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BY

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Abstract

An attempt was made to determine the effects of post-training strychnine treatment on the retention of specific memory attributes over extended temporal intervals. Heterogeneous strain (Binghamton HET) mice were given two training trials (1 trial per day) on a discrimination problem for which there was two relevant redundant stimulus cues, a brightness cue and a spatial-sequence cue. Immediately after the second training trial, mice were administered intraperitoneal injections of either strychnine sulphate (1.0 mg/kg) or physiological saline. After retention intervals of either 1, 3, or 27 days, mice were tested under either complete cue reversal (both training cues were reversed), partial cue reversal (one training cue was reversed while the other cue remained unchanged), or relearning conditions (both training cues were unchanged).

On the basis of subjects' performance upon initial exposure (first retention test trial) to cue reversal conditions, it was shown that strychnine had enhanced the memory of specific rather than more general-contextual aspects of the training situation. Strychnine-treated mice exhibited significantly greater impairment of initial test performance than saline-treated mice, when both cues were reversed during retention testing. Secondly, strychnine was shown to selectively enhance the memory of the brightness cue; the initial test performance of strychnine-treated mice was more impaired when the brightness

cue rather than the spatial-sequence cue was reversed during retention testing. No significant differences in initial test performance were observed between saline-treated mice as a function of which cue reversed during retention testing. Thirdly, the effects of post-training strychnine treatment appeared to be relatively short-lived or, at least, masked by whatever forgetting may have occurred over the 7 and 21 Day retention intervals. It was suggested that, while strychnine treatment may have strengthened specific memory attributes, strychnine may not have otherwise affected the rate of forgetting of specific memory attributes. The possibility was also raised that strychnine treatment may bias the manner in which the memory of a learning event is processed, in such a way that the memory may be less accessible for retrieval after long retention intervals.

Finally, because a progressive decrease in negative transfer was observed, as a function of retention interval duration, when mice were tested under cue reversal conditions, it was suggested that forgetting of specific memory attributes had occurred. In comparison, relatively little forgetting was indicated by the performance of mice on a relearning task. The discrepancy between these findings was argued to reflect the relative insensitivity of a relearning task as a measure of retention.

List of Illustrations

Various investigators (e.g., McGaugh, 1973) have proposed that strychnine sulphate and other central nervous system (CNS) stimulants enhance the memory of learning experiences. The facilitory effect of strychnine on memory has been inferred from the finding that animals, administered sub-convulsive doses of strychnine shortly after a learning experience, tend to exhibit enhanced performance on subsequent retention trials (e.g., McGaugh and Krivanek, 1970). For the most part, such findings have been attributed to a strychnine-induced enhancement of the neurobiological mechanisms underlying memory storage processes (Dawson and McGaugh, 1973). This supposition, however, has not been entirely free from debate. Some investigators (e.g., Thiessen, Schlesinger, and Clhoun, 1961; Whishaw and Cooper, 1970) have argued that the facilitory effects of strychnine on retention test performance may not necessarily represent an effect of strychnine on associative processes, but rather, may represent an effect of strychnine on various non-associative processes, such as attention or motivation, which influence the performance of a learned response. Because this controversy underscores one of the most fundamental issues that must be addressed in this area of research, it would be useful then to review some of the methodological problems and general findings of this area of research before detailing the specific concerns of the present studies.

Lashley (1917) was the first to suggest that strychnine may have a facilitory influence on learning and memory processes. Rats, that were administered strychnine 10 minutes prior to each daily training

session in a maze, required significantly fewer trials to attain a learning criterion than control subjects that were administered injections of distilled water. Lashley's discovery was not pursued in earnest until the late 1950's, when McGaugh and his associates (McGaugh, 1959; McGaugh and Petrinovich, 1959) "reactivated" interest in the potential implications of Lashley's findings. While McGaugh and Petrinovich (1959) and other investigators (e.g., McGaugh and Thomson, 1962; Petrinovich, 1963) demonstrated that pre-training injections of strychnine facilitated acquisition performance on a number of different behavioral tasks, these early studies did not constitute an unambiguous demonstration of the effects of strychnine on learning and memory processes.

Methodological Problems. The fact that, in these and many other early studies, animals were administered drug treatments prior to training precludes a clear interpretation of the effects of drug treatment on two accounts. First, it is impossible to determine whether the observed facilitory effects of strychnine were the result of a strychnine-induced enhancement of learning and memory processes, or resulted from some proactive influence of strychnine on attentional, motivational, or other non-associative processes. For example, when strychnine is administered prior to training, the facilitory effects on acquisition performance have been interpreted, in some cases, to be a result of a strychnine-induced alteration of subjects' sensitivity to reinforcement contingencies or a strychnine-induced depression of competing response

tendencies. Whishaw and Cooper (1970), for instance, have argued that Lashley's findings could be attributed to a depression of exploratory activity by strychnine rather than a direct enhancement of maze learning. Interpretation is further complicated when response latency is the principal dependent measure used in studies of strychnine-induced facilitation. In addition to the finding that strychnine-treated animals tend to exhibit longer latencies in maze tasks (Lashley, 1917; McGaugh and Petrinovich, 1959), strychnine also has been shown to depress open field activity (Theissen, Schlesinger, and Calhoun, 1961), home cage activity (Calhoun, 1965) and general exploratory activity (Theissen et al., 1961; Wishaw and Cooper, 1970).

Secondly, the practice of pre-training drug treatments also precludes a clear distinction between the effects of strychnine on the initial acquisition of stimulus information and the effects of strychnine on memory processes. Further, when strychnine is administered prior to both training and test sessions, it is unclear whether enhanced retention test performance in these situations represent the result of strychnine-induced enhancement of post-training memory processing or state-dependent learning (e.g., Overton, 1971).

In more recent studies, investigators have attempted to minimize these types of interpretive problems by administering drug injections at various intervals after training, and then testing subjects 24 to 48 hours after drug treatment. Under these conditions, facilitated retention test performance cannot be attributed to an effect of strychnine on the initial acquisition of information, because the drug treat-

ment is administered after the learning experience. Further, because strychnine is rapidly metabolized and should be completely eliminated from the animal's system within 24 hours (cf. Franz, 1975), enhanced retention test performance should reflect a retroactive influence of strychnine on the memory of prior training rather than state-dependent retention or non-specific proactive effects of strychnine on retention test performance.

While these assumptions have met with general acceptance, it should be noted that there have been some reports which have suggested that proactive effects of strychnine and other CNS stimulants may persist over drug treatment-test intervals of 24 to 72 hours. Cooper and Krass (1963) reported that strychnine-injected rats exhibited a faster rate of acquisition on a shock motivated maze task than blank-injected controls, even when rats were tested 72 hours after drug treatment. It is not clear, however, that Cooper and Krass demonstrated a proactive effect of strychnine. Cooper and Krass gave rats extensive (2 weeks) training on a "practice problem" in the maze prior to drug treatment, and as such, this introduces the possibility that the facilitated performance on the new (test) problem may have been due to enhanced positive transfer from prior training. Furthermore, Greenough and McGaugh (1965) failed to replicate Cooper and Krass' findings. In most of the other cases in which 24 hour proactive drug effects have been noted (Bauer, 1972; Bauer and Duncan, 1971), the general finding has been that proactive drug effects were observed only for animals that had received repeated daily drug injections (typically for 10 to 20 days)

prior to testing.

These latter types of findings raise another possible methodological problem, i.e., the potential cumulative effects of repeated drug injections. This problem is of some concern, given that, in most cases in which post-trial injections of strychnine or other CNS stimulants have been shown to facilitate retention test performance, subjects were administered repeated daily drug injections during the course of training. Some caution in this regard has been suggested by a recent finding by Izquierdo, Fernandez, Olivera, and Settineri (1975). These investigators observed that, when rats were administered daily injections of initially sub-convulsive doses of strychnine (1.0 mg/kg), pentylenetetrazol (30 mg/kg), or picrotoxin (1.2 mg/kg), rats eventually exhibited clonic convulsions to the same dose of these agents after 10 to 20 injections. While the basis of these findings is not clear at present, these results suggest a possible cumulative effect of repeated drug injections. As such, the distinction between possible proactive and retroactive effects of post-trial administration of CNS stimulants may become obscured when drug injections are administered throughout the course of training.

These methodological problems have been the central focus of much of the debate regarding the interpretation of the effects of strychnine and other CNS stimulants on retention test performance. While the results of many of the earlier studies have been subject to alternative interpretations, more recent studies (e.g., Gordon and Spear, 1973) have adequately addressed many of these methodological problems. In

these cases, a clear distinction was provided between possible proactive and retroactive effects of strychnine, in that no facilitory effects of strychnine were observed for non-trained control animals, administered strychnine 24 hours prior to testing. Furthermore, facilitory effects of strychnine were observed when animals received only a single post-training injection of strychnine.

The Generality of Drug Facilitation. While these methodological considerations must be kept in mind, it also should be noted that a rather persuasive case has been advanced for the generality of the basic facilitation phenomenon. Post-trial strychnine treatments have been shown to facilitate maze learning (e.g., McGaugh, Thomson, Westbrook, and Hudspeth, 1962), brightness discrimination learning (e.g., Krivanek and Hunt, 1967; McGaugh and Krivanek, 1970), sensory preconditioning (Humphrey, 1968), and the learning of an "oddity" problem (Hudspeth, 1964). Furthermore, strychnine-induced enhancement has been demonstrated in test situations in which either appetitive or aversive reinforcement contingencies were in effect. Suggestions that the facilitory effect of strychnine may be due to a proactive influence on response latency have been countered by the fact that both passive (Franchina and Moore, 1968) and active avoidance learning (Bovet, McGaugh, and Oliverio, 1966) have been shown to be enhanced by post-trial strychnine treatment.

While the effects of strychnine on memory processing have been studied more extensively than the effects of other CNS stimulants, a

similar pattern of results emerges when these other agents are employed. Post training administration of picrotoxin (Breen and McGaugh, 1962), pentylenetetrazol (Krivanek, 1971), 5-7-diphenyl-1-3-diazadamantan-9-ol (McGaugh, Westbrook, and Thomson, 1962), amphetamine (Evangelista and Izquierdo, 1971), and caffeine (Garg and Holland, 1967) all have been shown to enhance retention test performance. As with strychnine, the facilitory effects of these other agents have been demonstrated in a variety of behavioral test situations (cf. Calhoun, 1971; McGaugh, 1973).

Factors Affecting Drug-Induced Facilitation. There are, however, limits to the apparent generality of these findings. Some failures to obtain drug-induced facilitation have been reported (Carlson, 1966; Louttit, 1965; Oglesby and Winter, 1974; Pearl and McKean, 1967; Prien, Wayner, and Kahan, 1963; Shaeffer, 1968; Stein and Kimble, 1966). While these negative findings do question the generality of the phenomenon, these findings may be indicative primarily of subject and/or procedural differences between studies. Petrinovich (1967) has suggested that many of these negative findings may be attributed to the use of an inappropriate or non-optional drug dosages for inducing facilitation of retention test performance. Responding specifically to Louttit's (1965) finding, Petrinovich demonstrated that post-trial administration of strychnine enhanced the retention test performance of Long-Evans rats, but only when the rats were administered a low dose (0.125 mg/kg) of strychnine.

In studies, in which the effects of a wide range of different dose-levels have been investigated, the facilitory effects of strychnine and other CNS stimulants have been shown to be dose-dependent. McGaugh and Krivanek (1970), for example, reported enhancement of brightness discrimination learning for Swiss Webster mice administered either low (0.025 mg/kg) or high doses (1.0 and 1.25 mg/kg) of strychnine after each training trial; no facilitory effect of drug treatment was observed for mice administered intermediate dose levels (0.20 to 0.80 mg/kg) of strychnine. The optimal doses for facilitation, however, have been found to vary as a function of strain differences and training conditions.

McGaugh and his associates (e.g., McGaugh, Thomson, Westbrook, and Hudspeth, 1962) have reported differential effects of strychnine and 5-7-diphenyl-1-3-diazadamantan-9-ol (1757 IS, a synthetic compound which has similar effects on CNS neural activity as strychnine) between the Tryon S_1 (maze bright) and Tryon S_3 (maze dull) rat strains. In some cases (e.g., Westbrook and McGaugh, 1964), sex differences have been observed to correlate with differential effectiveness of drug treatment. The nature of these differences, however, was not consistent across studies. Garg and Holland (1967) and Garg (1970) also have reported differential facilitory effects of nicotine and picrotoxin between the Maudsley reactive and non-reactive rat strains, with greater facilitation observed for the Maudsley reactive strain.

Similar differences in the effectiveness of drug treatment have been observed between various inbred mouse strains. Krivanek and McGaugh (1968) noted differences in terms of the optimal facilitory dose of pentylenete-

trazol between Balb/c and C57BL/6 mice, with maximal facilitation observed for Balb/c mice at the 5 mg/kg dose and at the 10 mg/kg dose for C57BL/6 mice. At the 20 mg/kg dose, pentylenetetrazol was found to impair the retention test performance of Balb/c mice but not C57BL/6 mice. Castellano (e.g., 1976, 1977) has reported differential and often opposite effects of post-trial nicotine and caffeine administration between the Balb/cJ, DBA/2J, and C57BL/6J strains. For example, post-trial administration of nicotine (0.5 mg/kg) enhanced brightness discrimination learning by C57BL/6J mice but impaired the test performance of DBA/2J mice (Castellano, 1976). Comparisons between control animals, however, revealed that these two strains differed in terms of rate of learning, with the DBA/2J strain observed to have a faster rate of acquisition. While it is unclear whether the differential facilitory effects of CNS stimulants reflect strain differences in susceptibility to these agents (cf. Schlesinger, Boggan, and Griek, 1968) or strain differences in learning ability, or an interaction between these factors, the results of these studies underscore the rather pronounced influence various subject characteristics (see also, Buckholtz, 1974) may have on the demonstration of drug-induced facilitation of retention test performance.

At another level, Hall (1969) has shown that differences in task difficulty may account for some of the failures to obtain drug-induced facilitation. When rats were trained on a relatively easy discrimination task, no significant differences in test performance were observed between strychnine-treated and saline-treated animals; however, when rats were trained on a relatively more difficult discrimination problem,

a significant facilitory effect of post-trial strychnine treatment was observed (see also, Cooker and Albert, 1967). Hall argued that the discrepancy between these findings was not indicative of an absence of a facilitory effect of a facilitory effect of strychnine on the learning of the "easy" discrimination problem, but rather, reflected a difficulty in detecting a facilitory affect of strychnine due to a "ceiling effect". When learning is at or near asymptotic levels, it becomes more difficult to observe any further improvements in test performance as a function of drug treatment. A similar type of "ceiling effect" may be encountered when animals are given extended training on a given task prior to drug treatment (e.g., Bovet, McGaugh, and Oliverio, 1966).

The effectiveness of post-training drug treatment has also been shown to vary as a function of the duration of the training-drug treatment interval; the general finding has been that, with increases in the duration of the training-drug treatment interval, there is a corresponding decrease in the facilitory effect of drug treatment (e.g., McGaugh and Krivanek, 1970). Hunt and Bauer (1969) have demonstrated that the temporal gradient of facilitation may also interact with drug dosage.

