INFORMATION TO USERS

This material was produced from a microfilm copy of the original document. While the most advanced technological means to photograph and reproduce this document have been used, the quality is heavily dependent upon the quality of the original submitted.

The following explanation of techniques is provided to help you understand markings or patterns which may appear on this reproduction.

1. The sign or "target" for pages apparently lacking from the document photographed is "Missing Page(s)". If it was possible to obtain the missing page(s) or section, they are spliced into the film along with adjacent pages. This may have necessitated cutting thru an image and duplicating adjacent pages to insure you complete continuity.

2. When an image on the film is obliterated with a large round black mark, it is an indication that the photographer suspected that the copy may have moved during exposure and thus cause a blurred image. You will find a good image of the page in the adjacent frame.

3. When a map, drawing or chart, etc., was part of the material being photographed the photographer followed a definite method in "sectioning" the material. It is customary to begin photoing at the upper left hand corner of a large sheet and to continue photoing from left to right in equal sections with a small overlap. If necessary, sectioning is continued again — beginning below the first row and continuing on until complete.

4. The majority of users indicate that the textual content is of greatest value, however, a somewhat higher quality reproduction could be made from "photographs" if essential to the understanding of the dissertation. Silver prints of "photographs" may be ordered at additional charge by writing the Order Department, giving the catalog number, title, author and specific pages you wish reproduced.

5. PLEASE NOTE: Some pages may have indistinct print. Filmed as received.

Xerox University Microfilms
300 North Zeeb Road
Ann Arbor, Michigan 48106

AN ASSESSMENT OF THE RELEVANCE OF CORTICAL THETA RHYTHM FOR MEMORY PROCESSES IN THE RAT

by

Thomas Wesley Nicholas

A Dissertation Presented to the
FACULTY OF THE GRADUATE SCHOOL
UNIVERSITY OF SOUTHERN CALIFORNIA
In Partial Fulfillment of the
Requirements for the Degree
DOCTOR OF PHILOSOPHY
(Psychology)

June, 1974

UNIVERSITY OF SOUTHERN CALIFORNIA
THE GRADUATE SCHOOL
UNIVERSITY PARK
LOS ANGELES, CALIFORNIA 90007

This dissertation, written by

Thomas Wesley Nicholas

under the direction of his Dissertation Committee, and approved by all its members, has been presented to and accepted by The Graduate School, in partial fulfillment of requirements of the degree of

DOCTOR OF PHILOSOPHY

Charles G. Mayo

Dean

Date February 13, 1974

DISSERTATION COMMITTEE

Chairman

ACKNOWLEDGEMENTS

The list of those who contributed to the completion of this dissertation is lengthy, and space requirements demand that I acknowledge only those who were directly concerned. I wish to first express my appreciation to Norman Bregman, who developed many of the behavioral procedures for the maze task. I would also like to thank members of my dissertation committee, Dr. Ernest Greene and Dr. Louis Bishop, for their suggestions in the planning and implementation of this project. An additional task which the committee accepted was to comment on the initial dissertation drafts. Appreciation should also be extended to Dr. Gary Galbraith for his financial assistance and his collaboration in the computer analysis of the data. I owe special gratitude to Joe Rouge of the Engineering Computer Laboratory, University of Southern California, who spent many hours helping me to interact with the computer facilities. I would like to give acknowledgement to Dr. Donald J. Lewis who served as the chairman of the dissertation committee, and who provided support of various kinds to the project. Much of the dissertation can be directly traced to ideas which I have developed because of my association with him.

Finally, I would like to thank my wife, Lynda,

for her encouragement and understanding throughout the many hours she spent typing the dissertation.

This research was supported by Research Grant GB-12372 from the National Science Foundation to Donald J. Lewis, and a predoctoral fellowship awarded to the author from the National Institute of Mental Health, Grant MH-10554.

TABLE OF CONTENTS

INTRODUCTION

A great deal of the data for animal memory processes originates from studies using electroconvulsive shock (ECS) as a tool to disrupt brain electrical activity (McGaugh and Dawson, 1971). The earlier concept of a consolidation process in memory (Burnham, 1903) laid the basis for the contemporary consolidation theory (McGaugh, 1966). Under this notion memory is viewed as a two stage process. Thus a new memory is thought to require time in order to harden into a permanent memory. If brain electrical activity is disrupted with ECS, then memories which have not yet consolidated should also be disrupted. This rational for using ECS is supported by the observation that a performance decrement (an amnesia) is often produced when ECS follows a learning experience (Lewis, 1969).

Later formulations have cast doubt on the inclusiveness of a consolidation theory of memory (Lewis and Maher, 1965; Lewis, 1969; Miller and Springer, 1973; Spear, 1973). If ECS does interfere with consolidation then one must somehow deal with the evidence that an ECS-produced memory disruption may recover with time (Pagano et al., 1969; Thompson, Enter and Russell, 1967; Zinkin and Miller, 1967; Neilson, 1968; DeVietti and Larson, 1971; Riddell, 1969; DeVietti et al., 1972). There is also evidence that

such a disrupted memory may be returned by a reminder treatment; that is, exposing the animal to a portion of the cues of the original learning (Lewis, Miller and Misanin, 1968; Lewis and Nicholas, 1973; Quartermain, McEwen and Azmita, Jr., 1970, 1972; DeVietti and Hopfer (in preparation); Miller and Springer, 1972; Cherkin, 1972; Gordon and Spear, 1973; Galluscio, 1971). Finally other evidence indicates that a second ECS treatment (in some cases a footshock (FS) or other related stimulus followed by an ECS) may return an ECS disrupted memory (Neilson, 1968; Nachman and Meinecke, 1969; Pfingst and King, 1969; Kesner, McDonough, Jr., and Doty, 1970; Thompson and Neely, 1970; Thompson and Grossman, 1972). In addition to the notion of memory return there is evidence that an old (presumably consolidated) memory is not permanent; it too is subject to the effects of ECS (Schneider and Sherman, 1968; Misanin, Miller and Lewis, 1968; Lewis, Bregman and Mahan, Jr., 1972; Lewis and Bregman, 1972; DeVietti and Holliday 1972; Bregman, 1972; Robbins and Meyer, 1970; Howard and Meyer, 1971).

None of these phenomena should occur if a consolidation theory is correct. Logically, a labile memory disrupted by ECS should fail to consolidate, and it should be permanently lost. Moreover, an ECS-produced amnesia for an already consolidated memory cannot logically be due

to the disruption of the memory consolidation process. Thus an alternative explanation to a consolidation theory suggests that the amnesia produced by ECS may be due to an interference with the retrieval of the memory, rather than a disruption in the storage of the memory (Lewis and Maher, 1965; Lewis, 1969; Miller and Springer, 1973; Spear, 1973). Lewis, (1969) has pointed out that an amnesia may conceiveably derive from a failure of memory processes at several points. For example, the initial registration of the memory may be faulty, or the coding of the memory at the time of storage may be obscured, perhaps by agents such as ECS. Also the retrieval argumentt allows that even long after memories are stored the recall of a memory may be impaired, while the memory itself remains intact. Thus various factors could account for a retrieval failure; a lack of motivation, a response competition, or a response suppression (for example, fear) could easily occur without the impairment of the stored memory.

Much of the ECS data is derived from one-trial passive avoidance (PA) studies. In one example of this task, the stepdown apparatus, animals are placed on a raised platform, and the time required for them to step off the platform is recorded. Often three groups of animals are compared in the task. One group is given a footshock (FS) when they step off the platform; another group is given

FS followed by ECS; the third group is not given FS, but only an ECS. Twenty-four hours later the animals are tested for their latency to step off the raised platform. Typically the FS animals remain on the platform, while the FS-ECS animals rapidly leave it. Thus the FS-ECS animals appear ignorant of the FS event which immediately preceeded the ECS treatment. This ECS-produced retrograde amnesia (RA) in a passive avoidance task of one form or another has been the subject of many papers (Madsen and McGaugh, 1961; Chorover and Schiller, 1965, 1966; Lewis et al., 1968a, 1968b; Misanin, Miller and Lewis, 1968; Poslunds and Vanderwolf, 1970; Spevack and Suboski, 1969).

The ECS treatment itself has in the past been administered to rodents by electrodes attached to the ears (transpinnate) or in some cases to the eyes (transcorneal) (Schneider, Kapp, Aron and Jarvik, 1969; Zornetzer and McGaugh, 1971a, 1971b). In recent years RA has been obtained in one trial passive avoidance tasks by administering ECS (usually of a low intensity) to electrodes placed in the skull (transcortical) (Vandaris and Gehres, 1970; Zornetzer and McGaugh, 1970; Gold, Farrell and King, 1971; Robins and Thomas, 1968; Kesner, Gibson and LeClair, 1970; Paolino and Hine).

An ECS directly manipulates ongoing brain electrical activity; however, that activity has been

studied as a subject within itself. The continous electrical fluctuations of the human brain is often recorded as an index of health or disease. Small voltages can be displayed from electrodes placed on the intact skull or within the brain itself. The record of these small, alternating differences in electrical potential between two electrodes is called an electroencephalogram (EEG). Often a particular frequency may dominate a portion of the EEG. The alpha rhythm (8 - 14 Hz.), beta rhythm (14 - 60 Hz), theta rhythm (4 - 8 Hz.) and delta rhythm (4 Hz. and lower) are the terms applied to brain electrical activity within specific portions of the EEG band of frequencies (Towe, 1965).

CHAPTER I

AMNESIC AGENTS AND AN EEG CORRELATE OF EXPERIMENTAL AMNESIA

In addition to ECS many other agents have been shown to produce an amnesia for prior learning. Various anesthetics, ether, phenobarbital, and metrazol may function as amnesic agents (Pearlman, Sharpless and Jarvik, 1971; Pearlman, 1966, Alpern and Kimble, 1967; Hertz, et al., 1970; Cherkin, 1972; Penrod and Boice, 1971). Other drugs which have been implicated are puromycin (Flexner, Flexner and Roberts, 1967; Agranoff, Davis and Brink, 1965; Davis and Agranoff, 1966; Barondes and Cohen, 1965), acetoxycloheximide (Agranoff, Davis, Casola and Lim, 1967; Barondes and Cohen, 1967; Cohen and Barondes, 1968; Daniels, 1971), cycloheximide (Quartermain, McEwen and Azmitia, 1970; Barondes and Cohen, 1967), actinomycin-D (Agranoff et al., 1967) and various cholinergic agents (Deutsch, Hamburg and Dahl, 1966; Deutsch and Rocklin, 1972; Deutsch, 1969; Belluzzi, 1972). Application of potassium choride (KCL) to the cortex to elicit a depression of cortical electrical activity (Bures and Buresova, 1963; Pearlmam and Jarvik, 1961; Bivens and Ray, 1965) or to the hippocampus to depress hippocampal electrical activity (Avis and Carlton, 1968; Auerbach and Carlton, 1971; Kapp and Schneider, 1971; Hughes, 1968) have both produced RA. In

a similar manner breathing carbon dioxide (Paolino, Quartermain and Miller, 1966; Taber and Banuaziai, 1965; Nachman and Meinecke, 1969; Quinton, 1966), body heating or cooling (Jacobs and Sorenson, 1969; Kane and Jarvik, 1970; Ricco, Hodges and Randall, 1968; Riccio, Gaebelein and Cohen, 1968; Beitel and Porter, 1968; Misanin and Hoover, 1970; Ricco and Stikes, 1969; Jensen and Riccio, 1970), and electrical stimulation of discrete subcortical areas (Kesner and Doty, 1968; Wyers et al., 1968; Brunner et al., 1970; Lidsky and Slotnick, 1970, 1971; McDonough, Jr. and Kesner, 1971; Shrinkman and Kaufman, 1972; Kesner and Conner, 1972) have all demonstrated effectiveness in producing an amnesia for prior learning. Given the fact that similar behavior (an amnesia, usually in a passive avoidance task) is produced by different amnesic agents one might wonder if any consistant similarity could be detected in the cortical EEG recorded from animals made amnesic by the various agents. If a unique EEG correlate could be found for experimental amnesia across different amnesic agents, then this fact would be evidence that amnesia is produced by manipulating the brain in a particular manner.

Miscellaneous Amnesic Agents.

As Lewis (1969) has pointed out, many amnesic agents have convulsive properties. Thus these agents affect brain electrical activity by producing neural spiking

followed by a period of depressed electrical activity. Spreading cortical depression appears to deviate somewhat from this generalization, since it does not obviously manifest initial neural spiking (Bures and Buresova, 1960, 1970). However localized neural spiking may occur after hippocampal depression (Avis and Carlton, 1968; Kapp and Schneider, 1971), and alternating periods of hippocampal seizure and depression has also been reported (Bures et al., 1962). Greene (1971) has shown that application of KCL through cannula implanted in the rat hippocampus may produce perseverative behavior which is similar to that produced from hippocampal lesion. He suggests that hippocampal spreading depression produces a functional and reversible hippocampal lesion, and that this perseverative behavior may be different from the behavior observed during a hippocampal seizure. If this suggestion is true then an amnesia might be produced by either depression or disruption (seizure) of hippocampal electrical activity. Thus the observation of an amnesia would depend heavily on the particular behavior necessary for correct performance of the task.

Horsten (1949) found a cessation of EEG activity in rats cooled to 68° F. Lipp (1964) reported that both frequency and amplitude of cortical and subcortical EEG decreased in cooled, unanesthetized cats and rabbits.

Subcortical seizure was observed in these animals when the body temperature was reduced to 72° F.

Drug Agents

Puromycin disrupts hippocampal electrical activity five hours after temporal injection, but cycloheximide or acetoxycloheximide apparently do not (Cohen, Ervin and Barondes, 1966; Cohen and Barondes, 1967). It has been found that actinomycin-D, which produces a failure of long term storage similar to the above drugs, also produces hippocampal epileptiform spike discharges at three days following its injection into the hippocampus of the rat (Nakajima, 1969). Such a temporal period corresponds to some of the literature reporting failures of long term consolidation (Agranoff, Davis, Casola and Lim, 1967) with Act-D. The deficit in long term storage is more likely a proactive effect of the drug on the behavioral testing period, rather than a retroactive effect on the memory storage (Nakajima, 1972). Nevertheless the possiblity is presented that a drug which does not show an effect on brain electrical activity near the time of injection into the brain, may produce a change in that activity at a much later time.

Of those drugs used to manipulate cholinergic sites in the CNS, little information is available on the effect on electrical activity when diisopropylfluorophos-

phate or physiostigmine are injected into the brain, but carbachol injections can cause both EEG seizures and behavioral convulsions (Belluzzi, 1971; Grossman, 1963).

