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A Comparison of ECS and Drug Induced State-Dependent Learning

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A COMPARISON OF ECS AND DRUG INDUCED STATE-DEPENDENT LEARNING

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CHAPTER I

INTRODUCTION

Early work on state-dependent or "dissociated" learning has been credited to Girden and Culler (1937), who studied a leg flexion response in dogs. They found that dogs conditioned while nondrugged failed to elicit the conditioned response (CR) while drugged with crude curare. Dogs conditioned while drugged demonstrated no CRs when tested without the drug. However, the CR returned in both cases when the original drugged or nondrugged condition present during acquisition were reinstated. The absence of transfer between drug states was termed "dissociation of learning" by these experimenters.

Later experiments produced these additional results: (a) responses learned while under the influence of curare extracts such as dihydro-beta-erythroidine (Girden, 1942) and physostigmine (Case & Funderbunk, 1947) were not obtained when the subjects were tested in the nondrugged state, and (b) no dissociation effect was obtained with a refined form of curare, d-tubocurarine (Arbit, 1958; Gardner & McCulloch, 1962). Overton (1964) concluded that most central acting agents seem to produce the state-dependent effect while

peripheral agents do not. More recent work indicates that the state-dependent phenomenon is obtained with a variety of central acting drugs (Bloch & Silva, 1959; Evans & Patton, 1970; Mayse & Morris, 1969; Moroz, 1959; Otis, 1964; Overton, 1964; Rosenzweig, Krech, & Bennett, 1956) in a variety of situations (Evans & Patton, 1970; Mayse & Morris, 1969; Moroz, 1959; Otis, 1964; Overton, 1964; Rushton, Steinberg, & Tinson, 1963), and occurs in humans as well as infra-human species (Bustamante, Rossello, Jordan, Pradera, & Insua, 1968; Bustamante, Jordan, Vila, Gonzalez, & Insua, 1970; Goodwin, Powell, Bremer, Hoine, & Stern, 1969; Tarter, 1970).

Recently Neilson (1968) proposed a state-dependency hypothesis to explain the disruptive effect of electro-convulsive shock (ECS) on learning. Such experiments usually employ footshock (FS) as an integral part of either a single trial passive avoidance or conditioned fear paradigm. ECS is administered shortly after the trial and subjects tested later demonstrate little or no retention of the conditioning trial, i.e., amnesia. The usual interpretation of these data is in terms of the consolidation hypothesis, which states that ECS produces a disruption of the formation of memory at short acquisition-ECS intervals, such as .5 seconds. However, Neilson found that rats administered FS-ECS prior to passive avoidance training, where they again received ECS, showed retention when tested 24 hours later. Also, rats given

passive avoidance training followed by ECS showed amnesia at the 24 hour test, but then recovery of memory at the 96 hour test. In another experiment, Neilson found that ECS raised brain thresholds and that these returned to pre-ECS levels approximately 96 hours afterwards. Thus Neilson found that when training and recall sessions were given in the same brain excitability states, there was no retention deficit. He also found that if brain excitability states were not the same during acquisition and recall, then retention did not occur. DeVietti and Larson (1970) reported that rats administered FS-ECS 24 hours after a single fear conditioning trial showed attenuated performance when tested 24 hours later (amnesia), but showed retention at the 96 hour test. These results clearly supported Neilson's (1968) state-dependent hypothesis.

The purpose of the present experiment is twofold: (a) to determine if FS and ECS or just ECS can be used as an agent to produce "dissociated" learning in a multi-trial procedure, and (b) if shown, to determine the effectiveness of these agents relative to three different dosages of sodium pentobarbital preselected to produce no, moderate, and complete dissociation (Overton, 1964).

CHAPTER II

METHOD

Subjects

Subjects were 78 male Long-Evans rats from the Central Washington State College Psychology animal colony, aged 90-120 days at the start of the experiment, and were individually housed and maintained on water and Purina lab chow ad lib.

Apparatus

The apparatus was a water T maze. The maze was constructed of 1/4 inch plywood. The walls were 15 inches high. The start alley measured 6 inches wide by 10 inches long, the arms 6 inches wide by 12 1/2 inches long, and the goal platforms were 5 1/2 inches wide by 7 inches long. The maze was placed in a glass aquarium that measured 30 inches wide by 16 inches deep by 16 inches high. The water level in the maze was 8 inches and the goal platforms were 8 1/4 inches from the bottom of the aquarium. The goal platforms were covered with a fine wire mesh. Barriers, which were not visible from the choice point, could be inserted into the maze to prevent entrance onto the incorrect goal platform. The entire maze was painted flat gray, and a

sheet of paper painted the same color was wrapped around the outside of the aquarium to reduce reflection and visual cues. The maze was filled with fresh cold tap water (54°-60°) prior to each session.