These various findings suggest that, while strychnine may enhance retention test performance, the degree of enhancement that may be obtained in a given study may vary depending on the influence of various subject and experimental factors, as well as the characteristics of the post-training environment (Calhoun, 1966). It is difficult, however, to isolate the influence of these various factors, for more often than not, these factors have been found to interact in a complex fasion (e.g., Krivanek, 1971).

Theoretical Interpretations. The general pattern of results discussed thus far suggests that the facilitory effect of strychnine and other CNS stimulants is due mainly to enhancement of associative rather than non-associative processes. Granted this initial premise, the concern then becomes one of delineating the nature of the effects of these agents on associative processes. The memory consolidation model (e.g., McGaugh, 1966) has provided the principal theoretical framework for this area of research. Briefly, the basic assumption of this model is that, for a short period of time following a learning event, the memory of that event is represented in a relatively labile or transitory form before being consolidated and stored in a relatively more permanent form. During this labile phase, the memory trace is assumed to be susceptible to disruption or modification by environmental treatments (e.g., electroconvulsive shock, drug administration) which take place after the learning event. Once the memory trace is represented (stored) in long-term memory, it is assumed that the memory is no longer susceptible to further modification. The general finding that strychnine-induced facilitation is a time-dependent phenomenon is consistent with the assumptions of the memory consolidation model. Typically, strychnine-induced enhancement of retention test performance is only observed when animals are administered strychnine immediately or within minutes after a learning event (e.g., McGaugh and Krivanek, 1970).

The noted dependence of strychnine-induced facilitation on various subject characteristics and training parameters is, however, inconsistent with earlier assumptions (e.g., Hebb, 1949) that the labile con-

solidation phase of memory processing was of fixed duration. Recent revisions of the memory consolidation model (e.g., Gold and McGaugh, 1975; Mah and Albert, 1973) have been introduced to account for the influence of these factors. Gold and McGaugh have attributed the facilitory effect of strychnine and other CNS stimulants to an enhancement of non-specific processes (e.g., arousal level) which modulate the rate of perseveration or consolidation of the memory trace. Training conditions which might affect arousal level or induce phasic charges in hormonal levels (e.g., footshock) may in turn alter the effectiveness of subsequent drug treatment.

With these types of revisions, the memory consolidation model can account for most of the findings in the drug facilitation literature; however, even with these modifications, the memory consolidation model has considerable difficulty in accounting for some recent findings that strychnine may facilitate retention of prior training when administered 24 to 72 hours after a learning event (Alpern and Crabbe, 1972; Crabbe and Alpern, 1973b; Gordon, 1977; Gordon and Spear, 1973; Sara and Remacle, 1977). Based on the assumption that the consolidation of a memory trace should be completed within minutes after training, the memory of prior training should not be suseptible to the effects of strychnine treatment 24 hours after the original learning event. Gordon and Spear (1973) and Gordon (1977) however, demonstrated that the memory of prior passive avoidance training could be enhanced when rats were administered strychnine 72 hours after training, but only if rats were given a "memory reactivation" treatment (confinement in the training apparatus without presentation of the CS) shortly prior to drug treatment. These in-

vestigators argued that the memory of prior training was susceptible to the facilitory effects of strychnine in these instances because the "reactivation" treatment had induced a re-processing of the memory of prior training.

These findings are in contrast to those of Alpern and Crabbe (1972) and Crabbe and Alpern (1973) who demonstrated that a series of 10 daily injections of strychnine, beginning 24 hours after training, could facilitate subsequent retention test performance in the absence of providing a "reactivation" treatment. Gordon, Brennan, and Rose (1975), however, failed to replicate Alpern and Crabbe's findings. Sara and Remacle (1977) reported that when strychnine was administered 15 minutes prior to the retention test, strychnine treatment was found to enhance test performance of rats administered electroconvulsive shock shortly after passive avoidance training or "undertrained" rats (i.e., rats given passive avoidance training at low shock levels). Because test performances of various control groups suggested the absence of a proactive effect of strychnine, Sara and Remacle argued that strychnine had enhanced the retrieval of the memory of prior passive avoidance training.

These recent findings suggest that strychnine may not affect only the initial processing of a memory but also may influence subsequent reprocessing and/or retrieval of a memory. While these are initial findings, they do point to considering phases or aspects of memory processing that have been largely ignored by the memory consolidation model. These findings, particularly those of Gordon and Spear (1973) and Gordon (1977), also suggest alternative views of memory processing. In contrast to the memory consolidation model, some investigators (e.g.,

Lewis, 1976; Spear, 1973) have suggested that the memory of a learning event is relatively rapidly stored and subsequently is further organized or "elaborated" in order to facilitate later retrieval. These hypotheses, however, are only recent developments within animal memory research and have not received as much attention as the more traditional memory consolidation model. Nevertheless, these types of notions seem to provide an important alternative context in which to interpret the effects of drug treatment on memory processes.

Theoretical Limitations. Over the past 20 years, the memory consolidation model has provided the principal theoretical framework for drug facilitation research, and as noted, most of the findings in this area of research can be accounted for by various versions of the memory consolidation model. This success, however, may be paradoxically indicative of the limitations of this model; the model may be too general. The limitations of the memory consolidation model becomes apparent, when it is realized that there has been relatively little progress in this area of research. In this light, an earlier evaluation made by Cooper and Krass (1963) still seems to be appropriate: "In spite of the considerable amount of research carried out in this area there seems as yet little justification for concluding that much progress has been made beyond Lashley's original contribution" (p. 474). This suggestion is not intended to ignore the contributions that various researchers have made over the past 20 years. There indeed have been notable methodological refinements, the generality of the basic phenomenon has been extend-

ed and some of the factors which might influence the effectiveness of post-trial drug treatments have been identified. Despite these achievements, there has been little progress in the understanding of the nature of the effects of strychnine and othrr CNS stimulants on memory processes. Earlier hopes (e.g., McGaugh, 1959) that this line of research would delineate the neurochemical correlates of memory processing largely have not been realized. The specific physiological mechanisms by which strychnine and other CNS stimulants exert a facilitory influence on memory processing have not been well defined (cf. Appendix A).

At another level, little is known about the manner in which strychnine affects the various characteristics of the memory of a learning experience. It is in this context that the limitations of the memory consolidation model become most apparent. The principal emphasis of the memory consolidation model has been directed to the characteristic properties of initial (short-term) memory processing; little, if any, attention has been afforded to the characteristics of the memory itself. Within the consolidation model, the memory of a learning event has typically been discussed in very general terms; it would seem that the memory of a learning event is regarded as a unitary element, processed and stored as a single bit of information.

Memory Attributes. This conceptualization of the memory of a learning event, however, is not consistent with much of the recent evidence concerning learning and memory retrieval in animals. Within a given learning situation, an animal if confronted with a variety of stimuli

or discriminative stimuli for instrumental responding. It is also clear that when redundant relevant stimuli (i.e., compound stimuli, with each component being equally predictive of reinforcement) are present in a learning situation, certain stimuli tend to gain control over responding, whereas, other stimuli acquire only minimal control (e.g., D'Amato and Fazzaro, 1966). Furthermore, it has been demonstrated that, while a variety of stimuli from a learning situation may serve as retrieval cues on subsequent retention tests, certain cues are more effective than others in aiding memory retrieval (e.g., Spear, Gordon, and Martin, 1973).

These kinds of data suggest that the memory of a learning event may consist of a variety of attributes or components each representing some feature of the learning event (cf. Spear, 1971; Underwood, 1969), and that these attributes may be differentially processed or stored such that some attributes are more accessible than others for subsequent memory retrieval. Such a theoretical framework introduces a number of questions concerning the specific manner in which strychnine enhances retention test performance. It is possible, for example, that enhancement results almost entirely from the strengthening of memory attributes representing critical aspects of the learning event (i.e., specific stimulus-response associations), and that attributes representing more general aspects are too weak to benefit from drug treatment. On the other hand, it is possible that in many cases the critical memory attributes are at maximal strength following learning and that drug-induced enhancement results primarily from the strengthening of the attributes representing contextual stimuli. Finally, drug-induced facilitation could result from the strengthening of general memory attributes which have little

specific relevance to a particular learning situation. Such attributes might represent features of the learning situation, such as the experience of being handled or the use of general attentional strategies (e.g., an observing response), which could transfer positively to most retention test situations.

These and related alternatives have received little attention in the drug-facilitation literature. In addition to the already noted biases in research emphasis, most of the behavioral paradigm commonly employed to assess the effects of drug treatment on memory processes do not provide a means of distinguishing between these alternative modes of memory enhancement. In most studies, animals have been trained under similar stimulus conditions. Under such conditions, it is difficult to determine whether enhance retention test performance reflects drug-induced enhancement of relatively specific memory attributes or more general-contextual memory attributes. In either case, a facilitory effect of drug treatment would be expected to be expressed in terms of enhanced positive transfer from prior learning to the retention test.

The negative transfer paradigm (cf. Postman, 1971), however, seems to provide one means of distinguishing between these alternatives. Under such a paradigm, subjects are trained on a given task (e.g., passive avoidance) and are subsequently tested on a conflicting task (e.g., active avoidance). Under these conditions, retention of specific or critical training experiences should impair test performance, while retention of more general training experiences (e.g., prior handling) could potentially facilitate test performance. Using negative transfer designs, recent studies (e.g., Gordon, 1977; Brennan and Gordon, in press) have provided

some initial evidence that the effect of post-training strychnine treatment is expressed primarily in terms of an enhancement of specific rather than general memory attributes. In both studies, the test performance of strychnine-treated subjects was significantly more impaired than that of saline-treated subjects, when subjects were tested on a conflicting active avoidance task (Gordon, 1977) or discrimination reversal (Brennan and Gordon).

Brennan and Gordon also attempted to extend this type of analysis a step further. In a second experiment, mice were given training on a discrimination problem with two relevant redundant cues, a brightness cue and a spatial-sequence cue. Mice were administered either strychnine (1.0 mg/kg) or saline immediately after training. Twenty-four hours after drug treatment, mice were tested under partial cue reversal conditions (i.e., one training cue was reversed while the other cue remained unchanged). The results of this study suggested that strychnine had differentially enhanced the memory of the two discriminative stimuli; strychnine-treated mice were observed to make significantly more errors when the spatial sequence cue was reversed than when the brightness cue was reversed during the retention testing. Because no similar effect of test was observed for saline-treated mice, Brennan and Gordon suggested that strychnine may have induced some form of selective post-trial processing of the two stimulus cues.

The present studies represent an extension of Brennan and Gordon's study. As in previous study, the basic intent was to determine whether strychnine would differentially enhance the memory of redundant discriminative stimuli. The specific concern of the present studies, however,

was to determine the effects of post-training strychnine treatment on the retention of specific memory attributes over extended (1 to 21 days) retention intervals (i.e., attempt was made to determine whether the purported differential effects of strychnine would still be observed when mice were tested after relatively long retention intervals).

The attempt to extend the type of analysis used by Brennan and Gordon to an investigation of the effects of post-training strychnine treatment on the retention of discrimination training across long intervals not only distinguishes the present studies from the more traditional concerns of drug facilitation research, but also introduces questions which have received relatively little attention in studies investigating the retention of choice behavior by animals. The basic point of departure is reflected in the methods used to assess retention of discrimination training in the present studies.

With few exceptions, the relearning test has been the most commonly used means of assessing the effects of retention interval duration on the retention of a learned response. As noted, in most studies which have investigated the effects of post-training drug treatment on the memory of a learning experience, animals have also been typically trained and tested under similar stimulus conditions. In both instances, retention test performance provides relatively little information about the characteristics of the memory at the time of retention testing. It was because of this lack of specificity that Bunch (1941b) questioned the appropriateness of the relearning test performance as a measure of retention. The principal criticism which was raised by Bunch was the fact that specific and general memory attributes appeared to be

differentially affected by retention interval duration.

While rats were observed to exhibit considerable forgetting of prior training on a complex (14 unit) maze task over intervals of 60 to 120 days, the degree of positive transfer from training on a 5 unit maze task to subsequent training on a more complex 14 unit maze task was roughly equivalent, whether rats were tested within 2 days or 120 days after training on the 5 unit maze task (Bunch, 1941a). A similar distinction between specific and general transfer effects was suggested by the finding that, while prior training was found to impair reversal learning when rats were tested within 2 days of initial discrimination training was found to facilitate reversal learning when rats were tested after retention intervals of 14 to 28 days (Bunch, 1939). The suggestion in both cases was that, while animals exhibited considerable forgetting of the specific aspects of prior training, retention of more general aspects of prior training were less affected by retention interval duration and transferred positively to the learning of a related maze task or reversal learning.

These findings have a particular implication for the general finding that animals tend to exhibit relatively little forgetting of simple (one-choice) choice behavior, when tested under relearning conditions after extending retention intervals (cf. Gleitman, 1971). While it is possible that the memory of specific stimulus-response associations may not be affected or are less susceptible to the effects of retention interval duration in these paradigms, it is also possible that the retention of general memory attributes may mask whatever forgetting of

specific stimulus-response associations, which might have taken place over extended retention intervals. In this light, it is instructive to note that one of the few studies to observe some degree of forgetting of simple choice behavior after retention intervals of 3 to 14 days (Hill, Cotton, Spear, and Duncan, 1969), likewise provided some indication that there was differential retention of specific and general memory attributes. While no differences were observed in terms of "stem" (start box to choice point) speed, significant decreases in "arm" (choice point to goal area) speed were observed as a function of retention interval duration. It would seem that, while animals exhibited relatively little forgetting of more general training experiences (e.g., that they were reinforced in the T-maze), animals appeared to exhibit forgetting of more specific training experiences (i.e., the exact location or reinforcement).

The importance of providing some degree of distinction between general and specific transfer effects becomes more critical in the context of interpreting the effects of post-training drug treatment on retention test performance, particularly when relatively long intervals intervene between drug treatment and the retention test. Given the suggestion that strychnine enhances relatively specific memory attributes, a question may be raised as to whether post-training strychnine treatment may enhance the subsequent retrieval of specific memory attributes after extended retention intervals. It is possible, for example, that the effects of strychnine may be relatively short-lived; while strychnine may strengthen specific memory attributes, strychnine treatment may not

otherwise affect the rate of forgetting of specific memory attributes. If, on the other hand, strychnine enhances the "elaboration" of the memory of a learning experience (cf. Lewis, 1976), post-training strychnine treatment could potentially improve the accessibility of specific memory attributes for subsequent retrieval, even after extended intervals.

The few studies (Garg and Holland, 1967; McGaugh, Westbrook, and Thomson, 1962; and Stein and Kimble, 1966) which have included relatively long (14 to 30 days) drug treatment-test intervals, however, do not provide a basis of determining the consequences of drug treatment on the retention of prior training across long retention intervals. In all three studies, a facilitory effect of drug treatment was not observed when animals were tested after long retention intervals; this finding, however, was due largely to the fact that relatively little forgetting was exhibited by control animals. As such, it is difficult to interpret the findings of these studies. In addition to the fact that the use of a relearning test may have obscured forgetting of specific memory attributes, various methodological problems (e.g., failure to control for degree of training) may have also obscured any differences in the retention test performance between drug-treated and control animals.

