EFFECTS OF CHEMICALLY INDUCED BILATERAL AND UNILATERAL SPREADING CORTICAL DEPRESSION ON AVOIDANCE LEARNING IN RATS

A Thesis

Presented to

the Faculty of Graduate Studies and Research

University of Manitoba

In Partial Fulfillment

of the Requirements for the Degree

Master of Arts

---

by

Gordon Winocur

August 1964

ABSTRACT

Two experiments were conducted to investigate the effects of bilateral (BSD) and unilateral (USD) spreading depression in rats. Two avoidance problems (Tasks A and B) were used. These were equated for difficulty in normal animals but differed in their respective motor requirements. Task A required Ss to run through one of two open doors to avoid shock, while in Task B the doors were closed and Ss were required to climb through a small open window in one of the doors. Experiment I examined the effects that prior training might have on avoidance learning in a cortically depressed state. Experiment II studied the effects of USD on avoidance learning. Two groups were tested, one received SD applied to alternate hemispheres on two successive testing sessions, the other received SD applied to the same hemisphere for both sessions. Conclusions are: (a) When compared to sham Ss, animals under BSD and USD show a learning deficit which appears to be related to motor impairment induced by cortical SD. (b) Prior training in the normal state can facilitate avoidance learning in a cortically depressed state. (c) The functional cortex is not essential for the learning of simple avoidance responses.

ACKNOWLEDGMENTS

I wish to thank Dr. Kenneth R. Hughes for his guidance and helpful criticisms in serving as Chairman of my thesis committee. Special thanks are due to Dr. Roderick M. Cooper who provided a constant source of inspiration and encouragement, particularly during the early stages of this research. The critical reading of the manuscript by, and the many useful comments of Dr. David S. Abbey are gratefully acknowledged. This research was supported by the National Research Council, Grant No. Nr-81, held by Dr. Cooper, and by the Medical Research Council, Grant No. MA-1220, held by Dr. Hughes.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER I

INTRODUCTION

Our knowledge of the physiology of the brain and its functioning has been greatly advanced in recent years by the use of surgical decortication techniques. While such methods have been most valuable, surgical removal of the cortex presents a number of unavoidable problems which tend to confound the analysis of the behavioral consequences of decortication. For example, surgical decortication results in anatomical degeneration, extending deep into subcortical structures. Furthermore, the severe trauma often associated with such surgery permits the study of the effects of decortication only several days after operation, that is at a time when compensating mechanisms may have already begun to take over some of the lost cortical functions.

There would be obvious advantages to a technique which could eliminate some or all the complications of surgical ablation yet still produce complete disruption of cortical functioning. Such a technique is, in fact, now available in the "spreading cortical depression of Leao" and is being widely used in the study of brain functioning. Spreading depression (SD), generally elicited by topical application of KCl solution, is said to induce a kind of "functional decortication" by temporarily depressing all

electrical activity in the cortex. A 25% KCl solution will depress cortical activity for from three to five hours. SD has the added advantages of being easily produced and fully reversible. Moreover, SD inhibits cortical activity and does not directly affect subcortical functioning.

An investigation into the behavioral effects of various SD conditions will comprise the major topic of this thesis. However, before formally introducing the problems to be dealt with, an introduction to the SD phenomenon itself will be undertaken.

CHAPTER II

THE SPREADING DEPRESSION PHENOMENON

SD was first reported by A. A. P. Leao in 1944 in an investigation of the effects which electrical stimulation of the cortex has on subsequent cortical activity. The animals (rabbits) were anesthetized with Dial and the dorsolateral parts of both hemispheres were widely exposed. Stimulating and recording electrodes were applied to the surface of the pia mater. Electrical stimulation of the cortex was obtained with tetanizing currents of about one to five seconds in duration from a Harvard Induction Coil. Mechanical stimulation was administered with a few light strokes of a glass rod. Recording of electrical activity was achieved with a six-channel Grass ink writing oscillograph. Following a brief period of repetitive stimulation, Leao noted a decrease in the amplitude and frequency of normal spontaneous activity. This depression of electrical activity was observed initially at the point of stimulation but gradually spread out in all directions so that ultimately the whole cortex was included. Leao called this phenomenon cortical spreading depression.

Leao and Morison (1945) found that 1% KCl solution applied to the exposed cortex also induced SD. The authors observed, at the same time, that a single piece of filter

paper kept moist with KCl sustained the depressed state. Bures and Buresova (1960c) noted that the average minimum effective concentration of KCl solution required to elicit SD when applied with filter paper was approximately 0.6%.

Marshall (1959) and others (Sloan and Jasper, 1950; Bures, Buresova and Zahorva, 1958) report that SD is always accompanied by a wave of surface negativity which at the point of maximum deflection attains an amplitude of 5-15 millivolts and has a duration of one to two minutes. The negative phase is preceded and succeeded by smaller positive waves of about 0.5 millivolts in amplitude which last for three to five minutes. This change in surface potential makes up what Marshall (1959) refers to as the SPC or slow potential change. The SPC travels about three to six millimeters per minute and appears to have an equally depressing effect on all areas of the cortex. Complete electrical depression at any one point as measured by Leao (1944a), will last for five to ten minutes, although spontaneous activity may not return to normal for up to 20 minutes after the initial onset of the SPC. Increasing the amount of stimulation elicits a regular series of slow potential changes. Bures, Buresova and Zahorva (1958) report that increasing the concentration of KCl in solution produces a slow potential wave every five to ten minutes. There is no evidence that increasing the intensity of the stimulus has any effect on the amplitude

or duration of a single SPC. Spontaneous EEG activity remains depressed for the period during which the series of slow potential changes pass over the cortex.

Leao (1944a, 1944b) and Leao and Morison (1945) demonstrated that SD initiated in one hemisphere spreads to the opposite hemisphere, except when the stimulation was very weak. The authors do not define what is meant by a very weak stimulus. Sloan and Jasper (1950) present evidence in support of the Leao studies. They isolated a small area of the cortex leaving its pial blood supply intact and found that SD could enter the area after the surfaces of the incision had become adjoined. The authors concluded that neural continuity was not a requisite for SD propagation and all that is essential is "physical and neural contiguity" (Sloan and Jasper, 1950). On the other hand, van Harreveld, Terres, and Dernberg (1956) showed that an incision in the cortex as small as 0.1 millimeter in length is sufficient to inhibit the spread of depression. They argue, in opposition to Sloan and Jasper, that any break in the continuity of the cortex will disrupt the passage of SD. Ochs (1958) showed that lesions of the cerebral cortex will initially prevent the spread of depression. However, after a few hours, passage of SD across the lesion may be noted. Buresova, Bures, and Beran (1958) and Bures and Buresova (1960a) offer evidence that SD is restricted to one hemisphere.

They showed that SD in one hemisphere had no effect on the electrical activity of the other. While the electrophysiological evidence is inconclusive on the question of interhemispheric transfer of SD, it will be shown that there is greater agreement among the behavioral studies.

Existing evidence indicates that SD initiated in the cortex does not spread to subcortical centres. In a study to investigate more closely the spread of depression, Leao and Morison (1945) destroyed either by knife or by thermocoagulation, the upper cortical layers without damaging the subcortex. Stimulation of the remaining structures failed to elicit SD in any region other than the point immediately stimulated. The authors concluded that intact superficial cortical layers are necessary for SD and that subcortical connections could not serve as an alternate path for the propagation of SD in the absence of the cortex. It is interesting to note that depression failed to spread despite the fact that the lower two or three layers of the cortex were left intact. There is, however, recent evidence that repeated application of KCl to the cortex may result in some subcortical degeneration (Tapp, 1962). Tapp reported that 12 of 30 Ss showed tissue damage below the level of the cortex, although it is not clear if the degeneration was a result of the operational procedure or was, indeed, attributable to the application of KCl. There was no relationship

between the presence of subcortical degeration and Ss' performance under SD. Grafstein (1956b), in a study to evaluate the findings of Leao and Morison, isolated a small area of the cortex of cats, and by making radial cuts across the width of the isolated area was able to study the spread of depression at various cortical layers. She found that SD was not inhibited in the lower regions when layers I to III were incised, nor in the upper regions when layers IV to VI had been destroyed. Grafstein further demonstrated that incision in any one layer was insufficient in itself to hinder the spread of depression. SD could be arrested only by a cut extensive enough to involve almost every cortical layer. Grafstein concluded that all cortical layers are involved in the propagation of SD.

A number of investigators have reported that SD is accompanied by changes in subcortical activity (Weiss and Fifkova, 1961; Bures, Buresova, Fifkova, Olds, Olds, Travis, 1961; Bures, Buresova, Weiss, and Fifkova, 1963). These changes are usually attributed to secondary effects of the cortical depression, rather than a downward spread of the KCl induced depression itself (Weiss and Fifkova, 1961; Bures, et al, 1963). Weiss and Fifkova suggest that spontaneous activity in both the cerebral cortex and lower centres is a function of reverberatory cortico-subcortical neural circuits. Elimination of the cortex interrupts these circuits

and subsequently disrupts the generation of normal electrical activity in both centres. The effect of decreased spontaneous firing is particularly marked in such subcortical loci as the non-specific thalamic nuclei(Weiss and Fifkova, 1961), hippocampus and hypothalamus (Bures et al, 1963). Cortical SD does not appear to produce any changes on such thalamic structures as the lateral and medial geniculate bodies, and the nuclear masses which make up the ventral nuclei. On the other hand, Bures et al report that the prevalent effect is one of increased activity in the tegmental and reticular areas of the brain stem. It would seem that great differences exist in subcortical responses to cortical SD. They are differences which are not yet understood or clearly described.

At this time our knowledge of SD is limited largely to mere description. The nature of the mechanism underlying the arousal of the SPC and its propagation across the cortex is essentially unknown. The evidence that does exist is, for the most part, incomplete or speculative. It was first thought that SD is sustained solely by the neural conduction pathways within the cortical gray matter. Leao and Morison (1945) opposed this theory by showing that periods of anoxia up to one minute failed to interfere in any way with the spread of the phenomenon. If the neuronal network played a major role in the propagation of the depression, then

SD would have been severely affected by anoxia because synaptic transmission is particularly sensitive to changes in oxygen supply. Grafstein (1956a) confirmed that neural conduction alone is not directly responsible for the propagation of SD. She presented evidence that the initiation and transmission of depression depends on a substance which is found in resting cortical neurons and which is released during neural activity. Grafstein found that by repeatedly stimulating the cortex at a sub-threshold level prior to inducing SD, she could reduce the amplitude of the negative phase of the SD wave when it finally was aroused. She speculated that prolonged repetitive stimulation would exhaust the substance, leaving less available for release during the period of neural activity generally found just prior to the onset of the SD wave. Grafstein proposes that the critical substance released during the neural activity is K^+, which is known to be released during normal action. She supports this hypothesis by showing that the addition of KCl to the cortex just after sub-threshold stimulation and prior to SD serves to restore the amplitude of the negative potential. Grafstein reports that other ions do not have this effect.

Grafstein's theory of SD propagation is that upon initial stimulation of the cortex, neuronal activity results in the liberation of K^+ into the extracellular space. The

abundance of K^+ has the effect of lowering the membrane potential in adjacent neurons by enhancing depolarization, causing the neurons to fire at first. This firing in turn liberates more K^+ so that the cycle is repeated. Eventually a condition will arise where there is an excess of positive charges on the outside of the membrane with respect to the negative charges on the inside. The membrane would thus be in a state of hyperpolarization, making it impossible for normal stimulation to arouse further neural activity. The propagation of depression depends upon the concentration of liberated K^+ throughout the cortex.

The theory, although attractive, is not completely adequate. Grafstein does not show directly that it is the liberated K^+ which accounts for the early discharge and drop in membrane potential. As Marshall (1959) points out, the liberation of K^+ may be another concomitant of SD. A crucial test of the theory remains to be devised.