Additional apparatus consisted of a shock box and an ECS apparatus. The shock box was made of plexiglas and measured 20 cm. by 23 cm. by 20 cm. high. The grid floor was made of stainless steel rods 0.33 cm. in diameter, spaced 1 cm. apart. The footshock administered in the shock box was 2 sec., 1.0 ma., 60 Hz sine wave polarized electric shock to the grid floor. The ECS apparatus was designed to deliver 92 ma. for 200 msec. through modified alligator clips attached to the ears.

State Producing Agents

A high drug state was produced by a 25 mg./kg. injection of sodium pentobarbital. The medium drug state was produced by a lower dosage of 12 mg./kg. of sodium pentobarbital. The nondrugged state was produced by injection of isotonic saline in the same volume. Both the sodium pentobarbital and the isotonic saline were injected intraperitoneally 15-20 minutes before the start of the experimental session. Since the higher dosage of sodium pentobarbital produced a state of anesthesia deep enough that the subjects failed to respond to the water, the trials were given when the subjects had recovered enough to move through the maze.

Return of the righting response was used as an indicator of the subjects' ability to swim through the maze. These dosages and procedures were chosen from the results of previous work (Mayse & Morris, 1969; Overton, 1964).

The other two state producing agents tested were the ECS and the FS-ECS. In the case of the FS-ECS group, ECS was administered .5 seconds after the termination of the FS. Since these procedures produced unconsciousness, the ECS and FS-ECS subjects started training 24 hours after administration of either of these two treatments. Throughout this text, the terminology of O-Agent (training-treatment) will refer to the condition in which the group was trained with no agent and then retrained with the agent. Similarly, Agent-O (treatment-training) refers to the condition in which the group was trained under an agent and retrained with no agent.

Procedure

Each subject was handled for a 3-minute period for 3 days prior to administration of a state producing agent. Modified alligator clips were attached to the ears of the ECS and FS-ECS subjects during this time to familiarize them with the clips. Each of the 78 subjects was individually trained to escape from water in a T maze. Each subject was dropped, facing the experimenter, into the center arm of the maze and was allowed to swim freely until he reached and remained on either of the two accessible goal platforms. After

an interval of 5 seconds, the subject was removed from the goal platform and the opposite goal was assigned as the correct goal to which the subject had to complete 4 out of 4 correct responses to reach the learning criterion, chosen on the basis of pilot work. A record was made on every trial of which arm the subject entered first. A subject was judged to have entered an arm when half its body left the choice point, an area 6 inches square.

Each subject was then retrained to the same criterion 72 hours after the training session, i.e., 96 hours after the administration of FS-ECS or ECS in the case of the ECS groups.

The 78 subjects were divided into 13 groups of 6 each, differentiated on the basis of both treatment and order of treatment. These included 8 experimental groups which trained and retrained under different levels of the same agent and 5 control groups which trained and retrained under the same levels of an agent. The experiment was run in six replications, with one subject from each group being trained and retrained each week. Table 1, page 8, summarizes the groups and the treatments used.

TABLE 1

Groups and Treatments

Control Groups

Training	Retraining
High drug	High drug
Medium drug	Medium drug
No drug	No drug
FS-ECS	FS-ECS
ECS	ECS

Experimental Groups

Training	Retraining
High drug	No drug
No drug	High drug
Medium drug	No drug
No drug	Medium drug
FS-ECS	No FS-ECS
No FS-ECS	FS-ECS
ECS	No ECS
No ECS	ECS

CHAPTER III

RESULTS AND DISCUSSION

Control Groups

The control groups served three purposes: (a) to compare with the experimental groups, (b) to determine if the task used was sensitive, and (c) to determine if groups trained and retrained differently as a function of the agent used. Analysis of variance of the control groups' performance on training and retraining, summarized in Table 2, page 10, showed that the groups did not differ ($p > .05$) as a function of the agent used. Also, the lack of a reliable ($p > .05$) Training X Groups interaction indicated that all groups reached criterion in the same number of trials during training, and also reached criterion at the same rate during retraining. A reliable decrease ($p < .01$) in trials to criterion on retraining, relative to training, indicated that the task was sensitive to retention of memory, i.e., subjects showed a reliable savings during retraining.