In accord with the notion that many amnesic agents change brain electrical activity, recordings of such activity following temporal injection of puromycin have demonstrated that the drug does disrupt hippocampal electrical activity (Cohen et al., 1966; Cohen and Barondes, 1967). This finding encouraged Avis and Carlton (1968) to attempt to produce an amnesia by disrupting hippocampal electrical activity with an injection of potassium chloride (KCL) into the hippocampus. The resulting depression of electrical activity at the injection site was observed for KCL only, since saline injections did not affect hippocampal electrical activity. In like manner, when the animals were tested for their latency to drink in the presence of a tone which had previously been paired with electric shock, KCL animals had short latencies, while saline animals had long latencies. With specific reference to the EEG, Avis and Carlton (1968) suggested that the duration of the EEG depression was related in an inverse manner to retention. Thus the longer the observed depression, the shorter the observed drinking latency in a situation where the normal response would be a very long drinking latency.

Auerbach and Carlton (1971) showed that animals trained in the drink suppression task, injected in the hippocampus with KCL, and then tested for their latency to drink show shorter latency and lower blood and adrenal corticosteroid content than animals similiarly handled, but injected with saline. The authors suggested that the occurrance of electrical silence in the brain between training and testing decreases the animals' physilogical response to a fear-provoking stimulus.

Cortical Electrical Stimulation

For purposes of clarity, one can say that typical electrical brain stimulation through implanted electrodes differs from ECS in that the current applied to the brain is not intended to be large enough to produce a behavioral convulsion and render the animal unconscious. Seizures or afterdischarges (AD) of an area of cortex or a subcortical system are the usual result of such a treatment, and a behavioral manifestation of the stimulation (if present) is usually confined to momentary freezing or shivering.

In primates, electrical stimulation of inferotemporal cortex which is intense enough to set up afterdischarges there, is disruptive of learning when the cortical seizure occurs on each trial of discrimination training or at the start of short blocks of discrimination

trials (Chow, 1961; Goldrich and Stamm, 1971). In this paradigm the AD activity apparently disrupts the normal ongoing patterning of neuronal circuits during learning. Chow (1961) also showed that bilateral temporal AD during recall of an already learned visual discrimination will disrupt test performance. This effect he called a retention deficit since unilateral temporal AD did not disrupt test performance, nor did AD activity in the monkey's visual cortex.

In a somewhat different task electrical stimulation of prefrontal cortex in the monkey has been used to obtain a memory deficit. Stamm (1969) has found that stimulation applied at the end of cue presentation and during the early period of the delay in a two choice delayed response trial impairs correct performance. The same stimulation appeared not to affect correct performance if it was delivered at other times during the trial. In a similiar manner Kovner and Stamm (1972) have found that stimulation of inferotemporal cortex produced a graded impairment of a delayed matching task. The deficit in correct performance increased as stimulation was moved from the early period of the delay to the late period of the delay. The maximum deficit occurred when stimulation was delivered during the matching period (following the delay period). Also stimulation of inferotemporal cortex

did not affect a simultaneous matching task, and stimulation of prefrontal cortex did not produce a deficit for either the simultaneous matching or the delayed matching tasks.

The ability of electrical stimulation to produce an amnesia when the stimulation is delivered posttrial (the retroactive ECS paradigm) to large areas of cortex was questioned by Reitz and Gerbrant (1971). Those authors delivered electrical stimulation to inferotemporal cortex immediately (3-5 seconds) after each trial of a multitrial visual discrimination. Such stimulation did not produce a retroactive effect on visual discrimination learning. However, in a manner similar to Chow's (1961) work an impairment was produced if the inferotemporal stimulation was presented immediately pretrial, thereby causing AD activity during the presentation of the discriminitive stimuli.

Subcortical Electrical Stimulation

Discrete electrical stimulation of the subcortical areas of the brain may also initiate AD activity and produce an amnesia for prior learning. Both Wyer et al., (1968) and Wyer and Deadwyler (1970) obtained a PA deficit with stimulation of the caudate nuclei intense enough to elicit spindle activity from that area. In a Lashley III maze Peeke and Hertz (1970) demonstrated

that caudate nucleus stimulation could produce a retroactive memory impairment in an appetitive task. This finding perhaps reinforces an earlier report (Mahut, 1962) of a memory deficit produced in appetitive tasks by subcortical (reticular, tegmental, diencephalic) stimulation. In a later paper Herz and Peeke (1971) also found caudate stimulation to be an effective amnesic agent by examining extinction performance, again in an appetitive task.

Bilateral seizures of the amygdaloid complex elicited by chronic low intensity electrical stimulation has produced an amnesia for a conditioned emotional response (McIntyre, 1970). Kesner and Doty (1968) produced a PA deficit when stimulation of the amygdala produced AD at that site. Stimulation of the dorsal hippocampus produced RA only when AD activity spread to the amygdala. On the other hand, AD activity in the septum, fornix or ventral hippocampus produced no deficit. Both Brunner et al., (1970) and Vardaris and Schwartz (1970) have produced RA in one trial PA tasks by administering a single post-trial electrical stimulation to the hippocampus. Vardaris and Schwartz (1970) show that retention performance in the task had no relationship to the duration of either hippocampal AD activity or hippocampal post seizure depression. This finding is in agreement with Routtenberg, Zechmeister, and Benton (1970) who could find no obvious

difference in hippocampal activity after FS or FS-ECS which could be related to retention in a one trial PA task. Vandaris and Schwartz (1970) speculate that RA may be a result of AD propagation to other brain areas and not simply hippocampal seizures since a small number of rats in their study manifested hippocampal seizure, but no RA.

However, less intense electrical stimulation can also produce RA in the absence of AD, the involvement of adjacent brain centers, or behavioral seizure. McDonough and Kesner (1971) obtained a PA deficit in cats by delivering low level bilateral stimulation to the amygdala. These authors recorded the electrical activity of the amygdala and hippocampus after stimulation to verify that no AD activity took place. In a second experiment McDonough and Kesner (1971) selectively stimulated either the amygdala or the hippocampus. Brief, low intensity, bilateral stimulation caused disruption of the electrical activity of these centers only for the period of stimulation and produced no seizure in the EEG. Stimulation of either the amygdala or hippocampus caused an amnesia for a mouth-shock which the animals had received twenty-four hours before. In a manner similiar to that reported for ECS (Kesner et al., 1970; Neilson, 1968; Nachman and Meinecke, 1969; Pfingst and King, 1969) and body cooling (hypothermia) (Riccio and Stikes, 1969; Jensen and Riccio,

1970), a second mouth-shock and brain stimulation of the amygdala or hippocampus resulted in an avoidance of the mouth-shock when the animals were retested.

More data in support of the notion that discrete electrical stimulation can produce RA without producing AD can be found in Shinkman and Kaufman (1972). These authors delivered hippocampal stimulation to rats during a drink-suppression task and demonstrated RA in a group of animals with AD activity, but with no behavioral seizures. In the same experiment another group of rats received a different duration of stimulation, and these animals demonstrated RA with no AD activity. Also, although localized seizure activity was not specifically examined, Wyers et al., (1968) felt that their ventral hippocampal stimulation did not produce AD, yet it did produce a PA deficit. In a similar manner Wyers and Deadwyler (1970) point out that both 300 microampere and 900 microampere stimulation of the caudate nucleus are equally effective in producing RA, however, 300 microampere stimulation will not produce a spindle discharge in a resting, alert rat. Bresnahan and Routtenberg (1972) found disruption of retention for PA learning with low level (5 microampere) unilateral stimulation of the amygdala, but not with stimulation of the hippocampus. They present evidence that such stimulation to the amygdala produces no AD activity in either the

amygdala or hippocampus. These authors implicate the medial amygdaloid nucleus as the anatomical site mediating the memory disruption.

Amnesic Agents-Summary

Taken together the EEG data from the many amnesic agents suggest a general question of whether the various examples of performance deficit which are labeled amnesia are a unitary phenomenon. The opposite position would be that the various amnesic agents work in different ways to produce different deficits which only appear similar, perhaps because of the grossness of the behavioral measures used to assess the animals performance. Probably no clear resolution of this question can be made at this time, but some suggestions are possible.

Lewis, Miller and Misanin (1968a) have hypothesized that ECS prevents memory retrieval in the passive avoidance task because it renders the animal unconscious before it can complete what is called post-fixation coding. Without this process, the animal cannot form the association between the memory of footshock and the memory of where and how footshock occured. A similar notion of immediate post-trial memonic processing for animals is suggested by Wagner, et al. (1973). In that paper the authors develop the concept of a rehearsal process of limited capacity and suggest that what is commonly known

as an interference with consolidation by ECS may actually be an interference with rehearsal processes which occur after consolidation. In any case both the notions of post-fixation coding and rehearsal suggest that ECS acts on processes subsequent to fixation as Lewis (1969) has hypothesized. Additionally Lewis (1969) has suggested that it is active memories which are suceptible to ECS. Thus in the PA task it is an active memory, one undergoing post-fixation coding, which has been inhibited in the amnesic animals. It could well be that amnesic agents all work in this way. Although all amnesic agents do not render the animal unconscious, they may prevent post-fixation coding by distracting the animal. The point has been made that all amnesic agents have the ability to change ongoing brain electrical activity; it may be that this change is a manifestation of the animal's distraction from his coding task. This interpretation seems reasonable in view of the fact that there does not appear to be a specific EEG pattern which is a correlate of experimental amnesia when the several different amnesic agents are considered.

CHAPTER II

THE ECS SEIZURE PATTERN AND EXPERIMENTAL AMNESIA

Although a unique EEG pattern has not been found as a correlate of all forms of experimental amnesia, there is the possibility that such a correlate could be found for amnesia produced by a single amnesic agent. Thus within the ECS literature, a portion of the research in animal memory processes seeks EEG correlates of ECS-produced amnesia in the ECS seizure pattern. If ECS does manipulate animal memory, then the notion is that the EEG pattern within the first minutes after ECS may contain some implication for the amnesia which is observed at a later time. Contemporary research into the relation between cortical EEG and ECS-manipulation of animal memory might well begin with the Chorover and DeLuca (1969) study of the EEG of rats in the one-trial PA task. Behaviorally, in response to either ECS alone or to FS followed by ECS, all their animals exibited the same typical clonic-tonic reaction to ECS delivered across the pinnae. No change in that reaction was observed as a function of time (0.5-300 seconds) between FS and ECS.

However an examination of the EEG of animals that received ECS revealed the existence of three general

patterns which appeared to be highly dependent upon the animals' state of arousal. The normal pattern was obtained in animals that received an ECS without FS, or in animals with a long ($>$ 40 seconds) FS-ECS interval. This pattern is characterized during the 12-15 seconds following ECS by monophasic and biphasic spike activity coinciding with some high frequency discharge which outlasts the spike activity by 10-12 second. After an electrically flat period, monophasic sharp waves can often be observed approximately one minute after the seizure. Unlike the first discharge, this monophasic activity often occurs without observable muscle movement.

The two other EEG patterns seen in animals were classed as abnormal. Type A pattern consisted of asynchronous and bilaterally asymmetrical seizure activity, usually of delayed onset, variable frequency and reduced amplitude. These reactions were often observed when the ECS was given to animals engaged in active escape.
Type B pattern showed no detectable seizure activity and little departure from pre-ECS amplitude and frequency in spite of the presence of a behavioral convulsion. The EEG responses of this type occurred when the animal was visibly fearful at the time of ECS. In concise terms, the Type A pattern was described as an alteration of the normal seizure response, whereas the Type B pattern was described as an abolition of the normal seizure response.

Thus the Chorover and DeLuca paper established that the ECS seizure activity observed in typical one-trial PA studies is superimposed upon an ongoing neural background of FS-produced arousal. Such arousal may modify the EEG seizure pattern normally produced by ECS. It should be noted that with their description of normal seizure activity Chorover and DeLuca (1969) defined the three outstanding characteristics of the ECS seizure EEG---the initial neural discharge, the flat period and the occurrance of a later, or secondary, neural discharge.

As interesting as the Chorover and DeLuca paper is, it suffers from a failing. One is left with a question as to whether RA was established in their animals. That is, no behavioral measures of memory were taken, thus no firm correlation between the animals' performance in the PA task and their EEG can be made. Vandaris and Gehres (1970) took that fact into consideration in their experiment. They trained and tested rats in a stepthrough task, and they recorded EEG following treatment.

Four groups of animals were specified: FS; ECS; FS-ECS; and FS-ECS delayed. The FS-ECS group showed amnesia for the footshock, while the FS-ECS delayed (one hour) group did not. In testing, the ECS group showed no difference from initial stepthrough latencies, while the FS alone group manifested much longer test latencies

compared with initial latencies.

Vandaris and Gehres (1970) rated most of their seizure patterns as similiar to the normal seizure patterns reported in Chorover and DeLuca (1969). Further, four of their animals showed EEG's which were judged similar to the abnormal seizure patterns (type A) discussed above. After examining the stepthrough latencies of their animals, Vardaris and Gehres (1970) showed that of the four animals showing abnormal EEG after ECS all showed avoidance during testing, twenty-four hours later. Three of the four animals were in the FS-ECS group, while only one was in the FS-ECS delayed group. Thus Vardaris and Gehres (1970) suggest that anomalous stepthrough performance during testing was associated with the abnormal EEG taken immediately after ECS.

Lee-Teng (1969) reported that subconvulsive ECS currents produced RA much like the RA obtained from using an ECS strong enough to produce normal convulsions. More precisely, for an ECS of 10 ma. or 15 ma. given to chicks only 15 ma. produced an overt convulsion, while RA was obtained from both 10 ma. and 15 ma. Therefore Lee-Teng and Giaquinto (1969) gave three ECS intensities (5, 10, 15 ma.) to chicks and recorded their frontal EEG in an effort to find any commonality in the patterns of RA animals with a convulsion and RA animals without a convulsion.

Their results showed that the behavioral responses to 5 and 10 ma. ECS were equivalent; none of those animals showed a muscular convulsion. However spike activity was present in the 10 ma. group and absent in the 5 ma. group. Spike activity was also present in the 15 ma. group; this group manifested muscular convulsions. Hence Lee-Teng and Giaquinto (1969) concluded that there was an association between EEG spike activity and RA. They further concluded that the flat period in the EEG record following ECS had no relationship to the presence of RA.

Zornetzer and McGaugh (1970) studied the behavioral and EEG effects of ECS given to rats. They delivered ECS via clip electrodes located subadjacent to the pinnae and compared it with ECS given directly to frontal cortex via screws implanted in the skull. Although less current was delivered to the screw electrodes, behaviorally both modes of ECS resulted in complete RA for a PA task. In this study both cortical and subcortical (amygdala) activity was monitored. The EEG immediately following ECS was characterized by biphasic activity (spiking) which the authors termed primary afterdischarge (PAD). Following the PAD, the postictal depression period occured. For ECS intensities above 30 ma. a secondary afterdischarge (SAD) developed subcortically and rapidly spread to the cortex. SAD was characterised as monophasic waves which

grew in amplitude. The duration of the discharge was less than thirty seconds, and behaviorally there was little indication of seizure. Zornetzer and McGaugh (1970) speculated that the effect of the SAD activity was to make more complete the RA produced by PAD. Thus, temporary RA might be produced by a weak PAD. However no recovery of RA would be expected twenty-four hours after ECS if PAD was followed by SAD.