In summary, SD by inducing a reversible impairment of cortical function is thought to produce a state of functional decortication. When applied to a particular area of the cortex, SD travels in waves in all directions across the cortex at a rate of about three to six millimeters per minute. At each point on the cortex, complete depression lasts for about five to ten minutes, although normal activity often does not return for up to 20 minutes after the onset of

SD. Each SD wave is characterized by a slow negative potential (amplitude up to 15 millivolt, duration one to two minutes) which is followed by a less pronounced positivity. SD is most generally produced according to the techniques described by Bures and his associates. The usual procedure has been to apply a piece of filter paper, four to five millimeters in diameter, soaked in KCl solution over the cerebral cortex which has been previously exposed by trephine opening. A 25% KCl solution applied in this manner produces a series of SD waves lasting for three to five hours. Thus SD provides a valuable technique for studying the role of the cortex in various types of learning, and other complex behaviours.

CHAPTER III

THE PROBLEM IN HISTORICAL PERSPECTIVE

In recent years a number of experiments have been carried out to evaluate the behavioural effects of chemically induced SD. Bures (1959) referred to an animal under SD as being functionally decorticate and compared its deficit to that of an animal whose cortex had been removed surgically. SD has the effect of temporarily interfering with the function of the cortex without producing lasting structural changes. If cortical SD is capable of evoking a state similar to that brought about by surgical decortication, its use would be much preferred to the latter method. Functional decortication is accompanied by considerably less trauma, thus reducing the length of the recovery period. The short delay between operation and testing makes it possible to study the immediate effects of SD without the interference of compensating mechanisms which often develop when subcortical structures take over some of the cortical functions. Another factor favoring the use of SD is its reversible nature which makes possible the animal's behavior in both a normal and a cortically depressed state. Moreover, Bures claimed that SD does not produce any secondary subcortical degeneration as is generally found following surgical removal of the cortex. Recent evidence (Tapp, 1962) that repeated application of KCl may cause subcortical degeneration indicates

no clear relationship between the amount of such degeneration and an animal's behavior under SD.

Prior to the recent introduction of the SD technique experiments dealing with central nervous system function in learning have attempted in a variety of ways to remove or reduce cortical participation in the learning process. In assessing the relative importance of cortical and subcortical structures, three major approaches have been widely used: surgical ablation; curare injection; and more recently severance of interhemispheric connections ("split-brain"). Before proceeding with a discussion of the effects of SD, it will be useful to compare the findings of experiments which have used these other means of eliminating cortical function.

Using the surgical ablation technique, Culler and Mettler (1934) demonstrated that the decorticate dog is capable of establishing a conditioned leg withdrawal to visual and auditory stimuli, the US being shock to one of the other legs. Girden, Mettler, Finch, and Culler (1936) using much the same technique as Culler and Mettler were able to evoke similar CR's to auditory, thermal, and tactile stimulation. In neither case was the CR reported as being anything better than a generalized withdrawal from the shock source. The presentation of the CS aroused a diffuse jumping response in the animal. There appeared to be an inability to make localized adaptive responses with the appropriate limb. The number

of trials, i.e. CS-US pairings, required to elicit this CR was the same however, in both normal and decorticate Ss.

It is interesting to note that Girden et al (1936) encountered difficulty in evoking a clear CR in decorticate Ss to a tone of 12 db. above the minimum required by normal animals and could not get a consistent response until the tone was raised to 112 db. above normal limen. They found also in the thermal and tactile conditions that a strong CS was most efficacious in teaching the animal a CR. In other words, the greater the sensory stimulation, the better the animal learned.

That the nature of the CS and CR is an important factor in decorticate conditioning has been further suggested by the experiments of Pinto-Hamuy, Santibanez, and Rajas (1963), and Saavedra, Garcia, and Pinto-Hamuy (1963). Saavedra et al, using an avoidance task, showed that it is easier to condition neodecorticate rats to an auditory CS than to a visual CS. Pinto-Hamuy et al failed to condition decorticate rats to a visual CS. The authors generally concluded that the learning capacity of the neodecorticate rat depends on the nature of the CS and on the animal's ability to pair the CS with the instrumental response required by the experimental situation.

An earlier experiment by Bromiley (1948) demonstrated further the possibility of evoking an instrumental conditioned

avoidance response in the decorticate dog. However, Bromiley's animals, as well as those of Saavedra et al (1963) possessed more intact cortex than did those of Culler and Mettler (1934). Since that is the case, one is faced with the problem of attributing the results of Bromiley and Saavedra primarily to the function of the remaining cortex or to subcortical mechanisms that survived cortical extirpation. Culler and Mettler account for their undirected CR's in terms of subcortical functioning, but whether one is justified in attributing the ability to perform more precise instrumental CR's to such subcortical mechanisms cannot be ascertained at this time.

Further discussion of the relationship between cortical and subcortical mechanisms in learning is found in the literature concerned with curare. Curare is a drug which produces skeletal muscle paralysis by blocking the transmission of impulses from the motor axon to the muscle fibre. Harlow and Stagner (1933) demonstrated that an animal under curare was unable to learn a leg flexion response. Harlow (1940) found this to be so even when the dosage was not sufficient to induce complete muscular paralysis. The latter finding suggested to Harlow that in addition to paralyzing skeletal musculature, curare had a depressing effect on the central nervous system. Girden and Culler (1937), in support of Harlow's findings postulated that one of the

effects of curare is to "functionally decorticate" an animal forcing it to rely on subcortical centres for the mediation of learning. Girden and Culler demonstrated that learning is possible under curare by evoking a conditioned muscle twitch in the semi-tendinosus muscle of a curarized dog. At the same time, they showed that a CR acquired under curare was not manifested in the normal state and that CR's acquired in the normal state were not manifested under curare. Similar results were obtained by Harlow and Settlage (1939) who showed that except for a few minutes immediately following the injection of curare, a CR learned in the normal state did not transfer to the curarized state. Further support for what appears to be a dissociation of learning from drug to normal states is offered by Girden (1942) using erythroidine (a curare derivative) and by Girden (1947) employing monkeys as subjects instead of dogs. The general conclusion postulated in the Girden studies is that cortical and subcortical learning are independent of each other. That is, when the cortex is operating as in the normal state, several processes important for learning are at the cortical level, while those of the subcortex are less involved or suppressed. If the cortical system is disrupted, the subcortical neural mechanisms then become most important and take over the mediation of learning. Girden (1940) hypothesized that if this were the case, then a decorticate animal should not show dissociation,

because in such Ss all learning would have to be mediated by subcortical structures. Therefore, a CR established in either the normal or curarized animal should transfer to either state. Girden proceeded to extirpate the cortical auditory areas of a dog and after a reasonable recovery period, conditioned the animals either in the normal or drugged state. The CR was a twitch of the semi-tendinosus muscle, the US being shock. Girden reported that there was significant transfer from one state to the other, supporting his hypothesis that the cortex and subcortex are functionally independent. Culler, Coakley, Shurrager, and Ades (1939) attempted to validate the conclusions of Girden and Culler. They compared the minimum shock and time required to elicit a semi-tendinosus muscle twitch in curarized and normal animals by differential stimulation of the motor cortex and the ventral spinal roots which innervate the muscle. They demonstrated that stimulation of the motor cortex while the animal was under curare required more time to arouse the response than when it was normal. The reverse was found to be true when the ventral roots were stimulated. It was shown also that stimulation of the ventral roots of a curarized animal aroused a response far more readily than stimulation of the motor cortex. This evidence was in line with the proposed dual nature of the central nervous system. The authors postulated (re: the effects of curare) that

"somewhere between the cortex and the ventral root passes a plane of cleavage....To one side of the boundary (cephalad) is a zone of depression; to the other (caudad) is a non-depressed (possibly sensitized) area." (Culler, Coakely, Shurrager, and Ades, 1939).

The more recent literature does not corroborate this earlier notion of functional dissociation of the cortex and its lower connections. There is evidence that learning can be transferred from a curarized state to a normal state. Black (1958) showed that dogs who were taught a conditioned avoidance response in the normal state extinquished that response faster after having received a number of extinction trials under curare than did a control group which had received no previous extinction trials. There was no test for transfer for the reverse possibility, i.e. transfer from the normal to the curarized state. Gerall and Obrist (1962) were able to demonstrate transfer of learning from the curarized to the normal condition. They conditioned the pupillary dilation responses in six curarized cats and reported transfer of the learned response to the non-drugged state. They attributed the transfer, at least in part, to their use of Flaxedil, a purified curare compound which is unlike the raw drug in that it is believed to be free of any properties which may have a depressing effect on the central nervous system. Solomon and Turner (1962) conditioned normal

dogs to press a panel to avoid shock in response to a light CS. Ss were then curarized and presented with a number of tone-shock pairings. A contrasting tone not paired with the shock was interspersed throughout the curare period. Upon recovery, the animals showed discriminative capacity by responding to the light and to the tone that was paired with a shock, but not to the tone that was presented by itself. Thus the earlier idea of dissociation does not appear to be supported by more recent findings.

The last three studies reported employed curare derivatives rather than the raw drug itself. The pharmacological evidence appears divided on the improvements in the new compounds. Harlow (1940) and Girden and Culler (1937) have presented evidence which suggests that curare has an inhibitory effect on cortical functioning. However, Girden (1948) was unable to find any electrophysiological evidence for such inhibition. He reported that curarized animals showed no alteration in EEG activity from the normal state. On the other hand, Murlock and Ward (1961) offer evidence that intravenously injected curare produced up to 50% depression of spontaneous cortical activity. The effect, however, was highly variable and probably more closely related to the drop in blood pressure brought about by injection of the drug. Ochs (1959) using d-tubocurarine also got variable results, ranging from no effect to marked decrease in cortical

activity. Conversely, McCawley (1949) demonstrated that purified curare can have a stimulating effect on the nervous system and increase electrical activity. Salamus and Wright (1950) supported McCawley's findings and showed that the effect is greater on the cerebral cortex than on lower subcortical centres. Smith, Brown, Toman and Goodman (1947), on the other hand, used a human subject, and found that d-tubocurarine, while inducing skeletal muscle paralysis caused no measurable change in EEG activity, consciousness, or sensory capacity.

Thus, it is not possible at this time, to make a definite statement as to the effect of curare on the nervous system. The evidence which suggests that learning under curare is subcortically localized (eg. Harlow, 1940; Girden and Culler, 1937; Girden, 1942, 1947; Culler et al, 1939) is in line with Culler and Mettler's (1934) conclusion that decortication brings into operation learning mechanisms in subcortical structures. However, until it can be firmly established that curare serves as a cortical depressant rendering the cortex inactive, experimental findings involving the drug must remain inconclusive. Recently, a number of investigators have used chemically induced cortical SD as a decortication technique in learning experiments. Since, as has been earlier shown, SD depresses all normal cortical activity, an opportunity is provided to evaluate the findings of the

curare studies.

In addition to the approaches of the decortication and curare studies, a third method of studying brain functioning in learning is found in the use of the split-brain technique. Myers (1956) found that cats whose corpus callosum and optic chiasma had been sectioned were not able to show transfer of a visually discriminated CR. In this experiment following recovery from the operation, a blind was placed over one of the animal's eyes, durecting all the visual stimulation to one hemisphere. The animal was then trained on the task to a level of thirty-four correct responses in forty successive trials. After the animal had reached this criterion, the blindfold was switched to the other eye forcing utilization of the other hemisphere; no savings were reported. Stamm and Sperry (1957) confirmed Myers' results in "split-brain" cats trained on a somesthetic discrimination task to press a correct pedal for food. Sperry, Stamm, and Miner (1956) reported no visual transfer of a visual discrimination when both the optic chiasma and the corpus callosum were sectioned. Together, the findings suggest that the critical structure in mediating interhemispheric transfer is the intact corpus callosum.

