ELECTROCONVULSIVE SHOCK-INDUCED AMNESIA:

AN INVESTIGATION OF THE REINSTATEMENT EFFECT

by

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THESIS

Submitted to the Faculty of Arts

in Partial Fulfillment of the Requirements for

the Degree of Master of Arts

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1973

ABSTRACT

Three experiments were conducted to investigate the reinstatement effect, in which amnesia has been reported following the pairing of a noncontingent footshock and ECS. In Experiment I the possibility that a FS-ECS combination is more effective than a single ECS at disrupting memory consolidation was examined. Rats trained on a passive avoidance task which received ECS 15 seconds after training showed a partial amnesia. A noncontingent footshock preceding ECS at 15 seconds did not augment this amnesia but rather attenuated it, providing no support for a consolidation interpretation of the reinstatement effect.

In Experiment II an attempt was made to replicate the reinstatement effect through varying the conditions of training. Animals were not prehandled and received no pretraining familiarization with the apparatus. Under these conditions the reinstatement effect was still not observed.

In Experiment III the possibility that the reinstatement effect is dependent on the reactivation of the memory for original training was examined. Six hours after training, rats were administered ECS following 10 seconds of successful performance of the passive avoidance response. Although the memory for the original training must have been reactivated to mediate this performance, administration of ECS at this time again failed to produce amnesia.

The conditions necessary to obtain the reinstatement effect as well as the explanation for this effect are still unknown. The present

results add to a growing body of evidence indicating that amnesia is far more difficult to obtain in the reinstatement paradigm than in the consolidation paradigm, i.e., when ECS is administered shortly after training.

ACKNOWLEDGEMENTS

I sincerely wish to express my gratitude to Dr. John Jamieson for his untiring help and direction throughout the entire course of this undertaking. I also wish to thank Dr. Frank Colman for his useful comments during preparation of this thesis, and for his assistance in overcoming administrative difficulties. In addition, I wish to acknowledge the useful discussions with fellow students, especially Ted Ho and Jamie Arthur.

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to 60 minutes after acquisition. This period of susceptibility, as defined by the length of the ECS gradient, has been assumed to reflect the critical time necessary for the consolidation of memory traces.

Coons and Miller (1960) suggested an alternative to the consolidation interpretation of Duncan's (1949) study. They postulated that the performance deficit resulted not from amnesia, but from aversive properties of ECS. To support this position, they showed that ECS under some conditions had aversive effects.

However, Hudspeth, McGaugh, and Thompson (1964) demonstrated that aversive effects did not generally result from a single ECS administration. Nevertheless, to investigate retrograde amnesia without confounding aversive and amnesic effects, experimenters began using one-trial passive avoidance tasks. The most frequently used passive avoidance task utilizes the step-down box (e.g., Madsen & McGaugh, 1961). In this task, animals are punished with a footshock for stepping down from a platform. Retention of passive avoidance training is exhibited by increased step-down latencies, while amnesia is reflected by short latencies. Since any aversive effects of ECS should, like the footshock, increase step-down latencies, aversive and amnesic effects are not confounded in these tasks. An additional advantage of these tasks is that since only one training trial is required, a more precise definition of the temporal course of memory consolidation is possible. Investigations of retrograde amnesia have generally used ECS. although other treatments such as ether and pentobarbital anesthesia (Pearlman, Sharpless, & Jarvik, 1961), cortical spreading depression (Bures & Buresova, 1963), and hypothermia (Riccio, Hodges, & Randall, 1968) have also been used.

Investigations utilizing one-trial passive avoidance tasks have reliably demonstrated retrograde amnesia which cannot be explained by aversive effects (e.g., Heriot & Coleman, 1962; Madsen & McGaugh, 1961). While some alternative explanations have been offered for these ECS gradients (Lewis & Maher, 1965; Nielson, 1968; Spevack & Suboski, 1969), these explanations do not account for the bulk of experimental findings on retrograde amnesia as adequately as the consolidation hypothesis (see, for example, McGaugh & Dawson, 1971). However, several recent studies have demonstrated retrograde amnesia under conditions which are incompatible with the consolidation interpretation. These findings indicate that the ability of amnesic agents to disrupt memory can be "reinstated" long after the period usually thought to be necessary for memory consolidation has expired. The purpose of the present investigation was to examine this phenomenon and its implications for the consolidation hypothesis.

THE REINSTATEMENT EFFECT

Recently, several independent investigations have reported retrograde amnesia which depends not upon the time of ECS administration after training, but upon the time of ECS administration after some other subsequent event.

Schneider and Sherman (1968) trained rats in a step-down box in which a footshock was administered contingent upon stepping off an elevated platform. The authors showed that the administration of a single ECS at 0.5 seconds, but not either 30 seconds or 6 hours after training, impaired retention (i.e., the typical ECS gradient). However, if the presentation of an ECS at 30 seconds or 6 hours after training was immediately preceded by a second, noncontingent footshock, retention of training was significantly impaired. The duration of time between the administration of the second footshock and ECS was shown to be critical with amnesia being produced with an interval of 0.5 seconds but not with that of 30 seconds. Thus, it was demonstrated that retrograde amnesia was dependent not upon the training-ECS interval, but upon the footshock-ECS interval. These authors interpreted their findings as indicating that retrograde amnesia, observed in paradigms employing passive avoidance of footshock, resulted from the proactive effects of the combination of heightened arousal, produced by footshock, with ECS. These proactive effects are assumed to reduce freezing behaviour. They suggested that short step-down latencies exhibited by rats administered footshock followed immediately by ECS reflect impaired performance of the learned response, and not a loss of memory for the learning experience.

In an attempt to provide direct support for their position, Schneider, Malter and Advokat (1969) showed that the administration of footshock-ECS 30 minutes prior to one-trial passive avoidance training resulted in significantly shorter step-down latencies than were produced by a pretraining ECS alone. The authors suggested that the proactive effects of the footshock-ECS pairing inhibited freezing behavior during the retention test, since this pretreatment could not have disrupted memory consolidation. However, since these treatments preceded training by only 30 minutes, the differential effects of ECS and footshock-ECS might simply reflect a greater proactive interference with acquisition by the combined treatment. Aron, Glick, and Jarvik (1969) have shown that ECS can proactively interfere with acquisition of a passive avoidance response. The footshock-ECS pairing might simply augment this proactive effect on acquisition rather than inhibiting later freezing behavior as Schneider et al. (1969) have suggested.