Zornetzer and McGaugh (1971a) further elaborated characteristics of the PAD. Like Lee-Teng and Giaquinto (1969), it was found that in etherized mice the post-ictal depression was not a correlate of RA, and also that the seizure threshold of the brain is lower than the threshold for a convulsion. The authors pointed out that the occurrence of RA seemed to parallel the brain seizure threshold.

Therefore it would seem that the correlate of ECS-produced RA was PAD. The extent and duration of the PAD was thought to vary directly with the intensity of ECS current up to the point that SAD occured. Additional support for these notions came from Herz et al., (1970) using flurothyl in place of ECS.

The picture was soon to become clouded, however. That PAD activity might not be the critical event in the production of RA was suggested when Zornetzer and McGaugh

(1971b) found RA with eitherized mice in a one way active avoidance task in the absence of any cortical brain seizure. The authors suggested that the particular behavioral task used in an experiment may affect the occurrance of RA. Alternately they suggested that the brain seizure threshold might have changed because of the footshocks required in the acquisition of active avoidance.

However it was Zornetzer and McGaugh (1972) who conceded that many factors appear to influence the production of RA. Thus not only the intensity of the ECS current, but the motivational properties of the stimuli during learning may be important considerations. It was found that if rats were trained in a PA task with a brief mouthshock (low motivationsal stimulus) RA was manifest when any cortical seizure was produced. No difference in the PA deficit could be found regardless of whether an animal's seizure was a short PAD with no post-ictal period, or a full PAD, isoelectric, SAD sequence. On the other hand if rats were trained with a longer duration FS (high motivational stimulus) RA was maximal only when the cortical seizure showed both PAD and SAD activity.

Thus an analysis of the latency of a bar press twenty-four hours after treatment with a FS-ECS indicated that animals that manifested both PAD and SAD activity took less time to perform the task than animals that had

developed only PAD activity. While all animals manifested RA, the animals with the greater cortical response showed greater RA. Zornetzer (1972) again implicated the SAD. Instead of delivering current to the cortex, he applied it to the midbrain region (ventral tegmentum) and observed that RA was produced only if a cortical SAD developed.

More information concerning the ECS seizure pattern in a one trial passive avoidance task is supplied by Paolino and Hine (1973). Using the three group paradigm (FS, ECS, or FS-ECS), these authors delivered a range of ECS intensities directly to the rat cortex; different groups of animals received 2, 10, 50 or 100 ma. delivered transcortically. An additional two groups were given ECS or FS-ECS transpinnate for comparison purposes. Although the retention stepthrough latencies for the ECS-only and FS-ECS animals were uniformly low across all groups, they were also statistically different at all intensities except the 100 ma. transcortical ECS. Thus Paolino and Hine (1973) conclude that while the ECS treatment was not aversive for any of the intensities studied, only at the ECS of 100 ma. was RA truly complete. Additional groups of rats were given the same ECS discussed above, but at a 60 second delay following training. All these animals showed no RA, regardless of the intensity or mode of delivery of ECS.

Paolino and Hine (1973) then directed their attention to the ECS seizure pattern of the animals. The major finding was that long retention latency (no RA) was associated with anomalies of the SAD period. This conclusion came from examining the seizure EEG of those animals given ECS at a 60 second delay following training. On the other hand, the PAD period had no apparent significance for the production of RA. Further Paolino and Hine (1973) could find no reliable electrophysical distinction between amnesic animals (FS-ECS) and non-amnesic animals (ECS-only) regardless of ECS intensity or mode of delivery.

ECS Seizure Pattern-Summary

Thus much confusion surrounds the relationship between EEG and amnesia. The three cortical events following ECS---PAD, isoelectric period and SAD---have been clearly observed by many, yet the literature on these event contains many conflicting reports on major points. It is reported that ECS can produce RA without the occurrence of SAD, but SAD may contribute to RA (Zorneter and McGaugh, 1972). It is then reported that SAD is associated with the lack of RA (Paolino and Hine, 1973). It is suggested that a differentiation exists in the EEG seizure pattern of animals given ECS-only or FS-ECS in a one trial passive avoidance task (Chorover and DeLuca, 1959). It is then

suggested that only anomalous EEG is associated with lack of RA in animals given ECS (Vandaris and Gehres, 1970). Finally it is reported that no differentiation of the seizure patterns of amnesic and nonamnesic animals can be made, but that complete lack of RA seems to be associated with anomalous SAD (Paolino and Hine, 1973).

To further complicate the matter, electrical stimulation has produced RA in the absence of cortical seizure activity, and there is suspicion that electrical stimulation can produce RA without AD activity at the site of stimulation (McDonough and Kesner, 1971; Wyers et al., 1968; Shinkman and Kaufman, 1972; Bresnahan and Routtenberg, 1972).

Since amnesia can be produced by manipulation of discrete subcortical centers, and since ECS manipulates those centers in addition to other parts of the brain (Routtenberg, et al., 1970) it seems reasonable to assume that amnesia may be produced when the electrical activity of those subcortical centers is changed. Thus a correlate of amnesia quite conceivably may not exist in the EEG seizure pattern itself. Rather the question now becomes one of the sensitivity of the recording technique to discern subleties of neural response.

CHAPTER III

THETA

In addition the ECS seizure pattern, a correlate of ECS-produced amnesia, could conceivably exist in some special characteristic of the EEG waveform. Frequency information, particularly that of the theta range (4-9 Hz. in rats), has in the past been associated with learning and memory processes in animals.

Subcortical Theta

Early work with animals lesioned in the temporal lobe (Kluver and Bucy, 1937) contained suggestions that this area might be an important locus for memory processes. Scoville and Milner (1957) and Penfield and Milner (1958) implicated the integrety of the hippocampus as a necessary condition for normal learning and recall in humans. At about the same time several laboratories published reports of the slow wave electrical activity of the hippocampus (theta) in animals. Green and Arduini (1954) described an inverse relationship between activation of the cortex and hippocampus. Thus in association with neocortical desynchronization the hippocampal EEG record would manifest a series of large slow waves. Grastyan et al., (1959) reported that in response to a novel stimulus during conditioning the electrical activity of the hippocampus showed first desynchronization (as in the neocortex), but then

shortly later a synchronized response of large slow waves which:

> appear simultaneously with the appearance of the first somatic signs of the temporary connection and then, at the stabilization of the reflex, desynchronization follows again (Grastayan et al., 1959).

In other words the hippocampal theta activity was associated with orienting behavior in the initial phase of the animal's learning in the conditioning task (Grastyan, 1961). In a somewhat similar manner Pickenhain and Klingberg (1967) postulated that theta appears in all motivated, but non-automatized behavior. To these authors, however, theta was an expression of a dynamic comparator mechanism which compares actual sensory information with formerly stored information.

Adey (1967) has suggested that hippocampal theta activity in the cat is subtly related to discrimination performance, rather than orienting behavior. In a T-maze discrimination problem Adey et al. (1960) reported that trains of hippocampal theta (5-6 Hz.) from the dorsal hippocampus or entorhinal cortex appeared with each approach performance. Further research revealed that during early training the EEG of the entorhinal cortex lagged behind the EEG of the dorsal hippocampus by approximately 20-30 msec. However by the later periods of training the

theta activity of the entorhinal cortex led the dorsal hippocampus by as much as 65 msec. Adey et al. (1960) suggested that these differences in theta phase relationships might be the basis for a phase-comparator mechanism by which the brain could code information.

Another approach to the problem of the relationship of EEG to memory processes is suggested in the work of Elazar and Adey (1967). These authors trained cats to choose a left or right window at the end of a runway. One of the windows was illuminated randomly across training trials. The animals were given a food reward if they made a correct choice by running to the lighted window. EEG records were taken from the cats throughout training. In the later stages of training a very consistent EEG pattern emerged. The electrical activity of the hippocampus shifted upward to a dominant 6 Hz. frequency during the cat's correct approach in the runway. When the animal made an incorrect approach there was no shift of electrical activity to 6 Hz. Elazar and Adey (1967) suggested that the EEG effects which they observed were correlates of the memory consolidation process.

Cortical Theta

The work discussed thus far has in common the fact that theta was recorded directly from the hippocampus. Brain electrical activity of the theta frequency can also

be recorded from electrodes placed on the cortex. A logical question is whether theta activity recorded from the hippocampus is the same as theta activity recorded from the cortex. Yamaguchi, et al., (1967) used electrical stimulation to the brain stem of cats to elicit hippocampal theta activity. They then examined the resulting electrical activity of the cortex for theta activity which waxed and waned in synchrony with the hippocampal theta. Because much large amplititude hippocampal activity was not associated with the appearance of cortical theta, they concluded that cortical theta was not due to physical spread of the hippocampal electrical activity. Thus cortical theta appeared to derive from the cortex. However, it was not totally independent of the hippocampal activity, since well synchronised hippocampal theta appeared to facilitate the occurrence of cortical theta. Although not discussing cortical theta directly, Parmeggiani (1967) reported that large slow waves could be recorded on the cat cortex when sciatic nerve stimulation produced hippocampal theta. Again, the large slow waves were not due to physical spread of hippocampal activity because of their latency and the fact that they could be erased by cooling the neocortex. Nevertheless their appearance did depend on the hippocampal activity, and their origin was placed in thalamic non-specific nuclei.

Taking another position Lloyd and Gerbrant (1973) investigated an averaged cortical potential in the theta frequence range. By lowering an electrode through the brain and examining neural activity at various depths the authors were able to locate the source of the averaged cortical waveform in the pyramidal cell layer of the hippocampus.

Thus the conclusion drawn from these studies is that theta of hippocampal orgin can certainly be teased out from a cortical EEG waveform (especially by averaging techniques), and that some theta observed in the cortical EEG has been shown to be correlated with hippocampal theta. But it has yet to be proven that hippocampal theta and cortical theta are always the same thing, particularly in the unanesthetized and unrestrained animal. Nevertheless since there is a question of whether the theta recorded from the cortex has any existence apart from the theta which is recorded from the hippocampus, it seems reasonable to adopt the convention that the term cortical theta should refer to theta activity recorded between cortical electrodes. This convention is thus neutral with respect to the question of the ultimate origin of that activity.

Some of the ideas discussed in Elazar and Adey (1967) have found expression in the ECS literature. Noting that Elazar and Adey (1967) have implicated the

hippocampus (and its associated electrical activity, theta) in the consolidation of the memory trace, Landfield, McGaugh and Tusa (1972) investigated theta activity by recording from the cortex of rats trained in a one-trial PA task.

Immediately following treatment in a stepthrough task, Landfield, et al., (1972) placed each animal in a holding cage where EEG activity was sampled during a thirty minute period. Three groups of animals were used in the experiment (FS; FS-ECS; ECS), and two days following training and treatment all animals were returned to the apparatus for a behavioral measure of the animals' latency. The behavioral data and the EEG records indicated that the amount of theta activity recorded immediately following treatment was highly correlated with the animals' behavioral latency two days later. Thus animals that received FS showed large amounts of theta and had long latencies, while animals that received FS-ECS showed small amounts of theta and had latencies.

It should be noted that no relation was found for animals given only an ECS. However the relationship held for individual animals across FS groups. Thus a few FS-ECS animals that exhibited retention behaviorally also showed large amounts of theta, and a few FS animals with short latencies exhibited small amounts of theta. Hence

the amount of post trial theta was the best predictor of the animals' test performance.

Landfield, et al., (1972) then presented some evidence about the temporal course of theta. The animals from the first experiment were habituated to two boxes, one black and one white, each with a grid floor. After several days the animals were assigned to new groups (FS; FS-ECS; No FS-No ECS) and were placed in the white box for thirty minutes while EEG was sampled. Then they were treated according to their group and removed immediately to the black box. Two days after this training the animals were returned to the white box, and EEG again was sampled for thirty minutes.

These manipulations demonstrated that the pre-trial EEG of all the animals was the same; all groups showed high theta for the first few minutes, but then the amount of theta dropped across a thirty minute period. A FS, however, caused large amounts of theta for at least thirty minutes afterward. An ECS following a FS produced a suppression of theta followed by a gradual recovery. Two days later when the animals were placed in the white Box FS animals showed high theta. The FS-ECS and No Fs-No ECS animals showed high theta for the first few minutes, but then they habituated.

Landfield, et al., (1972) speculated that the

amount of theta in the cortical EEG could be used as a measure of retention. It must be noted that although there was clear distinction between groups when the amount of EEG theta was used to trace the temporal course of the activity across an experiment, there was no behavior with which to correlate the activity. Yet Landfield, et al., (1972) postulate that when consolidation processes are presumed to be active, theta is increased. When consolidation is decreased (by ECS) theta is also decreased. Without supposition however, the Landfield et al., (1972) paper does seem to support their conclusion that:

> in rats, the degree of retention of a one trial training experience varies with the amount of theta thythm activity recorded during the period after training.

Alternative Explanations of Theta

Douglas (1967) has discussed several hypothesis of hippocampal function and compared them with the data obtained from hippocampal lesions. Although a memory function is a possibility, his review suggests that it is more likely that the hippocampus is involved in an inhibitory efferent control of sensory reception. According to his notion the presence of theta, would signify that the hippocampus is, in fact, inactive.

Other authors have suggested that hippocampal theta is highly implicated in motor performance rather than in any memory function. Komisaruk (1970) has

observed a one to one correspondence between each beat of the theta rhythm and each twitch of rats' vibrissae during exploratory sniffing behavior. Heartbeat also manifested the same correspondence with theta. Since limbic, motor and cardiac function were so highly related with the theta rhythmn, Komisaruk (1970) suggested that theta was involved with modulating or driving the motor neurons controlling the muscles used in movement.

Kamp et al., (1971) has studied frequency shifts in hippocampal theta in a dog in an unrestrained field situation. Responding to the notion of progressive shifts in hippocampal theta during approach behavior in Elazar and Adey (1967), Kamp et al., (1971) reported that the frequency shifts were associated with the transition of one behavioral act to another.

Vanderwolf (1971) has reviewed much of the literature in hippocampal theta and concluded that theta is not related to the learning process. Rather, he presents the argument that theta is correlated with voluntary movement. He supports his argument with the observations that: (1) theta is not present during behaviors associated with reinforcement; (2) theta is not present in animals trained to remain motionless, and; (3) brainstem points that produce theta when stimulated can be neutral, rewarding, or punishing when tested by self

stimulation. On the other hand, Bennett (1969) has presented evidence that hippocampal theta can be present at times when the animal is motionless. He also contends that desynchronized hippocampal activity can occur during periods of voluntary movement. Somewhat like Grastyan et al. (1959), Bennett suggests that theta is involved with exploratory behavior.