There is evidence in the literature (Sperry, 1959, 1961) which indicates that the split-brain subject is in many respects like an animal with two separate brains. Each

hemisphere appears capable of acting alone, independent of the experiences of the other. Sperry demonstrated that the split-brain monkey could be conditioned to conflicting pattern discriminations in each eye with no apparent signs of interference. Myers (1959) showed that this was not possible in animals whose corpus callosum remained intact.

There is evidence (Schrier and Sperry, 1959; Glickstein and Sperry, 1960) that under certain conditions, visual information organized in one hemisphere of a split-brain animal can serve as a guide for limb responses for which the cortical centres lie in the opposite hemisphere. Schrier and Sperry sectioned the optic chiasma and the corpus callosum of cats and then trained them on a visual discrimination problem which required the animals to displace a wooden block with a forelimb in order to obtain food covered by the block. Ss were trained to perform the problem with one eye shielded (by a rubber mask) and then the other. After preliminary training, they received 50 trials a day, one forelimb being restrained for the first 25 trials, the other during the remaining trials. The order in which the limbs were restrained was alternated from day to day. It was found that regardless of which eye was shielded, either forelimb could be used equally well by all the animals. Glickstein and Sperry also demonstrated bilateral motor control by a single hemisphere. They showed that split-brain monkeys

trained to reach out and make a somesthetic discrimination for food were able to transfer the habit from one hand to the other.

It is possible that a system somewhat similar to Penfield's "centrencephalic system" operates in such cases. Penfield (1954) proposed a system located subcortically (including certain portions of the diencephalon, mid-brain, and pons) whose normal function is to transmit impulses to and from the cerebral cortex, but which in the absence of the cortex is capable itself of integrating impulses and initiating action. While Penfield's system is largely speculative, support for its existence is found in many studies of the brain stem reticular system. It has been shown that the reticular system plays a major role in controlling arousal, attention, wakefulness, sleep and learning (Jasper, 1958; Magoun, 1950, 1953; French, Hernandez-Peon, and Livingston, 1955). Magoun (1950) reported the existence of direct connections between the reticular formation and various parts of the diencephalon which are independent of the cerebral cortex and which are known to mediate sensory and motor impulses. It seems not unlikely then, that in the absence of the cortex, the centrencephalic system is potentially capable of controlling motor activity.

Sperry, Myers, and Schrier (1960) also argue in favour

of a subcortical mediating centre. After sectioning the corpus callosum of six cats, they removed all the cortex of one hemisphere except for the visual area. A blindfold was placed over one eye so as to restrict visual input to the isolated visual cortex, and Ss were trained to make a pattern discrimination for food. While Ss showed a general impairment of performance, they all retained the visual placing response. The authors noted further that the preferred paw bore no relation to the hemisphere which received the visual stimulation. Sperry (1959) showed that cats with their left sensori-motor cortex extirpated and the corresponding right structure isolated were able to maintain good visual-motor co-ordination. Ss were able to perform reaching, placing, centering, following, and jumping responses. Downer (1959) offered further evidence that monkeys trained on a visual discrimination task usually showed contralateral hand preference with respect to the unshielded eye. It appears then that while split-brain animals are capable of some co-ordinated motor movement, it is usually of a simple nature.

Our understanding of cortical and subcortical mechanisms has been greatly enhanced by the use of curare, decortication, and split-brain techniques. Further advancement has been made recently by the use of SD as a means of inducing functional decortication. Investigations by Bures, Buresova, Zahorva (1958), Tapp (1962) and Travis and Sparks

(1963), have all demonstrated that a rat under KCl-induced bilateral SD (BSD) is impaired in his ability to perform a conditioned avoidance response. Moreover, Bures et al and Tapp pointed out that the magnitude of the deficit is directly related to the concentration of the KCl solution. Such findings have been interpreted as indicating a disturbance of those mechanisms involved in the learning process. Bures and his colleagues have attributed losses in the performance of various CR's to a disruption of the cortical links of the memory forming mechanism (Bures and Buresova, 1963), or more generally, "to the impairment of associative cortical mechanisms" (Buresova, Bures, Fifkova, and Rudiger, 1963) involved in the consolidation of the learned response. It can be inferred from Bures' reports that whatever capacity an animal under KCl may still possess is due to important links of the learning process still intact and organized at the subcortical level.

Bures (1959) suggested that the duration and extent of impairment of a CR in a SD animal is a function of the difficulty of the task. He found that while animals under SD show some ability to perform a simple avoidance response, that response is no longer possible when the task is made more complex, e.g. by restricting the size of the doorway leading to the goal box. Bures contends that more complex neural mechanisms are involved in the second task, and that

they are affected more profoundly by SD than are the simple mechanisms required for the first problem.

There is evidence in the literature which raises certain questions as to the nature of the behavioral deficit accompanying cortical SD. This evidence suggests that SD may have a debilitating effect on sensori-motor co-ordination and in this way may contribute to poor performance. Tapp (1962), for example, noted a statistically significant relationship between the loss of a conditioned avoidance habit and general over-all motor impairment due to SD. Moreover, Tapp claimed that the animals did not appear to have lost all trace of the learned habit. He reported that while Ss generally failed to make the avoidance response, they nevertheless responded in some overt fashion to the CS (a light located in the ceiling of both sides of the testing apparatus). Tapp described these CR's as an increase in breathing rate and muscle tension as well as a pronounced pricking up of the ears. Those animals that were able to escape the US (shock) showed a lack of muscle control and usually staggered or fell over to the goal box. Tapp's observations appear to be in opposition to those of Bures (1959). Bures has contended that except for some decreased spontaneous motor activity and loss of the placing response, "the posture of the animal and its ability to move are completely undisturbed." (Bures, 1959).

In spite of this earlier statement of Bures, there is evidence in his own writings (Bures, 1959, 1960a) which further suggests that SD can have a severe effect on an animal's motor capacities. With the application of an appropriate amount of $CaCl_2$ or $MgCl_2$ to a particular part of the cortex, it was found that one could protect that area of the cortex from SD waves. Bures has demonstrated that when the sensori-motor cortex is protected by $MgCl_2$ and the rest of the cortex is subjected to KCl, the animal retains possession of a conditioned motor habit. As the task becomes more difficult and presumably involves greater cortical participation, $MgCl_2$ over the motor areas offers less protection. When $MgCl_2$ is applied to areas other than the motor cortex, the CR remains considerably impaired. These findings suggest that the motor cortex is particularly important in the learning of a motor response. Whether its role is directly related to the learning process or simply involves motor control cannot be unequivocably answered at this time. Bures and Buresova (1962a) showed that these results cannot be interpreted in terms of differential rates of K^+ diffusion from the site of application. They found that the duration of impairment was the same whether SD was initiated in the occipital, temporal, or frontal lobes.

There are thus two opposing points of view regarding the nature of the SD effect. Bures favours the idea that SD

has a disorganizing influence on the learning process. On the other hand, there is evidence, eg. Tapp (1962), that much of the loss can be accounted for in terms of specific sensori-motor loss.

The issue appears closely related to the questions raised by the work of Lashley. Lashley carried out a number of investigations which supported an equipotential interpretation of cortical function. He reported (1929) that rats with lesions in various parts of the cortex, including the sensory areas, exhibited equal loss on a maze learning habit. In another study (Lashley and Ball, 1929) it was demonstrated that rats whose sensory and motor spinal tracts had been sectioned showed no appreciable deficit in maze performance. He concluded, therefore, that learning is centrally controlled and that no part of the cortex contributes more to the learning process than any other. In other words, with respect to learning, the cortex acts as an equipotential system. Hunter (1930, 1940) objected to this equipotentiality interpretation and argued, on the basis of Lashley's data, that maze learning is controlled by a multiplicity of sensory cues. Hunter pointed out that Lashley's cortical lesions disrupted only a portion of the sensory projection areas, leaving others intact and capable of contributing to the learning process. Since a number of different stimuli are involved in learning the maze habit, removal of any <u>one</u> of them is not likely to seriously impair

the animal's performance. In an experiment by Honzik (as cited in Morgan and Stellar, 1950), requiring rats to learn a maze habit, no difference was found in performance between those who had been deprived of either the sense of sight or the sense of smell. However, serious retardation was found in those animals who had lost both of these senses. Destroying the auditory centres as well as the visual area and the olfactory bulbs had an even more appreciable effect. Pickett (1952) trained rats in an alley maze similar to that of Lashley's but restricted the stimuli controlling the maze habit to tactile and kinesthetic cues. After preliminary training, posterior lesions were made in one group and anterior lesions (sensori-motor) in another. The posterior animals showed no loss of the habit while the anteriors deteriorated markedly. Pickett concluded that when the cues controlling a habit can be isolated, removing these cues can interfere with learning. The findings of Pickett and Honzik have been interpreted to favour the arguments of Hunter in opposition to Lashley's theory.

Bures' view that SD disrupts the neural organization underlying the learning process seems to be in line with Lashley's interpretation that learning is centrally controlled. On the other hand, Tapp's findings that performance loss can be accounted for in terms of sensori-motor impairment seems to support the conclusions of Pickett and Hunter.

The SD studies thus far discussed have all involved bilateral application of KCl. Recent experiments (Bures and Buresova, 1960b; Travis and Sparks, 1963; Travis, 1964) have investigated the behavior of animals under SD applied unilaterally. The general findings are that the unilateral SD (USD) animal acquires a learned habit faster than BSD animals, but still considerably slower than normal animals. Travis and Sparks interpret these findings in terms of an equipotential or mass action theory arguing that the USD animal has more available neural tissue than the BSD animal but less than the normal. Such findings can, however, be interpreted as readily in terms of less sensori-motor loss since the SD is limited to one hemisphere.

Little work in the study of interhemispheric transfer has been done using USD. What evidence there is, suggests that a response learned while one hemisphere is under SD is not retained when the other is subsequently depressed. Bures and Buresova (1960b) and Travis and Sparks (1963) have shown that USD rats have been able to learn a simple shock avoidance as well as left-right discrimination problems. On retesting, Ss under ipsilateral SD showed good retention while those receiving contralateral SD showed no savings at all. Such evidence appears contrary to any theory that CR's may be mediated by subcortical mechanisms. Moreover, Bures and Buresova (1960b) found that Ss who had received

avoidance training under USD and then further training in the normal condition, performed significantly better when tested under contralateral SD than did Ss who had received no training between SD testing sessions. The authors interpret this finding as further evidence that avoidance learning is localized in the cerebral cortex. A recent study by Travis (1964) partially supports Bures and Buresova's findings. While Travis found that the number of inter-depression trials facilitates learning under contralateral SD, he also found that the number of original USD training trials can itself be a factor in influencing such learning. Thus, one might argue that applying SD to one side of the cortex does not entirely prevent the remaining structures of that hemisphere from playing some role in the learning process. What this role may be however, is a problem worthy of further investigation.

In summary then, the use of SD would appear to be a most effective means by which some of the problems of brain functioning may be studied. By providing a technique of functional decortication, it avoids many of the disadvantages characteristic of surgical procedures. SD is fully reversible and can be readily produced with a minimum of surgical shock to the animal. Moreover, SD primarily affects cortical structures without producing subcortical degeneration which generally accompanies surgical ablation.

Because of its effect on cortical functioning and

its reversible nature, SD lends itself to an evaluation of the early curare studies which have suggested that the cortex and the subcortex are functionally independent of each other. The uncertain effect of curare upon nervous functioning leaves such findings open to question. SD, on the other hand, is believed to depress completely all cortical activity, leaving subcortical activity relatively unimpaired.