Misanin, Miller, and Lewis (1968) reported a similar finding to that of Schneider and Sherman (1968). They established a conditioned emotional response (CER) in rats by pairing white noise with footshock. A single ECS given 24 hours after training did not interfere with subsequent performance of the CER. However, if the white noise preceded the ECS, retention of the CER was not exhibited on later testing. Misanin et al. (1968) suggested that the memory was transformed from an inactive to an active state by the presentation of the white noise. They suggested that the results of their study, as well as those of Schneider and Sherman (1968) can be adequately accounted for if it is assumed that ECS disrupts active memory traces irrespective of their age.

Subsequent to the publication of these findings, several attempts at replication failed completely to demonstrate this reinstatement effect.

In an attempt to replicate Schneider and Sherman's (1968) findings Banker, Hunt, and Pagano (1969) were unable to produce retrograde amnesia when a second noncontingent footshock, followed immediately by ECS, was administered 7 hours after passive avoidance training. They suggested that the short step-down latencies reported by Schneider and Sherman (1968) may have been caused by heightened emotionality of those animals receiving the double footshock condition, as indicated by an augmented frequency of animals "falling off" rather than "stepping down" purposely from the platform. However, this explanation does not account for the time dependence observed in Schneider and Sherman's (1968) study.

Jamieson and Albert (1970) reported that retention of the passive avoidance of a drinking response, previously paired with a strong footshock, was not only unimpaired but significantly enhanced by the administration of a second noncontingent footshock followed immediately by ECS 5 hours after training.

Dawson and McGaugh (1969) failed in an attempt at the exact replication of Misanin et al.'s (1968) findings. They concluded that the reactivation procedure was completely ineffective in the production of retrograde amnesia.

Lee-Teng (1970) reported a similar failure of this reactivation procedure. Chicks were trained to passively avoid pecking at a shiny object by presenting them with a lure coated with an unpalatable substance. One hour after training, the chicks were re-exposed to the lure and immediately administered ECS. Again, no retention deficits resulted.

More recently, however, two additional demonstrations of the reinstatement effect have been reported. DeVietti and Larson (1971) established a CER in rats by pairing a tone with an unavoidable footshock. A single ECS given 24 hours after training did not interfere with subsequent performance of the CER. However, if a second noncontingent footshock immediately preceded the ECS, performance of the CER was impaired. Furthermore, this deficit was observed to have dissipated when animals were tested 96 hours after training. They interpreted their findings within a state-dependent framework which postulates that retrograde amnesia results from a failure of retrieval, rather than disruption of memory consolidation. According to this interpretation, the interaction of footshock and ECS produces temporary states of abnormal brain excitability which impede normal retention. Although such cases of temporary amnesia can be adequately dealt with within a consolidation framework (McGaugh & Dawson, 1971), the effect of the second noncontingent footshock reflects the successful demonstration of the reinstatement effect.

Davis and his colleagues reported complementary findings using a multi-trial, one-way active avoidance training procedure with goldfish. They investigated the effects of re-exposing the fish to the training apparatus immediately prior to the administration of a number of amnesic treatments. Davis and Klinger (1969) found that re-exposure 24 hours after training, followed immediately by the administration of puromycin, acetoxycycloheximide, or potassium chloride resulted in impaired retention. By merely omitting re-exposure, retention was unimpaired by these treatments. However, when ECS was examined in this paradigm, no loss of memory resulted.

In a follow-up study, Davis and Hirtzel (1970) examined the re-exposure-ECS treatment using shorter time intervals between training and re-exposure-ECS. They found that the administration of ECS 4 hours after training resulted in impaired retention. However, when ECS was immediately preceded by re-exposure, this impairment was significantly increased. At 6 hours after training, ECS alone was much less effective in impairing retention (i.e., typical ECS gradient). Also, the effectiveness of re-exposure at 6 hours followed by ECS was greatly decreased as compared to that at 4 hours. These findings indicate on the one hand that the reinstatement effect in this situation can be obtained with ECS as well as with puromycin, acetoxycycloheximide and potassium chloride, and on the other hand that the reinstatement effect produced by ECS was time-dependent (i.e., that it depended on the interval between training and re-exposure-ECS).

IMPLICATIONS OF THE REINSTATEMENT EFFECT

The consolidation hypothesis predicts that the production of retrograde amnesia depends upon the length of the training-ECS interval, while those studies successfully demonstrating the reinstatement effect show that retrograde amnesia can depend upon the length of time between some other event and ECS. Therefore, the amnesia observed in these experiments does not appear to reflect the disruption of memory consolidation. These findings raise the possibility that all cases of retrograde amnesia may be caused by something other than disruption of consolidation.

On the other hand, the negative findings indicate that the inference is incorrect. The failures to replicate demonstrate that, although retrograde amnesia is reliably produced by the administration of ECS immediately after training, the reinstatement effect is not so easily obtained. Therefore, the reinstatement effect cannot account for the production of retrograde amnesia in all cases. Instead, the reinstatement effect may reflect a special case of retrograde amnesia dependent upon certain critical, but as yet unknown, parameters. Accordingly, this phenomenon may not be critical to the consolidation interpretation of retrograde amnesia.

However, the possibility that even some cases of retrograde amnesia may be caused by something other than disturbances of consolidation should not be overlooked. Although the reinstatement effect does not conclusively rule out the consolidation hypothesis, it does question the generality of its application. Accordingly, the possibility of such occurrences would necessitate the inclusion of appropriate controls in future investigations of memory consolidation. Also, the reinstatement effect may offer an additional source of information concerning the nature of the mechanisms by which the brain stores and retrieves information. Obviously, the means by which memories become susceptible to external disruption are of critical importance for our understanding of memory processes.

Before these implications, including the challenge which the reinstatement effect poses for the consolidation hypothesis, can be adequately evaluated, the mechanisms responsible for its production must be determined. Unfortunately, the positive findings are basically illustrative in nature and provide few clues to the basis of this phenomenon. Also the failures to replicate indicate that systematic investigation may be difficult.

