TEMPORAL PATTERNING OF ELECTROSHOCK AND RETROGRADE AMNESIA

by

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ABSTRACT

Treatments such as electroconvulsive shock (ECS) impair later performance of learned responses if presented shortly after learning, but not if delayed for a sufficient time. These gradients are frequently termed retrograde amnesia and interpreted as reflecting a memory consolidation process. The present investigation was concerned with the relationship of the length of the gradient produced by a single ECS to the duration of the memory consolidation process.

In the first experiment, rats were trained on a one-trial passive avoidance task and then presented with one of three ECS treatments. The treatments were five ECSs of 0.5 seconds duration spaced either 1 minute apart, 5 seconds apart, or in one continuous 2.5 second duration burst. The five ECSs spaced 1 minute apart were found to impair performance when presented immediately, 1 hour, 24 hours, and 48 hours but not 9 days after passive avoidance training. Five ECSs spaced 5 seconds apart impaired performance when presented immediately or 1 hour but not 24 hours after training. In contrast, the single 2.5 second duration ECS impaired performance when presented immediately but not 1 hour or longer after training. The impairments produced by the five ECSs spaced 1 minute apart at 1 hour and 24 hours were found to be permanent over 11 days.

The second experiment examined whether the long gradient produced by five ECSs spaced 1 minute apart was qualitatively different

from single ECS gradients. Five ECSs spaced 1 minute apart were presented following passive avoidance training to rats anesthetized with ether or sodium pentobarbital. In both cases, the series of ECSs still impaired performance when presented 1 or 24 hours but not 9 days following passive avoidance training. This finding does not provide support for a distinction between the gradients produced by a single ECS and a series of ECSs. These results were therefore interpreted as showing that the length of the gradient produced by a single ECS in a passive avoidance task is not a good estimate of the duration of time required for memory consolidation. In this passive avoidance task, consolidation appears to continue for a period of at least several days, while the gradient produced by a single ECS was less than 1 hour.

In the third experiment, rats were trained on a one-trial appetitive task and then presented with either five ECSs spaced 1 minute apart, or a single ECS of 0.5 seconds or 2.5 seconds duration. In contrast to the results in the passive avoidance task, the five ECSs spaced 1 minute apart did not produce a longer gradient than a single ECS of either 0.5 or 2.5 seconds duration. All three treatments impaired performance when presented 15 seconds but not 1 hour after training. Several possible explanations for the different effects of the series of ECSs in the two tasks are considered, and it is concluded that this difference probably reflects differences between the memory consolidation processes in the two tasks.

Supervisor_

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Memory Consolidation Theory

The possibility that memories require a period of time following learning in order to be properly stored was first suggested by Müller and Pilzecker (1900). They observed that humans learning a second list of words shortly after a first list showed impaired retention of the first list. As an explanation for the retroactive interference of the second list, they suggested that memories required a period of time following learning in order to be stored in their final, permanent form, and that any disturbance during this time might prevent the memories from becoming properly stored. They introduced the term "memory consolidation" to refer to the increasing resistance of the memories to disruption over time.

McDougall (1901) was the first to suggest that the notion of memory consolidation might account for the phenomenon of retrograde amnesia following head injury in humans. In many cases of head injury, patients report an inability to recall events which occurred during a period of time immediately preceding the injury (see Russell & Nathan, 1946 for an extensive examination of this problem). These memory losses often depend on the closeness of the event to the injury; memories of events which occurred closer to the injury are more likely to be lost than the memories of more distant events. McDougall explained the time-dependent character of these memory losses in terms

of a memory consolidation process. Presumably, memories which were lost were those which had been less completely consolidated.

Patients receiving electroconvulsive shock (ECS) therapy have also been observed to show a retrograde amnesia for antecedent events (Cronholm & Ottoson, 1963; Williams, 1950; Zubin & Barrera, 1941). In these studies, patients undergoing ECS therapy were presented with a set of stimuli at various intervals before ECS. In general, the results showed that retention of the stimuli presented closest to the ECS was most likely to be disrupted.

Retrograde amnesia has also been investigated in more controlled settings using experimental animals, usually rats or mice (see Lewis, 1969; McGaugh & Dawson, 1971; and Spevack & Suboski, 1969 for recent reviews of this work). In these studies, treatments such as ECS have generally been found to impair later performance of a learned response when presented soon after training, but not when delayed for a sufficient time. These impairments are usually found to be graded, with the shorter training-ECS delays producing larger impairments. Because of their similarity to the memory losses found with humans, these gradients are also usually interpreted as reflecting retrograde amnesias.

Experimental investigations of retrograde amnesia have largely been concerned with two issues. First, do these gradients actually reflect disturbances of a memory consolidation process? Second, assuming they do represent disturbances of memory consolidation what duration of time is required for the consolidation process to reach completion? Neither of these issues is completely resolved. The first issue has

received the most attention, and although a number of additional explanations have been offered for these gradients, there is still a substantial concensus in favor of the consolidation interpretation. With respect to the second issue, it has been a common practice to view the length of the gradient produced by ECS as an estimate of the duration of time required for memory consolidation to be completed, although recent findings suggest that this view may not be correct.

The present thesis is concerned with the relationship of the length of the amnesia gradient produced by ECS to the duration of the memory consolidation process. Before directly considering this question, the training procedures most widely used to investigate retrograde amnesia will be described, and an attempt will be made to show that the ECS gradients obtained with these procedures are best explained as disturbances of memory consolidation.

Rationale For Using One-Trial Learning Procedures to Investigate Retrograde Amnesia

Duncan (1949) provided the first demonstration of impaired performance of a learned response which depended on the time between training and ECS. He trained rats in a one-way avoidance apparatus, giving 1 trial per day. Following each daily trial, separate groups were given ECS either 20 sec., 40 sec., 60 sec., 4 min., 15 min., 1 hr., 4 hrs., or 14 hrs. later. Impaired acquisition was found in the groups given ECS at 15 minutes or less after each trial. The impairment was graded, with the shortest training-ECS delays showing the

slowest acquisition. Duncan attributed this ECS gradient to a disturbance of memory consolidation.

Coons and Miller (1960) replicated Duncan's experiment, and made the additional observation that the animals in the shortest training-ECS conditions tended to exhibit a great deal of emotional behaviour (defecation). On the basis of this observation, they suggested that ECS might have aversive effects which could interfere with the acquisition of the avoidance response. Since ECS was administered following entry into the non-shocked side, any aversive effects might have become conditioned to this side, thus decreasing the tendency to avoid. In order to test the possibility that ECS has aversive effects, they conducted a second experiment in which rats were first trained to run from a start box to a goal box to avoid shock. After acquisition of this response, the conditions were reversed so that the animals were now shocked in the goal box which previously had been "safe". ECS was administered to separate groups either 20 sec., 60 sec., or 1 hr. after the shock in the goal box. Coons and Miller found that the 20-second group learned to avoid the goal box faster than the 60-second group, and that both of these learned faster than the 1-hour group. This gradient is exactly the opposite of that which would be expected if ECS were disturbing memory consolidation. They suggested that ECS has aversive effects which may summate with the aversive effects of the footshock. They argued that the ECS gradient found by Duncan probably reflects a gradient of the aversive effects of ECS, and not a gradient of amnesia.

In another attack on the consolidation interpretation of Duncan's findings, Adams and Lewis (1962) showed that animals became immobile when placed in an apparatus in which they had received a series of ECSs. They suggested that repeated ECS treatments caused "fractional convulsions" to be conditioned to the place where ECS was administered. If fractional convulsions were conditioned to the training situation, they might be expected to inhibit later responding, and, in Duncan's experiment, such inhibition would appear as impaired acquisition. Convulsions would be more likely to become conditioned to the apparatus in the groups given ECS sooner after training, thereby accounting for the graded appearance of the ECS deficits. However, Spevack and Suboski (1969) have pointed out that Adams and Lewis' results can be explained simply by the aversive effects of a series of ECSs. Rats often become immobile when confronted with stimuli previously associated with aversive stimulation (Estes & Skinner, 1941). Moreover, there is no direct evidence supporting the claim that an ECS-produced convulsion can function as an unconditioned stimulus (Kent, Hawkins, & Sharpe, 1960).

To avoid the criticisms raised by Coons and Miller (1960) and Adams and Lewis (1962), experimenters began using one-trial passive avoidance training procedures (Hudson, 1950) to investigate memory consolidation. In these tasks, animals are punished, usually by footshock, for making a response such as stepping down from a platform, or pressing a bar. There are two advantages of one-trial passive avoidance tasks. First, since the animal learns to inhibit a

punished response, any aversive effects of ECS summate with the aversive effects of the shock to increase the latency to perform the response. However, if ECS produces a loss of memory for the footshock, the animal will continue to perform the response with a short latency on later testing. Secondly, the passive avoidance task, since it only involves a single training trial, has an additional advantage of only requiring the administration of a single ECS in contrast to Duncan's procedure in which ECS was administered following each daily trial. This is an advantage because a single ECS does not produce as strong aversive effects as multiple ECSs (Hudspeth, McGaugh, & Thompson, 1964).

A single ECS has generally been found to produce time-dependent impairments of passive avoidance responses (Chorover & Schiller, 1965; Heriot & Coleman, 1962; King, 1967; Kopp, Bohdenecky, & Jarvik, 1966; McGaugh, 1966; Miller, 1968; Quartermain, Paolino, & Miller, 1965; and others). For example, Heriot and Coleman (1962) trained rats to press a bar for food. After this response was acquired, a punishing shock was administered through the bar. Separate groups of rats received ECS either 1, 7, 26, 60 or 180 minutes after the punishment. A control group received only the punishing shock. Twenty-four hours later, the animals were returned to the bar and the number of presses in a 10-minute session was recorded. The punishment impaired the bar pressing response in the control group, but this impairment was attenuated by ECS in a graded fashion, the greatest attenuation appearing with the shortest ECS delays. The groups given ECS at 1, 7, 26, or 60 minutes after the punishment showed significantly less impairment than

the controls.

Recently, several other one-trial learning procedures have been used to investigate retrograde amnesia. One procedure, "appetitive" training, involves an increase in the strength of an appetitively motivated response as the result of a single experience with water. For example, Tenen (1965a) allowed thirsty rats to find water in a previously empty cul de sac. As a result of this single experience, the rats showed an increased tendency to return to the empty cul de sac on a later test session. Another procedure is "discriminated avoidance" training. In this paradigm two responses are available and one of them is followed by punishment. A single punishment is sufficient to establish a preference for the other response. For example, Pfingst and King (1969) trained hungry rats in a T-maze which had food available in both arms. After the rats were accustomed to running the maze for food, a punishing shock was administered upon entering one arm of the maze. As a result of this single punishment, the rats showed an increased preference for the other arm of the maze. Although aversive and amnesic effects are not opposed in these two tasks, it it generally possible to detect the presence of aversive effects. Providing the response baseline is sufficiently high before training, presenting ECS immediately after making the response in question should produce a decreased tendency to make this response on later testing. While this control is not completely satisfactory, a number of experiments have observed time-dependent effects of ECS which are not apparently due to aversive effects of ECS with both appetitive

(Pinel, 1969; Schiller & Chorover, 1967; Tenen, 1965a, 1965b) and discriminated avoidance procedures (Carew, 1970; Pfingst & King, 1969).

One-trial learning procedures have been popular not only because they permit an assessment of retrograde amnesia without the confounding factor of aversive effects, but also because they permit a clear determination of the training-ECS interval and consequently a more precise estimate of the duration of memory consolidation. This is an advantage over some other procedures in which a series of massed trials were used (Gerbrandt, Buresova, & Bures, 1966; Thompson & Pennington, 1957). Although only a single administration of ECS was required in these tasks, specification of the time during training at which memory consolidation began was not possible since consolidation may have started at any time during the training period.

It is now well established that time-dependent impairments of performance can be produced by ECS in a variety of training situations. Many other treatments have also been found to produce time-dependent deficits. These include ether and pentobarbital anesthesia (Pearlman, Sharpless, & Jarvik, 1961), CO_2 (Paolino, Quartermain, & Miller, 1966), cooling (Riccio, Hodges, & Randall, 1968), and cortical spreading depression (Bures & Buresova, 1963). These impairments are frequently interpreted as retrograde amnesia, their temporally graded nature being attributed to an underlying memory consolidation process.

Recently, a number of alternative explanations have also been offered for these gradients. Most of these alternative explanations are specifically directed at gradients obtained with a single ECS in

a passive avoidance training situation which is the most popular paradigm for investigating memory consolidation. These explanations, however, also apply in varying degrees to the gradients obtained with other treatments in other situations.

Alternatives to The Consolidation Interpretation of ECS Gradients

Pinel and Cooper (1966), while examining the strength of a passive avoidance response by testing different groups of rats at various times after training, found that passive avoidance improved over time. This improvement in passive avoidance over time has been referred to as the "incubation" effect and has been found in many (Irwin, Banuazizi, Kalsner, & Curtis, 1968; McGaugh, 1966) but not all (Bailey, Garman, & Cherkin, 1969; Pinel, 1970) passive avoidance tasks. Pinel and Cooper (1966) noted that the time course of improvement in passive avoidance corresponded to the length of their ECS gradient. They suggested that rather than disrupting a consolidation process, ECS could be viewed as simply halting the incubation of the response.

Spevack and Suboski (1969) have further elaborated this incubation hypothesis. They proposed that brief ECS gradients (less than 1 minute) reflect retrograde amnesia, while longer periods are due to the halting of incubation. They claimed that only brief gradients have been obtained in the other one-trial learning procedures, namely appetitive (Herz, 1969; Pinel, 1969; Schiller & Chorover, 1967) and discriminated avoidance (Carew, 1970; Pfingst & King, 1969), and they point out that incubation does not appear in these situations (Pinel,

1969; Suboski, Spevack, Litner, & Beaumaster, 1969). However, Spevack and Suboski's hypothesis is not consistent with all the available data. Tenen (1965b) has reported an ECS gradient of 3 hours in an appetitive task. In addition, several passive avoidance tasks in which long gradients were found do not show incubation (Bailey et al., 1969; Pinel, 1970).