Experimental Groups

Analysis of variance of the experimental groups' performance on training and retraining is shown in Table 3, page 11. As noted in Table 3, most of the main effects and

TABLE 2

Analysis of Variance: Control Groups

Source	df	MS	F
Groups	4	.52	.90
Ss within Groups	25	.58	
Training	1	86.40	193.46**
Training X Groups	4	.11	.24
Training X Ss within Groups	25	.45	

**$p < .01$

TABLE 3

Analysis of Variance: Experimental Groups

Source	df	MS	F
Between	47		
Order	1	.37	.37
Groups	3	10.47	10.27**
Order X Groups	3	6.24	6.11**
Ss within Groups	40	1.02	
Within	48		
Training	1	37.50	30.91**
Training X Order	1	7.05	5.81*
Training X Groups	3	4.75	3.92*
Training X Order X Groups	3	3.57	2.94*
Training X Ss within Groups	40	1.21	

*$p < .05$ **$p < .01$

all two-way interactions were reliable. The reader is directed to Tables 4-6, pages 13, 15, and 17 respectively, and Figures 1-3, pages 14, 16, and 18 respectively, for a complete description of the interactions.

The finding that the triple interaction (Training X Order X Groups) was reliable ($p < .05$) suggests that the interpretation of the main effects and the two-way interactions be tempered since one must consider the levels of the other two independent variables when looking at the effects of the remaining independent variable. The analysis of the simple effects (Kirk, 1968) of the Training X Order X Groups' interaction, presented in Table 7, page 19, and plotted in Figure 4, page 20, supplies this analysis.

The analysis showed that all 4 groups of both treatment orders reached the training criterion in the same number of trials ($p > .05$), but differences were found among the groups of both orders on the retraining. In the case of the O-Agent groups, application of the Neuman-Keuls multiple range test to the 4 retraining means indicated that the High and Medium drug groups were the same ($p > .05$), and these took more trials to reach criterion than the FS-ECS and ECS groups, which did not differ ($p > .05$). Therefore, in the O-Agent order, the drugs produced more dissociation than either the ECS or FS-ECS condition.

TABLE 4

Analysis of the Simple Effects of the Order X Groups' Interaction

Source	df	MS	F
Among Groups at O-Agent Order[a]	3	10.96	10.75**
Among Groups at Agent-O Order[b]	3	5.74	5.63**
Ss within Groups	40	1.02	
High group across Order	1	4.17	4.09*
Medium group across Order	1	1.04	1.02
ECS group across Order	1	.37	1
FS-ECS group across Order	1	13.50	13.23**
Ss within Groups	40	1.02	

*$p < .05$ **$p < .01$

[a]Neuman-Keuls multiple range test showed that both drug groups were equal ($p > .05$), but took more trials to criterion than the FS-ECS and ECS groups ($p < .01$), which were also equal ($p > .05$).

[b]Neuman-Keuls showed that the FS-ECS, High drug, and Medium drug groups were equal ($p > .05$), but all 3 groups took more trials to reach criterion than the ECS group ($p < .05$).

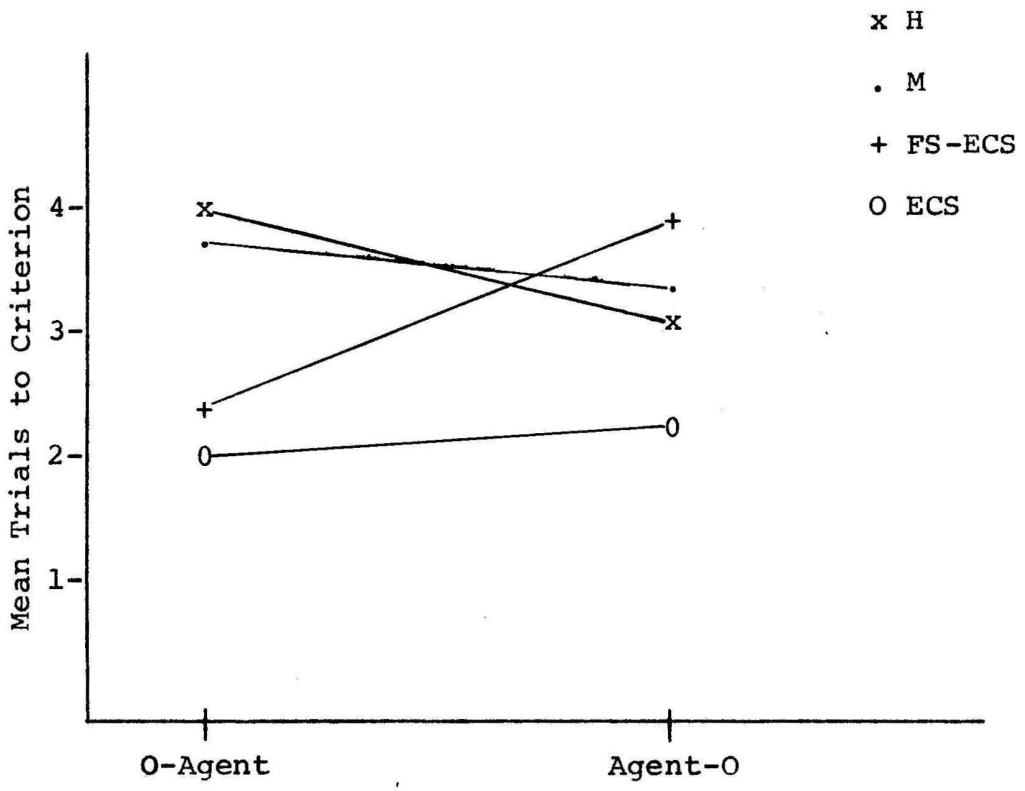

Figure 1. Order X Groups' Interaction showing the effects of the different agents as a function of order of presentation.

