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A Method for Sensing and Recording Simultaneous Behavioral and Electrophysiological Epileptiform Activity and the Observed Suppression of Paroxysmal Spiking Activity with Classical Conditioning Procedures

J. H. Tough
Western Michigan University

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A METHOD FOR SENSING AND RECORDING SIMULTANEOUS BEHAVIORAL
AND ELECTROPHYSIOLOGICAL EPILEPTIFORM ACTIVITY AND THE
OBSERVED SUPPRESSION OF PAROXYSMAL SPIKING ACTIVITY
WITH CLASSICAL CONDITIONING PROCEDURES

by

J. H. Tough

A Thesis
Submitted to the
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in partial fulfillment
of the
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August, 1972

A METHOD FOR SENSING AND RECORDING SIMULTANEOUS BEHAVIORAL
AND ELECTROPHYSIOLOGICAL EPILEPTIFORM ACTIVITY AND THE
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J. H. Tough, M.A.

Western Michigan University, 1972

A method for sensing and recording the simultaneous behavioral and electrophysiological activity of epileptic seizures was developed. An activity sensing cage consisting of an inverted loudspeaker translated motor behavior into voltage changes. The resultant voltage changes were integrated, amplified and recorded on a polygraph concurrently with electrophysiological data. The method was shown to 1) sense reliably a repeated standard input, 2) be sensitive to differing minute amounts of force and 3) produce data which lends itself to analysis with less variability than a more conventional technique.

Experimental manipulation of epileptiform activity revealed that a behavioral response to the onset of the CS developed over sessions in Experimental subjects but not in Control subjects. Also paroxysmal spiking activity was suppressed during the CS for approximately 70 per cent of the Experimental sessions. There was no change in the electrophysiological activity of the Control subjects during approximately 70 per cent of the Control sessions.

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J. H. Tough

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TABLE OF CONTENTS

CHAPTER		PAGE
I	INTRODUCTION	1
II	METHOD	7
	Subjects	7
	Apparatus	7
	Apparatus Reliability and Sensitivity . .	15
	Surgical Procedure	17
	Data Recording	18
	Procedure	19
	Data Analysis	23
	Histological Procedure	25
III	RESULTS	26
	Histological Results	62
IV	DISCUSSION	66
V	REFERENCES	71

INTRODUCTION

Hughlings Jackson was the first to take a modern scientific view of epilepsy (Gibbs and Gibbs, 1952). Jackson reasoned that the clinical manifestations of epilepsy were symptomatic of cerebral dysfunction (Jackson, 1870). Subsequently, Jackson's reasoning has been proven accurate by evidence arising from the fields of pathology, neurophysiology, and electroencephalography (Wilkins and Brody, 1970).

Gibbs, Davis and Lennox (1935) showed an immediate temporal association of seizure discharges and clinical seizures. Adrian and Moruzzi (1939) and Moruzzi (1939) demonstrated that individual muscle contractions closely follow each wave of cortical discharge with a latency of five to ten milliseconds. Jasper (Penfield and Jasper, 1954) states that close relationships between convulsive movements and electrical after-discharge from the pre-central gyrus may be demonstrated.

Although Jackson's deductive reasoning was highly accurate, Gibbs and Gibbs (1952) warn that "A purely clinical view of epilepsy is incomprehensible, and a purely electroencephalographic view is too narrow to be meaningful. The two views, when fused, produce a clear and understandable picture".

If clinical descriptions of epileptic episodes are to be used as a means of seizure classification, then the measurement and description of the clinical aspect should be accomplished in the most precise and scientific manner possible.

The present research concentrated on developing a reliable technique for simultaneously collecting behavioral and electrophysiological data surrounding epileptic episodes in infra-human subjects and to use this system in conjunction with conditioning experiments. The data which would be recorded using this technique should lend itself to systematic, objective, numerical analysis. The data should also be suitable for qualitative as well as quantitative analysis. Such a technique has been attempted by Ellinwood, Escalante, Mitchell and Hart (1970) using split screen video recordings of behavioral and electrophysiological activity of monkeys.

Various devices for sensing and recording behavioral activity in infra-human subjects have been produced. Hudson and Bussell (1972) report using photoelectric cells to monitor and translate swimming movements of fish for display with electromyographic (EMG) records of associated muscle activity. Capacitance circuits have been used by McClelland (1965) and Van Toller and De Sa (1968) to record behavioral activity of small animals.

McClelland's system was able to differentiate between such types of behavior as "rearing on two feet to top of cage, head movements, freezing on two feet and freezing on four feet". Ultrasonic devices have been employed in activity measurement, however according to Bolles and Sanders (1969) while these devices measure overall activity they give no indication as to what type of activity is occurring. Startle responses in mice have been measured using an oil damped, spring suspended lever, a strain gauge transducer and a polygraph (Wilson and Groves, 1972). Davis and Ellison (1964) produced an activity sensing device which recorded general movements of rats and dogs. Lateral movements of a ball bearing mounted base were converted to pulses by a free swinging pendulum in a circular contact. Zier and Tschannen (1968) measured activity in pigeons by attaching levers to the bottom of a free-floating plexiglas floor. The levers were then connected to a cardboard tube which rested on the cone of an inverted loudspeaker. Movements of the floor were mechanically transmitted to the loudspeaker. The output voltage of the speaker was then amplified and integrated into units which were recorded by a cumulative recorder. Word and Stern (1958) developed an activity sensing device which also used an inverted permanent magnet speaker. The cage floor acted as a diaphragm and the loudspeaker produced an electrical

output in response to the pressure changes caused by the movement of the diaphragm. The electrical output was then fed to an electroencephalographic (EEG) recorder for amplification and display.

Epileptiform activity may be triggered by a variety of stimuli (Penfield and Jasper, 1954). Various chemicals will produce seizure activity. Grim, Frazee, Kawasaki and Savic (1970) used cobalt applied to the cortex of the macaque to produce epileptiform activity. Epileptiform activity has been induced by hypothalamic stimulation in rats (Herberg and Watkins, 1966). Servit and Strejckova (1970) triggered epileptiform discharging in the frog brain by photic stimulation and also by direct electrical stimulation of the optic nerve. In the human literature Forster, Booker and Ansell (1966), Forster and Campos (1964), Forster, Ptacek and Peterson (1965) and Forster, Ptacek, Peterson, Chun, Bengzon and Campos (1964) investigated stroboscopic induced seizure discharges. Mani, Gopalakrishnan, Vyas and Pillai (1968) present 42 instances where hot water applied to various parts of the body triggered a type of reflex epilepsy. Chatrian, Lettich, Miller and Green (1970) discuss four cases of pattern-sensitive epilepsy. Rowan, Heathfield and Scott (1970) and Forster, Paulsen and Baughman (1969) present cases of epilepsy triggered by reading. Voice induced (Forster, Hansotia, Cleeland and Ludwig, (1969)

and musicogenic (Forster, Kløve, Peterson and Bengzon, 1965; Madison and Niedermeyer, 1970) seizures have been presented.

Electrical activity of the brain has been conditioned. Wells (Glasser, 1963) reviews and discusses the extensive literature pertaining to conditioned electrical activity of the brain. More recently, modification of amygdaloid spindling through instrumental conditioning has been demonstrated by Delgado, Johnson, Wallace and Bradley (1970).

Recent research reported by Forster and Campos (1964), Booker, Forster and Kløve (1965), Forster, Kløve, Peterson and Bengzon (1965), Forster, Ptacek and Peterson (1965), Forster, Booker and Ansell (1966), Forster, Booker and Gascon (1967), Forster, Hansotia, Cleeland and Ludwig (1969) and Forster, Paulsen and Baughman (1969) indicates that electrophysiological epileptiform activity may be modified by a desensitization technique. Mark and Ervin (1970) present and discuss several cases where Intra-Cranial Stimulation (ICS) of human subjects has modified behavior patterns associated with temporal lobe epilepsy.

The wide variety of triggering events and the fact that some forms of epilepsy may be desensitized, indicate that certain seizure activity may follow the laws of conditioning, though Forster (1969) in reviewing his own

and related research concludes that sensory-evoked seizures can not be conditioned in animals unless they have already been rendered epileptogenic, and that sensory-evoked seizures in humans are not the result of conditional reflexes. Nevertheless, considering the variety of eliciting stimuli and the fact that environmental manipulations have resulted in the modification of epileptic phenomena, preliminary investigation of classically conditioned epileptiform activity was undertaken concurrently with the development of a reliable behavioral seizure activity sensing device.

METHOD

Subjects

Subjects were six male albino rats, weighing between 375 and 455 grams at the beginning of the experiment. All subjects were housed individually in a temperature controlled animal colony room. Subjects were maintained on twenty grams of Purina Rat Chow and "ad libitum" water daily.

All subjects had an experimental history of use in an introductory psychology laboratory course.

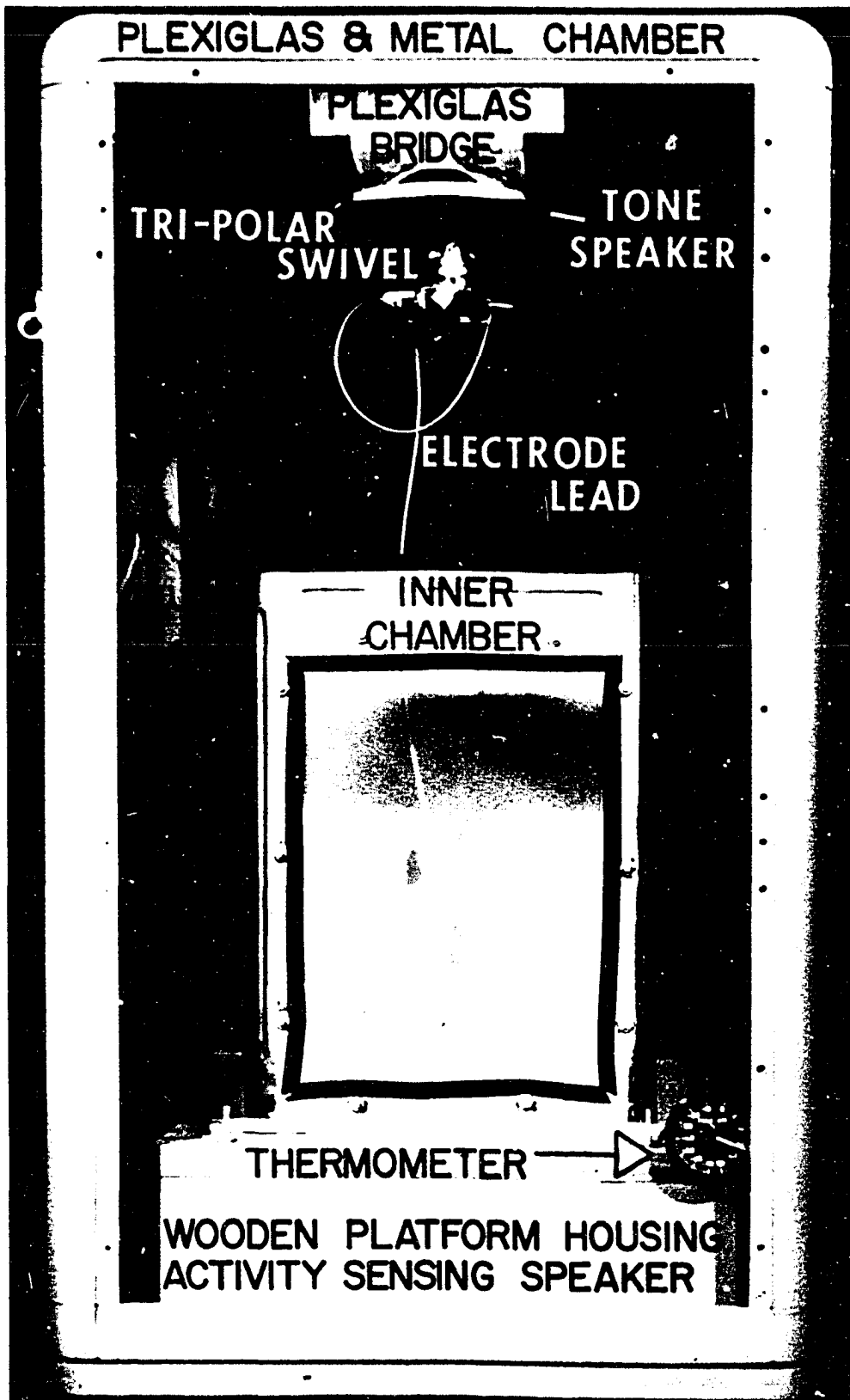
Apparatus

All sessions were run in an electrostatically shielded room which measured 5' x 5' x 7 1/2'. Acoustical tile applied to the four walls afforded sound attenuation. Two four ohm speakers suspended above the copper mesh ceiling provided white masking noise produced by a Grason Stadler Model 901 B white noise generator. Also above the wire mesh ceiling were two 100 watt light bulbs used for illumination.

