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Brain reward and brain seizure systems : an anatomical connection in the rat.

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BRAIN REWARD AND BRAIN SEIZURE SYSTEMS- AN ANATOMICAL CONNECTION IN THE RAT

by

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ABSTRACT

Various organisms, including man, will repeatedly press a bar or a switch to obtain electric shock to specific points in the brain. The phenomenon, now called electrical self stimulation (ESS) has been demonstrated from various brain areas. Attempts to control epileptic seizure have revealed seizure systems from various brain areas. The observation that rats may go into seizure following ESS raises the possibility that brain reward and brain seizure systems overlap. The purpose of this study was to examine the possibility that systems mediating reward may interact with brain areas mediating seizure.

A series of rats, implanted with chronic electrodes with stimulating tips in and near the basal septum, was tested for incidence of ESS. Subjects (Ss) demonstrating ESS were divided into two groups. The first group was allowed to self stimulate (SS) at successively higher current levels until either seizure occurred or 1000 microamperes (ua.) was reached. Seizure thresholds were recorded and then programmed stimulation (PES) was applied to these animals and seizure thresholds re-established. The second group of self stimulators together with a third group of Ss who did not demonstrate SS, were given comparable levels of PES as were recorded for the first group under SS. This was done to determine if convulsive seizures could be induced in these animals.

For Ss demonstrating ESS and seizure, ESS occurred at a

lower intensity level than seizure. A significantly greater incidence of seizure was found for Ss demonstrating ESS than for Ss who did not self stimulate. However no difference in seizure incidence was found for animals during SS compared to PES. No changes could be demonstrated in brain impedance for the three groups before, during and after seizure.

It was concluded that for some electrode placements, electrical stimulation could be activating two brain systems at the same time- one mediating reward and the other manifesting seizure. Some types of seizures may therefore have reinforcing properties. For some seizures, a treatment program that uses conditioning techniques may be ignoring a crucial reward variable affecting seizure frequency.

PREFACE

I would like to dedicate this thesis to my advisor, Dr. David Reynolds, who gave me a free hand in completing the project, but at the same time was always available for guidance whenever I needed it. He always seemed to have a way of putting those things in clear perspective which were often the cloudiest to me.

I would like to extend a special thanks to my committee members, Dr. Theodore Hirota and Father Claude Vincent, for showing exceptional patience over the long haul, especially toward the end.

A big thanks goes out to Marilyn Bell without whose help I would never have finished this manuscript on time.

The final acknowledgement must go to my parents. Their hard work and faith in me provided the final spark with which I could accomplish my goal.

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CHAPTER 1
INTRODUCTION

Twenty years ago, Olds and Milner (1954) reported that rats would repeatedly press a bar to obtain brief electric shocks to the brain. The animals pressed the bar in the absence of any conventional primary reinforcer such as food or drink. Since this initial report, the phenomenon, which has come to be called electrical self stimulation (ESS), has been used to demonstrate many interesting brain-behaviour relationships (Bishop, Elder and Heath 1963; Herberg 1963; Wilkinson and Peele 1962) from divergent brain areas (Olds 1956; Olds 1960; Lilly 1958).

Attempts to control epileptic seizures have also yielded fascinating discoveries regarding brain-behaviour relationships (Penfield and Jasper 1954; Sperry, Gazzaniga and Bogen 1969; Mark and Ervin 1970) from different brain areas (Penfield and Roberts 1958). At the same time, surgical intervention for epilepsy control has not been without cost to the patient (Penfield and Milner 1957). Because of this, drug therapy has been used for seizure control. But side effects from chronic drug taking are well documented, and increased drug dosage does not always control seizure activity. The resistance of seizures to control by drugs has often been

attributed to "sensitization"- an increased susceptibility of the brain to seizures as a consequence of previous repeated seizure activity. There is considerable evidence to support this (Goddard, McIntyre and Leech 1969; Tress and Herberg 1972).

With the emergence of behaviour modification techniques, it was only a matter of time before an attempt was made to reduce or eliminate seizures through conditioning techniques. Some success has been reported (Efron 1957; Delgado 1970). The extent to which this approach will be either practical or successful depends on a variety of factors. One factor is the extent to which the seizures themselves may be reinforcing. This unlikely possibility suggested itself as a result of an incidental finding in our laboratory and has also been reported by others (Porter, Brady and Conrad 1959; Malsbury 1971). One of the consequences of self stimulation in rats is the self induction of epileptic seizures. These seizures seemed to originate, however, only from electrodes in and around the diagonal band of the basal septum. The fact that seizures might have a close anatomical relationship to brain systems mediating reward has obvious implications for any attempt to control seizures through reinforcement techniques. The present experiment was carried out to determine if, in fact, a common anatomical substrate does exist, and if it does, to determine the likelihood that seizure activity originating in or involving basal septal regions may be activating

brain reward mechanisms.

The basic electrical self stimulation paradigm allows the subject (S) access to a switch, which if depressed, delivers brief electric shocks to specific points in the brain through permanently implanted electrodes(coated needles exposed only at the tip)(Grossman 1967). Some tissue damage results from electrode implantation. However, investigators have reported that after initial damage, repeated stimulation does not result in further tissue damage (Valenstein and Beer 1964; Goddard et al 1969).

Since the first study involving rats (Olds and Milner 1954), the phenomenon has been confirmed in cats (Wilkinson and Peele 1963), monkeys (Bursten and Delgado 1958; Briese and Olds 1964), and man (Bishop et al 1963).

Instrumental responses can be acquired with intracranial reward (ICR) when no other "incentive" or reward is used (Schhitzer, Reed and Porter 1965). However, an analysis of ESS paired with primary rewards offers some insight into the underlying mechanisms of the reinforcement properties of ESS. Stimulation of the lateral hypothalamus produces both "stimulus bound" eating and high self stimulation rates. Food deprivation in the same Ss was often found to result in a major increase in self stimulation rates (Margules and Olds 1962; Hoebel and Teitelbaum 1962; Robinson and Mishkin 1962). "Stimulus bound" drinking as well as high self stimulation rates have been demonstrated in the lateral hypothalamus (Mogenson and Steven-

son 1966; Mendelson 1970). Water deprivation was also found to affect ESS rates in a similar manner (Brady 1958). Prescott (1966) reported that vaginal cornification in female rats, indicating increased sexual receptivity during estrus, is associated with increased self stimulation rates in the posterior hypothalamus. Electrical self stimulation rates were found to increase with the systemic injection of testosterone (a male hormone) in male rats. Constant stimulation of the same site elicited immediate copulation with female rats (Caggiula and Hoebel 1966). Similar sexual responsiveness and self stimulation has been reported from the same neural region, often accompanied by ejaculation (Herberg 1963; Robinson and Mishkin 1962; Caggiula 1970).

Fluctuations in ESS rates have been demonstrated to be specific to certain drives. Wilkinson and Peele (1962) found that food deprivation increased ESS rates only in certain areas of the lateral hypothalamus but did not affect rates at other electrode placements. More recent research however has shown that eating and drinking can be elicited through stimulation of the same hypothalamic electrode. Different current intensities were used to demonstrate that stimulation produces eating at a lower current level and drinking at a higher level (Wise 1968).

Intracranial stimulation can therefore act as a "primary reinforcer" and its effects appear to be associated with "primary" drives such as hunger, thirst and sex.

Electrical self stimulation in rats has also been demonstrated to result in epileptic-type afterdischarges in widespread brain areas. This sometimes leads to convulsive seizures, or more commonly, to brief behavioural pauses. During these pauses, animals "freeze" for some seconds before they resume responding (Porter, Brady and Conrad 1959; Newman and Feldman 1964; Bogacz, St. Laurent and Olds 1965). Both types of attacks show a reduced incidence after administration of anti-convulsant drugs (Reed, Gibson, Gledhill and Porter 1964; Mogenson 1964).

Incidence of epileptic afterdischarges during ESS has prompted the suggestion that ESS might be directly related to seizure activity (Porter et al 1959; Newman and Feldman 1964). In effect, the electrical stimulation could result in "small" seizures sometimes developing into "full blown" convulsions. It has been suggested that the seizures themselves might be responsible for the reinforcing property of the brain shock (Bogacz et al 1965). To test for this possibility, rats were implanted with electrodes in various brain areas (ventro-lateral tegmentum, posterior lateral hypothalamus, anterior lateral hypothalamus, epithalamus, tectotegmental area and visual cortex) and tested for self stimulation (SS) at the various electrode placements. If SS developed, a response sequence was arranged allowing 10 SS responses to be followed by 10 free but unreinforced responses. This procedure was repeated three times during any one session. EEG recordings were taken during

the unreinforced response periods. If SS failed to develop with a given electrical stimulus, a similar response sequence was arranged. Ten forced stimulations (administered by the experimenter) were followed by a 12 second interval of no stimulation. This procedure was repeated three times with EEG recordings taken during the 12 second non-stimulation period. The experimenters found that epileptiform activity was produced equally in electrodes that did, as well as electrodes that did not, yield self stimulation. The authors concluded that "no significant relationships could be demonstrated between self stimulation and epileptiform activity, at least judging from the threshold values for the latter or from its duration and generalization which did not seem enhanced when induced in optimal sites for self stimulation".