Weiskrantz (1966) has proposed an alternative model for the effects of treatments such as ECS. He suggests that while very short ECS gradients (20 seconds) might reflect disturbances of consolidation, longer ECS gradients reflect impairments of memory retrieval. He assumes that memories continue to increase in strength over a period of weeks (in the sense of the neural signal underlying memory becoming stronger to produce a larger "signal to noise" ratio). He also assumes that treatments such as ECS introduce additional noise which prevents the recall of weaker traces by decreasing the signal to noise ratio. As the trace continues to increase in strength, it eventually stands out sufficiently from the noise level to be recalled. This model predicts that performance deficits produced by ECS will be temporary, disappearing with time. In fact, temporary deficits have been found by a number of investigators (e.g., Zinkin & Miller, 1967). However, this model also predicts that the time between training and testing should be more important than the interval between training and ECS, a finding that is not consistent with the available data.

Nielson (1968) attempted to explain ECS effects on performance through suggesting that ECS produces brain excitability changes.

These changes were thought to impair recall through a "state-dependent" mechanism. He suggested that performance is impaired for up to 4 days after ECS because the brain is in a different state than it was during training. Nielson provided some direct evidence for temporary changes in brain excitability as a result of ECS. He showed that the intensity of subcortical electrical stimulation necessary to elicit a conditioned response increased following ECS and then decreased over 4 days. Nielson's model, like Weiskrantz's, predicts that the impairment produced by ECS would only be temporary. However, Nielson makes no attempt to account for the time-dependent nature of these impairments.

Posluns and Vanderwolf (1970) have suggested that ECS has two effects: a disruption of consolidation and an impairment of response inhibition. These two effects are viewed as combining in tasks requiring immobility (such as the passive avoidance) to produce longer gradients than in tasks not requiring immobility. However, it is not clear from their model how a time-dependent effect (amnesia) can combine with a non-time-dependent effect (disinhibition) to produce a longer time-dependent effect.

In addition to the theoretical models which have been presented as alternatives to the consolidation hypothesis, there is also some recent evidence which is difficult to reconcile with the memory consolidation interpretation, but which has not yet given rise to adequate alternative explanations. Several studies have demonstrated impairments of performance which are not dependent on the time between

training and ECS, but rather on the time between some other event and ECS. Schneider and Sherman (1968) presented ECS to rats either 0.5 seconds, 30 seconds, or 6 hours after a single passive avoidance training trial. They found that performance of the passive avoidance response was impaired in the 0.5 second but not 30 second or 6 hour conditions. They found, however, that if an additional, noncontingent footshock was delivered 0.5 seconds before the 30 second or 6 hour ECS, performance was also impaired. Similar findings were reported by Misanin, Miller, and Lewis (1968). They established a conditioned emotional response (CER) to a light by pairing it with shock, and showed that if ECS given 24 hours after training was preceded by the light, performance of the CER was impaired. In both these cases, performance impairments were reported which were dependent not on the time between training and ECS, but rather on the time between some other event such as footshock or light and ECS. These findings can be described as reflecting the "reinstatement" of the ability of ECS to disrupt performance.

Schneider and Sherman (1968) contended that the pairing of ECS and footshock-produced arousal caused "after effects" which impaired the later performance of the passive avoidance response. Misanin et al. (1968), on the other hand, suggested that presentation of the light caused the memory to be recalled, and thus to enter a state in which it was more susceptible to disruption. Neither of these explanations is very explicit, and neither has been directly supported. Moreover, these phenomena are difficult to replicate. Banker, Hunt,

and Pagano (1969), Dawson and McGaugh (1969), Jamieson and Albert (1970), and Lee-Teng (1970a) have all failed to obtain these effects, the first two experiments being attempts at exact replication. However, Davis and Klinger (1969) have reported a similar finding using goldfish and a one-way avoidance training procedure. Re-exposure to the training apparatus 24 hours after training was found to allow a number of agents which would normally be ineffective at this time to impair performance. DeVietti and Larson (1971) have also reported a successful replication of this effect using rats and a CER procedure.

Another finding has recently been reported (Howard & Meyer, 1971; Robbins & Meyer, 1970) that bears substantial similarity to the "reinstatement effect". In these experiments, rats were trained on three discriminations, and given ECS following criterion on the third task. The results indicated that not only was performance of the third discrimination impaired by the ECS, but other discriminations which involved the same type of motivation as the third discrimination were also impaired, even when the other discrimination was the first learned. ECS seemed to disrupt a class of responses, impairment being dependent on the nature of the motivational state most recently aroused, not on the age of the memories.

The interpretation of the reinstatement effect is a very real problem. None of the explanations so far offered can adequately explain all the data including the difficulty with replication. These findings are difficult to reconcile with the consolidation interpretation of ECS gradients since these gradients can be obtained at

times when consolidation is presumably not occurring. However, it is important to point out that these data are not necessarily inconsistent with the notion that ECS presented shortly after training normally disrupts a memory consolidation process. It is possible, for example, that consolidated memories can become susceptible to disruption for some reason quite different from that responsible for most ECS gradients.

There is another finding which raises some question about the interpretation of ECS gradients. Chorover and DeLuca (1969) recently found that ECS did not produce seizure discharge in the cortex if it followed within 0.5 seconds after a footshock, but it did produce seizure discharge if delayed for 30 seconds or if ECS was not preceded by footshock. This finding indicates that the seizure produced by ECS is not of a constant form, but can be modified by prior presentation of footshock. Since footshock is generally used in passive avoidance training, this finding raises the possibility that ECS gradients might be due to a change in the seizure produced by ECS, rather than a change in the underlying consolidation process.

Processes other than memory consolidation have not been shown to adequately account for most ECS gradients, and, although some aspects of ECS gradients are not completely understood, a disturbance of memory consolidation still appears to be the best explanation. While there is no direct way of demonstrating that these gradients reflect memory consolidation, there is indirect support for the assumption that they reflect memory losses rather than some other disturbance. Such support comes from their similarity to human retrograde amnesia,

as well as from the fact that they are obtained in a variety of situations and with a number of different treatments. Assuming that the gradients reflect memory loss, the best explanation for their temporally graded character seems to be that they reflect an underlying consolidation process. However, because there is still some uncertainty as to whether the deficits at retest are on retention or performance, the term "ECS gradient" will be used instead of the more common "amnesia gradient" to refer to an impairment of a learned response which is produced by ECS and which depends, in a graded fashion, on the time between training and ECS. This is done to emphasize that "amnesia" is an interpretation of the gradient and not just a description.

ECS Gradients and the Duration of Memory Consolidation

This section will first consider the reasons why the lengths of ECS gradients have been interpreted as reflecting the duration of consolidation. Recent evidence will then be presented showing that the length of the gradient produced by ECS is not constant but depends to a limited extent on ECS current parameters. This limit might reflect the point at which the memory not yet consolidated is completely disturbed, or it may simply reflect the fact that a single ECS produces only a limited physiological disturbance. As a means of exploring this question, the possibility that a series of ECS treatments may produce a longer gradient than a single ECS will be examined.

The duration of time required for memory consolidation has frequently been estimated from the length of the ECS gradient. The

reason for choosing ECS for this purpose seems to be based, at least in part, on the view that ECS maximally disrupts the memory consolidation process. Such a view is supported by two widely held assumptions. First, consolidation has been assumed to involve patterned neural firing which persists for a period of time following learning and which is necessary for memories to be permanently stored (Gerard, 1955; Hebb, 1949; John, 1967). Second, ECS has been assumed to produce a maximal disturbance of neural firing providing that a "complete behavioral convulsion" is produced (Toman, Swinyard, & Goodman, 1946).

The most influential statement of the patterned firing hypothesis is that of Hebb (1949). Hebb suggested that memory was held initially as patterns of neural firing reverberating in closed circuits, and later in the form of altered structural relations between the neurons in the circuit. The reverberating activity was thought to continue until the permanent structural changes constituting the memory were formed and to be necessary for their formation. Since consolidation was assumed to involve patterns of neural firing, any treatment which produced a severe disruption of neural firing would be expected to produce a complete disruption of memories not yet consolidated and still held in the form of reverberating activity. Only those memories already permanently stored would remain intact.

ECS, providing the current intensity is sufficiently strong, typically produces a period of high voltage synchronous seizure discharge which appears throughout the brain and which is followed by a period of depression of neural activity. This massive disturbance

of neural activity should completely disrupt any ongoing patterns of neural firing, and therefore produce a complete cessation of the consolidation process. The memories still held in this form should be lost, while those which had already been permanently stored should remain intact. Accordingly, if memory consolidation is assumed to involve only this one phase, namely the transcribing of permanent memory from a labile memory trace consisting of patterned neural firing, the length of the ECS gradient should reflect the duration of time normally required for consolidation to reach completion.

The seizure discharge produced by ECS is usually accompanied by an overt behavioral convulsion in which all the skeletal muscles contract. The convulsion produced by a sufficiently strong ECS is highly stereo-typed, involving a brief tonic flexion of the body followed by a tonic extension. The tonic extension spreads caudally along the body, and hindlimb tonic extension has generally been taken to indicate a complete behavioral convulsion. The tonic extension phase is followed by a period of clonus and the postictal coma. Toman et al. (1946) observed that the form of the tonic convulsion did not vary with ECS parameters, and concluded that "the brain is maximally active during a tonic extensor seizure, and the discharge once initiated is independent of the stimulus" (p. 238). Largely on the basis of this conclusion the appearance of a tonic behavioral convulsion has been incorrectly assumed to reflect a maximal neural seizure. Recently, Chorover and DeLuca (1969) found that ECS following a footshock can produce a tonic convulsion without producing cortical seizure discharge.

Length of ECS Gradients

The lengths of ECS gradients have been found to vary greatly; gradients have been obtained which extend for 10 seconds (Chorover & Schiller, 1965), 20 seconds (Pfingst & King, 1969), 60 seconds (Quartermain et al., 1965), 1 hour (Heriot & Coleman, 1962), 3 hours (McGaugh, 1966), and even 6 hours (Kopp et al., 1966). A claim by Robustelli, Geller, and Jarvik (1970) to have demonstrated a gradient of 23 hours is invalid, since their effect was not shown to be time-dependent. The longest gradient demonstrated with a single ECS is 6 hours.

A number of variables have been found to affect the length of the ECS gradient. These include prior experience with the training apparatus (Miller, 1970), the level of footshock used (Ray & Bivens, 1968), the nature of the training procedure (Chorover & Schiller, 1966; Thompson & Pennington, 1957), and even the time of day (Stephens & McGaugh, 1968). The explanations for the effects of these treatments on the length of the ECS gradient have not been established. However, one possibility is that the duration of time required for consolidation is not constant but varies with both the nature of the memory and the state of the animal.

Another variable which has been found to affect the length of the ECS gradient is the nature of the ECS treatment. The disruptive effects of ECS have been found to vary depending on the manner in which ECS is administered. Ray and Barrett (1969) found that ECS across the eyes (via corneal electrodes) disrupted performance at

lower intensities than current across the ears. Likewise, King (1969) found that current passed between screw electrodes over the anterior cortex disrupted performance at lower intensities than that required across electrodes over the posterior cortex. In both these experiments, the amount of impairment was found to be more dependent on the mode of delivery than on the form of the behavioral convulsion, since the lower intensities of ECS did not produce tonic convulsions.

In addition to the importance of the locus of ECS administration, a number of experiments have found that the length of the ECS gradient depends on the current parameters, even when all parameters produce tonic convulsions. Both current intensity and duration have been found to affect the length of the gradient. Miller (1968) found that increasing the intensity of the current from 35 ma to 100 ma increased the length of the gradient from 5 minutes to 50 minutes. Most of the other experiments investigating the effect of varying ECS intensity have also found greater impairments with higher intensities (Dorfman & Jarvik, 1968; Hughes, Barrett, & Ray, 1970; Lee-Teng, 1969; Pagano, Bush, Martin, & Hunt, 1969). However, two studies (Quartermain et al., 1965; Weissman, 1963) failed to find an effect of ECS intensity. A possible reason for these two negative findings is that the effect of ECS intensity only increases up to an asymptote. This has been shown by the two studies which have systematically examined the effect of increasing ECS intensity (Dorfman & Jarvik, 1968; Lee-Teng, 1969). In both experiments, the amount of disturbance was found to increase with intensity up to a point, beyond which further increases in

intensity did not produce greater disturbances of performance.

The effect of ECS duration has not been found to be as significant as intensity. Dorfman and Jarvik (1968), Miller (1968), and Paolino, Quartermain, and Levy (1969) have all failed to detect any effect of varying ECS duration. In the most thorough of these studies, Dorfman and Jarvik (1968) found no differences over a very wide range of durations (0.1 to 3.0 seconds). On the other hand, positive results have been found by Alpern and McGaugh (1968). They found that a 0.2 second duration ECS impaired performance only when administered immediately after passive avoidance training, while longer duration ECSs (0.4 or 0.8 seconds) produced gradients of up to 3 hours. The difference between these results may somehow be tied to the fact that Alpern and McGaugh (1968) simultaneously varied both intensity and duration (using lower intensities with higher durations to keep the total amount of energy approximately equal).