Within the shielded room, a plexiglas and metal chamber (see Figure 1, p. 9) measuring 22" x 17" x 31" with four Barry-Mount 915-25 shock absorbers on the underside was mounted on top of a 175 lb. marble slab which

FIGURE 1

Front view of the experimental chamber which was mounted on four shock absorbers and rested on top of a marble slab which rested on top of three opposing layers of concrete blocks in the electrostatically shielded room.



rested on a foundation of three opposing layers of concrete blocks. The chamber supported a 4" x 22" plexiglas bridge approximately 3 1/2" from the top of the chamber. This bridge held two Jenson V-1574 circular speakerd, four 24 VDC stimulus lights, and one tripolar mercury swivel. On the bottom of the chamber was a wooden platform containing an inverted Utah Micro-Gap four ohm speaker packed in foam rubber (Figure 2, p. 12). The face of the speaker was suspended beneath an opening in the wooden platform. Directly above the hole in the platform was placed a 9" square five gallon tin container which had one side of plexiglas and an open top.

Also in the shielded room was a Panasonic WV220P television camera. The camera along with its AC power cord were shielded and grounded.

Figure 3 (p. 14) is a block diagram of all equipment used. Digital Equipment Corporation logic modules and two two-channel tape readers provided for the automatic delivery of the stimuli. A Grass S-8 stimulator with associated Stimulation Isolation Units supplied a 50 Hertz (Hz) bi-phasic square wave pulse of varying intensity for ICS. A 1,000 Hz sine wave was generated by a Hewlet Packard Audio Oscillator Model 2010. The wave form of the electrical stimulus was monitored on a Tektronix 502-A Dual Beam oscilloscope. All data were collected on a Grass Model 5 polygraph using three 5P5 (EEG) pre-amplifiers

FIGURE 2

Top view of the inverted activity sensing speaker mounted in the wooden base which supported the activity cage in the experimental chamber.

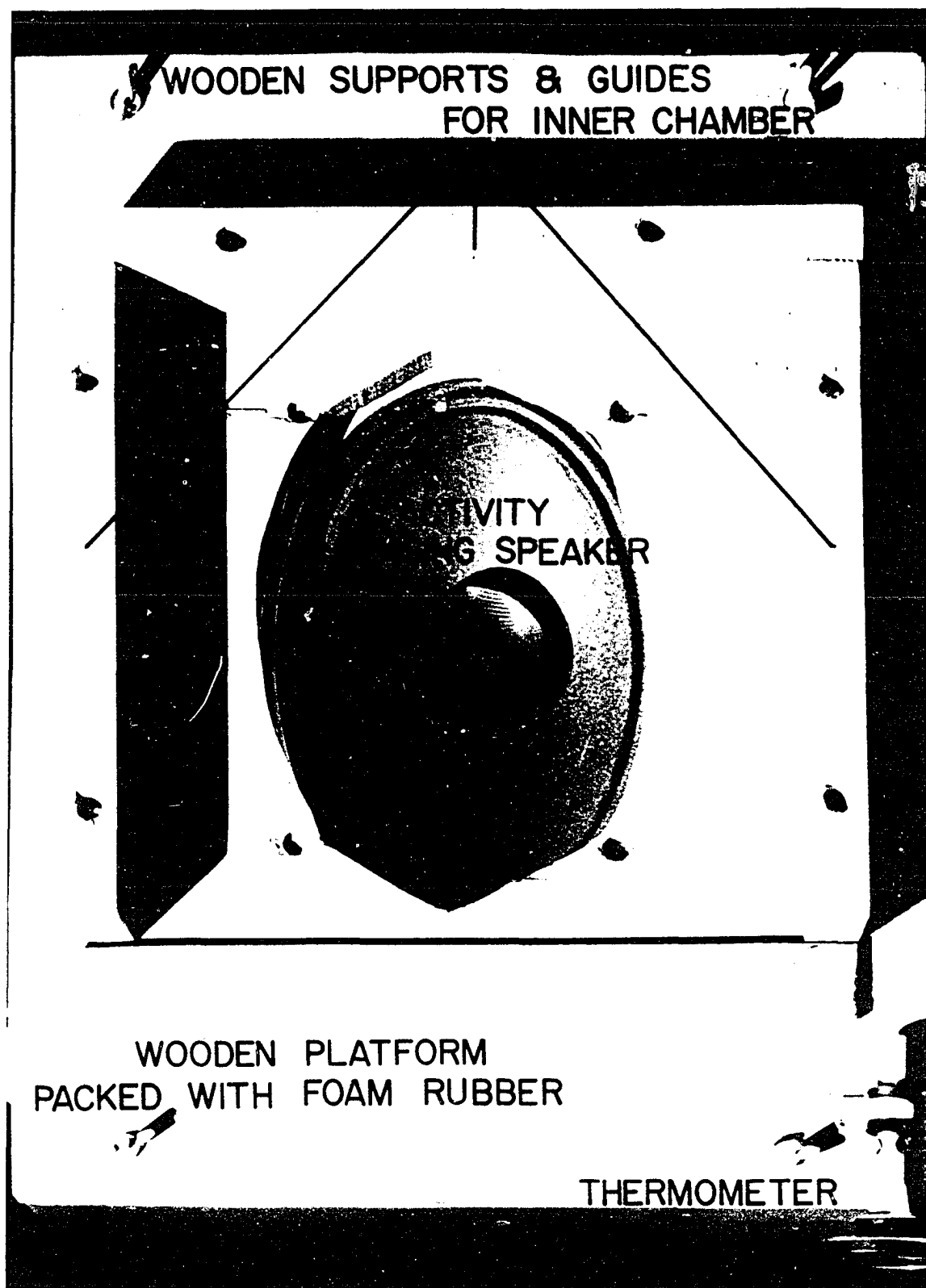
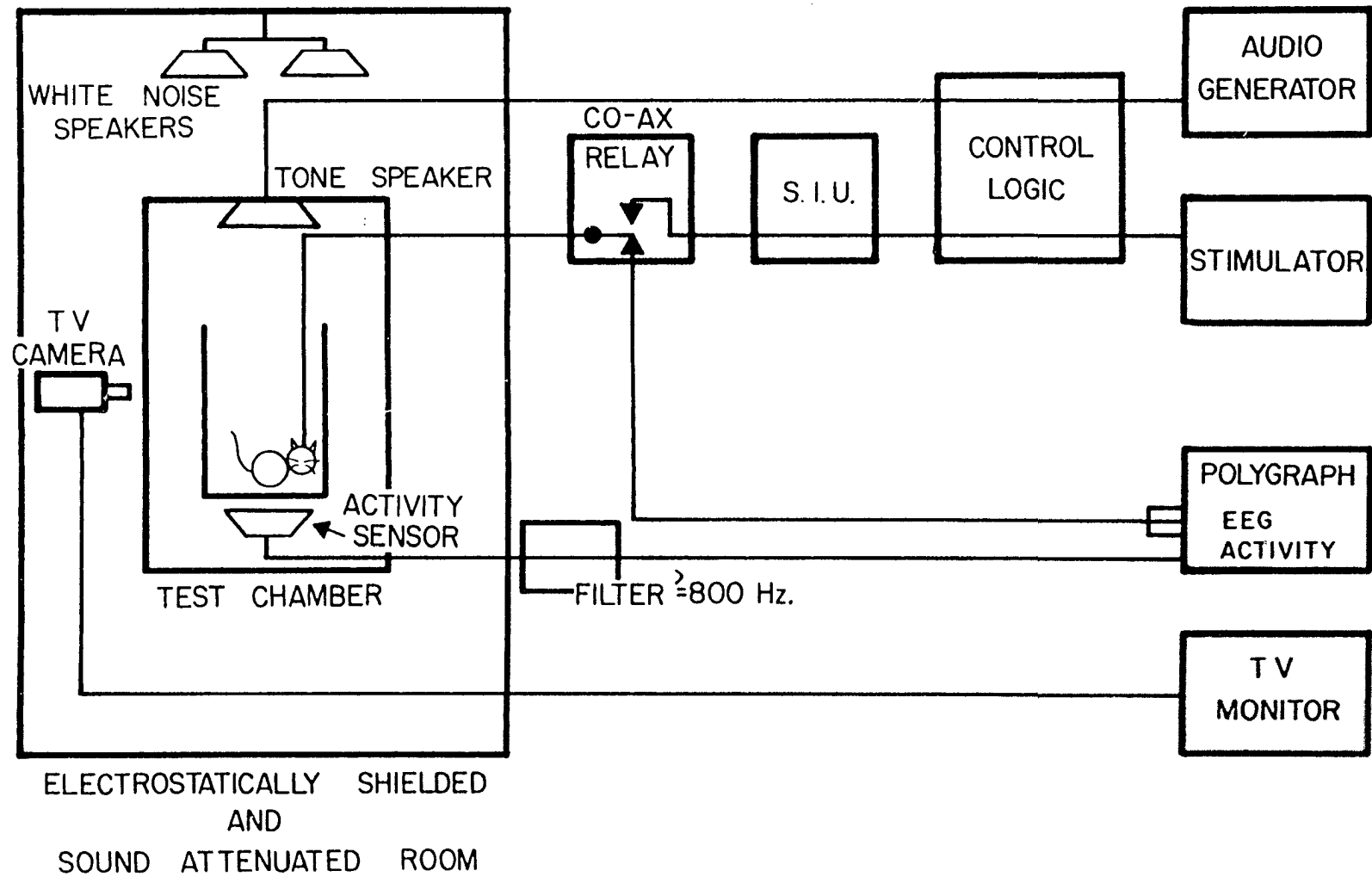


FIGURE 3

Block diagram of apparatus used for sensing and recording behavioral and electrophysiological data. Also included are the modules for stimulus generation and presentation.



and one GFS (EMG and Integrator) pre-amplifier. In later sessions a Krohn-Hite Model 330-A Ultra-Low Frequency band pass filter was used to block the 1,000 Hz tone from the pre-amplification stage of the Grass polygraph. A Panasonic television monitor which was connected to the camera in the shielded room provided for remote observation of subjects during the session. A Panasonic Tape-A-Vision video tape recorder and a Panasonic WV600P Special Effects Generator were used during one session to make a split-screen video recording of the subjects and their polygraph records.

Apparatus Reliability and Sensitivity

Three measures of reliability and sensitivity were employed to ascertain if the activity sensing technique would: (1) accurately report the same response to the same input over N trials; (2) be sensitive to differing forces and if so in what manner; (3) lend itself to data analysis more reliably than more conventional techniques.

Reliability: A 28 VDC relay was mounted in a cardboard tube and placed in the center of the activity sensing device. When activated by a remote pushbutton, the relay closure and release was sensed by the activity sensing device. All calibrations were of the same value as in the Experimental setting. A series of 190 trials of relay closure and release were recorded over a period of

32 minutes. The relay was activated in the following temporal order: the contacts were closed, five seconds later the contacts were released and twenty seconds later the contacts were again closed.

Sensitivity to differing forces: Using the same calibration values as in the Experimental setting, a spherical metal ball weighing .3528 g was allowed to free fall from 1, 2, 3, 4 and 5 cm above the floor of the activity chamber. Five trials were made at each height.

Reliability of data analysis: Four observers analysed the same 60 second segment of a polygraph record of both electrophysiological and behavioral activity. This record included an overt seizure. The use of the planimeter was explained and demonstrated to each observer. The observers traced the time the activity pen was deflected above the baseline (i.e. any and all behavior recorded by the activity sensor). Each observer analysed the data five times. The mean, variance and standard deviation were extracted from data produced by each observer and also for all observers.

The same observers then analysed the same data, which had been recorded using the method previously described by Ellinwood et al (1970) where the subject's behavioral activity is video tape recorded. The observers were given a pushbutton which controlled a Standard timer. Whenever the pushbutton was depressed the timer

would be activated. The timer stopped with the release of the pushbutton. The observers were instructed to depress the pushbutton whenever the subject moved and to release the pushbutton whenever movement stopped. Each observer analysed the same video tape record five times. The mean, variance and standard deviation for these data were extracted for each observer and for all observers.

