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Effect of reminder stimuli on weak memories

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THE EFFECT OF REMINDER STIMULI ON WEAK MEMORIES

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Electroconvulsive shock (ECS) was once thought by most researchers to disrupt memory by preventing storage of information when learning was followed closely by ECS. Many recent studies have indicated that retrieval processes may be disrupted rather than storage. The major reason for alternative interpretation is the finding of recovery of memory after administration of a non-training treatment known as a reminder.

It is not now known whether reminders facilitate memory recovery by somehow promoting better retrieval or instead summating with subthreshold memories to improve retention. If summation is occurring, memories that are weak because of less efficient training should also be improved by reminders. This experiment tests that hypothesis.

Forty-six rats were either given ECS or trained to a criterion less strict than those given ECS on a two-way active avoidance task. This less strict training constituted a "weak training" group. All animals were then given either no reminder, exposure to the conditional stimulus and training apparatus, or this exposure followed by strychnine injection. Since strychnine improves retention after acquisition, it should serve to improve recovery after a reminder.

Improvement with reminder and reminder+strychnine was much greater in groups given ECS than in weakly trained groups. This indicates that these traces, although similar in strength, are not really the same in nature and that retrieval promotion is the stronger interpretation of these results.

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CHAPTER I

Experimenters attempting to study memory by its disruption have typically used electroconvulsive shock (ECS) or various drugs administered soon after learning and observed their effects on retention some time later. The deficits observed were originally interpreted in terms of disruption of a consolidation process, which involves transfer of a trace from a short-term "holding" process to a more permanent form (e.g., John, 1967). This would consequently lead to loss of the memory trace. Unfortunately for this point of view, spontaneous recovery of the memory was found in a few cases (Zinkin and Miller, 1967). Prompted by this development, researchers began to check for savings at various time intervals past the initial test and after the animal was exposed to certain "reminder" stimuli. Reminders, also known as reactivation treatments (Spear, 1973), are presumably some subset of the stimuli impinging on the organism during acquisition of the trace and include both external and internal stimuli. They are most often given in a form not sufficient for training to occur. Common reminders include non-contingent footshock (e.g., Miller and Springer, 1972), presentation of the training cues (Kesner and Conner, 1974), injection of ACTH or the fragment $ACTH_{4-9}$ (Klein, 1972; Keyes, 1974; Rigter, Van Riezen and deWied, 1974), and confinement in the experimental apparatus (Davis and Hirtzel, 1970). Confinement, or detention, has been found to facilitate retrieval by Davis and Hirtzel, as well as others, but instead was additive to the effects of the amnesic agent in experiments by Geller, Robustelli and Jarvik (1971). Since the experimental manipulations of detention are the same as those for extinction, it is possible that this procedure works both to recall weak memories and to also decrease their strength. Some chemical agents which facilitate acquisition, such as strychnine, have been tried as reminders, but have not been able to improve retention when not administered at a time the trace is presumably activated, such as during acquisition or after a reminder (Gordon and Spear, 1973; Springer and Miller, 1972; Duncan and Hunt, 1972).

Results such as these have caused examination of a number of subissues not previously considered in detail in memory research. The two major questions in this category would be: in what form is a memory trace left after an ECS, and how does a reminder serve to improve retention? A great deal of attention has been devoted to the possible effects of ECS apart from the originally assumed amnesic effect. Many researchers (e.g., Coons and Miller, 1960) have suggested that an ECS, if felt, could serve as a punishing stimulus that would account for many apparent findings of amnesia, particularly in active avoidance tasks, where an ECS delivered upon successful escape to the "safe" side of a shuttle box could, if felt, prove more aversive than the shock used as the training stimulus for that task. This interpretation does not account for a large range of studies finding amnesia in other tasks, particularly where a passive avoidance paradigm is used. Here, as Madsen and McGaugh (1961) point out, a punishing ECS should act additively to the punishing stimulus to yield an even stronger avoidance tendency, rather than the amnesia usually found.

The apparent amnesia found after passive avoidance tasks has been otherwise explained as simply a decrease in response latency after ECS (Routtenberg and Kay, 1965). Any such effect, while indicating caution in using latency measures, still fails to explain why small differences in time of ECS after learning are critical in amount of amnesia produced or why amnesia is found when non-latency measures are used (Deutsch, 1973).

A further attempt to weaken the retrograde amnesia interpretation comes from researchers who propose that ECS disrupts an incubation process wherein an avoidance response increases in strength (incubates) over time (Spevack and Suboski, 1969; Pinel and Cooper, 1966; Chorover and Schiller, 1965). In the normal avoidance paradigm, little retention is shown after training, but progressively increases, as is demonstrated when different groups are tested at various intervals after acquisition. If ECS disrupts this incubation process, then apparent amnesia will result. Spevack and Suboski (1969) review the relevant literature and conclude that three separate effects of ECS are demonstrable. The first is a punishing effect, found after many administrations, but not usually demonstrable after a single application of ECS. The second is the incubation disruption process and the third the usual retrograde amnesia interpretation. Dawson (1971) points out, however, that similar and very long gradients of amnesia can be found in tasks with no demonstrable incubation gradients and in general little variance can be attributed to this sort of interpretation. In particular, appetetive tasks have no incubation gradients at all. It seems that the similarity of the incubation curve to the ECS gradient is merely a property of a few isolated cases and is not generally successful as an explanatory device. Buckholtz and Bowman (1972) found a clear disjunction between the retrograde amnesia and incubation curves, suggesting that even all avoidance tasks do not produce incubation curves like those produced by ECS gradients.

Other experimenters have attempted to explain the gradients obtained with ECS-produced amnesia by resorting to a state-dependent learning interpretation. This line of reasoning stems largely from the finding that a pre-acquisition ECS attenuates the amnesia produced by an ECS following acquisition. ECS may then produce an altered state that lasts for days, such that learning in the normal state, usually prior to ECS, is not easily recovered (DeVietti and Larson, 1971a,b). If this were the important variable, nevertheless, then this would predict far more spontaneous recovery of the task after the ECS-induced state has worn off than is actually found. Further, retention would be better in the pre-acquisition ECS, post-acquisition ECS paradigm than normally found, since the state is identical in both cases. A modification of this position suggests that good retrieval must occur in the presence of the same state in which consolidation occurs, i.e., that present immediately after acquisition. Good evidence for this is that retention tests given soon after an ECS do yield good retention (Thompson and Grossman, 1972). This theory, however, would predict that when the animal once again returns to the normal state retrieval failure would occur and amnesia would again result. Although retention is improved after a second ECS, which presumably could also function as a reminder stimulus, memories regained at this time do not fade after the normal physiological state is regained (Miller, Malinowski, Puk and Springer, 1972). This theory further does not account well for improved retention found after reminders less likely to involve any state changes, such as apparatus exposure.

It seems likely that any experimental paradigm employing ECS will have certain alternatives to a strict retrograde amnesia interpretation that are not only justifiable, but even perhaps indistinguishable in prediction from the amnesic viewpoint. Nevertheless, a great lack of generality for all such interpretations seems to be the rule for all such alternatives; only the retrograde amnesia interpretation seems robust across a great variety of reinforcers, tasks, and other procedural variables. Perhaps the best point to be derived from these studies is that a gross manipulation such as ECS is certain to have a wide variety of effects and care must be taken to choose a task that will not exploit unintended variables.

While a retrograde amnesia interpretation of the effects of ECS seems still preferable to the alternatives, the consolidation disruption hypothesis has come under somewhat heavier attack as the specific mechanism involved in the memory loss. The reminder studies have caused many researchers to suggest that no loss of information is caused by an ECS, but instead retrieval failure is induced in some manner (e.g., Spear, 1973; Miller and Springer, 1973). Retrieval might be defined as that set of neural traces that is necessary to recall and express a trace which has been formed, while the trace itself is the set of informational attributes otherwise required for performance of the learned response (Miller and Springer, 1973), such as the CS-UCS association. Miller and Springer suggest that memories may be very quickly encoded and thus immune to present manipulations, but that access to this engram can be lost. Logically, therefore, consolidation theory must suffer from any comparison with retrieval theory, as any savings shown by the organism demonstrates that some storage has occurred, while failure to find savings cannot rule out retrieval failure, as the memory might still be accessible under a different set of manipulations.