More recently Klemm (1972a) has pointed out that the conclusions made in Landfield et al., (1972) linking cortical theta with memory storage might be completely erroneous. Klemm (1972b) prefers the explanation that hippocampal theta rhythm is a nonspecific result of sensory stimulation of the brainstem reticular formation. Thus animals given a FS (as in Landfield et al., 1972) would be expected to exhibit theta simply because the FS would cause the animals to be highly aroused.

Theta-Summary

Thus much research suggests that theta activity may be involved with various aspects of motor performance or arousal processes, and not with learning or memory. Obviously the problem of resolving whether theta activity is strictly concerned with motor processes or strictly concerned with learning or memory processes is a sticky one. At the present level of science an animal's memory of previous learning is inferred from his performance

during a retention test. Therefore, without some motor behavior one can know nothing about memory. Nevertheless sufficient attention can be given to the design of experiments so that it will be possible to learn something of the relative importance of theta in motor or memory processes. Specifically one would prefer a task in which all animals perform the same motor behaviors, but differ in their memory ability. A task like passive avoidance, for example, where control animals remain on a platform while experimental animals step off would not be desirable, since both groups perform different motor behaviors.

CHAPTER IV

THE EXPERIMENTAL PROBLEM

The proposed experiment seeks to resolve some of the confusion surrounding theta and animal memory by showing that cortical theta does or does not have broad implications for memory processes. This will be accomplished by training the animals in an appetitive maze task in which consolidation processes are separated from retrieval processes (Lewis, Bregman and Mahan, 1972). In this task animals learn to run without error a four box Krechevsky maze (K-maze). The maze consists of a series of four left or right choices. Then the animals are left in their cages throughout a seven day retention period. On the seventh day the animals are returned to the start box (SB) of the K-maze, and an ECS or no-ECS sham (NECS) treatment is administered. The animals are placed in their cages for twenty-four hours, then they are returned to the K-maze for testing. Testing consists of retraining the animals to run the K-maze; typically ECS animals make more errors than NECS animals.

Since the ECS treatment is given to the animals seven days after they have learned the K-maze, the resulting deficit cannot be attributed to an interference with consolidation processes. The K-maze amnesia is not

indexed by an animal's failure to perform, but by the number of errors it makes in running the maze after ECS. Thus a gross impairment in motor performance due to a debilitating effect of ECS is not demonstrated. Also explanations of the amnesia based on notions of fear (Coons and Miller, 1960) or changed activity levels (Routtenberg and Kay, 1965) are not likely, since the animal's specific choice is the measure of retention. Rather, the amnesia is assumed to be an example of a memory retrieval deficit caused by administering ECS upon presentation of the cues related to a learned task (Misanin, Miller and Lewis, 1968; Lewis, Bregman and Mahan, 1972; Lewis and Bregman, 1973; Bregman, 1972). Such a presentation produces an active memory state which is then susceptible to inhibition from the ECS (Lewis, 1969). Bregman (1972) has presented evidence that ECS will produce the K-maze retention deficit if the ECS treatment is given in the SB of the maze, but not if the ECS treatment is given in another box (NB) obviously different from the SB and therefore neutral with respect to the cues of the SB and maze. In this manner the K-maze offers the opportunity to contrast the EEG of two groups of animals in an appetitive task that both receive ECS, with the result that one group (SB-ECS) will be amnesic and the other (NB-ECS) will not.

If EEG records of the thirty minute period following ECS or NECS treatment in the K-maze show that the amount of theta is related to the amount of retention, then it will be established that theta has implications for processes beyond that of consolidation. Further since the K-maze is an appetitive task, Klemm's criticism (Klemm, 1972b) of FS-produced arousal can be dealt with directly. Thus if there is a relationship between post-ECS theta and relearning performance it should be possible to attribute the relationship to either memory processes or to other processes. If post ECS theta fails to differentiate relearning performance in ECS and NECS animals, or if the theta relationship does not follow specific predictions for NB-ECS and SB-ECS animals the correlation is most likely due to processes like those suggested for hippocampal theta by Kamp et al., (1971), Komisaruk (1970), or Vanderwolf (1971).

Additionally the proposed experiment offers an opportunity to further test notions of theta and memory storage if a relationship is established as discussed above. Logically, if theta has any implication for retention in the K-maze then it should have direct relation to the active memory state hypothesized by Lewis (1969) and Bregman (1972). Cortical EEG records can also be taken during training and at the time of reinstatement to better

establish the temporal course of theta throughout the experiment. Thus if theta is related to more than simple memory storage it should be present during reinstatement, and the reinstated ECS animals should make errors when they are tested in the K-maze twenty-four hours later.

CHAPTER V

METHOD

Subjects

The animals participating in experiments I, II and III were obtained from Horton Labs, Inc. of Oakland, California. All the animals were male albino rats (Sprague-Dawley derived) between 40-50 days old at the time of delivery. During training in the maze task, and until the animals were discarded each animal was fed approximately ten grams of food, once each day. This amount was in addition to the food the animal received on each trial for his performance in the maze. The animals were caged individually with water available to them at all times.

Surgery

At the time of surgery the animals ranged in weight from 190 to 294 grams ($\bar{X}$ = 245 grams). They were anesthetized with pentobarbital (50 mg./kg.), placed in a stereotaxic frame, and prepared with a cortical electrode assembly (amphenol connectors). The assembly was connected by size 008 nichrome wire to stainless steel screw electrodes which were secured in the rat's skull. The electrodes were placed approximately 2 mm. lateral to midline. There were four electrodes; two were placed posterior (2 mm. anterior to lambda), and two were placed anterior (2 mm. posterior to bregma), thus allowing

an anterior to posterior pair of electrodes over the cortex on each side of the brain. The electrode assembly was bonded with dental cement to the screw electrodes.

After surgery the animals were placed in their individual cages and allowed a recovery period of five days, during which the animals were given continous access to both food and water. At the end of this period the animals were placed on a food deprivation schedule of ten grams of food per day for five days before behavioral training began. Throughout the ten days following surgery the animals were handled daily.

Apparatus

The apparatus was a sequential maze (K-maze), modified from that of Krechevsky (1932). The maze is made up of a start box (SB), four maze boxes, each with a left-right choice option, and a goal box (GB). All the boxes are separated from each other by guillotine doors. Unlike the original Krechevsky maze, the four maze boxes are each designed to force the animal to make a left or right choice without an actual visual discrimination.

Cortical EEG was recorded using a 4 channel Grass EEG unit. The records were stored on 1/2" magnetic tape (Honeywell model 7600 recorder) for later analysis by computer. The ECS was delivered from a Beckman 735B Liberson Brief Stimulus Therapy Apparatus from a duration

of 0.5 seconds.

Experimental Design

Three groups were included in Experiments I and II. Two groups of animals received ECS or NECS treatment in the start box of the K-maze (SB-ECS; SB-NECS). One group received ECS in a box (NB-ECS) outside of the maze. In Experiments I and II ECS was delivered to the two posterior cortical screw electrodes. The ECS intensity in Experiment I was 20 ma.; in Experiment II it was 10 ma.

Two groups were included in Experiment III, SB-ECS and NB-ECS. An ECS intensity of 55 ma. was delivered transpinate.

Pretraining

Upon recovery from surgery the animals were pretrained in the K-maze. Basically pretraining consisted of allowing each animal, one at a time, to travel without barriers from the SB, through the maze and into the GB where it received a food reward. This procedure was repeated for ten trials, after which the barriers were placed in the maze.

Training

Following the ten pretraining trials the animals were then trained to run through the maze to a a particular sequence of left and right turns. Half the animals were trained to run right, left, left and right

at the choice options in the maze; the other half were trained to run left, right, right, and left. All animals were trained to a criterion of eleven out of twelve correct choices. This criterion corresponded to the animal running through the maze three consecutive times while making only one incorrect turn.

Handling

Following the training period all animals were left in their home cages for seven days. Throughout this retention period they were handled daily. Handling consisted of removing each animal individually from its home cage and transporting it to the NB. The animals were left in the NB for fifteen seconds, and then they were returned to their cages. This procedure was followed three times daily. It was designed to eliminate as a cue for the maze the routine handling which occurs during the training period.

Reinstatement and Treatment

On the seventh day of the retention period the animals received ECS or NECS treatment. Following handling, one group was connected to the recording leads, placed in the SB, the SB gate was opened, and the animal was given an ECS. Another group was treated the same way except that they received NECS. A third group was connected to the recording leads, placed in the

neutral box (NB), and given an ECS.

Testing

All animals were returned to the K-maze twenty-four hours after ECS or NECS in order to assess the effect of the treatment. Retention was inferred by recording the number of errors each animal made in relearning the K-maze to the original learning criterion of eleven out of twelve correct choices.

Recording Procedures

The electrode assembly contained four electrodes. Cortical EEG was recorded from anterior and posterior electrode pairs as well as from the two anterior electrodes. Cortical EEG records were taken from all animals at five particular periods within the behavioral training, handling and treatment procedures (Table 1). The first and second recording periods were two recording trials during K-maze training. For a recording trial the animals were not allowed to run the maze. Instead each animal was connected to the recording leads, placed in the SB, and the SB-gate was slightly raised. Then the animal was removed from the SB and replaced in its cage to await the next training trial. The first recording trial followed the initial trial of the training period. The second recording followed the second consecutive training trial in which the animal ran the maze with a total of one error or less

TABLE 1

K-MAZE PROCEDURES AND EEG RECORDING

Pretraining	
-10 Maze Trials	
Training	Early Learning EEG
-Learn to Criterion	Late Learning EEG
Retention Interval	Handling EEG
-Handling for Seven Days	
Reinstatement and Treatment	
-Place in SB (ECS)	Reinstatement EEG
-Place in SB (NECS)	
-Place in NB(ECS)	
Recovery from Treatment	ECS Seizure Pattern
-Place in NB	30 Minute Post-ECS EEG

for both trials (7 out of 8 correct choices).

Cortical EEG records were again taken from all animals in one handling period during the seven day retention interval. On the sixth day of the retention period the animals were connected to the recording leads, and a record was taken when they were placed in the NB.

During the reinstatement period, approximately five seconds in duration, EEG records were taken from the animals placed in the SB of the K-maze. Cortical EEG records were also taken from those animals placed in the NB. After ECS or NECS treatment, EEG records were continously recorded for thirty minutes, and all animals were left in the NB during this time.

Cortical EEG Analysis

There were three different kinds of EEG data obtained from the different recording periods in Experiments I, II and III. One kind of EEG data was that of the neural seizure pattern which was recorded in the two minute period immediately after ECS. This EEG data was analyzed from all three Experiments. The second kind of EEG data, amount of theta, was obtained from a continuously recorded 30 minute period which followed ECS or NECS treatment. The third kind of EEG data (EEG pattern) was obtained from the four pre-ECS recording periods: Table 1 displays the different recording periods in

conjunction with the behavioral procedures for the K-maze.

In Experiments I, II and III the ECS-produced neural seizure pattern was recorded on the paper record produced directly from the Grass EEG unit. The duration frequency and amplititude of the various portions of the seizure pattern reported in the data were obtained by measuring with a millimeter ruler the paper EEG record which was taken from each animal at the time of treatment.

In Experiment III each animal's EEG was evaluated for the amount of theta activity in the 30 minute post-ECS period by passing the FM tape recorded waveform through a bandpass filter (3 - 10 Hz.) and then into a digital logic circuit containing a Schmidtt trigger and counter. The digital logic circuit was designed to analyze the filtered EEG every other second and detect frequencies of 4 to 9 Hz. which were greater than 30 microvolts in amplititude. The 30 minutes of EEG was sampled in 5 periods of 4 minutes each, but sampling did not begin until the fourth minute following ECS or NECS treatment. Each second of theta that the digital logic circuit detected was recorded on a cumulative electromechanical counter.

Also in Experiment III a five second block of the analog waveforms for each of the pre-ECS recording periods stored on magnetic tape was digitized (128 samples/ sec.). The power spectrum in the band 1 to 64 Hz. was then

computed by fast fourier analysis on an IBM 360/44 computer for each of the five second blocks. For the statistical analysis of this data, only those animals for whom EEG data was available throughout the experiment were used in the analysis. Thus each animal was required to have an EEG record from the early and late learning periods, the handling period, and the reinstatement period. Two of the animals for whom post ECS cortical theta was counted failed to meet this requirement, and thus were not used in this analysis.

The first problem to be addressed was to decide upon a method of assessing the similarity of two EEG patterns. The spectral analysis computed on the data defined the power of each frequency component in the band 4 to 9 Hz. The power of each frequency component describes the relative intensity each frequency attains in the overall waveform. To illustrate, one could consider two different waveforms, a pure sine wave and white noise. If a graph of power across frequency (a power spectrum) is plotted for the sine wave all the power of the waveform will be located at the frequency of the sine wave, and there will be no power at other frequencies. In contrast, if a power spectrum is computed for white noise there will be equal power at all frequencies. An EEG waveform is similar to these examples. Numbers

are assigned to each frequency in the band; those numbers scale the extent to which any frequency in the band is active in the EEG pattern.

The data obtained from the spectral analysis is often displayed as a graph with frequency as the abcissa and power as the ordinate. Those frequencies which are most active in the EEG will have the highest power. Thus one can see that two separate EEG power spectra with identical power values at each frequency have the same power spectrum. A graph of the power spectrum of one waveform could be superimposed upon the graph of the power spectrum of the other waveform, and there would be no deviation between the curves. On the other hand two power spectra with very different power values at each frequency would be dissimilar waveforms; a graph of one spectrum superimposed upon the other would show large deviations at each frequency. This was the logic used to assess EEG pattern similarity.

The computation of EEG pattern deviation is easily demonstrated. For example let the power values for frequencies 1 through 9 Hz. for one animal's EEG during early learning be represented by the array, X_I where I = 1 to 6 (Table 2). In X_1, put the power value for 4 Hz., in X_2 put the power value for 5 Hz., and so on until 9 Hz. Now let the spectral analysis of the same animal's

TABLE 2

COMPUTATION OF EEG DEVIATION SCORES

EEG FREQUENCY	POWER VALUES		POWER VALUES		ABSOLUTE VALUE OF DIFFERENCE
4 Hz.	X_1	-	Y_1	=	$\lvert X_1 - Y_1 \rvert$
5 Hz.	X_2	-	Y_2	=	$\lvert X_2 - Y_2 \rvert$
6 Hz.	X_3	-	Y_3	=	$\lvert X_3 - Y_3 \rvert$
7 Hz.	X_4	-	Y_4	=	$\lvert X_4 - Y_4 \rvert$
8 Hz.	X_5	-	Y_5	=	$\lvert X_5 - Y_5 \rvert$
9 Hz.	X_6	-	Y_6	=	$\lvert X_6 - Y_6 \rvert$
					$\sum_{I=1}^{6} \lvert X_I - Y_I \rvert$ I

EEG for frequencies 4 through 9 Hz. during late learning be represented by the array, Y_I, where I = 1 to 6. As before place the late learning EEG power values for 4 Hz. in Y_1, for 5 Hz. in Y_2, and so on.