Surgical Procedure

Surgery was performed under clean but not aseptic conditions. Subjects were anesthetized with 50 mg./kg. sodium pentobarbital and placed in the stereotaxic instrument. The electrodes were stereotaxically placed in the brain of each subject. The intended placements of the electrodes were: the basal lateral, the central and the cortical amygdaloid nuclei.

Electrodes were Plastic Products #MS-333 tripolar electrodes. Two of the three electrodes were twisted together with their tips being separated vertically by approximately 1/2 mm. The third electrode was stripped of its insulation and used as a reference electrode. Three stainless steel jewelers screws were placed in the calvarium so that the bottom tip of the screw would make contact with the dura mater but not penetrate it. The reference electrode was attached to the tops of the three screws. Dental acrylic was applied so that it was

anchored by the protruding screw heads and supported the electrode connection.

Terra Cortil ointment was applied to the wound prior to closure and 200,000 units of procaine penicillin was administered post-operatively to prevent infection.

All subjects had a minimum ten day recovery period before being introduced to the experimental setting.

Data Recording

Three channels of electrophysiological data were recorded for each subject. The tripolar electrode arrangement allowed recording in either a mono- or bipolar mode. Channels one and two recorded bipolar data while channel three recorded monopolar data. The remaining channel (channel four) was used to record behavioral activity data. An event pen signalled onset and duration of tone by an upward deflection and vibration and the onset and duration of ICS by a downward deflection and vibration.

Prior to each day's sessions, the polygraph was turned on for an hour before calibration. This was done to allow the circuitry to warm up and stabilize. Driver amplifiers for channels one, two and three were calibrated in the conventional manner with negative polarity being up and the half-amplitude high frequency filter settings at three Hz for channel one and sixty Hz for channels

two, three and four. The 5P5 pre-amplifiers were conventionally calibrated with the half-amplitude low frequency filter settings at .25 Hz for channel one and 1.5 Hz for channels two and three. Signal amplification varied across subjects.

The input for channel four originated from the speaker located under the container in the experimental chamber. Movement of the floor of the container caused a sympathetic movement of the speaker cone which induced an electromotive force in the voice coil of the speaker. The resultant signal was amplified by the Grass 5P3 pre-amplifier. The driver amplifier for the 5P3 pre-amplifier was calibrated to meet the needs of the specific experimental setting. The baseline trace was shifted to two centimeters below the standard baseline and the sensitivity adjusted so that a deflection of 34 mm occurred in response to the calibrated input. The 5P3 pre-amplifier EMG sensitivity was set for a 7 mm pen deflection in response to a 20 uVolt DC calibration input. The EMG and Integrator sensitivity was set for a 12 mm pen deflection in response to a 500 uVolt calibration input.

Procedure

A tripolar electrode lead was attached to the subject before each session. The subject was then placed in the

experimental chamber. During all sessions white noise was used to mask sound insufficiently attenuated by the shielded room. The room was constantly illuminated with two 100 watt light bulbs during all sessions.

Baseline procedure: During baseline procedures each subject remained in the experimental chamber for thirty minutes. Electrophysiological and behavioral data were recorded by the polygraph throughout the entire thirty minute session. Baseline sessions also served as an adaptation period for all subjects.

Threshold testing: Stimulus thresholds (electrical) at which electrophysiological seizures were elicited were determined for each subject. Stimulation was increased by ten micro-ampere increments until electrophysiological evidence of seizure activity was present. Threshold testing was continued at values above the actual threshold values. Subjects were then arbitrarily assigned to Experimental and Control groups. Experimental subjects received tone paired with ICS and Control subjects received only tone.

Control procedure: Subjects R-8 and R-14 had 22 thirty minute Control sessions. Seven minutes after the session started the polygraph was started and at ten and twenty minutes a five second 1,000 Hz tone was presented.

Experimental procedure: Subjects R-6 and R-12 were tested over 33 thirty minute experimental sessions. At minute

seven the polygraph was started and at ten and twenty minutes the subjects received five seconds of tone and three seconds of ICS. The stimuli were coterminous.

Subject R-7 had a total of twenty experimental sessions. Sessions one through nine were thirty minutes long with stimulus pairings occurring at minute ten and minute twenty in the session. Sessions ten through twenty were 45 minutes long with six stimulus presentations. The stimulus presentations began at minute ten with a five minute inter-trial interval. Tone duration was eight seconds and ICS duration was three seconds. The stimuli were coterminous.

Subject R-10 had a total of eighteen experimental sessions. During sessions one through five there were two stimulus presentations with an inter-trial interval of ten minutes. The session length was thirty minutes. During sessions six through eight the inter-trial interval was five minutes and there were two stimulus presentations. The session length remained at thirty minutes. For sessions nine through eighteen, six stimulus pairings were given with an inter-trial interval of five minutes. Sessions were forty-five minutes in length. Tone duration was thirteen seconds and ICS duration was three seconds. The stimuli were coterminous.

Table 1 (p. 22) presents the various schedules for each subject and also the stimulus parameters.

Table 1

	Session	Inter-Trial Interval	Stimulus Pairings	Stimuli Presented	Tone Duration	Shock Duration	Shock Intensity	Tone Frequency
R-6	1-33	10'	2	ICS-Tone	5 sec	3 sec	85uA	1,000 Hz
R-7	1-9	5'	2	ICS-Tone	8 sec	3 sec	75uA	1,000 Hz
	10-20	5'	6	ICS-Tone	8 sec	3 sec	75uA	1,000 Hz
R-10	1-5	10'	2	ICS-Tone	13 sec	3 sec	75uA	1,000 Hz
	6-8	5'	2	ICS-Tone	13 sec	3 sec	75uA	1,000 Hz
	9-18	5'	6	ICS-Tone	13 sec	3 sec	75uA	1,000 Hz
R-12	1-33	10'	2	ICS-Tone	5 sec	3 sec	75uA	1,000 Hz
R-8	1-22	10'	2	Tone	5 sec	---	---	1,000 Hz
R-14	1-22	10'	2	Tone	5 sec	---	---	1,000 Hz

Data Analysis

Electrophysiological data: All electrophysiological data which were analysed were selected from the second channel. A section of record which occurred before the first stimulus presentation of the first experimental session was examined for each subject. The amplitude of the negative pen deflections usually remained below the 100 uVolt level. Class intervals were then determined for higher voltage deflections, in 100 uVolt increments. A ten second sample of electrophysiological data immediately prior to the onset of the CS (Pre-Tone) was examined for each stimulus pairing, and the number of high amplitude spikes falling in each class interval was recorded. Each CS duration (During-Tone) was analysed in the same manner. Due to electrical artifact during the administration of ICS, the electrophysiological data were lost for the duration of ICS. The resulting data were converted into spikes per second (SPS) by dividing the total number of spikes by the duration of the sample in seconds. These data were then averaged per session so that for each session there was one SPS frequency for Pre-Tone activity and one for During-Tone activity. For each session a suppression ratio was calculated using the formula $SR = \frac{D-P}{D+P}$ where SR is equal to suppression ratio, D is equal to the average SPS During-Tone and P is equal

to the average SPS Pre-Tone. The construction of this formula resulted in positive ratios indicating facilitation and negative ratios indicating suppression. In the actual presentation of data, suppression is defined as ratios which have values of -1 to $-.4$. Facilitation is defined as ratios which have values of $.4$ to 1 . The area $-.4$ to $.4$ is designated the "No Change" area. SPS data were calculated for the total number of spikes rather than for the individual class intervals.

Behavioral activity data: The analysis of the behavioral data from the fourth channel consisted of initially segmenting the records into fifteen second intervals. Data were scored for two minutes prior to onset of CS. Data recorded ~~post CS-UCS~~ varied in total time due to the variability of the inter-trial intervals. A planimeter with a scale which was easily converted into seconds was used to determine the time the pen was deflected above the 417 uVolt level. This was accomplished by tracing over the 417 uVolt boundary line wherever the pen was deflected above the boundary. The 417 uVolt boundary negated the possibility of timing deflections which reflected transmitted artifact and eliminated the low magnitude behavioral activity of the subject. Total time during each fifteen second period in which the pen was above the voltage minimum was then recorded.

Histological Procedure

At the conclusion of the experiments all subjects were sacrificed with a lethal dose of sodium pentobarbital. The cardiac perfusion technique described by Hart (1969) was used.

The brains were blocked in the stereotaxic instrument. Forty-eight micra frozen sections were made using an American Optical Co. Model 860 microtome. The sections were temporarily slide mounted for independent histological localization of electrode placement¹.

¹Dr. J. Renfrew performed the localization of electrode placements using coordinates from Pellagrino and Cushman (1967).

RESULTS

The method for simultaneously sensing and recording behavioral and electrophysiological activity as described was tested. Figure 1 (p. 9) shows the experimental chamber housing the device for sensing behavioral activity. The tripolar swivel for the transmission of electrophysiological data and the administration of the UCS can be seen. The speaker used to deliver the CS can also be seen in this figure. Figure 2 (p. 12) illustrates in detail the activity sensing speaker.

Table 2 (p. 27) presents the results of repeated relay release (standard input) as sensed and recorded by the current technique. Over 190 relay releases the mean pen deflection was 3.8 mm, with the range being from 3 mm to 4.5 mm of pen deflection. The frequency of each of the measured deflections is also given in this table. From the data presented in this table it can be seen that the probability of a pen deflection being within .5 mm of the mean in response to a standard input would be $p = .964$.

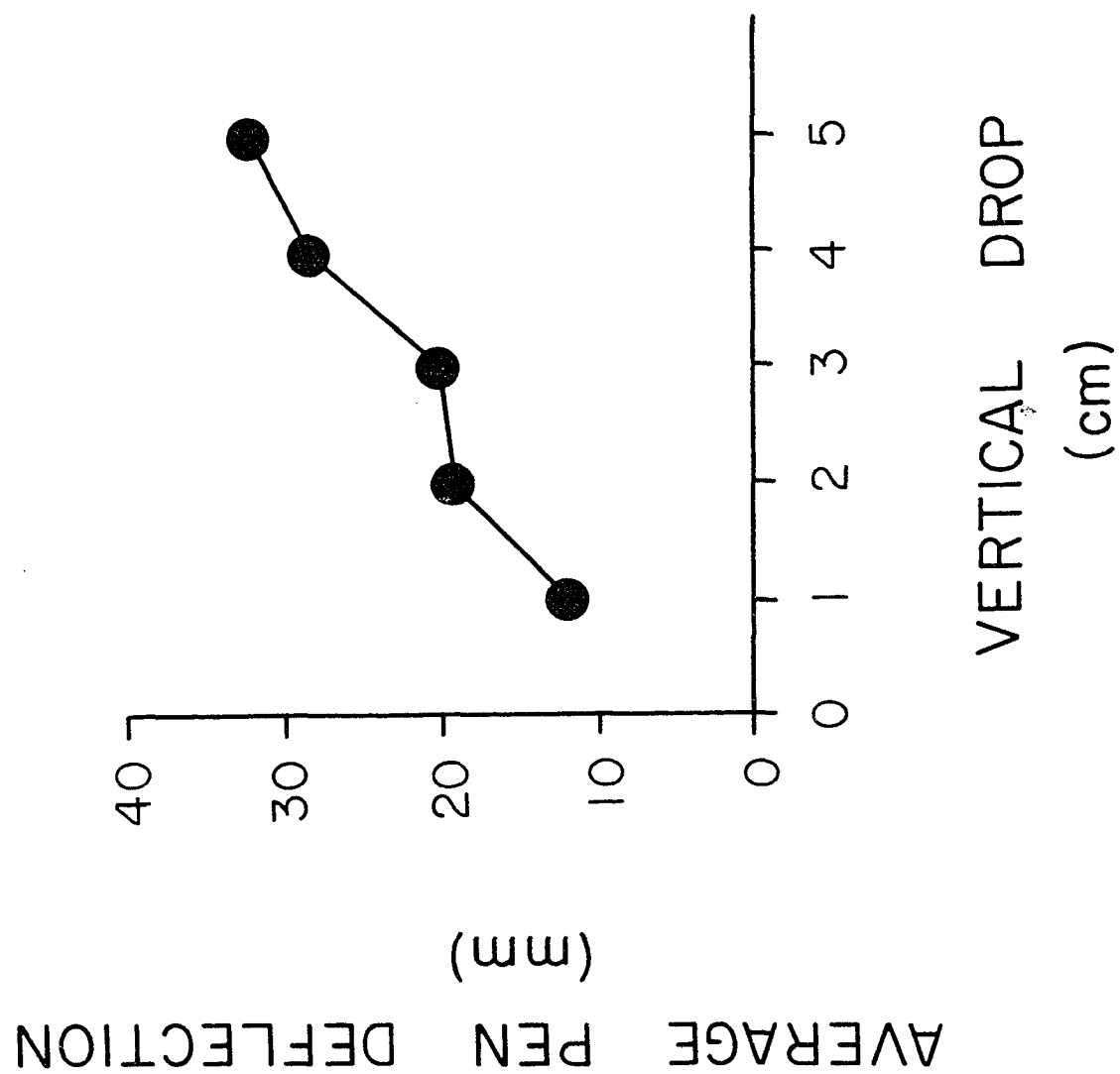
Figure 4 (p. 29) presents the average pen deflection (over five trials) in mm as a function of height from which a .3528 g mass is allowed to free fall. The deflection increases as a function of height. It was found that

Table 2

Mean pen excursion for 190 trials.....	3.8 mm
Range of pen excursions for 190 trials.....	3 mm - 4.5 mm
Frequency of pen excursions at the 3.0 mm level over 190 trials...	1
" " " " " " 3.5 mm " " " " ...	82
" " " " " " 4.0 mm " " " " ...	101
" " " " " " 4.5 mm " " " " ...	6
Probability of pen excursion being within .5 mm of the mean.....	.964

FIGURE 4

Average behavioral activity pen deflection in millimeters as a function of height (Vertical Drop) from which a .3528 gram mass is allowed to free fall.



the force with which an object strikes the sensing device is approximately proportional to the square root of the height from which it falls¹. The deflection which occurred at the 1 cm level would correspond to deflections occurring at C in Figure 5 (p. 32), the deflection which occurred at the 3 cm level would correspond to deflections occurring at B in Figure 5 and the deflection which occurred at the 5 cm level would correspond to the initial deflection at A in Figure 5.