TABLE 5

Analysis of the Simple Effects of the Training X Order Interaction

Source	df	MS	F
Between Orders at Trn.	1	5.33	4.76*
Between Orders at Retrn.	1	2.08	1.86
Pooled Error Term	80	1.12	
O-Agent across Trn. and Retrn.	1	6.02	4.97*
Agent-O across Trn. and Retrn.	1	38.52	31.83**
Trn. X Ss within Groups	40	1.21	

*$p < .05$ **$p < .01$

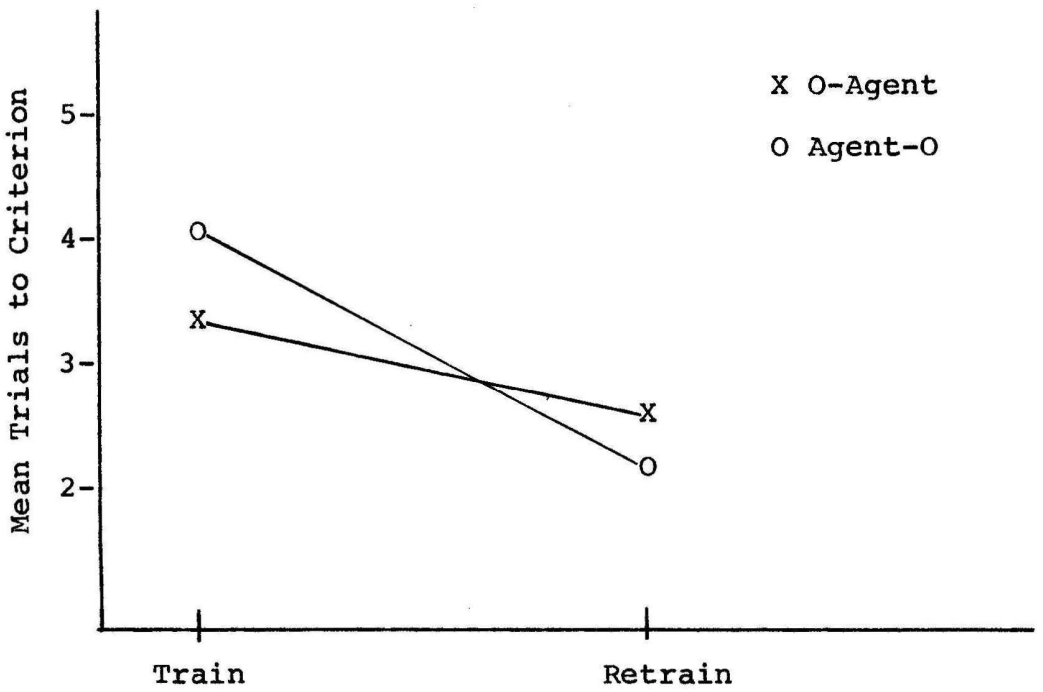

Figure 2. Training X Order Interaction showing the effects of the order of agent presentation on training and retraining.

TABLE 6

Analysis of the Simple Effects of the Training X Groups Interaction

Source	df	MS	F
Training	3	2.97	2.65
Retraining[a]	3	12.25	10.94**
Pooled Error Term	80	1.12	
High across Trn. and Retrn.	1	0	0
Medium across Trn. and Retrn.	1	15.04	12.43**
FS-ECS across Trn. and Retrn.	1	10.67	8.81**
ECS across Trn. and Retrn.	1	26.04	21.52**
Error Term	40	1.21	

**$p < .01$

[a]Neuman-Keuls showed the ECS group retrained in fewer trials than the other 3 groups ($p < .01$), which did not differ from one another ($p > .05$).