Now if each X_I is subtracted from its corresponding YI and the absolute value of that different taken, the result is a new array, $|X_I - Y_I|I$, where I = 1 to 6. This new array represents the absolute difference between each power value in array X_I and its corresponding power value in the array Y_I. Or in simpler terms the amount of deviation at each frequency between early learning and late learning is now contained in the array $|X_I - Y_I|I$. If each $|X_I - Y_I|I$ is added together the result will be one number, $\sum_{I=1}^{6} |X_I - Y_I|_I$, a deviation score which represents the total amount that one EEG pattern deviates from another EEG pattern. Again, two similar waveforms will produce a small EEG deviation score, two dissimilar waveforms will produce a large deviation score.

CHAPTER VI

RESULTS

Experiment I

A total of 12 rats completed Experiment I, an initial experiment in which parameters and procedures were tested. A description of the ECS seizure for SB-ECS and NB-ECS animals is presented in Table 3. The ECS intensity was an average current of 20 ma. for 0.5 seconds delivered directly to the brain. This ECS treatment resulted in little scoreable PAD activity. After a complete flattening of the EEG record and at approximately one minute after ECS, an SAD period could be easily observed between the anterior and posterior electrode pair.

All animals that received an ECS treatment manifested large amplitude ($>$ 150 uv) spike activity in their EEG record throughout the 30 minute post-ECS period. Many of these animals were directly observed in shaking episodes; a few fell over and manifested a full clonic seizure late in the 30 minute period. Twenty-four hours after ECS or NECS treatment the animals were returned to the K-maze for behavioral testing. The number of trials to relearning criterior (11/12 trials) is presented in Table 4.

Although the distributions of relearning scores

TABLE 3

SEIZURE DURATIONS FOR THREE INTENSITIES OF ECS

MEASURED IN SECONDS FROM ONSET OF PAD TO END OF SAD

EXPERIMENT I TRANSCORTICAL 20 ma		EXPERIMENT II TRANSCORTICAL 10 ma		EXPERIMENT III TRANSPINNATE 55 ma	
SB-ECS	NB-ECS	SB-ECS	NB-ECS	SB-ECS	NB-ECS
60	60	62	65	59	58
60	63	69	66	60	60
66	66	77	72	62	63
76		72	72	67	64
		74	73	67	66
			73	67	66
			76	68	66
				69	76
				72	

TABLE 4

K-MAZE RELEARNING ERRORS TO CRITERION

EXPERIMENT I TRANSCORTICAL ECS 20 ma			EXPERIMENT II TRANSCORTICAL ECS 10 ma			EXPERIMENT III TRANSPINNATE ECS 55 ma	
SB-ECS	NB-ECS	SB-NECS	SB-ECS	NB-ECS	SB-NECS	SB-ECS	NB-ECS
4	14	0	4	11	0	1	2
22	1	3	8	0	1	3	0
6	37	2	2	4	0	0	1
6	13	2	0	4	1	4	0
			1	0	1	0	1
			4	2	2	3	1
				1	0	1	0
						4	0
						5	0

for SB-ECS and SB-NECS animals are clearly different (the distributions do not overlap), it is also apparent that there is no difference in relearning performance between SB-ECS and NB-ECS animals (Mann Whitney U test (Seigal, 1956) N1 = 4; N2 = 4; U = 6; P = .343). Because a cue-dependent amnesia was not observed in the data, the pre-ECS recording periods were not analyzed. Since seizure was observed throughout the thirty minute period in ECS animals, it seemed reasonable that the ECS intensity of 20 ma. delivered to the brain had been too large. Thus the 30 minute post-ECS EEG record was also not analyzed.

Experiment II

In Experiment II 22 male, albino rats were prepared with cortical electrodes. In the course of the experiment two animals died. The ECS intensity was an average current of 10 ma. delivered for 0.5 seconds as before, directly to the brain. A description of the SB-ECS and NB-ECS ECS seizure is presented in Table 3. As in Experiment I, the PAD period was not prominent, while an easily observable SAD period appeared between the anterior and posterior electrodes at approximately one minute after ECS. Twenty-four hours after ECS or NECS treatment the animals were returned to the K-maze for behavioral testing. The number of trials to relearning criterion 11/12 trials) is presented in Table 4. Again there

seemed to be no clear difference in relearning between SB-ECS and NB-ECS animals, although a Mann-Whitney U test showed the SB-ECS animals to be amnesic (N1 = 6, N2 = 7; U = 8.5; p = .047) when compared with SB-NECS animals. As in Experiment I, the pre-ECS EEG and the 30 minute post-ECS EEG were not analyzed.

Experiment III

In Experiment III the 55 ma. (average current for 0.5 sec.) transpinnate ECS intensity used by Bregman (1972) was substituted in place of ECS delivered to the brain. A further change from Experiments I and II was to move the neutral box to a room adjoining the room in which the K-maze was set up. Although Bregman (1972) handled his animals in the NB and trained and tested them in the same room, it is possible that the reason that SB-ECS and NB-ECS animals were not different in Experiment II was that the handling cues associated with the maze during training were not adequately extinguished. Thus by replicating the same type and intensity of ECS treatment as Bregman (1972) and by increasing the cue differences between the NB and SB, it was hoped to maximize the conditions to bring about amnesia in the SB-ECS animals and no amnesia in the NB-ECS animals.

The number of trials to relearning criterion (11/12 trials) in the K-maze is presented in Table 4;

a Mann-Whitney U test of the number of errors to relearning criterion shows the errors of SB-ECS groups to be statistically greater ($N1 = 9$; $N2 = 9$; $U = 19$; $p < .05$) than the errors of the NB-ECS group. Thus a cue-dependent amnesia was produced in Experiment III.

Post-ECS EEG

In contrast to the ECS EEG seizure observed in Experiments I and II, a very well defined PAD period was elicited with the 55 ma. transpinnate ECS. A description of the ECS seizure pattern in SB-ECS and NB-ECS animals in Experiment III is presented in Table 3, and in Table 5.

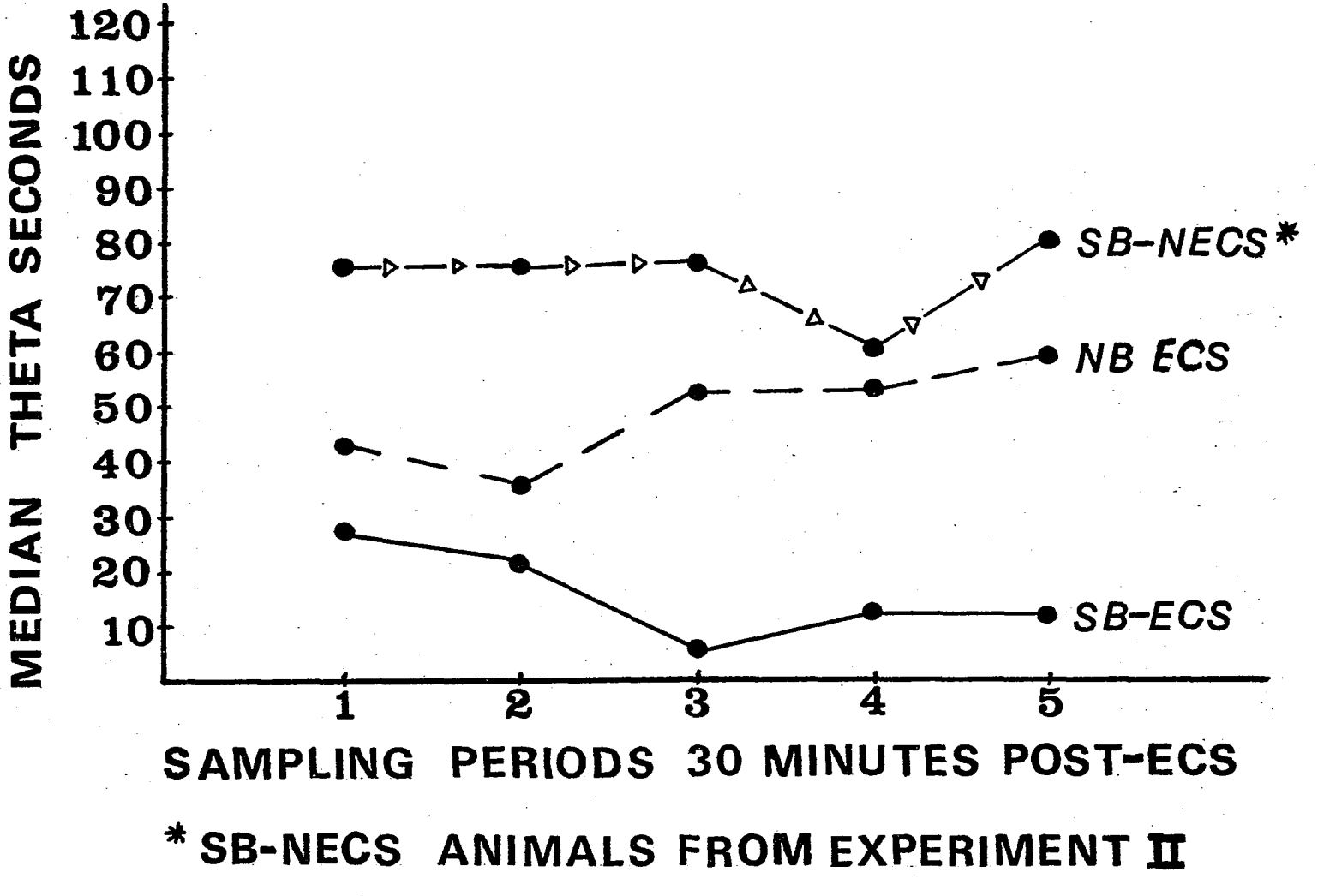
Figure 1 displays the mean cumulative amount of theta for SB-ECS and NB-ECS animals of Experiment III at each of the five sampled periods during the post-ECS period. Included in the figure is the theta count of SB-NECS animals from Experiment II. A Friedman two-way analysis of variance over the scores of sampling periods 1, 3 and 5 shows an overall significance ($X^2r = 9.42$; $df = 2$; $p < .01$) among those sampling periods. A Mann Whitney U test of the SB-ECS and NB-ECS animals in sampling period 1 shows them not to differ statistically ($N1 = 9$; $N2 = 9$; $U = 31.5$; $p > .05$) while a Mann Whitney U test of those same groups at sampling period 5 shows the SB-ECS animals to be significantly lower ($N1 = 9$; $N2 = 9$; $U = 20$; $p < .05$) than NB-ECS animals in the amount of

TABLE 5

ECS SEIZURE PARAMETERS FOR AMNESIC AND NON-AMNESIC ANIMALS

EXPERIMENT III

	OVERALL SEIZURE DURATION	PAD DURATION	FREQ.	AMPLITUDE	SAD DURATION	FREQ.	AMPLITUDE
	67	16	3.56	15.26	16	1.64	1.22
	67	14	3.21	16.28	10	1.70	5.62
	62	12	3.75	16.80	11	2.45	11.30
	67	12	3.50	9.70	19	1.73	10.42
SB-ECS	69	15	3.80	9.50	16	2.13	12.60
	72	11	4.81	8.11	18	1.80	11.66
	60	15	3.66	13.26	8	2.50	4.69
	59	14	3.85	12.41	9	1.66	5.22
	68	13	3.08	9.07	14	1.84	12.50
	76	13	3.38	14.25	23	1.26	6.00
	66	12	4.90	14.25	15	1.50	12.83
	60	12	3.08	9.70	12	1.72	10.50
	63	25	3.15	12.50	14	1.38	12.00
NB-ECS	58	24	1.93	7.83	8	1.37	5.83
	66	20	3.00	16.20	8	1.52	4.00
	66	12	3.40	9.58	13	1.72	9.60
	64	11	4.54	15.00	12	2.16	4.00



* SB-NECS ANIMALS FROM EXPERIMENT II

theta that they exhibit. Further, two additional Mann Whitney U tests showed that NB-ECS animals were significantly lower in amounts of theta than SB-NECS animals at sampling period 1 ($N1 = 7$; $N2 = 9$; $U = 14$; $p < .05$) but not at sampling period 5 ($N1 = 7$; $N2 = 9$; $U = 20$; $p > .05$).

Pre-ECS EEG

Within the pre-ECS EEG data, the first hypothesis to be tested was whether the EEG patterns obtained during K-maze training (early and late) and handling were reliably different from each other. For each animal in Experiment III three EEG deviation scores were computed. One score represents the total deviation between early and late learning EEG patterns; the second score represents the total deviation between handling EEG and late learning EEG; and the third score represents the total deviation between handling EEG and early learning EEG. The scores were then ranked in order of magnitude and a Friedman two way analysis of variance (Siegel, 1956) was used to test the null hypothesis that each column of deviation scores came from the same population of values. Table 6 displays the deviation scores for EEG frequencies from 4 to 9 Hz. recorded between anterior and posterior electrodes on one side of the brain; Table 7 displays the same information for EEG recorded between the two anterior electrodes.

TABLE 6

DEVIATION SCORES

ANTERIOR TO POSTERIOR ELECTRODES

4 to 9 Hz.

EARLY-LATE	LATE-HANDLING	HANDLING-EARLY
1425	2957	2295
165	127	205
609	432	224
166	133	144
205	255	346
434	208	315
84	143	109
244	284	80
180	171	182
166	195	168
929	297	1129
301	220	493
89	105	98
161	98	149

TABLE 7

EEG DEVIATION SCORES

ANTERIOR TO ANTERIOR ELECTRODES

4 to 9 Hz.

EARLY-LATE	LATE-HANDLING	HANDLING-EARLY
334	173	340
104	110	63
184	314	253
210	210	81
301	315	87
140	123	154
269	390	164
214	288	222
179	259	212
113	177	178
490	404	762
221	291	202
180	183	130
159	204	182

The columns of deviation scores do not differ significantly for EEG recorded between anterior and posterior electrodes ($X^2r = 1$; df = 2; $p > .50$) or for EEG recorded between the two anterior electrodes ($X^2r = 4$; df = 2; $p > .10$) in the frequency band 4 to 9 Hz. Thus there was no reliable difference in the pattern of theta frequencies for EEG obtained during training and handling.