The advantages of SD can also be applied to the investigation of interhemispheric transfer as frequently studied in split-brain animals. As well as eliminating some of the negative aspects of surgery, SD not only interferes with interhemispheric connections, but also has the advantage of rendering one cortical hemisphere temporarily inoperable without affecting the other hemisphere. In this condition, the depressed cortex is prevented from directly participating in the operations of the functional hemisphere.

While SD offers many possibilities for research regarding the brain and learning, there are still some very important questions regarding its behavioral consequences. A major purpose of this thesis is to examine some of the behavioral effects of SD.

CHAPTER IV

STATEMENT OF THE PROBLEM

A number of investigators have found that rats under SD are seriously impaired in their ability to learn certain avoidance problems. Bures and his associates have argued that such losses are due to a disturbance involving those cortical mechanisms important to the learning process. Tapp (1962), on the other hand, has presented evidence that animals under SD may suffer a severe motor loss which may account for the difference in error scores obtained by one group versus another group. The issue then is whether SD impairs the animal's capacity to <u>learn</u> a particular habit or rather his ability to <u>perform</u> the required response. The problem is a complex one and it is not unlikely that both arguments are partially valid. However, if the latter is true, it should be possible to impair an animal's performance under SD merely by increasing a task's motor complexity without necessarily adding to its difficulty as a learning task. According to Bures, since it is the animal's learning ability that is impaired by SD, and since "the posture of an animal and its ability to move are completely undisturbed," (1959) simply increasing the motor requirements of the task without making it a more complex problem should have no effect on performance. This problem will be examined in the present study by testing rats under BSD on tasks differing only in

their motor requirements.

Another problem to be studied is one suggested by the findings of some of the early curare studies. A number of investigators (Culler and Mettler, 1934; Girden and Culler, 1937; Culler, Coakely, Shurrager, and Ades, 1939) have argued that the drug curare has a depressing effect on cortical activity. Thus any learning manifested by a curarized animal would have to be localized at the subcortical level. It was subsequently found that learning which occurred in curarized animals was not retained in the normal state and vice versa. It was, therefore, concluded that with respect to learning, the cerebral cortex and the subcortex could operate independently of each other. The failure of recent studies (Black, 1948; Gerall and Obrist, 1962; Solomon and Turner, 1962) to confirm these results has raised the question of the effectiveness of curare as a cortical depressing agent. Moreover, current physiological evidence is not in agreement as to the cortical effects of curare (Girden, 1948; McCawley, 1949; Ochs, 1959; Murlock and Ward, 1961).

On the other hand, the studies of Leao and Bures suggest that SD is a most reliable means by which depression of cortical activity may be induced. As it is applied topically, directly above the cortex, SD is free of complications which may accompany the intramuscular injection of curare. Furthermore, its reversible nature and the fact

that its effect is for the most part limited to cortical structures indicated that SD can be a most valuable means by which the relationship of cortical and subcortical structures may be studied. This study will investigate the learning ability of animals under BSD, and the possibility of transfer of training from the normal to the SD state.

A third problem to be investigated using SD techniques is that of interhemispheric transfer. There is evidence from the examination of hemi-decorticate animals (Schrier and Sperry, 1958; Downer, 1959; Glickstein and Sperry, 1960; Sperry, Myers, and Schrier, 1960) that on certain tasks requiring a general type of motor response, a split-brain animal is able to control motor activity of both his right and left sides with only one functional hemisphere. Such findings have suggested the presence of a subcortical mediating centre which functions in the absence of intact cortical connections (Penfield, 1954).

A number of investigators (Bures and Buresova, 1960b; Travis and Sparks, 1963; Travis, 1964) have investigated such transfer using SD to inhibit the function of one hemisphere. Animals under USD are severely impaired in avoidance learning, although not to the extent found in BSD animals. It has been reported that rats given avoidance training on Day 1 under SD applied unilaterally, show no retention of the habit when tested on Day 2, SD having been applied to the

opposite hemisphere. This evidence suggests that the hemisphere depressed on Day 1 was not involved in learning. The findings of the SD studies then are at variance with some of the split-brain experiments which have demonstrated that hemi-decorticate animals are capable of controlling a learned response with the hemisphere not directly involved during acquisition. It has been suggested, however, that the nature of the CR may be an important factor in controlling such transfer. The problem of demonstrating interhemispheric transfer using SD is examined in the present study by employing two avoidance problems, one involving a specific localized response, the other a simple type of response requiring little specific motor ability.

In summary, the present research is intended to deal with three major issues which centre about the use of cortical spreading depression as a means of inducing functional decortication:

1. An attempt is made to determine whether motor impairment can account for the learning deficit demonstrated in rats under SD on avoidance learning problems. This will be accomplished by testing Ss under SD on two tasks of equal difficulty (for normal animals) but of varying motor complexity.

2. An examination is made of the suggestion in the curare studies that the cortex and subcortex may be dissociated

during learning, functioning independently of each other. It is argued that a habit acquired while the cortex is normal is not retained when the animal is functionally decorticate and presumably relies on subcortical structures for learning. This will be studied by determining whether animals under BSD can benefit from prior training in the normal state.

3. Interhemispheric transfer of training is the third problem to be dealt with. Although SD studies have previously failed to demonstrate such transfer, there is evidence from some of the split-brain studies that under certain conditions related to the nature of the required response, such transfer may occur. In this study the problem is investigated by determining the relative learning ability of animals who are given training for two days, one day under USD and a second day under ipsilateral or contralateral USD.

CHAPTER V

EXPERIMENT I

Introduction

Experiment I was designed to study the performance of rats in two conditioned avoidance situations following the application of cortical SD. The apparatus used for both problems was a modified Yerkes-Thompson box. The first task (Task A) required the animals to avoid shock by crossing from the start box over to the safe compartment at the other end of the testing box. Entrance to the safe compartment was gained through one of two open doors. The second task (Task B) required Ss to locate a small opening in one of the doors and climb through it to avoid shock. Preliminary investigation indicated that normal animals committed an equal number of errors and required the same number of trials to learn either avoidance task to a criterion of nine correct responses on ten successive trials. It was, therefore, assumed that the tasks were equated for difficulty in normal animals.

If, as Bures suggests, the effect of SD is limited to disrupting the organization of the learning engram, Ss under SD should show equal loss on both tasks. Since the tasks are equated in difficulty for animals and since Task B differs from Task A in requiring a more precise motor response

any difference would suggest that the animals were actually unable to make the appropriate motor responses. In that case one might argue that animals under SD experience a severe motor impairment.

The first experiment also attempted to evaluate the argument that learning in the normal state does not transfer to the functionally decorticate state. While the early curare studies suggest a lack of transfer between such states, the evicence obtained in studies using SD is inconclusive. Travis and Sparks (1963), using an avoidance problem, found that training under BSD seemed to make learning in the normal state more difficult. Overton (1964), using sodium pentobarbital as a cortical depressant, found that rats trained to escape shock in a T-maze while normal did not show retention of the habit while in a drugged state. Conversely, if the habit was learned in the drugged state, it did not appear when Ss were normal. He called such learning "state dependent". A study by Thompson (1962), on the other hand, demonstrated that animals pretrained on an avoidance problem with a functional cortex required fewer trials to relearn the habit under SD than did Ss with no such pretraining. He failed, however, to demonstrate transfer from SD state to normal state.

The hypothesis that learning in the normal state does not transfer to the SD state is examined in this experiment by giving half the animals preoperative training on their

appropriate task and comparing their performance under SD to Ss who had received no preoperative training. If learning is dependent upon the state of the animal, giving Ss practice while normal should not affect performance when SD is introduced.

With respect to savings within the functionally decorticate state, i.e. from one SD state to another, the evidence indicates that animals do not appear to benefit from prior experience under SD. The Travis and Sparks study appears to be the only one which has looked at the problem and it reports no savings from one SD testing session to another. These results are somewhat surprising if we accept the conclusion that learning is "state-dependent" (Overton, 1964). Curare studies by Harlow and Stagner (1933) and Girden (1942, 1947) have invariably demonstrated that while no transfer occurred from the drugged to the non-drugged state, curarized animals retained CR's acquired under the drug. The hypothesis that there is no savings from one SD testing session to another is evaluated in this study by testing the animals under SD on two successive days.

In summary, Experiment I investigates the nature of the loss displayed by rats under BSD when tested on two avoidance tasks of equated difficulty, but differing in sensori-motor complexity. Thus any difference in the animals' learning of the two tasks would suggest a motor impairment

attributable to SD. Another purpose of this study was to determine the effects of prior training in the normal state on Ss' performance under BSD. This aspect of the experiment attempted to evaluate the argument that cortical and subcortical learning are independent of each other. Another aim of this study was to investigate the claim made by Travis and Sparks (1963) that Ss under SD show no savings from one testing session to another. The hypothesis of no savings is evaluated by testing all Ss under SD on two consecutive days.