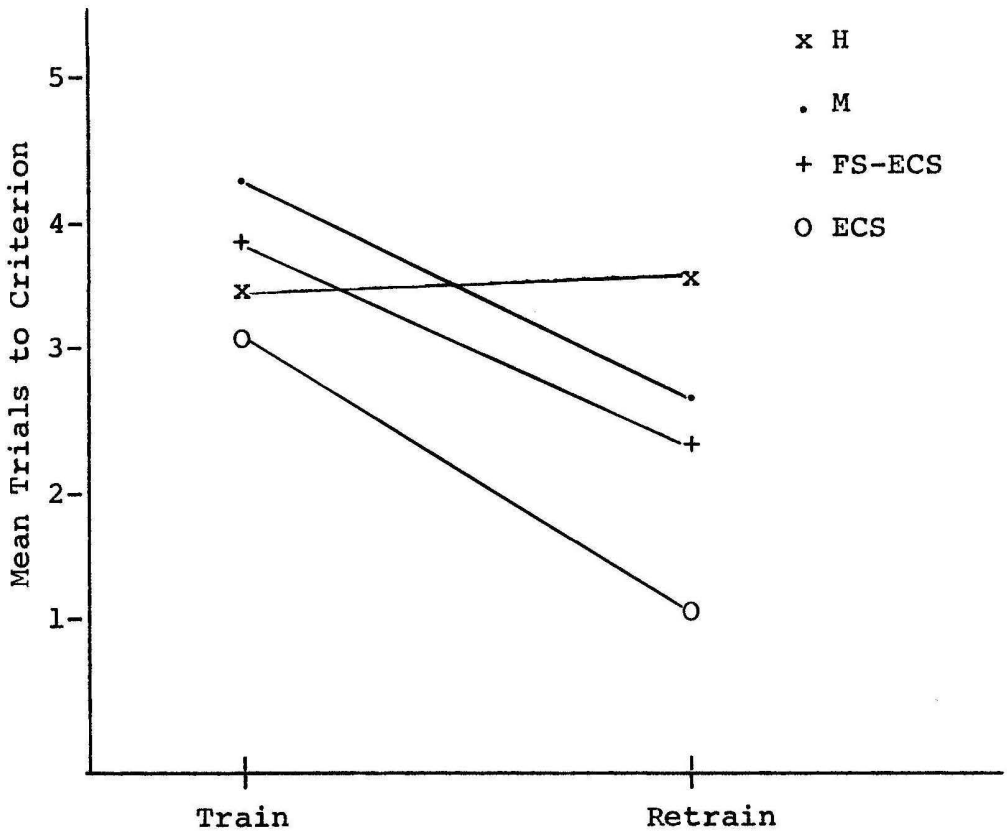

Figure 3. Training X Groups' Interaction showing the effect of the various agents at training and retraining.

TABLE 7

Analysis of Variance: Training X Order X Groups Effects on Experimental Groups Analysis

Source	df	MS	F
Between Ss			
O-Agent Groups at Trn.	3	1.37	1.22
Agent-O Groups at Trn.	3	1.82	1.62
O-Agent Groups at Retrn.[a]	3	15.33	13.69**
Agent-O Groups at Retrn.[b]	3	6.50	5.80**
Pooled Error Term	80	1.12	
Within Ss			
O-High across Trn. and Retrn.	1	4.08	3.37
O-Medium across Trn. and Retrn.	1	.75	1
O-FS-ECS across Trn. and Retrn.	1	10.08	8.33**
O-ECS across Trn. and Retrn.	1	8.33	6.88**
High-O across Trn. and Retrn.	1	4.08	3.37
Medium-O across Trn. and Retrn.	1	21.33	17.63**
FS-ECS-O across Trn. and Retrn.	1	2.08	1.72
ECS-O across Trn. and Retrn.	1	18.75	15.49**
Training X Ss within Groups	40	1.21	

**$p < .01$

[a]Neuman-Keuls showed that the High and Medium groups did not differ in trials to retraining criterion ($p > .05$), but took more trials than the FS-ECS and ECS groups ($p < .01$), which were the same ($p > .05$).

[b]Neuman-Keuls showed that the FS-ECS, High, and Medium groups did not differ in retraining trials to criterion ($p > .05$), but the FS-ECS group took more trials than the ECS group ($p < .01$), and the High and Medium groups did not differ from the ECS group ($p > .05$).