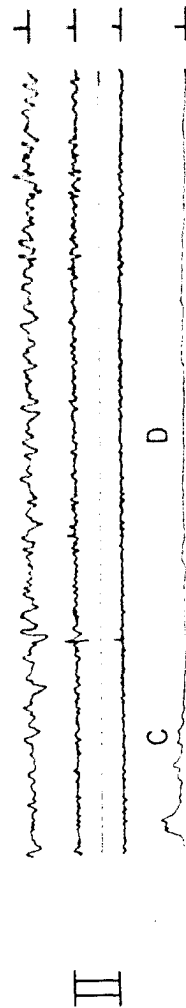
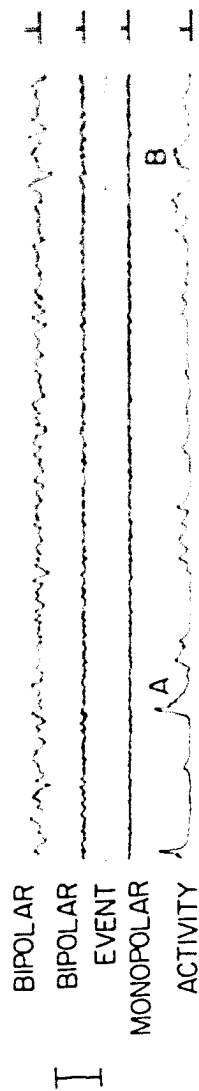
The analysis of behavioral data recorded by the current technique was found to be less variable than the analysis of the same data recorded by a more conventional technique (visual observation of a video tape). Analysis of behavioral data obtained using the activity sensing device and the polygraph indicated that data could be extracted repeatedly by the same and different observers with very little variability. The variance within observers (Table 3, p. 33) ranged from .033 to .140 while the variance across 20 observations was .515. When the observers analysed the same data using visual observation of the behavior (video tape recording), the variance within observers ranged from .046 to 2.55 while

¹ In order to compute the actual force involved in a free falling object striking a surface, the time that it takes the object to stop moving (i.e. when distortion of both surfaces ceases) must be found. These data were not available.

FIGURE 5

Polygraph record of a single subject showing electro-physiological data from the basolateral amygdaloid nucleus and behavioral data recorded by the activity sensing apparatus. (A) indicates subject standing on hind feet. (B) indicates ambulatory movements. (C) indicates exploratory behavior. (D) is a motionless subject

R-6



500 μ V

10 SECONDS

Table 3

Observer	Polygraph Record					Video Tape Record				
	N	X	S ²	S	Range	N	X	S ²	S	Range
1	5	33.6	.040	.200	33.5 - 34.0	5	41.7	2.550	1.597	40.5 - 44.5
2	5	33.3	.060	.245	33.0 - 33.5	4	43.2	.505	.711	42.1 - 44.0
3	5	33.3	.033	.182	32.5 - 33.5	5	40.7	.046	.215	40.4 - 41.0
4	5	34.4	.140	.374	34.0 - 35.0	5	41.9	.686	.828	40.6 - 43.0
Total	20	33.7	.265	.515	32.5 - 35.0	19	41.8	1.741	1.320	40.4 - 44.8

the variance for 19 observations was 1.320. Also apparent in Table 3 is an 8.1 second difference in the mean values for all observations. This discrepancy was attributed to the observers' reaction time in depressing and releasing the pushbutton.

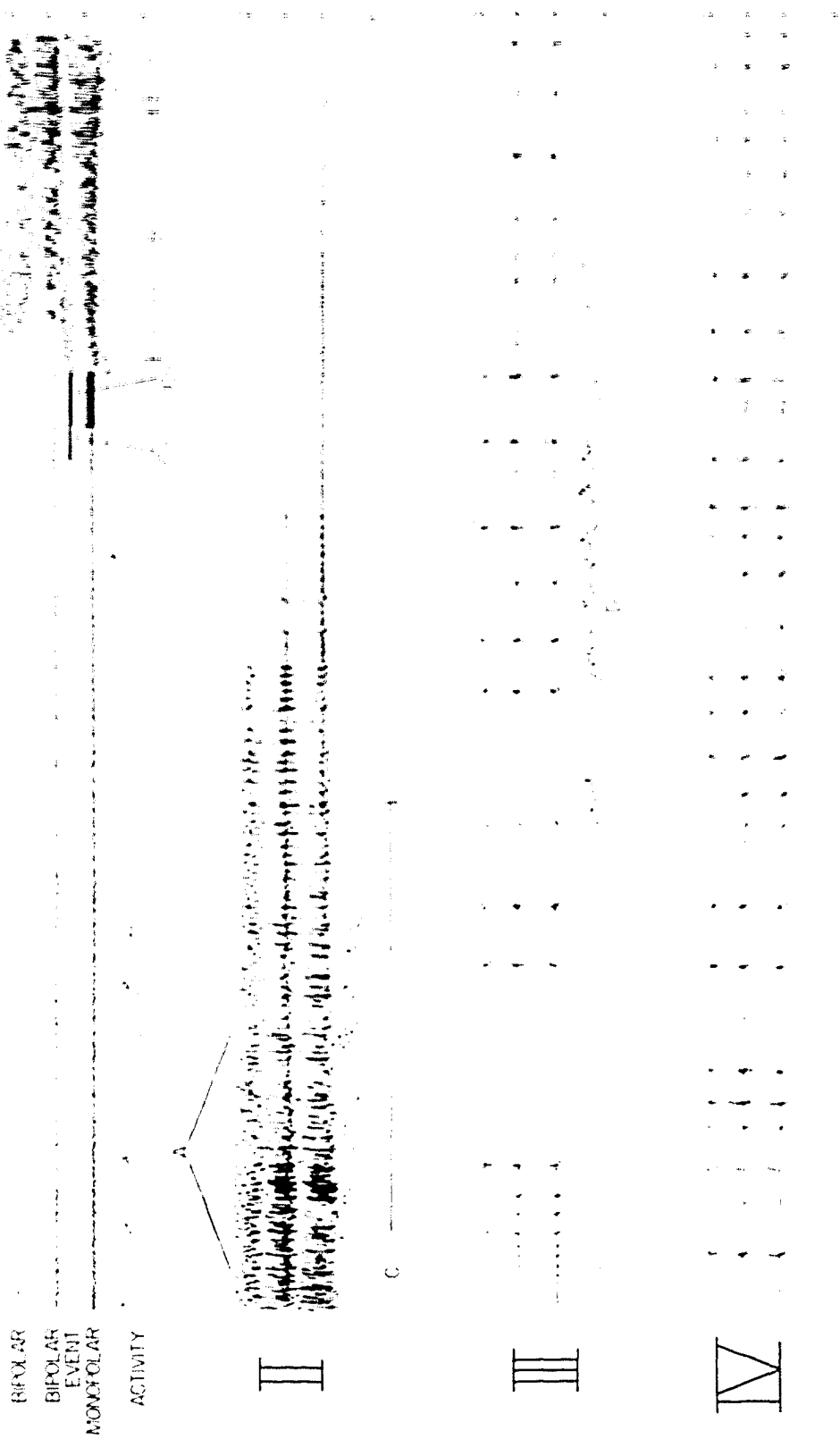
Normal behavioral and electrophysiological activity of subjects was simultaneously recorded by the present method. Figure 5 (p. 32) indicates patterns of normal activity for one subject. Behavioral events which produced the activity at A in Figure 5 are behaviors of the greatest magnitude, such as the subject rearing up on hind legs. Sniffing and exploratory behavior are represented by the behavioral record at B. C is an example of shifting of position or slight ambulatory movements, and D is a motionless subject.

During seizure activity, the activity sensor provided a reliable means for recording behavioral and electrophysiological activity. Figure 6 (p. 36) illustrates a typical seizure episode. The onset and duration of the CS and the UCS are marked. Segment A of the electrophysiological data is the paroxysmal slow wave discharging (PSD) which was evident for 48 seconds following ICS. For nine seconds after stimulation there is no behavioral activity present (segment B) and then motor involvement occurs during segment C. At the termination of the continuous PSD (48 seconds after termination of ICS) motor activity

FIGURE 6

Polygraph record of a single subject showing electrophysiological data from the basolateral amygdaloid nucleus and behavioral data surrounding the presentation of the conditional (CS) - un-conditional (UCS) stimulus compound recorded by the activity sensing apparatus. (A) continuous paroxysmal slow wave discharging, (B) absence of behavioral activity, (C) behavioral activity during continuous paroxysmal slow wave discharging, (D) recovery of behavior, (CS) onset and duration of CS, (UCS) onset and duration of UCS.

R-6



drops out to re-appear during the later behavioral recovery stage (segment D).

The average continuous PSD duration followed a similar pattern for all Experimental subjects. Increased average duration was shown in sessions which occurred during the middle of the study as opposed to sessions occurring during the early part of the study. Sessions which occurred later in the study evidenced PSD of shorter duration than the middle sessions but similar to the early sessions (Figures 7, p. 39; 8, p. 41; 9, p. 43)

Manipulation of inter-trial intervals and the number of stimulus pairings effected the electrophysiological data. Seizure activity produced by ICS in subjects which had two trials per session with an inter-trial interval of ten minutes (R-6 and R-12) resulted in a continuous PSD which was of shorter duration for the second trial than the first trial (Figures 7, p. 39 and 9, p. 43). However when the inter-trial interval was reduced to five minutes (R-7, Figure 8, p. 41) the continuous PSD for the second trial was of longer duration than that of the first trial. When the inter-trial interval was shortened from ten minutes to five minutes and the number of trials increased from two to six, the continuous PSD duration for trials two through six was reduced as can be seen in Figure 9 (R-10).

During the majority of sessions the CS (tone) was

FIGURE 7

Average duration, in seconds, of continuous paroxysmal slow wave discharging as a function of Trials and Sessions for Subjects R-6 and R-12.