Because of the problems of the above cited studies, the initial concern of the present studies was to determine whether non-injected mice would exhibit some degree of forgetting of prior discrimination training as a function of retention interval duration (Experiment 1). Given that some degree of forgetting was observed in Experiment 1, an initial attempt was made in Experiment 2 to determine the effects of post-training strychnine treatment on the retention of discrimination training. In this study,

mice were given a single injection of either strychnine or saline immediately after discrimination training and were then tested on the same discrimination problem after various retention intervals (1 to 21 days). While the use of a relearning test in Experiment 2 is subject to criticisms already noted, the decision was made to test mice under these conditions to maintain some commonality with prior research in this area.

The principal purpose of the present studies, however, was not only to determine whether strychnine would enhance the test performance of mice tested after relatively long retention intervals, but also to determine the specificity of the effects of post-training strychnine treatment on the retention of discrimination training. In order to obtain some index of the specificity of the effects of strychnine treatment, mice in Experiment 3 were injected with either strychnine or saline immediately after discrimination training and were then tested under various cue reversal conditions after extended retention intervals (1 to 21 days).

General Methods

Since the apparatus and training procedure are similar in all three experiments, they will be reported in detail in this section and subsequently only variations in testing procedures and drug treatment conditions will be indicated.

Subjects The subjects for all three experiments were male Heterogenous (Binghamton HET) mice, 60 days old at the start of training. The Binghamton HET stock was derived from an eight-way cross (LP/J, Balb/cJ, MA/J, LG/J, SM/J, 129/J, DBA/2J, and C57BL/6J). Mice were housed 4-5 to a cage in a temperature-controlled vivarium, with a 12 hr/12 hr light-dark cycle (lights on 0800-2000 hrs) in effect. Mice were trained and tested between 1100 and 1400 hrs.

Apparatus All training and testing took place in a 6 unit discrimination maze, similar to that used by Crabbe and Alpern (1973a) and by Brennan and Gordon (in press). The maze and basic training conditions are shown in Figure 1. The maze was constructed

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Insert Figure 1 about here

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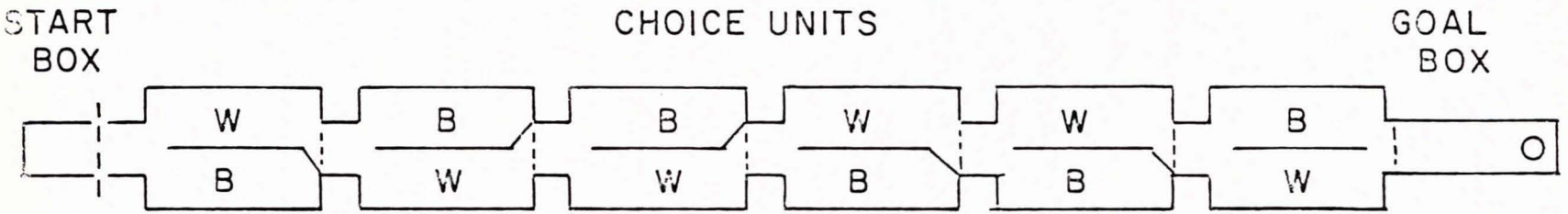
of Plexiglas and consisted of a start compartment, 6 separate dis-

Figure 1. Schematic representation of discrimination maze and training conditions.


START
BOX
CHOICE UNITS
GOAL
BOX
W
B
B
W
B
W
W
B
W
B
B
W
B
W
B
W
O

crimination units, and a goal compartment.

The start compartment was 10 cm long, 3.5 cm wide, and 5 cm high and was painted flat grey. Each of the 6 discrimination units consisted of an 8 x 3.5 x 5 cm flat grey entryway which led to a chamber divided into 2 alleyways - one painted flat white and the other flat black. A 5 cm high barrier, beginning 3 cm past the end of the entryway, separated the two alleyways. Each alleyway was 25 cm long, 3.5 cm wide, and 5 cm high. A piece of clear vinyl was used to block the incorrect alleyway of each discrimination unit. The vinyl barrier was placed so that it could not be seen from the choice point of each discrimination unit.

The discrimination units were positioned linearly such that the entryway of each unit followed either the start compartment (in the case of discrimination unit 1) or the exit from the preceding discrimination unit. Sliding doors, painted flat grey, could be inserted between any compartment of the maze and the entryway to the next compartment.

Following the last discrimination unit was a goal compartment which consisted of an entryway (7 x 3.5 x 5 cm) painted flat grey and a goal area painted either flat white or flat black, depending on the particular training or test condition. A plastic drinking cup, 1.5 cm in dia., was mounted on the floor of the goal area, 1 cm from the end of the goal compartment. The entire maze was covered with a sheet of clear Plexiglas, with separate removable sheets of Plexiglas covering the start and goal compartments.

General Training Procedures. Prior to the start of training, all mice were placed on water deprivation for 48 hours. Subjects in each of the three experiments were given two acquisition trials in the maze (1 trial per day). During training, choice of the white alleyway of each discrimination unit allowed the subject entry into either subsequent discrimination units or the goal compartment (painted flat white). The discrimination units were arranged such that the white alleyways appeared in a LRRLLR sequence (L=left, R=right) during training. The decision to make the white alleyway correct for all animals during acquisition was based on the fact that pilot animals tended to show an initial preference for the black alleyways in the maze (see also, Crabbe and Alpern, 1973a). Thus, all animals were trained to enter the non-preferred alleyway.

At the start of training trials, the door between the start compartment and the first discrimination unit was closed; the doors between all other maze units were open. The subject was placed into the start compartment and the door between the start compartment and the first discrimination unit was opened. A correctional procedure was in effect during training and testing; i.e., within a given discrimination unit, subjects could repeatedly enter the incorrect alleyway. Once a subject had entered either a discrimination unit or the goal compartment, a sliding door was closed behind the subject to prevent re-entry of the preceding maze unit. Three response measures were recorded: Choice errors (the initial entry of an incorrect alleyway), repeated errors (all subsequent re-entries of an incorrect alleyway), and the latency to traverse the maze.

Following entry into the goal compartment, mice were given a 10 second access to a 0.3% saccharin solution. Immediately after removal from the goal compartment on Training Day 1, mice were returned to their home cages. On Training Day 2, mice were either returned to their home cages (Experiment 1) or were administered drug treatment and then returned to their home cages (experiment 2 and 3).

Throughout all phases (i.e., training, retention interval, testing) of each of the three experiments, mice were maintained on a 23 hr 50 min water deprivation schedule. During both training and testing, mice were given a 10 min access to water in their home cages, approximately 30 min after each experimental session. During the retention interval, mice were left undisturbed, except for normal (once a week) cage changing, in their home cages, which were placed in the vivarium.

Data Analysis

Separate repeated measures analyses of variances (cf. Keppel, 1973) were performed on each of the three response measures, with trials as the within factor. In prior research (e.g., Brennan and Gordon, in press), in which similar maze tasks were used, the major effects of drug treatment were often observed in terms of the tendency of mice in various treatment groups to exhibit differential error responding within specific discrimination units. For this reason, the analyses of variance that were performed on choice and repeated error responding during testing, in the present experiments included discrimination unit as an additional within factor. When differential patterning of error responding was indicated by the overall analysis, subsequent analyses of variance were conducted on error responding within the first 3 discrimination units and final 3 discrimination units of the maze. The decision to examine the patterns of error responding in this particular manner was governed by the fact that these were the two distinct patterns of error responding that were typically observed in the present experiments. All subsequent comparisons between individual treatment group means were made in terms of the Duncan Multiple Range Test (Duncan, 1955).

Summary tables for all the analyses of variance that were conducted are presented in separate appendices for each experiment: Experiment 1 (Appendix B), Experiment 2 (Appendix C), and Experiment 3 (Appendix D).

Experiment 1

Before an attempt could be made to determine whether post-training strychnine treatment would have an effect on the retention of discrimination training across extended temporal intervals, it was important to determine whether non-drugged mice would exhibit some degree of forgetting as a function of retention interval duration. The importance of this preliminary investigation is underscored by the fact that one of the critical problems, that is common to the three principal studies (Garg and Holland, 1967; McGaugh, Westbrook, and Thomson, 1962; and Stein and Kimble, 1966) that failed to observe a facilitory effect of post-training drug treatment, when animals were tested 14 to 30 days after drug treatment, was the general absence of any appreciable forgetting by control animals in these studies. Under these circumstances, it is unclear whether the failure to observe a facilitory effect of drug treatment represented an absence of an effect of drug treatment, or rather, a "ceiling effect". Some aspects of the experimental protocol in these studies suggest that it may have been difficult to detect an effect of drug treatment, given the near asymptotic retention test performance by control animals.

In all three studies, animals either were trained to criterion or were given extended training prior to retention testing. Under these training conditions, relatively little forgetting of a well learned response might be expected to occur over retention intervals

of 14 to 30 days (cf. Gleitman, 1971).

In two of these studies (Garg and Holland, 1967; McGaugh et al., 1962) animals were trained under either food or water deprivation conditions. At the end of training, animals were placed on an ad libitum schedule until a few days prior to retention testing, when deprivation conditions were re-instated. The re-introduction of deprivation conditions may have enhanced the retention test performance of animals by providing for a clear discrimination between training and non-training cues. The re-introduction of deprivation conditions may have also facilitated the retrieval of the memory of prior training by placing the animals in a motivational state similar to that of original training (cf. Spear, 1973).

An attempt was made to minimize some of these problems in the present study. First, mice were given only two discrimination training trials prior to the imposition of retention intervals of either 1, 3, 7, or 21 days. In addition to an attempt to maintain some commonality with the parameters used in previous work in this laboratory, it was felt that the memory of discrimination training would not have acquired maximal strength by the end of training, and as such, might have increased the possibility that some degree of forgetting would be observed. In previous work, HET mice were typically not observed to attain a learning criterion (i.e., no more than 1 choice error over 2 consecutive trials) until after 4 to 6 training trials (see also, Crabbe and Alpern, 1973a). Second, mice were maintained on the same

deprivation schedule throughout all three phases (training, retention interval, and retention test) of the present study to minimize the possibility that motivational cues might serve as distinctive training cues.

Methods

Procedure. Two days prior to training, all mice were placed on water deprivation and were randomly assigned to 1 of 4 retention interval conditions: 1 Day (RI1, n=8), 3 Day (RI3, n=8), 7 Day (RI7, n=7), and 21 Day (RI21, n=7) retention intervals. All mice were given two discrimination training trials (1 trial per day) on the previously described discrimination problems. After the designated retention intervals, mice in each of the four groups were given 4 retention test trials (1 trial per day) on the same discrimination problem. No drug treatments were administered at any time during the course of the present experiment.

Results and Discussion

During training, no significant differences in either choice error or repeated error were observed between the four treatment groups. While no reduction in choice error responding was observed during training, mice did make significantly fewer repeated errors on the second training trial (F 1,26=14.0, $p<.001$), suggesting that some learning

did take place over the two training trials. Mice also exhibited a significant reduction in the latency to traverse the maze on the second training trial (F 1,26=20.89, $p<.001$). While no significant main effect of retention interval condition was observed in terms of the latency measure, a significant groups x trials interaction was noted (F 3,26= 3.10, $p<.05$). This latter finding was due mainly to the fact that the RI21 group had a significantly longer mean latency than the other 3 treatment groups ($p<.05$ in all cases) on the second training trial.

During the four trials of retention testing, a significant main effect of retention interval duration was observed in terms of choice error responding (F 3,26=3.62, $p<.05$). As illustrated in Figure 2a, mice tested 21 days after initial discrimination training made signifi-

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Insert Figures 2a and 2b about here

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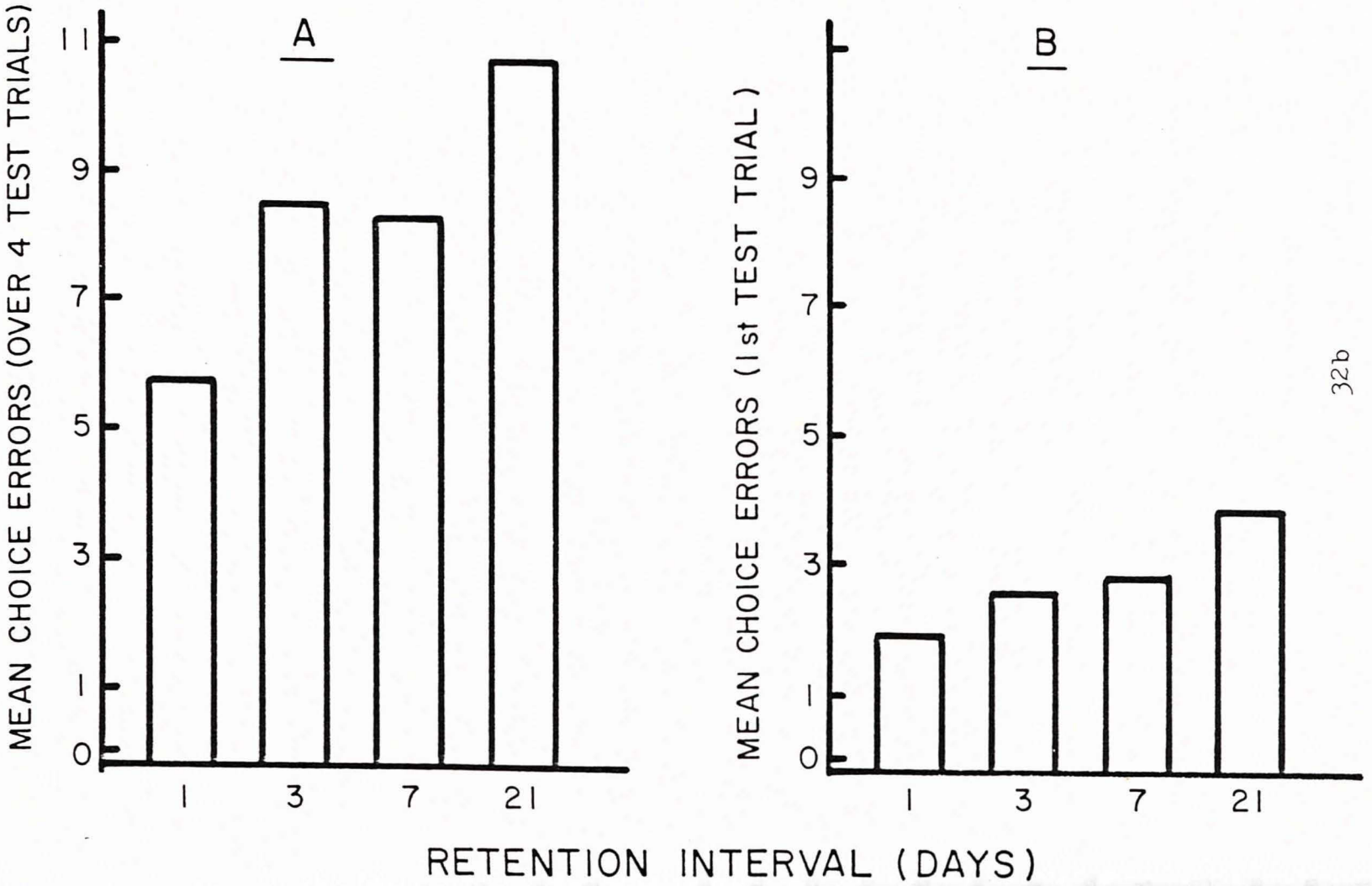
cantly more choice errors than mice in either the RI1 ($p<.01$), RI3 ($p<.05$), or the RI7 ($p<.05$) conditions. While no significant differences in choice error responding were observed between the RI3 and RI7 groups, mice in both groups were observed to make significantly more choice errors over the four test trials than mice in the RI1 group ($p<.05$ in both cases). The observed differences in choice error responding were most evident on the first retention test trial (F 3,26=4.56, $p<.025$). As illustrated in Figure 2b, RI21 mice made significantly more choice errors than mice in either the RI1 ($p<.01$) or RI3 ($p<.05$) groups on the first retention test trial. No significant differences were ob-

Figure 2. A. The mean number of choice errors over four test trials for each of the treatment groups in Experiment 1 is shown as a function of retention interval duration.