The conclusions of Bogacz et al (1965) seemed to dissociate ESS and epileptiform activity. However, some Ss demonstrated full blown convulsions following ESS. This has also been reported by others (Newman and Feldman 1964; Malsbury 1971). This finding could be explained by inferring that ESS is concurrently activating brain reward and brain seizure systems. The reinforcing property of ESS need not be due to seizure onset, but ESS may be contiguously activating anatomically proximal brain systems- one mediating reward and another manifesting seizure.

To imply different but overlapping systems for brain reward and brain seizure, it would seem necessary to demon-

strate that ESS and seizure can occur separately (i.e. independent of one another), as well as together. Specifically, it should be possible to demonstrate SS without seizure, seizure without SS, and both SS and seizure together.

Reference has been made in the literature to human patients bringing on their own seizures, i.e. self induction of seizures (Gastaut and Broughton 1972). Since seizures have been shown to be initiated by rats during SS, this raises a question as to the role of the subject as an active or passive participant in seizure elicitation. There is some evidence in aversive situations that the subject's involvement (active or passive) can lead to different results. Weiss (1968) yoked three rats together to receive aversive electric shock. One S was given a warning light before the shock was delivered, and could press a switch to defer the shock for himself and his yoked partners. His partners could also depress a switch, but this had no effect on delivery of the shock. Weiss found that those Ss who could not control the occurrence of shock were more likely to develop ulcers, even though all three Ss received the same number of shocks. In an SS situation, Ss might be able either to hasten or defer seizures by subtle shifts in bar pressing, whereas Ss receiving programmed stimulation might not. Thus, the role of self involvement in the seizure process could yield some valuable information regarding the extent of control an organism might exert over brain seizures.

In a somewhat different but related problem, brain impedance has been shown to change during and after SS (Reynolds 1963). More recently however, no relationship between brain impedance and seizure afterdischarges could be established (Racine 1971). Brain impedance measures the total opposition of tissue to current within the stimulating circuit (Delgado 1960). If, as some have suggested, impedance decrease reflects increased activity of neuronal tissue surrounding the recording electrode, sytematic changes in impedance may help clarify the relationship of brain activity, SS and seizures.

HYPOTHESES

The preceding review raises the following specific questions-

1. Seizure and self stimulation have been elicited from the same electrode. Can seizure and self stimulation be elicited separately? If so, then it would support the notion that there are separate but overlapping systems within the brain that mediate seizure and self stimulation.

Seizures have classically been considered aversive. However, the possibility of anatomically overlapping brain reward and brain seizure systems raises the possibility that some seizures may have reinforcing effects. What is the relative incidence of seizures among self stimulating and non self stimulating Ss? If a greater incidence of seizures is found among SS Ss than non SS Ss, this would suggest that seizures in some cases may have rewarding concomitants. If no difference is found, then there is no reason to believe that there is any special relationship between the two. If a greater incidence of seizure is found among non SS Ss than among SS Ss, this would suggest that seizures have little or no direct effect on reward systems.

2. Some experiments have used active ESS while testing for seizures (Bogacz et al 1965), while others have used programmed stimulation (PES) after ESS had been demonstrated (Herberg et al 1969; Tress and Herberg 1972). What, if any, is the role of self involvement on the incidence of seizures?

If for SS Ss, active ESS hastens seizures, it could be said that SS Ss are seeking seizures. If during active ESS seizures take longer to develop, then it could be argued that self stimulators are deferring seizures, and that seizures are aversive. If no difference is found, then it can be presumed that seizures are basically neither reinforcing or aversive in the area studied or that the experimental method cannot discriminate as to the reinforcing properties of seizures.

3. Is there any relationship between brain impedance, ESS and seizures? The investigation of impedance changes during ESS and during behavioural seizures from the septal region may be helpful in determining neural mechanisms basic to each.

CHAPTER 2
METHOD

Subjects

Twenty four male albino rats (Wistar strain) were used with a weight range between 350 and 450 grams. The majority of subjects were bred at the University of Windsor, Windsor Ontario. Three were obtained from Woodlyn Farms, Guelph, Ontario. Food and water was available ad lib throughout the study.

Apparatus

Solid state programming units (BRS Digi-Bits) connected to a test chamber (Lehigh Valley, Model # 1417) were used to set up the basic 10 minute stimulation session during which brain stimulation was delivered. Self stimulation and programmed stimulation procedures were both programmed in the same unit, allowing either procedure separately. At the end of the 10 minute session, the unit was programmed to open a relay to discontinue any further brain shocks. A 5 minute "extinction" phase was then initiated. Termination of the extinction phase ended the session. A pulse generator (Berl-Model 210, constant current source), monitored on an oscilloscope, (Tektronix Inc., Type 422) was used to deliver brain shocks.

The subjects' bar presses and brain shocks were both separately connected to a cumulative counter. Delivered brain shocks were alsorecorded on a cumulative recorder (R. Gerbrands Co.).

Electrodes

The electrodes (Clay Adams, Type O), were coated with FORMVAR. A reducer was then applied to thin the coat. Electrodes were coated at least four times, and were then baked for 48 hours after each coat at about 350°F. The electrode tips were then exposed by scraping them on sandpaper. Electrode stems were tested for leaks in a saline solution by applying a 30 volt stimulus to the electrodes from an AC power source.

Surgery

All Ss were anesthetized with sodium pentobarbital (NEMBUTAL), supplemented with ether, prior to surgery. One c.c. of NEMBUTAL, diluted in a solution of 10 parts water, was injected per 100 grams of subject's body weight. Unilateral monopolar electrodes were then implanted in all Ss using a stereotaxic procedure described by Hart (1969). The target area was the basal septum and neighbouring structures, in particular the diagonal band of Broca, as specified in De Groot (1961).

Stimulus Parameters

Pulse trains, 0.2 seconds in length, of negative going rectangular wave stimulation (0.5 milleseconds in duration) at a frequency of 100 Hertz were used throughout pretest and test sessions. The amplitude of constant current stimulation

during pretest originated from a base of 50 ua. and was increased in 50 ua. steps from SS threshold levels during daily test session for all Ss.

Procedure

Pretest

The experimental procedure is summarized in Table 1.

After a three day recovery from surgery, a pretest period of up to five daily sessions was used to determine which electrodes would show self stimulation using the method of successive approximations. This involves the experimenter stimulating the S on repeatedly closer approaches to the lever until the S begins to self stimulate. Subjects showing aversive affects to stimulation during pretest were not included in further testing. All Ss responding to shaping with an average of at least 10 self applied brain shocks per minute for any one session were classified as self stimulators. Thresholds for SS were determined by decreasing the current level by 25 ua. during the next session from the level at which SS was first noticed. The lowest level at which SS met the above criterion was regarded as the SS threshold level. All Ss not demonstrating an average of at least 10 bar presses per minute were classified as non self stimulators. Electrical self stimulation was delivered on a continuous reinforcement schedule (CRF).

