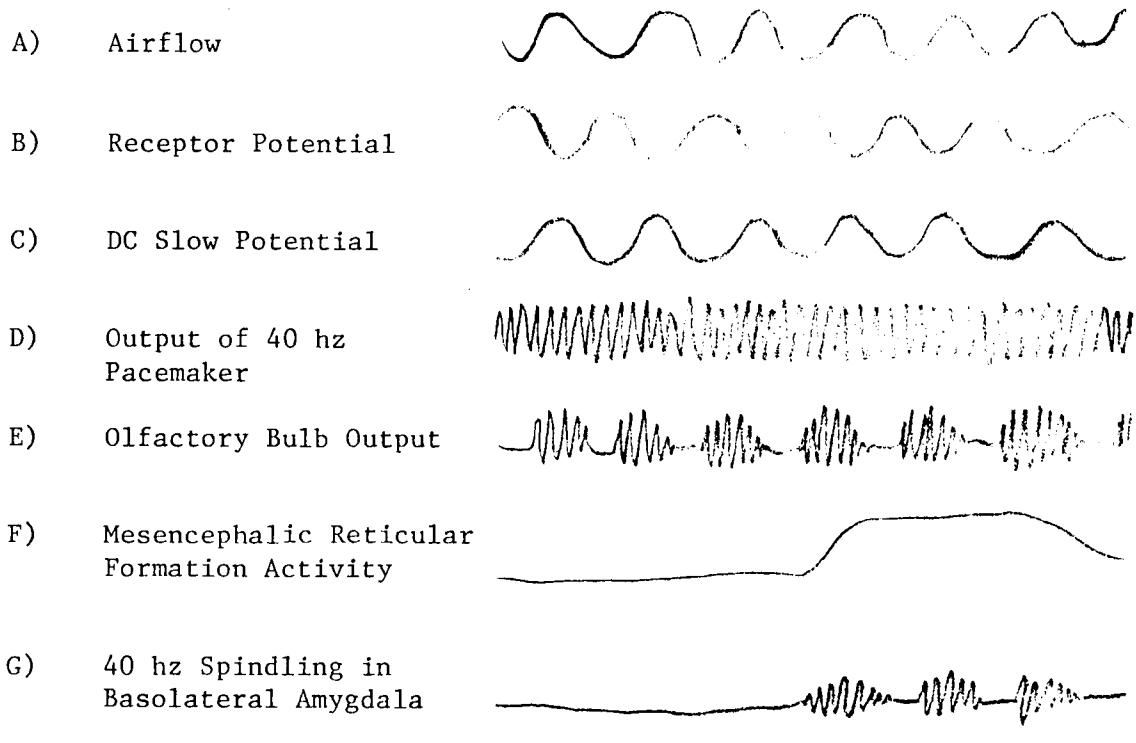
To summarize, nearly all of the investigators noted some degree of dissociation between respiration and rhinencephalic 40 hz activity. The extent of the autonomy of the two phenomena across situations, an indicator of its value to neurobehaviroal investigators, was dependent upon both the recording topography and the degree of arousal. The simplest response, having the least dissociation from respiration, is found in the olfactory bulb, followed by the prepiriform cortex and lastly the amygdala. In a study using the curarized cat, Kerr and Hagbarth (1955) observed the effect of exciting centrifugal fibers on the resting activity of the bulb. Depressive effects were seen while stimulating the prepiriform cortex, cortical amygdaloid nucleus and olfactory tubercle. Similar effects were seen with high frequency stimulation of the anterior limbs of the anterior commissure. Specifically, the depressive effects referred to were a reduction of

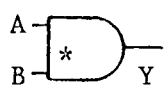
spontaneous discharge in the bulb or as a reduction or abolition of the recurrent spindles induced through olfactory stimulation. Light central anesthesia sufficient to block the centrifugal depression causes increases in spindling. (It should be noted that authors (Freeman, 1959; Adrian 1942) have reported curare effects on unit behavior in the basal rhinecephalon which could possibly effect the data in this study.) Other investigators have identified mesencephalic influences on bulbar EEG and unit activity (Arduini and Moruzzi, 1952; Yamota and Iwana, 1961). The reader's attention is called to Figure 4 on the next page which is a graphic synopsis of the circuitry producing 40 hz activity.

Note that the central influences reported by Kerr and Hagbarth (1955) were in the opposite direction from those reported by Lavin et al. (1959). Early assumptions that the functions of these connections are facilatory, which would increase receptor acuity to aid in shifting attention at the onset of a change in the environment. More recent evidence is that these influences are inhibitory to aid in reducing attention spent in attending stimuli having little survival significance (John, 1960).

The centrifugal projections to the olfactory bulb have been as problematic to the anatomists as they have been to those investigators using electrographics. In the rabbit, almost complete transection from the anterior piriform cortex, olfactory tubercle, anterior commissure and anterior neocortex was made unilaterally (Cragg, 1962). Interruption of the centrifugal fibers in this manner cause dense fiber degeneration throughout the bulb in all the internal layers. Many fine fibers were







NOTE- Logical AND function presupposes simultaneous inputs at A and B for the occurrence of an output at Y

Figure 4. Model illustrating interaction of olfactory, amygdaloid and mesencephalic components in the production of 40 hz spindles.

found to pass through the mitral and tufted cell layers and surround the glommeruli, ending in relation to the granule cells. These fibers are absent in the accessory bulb. The bulk of these fibers originate in the prepiriform cortex with a few projecting from the midbrain, thalamus and hypothalamus. The paucity of direct bulbar connections from the reticular formation in no way contradicts the assumption of powerful mesencephalic control on the bulb as there is ample opportunity for these influences to occur through secondary connections from either the preoptic area or the olfactory tubercle which are rich in mesencephalic projections (Cragg, 1962; Powell et al., 1965). Heimer (1968) supported these findings in the rat, reporting bulbo-petal projections involving the prepiriform cortex which is part of a system of forward projecting fibers "involving at least the entire extent of the prepiriform and periamygdaloid cortices." Two rat studies have identified efferents in the lateral olfactory tract that contrast with commissural deep bulbar endings in that they terminate on the peripheral dendrites in the outer plexiform layers (Price, 1968; Heimer, 1968).

Investigations on the unit level directed at centrifugal projections to the amygdala are not as numerous as the olfactory studies but they are provocative. Testing Johnson's (1923) hypothesis on the amygdala's role as a olfactory-somatic coordination center, Machne and Segundo (1955) investigated amygdaloid unit responses to peripheral stimulation and their response to various interoceptive systems in the cat. Slow wave observations (EEG) were the same as those reported by previous investigators. Spontaneous unit firing rates were variable with the

highest rate being approximately 50 hz. Localization was evident to the extent that the effectiveness of the eliciting stimuli depended upon the nuclear group hosting the recording electrode. The anterior amygdaloid area contained units responding to sciatic, olfactory, vagal, mesencephalic and auditory (order indicates relative effectiveness) stimulation. The basal nuclear units responded to sciatic, olfactory, vagal and mesencephalic stimulation. Sciatic, olfactory vagal, mesencephalic, auditory and mesencephalic stimulation elicited central nuclear responses. No stimulation modalities elicited responses in the cortical or medial nuclei. Units in these areas also had multisensory convergence with variations in what senses converged depending on the recording topography. Latencies from stimulus onset varied from 50 to 200 msec. with the shortest being 20 msec., indicating that there is a great deal of variation in the number of synapses occurring between receptors and their eventual connection in the amygdala. Typical responses were similar to those found in the mesencephalic reticular system, they showed long and variable latencies, rapid habituation and fatigueability—evidence of an indirect pathway since central processing further back in the pathway is obviated. Amygdaloid cell population responses recorded from macroelectrodes, were of characteristically shorter duration than were the responses of mesencephalic units to novel stimuli or situations eliciting generalized cortical EEG arousal.

In further cat unit studies, Creuztfeldt et al. (1962) observed relatively low levels of spontaneous firing and a moderate positive correlation with the EEG. This study found similar topographic

distributions to those which were described in the above study but was more meticulous in distinguishing between direct and indirect and specific and nonspecific unit responses. This study largely concurred with Machne and Segundo in acknowledging that the primary amygdaloid afferentation is olfactory and sciatic, and added that the olfactory pathways are largely direct projections whereas the sciatic projections are indirect and nonspecific. These studies support conjecture from neuroanatomical studies which have suggested that there are both direct olfactory-amygdaloid projections which have been described at length, and a second set of indirect, secondary olfactory projections coming in from the prepiriform and piriform cortices. The indirect projections are to nuclear areas which lack primary input. These mutual exclusivities suggest a functional differentiation of the amygdala. Creutzfelt et al. showed clear multi-sensory convergence only in the central lateral nucleus. These olfactory, sciatic, auditory and somesthetic responses were specific and stimulus bound. One unit made a specific response to tactile stimulation at the base of the tail, probably having sexual functions. The authors acknowledged that their failure to identify units responding photic, auditory and somato-sensory unit such as those reported by Machne and Segundo could have been due to either the nonspecificity of their stimulus or to differences in technique and does not necessarily mean that the units reported by these investigators are not really there.

In conclusion, the amygdala has been shown to have multisensory afferentation from all of the sensory modalities (Gloor, 1960; Sawa and

Delgado, 1968) and that these projections are richest in the basolateral areas. Such a reception field is highly reminiscent of the reticular system and it has been demonstrated does indeed respond in a similar fashion (Ursin and Kaada, 1960; Fendel and Gloor, 1954) in that the amygdaloid response is indistinguishable from the reticular response at unit levels and has been implicated in eliciting aroused cortical EEG patterns.

Review of Amygdaloid Functional Studies

The first study using the technique of restricted ablation in the amygdala was made by Spiegel et al. in 1940. Since then 800 to 900 papers have been written which incorporate the techniques of lesioning, stimulation and behavioral observations in various combinations. A large number of these studies have been directly contradictory, leaving investigators with a picture of the amygdala which exaggerates its lack of functional specificity (Kaada, 1972). The sources of these erroneous findings are multiple and should be addressed prior to any in-depth discussion of amygdaloid function. Many of the contradictory findings are born from the real functional complexity of the amygdala which occur in very compact areas. When the classical methods of stimulation and/or lesioning are employed there will very likely be ensuing contamination of the data as it is nearly impossible to experimentally affect an efferent without similarly effecting an afferent or vice-versa. The lateral amygdala is especially susceptible to these difficulties. These dilemmas can be overcome by the careful mapping of stimulation

thresholds or by using chemostimulation which limits its effects to dendrites and cell bodies without affecting fibers of passage (Kaada, 1972).

An experimental design must take many hidden variables into account. For example not only does curare affect unit behavior in the rhinecephalon as was discussed earlier, general anesthetics can effect other important factors such as the depth of respiration which has been shown to be an important factor (Ursin and Kaada, 1960). Varying parameters such as the stimulation frequency may even cause a reversal in the achieved results and such effects have been demonstrated in the cardiovascular influences exerted by the amygdala (koikegami et al., 1955).

Finally, it has been demonstrated that amygdala has one of the lowest seizure discharge thresholds of any structure in the brain. Electrical afterdischarges following amygdaloid stimulation are frequent concomitants. These afterdischarges spread across naturally occurring functional borders which seriously distort the obtained functional topography. Kaada and Goddard (1972) have noted that the great majority of the studies they have reviewed have failed to include simultaneous recording of amygdaloid responses to stimulation and have been doing "blind" stimulating without being aware of the electrical consequences of stimulation. Such lack of experimental control could well account for the variety and contradictions in reported affective behaviors seen across studies.

In his review of the amygdala, Kaada (1972) has divided the amygdaloid function into five general categories which are: (a) arousal,

orienting and sleep; (b) agonistic and social behaviors; (c) feeding; (d) sexual activities and (e) reward and punishment in self-stimulation studies. Those activities included in the first two categories are of primary interest to this study but brief summaries of the latter three categories will be included in the interest of the presentation of an integrated picture of amygdaloid function.

The Role of the Amygdala in Feeding and Drinking

There is very little doubt that bilateral ablation in the amygdala affects food intake. There has been significant variation in which direction the effects of ablation take. The most consistent picture which emerges is that amygdaloid ablation caused a severe but transient depression of an animal's appetite followed by acute hyperphagia. It is quite possible that the transiency of the depressive effects may be an artifact of surgical shock. The increase in food intake does not always cause an increase in body weight. Kluver and Bucy (1938) described a peculiar form of "oral blindness" where an animal inserts all available small objects into its mouth, ejecting those which are not edible.

Fonberg and Delgado (1961) demonstrated that telestimulation of the anterior and basolateral amygdala inhibited the spontaneous ingestion of food in cats, while leaving playful behavior unmodified. Learned instrumental alimentary responses were also inhibited. The inhibition was not stimulus bound inducing appetitive depression from seconds to hours or days after the stimulation.

In further stimulation studies in the cat basolateral region, Lewinska (1968) produced inhibition of food intake in which the animal showed more aversion to the food. Nausea and retching were induced at high intensities, while at lower stimulation currents the animals would sniff at the food but not eat. The sniffing was indicative that the animal was not experiencing satiety. It was also demonstrated that infrathreshold stimulation of those regions evoking defense-flight reactions will inhibit appetitive behaviors. Robinson and Mishkin (1962, 1968) have demonstrated areas in the monkey cortical and medial nuclei and in the parvocellular region of the basal nucleus which augment appetitive behaviors.

In a highly refined set of experiments using chemoceptive stimulation with highly specific neuropharmacological agents, Grossman (1964) mapped out anatomically overlapping neuronal circuits of the lateral hypothalamus controlling food and water intake. His experiments showed that circuits mediating water regulation are selectively responsive to cholinergic agents where food intake systems are responsive to adrenergic stimulation. These studies alert us to the possibility that pharmacologic coding may be as important as topography. Grossman duplicated these experiments in the amygdala. Adrenergic stimulation in the cortical nucleus produced eating behaviors and suppressed water ingestion. Conversely, water intake was enhanced with a concomitant reduction of eating behavior with the introduction of carbacol which is a parasympathomimetic and is metabolized at a much slower rate than acetlychloline.

Aphagia has been produced in dogs with the destruction of the medial and central nuclei, while destruction of the basolateral area induces hyperphagia (Fonberg and Sychowa, 1968; Fonberg, 1968). Brutowski (1968) concluded that the inability of the dog to inhibit its eating behavior after basolateral lesions is actually due to an enhanced drive state indicating a removal of inhibition.

Specific motor movements such as sniffing, licking and mastication have been elicited by stimulation of the pre- and piriamygdaloid cortex and from very diverse points within it (Kaada, 1951; Hilton and Zybrosna, 1963); MacLean and Delgado, 1953). Increases in gastric motility have been seen in anesthetized cats (Shealy and Peele, 1957) while stimulating the central and medial nuclei or the magnocellular portions of the basal nucleus (Koikegami, 1964). Inhibition has been produced by stimulation of the magnocellular basal nucleus, an areas which has been identified as having strong sympathetic influences.

Control or modulation of appetitive motivational states and process processes have their strongest representations in the medial and cortical nuclei and in the parvocellular portion of the basal nucleus.

Sexual Functions and Amygdaloid Representation

The amygdala and preoptic area which are intimately related, are two areas of the brain where sexual dimorphism is apparent at the micro-structural level. The existence of estradiol concentrating neurons in the hypothalamus and preoptic areas receiving rich, direct connections from the amygdala suggests the existence of a neuroendocrine circuit

involving these three areas (Stumpf, 1972). Raisman and Field (1972) observed significant microstructural sexual dimorphism in the preoptic area of adult rats. They found that female rats have twice as many synaptic dendritic spines in this area than do the males. This area is rich in amygdalo-preoptic synapses. The amygdala has been shown to participate in limbic circuitry which is uniquely sensitive to gonandal steroids. These neurons have been depicted autoradiographically (Stumpf, 1968) and by scintillation techniques (McEwin and Pfaff, 1970), to have a topographic distribution in the hypothalamus, preoptic area (Stumpf and Sar, 1969), and amygdala (Stumpf and Sar, 1961; 1971). One of the areas having the highest density of estradiol concentrating neurons is the amygdala and olfactory tubercle (Pfaff and Keiner, 1972). It is widely known that olfactory acuity is related to estrogen levels in all species down to the goldfish (Hara, 1967).

Understanding of the functional implications of these microstructural and biochemical differences can best be understood in conjunction with data from ablation and stimulation studies. It has been shown that the amygdala plays a role in gonadal maintenance of male cats. Bilateral amygdalectomy induces gonadal atrophy (Kling et al., 1960; Yamada and Greer, 1960) and probably caused by a reduction of gonadotropin levels. Paradoxically, amygdalectomy causes precocious development of ovarian, uterine and vaginal tissues (Elwers and Critlow, 1961) in young females but has no effect on the adult reproductive structures. Uterine contractions can be either initiated or augmented through amygdaloid stimulation in either the central or basal nucleus (Shealy and Peele,

1957). Penile erections have been elicited in Macacca mulatta following cortico-medial nuclear stimulation or by stimulating the stria terminalis (Robinson and Mishkin, 1968). These sites are very close to areas having high densities of neurones which are selectively sensitive to testosterone (Stumpf, 1971).

Earlier reports describing hypersexuality following amygdalectomy (Kluver and Bucy, 1938) have needed some revision because the associated surgeries included more than amygdaloid tissues, involving cortical area which is a source of confounding data in discussions of amygdaloid function. Various investigators have shown that ablations of tissues surrounding the amygdala will result in hypersexuality. Lesions in adjacent temporal cortex, septum and habenular nuclei will cause similar sexual behavior (Kaada, 1972) after amygdaloid damage. In that the temporal cortices and piriform cortex have equally intimate locations in relation to the amygdala it is difficult to introduce amygdaloid lesions without disturbing the neighboring cortices. Many of the earlier studies using cats and finding hypersexuality to be a result of amygdaloid extirpation have been misleading in that male cats can normally become hypersexual if repeatedly tested in the same environment (Goddard, 1972a). Undoubtably, amygdalectomy does induce changes in sexuality. Hypersexuality is seen in males of several species (Shreiner and Kling, 1953; 1954; 1956) and can be eliminated by castration and subsequently reinduced by the introduction of exogenous testosterones. Such behavior has been reported in humans after anterior temporal lobe lesions (Terzian and Ore, 1955). Hypersexuality has been demonstrated in male and female cats as a result of lesions in the central nucleus (Wood, 1958).

Hyposexuality has also appeared after corticomedial damage which has been a region implicated in producing aphagias. In these cases rats were force fed to keep them alive. On going spermatogenesis and seminal vesicles having normal weight and proper anterior hypothalmic function all indicated that the reproductive systems were intact, however no sexual behavior occurred (Schwartz and Kling, 1964).

Amygdalectomy has been shown to cause significant changes in parenting behavior. Kling (1972) states that amygdalectomized mother monkeys will probably be unsuccessful in rearing infants. He cites two cases where amygdalectomized mothers were very rough with their infants, biting them, kicking and bouncing them around "as if they were rubber balls" in a manner suggesting that they were unable to recognize what they were. He also watched a mother having a bilateral lesion of the dorso-lateral frontal cortex reject her yearling and leaving the colony. A fourth multiparous mother, sustaining bilateral lesions of the superior temporal neocortex showed exemplary maternal behavior.

The sexually facilitating regions of the amygdala seem to be the corticomedial nucleus and perhaps the parvocellular basal nucleus. They exhibit significant estrogen uptake and stimulation of these regions produce ovulation (Shealy and Peele, 1957), lactogenesis (Tindal et al., 1967) and penile erection. Removal induces hyposexual behavior. It appears then that there is an antagonistic grouping in the ventral part of the basolateral complex. Such a functional organization parallels the systems seen in the hypothalamus which are responsible for appetitive behaviors.

Self Stimulation and Avoidance

Functional explorations of the hypothalamus were greatly aided through mapping the topography of reward valence for self stimulation (Olds and Olds, 1963). It was found that antagonistic loci mediating drive initiation and inhibition were positively and negatively reinforcing for self stimulation behaviors. In that the amygdala is known to be involved in motivated behaviors, affecting food intake and sexuality, it is quite logical to investigate it in terms of identifying areas which are rewarding or negatively reinforcing upon stimulation. Areas have been localized that are rewarding and negatively reinforcing and that produce ambivalent approach and avoidance responses (Kaada, 1972). In studies using other techniques many of the investigators have reported conflicting results and observed much functional overlap (Goddard, 1964), but there is enough consistency to state that stimulation of the corticomedial nuclear group is positively reinforcing and the basolateral group is negatively reinforcing in the rat. Strongest reinforcing effects were found on the medial edge of the corticomedial group. Highest escape rates were elicited from stimulation of the magnocellular basal nucleus. Mesencephalic self stimulation rates were higher than those from the amygdala whereas the amygdala elicited higher rates of escape behavior (Wurtz and Olds, 1963). Stimulation intensity has been found to be a parameter of reward valence in humans when the locus of stimulation is held constant (Bishop, Elder and Heath, 1963).

The amygdala has been involved largely in attaching an affective loading or significance to stimuli normally eliciting fear. If this is the case, then it follows that avoidance learning tasks will be especially difficult for the amygdalectomized animal (Goddard, 1969). Active avoidance deficits in cats were seen after sustaining lateral nuclear damage or transection of the VAF, however performance of passive avoidance was left unimpaired (Ursin, 1965). Hovrath (1963) supported these findings and extended regions involved in the acquisition and retention of active and passive avoidance to the central nucleus and parts of the basolateral complex. Kling et al. (1960) showed that although amygdalectomized cats do not differ in the total number of trials to reach criterion in a shuttlebox, they take significantly more trials to begin making avoidance responses. Such behavior suggests a deficit in interpreting the meaning of a conditioned stimulus but not in making the response or in learning it. Other investigators have demonstrated that the retention and performance of presurgically acquired avoidance tasks are not affected but the acquisition of new ones are impaired (Brady et al., 1954).

These experiments reify the amygdala's involvement in motivated or approach behaviors, they illustrate the complex involvement in the interpretation of the meaning of aversive stimuli. In humans, epileptic discharges in the amygdala are experienced as states of confusion, sensory illusions and as feelings of nonreality (Feindel, 1961). Sawa et al. (1954) have reported confusion and the inability to recognize people for up to two months after bilateral amygdalectomy in schizophrenics. These symptoms would suggest the inability to interpret sensory input.

Agonistic, Affective and Social Behaviors

Evolutionary development in the nervous system is manifested by increased structural complexity and intercommunication within the brain. Highly correlated with emerging CNS complexities are the appearance of complex and frequent social interactions. In land mammals, survival of the individual becomes increasingly dependent on a delicate set of checks and balances based on social releasers (Holloway, 1968; Jerison, 1973). There is evidence indicating that the interpretation of these releasers have functional bases, at least in part, in the amygdala (Eleftheriou, 1972a).

Immediately obvious examples are pheromonal control of interactive behaviors. Territorial marking is a pheromonally based process through which many mammals mark their own specific territories. These cues are rarely neutral. They maintain dominance, elicit mating behavior, or provoke fear or aggression. Olfactory experiences in humans are typically charged. For example, nothing produces a stronger feeling of disgust than the odor of putrefaction (Gloor, 1972). There are more subtle examples than the molar motoric forms exemplified here. The "Bruce" effect describes a process where pheromonal releasers are responsible for the synchronization of oestrus cycles in nonpregnant mice. Similarly, the "Whitten" effect is a process where the presence of urine from a strange male mouse will abort a pregnancy of a female mouse (Sawyer, 1972). Here are examples where olfactory cues induce widespread internal hormonal changes through an amygdaloid-hypothalamic-pituitary circuit which is well mapped and understood.

Less intuitively obvious and well understood are the mechanisms for powerful visual influences on these basic behaviors. There is much reason to include the amygdala as an important component of the interpretive circuitry for visual input and the attaching of motivational and affective responses to it. Everyday experience with advanced mammals and primates show us that visual patterns are powerful in their ability to motivate behaviors. Neuroanatomical questions concerning how the information received in the visual cortex effects hypothalamic motivational substrates are inevitable. There are no primary visual cortical projections to the hypothalamus. It has been demonstrated that the principle interpretive cortex for visual form perception and interpretation is located in the inferior temporal neocortex which lacks any direct connections to the hypothalamus (Kluver and Bucy, 1937; 1938; Cowey and Gross, 1970), however it has been shown that the amygdala receives a rich representation from this cortex (Whitlock and Nauta, 1970). Each cortical sensory system has an orderly sequence of projections from primary, to secondary receiving areas and on to the superior temporal sulcus and frontal pole and orbital cortex. The amygdaloid visual projection from the visual system is unique (Jones and Powell, 1970) among the senses. A study by Downer (1961) provides a graphic illustration of both the importance of the amygdaloid-visual affective circuitry and the strength of the visual-amygdaloid influences on the hypothalamus. A unilateral amygdalectomy was done on a monkey that had previously been subjected to a complete split brain preparation. The monkey was extremely aggressive towards humans and was unapproachable.

After the amygdalectomy it remained unapproachable when the eye ipsilateral to the removed amygdala was occluded leaving visual input only to the intact hemisphere. The opposite behavior was seen when the intact hemisphere's visual input was removed through occlusion and restoring it to the amygdalectomized side. The animal remained very placid, approaching humans and eating from their hands. Touching or prodding the animal however, threw it into a rage meaning that the placidity was only to visual input. The conclusion here is that the visual information causing either the fear or aggression in the animal had to be processed by the amygdala before it acquired the powerful emotional motiviation seen in the animal's response. The ability to show emotional behavior was still intact because it would respond violently to tactile stimulation. These findings support existing conceptualizations about amygdaloid influences on the interpretation and "emotional coloring" of environmental sensory events impinging on an animal.

These explanations prove to be adequate for the observations that animals with bilateral amygdalectomies exhibit extreme placidity and docility. These effects are probably brought about by destroying the integrity of the amygdaloid circuitry related to arousal. This result would certainly be anticipated in a system as intimately connected with motivational processes as the amygdala is. The placidity has been identified as a cause for the dropping in social dominance of monkeys in their colonies (Pribram, 1962; Rosvold et al., 1954). This response to amygdalectomy has been seen in all species investigated including

humans (Goddard, 1964). Two avenues of research have shown the opposite response. A number of studies have noted increased aggressiveness after amygdalectomy (Wood, 1958; Green et al., 1957). Additionally, stimulation studies have implicated the amygdala in attack behaviors (Shealy and Peel, 1957; MacLean and Delgado, 1953). The genesis of these agonistic behaviors, mostly uncoordinated and undirected, has been attributed to artifacts in the experimental preparation. In studies where rage is seen, it has generally been seen several weeks post operatively and frequently appears along with convulsions. In these cases it seems that the rage is due to the development of epileptic foci around the periphery of the site of the preparation (Goddard, 1964; 1972). Rage is only seen in stimulation studies under high intensity levels and is accompanied by clonic movements of all limbs (Goddard, 1964). These parameters are precisely the conditions discussed by several authors (Kaada, 1972; Gloor, 1972; Eleftheriou, 1972a) as being likely to generate amygdaloid afterdischarges and seizures. Goddard (1972a; 1972b) has expanded our understandings of the conditions under which amygdaloid stimulation may lower the threshold for these seizures. Singular stimulations, having long interstimulus intervals (exceeding 8 hours) will cause significant decreases in seizure thresholds. The lowered seizure threshold can persist for periods of months. Goddard does not specify a maximum period for the effect to last. He does acknowledge however, that the response shows no decrement with interstimulus applications several months apart suggesting that the change may be permanent. A paradoxical aspect of the "kindling phenomenon" is that massing the stimulations will not cause

a change in seizure thresholds. Goddard (1972b) has shown that animals can even "habituate" to constant stimulation. An interstimulation interval of approximately 8 hours is necessary to produce kindling. Goddard's (1972b) work with cats shows that singular events can cause long term, if not permanent modification of the amygdala's electro-behavioral response. It is not known whether natural circumstances can produce the same effects. These effects have been replicated in humans where the first stimulation experienced was amusing but subsequent stimulation led to intense fear and an impulse to flee. Heath et al. (1955) and King (1961) have reported that stimulating humans has different effects from experience to experience.

Amygdaloid stimulation will elicit flight and defense reaction in cats but no findings have reported a directed attack response (Kaada, 1972). Flynn et al. (1970) have made the distinction between a directed attack which is marked by a quiet, efficient stalking and well directed killing in the absense of sympathetic behaviors, and an affective attack which characteristically is quite vocal, undirected and lacks any species specificity, meaning that the experimenter is fair game also. The "affective attack" has many emotional and sympathetic concomitants. These two different forms of agonistic behavior can be elicited from separate loci in the hypothalamus. Simultaneous stimulation of the amygdala may either augment or depress these froms of aggressive behavior elicited from hypothalamic stimulation (Egger and Flynn, 1962; 1962; 1967) in cats. The dorsolateral portion of the posterior lateral nucleus is a facillitating site where suppression can be elicited from

the lateral basal nucleus and from the anterior and medial portions of the lateral nucleus.

Karli (1956; 1972) has described naturally occurring attacks on mice in the rat, both domestic and wild. Although Karli has concluded that this behavior is "innate" it is a form of interspecific aggression rarely seen in nature. It occurs in varying percentages of rat populations, 66 % in wild rats and 12% in laboratory animals (albinos). Apparently strain differences are an important variable—our own results in several (3) groups (N = approximately 30 in each) shows that almost 90% of hooded rats will kill. Although Karli labels the response as being preditory he reports (we concur) the animals rarely consume the mouse after the first kill and nonkillers (Karli, 1956) will starve to death in the presence of a mouse. Deneberg et al. (1968) have shown that the animals social-affiliative history will effect the probability that it will show spontaneous mouse killing. Social isolation will enhance the probability that an animal will be a killer (Myer, 1969) and experience in killing increases the probability of a kill and decreases the latency between exposure to a mouse and the act of killing (Karli, 1956; Karlie et al., 1972). Whether or not the animal is in its home cage will effect the latency of killing. The "innateness" of the response is a question of definition but there is little doubt that the plasticity of the response must be considered in making such a classification.

Mouse killing rats that do not kill rat pups use olfaction to make the discrimination between the two. However, when a rat pup's odor is

masked by lavender toilet water, it is killed instantly by rats that ordinarily would not (Myer, 1964).

A bilateral amygdalectomy will eliminate mouse killing in natural killers. The region in the amygdala mediating the facilitation overlaps several nuclei and has been called the centromedial region (Karli et al., 1972). It is composed of the central nucleus and dorsal aspect of the medial nucleus. Lesions in this area will cause a permanent cessation of muricidal behavior. Bilateral transection of the stria terminalis leaves the behavior unchanged where transection of the fibers of the VAF passing through the ansa lenticularis will eliminate it but not effect conspecific interactions (Grossman, 1970) showing that the circuitry mediating the muricidal behavior is rather specific.

It appears that the facilitating centromedial region projects to the lateral hypothalamus to regions where aggression can be elicited upon stimulation. The centromedial region is inhibited by direct and indirect olfactory input as bilateral transection of the lateral olfactory tract anterior to the piriform cortex will cause killing to occur in natural nonkillers (Karli et al., 1972).

The last highly charged emotional states reliably elicited from the amygdala are the defense and flight behaviors which have been described by many investigators (of Goddard, 1964; Zybrozyna, 1972). These behaviors occur on a continuum of intensities and at their most intense points involve a completely activated animal. In the cat, threatening vocalizations are heard with growling and hissing, pupillary dilation, piloerection and the characteristic feline threat posture. This is the

unmistakable constellation of full sympathetic activation. The profile of somatic activation of the amygdaloid defense reaction is essentially the same one as is seen in the hypothalamic reaction. There is some difference however in the time course of the two responses. Elicitation of the hypothalamically stimulated reaction is stimulus bound with no latency between stimulus and response. This is not the case in the amygdala as it is delayed to an extent, and is seen to take time in its development even under high stimulating current levels. Full expression of the response can take between 20 to 40 seconds or longer. Similarly, the amygdaloid reaction can take much longer in its dissipation lasting from 20 seconds to two minutes after stimulus offset. The amygdaloid reaction seems to show a higher level of integration and control of the timing of the response. The topography of the reaction is not localized to any one nucleus. Elicitation can occur in parts of the anterior, basal and medial nuclei (Zybrozyna, 1972). The main pathway for communication of the defense reaction to the hypothalamus is the stria terminalis (Hilton and Zybrozyna, 1963).

A great deal of evidence has been presented showing the amygdala's role in emotional expression and in making adaptive responses to highly motivating stimuli. It is a multisensory area rich in visual and olfactory input which are two of the senses communicating distant environmental happenings that are highly relied upon by the vertebrate. Goddard (1972b) has demonstrated in his kindling effect, how short intervals of low level stimulation can cause long lasting, even permanent changes in amygdaloid responses. This suggests the possibility of a

consolidative learning mechanism functionally localized in the amygdala. Important social behaviors are represented in the amygdala, ranging from conspecific relations to maternal patterns. These behaviors are possible through complex interpretive functions, possible only through interactions of some behavioral substrates having "innate" origins tempered and modified through learning. The amygdala seems to be a primary center involved in these pattern recognitions and interpretations as it adds motivational valence or affective coloring through its intimate connections with the hypothalamus. Mediation of interspecific interactions as well as those with conspecifics are influenced by the amygdaloid complex. Many of these patterns of behavior are inborn but are modifiable. An example of this would be the change in muricidal propensities in the rat due to its early social experience with mice as well as other rats. Through the shear mass of the data one can not help but wonder that amygdala plays a major part in these interactions.

Amygdaloid Arousal and Orienting

Before an animal can engage in food seeking, social, sexual, agonistic, defensive or other adaptive activities, the animal has to be aroused. In order to properly interpret a stimulus and classify the event as relevant or irrelevant to its survival the animal must be able to orient to the stimulus so that the animal's receptors can take in as much data as is needed. Although they are basic responses, the orienting and arousal responses are among the most important of those mediated by the amygdaloid complex.

In the unanesthetized animal the orienting response is the most commonly elicited response to stimulation. Following stimulation, the animal will immediately cease all spontaneous behaviors such as grooming. The animals then show signs of arousal becoming alert and attentive. Orienting behaviors ensue as the animals begin to inspect the environment. Very frequently the orientation is to the side contralateral to the stimulation. Pupillary dilation and sniffing ensue and during this time the animal responds quite normally to stimulation. This is done at stimulation levels below those causing afterdischarges. The response is identical to responses elicited from mesencephalic regions, including cortical EEG desynchronization (Ursin and Kaada, 1960; Fendel and Gloor, 1964). However when compared to the mesencephalic response the amygdaloid response shows a much higher rate of habituation to stimulation. The arousal response seems to be localized in the lateral and magnocellular parts of the basal nucleus and to a medially extending portion entering the internal capsule. This region exactly parallels the diffuse fiber projections of the VAF (Kaada, 1972).

Inhibition of respiration rates, blood pressure and somatomotor reflexes upon stimulation of the olfactory tubercle and periamygdaloid cortex suggests the existence of an area which depresses arousal functions. In humans, stimulation of these areas will induce impairment of consciousness, feelings of fatigue and tendency to close the eyes. Again these stimulation levels were made at levels too low to produce an afterdischarge (Kaada and Jasper, 1952). Other aspects of amygdaolid arousal have been included in the section discussing amygdaloid 40 hz and its relation to arousal.

Behavior and Olfactory Bulb Ablation Studies

Historically, the behavioral effects of olfactory bulb removal have been highly debated and is perhaps an area that only the closest adherence to the best empirical techniques will unravel. For many years it has been widely accepted that removal of the bulb causes a hyper-emotionality and viciousness more pronounced than the septal and ventromedial hypothalamic syndromes. The work of Douglas et al. (1969) formalized these assumptions and launched experimentation from several investigators. Since then there has been a consistent inability of the most competent investigators to replicate each other's work (Thorne et al., 1973). Worse yet, several investigators have reported that there were no differences between successfully operated animals and normal controls in varying portions of the operated population, while the remaining show hyperemotionality (Douglas et al., 1961; Seago et al., 1970; 1971). This indicates that investigators lack uniformity in their preparations within their laboratory. Still other investigators have reported no change in emotionality following bulbectomy (Thorne et al., 1974; Bandler and Chi, 1972; Phillips, 1970; Thorne et al., 1973) raising the question: is the olfactory bulb syndrome real or artifact? There is no doubt that contradictory results can be explained when the proper controls are exerted. The syndrome is multidetermined, and the relevant parameters have been identified as being the sex of the animals (rats) (Sieck, 1973; Thorne et al., 1971), lesion topography and depth (Sieck, 1972; Thorne et al., 1974; Cain, 1974), social experience (Bernstein and Moyer, 1970), strain differences (Thorne et al., 1974)

and procedural differences, such as the use of Gelfoam to pack a lesioned site (Thorne, 1974). These have all been shown to be important determinants which are frequently neglected or over which there is a lack of experimental control.

Cain (1974) asserts that lack of detail in reporting histological findings renders the data from almost all of the studies in this area to be incomparable. Even so, recent highly controlled studies have yielded some very reliable data on the olfactory bulb syndrome.

Hyperemotionality is <u>not</u> a product of bulbar extirpation. Clearly the damage must involve extrabulbar areas such as the piriform, orbital, frontal or periamygdaloid cortices or anterior olfactory nucleus (Thorne et al., 1974; 1972; 1971; Bandler and Chi, 1972). The degree of affective change is continuous and can be related to lesion size and topography (Sieck, 1973). Thomas (1973) reports bulbectomized animals to be deficient in one way avoidance and facilitated in two way avoidance tasks.

Bulbectomies cause deficits that are seemingly unrelated to anosmia. Animals sustaining complete olfactory bulb damage fail to learn passive avoidance tasks and extinguish much slower in CRF (continuous reinforcement) schedules than do normal controls. Startle responses are augmented and olfactory bulb animals fail to habituate to extraneous stimuli in a Y-maze as exhibited by the fact that they never reach choice point latency criteria and hence never demonstrate that they have learned the task (Sieck, 1973).

It is not surprising that muricidal behaviors are seen in a significantly higher percentage (63%) of olfactory bulb groups than in

operated controls (10% - N = Ss per group) (Thorne et al., 1974). Studies have been included demonstrating the inhibitory role of olfaction on mouse killing rats who do not kill rat pups (Myer, 1964).

The mechanisms interrupted by olfactory bulb removals have yet to be satisfactorily identified but some rather provocative correlative relationships have been identified.

Olfactory bulb lesions have been shown to shift the animal's position on stimulus reactivity continua (rats). The same animals showed correlated shifts in brain serotonin and norepinephrine (Sieck, 1973), which are two of the most important amines in transneuronal communication. Serotonin depletion has been linked with basic behavioral components such as the ability to habituate to a stimulus (Sheard et al., 1967; 1968) which was an aspect of the olfactory bulb syndrome reported by Sieck (1973).

The olfactory system exerts important inhibitory effects on the amygdala (Karli, 1972; Bandler and Chi, 1972; Myer, 1964). It has been shown that many biochemical and visceral systems are at least under partial amygdaloid control and how the effects of pheromones through amygdaloid and hypothalamic influences can cause fluctuations in the output of many diverse somatic and endocrine systems. In short the olfactory-amygdaloid circuitry is a powerful source of control on the internal homeostasis of the organism.

External Control of CNS Electrical Activity

The earliest research on the EEG was purely correlative. Nearly all efforts revolved around and sought to establish relationships between

specific behaviors and the appearance of certain EEG waveforms. Eventually, in making further explorations a number of independent variables were administered either directly on the neural mechanisms generating the EEG, surgically or pharmacologically perhaps, or by stimulation of an intact individual. Examples would be sleep deprivation, exercise, sudden darkness etc., but the designs were inherently confounded because investigators lacked a treatment that they could be certain acted only on the site generating the EEG and not on the behavior. The designs were awkward perhaps because the questions being asked were. True breakthroughs in determining the relationship between CNS electrical activity and overt states of behavior would have to wait until a less obtrusive method of intervention was available.

The first successful demonstration of exerting external behavioral control on the EEG was made by Jasper and Shagass (1941) using a classical conditioning paradigm. The unconditioned response was the alpha blocking response, and using an auditory stimulus as a conditioned response, they were able to demonstrate nearly all of the forms of Pavlovian conditioning including simple, differential, delayed, cyclic and trace conditioning. Although the experiment demonstrated the possibility of temporary behavioral connections exerting control over spontaneous EEG it generated little interest in the following years.

Operant techniques were first applied to CNS electrical activity at the unit level where the operant behavior was the spontaneous discharge rate of individual units in the sensory motor cortices of lightly anesthetized cats (Olds and Olds, 1961; Olds, 1963). Units in the

precentral cortex of monkeys (Maccaca Mulatta) have shown increases in discharge rates of up to 100% above basal rates using food reinforcers (Fetz, 1969).

Studies paralleling the Olds work demonstrating the feasibility of exerting operant control on CNS controlled somatic and visceral responses previously thought to be "autonomous" from external contingencies were conducted by Miller (1967, 1969). The AEP (averaged evoked potential), a response reflecting integrative functions of the whole CNS was also conditioned. In an experiment using yoked controls Fox and Ruddel (1968) demonstrated that components of the visual AEP were plastic and subject to operant control. Those dimensions changed bidirectionally were the polarity of specific components of the AEP in cats, occurring between 170 and 190 msec.

Reinforcement contingencies are capable of changing the interrelationships of the individual components of the AEP which raises the question of conditioning specificity. A technique capable of independently modifying individual components of a response as fast as the AEP demonstrates an amazingly high degree of specificity. In turn, this raises the question of dissociative conditioning, where the normal significance of the physiological process being modified is completely altered. A demonstration of this possibility was made by Fetz and Finnochio (1971) where the investigators, using monkeys made simultaneous recordings of specific unit activity in the motor cortex and the EMG (electromyographic response). They localized a unit having a highly correlated firing rate with the EMG of the bicep. At this point they

placed the arm in a special cast rendering it useless but maintained the capability to monitor and reinforce the EMG activity from four of the arm muscles. As part of a control procedure they once again demonstrated the high positive correlation between the cortical unit and the bicep EMG. In the next stage they successfully rewarded high firing rates of the unit and low basal EMG rates. The monkey learned to increase the firing rates in the absence of any EMG activity. The monkey also learned to reverse this task in part, that is it learned to produce high EMG in the biceps while reducing the firing rate of the unit. Here is a case of complete dissociative conditioning where feedback procedures through their specificity have produced a physiologically unnatural state. This is an important theoretical caveat when using such procedures.

Operant control of unit responses can be considered to be molecular when contrasted to the modification of whole populations of responses such as is the inevitable result of conditioning the EEG. EEG conditioning has been demonstrated cortically and subcortically in both animals and humans and an in depth review has been made by Black (1972). A systematic review of the relevant results can be made and can be cogently organized or classified if they are related according to the particular spindle or type of activity being conditioned.

In humans, with scalp electrodes, Green et al. (1972) has reported conditioning of theta spindles which are high amplitude spindles having frequencies between 4 and 7 hz. The occurrence of such theta activity has been reported to be correlated with shifts in cognitive states such as reduced arousal accompanied by hypnagogic imagery. Beatty (1974)

has demonstrated that when two groups are reinforced for high and low theta density respectively, that the high theta group shows deterioration on a monitoring task requiring high vigilance where the latter group shows a facilitation in the task. Theta conditioning then, is associated with the reduction of arousal with mood-shift alterations.

One of the first spindles to be conditioned in humans was the alpha spindle, a second high amplitude spindle occurring in the frequency range of 8 to 12 hz. Dewan (1967) first reported the conditionability of the response and the fact that the occurrence of alpha is linked to such mediators as occular accommodation, eye position and degree of occular fixation. Dewan's subjects achieved such a degree of volitional control over the spindle that they could use it to send Morse code messages. Human subjects have demonstrated that they can readily discriminate between alpha states and nonalpha states (Stoyva and Kamiya, 1968). There is a low state of arousal associated with alpha. Subjective reports have described the state as being pleasant and relaxed with an accompanying narrowing of awareness (Brown, 1970). Kamiya (1969) in fact used the pleasant and rewarding states reported by Ss, plus the fact that it is discriminable to explain the phenomenon of alpha conditioning by saying that the Ss doing well in the task found it to be a preferred state after it was induced through the use of external feedback equipment.

In an experiment which examined the effects of the convulsant monomethylhydrazine, Sterman (1973) found that cats having been reinforced for producing 12-14 hz activity in the sensorimotor cortex,

manifested significantly extended seizure onset latency, or showed no motor seizure response at all. Chase and Harper (1971) later referred to this relatively low amplitude spindle as SMR (sensorimotor or somatomotor rhythm). This rhythm which seems to be indigenous to the sensorimotor cortex has been functionally related to motor inhibitory phenomena. Clinical applicability of this rhythm has been demonstrated by Sterman (1971; 1972; 1973; Sterman et al., 1974; Lubar et al., 1976; Finley, 1976) in the control of certain epileptic seizures. Shouse (1976) has shown beneficial results in hyperkinetic populations using SMR conditioning.

The conditioning studies above have dealt with the conditioning of low frequency spindles and there are several commonalities between them which suggest a common property. All of the rhythms, including SMR, which is believed to be the same as a stage II sleep spindle, are associated with concomitant body states in which decreases in arousal and motor activity are seen. This is not at all unexpected when one considers what these waveforms are indicative of. All of the conditioned activities are synchronous spindles in which the underlying cell populations are synchronized and working in unison. The cell populations are not engaged in differentiated activity. These activities contrast sharply with cortically activated states which are characterized by a desynchronized EEG having very low amplitude heterogeneous frequency components (Morrel and Jasper, 1956). Such a lack of synchrony is indicative of highly differentiated activity of the cells which are generating the EEG as would be the case during rates of high information

processing. The spindle has been explained as a mechanism of cortical idling, where the cortex is in a state of waiting (Andersen and Anderson, 1968).

In contrast to the low frequency spindling behaviors and their concomitant inhibitory states, the higher frequencies accompany states of activation and arousal. An example of this is alpha blocking where there is a sudden shift from occipital alpha to beta activity with the presentation of a novel stimulus (Jasper and Shagass, 1941, Andersen and Anderson, 1968). This principle holds true in the olfactory bulb (Lavin et al., 1959) and in the amygdala (Gault and Leaton, 1962). The relationship between rhinencephalic 40 hz and arousal has been discussed at length earlier. It was shown that in order for 40 hz amygdaloid activity to occur there must also be an arousal component projected to the amygdala from the mesencephalic reticular activating system. Forty hertz activity at the neocortical level has a smaller amplitude and has been related to the acquisition phase of a serial learning task and is thought to have a role in the consolidation process of the stimulus-response connections (Sheer, 1970; Sheer and Grandstaff, 1970).

The consensus is almost unanimous among investigators of the amygdala that its role is a modulatory one through which information is integrated. It works in conjunction with the rest of the limbic system weighing the net effect of current external events, past experience, and current internal states, biasing the hypothalamus as it controls effector outflow (Egger, 1972; Kaada, 1972). It has been suggested that the amygdala's own plasticity is the neural substrate

involved in reconciling more rigid innate pattern recognitions with current and past realities (Kaada, 1972). Once again this is accomplished through rich reciprocal connections with the hypothalamus. These connections are organized to the point that several investigators have suggested the idea of a topologic representation of the amygdala on the hypothalamus (Kaada, 1972; Egger, 1972).