The findings that ECS gradients vary in length depending on current parameters clearly show that the early view of ECS as a unitary treatment is incorrect. These findings also do not support a simple hypothesis of patterned neural firing, since the seizure produced by a low intensity ECS would be expected to disrupt such a process to the same degree as the seizure produced by a high intensity ECS. Consequently these findings necessitate a reconsideration of the relationship of the length of ECS gradients to the duration of memory consolidation

Two Possible Relationships Between the Length of ECS Gradients and the Duration of Memory Consolidation

There are two hypotheses concerning the duration of consolidation which follow from the findings of variations in ECS gradients with current parameters. One possibility is that memory consolidation is not completely disrupted by every ECS, but only by those of sufficiently high intensity. Lee-Teng (1969), and Dorfman and Jarvik (1968) both found that increasing ECS intensity only increased the amount of disturbance of performance up to an asymptote. This asymptote might reflect the point at which ECS disrupted all the memory not yet consolidated. If this possibility is correct, the length of the amnesia gradient produced by a high intensity ECS would correspond to the duration of time required for the consolidation of memory.

The other hypothesis is that consolidation continues for longer than the length of ECS gradients, even those obtained with a high intensity ECS. This is supported by a recent finding that flurothyl, a convulsant vapour, produces a much longer gradient than any which have been found with ECS (Cherkin, 1969). Cherkin, using chicks, found that a high concentration of flurothyl impaired performance of a passive avoidance response when administered 24 hours but not 48 hours after training. This very long gradient is of particular interest since it was obtained in the same situation in which Lee-Teng (1970b) found an asymptotic gradient of approximately one minute using ECS.

The asymptote found with ECS intensity (Dorfman & Jarvik, 1968; Lee-Teng, 1969) is not inconsistent with this latter hypothesis.

Instead of reflecting a complete disturbance of consolidation, the asymptote may reflect some characteristic of the seizure produced by ECS. There is evidence indicating that several aspects of the seizure produced by ECS increase with ECS intensity up to a certain level but beyond this level further increases in ECS intensity do not produce increments in the seizure. For example, Minz and Domino (1953) found that the duration of cortical seizure discharge produced by ECS in spinal cats increased with ECS intensity up to a point beyond which further increases in intensity did not result in longer durations of discharge. Zornetzer and McGaugh (1970) recently examined the seizure discharge produced by ECS in rats. Contrary to Minz and Domino (1953), they found that the duration of seizure discharge continued to increase with intensity. The reason for this difference is unclear. Zornetzer and McGaugh did, however, report that the frequency of the seizure discharge only increased up to a point. While more research needs to be done on the relationship of seizure discharge to ECS intensity, these findings indicate that some aspects of the seizure produced by ECS may not continue to increase with ECS intensity.

On the basis of the available evidence, it is not possible to decide with certainty whether the asymptote found with ECS intensity reflects a maximal disturbance of unconsolidated memory, or whether it reflects a failure of the neuronal disturbance produced by ECS to continue to increase with intensity. A possible way of clarifying this issue might be to examine whether increasing the neuronal disturbance produced by ECS will result in further increases in the amount of

impairment. A series of ECSs, each of which produces a separate seizure, should produce a greater disturbance than a single ECS.

Multiple ECSs

Several early experiments have observed time-dependent impairments using multiple ECSs which were of greater duration than any reported with a single ECS. Hunt and Brady (1951) and Brady (1952) found that a series of 21 ECSs presented three times per day impaired the performance of a CER acquired through eight trials spaced over a 31-day period, if the treatments were started 1 or 2 days after the last training trial. However, the effect of the ECSs was markedly reduced if the ECSs were delayed 30 days, and only slight impairment appeared if the delay was 90 days. Williams (1961, 1963) gave eight daily training trials on a conflict training procedure, in which rats were trained to cross an electrified grid to obtain water. A series of eight daily ECSs were found to eliminate grid hesitation, the measure of conflict, when started 1 day but not 13 days after the last training trial.

In both these sets of experiments, the training procedure involved many trials spaced over a period of days, creating difficulty for comparing these findings to those obtained with a single ECS following one trial learning. Nevertheless, these impairments are not generally interpreted as extensions of the sort of deficit produced by a single ECS (Hunt, 1965; McGaugh, 1968), but rather are usually distinguished on the basis of several supposedly apparent empirical differences.

There are three ways in which the deficits produced by single and multiple ECSs have been thought to differ. First, the impairment produced by multiple ECS has been reported to be only temporary (Brady, 1951), not appearing if testing was given 30 days after the series of ECSs instead of the usual 4 days. On the other hand, the performance deficits produced by a single ECS are usually permanent (Chevalier, 1965; Luttges & McGaugh, 1967). However, several studies have shown that responses disturbed by a single ECS may also reappear spontaneously over time (e.g., Pagano et al., 1969) or following a "reminder" (Lewis, Miller, & Misanin, 1968). Moreover, the deficit observed by Williams (1961) was apparently permanent for at least 52 days.

Second, multiple ECS was thought to selectively impair a CER and not to disturb other responses. Geller, Sidman, and Brady (1955) reported that multiple ECS impaired a CER, but not a bar press response for water even though the bar press response was acquired after the CER, i.e. the CER was selectively disturbed, not just the most recently acquired response. However, there is also some evidence showing that a single ECS may be more effective in disturbing CERs than other sorts of responses. Chorover and Schiller (1966) found that a single ECS produced longer gradients in a CER task than in two other variants of passive avoidance training procedures.

The third apparent difference between the effects of single and multiple ECS is the reported requirement of the overt convulsion for the disturbance produced by multiple but not by single ECS. Hunt, Jernberg, and Lawlor (1953) found that the series of 21 ECSs did not

produce impairment of a CER if they were presented while the animals were anesthetized with ether. Hunt and Beckwith (1955) found that presenting the ECSs under phenacemide but not diphenylhydantoin also blocked the effect of ECS. Both ether and phenacemide prevented the appearance of overt convulsions, while diphenylhydantoin prevented the appearance of a tonic extension but not a running seizure. McGaugh and Alpern (1966) showed that the impairment produced by a single ECS still appeared even though the ECS was given under ether anesthesia which blocked the overt convulsion. The same result was obtained by Essman (1968) using lidocaine and 2, 4, dichlorophenoxyacetic acid, and Weissman (1965) using phenobarbital, diphenylhydantoin, and phenacemide, all of which blocked the overt convulsion.

The gradients produced by single and multiple ECSs do not appear to differ qualitatively on the basis of either the permanence of the effect or the selective disturbance of CERs. On the other hand, the apparent differential requirement of the convulsion does provide support for the possibility that the gradients produced by single and multiple ECSs reflect different processes. However, closer examination of this latter difference reveals several factors which create difficulties for drawing a firm distinction. First, these data are from different experiments and it is impossible to be certain that the treatments (anticonvulsant drug doses and ECS levels) were comparable. This is a problem because it is possible that the seizure discharge produced by ECS was not blocked even though the overt convulsion was. Stille and Sayers (1967) examined a number of drugs which blocked the

overt convulsion (including phenacemide, diphenylhydantoin, and phenobarbital) and found that the cortical seizure discharge was unaffected by the drugs. The differential effects observed between single and multiple ECS when the convulsion was blocked, may reflect the seizure being blocked in the multiple, but not in the single ECS experiments. Whether or not the seizures were blocked probably depends on an interaction between the amount of drug and ECS parameters, and is difficult to evaluate in the absence of recordings. Second, both sets of experiments finding long gradients with multiple ECS treatments used training procedures involving many trials spaced over a period of days, creating difficulty for comparing these findings to those obtained with a single ECS following one-trial learning.

Summary and Rationale of the Present Investigation

The early view that the length of the ECS gradient corresponded to the duration of consolidation is no longer tenable. The length of the gradient produced by ECS has been found to vary with ECS parameters. Since the length of the ECS gradient is not constant, it is not meaningful to identify the duration of consolidation as the length of the gradient obtained with an arbitrary ECS. There remain two possibilities for the relation of the length of the ECS gradient to the duration of consolidation. One possibility is that the duration of consolidation corresponds not to the length of any arbitrary ECS gradient, but only to those obtained with an ECS of sufficient intensity. The second possibility is that memory consolidation continues for longer

than the length of even a high intensity ECS gradient.

Support for the first possibility comes primarily from the finding that ECS intensity only increases the ECS gradient to an asymptotic level. The latter possibility requires that this asymptote reflects the limited neuronal disturbance which a single ECS is capable of producing. There is evidence that al least some aspects of the seizure discharge produced by ECS reach an asymptote with increasing ECS intensity.

Tentative support for the second possibility is provided by several early studies (Brady, 1952; Williams, 1963) which have found gradients of much greater length than those obtained with a single ECS. However, inferences from these studies are complicated by the possibility that these longer gradients may reflect a different process than single ECS gradients. This possibility is suggested primarily by the apparent differential effects found when the convulsion was blocked.

The purpose of the present investigation is to determine whether a series of ECSs can produce gradients which do not reflect a qualitatively different process than gradients produced by a single ECS, but which are of greater length. If such gradients can be obtained, they should provide strong support for the possibility that memory consolidation continues for longer than the length of single ECS gradients.

Two possible ways of investigating the effects of a series of ECSs are to vary the number of ECSs or to keep the number constant but vary the spacings between them. This latter approach was used by Brady,

Hunt, and Geller (1954). They found that a series of 21 ECSs produced substantial impairment of a CER when spaced 1, 8, or 24 hours apart. However, when the 21 ECSs were spaced 30 minutes apart, less impairment of the CER was found and when spaced 1 second apart no impairment was observed. The advantage of this latter approach is that the effect of a series of ECSs can be examined without varying the amount of current administered to the animals in the various conditions. In addition, this latter approach appears to be better suited for the purpose of the present investigation, since by presenting a series of ECSs spaced closely together an effect only slightly greater than that produced by a single ECS may be obtained. As the spacings are gradually increased, the effect of the ECS may also gradually increase. The obtained results may therefore be comparable to those obtained with a single ECS except greater in magnitude.

The present experiments are divided into three parts. The first experiment investigated the effect of a series of ECSs on performance of a passive avoidance response acquired in a single trial. The purpose of this experiment was to determine whether the length of the gradient could be increased as the spacings between the ECSs were increased.

Since the first experiment showed that a longer gradient was produced by a series of spaced ECSs, a second experiment was conducted to determine whether this longer gradient would be attenuated as a result of blocking the behavioral convulsion. This experiment was included to evaluate the possibility that the series of ECSs produced

a qualitatively different effect than a single ECS.

A final experiment was included to determine whether the series of ECSs would also produce a prolonged gradient for an appetitive response acquired in a single trial.

EXPERIMENT 1: THE EFFECT OF A SERIES OF ECSS ON RETENTION OF A PASSIVE AVOIDANCE RESPONSE

The purpose of this first experiment was to ascertain whether a series of ECSs would produce a time-dependent impairment of performance which is of greater magnitude than those produced by a single ECS. In order to do this, 5 ECSs were presented, spaced 5 seconds apart or spaced 1 minute apart. The performance of these two groups was compared with that of a group which received only one ECS but of five times the duration. This group served as a control for any possible effect of the amount of current per se. A passive avoidance task was used since this is the type of learning procedure in which the effects of a single ECS have been most thoroughly documented.

Method

Subjects

Naive, male, hooded, 200-300 gm rats obtained from Quebec Breeding Farm (now Canadian Breeding Laboratories) served as subjects.

Surgery

The animal (under sodium pentobarbital anesthesia, 45 mg/kg) was placed in a stereotaxic head holder and its skull exposed. Two small holes were drilled bilaterally to receive the stainless-steel screw electrodes (0.8 mm diamter). These were positioned 1 mm posterior to the bregma and 4 mm lateral to the sagittal suture.

These screw electrodes, attached via connecting wires to pins,

penetrated just through the skull and were in contact with the dural surface. Two other screws were placed in the skull to provide additional support. After the supporting and electrode screws were in place, the skull was wiped dry and dental acrylic cement was applied to cover the screws and the wound area in such a way that only the pins protruded. Immediately following surgery, the animals were injected intraperitoneally with 40 mg/kg pentylenetetrazol and intramuscularly with 0.2 cc sodium penicillin (Crysticillin). Penicillin was also routinely given on the day following surgery and on the second from last pretraining day.

Apparatus

The training apparatus was a gray plywood alley 122 cm long, 11 cm wide, and 20 cm high. A stainless steel drinking spout similar to those used in the home cages, but covered with masking tape except for the tip, protruded for 2 cm through one end wall. A Physiological Electronics Inc. drinkometer was connected to the water spout and the grid floor below the spout. The tape on the drinking spout was to prevent the drinkometer from being activated except through the tip.

The grid floor consisted of 3 mm diameter brass rods spaced 13 mm apart and which extended for 18 cm, the last rod being joined to the hardware cloth which comprised the floor of the rest of the alley. The grid floor was connected to a constant current shock source which could deliver 2.0 ma, AC footshock.

ECS was a 60 Hz sine wave from an 840 volt transformer in series with a 44,000 ohm resistance. ECS was delivered from the transformer

via flexible wires terminating in butterfly clips which could be attached to the pin extensions of the screw electrodes.

In order to determine the ECS current intensity, as well as the impedance between the cortical screw electrodes, in a number of animals the voltage drop across either the 44,000 ohm resistance or the screw electrodes was measured during ECS with a Tektronics 565 Storage Oscilloscope. The impedance between the screw electrodes was found to vary between 1,500 and 3,000 ohms, and the current between 17.9 and 18.4 milliamps.

Training Procedure

The animals were housed in group cages and maintained on freely available water and Purina food chunks for at least a week before surgery. Following surgery, the animals were housed individually. Food continued to be freely available throughout the experiment, but on the second day after surgery, the water bottles were removed and 23-hour water deprivation was maintained for the rest of the experiment. The animals were briefly handled on the two days following surgery. On the third day after surgery, each animal, 21 to 23 hours water deprived, was placed in the apparatus for 10 minutes. Animals were always placed at the end opposite the drinking spout, facing the spout. One hour access to water was given in the home cages following each pretraining session. On the fourth day, the animals were placed in the apparatus for 5 minutes and on the fifth day, for two periods, first for 3 minutes and then, 1-2 hours later, for 2 minutes. On the sixth and seventh days (the last two pretraining days) the animals

were given 3 trials, each of 1 minute duration, separated by 30-45 minutes. This pretraining procedure was used because preliminary experiments showed it to be an efficient way of establishing a strong drinking response.