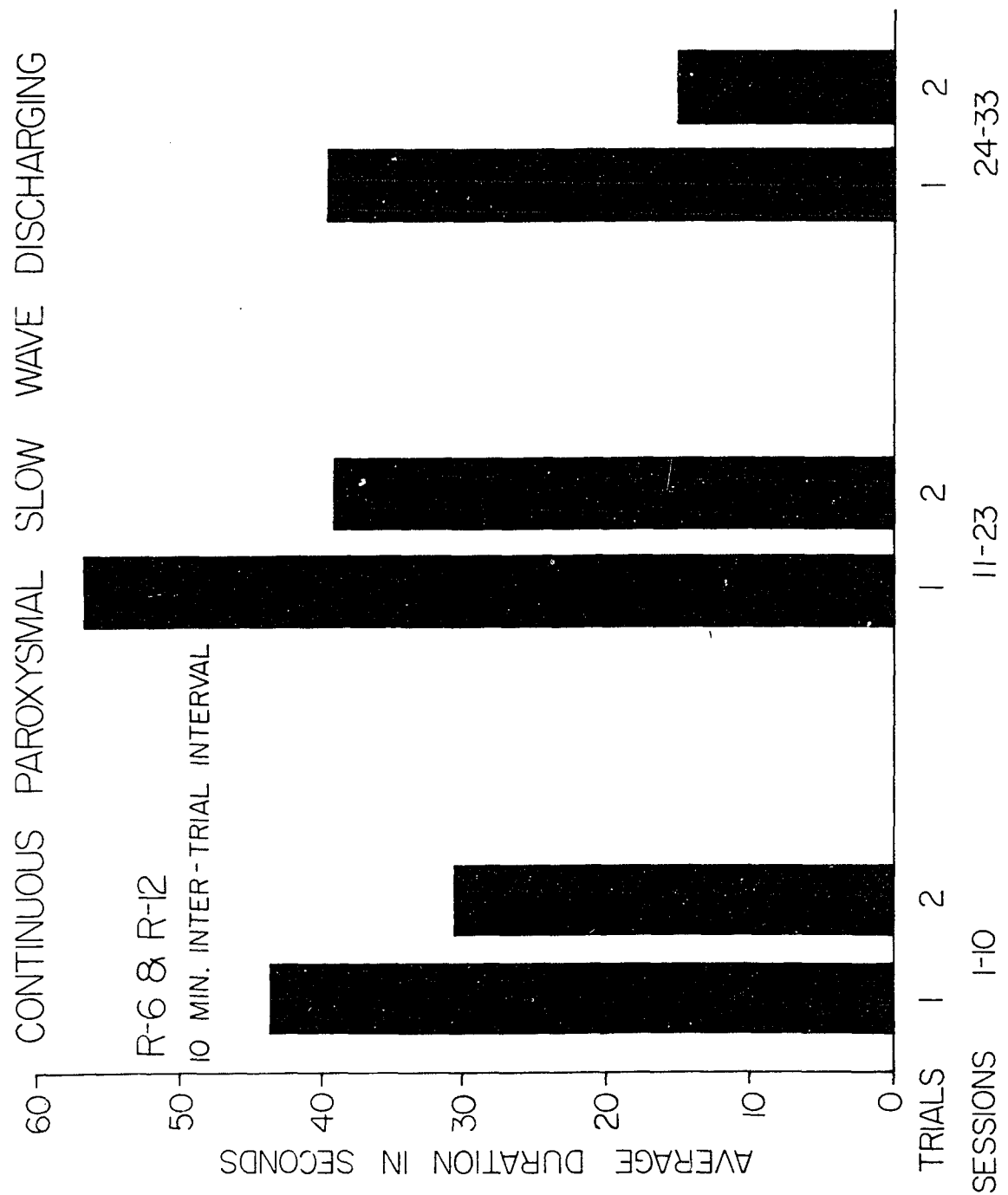


FIGURE 8

Average duration, in seconds, of continuous paroxysmal slow wave discharging as a function of Trials and Sessions for Subject R-7.

CONTINUOUS PAROXYSMAL SLOW WAVE DISCHARGING

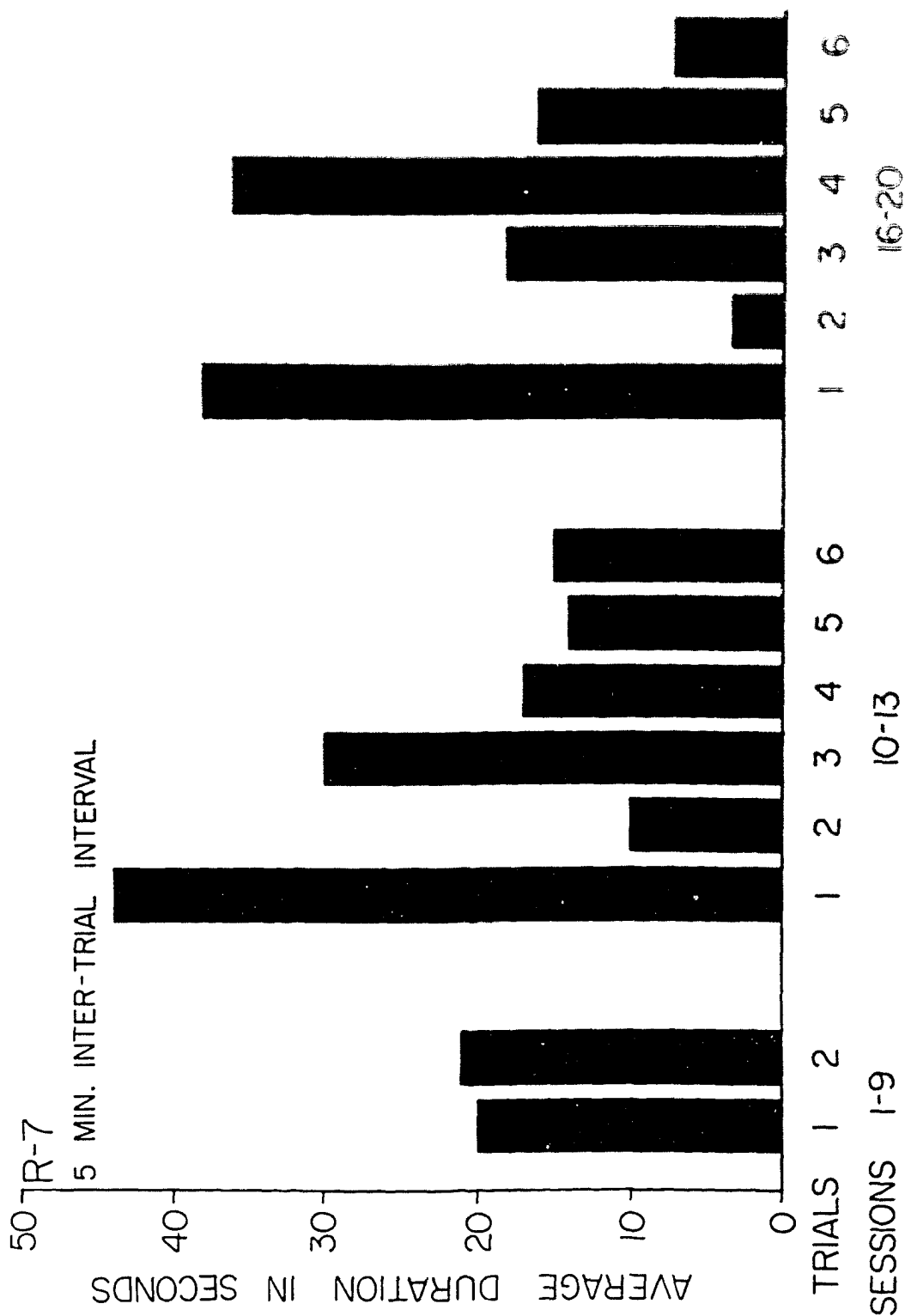
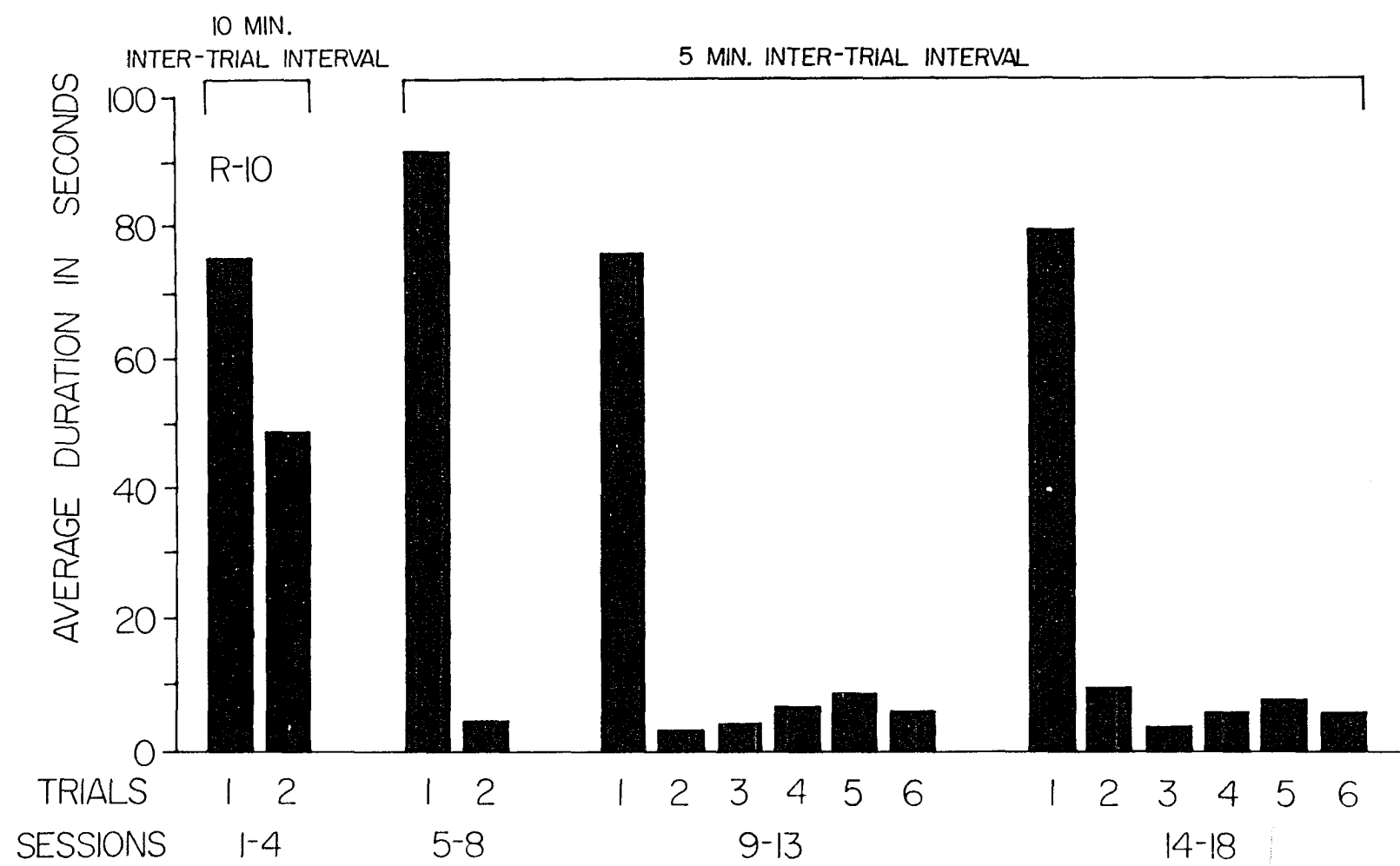


FIGURE 9

Average duration, in seconds, of continuous paroxysmal slow wave discharging as a function of Trials and Sessions for Subject R-10.



CONTINUOUS PAROXYSMAL SLOW WAVE DISCHARGING



not filtered from the pre-amplification stage of the activity channel. Therefore an artifact was produced by the activity sensor in response to the CS presentation, obliterating the activity channel. An example of the artifact produced by the onset and duration of the CS when the filter was not utilized is presented in Figure 10, segment A (p. 46). When the filtering of the activity channel had been accomplished, in the last sessions of the study, behavioral responses during the CS could be recorded.

Control subjects habituated to the presentation of the CS. Figure 11 (p. 48) presents the duration of activity for a Control subject surrounding the presentation of the CS. Figure 12 (p. 50) shows the filtered activity channel of the last session for the same subject. There is no behavioral activity in response to the presentation of the CS.

Activity surrounding the presentation of the CS-UCS compound for Experimental subjects is shown in Figures 13 (p. 52) and 14 (p. 54). As with the electrophysiological activity, manipulation of the inter-trial interval and the frequency of stimulus pairings per session effected the behavioral activity. With the reduction of the inter-trial interval from ten minutes to five minutes there is a reduction of behavioral activity following the second presentation of ICS, as is shown in Figure 14, session 5, trial 2. Also when additional stimulus pairings were presented,

FIGURE 10

Polygraph record for one subject with an intended electrode placement in the cortical amygdaloid nucleus showing artifact (A) in the behavioral activity channel in response to the onset and duration of the conditional stimulus (CS).