The proposed research is directed at modifying the molar electrical (EEG) behavior of the amygdala through augmented feedback and alimentary reinforcement. The amygdala enjoys both nonspecific sensory projections that are related to arousal (Gault, 1963) and very specific sensory projections. Machne and Segundo (1955) and Creuzfeldt et al. (1962) both have demonstrated specific units which will respond to very complex stimulus patterns. O'keffe and Bouma (1969) have described amygdaloid units which respond to meows rather than clicks and mice rather than flashes of light. Such specificity demonstrates that the amygdala is getting very specific sensory input which in turn enables it to make specialized responses. This is interesting in respect to its nonspecific arousal functions. It is anticipated that operant augmentation of the electrical activity in the amygdala will cause a general activation of the animal.

The present study will investigate the effects of modulating 40 hz activity in the amygdaloid complex in hopes of illuminating the role of this activity in amygdaloid function and adding to the existing body of knowledge concerning amygdaloid mechanisms and function.

CHAPTER II

METHODOLOGY AND RESULTS

Method

Subjects. The initial subject pool consisted of eight male hooded rats received from Blue Spruce Farms. These rats weighed 300 grams ± 10 grams. Upon receipt the animals were individually housed and placed on an adlib feeding schedule. A normal day-night cycle (12 hours on and 12 hours off) was maintained for the duration of the experiment. Animals were allowed to increase size and weight until a weight of 380 (±10 grams) was attained prior to surgical implantation of the electrodes, connector and cranial skull cap.

Surgical procedure. All surgical procedures were performed under aseptic conditions using .001 cc Nembutal (sodium pentobarbital) anesthetic per gram of body weight. Presurgical preparation including shaving the animal's head, cleaning with phisohex and securing the animal rigidly in a Kopf Model 1404 stereotaxic holder adapted for rat surgery. A longitudinal incision was made followed by a blunt dissection of the periosteum and cranial musculature. The cranium was visualized and allowed to dry thoroughly. Any bone hemorrhaging was eliminated by thermocoagulation. Stainless steel bone screws were fixed in a pentagonal pattern at the anterior and posterior extremes of the dorsal cranium. The screw at the anterior apex of the pentagon was soldered to a 20 gauge wire prior to implantation. This wire was used as a

reference for making bipolar recordings. Care was exercised to maintain the integrity of the underlying cortex at all times during the preparation.

Nichrome electrodes were made in the laboratory prior to surgery and were made in a twisted pair configuration. The wire diameter was .127 mm and was Formvar coated. Twisting was done with an electric motor under 10 to 15 lbs. of linear tension to insure straightness and uniformity of pitch. After twisting, the electrodes were dipped automatically in Epoxylite and baked for 24 hours at approximately 95° C. The curing procedure was repeated three times. Electrode tips were made by cutting the electrode shaft at a 30° angle with a pair of sharp scissors. There was no further spreading or scraping of the tips. The nominal impedance at 10 hz of this preparation was approximately 100 K-ohms (Kilohms) as measured by a Grass Model EZM impedance meter, and was relatively constant (± 10 K-ohms) across animals.

These electrodes were placed stereotaxically and bilaterally using the De Groot (1959) atlas. Coordinates for implantation were: A-P + 5.4; D-V - 2.0; and M-L ± 4.0 mm. Entry holes for the electrodes were located with the electrodes while in their stereotaxic holders and made with a .79 mm drill bit in a dental drill. The dura and pia mater were punctured by a 20 gauge needle to minimize deflection of the electrode. The electrodes were fixed to the skull using Cranioplastic acrylic dental cement. After the cement cured, the electrodes were unraveled at the top and were prepared for soldering to Amphenol SLE-7, seven pin sockets. After heatsinking the electrodes and reference wire, the

connector was cemented securely to the skull and bone screws. The wound was thoroughly cleaned and received an application of sulfathiozone powder for antiseptsis. The wound was closed using absorbable catgut sutures in a manner which would minimize tissue recession from the skull cap. This preparation proved to be very durable, lasting for over a year when required.

Significantly larger nichrome "side by side" electrodes were implanted and used as bipolar recording electrodes in earlier pilot work. Subsequent histological examination showed that these electrodes were placed with a great deal of precision, but because of their relatively large size left relatively large and obtrusive tracks. These tracks indicated that the electrodes themselves caused much damage and were an intrusive preparation. The much smaller diameter twisted pair electrodes used in this study were quite the opposite. These electrode tracks were so small that it was very difficult to see the electrode tracks, even with a high quality microscope. The disadvantages of these electrodes is that they were liss rigid and more sensitive to the effects of variations of neural tissue density as they traversed the various strata of brain tissue during implantation. For example, a fiber tract such as the optic tract is much denser and harder to penetrate than are the surrounding cortices or a nuclear mass such as the amydgala. Variations in tissue density did increase the "spread" of the placements of the twisted pair electrodes when compared to the more rigid side by side electrodes; however there was virtually no tissue damage. Histological examinations showed that all electrodes were in the amygdala. No

histological evaluation was possible on the left hemisphere of rat 3K because the post morten fixing of the brain tissue was relatively poor and the left hemisphere tissue from the histological sections were frequently torn or lost.

Pre-experimental behavioral training and screening. The animals were placed on adlib food and water for a two-week post surgical recovery period. Following recovery they were placed on a 23 hour water deprivation schedule with adlib food. During the course of the experiment body weights were monitored and not allowed to drop below 80% of the weight prior to implementing the deprivation schedule. Ss (subjects) were allowed to habituate to an aluminum skinner box (25 cm High x 30 cm Wide x 20 cm Deep). The floor of the cage was a nonelectrified grid approximately 2.7 cm above the bottom of the cage. Centered on one wall was a brass drinking spout mounted 2.7 cm above the cage floor. The spout had a water capacity of approximately .2 cc. Two CM 47 light bulbs were mounted 9 cm above the spout and were laterally displaced 5 cm to either side of the spout. The animals were manually dipper trained to the spout. During this period one of the CM 47 lights was illuminated at all times. When reinforcement was available, the glowing CM 47 was extinguished for 500 msec (milliseconds); and simultaneously the quiesent bulb was illuminated. The net effect was a luminous stimulus to the animal which was a highly discriminable event. The second light added to the discriminability and maintained the level of illumination in the apparatus. This addition minimized a startle response to this stimulus. A 60 dbm tone at 2400 hz was emitted

simultaneously with the light alternation. When this stimulus complex was repeatedly paired with the presentation of water at the spout it acquired very immediate secondary reinforcing capabilities. This was important because a water reward is not as intrinsically visible or audible as is the traditional food pellet reinforcer and therefore can arrive unannounced to the animal. This would of course significantly reduce the effectiveness of a reinforcer. Furthermore, such a noticeable secondary reinforcer was advantageous because the eventual operant was an EEG response as opposed to a motor response. Reafference from a motor response is part of a stimulus complex used by the animal in an instrumental learning task. Such reafference is lacking in an EEG operant response. Finally, the response was one that could occur in the absence of any specific orientation in the apparatus, even if the animal had its back turned to the reinforcing apparatus and an effective secondary reinforcer was needed to announce the presence of the primary reinforcer.

After Ss were dipper trained and learned the significance of the secondary reinforcer, a standard rat bar manipulandum was installed in the cage at the same height of the drinking spout and 5 cm to the left. Deprived Ss were left in the cage over night for autoshaping to the bar response. All Ss autoshaped in one night. After this Ss were run daily for eight days until they had made a minimum of 2000 cumulative presses. This demonstrated that the water was an effective reinforcer and insured that the significance of the secondary reinforcer was well learned. Following this period Ss received similar training, with the addition

of alternating periods where the availability of reinforcement and the secondary reinforcer were turned on and off for 5 minute periods. Ss were run on this schedule for 2 hours per day for eight days. Here the presence of the light used as the secondary reinforcer served as a cue that reinforcement was available in an SD-S_{Δ} fashion (discriminative stimulus and S_{Δ} meaning change is the discriminative stimulus.) Over the eight days recording equipment indicated that rats learned behavioral suppression to the S_{Δ} condition where the cue lights were extinguished.

Ss were subjected to muricidal testing where it was determined that four of the five animals (3K, 5K, 8K and 10K) were vicious and effective mouse killers. There was virtually no latency between introduction of a mouse into the home cage and the onset of a lethal attack. The remaining rat (4N) was a nonkiller. During the entire experiment this rat was housed with a 30 gram white mouse. There was never any evidence of aggression from 4N towards this mouse, in fact they habitually slept together during sleeping periods. The behavior of the other rats was unchanged towards mice during the course of the experiment. Upon exposure to a mouse they killed instantly.

Experimental design and intrasession paradigm. A simple A-B-A, pretest, test, posttest design was incorporated for the experiment. The one parameter that was changed across conditions was the contingency of the reinforcer. During the pretest and posttest conditions, respectively referred to as habituation and extinction, there was no contingent relationship between the observed 40 hz spindling and the reinforcer. A baseline rate of 40 hz spindling behavior was recorded while the

animal received completely random reinforcement during the 10 day habituation period. Reinforcement was made contingent upon the occurence of 40 hz during the acquisition or test phase of the design for forty days in an attempt to operantly augment the 40 hz activity. Finally, the random schedule of reinforcement was restored during the extinction or posttest part of the experiment. The extinction phase lasted 20 days. Much care was taken to insure that the Ss were subjected to no changes across the cells other than the reinforcement contingencies.

Behavioral testing. At the completion of the three cells, Ss were subjected to a variety of behavioral tests measuring emotionality and reactivity to various stimuli. Specifically these tests were vocalization upon handling with a glove, presentation of a pencil in the cage, current threshold for vocalization while in a shock box and an open field test. These tests were repeated once per day for five days and an average score was reported for them. These tests have been described in detail by Bernstein and Moyer (1970). The measures obtained from these tests were well quantified where possible. The attack toward a pencil when it was presented was rated on a scale from 0 (complete indifference) to 5 (vicious attack) the same is true for the measure relating to emotionality seen when handled with a gloved hand in the cage. The open field test requires no judgements, yielding to objective measures such as the number of square crossings. The reactivity test, current threshold for vocalization, could be directly measured from a meter while the current was advanced at a steady rate. Because of disruptive effects the shock test was always given last.

Animals were maintained on their 23 hr deprivation cycle at all times during these measurements to avoid confounding effects of variations in motivation. Emotional tests were made approximately five hours after Ss daily watering to reduce the moderating effects of complete satiation.

The day to day handling and treatment of the individual S is described in the intrasession paradigm. The intrasession paradigm was fully automated and required no intervention or supervision from E eliminating experimenter bias. The apparatus which accomplished this is fully illustrated in Figure 5. Each session lasted for 40 minutes and occurred daily. Ss were run for six days per week on the 23 hr. deprivation schedule and given adlib water for 24 hrs. after the session on the sixth day. The animal was not run on the seventh but was returned to the 23 hr. deprivation schedule. This was to minimize the stress to Ss caused by a constant deprivation schedule.

The availability of equipment necessitated monitoring and reinforcing only one hemisphere at a time. During every session however, both hemispheres were conditioned in a highly prescribed fashion. A session was initiated by selecting either the right or left hemisphere to be the contingent (hemishpere being conditioned) hemisphere. Each 40 minute session can best be conceptualized if it is subdivided into eight, five minute blocks. The first (1st through 5th minutes) block and last (36th through 40th minutes) were blocks during which the cue light was extinguished and there was no reinforcement available. After the first block which was a passive recording interval for

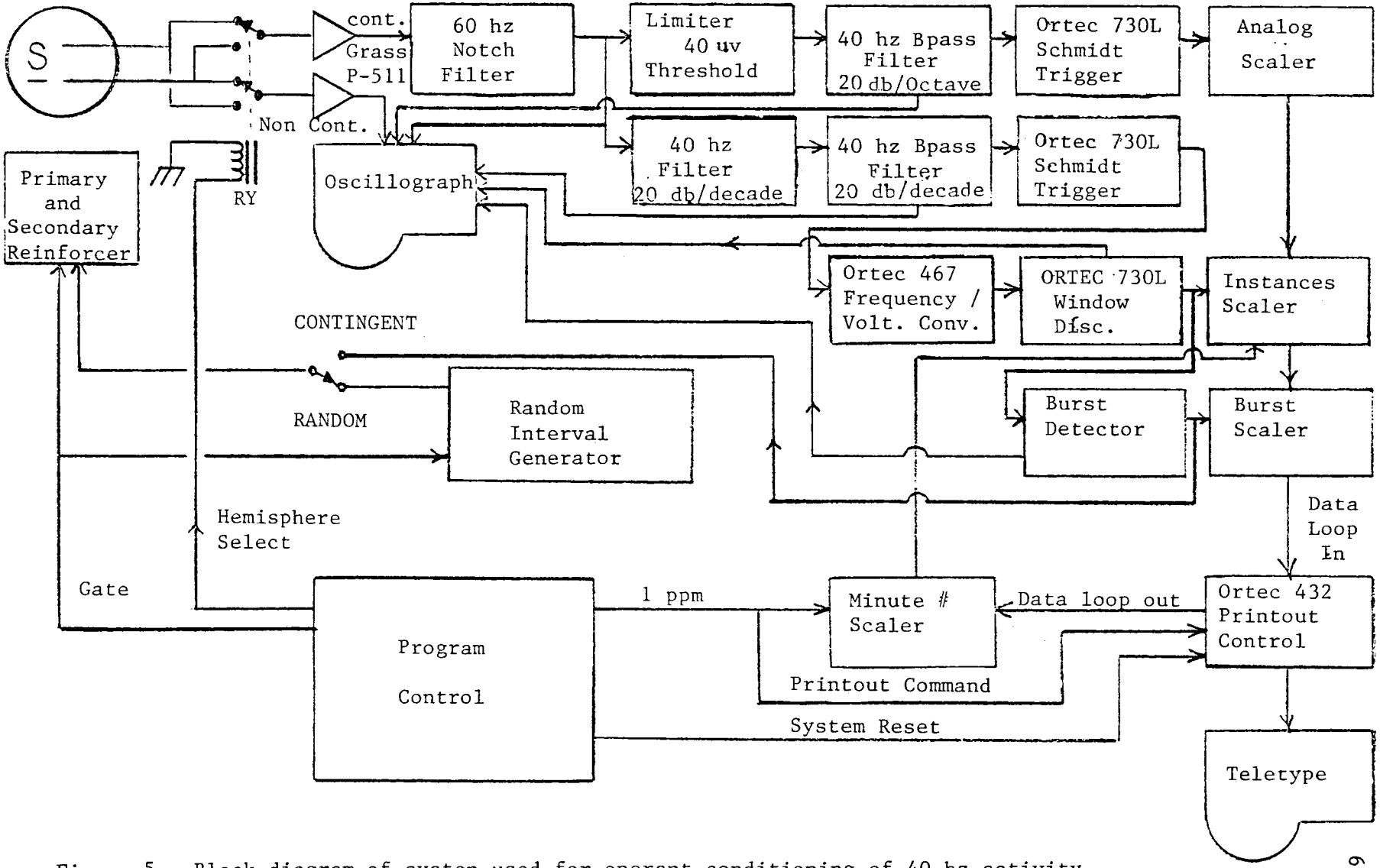
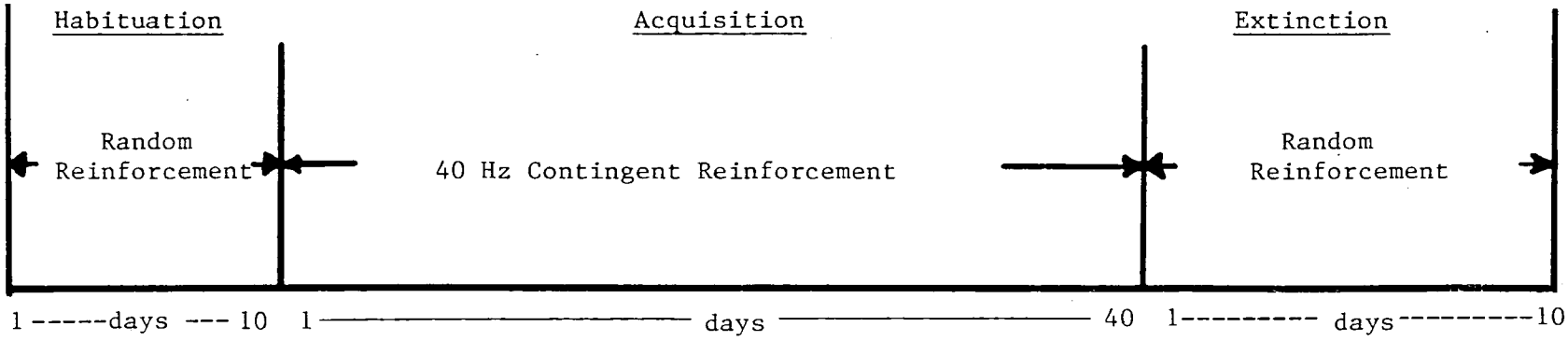


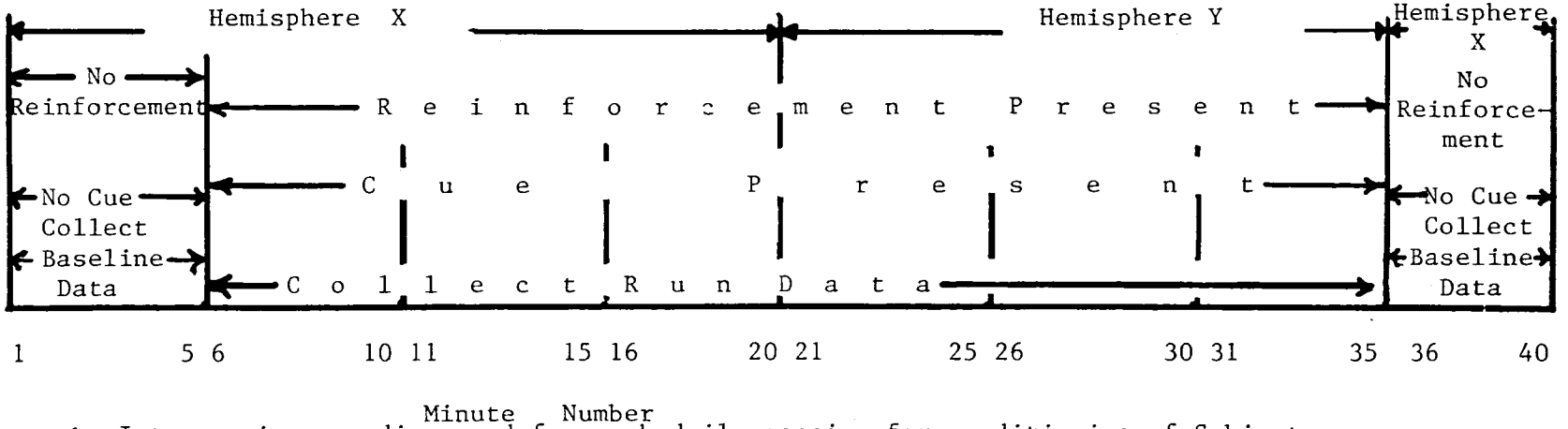
Figure 5. Block diagram of systen used for operant conditioning of 40 hz activity and data acquisition.

recording the animals baseline spindle density, the conditioning periods began marked by the illumination of the cue light and availability of reinforcement. The initial hemisphere, either the left or the right, had its baseline measured during the first block and was conditioned during the next three blocks (minute 6 through 20). The equipment then alternated hemispheres and began conditioning the contralateral hemisphere for the next 15 minutes or three blocks (minutes 21 through 35). The equipment then automatically switched back to the original hemisphere, removed the reinforcement while monitoring the hemisphere's performance, and extinguished the cue light.

A pictorial representation of the basic experimental design is illustrated in Figure 6a. Figure 6b illustrates the somewhat more complex intrasession paradigm. Data representing the various categories of dependent variables were accumulated and printed out at one minute intervals. Fifteen minute averages of a given dependent variable were averaged for each reinforcement block (minutes 6 through 20 and minutes 21 through 25) and graphed to attain "RUN" scores. "BASELINE" scores, plotted with RUN averages were attained by averaging the dependent variable scores of the first and last baseline intervals. Since baseline scores could only be collected for the initiating hemisphere on a given day, the hemisphere of initiation was alternated systematically daily. This allowed baseline data acquisition for a given hemisphere to be collected every other day. The practice also provided a convenient method for counterbalancing of sequential conditioning effects which may be related to satiation or task fatigue in the S.



a . Experimental design showing reinforcement contingencies.



b . Intrasession paradigm used for each daily session for conditioning of Subjects.

Figure 6 . Diagrams illustrating the experimental design and intrasession paradigm for daily conditioning.

Apparatus for recording reinforcement and data acquisition. A block diagram of the apparatus is provided in Figure 5 (page 68). EEG recordings were made using Grass P-511 AC (alternating current) coupled differential amplifiers. The contingent hemisphere was selected automatically by relays to feed the input of the contingent amplifier which drove the data analysis and reinforcement equipment at all times. This manner of hemisphere selection, i.e., low-level switching of the inputs, was used in preference to high level switching to eliminate the possibility of differences between the amplifiers affecting the data. The remaining amplifier was the noncontingent amplifier which had the singular function of amplifying activity in the noncontingent hemisphere for oscillographic display. The contingent amplifier was set to have a low frequency rolloff at 10 hz at a 6 db (decibel) per octave rate. The upper rolloff began at 100 hz at a rate of 6 db per octave. The amplifiers were operated at a gain of 10,000.

The 60 hz notch filters in the Grass P-511 are passive R-C (resistance and capacitive network) filters which are very broad in their response. They are broad enough that using them would produce several db of attenuation at 40 hz. This was not tolerable so the contingent amplifier was operated using an external active 60 hz notch filter (Mentor, Inc.) having extremely sharp rejection (60 to 70 db) at 60 hz ± 1 hz. The noncontingent amplifier used for the oscillographic display was operated using internal 60 hz notch and showed a resulting lowered high frequency response on the noncontingent write out. The contingent channel was split at the output of the Mentor filter into a

data acquisition channel and the actual reinforcement channel which is also a data channel. The reinforcement channel used a frequency discrimination method which was based on zero-crossing analysis. Zero-crossing frequency discrimination is one of the most accurate frequency discrimination techniques but as a technique it has some limitations. One of the most troublesome is that low frequency components can offset higher frequency components to the point that internal discriminators do not "see" them.

A digitally based zero-crossing technique can be used when a heterogenous EEG signal is preprocessed using broadly tuned bandpass filters to eliminate the low frequency components. This has the effect of eliminating any sustained baseline shift which can have a very deleterious effect on the zero-crossing discriminator. Two broadbanded 40 hz bandpass filters were constructed in the laboratory for the present research. Each filter had a rolloff of 20 db/decade on either side of the center frequency. The filters were cascaded to achieve an attenuation of 40 db per cecade. This yielded a 40 db attenuation at the 1/10F (4 hz) and 10F (400 hz) points. When combined with the rolloffs in the Grass P511s the attenuation at 4 and 400 hz were approximately 50 db referred to the amplifier's input. The filters were adjusted to have unity gain at their 40 hz center frequency.

This system, used in conjunction with a zero-crossing analysis was more than adequate for the detection and reinforcement of 40 hz activity. The filters were free of "ringing" and any artifact caused by transients introduced by the Ss movements. An Ortec 730-L Single

Channel Analyzer used as a schmidt trigger (integral mode) with a trailing edge pulsed output (.5 usec @ 5 volts) was used to monitor the output of the 40 hz filters and to make an amplitude discrimination when the amplitude of the amplified EEG exceeded a voltage level which corresponded to a voltage level which corresponded to 5 uvolts of raw EEG. It should be noted that daily low level voltage calibration of all equipment was standard operating procedure. The output of the 730-L was connected to the input of an Ortec 4672 Instantaneous Time/Frequency Meter. The Time/Frequency meter functioned as a frequency to voltage converter and worked on a cycle-to-cycle basis, insuring as close to an instantaneous response as is possible. The analog signal from this converter was monitored by a second Ortec 730-L Single Channel Analyzer operated as a window discriminator (differential mode), enabling the E to predetermine a digitally detected frequency bandpass. When activity occurred in the 38-42 hz the second 730-L responded with a logic pulse (.5 usec @ 5 volts).

Dependent variables and their instrumentation. Individual EEG events exceeding 5 uvolts were accumulated and constituted the dependent variable referred to as "INSTANCES" data. The INSTANCES pulses were monitored by a digital burst detector. This detector had the capability of responding when a preset number of pulses occurred in a preset number of milliseconds (100 millisecond increments). When the criterion was met the detector emitted a "burst" pulse. The burst pulse appearing at the reinforcement apparatus when the paradigm was in reinforce mode (minute 6 through 35) would cause the sonalert tone and lights to

alternate as the animal received approximately .2 cc of water. These burst pulses were written out oscillographically as were the instances pulse. The number of burst pulses were synonymous with the number of reinforcements and as such became a second dependent variable hereafter denoted as "BURSTS." During portions of the design calling for random reinforcement, the reinforcement apparatus could be activated by a digital random interval generator which generated pulses having random spacing in time. The mean interval could be controlled by presetting the longest possible interval desired. In this case then, the mean interval would equal one half the maximum interval. During the experiment the interval was set at 30 seconds. The random interval generator would reinforce on the average once every 15 seconds which was a nominal reinforcement rate.

An additional dependent variable was one that is derived from the raw EEG where it branched to the INSTANCES 40 hz filters. At this point, the EEG was amplitude limited, where it exerted its limiting action on signals exceeding amplitudes of 40 uvolts. This method is superior to clipping which introduces harmonics into the processed signal that were not there prior to clipping. A limiter minimizes these effects because its limiting action is not as severe as a clipper. The purpose of the limiter was to eliminate high amplitude transients from ringing the White Instrument Company 4-pole active bandpass filter. The output of the bandpass filter (38-42 hz) was adjusted to have a unity gain at the center (40 hz) of its bandpass. The output of the filter drove a third Ortec 730-L Single channel analyzer (integral mode) which was used as a

schmidt trigger. The output pulses of this circuit were accumulated as a dependent variable called "ANALOG," meaning that the system was accumulating the number of events exceeding 5 uvolts as measured by a sharp bandpass filter.

Tha ANALOG measure was accomplished by filtering the EEG with a relatively sharp bandpass filter followed by a schmidt trigger. The pulses from the schmidt trigger (Ortec 730-L) were then accumulated in a binary fashion. Such a configuration was used to provide a rough indication of the number of events exceeding a preset threshold (5 uvolts). The method has proven to be unreliable at lower frequencies (12-15 hz) in previous studies (Luber et al., 1976; Shouse, 1976). Commercial filters used in the lower ranges were found to be much more sensitive to artifact than was an equivalent filter in the 38-42 hz range.

Even with the reduction of the filter's transient response the information yielded from such a measure was limited by the inherent loss of analog information relating to power or voltage when translated by a binary schmidt trigger. The information yielded by the ANALOG measure is problematical at best, but it was included in hopes that when compared to and with the other measures that a clearer picture of the conditioning process might emerge.

Daily sessions. The entire daily session was completely automated from start to finish using sequential logic. This included hemiphere selection and switching, gating (enabling) the reinforcement mechanism and timing the printout command to the teletype printout control.

Figure 7 is an exemplary oscillographic write-out obtained from the system. Here the top channel is the raw or unprocessed contingent EEG signal. Channel 2 is the filtered output of the contingent EEG. Channel three is the burst channel and shows one reinforcement. Channel 4 is the output of the 40 hz filter and of course is an analog signal. Channel 5 is the contralateral or noncontingent hemisphere. Channel 6 shows the instances output in the form of the small digital logic pulses. There are a number of notable aspects to this sample of the write-out. The high amplitude rhythmic signal appearing in both hemispheres was the only "artifact" seen in the course of the experiment. It occurred when the animal was licking water from the spout as a result of being reinforced. The activity was uniformly 6 hz. It is important to note that reinforcement is not obtained for the behavior nor does it generate spurious responses in the data acquisition circuitry as it is monitored in every step on the oscillographic write-out. It is equally notable that the high amplitude transient activity did not cause any problematic response in the 40 hz filter output. Complete assurance the system was artifact-free is a necessity, for no presumption of 40 hz conditioning is admissable until it can demonstrate positively that the system is successfully rejecting artifacts and is only reinforcing for 40 hz spindles. Note the licking artifact in Figure 7 is not reinforced.

Interpretation of the dependent variables. During the course of the experiment the apparatus determined that an INSTANCE had occurred if one cycle of 40 hz activity occurred having an amplitude greater than 5 uvolts. The graphs show separately, the daily mean number of INSTANCES

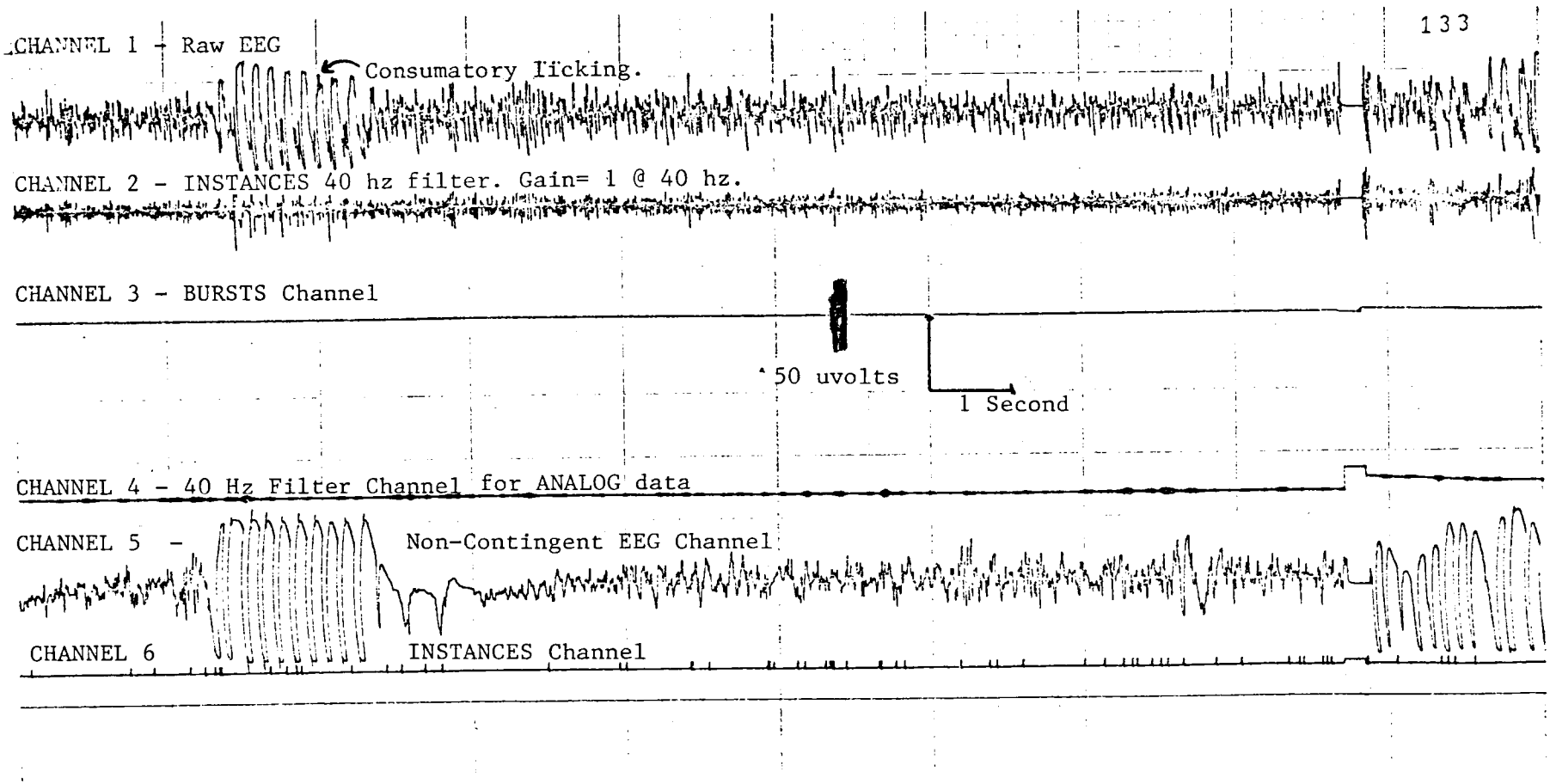


Figure 7. Exemplary write-out showing relationships of data channels on oscillograph.

per minute for each hemisphere. As with all of the variables, baseline data for a given hemisphere was collected on alternate days. INSTANCES pulses coming in large numbers in a short period of time would be the natural consequence of a 40 hz spindle. When the stream of pulses met the burst detector's numeric and temporal criteria a BURST pulse was emitted. In the course of the experiment the criteria were 4 pulses in 200 milliseconds. The fact that high rates of INSTANCES would cause high rates of BURSTS means that the two measures are highly correlated because of the dependence of BURSTS on INSTANCES. The third measure was electronically independent but should reflect the same phenomenon monitored by the first two measures and therefore should ideally show a high correlation with the first two measures. The ANALOG measure had nothing to do with reinforcement. Since it was independently measuring the output of a 40 hz filter corresponding to the amount of 40 hz energy in the signal and exerted no influence on reward to the animal it should be the source of an excellent independent measure of conditioning.

The intercorrelations between these measures would vary according to the underlying mechanisms influenced by the operant conditioning process. Specifically, the interrelationships should depend on the method of "strategy" used by S to produce the behavior. This will be discussed in the chapter on conclusions and discussion.

Statistical analysis. Selection of the appropriate statistical analysis for the conditioning studies involves making a set of a priori assumptions about the treatment received by the Ss. Group statistics

would be applicable if all of the electrodes were recording in exactly the same site. This is not the case. Electrodes having very small surfaces tend to record with a great deal of specificity. For this reason and distribution of electrodes after histology it was decided that individual statistics for each hemisphere of each animal would be applied.

The analysis was a two way analysis of variance with one score for one subject's hemisphere in each cell. The design broke the data into seven sequential blocks each containing data for ten days which in turn contained the averaged minute scores for each of the seventy days. The 10 day blocks were the collapsed columns of the matrix. The collapsed data in the rows provided days data. The two effects analyzed then were rows and days. This is a very powerful analysis albeit an unusual one. The practice of assigning one measurement to one cell eliminates within cell variations from differences between subjects assigned to the same cell. After obtaining the matrix F value, a Tukey A Multigroup Comparison was used to determine which blocks were significantly different from each other. The p value for the F was $\simeq .01$ ($df = 69$) for significance. Intercorrelations for each measure were also obtained. Plots of the original data, the block means of the data and Tukey A comparison summaries are included.

Results

EEG conditioning. During the course of the experiment there were no facilities in the laboratory for making either an on-line spectral

analysis, or to make analog recordings for later analysis. This is one of the reasons that three measures were used. The sacrifice is the loss of information concerning relative densities of other components of the spectral densities. Figure 8 is an exemplary EEG writeout from Rat 10K during the habituation period. Typically the patterns seen during habituation were "quiet" such as the write-out seen here. These patterns contrasted sharply with the patterns seen on days in the acquisition blocks when the animal was receiving high rates of reinforcement. Such a pattern is depicted in Figure 9 which was made during the animal's final day of acquisition. Here the EEG shows an elevated average power and much more activity in the 40 hz range. This is evidenced in the raw EEG, output of the differentiator, 40 hz filter, instances measure and bursts. The lower roll-off of the noncontingent channel is very apparent here in that there is an attenuation of high frequencies. Typical post-extinction activity resembled habituation activity with variations. At times habituated activity was less activated than extinction and at times the converse was true depending on the relative degree of habituation and extinction. An illustration of an extinguished EEG is seen in Figure 10. Here the activity has not quite returned to baseline behavior. Figure 11 is a write-out having a higher speed, providing a clearer picture of the reinforced activity. The changes in the EEG were not always as pronounced as these pictures indicate, on the other hand there were other rats that showed more pronounced changes than the ones shown here.

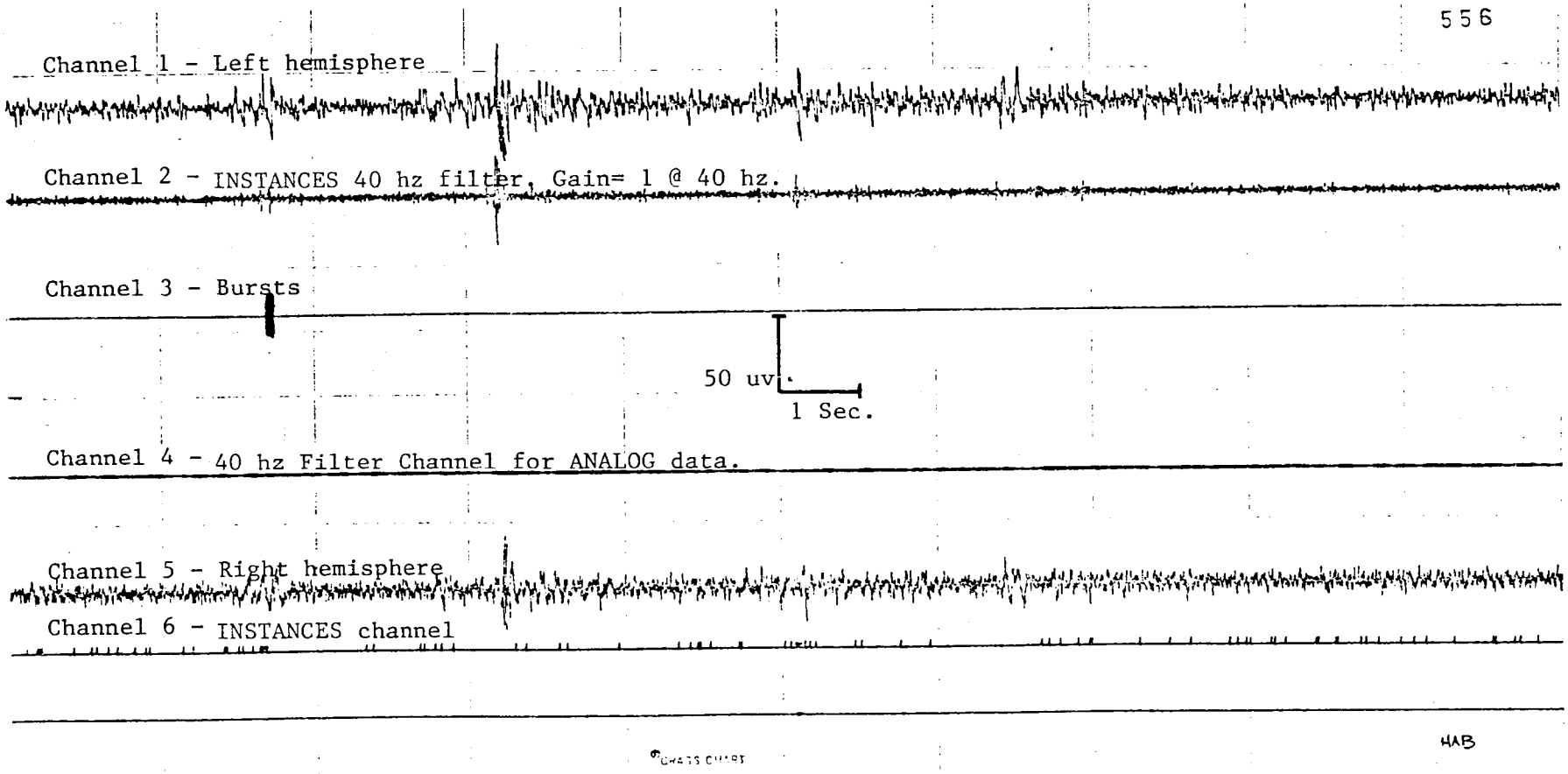


Figure 8. Habituation Day 10. Left hemishere contingent. Rat 10K.

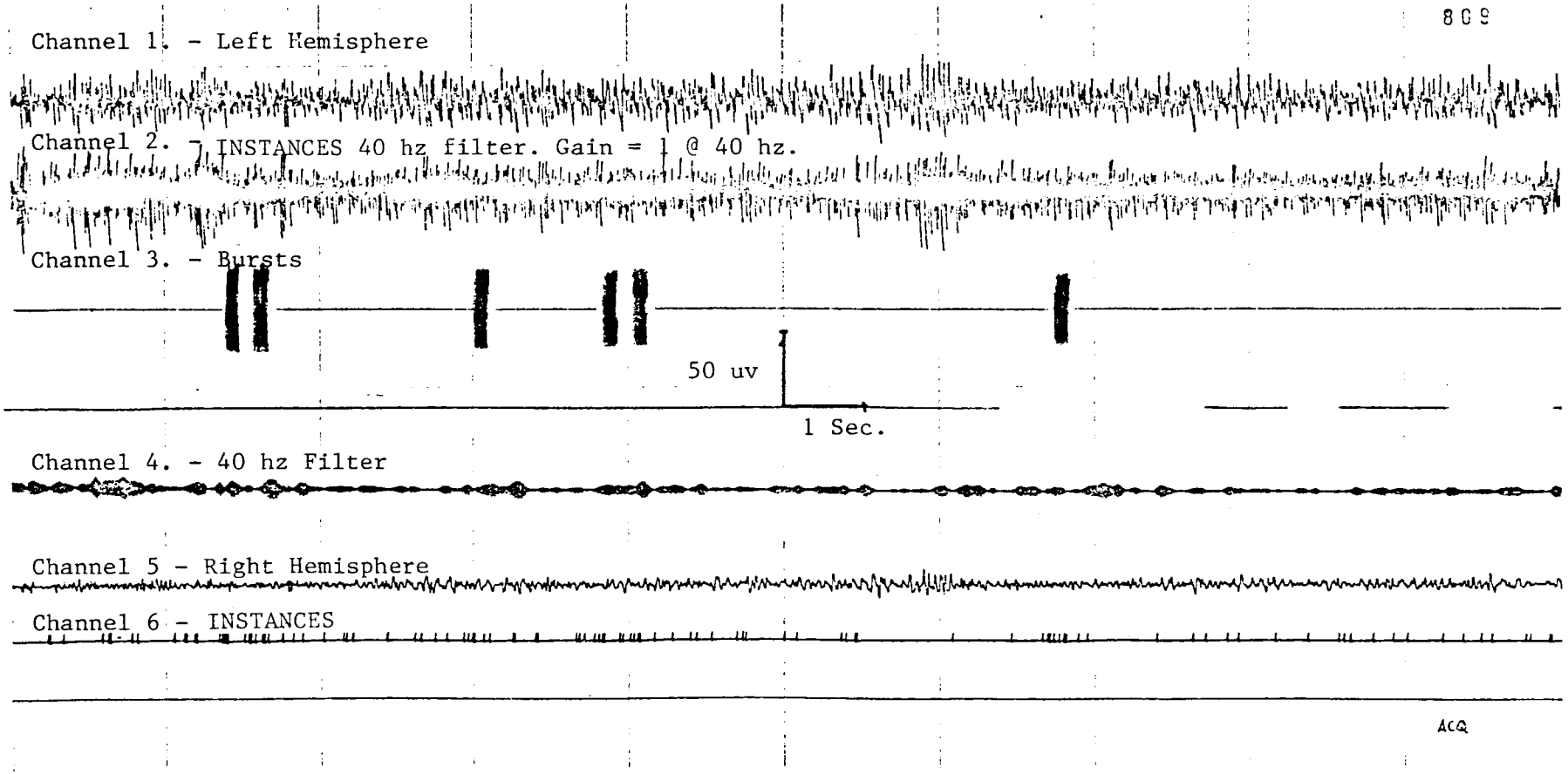


Figure 9. Day 40 acquisition - left hemisphere contingent. Rat 10K.

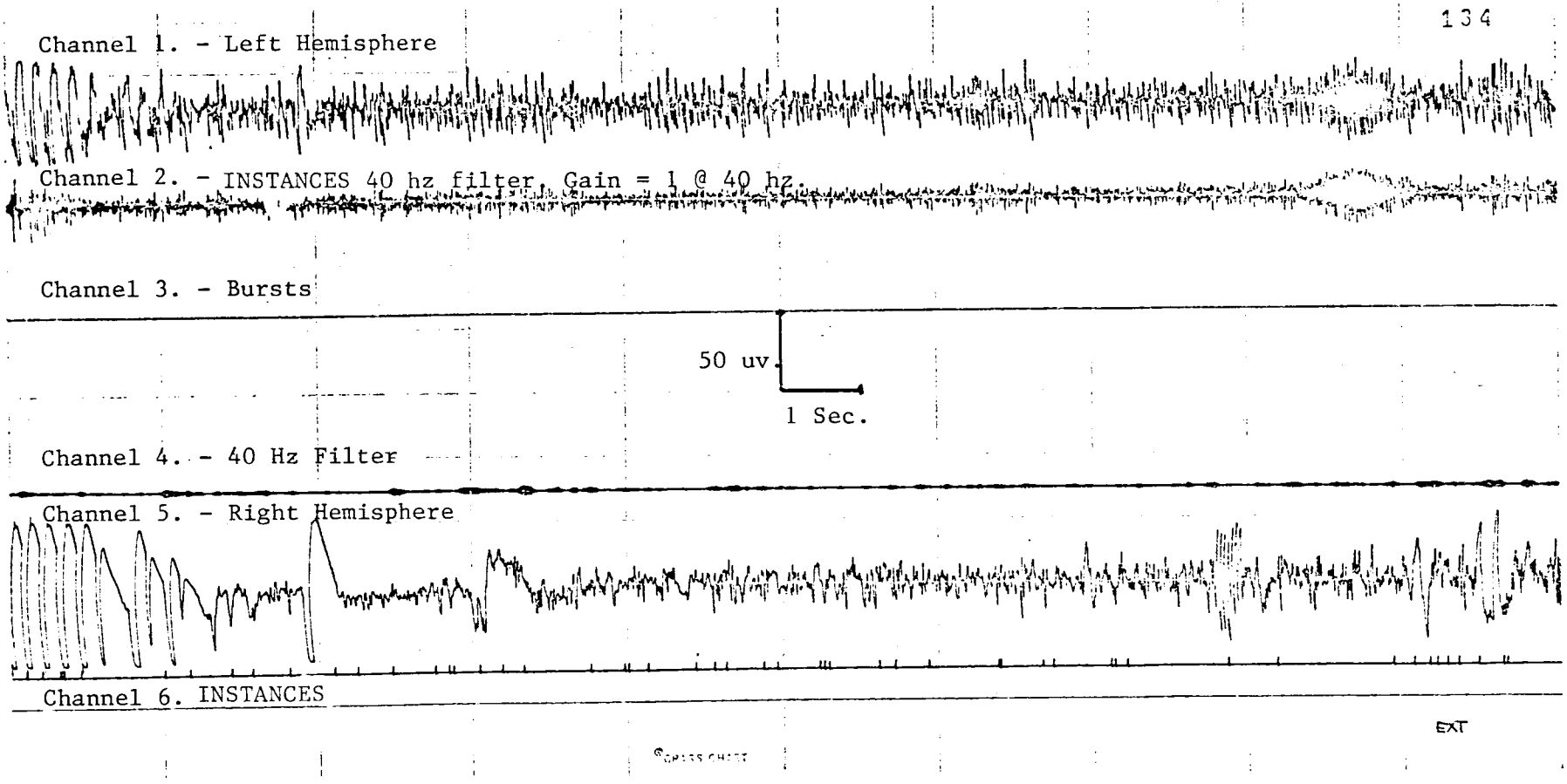


Figure 10. Day 10 extinction - left hemisphere contingent. Rat 10K.