On the last two days of pretraining, the drinking latency was recorded with a stopwatch. Animals not drinking during each 1 minute trial were assigned a score of 60 seconds. Those with mean latencies over the three trials on the last pretraining day of greater than 23 seconds were discarded. Approximately 10 percent of the animals were excluded for this reason.

On the passive avoidance training day (eighth day following surgery), the animals were placed on a stand beside the apparatus and wires for administering the ECS were attached. After 1 minute of adaptation to the wires, all animals were given a single trial. Upon touching the spout the animals received one of several treatments depending on the experimental condition.

Experimental Conditions

This experiment involved a number of stages which were run sequentially but which will be presented together for simplicity. Animals were generally run in lots of 30, with each lot containing animals in 3 to 5 different treatment conditions. In order to minimize differences between treatment groups due to variation in lots of animals, the animals were assigned to groups on the basis of their pretraining latencies and all treatment groups were equated on this measure. There were generally between 5 and 7 animals per treatment

group (see Table 1 for the exact number of animals in each group).

The animals receiving passive avoidance training were all given a 1.0 second, 2.0 ma footshock upon touching the spout. In the immediate ECS condition, ECS onset coincided with the offset of the footshock and was administered in the alley. Delayed ECS groups were returned to their home cages following the footshock and were later given ECS on the feeding stand beside beside the alley.

Within this framework, the effects of three ECS treatments were examined. These were five ECSs each of 0.5 seconds duration spaced 5 seconds apart, five ECSs of 0.5 seconds duration spaced 1 minute apart, and one ECS of 2.5 seconds duration. The treatment conditions are presented in Table 1. The original design included only the immediate, 1 hour and 24 hour ECS delays. When it became apparent that the five ECSs spaced 1 minute apart impaired performance even when presented 24 hours after training, additional groups were added to evaluate whether this impairment was time-dependent.

In addition to these experimental groups, a number of control conditions were included. First, to confirm that the drinking response established during pretraining was stable over the duration of the experiment, two groups of animals were given neither footshock nor ECS on the training day, but were simply removed from the apparatus upon touching the water spout. One group was tested 48 hours after the training session and the other was tested at 11 days. To show that the passive avoidance response was also stable, two other groups of rats were given a footshock on the training day, but no ECS.

Table 1

The Number of Subjects in Each Treatment Condition in Experiment 1

Treatment	Time of[a] Testing	No[b] FS	FS Only	FS-ECS Delay				
				Immed.	1 hr.	24 hr.	48 hr.	9 days
No ECS	48 hrs.	N=5	N=10	-	-	-	-	-
No ECS	11 days	N=7	N=10	-	-	-	-	-
1 ECS, 2.5 sec. duration	48 hrs.	N=5	-	N=5	N=7	N=6	-	N=7
5 ECS, 5 sec. apart	48 hrs.	N=5	-	N=5	N=7	N=8	-	-
5 ECS, 1 min. apart	48 hrs.	N=5	-	N=8	N=7	N=7	N=11	N=8
5 ECS, 1 min. apart	11 days	-	-	-	N=6	N=5	-	-

[a]Following ECS, or training (in the no ECS conditions)

[b]FS = footshock (passive avoidance training)

These animals were tested either 48 hours or 11 days later.

Several other control conditions were included to evaluate alternatives to the interpretation that the ECS treatments were producing a disturbance of memory consolidation. First, three groups were included to determine whether any aversive effects of the ECS treatments were sufficiently strong to affect the drinking response. These received one of the three ECS treatments instead of footshock upon touching the water spout. Second, to examine whether the impairments produced by the five ECSs spaced 1 minute apart were permanent, two groups were given this treatment at 1 hour or 24 hours after training and tested 11 days following training.

Animals in all conditions received 1 hour access to water in their home cages on each day of the experiment. On days when ECS was administered, water was given starting 1 hour after ECS. If the animal received only training, water was given 1 hour after training. All animals were approximately 23 hours water deprived during testing.

Retention tests were given either 48 hours after ECS, 48 hours after training, or 11 days after training, depending on the experimental condition (Table 1). Testing for all groups took the form of three trials, 30-45 minutes apart, identical to those on the last pretraining days. Animals failing to drink during the 60 second test were removed and assigned a score of 60 seconds for that trial. The latencies of the drinking response on each of the three trials on the test day were averaged for each animal.

All statisical analyses were performed on the mean drinking

latency for each animal on the test day. These mean latencies did not satisfy the requirements for parametric analysis, since the maximum score of 60 was obtained by a number of animals. Consequently, Halperin's (1960) extension of the Mann-Whitney test to samples censored at the same fixed point was used.

Results

The drinking latencies for the control groups not receiving ECS are presented in Table 2. In the groups not receiving passive avoidance training, the drinking latencies of animals tested 48 hours after the training day did not differ from those of animals not tested until 11 days after the training day. These groups were therefore combined. With passive avoidance training the situation was similar. The drinking latencies of the groups receiving passive avoidance training (footshock) did not differ between the 48 hour and 11 day testings. At both times of testing the latencies were significantly longer than the latencies of the corresponding groups not receiving passive avoidance training. This finding indicates that the passive avoidance training procedure produced significant learning which was stable over 11 days. The groups receiving passive avoidance training were also combined.

Figure 1 illustrates the median drinking latencies for the groups receiving one of the ECS treatments following passive avoidance training. The drinking latency varies with both the type of ECS and the time of ECS administration. The single 2.5 second ECS significantly impaired passive avoidance performance when presented

Table 2

Drinking Latencies for the Groups in Experiment 1

Which Did Not Receive ECS

Group	N	Test Latency (seconds) Median	Range
FS test 48 hrs.	10	60.0[a]	15.6 - 60.0
FS test 11 days	10	60.0[b]	23.3 - 60.0
FS Combined[d]	20	60.0[c]	15.6 - 60.0
No FS test 48 hrs.	5	2.3	1.6 - 4.3
No FS test 11 days	7	2.0	2.0 - 4.0
No FS Combined[d]	12	2.0	1.6 - 4.3

[a]Significantly different from No FS test 48 hours ($p < .001$).

[b]Significantly different from No FS test 11 days ($p < .001$).

[c]Significantly different from Combined No FS group ($p < .001$).

[d]The difference between the 48 hour and 11 day testings is not significant.

immediately after training ($p < .001$), but not when presented 1 hour, 24 hours, or 9 days later (all comparisons are to the combined footshock-no ECS controls, one-tailed). The five ECSs spaced 5 seconds apart impaired performance when presented immediately ($p < .001$) or 1 hour ($p < .025$) after training, but not when presented at 24 hours. In contrast, the five ECSs spaced 1 minute apart impaired performance when presented immediately ($p < .001$), 1 hour ($p < .001$), 24 hours ($p < .01$) and 48 hours ($p < .02$) but not 9 days after training. These results show that each ECS treatment produced an impairment of performance which was time-dependent. These results also show that each of the ECS treatments produced a gradient of a different length. Medians, ranges and further statistical comparisons between these groups are presented in Appendix A.

None of the immediate ECS groups differed significantly from the combined No FS control. All other training-ECS groups were significantly different from the No FS controls.

The impairment of passive avoidance performance produced by the five ECSs spaced 1 minute apart was permanent over at least 11 days appearing when testing was given 11 days rather than 48 hours after training, in both the 1 hour (Median = 11.0, Range = 1.6 - 21.6; $p < .001$) and the 24 hour (Median = 40.6, Range = 9.3 - 44.0; $p < .025$) conditions (compared to the combined footshock-no ECS controls, one-tailed). These groups did not differ from the corresponding groups tested at 48 hours.

Finally, the three ECS treatments given to animals not receiving

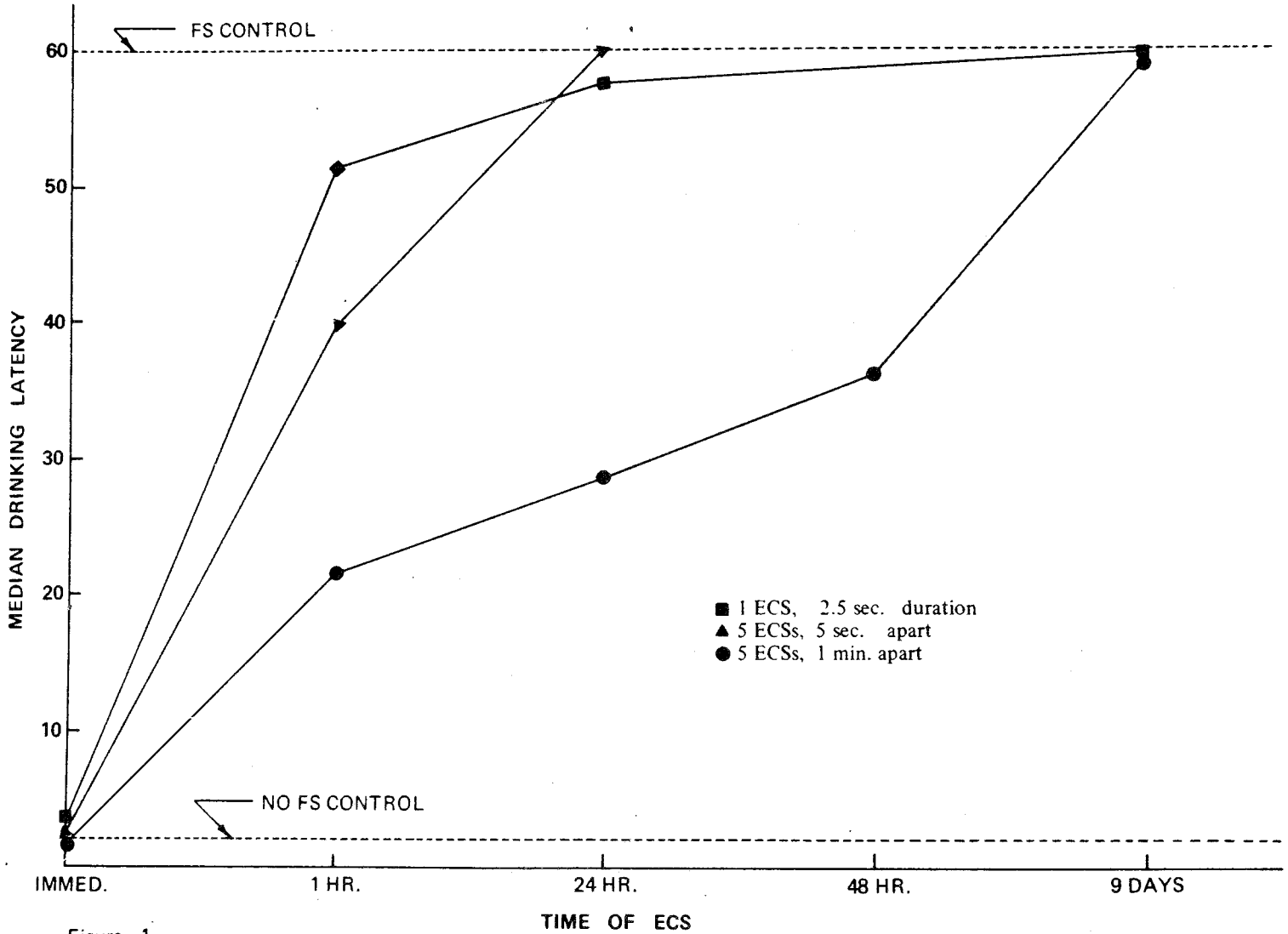

Figure 1.

Median Drinking Latencies for the Groups Receiving Passive Avoidance Training Followed by one of the ECS Treatments.

footshock did not produce increased latencies as compared to the combined no footshock-no ECS controls (2.5 second ECS: Median = 2.0; five ECSs, 5 seconds apart: Median = 2.3; five ECSs, 1 minute apart: Median = 2.3), showing that none of these treatments had a direct effect on the latency of the drinking response.

Behavioral Observations

The 2.5 second ECS consistently evoked a full tonic-clonic convulsion. The five ECSs spaced 5 seconds apart resulted in only one full convulsion; however, each current onset was marked by a slight jerk. The five ECSs spaced 1 minute apart produced a separate response to each stimulus: to the first a tonic-clonic convulsion, to the second and third usually an initial extension of the forelegs and opening of the mouth followed by a running seizure. The fourth and fifth ECSs produced similar effects, but were usually followed by more vigorous thrashing and running behavior. These were often accompanied by vocalization. It was frequently necessary to hold the animal by the tail during these seizures to prevent his running off the feeding stand.

Histology

Following testing, the animals were killed; the brains were removed and fixed in formal saline. No hemorrhages were observed on the cortex of any animal. Two brains from animals which had received the five ECSs spaced 1 minute apart were sectioned at 40 microns and every fifth section for 1.5 millimeters anterior and posterior to the electrodes was taken and stained with thionin. Microscopic examination

revealed no gross morphological damage.

Discussion

All three ECS treatments produced impairments of passive avoidance which were time-dependent. The time during which they were effective differed for each treatment; the single 2.5 second ECS produced a gradient of less than 1 hour, the five ECSs spaced 5 seconds apart a gradient of between 1 and 24 hours, and the five ECSs spaced 1 minute apart a gradient of between 48 hours and 9 days. The greater impairment produced by the longer spacings is similar to the findings reported by Brady et al. (1954), and the present results confirm the reports of Brady (1952) and Williams (1963) that a series of ECSs can produce a long gradient. In fact, the gradient of 48 hours produced by the five ECSs spaced 1 minute apart is far greater than the longest gradient (6 hours) which has been reported with a single ECS (Kopp et al., 1966).