R-14

ACO

BIPOLAR



BIPOLAR



EVENT

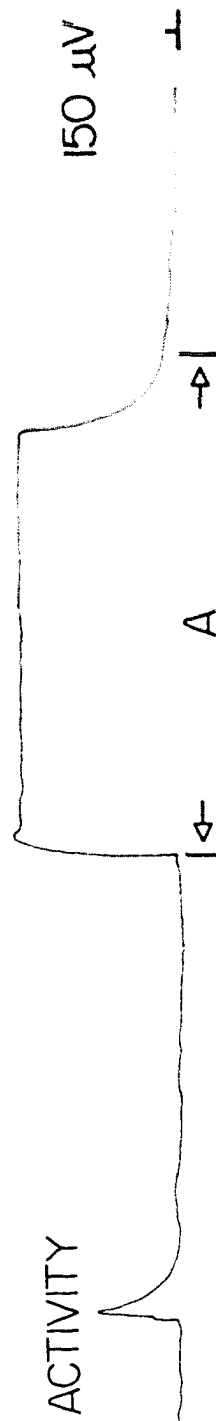
CS



MONOPOLAR



ACTIVITY



5 SECONDS

FIGURE 11

Duration of behavioral activity in seconds across the several fifteen second segments pre- and post-conditional stimulus presentation during Sessions 1 and 4 for Control Subject R-14.

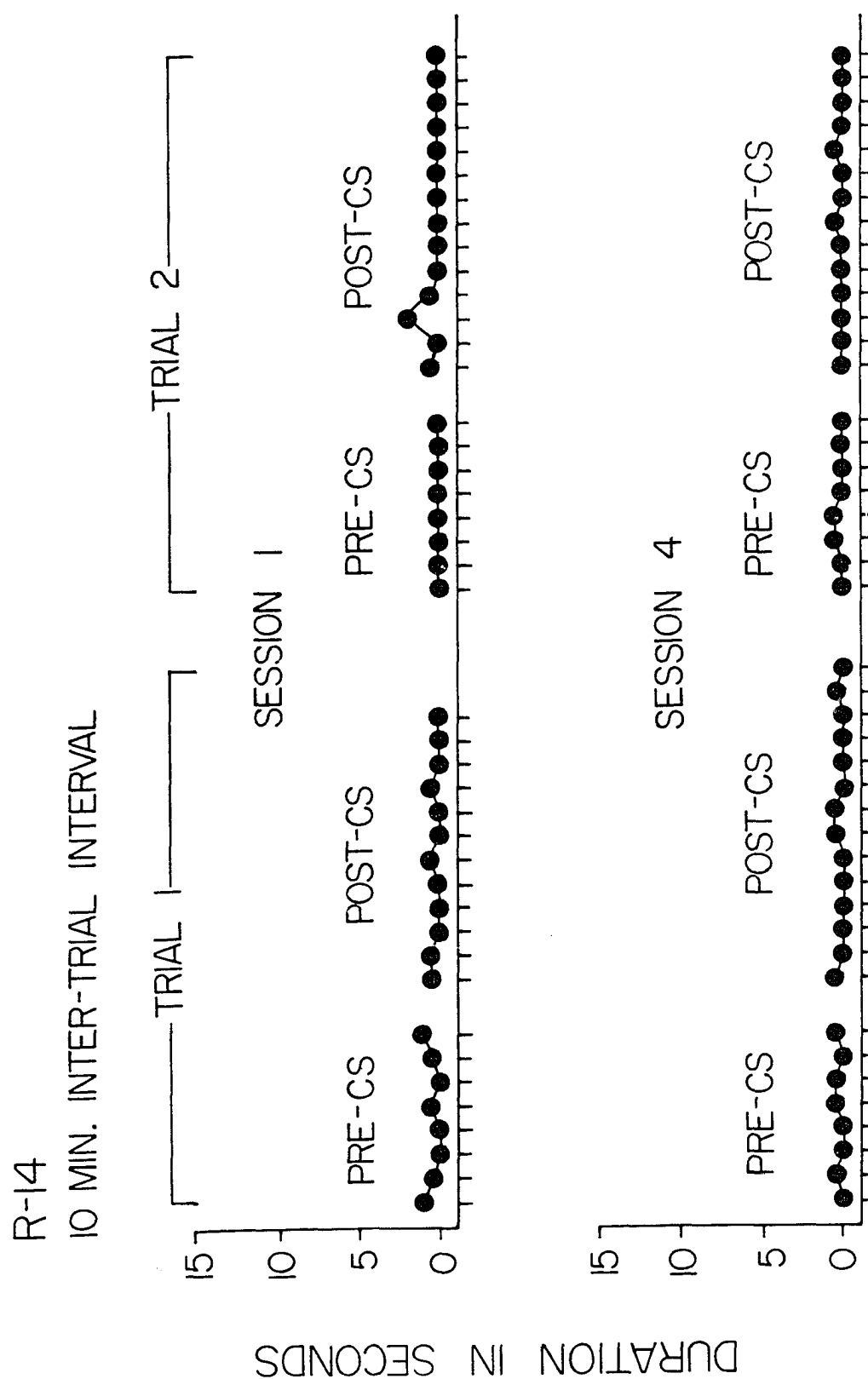


FIGURE 12

Polygraph record for a Control Subject with the intended electrode placement in the cortical amygdaloid nucleus showing the conditional stimulus (CS) induced artifact filtered from the behavioral activity channel.



R-14
ACO

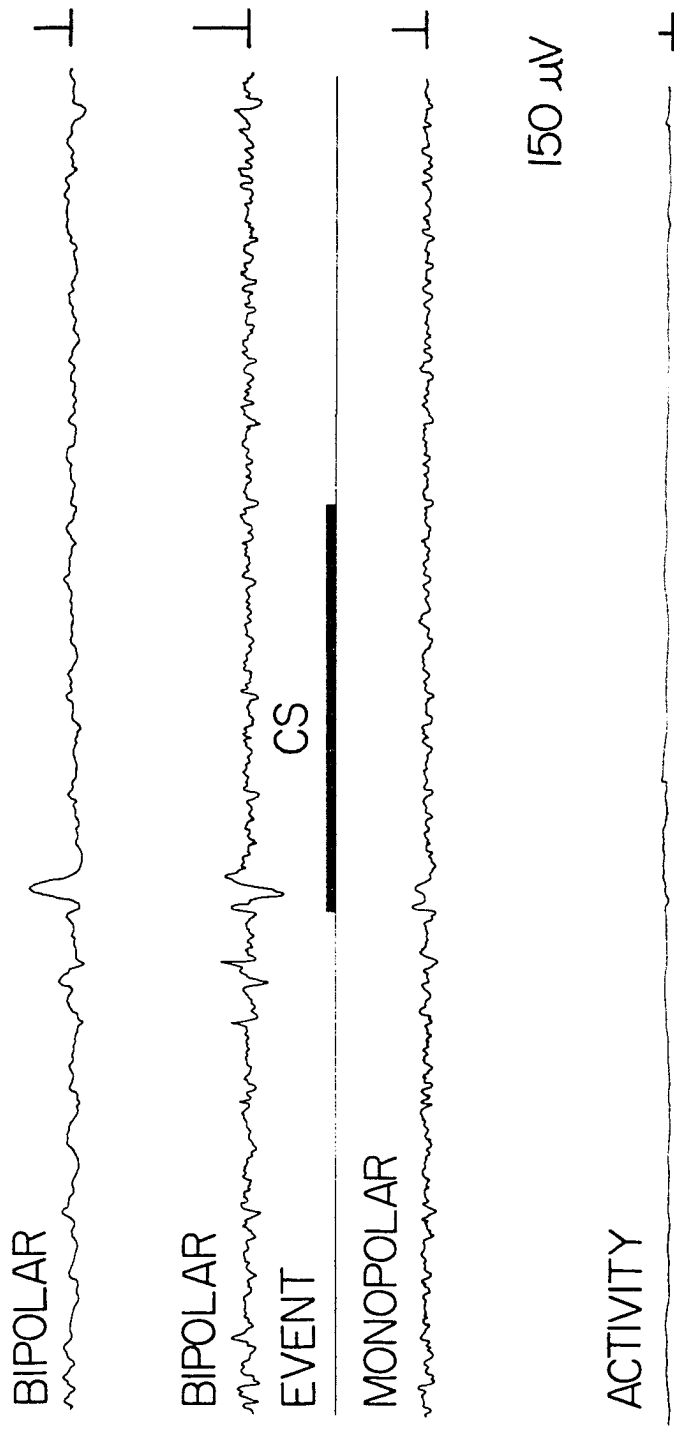
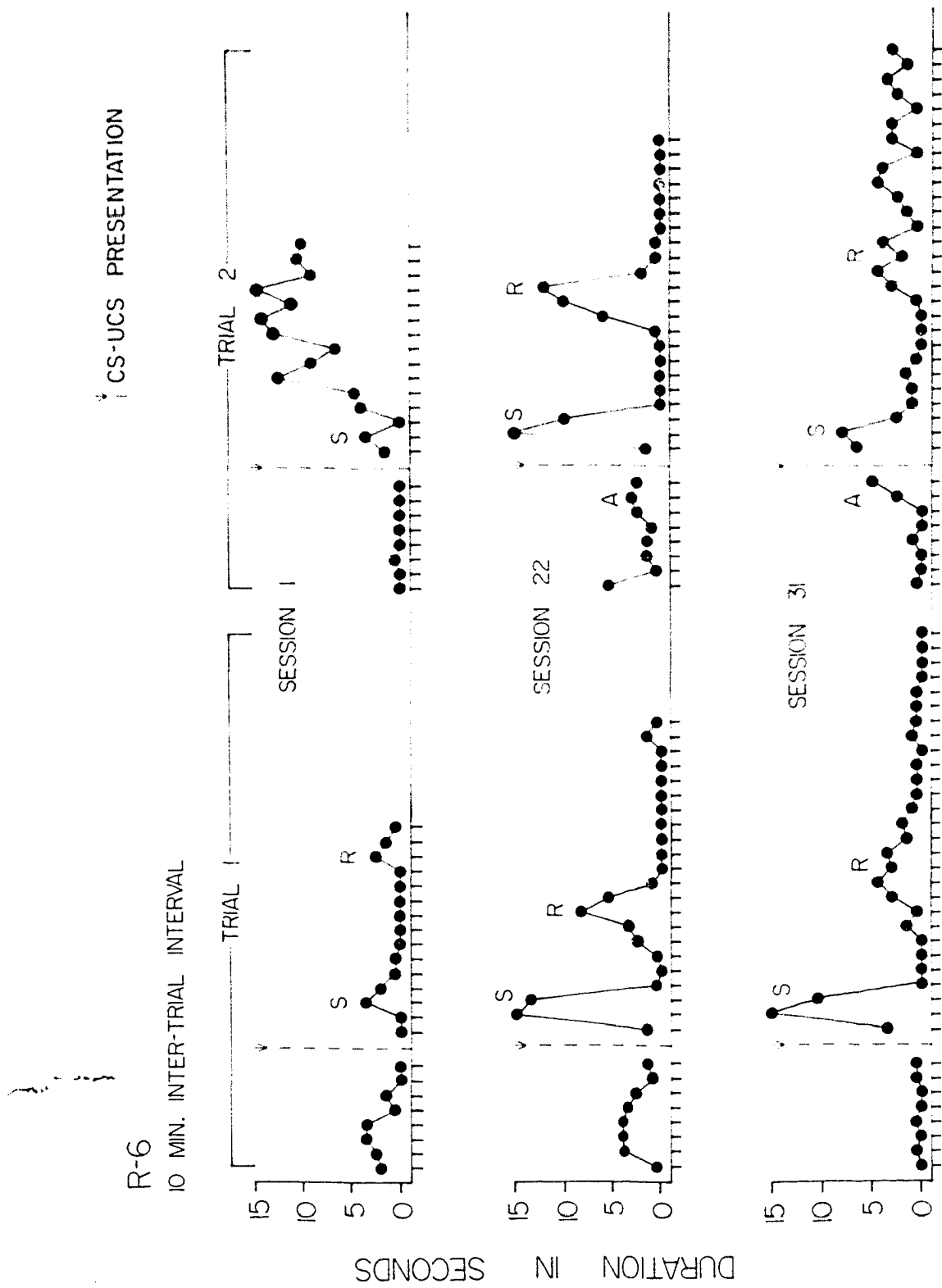


FIGURE 13

Duration of behavioral activity in seconds across the several fifteen second segments surrounding the presentation of the conditional (CS) and unconditional (UCS) stimulus compounds for Sessions 1, 22 and 31 for Experimental Subject R-6. (A) indicates behavioral activity prior to delivery of the second CS-UCS compound. (S) indicates behavioral activity during paroxysmal slow wave discharging. (R) indicates behavioral activity during behavioral recovery.