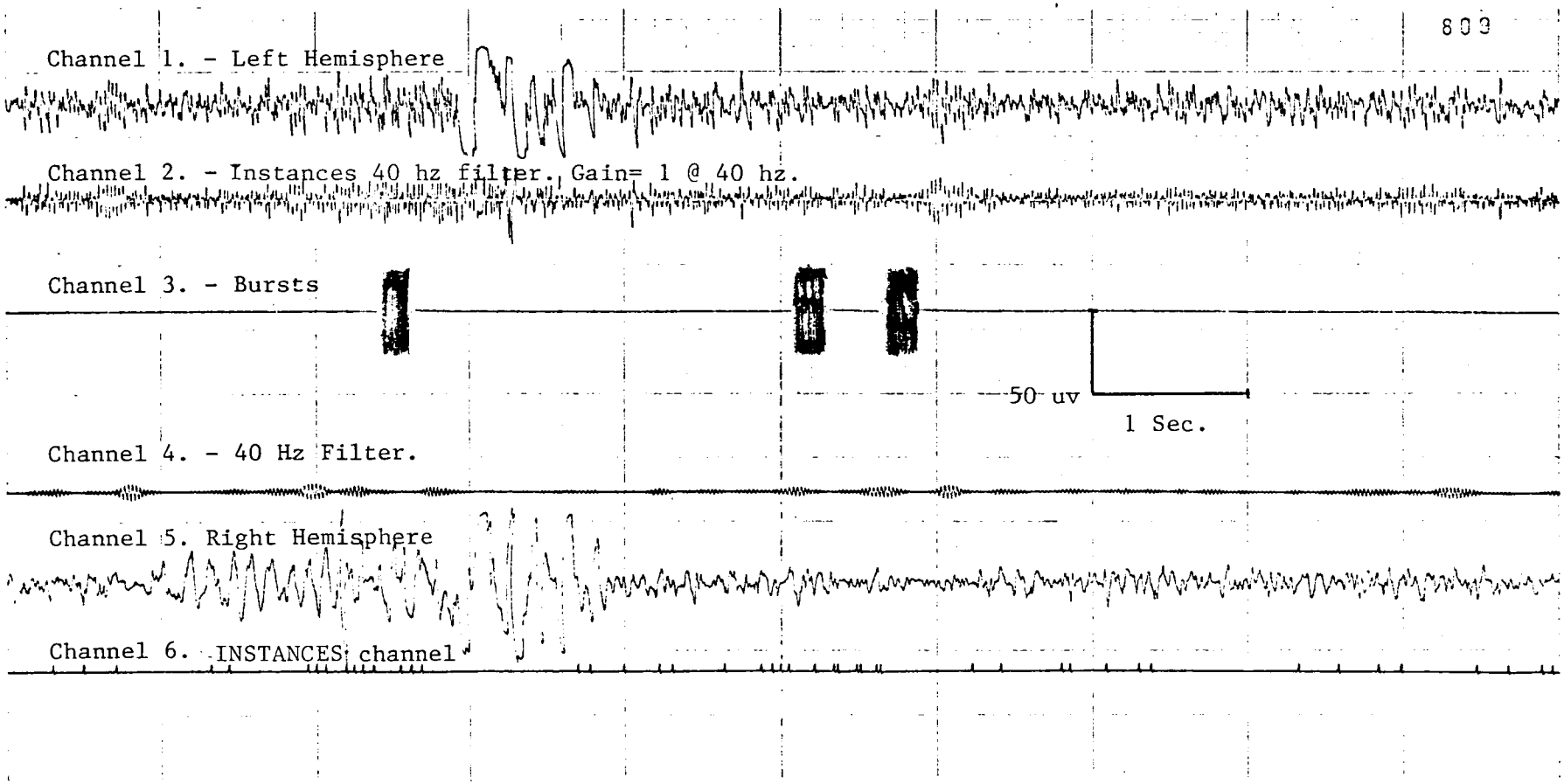


Figure 11. Rat 10K left hemisphere during acquisition day 32 showing reinforcement at a higher write-out rate.

Rat 4N

Histology. Rat 4N's placements were in the amygdala. The electrode in the left hemisphere was found at the junction of the central nucleus and junction of the optic tract. The coordinates were A 5.2, ML - 4.4 and DV - 1.7. The right hemisphere recording site was in the medial nucleus at coordinates A + 5.8, ML - 3.2 and DV - 2.5. A difference of approximately .6 mm in the AP (anterior-posterior) plane that made the difference in the placement this small error however was enough to appreciably change the implantation locus of the electrodes to the point that individual statistics are not justifiable. Figures 12a and 12b illustrate the reconstructed electrode site.

Left hemisphere conditioning data. The ANALOG data showed no conditioning in this hemisphere. It is characterized by a very high baseline during habituation and extreme variability in acquisition. The F value (2.21) was not significant for this matrix. The correlation between ANALOG and INSTANCES (-.3221) and BURSTS (-.0688) were low and negative. ANALOG data is plotted in Figure 13 and the plot of the means and ANOVA are shown in Figure 14. The disparity between the ANALOG data and INSTANCES and BURSTS is the largest seen in all of the animals. INSTANCES data were significant F = 14.28) showing that there were significant differences between block means. There are no significant differences between the Tukey A's between blocks 1, 2, 3, and 6. This shows that S showed no difference between habituation and the second block of extinction. The fact that blocks 2, 3, and 6 are not significant

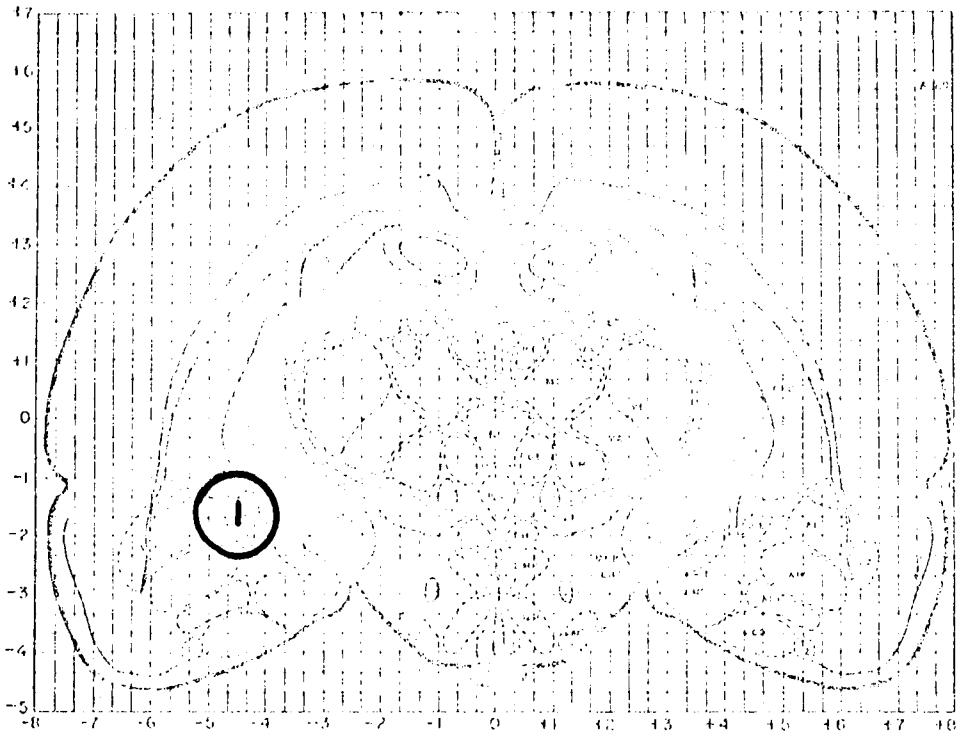


Figure 12a. Left hemisphere implantation site.

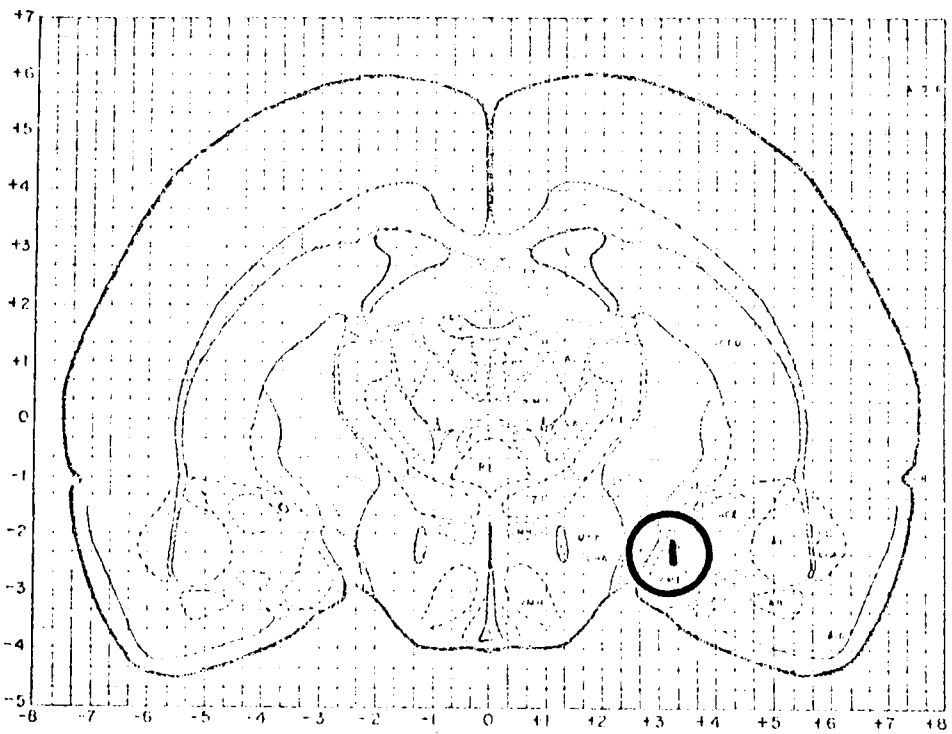


Figure 12b. Right hemisphere implantation site.

Figure 12. Reconstructed sites for rat 4N. The left hemisphere implant is in the central nucleus and the right is in the medial nucleus.

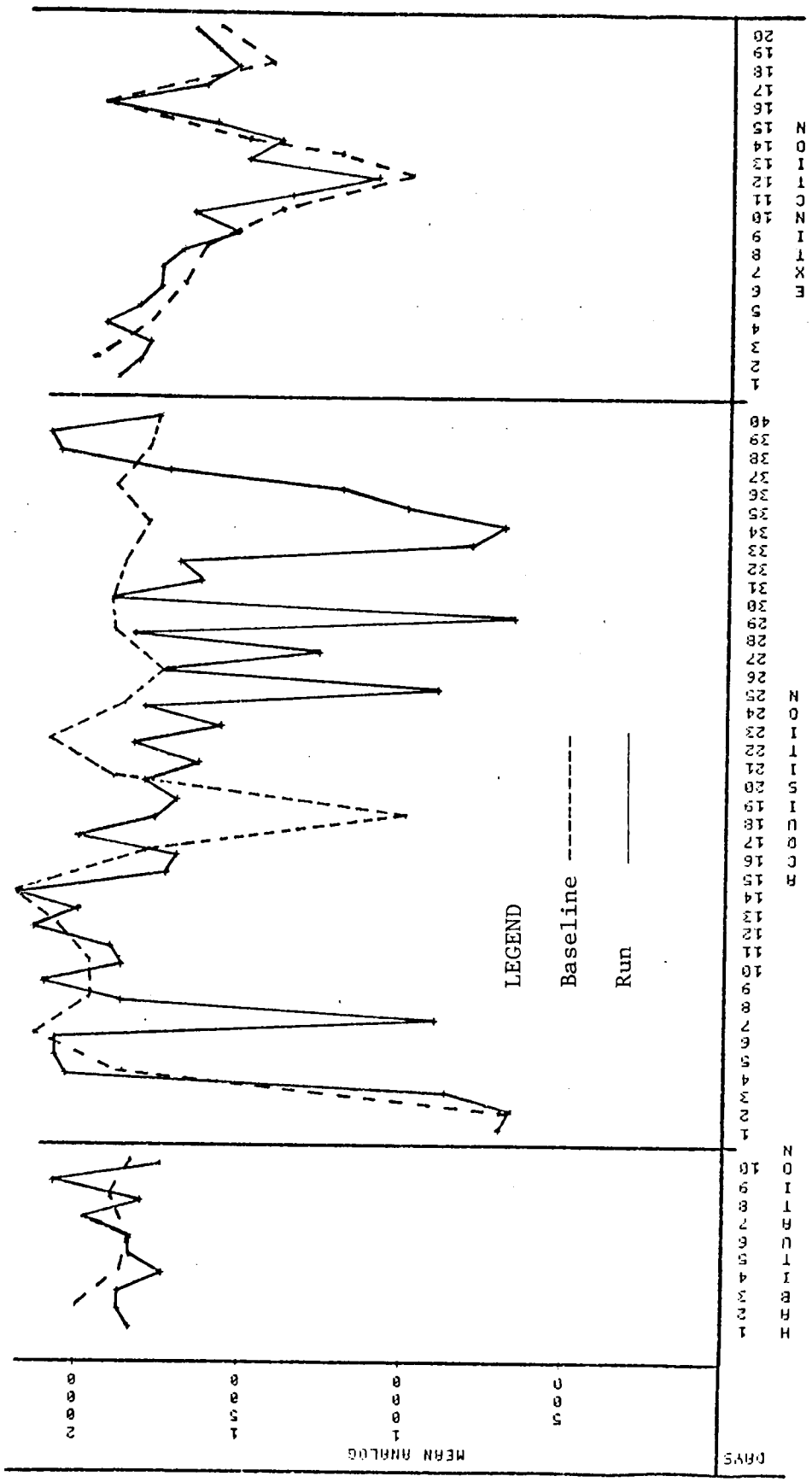
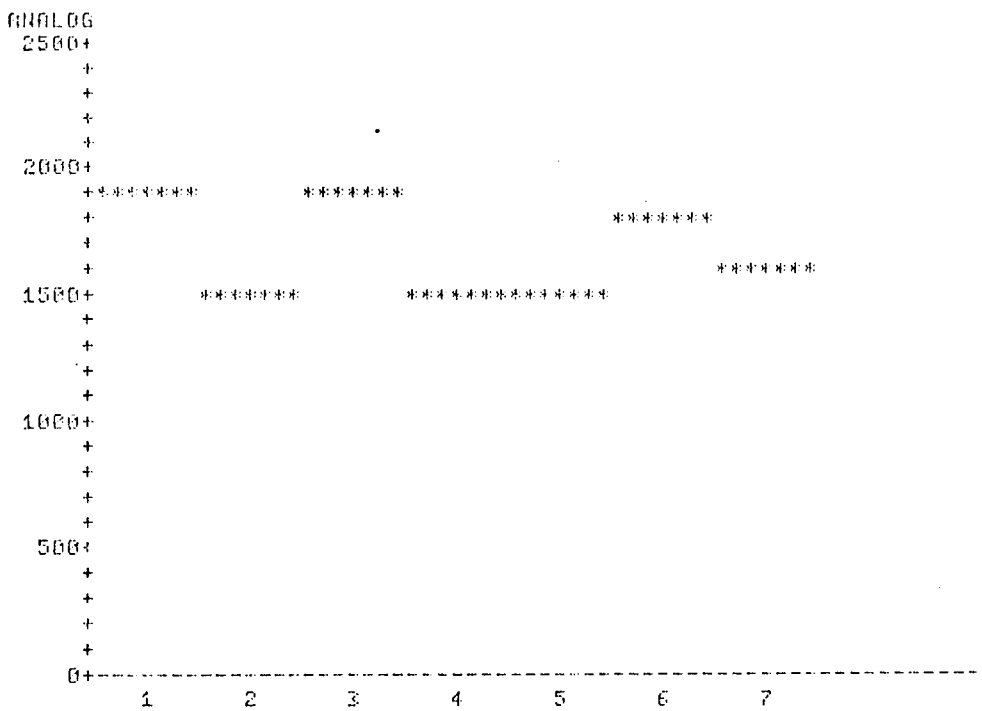


Figure 13. Mean ANALOG over days. Rat 4N - left hemisphere.



BLOCKS X MEAN

TUKEY A - MULTIPLE COMPARISONS TEST

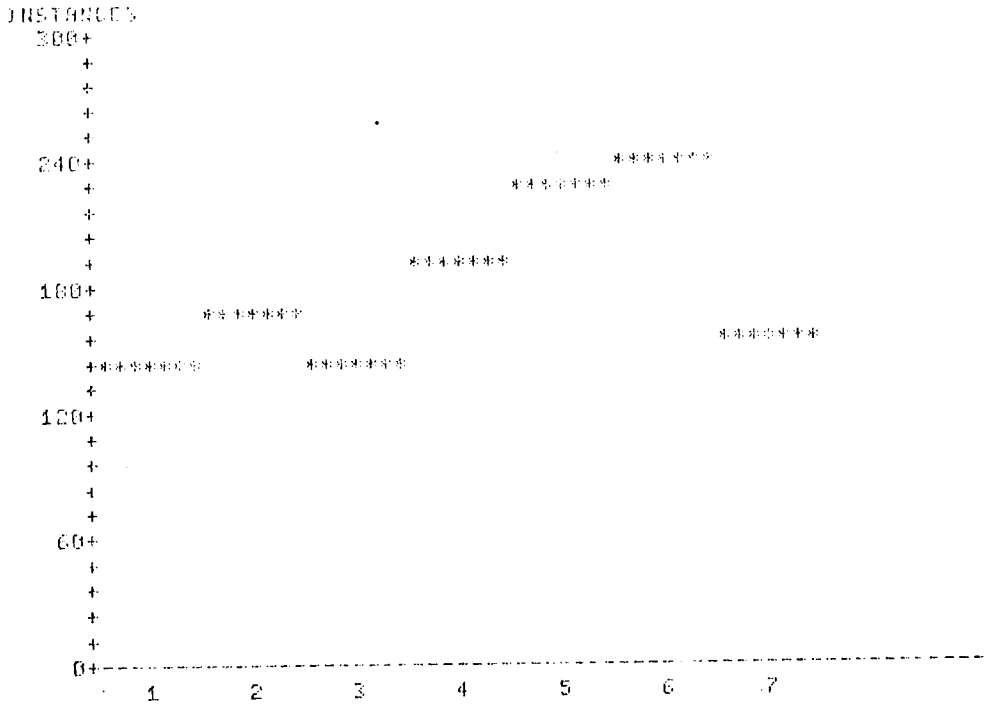
	5	4	2	7	6	1	3
	1490.20	1530.00	1533.20	1550.90	1787.70	1869.00	1910.90
5 1490.20		39.80	43.00	60.70	297.50	378.80	420.70
4 1530.00			3.20	20.90	257.70	339.00	380.90
2 1533.20				17.70	254.50	335.80	377.70
7 1550.90					236.80	318.10	360.00
6 1787.70						81.30	123.20
1 1869.00							41.90
3 1910.90							

CRITICAL VALUE = 623.85 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 14. Blocks X Mean ANALOG. Rat 4N - Left Hemisphere.

indicates that acquisition and extinction took time to occur which may indicate that S had some difficulty discriminating the 40 hz state in this location. The lower mean of block 5 when compared to extinction block 6 shown in Figure 15 is easily interpreted by referring to Figure 16 which shows a large dip (not large enough to effect the significance) in the INSTANCES rate during block 5. These dips were seen in all animals for all measures from time to time during blocks 4 and 5, and were due to electrode cable fatigue and deterioration. INSTANCES data contrary to ANALOG data did indicate learning. Once again these were not directly effecting the reinforcement to the animal. Overall acquisition peak days showed a two-fold increase over habituation for INSTANCES data. The mean relative change was +29.7% for INSTANCES (relative change is calculated on the basis of % relative change of A to B = (B-A)/A)*100).

It would be expected that the clearest differences would be in the response that is reinforced and this is exactly the case. BURSTS data graphed in Figure 17 shows a reasonable profile. There is no significant difference between blocks 1 and 7, showing that BURST rates between habituation and extinction are the same. There is no difference between habituation and block 2 which supports the INSTANCES data indicating that acquisition was not significantly different from habituation until the 3rd, 4th and 5th blocks. Block 6, the first extinction block, is not different from 3, 4, or 5. It is however different from habituation, but not the first acquisition block. These are all indicators that acquisition and extinction took time, meaning that the operant, a 40 hz



BLOCKS X MEAN

TUKEY A - MULTIPLE COMPARISONS TEST

		1	3	7	2	4	5	6
		141.00	147.00	152.00	167.10	188.10	228.60	235.10
1	141.00		6.00	11.00	26.10	47.10	87.60	94.10
3	147.00			5.00	19.30	40.30	80.80	87.30
7	152.00				14.30	35.30	75.80	82.30
2	167.10					21.00	61.50	68.00
4	188.10						40.50	47.00
5	228.60							6.50
6	235.10							

CRITICAL VALUE = 52.36 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 15. Blocks X mean INSTANCES. Rat 4N - left hemisphere.

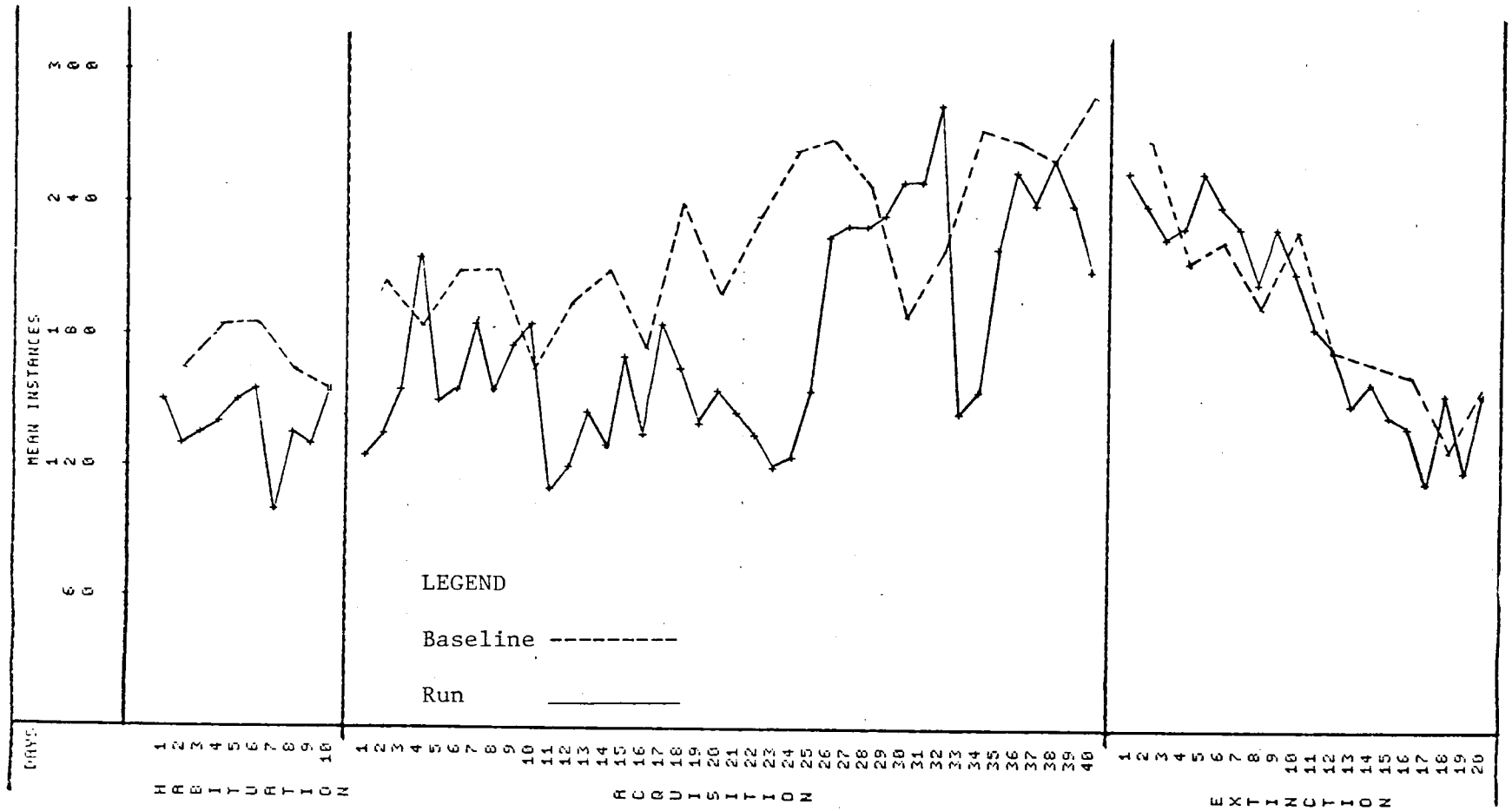


Figure 16. Mean INSTANCES over days - rat 4N - left hemisphere.

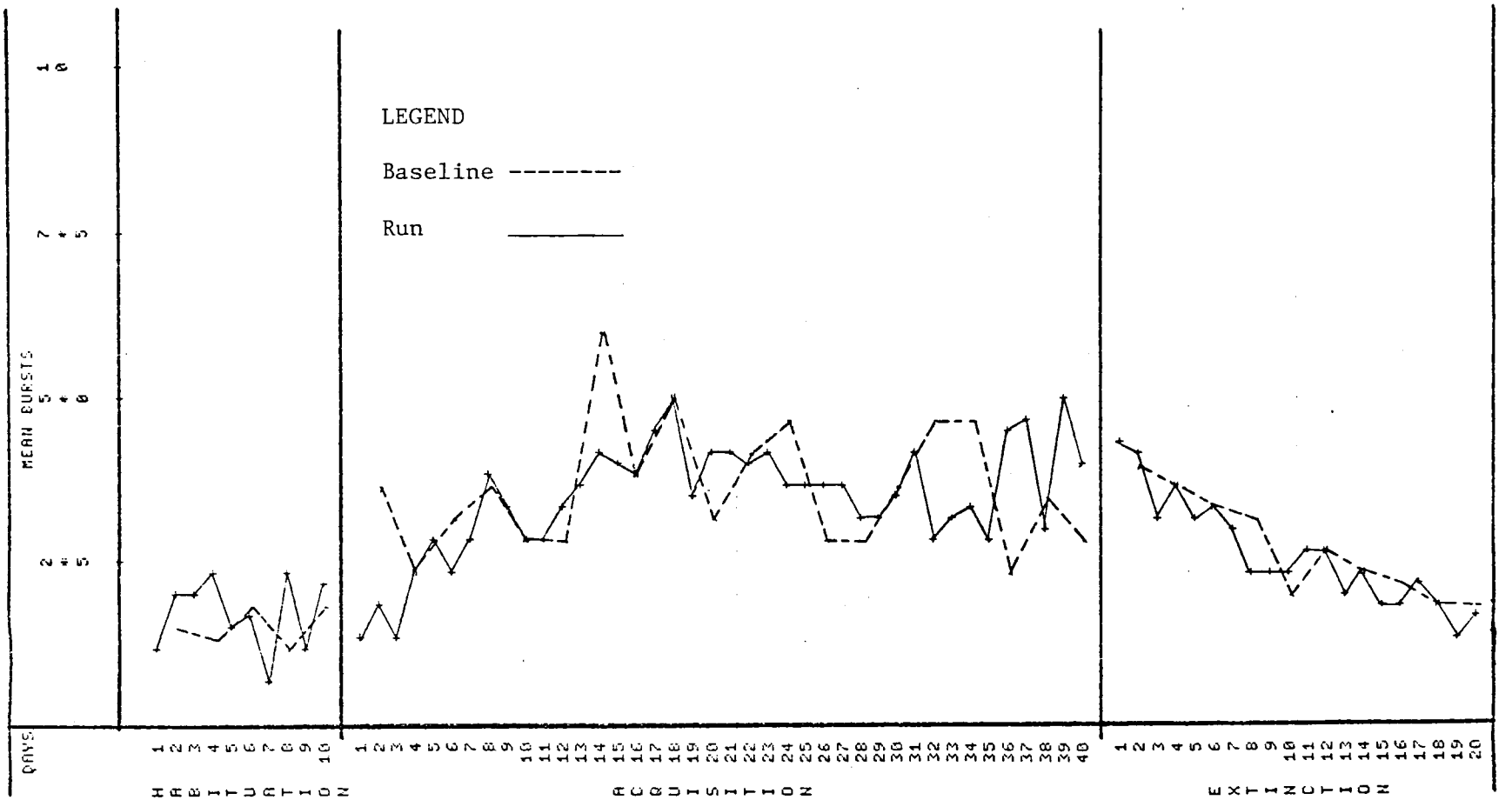
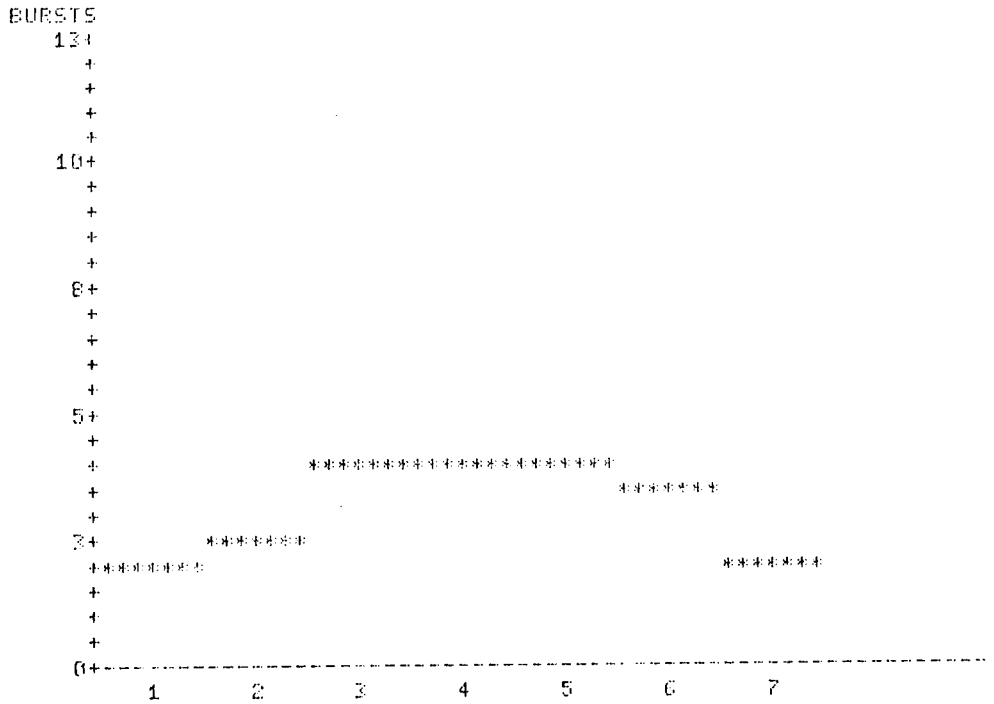


Figure 17. Mean BURSTS over days. Rat 4N - left hemisphere.

spindle was discriminable but with some difficulty. It could therefore be brought under control in time.

BURSTS showed a mean relative increase of 99.9% over habituation. The fact that extinction was slow reduced the relative mean change of acquisition to extinction to only -23.56%. The slow extinction caused what might be considered to be a deflated ratio of the means. The anova shows no differences between habituation and extinction indicating that extinction was complete. Figure 18 shows the mean blocks data for BURSTS.

The analysis will allow intelligent speculation concerning what process occurred or actually what happened to the EEG during conditioning. ANALOG shows no real change across conditions at all. The conclusion that must be drawn therefore is that there were no changes in the distribution of the spectral energy. The increase in instances, which would naturally cause an increase in BURSTS seems to come from a slight increase in the amount of 40 hz activity that is immediately below the 5 uv threshold for ANALOG. This is the strategy of change that could occur in view of the data for this hemisphere. It would adequately explain the dissociation between ANALOG and the other two measures. The location of the electrode in this hemisphere was unique and observed effects were also unique, i.e., this is the only occurrence of such complete dissociation. It is tempting to relate these results to the electrodes recording site but it should be remembered that such a conclusion would be based on a correlation where N equals 1 and would therefore be unwarranted.



BLOCKS X MEAN

TUKEY A - MULTIPLE COMPARISONS TEST

		1	7	2	6	4	5	3
		1.82	2.18	2.65	3.38	3.87	3.94	4.10
1	1.82		0.36	0.83	1.56	2.05	2.12	2.28
7	2.18			0.46	1.19	1.69	1.75	1.91
2	2.65				0.73	1.22	1.29	1.45
6	3.38					0.49	0.56	0.72
4	3.87						0.07	0.23
5	3.94							0.16
3	4.10							

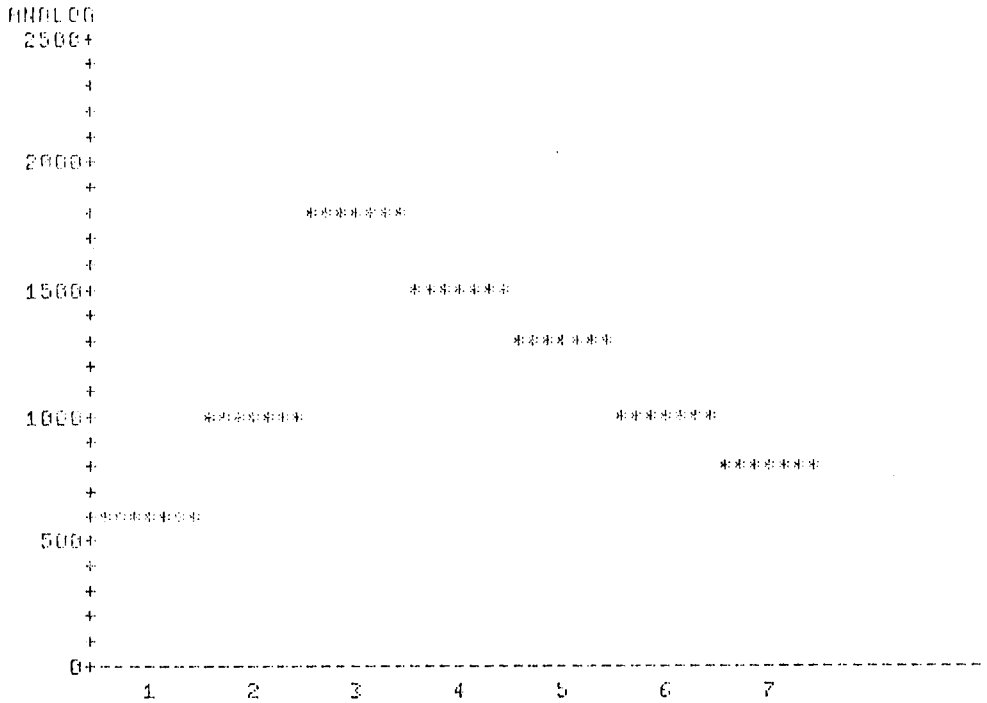
CRITICAL VALUE = 1.10 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 18. Blocks X mean BURSTS. Rat 4N - left hemisphere.

Right hemisphere conditioning data. ANALOG data for 4N shows significant differences (F = 20.6) between blocks. Once again the data is difficult to interpret.

There are no differences between blocks 1, 2, 6 and 7 which is what would be expected ideally. However, the peak of acquisition occurs during the second acquisition block and falls off linearly after that. Such occurrences are seen clearly in Figure 19 which is a plot of the block means and in Figure 20 which is a plot of the daily ANALOG performance of the animal. Block 2 was different from 1 demonstrating that acquisition came rapidly, but was the same as blocks 5 and 6 showing a real decrement in the acquisition period. This could be attributed to either equipment problems which is dubious but possible or a learning strategy. If 4N was superstitiously doing things to change the reinforcement rate only to find it was not necessary this would explain the acquisition's sharp rise and fall. Block 4, the final acquisition was still significantly above extinction but was significantly lower than the activity seen in block 3. There are no significant differences between 3 and 4 or between 4 and 5 which shows that the rate decrement seen in Figure 17, page 92 is both linear and real.

There was a mean relative increase of 167.5% between habituation and extinction and a decrease of 17% between acquisition and extinction. The final decrease was much greater than the former statistic suggests because it includes the portion of extinction that begins where acquisition ends (blocks 5 and 6). There are no significant differences between blocks 1 and 2, and 6 and 7. Intercorrelation between ANALOG



BLOCKS X MEAN

TUKEY A - MULTIPLE COMPARISONS TEST

		1	7	2	6	5	4	3
		613.80	753.30	967.30	1014.60	1293.60	1492.80	1786.10
1	613.80		139.50	353.50	400.80	679.80	879.00	1172.30
7	753.30			214.00	261.30	540.30	739.50	1032.80
2	967.30				47.30	326.30	525.50	818.80
6	1014.60					279.00	478.20	771.50
5	1293.60						199.20	492.50
4	1492.80							293.30
3	1786.10							

CRITICAL VALUE = 468.87 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 19. Blocks X mean ANALOG. Rat 4N - right hemisphere.

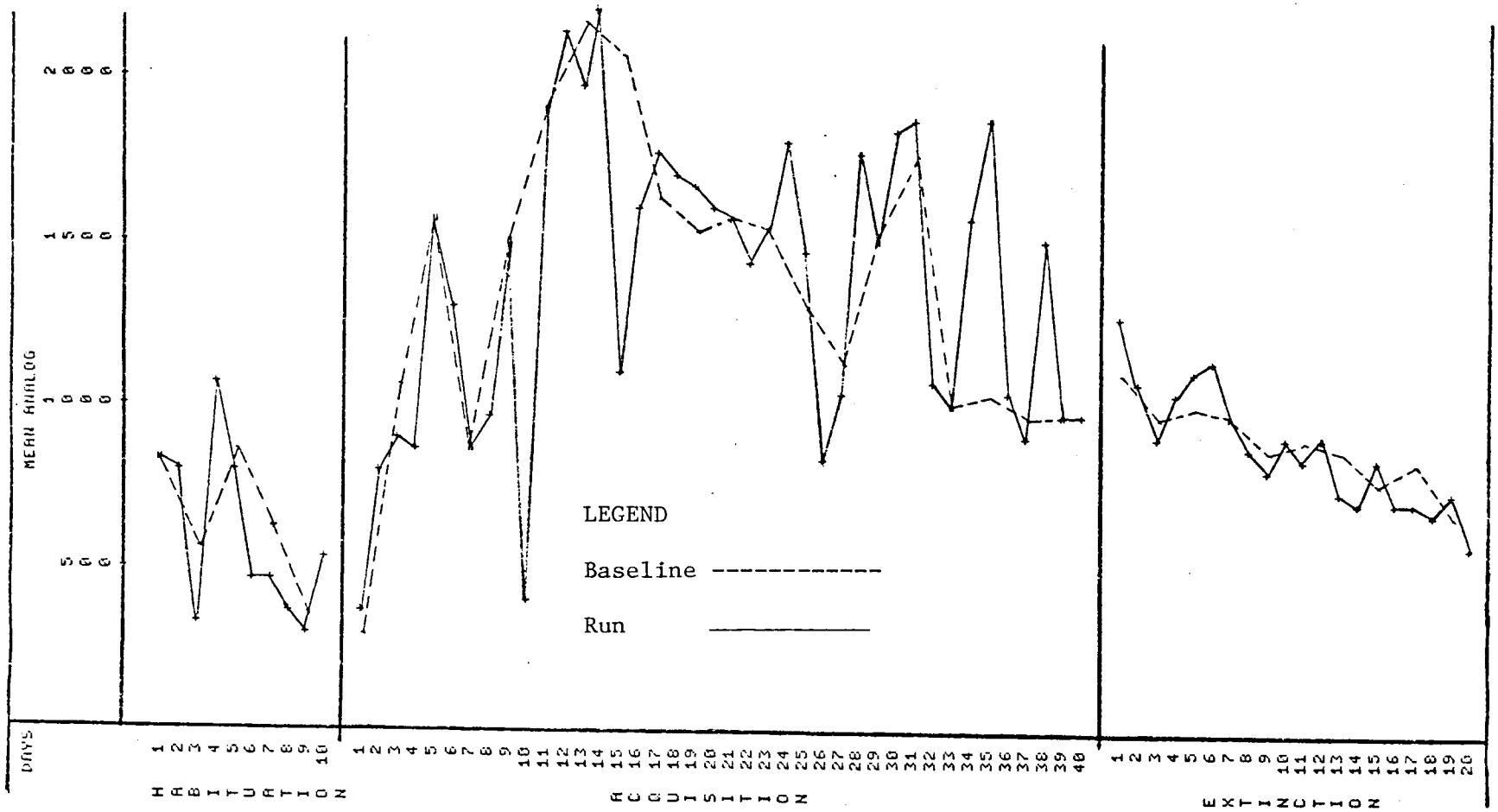


Figure 20. Mean ANALOG over days. Rat 4N - right hemisphere.

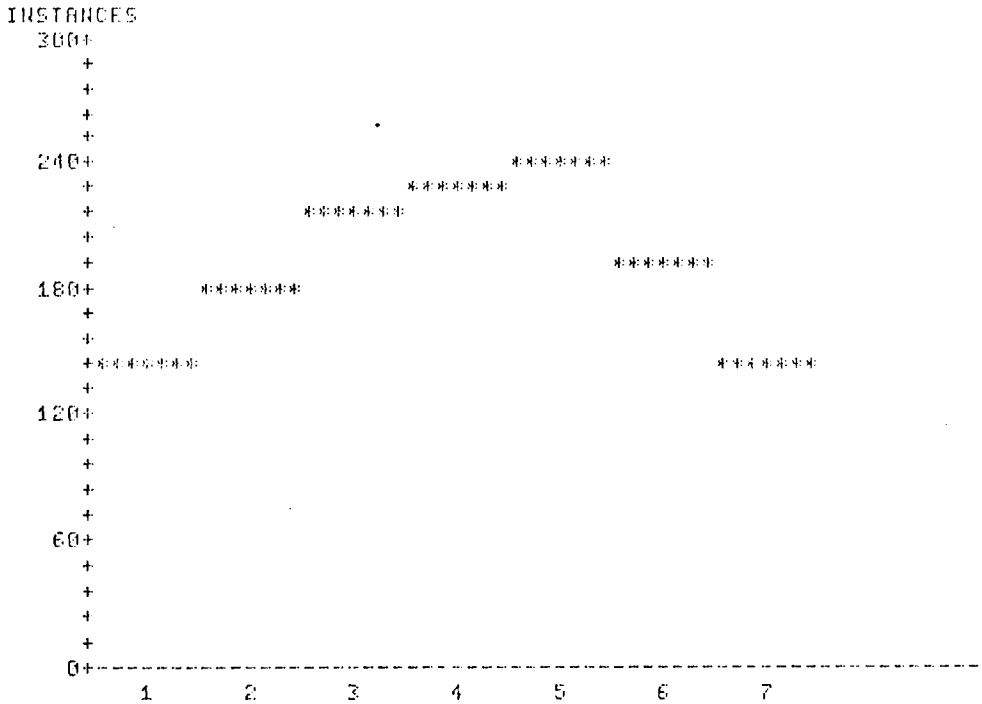
and BURSTS and ANALOG and INSTANCES were high, positive and significant (.8246 and .83 respectively; $p < .01$; $df = 8$).

In spite of the high intercorrelation between measures a slightly different profile of performance is seen in the INSTANCES data in Figure 21. Where the mean daily INSTANCES scores show a marked drop in activity in Figure 22, after an initial strong acquisition, the mean blocks graph indicates a steady acquisition. There are no significant differences between blocks 1, 2, 3, and 4. This indicates a slow but steady acquisition with no sign of an asymptote. In all probability the animal would have shown more improvement if the acquisition period had been prolonged. The mean relative increase in INSTANCES was + 48%. During peak periods the INSTANCES rates showed more than a two-fold increase over the baseline.

The BURSTS data showed definite learning. There are no significant differences between blocks 1, 2 and 6. This pattern shows a moderately slow acquisition and asymptote. There are no differences between extinction and habituation which shows that the activity went up and came back down and was thusly under behavioral control. See Figures 23 and 24 for BURSTS data.

Overall Rat 4N showed similar patterns in both hemispheres. Behavioral control of 40 hz was demonstrated.

Behavioral data. Rat 4N was the only S in the group that was a natural nonkiller and remained so during the course of the experiment. After determining that the rat would not kill a mouse one was housed in the cage with the S at the onset of the experiment. There was never any



BLOCKS X MEAN

TUKEY A - MULTIPLE COMPARISONS TEST

		1	7	2	6	3	4	5
		144.10	145.50	182.80	191.60	210.50	222.90	237.40
1	144.10		1.40	38.70	47.50	66.40	78.80	93.30
7	145.50			37.30	46.10	65.00	77.40	91.90
2	182.80				8.80	27.70	40.10	54.60
6	191.60					18.90	31.30	45.80
3	210.50						12.40	26.90
4	222.90							14.50
5	237.40							

CRITICAL VALUE = 52.34 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 21. Blocks X mean INSTANCES. Rat 4N - right hemisphere.