Test

Subjects demonstrating SS were randomly subdivided into two groups. Group 1 was allowed free access to a bar and was

TABLE 1

Experimental Procedure

Groups	Pre-test	Test
Group 1	1) Subjects (Ss) tested for self stimulation (SS) 2) SS threshold established	1) Ss allowed to self stimulate -daily increase of 50 ua. from SS threshold level -SS until seizure developed or 1000 ua. reached -seizure threshold established -seizure threshold re-established with programmed stimulation (PES) -SS threshold re-established
Group 2	1) Ss tested for SS 2) SS threshold established	1) Ss given PES -each member yoked to one S in Group 1 -stimulus parameters equated with Group 1 partners -PES until seizure developed or 1000 ua. reached -PES seizure threshold established
Group 3	1) Ss tested for SS to maximum of 1000 ua. 2) No SS demonstrated	1) Ss given PES -procedure identical to Group 2 test procedure

tested at successively higher current levels. An increase of 50 ua. per day from individual SS threshold levels was used. The remaining self stimulators (Group 2) and the non self stimulators (Group 3) were individually paired with one of the Ss from Group 1. Similar thresholds for SS were used in pairing Group 1 and Group 2 Ss. Subjects from Group 2 and 3 received programmed stimulation at the approximate daily rate and current intensities (± 5%) recorded for their individual partners from Group 1. Daily sessions continued for the three groups either until seizures occurred, hindering side effects developed (squeaking, high locomotor activity), or a maximum of 1000 ua. was reached. With the onset of seizure, current levels were decreased by one-half the daily increment (25 ua.) for the next session. Seizure thresholds were regarded as the lowest of these two levels during which seizure was elicited for one session. The threshold for seizures was recorded as well as the number of stimulations to seizure, seizure duration, seizure severity and seizure latency (amount of time from beginning of session to occurrence of seizure). Programmed stimulation was discontinued for Group 2 and 3 as soon as seizures were initiated. A behavioural seizure was operationally defined as bilateral clonic activity involving the forequarters and continuing during stimulation as well as after stimulation termination. Stimulation was reinstated when it appeared that the S had sufficiently recovered from the seizure (ranging from about 15 seconds to 3 minutes).

Seizure severity was recorded on a five point scale as utilized by Racine (1971).

Following testing for seizure threshold, Group 1 was retested with programmed stimulation at a rate comparable to that which elicited the initial seizure (± 5%). Stimulation parameters were equated with initial levels recorded during seizure sessions. If seizure was observed on the first day, then current levels were decreased daily by 50 ua. until seizure was no longer elicited in any one session. If seizure was not observed on the first day, then current was increased by 50 ua. daily until either seizure or 1000 ua. reached. Seizure threshold was determined as before.

Groups 1 and 2 were then retested for SS threshold levels in the same manner that was used during pretest.

Histology

Sacrifice

All Ss were sacrificed following the last day of testing and the heads placed in formalin (10%) for a week. The brains were then removed from the skull and left in formalin (10%) for another 10 days. The removed electrodes were then tested for leaks in a saline solution using a 30 volt, 60 Hertz stimulus.

Sectioning

Sections of 50 microns were made using a freezing microtome (AO Model #880). Each third section from the

initial discovery of the electrode tract was preserved. Hand drawings were taken to verify electrode placements. Brain sections were preserved in formalin (10%) for photographing.

Photography

Brain sections were mounted on an overhead projector and exposed to photosensitive paper (Kodak Polycontrast RC paper) for 10-12 seconds. The paper was then placed in a developer (Ilford Bromophen) for 1½-2 minutes, rinsed in clean water and placed in a fixer (Kodak Fixer) for 5-10 minutes. The 4"x5" pictures were then rinsed in water again and dried.

CHAPTER 3
RESULTS

Table 2 indicates the differing incidence of SS and seizure in different subjects. Self stimulation and seizures were demonstrated both separately and together.

Table 3 shows the Group by Group incidence of motor seizures in self stimulating and non self stimulating Ss. A chi square analysis (Ferguson 1971) revealed a significantly greater incidence of seizures among self stimulating Ss (Group 1 and 2) than among non self stimulating Ss (Group 3) ($\chi^2 = 4.26$, d.f. = 1, $p \leq .05$). Individual group comparisons, however, did not reveal a difference in seizure incidence for Group 1 and Group 2 individually when compared to Group 3. A chi square analysis also revealed no difference between Group 1 and Group 2 Ss for incidence of seizures.

Table 4 indicates seizure thresholds for Group 1 during SS and PES and for Group 2 during PES. A comparison of seizure thresholds for Group 1 Ss during SS showed no difference from seizure thresholds recorded for Group 2 Ss under PES. Similarly a comparison of seizure thresholds for Group 1 Ss under SS and PES revealed no difference in seizure threshold. Table 5 indicates a seizure latency and seizure threshold comparison for Group 1 Ss under SS and PES. A significantly shorter latency to seizure onset was recorded during programmed stimulation compared to self

TABLE 2

Combinations of SS and Seizure Within Ss Across Groups

Ss showing only SS	2
Ss showing only seizure	3
Ss showing both SS and seizure	14
Ss showing neither SS nor seizure	5
TOTAL N =	24

TABLE 3

Incidence of Motor Seizures in Each Group

Group 1 (SS-SS)	Group 2 (SS-PES)	Group 3 (no SS-PES)	
#70+	#92+	#109+	
#74-	#97+	#98-	
#78+	#85+	#103-	
#79+	#106+	#110+	
#80+	#82+	#83+	
#89+	#111+	#87-	
#91+	#101-	#90-	
#95+	#96+	#102-	
7	7	3	= TOTAL SEIZURES (per Group)

+ = seizure recorded

- = no seizure recorded

$x^2 = 4.26$, d.f. =1, $p \leq .05$ for Group 1 and 2 vs. Group 3

$x^2 = 2.40$, d.f. =1, $p \geq .05$ for Group 1 vs. Group 3 and Group 2 vs. Group 3

$x^2 = .57$, d.f. =1, $p \geq .05$ for Group 1 vs. Group 2

TABLE 4

Comparison of Seizure Threshold for Group 1 Ss during SS and PES and Group 2 Ss during PES

	Group 1		Group 2	
S	SS(ua.)	PES(ua.)	S	PES(ua.)
#70	600	525	#92	1000
#74	---*	---*	#97	375
#78	850	850	#85	825
#79	150	200	#106	200
#80	975	1000	#82	500
#89	775	800	#111	550
#91	975	875	#101	---*
#95	975 (7!)	1000 (7!)	#96	950 (7!)

Wilcoxon Rank Sum Test, R= 52.5, $p \geq .05$ for Group 1 Ss during SS and Group 2 Ss during PES

Wilcoxon T = 10, $p \geq .05$, for Group 1 Ss during SS and PES

*no seizure elicited

!=# of Ss demonstrating seizure in respective column

TABLE 5

Comparison of Seizure Threshold and Seizure Latency for Group 1 1 Ss during SS and PES

S	Group 1 (SS) Seizure Latency (min.)	Group 1 (SS) Seizure Threshold (ua.)	Group 1 (PES) Seizure Latency (ua.)	Group 1 (PES) Seizure Threshold (ua.)
#70	6.5	600	1.1	525
#74	---*	---*	---*	---*
#78	7.9	850	9.9	850
#79	10.2	150	9.0	200
#80	9.5	975	9.5	1000
#89	6.8	775	.6	800
#91	6.8	975	4.0	875
#95	7.2	975	5.0	1000

Wilcoxon T = 1, N= 6, $p \leq .05$, for seizure latency comparison during SS and PES

*no seizure elicited

stimulation (Wilcoxon T= 1, N=6, $p \leq .05$).

Figure 1 is a composite diagram of electrode placements for the three groups. Table 6 lists the approximate brain areas for electrode placements. Brain areas demonstrating seizure are also indicated. For self stimulators, the majority of electrode tips were located in either the diagonal band of Broca or the medial preoptic area. Group 3 electrode tips had no consistent location. The composite diagram (Figure 2) of electrode placements for Group 1 and Group 2 Ss indicates no great difference between Group 1 and Group 2 Ss.

Figures 3a through 3e present brain impedance recordings for the three groups at different stimulus intensity levels. The recordings are presented for the beginning (first minute), middle (fifth minute), and end (tenth minute) of each test session. The impedance levels are presented as group means. The standard deviations about the means are also presented. Inspection of the Figures reveals a higher brain impedance for Group 2 than Group 3 at .1 milleamperes (ma.) but no other difference in impedance means was found at other stimulus intensity levels.