The numerous failures to replicate imply that, whatever the ultimate explanation of the reinstatement effect might be, it must be able to deal with these negative findings as well as the positive instances. For example, if Schneider and Sherman's (1968) proactive hypothesis were correct, the reinstatement effect should be relatively easy to replicate. But this is not the case. DeVeitti and Larson's (1971) state-dependent interpretation can be criticized on similar grounds because of its apparent inability to adequately account for the failures to replicate.

Conversely, Misanin et al.'s (1968) reactivation hypothesis allows for a possible source of variation among experimental findings.

Negative instances can be explained in terms of the inability of experimental manipulation to adequately 'reactivate' inactive memory. Moreover, this conjecture that ECS selectively disrupts active memory can account for the retrograde effects of amnesic agents as adequately as does the consolidation hypothesis. Lewis (1969a) suggested that the importance of the training-ECS interval lies not in the degree of memory consolidation attained prior to the administration of ECS, but in the degree to which memory had receded into an inactive state following training. The major limitation of this hypothesis is its lack of direct, empirical support.

However, before alternative explanations are considered, the possibility that the reinstatement effect may be attributable to the disruption of memory consolidation should be examined. The importance of the reinstatement effect for the consolidation hypothesis stems from its raising the possibility that not all retrograde amnesia results from the disruption of memory consolidation. Previous findings have only provided indirect support for this conjecture. For this conclusion to be justified, disruption of consolidation must be ruled out as a possible explanation.

A CONSOLIDATION INTERPRETATION OF THE REINSTATEMENT EFFECT

The positive instances of the reinstatement effect have been interpreted as indicating that the ability of ECS to disrupt memory can be reinstated long after the critical period for memory consolidation has expired. This conclusion is based on the assumption that the length of the ECS gradient represents the amount of time necessary for the completion of memory consolidation. Thus, any impairment of retention, caused by certain treatments administered beyond the point in time at which ECS becomes ineffective has been interpreted as involving something other than disruption of consolidation.

However, it is becoming clear that the length of the ECS gradient represents not the duration of consolidation, but the degree of susceptibility of this process to the disruptive properties of ECS (McGaugh & Dawson, 1971). This conclusion is supported by recent studies which indicate that the memory impairment produced by ECS administration is not maximal. For example, Bohdanecky, Kopp, and Jarvik (1968) showed that the administration of flurothyl (a highly convulsive vapour) produces a much flatter and longer temporal gradient than that produced by a single ECS. Similarly, Robustelli, Geller, and Jarvik (1969) reported that the combined action of two amnesic treatments, namely detention in the passive avoidance apparatus and ECS, produced a significantly greater memory deficit than that produced by ECS alone. These findings suggest that the processes underlying memory consolidation may be susceptible to disruption by other amnesic agents for a longer period of time than by ECS alone.

In relation to the present problem, Davis' work indicates that the re-exposure-ECS treatment may be time-dependent, and that its amnesic properties are superior to those of ECS alone. This suggests that the "reinstatement" of the ability of ECS to disrupt retention by pairing ECS with a second noncontingent footshock long after ECS alone is ineffective, may be caused by the ability of the second footshock to potentiate, or enhance the amnesic properties of ECS. If this is the case, the combination of footshock and ECS should be able to produce a longer temporal gradient than ECS alone.

Some recent evidence concerning the physiological interaction of footshock and ECS lends support to this hypothesis. Nielson and Fleming (1968) found that ECS produces significantly greater changes in catecholamine levels of the brain when preceded by stress, such as that produced by multiple footshock, than when ECS is administered alone. Chorover and DeLuca (1969) found that the cortical seizure activity produced by the administration of ECS can be altered or abolished by a prior footshock. Also, the frequency and type of abnormal reaction was shown to vary inversely with the duration of the footshock-ECS interval. Furthermore, Schneider et al.'s (1969) finding that footshock-ECS has greater proactive effects than ECS alone upon step-down latencies supports this position.

These findings concerning the existence of a physiological interaction between footshock and ECS, along with those of longer temporal gradients than produced by ECS alone, constitute the major empirical support for the assumption that, by pairing a footshock with ECS, the ability of ECS to disrupt memory consolidation may be enhanced.

It should be noted that a consolidation interpretation of the reinstatement effect can adequately account for failures to replicate. Various factors have been shown to alter the length of the ECS gradient, presumably through speeding the rate of memory consolidation. Training-related variables such as amount of pretraining familiarization (Lewis, Miller, & Misanin, 1968), nature of the training (Chorover & Schiller, 1966; Thompson & Pennington, 1957), intensity of footshock used in training (Ray & Bivens, 1968), and even time of day (Stevens & McGaugh, 1968) have been shown to substantially alter the length of this period of susceptibility to external disruption. Such factors might adequately account for the differential results obtained since, in some cases, memory consolidation may be completed more quickly.

RATIONALE FOR THE PRESENT INVESTIGATION

Experiment I was designed to test this consolidation interpretation of the reinstatement effect. If in fact the amnesic properties of ECS can be enhanced by a footshock given immediately prior to its administration, then the amount of amnesia produced by this treatment should be greater than that produced by ECS alone, when administered within an appropriate training-treatment interval. In Experiment I a footshock-ECS combination was presented 15 seconds after training, a time when a single ECS produces only a partial disturbance of retention. If this combined treatment produces a greater disturbance of consolidation than ECS alone, an increased impairment should be exhibited.

When Experiment I failed to demonstrate the reinstatement effect, Experiments II and III were conducted in an attempt to determine the conditions necessary for its production.

Failures at exact replication suggest that the conditions necessary for the production of the reinstatement effect may be of a nature which is difficult to control operationally. Subject-related factors such as varying degrees of pretraining familiarization or emotionality may be implicated since these are especially difficult to control from study to study. Several recent investigations by Lewis and his colleagues demonstrated that, in a typical step-down task, the amount of retrograde amnesia, produced by ECS administered at various times after training, varies inversely with the degree of pretraining familiarization experience in the apparatus (Lewis, Miller, & Misanin, 1968; 1969).

The amount of pretraining familiarization given an animal is generally reported in terms of time. However, Miller (1970) showed that total amount of pretraining time spent in the apparatus may not be an adequate criterion for measuring the degree of familiarization. The effectiveness of familiarization in attenuating the amnesic properties of ECS was shown to be a function of the length of these pretraining trials as well as the complexity of the training environment. Also, Galosy and Thompson's (1971) recent failure to replicate the familiarization effect indicates difficulties encountered in control of this variable. Accordingly, inadvertent variations in the degree of pretraining familiarization might account for the differential results obtained in attempts to demonstrate the reinstatement effect.