B. The mean number of choice errors on the first retention test trial for each of the treatment groups in Experiment 1 is shown as a function of retention interval duration.


A
B
MEAN CHOICE ERRORS (OVER 4 TEST TRIALS)
MEAN CHOICE ERRORS (1st TEST TRIAL)
0
1
3
5
7
9
11
1
3
7
21
RETENTION INTERVAL (DAYS)

served between the RI21 and RI7 groups or between the RI1, RI3, and RI7 groups on the first retention test trial. On all subsequent test trials, no statistically significant differences in choice error responding were noted between any of the four treatment groups. The relatively transitory retention deficit observed for mice tested 21 days after discrimination training is similar to that noted by other investigators (cf. Gleitman, 1971). Animals have typically been found to exhibit relatively little forgetting of choice behavior over retention intervals ranging from 5 to 44 days (e.g., Gleitman and Jung, 1963; Maier and Gleitman, 1967), except in situations in which animals are trained on an opposing task or discrimination reversal shortly after initial discrimination training (e.g., Chiszar and Spear, 1968; Maier and Gleitman, 1967).

The effect of retention interval duration was less apparent in terms of repeated error responding during retention testing. While no significant main effect of retention interval duration was noted, a significant retention interval x discrimination unit interaction was noted (F 5, 130=1.87, $p<.05$). Separate analyses of variance on repeated error responding in the first 3 and final 3 discrimination units revealed that, while no significant differences were observed in terms of repeated error responding in the first 3 discrimination units, significant differences in repeated error responding in the final 3 discrimination units were observed among the various retention interval groups (F 3,26=4.47, $p<.025$). Mice in the RI21 group made significantly more repeated errors in the final 3 discrimination units than the other 3 treatment groups ($p<.01$ in all cases) during the four trials of retention testing. As was the case for choice error responding, between group dif-

ferences in repeated error responding in the final 3 discrimination units were observed only on the first retention test trial (F 3,26=3.71, $p<.05$).

This latter finding might suggest that, while all mice were exhibiting comparable levels of repeated error responding upon initial exposure to the maze (i.e., the first 3 discrimination units) on the first retention test trial, mice in the RI21 group may have been attending to inappropriate stimulus cues, which could have interfered with subsequent choice behavior. In comparison to the increase in repeated error responding in the final 3 discrimination units that was observed for RI21 mice on the first retention test trial, mice in the 3 other retention interval conditions exhibited a reduction in repeated error responding in the final 3 discrimination units. It is difficult, however, to determine which stimulus cues were controlling the test performance of RI21 mice.

While the pattern of results for the latency measure likewise suggested a retention deficit on the part of mice in the RI21 group, the main effect of retention interval duration was only marginally significant (F 3,26=2.96, $.10>p>.05$). In an attempt to correct for the noted differences in maze latency on the second training trial, latency difference scores were computed (i.e., latency second training trial - latency first test trial). An analysis of variance on the latency difference scores, however, also yielded only a marginally significant effect of retention interval duration (F 3,26=2.28 $.10>p>.05$). Nevertheless, post-hoc comparisons revealed that, on the first retention test trial, the RI21 group was found to have a significantly longer mean latency than the RI1 and RI3 groups ($p<.05$ in both cases); no significant

differences in mean latency were observed between the RI1, RI3, and RI7 groups on the first retention test trial.

The general pattern of results suggests that the present paradigm may be appropriate for examining the effects of post-training strychnine treatment on the retention of discrimination training across long retention intervals, since some degree of forgetting was shown to occur as a function of retention interval duration. The present test conditions (i.e., relearning), however, may not be appropriate for identifying the specific nature of the retention deficits which are observed; for example, under these conditions it is difficult to determine which stimulus cues are controlling retention test performance.

Experiment 2

Within the area of drug facilitation research, the principal concern of research has been to delineate the effects of strychnine and other CNS stimulants on the initial processing (or consolidation) of the memory of a learning experience. It is unclear, however, how the proposed enhancement of initial memory processing by these agents may affect the retention and retrieval of the memory of a learning experience, when animals are tested after relatively long temporal intervals.

The few studies, which have investigated the effects of post-training drug treatments on retention test performance after extended intervals, would tend to suggest that the facilitory effects of drug treatment are relatively short-lived. Garg and Holland (1967) and McGaugh, Westbrook, and Thomson (1962) reported that drug treatment enhanced test performance, when animals were tested 24 to 48 hours after drug treatment; however, when these same animals were given a second retention test 30 days after the initial test phase, no significant differences in retention test performances were observed between drug-treated and control animals. Some of the methodological problems of these two studies have already been discussed in Experiment 1. The within-subject design of these two studies introduces an additional problem, in that there was no independent test of the effects of post-training drug treatment on retention over long intervals.

In the present experiment, separate groups of mice were administ-

ered either strychnine or saline immediately after discrimination training and were then tested either 1, 3, 7, or 21 days after drug treatment. Because the present experiment was intended as an initial investigation of the effects of strychnine on the retention of prior discrimination training, mice were trained and tested on the same discrimination problem. Despite the limitations of the relearning test condition as an index of retention, it was felt that it would be useful to first examine the effects of strychnine under these conditions, not only to maintain some degrees of commonality with prior research, but also to provide a basis of comparison for a more detailed analysis of the effects of strychnine treatment on the retention of specific memory attributes (cf. Experiment 3).

Methods

Procedure. Two days prior to discrimination training mice were placed on water deprivation and were randomly assigned to 1 of 4 retention interval conditions (1, 3, 7, or 21 Day retention intervals). Following the first discrimination training trial, mice within each of the 4 retention interval conditions were matched on the basis of the number of choice errors and were randomly assigned to 1 of 2 drug treatment conditions, either ST (1.0 mg/kg strychnine sulphate) or SA (0.9% saline) resulting in a total of 8 treatment conditions: ST1 (n=8), SA1 (n=8), ST3 (n=6), SA3 (n=7), ST7 (n=8), SA7 (n=7), ST21 (n=6), and SA21 (n=7).

Immediately following removal from the goal compartment on the second discrimination training trial, mice were administered equal volume (1cc/0.1 kg body weight) intraperitoneal injections of either physiological saline or 1.0 mg/kg strychnine sulphate (dissolved in a 0.9% saline solution). In pilot studies with HET mice, the 1.0 mg/kg dose of strychnine appeared to be the most effective facilitory dose of the various levels of strychnine that were tested. The LD_{50} for strychnine for HET mice was found to be 2.0 mg/kg. Immediately after drug treatment, mice were returned to their home cages. After the designated retention intervals, mice in each of the 8 treatment groups were given 4 retention test trials (1 trial per day) on the same discrimination problem (i.e., white=correct brightness and the sequence of correct choices=LRRLLR). No further drug treatments were administered during either the retention interval or retention testing.

Results and Discussion

Both training and test data were analysed in terms of repeated measures analyses of variance, with retention interval duration and drug treatment condition as the between factors. Prior to drug treatment, significant differences in choice error responding were observed as a function of assignment to retention interval condition ($\underline{F}$ 3,49= 4.14, $\underline{p}<.01$). This finding was due mainly to the fact that mice in the RI7 condition made significantly fewer choice errors ($\overline{X}$=6.0) than mice assigned to either the RI3 ($\overline{X}$=7.85, $\underline{p}$ .01) or the RI21 conditions ($\overline{X}$=7.92, $\underline{p}$ .01). No significant differences in choice error respond-

ing were observed between either the RI($\overline{X}$=6.88) and the RI7 conditions or between mice in either the RI1, RI3, or RI21 conditions during discrimination training. These differences in choice error responding were observed primarily on the second training trial (F 3,49=3.68, $p<.05$). The basis of the observed differences in choice error responding during training is unclear in that all mice were trained and tested under similar conditions. No significant differences of repeated error responding or mean latency was observed among the various treatment groups during training. As was the case in Experiment 1, no significant reductions in choice error responding were observed during training, while significant reductions in repeated error responding (F 1,49=21.99, $p<.001$) and latency (F 1,49=101.94, $p<.001$) were observed over the two training trials.

During retention testing, significant differences in choice error responding were observed as a function of retention interval duration (F 3,49=5.80, $p<.01$) and the interaction of retention interval and drug treatment conditions (F 3,49=7.14, p .001). As illustrated in Figure 3, various anomalous findings were noted. First, most studies, which have

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Insert Figure 3 about here

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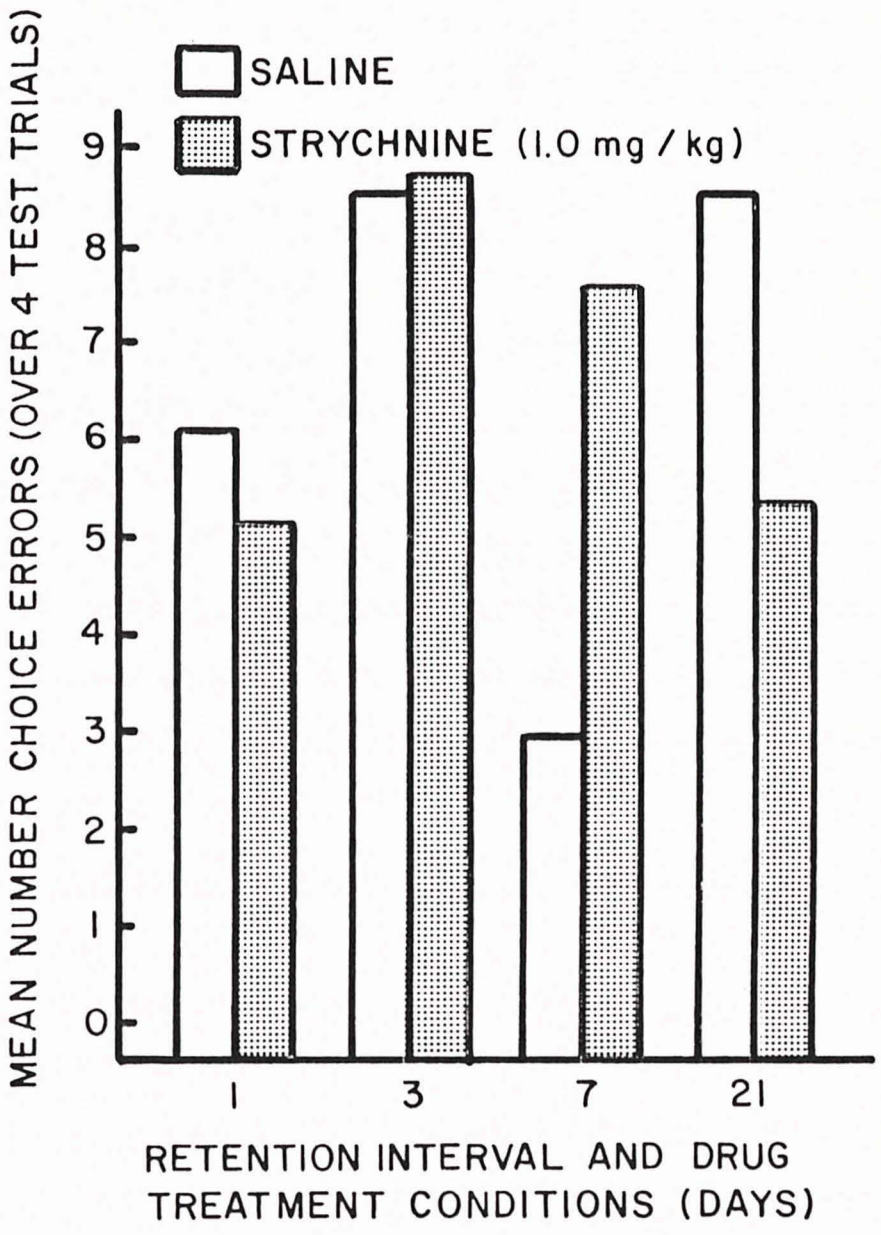
reported a facilitory effect of strychnine on retention test performance, tend to observe this effect when animals are tested 24 to 48 hours after

Figure 3. The mean number of choice errors (over four test trials) of each of the treatment groups in Experiment 2 is shown as a function of post-training drug treatment and retention interval duration.


SALINE
STRYCHNINE (1.0 mg / kg)
MEAN NUMBER CHOICE ERRORS (OVER 4 TEST TRIALS)
0
1
2
3
4
5
6
7
8
9
1
3
7
21
RETENTION INTERVAL AND DRUG TREATMENT CONDITIONS (DAYS)

drug treatment. In the present study, while ST1 mice tended to make fewer choice errors than SA1 mice, this difference was not found to be statistically significant. In contrast, ST21 mice were observed to make significantly fewer choice errors than SA21 mice ($p<.05$) during retention testing. This finding may, in part, reflect a "ceiling effect". In various pilot studies, we have failed to observe a clear facilitory effect of strychnine, when mice were tested under similar conditions 24 hours after drug treatment. It is possible that, under these training and test conditions, the memory of prior discrimination training may be readily accessible for both saline-treated and strychnine-treated mice. With some degree of forgetting on the part of saline-treated mice over the 21 Day retention interval, the facilitory effect of post-training strychnine treatment was more apparent. While the absence of any significant differences in choice error responding between the ST1 and ST21 groups might suggest that post-training strychnine treatment had "protected" the memory of prior discrimination training from the detrimental effects of extended retention interval duration, this suggestion, however, must be qualified in terms of the more general pattern of results in the present study.

The fact that both the SA3 and ST3 groups exhibited relatively poor performance during retention testing introduces some problems for the suggestion that post-training strychnine treatment had enhanced the retention of discrimination training. Even more problematic is the finding that the SA7 group made significantly fewer choice errors during testing than all other treatment groups ($p<.01$ in all cases), with the exception of the ST1 and ST21 groups ($.10>p>.05$ in these latter two

cases). The superior performance of the SA7 group was in sharp contrast to that observed for non-injected mice that were tested 7 days after discrimination training in Experiment 1. The interpretation of this finding is further complicated by the fact that the RI7 group in the present study was also observed to exhibit superior performance during initial discrimination training.