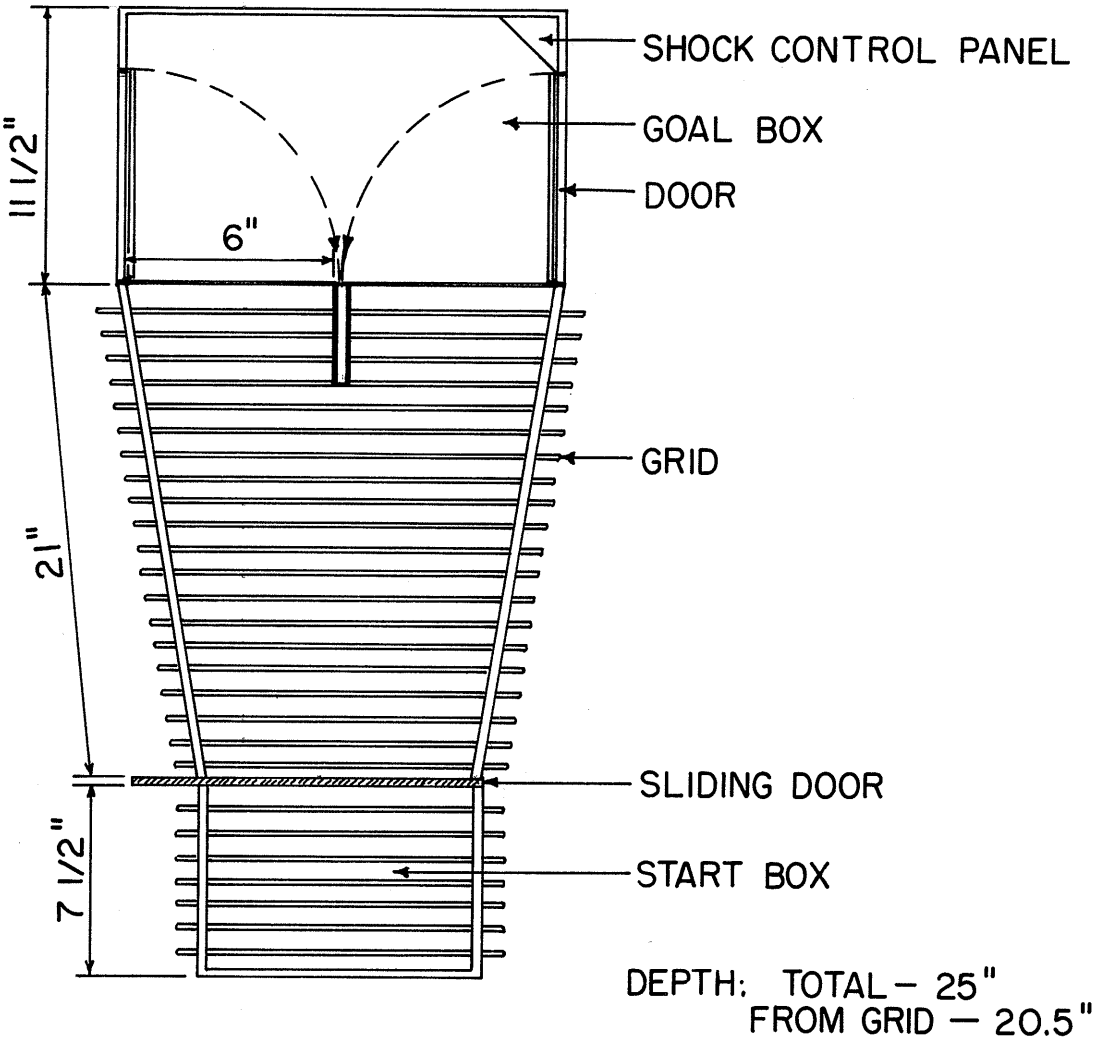
Method

Subjects

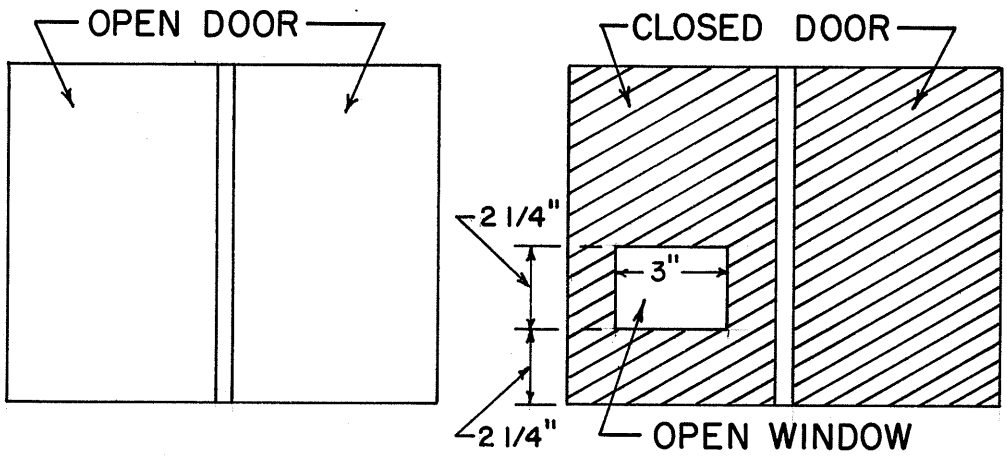
Ss used in this experiment were 90 male, experimentally naive hooded rats approximately 250 grams in weight and between 90 and 120 days old, obtained from the Canadian Research Animal Farm at Bradford, Ontario.

Apparatus

The testing apparatus (a modified Yerkes-Thompson box--see Figure I) consisted of a wooden chamber (40" long) divided into a start box (7 1/2" long), a runway (21" long) and a safe goal compartment (11 1/2" long). Access to the runway was gained through a manually controlled sliding door. The floor of the start box and runway was an electrifiable grid controlled by E. Shock was administered from a 150 volt DC shock source in series with a variable resistor set at 47 K.



PLAN VIEW n.t.s.



TASK 'A' TASK 'B'

FRONT VIEW OF ENTRANCE TO SAFE COMPARTMENTS OF TASKS A AND B.

MODIFIED YERKES – THOMPSON TESTING APPARATUS.

FIGURE I

Assuming the resistance of the animal to range from 10 to 20 K. the intensity of the shock was calculated to be between 2 - 2 1/2 milliamperes.

Surgery

Ss were anesthetized under ether and placed in a Krieg-Johnson stereotaxis instrument. A midline incision about 3 cm. in length was made in the scalp which was then retracted. Exposure of the parieto-occipital cortex of both hemispheres was achieved by a trephine opening about 4 mm. in diameter. Care was taken not to break the dura. The wound was then cleansed with zephran (Winthrop-Benzalkonium Chloride solution), the skin was replaced over the skull and secured with two or three wound clips. The operation generally took about 15 or 20 minutes. A 24-hour recovery period followed during which S remained isolated in his home cage.

Spreading Depression

Spreading Depression (SD) was elicited according to the technique described by Bures, Bures, and Zahorva (1958). The day following the operation and about 20 minutes prior to testing, the animal was lightly anesthetized under ether and the wound reopened. A small piece of filter paper (about 4 mm. in diameter) soaked in 33% KCl solution was placed directly upon the exposed dura. The skin was then placed over the skull and secured with two or three wound clips.

Ss were then placed in a cage for 10 to 15 minutes prior to avoidance testing. Following each testing session, the filter paper was removed, and the scalp secured again by wound clips. Ss whose dura appeared punctured or discolored were eliminated.

Groups

Ss were divided into three major groups--KCl Experimental group (N = 40), Sham Control group (N = 40), and Normal Control group (N = 10).

KCl Experimental: The 40 rats in this group were divided into two equal groups, Task A group and Task B group. Within each task, the animals were further subdivided into Practice (N = 10) and No Practice (N = 10) conditions. Ss in the Practice condition were trained immediately prior to operation on their respective task to a criterion of 9 correct responses in 10 successive trials. During this time the No Practice animals remained in their home cages. All experimental Ss were tested under BSD.

Sham Control: The sham group (N = 40) similarly consisted of a Task A and a Task B group with half the animals receiving the Practice condition and half the No Practice condition. The sham group was subjected to the same pretesting surgical procedures as the experimental group. Prior to each post-operative testing session, Ss were reopened and a dry piece of filter paper (approximately 4 mm. in diameter)

was applied to the dura. The skin was then secured with two or three wound clips and the animals were placed in a cage to recover from the ether. After testing, the filter paper was removed, the skin secured again with wound clips, and the rat was returned to his home cage.

Normal Control: A normal group (N = 10) was tested on Task A with no prior practice on two consecutive days. The purpose of this group was to control for the effects of operational procedure.

Tasks

Both tasks required Ss to move from the start box to the safe compartment to avoid shock. In Task A, the safe compartment was entered through one of two open doors (6" wide) separated by a 1/4" thick centre post extending the height of the box. For Task B, one door was closed and a white translucent plastic plate was placed in the other doorway. Entrance to the safe compartment was gained through an aperture (2 1/4" x 3") centrally located in the plastic about 2 1/4" from the bottom of the plate.

Testing Procedures

The testing procedures were identical for experimental and control groups on both Tasks A and B. Ss were given two 30-trial testing sessions separated by about 24 hours. On each trial, S was placed in the start box, and allowed 5 seconds to

reach the safe compartment. After 5 seconds shock was delivered through the grid floor. The shock was administered every 5 seconds until the animal escaped into the safe compartment. In the event that S failed to escape within 60 seconds, he was removed from the grid floor and placed in the safe compartment for 30 seconds, the usual inter-trial interval. A record was kept of the number of times he was successful in reaching the safe compartment within 5 seconds of having been placed in the start box.

Results

The results of Experiment I are represented in Figure II and Table I. An analysis of the data (Table II) shows that the number of errors made on Days 1 and 2 by Ss under BSD differed significantly from that of shams and normals. This was true in the Task A condition for the Practice ($U = 12.5$, $P < .01$) and No Practice ($U = 8$, $P < .001$) groups, as well as for the Practice ($U = 0$, $P < .001$) and No Practice ($U = 0$, $P < .001$) groups in the Task B condition. A comparison between the combined error scores of Days 1 and 2 of the normal control group and its corresponding No Practice sham control (Table I) also revealed a significant difference ($U = 2$, $P < .001$). One may infer, therefore, that while operational procedure can account in part for the poorer performance of the experimental animals, there is a large additional impair-

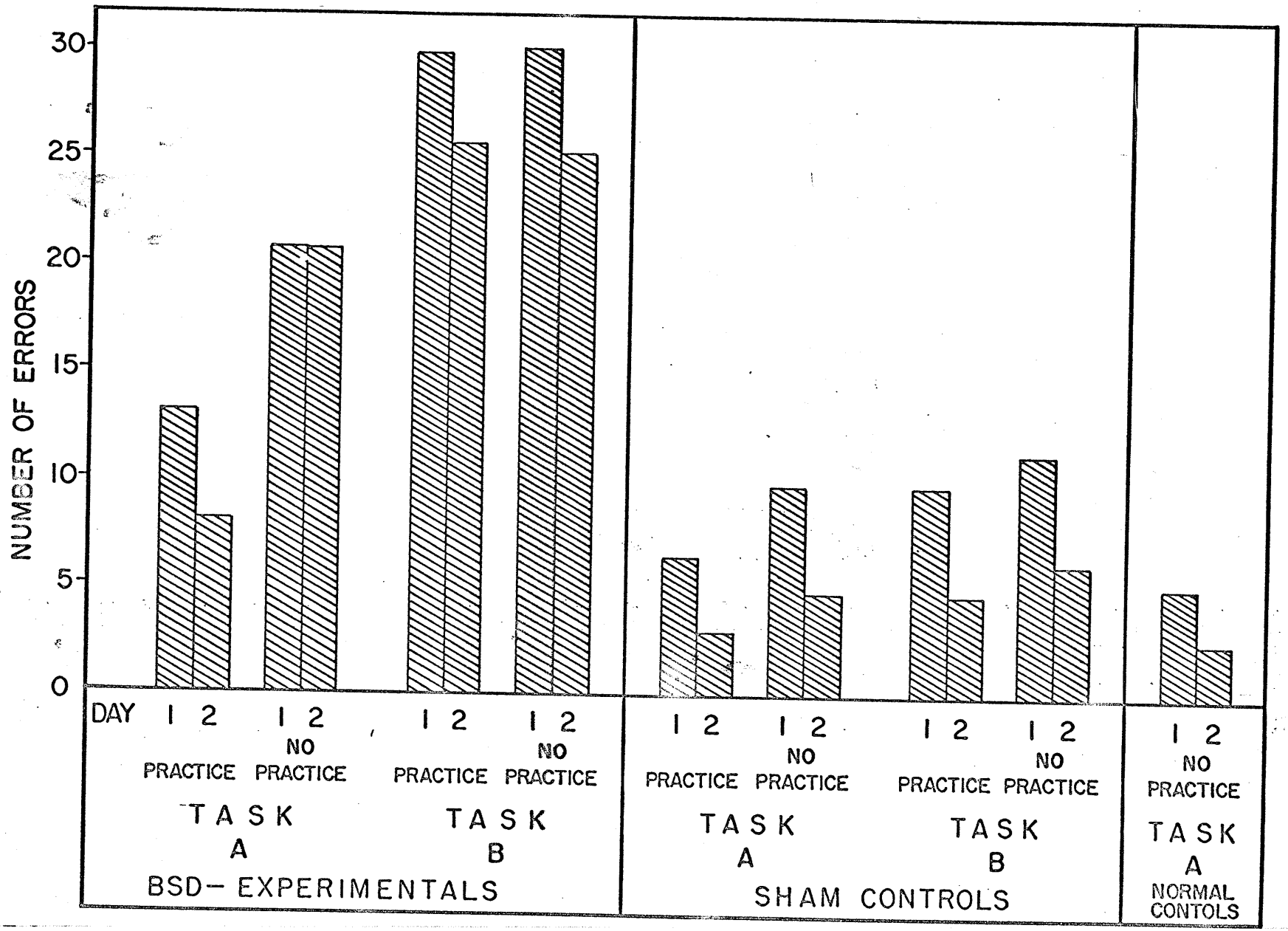


FIGURE II. MEAN NUMBER OF ERRORS MADE BY BSD AND SHAM GROUPS ON TWO 30 TRIAL TESTING SESSIONS FOLLOWING CONDITIONS OF PRE-OPERATIVE TRAINING AS COMPARED TO THAT OF A NORMAL GROUP FOLLOWING NO PRE-OPERATIVE TRAINING

ment attributable to the SD treatment.