Experiment II examined this possible source of variability within a reinstatement paradigm. In Experiment I, much care was taken in familiarizing the animals with the apparatus prior to training as well as in gentling them before being placed on the platform. Under these conditions, the reinstatement procedure failed to produce retrograde amnesia. The purpose of Experiment II was to determine if the reversal of these conditions would result in the successful demonstration of the reinstatement effect. Since the results of Experiment I indicated that the reinstatement effect is not time-dependent, a training-treatment interval of 6 hours was used in order to replicate the conditions of Schneider and Sherman (1968).

Since Experiment II was also unsuccessful, Experiment III was conducted. One possible explanation for failures to obtain the reinstatement effect is provided by Misanin et al.'s (1968) interpretation, namely that ECS disrupts active memory processes. Therefore, in order to obtain the reinstatement effect, it may be necessary to ensure that the memory is reactivated. Experiment III provided an operational definition of reactivation. In other words, an objective measure was used to ensure that the memory for the training was recalled at the time of ECS administration.

Accordingly, in Experiment III, a variation of the reinstatement procedure was used in which rats received ECS 6 hours after training and immediately following 10 seconds of successful passive avoidance on the platform. Previous work indicated that naive rats step down more quickly, especially after several habituation trials. Therefore, this passive avoidance should indicate that the memory is being reactivated. If the "reactivation" hypothesis is correct, the administration of ECS at a time when the conditioned response of passive avoidance is being performed should result in the production of retrograde amnesia.

EXPERIMENT I

AN EXAMINATION OF A CONSOLIDATION INTERPRETATION OF THE REINSTATEMENT EFFECT

The purpose of this experiment was to examine the possibility that a FS-ECS combination is more effective than a single ECS at disrupting memory consolidation. A footshock-ECS combination was administered 15 seconds after one-trial, passive avoidance training, a time when ECS alone produces only a partial disturbance in retention. If the combined treatment has superior amnesic properties than ECS alone, an increased deficit should result.

Method

Subjects

Forty-eight experimentally naive, male, hooded, 200-250 gram rats, obtained from the Canadian Breeding Laboratories, Laprairie, Quebec, served as subjects.

Apparatus

The training appratus consisted of a modified step-down box constructed according to the specifications of Carew (1970). The dimensions of this open-topped, Plexiglas box were 40 cm. by 40 cm. by 30 cm. high. Half of the compartment, from the centre of one wall to that of the opposite wall, was painted flat black, while the other half was painted gloss white. Immediately above the floor of the box, which was also half black and half white, was a grid floor which consisted of stainless steel bars 0.2 cm. in diameter spaced 1.3 cm. apart. In the centre of this grid floor, a 12.5 sq. cm. Plexiglas platform 5 cm. high, which was also half black and half white, was constructed with small walls on two opposite sides of the platform, appropriately painted, to prevent animals from stepping down onto a black-white border.

This modification of the standard step-down apparatus was used because it permits retention of footshock to be measured in terms of choice preference as well as the usual step-down latency. By utilizing this dual criterion of retention, confounding factors such as "motor disinhibition" (Schneider & Sherman, 1968), and "excitability" (Banker et al., 1969) may be differentiated from retrograde amnesia.

ECS consisted of a 60 milliampere current produced by a 730 volt transformer in series with a 10,000 ohm resistance, for a duration of 0.5 seconds. This current was administered via gauze covered saline soaked alligator clips attached to the pinnae of the rat's ears. These ear clips were connected to the power source by flexible wires. The wires were suspended above the training apparatus by an elastic cable in order to minimize impairments of mobility.

Footshock was administered via the grid floor of the training apparatus and consisted of a constant A.C. current of 0.5 ma for a duration of 1.0 seconds.

Procedure

During the course of the experiment, all Ss were maintained on ad lib. food and water. For approximately 6 days after arrival from the supplier, Ss were housed two per cage. On the day before training began, the animals were separated, handled for 3 to 5 minutes each, and placed in individual cages.

(a) Habituation: For four consecutive daily trials, each rat was carried by hand from the colony room to the laboratory. Each animal was placed in the centre of the platform, facing the black-white border of the restraining wall away from the E. Upon stepping down (all four feet on the grid floor), each S was allowed 30 seconds to explore the apparatus. Step-down latencies (seconds) and choice (black or white) were recorded. None of the animals wore ear clips during these pretraining familiarization trials.

(b) Treatment: On Day 5 Ss were randomly assigned to four treatment groups with 12 Ss per group. The training procedure was identical to that of the previous four habituation trials for all animals with two exceptions. First, ear clips were attached and a 15 second adaptation period was given outside the apparatus prior to positioning on the platform. Second, each S received a footshock immediately upon stepping down onto the grid floor. Step-down latencies and choice were again recorded for each rat. Subsequent treatment depended upon the group to which Ss had been assigned. Group FS-ECS received ECS 15 seconds after training in order to evaluate the effects of delayed ECS upon retention. Group FS-FS, ECS received a second noncontingent footshock 15 seconds after training followed 0.5 seconds later by ECS to determine the influence of a second footshock immediately prior to ECS upon the effectiveness of a delayed ECS (i.e., the reinstatement paradigm). Two additional groups served as controls. Group FS received no further treatment after training to evaluate retention in untreated animals. Group FS, ECS received ECS 0.5 seconds after training to determine the effects of immediate ECS upon retention. All Ss receiving ECS were removed from the apparatus while unconscious and returned to their home cages. Those Ss receiving training only (Group FS) were removed approximately 15 seconds after stepping down from the platform.

(c) Retention: Twenty-four hours after training, each S was again placed on the platform. Step-down latencies and choice were again recorded. None of the animals wore ear clips during retention testing.

Results

Behavioural Observations

The administration of ECS reliably produced full tonic convulsions, characterized by the extension of the hindlegs, in all Ss. Five Ss were disabled by ECS-induced paraplegia and were replaced during the course of the experiment.