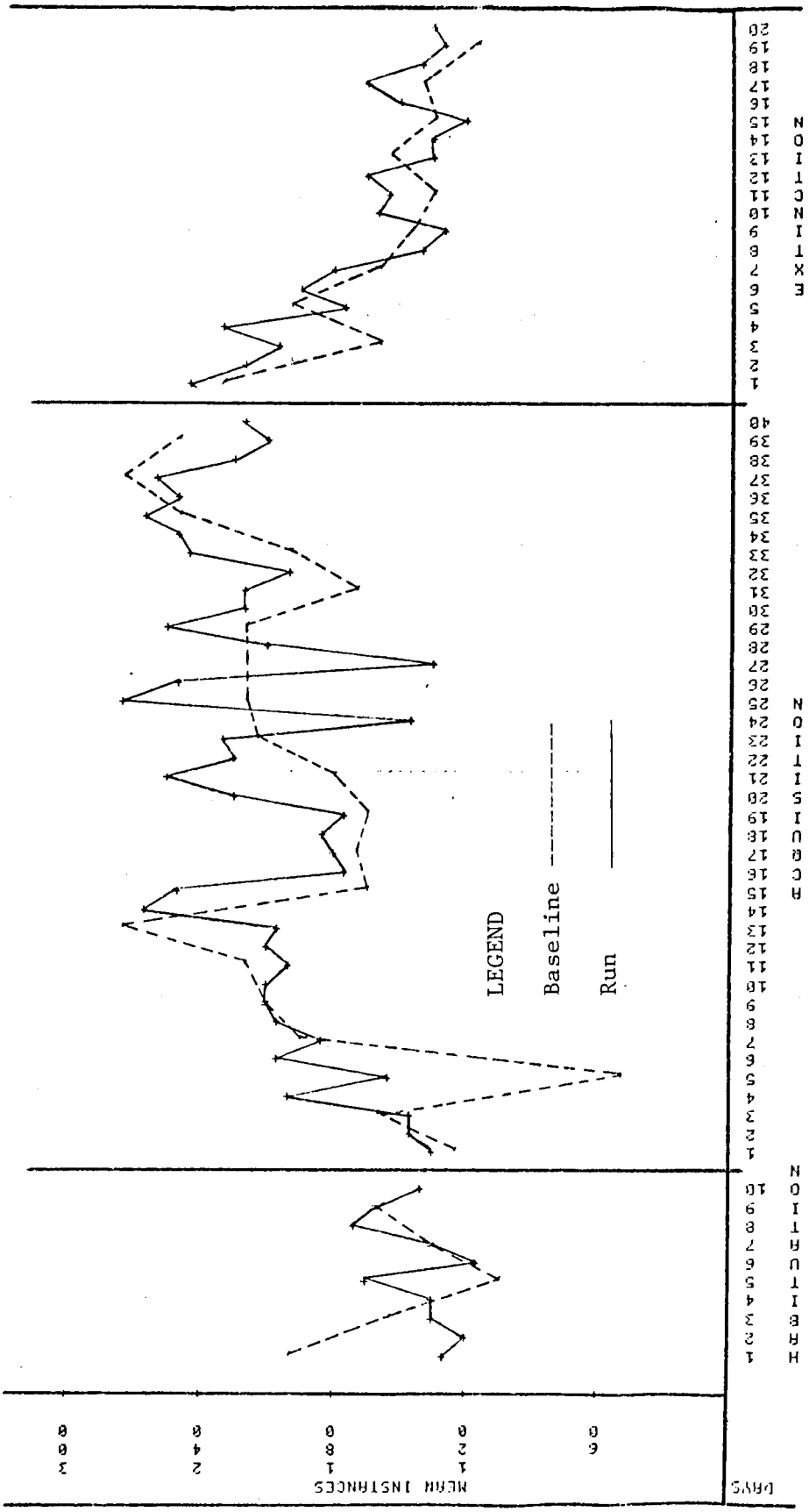


Figure 22. Mean INSTANCES over days. Rat 4N - right hemisphere.

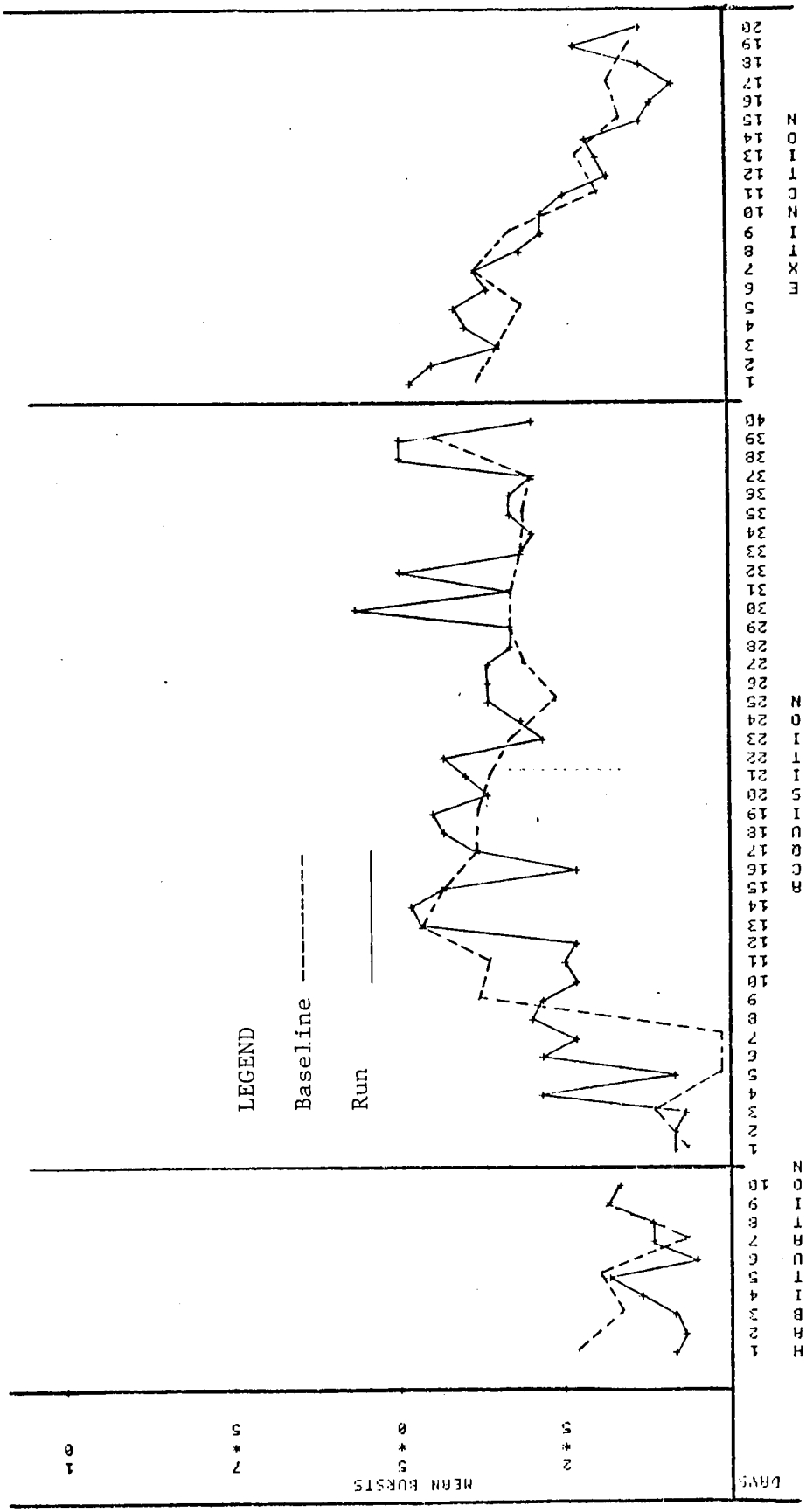
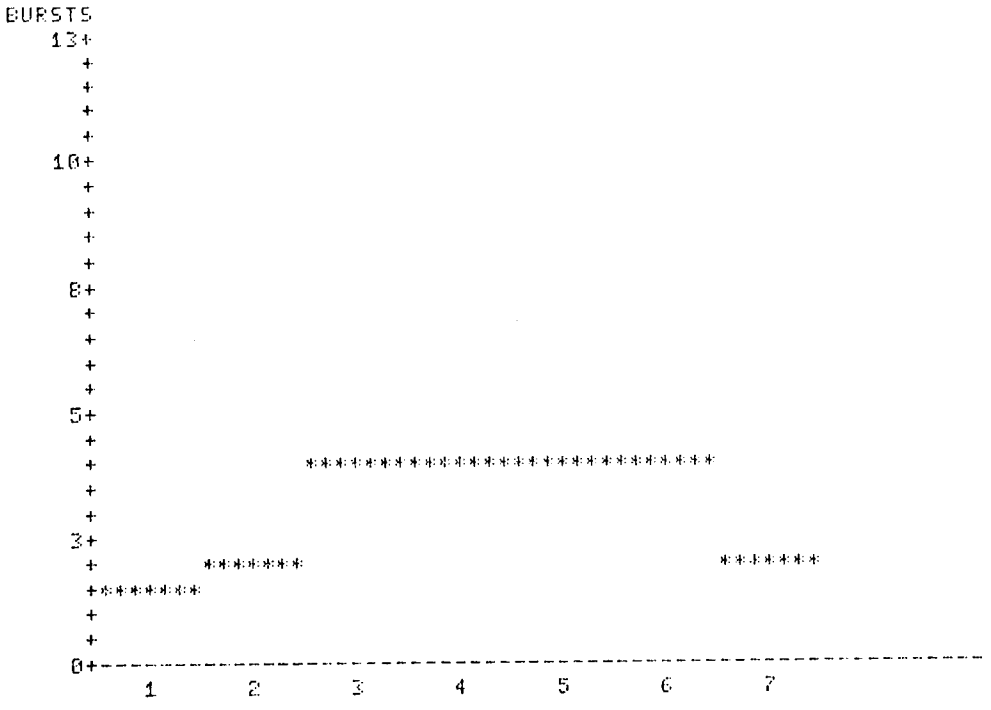


Figure 23. Mean BURSTS over days. Rat 4N - right hemisphere.



BLOCKS X MEAN

TUKEY A - MULTIPLE COMPARISONS TEST

		1	7	2	6	5	3	4
		1.30	1.84	2.11	3.91	3.93	3.94	3.97
1	1.30		0.54	0.81	2.61	2.63	2.64	2.66
7	1.84			0.27	2.07	2.09	2.10	2.13
2	2.11				1.80	1.82	1.83	1.86
6	3.91					0.02	0.03	0.05
5	3.93						0.01	0.04
3	3.94							0.03
4	3.97							

CRITICAL VALUE = 1.31 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 24. Blocks X mean BURSTS. Rat 4N - right hemisphere.

evidence that the treatment increased the Ss aggression. The S showed an increase in activity in the open field apparatus. A standard open field apparatus was used. Crossings were counted in 1 minute blocks for six minutes per day for five days after all conditions. Rat 4N showed an increase in open field crossings after habituation ($\overline{X}$ = 35.5, sd = 12.5). Post acquisition testing showed an increase in crossings ($\overline{X}$ = 49.1, sd - 12.05). After extinction the mean rate of crossing returned to 36.9 (sd - 13.8) per minute. There were no significant changes in tendency to vocalize when handled. Neither was there any significant change in the threshold current needed to elicit vocalization. It remained constant at approximately .13 ma (milliamperes) across all conditions. A graphic summary of the behavioral results are shown in Figure 25.

After conditioning of 40 hz spindles 4N showed an elevation in activation levels in the open field apparatus. No other changes were seen in its behavior.

Data for Rat 3K

Histological data. Rat 3K was an anomalous animal in virtually every aspect. The animal contracted an acute respiratory infection during the interval between the final behavioral testing and the time it was due to be sacrificed. There was no sign of an infection prior to its death. The animal had its brain removed 5 hours post-mortem, but even this interval radically affected the ability of the fixatives to harden the brain tissue in preparation for histological evaluation. Consequently, the tissue showed appreciable disintegration as it was mounted

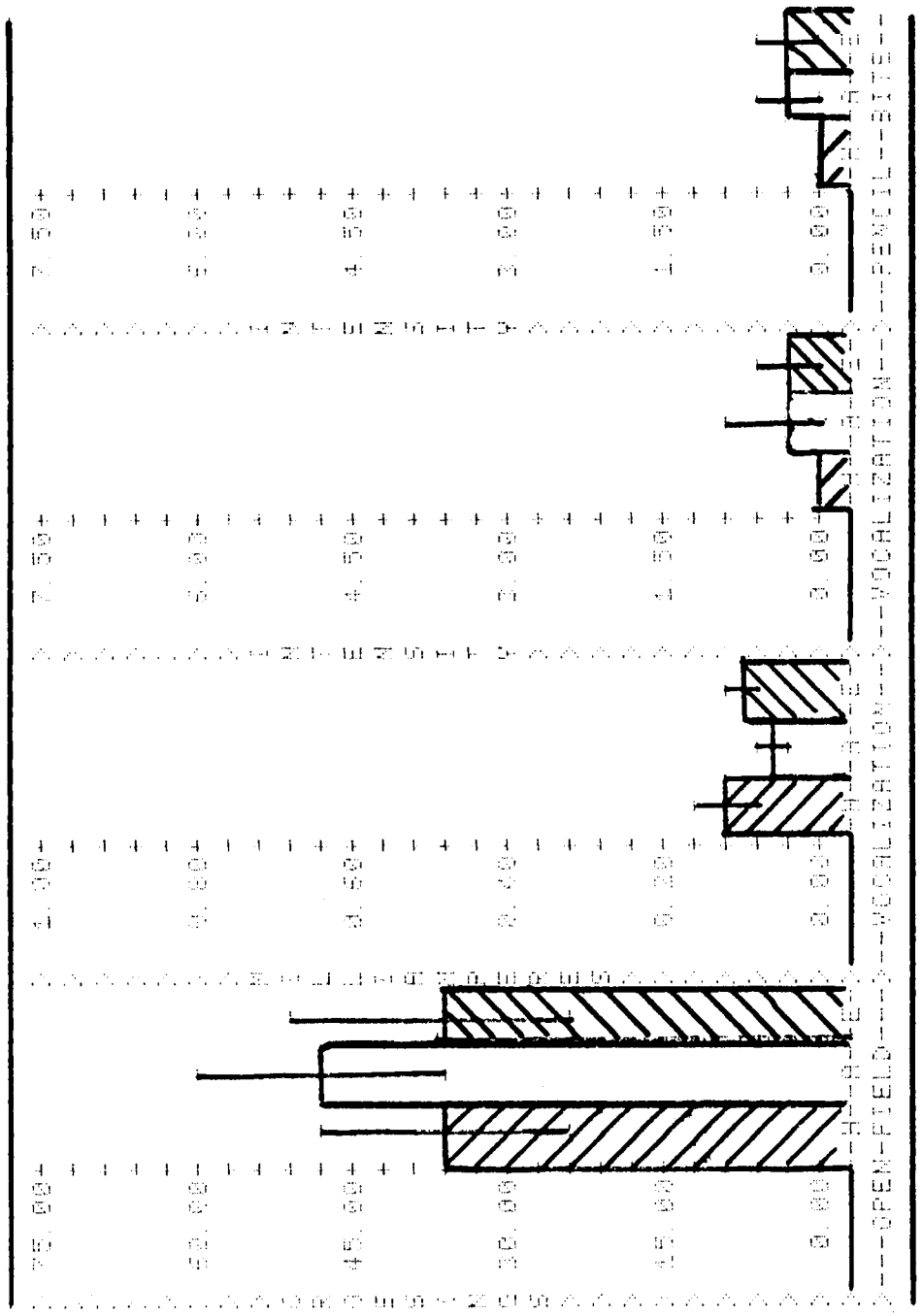


Figure 25. Post contingency means and standard deviations for behavioral tests. Rat 4N.

on glass slides for evaluation. The tissue containing the right hemisphere electrode tracks was lost in mounting.

The left hemisphere electrode was found at coordinates A + 6.6, ML - 4.0 and DV - 2.0. These coordinates correspond with the central nucleus. The placement of this electrode is illustrated in Figure 26.

Left hemisphere conditioning. ANALOG data for Rat 3K is significant as the overall F = 18.6337 showing that there are significant differences between groups. Blocks 1, 2, and 6 do not differ significantly meaning that there is no significant difference between habituation, the first acquisition block and the late block of extinction. These blocks did differ significantly with blocks 3, 5, and 6, which demonstrates that learning occurred here. It is interesting to note that there was no difference between blocks 3 and 6 suggesting a long slow acquisition. There was a relative increase of + 42% between habituation which is notable in view of the long acquisition period. Intercorrelations between ANALOG and INSTANCES were positive but insignificant (r - .638, Critical Value = .676).

Clear learning is demonstrated as there are no significant differences between habituation, the first acquisition block and both extinction periods. The latter three acquisition blocks are significantly different from these periods. There is a large but insignificant negative difference between blocks 1 and 7 suggesting that the animal may not have been adequately habituated prior to starting acquisition. The intercorrelation of +.6743 is significant between INSTANCES and BURSTS. INSTANCES showed a mean relative increase of +57.36% from

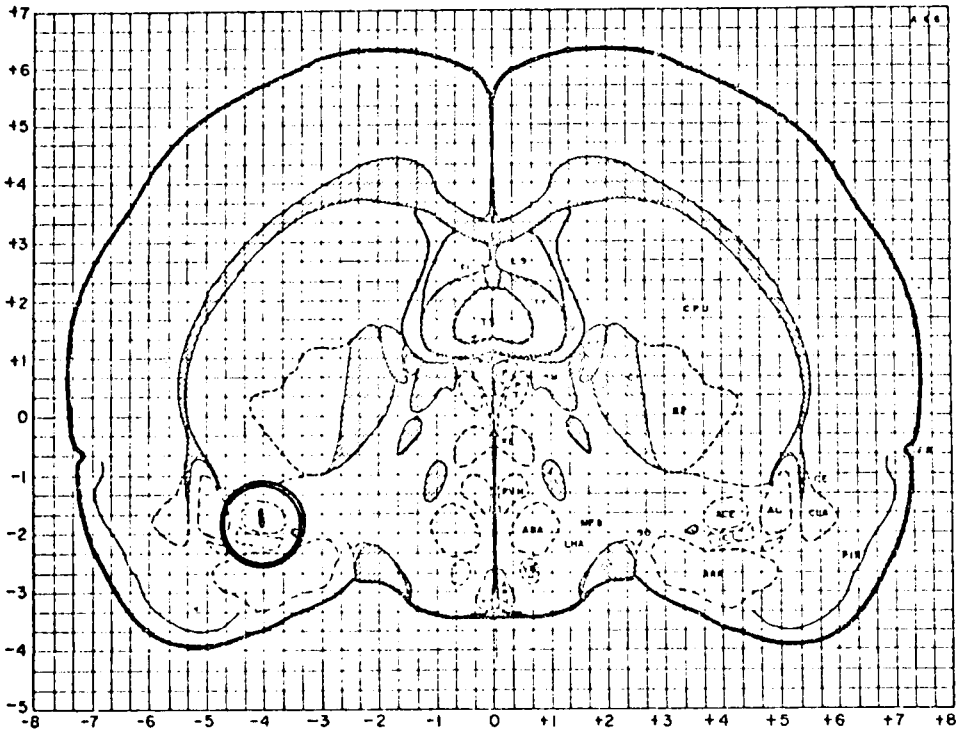


Figure 26. The singular verified electrode placement for rat 3K. The coordinates were A 6.6, ML -4 and DV - 2.0. The electrode tip was lodged in the central nucleus.

habituation to acquisition. Graphs of the daily data are seen in Figure 27 and blocks means are shown in Figure 28.

INSTANCES data for this hemisphere is ideal and rather unremarkable. Assymptote is hampered by the problem with cable fatigue in the mid-acquisition blocks. Recovery ensues after the cable was repaired. The daily data is seen in Figure 29 and the blocks data are seen in Figure 30.

The clearest picture of conditioning seen so far is seen in Figures 31 and 32 which are graphs of BURSTS daily data and block means respectively. Blocks 1, 2 and 7 do not differ significantly nor do blocks 3, 4 and 6. Block 5, the final block in acquisition is significantly different from all other blocks. There is a +387% increase between habituation and acquisition. Such a large relative relationship may be deceptive in that the habituation operant level may be spuriously low and relating it to any increase at all will produce an inflated number.

Right hemisphere data—Rat 3K. ANALOG data is graphed daily in Figure 33 and the blocks means are shown in Figure 34. Figure 34 shows a rapid acquisition with some rather pronounced variations. Finally, learning assymptotes. There are no differences between blocks 1, 2, 6 and 7 at a p level of .01. However 7 does differ from 1 at the .05 level. The means appear to be very different in both of these figures. Blocks 3, 4 and 5 do not differ from each other but are different from habituation, early acquisition and late extinction. The difference at the .05 level between blocks 7 and 1 suggest that there was an

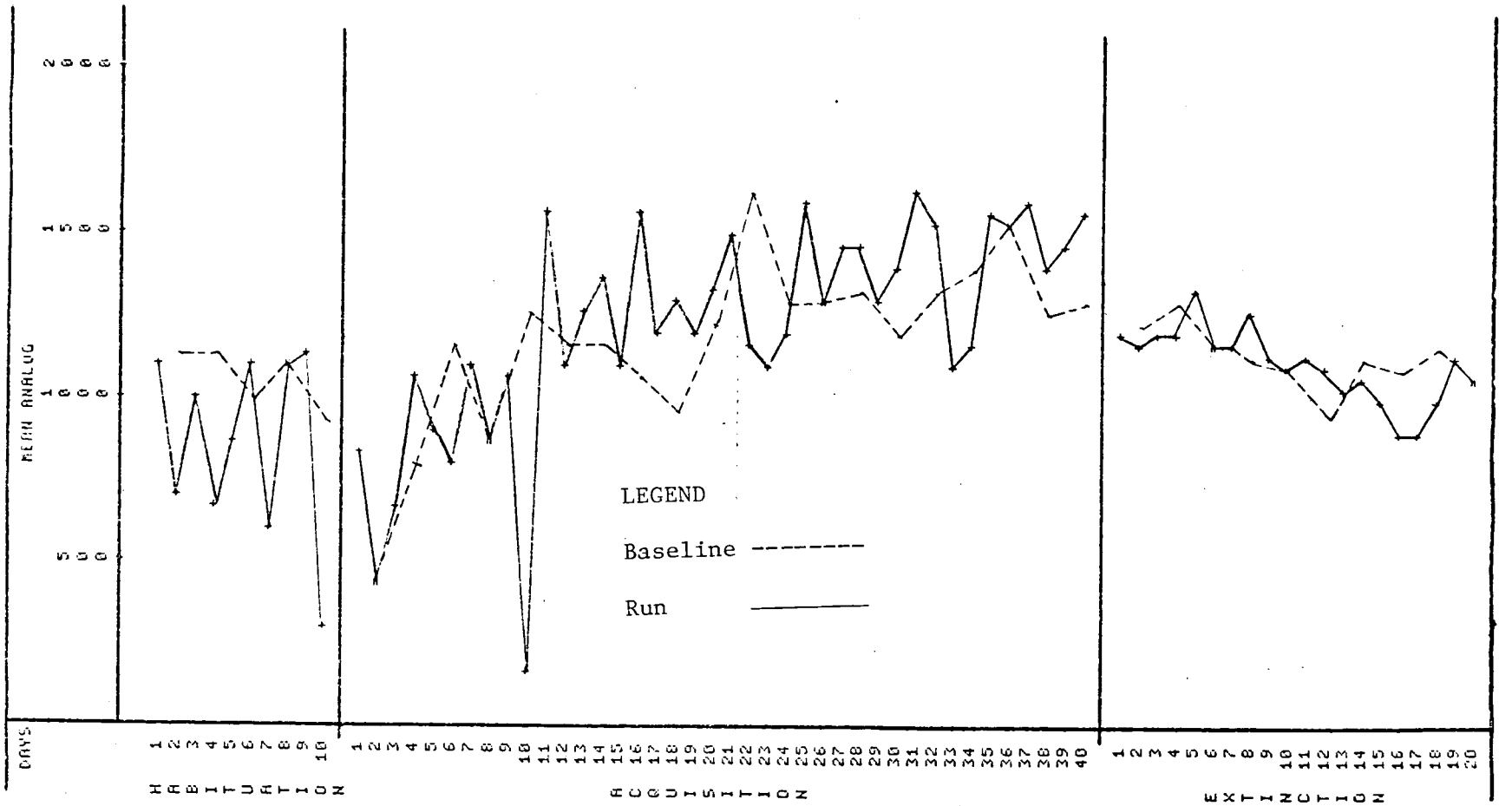
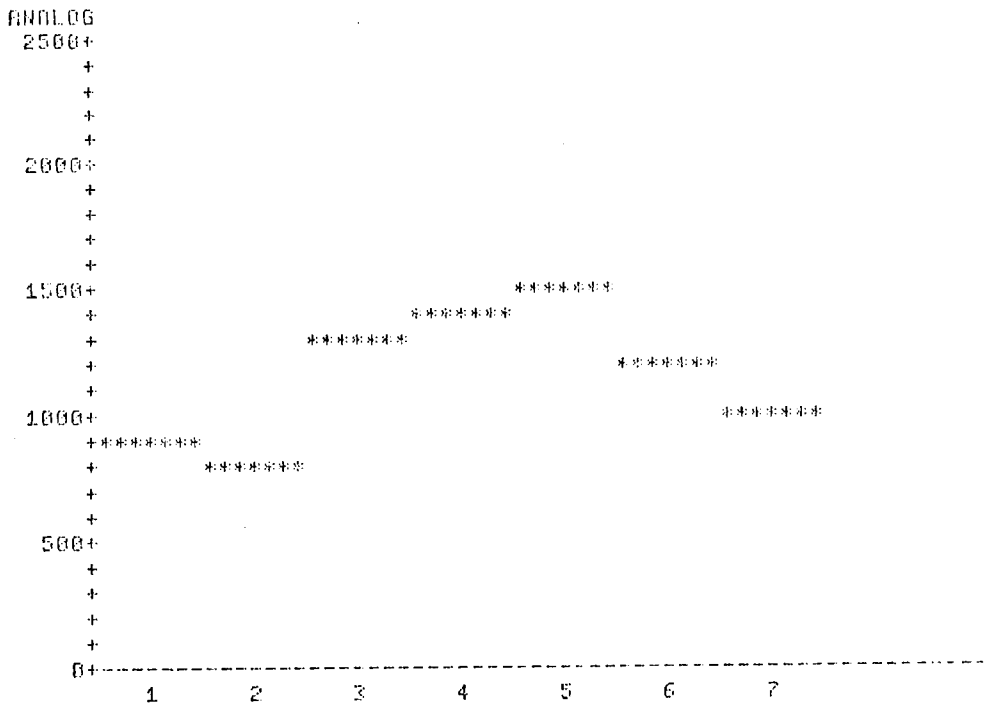


Figure 27. Mean ANALOG over days. Rat 3K - left hemisphere.



BLOCKS X MEAN

TUKEY A - MULTIPLE COMPARISONS TEST

	2	1	7	6	3	4	5
	809.00	873.60	1049.20	1208.80	1316.60	1365.90	1473.30
2 809.00		64.60	240.20	399.80	507.60	556.90	664.30
1 873.60			175.60	335.20	443.00	492.30	599.70
7 1049.20				159.60	267.40	316.70	424.10
6 1208.80					107.80	157.10	264.50
3 1316.60						49.30	156.70
4 1365.90							107.40
5 1473.30							

CRITICAL VALUE = 300.99 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 28. Blocks X mean ANALOG over days. Rat 3K - left hemisphere.

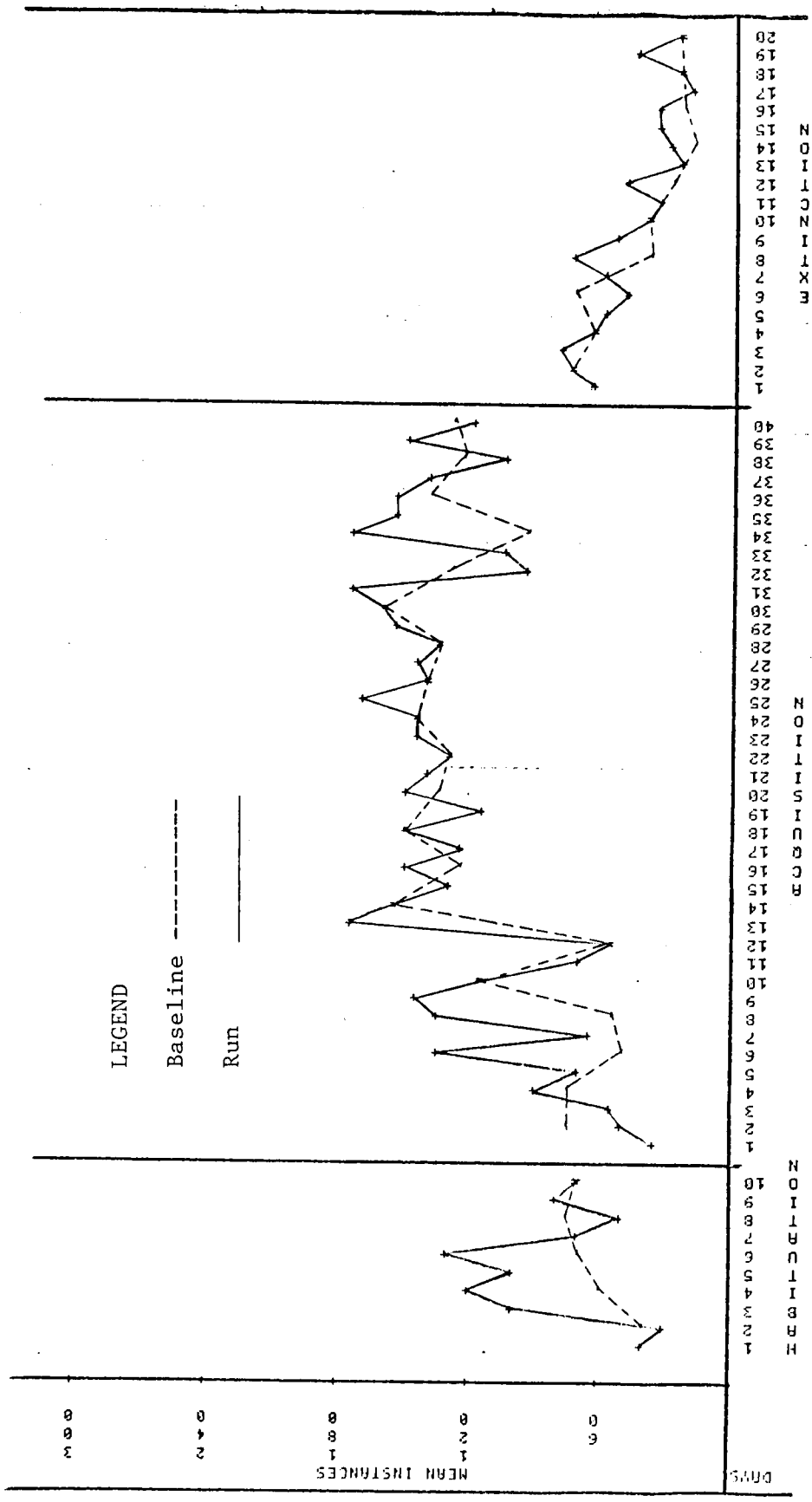
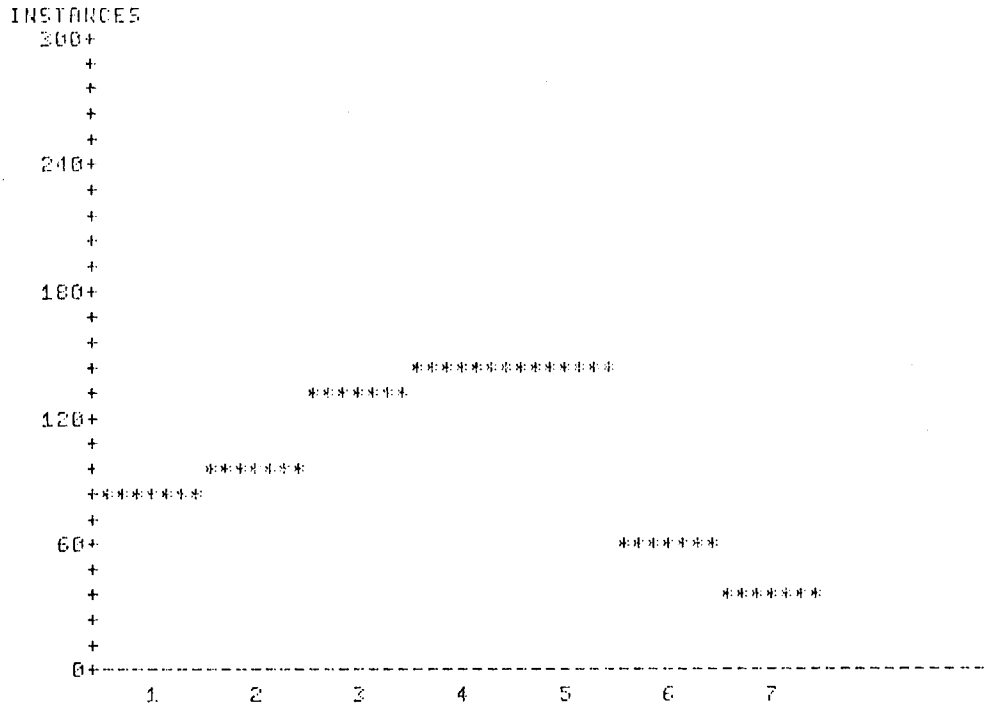


Figure 29. Mean INSTANCES over days. Rat 3K - left hemisphere.



BLOCKS X MEAN

TUKEY A - MULTIPLE COMPARISONS TEST

		7	6	1	2	3	5	4
		35.70	65.10	81.50	92.30	130.50	140.60	149.60
7	35.70		29.40	45.80	56.60	94.80	104.90	113.90
6	65.10			16.40	27.20	65.40	75.50	84.50
1	81.50				10.80	49.00	59.10	68.10
2	92.30					38.20	48.30	57.30
3	130.50						10.10	19.10
5	140.60							9.00
4	149.60							

CRITICAL VALUE = 42.78 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 30. Blocks X mean INSTANCES. Rat 3K - left hemisphere.

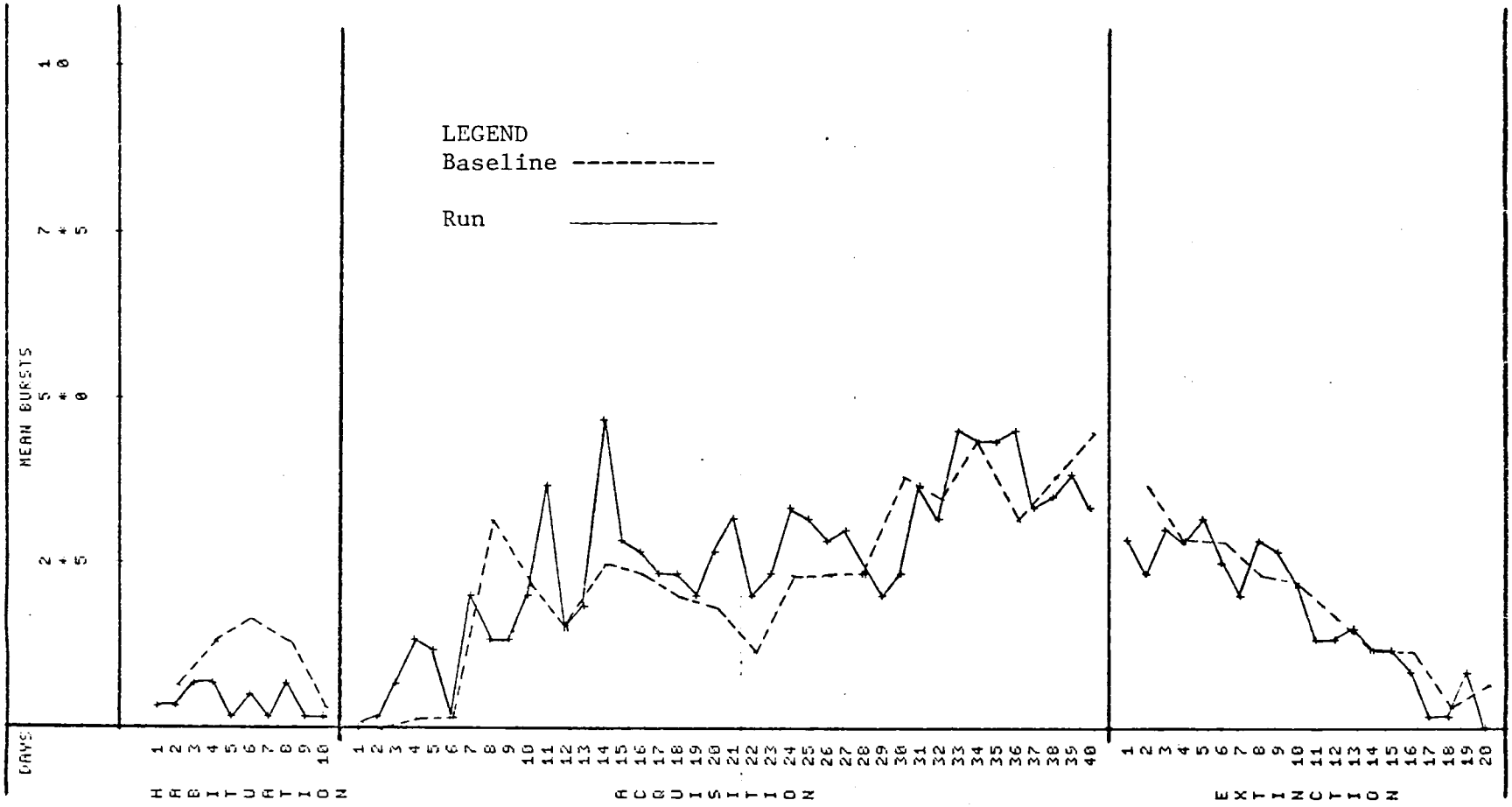
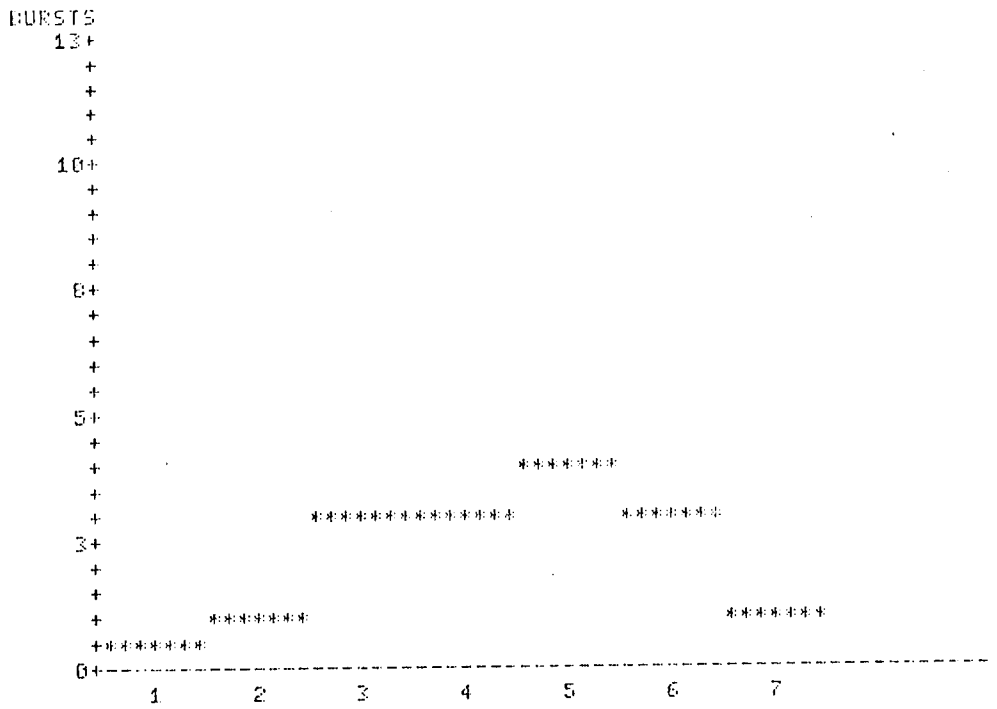


Figure 31. Mean BURSTS over days. Rat 3K - left hemisphere.



BLOCKS X MEAN

TUKEY A - MULTIPLE COMPARISONS TEST

		1	7	2	6	3	4	5
		0.56	1.05	1.15	2.81	2.84	2.87	4.05
1	0.56		0.49	0.59	2.25	2.28	2.31	3.49
7	1.05			0.10	1.76	1.79	1.82	3.00
2	1.15				1.66	1.69	1.72	2.90
6	2.81					0.03	0.06	1.24
3	2.84						0.03	1.21
4	2.87							1.18
5	4.05							

CRITICAL VALUE = 0.91 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 32. Blocks X mean BURSTS. Rat 3K - left hemisphere.

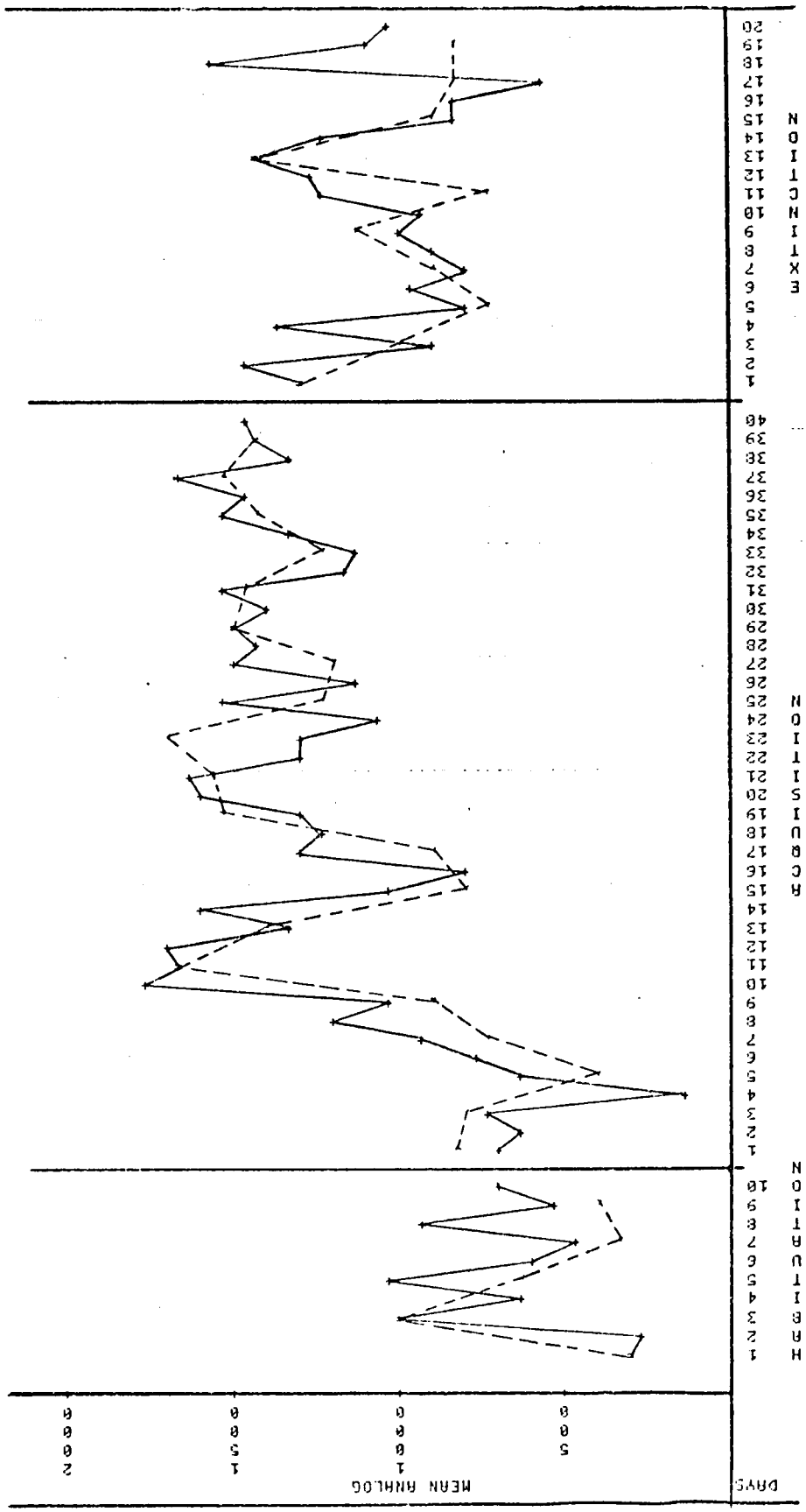
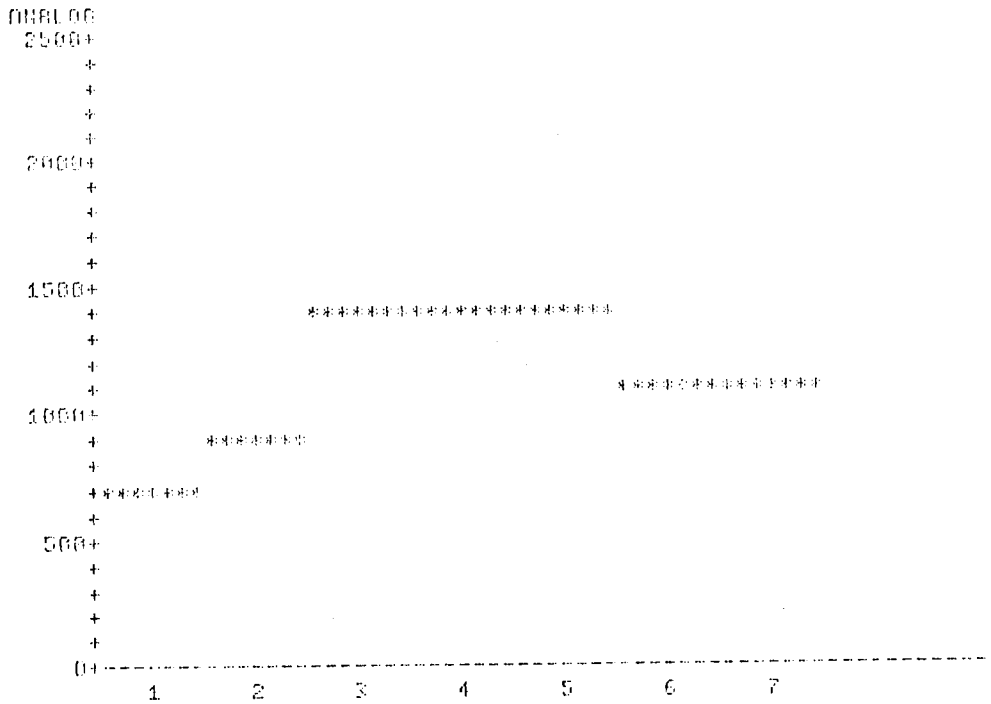


Figure 33. Mean ANALOG over days. Rat 3K - right hemisphere.



TUKEY A - MULTIPLE COMPARISONS TEST

	1	2	6	7	3	4	5
	665.50	869.70	1060.10	1123.30	1371.80	1396.80	1424.30
1 665.50		204.20	394.60	457.80	706.30	731.30	758.80
2 869.70			190.40	253.60	502.10	527.10	554.60
6 1060.10				63.20	311.70	336.70	364.20
7 1123.30					248.50	273.50	301.00
3 1371.80						25.00	52.50
4 1396.80							27.50
5 1424.30							

CRITICAL VALUE = 459.66 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 34. Blocks X mean ANALOG. Rat 3K - right hemisphere.

incomplete extinction in this hemisphere. In behavioral terms this would be called perseveration. It is notable that rat 3K showed strong behavioral perseverance in the apparatus, continuing to lick the spout long after the reinforcement was delivered. This behavior only occurred when the apparatus lights signaled that reinforcement was available.

There was a high positive significant intercorrelation ($r = .802$) between ANALOG and BURSTS. The mean relative increase between habituation and extinction was + 90.0% for ANALOG.

Figure 35, the daily INSTANCES data strongly resembles the analogous graph for ANALOG, where Figure 36, the block means graph does not. Again there are no differences between blocks 1, 2, 6 and 7. Blocks 3, 4 and 5 are different however. The large variations occurring in this animal are more apparent in the mean blocks INSTANCES graph than they are in the ANALOG graph even though statistically they are not significant. The INSTANCES rate of occurrence increased 79.1% from habituation to acquisition.