It is unclear then whether the enhanced retention test performance of the SA7 group represented an effect of degree of learning, retention interval duration, drug treatment, or an interaction between these various factors. The potential influence of the degree of original learning was suggested by the fact that, when difference scores were computed (i.e., choice errors second training trial - choice errors first retention test trial), no significant main effects of retention interval duration or drug treatment were observed. Whatever the case, the present pattern of results introduces the need for caution in interpreting the effects of drug treatment and retention interval duration.

In addition to overall differences in choice error responding during retention testing, differences were also observed in terms of the patterning of choice error responding (cf. Appendix C). The mean number of choice errors in the first 3 and final 3 discrimination units during retention testing are presented for each of the treatment groups in Figure 4. The superior performance of the SA7 group was reflected by

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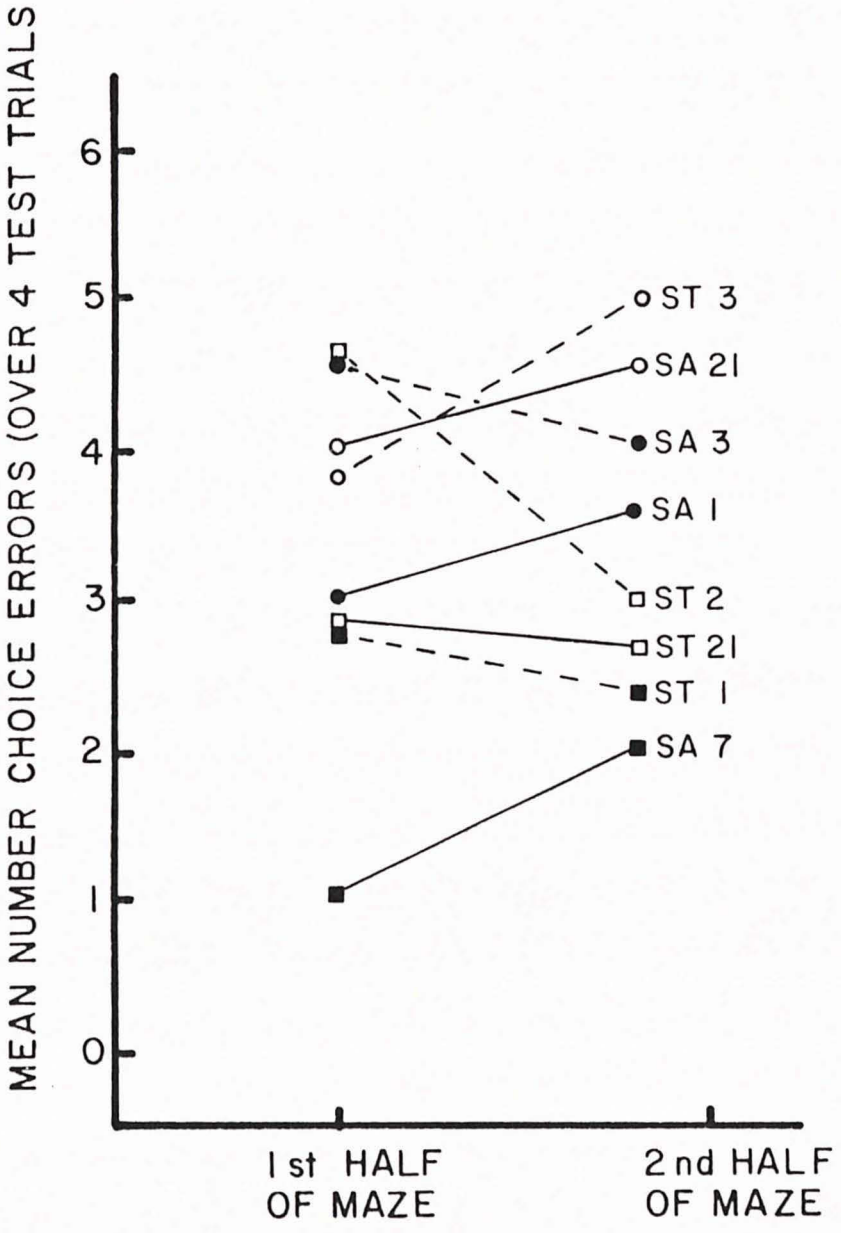
Insert Figure 4 about here

Figure 4. The mean number of choice errors in the first 3 and final 3 discrimination units (over four test trials) for each of the treatment groups in Experiment 2 is shown as a function of post-training drug treatment and retention interval duration.


MEAN NUMBER CHOICE ERRORS (OVER 4 TEST TRIALS
6
5
4
3
2
1
0
ST 3
SA 21
SA 3
SA 1
ST 2
ST 21
ST 1
SA 7
1st HALF OF MAZE
2nd HALF OF MAZE

the fact that the SA7 group was found to make significantly fewer choice errors in the first 3 discrimination units than all other treatment groups ($p<.05$) during retention testing. While the ST1 and ST21 groups were also observed to make significantly fewer choice errors in the first 3 discrimination units than the ST7 ($p<.05$ in both cases) and the SA3 ($p<.05$ in both cases) groups, perhaps the most interesting finding was that, with the exception of the ST3 group, strychnine-treated mice tended to exhibit a reduction in choice error responding in the final 3 discrimination units. In comparison, saline-treated mice tended to exhibit an increase in choice error responding in the final 3 discrimination units during retention testing. While these findings are admittedly difficult to interpret in the context of the noted differences in acquisition performance, these patterns of choice error responding may be suggestive of distinction between the stimuli that were controlling the choice behavior of saline-treated and strychnine-treated mice during retention testing. The present test conditions, however, do not provide a means of determining the specific stimulus cues which were controlling choice behavior.

While differences in choice error responding were observed during retention testing, no significant differences in repeated error responding were observed between the various treatment groups during retention testing. This finding was due to the fact that mice tended to make relatively few repeated errors during retention testing in the present study.

During retention testing, significant differences in mean latency were observed between the various treatment groups. An analysis of variance on the latency measure revealed a significant interaction of

drug treatment x retention interval condition (F 3,49=4.29, $p<.05$) and a significant interaction of drug treatment x retention interval duration x test trial (F 9,147=1.88, $p<.05$). These findings were due primarily to the fact that the SA21 group was observed to have a significantly longer mean latency than all other treatment groups ($p<.05$) on the first retention test trial. No significant differences in mean latency were observed between any of the other treatment groups on the first retention test trial. While a retention deficit on the part of the SA21 group was suggested by the impaired choice behavior of this treatment group during retention testing, the latency measure provides perhaps, the clearest evidence that there was some degree of forgetting by saline-treated mice after a 21 Day retention interval. The significant difference in mean latency between the SA21 and ST21 groups on the first retention test trial might suggest that post-training strychnine treatment had enhanced the retention of the memory of prior discrimination training; this suggestion, however, must be qualified by the more general pattern of results.

In the present study, the various treatment groups were found to differ during initial discrimination training. These differences in acquisition performance apparently were reflected in terms of the differences noted in test performance. The problematic features of the present results may, however, be important, in that they underscore the limitations of the present paradigm for investigating the effects of post-training strychnine treatment on the retention of prior training over long intervals. While some degree of forgetting was observed for

non-injected mice (RI21) in Experiment 1 and by the SA21 groups in the present study, the particular patterns of error responding by mice in these groups (i.e., increased error responding in the final 3 discrimination units) may be indicative of a more important characteristic of the retention deficits which were observed. In both cases, it was suggested that, after 21 Day retention intervals, mice may have been attending to inappropriate stimulus cues at the time of retention testing. The present test conditions (i.e., a relearning task) do not provide a clear means of determining the relative saliency of various training cues, and further, the present test conditions do not provide a way of assessing whether there were any changes in cue saliency as a function of retention interval duration.

These limitations of the relearning test condition have already been suggested in Experiment 1; in the present study, these limitations may be more critical, given that strychnine-treated and saline-treated mice were observed to exhibit differential responding. In addition to the fact that the present test conditions do not provide a means of identifying the specific characteristics of the retention deficits which were observed, the present test conditions may obscure the effects of post-training strychnine treatment on the retention of prior discrimination training. For example, due to the fact that the present test conditions represent an optimal situation for both specific and general positive transfer from prior training, any strychnine-induced enhancement of specific memory attributes may have been masked by the effects of general positive transfer on the retention test performance of saline-treated mice. As such, the present test conditions may not provide a sensitive index of

the effects of post-training strychnine treatment on the retention of prior discrimination training.

Experiment 3

In both Experiment 1 and 2, the possibility was raised that, after relatively long retention intervals, there may have been a change in the stimulus cues which were controlling sugjects' retention test performance. This possible characteristic of forgetting (i.e., a change in stimulus control), however, may often go undetected when animals are tested under relearning conditions. For this reason, the general finding that there is relatively little forgetting of choice behavior over extended retention intervals (cf. Gleitman, 1971) may reflect the fact that the commonly used relearning test condition may not provide a sensitive index of forgetting. Because the relearning task represents an optimal condition for both specific and general positive transfer from prior training, forgetting of specific stimulus-response associations may be obscured by the retention of more general aspects of prior training (cf. Bunch, 1941b). This is, in part, suggested by the finding that the amount of negative transfer, which is observed when subjects are tested on a discrimination reversal, is an inverse function of retention interval duration (e.g., Bunch, 1939; Gollin, 1964; Stevenson and Weir, 1959). These findings suggest that there is some forgetting, even relatively rapid forgetting (e.g., Gollin, 1964), of specific stimulus-response associations in choice situations as a function of retention interval duration.

The attempt to provide some distinction between possible specific and general transfer effects takes on an additional dimension within the present paradigm. In both Experiments 1 and 2, mice were given training

on a discrimination problem for which there were two relevant and redundant stumulus cues, a brightness cue and a spatial-sequence cue; the discrimination problem could be solved by utilizing either stimulus cue. Under these conditions, the two stimulus cues could potentially exercise differential control over responding. In previous studies (e.g., Brennan, Gordon, and Komoda, in preparation), there was evidence that, when mice were trained under these types of conditions, one stimulus cue tended to acquire maximal control over responding, while the other stimulus cue exercised only minimal control over responding. Because mice were trained and tested under similar stimulus conditions in Experiments 1 and 2, there was no clear means of assessing the relative saliency of the two stimulus cues, and there was also no clear way of determining whether there were any changes in cue saliency as a function of retention interval duration.

The possibility that the two stimulus cues may acquire differential control over responding also introduces questions regarding the manner in which strychnine treatment may affect the memory of the two stimulus cues. Strychnine, for example, could enhance the memory of the two stimulus cues to the same degree. On the other hand, it might be suggested that strychnine may differentially enhance the memory of the two stimulus cues as a function of cue salience. Experiment 2 unfortunately did not provide a means of determining the manner in which strychnine may have affected the memory of the two stimulus cues. Further, the use of a relearning test in Experiment 2 did not provide a clear means of assessing the effects of post-training strychnine treatment on the retention of the two stimulus cues across long temporal intervals. Using similar train-

ing conditions, Brennan and Gordon (in press) have, however, provided some initial evidence that strychnine may differentially enhance the memory of relevant, redundant stimulus cues; when mice were tested under partial cue reversal conditions (i.e., one training cue was reversed while the other cue remained unchanged) 24 hours after drug treatment, significant differences in error responding by strychnine-treated mice were observed as a function of which training cue was reversed during testing.

The intent of the present study was to extend this type of analysis to the investigation of the effects of post-training strychnine treatment on the retention of prior discrimination training across relatively long intervals. Attempt was made to determine: 1) whether strychnine would differentially enhance the memory of the two training cues, and 2) whether the proposed selective effect of strychnine induced enhancement would affect test performance, when mice were tested after extended retention intervals. To this end, separate groups of strychnine-treated and saline-treated mice were tested under partial cue reversal conditions after retention intervals of either 1, 7, or 21 days. In order to provide a reference condition against which the proposed selective effect of strychnine-induced enhancement might be further assessed, separate groups of strychnine-treated and saline-treated mice were tested under complete cue reversal conditions (i.e., both training cues were reversed during testing) after these same retention intervals.

The present experiment may also be viewed, in part, as an attempt to assess the relative sensitivity of these various cue reversal conditions and the relearning test condition as indices of the retention of

prior discrimination training. Because mice were found to differ in terms of acquisition performance in Experiment 2, separate groups of strychnine-treated and saline-treated mice were also tested under relearning conditions in the present experiment.

The working assumptions for the present experiment were derived largely from Brennan and Gordon's findings. First, it was assumed that strychnine would primarily enhance the memory of specific stimulus-response associations rather than the memory of more general contextual stimuli. If strychnine had enhanced the memory of specific stimulus-response associations, greater impairment of test performance should be observed for strychnine-treated than saline-treated mice, when both training cues were reversed during testing. If, on the other hand, strychnine had primarily enhanced the memory of more general contextual stimuli, the strychnine treatment might be expected to facilitate test performance (cf. Brennan and Gordon, Experiment 1).

Secondly, it was assumed that strychnine would differentially enhance the memory of the two training cues. In order to establish this fact, two sets of comparisons must be made. First, differences should be evident between strychnine-treated mice tested under partial cue reversal conditions. Secondly, the differences in test performance that are observed between strychnine-treated mice should be of a greater magnitude than those observed between saline-treated mice tested under partial cue reversal conditions.

Methods

Procedure. Prior to the start of discrimination training, all mice were placed on water deprivation for a 48 hour period. All experimental subjects were given two discrimination training trials (1 trial per day). After the first discrimination training trial, experimental subjects were matched on the basis of the total number of choice errors and were randomly assigned to 1 of 2 drug treatment conditions, ST(1.0 mg/kg strychnine sulphate) or SA(0.9% saline). Mice within each drug treatment condition were then randomly assigned to 1 of 3 retention interval conditions (1, 7, or 21 Day retention intervals) and 1 of 4 test conditions, resulting in a total of 24 independent experimental groups (n=8 in each group). The design of the present experiment is summarized in Table 1.

Insert Table 1 about here

Immediately following removal from the goal box on the second discrimination training trial, mice were administered intraperitoneal injections of either strychnine or saline and were then returned to their home cages. After the designated retention intervals, mice were tested under 1 of 4 conditions: 1) complete cue reversal (CR; correct brightness=black and the sequence of correct choice=RLLRRL), 1 of 2 partial cue reversal conditions with either 2) the brightness cue reversed and the sequence unchanged (BR; correct brightness=black and the sequence

Table 1

Summary of training, post-training drug treatment,

and retention test conditions in Experiment 3.

A. Experimental (trained) subjects: Mice received two discrimination training trials (1 trial per day) prior to drug treatment and retention testing.

Post-Training Drug Treatment	Retention Interval	Retention Test Conditions*			
		CR	BR	SR	RL
1. Strychnine (1.0 mg/kg)	a. 1 Day				
	b. 7 Days				
	c. 21 Days				
2. Saline	a. 1 Day				
	b. 7 Days				
	c. 21 Days				

B. Control (non-trained) subjects: Mice were not given discrimination training, but were given two goal box adaptation trials (1 trial per day) prior to drug treatment and testing.