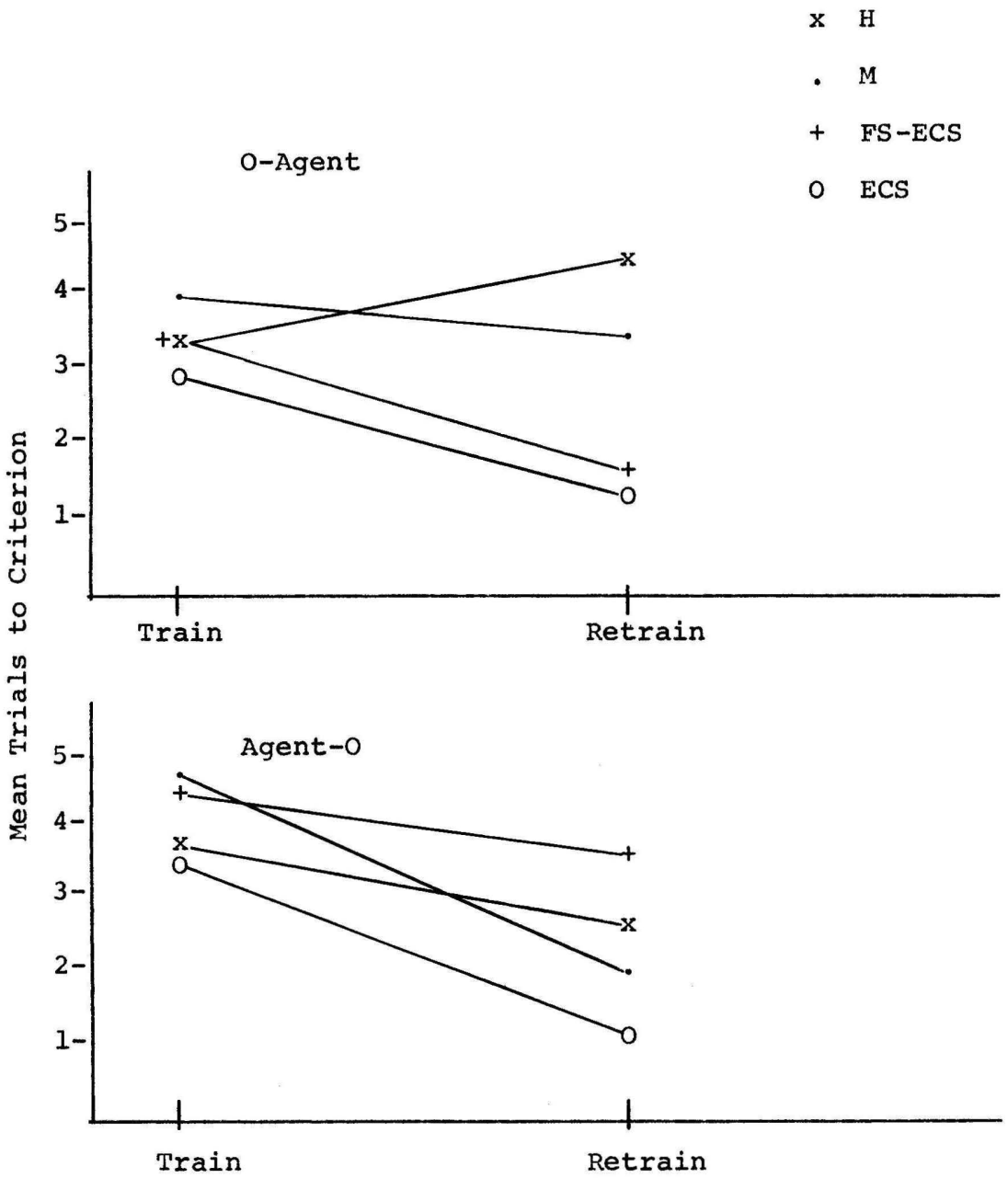

Figure 4. Training X Groups X Order Interaction showing the effects of each agent in each treatment order at both training and retraining.

In the Agent-O order, the FS-ECS group required more trials to retrain ($p < .01$) than the ECS group; the FS-ECS group did not differ from the High and Medium drug groups ($p > .05$), and the High and Medium drug groups did not differ from the ECS group ($p > .05$). Thus, in the Agent-O order, FS-ECS condition was more clearly effective in producing a dissociation effect than the ECS, High, or Medium drug conditions.

Comparisons across training and retraining reflect the degree of dissociation produced by the agents. The lack of a significant effect ($p > .05$) indicates an effect consistent with a dissociation effect since the group showed no reliable savings during retraining. Thus, in the O-Agent treatment order both levels of drugs produced a dissociation effect ($p > .05$), while ECS and FS-ECS did not ($p < .01$).

In the Agent-O order, the FS-ECS and High drug treatments produced dissociation ($p > .05$), while the ECS and Medium drug treatments did not ($p < .01$).

Control versus Experimental Groups

Analysis of variance on only the retraining data of all control groups and experimental groups was performed to determine the effectiveness of the agents used relative to control groups which did not receive agent shifts between training and retraining. The analysis is shown in Table 8, page 22, and the plot in Figure 5, page 23. A reliable Groups effect ($p < .01$) indicated that groups retrained

TABLE 8

Analysis of Variance: Experimental and Control Groups Retraining

Source	df	MS	F
Groups	12	8.51	11.99**
Ss within Groups	65	.71	

**$p < .01$

differently depending on the state producing agent used. A series of comparisons among groups was done using the Neuman-Keuls multiple range test comparing: (a) control groups, (b) O-Agent groups versus appropriate controls, (c) Agent-O groups versus appropriate controls, (d) O-Agent groups, (e) Agent-O groups, and (f) O-Agent versus Agent-O for each agent.