An examination of the error scores of BSD animals on Days 1 and 2 revealed that Ss tested on Task A demonstrated superior performance to those tested on Task B. This was so in both Practice (Task A-Practice vs. Task B-Practice, $U = 0$, $P < .001$) and No Practice (Task A-No Practice vs. Task B-No Practice, $U = 23.5$, $P < .05$) conditions.

An analysis of the effect of preoperative practice on the number of errors made on Day 1 by BSD animals revealed that only those Ss in the Task A, SD condition were affected by the preoperative practice ($U = 14.5$, $P < .02$). There was no difference in performance between Ss in the Task B Practice and Task B No Practice conditions. An analysis of the effects of such practice on shams indicated a significant difference for the Task A Ss ($U = 14$, $P < .02$) and an effect approaching significance for the Task B Ss ($U = 29$, $.05 < P < .10$).

A Walsh test of related samples (Siegel, 1961) was applied to the data to test for a savings effect from Day 1 to Day 2. As can be seen from Table II all control Groups showed a significant savings while the only SD group to show significant savings was the Task A-Practice group ($P < .025$).

TABLE I

MEAN ERRORS AND PER CENT SAVINGS MADE BY BSD, SHAM, AND NORMAL RATS DURING 30 TRIAL TESTING SESSIONS ON AVOIDANCE TASKS A AND B FOLLOWING CONDITIONS OF PRE-OPERATIVE PRACTICE AND NO PRE-OPERATIVE PRACTICE

	Pre-op. Practice		BSD-EXPERIMENTALS			
	Trials to Crit.	Errors to Crit.	Errors on Day 1	Errors on Day 2	Total Errors Days 1 & 2	% Savings Days 1 & 2
Task A						
No Practice	-	-	21.7	21.6	43.3	00.00
Practice	13.9	4.4	13.4	8.8	22.2	34.33
Task B						
No Practice	-	-	30.0	25.4	55.4	15.33
Practice	13.9	4.3	29.2	26.8	56.0	8.22
	SHAM CONTROLS					
Task A						
No Practice	-	-	9.4	4.6	14.0	51.06
Practice	13.9	4.8	6.5	3.0	9.5	53.85
Task B						
No Practice	-	-	11.3	5.3	16.6	53.10
Practice	14.4	5.1	9.4	4.3	13.7	54.26
	NORMAL CONTROLS					
Task A						
No Practice			5.4	2.2	7.6	59.26

TABLE II

ANALYSIS OF THE RELEVANT DATA OF EXPERIMENT I

	Conditions Tested	Mann-Whitney U-Values	P-Values
Comparison of the error scores of BSD. Experimental, sham, and normal control groups on each task	Task A-BSD, Practice vs. Task A-Sham, Practice	12.5	$P < .01$
	Task A-BSD, No Practice vs. Task A-Sham, No Practice	8.0	$P < .001$
	Task B-BSD, Practice vs. Task B-Sham, Practice	0.0	$P < .001$
	Task B-BSD, No Practice vs. Task B-Sham, No Practice	0.0	$P < .001$
	Task A-Normal, No Practice vs. Task A-Sham, No Practice	2.0	$P < .001$
	Task A-Normal, No Practice vs. Task A-BSD, No Practice	0.0	$P < .001$
Comparison of Task A vs. Task B performance of BSD, sham, and normal animals	Task A-BSD, Practice vs. Task B-BSD, Practice	0.0	$P < .001$
	Task A-BSD, No Practice vs. Task B-BSD, No Practice	23.5	$P < .05$
	Task A-Sham, Practice vs. Task B-Sham, Practice	27.5	$P > .05$
	Task A-Sham, No Practice vs. Task B-Sham, No Practice	29.0	$P > .05$
	Task A-Normals, Pre-op. Trials to Crit. vs. Task B-Normals, Pre-op. Trials to Crit.	180.0	$P > .05$
	Task A-Normals, Pre-op. Errors to Crit. vs. Task B-Normals Pre-op. Errors to Crit.	176.0	$P > .05$

continued . . .

TABLE II continued

	Conditions Tested	Mann-Whitney U-Values	P-Values
Analysis of the effects of pre-op. practice on BSD and sham animals	Task A-BSD, Practice vs. Task A-BSD, No Practice	14.5	$P < .025$
	Task B-BSD, Practice vs. Task B-BSD, No Practice	57.0	$P > .05$
	Task A-Sham, Practice vs. Task A-Sham, No Practice	14.0	$P < .01$
	Task B-Sham, Practice vs. Task B-Sham, No Practice	29.0	$.05 < P < .10$
		Walsh Test P-Values	
Analysis of savings effect from Day 1 to Day 2 in BSD, sham, and normal animals	Task A-BSD, Practice, Day 1 vs. Task A, BSD, Practice Day 2	$P < .05$	
	Task A-BSD, No Practice, Day 1 vs. Task A, BSD, No Practice Day 2	$P > .05$	
	Task B-BSD, Practice, Day 1 vs. Task B, BSD, Practice Day 2	$P > .05$	
	Task B-BSD, No Practice, Day 1 vs. Task B, BSD, No Practice Day 2	$P > .05$	
	Task A-Sham, Practice, Day 1 vs. Task A, Sham, Practice Day 2	$P < .01$	
	Task A-Sham, No Practice, Day 1 vs. Task A, Sham, No Practice Day 2	$P < .01$	
	Task B-Sham, Practice, Day 1 vs. Task B-Sham, Practice Day 2	$P < .01$	
	Task B-Sham, No Practice, Day 1 vs. Task B-Sham, No Practice Day 2	$P < .01$	
	Task A-Normal, No Practice Day 1 vs. Task A-Normal, No Practice Day 2	$P < .01$	

CHAPTER VI

EXPERIMENT II

Introduction

Experiment II was carried out to evaluate the effects of USD on the performance of rats on the tasks of Experiment I. One purpose of this study was to compare the behavioral loss of USD animals to that of animals under BSD. The comparison is an interesting one in the light of Bures and Buresova's (1960c) contention that the difference between the effects of BSD and USD on rats is primarily one of degree of impairment.

Another purpose of this study was to test Bures and Buresova's (1960b) hypothesis that the neocortex plays an essential role in mediating avoidance learning. Since USD severely impairs cortical functioning in one hemisphere, according to Bures and Buresova's argument, an animal trained under USD on Day 1 would show no savings if he were tested on Day 2 with SD applied to the opposite hemisphere. However, if, as we may assume, the ipsilateral and contralateral subcortex remains intact and operable during USD, then reversing the locus of SD on Day 2 may not necessarily affect recall of the habit learned on Day 1. If indeed, Ss who received SD on the contralateral hemisphere on Day 2 were to show savings from one SD testing session to another,

one might argue in favour of the existence of a subcortical centre capable of mediating the conditioned and unconditioned components of the avoidance habit.

Method

Subjects

Forty male hooded rats approximately 250 grams in weight and between three to four months old from the Canadian Research Animal Farm were used.

Apparatus

The testing chamber described in Experiment I was again used in this experiment.

Surgery

All Ss were subjected to the same surgical procedures, 24 hours before the first testing session. S was anesthetized under ether and a trephine opening of about 3 cm. in diameter was made in the skull over the parieto-occipital area of both hemispheres. The skin was then replaced over the skull and secured with two or three wound clips. S was then returned to his home cage and allowed a 24 hour recovery period.

Procedure

Ss were divided into two equal size groups and assigned

to either Task A (N = 20) or Task B (N = 20) groups. Within each condition, Ss were further subdivided into Ipsilateral and Contralateral groups. Ss in the Ipsilateral group received USD to the same hemisphere on two successive testing sessions; Ss in the Contralateral group received USD on the opposite hemisphere for the second testing session.

Approximately 24 hours after the operation, those animals that had made sufficient recovery from surgery were again anesthetized under ether, the skull was reopened and filter paper soaked in 33% KCl solution was applied to the right hemisphere of half the animals, and to the left hemisphere of the other half. The skin over the wound was secured with wound clips and the animals were allowed a 10 to 15 minute recovery period. Ss were then tested on their respective task. Testing procedures were exactly the same as those employed in Experiment I. After testing, the animal was again anesthetized, the wound reopened, and the filter paper removed. The skin was secured with wound clips and the animal returned to his home cage. The following day, the procedure was repeated except that the Contralateral group was tested with KCl applied to the opposite hemisphere. The Ipsilateral group was tested with KCl applied to the same hemisphere as on Day 1. A record was kept of each animal's successful avoidance responses in each 30 trial session.

Results

In order to evaluate the relative effects of BSD, USD, and sham procedures on learning ability, an analysis was made of Ss error scores on Day 1. As expected there was no significant difference between animals who received left SD on Task A, Day 1 ($N = 10$, $\bar{X}$ errors = 13.0) and those who received right SD on Task A, Day 1 ($N = 10$, $\bar{X}$ errors = 15.3) [$U = 44.5$; $P > .10$], nor was there any difference found between Ss who received left SD on Task B, Day 1 ($N = 10$, $\bar{X}$ errors = 18.9) and those receiving right SD on Task B, Day 1 ($N = 10$, $\bar{X}$ errors = 19.2) [$U = 48.5$; $P > .10$]

Since there was no difference between Ss who received right SD on Day 1 and those who received left SD on Day 1, the Day 1 error scores were combined within each condition (Ipsilateral and Contralateral) yielding a Task A, USD mean error score of 14.2 and a Task B, USD mean error score of 19.1 (see Table III). This permits comparison of error scores in a single Day 1, USD, Task A group with the Day 1 error scores of Task A, BSD and sham groups, and similarly permits comparison of the Day 1 scores of a single USD Task B group with the Day 1 scores of BSD and sham Ss on Task B.

As can be noted from Table IV, the Day 1 error scores of Ss under USD differed significantly from those of BSD and sham animals in both Tasks A and B. Ss under USD demonstrated better learning ability on both tasks than did BSD

animals. For example, the Day 2 error score for the USD Ss was comparable to the error score of the sham group on Day 1, indicating a much higher level of learning than that shown by BSD Ss (Table III). In addition it was found that the errors made by Ss under USD on Task A were significantly lower than those of USD Ss on Task B ($U = 82.5$; $P < .001$).

An analysis of the error scores recorded on Day 2 revealed no significant differences between Ipsilateral and Contralateral groups on Task A ($U = 42.5$; $P > .10$) nor on Task B ($U = 48$; $P > .10$). All USD Ss showed significant improvement from Day 1 to Day 2 (Tables III and IV).

TABLE III

MEAN NUMBER OF ERRORS ON TASKS A AND B MADE BY BSD, USD, AND SHAM GROUPS ON TWO SUCCESSIVE DAILY 30 TRIAL TESTING SESSIONS

	USD (N = 10/gp)			Sham (N = 10/gp)		BSD (N = 10/gp)	
	Day 1	Day 2		Day 1	Day 2	Day 1	Day 2
Task A	13.3*	8.4	Ipsilateral	9.4	9.6	21.7	21.6
	15.0*	8.4	Contralateral				
$\bar{X}$(N = 20)	14.2	8.4					
Task B	19.5*	11.9	Ipsilateral	11.3	5.3	30.0	25.4
	18.6*	11.7	Contralateral				
$\bar{X}$(N = 20)	19.1	11.8					

*N = 10: 5 left SD, 5 right SD

TABLE IV

STATISTICAL COMPARISON OF ERRORS ON DAY 1 MADE BY BSD, USD, AND SHAM GROUPS AND OF SAVINGS FROM DAY 1 TO DAY 2 IN USD GROUPS

Conditions Tested	Task A		Task B	
	Statistic	P-Value	Statistic	P-Value
Errors on Day 1:				
BSD (N = 10) vs. USD (N = 20)	$U = 53.5$	$P < .025$	$U = 0$	$P < .001$
Sham (N = 10) vs. USD (N = 20)	$U = 1$	$P < .001$	$U = 17$	$P < .001$
Sham (N = 10) vs. BSD (N = 10)	$U = 8$	$P < .001$	$U = 0$	$P < .001$
Savings Day 1 to Day 2:				
USD - Ipsilateral	Sign	$P < .01$	Sign	$P < .05$
USD - Contralateral	Sign	$P < .01$	Sign	$P < .01$

CHAPTER VII

DISCUSSION OF RESULTS

Experiment I

It was found in Experiment I that Ss under BSD on Task A showed better learning, that is, made fewer errors, than did Ss under BSD on Task B. Sham groups showed equal learning ability on both tasks. There are two possible explanations for the observed difference between Ss under BSD. It can be argued that Tasks A and B differ as tests of learning ability, Task B presenting a more difficult problem in that it requires a more complex avoidance response than does Task A. If normal animals do, in fact, differ in the ease with which they are able to master Tasks A and B, then one would expect these differences to persist or even be exaggerated when Ss are subjected to "functional decortication". However, this does not appear to be the case. Normal animals mastered Tasks A and B with equal facility, indicated by errors and trials to criterion (Table I). Similarly, there were no differences between error scores of sham animals from Task A to Task B (Table II).