Post-Adaptation Drug Treatment	Retention Interval	Retention Test Conditions			
		CR	BR	SR	RL
1. Strychnine (1.0 mg/kg)	1 Day				
2. Saline	1 Day				

* Training Conditions: Correct brightness=white, and the sequence of correct choices=LRRLLR (L=left, R=right).

CR (Complete cue reversal): Correct brightness=black, and the sequence of correct choices=RLLRRL

BR (Brightness cue reversal): Correct brightness=black, and the sequence of correct choices=LRRLLR.

SR (Sequence cue reversal): Correct brightness=white, and the sequence of correct choices=RLLRRL

RL (Relearning Condition): Correct brightness=white, and the sequence of correct choices=LRRLLR.

of correct choices=LRRLLR), or 3) the sequence cue reversed and the brightness cue unchanged (SR; correct brightness=white and the sequence of correct choices=RLLRRL), or 4) the relearning (RL) test condition, in which neither training cue was reversed (correct brightness=white and the sequence of correct choices=LRRLLR). Mice were tested for 4 days (1 trial per day). During testing, mice in the CR and BR conditions were reinforced in a goal box painted flat black; for mice in the SR and RL conditions the goal box was painted flat white.

In order to control for possible proactive effects of strychnine on test performance, 8 additional groups of non-trained but drug-injected mice were included in the present study. Instead of discrimination training, control animals were simply placed into the goal box, with the door separating the goal box and the sixth discrimination unit closed, and were given a 10 second access to a 0.3% saccharin solution, once a day for 2 consecutive days. Following removal from the goal box on Day 2, control animals were immediately administered intraperitoneal injections of either strychnine (1.0 mg/kg) or saline. Twenty-four hours after drug treatment, control animals were tested under 1 of 4 conditions (CR, BR, SR, or RL) for 4 days (1 trial per day). No further drug treatments were administered to either experimental or control animals during either the retention interval or testing.

Results and Discussion

Separate repeated measures analyses of variance were performed on both training and test data, with drug treatment, retention interval,

duration, and test condition as between factors.

Training

While no significant effects of treatment conditions were observed in terms of choice error responding across the two training trials, significant differences in repeated error responding were observed as a function of the interaction of assigned drug treatment and retention interval conditions (F 2,168=3.31, $p<.05$) and in the latency to traverse the maze as a function of assigned retention interval condition (F 2,168=3.21, $p<.05$). Subsequent comparisons revealed that these latter two findings were due to between group differences in repeated error responding and mean latency on the first training trial; no significant differences were observed in terms of any of the three response measures on the second training trial. Furthermore, while significant reductions in repeated error responding (F 1,168=84.41, $p<.001$) and mean latency (F 1,168=291.27, $p<.001$) were observed over the two training trials, no significant trials x treatment condition interactions were observed for either response measure. These findings would suggest that, in contrast to the findings of Experiment 2, mice in the present experiment were exhibiting comparable degrees of acquisition at the time of drug treatment.

Retention Test

The effects of the various treatment conditions were found to interact in a complex fashion. In part, this was due to the fact that mice were tested under various cue reversal conditions. In order to place the

present findings in proper perspective, it would be useful to consider some of the aspects of these test conditions before detailing the present findings.

When animals are tested under reversal conditions, retention test performance may not be indicative only of the characteristics of the memory of prior discrimination training, but may also reflect the fact that animals are given an opportunity for new learning, or the interaction between whatever new learning may be taking place and the memory of prior training. Under these circumstances, the least ambiguous index of the characteristics of the memory of prior training would seem to be provided by subjects' performance upon initial exposure to the reversal conditions. In the absence of any intervening training, subjects' initial retention test performance should be in terms of the memory of prior training. After animals have had exposure to reversal conditions, it becomes increasingly more difficult to distinguish between the characteristics of the memory of prior training and whatever new learning may have taken place.

The importance of this consideration is further underscored when it is realized that mice were tested under a "correction procedure" in the present experiment. Under these conditions, an animal that tended to exhibit a high degree of repeated error responding upon initial exposure to cue reversal conditions would also have more opportunities to learn about the altered contingencies than an animal that tended to make fewer repeated errors. In this context, the possibility exists that post-training treatments (e.g., strychnine administration), which

enhance the memory of prior training, may have dual effects on retention test performance. If strychnine treatment had enhanced the memory of specific stimulus-response associations, strychnine-treated mice would be expected to exhibit enhanced negative transfer upon initial exposure to a reversal of relevant stimulus cues, but given exposure to the altered stimulus contingencies, strychnine-treated mice might exhibit facilitated reversal learning. This pattern of results was suggested by the findings of Brennan and Gordon. In the present experiment, strychnine was likewise found to have a dual influence on retention test performance.

In contrast to the findings of Experiments 1 and 2, the effects of the various treatment conditions in the present experiment were evident primarily in terms of differences in repeated error responding between the various treatment groups. While the various treatment groups were also found to differ in terms of choice error responding, these differences were observed mainly on the second test trial and, as such, do not provide an unambiguous index of the effects of drug treatment on the memory of prior discrimination training. For this reason, consideration will be given first to the differences in repeated error responding that were observed in the present experiment.

Repeated Error Responding. The post-training strychnine treatment was shown to enhance relatively specific attributes of the memory of prior training, in that strychnine-treated mice were observed to make significantly more repeated errors upon initial exposure (i.e., the first 3 discrimination units) to the complete cue reversal (CR) condi-

tion than saline-treated mice on the first retention test trial ($p<.01$). Further, an analysis of variance on repeated error responding in the first 3 discrimination units on the first retention test trial suggested that strychnine had differentially enhanced the memory of the two training cues as indicated by a significant interaction of drug treatment x test condition (F 3,168=4.83, $p<.01$). Strychnine-treated mice were observed to make significantly more repeated errors in the first 3 discrimination units when the brightness cue alone was reversed (BR condition) than when either the sequence cue alone was reversed (SR condition, $p<.01$) or both the brightness and sequence cues were unchanged (RL condition, $p<.01$) on the first retention test trial. These findings suggest that strychnine had selectively enhanced the memory of the brightness cue. In contrast, no significant differences in repeated error responding in the first 3 discrimination units were observed between saline-treated mice as a function of test condition. As illustrated in Figure 5, the effect of post-training strychnine

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Insert Figure 5 about here

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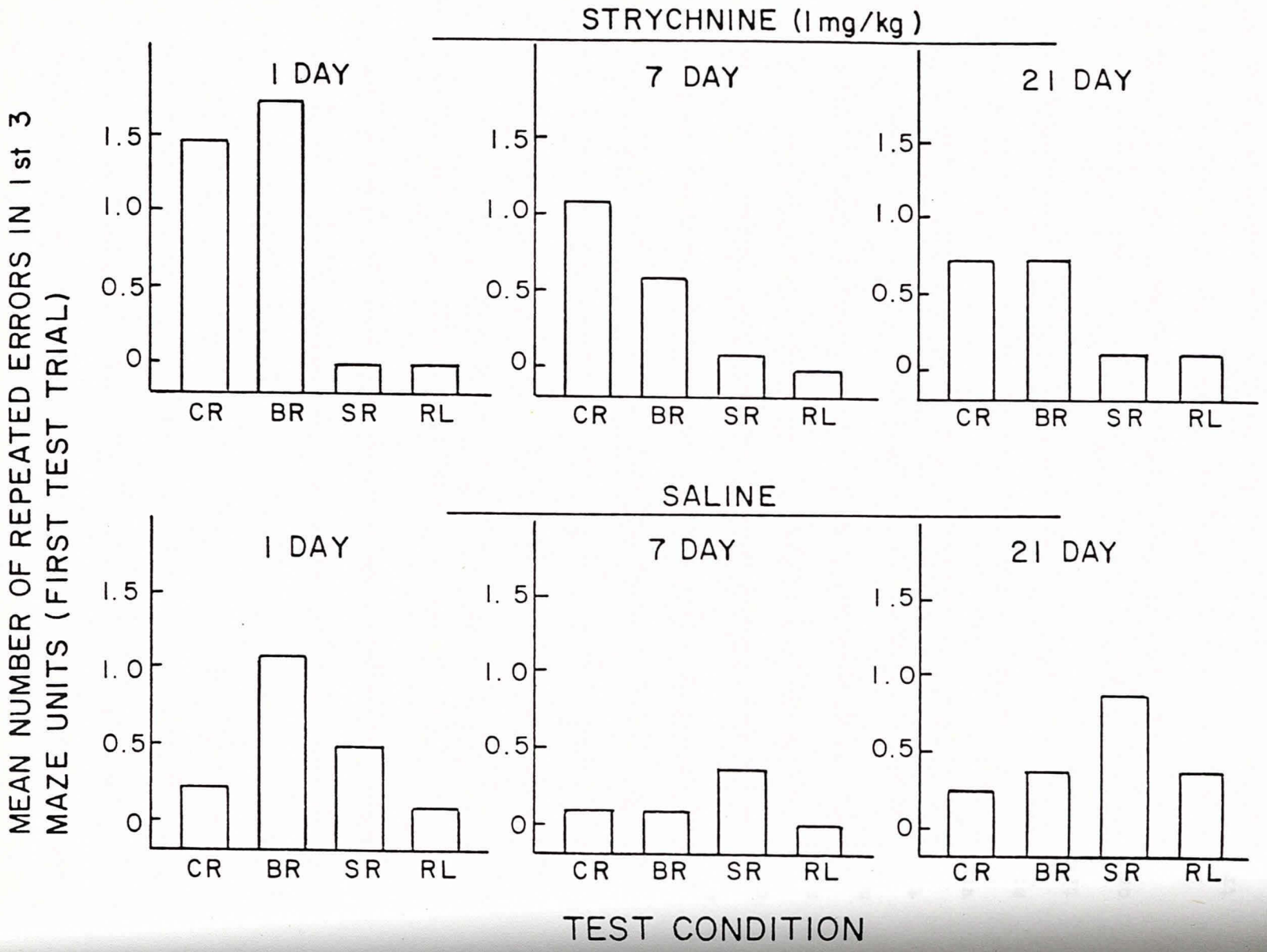
treatment on retention test performance was influenced by the duration of the retention test interval.

The differential effects of strychnine treatment were most evident in terms of the test performance of strychnine-treated mice that were tested 1 day after discrimination training. At the 1 Day retention

Figure 5. The mean number of repeated errors in the first 3 discrimination units on the first retention test trial for each of the treatment groups in Experiment 3 is shown as a function of post-training drug treatment, retention interval duration, and test condition.


STRYCHNINE (1 mg/kg)
1 DAY
7 DAY
21 DAY
SALINE
1 DAY
7 DAY
21 DAY
MEAN NUMBER OF REPEATED ERRORS IN 1st 3 MAZE UNITS (FIRST TEST TRIAL)
1.5
1.0
0.5
0
CR
BR
SR
RL
TEST CONDITION

55b

interval, mice in the STCR and STBR conditions made significantly more repeated errors in the first 3 discrimination units than mice in either the STSR ($p<.01$ in both cases) or the STRL conditions ($p<.01$ in both cases) on the first retention test trial. The fact that no significant differences were observed between the STCR and STBR groups (brightness cue reversed in both test conditions) or between the STSR and STRL groups (brightness cue unchanged in both test conditions) suggests that the memory of the brightness cue exercised maximal control over responding on the initial test trial.

The differential effects of strychnine-induced enhancement appeared to be relatively short-lived, or at least, masked by any forgetting that may have occurred over the 7 and 21 Day retention intervals. While strychnine-treated mice did tend to make more repeated errors in the first 3 discrimination units when the brightness cue (BR) rather than the sequence cue (SR) was reversed, these differences were not found to be statistically significant for mice tested either 7 or 21 days after strychnine treatment. There was, however, some suggestion that the effects of strychnine treatment may have persisted beyond a 24 hour drug treatment-test interval; at the 7 Day retention interval, STCR mice were observed to make significantly more repeated errors in the first 3 discrimination units than mice in either the STRL group ($p<.05$) or the SACR group ($.10>p>.05$) on the first retention test trial.

The general patterns of repeated error responding by strychnine-treated mice were in sharp contrast to those observed for saline-treated mice on the first retention test trial. First, the effect of test condition was less evident in terms of repeated error responding by saline-

treated mice. Only at the 1 Day retention interval was there some suggestion that the test performance of saline-treated mice was more impaired when the brightness cue rather than the sequence cue was reversed; SABR mice were observed to make more repeated errors in the first 3 discrimination units than SASR mice ($.10>p>.05$) on the first retention test trial. Second, in contrast to the initial test performance of strychnine-treated mice, saline-treated mice, which were tested 7 or 21 days after discrimination training, tended to make more repeated errors in the first 3 discrimination units when the sequence rather than the brightness cue was reversed. While these differences were not found to be statistically significant, these findings might suggest that, after the 7 Day and especially after the 21 Day retention intervals, saline-treated mice were responding more in terms of a brightness preference than in terms of the memory of prior training. Non-trained control animals in the present experiment were observed to exhibit greater error responding when white was the correct brightness (SR condition) than when black was the correct brightness (BR condition) during test trials (cf. section on control data).

After mice had had initial exposure to cue reversal conditions on the first test trial, two different patterns of repeated error responding were observed. First, there was some suggestion of differential stimulus control in terms of repeated error responding by saline-treated mice. Second, strychnine-treated mice tended to exhibit a reduction in repeated error responding. While there was some suggestion of these two patterns in terms of repeated error responding in the final 3 discrimination units on the first retention test trial, an analysis of

variance revealed no significant main effects or interactions. These patterns were more apparent in terms of repeated error responding in the first 3 discrimination units on the second test trial. In contrast to the general absence of differential repeated error responding by saline-treated mice upon initial exposure to cue reversal conditions, on the second retention test trial saline-treated mice were observed to make significantly more repeated errors when tested under the BR condition than when tested under either the SR or RL conditions ($p < .05$ in both cases). This distinction between the repeated error responding by saline-treated mice on the first and second retention test trials might suggest that, while the memory of prior training may not have been readily accessible on the initial exposure to cue reversal conditions, exposure to stimulus conditions on the first test trial may have served to "re-activate" the memory of prior discrimination training.

In contrast, no significant differences in repeated error responding were observed between strychnine-treated mice on the second retention test trial. Further, strychnine-treated mice tended to make fewer repeated errors in the first 3 discrimination units than saline-treated mice ($.10 > p > .05$) on the second test trial. These findings were similar to those reported by Brennan and Gordon; after strychnine-treated mice had exhibited enhanced negative transfer upon initial exposure to cue reversal conditions, strychnine-treated mice were observed to exhibit a significant reduction in error responding on subsequent test trials. This finding may be the result of a number of different factors. The general reduction in repeated error responding by strychnine-treated mice in the CR and BR test conditions may reflect the fact that, due to

the high degree of repeated error responding by STCR and STBR mice upon initial exposure to cue reversal conditions, mice in these groups had more opportunities to learn about the altered stimulus contingencies. This finding may also suggest that strychnine may have also enhanced general memory attributes to a certain degree, such that after initial exposure to the reversal of critical stimulus cues, strychnine-treated mice may have had an enhanced tendency to alter attentional or response strategies.