A recent study (Weiner, 1970) has also found that a series of ECSs produced a longer gradient than a single ECS. Using a multi-trial shock-escape training procedure, he found that a series of four ECSs spaced 5 minutes apart impaired later performance when presented 5 or 30 minutes but not 24 hours after training. In contrast, a single ECS did not impair performance when presented at these times. However, Weiner also observed deficits when either the series of ECSs or a single ECS were presented 7 or 14 days after training, similar to the effects found with anticholinesterase drugs (see page 69).

EXPERIMENT 2: THE EFFECT OF PRESENTING A SERIES OF ECSS TO ANESTHETIZED ANIMALS

A distinction has been drawn between the impairments of learned responses produced by single and multiple ECSs on the basis of observations that these two treatments are differentially affected by anticonvulsant drugs (i.e., McGaugh, 1968). In the case of a single ECS, the disturbing effect on performance is supposedly unaffected by anticonvulsants (Essman, 1968; McGaugh & Alpern, 1966; Weissman, 1965). In contrast, multiple ECS does not appear to have any effect on performance when the convulsion is blocked (Hunt et al., 1953; Hunt & Beckwith, 1955). However, this distinction is based on comparisons between studies, and it is not possible to be sure that the levels of anesthesia in the two sets of experiments were comparable. Specifically, the differential effects of anticonvulsants may simply have been due to the use of different drug levels in the two sets of experiments. For example, neural seizure discharge may be necessary for both effects, but only the drug levels used in the multiple ECS studies might have been sufficient to block the seizure discharge. It is difficult to compare the drug and ECS levels used in these experiments, and none of these experiments have included electrical recordings to confirm that the anticonvulsant drugs blocked the seizure discharge as well as the overt convulsion.

The present experiment examined the effect of blocking the

convulsion on the impairment of passive avoidance performance produced by five ECSs spaced 1 minute apart. In order to examine the possibility that the reported differential effects of anticonvulsants might be an artifact of different drug levels, the present experiment used two drugs, both of which block the overt convusion, but which were found, through preliminary recordings, to have quite different effects on cortical seizure discharge. One drug, ether (diethyl ether), was found to have little effect on seizure discharge, while the other drug, sodium pentobarbital, was found to block or at least greatly attenuate seizure discharge (representative records are presented in Appendix C).

Method

Seventy-seven male rats of the same age and strain as those in Experiment 1 were used here.

The apparatus, surgical and training procedures were identical to those used in Experiment 1.

The design of the experiment was as follows. Ten groups, all of which received passive avoidance training, were tested. Three groups were given the five ECSs spaced 1 minute apart while anesthetized with ether (Anesthetic ether, Squibb) at 1 hour (n = 6), 24 hours (n = 10), or 9 days (n = 10) after training. Three other groups received five ECSs spaced 1 minute apart under sodium pentobarbital anesthesia (Nembutal, Abbott Laboratories) at 1 hour (n = 7), 24 hours (n = 9), or 9 days (n = 6).

To control for effects of ether or sodium pentobarbital alone

on performance two groups were not given ECS but only ether (n = 6) or sodium pentobarbital (n = 7) anesthesia 1 hour after training. Two additional groups were included; these received the 2.5 second duration ECS under ether (n = 8) or sodium pentobarbital (n = 8) 24 hours after training. These groups were included simply to examine the possibility that ether or sodium pentobarbital might somehow augment the effect of ECS on performance.

Sodium pentobarbital anesthesia was produced by injecting, intraperitoneally, 45 mg/kg of sodium pentobarbital 15 minutes prior to ECS administration. A standard method was used to administer ether anesthesia. First, the animals were placed in a 3-litre ether saturated jar for approximately 45 seconds (until the righting reflex was lost). They were then removed and the ECS clips were attached. Fifteen seconds after being removed from the jar ether was again administered (a small vial containing ether-saturated cotton was fitted over the snout). This second administration of ether was necessary to maintain anesthesia. The vial was only kept over the snout for 15 seconds, and 15 seconds was always allowed to elapse between administration of ether and ECS. Additional 15-second administrations of ether were included between each ECS. All administrations of ether took the same form whether ECS was administered or not.

All analyses, as in the previous experiment, were performed on the mean drinking latencies for each animal on the test day, using Halperin's (1960) extension of the Mann-Whitney test.

Results

The five ECSs spaced 1 minute apart, when presented to animals anesthetized with ether or sodium pentobarbital, produced the same impairments of passive avoidance performance as had been found in the previous experiment using unanesthetized animals (Figure 2). The five ECSs spaced 1 minute apart under ether produced significantly lower drinking latencies than the ether only controls when administered at 1 hour ($p < .02$) and 24 hours ($p < .02$), but not at 9 days after training. Similarly, the five ECSs spaced 1 minute apart under sodium pentobarbital produced significantly lower drinking latencies when administered at 1 hour ($p < .01$) or 24 hours ($p < .01$), but not at 9 days after training. Additional comparisons between these groups are presented in Appendix B.

There were no differences between the ether and sodium pentobarbital groups under any of the conditions. Moreover, none of these groups differed significantly from the corresponding groups in Experiment 1.

The 2.5 second ECS at 24 hours under ether (Median = 60.0, Range = 12.0 - 60.0) or sodium pentobarbital (Median = 60.0, Range = 26.6 - 60.0) did not significantly impair performance relative to the groups receiving only ether or sodium pentobarbital. This finding suggests that anesthesia did not augment the effect of ECS on performance.

Behavioral Observations

Both ether and sodium pentobarbital blocked the overt convulsion

to the extent that the response to ECS was only a brief jerk or stiffening during current presentation. Two animals receiving ECS under ether showed evidence of a motor seizure during ECS and were discarded from the experiment.

Discussion

Ether and sodium pentobarbital anesthesia, both of which blocked overt signs of a seizure, did not attenuate the effect of a series of five ECSs. Under both drugs, the five ECSs spaced 1 minute apart impaired performance of the passive avoidance response to the same degree as had been found with unanesthetized animals in the previous experiment.

The present findings are in contrast to those of Hunt, et al., (1953) and Hunt and Beckwith (1955) who found that blocking the behavioral convulsion also blocked the effect of a series of ECSs on performance. Conversely, the present findings are consistent with the results usually obtained with a single ECS (Essman, 1968; McGaugh & Alpern, 1966; Weissman, 1965). These results, therefore, do not support the hypothesis that the gradient produced by the series of ECSs spaced 1 minute apart represents a different process than that responsible for single ECS gradients.

McGaugh and Zornetzer (1970) have recently reported evidence which also questions the distinction between single and multiple ECS gradients. In their experiment, mice trained in a passive avoidance task were later given ECS either while anesthetized with ether or while unanesthetized. They found the ECS gradient was blocked if a

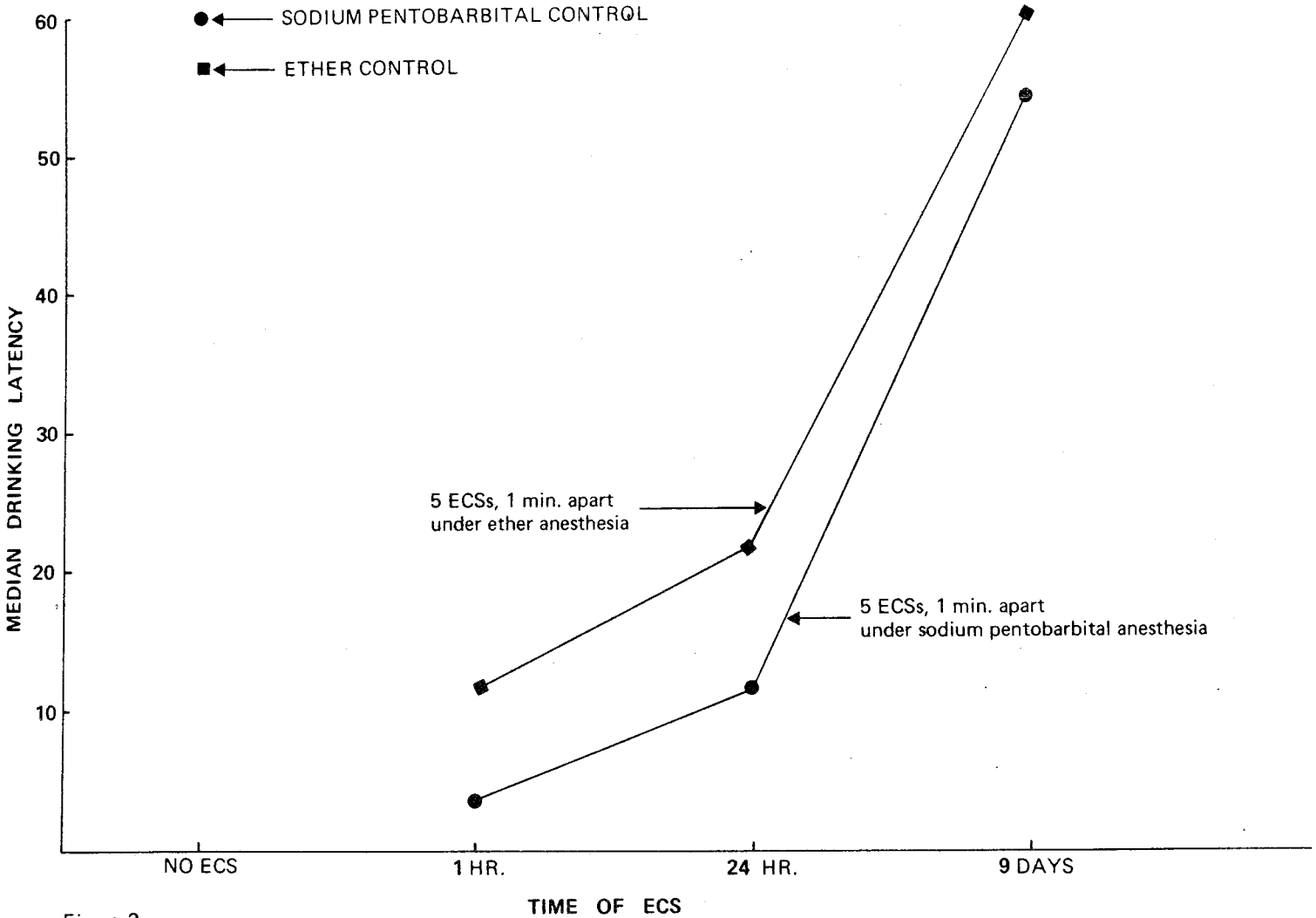

Figure 2.

Median Drinking Latencies for the Groups Receiving 5 ECS'S Spaced 1 Minute apart Under Ether or Sodium Pentobarbital Anesthesia Following Passive Avoidance Training.

low intensity ECS and high concentration of ether were used, but not when either a high intensity ECS or low concentration of ether was used. It now appears that both single and multiple ECS gradients may or may not be blocked by anticonvulsant drugs.

The reason why anticonvulsant drugs in some cases block the ECS gradient is presumably because in those cases some aspect of the neuronal disturbance which is normally produced by ECS and which is necessary to produce the ECS gradient is blocked. McGaugh and Zornetzer (1970) reported that animals administered low intensity ECS under high concentrations of ether did not exhibit any disturbance of cortical neuronal activity as a result of the ECS, although cortical seizures were observed in those animals administered either high intensity ECS or low intensity ECS under low concentrations of ether. Therefore the condition in which they observed the ECS gradient to be blocked corresponded to the condition in which ECS did not produce a detectable neuronal disturbance.

In this experiment the ECS gradient appeared under all conditions, presumably because the ECS intensity was high relative to the levels of drugs used. Nevertheless, in the case of sodium pentobarbital anesthesia an interesting result was obtained. The level of sodium pentobarbital anesthesia used here was found to block or greatly attenuate the cortical seizure discharge normally produced by ECS suggesting that seizure discharge, at least in the cortex, is not necessary for the gradient produced by the series of ECSs. This result is not inconsistent with the results of McGaugh and Zornetzer

(1970), since in the present experiment other aspects of the neuronal disturbance such as the period of post-ictal depression were not blocked by the drug. More research is needed to clarify which aspects of the disturbance produced by ECS are responsible for producing the ECS gradient.

EXPERIMENT 3: EFFECT OF A SERIES OF ECSS ON AN APPETITIVE RESPONSE ACQUIRED IN A SINGLE TRIAL

The first two experiments established that five ECSs spaced 1 minute apart produced a longer gradient in a passive avoidance task than has been found with a single ECS. This gradient does not appear to differ except in magnitude from those produced by a single ECS. The present experiment examined the generality of this increased impairment by using a one-trial appetitive training procedure. This task involves a quite different response (approach) than the previous passive avoidance task (inhibition of approach).

Method

One hundred and thirteen rats of the same strain as in Experiments 1 and 2 were used in this experiment. Of these, 40 were excluded for failing to lick the spout with 10 minutes on the training day, leaving only 73 subjects.

The apparatus and surgical procedures were identical to those of Experiments 1 and 2. The animals also received the same treatment as those in the previous experiments until the first pretraining day. On this day, they were each placed in the alley for 10 minutes with the water spout empty. The number of licks at the empty spout was recorded on the drinkometer. For the next two days the identical procedure was followed. The animals received 1 hour of access to water in their home cages following removal from the alley.

On the fourth day, appetitive training was carried out. The animals were placed in the alley as usual, only on this day the water spout contained water. Those animals finding the water were allowed to drink for 15 seconds. They were then removed and the wires for administering ECS were attached. Three ECS treatments were used in this experiment. Two of these, five ECSs spaced 1 minute apart and one 2.5 second duration ECS were the same as those used in the previous experiments. A third ECS treatment, one 0.5 second duration ECS, was also examined.