Since tetrieval cues are also a form of memory and presumably must also be encoded and consolidated, some uncertainty must exist as to why one trace and not the other should be disrupted by ECS; additionally, the separability of the two may not always be easy. Consolidation, as stated earlier, refers to the transfer of information from a temporary to a longer-lasting form. While consolidation theorists may speak of "interruption" and "restarting" of consolidation under certain circumstances (Albert, 1966), still, at some interval any information not consolidated must necessarily be lost; the only way of regaining it should be through a training experience containing at least that lost information. If a test shows information is present not found with a prior test, and no training intervenes, then the prior deficit must be attributed to a retrieval failure at that time. To refer to a restarting of consolidation after a long interval would imply that the information to be consolidated is still available; this would imply that this information is already in some form of long term storage. A common example of such a deficit, independent of any experimental manipulations, is the Kamin effect (Spear, 1973). Animals trained on an avoidance task show deficits at 24 hours with respect to animals tested at 3, 48, or 96 hours. Since consolidation is not interrupted by an amnesic agent and the information is available at longer intervals, obviously the deficit at 24 hours must be attributed to some form of retrieval or motivational failure. Perhaps a similar sort of process is occurring in paradigms involving experimentally induced amnesia.

In trying to distinguish the retrieval theory from the consolidation interpretation, perhaps the first consideration concerns the permanence of the memory deficit seen after ECS. If information is lost, then amnesia should be permanent barring replacement of the lost information. Zinkin and Miller (1967), as noted previously, found "spontaneous recovery" of the memory trace in animals repeatedly tested at various intervals after the ECS. Most researchers have found permanence of amnesia when the repeated testing procedure is replaced by groups tested separately at only one interval per group (Luttges and McGaugh, 1967; Herz and Peeke, 1968). King and Glasser (1970) found permanence with separate groups up to four weeks, but gradual recovery was seen when the groups, after their initial test, were given repeated tests. It seems certain that the reexposure to the training apparatus is the causative agent in recovery of the memory. Nevertheless, this recovery seems to speak against a strict loss of information interpretation of the retrograde amnesia effect. Apparatus cues are not normally considered information critical to the performance of an avoidance task. It could be that certain secondary reinforcing properties of the apparatus survives the ECS and could serve as an additional training experience upon reexposure to the training environment. Schneider et al. (1974) suggest that this is occurring and find that the repeated trials procedure is ineffective when the conditioning properties of the test trials are reduced, as by eliminating the response, altering the apparatus cues or extinguishing the conditioned fear by confining the animals to the apparatus in the first test trial. It should be noted, however, that secondary reinforcement is typically a weak, if reliable, phenomenon, whereas reminder studies show dramatic increases in response strength probably unparalleled in any higher order conditioning studies, with the reminder being almost any fractional portion of the training situation (Spear, 1973). Furthermore, since severity of amnesia tends to vary directly with complexity of the training situation and inversely with intensity of the reinforcer, one would expect the weak and less easily formed secondary associations to be the most subsceptible to the amnesic agent, rather than the ones which survive the treatment. Also, almost all responses show decrements proportional to the similarities between training and testing cues. The manipulations of Schneider et al. would seem to only prove that retrieved memories are subject to the same rules of extinction and generalization decrement as normal memories and that effective retrieval depends upon similarity between training and testing cues.

The reminder effect, which perhaps appeared a little tenuous when it first appeared, has now been replicated to such an extent that its existence now seems unquestionable. Further, the return of memory seems relatively permanent (Miller and Springer, 1972), lasting at least five days after the reactivation treatment. Additionally, many different types of reminders have been found effective in producing recovery from retrograde amnesia. Re-exposure to the training apparatus is, of course, one of those commonly used, both for aversive studies (Zinkin and Miller, 1967) and appetetive tasks (Miller, Ott, Berk and Springer, 1974). Importantly, this reminder is effective for both active avoidance (Lewis and Nicholas, 1973) and passive avoidance tasks (Sara, 1973), unlike many physiological manipulations. The reinforcer used in training is also an effective reminder. Miller et al., (1974) found the sucrose reinforcer returned the memory of an appetetive task, while non-contingent footshock is effective in avoidance tasks (Miller and Springer, 1972; DeVietti and Bucy, 1975). DeVietti and Hopfer (1974a) compared the effects of apparatus cues and non-contingent footshock and their interaction and found their level of footshock somewhat more effective than training cues, with animals receiving both types of reminder showing the most improvement in retention. In another study, these authors found recovery after a second ECS, delivered without additional training (DeVietti and Hopfer, 1974b). Although they interpret their results from a state dependency framework, it may be that the ECS itself or its persisting physiological effects can serve as a reminder; the two interpretations are not very different. Amnesia produced by hypoxia, cycloheximide, flurothyl, and puromycin have been shown to parallel the effects of ECS closely (Sara, 1973; Quartermain, McEwen and Azmitia, 1972; Cherkin, 1972).

Much of the interpretational problems with recovery phenomena hinge on whether reminders replace new information lost after the amnesic treatment (c.f., Gold and King, 1974; Miller and Springer, 1974). Retrieval theorists assume that because reminders are given non-contingently or resemble extinction trials that no information is transmitted to the animal. In any case, a series of reminders alone would not be sufficient to produce learning resembling the original training task in most studies. Nevertheless, there is some evidence that this sort of experience can summate with a weakened memory trace to produce a significant attenuation of retrograde amnesia. Cherkin (1972), using flurothyl amnesia in chicks, found that reminder treatments only improve retention in those animals that received mild doses of flurothyl; if amnesia was greater, the reminder was ineffective. Gold and his coworkers have produced evidence that animals rendered amnesic by transcorneal ECS (Haycock, Gold, Macri and McGaugh, 1973), cortical stimulation (Gold, Haycock, Macri and McGaugh, 1973), and amygdala stimulation (Gold, Macri and McGaugh, 1973) show reminder effects that can be interpreted in a summation framework. DeVietti and Haynes (1975), however, found much less summation in a paradigm similar to the Haycock et al. (1973) study. These studies once again seem to focus upon the exact naure of the trace left after ECS. Mah and Albert (1973) examine studies employing ECS and suggest that the variance found is related to two basic variables. The first concerns the characteristics of the task itself. One reliably finds that when task complexity is parametrically increased, a corresponding increase in the severity of the amnesia produced by a given level of ECS is obtained. A correspondingly increasing amount of familiarity with the training apparatus, a variable that decreases amnesia, is necessary to offset the retrograde amnesia developed by those increasingly complex environments. A second task characteristic affecting retrograde amnesia gradients is the strength of reinforcement used during training. Increasing either the intensity or duration of footshock used in acquisition will attenuate the amount of amnesia found (Chorover and Schiller, 1965; Ray and Bivens, 1968). These variations can be fitted into a consolidation theory if it is assumed that the rate of consolidation is affected by learning conditions. Evidence that consolidation rates can vary is that hypothermia after training can prolong the length of time that an ECS is disruptive. This implies that consolidation, like other bodily processes, may be slowed by temperature changes. Similarly, a long latency ECS, given five minutes after acquisition, prolongs the period of time a second ECS can interfere with memory (Mah, Albert and Jamieson, 1972). Other procedures, including anodal polarization (Albert, 1966), strychnine injection (Duncan and Hunt, 1972), and reticular formation stimulation (Bloch, DeWeer and Hennevin, 1970) seem to decrease this period, as well as attenuating amnesia when applied before the ECS or drug administration.

The other parameter affecting variations in retention is the severity of the amnesic treatment. As one might expect, the extent of amnesia increases with the severity of the amnesic agent, whether duration or intensity of ECS or dosage level of an amnesic drug is used as the independent variable (Haycock and McGaugh, 1973; Buckholtz and Bowman, 1972; Cherkin, 1969). These findings hold true, of course, for either a consolidation or retrieval interpretation if one assumes that either can be affected by these variable; it can therefore not be determined from this type of evidence which theory is more acceptable.

If both consolidation and retrieval processes can be considered to show similar lability to training characteristics, one must turn to other manipulations to help discriminate between the two positions. A number of unusual recovery procedures may bear upon this point. Azmitia, Efrain, McEwen and Quartermain (1972) found that allowing the animals to recover in the experimental apparatus instead of the home cage prevented the development of amnesia, a finding replicated by Mah and Albert (1974). Similarly, allowing the animals to recover in a sensory restricted environment seems to decrease the severity of the retrograde amnesia found (Peters, Douglas, Calhoun and Adams, 1973; Calhoun, Prewett, Peters, Douglas and Adams, 1975; but c.f. Adams, Calhoun, Davis and Peters 1974). Retrieval theorists suggest that since memory still survives a short time after ECS (McGaugh and Landfield, 1970; Miller and Springer, 1971), perhaps these procedures allow incorporation of the training cues into retrieval systems in a manner not possible where the apparatus cues are not available. The effect of the sensory restricted environment is somewhat harder to understand, but may be related to the distracting effects of a change in environment in a manner similar to the effects of disrupting "rehearsal" process in human memory reserrch (Peterson and Peterson, 1959).