An effect of retention interval duration was also suggested by the fact that on the second retention test trial no significant differences in repeated error responding were observed between saline-treated mice in the 21 Day retention interval condition. Further, strychnine-treated mice in the 21 Day retention interval condition were not found to exhibit a reduction in repeated error responding on the second retention test trial to the same degree as was observed for strychnine-treated mice in the 1 and 7 Day retention interval conditions. As was the case for initial test performance, the test performance of mice, in the 21 Day retention interval condition, on the second retention test trial suggests that the memory of specific training stimulus cues may not have been accessible to the degree that it exerted a clear influence on the retention test performance of mice in these groups.

Both saline-treated and strychnine-treated mice tended to make relatively few repeated errors on Test Trials 3 and 4. While some differences in repeated error responding were noted on these later test trials (cf. Appendix D), these differences primarily reflected repeated error responding on the part of 1 or 2 mice within a given treatment

group.

The patterns of repeated error responding that were observed on the first 2 retention test trials were reflective of a complex interaction of the effects of drug treatment and retention interval duration. Not only was there an indication that post-training strychnine treatment had differentially enhanced the memory of the two training cues, but there was also a suggestion that there was a progressive decrease in differential stimulus control as a function of retention interval duration. There was also a suggestion that the relative accessibility of the memory of prior discrimination training on the first retention test trial may have influenced the particular patterns of repeated error responding that were observed on the subsequent test trials.

Choice Error Responding. This pattern of results, however, was not as evident in terms of the differences in choice error responding that were noted between the various treatment groups during retention testing. In contrast to the differences in repeated error responding that were observed on the first retention test trial, no significant differences in choice error responding in the first 3 discrimination units were observed on the first retention test trial.

Following initial exposure to cue reversal conditions, strychnine-treated mice were observed to make fewer choice errors in the final 3 discrimination units than saline-treated mice on the first retention test trial. This tendency was most pronounced for mice tested 1 day after discrimination training. ST1 mice were observed to make significantly fewer choice errors in the final 3 discrimination units than

SAl mice ($p<.05$) on the first retention test trial. While this finding was similar to that which was noted in terms of repeated error responding by strychnine treated mice on the first retention test trial, this reduction in choice error responding appeared to be more of a within-trial phenomenon, for on the second test trial differential choice error responding was observed for both strychnine-treated and saline-treated mice.

On the second test trial, both strychnine-treated and saline-treated mice exhibited greater error responding either when both training cues were reversed (CR) or when only the brightness cue (BR) was reversed than when tested under the RL condition. While this finding might suggest that the brightness cue exerted greater control over choice error responding, neither the brightness nor sequence cues appeared to have exercised maximal control over choice error responding on the second test trial; no significant differences in choice error responding were observed either between strychnine-treated or between saline-treated mice tested under the two partial cue reversal conditions. As was the case for the repeated error measure, the effect of retention interval duration was reflected in the fact that there was a general absence of differential choice error responding by either strychnine-treated or saline-treated mice in the 21 Day retention interval condition.

The effects of post-training drug treatment were less apparent in terms of the choice error measure, since differential choice error responding was observed for both strychnine-treated and saline-treated mice on the second retention test trial. The principal distinctions be-

tween the patterns of choice error responding by strychnine-treated and saline-treated mice on the second test trial were that, first, strychnine-treated mice tended to make more choice errors under the complete cue reversal condition than saline-treated mice ($p < .05$). Secondly, while both saline-treated and strychnine-treated mice exhibited differential choice error responding in the first 3 and final 3 discrimination units on the second test trial, strychnine-treat mice tended to exhibit greater differential choice error responding in the final 3 discrimination units. Given that strychnine-treated mice were observed to exhibit a reduction in choice error responding in the final 3 discrimination units on the first test trial, the absence of clear patterns of differential choice error responding by strychnine-treated mice in the first 3 discrimination units on the second test trial may indicate that whatever new learning may have occurred on the first test trial may have interferred with initial choice responding by strychnine-treated mice on the second test trial. No differential effects of drug treatment were observed in terms of choice error responding on Test Trials 3 and 4.

In comparison to the relatively straightforward pattern of results which was observed in terms of repeated error responding, the interpretation of the differences in choice error responding is more problematic. Due to the fact that the major differences in choice error responding were observed on the second test trial, it is difficult to attribute these differences unambiguously to an effect of post-training drug treatment on the memory of prior discrimination training. While it is difficult to resolve the differences between the patterns of results observed in terms of the repeated error and choice error

measures, the discrepancy between these patterns of results may by indicative of the differential sensitivity of these two response measures. Using related maze tasks, some other investigators (e.g., Chin, Donovick, and Burright, 1976; Sikorszky, Donovick, Burright, and Chin, 1977) have found the repeated error measure to provide a more sensitive index of the effects of certain experimental treatments (e.g., septal lesions).

Latency. The differences in mean latency, that were observed on the first retention test trial, largely reflected the differences that were noted in terms of repeated error responding. As indicated by a marginally significant interaction of drug treatment x test condition (F 3,168=2.11, $.10 > p > .05$), there was a general absence of any significant differences in mean latency between saline-treated mice. The exception to this general pattern was the finding that SABR mice had a significantly longer mean latency on the first trial than SARL mice ($.10 > p > .05$). In contrast, clear differences in mean latency were observed between strychnine-treated mice on the first retention test trial. STCR mice and STBR mice were found to have significantly longer mean latencies than either STSR ($p < .01$ and $.10 > p > .05$, respectively) and STRL mice ($p < .01$ and $p < .05$, respectively). These differences in mean latency to traverse the maze were primarily observed between strychnine-treated mice in the 1 Day retention interval condition; no reliable differences in mean latency were observed between mice in

the 7 and 21 Day retention interval conditions.

Test Performance: Control Animals. While the general pattern of results suggests that post-training strychnine treatment had enhanced the memory of prior discrimination training, it was also important to distinguish between the proposed effects of strychnine on the memory of prior discrimination training and the possible proactive effects of strychnine on test performance. The impairment of initial test performance, which was observed for strychnine-treated mice tested under complete cue reversal and brightness reversal conditions, may have been due to a proactive influence of strychnine on test performance. Strychnine could have enhanced or altered existing brightness preferences, independent of any effect on the memory of prior discrimination training.

It was particularly important to provide a distinction between the effects of strychnine on the memory of prior discrimination training and possible proactive effects of strychnine on test performance, since the most pronounced effects of post-training strychnine treatment were observed in terms of the initial test performance of mice that were tested 1 day after drug treatment. This distinction was clearly provided when comparisons were made between the test performance of control and experimental (1 Day retention interval) animals.

The effect of prior discrimination training was evident in terms of the differential effects of the various test conditions on the per-

formance of control and experimental animals; analyses of variance on each of the three response measures (cf. Appendix D) revealed a significant interaction of training x test condition in each case. The basic characteristics of this interaction are illustrated in Figure 6, in which the mean choice errors (over 4 test trials) are presented for con-

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Insert Figure 6 about here

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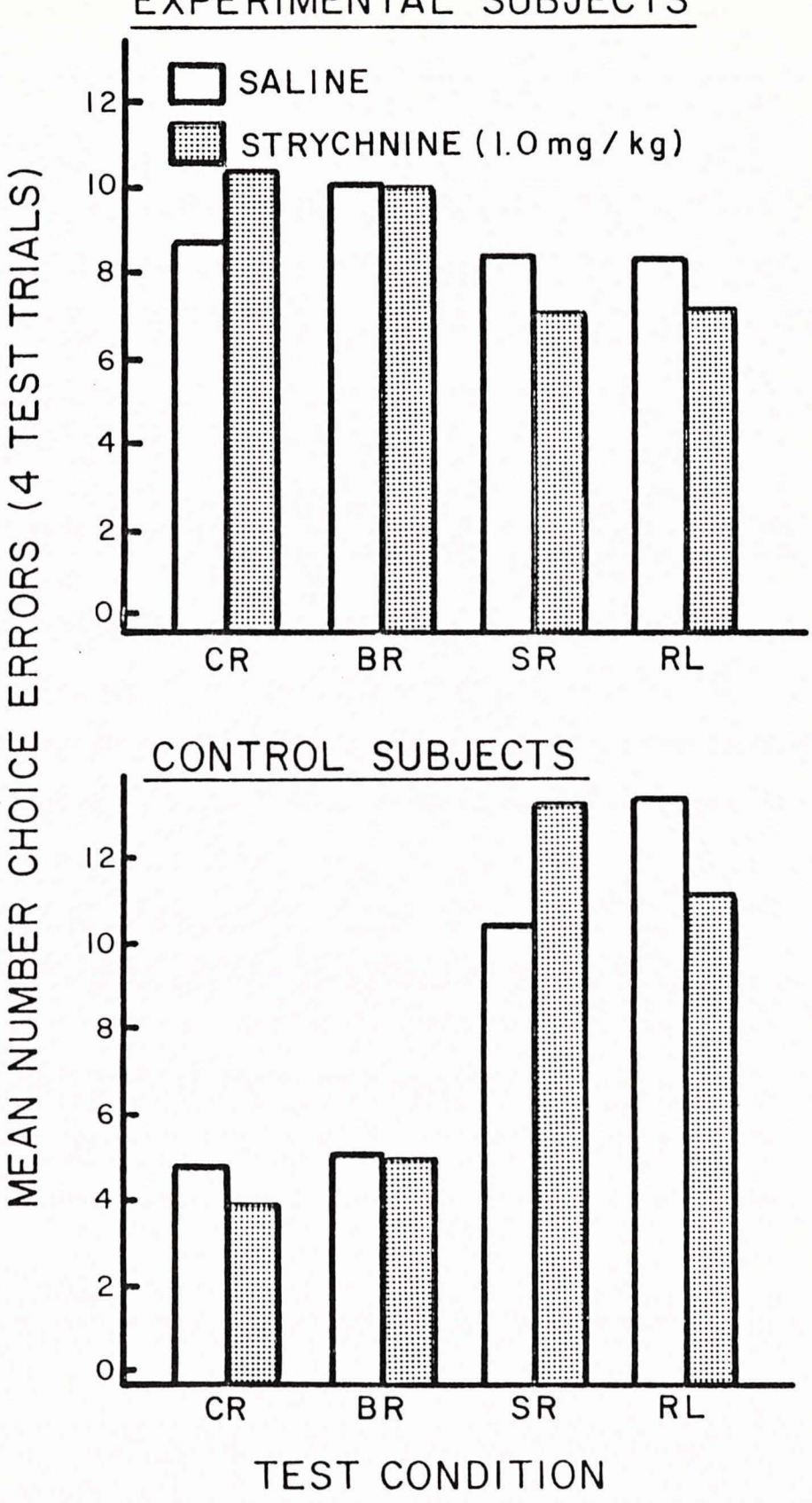
trol and experimental animals as a function of test condition. During discrimination training, experimental animals were trained to choose the non-preferred white alleyway of each discrimination unit. The effect of prior training was reflected in the finding that experimental animals made significantly more choice errors than control animals, when the correct brightness was reversed during the testing (i.e., the CR and BR test conditions, $p < .001$ in both cases). When the correct brightness was unchanged during testing (i.e., the SR and RL test conditions), experimental animals were observed to make significantly fewer choice errors than control animals ($p < .001$ in both cases).

There was little evidence that strychnine had altered the brightness preference of control animals. Both strychnine-treated and saline-treated controls tended to make relatively few errors under the CR and BR test conditions. While both strychnine-treated and saline-treated controls were observed to exhibit greater error responding under the SR and RL test conditions, there was, as indicated in Figure 6, a ten-

Figure 6. The mean number of choice errors (over four test trials) for experimental (1 Day retention interval) and control groups is shown as a function of drug treatment and test condition.


EXPERIMENTAL SUBJECTS
SALINE
STRYCHNINE (1.0 mg / kg)
MEAN NUMBER CHOICE ERRORS (4 TEST TRIALS)
0
2
4
6
8
10
12
CR
BR
SR
RL
CONTROL SUBJECTS
0
2
4
6
8
10
12
CR
BR
SR
RL
TEST CONDITION

dency for strychnine-treated controls to make more choice errors under the SR condition and fewer choice errors under the RL condition than saline-treated controls. In most cases, these differences proved to be either non-significant or only marginally significant. While the basis of this difference between control animals is unclear, the important fact is that, despite this difference between control animals, both strychnine-treated and saline-treated controls tended to exhibit greater error responding under the SR and RL test conditions than experimental animals.

Also in contrast to the test performance of experimental animals, there was a general absence of significant differences in repeated error responding by control animals during testing. On the first test trial, however, strychnine-treated controls were observed to make significantly fewer repeated errors in the first 3 discrimination units than saline-treated controls ($p < .05$) tested under the RL condition. The general pattern of results, however, would tend to argue against the suggestion that the differences initial repeated error responding, which were observed between strychnine-treated and saline-treated experimental animals, were due to a proactive effect of strychnine on test performance. As illustratedin Figure 7, there was a clear distinction between the patterns of re-

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Insert Figure 7 about here

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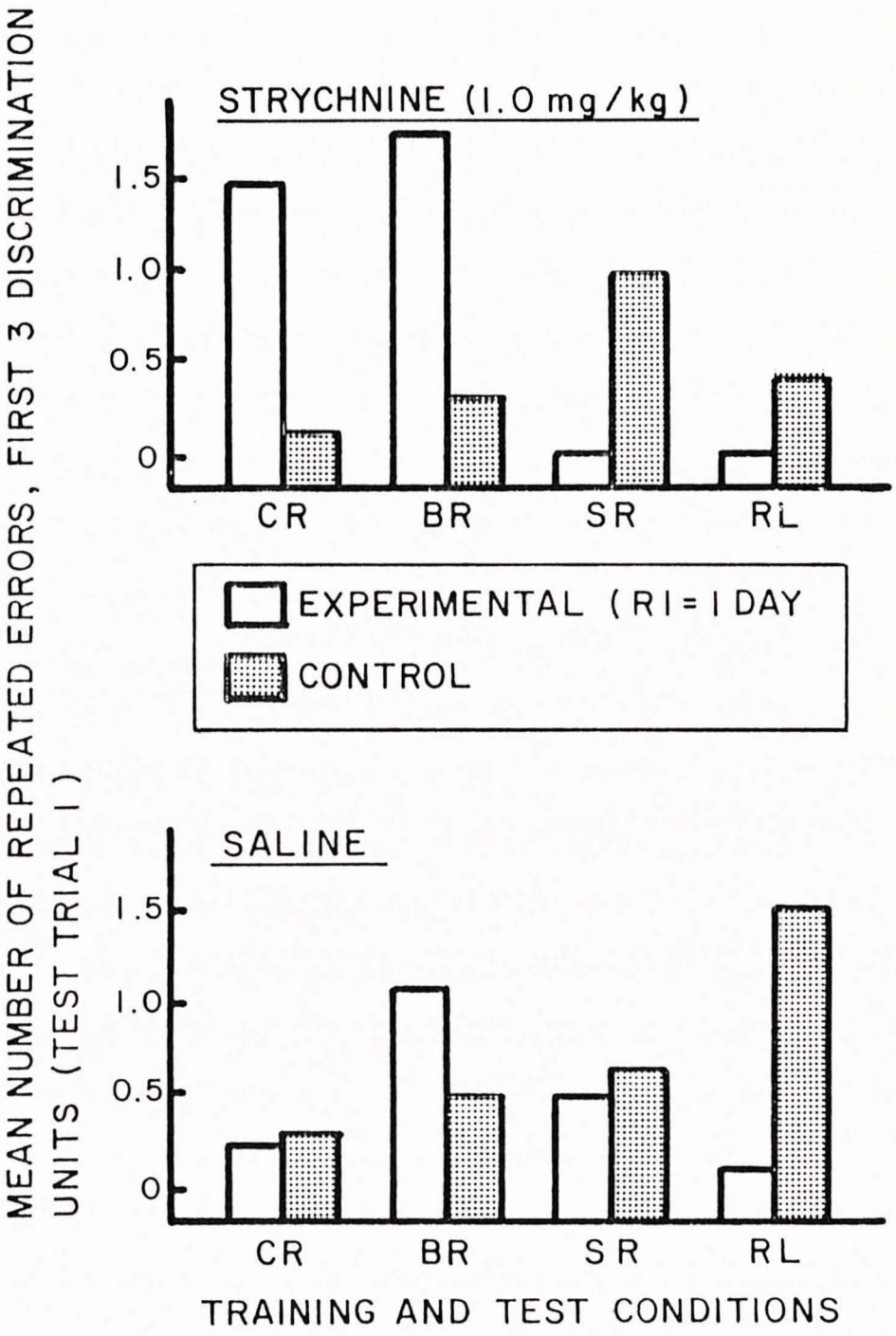
peated error responding by experimental (1 Day retention interval condi-

Figure 7. The mean number of repeated errors in the first 3 discrimination units on the first test trial for experimental (1 Day retention interval) and control groups in Experiment 3 is shown as a function of drug treatment and test condition.