Analysis of Step-Down Latencies

(a) Logarithmic Transformation: Table 1 contains the group means and variances of the step-down latencies for Days 5 and 6. Bartlett's test indicated heterogeneity of variance between the Day 6 latencies for the four groups (B' of 11.44 with three degrees of freedom, $p < .01$). To remove the heterogeneity of variance, a logarithmic transformation was performed on the step-down latencies. Table 2 contains the group

TABLE 1

Group Means and (Variances) of Step-Down Latencies in Experiment I

Groups	Day 5	Day 6
FS	4.967 (8.779)	54.908 (2550.734)
FS, ECS	4.958 (11.817)	12.150 (347.570)
FS-ECS	6.000 (12.196)	28.533 (724.617)
FS-FS′, ECS	6.583 (42.943)	73.183 (1574.658)

TABLE 2

Group Means and (Variances) of Logarithmic Transformations of Step-Down Latencies for Experiment I

Groups	Day 5	Day 6	t	p*
FS	1.445 (0.352)	3.322 (1.993)	3.820	.01
FS, ECS	1.436 (0.334)	1.660 (1.814)	0.582	NS
FS-ECS	1.606 (0.472)	2.570 (2.501)	2.057	.10
FS-FS, ECS	1.519 (0.765)	3.967 (1.217)	7.894	.001

* Within Group Comparisons (t-tests for correlated samples)

means and variances of the transformed latencies. Bartlett's test, applied to the Day 6 transformed latencies, yielded a B' of 1.36 with three degrees of freedom (n.s.) indicating that the logarithmic transformation effectively eliminated the heterogeneity of variance.

(b) Within Group Comparisons: In order to evaluate the effects of Day 5 treatments upon the latencies of Day 6, t-tests for correlated samples (Table 2) were used to compare Day 5 latencies with those of Day 6 for each group. The step-down latencies of Group FS significantly increased from Day 5 to Day 6 ($p < .01$), indicating retention of training. Group FS, ECS did not change significantly indicating that retention was severely impaired by immediate ECS. Group FS-ECS showed a substantial increase which failed to reach significance ($.05 < p < .10$) indicating that ECS delayed for 15 seconds after training still produced some impairment of retention. Group FS-FS, ECS had significantly elevated latencies from Day 5 to Day 6 ($p < .01$) which indicates that, when delayed ECS was preceded by a second noncontingent footshock, retention was unimpaired.

(c) Between Group Comparisons: Analysis of variance indicated no significant differences between groups on Day 5, prior to training. Analysis of variance for Day 6 latencies yielded a significant F of 6.296 with 3 and 44 degrees of freedom ($p < .01$) indicating differential treatment effects.

To evaluate the relative contribution of each treatment to this overall difference, Neuman-Keuls Multiple Comparisons were performed. The results of these comparisons indicated that:

(1) the latencies of Group FS, ECS were significantly shorter than those of Group FS ($p < .001$) which reflects greatly impaired retention as the result of immediate ECS;

(2) the latencies of Group FS-ECS were neither significantly shorter than those of Group FS nor longer than those of Group FS, ECS which indicates partially impaired retention caused by delayed ECS;

(3) the latencies of Group FS-FS, ECS were significantly longer than those of either Group FS, ECS ($p < .01$) or Group FS-ECS ($p < .05$). This indicates that the FS-ECS combination not only failed to increase the amount of memory loss as predicted by the reinstatement effect, but also attenuated its production.

(4) The difference between Group FS-FS, ECS and Group FS was not significant, which indicates that the second footshock-ECS treatment did not affect retention.

Analysis of Choice Data

For analytic purposes, choice data is reported in terms of the percentage of animals alternating place preference between a given pair of trials (black to white, or white to black) for each group. The percentages of alternation for each group from Day 4 to 5, and Day 5 to 6 are presented in Table 3. Each cell represents the number of animals alternating place preference from the previous day's choice, divided by the total number of Ss in that group times one hundred percent.

(a) Within Group Comparisons: t-tests for evaluating differences between two correlated proportions were applied to this data for each

TABLE 3

Percentage of Alternation for Experiment I

Groups	Day 5	Day 6	p*
FS	16.67	83.35	.01
FS, ECS	25.00	8.33	NS
FS-ECS	25.00	33.33	NS
FS-FS, ECS	25.00	25.00	NS

* Within Group Comparisons (t-tests for correlated proportions)

treatment group, comparing percentages of alternation on Day 5 to that on Day 6. These comparisons indicated that only Group FS increased significantly from Day 5 to Day 6 ($p < .01$), indicating retention of training. All other comparisons were not significant which indicates impairment of retention of the discriminated avoidance training for all ECS groups.

(b) Between Group Comparisons: To determine the significance of differences in percentage alternation between groups for Days 5 and 6, chi square tests of independence were performed. No differences were found on Day 5. For Day 6 alternations, a significant chi square of 15.98 with three degrees of freedom was obtained ($p < .01$).

To evaluate the relative contribution of each treatment to this overall difference, individual chi squares were calculated for all possible combinations. These showed that the percentage alternation on Day 6 for Group FS was significantly greater than any of the other three groups (p's $< .05$). Also, no significant differences existed among these other three groups indicating comparable degrees of retention deficits for these groups.

Discussion

Analysis of the latency data indicates that the present experiment failed to demonstrate the reinstatement effect. These results do not support a consolidation interpretation of this phenomenon. While the administration of a single ECS 15 seconds after training produced a partial impairment of retention when tested 24 hours later, a second noncontingent footshock administered 0.5 seconds prior to this ECS failed to enhance this partial impairment, as would be expected if footshock-ECS pairing was a more effective amnesic agent than ECS alone. These results are inconsistent with those of Davis and Hirtzel (1970) which indicated that the reinstatement effect may be time-dependent, and that its amnesic properties are superior to those of ECS alone.

In this experiment the reinstatement procedure not only failed to produce amnesia, but resulted in better passive avoidance performance than was exhibited by the group receiving only ECS. While the footshock-ECS pairing has been reported to produce amnesia (i.e., the reinstatement effect) there are now several reports that it can also have the opposite effect, namely an attenuation of amnesia (the present experiment) or an increase in retention of the passive avoidance response above the level shown by groups receiving only passive avoidance training (Dawson &McGaugh, 1969; Gold & King, 1972; Jamieson & Albert, 1970). The reason why this second footshock was able to survive or block the disruptive powers of immediate ECS, when typically the memory of initial training can be effectively eliminated by immediate ECS, is unclear. According to consolidation theory the memory trace of the second footshock should have been equally disrupted.