Separate groups received the five ECSs spaced 1 minute apart at 15 seconds (n = 5) or 1 hour (n = 7) following training. Similarly, the one ECS of 2.5 seconds duration was given at 15 seconds (n = 5) and 1 hour (n = 9) after training. The one ECS of 0.5 seconds duration was also given at 15 seconds (n = 5) and 1 hour (n = 8). The 15 second delay was required to attach the wires. ECS was always given on a feeding stand beside the alley. The 1 hour delay animals were returned to their home cages for the hour.

To determine the aversiveness of the three ECS treatments, three control groups (n = 5 each) were not given water on the training day but were removed 15 seconds after first touching the spout (the time allowed the other groups for drinking) and were given one of the three ECS treatments 15 seconds later.

Two groups were not given ECS: one received water (appetitive training, n = 10), the other (n = 9) did not. All animals were given 1 hour access to water in their home cages either 1 hour after ECS or

1 hour after the training trial.

For all groups, testing was given 48 hours after training, and consisted of recording the number of licks at the empty spout in a 10 minute session as on pretraining days. Comparisons between groups were made on the basis of the number of licks on the test day. The data were analysed using non-parametric tests (Mann-Whitney U).

Results

The appetitive training procedure produced an increase in the amount of licking at the empty spout on the test day. The group receiving water (appetitive training) on the training day (Median = 95, Range = 4 - 266) showed a significantly ($U = 7$, $p < .001$) greater number of licks at the spout on the test day than the group not given water (Median = 8, Range = 1 - 24). This result demonstrates that the drinking experience on the training day produced substantial learning of the presence of water in the spout.

Results for the groups receiving appetitive training followed by one of the ECS treatments are presented in Table 3. No differences were observed between the three ECS treatments. Each ECS treatment produced significant impairment of the appetitive response when presented 15 seconds after training, but not when presented 1 hour after training.

Inspection of the median number of licks for the three groups receiving ECS at 1 hour after training shows that these scores are somewhat lower than the median for the no ECS, H_2O control. This difference might suggest that some impairment was still produced by

Table 3

Number of Licks at the Empty Water Spout on the Test Day for the Groups in Experiment 3

Type of ECS	Time of ECS	N	Median	Range	U^a	U^b
No ECS H_2O Control	-	10	95	4 - 266	7***	-
No ECS No H_2O Control	-	9	8	1 - 24	-	7***
1 ECS, 0.5 sec. duration	15 sec.	5	22	17 - 42	4**	9*
	1 hr.	8	53	22 - 254	1***	35
1 ECS, 2.5 sec. duration	15 sec.	5	43	14 - 68	4**	10*
	1 hr.	9	54	30 - 248	0***	43
5 ECSs, 1 min. apart	15 sec.	5	39	11 - 48	4**	9*
	1 hr.	7	62	17 - 234	3**	32

[a]Compared to No ECS, No H_2O Control

[b]Compared to No ECS, H_2O Control

* $p < .05$ (one-tailed)

** $p < .01$ (one-tailed)

*** $p < .001$ (one-tailed)

the ECS treatments when administered at this time, even though the individual comparisons to the no ECS, H_2O control were not significant. However, this possibility is not supported by the finding that even when combined, these three groups do not differ from the no ECS, H_2O control ($U = 110$, n.s.).

All groups receiving appetitive training followed by ECS showed significantly higher numbers of licks at the empty spout than the control group which had not received appetitive training (Table 3). These differences suggest that significant retention of the appetitive training was present in every group.

The results from the control groups receiving only ECS on the training day indicate that the impaired performance found with the five ECSs spaced 1 minute apart and the 2.5 second duration ECS were not due to punishment. ECS alone did not affect the number of licks (relative to the control group not receiving appetitive training) in the five ECSs spaced 1 minute apart condition (Median = 4, Range = 0 - 76, $U = 19$) or the 2.5 second duration ECS condition (Median = 0, Range = 0 - 106, $U = 17$). If ECS was aversive, it would be expected to decrease the frequency of a response which preceded it. Because these two treatments did not decrease the number of licks, the impairment found in the groups given these treatments 15 seconds after appetitive training cannot be explained by punishment. On the other hand, the single 0.5 second duration ECS produced a significantly lower number of licks (Median = 1, Range = 0 - 2, $U = 3$; $p < .01$), indicating that administration of this treatment may have been aversive.

Discussion

In the appetitive task used here, there were no differences between the lengths of the gradients produced by the three ECS treatments. The five ECSs spaced 1 minute apart produced only a slight impairment of performance when presented 15 seconds after training, and no impairment when presented 1 hour after training. It should be pointed out that the subjects receiving appetitive training showed considerable variability in the response measure used in this task. It is possible that this variability masked small differences between the ECS treatments, although it is quite unlikely that differences of the magnitude observed in Experiments 1 and 2 would not have been detected.

Because of the low response level in the groups not given appetitive training, the adequacy of the controls for aversive effects of ECS might be questioned. Aversive effects might not have been detected because the animals were already responding at such a low rate. However, in the case of the five ECSs spaced 1 minute apart and the single 2.5 second duration ECS, no aversive effects were detected in Experiment 1 (or in this experiment) and it therefore appears safe to interpret the deficits produced by these treatments in this appetitive task as amnesia. On the other hand, the single 0.5 second duration ECS, which was not examined in Experiment 1, appeared to produce significant aversive effects in this appetitive task. Therefore it is possible that the gradient produced by this treatment was due to punishment, not amnesia.

The length of the gradients produced by each of the ECS treatments

in this task, between 15 seconds and 1 hour, is shorter than the 3 hours found by Tenen (1965b) but is somewhat comparable to those reported by Pinel (1969), 1 minute, and Herz (1969), 20 seconds, all of whom used a single ECS and appetitive tasks. However, this gradient is much shorter than the gradient found with five ECSs spaced 1 minute apart in the passive avoidance task (Experiments 1 and 2). It should be noted that even if all three gradients are interpreted as reflecting aversive effects, the main conclusion of this experiment, namely that the series of ECSs did not produce a longer gradient than a single ECS in this task, is unchanged.

The failure to observe variability in the lengths of the gradients produced by the different ECS treatments is not inconsistent with available data. No study has previously examined the effects of varying ECS parameters in a one-trial appetitive task, although a comparison of the results of Pinel (1969) and Tenen (1965b) suggests that ECS intensity may affect the length of the gradient in an appetitive task. Pinel used 60 ma. and found a gradient of 1 minute; Tenen used 150 ma. and found a gradient of 3 hours.

The present results are consistent with those of Sidman et al., (1955) who found that a series of ECSs impaired the performance of a CER, but not a more recently acquired appetitive response (bar press). The results of Sidman et al. (1955) and of the present experiment suggest that a series of ECSs is more effective in producing a long gradient when a shock-motivated inhibitory response is used than when an appetitive response is used.

GENERAL DISCUSSION

Three issues will be discussed here: first, the possibility that memory consolidation is relatively brief and is maximally disturbed by a single ECS; second, possible explanations for the different results obtained in the passive avoidance and appetitive tasks; and third, the effect of ECS on the consolidation process.

ECS Gradients and the Duration of Memory Consolidation

The duration of time required for memory consolidation is usually estimated from the length of the gradients produced by treatments such as ECS. Because the lengths of such gradients vary somewhat with treatment parameters, it seems probable that consolidation continues for at least as long as the length of the longest gradient which can be obtained. However, there is another possibility, namely that memory consolidation is maximally disturbed by a single ECS, and that longer gradients obtained with other treatments reflect some other process. The view that a single ECS maximally disrupts the consolidation process originated from dual process theories of consolidation (e.g., Hebb, 1949), in which ECS was assumed to disrupt patterned neural firing. While such theories are seriously questioned by the finding of variability in ECS gradients with ECS parameters, the view that single ECS gradients reflect a maximal disturbance of consolidation has lingered on. Consolidation is generally assumed to

be complete within a few minutes or at longest a few hours after training, corresponding to the length of ECS gradients.

The present investigation attempted to show that gradients could be produced with a series of ECSs which were longer than single ECS gradients but not otherwise different. Such a finding would be inconsistent with the position that single ECS gradients reflect a maximal disruption of memory consolidation, and would instead suggest that memory consolidation continues for a longer period than is estimated from the length of single ECS gradients.

In Experiment 1, in which a passive avoidance training procedure was used, a series of five ECSs spaced 1 minute apart produced a gradient of 48 hours, substantially longer than the gradient (less than 1 hour) produced by a single ECS. This gradient is also of greater length than the longest gradient (6 hours) which has previously been reported with a single ECS (Kopp et al., 1966).

While the gradient of 48 hours found in Experiment 1 is considerably longer than the duration of time that memory consolidation is generally assumed to continue for, it is comparable in length to the gradients found in two other recent studies. Buresova and Bures (1971) found that KCl applied to the cortex of rats for a prolonged period impaired later performance of a shock-motivated pattern discrimination when administered 24 hours but not 14 days following training. Similarly, Cherkin (1969) showed that high concentrations of flurothyl impaired passive avoidance behavior in chicks when presented 24 hours but not 48 hours after training.

Experiment 2 examined whether the long gradient found with the series of ECSs in Experiment 1 was qualitatively different from single ECS gradients. The primary support for a distinction between single and multiple ECS gradients comes from studies showing that anticonvulsant drugs blocked the gradients produced by multiple ECSs (Hunt et al., 1953; Hunt & Beckwith, 1955) but not single ECSs (Essman, 1968; McGaugh & Alpern, 1966; Weissman, 1965). In Experiment 2 a series of five ECSs spaced 1 minute apart were still found to produce a long gradient when presented under ether or sodium pentobarbital anesthesia, both of which blocked overt signs of a convulsion. This finding is opposite to the results previously reported with multiple ECSs, but similar to those found with single ECSs. Therefore it is probable that the differences previously found between the effects of anticonvulsant drugs on single and multiple ECS gradients were due to different drug levels or ECS parameters in the different experiments, and not due to a qualitative difference between the gradients produced by single and multiple ECSs.

The results of a recent study by McGaugh and Zornetzer (1970) also indicate that the differences reported earlier between single and multiple ECS gradients are probably invalid. They found that single ECS gradients could be blocked by ether anesthesia if a low intensity ECS and a high concentration of ether were used, but not if either a high intensity ECS or low concentration of ether were used. The findings of McGaugh and Zornetzer (1970) together with the results of Experiment 2 suggest that a distinction between

single and multiple ECS gradients on the basis of supposed differential effects of anticonvulsant drugs is incorrect.

A qualitative distinction between single and multiple ECS gradients is not supported by the effects of anticonvulsant drugs, nor by any other evidence. The longer gradients produced by a series of ECSs likely reflect a greater disturbance of the same underlying process which is disturbed by a single ECS. Assuming that ECS gradients reflect the disturbance of memory consolidation, the conclusion follows from the results of Experiments 1 and 2 that the consolidation process for this passive avoidance response continues for at least 48 hours.

While a series of ECSs produced a long gradient in the passive avoidance task, it did not produce a longer gradient than a single ECS (of 0.5 or 2.5 seconds duration) in a one trial appetitive task. All three treatments produced only a slight impairment at 15 seconds, and none at 1 hour. This finding has a number of possible implications which will be considered in the next section.

Passive Avoidance - Appetitive Task Differences

The finding that a series of ECSs spaced 1 minute apart produced gradients of quite different lengths in the passive avoidance and appetitive tasks is not predicted by consolidation theory, but is from two other positions (Posluns & Vanderwolf, 1970; Spevack & Suboski, 1969) both of which do not view ECS gradients in passive avoidance tasks as evidence for memory consolidation. Nevertheless,

this finding is not inconsistent with consolidation theory, and can be explained from a consolidation position in two ways. These four viewpoints will be considered here.

Incubation theory, as presented by Spevack and Suboski (1969), holds that ECS gradients in passive avoidance tasks reflect the halting of an incubation process, not interference with memory consolidation. The strength of the learned response is assumed to increase (incubate) following training, and ECS is assumed to halt this incubation process. On the other hand, brief ECS gradients (less than 1 minute) which have been found in appetitive and discriminated avoidance tasks were assumed to reflect a true interference with consolidation since the learned responses in these tasks do not appear to incubate. According to their theory, a short gradient would be predicted in the appetitive task since responses in such tasks presumably do not incubate. The passive avoidance task might be expected to yield a longer gradient since the learned response might undergo a long incubation period.

However, there is some direct evidence against Spevack and Suboski's incubation hypothesis. Tenen (1966b) found a long gradient (3 hours) in a one trial appetitive task. In addition, Bailey et al. (1970) and Pinel (1970) found no evidence for incubation in passive avoidance tasks which yielded long gradients. Incubation theory has one other serious flaw; because ECS is assumed to halt the incubation process the theory is incapable of explaining variability in ECS gradients with current parameters. Therefore, while

incubation theory predicts different length gradients in passive avoidance and appetitive situations, as presently formulated it is inadequate to account for the present findings.

Posluns and Vanderwolf (1970) suggested that ECS has two effects: first, it impairs inhibition of responding; and second, if presented within a few seconds of training it can disrupt memory consolidation. They suggest that ECS produces long gradients in tasks where response inhibition facilitates the learned response, such as the passive avoidance, but not in tasks where response inhibition is incompatible with the learned response, such as appetitive tasks. However, their theory evades the critical question of how a time-dependent effect (amnesia) combines with the non-time-dependent effect (impairment of response inhibition) to produce a longer gradient. Therefore this theory is not able to account for the time dependence of the long gradient found here with a series of ECSs.

It should be pointed out the theory of Posluns and Vanderwolf offers an interesting explanation for the failure of the series of ECSs to produce a longer gradient than a single ECS in the appetitive task. They have shown that a series of ECSs produces greater impairment of response inhibition than a single ECS (Posluns & Vanderwolf, 1970). If a series of ECSs also produces a greater disturbance of memory consolidation than a single ECS, these two effects could have cancelled one another so that both treatments produced gradients of similar length.