TABLE 6

Brain Areas of Electrode Placements

Group 1	Group 2	Group 3
#70-DBB*	#92-OC* POA	#109-AC*
#74-DBB TUO	#97-POA*	#98-SO
#78-DBB*	#85-POA*	#103-OC
#79-DBB*	#106-ACB* DBB	#110-CPU*
#80-POA* (med.-lat.)	#83-ACB*	#83-DBB* ACB
#89-DBB*	#111-POA*	#87-SO
#91-POA* (med.-lat.)	#101-DBB	#90-POA
#95-DBB*	#96-DBB* ACB	#102-TUO DBB

AC-anterior commisure
ACB-accumbens nucleus
CPU-caudate/putamen
DBB-diagonal band of Broca
OC-optic chiasm
POA-medial preoptic nucleus
SO-supraoptic nucleus
TUO-olfactory tubercle

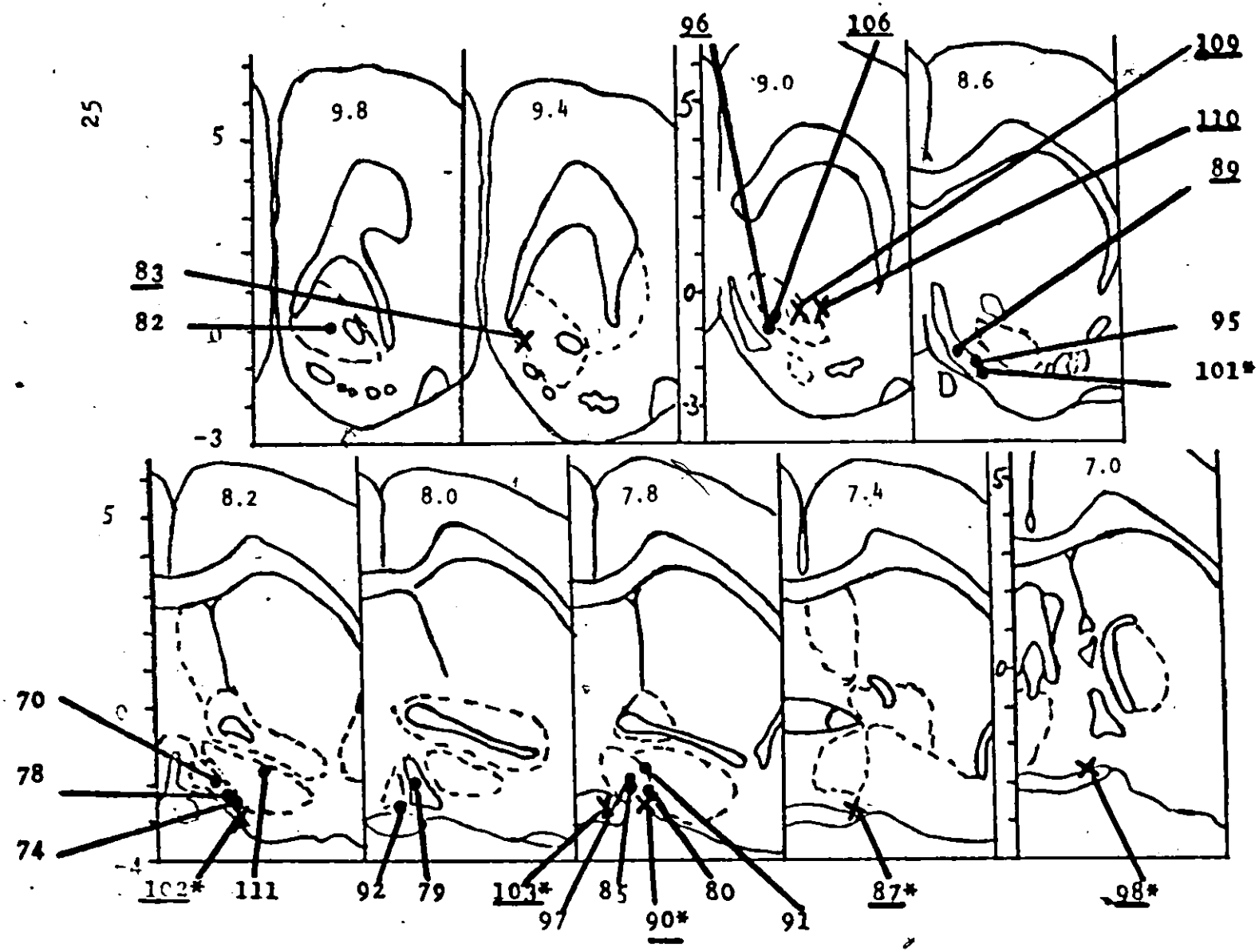

Fig. 1 Comparison of electrode placements between Groups 1&2 and Group 3

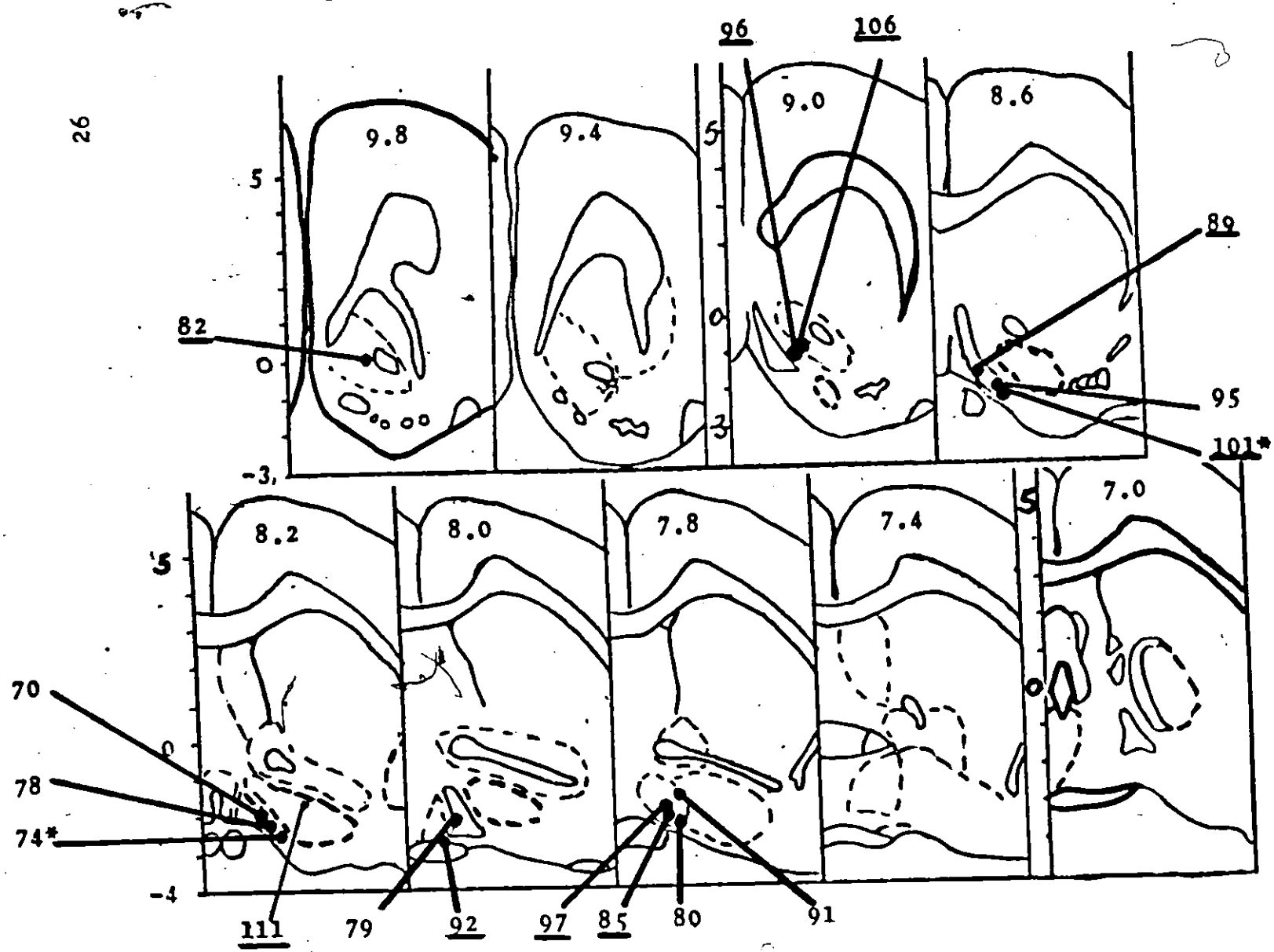

Fig. 2 Comparison of electrode placements between Group 1 and Group 2 Subjects

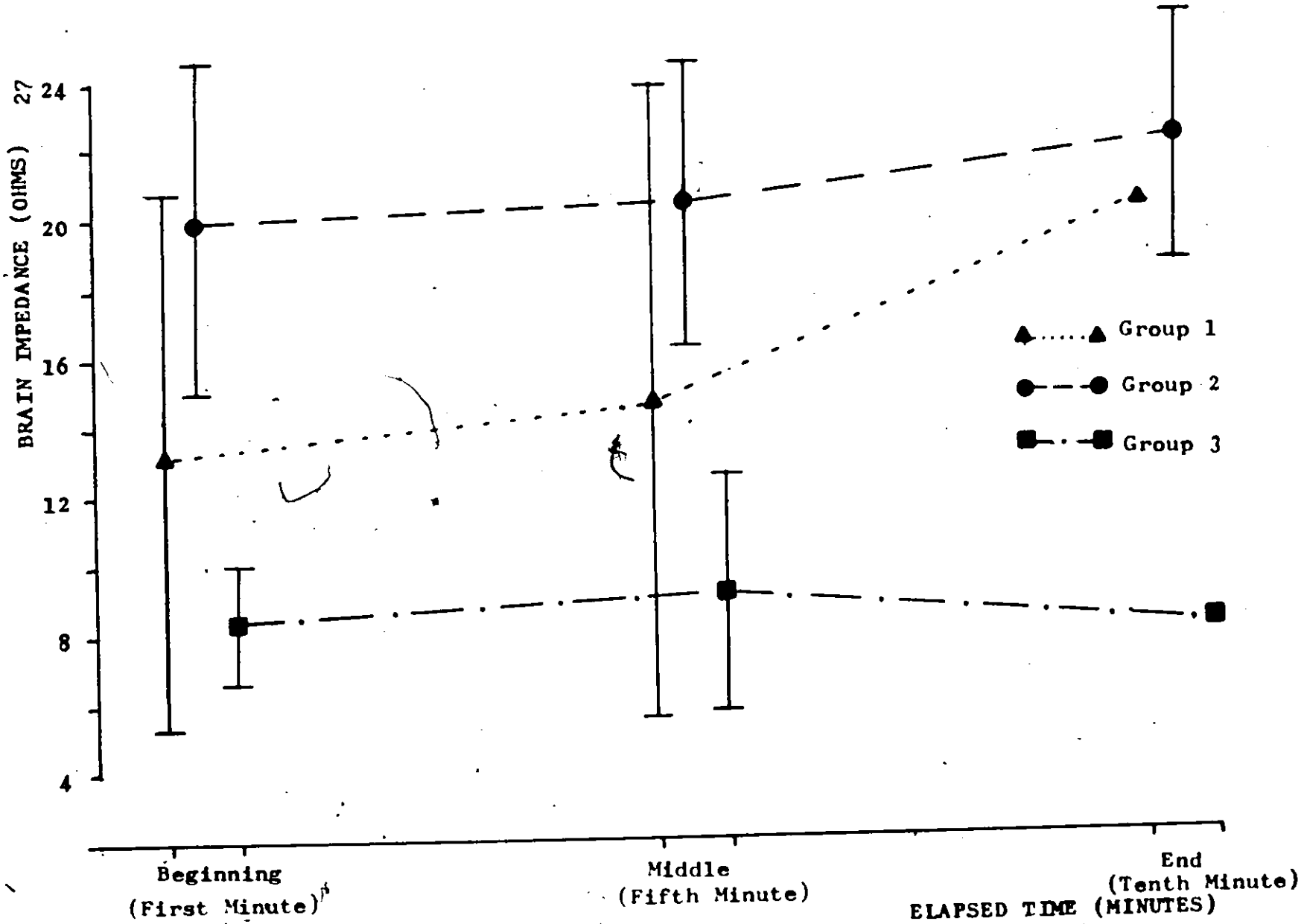

Figure 3a) Changes in Brain Impedance during 10 minute Test Sessions at .1 ma. stimulus intensity

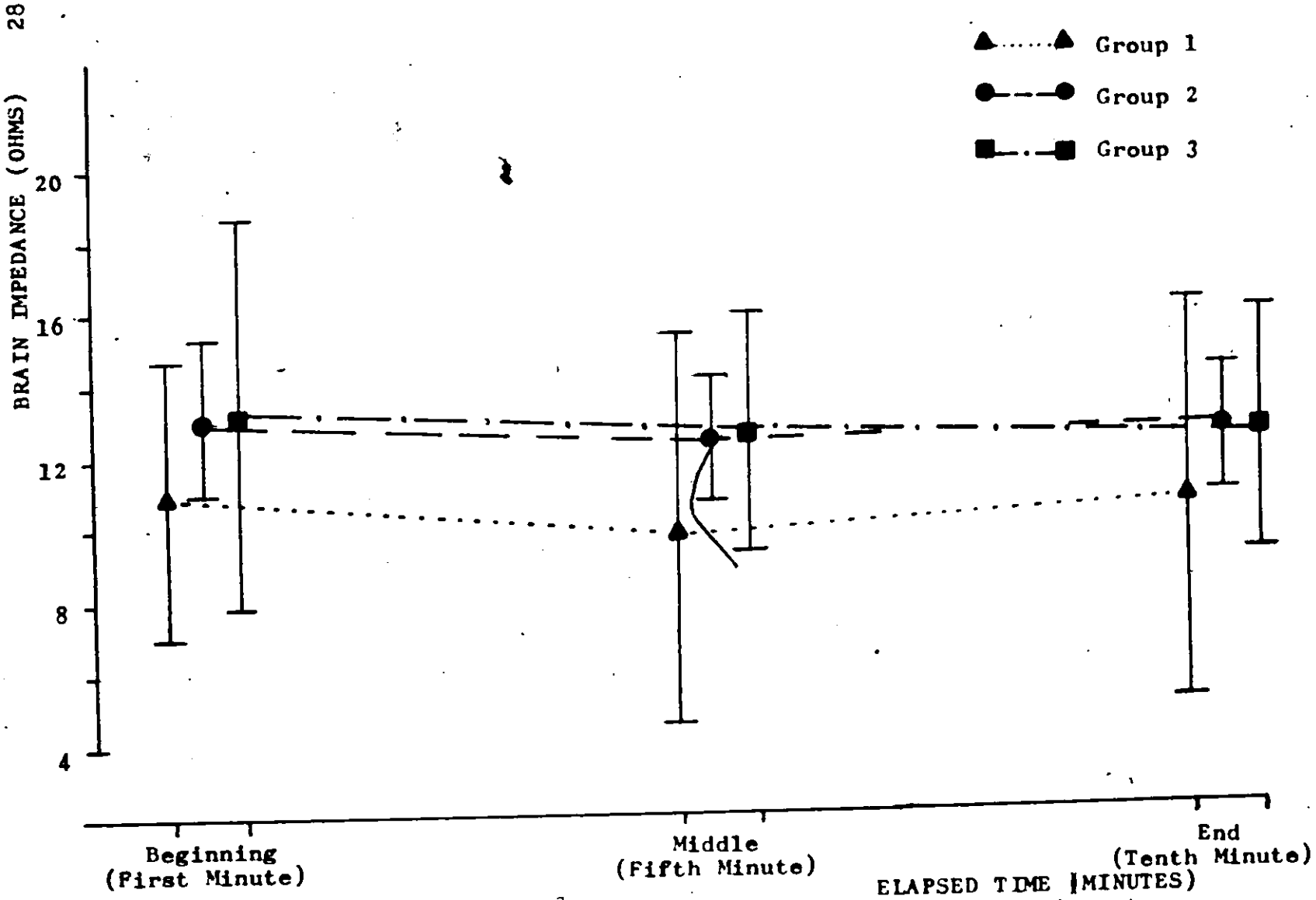

Figure 3b) Changes in Brain Impedance during 10 minute Test Session at .3 ma. stimulus intensity