The BURSTS data shows significant differences between blocks 1, 2, and 6 and block 5. There is no difference between early acquisition and early extinction (blocks 3, 4 and 6). This shows that learning definitely occurred. There are some anomalous periods of very high BURST rates for Rat 3K. Acquisition day 33 was such an example. However the animal was never able to muster such a reinforcement rate on subsequent days. Graphs for daily BURST data are shown in Figure 37 and block means are shown in Figure 38.

The 40 hz activity in Ss left hemisphere amygdaloid central nucleus and the activity occurring in the unknown location were both brought

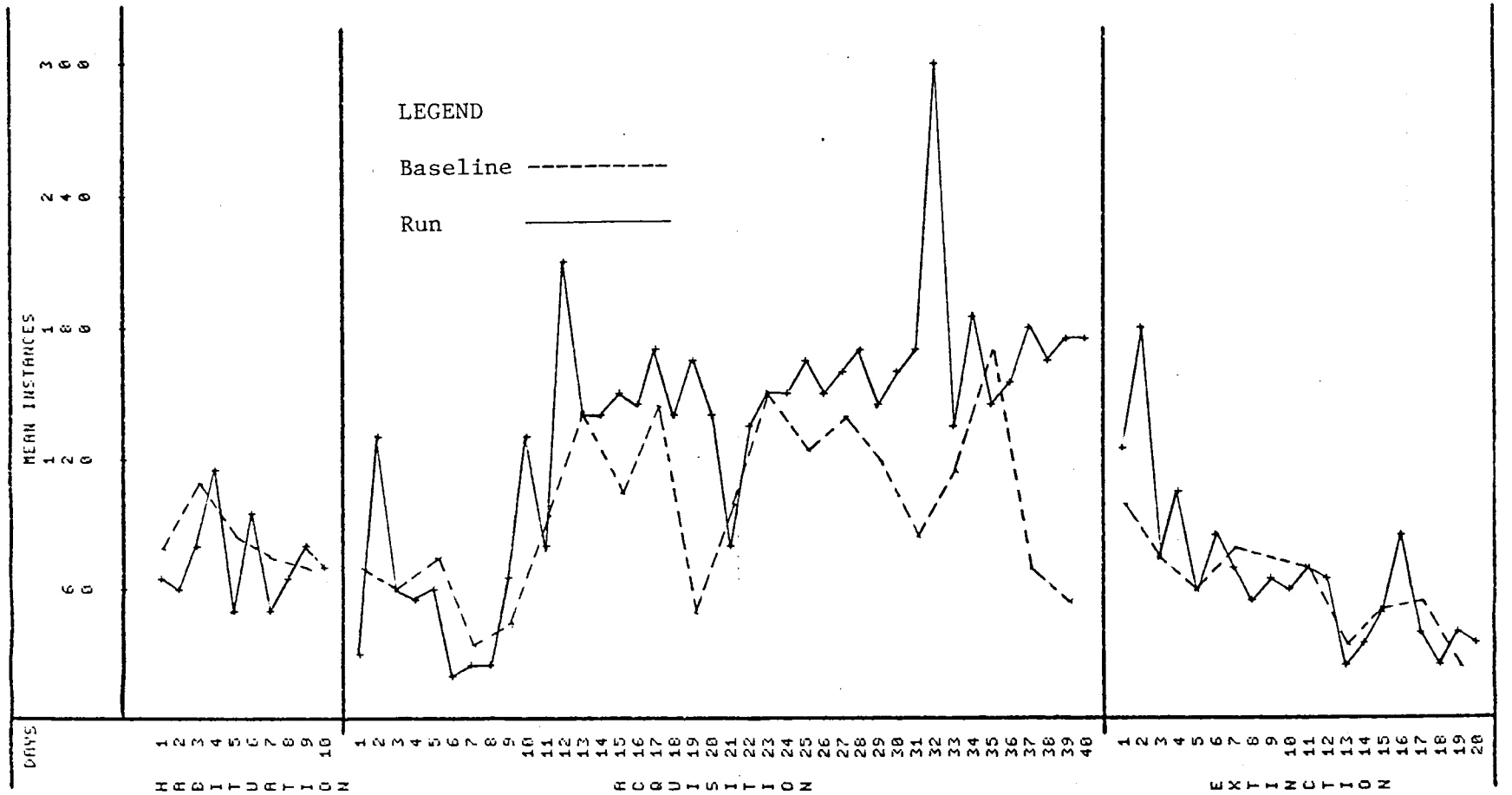
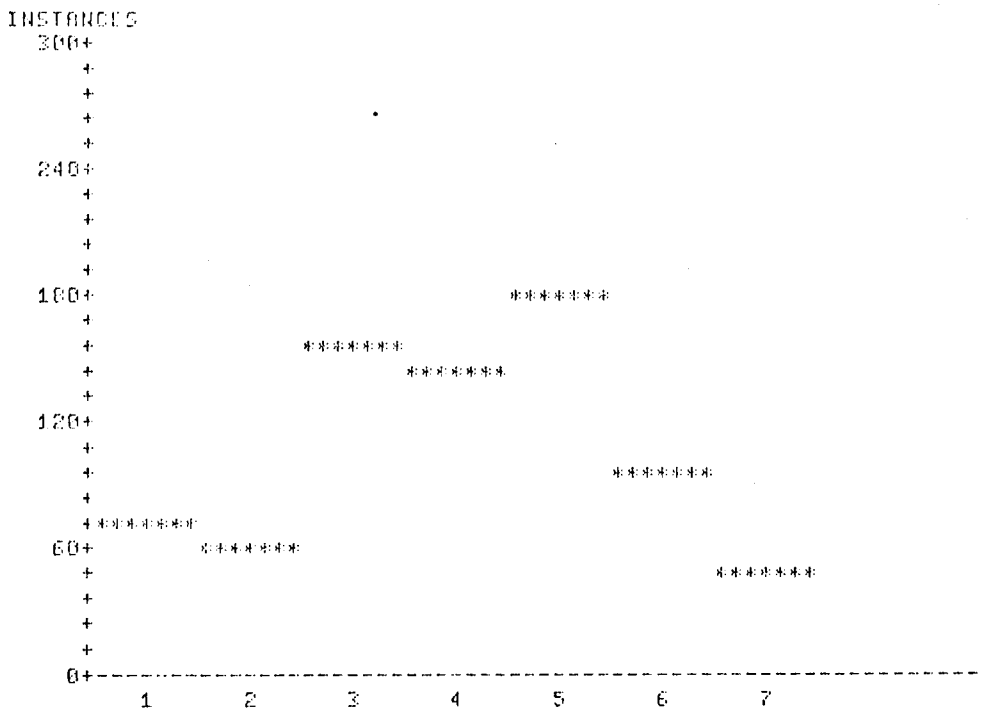


Figure 35. Mean INSTANCES over days. Rat 3K - right hemisphere.



BLOCKS X MEAN

TUKEY A - MULTIPLE COMPARISONS TEST

		7	2	1	6	4	3	5
		50.40	63.00	76.10	90.70	149.50	151.50	181.30
7	50.40		12.60	25.70	40.30	99.10	101.10	130.90
2	63.00			13.10	27.70	86.50	88.50	118.30
1	76.10				14.60	73.40	75.40	105.20
6	90.70					58.80	60.80	90.60
4	149.50						2.00	31.80
3	151.50							29.80
5	181.30							

CRITICAL VALUE = 48.52 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 36. Blocks X mean INSTANCES. Rat 3K - right hemisphere.

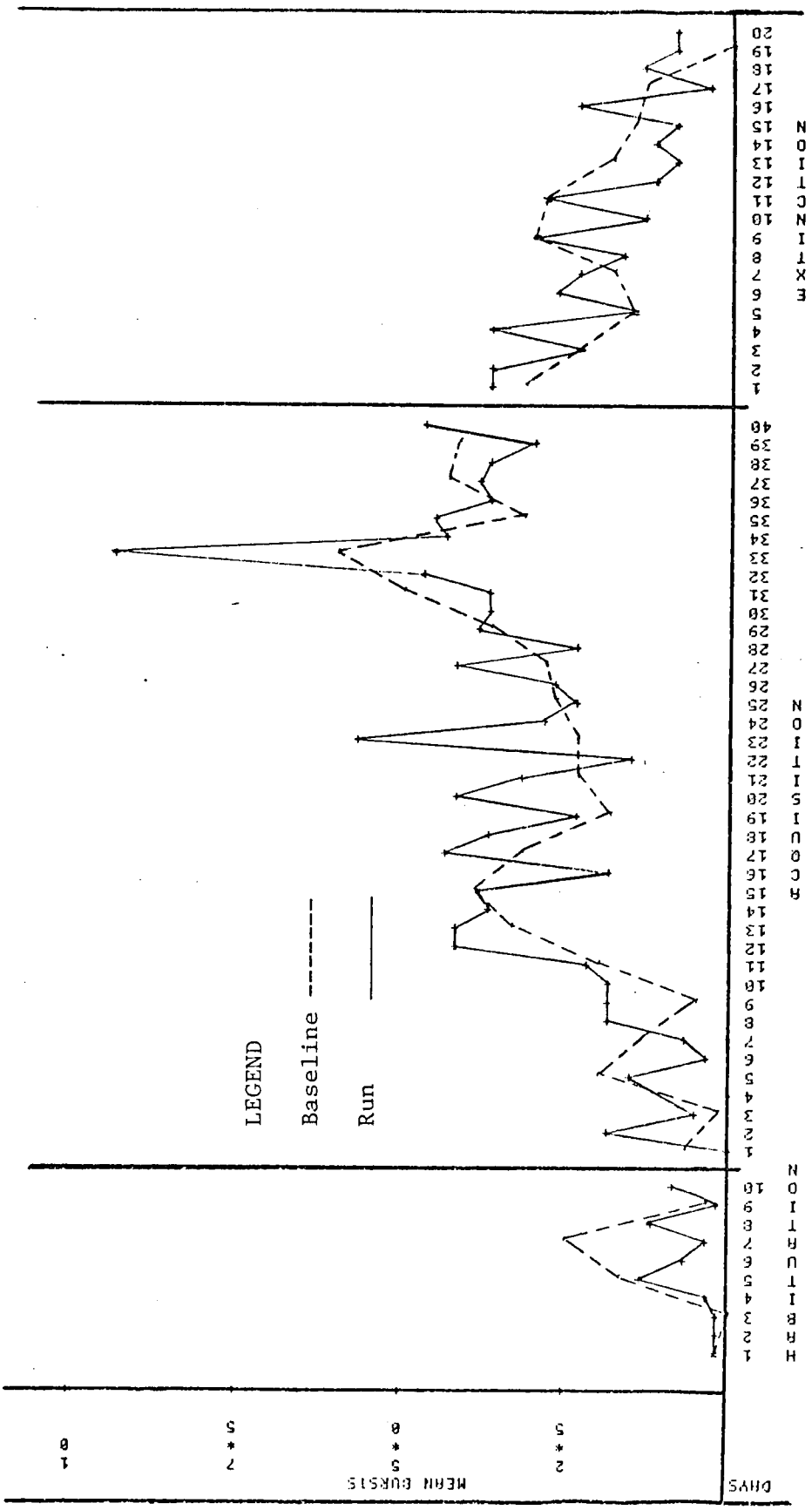
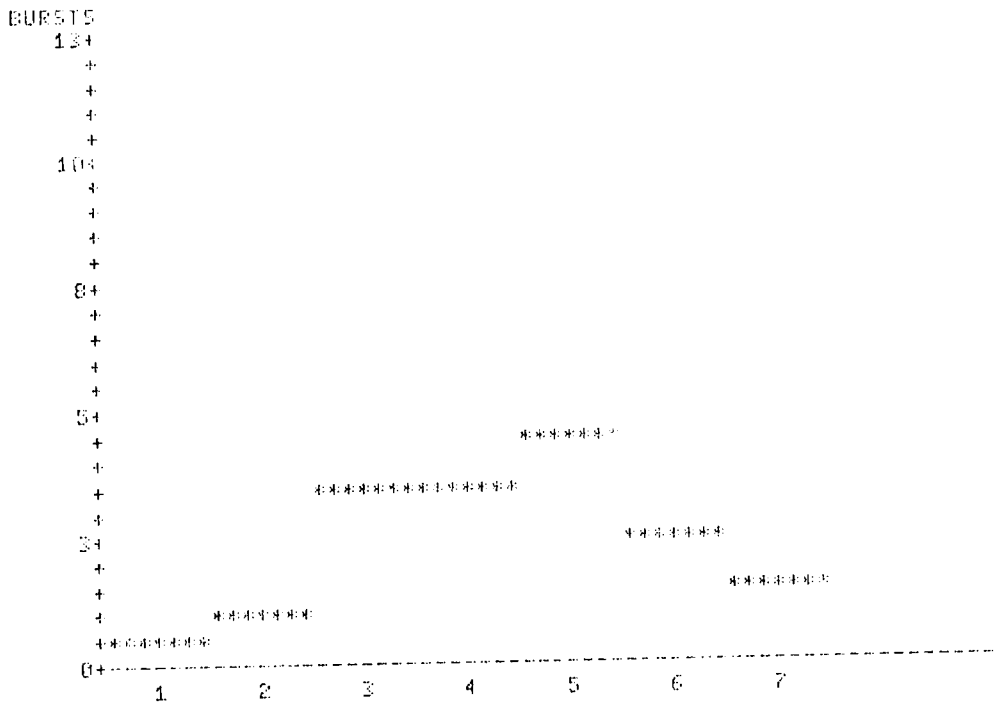


Figure 37. Mean BURSTS over days. Rat 3K - right hemisphere.



BLOCKS X MEAN

TUKEY A - MULTIPLE COMPARISONS TEST

		1	2	7	6	4	3	5
		0.69	1.15	1.41	2.73	3.40	3.61	4.71
1	0.69		0.46	0.72	2.04	2.71	2.92	4.02
2	1.15			0.26	1.58	2.25	2.46	3.56
7	1.41				1.32	1.99	2.20	3.30
6	2.73					0.67	0.88	1.98
4	3.40						0.21	1.31
3	3.61							1.10
5	4.71							

CRITICAL VALUE = 1.73 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 38. Blocks X mean BURSTS. Rat 3K - right hemisphere.

under strong behavioral control. Neither rapid acquisition nor extinction were seen in any case.

Behavioral data. The anomaly seen in 3K previously are reified in the behavioral data. Rat 3K ranked second in open field crossing on habituation ($\overline{X}$ = 44.70, sd - 14.2). There were no appreciable changes seen in either post-acquisition tests ($\overline{X}$ - 43.10, sd = 16.0) or post-extinction test ($\overline{X}$ = 42.6, sd = 13.7). No changes were seen in current threshold for vocalization.

The truly interesting changes were seen in the animals response to being handled by E. Intensity of vocalization went up on a rating scale of 1 (no vocalization) to 4 (extreme vocalization). Post-habituation scores were averaged .4 (sd - .89) in other words the animal was quiet and offered no resistance to handling prior to conditioning. After 40 hz conditioning 3K showed very strong, abrupt changes in its affect. It vocalized intensively on handling and rather unpredictably. The vocalization was not only related to a startle response upon initial contact but would often occur as the contact was of an intolerable duration to the animal. An example of this was when the electrode plug was being fastened to the animals head plug. There was no evidence that the animal was experiencing any pain from the plug itself. During the acquisition period the animal became increasingly difficult to manage and to control. The animal showed a high frequency of biting E where this never happened previously. The attack was sudden and without warning, or vocalization. It was quick, well directed and effective, frequently causing lacerations and bleeding in E.

These effects overlapped with 3K's attacks on anything inserted into its cage. When presented with a pencil, finger or car keys, 3K would instantly seek out and violently attack the object. This was done without piloerection or vocalization. The attack was swift, well directed and well organized. It did not have any of the elements of an affective attack but seemed much more predatory.

Post-extinction data showed a return to the original post-habituation behaviors. Vocalization on handling was diminished ($\overline{X}$ = .2, sd = .48). Pencil biting went to zero also ($\overline{X}$ = 0).

During the preliminary behavioral screening 3K was found to be a voracious mouse killer. There was no change in the animal's propensity to kill at any time during the experiment.

Behavioral control of 40 hz activity was demonstrated in the central nucleus and an unidentified site in the contralateral hemisphere. Concomitant changes in behaviors were observed. A graph of these behaviors is seen in Figure 39.

Data for Rat 5K

Histological evaluation. The electrode in the left hemisphere of 5K was lodged in coordinates A 5.2, ML - 4.2 and DV - 1.8. The electrode site was the central nucleus. This animal also showed a large subcortical tumor approximately 2.0 mm in diameter approximately 2 mm posterior to the cortical entry site.

The right hemisphere recording coordinates were A 4.6, ML 4.5 and DV 2.0. The electrode tip was found to be lodged in the medial nucleus. Electrode placements are illustrated in Figure 40.

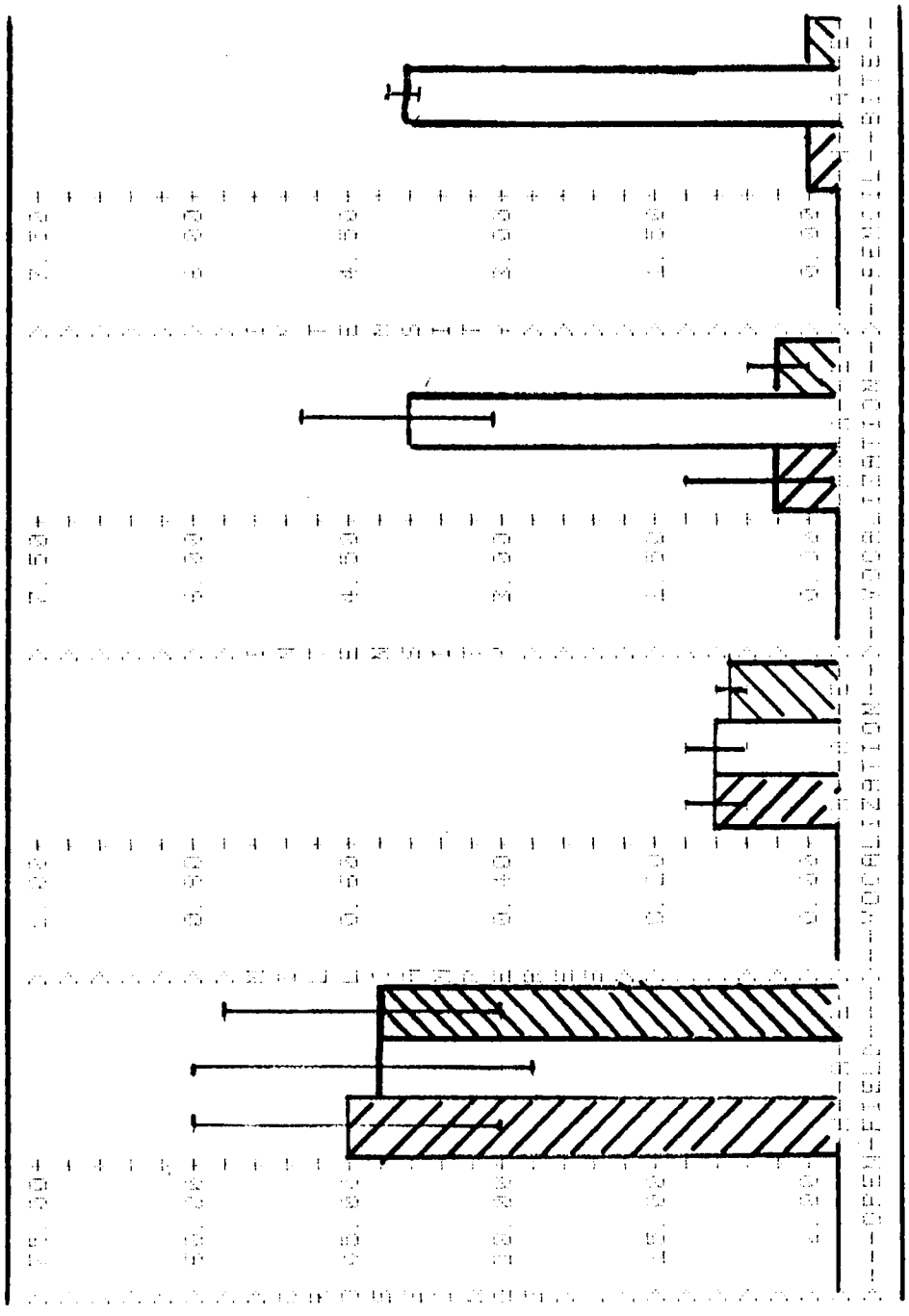


Figure 39. Post contingency means and standard deviations for behavioral tests. Rat 3K.

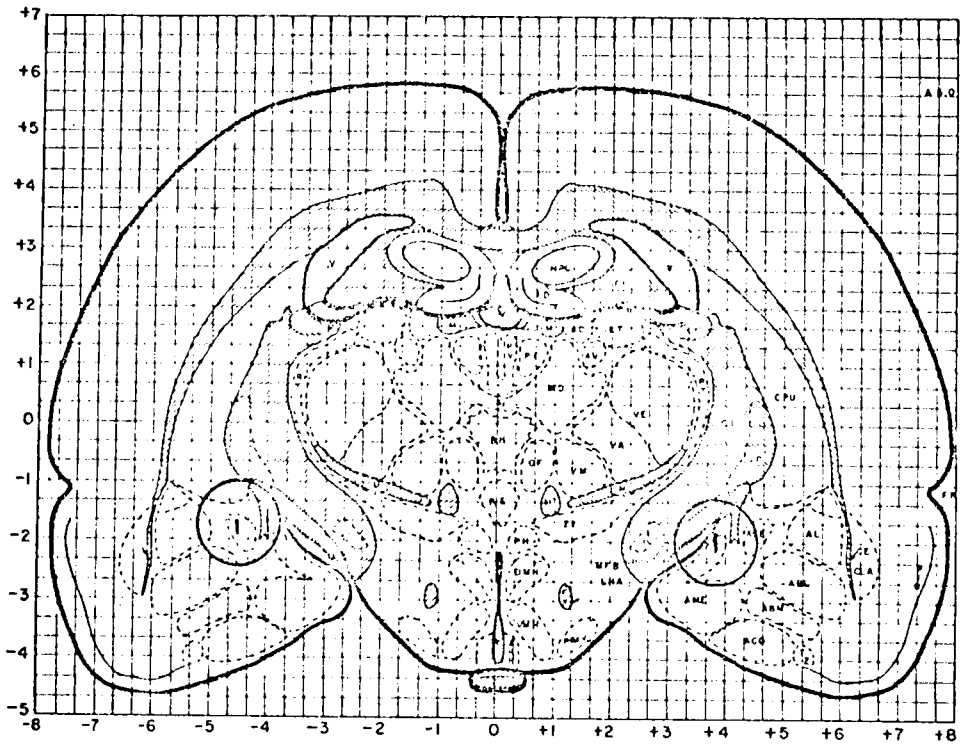


Figure 40. Electrode placements for rat 5K. The left electrode is in the central nucleus at coordinates A 5.2, ML -4.2 and DV - 1.8. The right electrode is in the medial nucleus at coordinates A 4.6, ML 4.5 and DV 2.0.

Left hemisphere conditioning data. The performance of Rat 5K is difficult to interpret. For ANALOG data the matrix is significant ($F = 7.024$, $p < .01$). The Tukey-A Multigroups comparisons test showed no significant differences between blocks 1, 2, 3, 5, 6 and 7. Nor are there any differences between blocks 3, 4, 5 and 6, but 3 is different from blocks 1, 2 and 7. The profile of a rapid acquisition followed by a highly variable pattern such as the one seen for 5K may be due to equipment problems which is doubtful because it did not appear in other animals. A second and more likely hypothesis would be superstitious learning as the animal attempts to find various correlated skeletal mediators of the behavior. When reinforcement first becomes contingent on the 40 hz spindle the animal learns that reinforcement is contingent on some aspect of its behavior. The rise in ANALOG is a reflection of an increase in activation as the S produces various behaviors only to learn that it will not produce reinforcement. In spite of the unorthodox acquisition seen in this measure the mean relative ratio between habituation and acquisition was 96%. ANALOG showed a low and insignificant correlation to INSTANCES ($r = .2683$) but was positively and significantly correlated with BURSTS ($r = .7399$).

Figure 41 is a graph of the daily ANALOG record and Figure 42 includes the block means.

The INSTANCES data is demonstrative of a rather weak effect. It is characterized by a very poor habituation. There are no differences between blocks 1, 2, 4, 5, 6 and 7. There is however some weak acquisition because block 5 is significantly different from block 7.

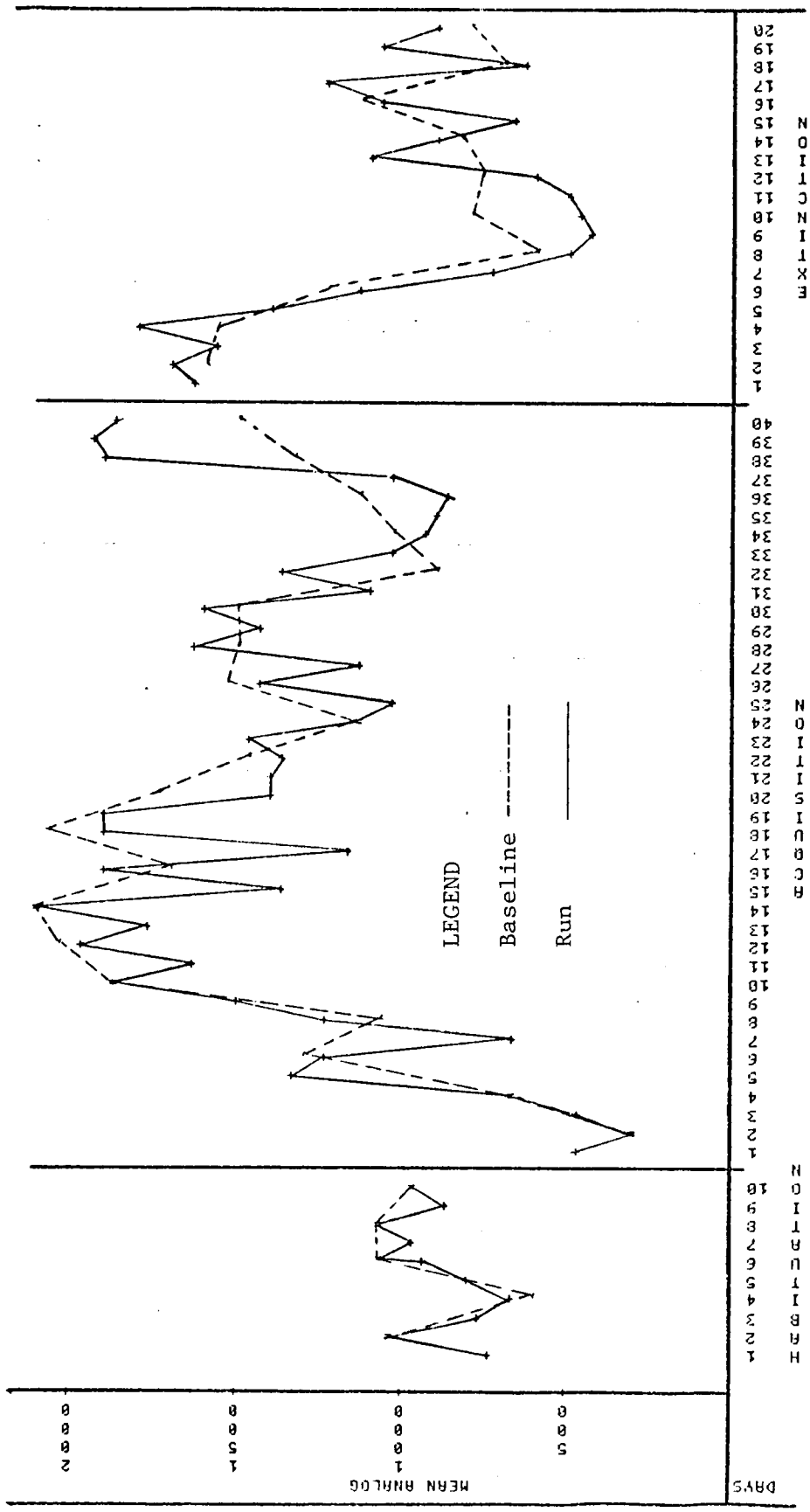
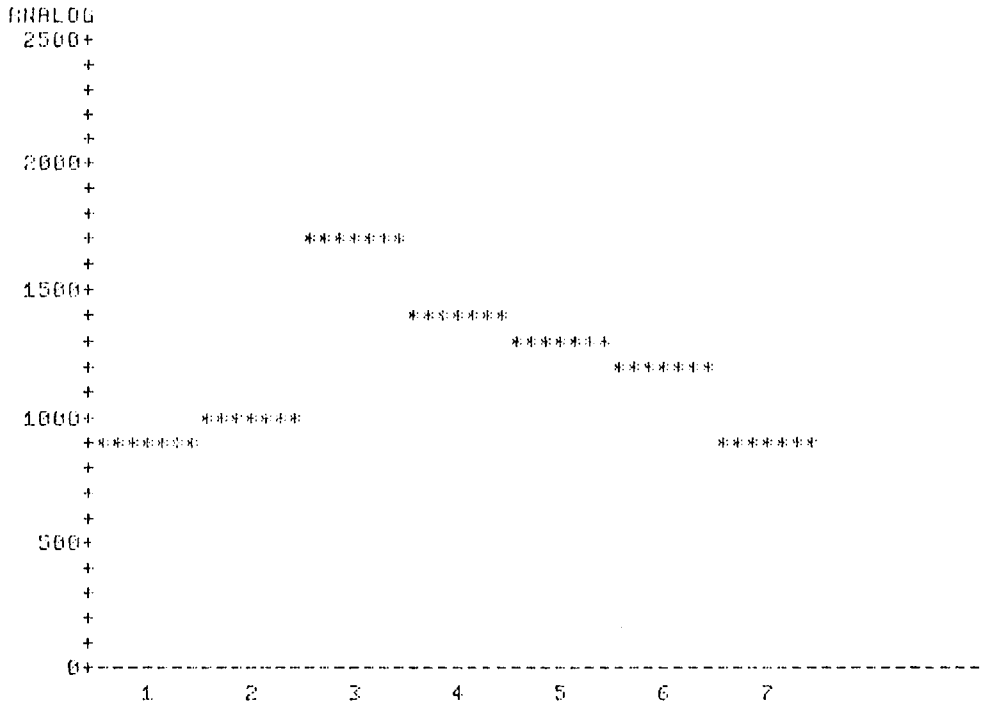


Figure 41. Mean ANALOG over days. Rat 5K - left hemisphere.



BLOCKS X MEAN

TUKEY A -- MULTIPLE COMPARISONS TEST

	7	1	2	6	5	4	3
	887.00	894.50	993.40	1152.10	1313.30	1381.60	1728.70
7 887.80		6.70	105.60	264.30	425.50	493.80	840.90
1 894.50			98.90	257.60	418.80	487.10	834.20
2 993.40				158.70	319.90	388.20	735.30
6 1152.10					161.20	229.50	576.60
5 1313.30						68.30	415.40
4 1381.60							347.10
3 1728.70							

CRITICAL VALUE = 620.13 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 42. Blocks X mean ANALOG. Rat 5K - left hemisphere.

Figure 43 is a graph of the daily INSTANCES and Figure 44 is the graph of the mean blocks.

The BURSTS data for 5K has significant differences but they are weaker than the ones found in previous animals. It is notable that BURSTS for habituation show an adequate habituation but it is higher than the extinction data. This is in keeping with the other measures but to a lesser degree. Figure 42, the graph of the blocks is very deceptive when compared to the data shown of the daily activity in Figure 45. Figure 46 shows a graph of almost ideal conditioning and suggests that mild acquisition occurred in block 2 and learning asymptotes in block 3, holding constant in blocks 4 and 5. The daily records show a rapid but highly erratic acquisition which occurs through block 3. There is a definite leveling out in block 4 with a return of the variation followed by recovery in block 5. The loss of acquisition seen in block 5 can be attributed to equipment difficulties. This is in keeping with the recovery seen in the second half of block 5. This data shows a consistent tendency for the daily Baseline data to be higher than the Run data. This is an artifact of the equipment and paradigm. During the Baseline periods 5K showed no approach behavior toward the drinking spout because of the cue lights. During the RUN periods the animal would stand over the drinking cup and lick the spout for an appreciable fraction of the Run interval. Hence the animal was not only being reinforced to produce 40 hz but to lick the drinking spout. This behavior produces the consummatory licking discussed earlier. Such behavior causes a suppression of the ANALOG, INSTANCES

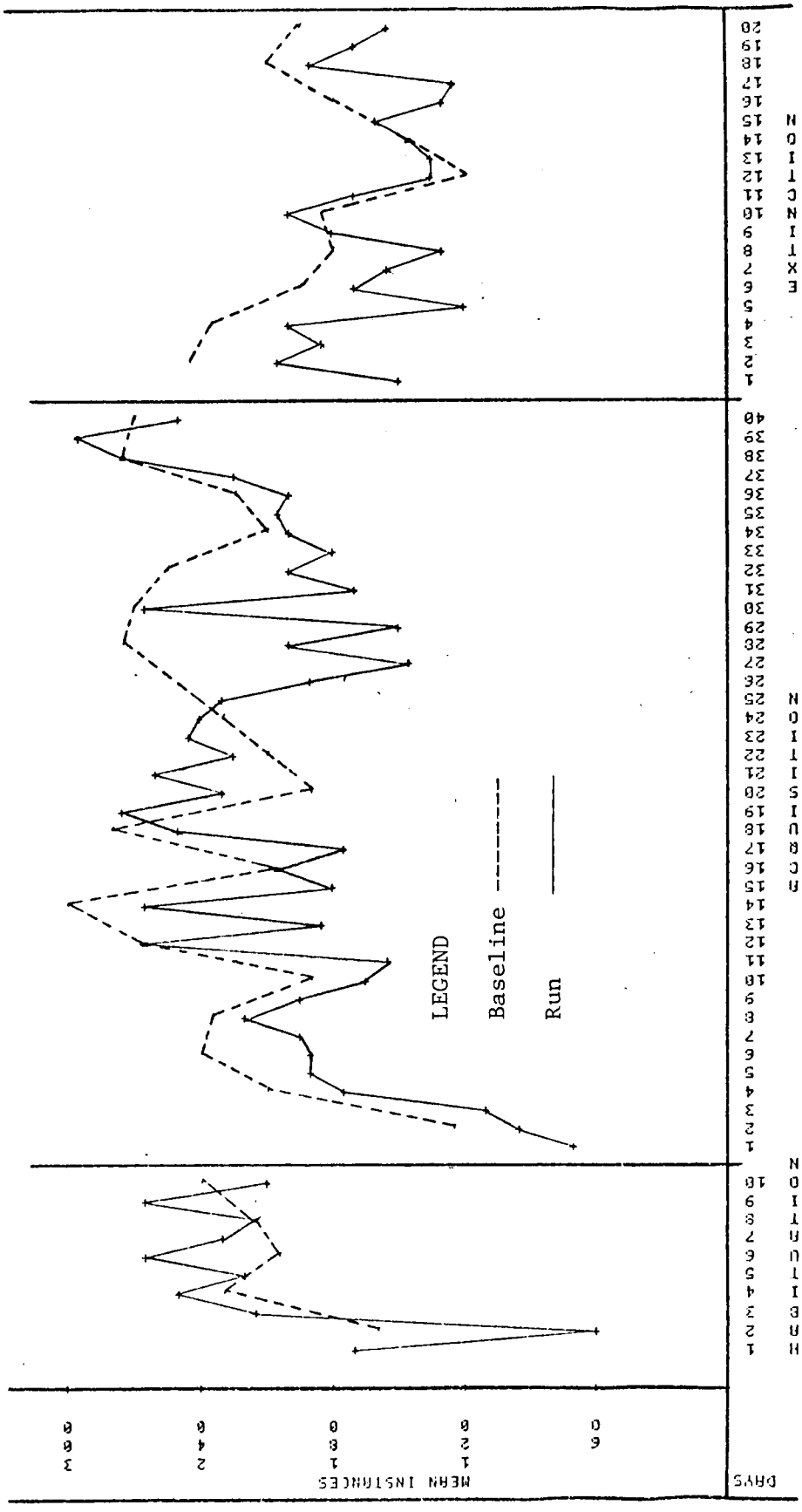
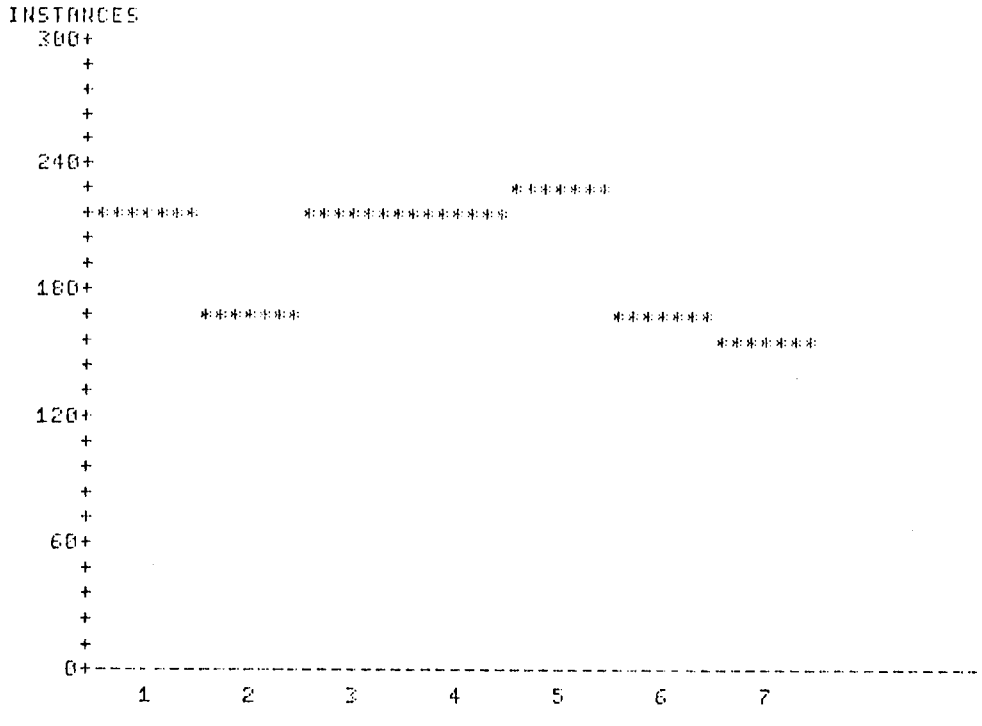


Figure 43. Mean INSTANCES over days. Rat 5K - left hemisphere.



BLOCKS X MEAN

TUKEY A - MULTIPLE COMPARISONS TEST

		7	2	6	1	4	3	5
		154.20	163.60	172.10	213.80	217.20	221.80	222.90
7	154.20		9.40	17.90	59.60	63.00	67.60	68.70
2	163.60			8.50	50.20	53.60	58.20	59.30
6	172.10				41.70	45.10	49.70	50.80
1	213.80					3.40	8.00	9.10
4	217.20						4.60	5.70
3	221.80							1.10
5	222.90							

CRITICAL VALUE = 66.77 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 44. Blocks X mean INSTANCES. Rat 5K - left hemisphere.

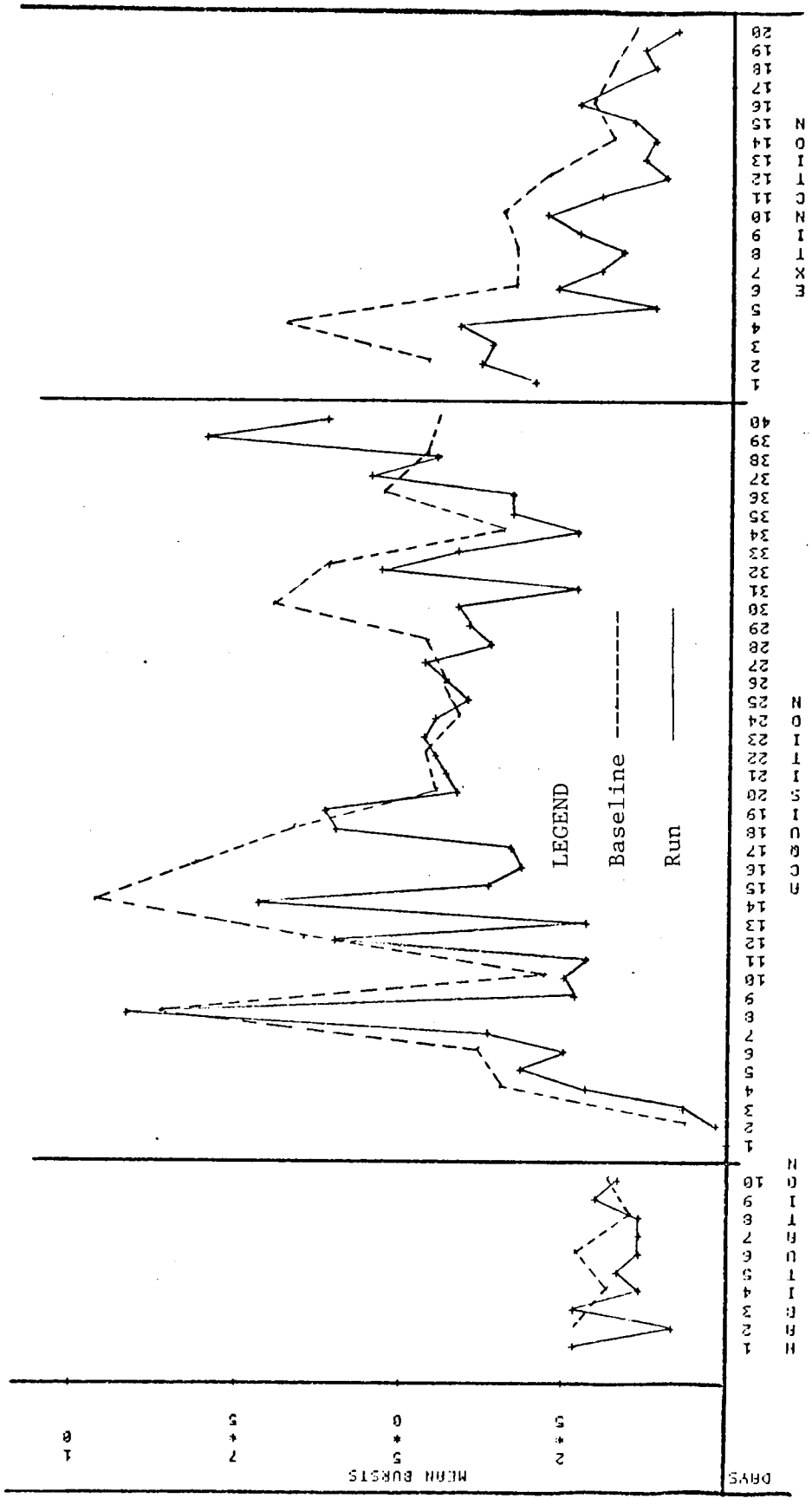
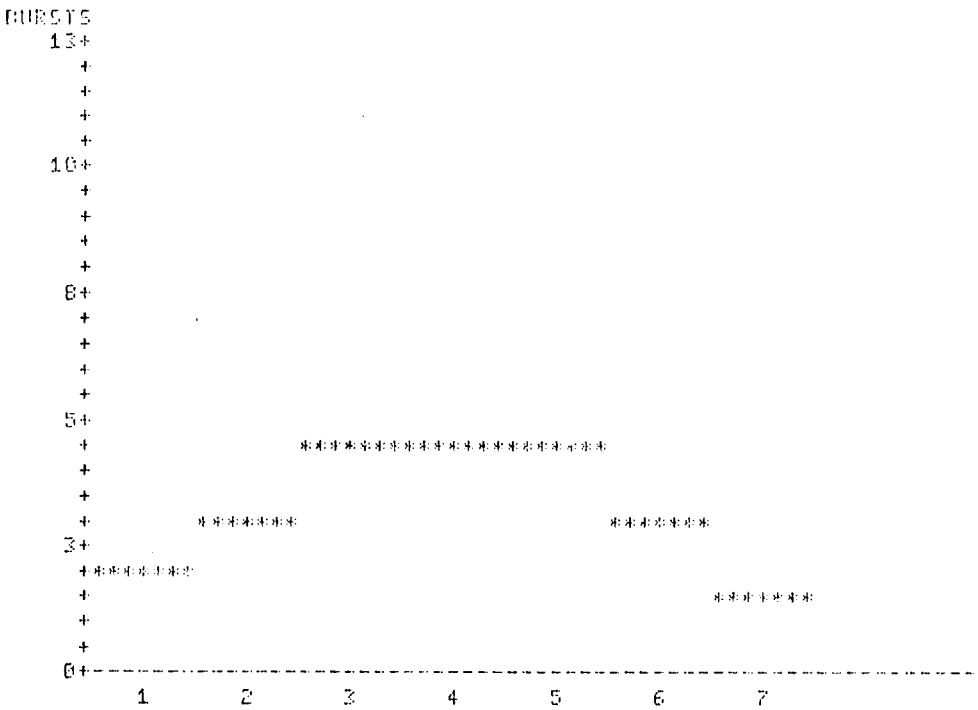


Figure 45. Mean BURSTS over days. Rat 5K - left hemisphere.



BLOCKS X MEAN

TUKEY A - MULTIPLE COMPARISONS TEST

		7	1	2	6	4	3	5
		1.45	1.77	2.79	2.90	4.45	4.57	4.68
7	1.45		0.32	1.34	1.46	3.00	3.12	3.23
1	1.77			1.02	1.14	2.68	2.80	2.91
2	2.79				0.11	1.65	1.78	1.89
6	2.90					1.54	1.66	1.77
4	4.45						0.12	0.23
3	4.57							0.11
5	4.68							

CRITICAL VALUE = 2.41 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 46. Blocks X mean BURSTS. Rat 5K - left hemisphere.

and BURSTS. The suppression is not real however and only appears to the equipment. This condition appears when reinforcement is contingent on the animals behavior because the differences between Baseline and Run are absent in habituation and later disappear in extinction. The erratic density of bursts fits the superstitious learning or "trial and error" learning models well.

A weak conditioning effect was seen in the left hemisphere central nucleus of Rat 5K. The data was highly variable and correlated with the animals response to changes in reinforcement contingencies.

Right hemisphere conditioning data. Right hemisphere data closely paralleled the left results obtained from the left hemisphere. The first notable difference is that the ANALOG habituation appears to be quite adequate. The same relationship between run and baseline appears in the daily activity graph shown in Figure 47. There is the same high peak at the end of block 1 which once again falls off during the period of equipment difficulty.

There is an acquisition effect for ANALOG in Rat 5K but it is weak and unusual. There are no significant differences between blocks 1, 2, 4, 5, 6 or 7. Block 3 is different from 1, 5, 6 and 7 but not blocks 2 and 4. From this it can be concluded that acquisition began to occur in block 2 and was definitely demonstrable in block 3. After these blocks it was lost. The graph for the block means can be seen in Figure 48.