Since, according to Bures, SD interferes with the cortical locus of learning, and since Tasks A and B are equally difficult to learn, one would expect the loss under SD to be comparable for both tasks. Such is not the case, however, for in these experiments, animals under SD show a

greater loss on Task B than they do on Task A.

An alternative explanation might be that although Tasks A and B are of equal difficulty as measured by trials and errors to criterion, they do, in fact, differ in requiring different patterns of organized motor responses for their solution. In Task A, Ss are required simply to run through one of two open doors to avoid shock. In Task B, however, both doors are closed and Ss are forced to locate a small open window and climb through it to enter the safe compartment. If an animal's motor ability was impaired to any extent, one would expect him to have trouble with the mechanics of Task B. Under SD, rats do appear, in fact, to suffer motor impairment. While posture was for the most part unimpaired, all placing and hopping responses were completely abolished. Ss under SD displayed a marked reduction in locomotor ability and exhibited little of the exploratory behavior commonly found in normal rats. Their movement was sluggish and poorly coordinated and they often bumped into the centre post of the testing apparatus while attempting to avoid or escape shock. On Task B, SD Ss often appeared to experience considerable difficulty in lifting themselves through the window into the safe compartment. The motor loss suffered by USD animals was similar to that of BSD animals but of a less severe nature. This would suggest that much of the difference in learning ability found in SD animals on Tasks A

and B could be attributed not to the disturbance of cortical links of the learning process, but rather to a motor or sensori-motor impairment. Such an argument would support Tapp's conclusion that much of the observed impairment in learning ability demonstrated under SD can be attributed to a severe motor deficit.

A comparison of the total number of errors made by BSD and sham groups revealed that although BSD Ss made more errors than sham Ss they still showed some evidence of learning on Task A. Ss under BSD were, however, incapable of learning Task B which required a more complex motor response. These results are relevant to the findings of some of the surgical decortication studies. For example, Culler and others (Culler and Mettler, 1934; Girden, Mettler, Finch, and Culler, 1936; Bromiley, 1948) have demonstrated that decorticate animals are capable of carrying out only CR's which require gross motor movements.

A second finding of Experiment I was that Ss who had received prior training on Task A while normal subsequently performed significantly better than other SD Ss who had received no prior practice. In other words, Ss in the cortically depressed state benefited from training they had received pre-operatively. These results are at variance with the conclusions of the curare studies in which Ss under curare showed no sign of profiting from prior training received in the

normal state. The findings, therefore, cast doubt on the general conclusion of the curare studies that cortical and subcortical learning can be independent of each other. Although this phenomenon of savings from normal to SD state was demonstrated only in the Task A and not in the Task B BSD Ss, this may be due to the complete inability of the latter Ss to perform the appropriate response.

The findings of Travis and Sparks (1963) that no savings occurs from one SD testing session to another were only partially supported in this experiment. Such savings from one SD testing session to the next were reported only in the Task A-Practice group. Although one might not expect to find savings in Task B Ss if they were not able to perform the avoidance response, it remains to be explained why the animals in the Task A-No Practice group who had shown some evidence of avoidance learning under BSD failed to show a reduction of errors from Day 1 to Day 2. It is somewhat perplexing to find savings occurring from the normal state to the SD state but not from one SD state to another, especially in view of Overton's (1964) conclusion that learning is state-dependent. Further experimentation will be required to clarify this problem.

Experiment II

An examination of the number of errors made on Day 1 by animals in this experiment indicated that Ss under USD showed a marked impairment in learning the avoidance tasks. The learning deficit displayed by Ss under USD was, however, not as great as that found in Ss under BSD. At the same time it was noted that while USD Ss suffered some loss of motor coordination, the loss did not appear to be as severe as in BSD Ss. This evidence, while supporting Bures' contention that USD produces the same symptoms as BSD but to a lesser degree, suggests further that the learning deficit displayed by Ss under SD is related to a corresponding loss in motor coordination. Moreover, it was found that USD Ss on Task A demonstrated better learning ability than USD Ss on Task B. Since Tasks A and B were found to be of equal difficulty, differing only in their motor requirements, the latter finding offers further support to the argument that motor impairment due to SD interferes with the animal's acquisition of an avoidance response.

The finding that both Ipsilateral and Contralateral groups made fewer errors on Day 2 than on Day 1 is very interesting. This evidence is in direct opposition to the findings of Bures and Buresova (1960b) and Travis and Sparks (1963) who failed to report such savings in contralateral Ss. In the present experiment, Ss on Day 1 were restricted to

learning with only one hemisphere functional, the other being cortically depressed. In contralateral Ss, the hemisphere which was normal on Day 1 was then subjected to SD on Day 2. Therefore, if we can assume, as Bures does, a cortical locus for avoidance learning, then any learning which occurred in the normal hemisphere on Day 1 should be supressed on Day 2 when the normal hemisphere on Day 1 is then under SD. The rat on Day 2 should show no evidence of benefiting from training received on Day 1. Since, in effect, improvement was found from Day 1 to Day 2 in contralateral Ss (Table III), it can be argued that for learning these avoidance problems a functional cortex is apparently not essential. An explanation of such savings might be that subcortical mechanisms were involved in the original learning. Support for this explanation is found in the finding of Experiment I that animals under BSD showed evidence of learning Task A and also showed savings under BSD from Day 1 to Day 2 on Task A. Additional support for such an argument may be found in the studies of Schrier and Sperry, 1958; Downer, 1959; Glickstein and Sperry, 1960; Sperry, Myers, and Schrier, 1960 using hemidecorticate animals. These investigators demonstrated that animals restricted to the use of only one hemisphere could still control motor activity of both sides of their body. It was concluded that the integration of such bilateral control took place in the

subcortex. Although more research is needed in this area, on the basis of this study, it would seem that animals deprived of normal cortical function and presumably dependent upon subcortical mechanisms for learning were still able to learn a simple avoidance response (Task A), but were less successful in mastering the requirements of a more complex response (Task B).

CHAPTER VIII

SUMMARY

Experiments were conducted to evaluate the effects of bilateral and unilateral spreading cortical depression on avoidance learning in rats. Testing was carried out on two tasks (A and B) equated for difficulty in normal animals but differing in their respective motor requirements.

Experiment I was made up of a BSD Experimental group (N = 40), a Sham Control group (N = 40), and a Normal Control group (N = 10). Half the experimental and sham Ss were tested on Task A, the other half on Task B. Within each task condition, ten Ss received training prior to receiving bilateral spreading depression (BSD) while the remainder received training only under BSD. Ss in the Normal Control group were tested only on Task A and received no pre-operative practice. Testing sessions consisted of two 30 trial periods separated by 24 hours. On each trial, Ss were allowed five seconds in which to run from a start box to a goal box in order to avoid shock.

In Experiment II, 40 rats were equally divided into Task A-Ipsilateral, Task A-Contralateral, Task B-Ipsilateral, and Task B-Contralateral groups. All Ss received two 30 trial testing sessions on their respective tasks according to the procedures of Experiment I. The contralateral Ss were tested with SD applied to one hemisphere on Day 1 and

to the other hemisphere on Day 2. The ipsilateral Ss were tested with SD applied to the same hemisphere on both days.

The two experiments demonstrated that Ss under SD were seriously impaired in the avoidance learning problems. When compared to normals, both BSD and unilateral spreading depression (USD) Ss made considerably more errors in the two testing sessions. The learning demonstrated by Ss under USD was superior to that of Ss under BSD. Ss under BSD were, however, capable of some learning in the simple avoidance task (Task A). The fact that they were unable to show learning on Task B which for normal rats was as difficult as Task A, (the only difference being that Task B required a more precise motor response), suggests motor impairment induced by cortical SD is a major factor affecting the performance of a learned habit. This argument is supported by the observation that Ss under SD suffered a severe motor impairment characterized by a loss of coordination and a decrease in normal activity. The deficit displayed by BSD Ss was noticeably greater than that of USD Ss. Another finding of Experiment I was that prior training in the normal state facilitated learning under BSD. This evidence suggests that learning acquired in the normal state can be recalled in the cortically depressed state.

A major finding of Experiment II was that Ss who had received avoidance training under USD on Day 1

showed significant savings on Day 2 regardless of whether SD was applied to the same or opposite hemisphere to Day 1. This evidence suggests that the cortex is not essential for the carrying out of a simple conditioned avoidance response and that at least some avoidance learning can be controlled by subcortical mechanisms.

BIBLIOGRAPHY

Black, A. H. The extinction of avoidance responses under curare. J. comp. physiol. Psychol., 1958, 51 519-524.

Bromiley, R. B. Conditioned responses in a dog after removal of the neocortex. J. comp. physiol. Psychol., 1948, 41, 102-110.

Bures, J. Reversible decortication and behavior. In M. A. Brazier (Ed.) Conference on the Central Nervous System and Behavior. New York: Josiah Macey, Jr. Foundation, 1959, 207-248.

Bures, J. and Buresova, O. The use of Leao's spreading cortical depression in research on conditioned reflexes. EEG clin. Neurophysiol., 1960, Suppl., 359-376.(a).

Bures, J. and Buresova, O. The use of Leao's spreading depression in the study of interhemispheric transfer of memory traces. J. comp. physiol. Psychol., 1960, 53, 558-563.(b).

Bures, J. and Buresova, O. Activation of latent foci of spreading cortical depression in rats. J. Neurophysiol., 1960, 23, 225-236.(c).

Bures, J. and Buresova, O. Cortical spreading depression as a memory disturbing factor. J. comp. physiol. Psychol., 1963, 56, 268-272.

Bures, J., Buresova, O., Fifkova, E., Olds, I., Olds, S., and Travis, R. P. Spreading depression and subcortical drive centres. Physiol. Bohemoslov., Prague, 1961, 10, 321-330.

Bures, J., Buresova, O., Weiss, F., and Fifkova, E. Excitability changes in non-specific thalamic nuclei during cortical spreading depression in the rat. EEG clin. Neurophysiol., 1963, 15, 73-85.

Bures, J., Buresova, O., and Zahorva, A. Conditioned reflexes and Leao's spreading cortical depression. J. comp. physiol. Psychol., 1958, 51, 263-268.

Buresova, O., Bures, J., and Beran, V. A contribution to the problem of the dominant hemisphere in rats. Physiol. Bohemoslov., Prague, 1958, 7, 29-37.

Buresova, O., Bures, J., Fifkova, E., and Rudiger, W. The use of spreading cortical depression in analyzing the mechanism of operant behavior. In E. Gutmann, P. Hnik (Eds.) Central and Peripheral Mechanisms of Motor Functions. Prague: Collet (Czechoslovak. Acad. of Sciences), 1963, 151-155.