Two possible explanations have been offered. Gold and King (1972) suggested that this decrease in the ability of ECS to disrupt the memory of the second footshock may be caused by the presence of a relevant memory trace, when the second footshock is received, speeding up the consolidation processes. Jamieson and Albert (1970) and Gold and King (1972) suggested that heightened arousal prior to the administration of the second footshock-ECS treatment caused by initial fear conditioning may account for this phenomenon either by decreasing the susceptibility of memory to ECS or by speeding up consolidation.

The alternation data are not as clearly interpretable as the latency data. Only Group FS showed a significantly greater proportion of alternations on Day 6 than on Day 5. This indicates good retention of the one-trial discriminated avoidance task for the unconvulsed group. However, all other groups failed to show significant increases in alternation. Unlike the latency data whose graded differences reflected differential treatment effects, all groups which were administered ECS after training, irregardless of varying conditions, showed no retention of the discrimination. These findings are inconsistent with those of Carew (1970) who found a shorter ECS gradient when using alternation as the dependent variable than when step-down latencies were employed. The basis of this inconsistency is unclear.

At least two possible explanations can be suggested for this apparent lack of sensitivity of the alternation measure in differentiating between treatment groups. Either a much longer ECS gradient exists for the alternation measure than for step-down latencies, as suggested by Pfingst and King (1969), or ECS may have a general proactive effect on this measure, irregardless of preceding manipulations.

EXPERIMENT II

AN EXAMINATION OF THE EFFECTS OF DIFFERENTIAL PRETRAINING FAMILIARIZATION AND GENTLING UPON THE REINSTATEMENT PARADIGM

In this experiment, an attempt was made to obtain the reinstatement effect by varying the conditions of training. In the previous experiment, much care was taken in familiarizing the Ss with the apparatus prior to training as well as in gentling them before being placed on the platform. Under these conditions, the reinstatement effect was not obtained. The purpose of this experiment was to determine if the reversal of these conditions would result in the successful demonstration of the reinstatement effect.

Method

Subjects

Forty-eight experimentally naive, male, hooded, 200-250 gram rats, obtained from the Canadian Breeding Laboratories, Laprairie, Quebec, served as subjects.

Apparatus

The training apparatus as well as the parameters and mode of administration of ECS and footshock were identical to those of Experiment I.

Procedure

All Ss were maintained on ad lib. food and water during the experiment. After arrival from the supplier Ss were housed two per cage for 6 days. One day prior to training, the animals were separated and housed individually.

On Day 1, Ss were randomly assigned to four treatment groups. Each rat was removed from his home cage and transported from the colony room to the laboratory in a plastic, open-topped box. No attempt was made to gentle these animals prior to training. Ss were positioned on the platform as in Experiment I and step-down latencies and choice data were recorded. Three of the four treatment groups received a footshock upon stepping down onto the grid floor. All Ss were removed from the apparatus 10 seconds after leaving the platform. Subsequent treatment given 6 hours afterwards depended upon the treatment group to which Ss were previously assigned.

Group NFS-NECS, which had received no training was returned to the laboratory 6 hours later. Ear clips were attached and each S was replaced in the carrying box for 15 seconds before being returned to his home cage. No ECS was administered. This group was run to provide (1) a baseline in order to evaluate retention in terms of step-down latencies and (2) a means of evaluating retention of the discrimination since a within group baseline of this measure could not be obtained as only two trials were given.

Group FS-NECS received identical posttraining treatment as Group NFS-NECS in order to evaluate retention of training in untreated rats.

Group FS-ECS was also returned 6 hours later. Ear clips were attached and Ss were replaced in the carrying box for 10 seconds.

Each S was then placed directly on the grid floor on that side where the initial footshock used in training had been received, and ECS was administered. This group was run to determine the effects of ECS, administered 6 hours after training, upon retention.

Group FS-FS, ECS received the same treatment as Group FS-ECS, except a second footshock was delivered 0.5 seconds prior to ECS administration. This group was run to evaluate the influence of a second noncontingent footshock upon the effects of ECS. All Ss who received ECS were immediately returned to home cages while still unconscious.

Twenty-four hours after training, all groups were tested for retention of training. Step-down latencies and choice data were again recorded. Ear clips were worn neither during training nor during the retention test, but only during treatment.

Results

Behavioural Observations

As in Experiment I, the administration of ECS reliably produced full tonic convulsions. Only one animal was disabled by ECS and was replaced.

Analysis of Step-Down Latencies

(a) Within Group Comparisons: Table 4 contains the group means and variances of the transformed latencies for Day 1 and Day 2. To evaluate the effects of differential manipulations of Day 1 upon the step-down latencies of Day 2, t-tests for correlated samples were

TABLE 4

Group Means and (Variances) of Logarithmic Transformations

of Latencies for Experiment II

Group	Day 1	Day 2	t	p*
NFS-NECS	1.355 (1.008)	1.853 (1.038)	1.813	NS
FS-NECS	1.292 (0.996)	3.377 (1.498)	7.136	.001
FS-ECS	0.749 (0.429)	3.244 (1.404)	6.297	.001
FS-FS, ECS	0.817 (0.375)	3.190 (3.017)	5.873	.001

* Within Group Comparisons (t-tests for correlated samples)

performed comparing Day 1 latencies with those of Day 2 for each group. The significance of these comparisons is also included in Table 4.

These within group comparisons indicate that all those groups which received training showed a significant increase in latency on Day 2 indicating retention (p's $<$ .001). Group NFS-NECS, which received no training showed no such increase.

(b) Between Group Comparisons: A one-way analysis of variance applied to the group latencies of Day 1 indicates that no significant differences existed between groups prior to treatment. However, analysis of variance for Day 2 latencies yielded a significant treatment effect ($F = 3.48$ with 3 and 44 degrees of freedom, $p < .05$).

Neuman-Keuls multiple comparisons indicate that Group NFS-NECS had significantly shorter latencies on Day 2 than did the other three groups. Further comparisons among the trained groups indicate no differences in the degree of this retention. This indicates the differential posttraining treatment had no effect upon subsequent retention.