The second hypothesis to be tested with the pre-ECS EEG data concerns the notion of memory reinstatement. An important assumption for a cue-dependent amnesia is that at the time of ECS the animal is somehow cognizant of the task for which it will be made amnesic. Thus, such an amnesia does not depend on the disruption of a memory consolidation process. If it could be shown that animals' EEG patterns immediately before ECS and seven days after learning uniquely described the EEG patterns shown during late learning in the K-maze then the assumption underlying a cue-dependent amnesia might gain support. Apparently however, the variability in EEG patterns is such that a K-maze late learning EEG pattern is not reliably different from one taken during the handling period, a time when the animal is not associated with the maze. For this reason it is necessary to test the reinstatement notion in a relative manner. Thus a deviation score was computed between the reinstatement EEG and the

late learning EEG for SB-ECS and NB-ECS animals (Tables 8 and 9). A Mann Whitney U test was used to determine if the deviation scores of the SB-ECS animals were less than the deviation scores of the NB-ECS animals. Although strictly speaking the Mann Whitney U test failed to reach the generally accepted criterion ($p = .05$) of significance ($N1 = 8$; $N2 = 8$; $U = 17$; $P = .065$), it is clear from the results of the test that there is some effect in the data. Because this comparison has importance for a theory of how ECS works in animal memory experiments, the hypothesis should not be rejected simply because the test lacks statistical power. It was decided to see if it was at all possible to reach the $P = .05$ level. Siegal (1956) has suggested that the randomization test may be more powerful than the U test in its ability to reject the null hypothesis. Thus the data were tested again with the randomization test. This comparison showed that the two groups of deviation scores do differ in the direction predicted for EEG in the band 4 through 9 Hz. recorded between the anterior and posterior electrodes ($df = 14$; $t = 2.16$; $.025 > p > .01$), but not for EEG recorded between the two anterior electrodes ($df = 14$; $t = 0.78$; $p > .10$). Therefore the EEG pattern at the time of reinstatement is statistically similar to the EEG pattern shown during late learning in the K-maze for SB-ECS

TABLE 8

EEG DEVIATION SCORES

REINSTATEMENT EEG - LATE LEARNING EEG

ANTERIOR TO POSTERIOR ELECTRODES

4 to 9 Hz.

EXPERIMENT III

SB-ECS	NB-ECS
83	50
1040	1465
367	1601
476	420
158	680
953	2228
710	1003
511	2312

TABLE 9

EEG DEVIATION SCORES

REINSTATEMENT EEG - LATE LEARNING EEG

ANTERIOR TO ANTERIOR ELECTRODES

4 to 9 Hz.

EXPERIMENT III

SB-ECS	NB-ECS
1212	284
328	3901
367	1922
828	180
928	443
715	422
476	603
1022	857

animals, but not for NB-ECS animals.

CHAPTER VII

DISCUSSION

ECS Seizure Pattern

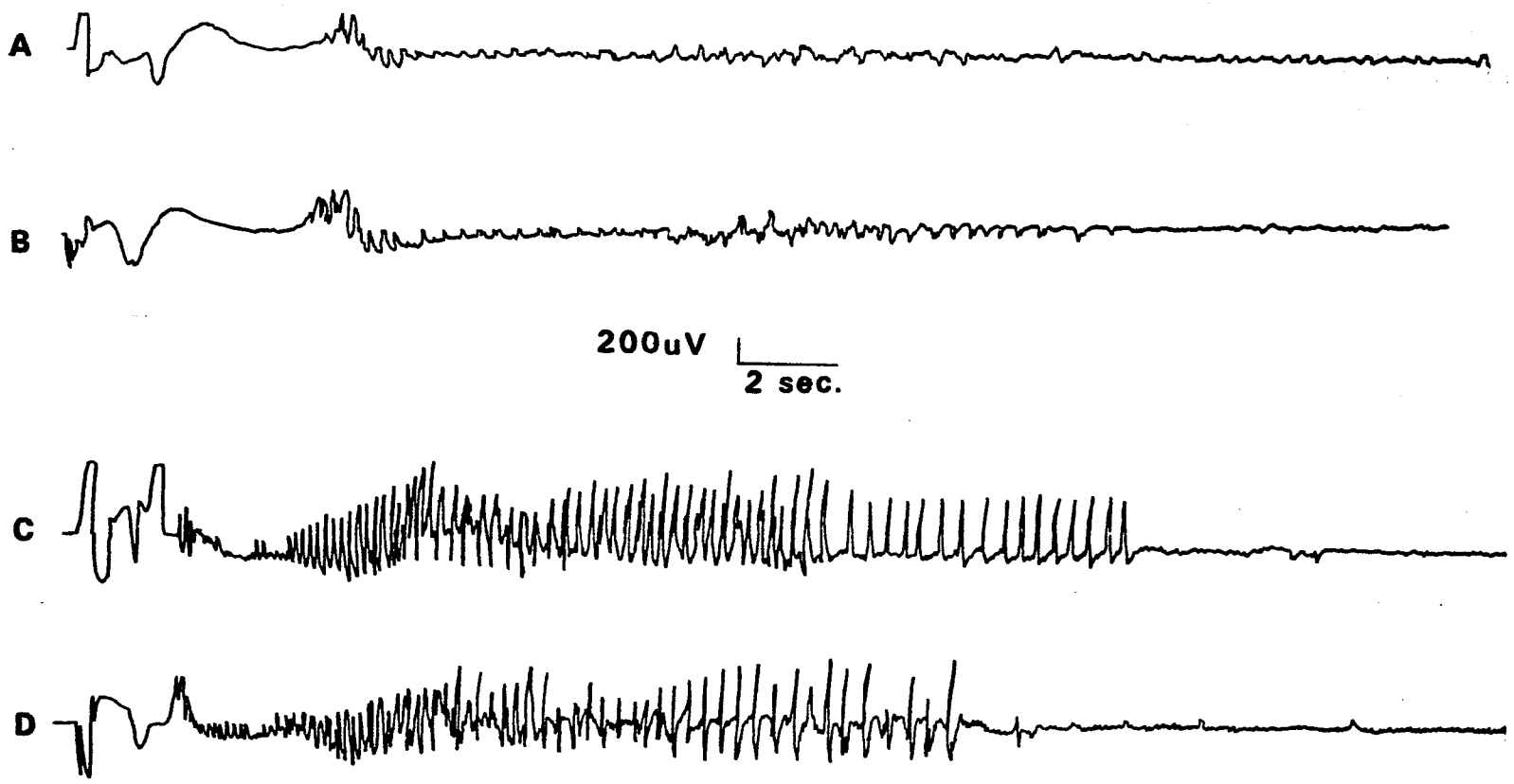
In a manner similar to other authors (Zorneter and McGaugh, 1970), the present data appear to support the notion that ECS intensity can modify the appearance of the PAD period. Zorneter and McGaugh have shown that below some ECS intensity SAD will not appear, but above the apparent threshold SAD is reliable. Although the ECS intensities in the present data are generally larger than theirs, SAD manifested no appreciable change across a range from 10 ma. transcortical ECS, to 10 ma. transcortical ECS to 55 ma. transpinnate ECS. Of what relevance for memory the various elements of the ECS seizure pattern hold is a question of some disagreement in the literature. In the present data none of the parameters of the ECS seizure pattern (Table 5) separated the amnesic from nonamnesic animals in Experiment III. In fact across a wide range of ECS intensity the overall duration of the ECS seizure appears equivalent. Thus the conclusion is inescapable. The PAD, SAD and isoelectric period are probably concerned with the brain's response to the ECS; in any case they hold no obvious relationship to the differentiation of amnesic and nonamnesic animals in the cue dependent amnesia paradigm.

As it was pointed out in Chapter II, most of the papers reporting correlation of memory with some aspect of the ECS seizure pattern use the passive avoidance task. Amnesia in this task is inferred from a comparison of animals that have received FS with animals that have recived FS and ECS. Chorover and DeLuca (1969) have shown that FS causes immediate cortical EEG effects which continue after the FS. An ECS also obviously manipulates cortical EEG. Perhaps these stimuli or an interaction between them account for the reported correlations between ECS seizure pattern and memory. If this were true then in an appetitive task like the K-maze one would not expect the ECS seizure pattern to show differential effects in amnesic and nonamnesic animals.

Although the ECS seizure pattern failed to differentiate amnesic from nonamnesic animals, the difference in the seizure pattern observed in Experiment I and Experiment II from that observed in Experiment III suggests that the seizure pattern may have some relevance for the production of cue dependent amnesia in the K-maze, although the data are not specifically clear in this regard. In all the experiments one purpose of handling during the seven day retention period was to extinguish any handling cues which might have become associated with the K-maze due to the lengthy training period. Since it

was always necessary to pick up the animal during each trial of pretraining and acquision, the pairing of such handling and the maze might cause any handling to evoke memory of the maze. Thus during the retention period the animals were handled and not put in the maze. Following the procedure of Lewis, Bregman and Mahan (1972) and Bregman (1972), the animals in Experiments I and II were all handled in the same room with the K-maze. In Experiment I the ECS intensity was 20 ma. transcortical; in Experiment II the ECS intensity was 10 ma. transcortical. In neither of the experiments was cue dependent amnesia observed (Table 4). The ECS seizure patterns from Experiments I and II appear quite similiar; a representative PAD period from two SB-ECS animals in Experiment II is presented in Figure 2 (EEG recordings A and B).

In Experiment III, conditions for the production of cue dependent amnesia were maximized. The animals were handled in a room adjoining the K-maze room during the retention interval and the 55 ma. transpinnate ECS of Lewis et al. (1972), Lewis and Bregman (1973) and Bregman (1972) was used. The seizure pattern produced by this ECS appears markedly different from the patterns produced by the transcortical ECS. The obvious difference is in the appearence of the PAD period immediately following the ECS. A representative PAD period from two SB-ECS animals


A
B
200uV
2 sec.
C
D

in Experiment III is presented in Figure 2 (EEG recordings C and D). Only in Experiment III was cue-dependent amnesia observed. This fact could be due to the handling during the seven day retention period, or it could be due to the transpinnate ECS.

In view of the fact that Bregman (1972) and Lewis and Bregman (1973) obtained cue dependent amnesia when handling took place in the same room as the K-maze, the ECS intensity is more likely implicated. Zornetzer and McGaugh (1970) have suggested that the total current delivered to the brain may be the critical variable in ECS memory disruption. In their paper a 3.0 ma. transcortical ECS produced memory disruption as effectively as a 40 ma. externally applied ECS. Thus the 10 ma. and 20 ma. transcortical ECS in Experiments I and II may well have been much more intense than the 55 ma. transpinnate ECS of Experiment III. If ECS intensity is a critical variable as Zornetzer and McGaugh (1970) suggest, then to produce a memory disruption the ECS must be sufficiently strong. However the present data suggests that with intensities above the current ranges they discuss, cue dependent amnesia may not be produced when the intensity is too great. Nevertheless, an inspection of Table 4 shows, an amnesia may well be produced, since during relearning the SB-ECS animals will make several

errors and SB-NECS animals will make only a few errors. A conclusion suggested by this data is that very high intensity ECS treatments may temporarly impair the animal's ability to perform the K-maze task. If this conclusion is true then lack of a PAD period in the ECS seizure may be correlated with the postulated impairment.

Post-ECS EEG

The present experiment has demonstrated a relationship between theta recorded in the 30 minute post-ECS period from electrodes on the cortex and amnesia in the appetitive K-maze. Landfield et al., (1972), using a one-trial PA task, linked post-ECS cortical theta with consolidation processes. Since the procedures which produce amnesia in the K-maze remove the animal from the time of acquisition of the task for a period of seven days following learning, then consolidation processes are assumed to be long completed at the time of ECS. Thus post-ECS cortical theta appears to have implications for processes beyond those of consolidation. Evidence that the cortical theta is related to memory processes comes from the finding that theta will differentiate amnesic from non-amnesic animals when both groups have had an ECS treatment. Thus post-ECS cortical theta appears to be related to animal memory not only in the consolidation paradigm, but in the retrieval paradigm as well.

Moreover in both paradigms the relationship between cortical theta and later behavioral testing is similar. In the Landfield et al., (1972) paper animals that had only FS showed high amounts of cortical theta. In addition recovery of memory in FS-ECS animals was related to recovery of cortical theta. In the present paper SB-NECS animals consistantly showed the highest amount of theta. In contrast both SB-ECS and NB-ECS animals began the 30 minute post-ECS period with a similarly low amount of theta; the NB-ECS animals then showed recovery of cortical theta while the SB-ECS animals did not. Twenty-four hours later the SB-ECS animals were amnesic in the K-maze while the NB-ECS animals were not.

Often the notion of retrieval processes in memory is contrasted against the consolidation theory of memory. The retrieval interpretation points out that many other variables may account for an amnesia, rather than just a failure of the memory to fixate or consolidate into permanent storage. A cue dependent amnesia, in particular, is difficult to account for in consolidation terms. This fact is not proof against the existence of consolidation processes, however; it merely points out a deficiency of consolidation theory. In spite of the fact that PA behavior and appetitive maze behavior are radically different, post-ECS cortical theta is related

to later retention in both tasks. Perhaps there does exist some common relationship between the PA task which purports to demonstrate consolidation and the appetitive maze in which cue dependent amnesia is found.

Cue dependent amnesia has in fact been demonstrated in PA, although the examples are few. The experiment by Schneider and Sherman (1968) may be the only example of a cue dependent amnesia in the stepdown task. Misanin et al., (1968) and DeVietti and Holliday (1972) have shown cue dependent amnesia in the drink suppression task.

A characteristic of PA is that acquisition takes place rapidly, typically in one trial. In contrast acquisition in the appetitive K-maze takes place over several trials. Because the K-maze task and the PA task differ in the length of acquisition, the K-maze is assumed to represent a task of increased complexity for the animal (Lewis, Bregman and Mahan, 1972; Lewis and Bregman, 1973). If this assertion is true, then it is reasonable that a cue dependent amnesia might be more often found in a complex task than in an easy one. Thus a continuum of complexity could represent a common relationship between memory process in PA and memory processes in the appetitive maze task. Such a continuum would account for the scarcity of examples of cue dependent amnesia in PA. However if PA

amnesia and cue dependent amnesia are basically related then it must be an active memory which is inhibited in the PA task. In this manner one could account for the fact that post-ECS cortical theta is related to later behavior in both PA and K-maze tasks.

Pre-ECS EEG

The amount of theta in the EEG of the thirty minute period following ECS was shown to differentiate amnesic from non-amnesia animals in the K-maze task. This data gives electrophysiological support to the notion of cue dependent amnesia, and it shows that simple frequency information in the post-ECS cortical EEG activity does have relevance for the later behavior of the animal. But EEG patterns as presented in the present experiment do not appear to have sufficient resolution to define the animals' gross behavior during periods of learning or handling. Moreover the patterning of frequencies within the theta band also do not seem precise enough to differentiate gross behavior during learning or handling. Thus the conclusion to be reached is that cortical theta activity (4-9 Hz.) was roughly the same among all phases of learning and handling. This fact may be related to the symmetry of the K-maze task. Unlike a PA task where different groups of animals typically perform radically different kinds of behavior, the K-maze task employs similar behaviors

throughout training and testing. Even during handling the animals are permitted to move about and explore. Thus the possibility of finding group EEG differences which may be inherent in the differential behavior of different groups of animals is minimized.