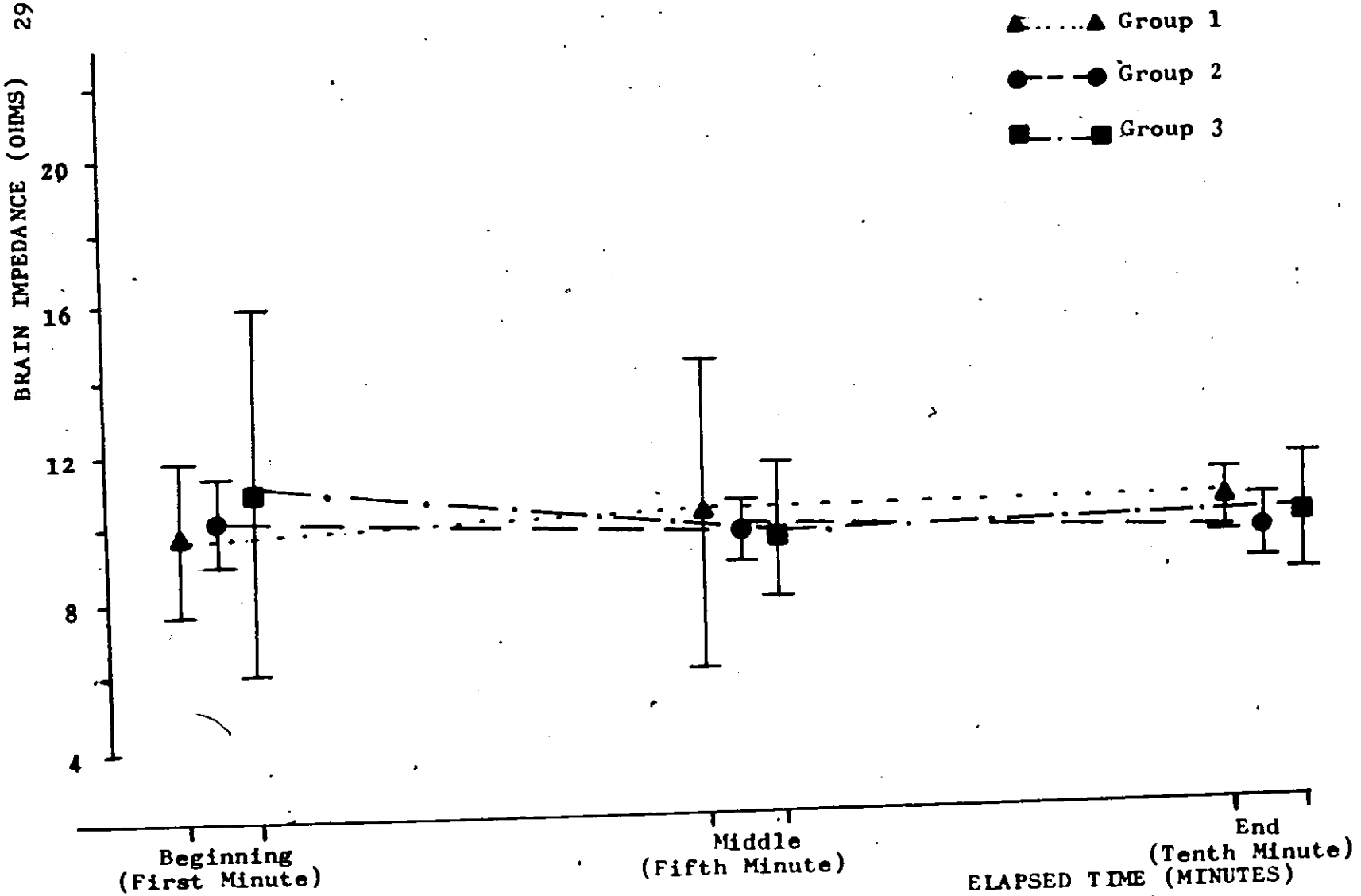

Figure 3c) Changes in Brain Impedance during 10 minute Test Session at .5 ma. stimulus intensity

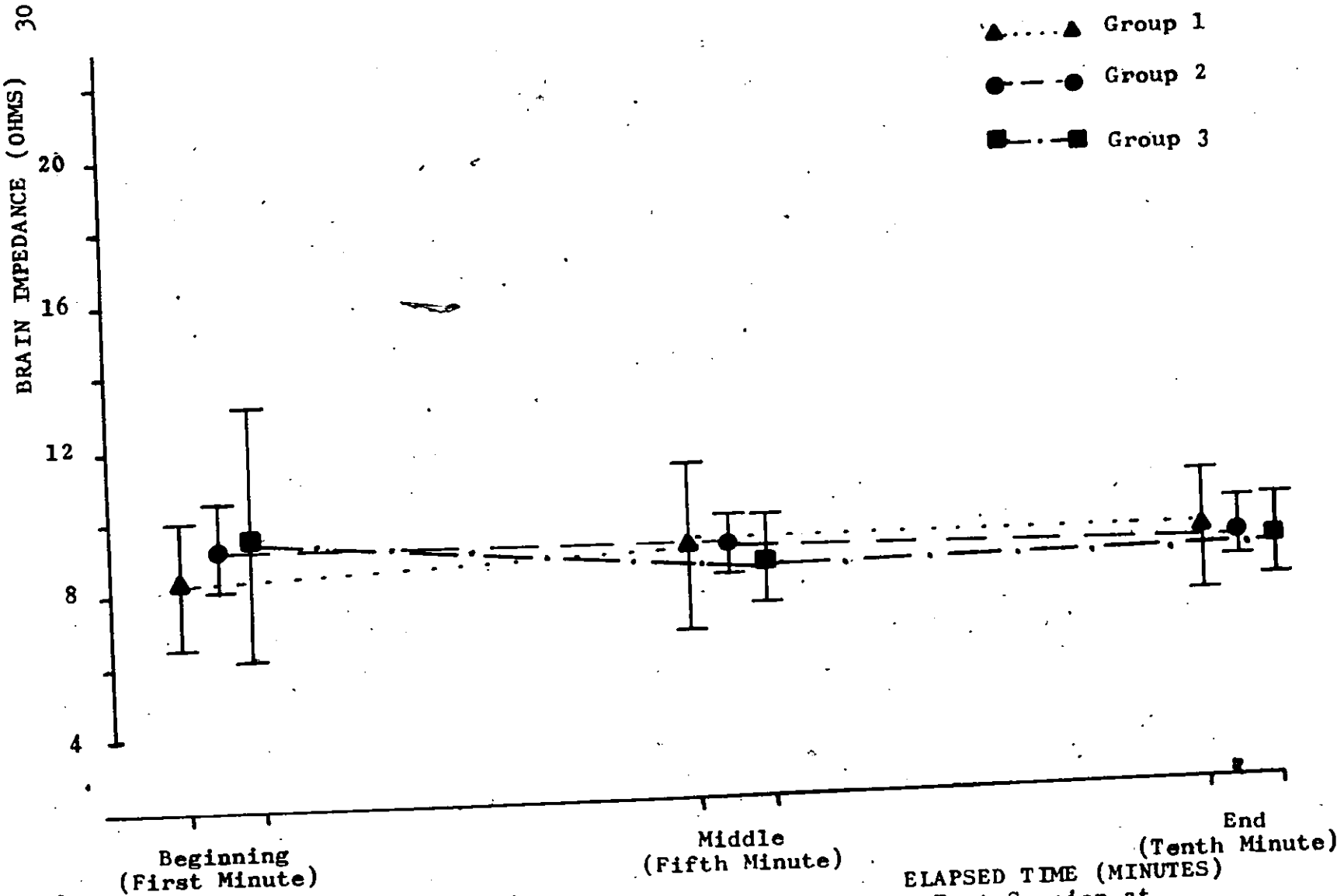

Figure 3d) Changes in Brain Impedance during 10 minute Test Session at .7 ma. stimulus intensity