Right hemisphere INSTANCES data closely parallel the data seen in the left hemisphere. This is seen in Figure 49 where the daily activity

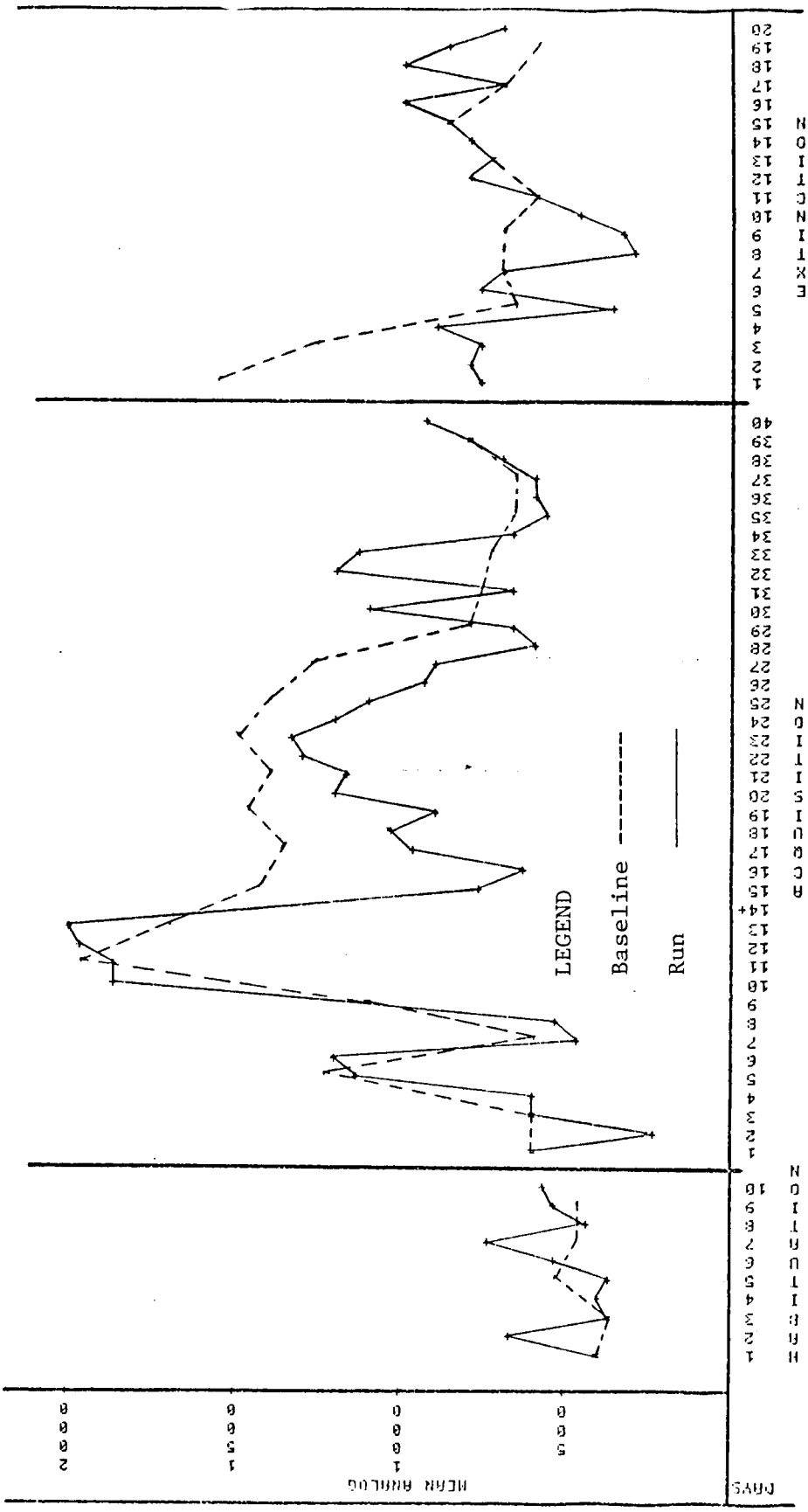
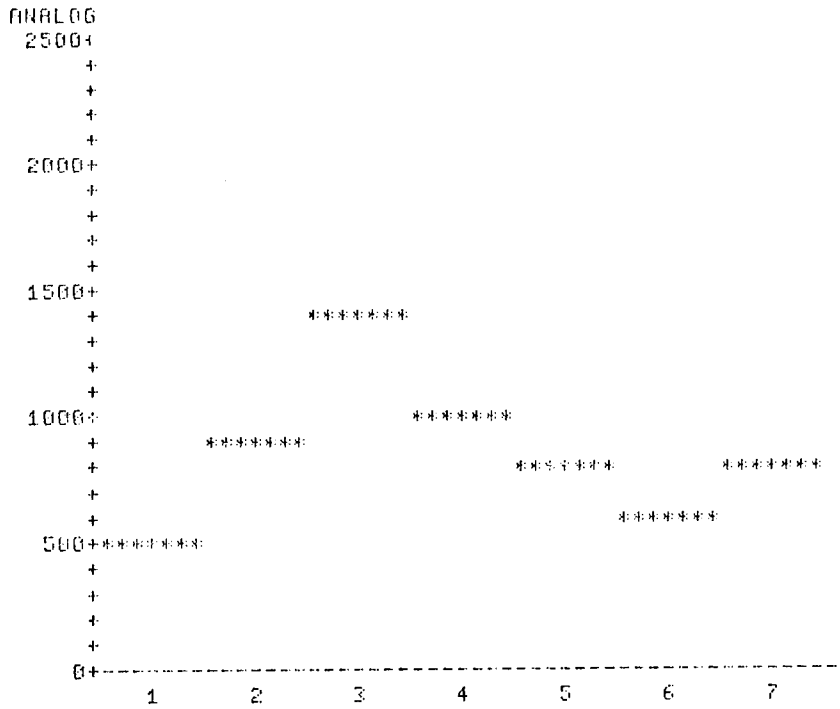


Figure 47. Mean ANALOG over days. Rat 5K - right hemisphere.



BLOCKS X MEAN

TUKEY A - MULTIPLE COMPARISONS TEST

		1	6	5	7	2	4	3
		518.80	629.90	803.10	821.20	851.40	1044.50	1369.70
1	518.80		111.10	284.30	302.50	332.60	525.70	850.90
6	629.90			173.20	191.40	221.50	414.60	739.80
5	803.10				18.20	48.30	241.40	566.60
7	821.30					30.10	223.20	548.40
2	851.40						193.10	518.30
4	1044.50							325.20
3	1369.70							

CRITICAL VALUE = 540.44 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 48. Blocks X mean ANALOG. Rat 5K - right hemisphere.

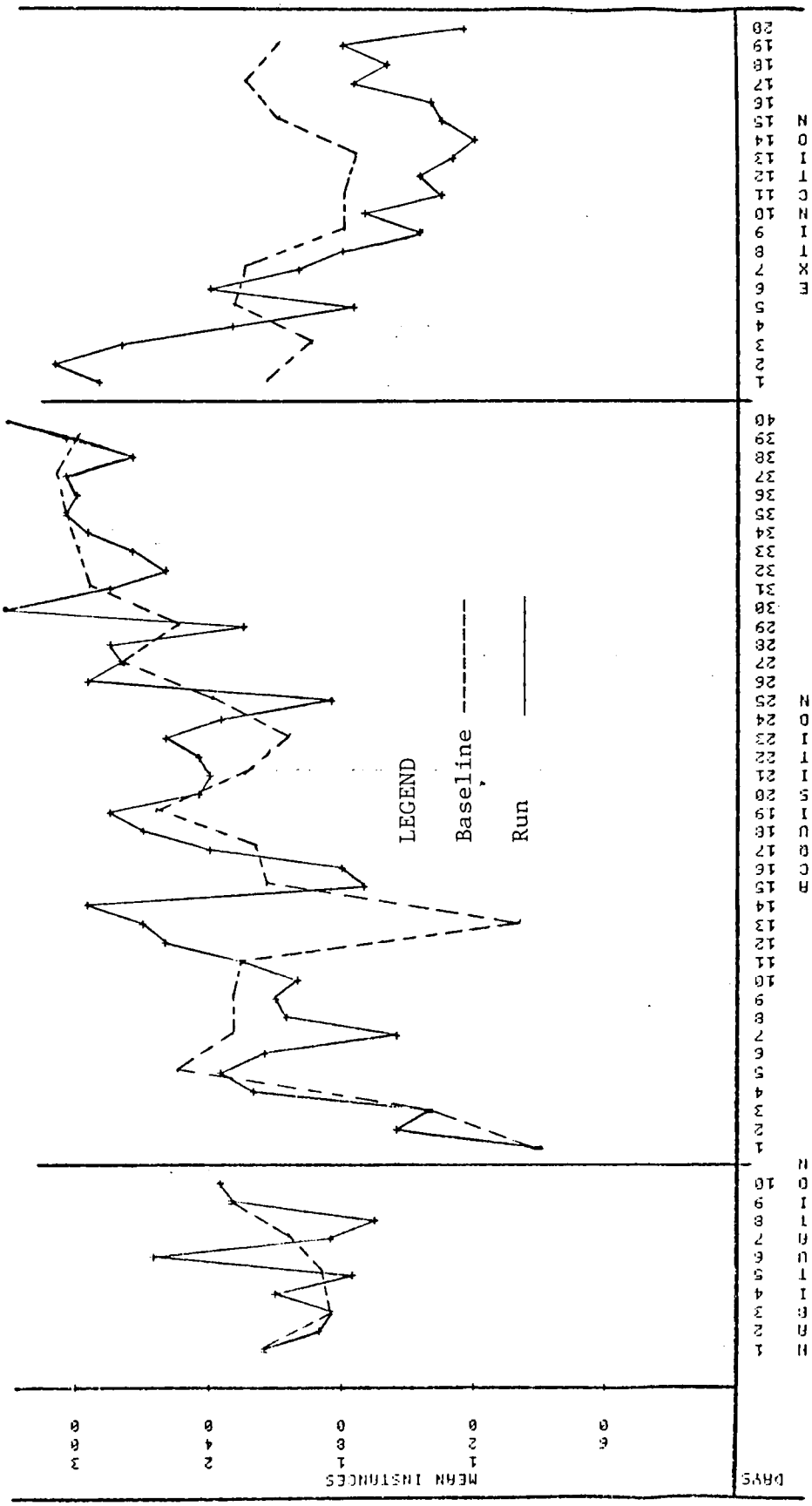


Figure 49. Mean INSTANCES over days. Rat 5K. Right hemisphere.

is graphed. The block means graphed in Figure 50 are closer to the expected results but reflect an inadequate habituation. There are no significant differences between blocks 1, 2 and 7 which are habituation, early acquisition and extinction. There are no differences between 1, 2, 3 and 7 which are habituation, early acquisition and early extinction and there are no differences between 3, 4 and 5 which are middle and late acquisition. Block 5 is clearly different from 1, 2, 6 and 7 which are habituation and extinction. Although INSTANCES data are removed from the ideal they show an increase of instances during acquisition.

BURSTS effects are not as ideal showing a very similar pattern to ANALOG ($r = .767$). The daily performance graph in Figure 51 shows the same rapid but erratic acquisition, with a decrement in block 4 and some recovery in block 5. There is a good strong extinction effect with a slow diminution between daily Baseline and Run data. The block graph, shown in Figure 52 offers a similar picture. Habituation, early acquisition and late extinction are not different. There are no differences between early acquisition, late acquisition and early extinction. Mid-acquisition (block 3) is significantly different from habituation, early acquisition and all of extinction but is not different from late acquisition. It can be concluded that a strong rapid initial acquisition took place followed by a highly variable acquisition. Acquisition and extinction occurred very rapidly allowing speculation that the 40 hz activity was highly discriminable. The fact that it was not maintained throughout acquisition suggests that the associated body



BLOCKS X MEAN

TUKEY A - MULTIPLE COMPARISONS TEST

		7	2	1	6	3	4	5
		147.80	185.60	208.20	225.20	246.80	261.30	299.50
7	147.80		37.80	60.40	77.40	99.00	113.50	151.70
2	185.60			22.60	39.60	61.20	75.70	113.90
1	208.20				17.00	38.60	53.10	91.30
6	225.20					21.60	36.10	74.30
3	246.80						14.50	52.70
4	261.30							38.20
5	299.50							

CRITICAL VALUE = 66.02 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 50. Blocks X mean INSTANCES. Rat 5K. Right hemisphere.

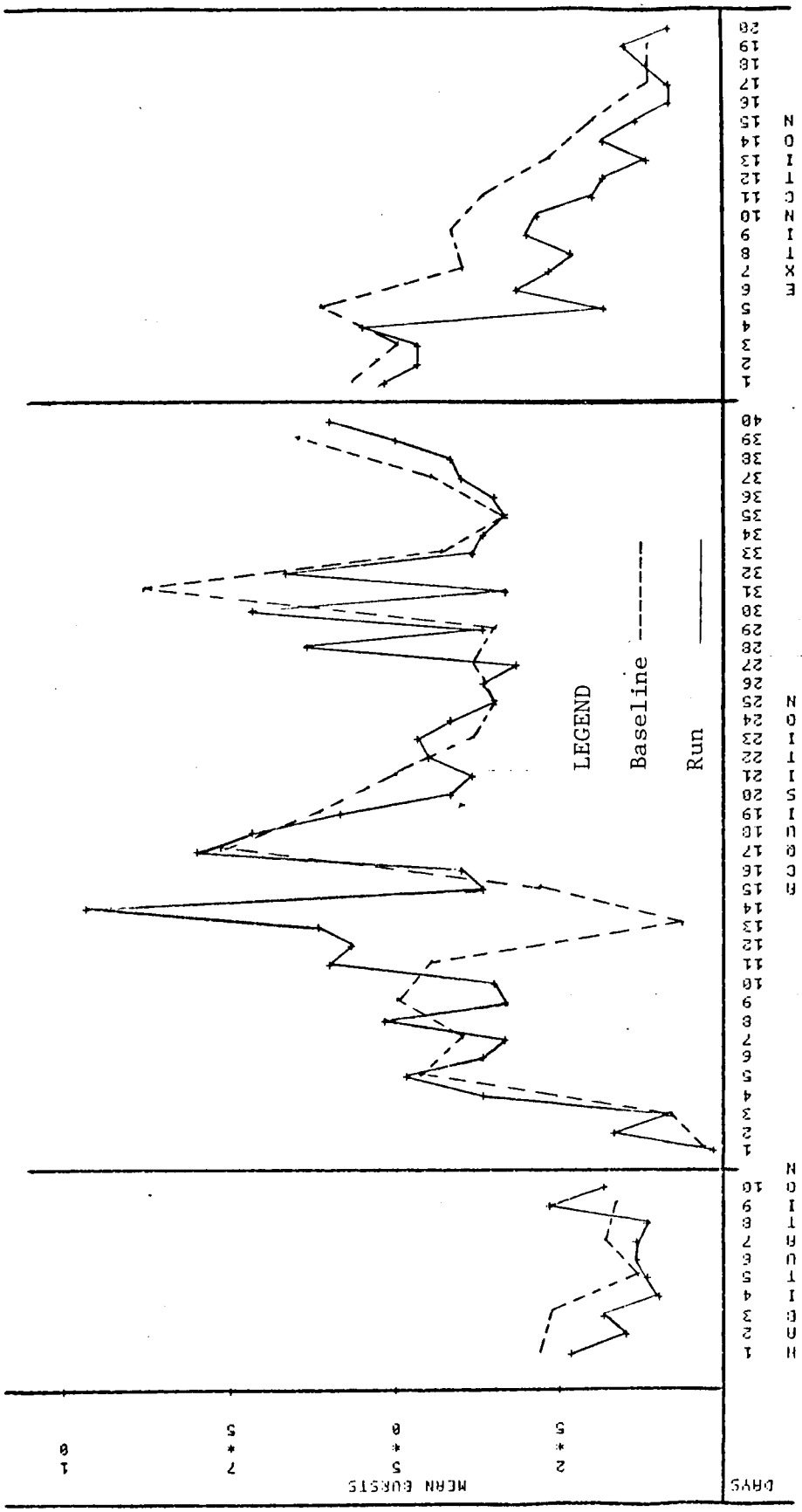
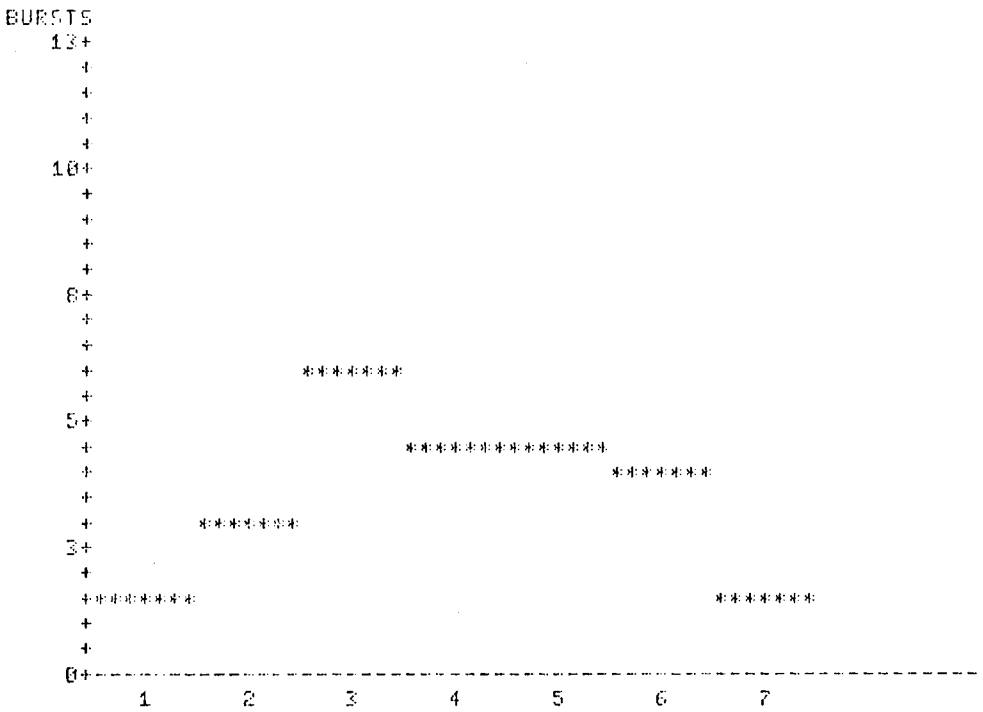


Figure 51. Mean BURSTS over days. Rat 5K - right hemisphere.



BLOCKS X MEAN

TUKEY A - MULTIPLE COMPARISONS TEST

		7	1	2	6	5	4	3
		1.51	1.75	3.21	3.76	4.53	4.65	6.20
7	1.51		0.24	1.70	2.25	3.02	3.14	4.69
1	1.75			1.46	2.01	2.78	2.90	4.45
2	3.21				0.55	1.31	1.44	2.99
6	3.76					0.77	0.89	2.44
5	4.53						0.12	1.67
4	4.65							1.55
3	6.20							

CRITICAL VALUE = 2.09 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 52. Blocks X mean BURSTS. Rat 5K - right hemisphere.

state was aversive to the rat. It would be premature to remove such a conclusion from the realm of conjecture however because equipment failure or superstitious learning can not be ruled out.

Behavioral data—Rat 5K. The emotional changes seen in 5K bore some similarity to those seen in 3K only they were greatly attenuated. There were no meaningful changes in open field crossings or in current threshold for vocalization. There was some increase in vocalization when handled and some increase in interest to a pencil when presented to its snout. There was no sustained attack as seen with 3K. There was no increase in attacks or bites inflicted on E. A graph of these behaviors can be seen in Figure 53.

Data for Rat 8K

Histological evaluation. Animal 8K had the closest to what can be called bilateral implants. The left hemisphere electrode in the ventral medial nucleus at coordinates A 5.4, ML - 3.6, DV - 2. The right hemisphere placement was verified to be the central medial nucleus at coordinates A 5.4, ML + 3.6 and DV = 2.6. These placements can be seen in relation to the amygdala in Figure 54.

Conditioning data—Rat 8K. The ANALOG data shows what is now becoming a familiar pattern. There are no differences between blocks 1, 2, 4, 5, 6 and 7. Blocks 3 and 5 are the same as block 4 but different from all others. This pattern shows no early acquisition followed by significant acquisition in block 3. These effects are lost in block 4

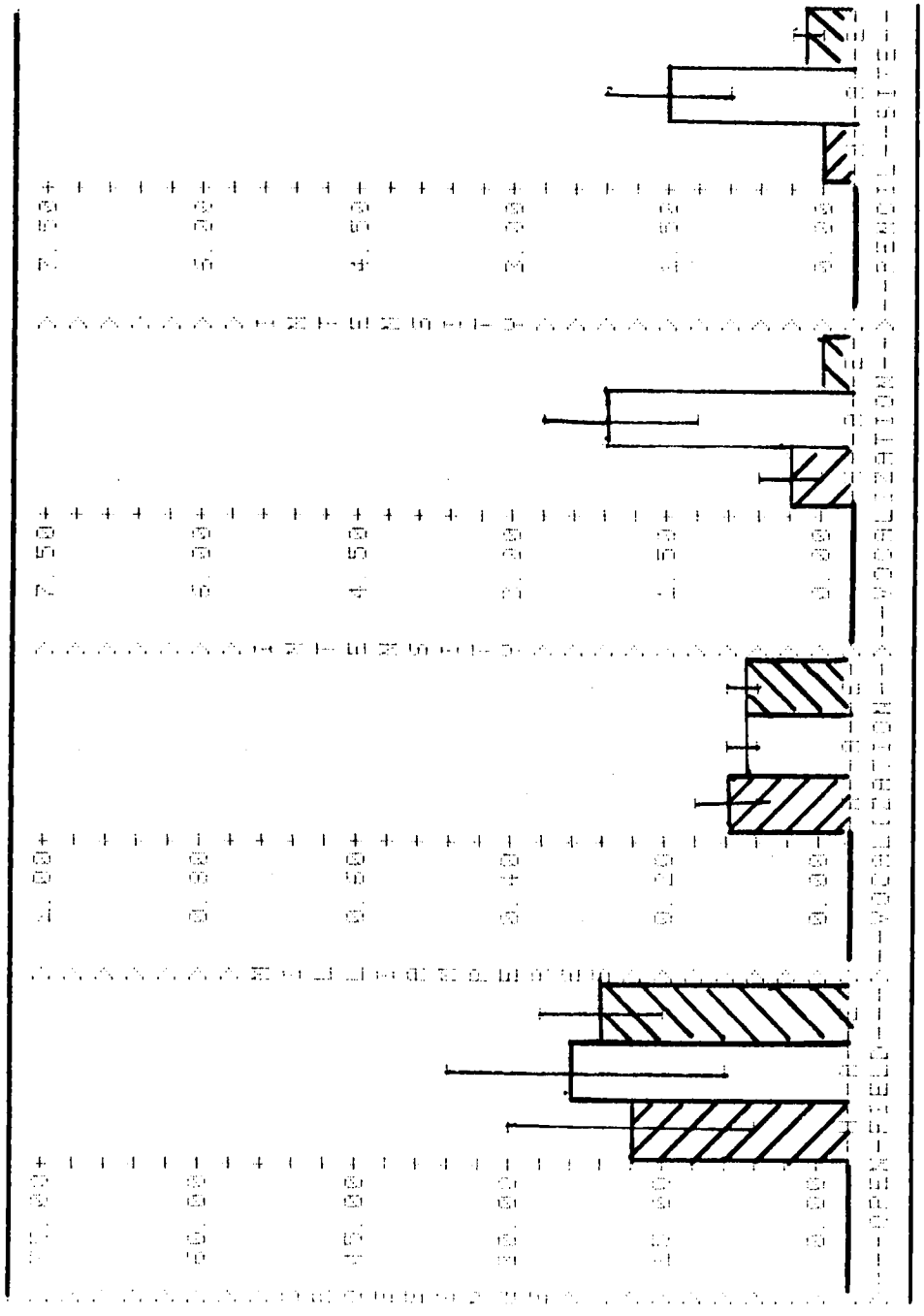


Figure 53. Post contingency means and standard deviations for behavioral tests for rat 5K.

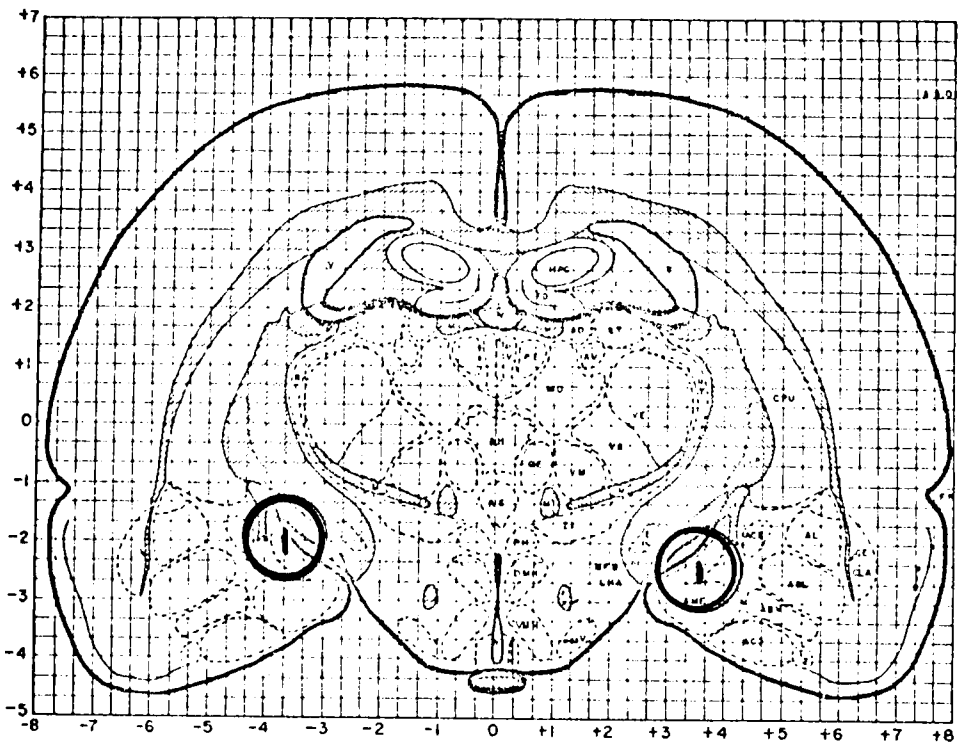


Figure 54. Bilateral medial nucleus implants. The coordinates for the left hemisphere are A 5.4, ML - 3.6, DV -2. The right hemisphere site is at coordinates A 5.4, ML + 3.6 and DV - 2. Rat 8K.

followed by recovery in block 5. Blocks 3, 4 and 5 are significantly above habituation. Extinction is complete. The daily data shown in Figure 55 and the blocks averages graphs Figure 56 are in close agreement. The intercorrelations between ANALOG and INSTANCES are positive and significant ($r = .770$). The same is true for BURSTS ($r = .681$). A relatively high basal ANALOG rate held the relative percentage increase between habituation and acquisition to 36.25%.

The INSTANCES daily data and mean blocks data shown in Figures 57 and 58 show a highly correlated performance record. Blocks 3, 4, 5 and 6 are significantly above baseline. Extinction is somewhat slower compared to past animals as evidenced by the significant difference between early extinction and habituation. Block 7, late extinction did fall to a point where it was not different from habituation.

BURSTS data showed a rapid acquisition in blocks 2 and 3 but a decline back to insignificant levels in block 4. (Here $p > .004$ but is significant at slightly lower levels. The critical value for .004 is 2.33 and $F = 2.23$). Block 5 shows a sharp increase before early and late extinction in Figure 59. Figure 60, the daily data graph shows rapid acquisition and then decline, followed by more acquisition. Extinction is good with one anomalous peak in early acquisition. The 210% mean relative increase between habituation and acquisition was quite respectable.

Right hemisphere conditioning data. This rat shows considerable consistency between hemispheres perhaps due to the bilaterality of the

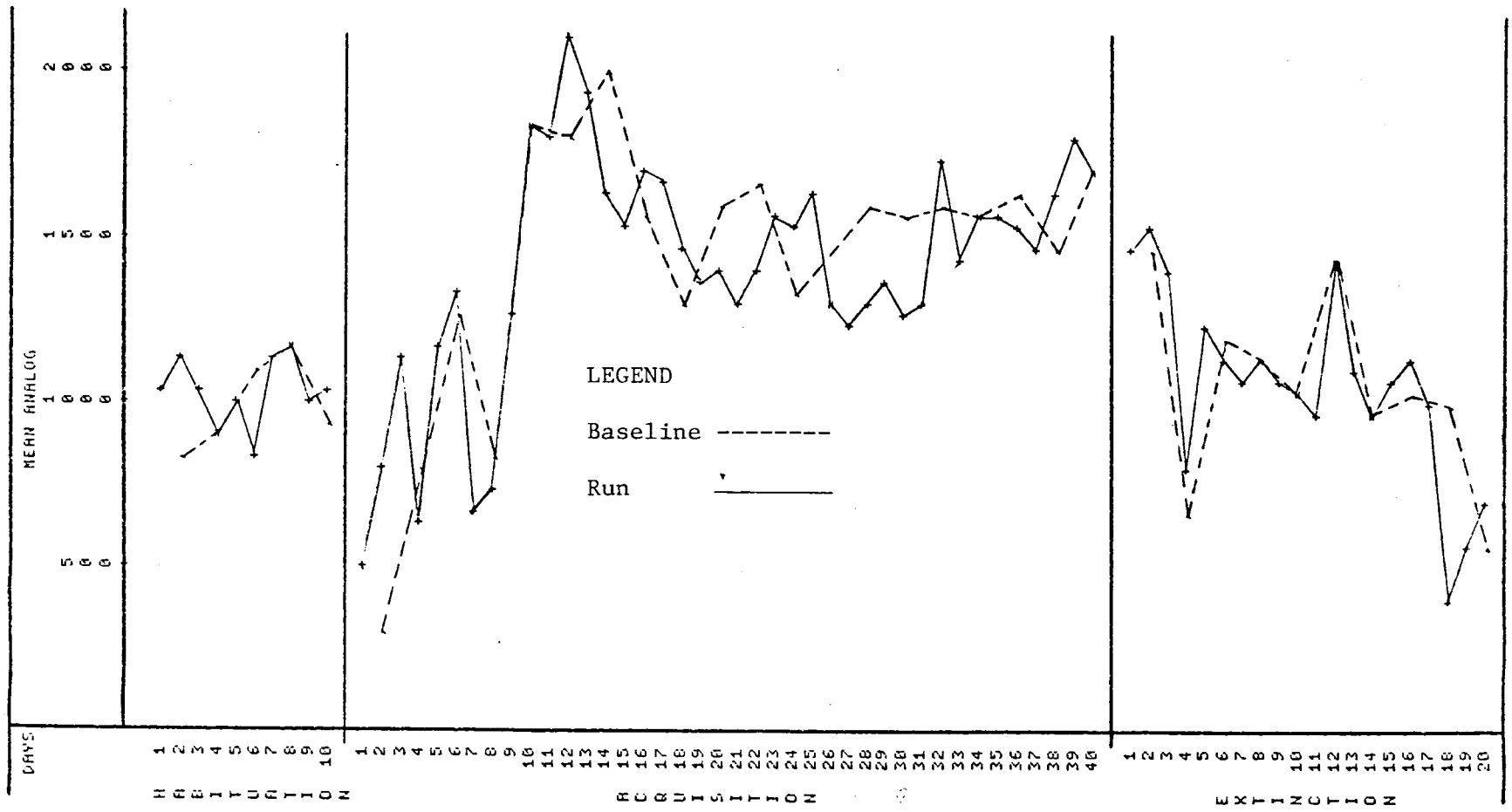
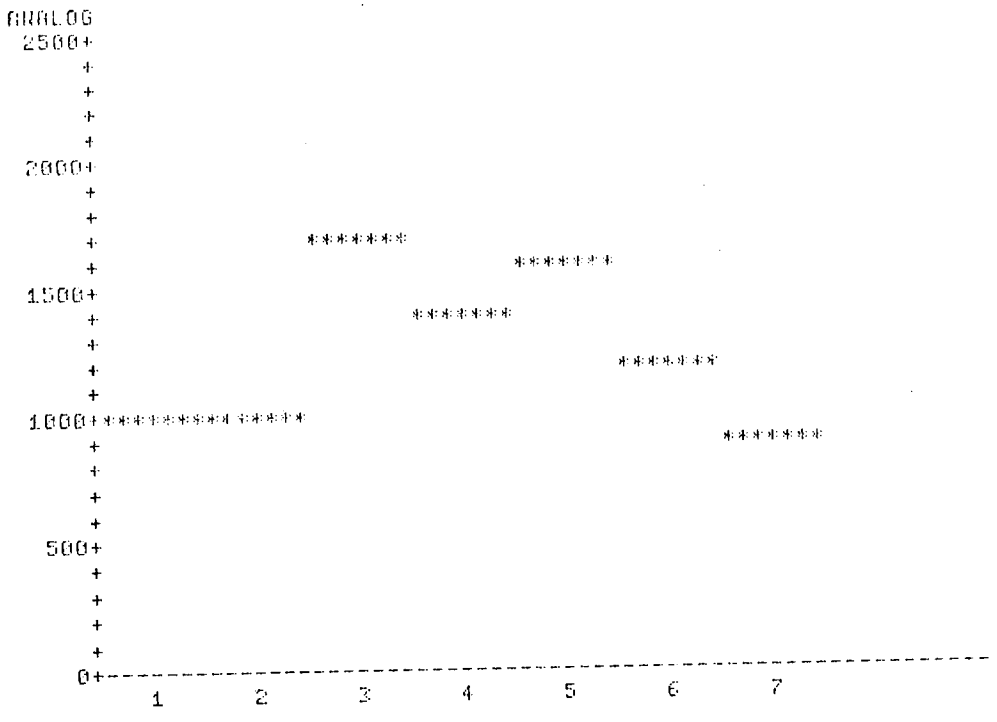


Figure 55. Mean ANALOG over days. Rat 8K - left hemisphere.



BLOCKS X MEAN

TUKEY A - MULTIPLE COMPARISONS TEST

	7	2	1	6	4	5	3
	947.10	1026.10	1044.20	1204.80	1401.70	1587.80	1675.50
7 947.10		79.00	97.10	257.70	454.60	640.70	728.40
2 1026.10			18.10	178.70	375.60	561.70	649.40
1 1044.20				160.60	357.50	543.60	631.30
6 1204.80					196.90	383.00	470.70
4 1401.70						186.10	273.80
5 1587.80							87.70
3 1675.50							

CRITICAL VALUE = 390.04 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 56. Blocks X mean ANALOG. Rat 8K - left hemisphere.

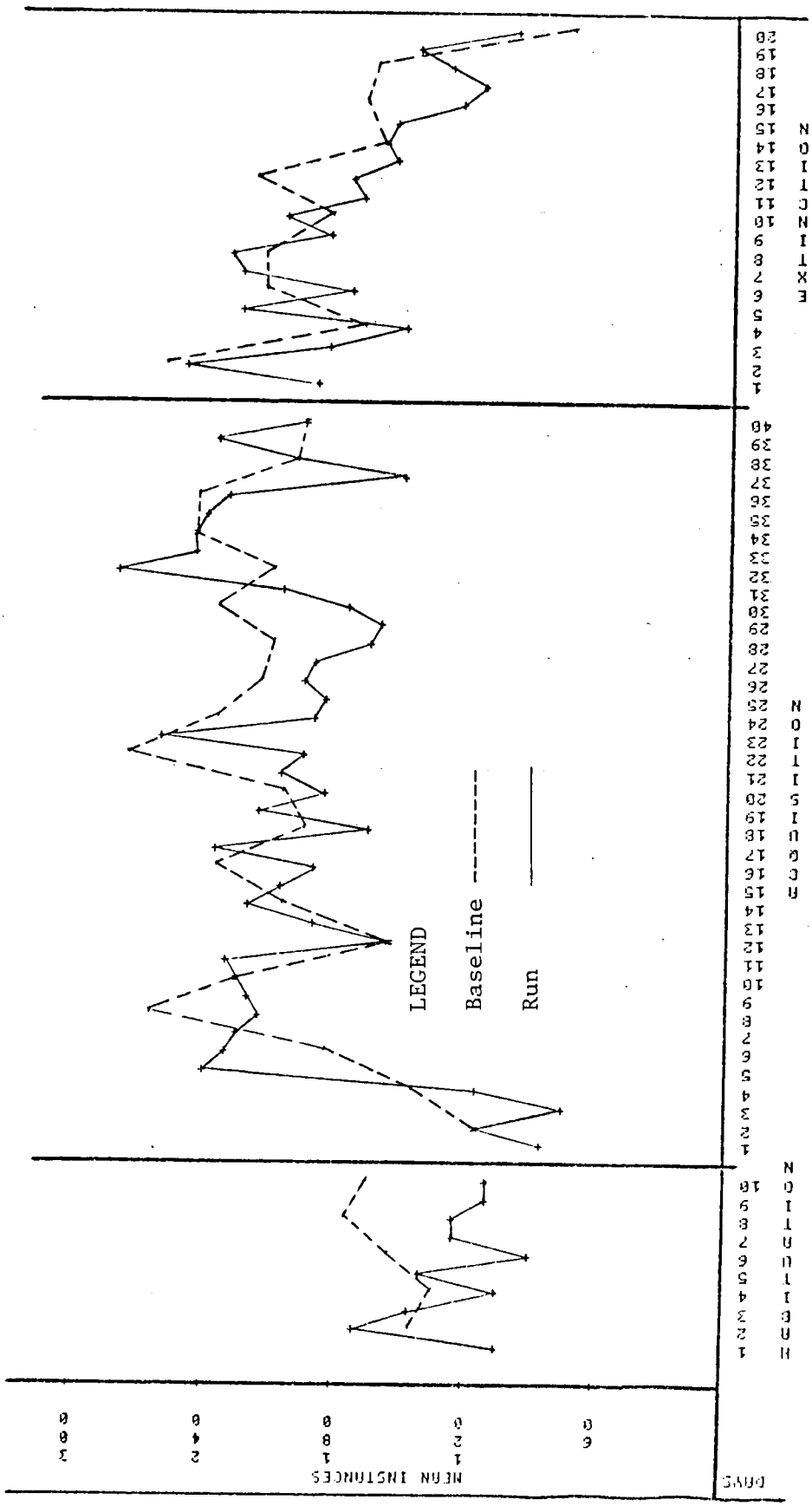
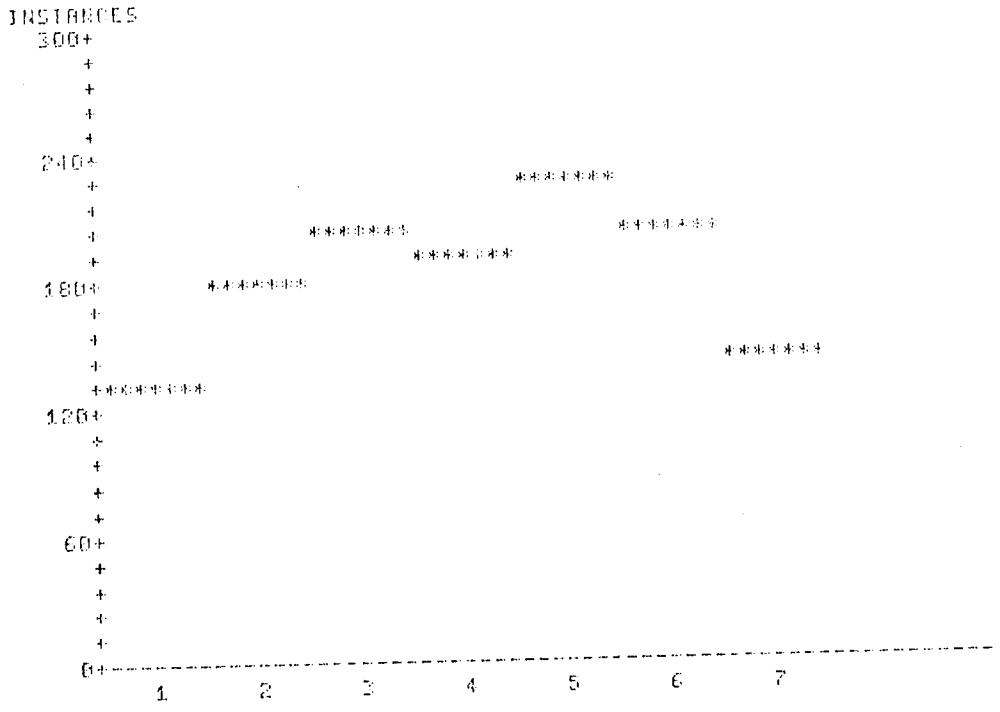


Figure 57. Mean INSTANCES over days. Rat 8K - left hemisphere.



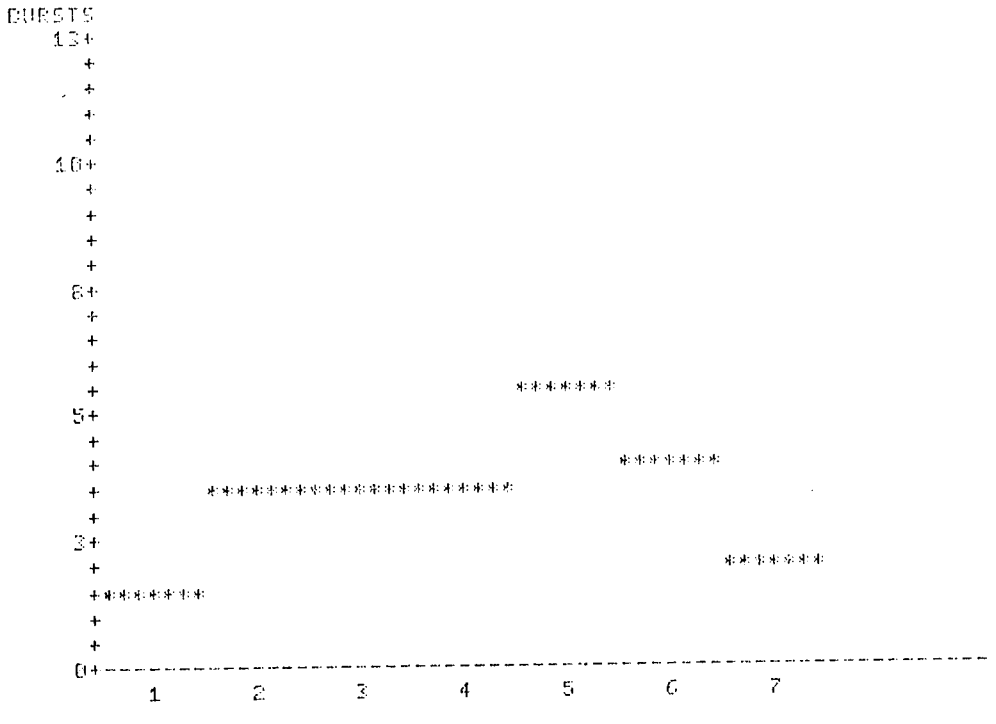
BLOCKS X MEAN

TUKEY A - MULTIPLE COMPARISONS TEST

		1	7	2	4	3	6	5
		126.10	145.80	177.50	194.50	202.30	205.30	225.90
1	126.10		19.70	51.40	68.40	76.20	79.20	99.80
7	145.80			31.70	48.70	56.50	59.50	80.10
2	177.50				17.00	24.80	27.80	48.40
4	194.50					7.80	10.80	31.40
3	202.30						3.00	23.60
6	205.30							20.60
5	225.90							

CRITICAL VALUE = 62.29 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 58. Blocks X mean INSTANCES. Rat 8K - left hemisphere.



BLOCKS X MEAN

TUKEY A - MULTIPLE COMPARISONS TEST

		1	7	4	2	3	6	5
		1.31	2.02	3.54	3.71	3.75	4.02	5.26
1	1.31		0.71	2.23	2.40	2.44	2.71	3.95
7	2.02			1.52	1.69	1.73	2.00	3.24
4	3.54				0.17	0.21	0.48	1.72
2	3.71					0.04	0.31	1.55
3	3.75						0.27	1.51
6	4.02							1.24
5	5.26							

CRITICAL VALUE = 2.33 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 59. Blocks X mean BURSTS. Rat 8K - left hemisphere.

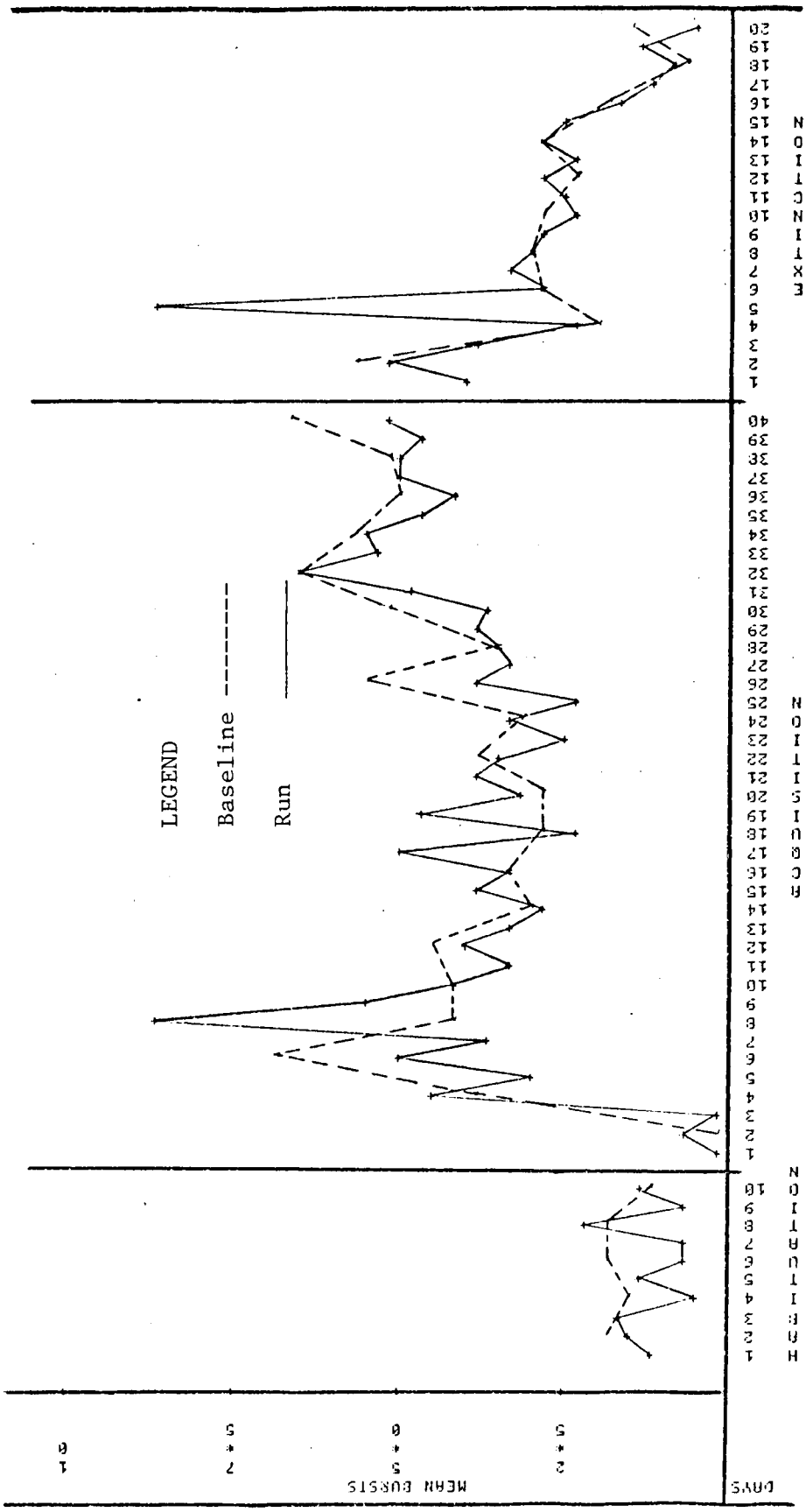


Figure 60. Mean BURSTS over days. Rat 8K - left hemisphere.

electrode implants. Forty hz activity between days is almost identical between hemispheres.