Exactly what remains after ECS is still uncertain. Even after amnesia develops, it appears some remnant of the training experience remains. Amnesia for autonomic indices such as heart rate increases in a chamber once associated with shock have proved to be fairly resistant to amnesic treatments (Mendoza and Adams, 1969; Hine and Paolino, 1969; but c.f., Springer, 1975). Everett and Corson (1973) present evidence they suggest indicates that the memory of a novel experience survives an ECS although the exact nature of the reinforcer does not. Incubation studies also imply that some portion of the training experience survives ECS. All of these are taken as evidence for some mnemonic foundation that may summate with a reminder to produce improved retention.

Other studies involving manipulations at times other than training may support the retrieval position somewhat more than the consolidation interpretation. Reactivation of the training experience with a reminder stimulus occurs upon every access to the trace, while consolidation should only be occurring after acquisition. If no amnesic treatment was given originally, and consolidation is given time to complete, then any amnesia observed after an ECS following reactivation must be attributed to disruptions of the retrieval process, not consolidation. Davis and Klinger (1969) found disruption after reactivation with ECS, puromycin, acetoxycycloheximide and potassium chloride each used as amnesic agents. Others have replicated this finding (Lewis and Bregman, 1973; Lewis, Bregman and Mahan, 1972). DeVietti, Holliday and Larson (1973) compared amnesia from an ECS given immediately after acquisition with a similar ECS given after reactivation and found the latter to be weak and transient relative to the ECS given after training. It would appear that a memory is somewhat subsceptible to disruption at any time it is active and not merely during consolidation. Parsimony would suggest that it is retrieval that is also disrupted by ECS at the original time of training. Two further studies deserve mention in relation to the reactivation phenomenon. Howard, Glendenning and Meyer (1974) found that ECS after a habit learned third in a sequence would disrupt a previously learned habit only if the two had similar reinforcing conditions. Potts (1971) gave ECS at various intervals following passive avoidance training, either in the goal box or the home cage. The latter condition proveded much less amnesia at all intervals than ECS in the goal box. Intervals at which home cage ECS was totally ineffective still produced a great deal of amnesia with goal box ECS. These studies all strongly indicate that a memory is subsceptible to disruption at any time it is active, and apparently degree of disruption is proportional to degree of activation.

Another group of experiments perhaps weakening the summation argument involve the administration of drugs prior to reactivation treatments, or as reminders themselves. It is difficult to see how a drug reminder, administered outside the training situation, can provide information for summation in the manner usually considered applicable for noncontingent footshock or apparatus cues. Adrenocorticotropic hormone (ACTH), $ACTH_{4-9}$ (Rigter, Van Riezen and deWied, 1974; Rigter and Van Riezen, 1975) and vasopressin have all been shown to be effective reminders. Each of these is an arousal-increasing drug; presumably they work by restoring a degree of arousal to the animal similar to that present during acquisition. It is interesting to note, with respect to this hypothesis that not all reminders are equally effective in retrieving all types of memory. Miller, Springer and Vega (1972, cited in Miller and Springer, 1973) found that a footshock was ineffective in restoring the memory of an appetetive task that had been followed by ECS. Exposure to the reinforcer or training apparatus would restore this type of memory. This series of experiments indicates that the arousal level increase produced by ACTH or its shorter analogues serves as a reminder of an aversive experience and should prove ineffective in an appetetive situation.

Other drugs used to interact with weak memories include scopolamine, which is thought to enhance weak traces in at least some experimental paradigms (Deutsch, 1973). It has been found to greatly enhance retention when administered before retesting in animals with retrograde amnesia (Adams, Hoblit and Sutker, 1969). Eserine, an anticholinesterase, augments amnesia in similar paradigms. This implies that there still exists a weak memory that is strengthened, as summation theorists would suggest, but without any information with which to summate. In any case, all the information must be there in the weak memory. Any increase in strength is strictly a non-training phenomenon. This clearly fits the retrieval interpretation better than the storage model.

Most drugs injected at time of reactivation tend to display effects similar to those they show at acquisition. Strychnine, a powerful learning agent during acquisition (Duncan and Hunt, 1972; Dawson and McGaugh, 1973), similarly strengthens the specific components of a trace after a reminder (Gordon and Spear, 1973). Nevertheless, unlike ACTH, it is ineffective as a reminder when administered alone (Springer and Miller, 1972; Gordon and Spear, 1973). This is presumably because its effects do not sufficiently resemble those of acquisition to induce reactivation of the memory trace.

A procedure similar to reminder phenomena and that may have some bearing on the retrieval vs. consolidation issue involves prior familiarization with the training apparatus (FAM). Jensen and Riccio (1970) gave three types of such experience, habituation to the apparatus, training followed by extinction and training followed by hypothermia. Further training, followed by hypothermia in all three groups, failed to produce the amnesia normally seen after hypothermia when prior experience is not given. Hinderliter, Smith and Misanin (1973) found a great reduction of amnesia by either noncontingent foot-shock or ECS given prior to acquisition. Sara and Lefevre (1973) found three minutes of apparatus exploration by rats attenuated amnesia from hypoxia or ECS. It appears that memories are not formed in any sort of manner that is independent of prior experience, but rather are incorporated into already existing systems. If a memory can be added to a system already functional, perhaps this aids in the development of retrieval cues such that their disruption by ECS or other amnesic agents is rendered less likely.

Since the major item of support for summation theory involves the nature of the improvement after a reminder treatment, perhaps these experiments should be considered in more detail. Gold, Macri and McGaugh (1973a) used sub-seizure amygdala stimulation to produce retrograde amnesia for a passive avoidance response 24 hours later. When given a second training trial followed by amygdala stimulation, only those animals showing partial amnesia show show a decrease in amnesia; those demonstrating total amnesia at the 24 hour test are still susceptible to the second amnesic treatment. All animals used in the retraining portion of the experiment had received four days of extinction prior to the retest and performed not significantly different from naive animals. Gold, Haycock, Macri and McGaugh (1973b) ran a similar experiment employing either strong footshock with ECS or weak footshock, also followed by ECS, along with several control groups. As in their previous experiment, animals were tested and classified as totally amnesic or partially amnesic by a test session. Noncontingent footshock only produced recovery in those animals judged partially amnesic by the test. Those receiving weak footshock (2.0 ma, .4 sec) and no ECS showed improvement similar in magnitude to those receiving a high footshock (2.0 ma, 1 sec) followed by

ECS when both groups receive a noncontingent footshock (2.0 ma, 1 sec) delivered in a different apparatus. The two main implications here are that a significant trace must remain before a reminder is given to allow improvement, and that this trace may be similar to that of animals trained less well. Schneider (1974) points out some of the difficulties with these interpretations. When the animals are separated into totally or partially amnesic groups by a post-hoc test, they may be so divided by a number of factors not necessarily related directly to trace strength, e.g., motivational level, differential subsceptiblility to the amnesic agent, and electrode placement. The effects of the noncontingent footshock are then not necessarily related to the trace strength. It is the responsibility of the experimenter to vary strength of amnesia directly, by changing current intensity, for example, and to let these other factors average out across groups rather than potentially become the main variable in group selection. Similarly, in Gold et al. (1973a), the same design flaws hold true. The fact that the second training and stimulation is effective may reflect merely the more effective electrode placements, which are aligned into the same group by the nature of the sorting procedure.

A related problem in Gold et al. (1973a) involves the choice of weak footshock as an analogy to amnesia in terms of trace strength. It may be that these animals have trace strengths similar to the high shock animals, but are only more poorly motivated. Westbrook and McGaugh (1964), for example, have shown that learning appears to be about equal in groups of rats learning a maze with and without reinforcement; upon receipt of reinforcement, the previously unreinforced groups immediately improve to the level of the continually reinforced groups. The implication is that they have learned as much and only the motivational levels differ. Additionally, extinction rates are not related well to magnitude of reward (Mackintosh, 1974), which shows again that, insofar as strenth of a trace is reflected by extinction rates, varying reinforcer magnitude is not a reliable way of varying trace strength. In any case, if these animals are given a noncontingent footshock equal in intensity and duration to that received by the high footshock group in training, it may increase the fear properties of the shock and increase performance independently of any of the mnemonic changes usually considered operable.