Analysis of Choice Data

Table 5 contains the percentage of alternations from Day 1 to Day 2. Since the design of this experiment precluded assessment of retention of the discriminated task by comparing baseline alternations with those following training for each group, the percentages of alternation from Day 1 to Day 2 for the trained groups were compared to those of the untrained control, Group NFS-NECS. A chi square test

TABLE 5

Percentage of Alternation for Experiment III

Group	NFS-NECS	FS-NECS	FS-ECS	FS-FS, ECS	p*
	33.33	41.66	58.33	66.66	NS

*Between Group Comparisons (χ^2)

of independence applied to the alternation data of Day 2 indicated no significant treatment effects between groups (χ^2 = 4.87 with 3 df). This failure of the trained groups to show significantly greater percentages of alternation on Day 2 than the untrained control group indicates poor retention of the discriminated response. Furthermore, since even Group FS-NECS failed to show retention, this suggests that the lack of retention reflects unsuccessful acquisition for all trained groups, and not ECS-induced amnesia for Group FS-ECS and Group FS-FS,ECS.

Discussion

As indicated by the latency data, Experiment II failed to demonstrate the reinstatement effect. The present results show that an ECS administered 6 hours after training had no detrimental effect upon retention of a one-trial passive avoidance task and that the administration of a second noncontingent footshock 0.5 seconds prior to ECS was equally ineffective in producing retrograde amnesia. This suggests that possible variations in pretraining familiarization and emotionality are not responsible for the differential results reported in previous attempts to replicate this phenomenon.

The alternation measure did not reveal significant retention in any of the groups. This finding indicates that alternation is not as sensitive a measure of retention as step-down latency in this task. Taken together with the results of Experiment I these results indicate that the discrimination in this one-trial learning procedure is not as reliable a measure of retention as the passive avoidance response.

EXPERIMENT III

AN EXAMINATION OF THE REACTIVATION INTERPRETATION OF THE REINSTATEMENT EFFECT

This experiment examined the possibility that the reinstatement effect is dependent on the reactivation of the memory for original training. Accordingly, rats received ECS immediately following 10 seconds of successful passive avoidance on the platform. Since the memory of original training must be reactivated to mediate the performance of the conditioned response, the administration of ECS at this time should result in the production of retrograde amnesia.

Method

Subjects

Twenty-seven experimentally naïve, male, hooded, 200-250 gram rats, obtained from the Canadian Breeding Laboratories, Laprairie, Quebec, served as subjects.

Apparatus

Same as that used in Experiments I and II.

Procedure

Pretraining, handling, and housing procedures were identical to those of Experiment I. Also, all Ss were given four daily habituation trials during which step-down latencies were recorded, and 30 seconds per trial allowed for rats to explore the training apparatus.

On Day 5, Ss were randomly assigned to three treatment groups.

All Ss received a footshock upon stepping down from the platform. Again, step-down latencies and choice data were recorded. Animals were removed from the apparatus within 10 seconds after footshock and returned to home cages. Six hours after training, all Ss were returned to the laboratory, had ear clips attached and were allowed 10 seconds for habituation in the carrying box. Subsequent treatment depended upon the treatment group to which the animals had been assigned.

Group FS-ECS received ECS outside the apparatus in the carrying box in order to minimize the probability of reactivation.

Group FS-FS, ECS was placed directly on the grid floor on that side where footshock used in training had been received. A second footshock was administered followed 0.5 seconds later by ECS. This group received a similar reinstatement treatment as that used by Schneider and Sherman (1968).

Group FS-R, ECS was positioned on the platform as during habituation, but with ear clips attached, and after 10 seconds of passive avoidance on the platform was administered ECS. This was done to maximize the probability of memory of training being in an active state at time of ECS. All Ss were removed from the apparatus while still unconscious and returned to home cages.

Twenty-four hours after training, the animals were tested for retention of training. The procedure utilized was identical to that of the pretraining habituation trials. Ear clips were worn only during treatment, and not during either habituation, training, or retention tests.

Results

Behavioural Observations

Again, ECS reliably produced full tonic convulsions in all Ss. Eight animals were disabled by the administration of ECS and were replaced. Three Ss, all from Group FS-FS, ECS jumped out of the apparatus during the retention test on Day 6. Because of this, step-down latencies and choice data could not be obtained for these animals. All Ss in Group FS-R, ECS remained immobile on the platform for the full 10 seconds prior to the administration of ECS.

Analysis of Step-Down Latencies

Because of our inability to obtain latencies for those animals who jumped out of the apparatus from the platform, parametric analyses were not applied. Because these Ss apparently exhibited strong evidence of avoiding stepping down onto the grid floor, the data could not be discarded since this would obviously bias the results. Therefore, it was assumed that the three Ss who jumped out would have obtained latency scores above the median had they not jumped out, and non-parametric median tests were used. Table 6 contains the median latencies for each treatment group on Day 5 and Day 6.

(a) Within Group Comparisons: Nonparametric sign tests for correlated pairs were employed to evaluate the significance of differences between the Day 5 and Day 6 median latencies, for each treatment group. The results of these sign tests are contained in Table 6. All three groups showed a significant increase in latencies from Day 5 to Day 6 (p's $< .05$). This indicates good retention of

TABLE 6

Median Step-Down Latencies for Experiment III

Group	Day 5	Day 6	p*
FS-ECS	2.1	36.0	.05
FS-FS, ECS	8.0	41.5	.05
FS-R, ECS	10.0	40.9	.05

*Within Group Comparisons (nonparametric sign test for two correlated samples) of training in all treatment groups.

(b) Between Group Comparisons: Nonparametric sign tests for independent samples were calculated to evaluate the differences between the median latencies for Day 5 and Day 6. Between group comparisons for Day 5 latencies indicate that no significant differences existed between groups prior to training. Comparisons for Day 6 data were also nonsignificant, which indicates no differential effect of the posttraining treatments upon subsequent retention.

Analysis of Choice Data

Although the three animals that jumped out of the apparatus exhibited strong avoidance of stepping down onto the floor, no evidence whatsoever was observed which suggested that the discrimination component was recalled since these animals refused to step down on either side. Therefore, it is impossible to predict which side of the box these Ss would have eventually chosen had they not jumped out.

Because choice data were unavailable for these three animals and because of the unreliability of this measure found in the first two experiments, the choice data were not analyzed.