From a consolidation point of view, the most likely explanation for the different length gradients produced by a series of ECSs in the two tasks is that the consolidation processes require different times to reach completion. Several studies have shown that the length of the gradient produced by ECS depends on a number of variables which do not likely affect the neural disturbance produced by ECS, but which may exert their effect through "speeding up" the consolidation process. These variables include prior experience with the training apparatus (Miller, 1970), the level of footshock used (Ray & Bivens, 1968), and the nature of the training procedure (Chorover & Schiller, 1966). Some characteristics of the appetitive training used here may have been more conducive to rapid consolidation than the characteristics of the passive avoidance training procedure.

There is a second explanation for the passive avoidance-appetitive difference which is also consistent with consolidation theory. Rather than reflecting differences in the duration of the two consolidation processes, the different length gradients might reflect differences in the susceptibility of the two consolidation processes to disruption. A series of ECSs might produce a more pronounced disturbance of the consolidating passive avoidance memory than of the consolidating appetitive memory, even though the two processes might require similar times to reach completion. This could happen for example if the two memories were being stored in different areas of the brain, which were differentially affected by ECS. There is evidence that limbic structures may be involved in the consolidation of passive avoidance responses

(Barcik, 1969; Kesner & Doty, 1968) and limbic areas are known to be highly susceptible to seizures. Unfortunately the brain structures involved in the storage of appetitive responses have not as yet been investigated.

The failure of the series of ECSs spaced 1 minute apart to produce a longer gradient than a single ECS in the one trial appetitive task suggests that the process being disturbed in this task differs from that responsible for the long gradient in the passive avoidance task. While the nature of the differences between these processes is still unclear, it should be emphasized that this finding does not imply that ECS gradients in the passive avoidance task do not reflect memory consolidation. On the contrary, the explanation for the gradient in the passive avoidance task which is consistent with the largest amount of data is that of a disruption of memory consolidation. The different findings obtained with a series of ECSs in the passive avoidance and appetitive tasks may indicate either that the consolidation processes in the two tasks require different times to reach completion or that somewhat different changes are involved in consolidation of the two memories.

The gradient of 48 hours found in Experiment 1 does not appear to be qualitatively different from shorter gradients produced by a single ECS, nor does it appear to be due to some process other than a disturbance of memory consolidation. Instead, this long gradient seems to be best explained by the assumption that memory consolidation continues for at least 48 hours after training in this passive

avoidance task. Although 48 hours is considerably longer than consolidation has been generally assumed to continue for, it appears necessary to conclude that the consolidation process may in some cases continue for at least this length of time. However, it is still necessary to explain why even though consolidation continues for this long, a single ECS may still produce only a brief gradient. In order to clarify the mechanism responsible for variations in ECS gradients with ECS parameters, the next section examines the nature of the effect of ECS on the consolidation process.

The Effect of ECS on the Consolidation Process

The early view of memory consolidation was a process by which information was transformed from a labile memory trace to a stable permanent memory (for example, Hebb, 1949). The initial labile trace was assumed to involve patterned neural firing, the continuation of which was necessary for the permanent memory to be established. Consequently, ECS was assumed to stop the consolidation process, since by disrupting the patterned firing further memory was prevented from entering the stable state. Accordingly, the amount of memory available to the animal at the time of testing corresponded to the amount which had entered the permanent state at the time ECS was administered.

However, the early dual trace theory of consolidation cannot adequately explain why, for example, the different intensities of ECS produce different length gradients. Clearly both intensities cannot be viewed as stopping the consolidation process. An alternative

formulation of the effect of ECS on the consolidation process is required to account for this variability in the ECS gradient with ECS parameters.

A second finding which is also difficult to reconcile with the early dual process model is that the gradients produced by ECS are occasionally only temporary and if the time of testing is delayed the deficit disappears (e.g., Pagano et al., 1969). If ECS had stopped the consolidation process through disturbing patterned firing, the strength of the permanent memory should have remained constant over time. Therefore this finding also necessitates the formulation of an alternative view of the effect of ECS on the consolidation process. Two approaches to this problem will be considered here.

One approach which has been taken to account for these two findings is to postulate that the memory trace continues to change over a long period and that ECS produces a disturbance which interferes with recall of the memory (Deutsch, 1971; Weiskrantz, 1966). Weiskrantz (1966) assumes that memory increases over a prolonged period of time, in the sense of achieving a greater signal to noise ratio (this time-dependent change in the memory might be termed consolidation although Weiskrantz does not refer to it as such). He suggests that ECS does not disrupt this process (except when administered within a few seconds of training), but rather adds more noise to the system. This noise impairs the recall of recent memories but not older memories which have a greater signal to noise ratio. Weiskrantz's model can explain the different gradients produced by

different intensities of ECS through assuming that the high intensity ECS produces more noise. His model also predicts that ECS gradients would only be temporary, since the signal to noise ratio continues to increase even after ECS is administered, so that when the signal becomes sufficiently strong, retention appears.

There is one major inadequacy of Weiskrantz's model. It implies that the critical variable determining whether ECS will impair performance is the time between training and testing, and not the time between training and ECS. This follows because the two processes, noise produced by ECS and increasing strength of the memory signal, are assumed to be independent. In other words, ECS is not assumed to directly affect the consolidation process at the time of administration; rather this process continues at its normal rate after ECS. Since the strength of the memory signal is assumed to only depend on the time between training and testing, and since the noise produced by ECS is independent of the time of ECS administration, presenting ECS between training and testing should have the same effect regardless of how long after training it is administered, so long as the time between training and testing is held constant. However, contrary to this prediction, the time between training and ECS has been found to be much more important than the time between training and testing; in fact, most experiments demonstrating ECS gradients keep the training-testing interval roughly constant. For example, in Experiment 1 the series of ECSs impaired performance when administered at 1 or 24 hours but not 9 days after training even when the training-

testing interval was held constant at 11 days.

Deutsch (1971) has proposed a similar model to Weiskrantz's although it is not simply intended to explain ECS gradients, but rather is also concerned with the nature of memory storage. Deutsch assumes that memory is stored in the form of decreased synaptic resistance in some cholinergic synaptic pathways. He assumes the resistance continues to decrease for a number of days after training (again, this time-dependent change in the memory is not specifically referred to as consolidation by Deutsch). As evidence for this change in resistance, he has shown that anticholinesterase drugs impair performance of several tasks when administered 5 or more days after training, but not when administered 1 or 3 days after training. Deutsch assumes that since the anticholinesterase drugs decrease the rate of breakdown of acetylcholine they will facilitate synaptic transmission. Since synaptic resistance is assumed to be high 1 or 3 days after training, the synaptic facilitation will facilitate (or at least not impair) recall. However, at 5 or more days after training, synaptic resistance is lower, and the synaptic facilitation produced by the drug will produce too great a facilitation of synaptic transmission resulting in a blockage of recall. As additional support for his theory Deutsch has shown that anticholinergic drugs which impair synaptic transmission through blocking the effect of acetylcholine produce the opposite effects of anticholinesterase drugs, namely an impairment of performance when administered at 1 or 3 days and no effect when administered at 5 or more days.

In Deutsch's experiments the drugs are assumed to produce a temporary impairment of recall, and the treatment-testing interval is kept constant at 24 hours, a time when acetylcholine or cholinesterase activity is presumably still being affected by the injected substance. While Deutsch's data support the notion that memory continues to change over a period of days following training, and also suggest that a change in cholinergic synapses is involved in the memory, his model does not directly bear on the interpretation of gradients produced by other treatments such ECS. If an attempt is made to extend Deutsch's model to other gradients, it will fail to adequately explain the findings, because Deutsch's model, like Weiskrantz's, involves two independent processes; the drug is not assumed to affect the change in synaptic resistance at the time of administration.

The second approach which has been taken to explain findings such as temporary gradients as well as variability in the ECS gradient with ECS parameters is to assume that ECS directly affects the consolidation process at the time of administration, and that the effect of ECS is not necessarily to stop consolidation, but simply to slow its rate. While several versions of this slowing hypothesis have been presented (Albert, 1966; Cherkin, 1969; McGaugh & Dawson, 1971) all basically assume that consolidation may continue after ECS and that the degree to which consolidation continues depends on the ECS parameters. The slowing hypothesis can be seen most clearly by contrasting it with the early view that ECS stopped consolidation. When ECS is assumed to stop consolidation, the amount of memory present at

testing would just correspond to the amount already consolidated when ECS was administered. According to the slowing hypothesis, some memory would also be consolidated after ECS administration. Therefore, at testing the animal would have available the amount of memory consolidated before ECS as well as the amount of memory consolidated after ECS.

A slowing hypothesis can explain temporary gradients since in some cases sufficient consolidation may continue following ECS to produce increased retention when tested at longer times after training than when tested soon after training. It can also explain the variability in the length of ECS gradients with ECS parameters since a weaker ECS treatment might only slightly retard consolidation so that a substantial amount of memory would be consolidated after ECS. A stronger ECS treatment on the other hand would slow consolidation to a greater degree, so that little memory would be consolidated after ECS and consequently, retention would be poorer.

Mah, Albert, and Jamieson (1972) have recently provided support for a slowing hypothesis. They found that a single ECS given 5 minutes after passive avoidance training produced only a slight impairment. However, when a second ECS was presented at 1 or 2 but not 3 hours after a first ECS at 5 minutes an additional deficit was observed. The time-dependent effect of the second ECS appears to reflect a disturbance of consolidation, indicating that consolidation was continuing following the first ECS.

The slowing hypothesis does not suffer from the problem of models

such as Weiskrantz's (1966), since the effect of ECS is assumed to be directly on the consolidation process. Because ECS is assumed to affect consolidation at the time of administration, the training-ECS interval should be a more important determinant of the effect of ECS than the training-testing interval, a prediction consistent with most available evidence. One slight difficulty with the slowing hypothesis is that some authors (e.g., McGaugh & Dawson, 1971) interpret it as predicting that consolidation would eventually reach completion in all groups regardless of the training-ECS interval. While this prediction does not necessarily follow (for example, if slowed sufficiently no further consolidation might take place), several modifications of the slowing hypothesis can eliminate this interpretation. For example, McGaugh and Dawson (1971) postulate that ECS affects a short term memory stage, and the amount of short term memory determines the level that long term memory eventually reaches. Another modification which eliminates this interpretation would be to assume that ECS blocked some of the memory outright, and that only part of it continued to consolidate. Nevertheless, some form of a slowing hypothesis appears to be the best explanation for the effects of ECS on the consolidation process.

Clearly, a revised view of the consolidation process is required. Rather than simply involving the formation of a permanent memory from neural firing patterns, consolidation must involve a gradual change in the stored representation of the memory which may continue for at least several days after training. Instead of being stopped by ECS, this

process may be slowed to varying degrees by different ECS treatments. However, two major questions are still unanswered. First, does consolidation in at least some cases continue indefinitely, so that the memory never reaches a permanent state? Second, is consolidation in some cases completed more quickly (within a few minutes or hours) than in other cases, as is suggested by the results of Experiment 3? Further research should provide answers to these questions as well as the more basic question of the nature of the mechanism which underly the storage of information in the brain.

CONCLUSIONS

A series of five ECSs produced greater impairment of a learned passive avoidance response when spaced 1 minute apart than when spaced 5 seconds apart or when presented in one continuous burst. In all three cases the impairment was time-dependent; the length of the gradient varying from less than 1 hour (single ECS) to between 2 and 9 days (five ECSs spaced 1 minute apart). The impairment produced by the five ECSs spaced 1 minute apart was permanent over 11 days, and was not attenuated when the ECSs were presented while the animals were anesthetized with ether or sodium pentobarbital, both of which blocked the convulsion normally produced by ECS. This long gradient does not appear to be qualitatively different from those found with a single ECS, and because of its greater length, probably reflects a greater disturbance of the same process response for single ECS gradients. The most likely explanation for this process is a time-dependent change in the memory (consolidation). Therefore, in this passive avoidance task the memory consolidation process appears to continue for at least several days.

In a one trial appetitive task, the five ECSs spaced 1 minute apart did not produce a longer gradient than a single ECS. This finding might indicate that the consolidation processes in the two tasks are qualitatively different and are differentially disturbed by ECS, or that the consolidation process is completed more quickly in the appetitive task.

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APPENDICES

Appendix Page

APPENDIX A

Additional Statistical Analyses on Data From Experiment 1

1. Data for experimental groups

Type of ECS	Time of ECS	N	Median	Range
5 ECSs spaced 1 minute apart	immed.	8	2.2	1.6 - 3.0
	1 hr.	7	21.3	2.3 - 23.6
	24 hrs.	7	28.3	4.0 - 60.0
	48 hrs.	11	36.0	9.0 - 60.0
	9 days	8	59.3	31.6 - 60.0
5 ECSs spaced 5 sec. apart	immed.	5	2.3	2.0 - 2.6
	1 hr.	7	39.6	19.0 - 60.0
	24 hrs.	8	60.0	33.6 - 60.0
1 ECS, 2.5 sec. duration	immed.	5	3.3	2.3 - 3.6
	1 hr.	7	51.3	2.0 - 60.0
	24 hrs.	6	57.8	31.6 - 60.0
	9 days	7	60.0	42.3 - 60.0

Appendix A (continued).

2. Comparison between ECS delays for each ECS condition. All analyses are done with Halperin's (1960) extension of the Mann-Whitney test. Probabilities are one-tailed since the longer ECS delays were not expected to produce greater impairments than the shorter delays.