The daily graph shown in Figure 61 and the means block graph shown in Figure 62 demonstrates good conditioning effects. There is an adequate habituation period for ANALOG data in block 1. There are significant differences between habituation and acquisition (blocks 1 and 2), but there are no differences between early acquisition and early extinction. Blocks 3, 4, 5 and 6 are significantly above habituation and extinction. Here acquisition is rapid. The depression effect following the rapid acquisition is here also in block 4 but it is not enough to make a significant difference from the other acquisition blocks. There is a mean relative increase of 268% between habituation and acquisition. The intercorrelation between ANALOG and BURSTS are positive and significant ($r = .935$) as is the correlation between ANALOG and INSTANCES ($r = .899$).

INSTANCES data is closer to the ideal. The daily instances graph in Figure 63 indicates that the animal may not have been fully habituated at the onset of acquisition. The conditioning effect does not appear to be a strong one for INSTANCES as the mean relative increase between habituation and acquisition is only 48%. Figure 64, the block means graph is difficult to interpret only because there was a slight mean decrease at the end of acquisition and a small recovery at the beginning of extinction.

There are no significant differences between habituation and late extinction. There are significant differences between blocks 3, 4, 5

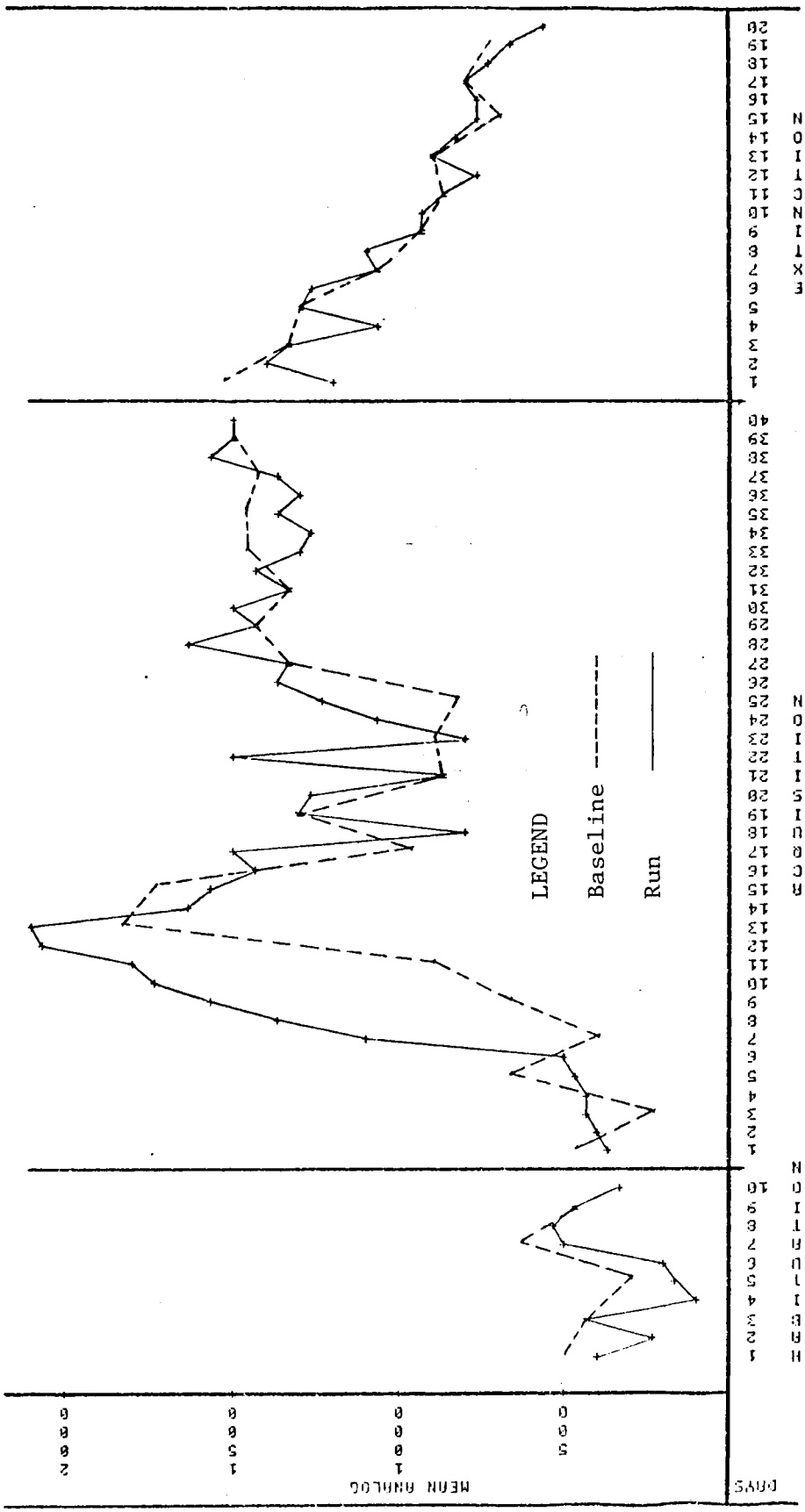
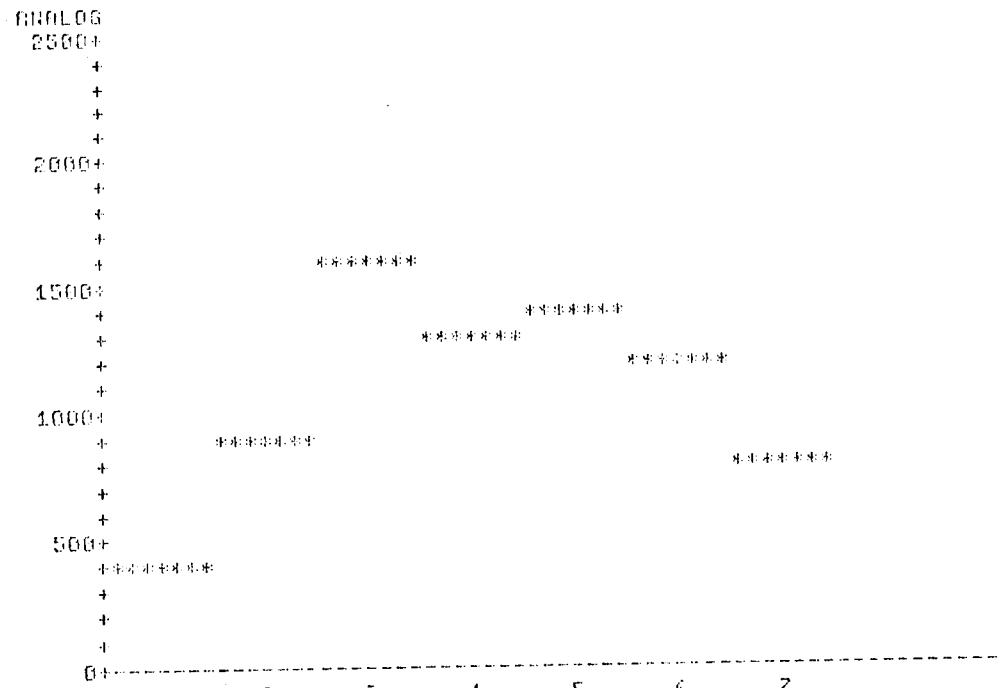


Figure 61. Mean ANALOG over days. Rat 8K - right hemisphere.



BLOCKS X MEAN

TUKEY A - MULTIPLE COMPARISONS TEST

		1	7	2	6	4	5	3
		354.80	790.30	852.80	1176.00	1291.70	1411.40	1564.80
1	354.80		435.50	498.00	821.20	936.90	1056.60	1210.00
7	790.30			62.50	385.70	501.40	621.10	774.50
2	852.80				323.20	438.90	558.60	712.00
6	1176.00					115.70	235.40	388.80
4	1291.70						119.70	273.10
5	1411.40							153.40
3	1564.80							

CRITICAL VALUE = 493.26 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 62. Blocks X mean ANALOG. Rat 8K - right hemisphere.

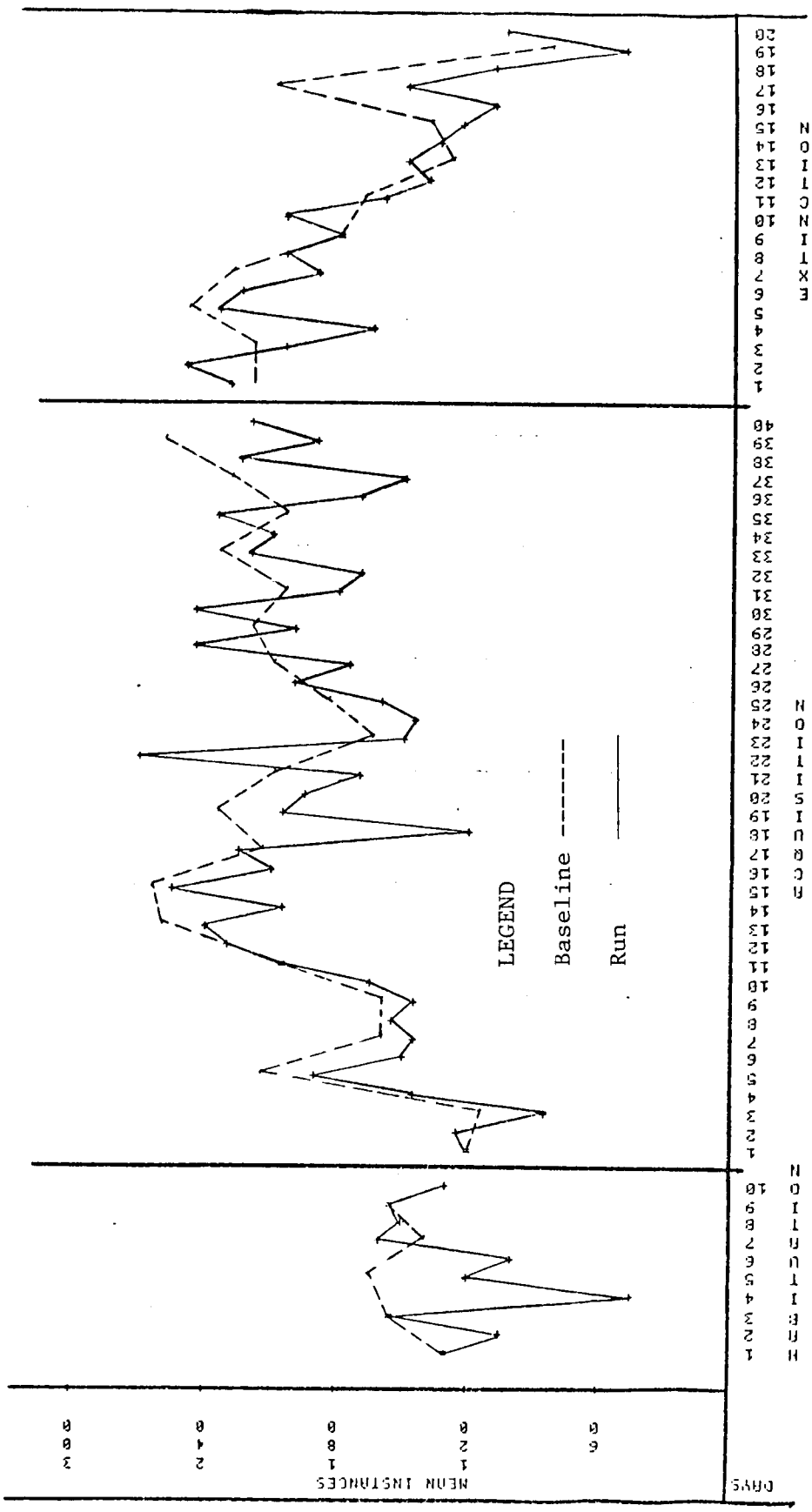
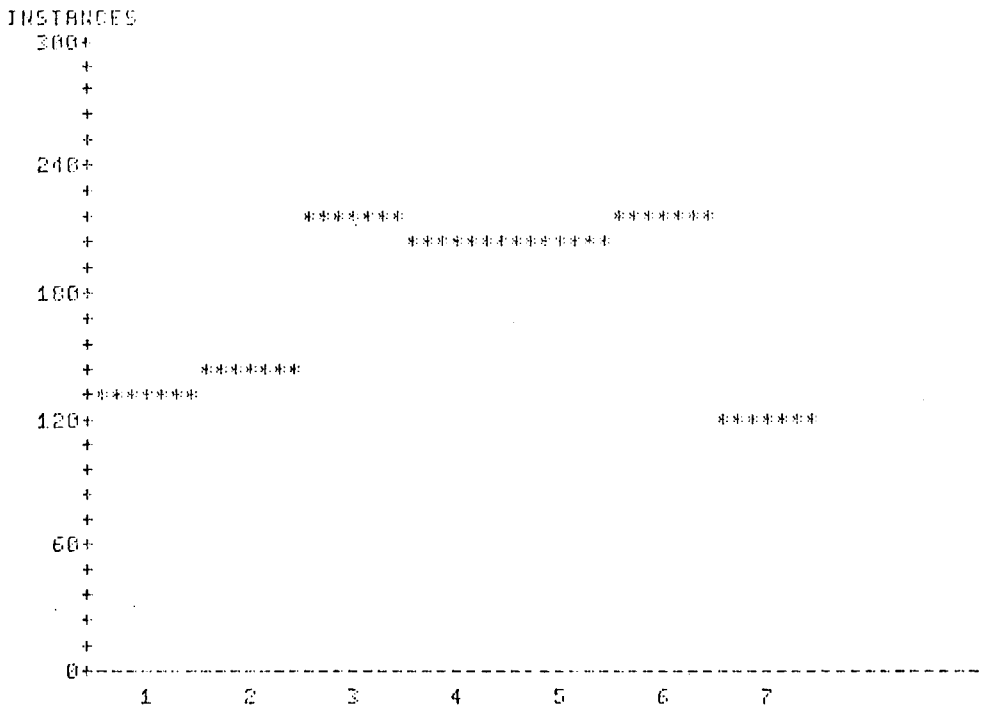


Figure 63. Mean INSTANCES over days. Rat 8K - right hemisphere.



BLOCKS X MEAN

TUKEY A - MULTIPLE COMPARISONS TEST

		7	1	2	4	5	6	3
		125.90	127.60	144.90	198.40	199.60	212.10	212.10
7	125.90		1.70	19.00	72.50	73.70	86.20	86.20
1	127.60			17.30	70.80	72.00	84.50	84.50
2	144.90				53.50	54.70	67.20	67.20
4	198.40					1.20	13.70	13.70
5	199.60						12.50	12.50
6	212.10							
3	212.10							

CRITICAL VALUE = 55.12 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 64. Blocks X mean INSTANCES. Rat 8K - right hemisphere.

and 6 and the habituation and extinction blocks. Blocks 4 and 5 are not significantly above block 2 at the .004 probability level (the calculated probability level for the individual Tukey A comparisons) but are different at the .01 probability level. Late extinction is significantly below early extinction.

Animal 8K showed very good conditioning. The relative increase from habituation to extinction is 167%. Daily BURST performance is graphed in Figure 65 and block means are displayed in Figure 66. There are no significant differences between habituation, early acquisition and late extinction. There are no significant differences between blocks 3, 4, 5 and 6. All of the former groups are significantly different from habituation and extinction. This is a good indication of learning.

Electrodes were planted bilaterally in the amygdaloid nucleus of Rat 8K. Both hemispheres showed acquisition and extinction in a fashion that suggested that the state associated with 40 hz activity is highly discriminable.

Behavioral data—Rat 8K. There were no notable changes in open field ambulation across conditions. Current thresholds for vocalization also failed to show any response to 40 hz density changes. There was a slight positive change in vocalization on handling which diminished again after extinction. The animals showed a slightly more aggressive posture towards a pencil when presented to its snout. This also disappeared after extinction. These behaviors are graphed in Figure 67.

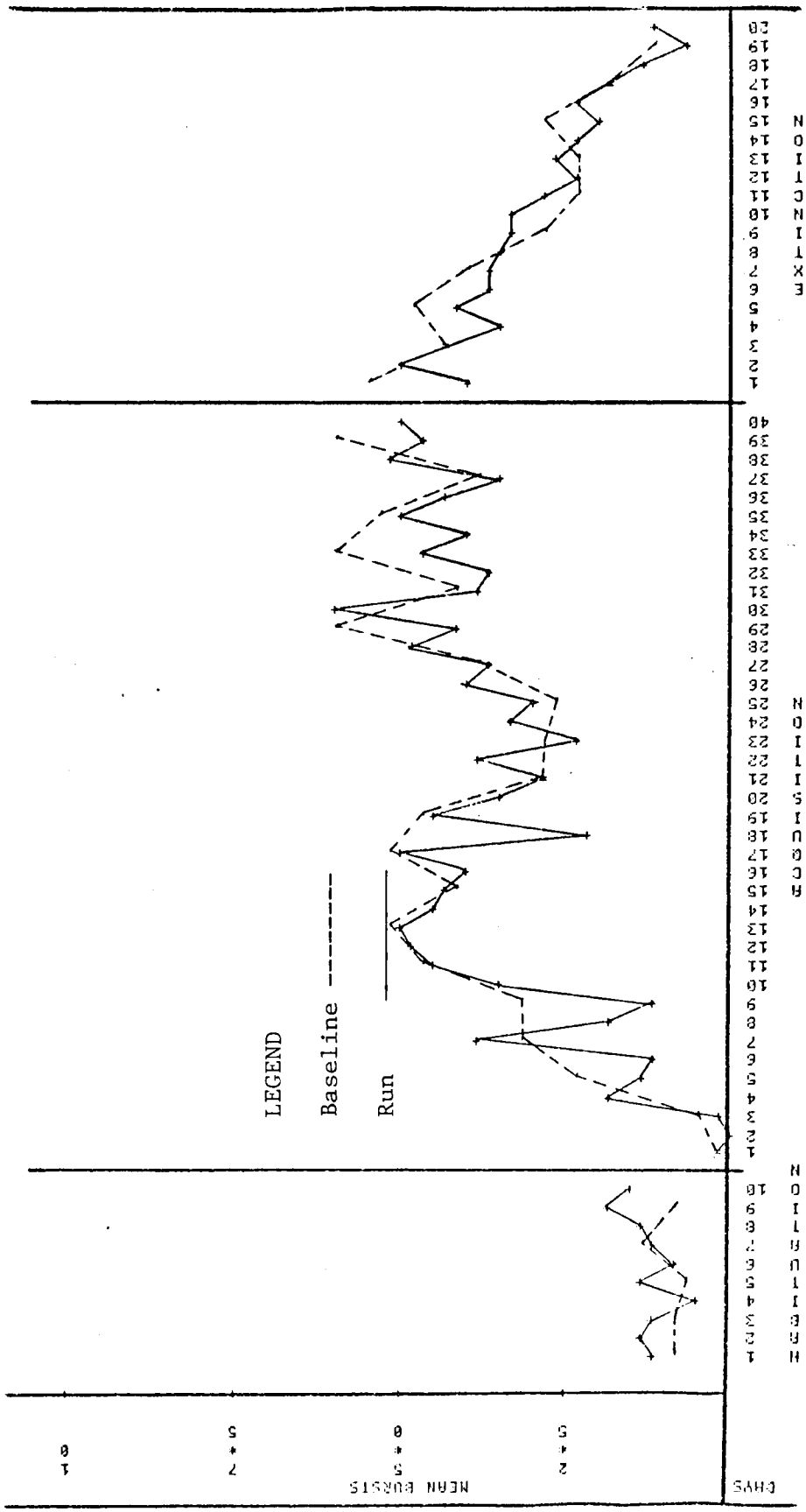
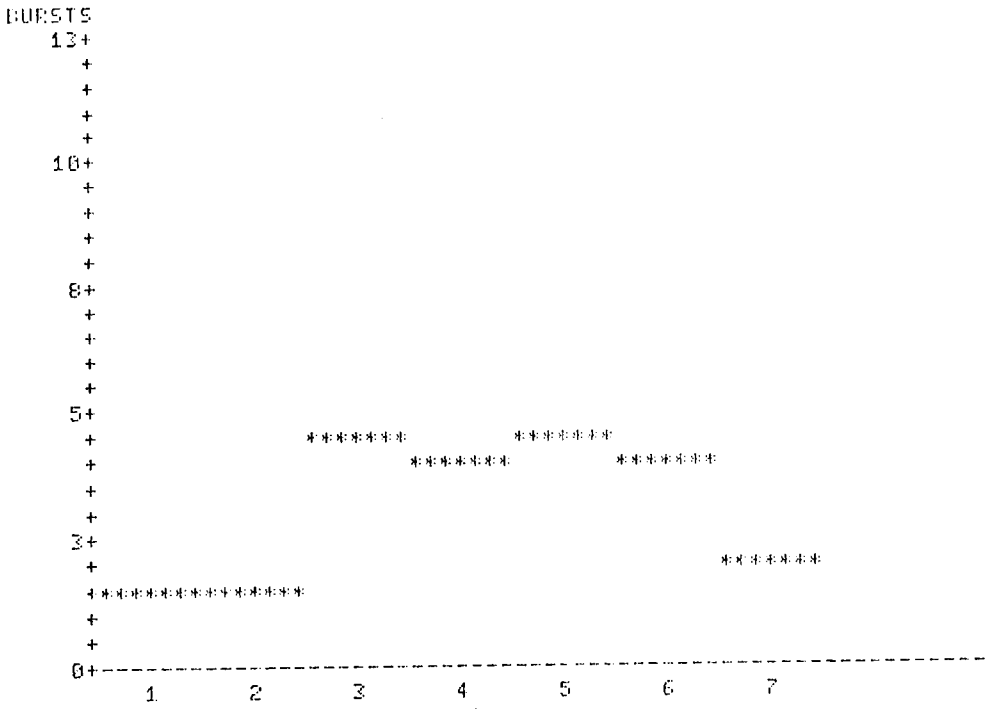


Figure 65. Mean BURSTS over days. Rat 8K - right hemisphere.



BLOCKS X MEAN

TUKEY A - MULTIPLE COMPARISONS TEST

		1	2	7	4	6	3	5
		1.36	1.65	2.07	4.00	4.03	4.37	4.55
1	1.36		0.29	0.71	2.64	2.67	3.01	3.19
2	1.65			0.42	2.35	2.38	2.72	2.90
7	2.07				1.92	1.96	2.30	2.48
4	4.00					0.03	0.37	0.55
6	4.03						0.34	0.52
3	4.37							0.18
5	4.55							

CRITICAL VALUE = 1.43 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 66. Blocks X mean BURSTS. Rat 8K - right hemisphere.

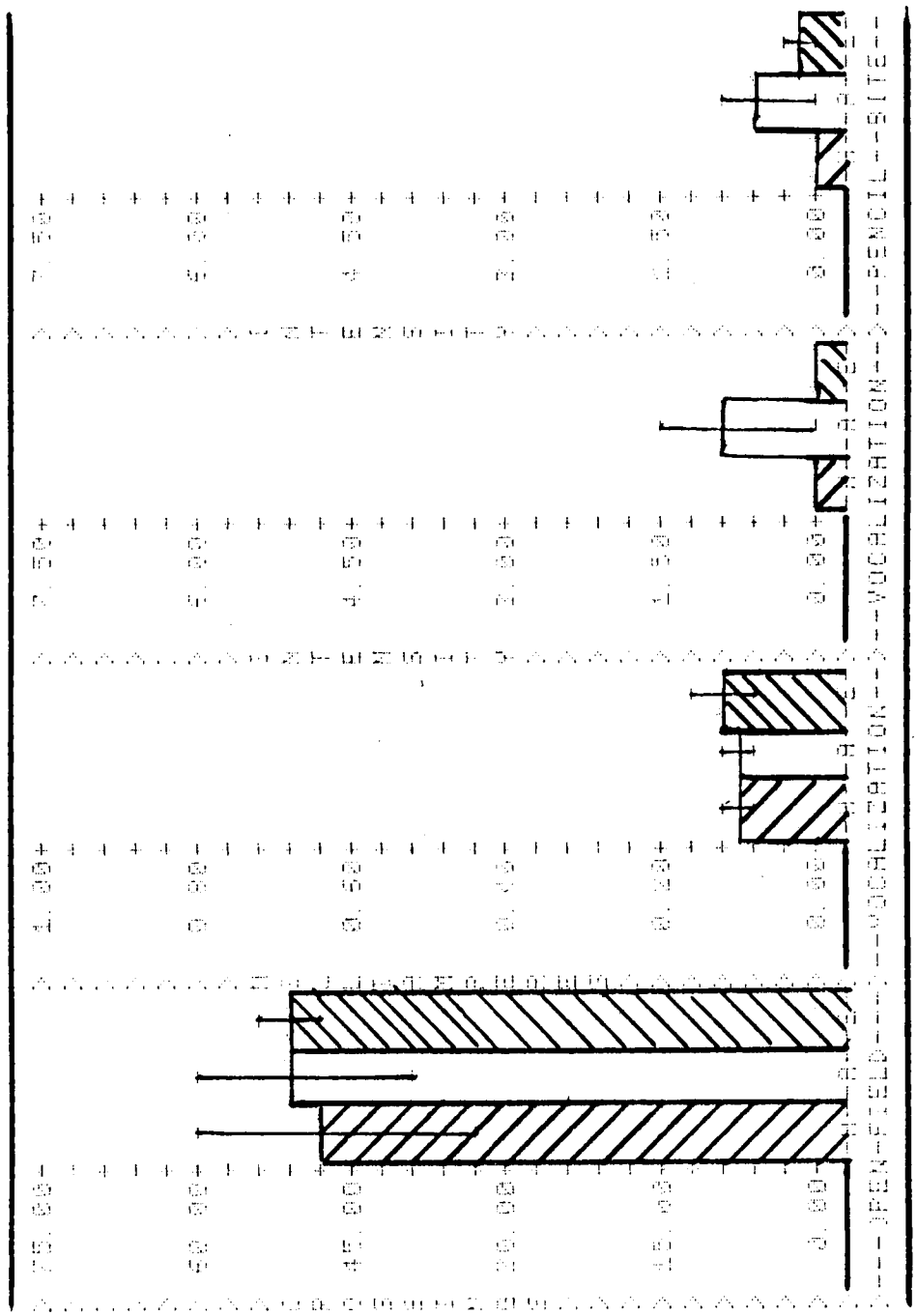


Figure 67. Post contingency means and standard deviations for behavioral tests for rat 8K.

Data for Rat 10K

Histological evaluation. The recording electrode in the left hemisphere was found lodged in the medial nucleus at coordinates A 4.8, ML - 3.3 and DV - 2.5. The largest AP error in the entire population of animals was seen in this animal. The right hemisphere electrode coordinates were A 7.0, ML + 3.3 and DV - 2.2. This location is the anterior amygdaloid area. These placements are illustrated in Figures 68a and 68b.

Left hemisphere recording data. The pattern seen in the conditioning of the left hemisphere is similar to the previous medial nucleus sites. The daily ANALOG graph shown in Figure 69 shows a rapid and variable acquisition. The peaks and troughs are not as pronounced in this animal as were seen in previous animals. The mean blocks graph shown in Figure 70, shows good habituation and extinction as there are no statistical differences between the two. Mid- and late acquisition are significantly above baseline and extinction. Extinction occurred rapidly as early extinction is not significantly different from late extinction. The intercorrelation between ANALOG and BURSTS ($r = .9731$) and ANALOG and INSTANCES are both positive and significant ($r = .9674$). The relative percent increase between habituation and extinction was +45.94%.

INSTANCES data is similar showing good acquisition in the daily performance graphs shown in Figure 71. The mean blocks graph shown in Figure 72 shows no acquisition in the first block but this is not the case. The acquisition started from a level below baseline. The step

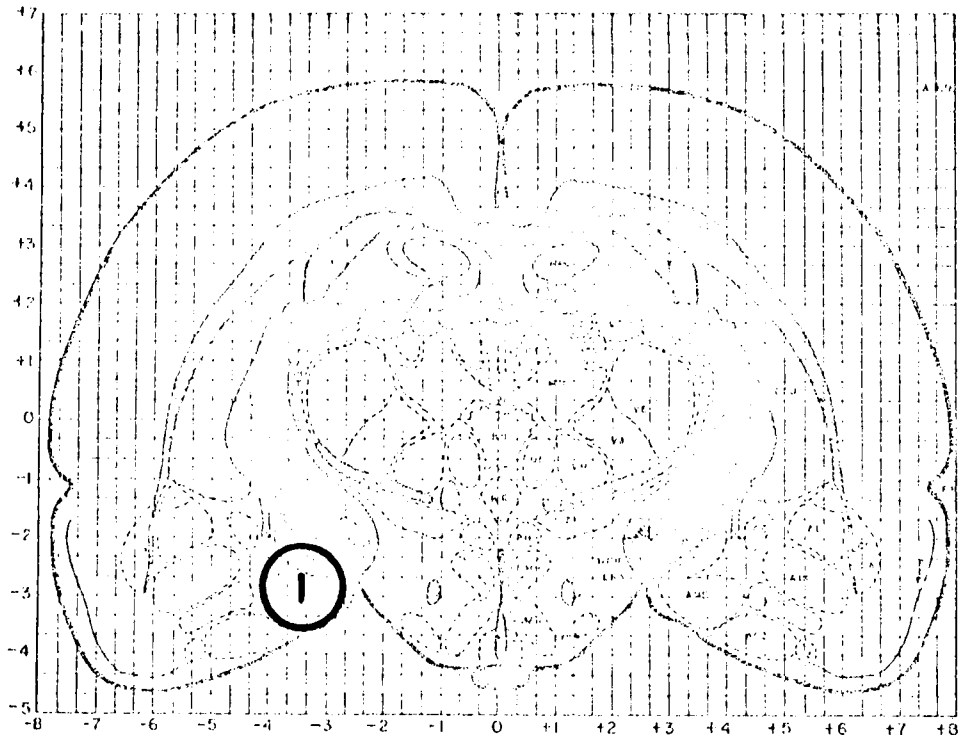


Figure 68a. Site of left Hemisphere Implant.

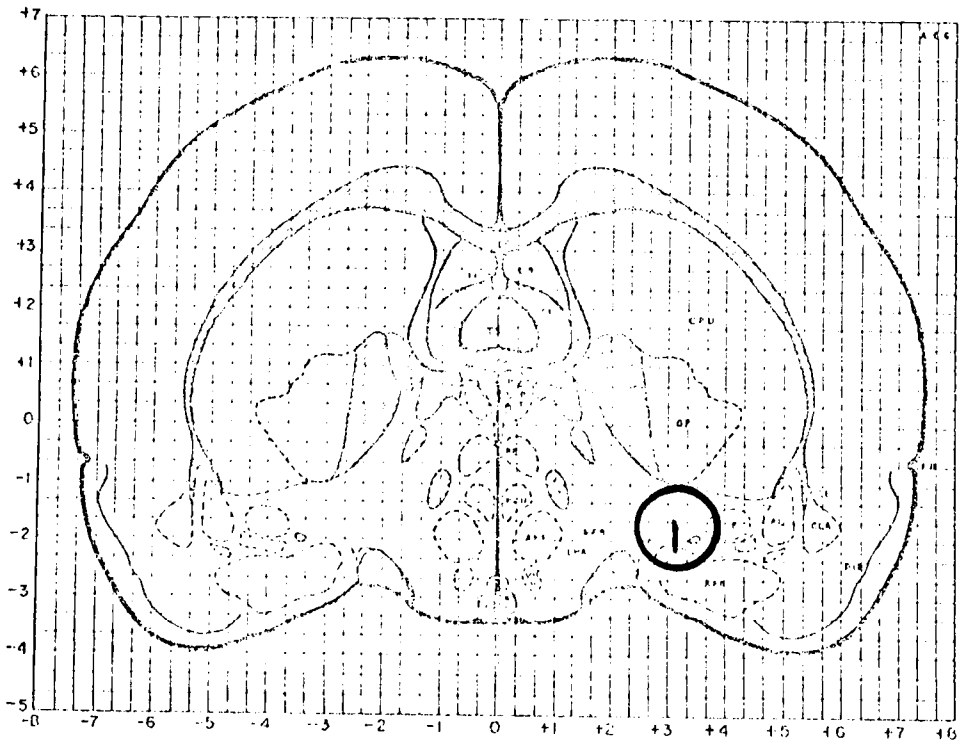


Figure 68b. Site of right hemisphere implant.

Figure 68. Illustration of implantation sites for rat 10K.

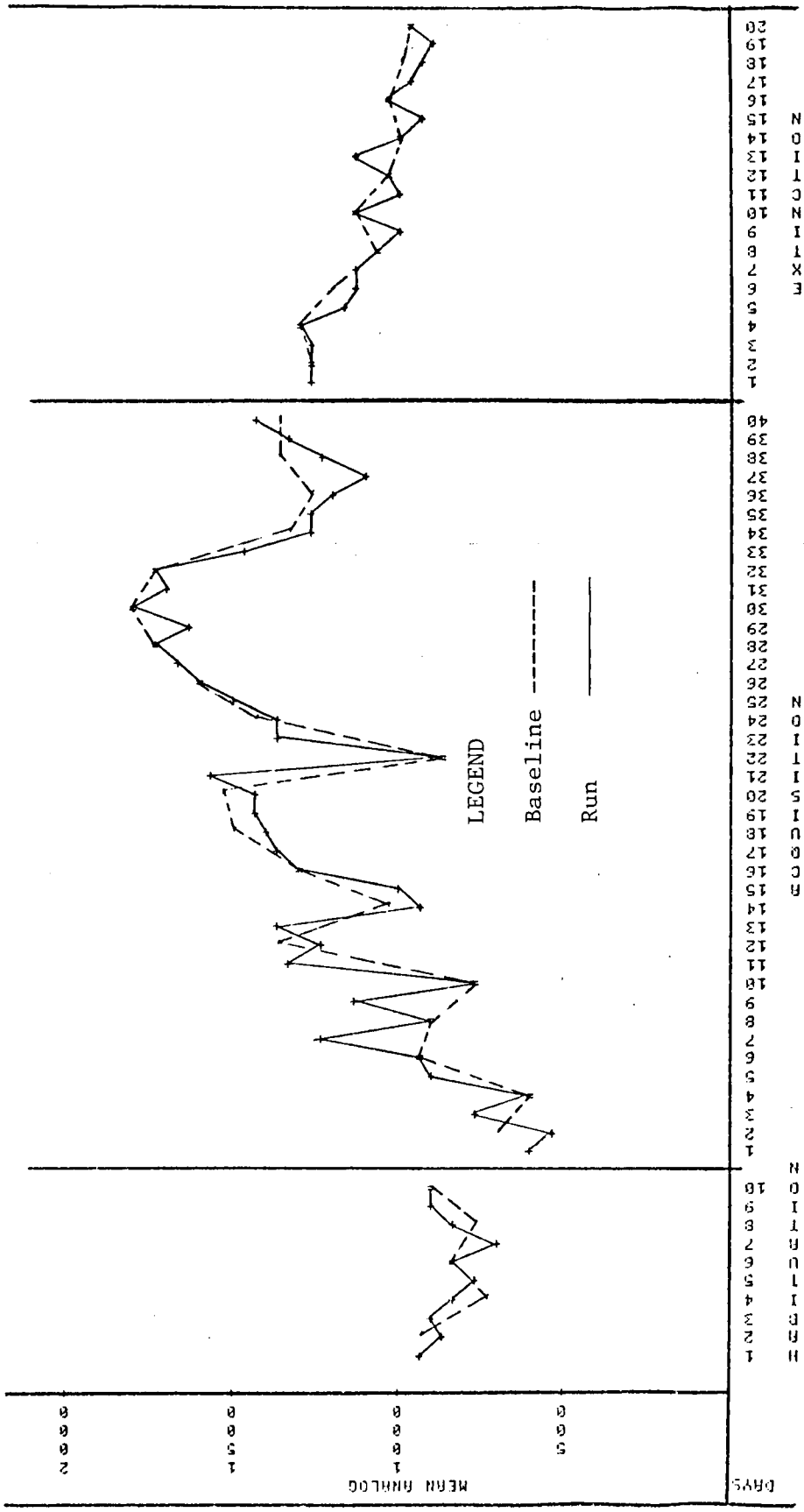
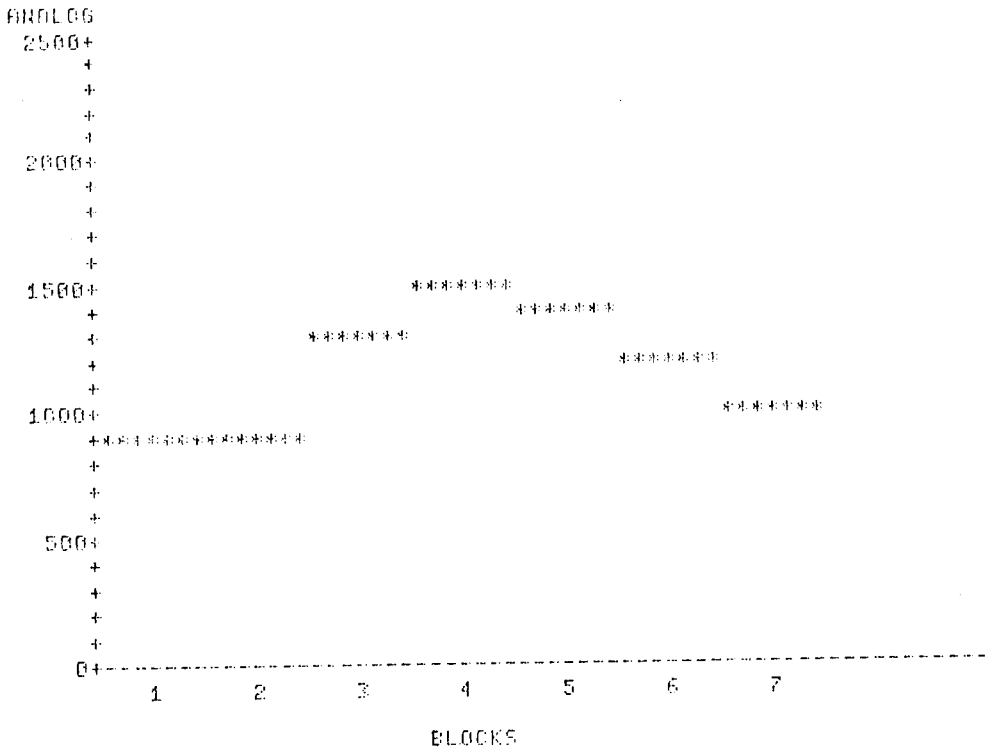


Figure 69. Mean ANALOG over days. Rat 10K - left hemisphere.



BLOCKS X MEAN

TUKEY B - MULTIPLE COMPARISONS TEST

	2	1	7	6	3	5	4
	859.60	868.60	1003.20	1188.50	1300.80	1387.00	1523.30
2 859.60		9.00	143.60	328.90	441.20	527.40	663.70
1 868.60			134.60	319.90	432.20	518.40	654.70
7 1003.20				185.30	297.60	383.80	520.10
6 1188.50					112.30	198.50	334.80
3 1300.80						86.20	222.50
5 1387.00							136.30
4 1523.30							

CRITICAL VALUE = 290.34 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 70. Blocks X mean ANALOG. Rat 10K - left hemisphere.

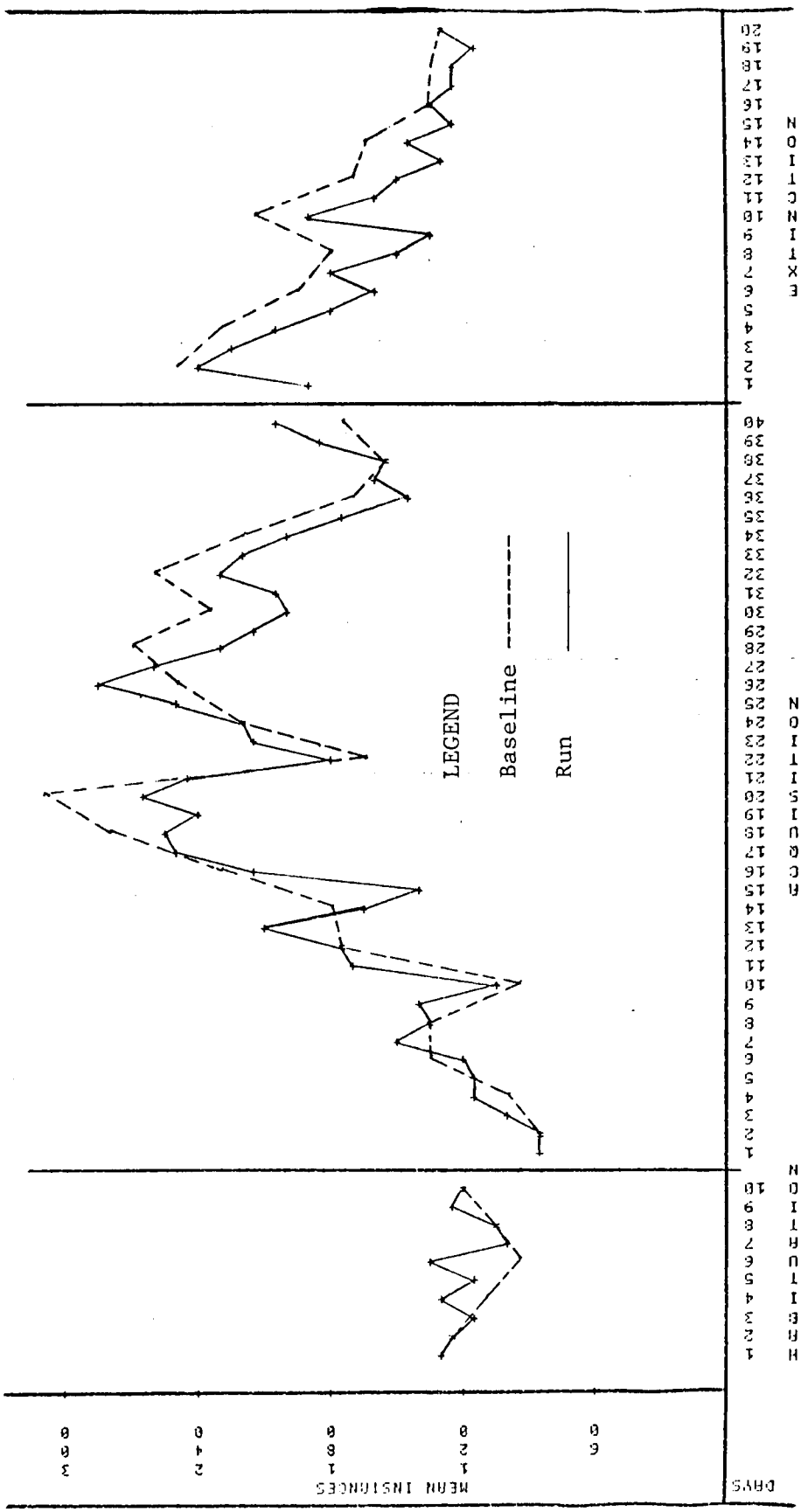
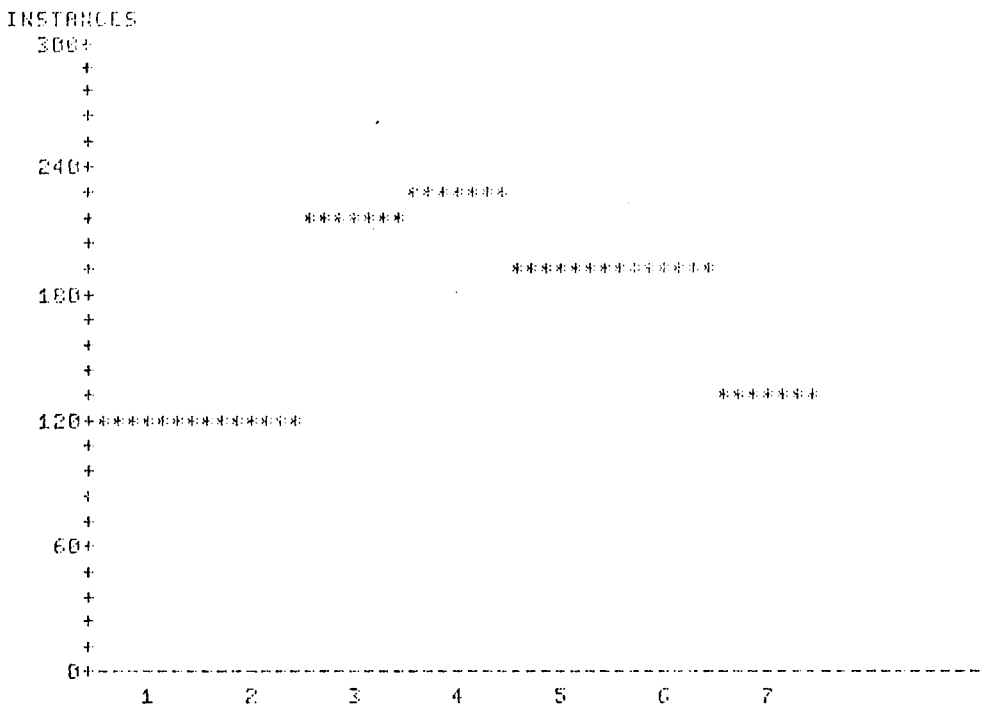


Figure 71. Mean INSTANCES over days. Rat 10K - left hemisphere.



BLOCKS X MEAN

TUKEY A - MULTIPLE COMPARISONS TEST

		2	1	7	6	5	3	4
		118.00	122.40	137.20	188.10	191.60	211.70	233.70
2	118.00		4.40	19.20	70.10	73.60	93.70	115.70
1	122.40			14.80	65.70	69.20	89.30	111.30
7	137.20				50.90	54.40	74.50	96.50
6	188.10					3.50	23.60	45.60
5	191.60						20.10	42.10
3	211.70							22.00
4	233.70							

CRITICAL VALUE = 48.89 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 72. Blocks X mean INSTANCES. Rat 10K - left hemisphere.

function increase between blocks 2 and three in Figure 72 is spurious and not real. The extinction is a regular one with a decreasing distance between baseline and run scores as extinction progresses.