Discussion

The reinstatement effect was not demonstrated in this experiment as indicated by the inability of any of the treatments to produce retrograde amnesia. The administration of ECS outside the apparatus 6 hours after training did not impair retention, and the presentation of a second noncontingent footshock 0.5 seconds prior to the administration of ECS, on the floor of the apparatus, was equally ineffective in disrupting memory of training. In addition, administration of ECS following 10 seconds of successful passive avoidance on the platform, also failed to produce amnesia.

The ineffectiveness of ECS administered at a time when trained rats were overtly freezing on the platform suggests that previous, inconsistent findings in the reinstatement paradigm may not be the result of possible variations in the degree to which memory of training is reactivated.

GENERAL DISCUSSION

Two major issues will be discussed in light of the findings of the present investigation: (1) implications of the reinstatement effect for the present status of consolidation theory, and (2) explanations for the reinstatement effect.

Implications of the Reinstatement Effect for the Present Status of Consolidation Theory

Experiment I examined the possibility that the production of retrograde amnesia within a reinstatement paradigm might reflect disruption of consolidation. It was suggested that a second non-contingent footshock might significantly enhance the amnesic properties of ECS. The results of this experiment showed that a second non-contingent footshock administered immediately prior to the administration of ECS at a time when ECS alone produces partial impairments of retention did not produce retrograde amnesia. This finding indicates that a prior footshock not only failed to enhance the amount of retrograde amnesia produced by ECS, but in fact, attenuated it. Therefore, the hypothesis that the production of retrograde amnesia within the reinstatement paradigm is caused by the disruption of memory consolidation was not supported.

From another point of view, the present investigation represents three consecutive failures to demonstrate the reinstatement effect. Lewis (1969b), referring to other failures to replicate the reinstatement effect wrote "failures to replicate an experiment can occur for a variety of reasons, and a single such failure is not convincingly negative to the phenomenon in question. If the phenomenon, or one like it in principle, has been found in other laboratories, then the idiosyncracies of a negative effort are not important (p. 772)". This statement causes a dilemma in regard to studies concerned with the reinstatement effect. The number of positive instances reported indicate the validity of this phenomenon. On the other hand, numerous failures to replicate, which now outnumber the positive findings, cannot be discarded as "idiosyncracies". Contrary to Lewis' opinion, examination of these "idiosyncracies" may provide a promising source of information. The present failures to replicate, combined with other unsuccessful attempts, cast serious doubt upon the generality of the positive findings. Moreover, the implication of the positive instances that all retrograde amnesia is produced by something other than the disruption of memory consolidation seems presently untenable.

The present investigation cannot rule out the possibility that, under certain conditions, retrograde amnesia may be caused by something other than disruption of consolidation. However, our attempts to delineate these conditions by examining possible sources of variability among previous studies proved to be unsuccessful. The results of the present investigation, combined with previous failures to replicate, suggest that the reinstatement effect is not a sufficient basis for rejecting the consolidation interpretation of retrograde amnesia.

Explanations for the Reinstatement Effect

The positive instances of the reinstatement effect have been interpreted as suggesting that the production of retrograde amnesia in these experiments is caused by something other than disruption of memory consolidation. Several alternative hypotheses have been offered to explain not only the production of retrograde amnesia observed in the reinstatement effect, but also the production of retrograde amnesia in general. Since the major support for these alternatives to consolidation theory stems from the positive instances of the reinstatement effect, the implications of the present investigation as well as other failures to replicate are of critical importance for these hypotheses.

The results of the present investigation lend no support for any of the hypotheses offered to account for the reinstatement effect. As pointed out previously, a satisfactory explanation of the reinstatement effect must be able to deal with both positive and negative findings. Schneider and Sherman's (1968) proactive hypothesis allows no such source of flexibility. The present findings, combined with those of Banker et al. (1969), Jamieson and Albert (1970), and Gold and King (1972) suggest that this explanation is unlikely. DeVietti and Larson's (1971) state dependent hypothesis seems equally unlikely for similar reasons, as well as its questionable premise that all retrograde amnesia is temporary.

Misanin et al.'s (1969) reactivation hypothesis has an advantage of allowing for negative findings. Moreover, their suggestion that

ECS disrupts active memory processes is an attractive alternative to consolidation theory. Experiment III was conducted in an attempt to evaluate this hypothesis. The results of this investigation suggest that the administration of ECS at a time when memory of training was actively being recalled, as inferred from the performance of the conditioned avoidance response, was ineffective in producing retrograde amnesia. Although additional research may show that other conditions are necessary for reactivation, the present findings offer no support for this conjecture.

Recently, a phenomenon similar to the reinstatement effect, which also suggests that the production of retrograde amnesia can be independent of the training-ECS interval, has been reported (Robbins & Meyer, 1970; Howard & Meyer, 1971). In these experiments, rats were trained on three discrimination tasks under various combinations of motivational states. Their results indicated that, when ECS was administered immediately following acquisition of the third task, not only was subsequent retention of this task impaired, but also that of previous tasks which involved the same type of incentive, irregardless of task sequencing. These findings were interpreted as indicating that the production of retrograde amnesia depends not upon the age of the memory, but upon the similarity of motivational states aroused during training and prior to the administration of ECS. More specifically, they suggest that ECS impairs recall of memories involving the same motivational state that was active at the time of ECS administration. However, this hypothesis also has difficulty dealing with the negative findings of the reinstatement effect. Specifically, in the present investigation, the reason why the second noncontingent footshock should not produce a similar motivational state as did the first, is unclear.

Thompson and Grossman (1972) reported a successful attempt at partial replication of Meyer's work. Furthermore, they found that the administration of a second ECS 15 minutes prior to retention testing completely restored retention. These authors suggested that memories of events, established under a similar motivational state as was evoked prior to the administration of ECS, become stored in abnormal brain states, resulting in impaired recall. The administration of a second ECS prior to retention testing is assumed to facilitate recall by reproducing the abnormal state in which these memories were stored. Obviously, the production of retrograde amnesia by means of motivational control necessitates a great deal of future research to determine the basis of this phenomenon.

At present, none of these explanations seem to account for all of the experimental findings on the reinstatement effect. Because this phenomenon has eluded adequate assessment, the reinstatement effect offers no conclusive support to any of these alternatives to the consolidation interpretation of retrograde amnesia.

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