Haycock et al. (1973) solved most of these problems by eliminating group selection through a post-acquisition test and instead administered two level of ECS to different groups to obtain different levels of amnesia. Noncontingent footshock was given either one hour before training, one hour after, or one hour after the first test. In comparing the high footshock-high ECS group high footshock-low ECS group, the low ECS animals showed approximately 78% amnesia, compared with about 100% amnesia for the high ECS groups. When given a reminder one hour after the first test, results on the second test indicated about 71% amnesia, or 29% recovery for the high ECS group, and 45% amnesia, or about 33% recovery for the low ECS group. This seems to indicate that reminder-stimulated recovery is not critically related to the strength of the trace left after ECS. The low footshock group that received no ECS showed a 41% recovery with non-contingent footshock after the first test, improving from 41% amnesia to no amnesia at all. This is roughly comparable to the approximately 30% recovery shown by the above groups. It should be noted, however, that the no reminder and low footshock group also showed a large increase in latency. Since they also received no ECS, perhaps this indicates an incubation-like effect that complicates interpretation. The initial amnesia for low footshock groups were also much less than for high footshock and improved to a much higher latency than any of the amnesic groups. Additionally, it is clear from other control groups that at least two processes were occurring here with repeated testing; one is a recovery phenomenon and the other an apparent extinction of the fear response where little amnesia is seen in the early test. These problems make interpretation more difficult; nevertheless, some support for the analogy of improvement by reminder of both amnesic and poorly trained groups can be derived subject to the criticisms and reinterpretations outlined above.

DeVietti and Haynes (1975) performed a similar experiment to those of Gold and his coworkers. They matched a group trained with weak footshock and given no amnesic treatment with one given stronger footshock in training, but followed by ECS. Their task was a passive avoidance where latency to drink in a box where shock was received was recorded. As in the Gold et al. (1973a, 1973b) studies, matching was on the basis of an initial test; hence it is subject to the same criticisms. Other groups also included were a noncontingent footshock group which never received training and one receiving strong footshock without ECS. Since the noncontingent footshock groups showed no learning, they are of no further interest. All of the other groups were further divided into groups receiving a strong reminder footshock, no footshock reminder, or a weak reminder footshock. On the second test, the groups trained with strong footshock and ECS showed a net increase in latency to drink, indicating attenuation of amnesia. The weak footshock groups all showed a decrease in latency. The divergency of these matched groups is taken by DeVietti and Haynes to show that the groups, although matched well, were not really similar at all and hence summation of reminders with weakly trained animals is at best a weak analogy with the process occurring after ECS. Figure 1, a graph extracted from DeVietti and Haynes (1975), illustrates some interesting comparisons between groups. The NR groups received neither the first test nor noncontingent footshock as a reminder. The proximity of groups receiving low shock and no reminder (TWFS/NR), and those with high shock followed by ECS and no reminder (TSFS/ECS/NR) indicates that these groups probably were matched fairly well by the test sortings, i.e., non-memorial factors seem less likely to have been exploited by these sortings since animals not sorted by this procedure still appear similar at the time they are first tested. As in Haycock et al.'s (1973) study, both recovery and extinction seem to be covarying, making the results more nebulous. All groups lowered their latency from test one to test two, indicating extinction of the fear response, except for the TSFS/ECS/SR group, that group trained with strong footshock, given ECS, then given a strong footshock reminder after the first test. Since Haycock et al. (1973) used strong footshock as a reminder for groups trained with weak footshock and retrieval is presumably related to the similarity between training and test or reminder, it is notable that only the TSFS/ECS/SR group showed an increase in latency, indicating promotion of retrieval. In all cases, greater extinction of the avoidance response was shown by

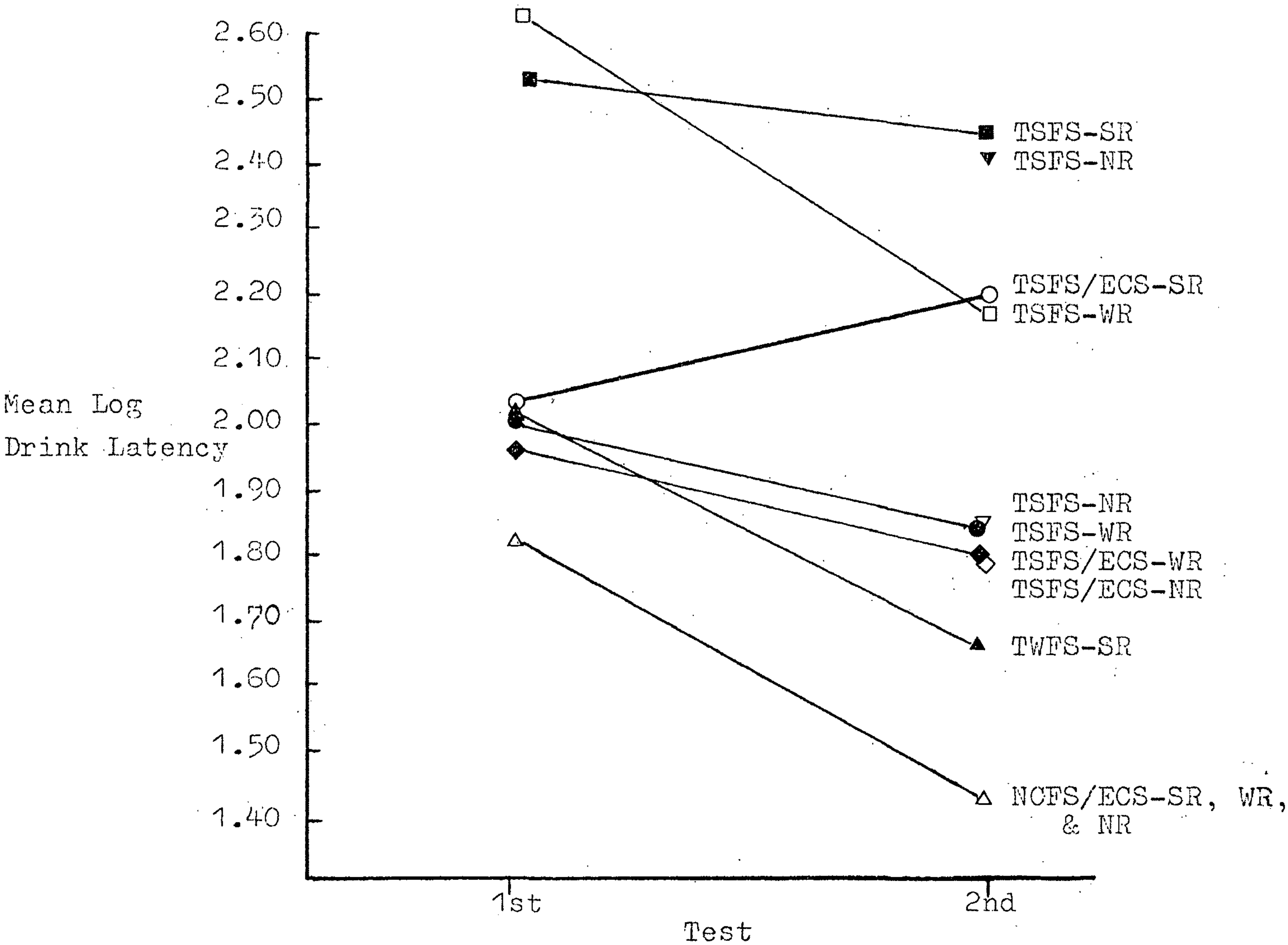


Figure 1. Graphic portrayal of a groups by test interaction. (extracted from DeVietti, et al., 1975; modification of their Figure 1

application of a reminder shock dissimilar to that given in training. It would seem that the conjunction of a test without footshock and a later noncontingent footshock would degrade the original correlation more than the test and a less similar footshock, thereby promoting more extinction in the prior case. Instead the opposite was found. It seems, then, that similarity of footshock reminder to training footshock serves to operate primarily to retrieve and strengthen the memory of the aversive experience and thereby weaken the extinction (and forgetting) process. Amount of strengthening or weakening would appear to be proportional to the amount of retrieval promoted, which depends upon the similarity of reminder and training conditions.

Another point to be derived from this design arises from the fact that a strong footshock reminder does not increase the fear properties of the shock in animals trained with weak footshock and then given a strong reminder. These animals, which never received ECS, decreased their latency to enter the shock compartment with a strong reminder, rather than increase it as would be predicted if their fear was increased. This is, of course, imposed upon the extinction of the first test, but it is nevertheless at least tentative evidence against this alternative interpretation.