5 ECSs 1 minute apart

	Immed.	1 hr.	24 hrs.	48 hrs.
1 hr.	.01			
24 hrs.	.001	n.s.		
48 hrs.	.001	.05	n.s.	
9 days	.001	.001	.02	.05

5 ECSs 5 seconds apart

	Immed.	1 hr.
1 hr.	.001	
24 hrs.	.001	.02

1 ECS, 2.5 seconds duration

	Immed.	1 hr.	24 hrs.
1 hr.	.001		
24 hrs.	.001	n.s.	
9 days	.001	n.s.	n.s.

Appendix A (continued).

3. Comparisons between ECS treatments for each ECS delay. All analyses are done with Halperin's (1960) extension of the Mann-Whitney test. Probabilities are one-tailed since the greater spacings were expected to produce greater impairments.

Immediate ECS

	1 ECS, 2.5 sec. duration	5 ECSs 5 sec. apart
5 ECSs 5 sec. apart	.01	
5 ECSs 1 min. apart	.02	n.s.

1 hour ECS

	1 ECS, 2.5 sec. duration	5 ECSs 5 sec. apart
5 ECSs 5 sec. apart	.025	
5 ECSs 1 min. apart	.001	.02

24 hour ECS

	1 ECS, 2.5 sec. duration	5 ECSs 5 sec. apart
5 ECSs 5 sec. apart	n.s.	
5 ECSs 1 min. apatt	.03	.01

9 day ECS

	1 ECS, 2.5 sec. duration
5 ECSs 1 min. apart	n.s.

APPENDIX B

Additional Statistical Analyses on Data from Experiment 2

1. Data for groups receiving 5 ECSs spaced 1 minute apart

Drug	Time of ECS	N	Median	Range
Ether	1 hr.	6	11.5	1.6 - 60.0
	24 hrs.	10	21.6	5.3 - 60.0
	9 days	10	60.0	42.6 - 60.0
Sodium Pentobarbital	1 hr.	7	3.3	2.0 - 15.6
	24 hrs.	9	11.3	1.6 - 60.0
	9 days	6	54.8	25.6 - 60.0

Appendix B (continued).

2. Comparisons between ECS delays for each drug condition. All analyses are done with Halperin's (1960) extension of the Mann-Whitney test. Probabilities are one-tailed since the longer ECS delays were not expected to produce greater impairments than the shorter delays.

5 ECSs 1 minute apart under ether

	1 hour	24 hours
24 hours	n.s.	
9 days	.01	.01

5 ECSs 1 minute apart under sodium pentobarbital

	1 hour	24 hours
24 hours	n.s.	
9 days	.001	.05

APPENDIX C

Electrical Recordings Under Ether and Sodium Pentobarbital Anesthesia

The recordings presented here were obtained in a preliminary investigation; these animals did not undergo training. Levels of anesthesia are the same as those used in Experiment 2.

The recordings were taken from a bipolar electrode consisting of twisted stainless steel wires, insulated except for 0.5 mm from the tip, with a 1.0 mm tip separation. The electrode was aimed at the cortex 2.0 mm anterior to bregma, 2.0 mm lateral to the saggital suture and 1.0 mm below the dural surface, and was implanted along with ECS screw electrodes identical to those used in Experiments 1, 2, and 3. All the recordings presented here are from animals in which the electrodes were confirmed histologically, to be in the cortex.

Recordings were taken about a week after surgery. Seizure discharge was recorded on an EEG channel of a Grass Model 7 polygraph. During passage of the ECS current, the polygraph leads were shorted to ground, and immediately after current offset were switched back to the animal. Two to three seconds were lost to "blocking". Recordings were taken with a time constant of 0.3, chart speed of 2.5 mm per second, and sensitivity of 150 microvolts per cm.

In both Figure 1 and Figure 2 the recordings from 10 different

Appendix C (continued).

animals are presented. The first segment starts with the onset of the current while the animal is unanesthetized. The first few seconds of the records contain stimulus artifacts indicating ECS onset and offset (the first two spikes) and the switching of the recording leads back to the animal from ground (third spike). The second segment is a recording taken 3 minutes after the ECS. The third segment starts with onset of an ECS given the following day while the animal was anesthetized with sodium pentobarbital (Figure 1) or ether (Figure 2). Again the three stimulus artifacts can be seen at the beginning of each record. The last segment is taken shortly (usually 10-30 seconds) before ECS, i.e., while the animal is anesthetized.

The unanesthetized (normal) seizure discharge was typically of high amplitude (300-500 microvolts) and lasted between 15 and 18 seconds. The frequency was highly variable between animals, although it typically slowed toward the end of the seizure to 2 or 3 per second. In some cases a few high amplitude spikes appeared after the seizure discharge had ended (animals 1, 2, 6, 7, 15). These may have been movement artifacts. In some records, the post seizure depression is masked by respiration artifact (1, 2, 3, 5, 10, 11, 12, 13, 15, 16, 19, 20).

The seizure discharge under sodium pentobarbital anesthesia was greatly attenuated or absent. In no case did the seizure discharge continue for longer than 12 seconds, nor was the amplitude higher than 75 microvolts (the large spike in record 8 was probably an artifact).

Appendix C (continued).

The post ECS depression is very marked (the lowered intensity of respiration caused by the anesthesia decreases the magnitude of artifact). The depression is not an effect of the anesthesia itself since the pre ECS record (last column Figure 1) typically shows high amplitude activity. It seems clear that the concentration of sodium pentobarbital used here greatly attenuates seizure discharge, although the period of post seizure depression is still present.

The recordings under ether anesthesia (Figure 2) are not as consistent. Two animals (11, 16) showed almost no seizure discharge; two animals (12, 19) showed attenuated seizure discharge, and the other six seemed to show a briefer period of high frequency activity than normal, followed by a long series of low frequency spikes (usually about 1 1/2 per sec.). This period of low frequency spiking is not seen in any of the unanesthetized recordings (although 3 approximates it), and in some cases (11, 14, 15) continues for longer than unanesthetized seizure discharge. Two conclusions can be drawn about the effect of ether anesthesia on seizure discharge: first, in most cases the seizure discharge is not blocked, and second, the pattern of seizure discharge under ether anesthesia is different from the unanesthetized pattern.

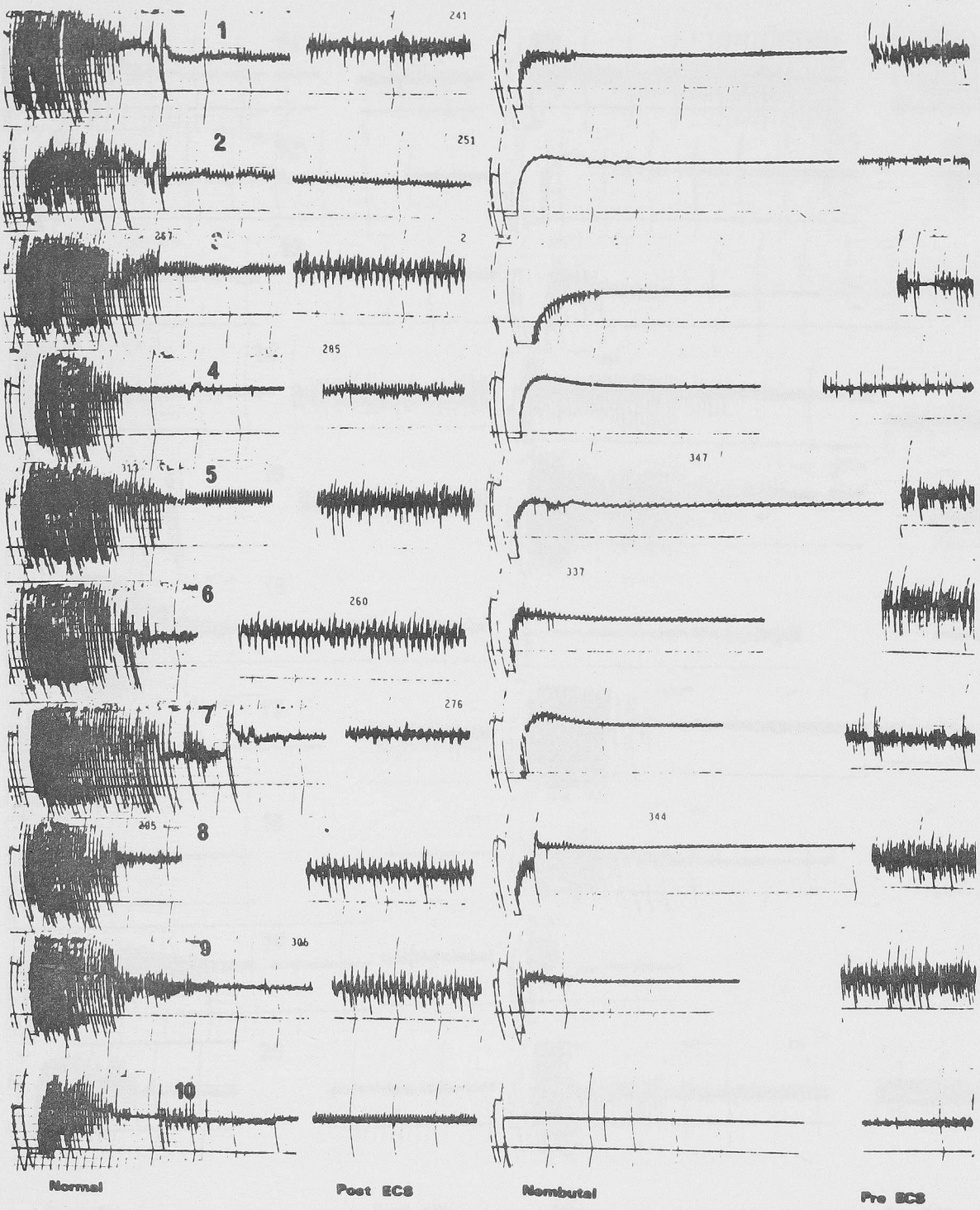

Figure 1. Seizure Discharge for 10 Rats Receiving ECS While Unanesthetized and Later Under Sodium Pentobarbital Anesthesia.

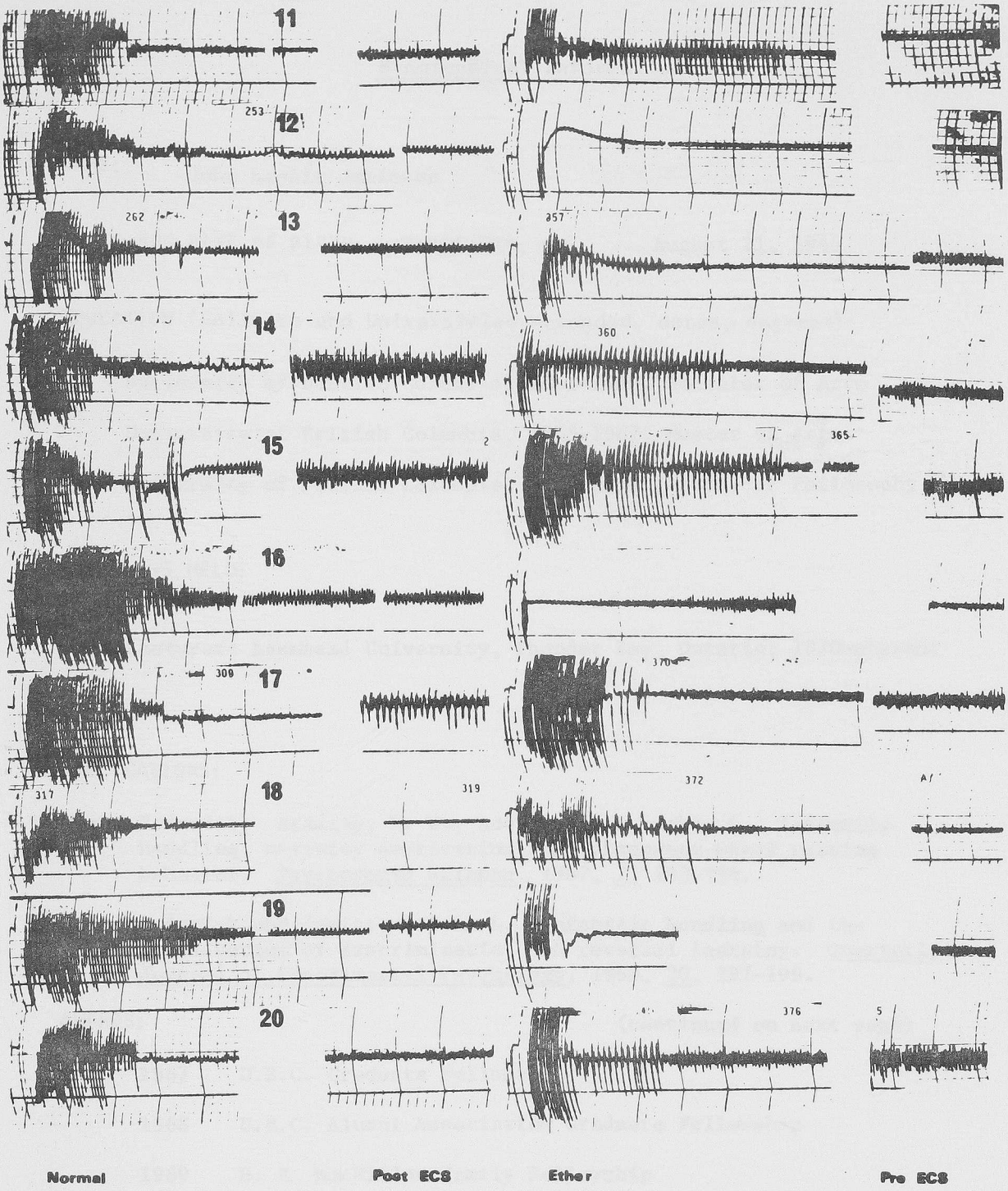

Figure 2. Seizure Discharge for 10 Rats Receiving ECS While Unanesthetized and Later Under Ether Anesthesia.