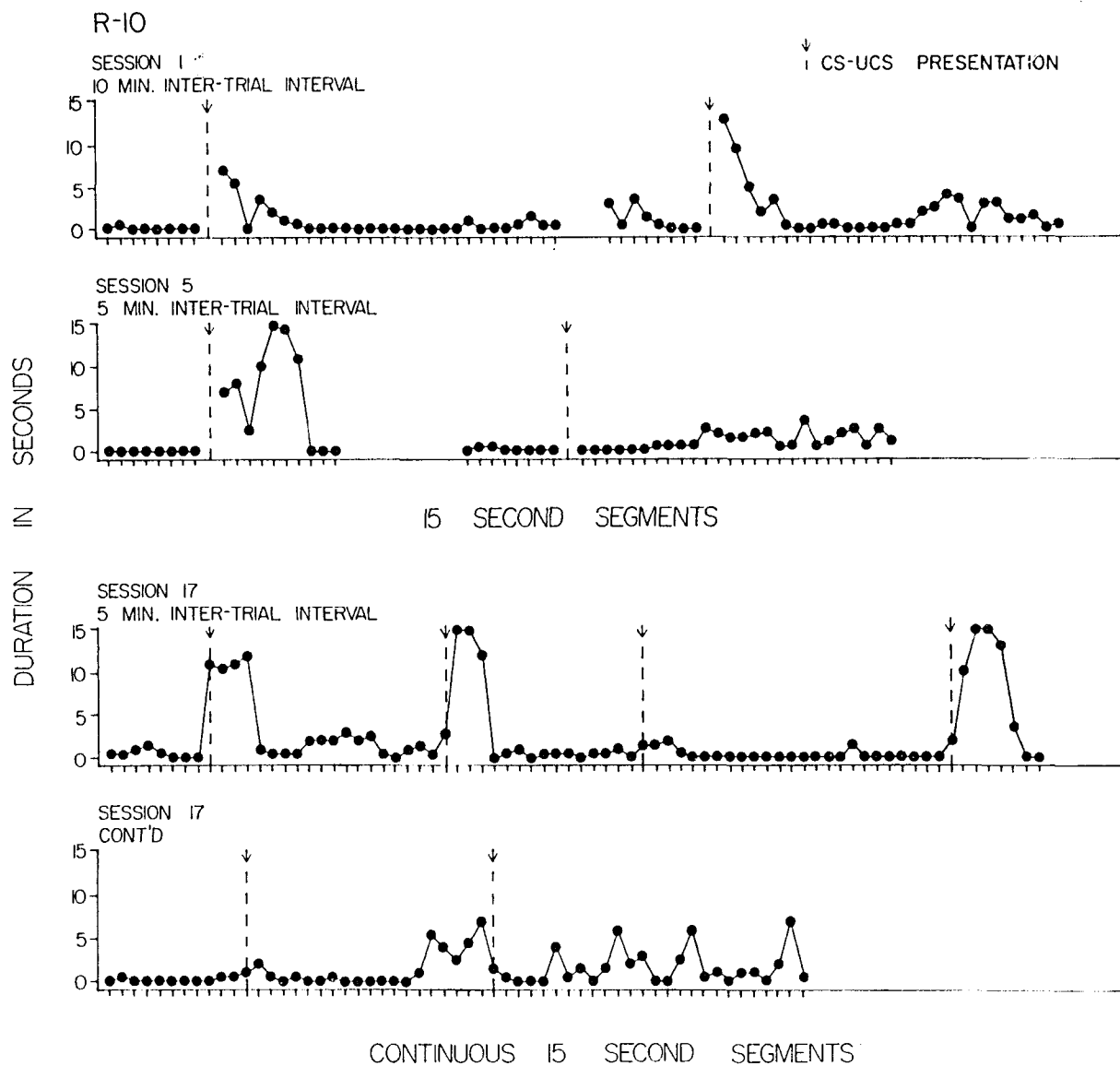


15 SECOND SEGMENTS

FIGURE 14

Duration of behavioral activity in seconds across the several fifteen second segments surrounding presentation of the conditional (CS) - unconditional (UCS) stimulus compounds for Sessions 1, 5 and 17 for Experimental Subject R-10.

:



behavioral activity following trials two through six showed an increase as a function of successive stimulus pairings, but still remained at a level lower than that following the initial stimulus presentation of the session (Figure 14, session 17). In Experimental subjects when the behavioral activity durations per 15 second segment of time were graphically depicted (Figure 13), certain behavioral components could be seen. In Figure 13, A is activity which is occurring just prior to onset of CS, S is seizure activity and R is behavior occurring during the recovery period. Also in Figure 13 can be seen the gradual increase of behavioral activity prior to onset of CS across sessions (Trial 2 sessions 1, 22, 31). Figure 15 (p. 57) presents the filtered activity channel for an Experimental subject. It can be seen that at the onset of CS there is an immediate behavioral response (segment A) lasting for two and 3/4 seconds.

Paroxysmal spiking activity was suppressed during the presentation of the CS in Experimental subjects. An example of this activity and the suppression of it is presented in Figure 16 (p. 59). Paroxysmal spikes appear at points A, B and C. During the CS, no paroxysmal spikes are present. Graphic representation of the effect of the CS on paroxysmal spiking activity is shown in Figure 17 (p. 61). Experimental subjects R-6, R-7 and R-12 show suppression of paroxysmal spiking during the CS in

FIGURE 15

Polygraph record for Experimental Subject R-12 with an electrode placement dorsal to the basolateral amygdaloid nucleus. (A) indicates the behavioral response to the onset of the conditional stimulus (CS) when the CS has been filtered from the activity channel.

R-12
ACO

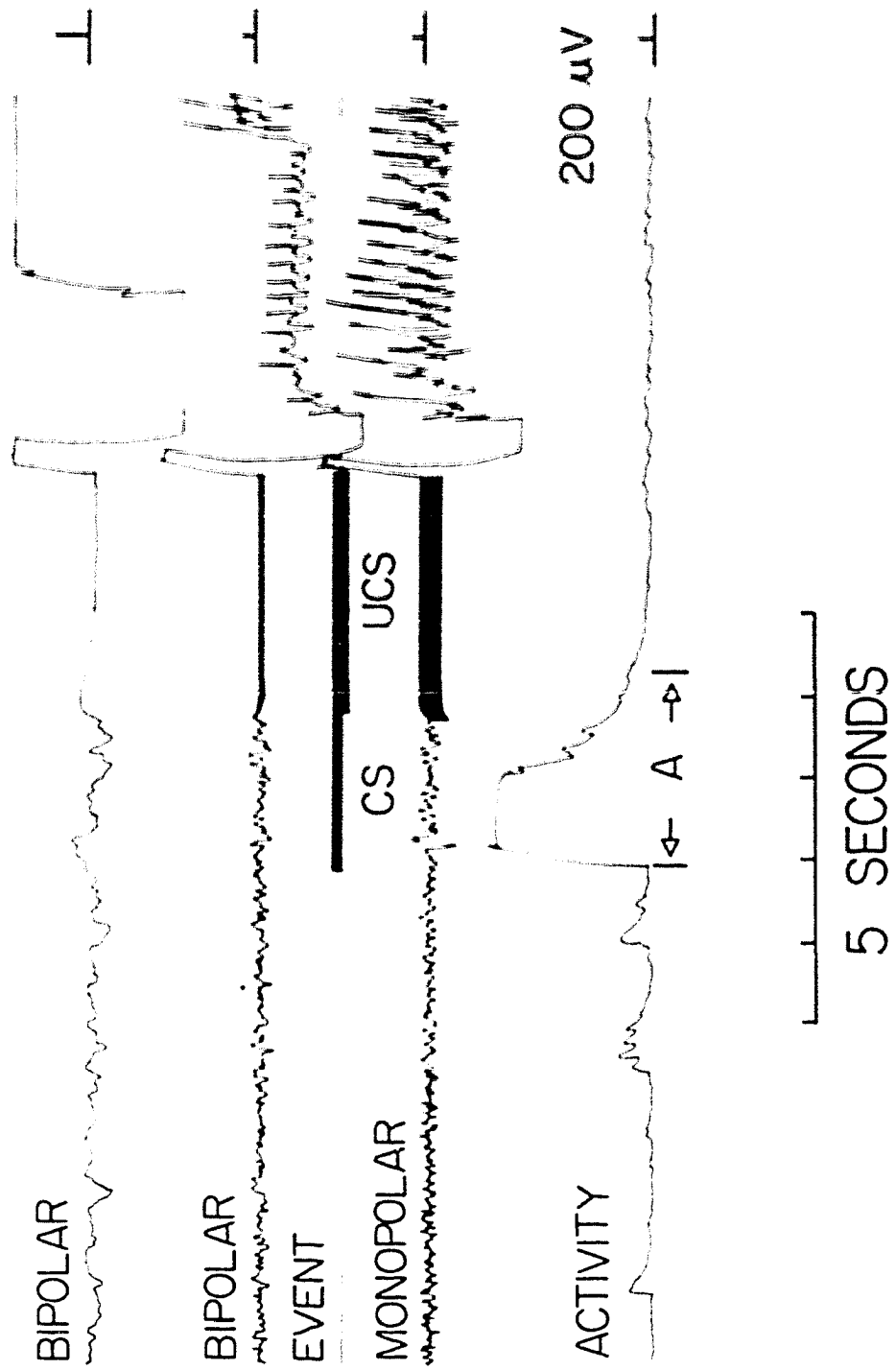


FIGURE 16

Polygraph record of Experimental Subject R-7 with an electrode placement in the basolateral amygdaloid nucleus showing paroxysmal spiking activity at (A), (B) and (C) prior to onset of the conditional stimulus (CS).