However, whether EEG patterns yield meaningful information depends to a great extent not only on what questions are asked, but also on how those questions are asked. Although the gross EEG patterns did not reliably differentitiate behavior during learning and handling, it was possible to show that during SB reinstatement the animal's EEG pattern in the Band, 4 - 9 Hz., does approximate the pattern of late learning within that frequency band. Therefore, it appears true that in the K-maze cue dependent amnesia paradigm the administration of ECS occurs in contiguity with EEG activity that is more similiar to the EEG activity of the later periods of learning for amnesic (SB) aminals, but not for non-amnesic (NB) animals. The difference in the brain electrical activity of amnesic and non-amnesic animals after ECS also seems to support the notion of an inhibition of that activity in the period after ECS. The activity in the theta band, which for the SB animals is similar to the theta activity during late learning, is the activity which appears suppressed in the 30 minute post-ECS period. On the other hand NB animals,

whose pre-ECS EEG is no similiar to the theta activity of late learning, significantly increase the amount of theta frequencies within 30 minutes. Thus the notion that ECS is an inhibitor of active memory traces (Lewis, 1969) may gain support from this data.

General Memory Model

Landfield, McGaugh, and Tusa (1972) suggested that cortical theta might be an electrophysiological correlate of a memory storage process. Earlier Elazar and Adey (1967) had suggested that shifts in the electrical activity of the hippocampus within the theta range were correlates of memory consolidation. The present experiment has shown that the amount of post ECS cortical theta frequencies is correlated with behavior in a task where amnesia is a retrieval deficit, not a consolidation failure. Moreover there appeared no great difference in the pattern of theta for EEG taken in early learning or late learning or, for that matter, during handling. Thus a role for cortical theta specific to a memory storage process as Landfield et al., (1972) suggest seems doubtful. If such a role were assumed one would expect at least a consistent difference in the EEG of early and later learning. If theta frequencies have anything to do with memory processes at all, it seems more reasonable to associate them with memory retrieval, rather than with memory storage.

In a manner similar to the active memory notion of Lewis (1969), John (1972) has suggested that during the retrieval of a specific memory, a unique pattern of electrical activity is released throughout the brain. According to his theory, this unique pattern reflects the activation and release of the specific memory. In the context of the present experiment theta activity appears to be associated with the retrieval of a memory of the K-maze. An ECS administered at the time of retrieval did suppress those frequencies, and later performance of the K-maze memory was impaired.

The data suggest that ECS did not destroy the K-maze memory, since the amnesic animals relearned the maze much faster than they originally acquired it. More evidence on this point comes from an experiment by Thompson and Grossman (1972) in which an ECS-produced amnesia in a sequential maze was removed by the administration of a second ECS treatment. Thus performance of a maze memory was returned, and one must conclude (as in the literature for PA) that ECS does not destroy memory for a sequential maze task. It could conceivably be the case that ECS does act on a stored, consolidated memory directly. If this thought is true, then the destruction of the memory is only partial. This would account for the savings shown by amnesic animals during relearning.

The evidence against this notion is found in the PA literature. It has been shown there that an ECS-produced amnesia can be returned by exposing the amnesic animal to a portion of the cues of original learning. Since relearning of the task is thought not to occur during these reminder treatments (Lewis and Nicholas, 1973), the interpretation is made that ECS does not affect the completed acquisition. Thus it seems reasonable to assume that the consolidated K-maze memory is also secure from a direct action of ECS. If ECS acts on memory processes, those processes are ones which occur long after the original learning is completed. Such processes cannot be concerned with memory consolidation.

In an earlier chapter it was suggested that the amnesia produced by a variety of amnesic agents might have a unitary mode of operation. If an amnesic agent is given to an animal shortly after learning it may prevent a proper coding of the memory through either distraction or by effectively removing the animal from the situation. A cue dependent amnesia seems difficult to incorporate into such a notion, however, since in the K-maze task learning is seven days apart from ECS treatment. Obviously ECS cannot prevent the post-fixation coding that also took place seven days before.

It is true, however, that a clear and revealing

definition of what memory actually is has remained elusive. In gross and intuitive terms memory is concerned with the storage and retrieval of past learning. Contemporary interpretations of memory retrieval stress the notion of memory as a dynamic process. Memory can be further conceived to be a process where already stored information is retrieved, reworked, and then stored again. Thus a process of new combinations and associations would be available to the inhibiting effects of ECS whenever a memory is active.

There is some evidence to support the notion that an already stored memory is modified at the time of reinstatement. Campbell and Jaynes (1966) showed that exposing animals to the conditions of original training at times throughout a retention interval caused those animals to show better retention of the task than animals that were not reexposed. It is their interpretation that reinstatement treatments can produce a memory enhancement while, in themselves, the reinstatement treatments do not permit learning of the task.

Thus it seems plausable that ECS can be expected to produce amnesia for a memory whenever ECS follows the activation of that memory, regardless of the temporal interval between original learning and ECS treatment. If such an interpretation is true then it is possible that

the mechanism through which ECS works is the same for ECS given immediately after learning or seven days after learning. In both cases ECS inhibits the dynamic aspects of an active memory.

BIBLIOGRAPHY

Adey, W.R. Hippocampal states and functional relations with corticosubcortical systems in attention and learning. In W. R. Adey and T. Tokizane (Eds.) Progress in Brain Research, Volume 27, Structure and Function of the Limbic System, Amsterdam: Elsevier, 1967.

Adey, W.R., Dunlop, C.W. and Hendrix, C.E. Hippocampal slow waves: distribution and phase relationships in the course of approach learning. Archives Neurology, 1960, 3, 74-90.

Agranoff, B.W., Davis, R.E. and Brink, J.J. Memory fixation in the goldfish. Proceedings, Natl. Acad. Sci., U.S.A., 1965, 54, 788-793.

Agranoff, B.W., Davis, R.E., Casola, L. and Lim, R. Actinomycin D blocks formation of memory of shock-avoidance in goldfish. Science, 1967, 158, 1600-1601.

Alpern, H.P. and Kimble, D.P. Retrograde amnesia effects of diethyl ether and bis (trifluoroethyl) ether. Journal of Comparative and Physiological Psychology, 1967, 63, 168-171.

Auerbach, P. and Carlton, P. L. Retention deficit correlated with a deficit in the corticoid response

to stress. Science, 1971, 173, 1148-1149.

Avis, H.A. and Carlton, P.L. Retrograde amnesia produced by hippocampal spreading depression. Science, 1968, 161, 73-75.

Barondes, S. H. and Cohen, H.D. Puromycin effect upon successive phases of memory storage. Science, 1966, 151, 594-594.

Barondes, S.H. and Cohen, H.D. Delayed and sustained effect of acetoxycloheximide on memory in mice. Proceedings, Natl. Acad. Sci., U.S.A., 1967, 58, 157-164.

Barondes, S.H. and Cohen, H.D. Arousal and the conversion of "short-term" to "long-term" memory. Proceedings, Natl. Acad. Sci., U.S.A., 1968, 61, 923-929.

Beitel, R. and Porter, P. Deficits in retention and impairments in learning induced by severe hypothermia in mice. Journal of Comparative and Physiological Psychology, 1968, 66, 53-59.

Belluzzi, J.D. Long lasting effects of cholinergic stimulation of the amygdaloid complex in the rat. Journal of Comparative and Physiological Psychology, 1972, 80, 269-282.

Bennett, T. Evidence against the theory that hippocampal theta is a correlate of voluntary movement.

Communications in Behavior Biology, 1969, 4, 165-169.

Bivens, L.W. and Ray, D.S. Memory trace disruption by cortical spreading depression. Psychological Reports, 1965, 17, 175-178.

Bregman, N.J. Cue dependent active memory and ECS produced memory occlusion. Unpublished doctoral dissertation, University of Southern California, 1972.

Bresnahan, E. and Routtenberg, A. Memory distruption by unilateral low level, sub-seizure stimulation of the medial amygdaloid nucleus. Physiology and Behavior, 1972, 9, 513-525.

Brunner, R. Rossi, R., Stutz, R.M., and Roth, T. Memory loss following postrial electrical stimulation of the hippocampus. Psychonomic Science, 1970, 18, 159-160.

Bures, J. and Buresova, O. The use of Leao's spreading depression in the study of interhemispheric transfer of memory traces. Journal of Comparative and Physiological Psychology, 1960, 53, 558-563.

Bures, J. and Buresova, O. Cortical spreading depression as a memory disturbing factor. Journal of Comparative and Physiological Psychology, 1963,

56, 268-272.

Bures, J. and Buresova, O. The reunified split brain. In R. E. Whalen, et al. (Eds.) The neural control of behavior. New York: Academic Press, 1970.

Bures, J. Buresova, O., Weiss, T., Fifkova, E. and Bohdanecky, Z. Experimental study of the role of hippocampus in conditioning and memory function. In P. Passouant (Ed.) Physiologie de l'Hippocampe. Paris: Centre National de Recherche Scientifique, 1962.

Burnham, W.H. Retroactive amnesia: Illustrative cases and tenative explanation. American Journal of Psychology, 1903, 14, 382-396.

Campbell, B.A. and Jaynes, J. Reinstatement. Psychological Review, 1966, 73, 478-480.

Cherkin, A. Retrograde amnesia in the chick: resistance to the reminder effect. Physiology and Behavior, 1972, 8, 949-955.

Chorover, S.L. and DeLuca, A.M. Transient change in electro-corticographic reaction to ECS in the rat following footshock. Journal of Comparative and Physiological Psychology, 1969, 69, 141-149.

Chorover, S.L. and Schiller, P.H. Short-term retrograde amnesia in rats. Journal of Comparative and Physiological Psychology, 1965, 59, 73-78.

Chorover, S.L. and Schiller, P.H. Re-examination of prolonged retrograde amnesia in one trial learning. Journal of Comparative and Physiological Psychology, 1966, 61, 34-41.

Chow, K.L. Effect of local electrographic afterdischarge on visual learning and retention in the monkey. Journal of Neurophysiology, 1961, 24, 391-400.

Cohen, H.D. and Barondes, S.H. Pruomycin effect on memory may be due to occult seizures. Science, 1967, 157, 333-334.

Cohen, H.D. and Barondes, S.H. Effect on acetoxycycloheximide on learning and memory of a light-dark discrimination. Nature, 1968, 218, 271-273.

Cohen, H.D., Ervin, F. and Barondes, S.H. Puromycin and cycloheximide: Different effects on hippocampal electrical activity. Science, 1966, 154, 1557-1558.

Coons, E. and Miller, N. Conflict versus consolidation of memory traces to explain "retrograde amnesia" produced by ECS. Journal of Comparative and Physiological Psychology, 1960, 53, 524-531.

Daniels, D. Acquision, storage and recall of memory for brightness discrimination by rats following intracerebral cerebral infusion of acetoxycycloheximide. Journal of Comparative and Physio-

logical Psychology, 1971, 76, 110-118.

Davis, R.E. and Agranoff, B.W. Stages of memory formation in goldfish: Evidence for an environmental trigger. Proceedings, Natl. Acad. Sci., U.S.A., 1966, 55, 555-559.

Deutsch, J.A. The physiological basis of memory. Annual Review of Psychology, 1969, 20, 85-104.

Deutsch, J.A., Hamburg, M.D. and Dahl, H. Anticholinesterase-induced amnesia and its temporal aspects. Science, 1966, 151, 221-223.

Deutsch, J.A. and Rocklin, K. Anticholinesterase amnesia as a function of massed or spaced retest. Journal of Comparative and Physiological Psychology, 1972, 81, 64-68.

DeVietti, T. and Holliday, J. Retrograde amnesia produced by electroconvulsive shock after reactivation of a consolidated memory trace: A replication. Psychonomic Science, 1972, 29, 137-138.

DeVietti, T. and Hopfer, T. Reinstatement of memory in rats: Dependence upon the interplay of two forms of retrieval deficit following, ECS. In preparation.

DeVietti, T.L. and Larson, R.C. ECS effects: Evidence supporting state-dependent learning in rats. Journal of Comparative and Physiological Psycho-

logy, 1971, 74, 407-415.

DeVietti, T.L., Mayse, J.F. and Morris, L.W. FS/ECS induced dissociation in rats: Parametric evaluation of ECS intensity and time of testing. Paper presented at the 52nd annual meeting of the Western Psychological Association, Portland, Oregon, April, 1972.

Douglas, R.J. The hippocampus and behavior. Psychological Bulletin, 1967, 67, 416-422.

Elazar, Z. and Adey, W.R. Spectral analysis of low frequency components in the electrical activity of the hippocampus during learning. Electroencephalography and Clinical Neurophysiology, 1967, 23, 225-240.

Flexner, L.B., Flexner, J.B. and Roberts, R.B. Memory in mice analyzed with antibiotics. Science, 1967, 155, 1377-1383.

Galluscio, E.H. Retrograde amnesia induced by electroconvulsive shock and carbon dioxide anesthesia in rats. Journal of Comparative and Physiological Psychology, 1971, 75, 136-140.

Gold, P., Farrell, W., and King, R. Retrograde amnesia after localized brain shock in passive avoidance learning. Physiology and Behavior, 1971, 7, 709-712.

Goldrich, S. and Stamm, J. Electrical stimulation of inferotemporal and occipital cortex in monkeys: Effects on visual discrimination and spatial reversal performance. Journal of Comparative and Physiological Psychology, 1971, 74, 448-458.

Gordon, W. and Spear, N. The effects of strychine on recently acquired and reactivated passive avoidance memories. Physiology and Behavior, 1973, In press.

Green, J.D. and Arduini, A. Hippocampal electrical activity in arousal. Journal of Neurophysiology, 1954, 17, 533-557.

Greene, E. Comparision of hippocampal depression and hippocampal lesion. Experimental Neurology, 1971, 31, 313-325.

Grastyan, E., Lissak, J., Madarasz., I., and Donhoffer, H. Hippocampal electrical activity during the development of conditioned reflexes. Electroencephalography and Clinical Neurophysiology, 1959, 11, 409-430.

Grossman, S.P. Chemically induced epileptiform seizures in the cat. Science, 1963, 142, 409-411.

Herz, M. and Peeke, H. Impairment of extinction with caudate nucleus stimulation. Brain Research,

1971, 33, 519-522.

Herz, M.J., Spooner, C.E. and Cherkin, A. Effects of the amnesic agent flurothyl on EEG and multiple-unit activity in the chick. Experimental Neurology, 1970, 27, 227-237.

Horsten, G.P. Influence of body temperature on the EEG. Acta. Brev. Neerl. Physiol., 1949, 17, 23-25.

Howard, R.L. and Meyer, D.R. Motivational control of retrograde amnesia in rats: A replication and extension. Journal of Comparative and Physiological Psychology, 1971, 74, 37-40.

Hughes, R.A. Retrograde amnesia in rats produced by hippocampal injections of potassium chloride: Gradient of effect and recovery. Journal of Comparative and Physiological Psychology, 1969, 68, 637-644.

Jacobs, B.L. and Sorenson, C.A. Memory disruption in mice by brief posttrial immersion in hot or cold water. Journal of Comparative and Physiological Psychology, 1969, 68, 239-244.