In a prior experiment, also reported in DeVietti and

Haynes (1975), groups had been given a weak reminder or no reminder rather than a test on day 5. Weakly trained groups as well as amnesic groups improved with weak reminder, which led to the second study. It appears that there is about a 50% reduction in the strength of the avoidance response attributable to the first test, which presumably acts through extinction. This figure is obtained by comparing their first and second experiments where the treatments are indentical except for the first test. It is against this background that the increase in latency of animals trained with strong footshock, given ECS, then a strong footshock reminder becomes most striking. Since the strong reminder groups provided the greatest drop in latency for the matched group trained with weak footshock, but not given ECS, it appears this disparity must be attributed to improved retrieval rather than some other hypothesis. Certainly the decrease in latency of the weak footshock group with strong reminder would argue against a motivational hypothesis. So long as one concedes the analogy implicit in the matching scheme, retrieval promotion seems to be the best interpretation of their data

Rationale

Almost all of the studies cited have employed some form of passive avoidance response, often with a drink latency measure. Gordon and Spear (1973) used a procedure of training on a passive avoidance response and testing on a conflicting active avoidance, while Lewis and Nicholas (1973) ran the reverse procedure. The latter study demonstrated that this was a more sensitive procedure than strict relearning of the same task. Almost all other aversive procedures have involved the latency measure, usually in passive avoidance tasks. Using ECS with this type of training paradigm has a number of advantages. It allows a control for punishing effects of ECS, since this should add to the effect of the footshock. Additionally, training and ECS is usually conveniently localized over a short period of time, so that differential ECS gradients effects for different subjects are minimized. King and Glasser (1973), however, have demonstrated that preexposure factors which vary considerably from study to study critically affect the latency measure common to passive avoidance tasks. Adams and Calhoun (1972) showed that a latency response measure can fail to show recovery from amnesia while a retention ratio measure for the same animals did indicate recovery. DeVietti and Hopfer (1974a) found that different results can be obtained by the use of different latency measures, e.g., latency to drink initially contrasted with latency to drink for 50 seconds. It seems possible, therefore, that the study of recovery phenomena may have suffered somewhat from a narrowness of approaches, and that other tasks should be investigated.

The two way active avoidance response, where an animal must respond to a signal by repeatedly fleeing from the side of the box where he is to the other side, has advantages and disadvantages almost opposite to those of the simple passive avoidance. It originally requires a large number of trials, thereby spreading the learning over a large time period compared to that of the passive avoidance task. It is much less sensitive, however, to the alternative interpretations that complicate interpretation of the latter, e.g., freezing behavior, changes in latencies, and punishing effects of ECS; since neither side is "safe", the animal is routinely required to enter the side where ECS was given originally. Disruption of incubation gradients, if present, should have a minimal effect, since shock follows unsuccessful responses. This guarantees that any complex secondary responses based on fear will be minimized in the presence of the primary reinforcer. As this task further represents a different degree of complexity than that normally used, it seems that it would serve as a worthwhile extension of present reminder paradigms.

As previously noted, a major problem with some designs comparing weak training with amnesic animals (e.g., Gold et al,. 1973a,b; DeVietti and Haynes, 1975) is the post-acquisition test that matches animals by performance, as well as the assumption that animals trained with weak shock are less well trained than those trained with high shock, rather than more poorly motivated. To attempt to replicate these findings with a different procedure, other matching schemes and criterion for "weak" training were used. For the latter, fewer training trials were used to lower trace strength, and to match groups, a pilot study was run to measure the number of trials required to provide retention equivalent to animals trained to a more stringent criterion, then given ECS. Additionally, changes in trace strength by artificial agents after a reminder deserve more study. To replicate Gordon and Spear's (1973) observation of enhancement of trace strength by strychnine injection after a reminder and to extend it to the summation framework, drug groups were added. Since strychnine is reported to enhance the strength of a trace after both acquisition and reminder, it should serve as a sort of extrapotent reminder.

The Problem of the Study

This study proposed to compare the effects of parametric variation in reminder, either no reminder, training cue reminder, or training cue reminder followed by strychnine injection, upon animals either trained well, then given ECS or animals trained to a less stringent criterion and not given contingent ECS. If matching has been effective, then these latter animals should be about equivalent in performance to the animals given ECS before a reminder is given. The response was a two-way shuttle avoidance response, where rats were required to alternate avoidance responses from one side to another in a two compartment shuttle box. Exposure to the CS, a tone presented five seconds before onset of shock was used as the reminder, as it seemed less likely to alter either activity levels or motivational variables than non-contingent footshock, since secondary reinforcers are reduced considerably in effectiveness when compared to the primary reinforcer. Further, the tone is meaningful only in the context of the memory and seems less likely in all ways to provide a training experience. It should be noted that the test apparatus and handling cues can also serve as reminders, and that exposure to the CS in the apparatus serves as an extinction trial mush as the commonly used first test trial may in other paradigms. Nevertheless, the extinction effects are bound to be less for a task learned over 50-100 trials than for a single trial paradigm. Also, there is no "unsafe" side to be extinguished and reintroduction of the shock on the first retraining trial should abolish any small effects of extinction that might persist from the reminder treatment.

Retesting was done 96 hours after training, since studies (DeVietti and Larson, 1971b; DeVietti, Mayse and Morris, 1974) had found testing 24 hours after acquisition or reminder to often be atypical of the retention curve as a whole and that residual effects of an ECS may perist that could complicate interpretation.

Animals were divided into a 2 X 3 factorial design with training experience varying with type of reminder. Half of the animals were trained to criterion, then given ECS immediately after the next response; the other half were trained to the less stringent criterion and given ECS when consolidation had presumably ceased. A comparison of the two groups receiving each training treatment with no reminder should help establish the validity of the matching procedure, but the major comparisons are between the other groups. Table I identifies all groups and the treatment each received.

Retrieval theory predicts that more recovery should be found in the amnesic groups than in the partially trained groups, since a fully elaborated memory has been rendered less accessible by ECS. Therefor, each group should improve to a degree proportionate to the strength of the reminder it receives. The strychnine plus reminder group (A-St) should show the most improvement, followed by the reminder only group (A-R). The partially trained groups and those receiving no reminder should all show little improvement by comparison.

TABLE I

Individual Group Treatments, Means, and Sample Sizes

	injection only— Ringer's solution	reminder + Ringer's inj.	reminder + strychnine inj.
:ained to :iterion- ımediate :S	A-NR n=5 $\bar{x}$=47.6	A-R n=8 $\bar{x}$=25.1	A-St n=9 $\bar{x}$=18.6
ırtially :ained- ·layed :S	PT-NR n=5 $\bar{x}$=48.8	PT-R n=8 $\bar{x}$=39.9	PT-St n=8 $\bar{x}$=34.3

CHAPTER II

METHOD

Subjects

Fifty-one male Long-Evans hooded rats obtained from Simonsen laboratories and weighing an average of 485 grams were trained as described below. Two were discarded due to training abnormalities induced by equipment malfunction; six showed severe motor deficits after ECS and were also omitted. Forty-three animals are included in the final data.

Apparatus

Training occurred in a two chambered box, with each chamber 33.2 cm X 18 cm X 26.6 cm. The left chamber was painted white on all sides, excepting one wall which was glass; this wall faced the experimenter. The other chamber was identical, but black. The two chambers were separated by a guillotine door with each side painted to match the chamber it faced. The floor was a series of electrifiable bars through which .5 ma shock was delivered. The shock source was a CJA Model 250 shock source; a Grid Shock Scrambler, model 255, from Davis Scientific Instruments scrambled the shock. ECS was delivered at 55 ma for .5 seconds by connecting in series a variable autotransformer, type 2PF 1010 from Staco Inc. and a Full Wave power transformer, model R-110A from Triad-Utrad Distributors. A decade interval timer, model 100C, series D, from Hunter Mfg. Co., Inc. was used to time the ECS; a second timer of the same type was used to initiate the tone and footshock. ECS was delivered through Propper nickel-silver Michel wound clips (11mm), from Propper Mfg. Co., Inc. which were attached to the ears of the animals. The transformers were connected to the ear clips by wires intertwined through a swivel mounted above the guillotine door and terminating in alligator clips. The swivel allowed the wire to be trailed from one chamber to the other without catching on edges of the box and thereby pulling loose the clips. A pulley above the box and a counterweight attached to the wire allowed constant tension to be kept on the wire, so that it remained above the animal. Strychnine sulphate crystals were obtained from Sigma Chemicals. A 2kHz tone was delivered by an audio frequency oscillator manufactured by Hewlitt-Packard Co.

Procedure

All animals were randomly separated into two groups and had ear clips attached about 18 hours prior to training. All training was initiated by placing the animal in the white compartment where he remained undisturbed for two minutes, followed by the first training trial. All trials consisted of the simultaneous opening of the door and initiation of the 2kHz tone, followed five seconds later by a .5 ma footshock. Tone and shock were terminated when the animal moved to the opposite compartment; the door was also closed behind him at this time. Shuttle responses from black to white alternated with white to black with an intertrial interval of thirty seconds.