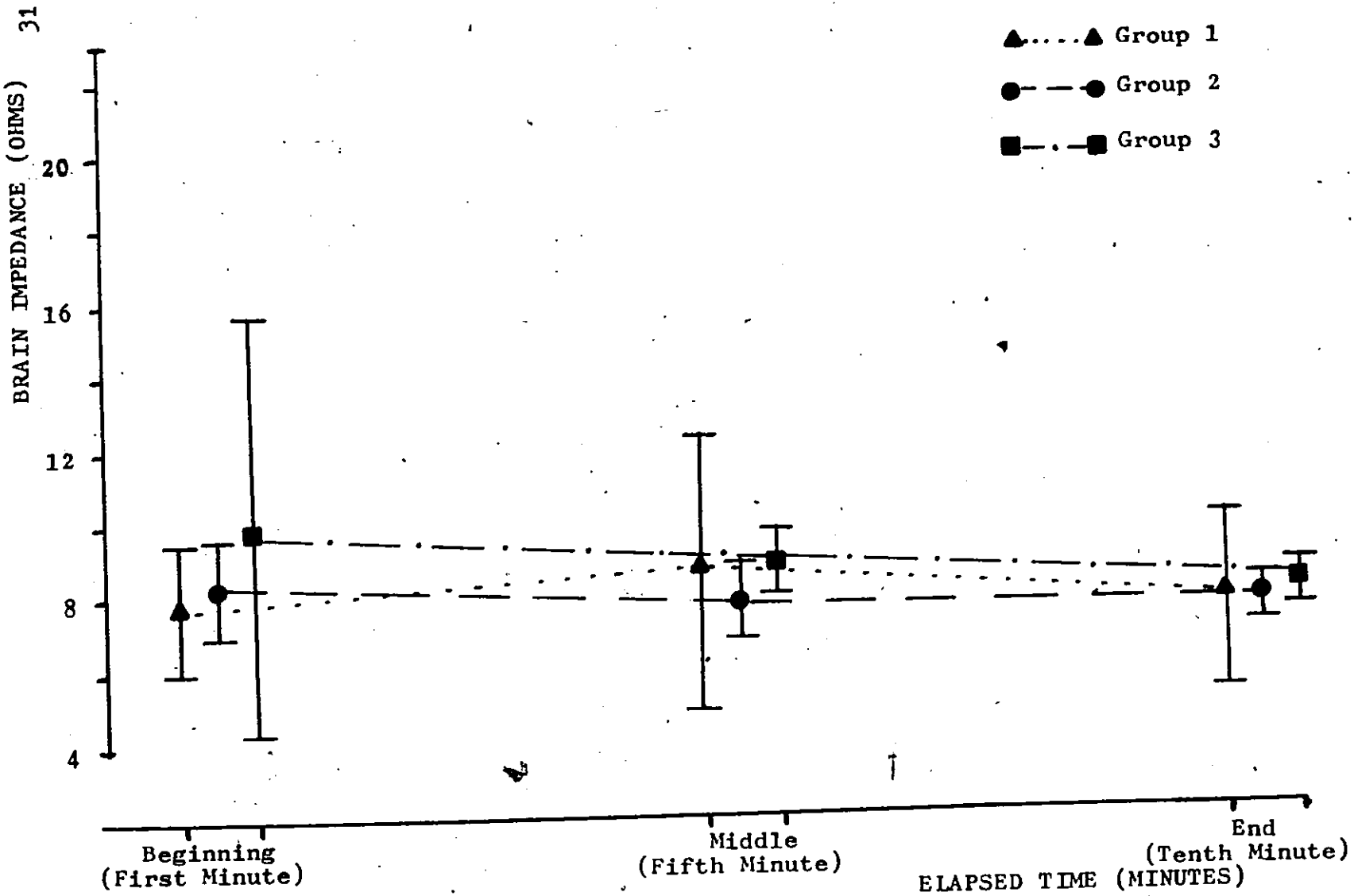

Figure 3e) Changes in Brain Impedance during 10 minute Test Session at .9 ma. stimulus intensity

CHAPTER 4
DISCUSSION

The study evolved from the incidental observation that rats would frequently go into seizure during self stimulation if the electrode tips were in and around the diagonal band area of the basal septum. The occurrence of presumably opposing phenomena- one pleasurable (self stimulation) and the other aversive (seizure)- was an apparent paradox. An experiment was initiated to determine the possibility of a relationship between self stimulation and seizure. A comparison of seizure susceptibility was obtained for electrodes in reward areas as well as for those in non-rewarding areas. The effect of active participation of the experimental animal in obtaining brain reward was also examined to see if this had an effect on seizure susceptibility. Brain impedance measures were recorded as a possible measure of brain activity around the electrode tip.

The original observation was that self stimulation and seizure could be elicited from the same electrode. To contend that there are separate but overlapping brain reward and brain seizure systems, it is necessary to demonstrate self stimulation and seizure from separate electrodes as well as together in other electrodes. Table 2 indicates the different combinations of self stimulation and seizure for the three groups. It is clear that self stimulation and

seizure were obtained separately, as well as together. In some locations, neither seizure nor self stimulation was elicited. It appears safe to conclude that reward and seizure systems in the brain areas studied are to some extent separable.

Table 2 indicates that self stimulation and seizures can be elicited separately as well as together. This raises the question as to the relative incidence of seizures for SS Ss compared to those who do not show SS. Expressed in another way, what is the seizure susceptibility due to stimulation of brain reward areas or to non-reward areas? The results are presented in Table 3. A significantly greater incidence of seizure was obtained for self stimulating Ss compared to non self stimulators ($\chi^2 = 4.26$). Seizures have traditionally been assumed to be aversive. However, the demonstration of seizure from reward areas raises the possibility that these seizures may have or may develop reinforcing properties.

It could be argued that the demonstration of a greater incidence of seizure among self stimulating Ss compared to non self self stimulators is an artificial finding, since only a relatively restricted brain area was sampled (principally the basal septum). The implication might be that the effect would disappear if a more extended brain area had been included in the subject sample. However, even if it were to be found that there is no significant difference in incidence of seizure between reward and non reward areas, the fact

still remains that both SS and seizure were reliably produced from the same electrode, and that therefore seizures may be rewarding for these Ss.

The demonstration of self stimulation and seizure from the same electrode raises the possibility that some seizures may be rewarding because during seizure, brain reward areas may be activated. However, alternate explanations are also possible. The seizures could be aversive and detract from the reinforcing properties of the SS. The occurrence of seizures could also be viewed as neither reinforcing or aversive and simply as a concomitant or side effect of electrical stimulation. To test these possibilities, self stimulators engaging in SS (Group 1-SS) were compared with self stimulators who received programmed stimulation (Group 1-PES and Group 2-PES). In other words, the effects of active versus passive involvement in brain stimulation was used to determine the nature of the reinforcing properties of seizure. Self stimulating Ss engaging in SS are in a position to control brain stimulation. They can press the bar at their own pace. If seizures are considered aversive, then it might be possible for the Ss by subtle manipulation of timing of bar presses to obtain brain shock but defer seizure onset. This presumes that the Ss are in some way forewarned of the oncoming seizure and can alter self stimulation to delay seizure. If the seizures themselves are rewarding, then the SS Ss might be able to alter their bar pressing pattern to hasten the onset of

seizure. Self stimulators receiving PES cannot control the occurrence of stimulation. Therefore, if seizures are aversive, Group 2 (PES) should show a greater susceptibility for seizure, and if rewarding, a lesser one. If no difference is found between Group 1 and Group 2, this would would suggest that the seizures are neither rewarding or aversive. The other possibility is of course that the experimental method cannot discriminate the nature of the reinforcing properties under the conditions of the experiment.

Self stimulating Ss engaging in SS showed no difference in relative seizure incidence when compared to SS Ss given PES (Table 3). The relative incidence of seizure is however a rather crude measure with which to differentiate relative seizure susceptibility. More sensitive measures could be more revealing. Seizure threshold and seizure latency can be viewed as more refined measures of seizure susceptibility, whereas seizure incidence is a discrete measure. A comparison of seizure threshold and seizure latency was used for this purpose. Table 4 compares seizure threshold for Group 1 Ss during SS and PES and also for Group 2 Ss during PES. A significant difference was found however for seizure latency for Group 1 Ss during SS compared to PES (Table 5). Group 1 Ss went into seizure significantly faster during PES than during SS.

This could be interpreted as evidence for the aversiveness of seizures, since the Ss during PES could not control

the occurrence of stimulation, and could therefore supposedly not defer seizure. This result is however confounded with the number of previous seizures recorded for the Ss at the time the seizure latency measure was taken. According to the experimental design (Table 1), Group 1 Ss had to first demonstrate seizure during SS before being given comparable stimulation during PES. In effect, all Ss tested during PES had already manifested one seizure whereas seizure latency scores during SS reflected the latency to initial seizure. There is evidence that previous seizures may have a crucial effect on subsequent seizures. Tress et al (1972) found that seizure threshold tended to decrease, seizure by seizure, i.e. seizures could be induced quicker following each seizure. Therefore, the importance of controlling the number of previous seizures when measuring seizure latency is crucial.

The results reported in Tables 3 and 4 suggest that since no difference was found in seizure incidence or threshold, for self stimulators during SS and PES, the seizures may not have either rewarding or aversive qualities. The forcefullness of this conclusion is clouded by the relatively small number of seizures recorded within subjects. Since the rats had not previously experienced seizures, the Ss may not have been able to associate either rewarding or aversive properties to the seizures (unless one trial learning is assumed). It could therefore be informative to see the influence of a greater number of trials at seizure producing intensities on seizure incidence,

threshold and latency. It was impractical to obtain this data in this study since numerous Ss were lost due to the violent nature of the seizures. The Ss were often noticed to contact the walls and ceiling of the test chamber, sometimes resulting in the Ss loosening the electrode attachments from their skulls. The use of a larger test chamber or a restraining device could overcome this difficulty.

Brain impedance changes have been used in the past as a possible indicator of brain activity (Racine 1971). Impedance was recorded in this study to see if any reliable changes could be detected during ESS or behavioural seizures. Except for an initial variability, impedance measures did not prove fruitful as a possible measure of brain activity (Fig. 3a through 3e). However, there was one subject (#109) who showed a large deviation from the other Ss, as exemplified in Appendix 1. This S demonstrated a consistently higher impedance level throughout testing, excluding the first day. The electrode tip was determined to be in the anterior commisure.

In brain stimulation research, effects from the same brain area are usually very similar across subjects. Self stimulation thresholds for similar hypothalamic placements, for example, are usually comparable. A greater variability in threshold levels for different electrode placements was observed in this research. The variability in seizure thresholds for subjects #96 and #106 is an example. While testing for leaks in the

electrode stems following the end of testing, a variability in electpode tip exposure was noticed, allowing a somewhat greater current density with some electrodes. This could account for threshold differences. The threshold variability could also be due to a large variability in seizure susceptibility between Ss.