Culler, E., Coakley, S. D., Shurrager, P. S., and Ades, H. W. Differential effects of curare upon higher and lower levels of the central nervous system. Amer. J. Psychol., 1939, 56, 266-273.

Culler, E., and Mettler, F. A. Conditioned behavior in a decorticate dog. J. comp. Psychol., 1934, 18, 291-303.

Downer, J. L. Changes in visually guided behavior following midsaggital division of optic chiasma and corpus callosum in monkey (macaca mulatta). Brain, 1959, 82, 251-259.

French, J. O., Hernandez-Peon, R., and Livingston, R. B. Projections from cortex to cephalic brain stem (reticular formation) in monkey. J. Neurophysiol., 1955, 18, 74-95.

Gerall, A. A. and Obrist, P. A. Classical conditioning of the pupillary dilation response of normal and curarized rats. J. comp. physiol. Psychol., 1962, 55, 486-491.

Girden, E. Cerebral mechanisms in conditioning under curare. Amer. J. Psychol., 1940, 53, 397-406.

Girden, E. Generalized conditioned responses under curare and erythroidine. J. exp. Psychol., 1942, 31, 105-119.

Girden, E. Conditioned responses in curarized monkeys. Amer. J. Psychol., 1947, 60, 571-587.

Girden, E. The EEG in curarized mammals. J. Neurophysiol., 1948, 11, 169-173.

Girden, E. and Culler, E. Conditioned responses in curarized striate muscle in dogs. J. comp. Psychol., 1937, 23, 261-274.

Girden, E., Mettler, F. A., Finch, G., and Culler, E. Conditioned responses in a decorticate dog to acoustic, thermal, and tactile stimulation. J. comp. Psychol., 1936, 21, 367-385.

Glickstein, M. and Sperry, R. W. Intermanual somesthetic transfer in split-brain rhesus monkeys. J. comp. physiol. Psychol., 1960, 53, 322-327.

Grafstein, B. Mechanism of spreading cortical depression. J. Neurophysiol., 1956, 19, 154-157.(a)

Grafstein, B. Locus of propagation of spreading cortical depression. J. Neurophysiol., 1956, 19, 308-316.(b)

Harlow, H. F. The effects of incomplete curare paralysis upon formation and elicitation of conditioned responses in cats. J. genet. Psychol., 1940, 56 273-282.

Harlow, H. F. and Settlage, P. The effect of curarization of the forepart of the body upon the retention of conditioned responses in cats. J. comp. Psychol., 1939, 27, 45-49.

Harlow, H. F. and Stagner, R. Effect of complete striate muscle paralysis upon the learning process. J. exp. Psychol., 1933, 16, 283-294.

Hunter, W. S. A consideration of Lashley's theory of the equipotentiality of cerebral action. J. gen. Psychol., 1930, 3, 455-469.

Hunter, W. S. A kinesthetically controlled maze habit in the rat. Science, 1940, 91, 267-269.

Jasper, H. H. Diffuse projection systems: the integrative action of the thalamic reticular system. EEG clin. Neurophysiol., 1949, 1, 405-419.

Lashley, K. S. Brain Mechanisms and Intelligence: A Quantitative Study of Injuries to the Brain. Chicago: Univer. Chicago Press, 1929.

Lashley, K. S. and Ball, J. Spinal conduction and kinesthetic sensitivity in the maze habit. J. comp. Psychol., 1929, 9, 71-105.

Leao, A. A. P. Spreading depression of activity in the cerebral cortex. J. Neurophysiol., 1944, 7, 359-390.(a).

Leao, A. A. P. Pial circulation and spreading depression of activity in the cerebral cortex. J. Neurophysiol., 1944, 7, 391-396.(b).

Leao, A. A. P. and Morison, R. S. Propagation of spreading depression. J. Neurophysiol., 1945, 8, 33-45.

Magoun, H. W. Caudal and cephalic influences of the brain stem reticular formation. J. Neurophysiol., 1950, 30, 459-474.

Magoun, H. W. Physiological interrelationships between cortex and subcortical structures. EEG. clin. Neurophysiol., 1953, Suppl. No. 4, 163-167.

Marshall, W. H. Spreading depression of Leao. J. Neurophysiol., 1959, 39, 239-279.

McCawley, E. L. Central actions of curare on the central nervous system. J. Pharmacol., 1949, 129.

Morgan, C. T. and Stellar, E. Physiological Psychology. New York: McGraw-Hill, 1950.

Murlock, N. and Ward, A. A. Jr. The effects of curare on cortical activity. EEG. clin. Neurophysiol., 1961, 13, 60-67.

Myers, R. E. Function of the corpus callosum in interocular transfer. Brain, 1956, 79, 358-363.

Myers, R. E. Interhemispheric communication through the corpus callosum: Limitations under conditions of conflict. J. comp. physiol. Psychol., 1959, 52, 6-9.

Ochs, S. Effects of cortical spreading depression on direct cortical response studied with an island technique. J. Neurophysiol., 1958,21, 159-169.

Ochs, S. Curare and low blood pressure effects on direct cortical responses. Amer. J. Physiol., 1959, 197, 1136-1140.

Overton, D. A. State dependent or "dissociated" learning produced with Pentibarbital. J. comp. physiol.Psychol., 1964, 57, 3-12.

Penfield, W. Mechanisms of voluntary movement. Brain, 1954, 77, 1-17.

Pickett, J. M. Nonequipotential cortical function in maze learning. Amer. J. Psychol., 1952, 65, 177-195.

Pinto-Hamuy, T., Santibanez, H. G. and Rojas, A. Learning and retention of a visual conditioned response in neocorticate rats. J. comp. physiol. Psychol., 1963, 56, 19-24.

Saavedra, M. A., Garcia, E. and Pinto-Hamuy, T. Acquisition of auditory conditioned responses in normal and neocorticate rats. J. comp. physiol. Psychol., 1963, 56, 31-35.

Salamus, S., and Wright, S. Action of d-tubocurarine chloride on the central nervous system of the rat. Brit. J. Pharmacol., 1950, 5, 49-61.

Schrier, A. M. and Sperry, R. W. Visuo-motor integration in split brain cats. Science, 1959, 125, 1275-1276.

Siegel, S. Nonparametric Statistics for the Behavioral Sciences, New York: McGraw-Hill, 1956.

Sloan, N. and Jasper, H. The identity of spreading depression and suppression. EEG. clin. Neurophysiol., 1950, 2, 59-78.

Smith, S. M., Brown, H. O., Toman, J. E. P., and Goodman, L. The lack of cerebral effects of d-tubocurarine. Anesthesiology, 1947, 8, 1-14.

Solomon, R. L. and Turner, L. H. Discriminative classical conditioning in dogs paralyzed by curare can later control discriminative avoidance responses in the normal state. Psych. Rev., 1962, 69, 202-219.

Sperry, R. W. Preservation of high order function in isolated somatic cortex in collosum sectioned cat. J. Neurophysiol., 1959, 22, 78-87.

Sperry, R. W., Myers, R. E., and Schrier, A. M. Perceptual capacity of the isolated visual cortex in the cat. Quart. J. exp. Psychol., 1960, 12, 65-71.

Sperry, R. W., Stamm, J. S., and Miner, N. Relearning tests for interocular transfer following division of optic chiasma and corpus callosum in cats. J. comp. physiol. Psychol., 1956, 49, 529-533.

Stamm, J. S. and Sperry, R. W. Function of corpus callosum in contralateral transfer of somesthetic discrimination in cats. J. comp. physiol. Psychol., 1957, 50, 138-143.

Tapp, J. T. Reversible cortical depression and avoidance behavior in the rat. J. comp. physiol. Psychol., 1962, 55, 306-308.

Thompson, R. W. Transfer of avoidance learning between normal and functionally decorticate states. J. comp. physiol. Psychol., 1964, 3, 321-325.

Travis, R. P. The role of cortical spreading depression in relating the amount of avoidance training to inter-hemispher transfer. J. comp. physiol. Psychol., 1964, 57, 42-46.

Travis, R. P. Jr. and Sparks, D. L. The influence of uni-lateral and bilateral spreading depression during learning upon subsequent relearning. J. comp. physiol. Psychol., 1963, 56, 56-57.

Van Harreveld, A., Terres, G., and Dernburg, E. A. Cortical discontinuity and propagation of spreading depression. Amer. J. Physiol., 1956, 184, 233-238.

Weis, T. and Fifkova, E. Bioelectric activity in the thalamus and hypothalamus of rats during cortical spreading EEG depression. EEG. clin. Neurophysiol., 1961, 13, 734-744.

APPENDIX I

RAW DATA OF EXPERIMENT I

Task A - BSD, Experimentals

I Pre-op. Practice Group		Day 1	Day 2
Trials to Crit.	Errors to Crit.	Errors on 30 trial test session	Errors on 30 trial test session
12	3	19	10
14	4	8	3
13	4	3	6
15	5	13	9
17	6	21	11
13	4	13	12
14	5	11	0
13	4	11	16
11	2	12	6
17	7	23	15
II No Practice Group			
		17	26
		16	2
		13	21
		29	30
		8	4
		30	30
		29	30
		15	17
		30	28
		30	28

Task B - BSD, Experimentals

I Pre-op. Practice Group		Day 1	Day 2
Trials to Crit.	Errors to Crit.	Errors on 30 trial test session	Errors on 30 trial test session
18	9	30	30
12	2	26	14
18	9	30	30
14	4	26	21
10	1	30	24
13	3	30	30
15	4	30	30
13	4	30	30
13	3	30	30
13	4	30	30
II No Practice Group			
		30	25
		30	30
		30	19
		30	13
		30	30
		30	22
		30	30
		30	30
		30	30
		30	30

Task A - Sham Controls

I Pre-op. Practice Group		Day 1	Day 2
Trials to Crit.	Errors to Crit.	Errors on 30 trial test session	Errors on 30 trial test session
12	3	7	3
13	5	7	2
17	8	8	2
14	5	9	3
13	4	6	5
14	4	5	2
14	5	6	1
13	4	3	2
14	5	6	5
15	5	8	5
II No Practice Group			
		9	2
		8	3
		13	6
		8	3
		8	11
		10	3
		9	3
		8	3
		10	5
		11	7

Task B - Sham Controls

I Pre-op. Practice Group		Day 1	Day 2
Trials to Crit.	Errors to Crit.	Errors on 30 trial test session	Errors on 30 trial test session
15	6	8	2
12	3	12	3
14	5	12	7
16	7	9	6
15	6	6	3
15	6	9	6
13	4	10	6
14	4	10	1
14	5	6	4
16	5	12	5
II No Practice Group			
		6	3
		8	7
		10	4
		11	4
		15	5
		17	4
		12	6
		11	7
		13	3
		10	10

Task A - Normal Controls (No Practice)

Day 1	Day 2
Errors on 30 trial test session	Errors on 30 trial test session
5	2
8	3
7	0
3	4
6	3
4	0
3	1
4	4
7	2
7	3

APPENDIX II

RAW DATA OF EXPERIMENT II

Task A

Ipsilateral		Contralateral	
Day 1	Day 2	Day 1	Day 2
17	12	15	4
19	30	17	12
11	8	16	28
9	3	23	14
17	3	9	3
10	7	16	9
10	2	13	6
10	4	10	3
17	10	19	7
13	5	12	8

Task B

Ipsilateral		Contralateral	
Day 1	Day 2	Day 1	Day 2
12	6	29	15
22	28	10	11
18	8	21	11
25	18	19	11
22	7	14	11
19	2	24	10
20	14	19	15
22	16	18	8
13	5	15	11
22	15	17	14

NOTE:

1. Scores represent number of errors on 30 trial testing session.
2. The first five Ss in each group received USD applied to the right hemisphere on Day 1 and the left hemisphere on Day 2. The last five Ss received left USD on Day 1 and right USD on Day 2.