The amnesic group was trained to a criterion of five consecutive successful avoidances, i.e., the animal successfully avoided shock each trial. Immediately upon completion of the fifth avoidance each rat was removed from the chamber, alligator clips attached to the wound clips on his ears, and returned to the same chamber. Another trial was initiated thirty seconds later and 55 ma ECS delivered for .5 seconds just as he stepped into the opposite chamber. He was then returned to his home cage to recover.

The partially trained animals (PT) were trained in a manner identical to the amnesic (A) animals above except that they were removed after completion of their first successful avoidance response and returned to their home cage. Eight hours later they received noncontingent ECS in a different room from that of training. This controlled for the effects of ECS not related to amnesia that may persist at later times.

Seventy-two hours after the initial training, animals in both groups were weighed and randomly assigned to one of three subgroups. Groups A-St and PT-St were replaced in the white compartment of the training apparatus, with the door open. After fifteen seconds the CS tone was presented for two minutes. Each rat was then removed and given 1.5 mg/kg strychnine sulphate dissolved in mammalian Ringer's solution injected intraperitoneally. He was then replaced in his home cage. The A-R and PT-R groups received identical treatment, but were injected only with the Ringer's carrier in a volume identical to that they would have received had they been in the strychnine group. The A-NR and PT-NR groups also received this type of injection, but had no exposure to the training apparatus at this time.

Twenty-four hours after this treatment, all groups were returned to the apparatus and retrained to the five consecutive avoidances criterion, using a procedure identical to that of training. This concluded the test phase.

CHAPTER III

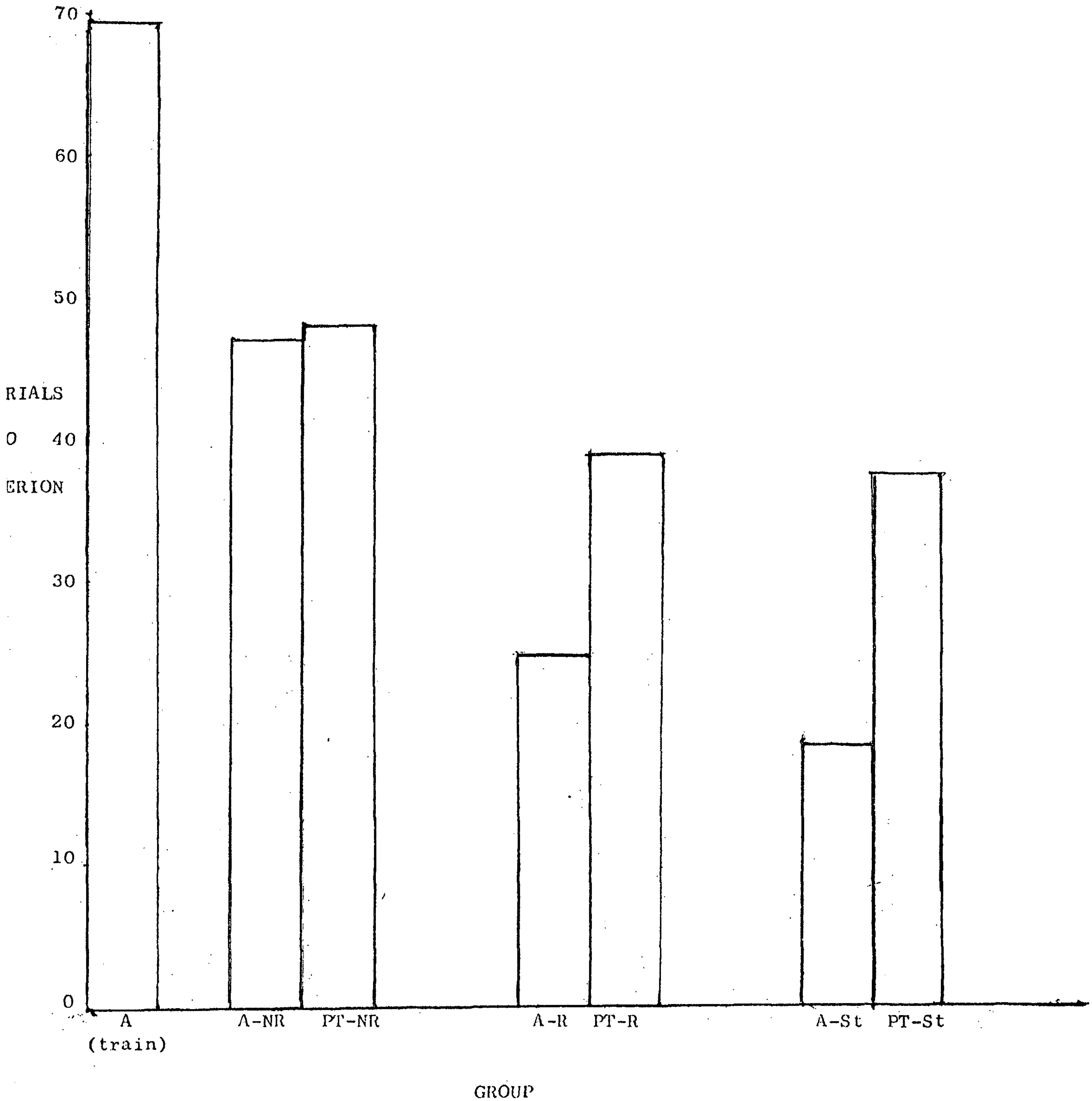
RESULTS

Figure II shows the mean trials to criterion for each of the six groups on the test trials. Also included is the mean for the three amnesic groups that had received identical training prior to ECS. These groups are combined for the best estimate of the mean. A two-way analysis of variance (ANOVA) was performed by reparamaterizing the data into a least squares matrix form as in Overall and Spiegel (1969) such that a harmonic mean need not be used. Both main effects reached statistical significance by this method while the interaction did not. Despite the fact that the A-NR and PT-NR groups were virtually identical, the other groups differed sufficiently that statistical significance ($F(1,37)=6.32$, $p<.05$) was reached. The reminder effect was also significant ($F(2,37)=7.73$, $p<.01$) at a high level. Despite the apparent bias toward an interaction by having the two NR groups equal and having significant main effects, the interaction factor nevertheless did not reach statistical significance ($F(2,37)=0.98$, $p>.05$).

A Newman-Keuls procedure revealed that the A-St group differed from the PT-NR and A-NR groups at the .01 level and from the PT-R group at the .05 level. Additionally, the A-R group differed from the PT-NR and A-NR group at

FIGURE II

Average number of responses to criterion for all groups



the .05 level. All other comparisons were non-significant.

A second ANOVA was performed by similarly reparamaterizing the number of trials to the first successful avoidance as the independent measure. The subjects within reminders by training treatment error term was estimated by subtracting total subject (row) variance from the variance attributable to reminders, training treatment, and their interaction, as described for trend analysis in Snedecor and Cochran (1967). The resulting ANOVA contains the same 2 X 3 independent measures of the previous test with a repeated measures test-retest in addition. Using the trial of the first successful avoidance as the dependent measure, neither the reminders effect ($F(2,37)=0.15$, p .05), the training treatment ($F(1,37)=0.00$, p .05), nor their interaction ($F(2,37)=0.25$, p .05) was significant. The trials effect of the difference between training and retraining was highly significant ($F(1,37)=17.41$, p .01), but the trials by training treatment ($F(1,37)=0.00$, p .05) trials by reminder ($F(2,37)=0.08$, p .05) and trials by reminder by reminder by training treatment ($F(2,37)=0.03$, p .05) were all non-significant. Figures III, IV, and V illustrate the mean trial of the first criterion response for all subgroups, collapsed across training treatment, and collapsed across reminder treatments, respectively.