Jensen, R.A. and Riccio, D. Effects of prior experience upon retrograde amnesia produced by hypothermia. Physiology and Behavior, 1970, 5, 1291-1294.

John, E.R. Switchboard versus statistical theories of learning and memory. Science, 1972, 177, 850-

864.

Kamp, A., DaSilva, L., and Storm Van Leeuwen, W. Hippocampal frequency shifts in different behavioural situations. Brain Research, 1971, 31, 287-294.

Kane, J. and Jarvik, M.E. Amnesia effects of cooling and heating in mice. Psychonomic Science, 1970, 18, 7-8.

Kapp, B.S. and Schneider, A.M. Selective recovery from retrograde amnesia produced by hippocampal spreading depression. Science, 1971, 173, 1149-1115.

Kesner, R.P. and Conner, H.S. Independence of short- and long-term memory: A neural system analysis. Science, 1972, 176, 432-434.

Kesner, R.P. and Doty, R.W. Amnesia produced in cats by local seizure activity initiated from the amygdala. Experimental Neurology, 1968, 21, 58-68.

Kesner, R. P., Gibson, W. and LeClair, M. ECS as a punishing stimulus: Dependency on route of administration. Physiology and Behavior, 1970, 5, 683-686.

Kesner, R. P., McDonough, Jr., J.H. and Doty, R.W. Diminished amnestic effect of a second electroconvulsive seizure. Experimental Neurology,

1970, 27, 527-533.

Klemm, W.R. Ascending and desending excitatory influences in the brain stem reticulum: A reexamination. Brain Research, 1972, 36, 444-452.(a)

Klemm, W.R. Theta rhythm and memory. Science, 1972, 175, 1449.(b)

Kluver, H. and Bucy, P. "Psychic blindness" and other symptoms following bilateral temporal lobetomy in Rhesus monkeys. American Journal of Physiology, 1937, 119, 352-353.

Kreschevsky, I. "Hypothesis" vs. "chance" in the presolution of sensory discrimination learning. University of California Publications in Psychology, 1932, 3, 27-44.

Komisaruk, B.R. Synchrony between limbic system theta activity and rhymical behavior in rats. Journal of Comparative and Physiological Psychology, 1970, 70, 482-492.

Kovner, R. and Stamm, J. Disruption of short term visual memory by electrical stimulation of inferotemporal cortex in the monkey. Journal of Comparative and Physiological Psychology, 1972, 81, 163-172.

Landfield, P., McGaugh, J. and Tusa, R. Theta rhythm: A temporal correlate of memory storage processes

in the rat. Science, 1972, 175, 87-89.

Lee-Teng, E. Retrograde amnesia in relation to subconvulsive currents in chicks. Journal of Comparative and Physiological Psychology, 1969, 67, 135-139.

Lee-Teng, E. and Giaquinto, S. Electrocortiograms following threshold transcranial electroshock for retrograde amnesia in chicks. Experimental Neurology, 1969, 23, 485-490.

Lewis, D.J. Sources of experimental amnesia. Psychological Review, 1969, 76, 461-472.

Lewis, D.J. and Bregman, N.J. The source of the cues for cue-dependent amnesia. Journal of Comparative and Physiological Psychology, 1973, In press.

Lewis, D.J., Bregman, N.J. and Mahan, J.J., Jr. Cue dependent amnesia in the K-maze. Journal of Comparative and Physiological Psychology, 1972, In press.

Lewis, D.J. and Maher, B.A. Neural consolidation and electroconvulsive shock. Psychological Review, 1965, 72, 225-239.

Lewis, D.J., Miller, R.R. and Misanin, J.R. Control of retrograde amnesia. Journal of Comparative and Physiological Psychology, 1968, 66, 48-52.

(a).

Lewis, D.J., Miller, R.R. and Misanin, J.R. Recovery of memory following amnesia. Nature, 1968, 220, 704-705. (b)

Lewis, D.J. and Nicholas, T. Amnesia for active avoidance produced by a competing response. Physiology and Behavior, 1973, In press.

Lidsky, A. and Slotnick, B.M. Electrical stimulation of the hippocampus and electroconvulsive shock produce similiar amnestic effects in mice. Neuropsychologia, 1970, 8, 363-369.

Lidsky, A. and Slotnick, B.M. Effects of posttrial limbic stimulation on retention of a one-trial passive avoidance response. Journal of Comparative and Physiological Psychology, 1971, 76, 337-348.

Lipp, J. Effect of deep hypothermia on the electrical activity of the brain. Electroencephalography and Clinical Neurophysiology, 1964, 17, 46-51.

Lloyd, R. and Gerbrant, L. Origin of the so-called theta rhythm in rats. Paper presented at the 53rd Annual Meeting of the Western Psychological Association, Anaheim, California, April, 1973.

Madsen, M.C. and McGaugh, J.L. The effect of ECS on one-trial avoidance learning. Journal of Comparative and Physiological Psychology, 1961, 54, 522-

523.

Mahut, H. Effects of subcortical electrical stimulation on learning in the rat. Journal of Comparative and Physiological Psychology, 1962, 55, 472-477.

McDonough, Jr., J.H. and Kesner, R.P. Amnesia produced by brief electrical stimulation of amygdala or dorsal hippocampus in cats. Journal of Comparative and Physiological Psychology, 1971, 77, 171-178.

McGaugh, J.L. Time-Dependent processes in memory storage. Science, 1966, 153, 1351-1358.

McGaugh, J.L. and Dawson, R.G. Modification of memory storage processes. Behavioral Science, 1971, 16, 45-63.

McIntyre, D. Differential amnestic effect of cortical vs. amygdaloid elicited convulsions in rats. Physiology and Behavior, 1970, 5, 747-753.

Miller, R. and Springer, A. Induced recovery of memory in rats following electroconvulsive shock. Physiology and Behavior, 1972, 8, 645-651.

Miller and Springer, A. Amnesia consolidation and retrieval. Psychological Bulletin, 1973, 80, 69-70.

Misanin, J. and Hoover, M. Recovery rate as a determinate of the amnesic-like effect of hypothermia. Physiology and Behavior, 1971, 6, 689-693.

Misanin, J.R., Miller, R.P. and Lewis, D.J. Retrograde amnesia produced by electroconvulsive shock after reactivation of a consolidated memory trace. Science, 1968, 160, 554-555.

Nachman, M. and Meinecke, R.O. Lack of retrograde amnesia effects of repeated electroconvulsive shock and carbon dioxide treatments. Journal of Comparative and Physiological Psychology, 1969, 68, 631-636.

Nakajima, S. Interference with relearning in the rat after hippocampal injection of actinomycin D. Journal of Comparative and Physiological Psychology, 1969, 67, 457-461.

Nakajima, S. Proactive effect of actinomycin D on maze performance in the rat. Physiology and Behavior, 1972, 8, 1063-1067.

Nielson, H.C. Evidence that electroconvulsive shock alters memory retrieval rather than memory consolidation. Experimental Neurology, 1968, 20, 3-20.

Paolino, R.M. and Hine, B. EEG seizure anomalies following supramaximal intensities of cortical stimulation: Relationships with passive-avoidance retention in rats. Journal of Comparative and Physiological Psychology, 1973, 83,

285-293.

Parmeggian, P.L. On the functional significance of the hippocampal O-rhythm. In W. R. Adey and T. Tokizane, (Eds.) Progress in brain research Volume 27, Structure and function of the limbic system. Amsterdam: Elsevier Publishing Company, 1967.

Pearlman, Jr., C. Similar retrograde amnesia effects of ether and spreading cortical depression. Journal of Comparative and Physiological Psychology, 1966, 61, 306-308.

Pearlman, Jr., C. and Jarvik, M.E. Retrograde amnesia produced by spreading cortical depression. Federation Proceedings, 1961, 20, 340.

Pearlman, Jr., C., Sharpless, S.K. and Jarvik, M.E. Retrograde amnesia produced by anesthetic and convulsant agents. Journal of Comparative and Physiological Psychology, 1961, 54, 109-112.

Peeke, H. and Herz, M. Caudate nucleus stimulation retroactively impairs complex maze learning in the rat. Science, 1971, 173, 80-82.

Penrod, W. and Boice, R. Effects of halothane anesthesia on the retention of a passive avoidance task in rats. Psychonomic Science, 1971, 23, 205-207.

Pfingst, B.E. and King, R.A. Effects of posttraining

electroconvulsive shock on retention test performance involving choice. Journal of Comparative and Physiological Psychology, 1969, 68, 645-649.

Pickenhain, L. and Klingberg, F. Hippocampal slow wave activity as a correlate of basic behavioral mechanisms in the rat. In W.R. Adey and T. Tokizane (Eds.) Progress in Brain Research, Volume 27, Structure and Function of the Limbic System. Amsterdam: Elsevier, 1967.

Posluns, D. and Vanderwolf, C.H. Amnesic and disinhibitory effects of electroconvulsive shock in the rat. Journal of Comparative and Physiological Psychology, 1970, 73, 291-306.

Quartermain, D., McEwen, B.S. and Azmitia, Jr., E.C., Amnesia produced by ECS or cycloexmide: Conditions for recovery, Science, 1970, 169, 683-686.

Quartermain, D., McEwen, B.S. and Azmitia, Jr., E.C. Recovery of memory following amnesia in the rat and mouse. Journal of Comparative and Physiological Psychology, 1972, 78, 360-370.

Quinton, E.E. Retrograde amnesia induced by carbon dioxide inhalation. Psychonomic Science, 1966, 5, 417-418.

Riccio, D. Gaebelin, C., and Cohen, P. Some behavioral aspects of retrograde amnesia produced by hypothermia. Physiology and Behavior, 1968, 3, 973-976.

Riccio, D., Hodges, L., and Randall, P. Retrograde amnesia produced by hypothermia in rats. Journal of Comparative and Physiological Psychology, 1968, 66, 618-622.

Riccio, D.C. and Stikes, E.R. Persistent but modifiable retrograde amnesia produced by hypothermia. Physiology and Behavior, 1969, 4, 649-652.

Riddell, W.I. Effect of Electroconvulsive shock: Permanent or temporary retrograde amnesia. Journal of Comparative and Physiological Psychology, 1969, 67, 140-143.

Robins, A.B. and Thomas, G. Retrograde amnesia produced by localized electrical stimulation of brain through chronically implanted electrodes. Psychonomic Science, 1968, 12, 291-292.

Robbins, M.J. and Meyer, D.R. Motivational control of retrograde amnesia. Journal of Experimental Psychology, 1970, 84, 220-225.

Schneider, A.M., Kapp, B., Aron, C., and Jarvik, M. Retroactive effects of transcorneal and transpinnate ECS on stepthrough latencies of mice

and rats. Journal of Comparative and Physiological Psychology, 1969, 69, 506-509.

Schneider, A. and Sherman, W. Amnesia: A function of the temporal relation of footshock to electroconvulsive shock. Science, 1968, 159, 219-221.

Routtenberg, A. and Kay, K. Effect of one electroconvulsive seizure on rat behavior. Journal of Comparative and Physiological Psychology, 1965, 59, 285-288.

Routtenberg, A., Zechmeister, E. and Benton, C. Hippocampal activity during memory disruption of passive avoidance by electroconvulsive shock. Life Sciences, 1970, 9, 909-918.

Shinkman, P.G. and Kaufman, K.P. Posttrial hippocampal stimulation and cer acquisition in the rat. Journal of Comparative and Physiological Psychology. 1972, 80, 283-292.

Siegel, S. Nonparametric statistics for the behavioral sciences. New York: McGaw-Hill, 1956.

Spear, N. Retrieval of memory in animals. Psychological Review, 1973, 80, 163-194.

Spevack, A. and Suboski, M. Retrograde effects of electroconvulsive shock on learned responses. Psychological Bulletin, 1969, 72, 66-76.

Stamm, J.S. Electrical stimulation of monkeys' prefrontal

cortex during delayed response performance. Journal of Comparative and Physiological Psychology, 1969, 67, 535-536.

Taber, R. and Banuazizi, A. CO2-induced retrograde amnesia in a one trial learning situation. Psychopharmacologia, 1966, 9, 382-391.

Thompson, C.I. and Grossman, L.B. Loss and recovery of long-term memories after ECS in rats: Evidence for state-dependent recall. Journal of Comparative and Physiological Psychology, 1972, 78, 248-254.

Thompson, R.W., Enter, R. and Russell, N. Effect of ECS on retention of a passive avoidance response in rats. Psychological Reports, 1967, 21, 150-152.

Towe, A.L. Electrophysiology of the cerebral cortex: Consciousness. In T.C. Ruch and H.D. Patton (Eds.) Physiology and Biophysics. Philadelphia: Saunders, 1965.

Vanderwolf, C.H. Limbic-diencephalic mechanisms of voluntary movement. Psychological Review, 1971, 78, 83-113.

Vardaris, R.M. and Gehres, L.D. Brain seizure patterns and ESB-induced amnesia for passive avoidance. Physiology and Behavior, 1970, 5, 1271-

1275.

Wagner, A., Rudy, J., and Whitlow, J. Rehearsal in animal conditioning. Journal of Experimental Psychology, 1973, 97, 407-426.

Wyers, E. and Deadwyler, S. Duration and nature of retrograde amnesia produced by stimulation of caudate nucleus. Physiology and Behavior, 1971, 6, 97-103.

Wyers, E.J., Peeke, H., Williston, J.S. and Herz, M.J. Retroactive impairment of passive avoidance learning by stimulation of the caudate nucleus. Experimental Neurology, 1968, 22, 350-366.

Yamaguchi, Y., Yoshi, N., Miyamoto, K., and Itoigawa, N. A study of the invasive hippocampal theta-waves to the cortex. In W.R. Adey and T. Tokizane (Eds.) Progress in Brain Research, Volume 27, Structure and Function of the Limbic System. Amsterdam: Elsevier, 1967.

Zinken, S. and Miller, A.J. Recovery of memory after amnesia induced by electroconvulsive shock. Science, 1967, 155, 102-103.

Zornetzer, S.F. Brain stimulation and retrograde amnesia in rats: A neuroanatomical approach. Physiology and Behavior, 1972, 8, 239-244.

Zornetzer, S., and McGaugh, J. Effects of frontal brain electroshock stimulation on EEG activity and memory in rats: Relationship to ECS produced retrograde amnesia. Journal of Neurobiology, 1970, 1, 379-394.

Zornetzer, S. and McGaugh, Jr. Retrograde amnesia and brain seizures in mice. Physiology and Behavior, 1971, 7, 401-408. (a)

Zornetzer, S. and McGaugh, J. Retrograde amnesia and brain seizures in mice: A further analysis. Physiology and Behavior, 1971, 7, 841-845. (b)

Zornetzer, S. and McGaugh, J. Electrophysiological correlates of frontal cortex induced retrograde amnesia in rats. Physiology and Behavior, 1972, 8, 233-238.