Control groups. Neuman-Keuls multiple range test showed that all control groups were equal ($p > .05$), requiring the same number of trials to attain the retraining criterion.

O-Agent groups versus appropriate controls. The High and Medium drug groups differed ($p < .01$) from the O control group, taking more trials to reach the retraining criterion. The FS-ECS and ECS groups did not differ ($p > .05$) from the O control group. Thus, additional evidence was obtained demonstrating the dissociation effects of the drug treatment

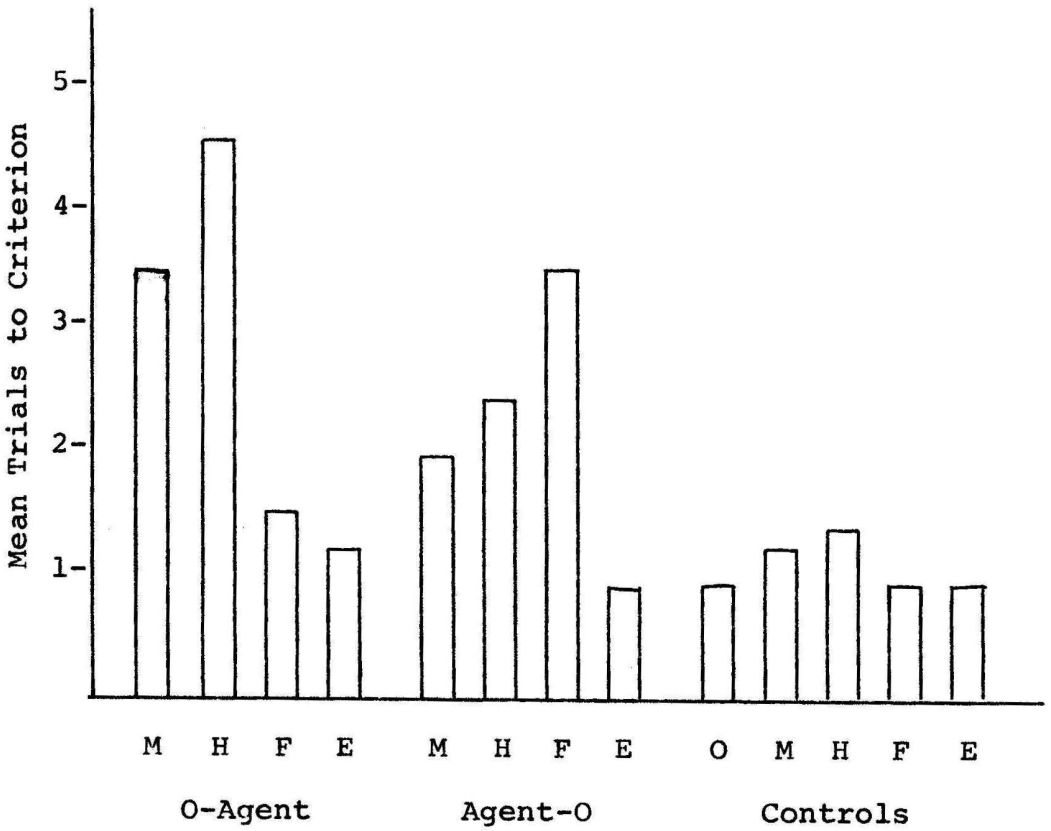

Figure 5. Control groups and Experimental groups retraining data. M - Medium drug, H - High drug, F - FS-ECS, and E - ECS.

and the lack of this effect in the case of the ECS and FS-ECS treatments in this order.

Agent-O versus appropriate controls. The High drug, Medium drug, and ECS groups did not differ from their respective control groups ($p > .05$), taking the same number of trials to reach the retraining criterion. The FS-ECS group required more trials ($p < .01$) to retrain than its control group. This analysis clearly shows that only the FS-ECS treatment produced dissociation effects in this order and that both drug treatments and the ECS treatment were ineffective in this order.

O-Agent groups. The High drug group was different ($p < .05$) from the Medium drug group, and different ($p < .01$) from all other O-Agent groups, requiring more trials to reach the retraining criterion. The Medium drug group took more trials to reach the retraining criterion ($p < .01$) than the FS-ECS and ECS groups, which were equal ($p > .05$). Again, a clear differentiation between the drug treatments and the FS-ECS and ECS treatments was found. In addition, a graded effect between drug treatments was obtained.

Agent-O groups. The FS-ECS group took more trials to reach the retraining criterion than the High drug group ($p < .05$), and more trials than all other Agent-O groups ($p < .01$). The reader will notice that this finding is not consistent with a previous statement (page 21). However, the

present analysis is considered more sensitive because of the smaller error term (Table 8, page 22). The larger error term in Table 7, page 19, was due to the fact that both training and retraining data were used and the training variability served to inflate the error term, thus hindering retraining comparisons. The High drug, Medium drug, and ECS groups were equal ($p > .05$), retraining in the same number of trials. This analysis shows the superiority of the FS-ECS treatment in producing dissociation effects in the Agent-O order.