FIGURE III

Trial of first successful avoidance for all subgroups

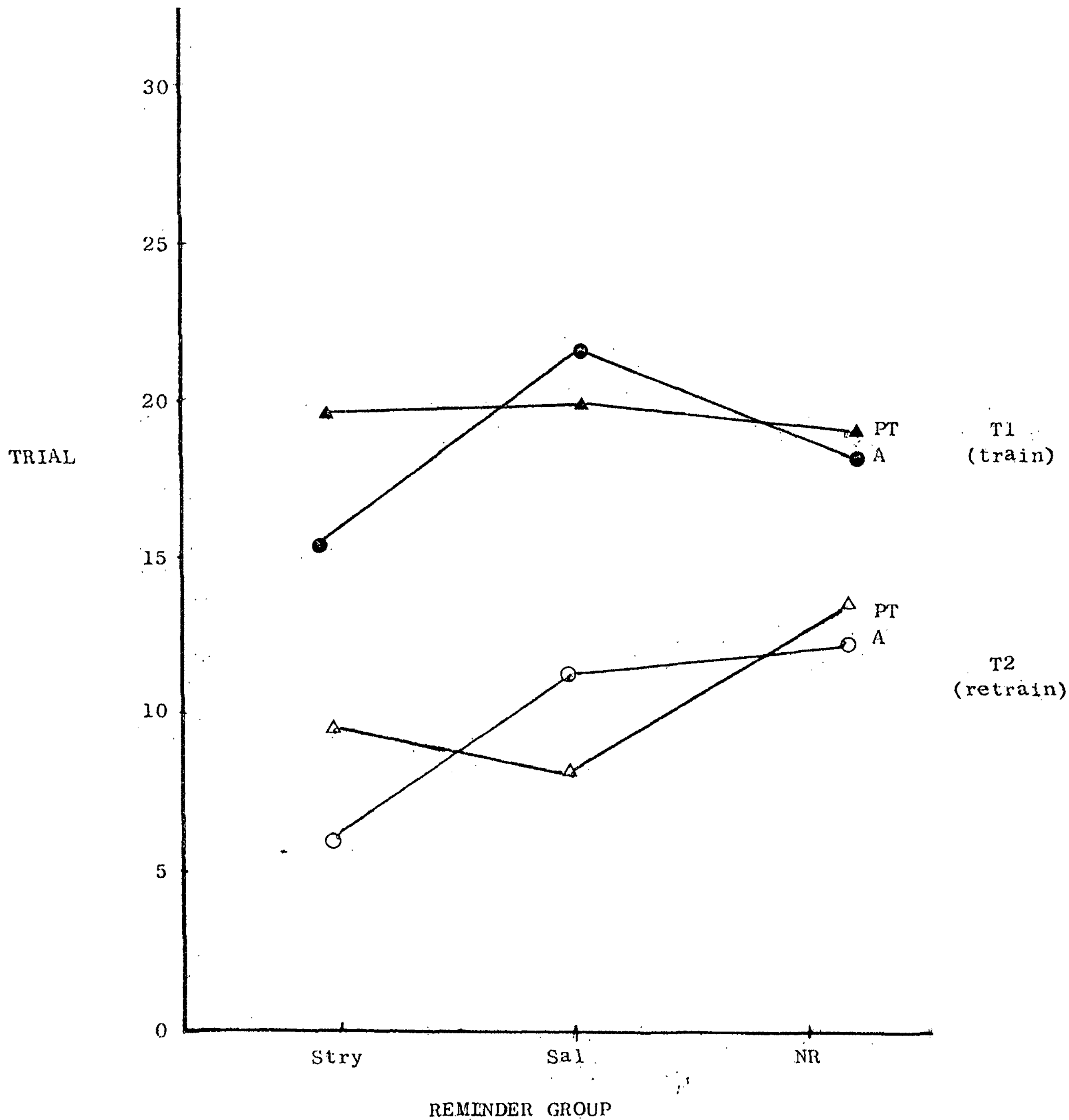


FIGURE IV

Trial of first successful avoidance for all subgroups collapsed across training treatment

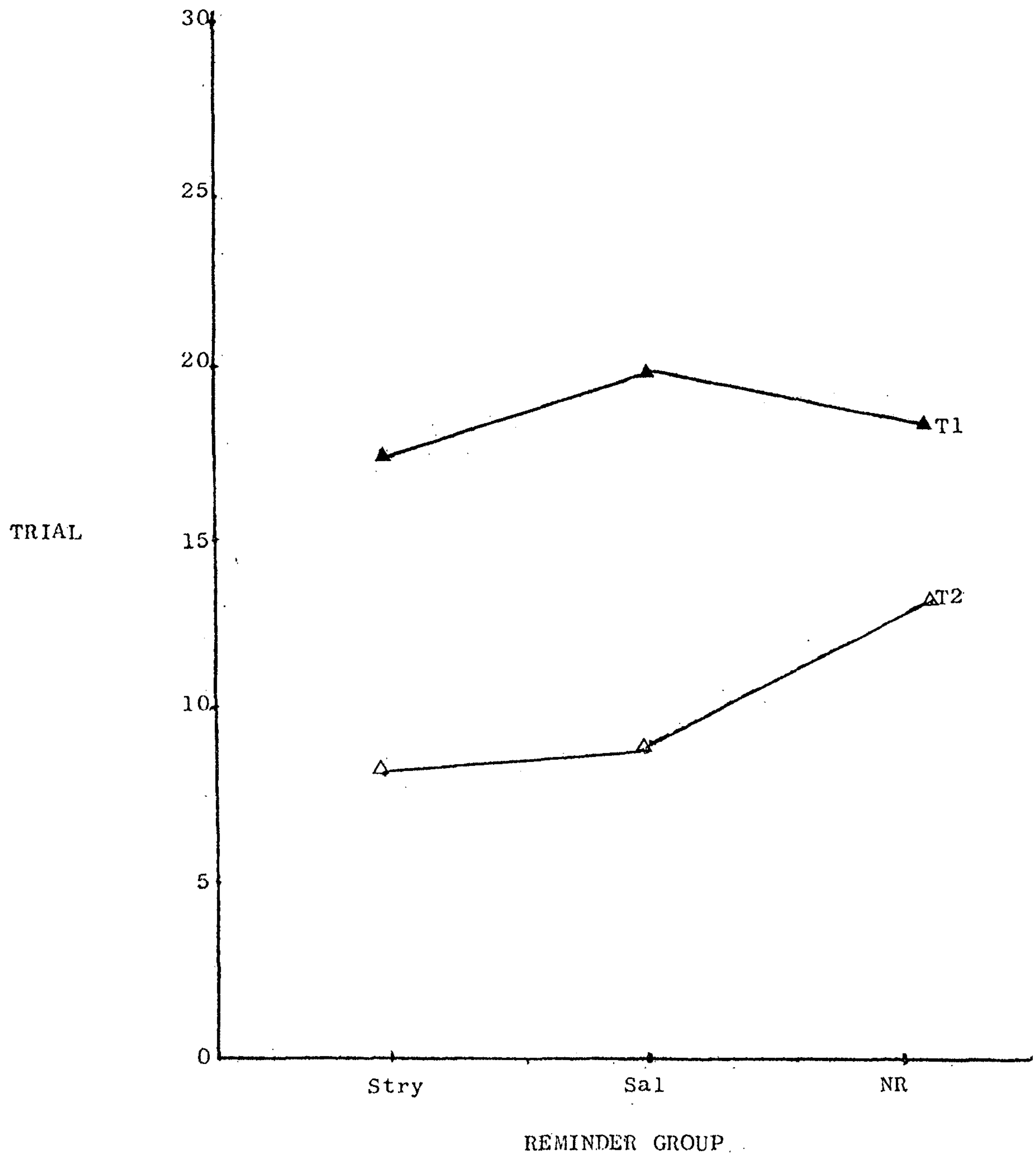
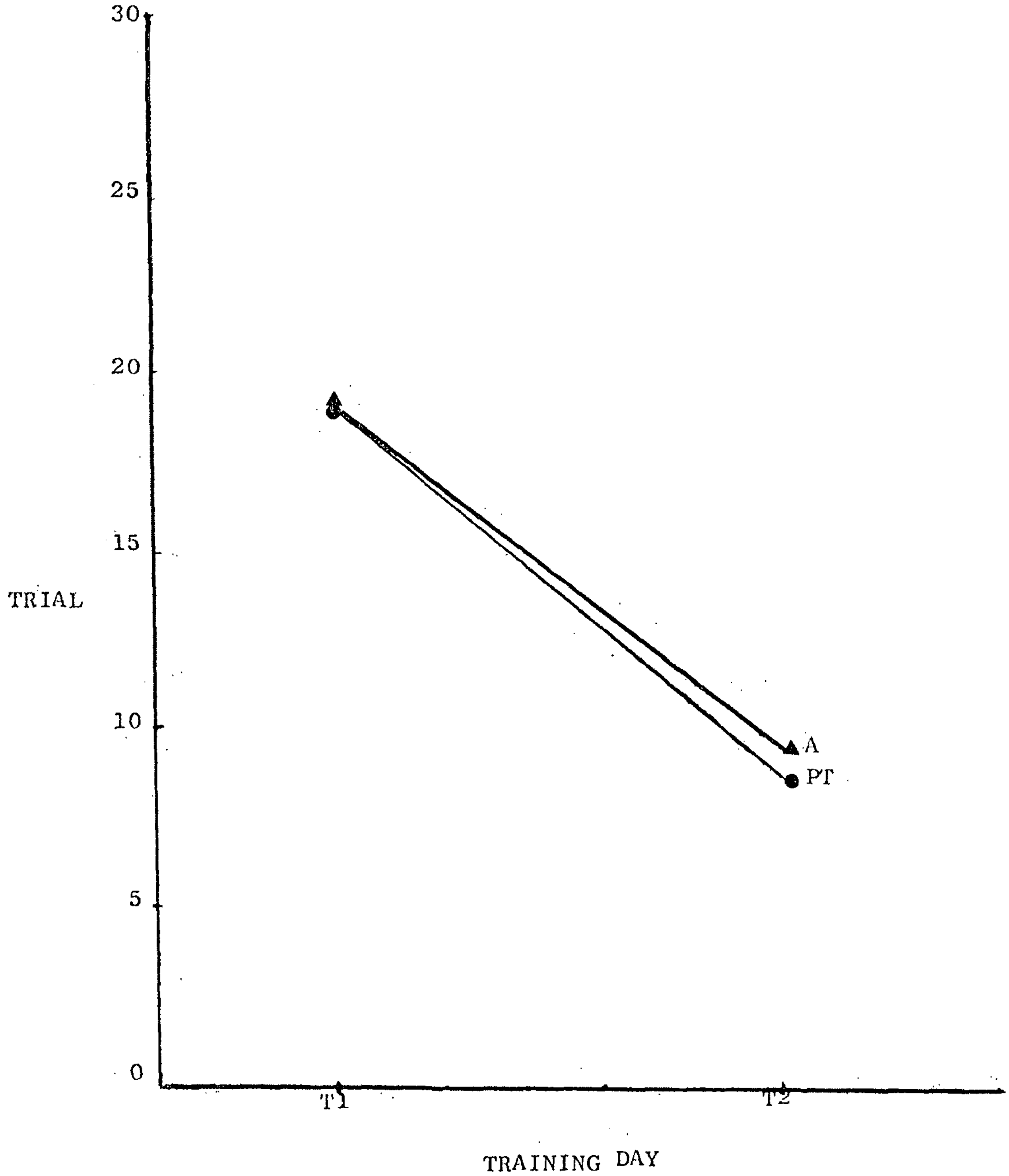