The profile of the daily BURSTS data depicted in Figure 73 is unremarkable other than an incomplete extinction. These relationships can best be seen in Figure 74, the mean blocks graph. Extinction is greater than habituation. There is a clear increase from baseline to acquisition. Once again equipment difficulty in the form of cable fatigue caused the depression or leveling off seen in the late acquisition blocks.

Right hemisphere conditioning. The recording for the right hemisphere is from the anterior amygdaloid area and is unique in the population. The picture revealed by Figure 75 the daily performance graph and by Figure 76, the mean blocks graph for ANALOG data is a subdued one.

The habituation was adequate. Acquisition was slow and almost absent in the first block. After acquisition extinction was slow in droping off. The depressions seen during the equipment problem are not as pronounced. These are consistent indications that the 40 hz activity is more difficult to discriminate in the anterior amygdaloid area than in other areas.

INSTANCES data shown in Figure 77 and 78 parallel the ANALOG data. Baseline and extinction are different from all other blocks except early acquisition. Blocks 3, 4 and 5 are significantly above baseline and extinction. Early extinction is not different from early acquisition.

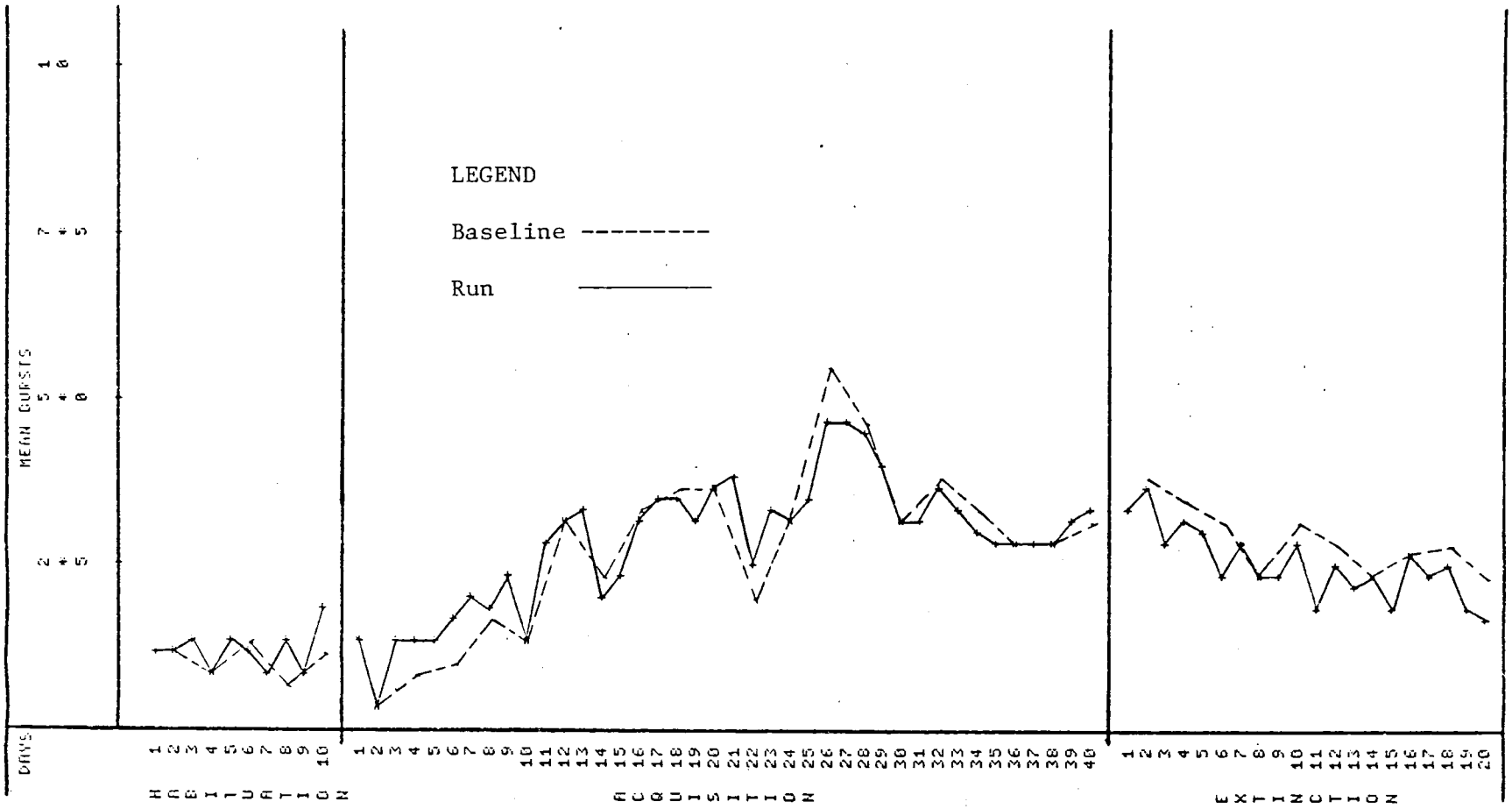
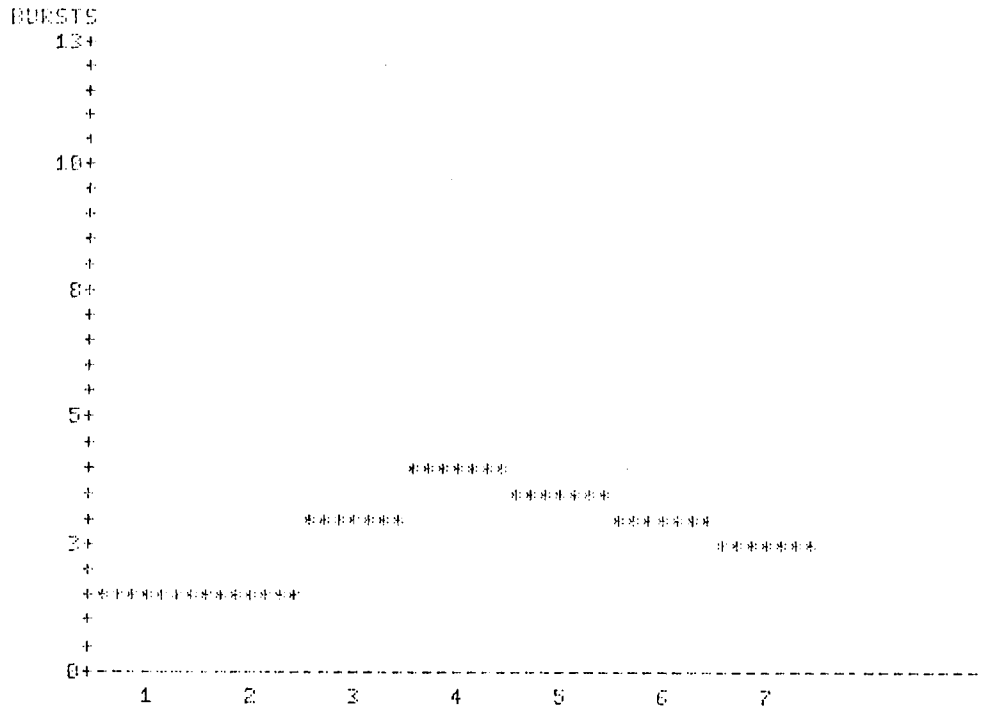


Figure 73. Mean BURSTS over days. Rat 10K - left hemisphere.



BLOCKS X MEAN

TUKEY A - MULTIPLE COMPARISONS TEST

		1	2	7	6	3	5	4
		1.34	1.64	2.34	3.08	3.25	3.28	3.90
1	1.34		0.30	1.00	1.74	1.91	1.94	2.56
2	1.64			0.70	1.44	1.61	1.64	2.26
7	2.34				0.74	0.91	0.94	1.56
6	3.08					0.17	0.20	0.82
3	3.25						0.03	0.65
5	3.28							0.62
4	3.90							

CRITICAL VALUE = 0.81 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 74. Blocks X mean BURSTS. Rat 10K - left hemisphere.

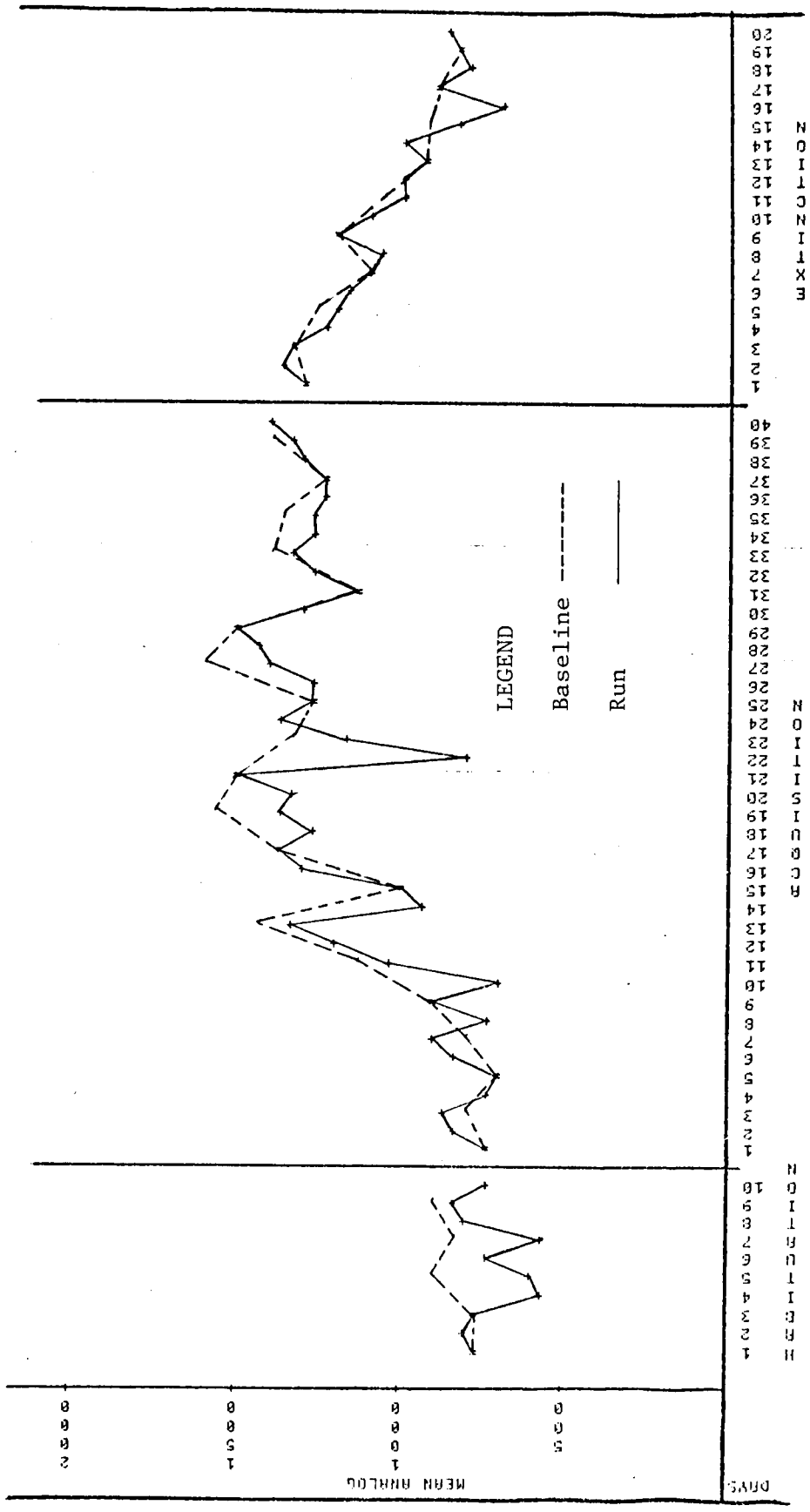
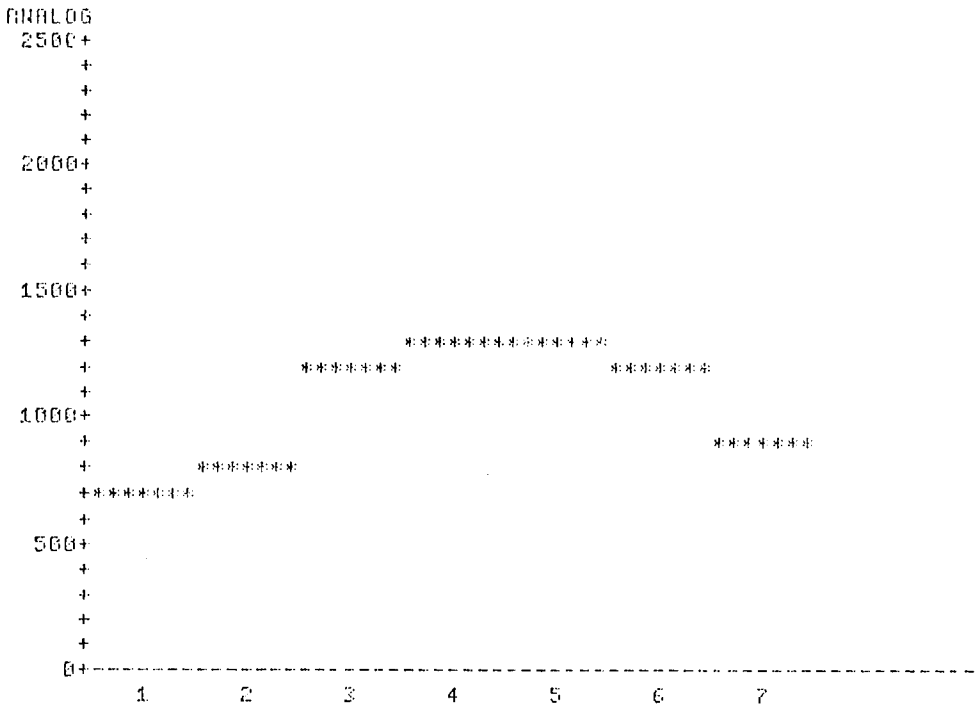


Figure 75. Mean ANALOG over days. Rat 10K - right hemisphere.



BLOCKS X MEAN

TUKEY A - MULTIPLE COMPARISONS TEST

		1	2	7	6	3	5	4
		732.00	810.10	907.50	1221.30	1231.10	1293.50	1316.40
1	732.00		78.10	175.50	489.30	499.10	561.50	584.40
2	810.10			97.40	411.20	421.00	483.40	506.30
7	907.50				313.80	323.60	386.00	408.90
6	1221.30					9.80	72.20	95.10
3	1231.10						62.40	85.30
5	1293.50							22.90
4	1316.40							

CRITICAL VALUE = 208.60 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 76. Blocks X mean ANALOG. Rat 10K - right hemisphere.

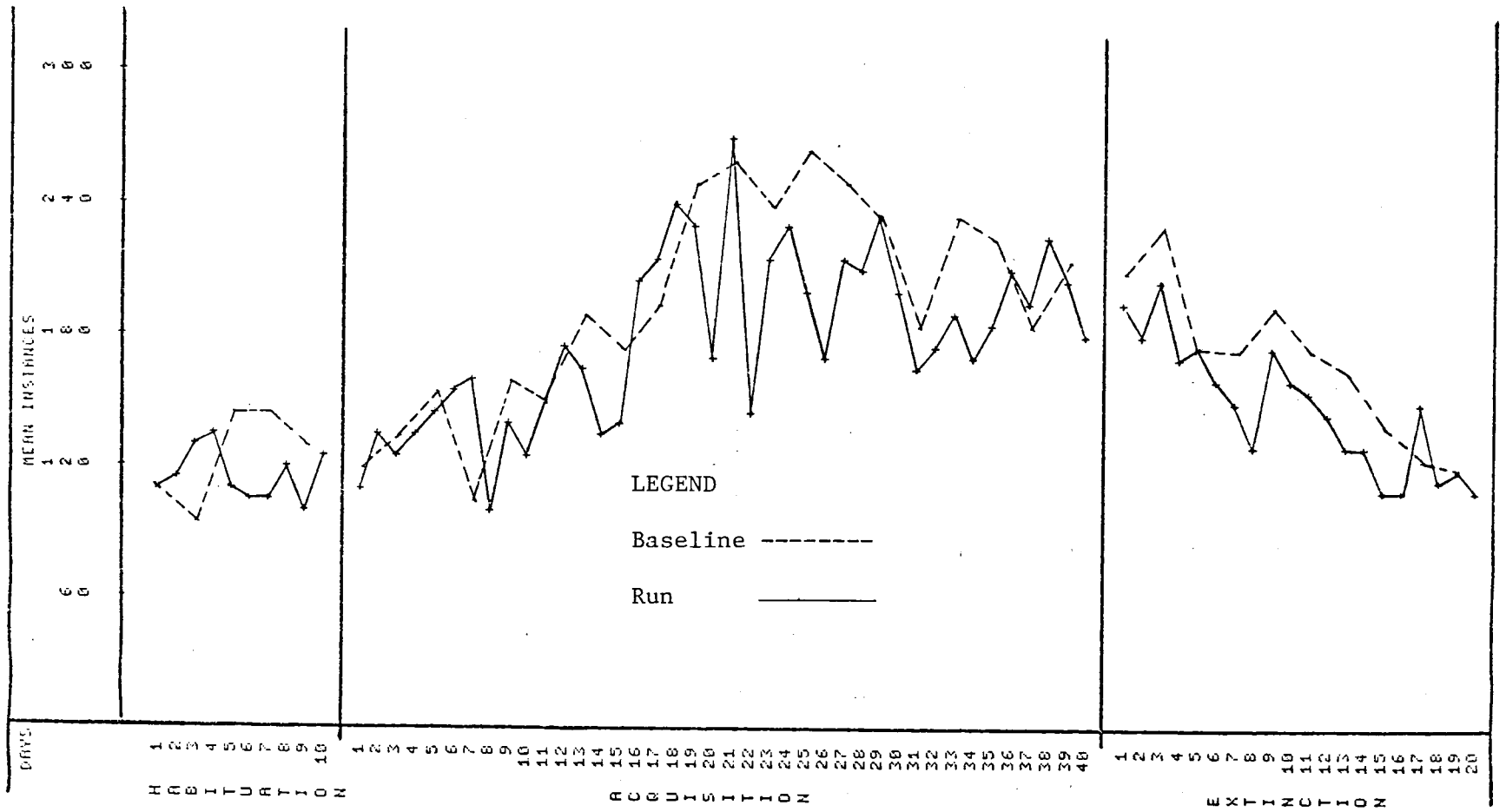
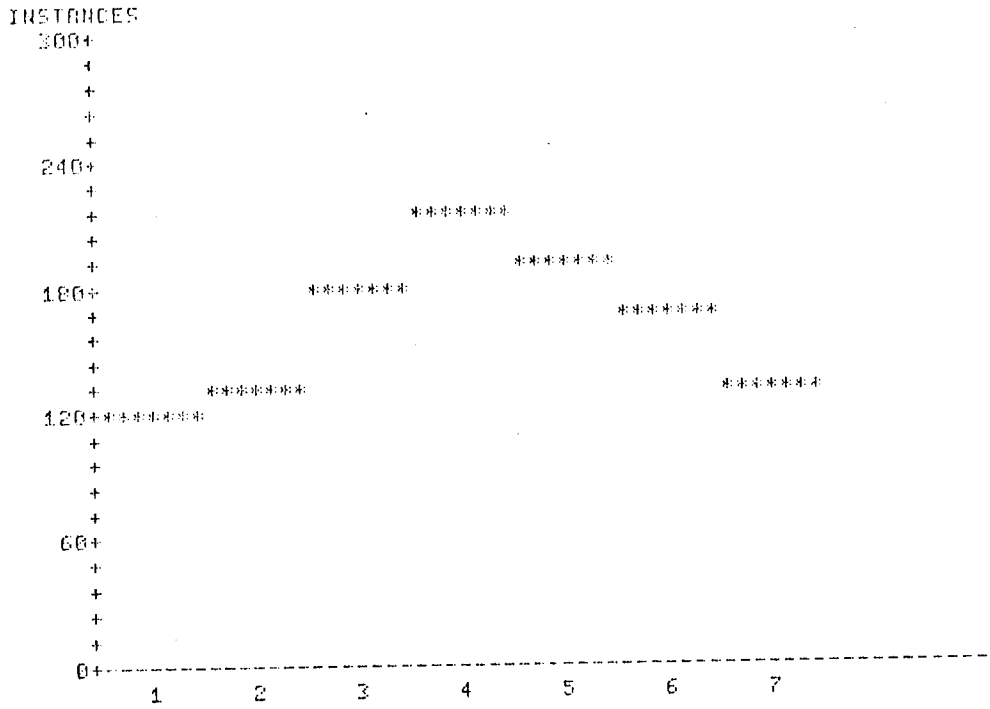


Figure 77. Mean INSTANCES over days. Rat 10K - right hemisphere.



BLOCKS X MEAN

TUKEY A - MULTIPLE COMPARISONS TEST

		1	7	2	6	3	5	4
		119.30	130.40	135.00	172.90	185.30	193.20	212.30
1	119.30		11.10	15.70	53.60	66.00	73.90	93.00
7	130.40			4.60	42.50	54.90	62.80	81.90
2	135.00				37.90	50.30	58.20	77.30
6	172.90					12.40	20.30	39.40
3	185.30						7.90	27.00
5	193.20							19.10
4	212.30							

CRITICAL VALUE = 41.48 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 78. Blocks X mean INSTANCES. Rat 10K - right hemisphere.

The BURSTS data is distinctive in its low levels. It would appear that the anterior amygdaloid area has a relatively low level of 40 hz activity in it. The activity is characterized by low variance and slow steady acquisition and extinction. Extinction never returned to baseline but is not significantly different from it. The daily performance data are seen in Figure 79 and the means blocks data are seen in Figure 80.

Behavioral data-- Rat 10K. There were few changes in the behaviors measured in Rat 10K. There may be some increase in open field activity but the standard deviations of habituation and extinction data overlap the acquisition mean so this interpretation should be viewed with caution. There were no changes seen in current threshold for vocalization, or in vocalization on handling. Pencil biting showed the slightest elevation during acquisition but once again there was no consistency seen in this measure while it was being taken. Here the standard deviation is greater than the score.

Rat 10K was implanted in the medial nucleus and in the anterior amygdaloid area. Forty hz conditioning in these areas was successful. Conditioning seen in the medial nucleus was consistent with patterns seen in the same locus in other animals. The operant and conditioned levels obtained from the anterior amygdaloid areas were lower than those seen in other sites. Few or no changes in behavior were seen in Rat 10K. A graph of these behaviors are seen in Figure 81.

A summary of all implants is included in Table 1 and a summary of all behavioral tests is included in Table 2.

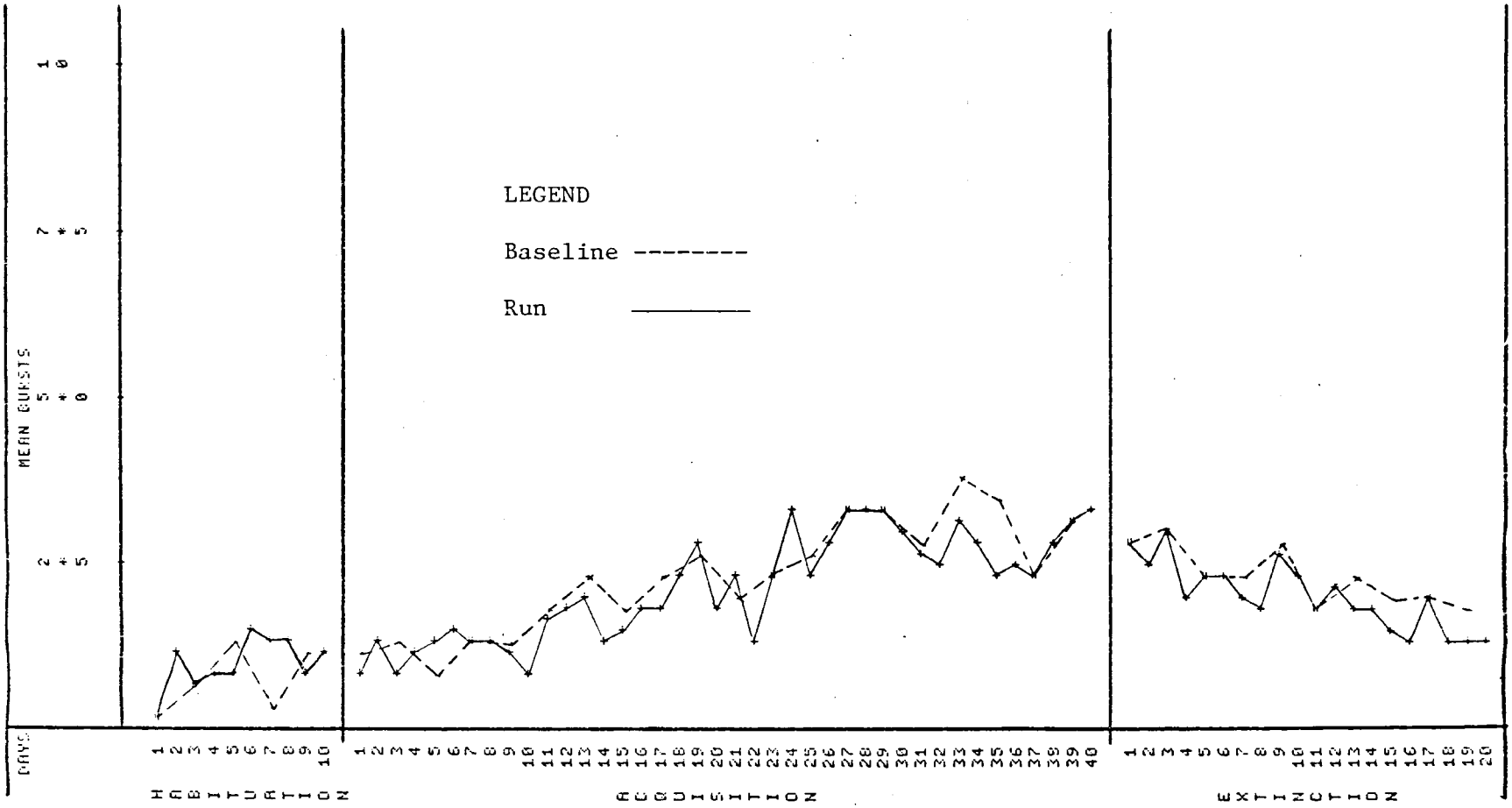
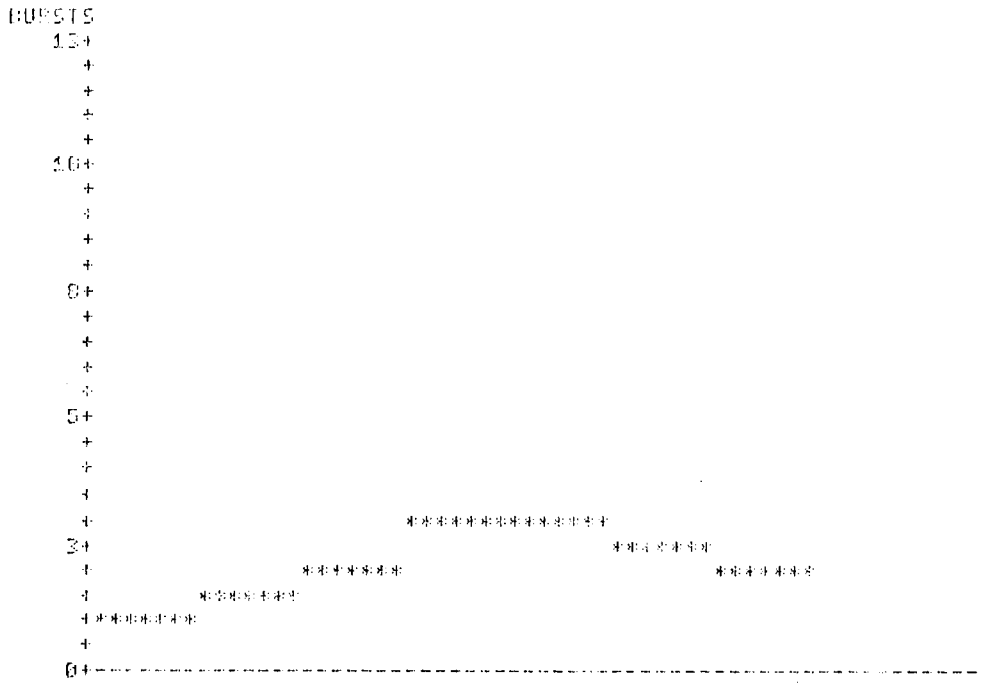


Figure 79. Mean BURSTS over days. Rat 10K - right hemisphere.



BLOCKS X MEAN

TUKEY A - MULTIPLE COMPARISONS TEST

		1	2	7	3	6	5	4
		1.14	1.30	1.83	2.09	2.59	2.95	2.96
1	1.14		0.16	0.69	0.95	1.45	1.81	1.82
2	1.30			0.53	0.79	1.29	1.65	1.66
7	1.83				0.26	0.76	1.12	1.13
3	2.09					0.50	0.86	0.87
6	2.59						0.36	0.37
5	2.95							0.01
4	2.96							

CRITICAL VALUE = 0.69 SIGNIFICANT VALUES ARE UNDERSCORED

Figure 80. Blocks X mean BURSTS. Rat 10K - right hemisphere.

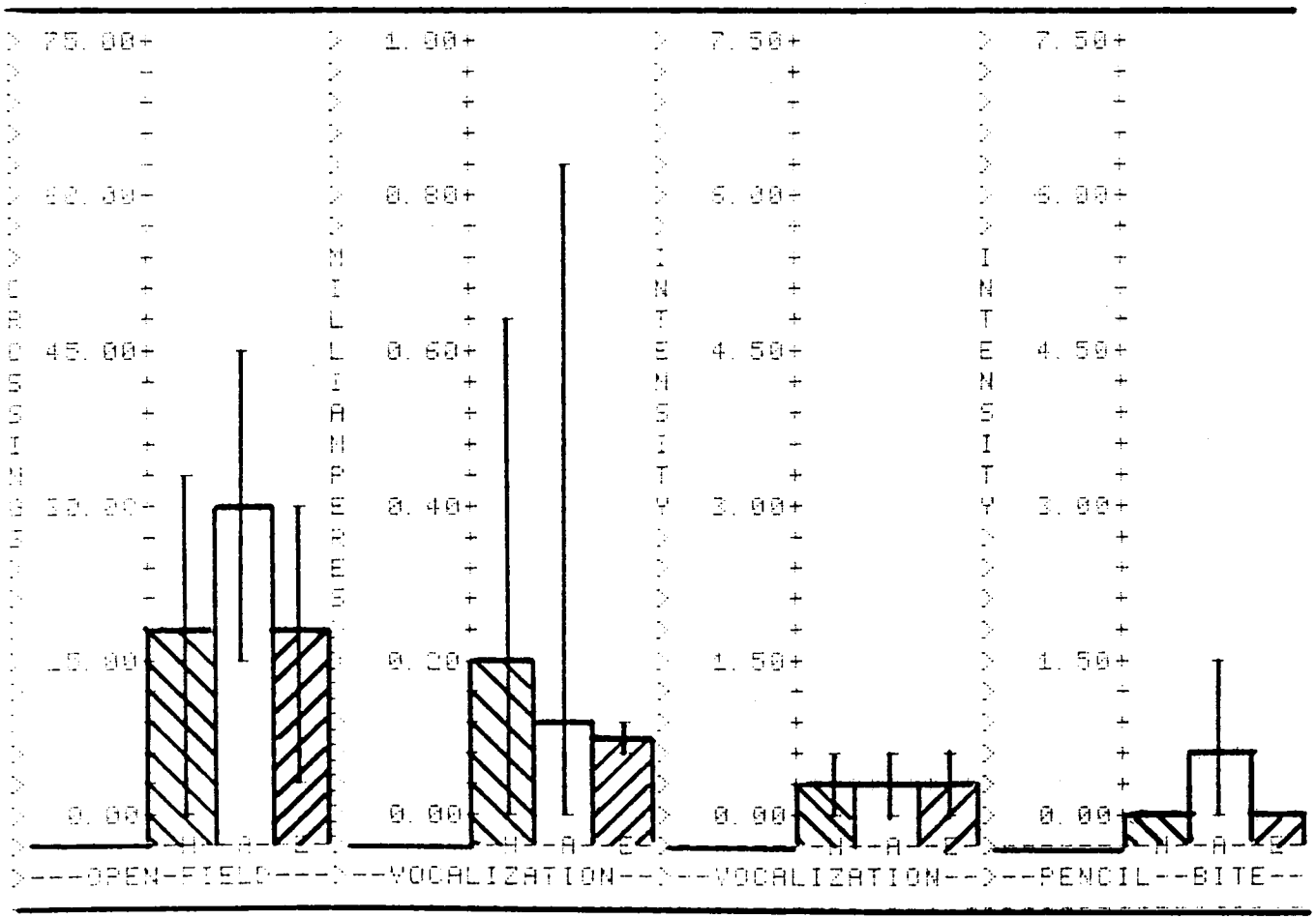


Figure 81. Post contingency means and standard deviations for behavioral tests for rat 8K.

Table 1

Summary of Electrode Implantation Sites

Animal	Hemisphere	Slide #	Ant. Coord.	Implantation Locus
4N	Left	7	A 5.2	Electrode deflected by optic tract. Junction of dorsomedial amygdala, anterior aspect of central nucleus and internal capsule.
	Right	7	A 5.2	Medial nucleus.
3K	Left	3-3	A 6.6	Central Nucleus.
	Right	Histological evaluation not possible in this hemisphere.		
5K	Left	5-6	A 5.2	Medial nucleus. Cortical tumor seen several mm posterior to electrode.
	Right	5-7	A 4.6	Central nucleus.
8K	Left	8-5	A 5.4	Medial nucleus.
	Right	8-5	A 5.4	Border of optic tract and medial nucleus.
10K	Left	15	A 4.8	Medial nucleus.
	Right	8	A 7.0	Ventral border of daudate nucleus. Dorsal border of anterior amygdalo area.

Total Sites	Anterior Amygdaloid Area	Medial Nucleus	Central Nucleus	No Determination Possible
10	1	5	3	1
100%	10%	50%	30%	10%

Table 2

Summary Table for Behavioral Test Scores

MAT	PARAMETER	MEASURE	ACQ		HAB		EXT	
			MEAN	STDV	MEAN	STDV	MEAN	STDV
3K	-OPEN-FIELD-(CROSSINGS)		44.70	14.20	43.10	16.00	42.64	13.70
3K	VOCALIZATION(	MA)	0.12	0.04	0.14	0.04	0.10	0.31
3K	VOCALIZATION(INTENSITY)		0.40	0.89	4.00	0.00	0.20	0.48
3K	PENCIL--BITE(FERROCITY)		0.00	0.00	4.00	0.84	0.00	0.00
4N	-OPEN-FIELD-(CROSSINGS)		35.50	12.50	49.10	12.05	36.60	13.80
4N	VOCALIZATION(	MA)	0.13	0.04	0.10	0.02	0.10	0.02
4N	VOCALIZATION(INTENSITY)		0.00	0.00	0.40	0.55	0.20	0.45
4N	PENCIL--BITE(FERROCITY)		0.00	0.00	0.20	0.45	0.10	0.44
5K	-OPEN-FIELD-(CROSSINGS)		18.60	12.90	22.96	13.07	20.33	5.70
5K	VOCALIZATION(	MA)	0.13	0.04	0.10	0.02	0.10	0.03
5K	VOCALIZATION(INTENSITY)		0.20	0.44	2.00	0.71	0.00	0.20
5K	PENCIL--BITE(FERROCITY)		0.00	0.00	1.60	0.55	0.13	0.34
8K	-OPEN-FIELD-(CROSSINGS)		47.50	13.50	49.62	10.95	50.66	3.50
8K	VOCALIZATION(	MA)	0.11	0.02	0.11	0.02	0.11	0.05
8K	VOCALIZATION(INTENSITY)		0.00	0.00	0.30	0.65	0.20	0.40
8K	PENCIL--BITE(FERROCITY)		0.00	0.00	0.50	0.50	0.20	0.20
10K	-OPEN-FIELD-(CROSSINGS)		16.60	15.90	29.50	15.40	17.00	13.30
10K	VOCALIZATION(	MA)	0.20	0.45	1.00	0.71	0.11	0.03
10K	VOCALIZATION(INTENSITY)		0.20	0.45	0.20	0.45	0.20	0.45
10K	PENCIL--BITE(FERROCITY)		0.20	0.00	0.60	0.89	0.00	0.00

CHAPTER III

CONCLUSIONS AND DISCUSSION

Conclusions

The most unequivocable finding is that learning of the 40 hz contingency occurred. Acquisition and extinction was demonstrated in all five animals with three highly intercorrelated measures. In several cases there were statistically significant drops in acquisition due to cable fatigue. After the cable was repaired the acquisition curve recovered.

The fact that there was generally a fairly rapid acquisition, occurring at least by the second 10-day block in the acquisition condition, is indicative that the associated physiological state is discriminable. At the same time it must be remembered that the animal had a very rich source of secondary reinforcers present which means that external feedback was certainly available, negating the necessity for reliance on internal cues to acquire the task. At the onset of the experiment a decision was made to use an appetitive reinforcer in preference to electrical stimulation of centrally rewarding regions. Structures having the highest reward value such as the medial forebrain bundle are an integral component of amygaloid and hypothalmic interactions. The use of such a reinforcement modality could possibly induce a very unnatural set of conditions in the structures involved. It would therefore be difficult to interpret the significance of any change in

40 hz activity. Appetitive reinforcers were a second alternative. Water delivery was chosen for reliability and economy. However, because of the intrinsic qualities of water reinforcement (i.e., silent arrival and practical invisibility inside the drinking spout) rich secondary reinforcers were necessitated in order to "announce" the presence of the primary reinforcer to insure that its immediate presence after the response would indeed be reinforcing.

There was no increase in 40 hz activity during habituation, in the presence of noncontingent randomly presented reinforcement and secondary reinforcement. Making reinforcement contingent on the production of 40 hz did indeed augment spindle density. Removal of the contingency was followed by a rapid decrease in spindle density. Two possibilities are suggested herein. The rapid decrease may indicate that the associated physiological state is highly discriminable and that it may be aversive.

There was no statistical difference between the daily Baseline and Run scores. There were animals in which perserveration of consummatory licking effectively reduced the Run time. The effect of this licking is the production of a large amplitude 6 hz signal in the raw EEG overwhelming other activity. Such behavior however, was not reinforced or cause false positive responses in the data acquisition circuitry.

The animals did not engage in the behavior in the no-cue Baseline periods but did enter into it in the Run period when the cue was on. Prolonged consummatory licking has the net effect of reducing the effective data acquisition time per minute, artifically deflating the Run score. The result was the reliable elevation of the Baseline over

the Run score. 5K and 4N were two animals in which this form of behavior was prevalent. This artifact appeared late in the experiment after it was too late to control for it. A possibility would have been to inhibit the clock in the program control and associated data acquisition circuitry in the presence of the licking behavior. Such a control however would have introduced other additional problems. One would have to carefully consider the effects of having sessions of unequal duration.

It is significant that there is no real difference between Baseline and Run conditions. Specificity of operant modification of internal processes has been discussed by Black (1972) and is dimension requiring consideration in any experiment of this nature. A constant concern is the extent to which the conditioned body state has "carry-over" effects to situations other than the room or apparatus in which the conditioning occurred. The lack of difference between Baseline and Run performance indicates that the increase in 40 hz spindling performance is not under immediate and simple stimulus control. Were this not the case, the value of this form of biofeedback as a research tool would be greatly diminished. Still the design permits no extrapolation concerning the EEG activity in the animal after it leaves the conditioning apparatus.

The shape of the envelope of the acquisition curve was independent of the implantation site of the electrode. The largest variation in the data is in the basal rates of the spindling behavior.

Changes in emotionality. Changes in emotionality and reactivity associated with changes in experimental conditions were highly variable across animals.

The measure requiring least judgement from E and that could be measured with the greatest degree of precision was the open field test. There is one particular trend that is rather important. Increases in ambulation were seen in animals which showed relatively low basal rates. Animals having high basal rates showed little or no increases. The validity of this observation is lessened by the small number in the experimental population.

There are two possible inferences that can be made from this data. It is possible that conditioning of the 40 hz activity will increase ambulation up to levels that occur naturally but not beyond. The increases then could be related to fear reduction or increased activation in the open field apparatus. Another possibility is that rats not showing increased scores in the open field tests may not have had electrodes in sites which would cause the behavioral change.

The vocalization intensity to handling measure was subjective and only as precise as a four-point rating scale would permit. Only in animal 3K were there clear cut unvaryingly significant changes in vocalization. Other animals showing changes showed an appreciable day-to-day variation which in turn generated large standard deviations in the descriptive statistics. Yet the data does communicate the reality that three animals were appreciably more vocal on handling them.

The same criticism and set of statements can be made of the pencil biting test. In all animals with the exception of 3K there was an appreciable degree of day-to-day variability. There were mild changes in two animals and radical changes in a third. Two animals showing a

mild affective shift showed a slightly elevated tendency toward attacking the pencil when it was presented. 3K managed to inflict much more damage than one would think a rat could muster in very short period of time. It should be noted that the attacks were not affective attacks, indeed they were very quiet. It is also possible that the change in behavior was not an attack but an investigation on the part of the animal. However, there is little doubt that 3K and the other affected rats were not investigating E during the many unexpected lacerations and bloodlettings inflicted by the Ss. The animals definitely became more difficult to manage during the acquisition period. All of these changes returned to basal levels by the end of extinction.

Commentary of the relative efficacy of inducing affective changes related to recording locus. Kaada (1972) has stated that tremendous topographic specialization occurs in the amygdala. He has shown where stimulation at points separated by tenths of a millimeter will produce entirely different results. Table 1, page 177, is a summary of the implanted electrodes. The medial nucleus was most frequently hit (5, 50%) an understandable outcome in view of the fact that the medial nucleus is the largest in the amygdaloid complex. The central nucleus was the second most frequently hit nucleus (3, 30%). One hit was in the anterior amygdaloid area and one unknown location. None of the animals could be considered to have truly symmetrical electrode placements. Once again the numbers of observations should be accepted with caution. It seems that the animals with central nucleus implants were more reactive after conditioning. This does not say that subsequent

testing in the medial nucleus would not yield similar results. The medial nucleus, is so large that a thorough examination of the nucleus using these techniques would comprise a large study itself.

Discussion

The central and medial aspects of the amygdala have been functionally implicated in the modulation and facilitation of arousal states (Karli, and Vergnes, 1965; Egger and Flynn, 1963; 1967). There are a number of additional studies paralleling this one. The most impressive was conducted by Delgado et al. (1970). Using telereception and telestimulation from an array of chronically implanted electrodes in a chimpanzee, he made several pertinent observations concerning olfactory spindles in the amygdala. The center frequency of these spindles were 26 hz which is one half of the olfactory spindle frequency seen in the chimpanzee olfactory bulb. The frequency is divided by two as it is transmitted to the amygdala by the process described by Freeman (1960). (Please see page 21 for a discussion.) In the laboratory, Delgado found a high correlation disappeared in a more antural setting. Using reticular stimulation as an aversive reinforcer, either bilateral or ipsilateral conditioning was possible. The conditioning process was specific enough to suppress spindling in one amygdala but not the other or both if desired. Spindling could be suppressed to 1% of its basal level. It was most notable that during periods of bilateral suppression, the animal was lethargic and placid and showed a marked decrease in motivation.

The spindling was elicited by novel stimulation. The spindling response to novel visual stimulation showed habituation. There was no

habituation to olfactory stimulation leading investigators to conclude that spindling was a component of olfaction.

Knapp (1973) made contradictory findings in cats. After conditioning amygdaloid 40 hz activity he found a decrease in reactivity in the animals. He related these findings to the fact that his recording sites were in the lateral nucleus which has been implicated in causing decreases in arousal in response to stimulation.

In studies of 40 hz conditioning in the visual cortex and hippocampus of cats effective conditioning has been demonstrated using appetitive reinforcers in a design similar to this study (Bauer and Jones, 1976). Increases of 600% in 40 hz activity were attained. Acquisition was rapid and monotonic. Notable results of this study were that when 40 hz activity was augmented in the visual cortex or hippocampus, there were associated increases in 40 hz activity in other regions of the brain. One of the areas mentioned specifically was the reticular formation an important structure involved in arousal. During the conditioning process the animals typically showed immobilization and were seen to "stare out into space." Identical behaviors were seen in the present study in unrestrained animals. Thusly the possibility exists that the animals are mediating the production of 40 hz by modifying sensory input and/or reducing proprioceptive input from skeletal motion.

Delgado et al. (1970) have depicted the 40 hz spindle as being part of an olfactory consolidation mechanism. Sheer (1970) has also speculated that the spindle is a mechanism of consolidation as did Bauer and Jones (1976).

We have no argument with the consolidation theory offered by the above authors. The present study does not address this dimension of 40 hz activity. The research herein was specifically designed to explore the effects of operant modulation of 40 hz activity on emotional and activation continua. In our opinion modulation of these behaviors is brought about through modification of activity levels in the basic arousal substrates of the animal. It has been shown that mesencephalic input is necessary for the occurence of 40 hz activity to appear in the amygdala. Therefore changing amygdaloid 40 hz activity must cause changes in mesencephalic activity.

With the experience gained from this research it is rewarding to point out what things might be changed to improve the experiment were it replicated. A basic problem were the electrode placements. Lacking truly identical implantation sites within the animal, there was no assurance that functionally similar cell populations were being conditioned bilaterally. It is quite conceivable the antagonistic centers were being stimulated which would obscure any possible changes. Such difficulties have plagued investigators in the past in one form or another prompting Goddard (1964) to suggest a control methodology. He recommends a design for lesion work that would be applicable in this work also. It would be quite sound experimentally and anatomically to eliminate the amygdala unilaterally and place a recording electrode in the contralateral amygdala. Such a practice requires the animal to rely wholly on the implanted amygdala for a given amygdaloid function. This is a novel approach to biofeedback but could be profitably used as a research tool in animals.

The conditioning apparatus was quite adequate but it may be profitable to inhibit the system's clock during consummatory licking.

The data in the present study is descriptive at a molar level. Further studies must answer questions at a more molecular level. For example, the biochemical basis for these behavioral changes must be explored. What if any changes are seen in the levels of the biogenic amines or somatic hormones such as ACTH (adrenal corticotropic hormones)? What microstructural changes if any are seen in the cell populations that were conditioned?

EEG conditioning has been demonstrated in both humans and animals in both cortical and subcortical structures. It is a highly specific technique and when used properly it can be a powerful research tool. It has been applied clinically to ameliorate a wide spectrum of symptoms and suffering. Further research is needed in both pure and applied areas to determine the properties of biofeedback. Research in more applied areas will supply information on the applications of the technique. Such research will undoubtedly be rewarding to humankind in a wide variety of health related fields.

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