O-Agent versus Agent O. The O-High drug group took more trials to reach the retraining criterion than the High drug-O group, but the difference was not significant ($p > .05$), indicating that the High drug condition produced a comparable dissociation effect in both orders. The O-Medium drug group required more trials to reach the retraining criterion than the Medium drug-O group ($p < .01$), which shows a greater dissociation effect was found in the O-Agent order. The FS-ECS-O group took more trials than the O-FS-ECS group to retrain ($p < .01$), showing a greater dissociation effect in the Agent-O order. The ECS-O and O-ECS groups did not differ in trials to criterion ($p > .05$), showing that this treatment produced the same effect in both orders. However, all other analyses showed no state dependent effect was obtained with this treatment.

CHAPTER IV

GENERAL DISCUSSION

The results showed that FS-ECS can be used as an agent to produce state dependent learning. However, this effect was noted only in the treatment-training order. Contrary to recent findings (Thompson & Neely, 1970), ECS only showed no dissociation effects in either treatment-training order. This finding that ECS administered 72 hours after training, i.e., 24 hours before retraining, or 24 hours before training, i.e., 96 hours before retraining, produced no dissociation effects indicates that ECS alone produces no state change without being preceded by FS, when administration and testing intervals are a matter of days rather than minutes, as used by Thompson and Neely (1970).

Again, the combination of FS and ECS produced a state dependent effect only in the treatment-training order. DeVietti and Larson (1970) also found a greater state dependent effect in the treatment-training order. The fact that the FS-ECS group showed the effect in the Agent-O order and the drug groups did not, suggests that the FS-ECS effectiveness might be as complete as the drugs were in the O-Agent order.

The tendency for drugs to produce a more complete dissociation in the training-treatment order has been shown (Evans & Patton, 1970; Mayse & Morris, 1969; Overton, 1964). Recently, however, Goodwin, et al. (1969), in a study using alcohol and humans, found that the treatment-training order produced a greater dissociation effect than the reverse order. Tarter's (1970) findings with alcohol support these conclusions as well. Thus, the state dependent effects of FS-ECS in the present study seem more related to the dissociation produced by alcohol than that produced by sodium pentobarbital since the more complete dissociation was obtained in the treatment-training order.

The results showed that both dosages of sodium pentobarbital produced a state change in the O-Agent order, but it also produced ataxia which may have added to the effect. This interpretation could help to explain the effect in the training-treatment order and the lack of such an effect in the reverse order.

An explanation of the dissociation of FS-ECS in the treatment-training order only may be that the dissociation effect of FS and ECS differs in degree depending on the treatment-training order. Another possibility may be the task and measures used. Most ECS work employs a single trial paradigm. The use of the repeated trials task may serve to confound the effect of state change.

The complexity of the task has been shown to be critical in obtaining state dependent effects (Goodwin, et al., 1969). It may be that other tasks are more sensitive to the effects of FS-ECS in the treatment-training order and to ECS only in both orders.

To summarize, this study shows that FS and ECS can produce state dependent learning and that the completeness of the state produced is comparable to that produced by drugs.

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APPENDIX

APPENDIX

FIRST CRITERION TRIAL ON TRAINING AND RETRAINING FOR CONTROL GROUPS AND EXPERIMENTAL GROUPS

Subject	CONTROLS									
	O		Medium		High		FS-ECS		ECS	
	T	R	T	R	T	R	T	R	T	R
1	3	1	3	2	6	1	4	1	4	1
2	5	1	3	1	5	3	4	1	4	1
3	3	1	3	1	4	1	3	1	4	1
4	4	1	4	1	2	1	3	1	3	1
5	2	1	3	1	4	1	3	1	4	1
6	3	1	4	1	3	1	3	1	4	1

Subject	O-Agent							
	Medium		High		FS-ECS		ECS	
	T	R	T	R	T	R	T	R
1	5	5	2	5	6	1	3	1
2	3	4	3	5	2	1	2	2
3	4	2	3	2	3	2	3	1
4	4	3	3	4	3	1	3	1
5	4	4	5	6	3	3	3	1
6	4	3	4	5	3	1	3	1

Subject	Agent-O							
	Medium		High		FS-ECS		ECS	
	T	R	T	R	T	R	T	R
1	8	2	5	3	5	1	5	1
2	5	1	4	1	4	3	3	1
3	3	3	3	4	6	3	3	1
4	4	2	4	2	4	5	3	1
5	5	2	3	3	4	6	3	1
6	3	2	3	2	3	3	4	1