FIGURE V

Trial of first successful avoidance for all subgroups collapsed across reminder treatments



CHAPTER IV

DISCUSSION

The consolidation position suggests that the trace remaining after ECS is merely one reduced in strength and therefore similar to that of partially trained animals. This position must therefore predict no significant main effect of the training variable if animals are matched well. A comparison of the two NR groups would suggest that they are indeed matched well. No significant interaction should be found since similar traces should respond similarly to identical manipulations.

The outcome of this experiment seems to unequivocally favor the predictions made by the retrieval position rather than that of summation theorists. Rather than responding similarly to reminder stimuli, amnesic animals and partially trained animals differ greatly in magnitude of response to reminder or reminder with strychnine. Although the direction of response in both groups is in the same direction, the effect in partially trained animals is small and non-significant. The improvement of the animals given ECS is much greater by contrast, and very great indeed where strychnine was also given. Since the A-NR and PT-NT groups were virtually identical, the size of this effect is even underestimated by the test used. The best explanation of these results seems to be an enhancement of retrieval. The size of the strychnine effect, if not significantly different from the reminder alone, still tended to replicate the findings of Gordon and Spear (1973) and indicate that the memory strengthening properties of this drug are effective after reactivation as well as after acquisition.

The lack of a significant interaction, on the other hand, is surprising. It would appear that the test is biased in favor of an interaction, since the two NR groups are the same and the main effects are significant. The absence of such an interaction may only reflect the small sample size of the NR groups and their large variance respective to the other treatments.

Since memories may not be single, unitary traces, it is of interest to attempt to see if there is some differential amnesia for different components of the trace. Some data suggest that perhaps there is. Long latency responses, where a rat failed to escape to the other compartment within five seconds of shock onset, were recorded during training and testing. While every animal made at least one such response in initial training and the 46 animals made a combined total of about 140 such responses, a total of only one was made by all animals combined in the retraining phase. These responses, which were always in the first few trials, seemed to indicate that the proper escape response of fleeing to the other compartment was learned at this time. The lack of such responses in both A and PT groups on retesting seemed to indicate that this memory survived ECS. This may be attributable to the generally long interval between the last such response and the time ECS was usually delivered, but in any case indicates that this phase of the memory of the complete task is separate from some portion that is required for complete performance.

Additional evidence for this interpretation comes from the number of trials required for the first successful avoidance on the original learning when compared to the relearning. Although the trials variable was highly significant, the training treatment variable was negligible. This indicates that the groups given ECS retained this memory as well as the PT animals. If the long latency responses indicate that a fleeing response to shock is learned during the first few trials, this latter data probably reflects the learning of a fleeing response in response to the CS during the subsequent trials, and that it is equally insubsceptible to ECS at the latencies it is given with respect to these trials. This memory component must also be independent of the "final solution" memory. The lack of a reminders effect or any significant interactions in the trial of first avoidance data probably indicates that the memories are near full strength and further retrieval enhancement of these portions is unlikely.

A related point of interest is that some savings is demonstrable in even the no reminder groups. It is possible that the handling, weighing and injection these animals received was sufficiently stressful to serve as a reminder in the manner of ACTH injections. Pilot animals not given injections tended to show more complete amnesia, indicating that the partial amnesia was not merely a failure of the ECS level to cause complete amnesia, but a rigorous comparison is not possible.

The recovery shown by the amnesic groups was, as is normally found, not complete. Nevertheless, the A-St groups compared fovorably with pilot animals not given ECS and experimental animals retested 96 hours after the completion of their retraining trials. The A-St animals averaged eighteen trials to criterion, compared to about nine trials for the latter groups of animals. While not complete, the recovery is sufficient to indicate that the limits on improvement are not so great as often stated.

The concept of a unitary trace varying only in strength with training or ECS and summating with reminders is an attractively simple hypothesis. Unfortunately it seems to have proved inadequate both in the simple fear conditioning task of DeVietti and Haynes (1975) and the more complex task used here. It is difficult to see how any fear properties associated with the CS and training apparatus would have a great effect on trials required to relearn a two-way shuttle avoidance where the number of relearning trials if fairly large and the primary reinforcer is reinstated in full at the beginning of these trials. Consequently, little effect of the reminder should be expected if summation is the only factor operating in reminder treatments. The small amount of improvement seen in PT animals may reflect this effect or merely the improved retrieval of a task never altered by ECS, but perhaps forgotten slightly over time. In any case, the great difference between the A and PT groups given reminder treatments indicates that summation cannot be the only factor operating. The hypothesis that best accounts for the most data seems to be that advanced by retrieval theorists.

Types of Information

The mechanisms of memory are so poorly understood it seems that any attempt at definition or observation must make at least some assumptions beforehand. For example, the fractionation of the mnemonic process into storage and retrieval components seems to assume separate mechanisms that can be manipulated independently, when a content adressible memory may as well apply. The simplest such system would be a unitary trace of varying strength. Since retrieval and storage seem to vary independently insofar as amnesic animals have trace strengths similar to weakly trained animals, this study would argue against this interpetation. It does not exclude, however, all content-addressible models.

Since both retrieval and training cues are forms of information, it is perhaps misleading to refer to ECS as failing to cause a loss of information, which reminders do not replace. A distinction between environmentally produced information, such as the learning of the paradigm contingencies, and intrinsic information required for storage and retrieval might be useful. In this light, the thrust of this and recent studies is that amnesic agents fail to cause loss of external information, since no new training is needed. Reminders may serve to somehow alter patterns of information present in the system and somehow make them again available. This then may be the basis of the distinction between retrieval and storage positions. This study would then support neither idea so much as a redefinition of terms.

CHAPTER V

SUMMARY

Electroconvulsive shock (ECS) was once thought by most researchers to disrupt memory by preventing storage of information when learning was followed closely by ECS. Many recent studies have indicated that retrieval processes may be disrupted rather than storage. The major reason for this alternative interpretation is the finding of recovery of memory after administration of a non-training treatment known as a reminder.

It is not now known whether reminders facilitate memory recovery by somehow promoting better retrieval or instead summating with subthreshold memories to improve retention. If summation is occurring, memories that are weak because of less efficient training should also be improved by reminders. This experiment tests that hypothesis.

Forty-six rats were either given ECS or trained to a less strict criterion than those given ECS . This less strict criterion represented a "weak training" group. All animals were given either no reminder, exposure to the conditional stimulus and training apparatus, or this exposure followed by strychnine injection. Since strychnine improves retention after acquisition, it should serve improve recovery after a reminder.

Improvement with reminder and reminder+strychnine was much greater in groups given ECS than in weakly trained groups. This indicates that these traces, although similar in strength, are not really the same in nature and that retrieval promotion is the stronger interpretation of these results.

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