R-7
ABL

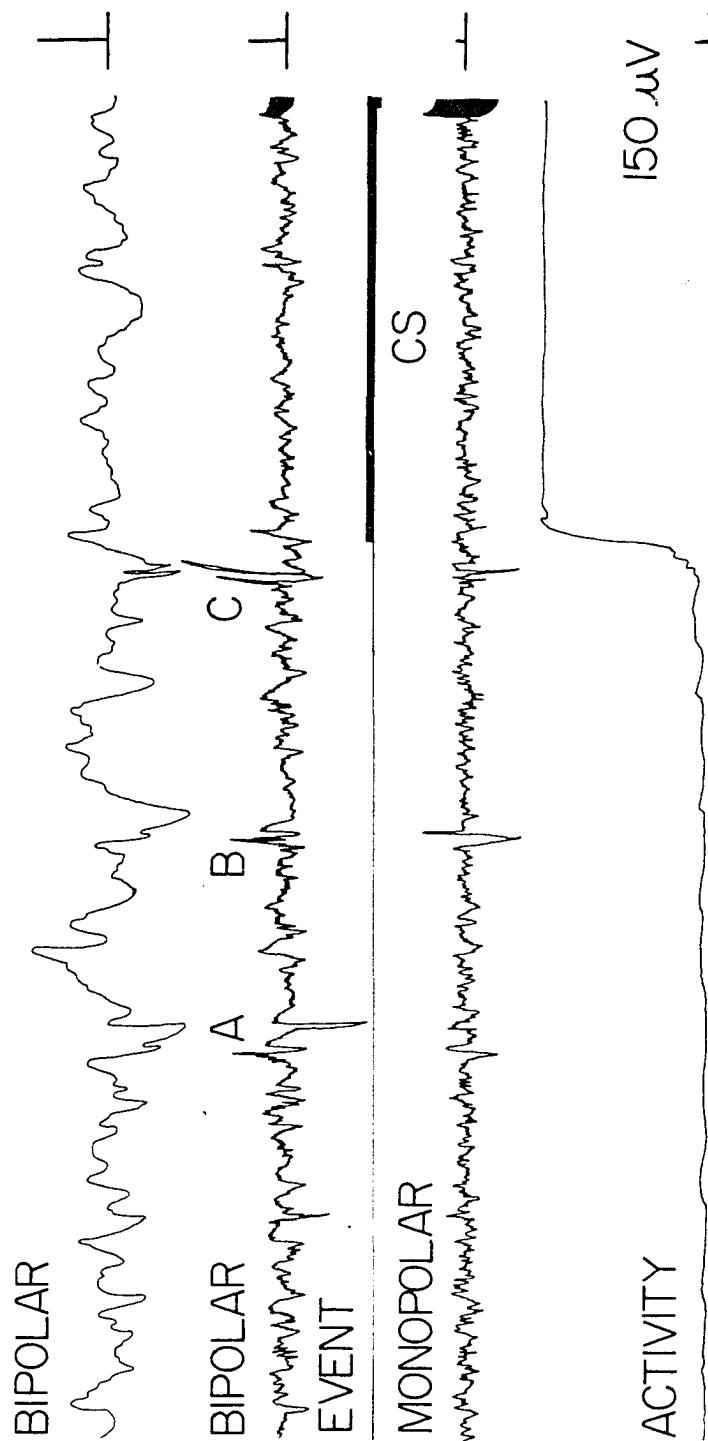
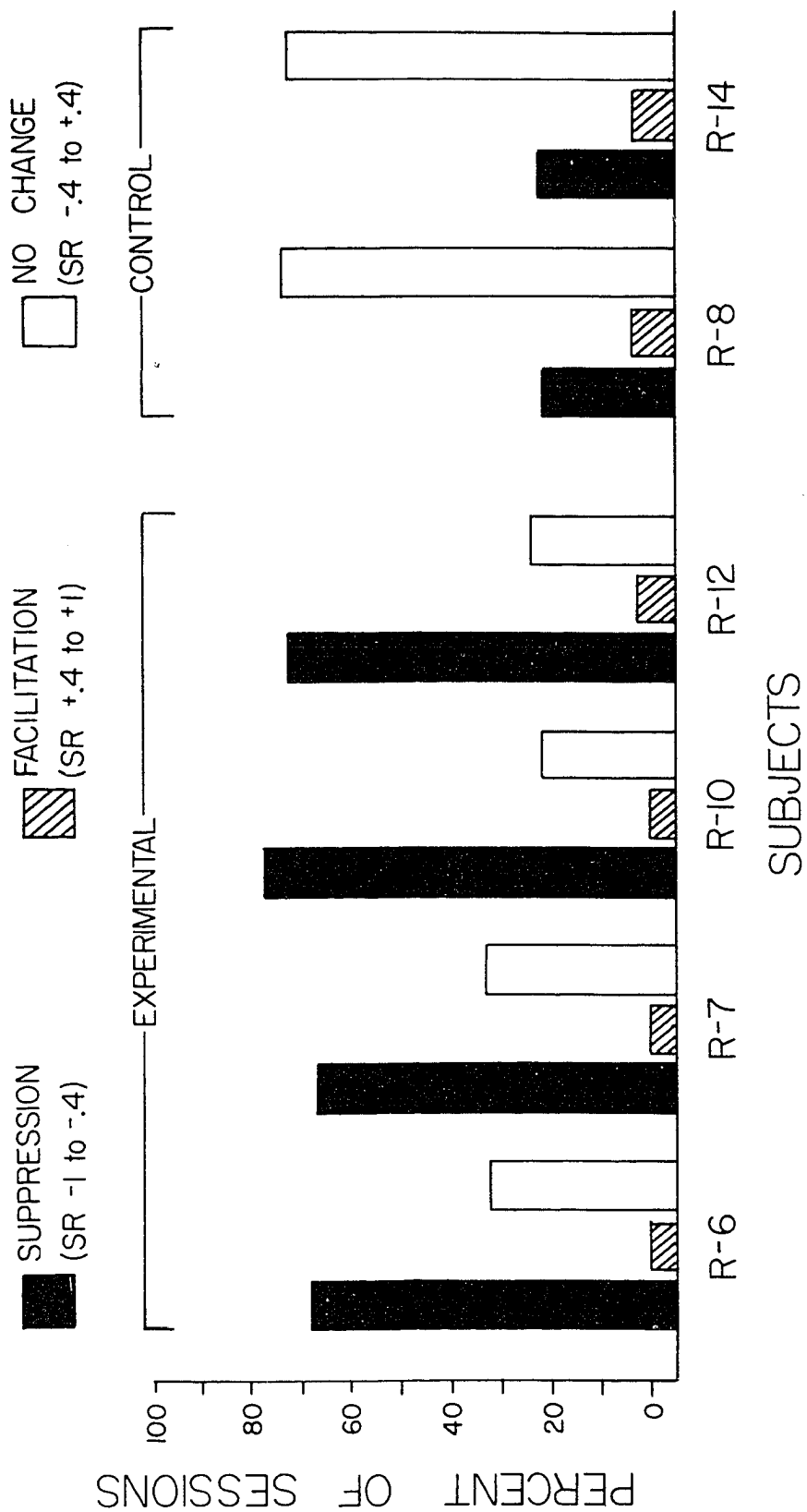


FIGURE 17

Per cent of sessions showing Suppression, Facilitation or No Change in paroxysmal spiking as a function of Experimental and Control Subjects. Ratios were computed using the formula $SR = \frac{D-P}{D+P}$, where SR is equal to Suppression ratio, D is equal to the number of spikes per second During-Tone (conditional stimulus) and P is equal to the number of spikes per second in a ten second sample Pre-Tone.



68, 67, 78 and 73 per cent of the sessions respectively, while Control subjects R-8 and R-14 evidence suppression in 22 and 23 per cent of the sessions respectively. Control subjects fell mainly in the "No Change" category (74 and 73 per cent for R-8 and R-14 respectively). Both Experimental and Control subjects showed little if any facilitation during the course of the experiment (none for Experimental subjects R-6, R-7 and R-10, three per cent of the sessions for Experimental subject R-12, and four per cent of the sessions for both Control subjects). A one way analysis of variance was performed on the per cent of sessions showing Suppression for Experimental and Control subjects to determine if there was a significant difference between the two groups. The summary table is presented in Table 4 (p. 63). As can be seen an F value of 35.28 was obtained with an F value of 21.20 needed at the .99 confidence level.

Histological Results

All intended electrode placements were within the amygdaloid complex. Histology verified the intended amygdaloid placements in two subjects (R-6 and R-7, basolateral amygdaloid nucleus). Electrode placement for R-10 was intended for the basolateral amygdaloid nucleus and was verified as being in the lateral amygdaloid nucleus. Electrode placement for R-12 was

Table 4

Summary Table for One Way Analysis of Variance

<u>Source</u>	<u>Sum of squares</u>	<u>D.F.</u>	<u>Mean square</u>	<u>F.</u>
Between	3536.33326	1	3536.33326	35.28
Within	401.00000	4	100.25000	
Total	3937.33323	5		

$F = 7.71$ at the .95 Confidence level

$F = 21.20$ at the .99 Confidence level

intended for the cortical amygdaloid nucleus and was verified as being in the area dorsal to the basolateral amygdaloid nucleus and ventral to the caudate nucleus of the putamen. Subject R-8 had an intended placement within the central amygdaloid nucleus and was verified as having a placement at the ventral border of the optic tract. The sixth subject was lost during perfusion and was not available for histological localization. Histological coordinates are presented in Table 5 (p. 65).

Table 5

Histological Results*

<u>Subject</u>	<u>Structure</u>	<u>Anterior- posterior</u>	<u>Lateral</u>	<u>Horizontal</u>
R-6	Cortical-basolateral Amygdaloid nucleus	3.8	5.0	-3.5
R-7	Basolateral Amygdaloid nucleus	3.6	6.0	-3.6
R-8	Globus pallidus-Optic tract	4.8	4.0	-1.5
R-10	Lateral Amygdaloid nucleus	6.4	4.7	2.0
R-12	Basolateral Amygdaloid nucleus-Putamen; Caudate nucleus	3.8	5.5	-2.5
R-14	Lost in Perfusion			

*Coordinates from Pellegrino and Cushman (1967)

DISCUSSION

The present research had two main goals, the first of which was to develop a reliable technique for simultaneously sensing and recording behavioral and electrophysiological activity associated with seizure activity. Other activity sensing devices have already been discussed. The present technique was demonstrated to lend itself more reliably to data analysis than a system which incorporated a video tape recorder (Ellinwood et al, 1970). Repeated standard inputs were shown to produce the same response using this technique and the system was sensitive to differing amounts of force. Temporal relationships between electrophysiological events and behavioral events are readily accessible. Also available in their correct temporal relationships are variables which are manipulated during the course of research. Figure 15 (p. 57) is an illustration of the immediate availability of the temporal relationships between the electrophysiological data, the behavioral data, the onset and duration of the CS and the onset and duration of the UCS.

Utilization of the polygraph to record the behavioral activity also reduces some of the analytical problems inherent in such data. With simple analysis involving the use of the planimeter as previously described,

behavioral activity may be presented as in Figures 11 (p. 48), 13 (p. 52) and 14 (p. 54). Utilizing different voltage levels as a means of describing classes or magnitudes of behavior, duration of different magnitudes of behavior can be extracted from the raw data. For more sophisticated analysis, the behavioral activity data is available as an analog signal. With analog to digital conversion, high speed, complicated analysis could be conducted using a computer.

A previous attempt to record behavioral and electrophysiological activity has been presented by Ellinwood et al (1970). Split screen video recording of the behavioral activity and the electroencephalographic record of cats was used. Limitations of such a technique are that only a fractional part of the total record can be viewed at one time, and that analysis other than visual scanning of the video recording is nearly impossible. Also when this system was compared to the present method, data analysis using the present method proved to be less variable both within and across observers than data analysis using the video recording.

Even though the development of the activity sensing technique was successful, there are areas which need improvement. In obtaining an area of sensitivity which would be able to detect the higher magnitude of motor behavior in seizures, the very low magnitude behaviors

such as a slight head movement or jawing were not sensed. Therefore a means of broadening the range of sensitivity so that the entire continuum of motor behavior may be sensed, is indicated. Also the present method is not as specific in its differentiation of behaviors as McClelland's (1965) previously described capacitance method.

The second goal of the present research was to attempt preliminary investigation in the area of classically conditioned epileptiform activity. Indication of a conditioning effect could be expected to occur either in behavioral activity or electrophysiological activity.

This investigation utilized the activity sensing device as an integral process for recording the behavioral data. The occurrence of a behavioral response at the onset of the CS for Experimental subjects was shown by the activity sensing device. If the filtering of the activity channel had occurred at an earlier point in the study, the development of the behavioral response over sessions might very well have been seen. Substantiating data in the form of activity duration prior to the onset of the CS are presented in Figures 13 (p. 52) and 14 (p. 54). These figures indicate that there is an increase in behavioral activity prior to onset of the CS over sessions. This is to be compared with the behavioral habituation to the CS prior to and post-CS delivery in the Control subjects

(Figure 11, p. 48) and also the lack of a behavioral response to the CS when the activity channel had been filtered (Figure 12, p. 50).

The data presented in Figure 17 (p. 61) indicate that paroxysmal spiking activity is occurring in the Control subjects (i.e. the occurrence of facilitation and suppression for the Control subjects). Actually the presence of the suppression and facilitation in the Control subjects reflects the fact that the SPS was calculated for all activity occurring above the minimum voltage requirement. Therefore Figure 17 reflects activity which just barely enters the lowest class interval of spiking activity.

Precursor slow wave activity in the cat has been described by Wyss, Frankhauser and Crowell (1969). This high amplitude wave form initially appears prior to any clinical or electrophysiological indication of seizure activity. Eventually the precursor slow wave initiates full epileptic seizures. DeFrance and Hutchinson (1971) also report finding this wave form preceding epileptiform activity in the monkey.

The paroxysmal spiking activity which was suppressed in the Experimental subjects would most likely be explained as being resultant of the previous seizure rather than causative of a succeeding seizure. However there could possibly be some relationship between the

precursor slow wave activity and the present spiking activity. If, in fact, they are related then manipulation of this activity would be a valuable technique for further investigation of electrophysiological seizure activity.

The present results would indicate that learning is evident in terms of both behavioral and electrophysiological activity. These results seem to be in direct opposition to the conclusions of McIntyre (1970) and Herz and Peeke (1968) who found that administration of ICS of such a magnitude as to produce seizures also produced retrograde amnesia which precludes learning immediately prior to the ICS.

In summary, the present research produced a reliable method for sensing and recording simultaneous behavioral and electrophysiological activity. Concurrently with the development of this method, preliminary investigation as to the possibility of classically conditioned epileptiform activity was attempted. It was found that a behavioral response to the onset of the CS developed over sessions in Experimental subjects but did not develop in Control subjects. Also paroxysmal spiking activity was suppressed during the CS for approximately 70 per cent of the Experimental sessions. There was "No Change" in the electrophysiological activity of the Control subjects during approximately 70 per cent of the Control sessions.

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