Another source of evidence to account for the inter-subject variability deals with the location of the majority of the electrodes. They were determined to be within the rhinencephalon, or "olfactory brain". Gloor (1960) has noted with rhinencephalic stimulation that in "... animals, electrical stimulation brings forth not only reactions of fear and anger but also behavioral patterns of an opposite character, suggesting that a 'rewarding' experience can be elicited by stimulation...From the study of the experimental records it seems unlikely that differences in the anatomical location of the site of stimulation or of the lesion could adequately account for these opposite effects." This great lability of rhinencephalic function based upon "flexible neuronal mechanisms" could account for threshold variability.

Speculation as to a possible explanation for the occurrence of seizure leads to an anatomical evaluation of the areas from which seizures were recorded. The electrode tips were histologically determined to be principally in the area of the diagonal band of Broca (horizontal limb)- medial preoptic area (Figure 1 and 2).

The diagonal band (DBB) is a fiber bundle and a part of the septum (Raisman 1966). It is known to project to the hippocampus (Raisman 1966) as well as to the amygdala (Nauta 1962; Cowan, Raisman and Powell 1965; Gloor 1960). The DBB is known to receive impulses from the hippocampus (Raisman 1966) as well as from the amygdala (baso-lateral group) and pyriform cortex (Cowan et al 1965; Raisman 1966; Romanes 1972). Lesions in the lateral hypothalamus have also produced degeneration in the horizontal limb of the DBB. Strong intra-septal connections between the lateral septal area and the DBB have also been noted (Raisman 1966).

The medial preoptic area (MPO), though belonging to the forebrain, is closely related to hypothalamic structures (Truex and Carpenter 1968). The MPO has strong connections with the amygdala via the stria terminalis and the ventral amygdalo-subcortical pathway (Gloor 1960). Stimulation of the amygdala, septum, hypothalamus, MPO and hippocampus has been shown to elicit seizures in rats (Goddard 1967; Bogacz et al 1965; Malsbury 1971). Because of the complexity of the anatomical connections, it is difficult to specify the origin of the seizure activity demonstrated in this experiment. However, the strength of the anatomical connections to the hippocampus (Green and Arduini 1954; Raisman 1966) as well as the similarity of the seizure behavioural pattern to amygdala seizures (Racine 1971), suggests these two structures as good possibilities for closer analysis. Lesions in the hippo-

campus and amygdala (CA3 and CA4, and baso-lateral group respectively) in separate groups of animals, following demonstration of seizure from the DBB would prove helpful in localizing brain areas involved in the seizure activity elicited from the DBB-MPO area.

It has been reported that stimulation of the MPO leads to a facilitation of male rat copulatory behaviour and ejaculation in monkeys (Malsbury 1971; Robinson and Mishkin 1966). It was noticed in this experiment that a majority of Ss who went into seizure and demonstrated self stimulation, also discharged seminal fluid during the testing sessions. This observation is accordance with the above mentioned results. It is believed that a sexual basis can account for at least part of the reinforcement effect of MPO stimulation.

The observed seizures of Ss #109 and #110 did not follow the seizure pattern of the seizures in other Ss, but were similar to each other. Seizures in these animals were more violent and "jerky" than the seizures of the other Ss who demonstrated a more "rhythmical clonus". Neither S#109 nor S #110 could be induced to self stimulate. This suggests that seizures in these subjects may involve different structures that do not overlap brain systems of reward. This finding emphasizes that the reward characteristics of seizures must be carefully delineated with respect to specific brain structures.

Implications

Within the considerable limitations imposed by differences between rat and man, discoveries that relate brain seizure systems with those mediating reward are of both theoretical and practical importance for basic research on epilepsy. The demonstration of an interaction between reward and seizure systems suggests that at least in some cases, epileptic seizures may become associated with brain activity that is positively reinforcing. If this is so, increased seizure activity may be partly due to activation of brain systems mediating reward. The experimental animal could be used as a model to determine the extent to which epileptic seizures could be reduced with negative reinforcement. The implications at the human level are the possible application of reinforcement procedures to counteract rewarding concomitants of seizure. The eventual goal of course, is to reduce the total number of seizures without medication.

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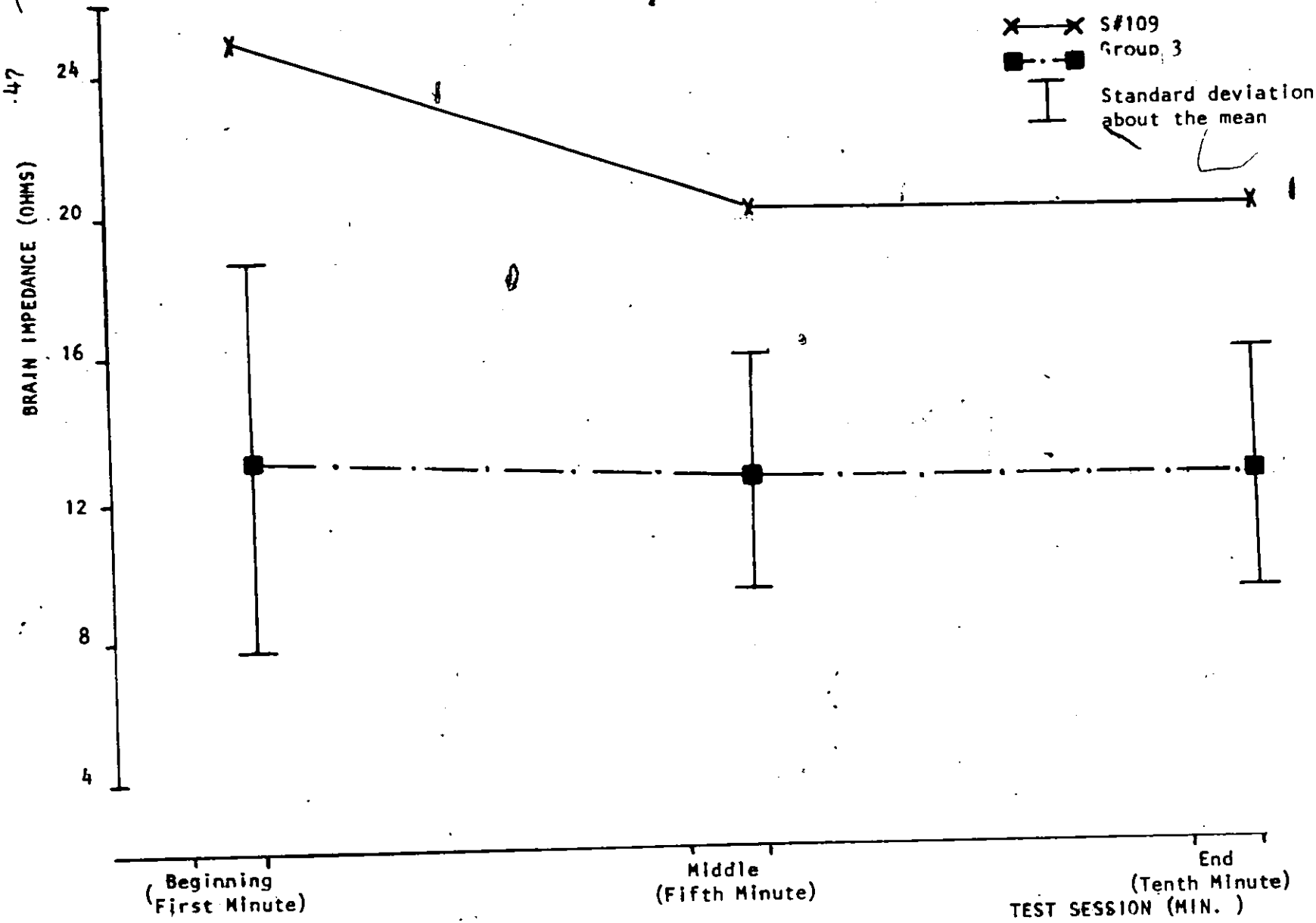

Appendix 1 - Comparison of Brain Impedance measures for S#109 and for Group 3 Ss at .3 ma. stimulus intensity

VITA AUCTORIS

1949	Born in Bradford, England to Jonas and Aldona Petrauskas
1954-62	Educated at Saint Anthony's Public School in Toronto, Ontario
1962-63	Attended Saint Anthony's High School in Kennebunkport, Maine
1963-67	Attended Michael Power High School in Islington, Ontario and graduated with senior matriculation diploma
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