STRYCHNINE (1.0 mg/kg)
1.5
1.0
0.5
0
CR
BR
SR
RL
EXPERIMENTAL (RI = 1 DAY
CONTROL
SALINE
1.5
1.0
0.5
0
CR
BR
SR
RL
MEAN NUMBER OF REPEATED ERRORS, FIRST 3 DISCRIMINATION UNITS (TEST TRIAL 1)
TRAINING AND TEST CONDITIONS

tion) and control strychnine-treated mice in the first 3 discrimination units on the first test trial. In contrast, the distinction between the patterns of repeated error responding by experimental and control saline-treated mice was less apparent; the only significant difference, which was noted between experimental and control saline-treated mice on the first test trial, was the tendency of saline-treated control to make more repeated errors in the first 3 discrimination units than saline-treated experimental subjects ($p<.05$) tested under the RL condition. These general findings provide a further basis of support for the suggestion that strychnine had differentially enhanced the memory of the two training cues.

Summary

While a more complete discussion of the implications of the present findings is reserved for the following section, it would be useful to review some of the general findings at this point.

First, there was evidence that a single post-training injection of strychnine sulphate had enhanced relatively specific attributes of the memory of prior discrimination training. Both in terms of initial repeated error responding and mean latency on the first retention test trial, strychnine-treated mice were found to exhibit significantly greater impairment of test performance than saline-treated mice, upon initial exposure to complete cue reversal conditions. Further, the fact that strychnine-treated mice exhibited greater impairment of ini-

tial test performance when the brightness cue rather than the sequence cue was reversed suggested that strychnine had selectively enhanced the memory of the brightness cue.

In contrast, there was relatively little evidence of differential response impairment on the part of salinetreated experimental subjects on the first retention test trial. While non-trained control animals were observed to exhibit differential error responding during testing, there was a clear distinction between the test performance of strychnine, treated experimental and control animals, suggesting the absence of a proactive influence of strychnine on test performance. The differences in test performance, which were observed between control animals as a function of test condition, suggested that control animals were responding primarily in terms of a brightness preference (see also, Crabbe and Alpern, 1973a).

Second, the suggestion that strychnine had differentially enhanced the memory of the two training cues must be qualified by the fact that this effect appeared to be relatively short-lived. While there was some suggestion of differential error responding by strychnine-treated mice in the 7 Day retention interval condition, no significant differences in test performance were observed between strychnine-treated mice that were tested 21 days after drug treatment. The progressive decrease in differential stimulus control, which was observed as a function of retention interval duration, suggests that there was some degree of forgetting of prior discrimination training at the 7 and 21 Day retention intervals. In contrast, there was relatively little indication of any forgetting, when mice were tested under relearning (RL) conditions.

Further, when mice were tested under RL conditions, there was no clear evidence of a facilitory effect of strychnine treatment.

The contrasting patterns of results, which were obtained when mice were tested under the various cue reversal conditions and the RL condition, point to the differential sensitivity of these various test conditions as indices of the effects of post-training drug treatment and retention interval duration. Other researchers (e.g., Bunch, 1941b) have question the sensitivity of the relearning task as an index of forgetting. The present findings provide an additional basis of support for the contention that the relearning task may not be sensitive enough to detect the specific characteristics of forgetting over extended retention intervals.

Some comment should be made at this point regarding an apparent discrepancy between the results of the present study and those of Experiment 1. When mice were tested on a relearning task in the present study, no significant differences in initial test performance were observed as a function of retention interval duration. In contrast, non-injected mice in Experiment 1 were observed to exhibit a significant impairment of initial test performance, when tested 21 days after discriminating training. Though the actual basis of this discrepancy is unclear, other investigators (e.g., Garg and Holland, 1967) have reported a similar difference in retention test performance between injected and non-injected subjects. While there was some suggestion, in Experiment 2, of a retention deficit on the part of saline-injected mice tested 21 days after discrimination training, this finding should be regarded with some caution, given the noted differences in acquisition performance, which

were observed in Experiment 2.

Finally, while strychnine treatment was shown to differentially enhance the memory of relevant, redundant stimulus cues in both the present study and in Brennan and Gordon's study, differences in cue salience were noted between these two studies. Brennan and Gordon reported that strychnine-treated mice exhibited greater response impairment when the spatial-sequence cue was reversed during testing; in the present study, strychnine-treated mice were observed to exhibit greater response impairment when the brightness cue was reversed. Because mice were given two discrimination training trials prior to drug treatment in both studies, it is difficult to clearly isolate the source of variance between these two studies; there is, however, some suggestion that these differences may reflect the fact that, at the time of drug treatment, subjects in these two studies may have differed in terms of degree of learning.

In various pilot studies, we have noted that the relative salience of the two stimulus cues may be subject to the influence of a number of variables (e.g., prior handling, degree of training, and task difficulty). The general finding has been that, when mice are given between 4 and 12 training trials on the present discrimination problem, mice tend to exhibit greater response impairment when the brightness cue rather than the spatial-sequence cue is reversed on test trials. As such, the differences in cue salience, which were noted between the present study and that of Brennan and Gordon, may suggest that, in the present study, mice were at a relatively higher degree of learning at the time of drug treatment. Whatever the basis of the differences between these two studies,

the findings in both cases underscore the importance of considering the characteristics of the memory, which are enhanced by post-training strychnine treatment.

General Discussion

An attempt was made in the present studies to address questions, which have received relatively little attention in prior research concerning the effects of CNS stimulants on memory processing. The principal intent of the present studies was to determine the effects of post-training strychnine treatment on the retention of specific memory attributes across extended temporal intervals. The results of these studies do not provide for a simple summary statement regarding the effects of strychnine on the memory of a learning experience, but rather, point to the complexity of the effects of strychnine on retention test performance.

The present findings add to a growing body of evidence, which suggests that strychnine primarily enhances relatively specific attributes of the memory of a learning experience. Gordon and Spear (1973) and Gordon (1977) have shown that, when rats were administered strychnine after passive avoidance training, strychnine-treated rats required significantly more trials to learn a conflicting active avoidance response than saline-treated rats. These findings suggest that strychnine had enhanced the memory of a specific response tendency. If strychnine had primarily enhanced the memory of more general or less relevant training experiences (e.g., handling experiences or exposure to the apparatus), the retention of these more general training experiences might be expected to transfer positively to the test situation and, as such, facilitate rather than impair active avoidance learning.

In the present studies (Experiment 3), strychnine treatment was shown to impair initial test performance, when the relevant stimulus cues were reversed during testing, suggesting that strychnine had enhanced the memory of specific stimulus-response associations. Not only were strychnine-treated mice observed to exhibit greater negative transfer upon initial exposure to complete cue reversal conditions than saline-treated mice, but the effects of post-training strychnine treatment were also shown not to be due to a proactive effect of strychnine on test performance. As such, these findings replicated the findings of Brennan and Gordon (in press, Experiment 1).

Beyond a basic distinction between the effects of strychnine on specific and general memory attributes, the results of Experiment 3 also suggested that post-training strychnine treatment had differentially enhanced the memory of the two redundant, relevant stimulus cues (a brightness cue and a spatial-sequence cue). In the present instance, it appeared that strychnine had selectively enhanced the memory of the brightness cue, since strychnine-treated mice were observed to exhibit greater response impairment when the brightness cue rather than the spatial-sequence cue was reversed during retention testing. In comparison, there was relatively little evidence of differential response impairment in terms of the initial test performance of saline-treated mice.

While the basic character of this finding was similar to that which was reported by Brennan and Gordon, differences were noted between these studies. In Brennan and Gordon's study, strychnine appeared to selectively enhance the memory of the spatial-sequence cue; in the present study, strychnine appeared to selectively enhance the memory of the

brightness cue. The suggestion was made that these differences may reflect the fact that the subjects in these two studies differed in terms of degree of learning at the time of drug treatment. This suggestion is not without some precedent. There is some evidence (e.g., Hicks, 1964; MacKintosh, 1965) that, during the course of maze learning, there may be a change in the particular stimulus cues, which are controlling choice responding by rats. While this possible phenomenon needs to be established more convincingly in the present paradigm, there is at least an initial suggestion that the specific effects of strychnine-induced enhancement may vary as a function of the relative salience of stimulus cues at the time of drug treatment.

In addition to providing an indication of the specificity of the effects of strychnine, the present findings also suggest that the effects of strychnine-induced enhancement are more complex than can be ascertained within the context of a simple relearning task. Because a relearning task represents an optimal situation for both specific and general positive transfer from prior training, not only is it difficult to determine the specificity of the effects of strychnine under these conditions, but effects of general positive transfer on the test performance of control subjects may, in some cases, further obscure the effects strychnine-induced enhancement of specific memory attributes. In this latter respect, it is noteworthy that while there was no clear evidence of a facilitory effect of strychnine treatment, when mice were tested on a relearning task 24 hours after drug treatment in both Experiments 2 and 3, the finding that strychnine-treated mice exhibited significantly greater response impairment than saline-treated mice, upon initial exposure to

complete cue reversal conditions in Experiment 3, does, however, suggest that strychnine had enhanced the memory of specific stimulus-response associations.

The limitations of the relearning test condition become an even more critical issue, when animals are tested after extended drug treatment-retention test intervals. Bunch (1941b) has discussed some of the problems of using a relearning task as an index of the retention of prior training; because there appears to be differential forgetting of specific and general memory attributes, any forgetting of specific memory attributes, which may occur as a function of retention interval duration, may be masked by the retention of more general memory attributes. The relearning task does not provide a clear means of assessing the specific characteristics of a memory at the time of retention testing. This problem was brought to light by the results of the present studies. In both Experiments 1 and 2, the suggestion was made that, after relatively long retention intervals, mice may have been attending to inappropriate or different stimulus cues at the time of retention testing, because qualitative differences in the patterning of choice responding were observed as a function of retention interval duration. The fact that, in Experiment 2, differences were also observed between the patterns of error responding by strychnine-treated and saline-treated mice further suggested that there may have been differences in the stimuli which were controlling the retention test performance of strychnine-treated and saline-treated mice. In both cases, however, there was no clear means of specifying the nature of the particular differences in test performance, which were observed in Experiments 1 and 2, because mice were

tested on a relearning task.

When mice were tested under various cue reversal conditions in Experiment 3, however, an initial basis was provided for specifying the interactive effects of drug treatment and retention interval duration. At a general level, a comparison between the performance of mice tested under complete cue reversal conditions and the test performance of mice tested on a relearning task suggested a distinction between the retention of specific and general memory attributes across extended retention intervals. The progressive decrease in negative transfer which was observed as function of retention interval duration, when mice were tested under complete cue reversal conditions, suggested that some forgetting of specific stimulus-response associations had occurred. However, the finding that, even after a 21 Day retention interval, mice exhibited relatively little impairment of test performance under relearning conditions, indicated that there was relatively little forgetting of more general training experiences.

While this distinction between the retention of specific and general memory attributes is important and in agreement with some earlier findings (e.g., Bunch, 1939), perhaps the most interesting findings were reflected in terms of the differential effects of retention interval duration on the initial test performance of strychnine-treated and saline-treated mice.

The effects of post-training strychnine treatment appeared to be relatively short-lived, in that the effects of strychnine treatment were clearly evident, only when mice were tested 24 hours after drug treatment. After the 7 and 21 Day retention intervals, the effects of

post-training strychnine treatment appeared to be masked by the forgetting of specific stimulus-response associations, which had taken place over these retention intervals. Some qualifications should, however, be introduced.

While the progressive decrease in negative transfer, which was observed when strychnine-treated mice were tested under complete cue reversal conditions after the 7 and 21 Day retention intervals, suggested that there was some forgetting of specific stimulus-response associations, there was nevertheless, some indication that the memory of specific stimulus-response associations was still accessible to a certain degree, when strychnine-treated mice were tested 7 days after drug treatment. At the 7 Day retention interval, strychnine-treated mice were observed to make significantly more repeated errors on the initial retention test trial, when tested under complete cue reversal conditions than when tested under relearning conditions. In contrast, there was relatively little evidence that the initial test performance of saline-treated mice was mediated by the retention of specific stimulus-response associations, since no significant differences in initial repeated error responding were observed between saline-treated mice tested under complete cue reversal conditions and saline-treated mice tested under relearning conditions, at any of the three retention intervals.

The effects of retention interval duration were revealed in a more complex fashion, when mice were tested under partial cue reversal conditions. While there was a suggestion that strychnine had selectively enhanced the memory of the brightness cue, this effect was only evident in terms of the initial test performance of strychnine-treated mice test-

ed 24 hours after drug treatment. No significant differences in initial test performance were observed between strychnine-treated mice tested under partial cue reversal conditions, at either the 7 or the 21 Day retention intervals. This decrease in differential stimulus control would suggest a relatively more rapid rate of forgetting of specific stimulus-response associations than would seem to be the case, when the initial test performance of strychnine-treated mice tested under complete cue reversal conditions is considered.

This discrepancy may be a function of a number of different factors. It is possible, for example, that in addition to whatever forgetting that may have occurred, the fact that, under BR condition, the less salient spatial sequence cue was unchanged during testing may have also represented a source of interference; i.e., there may have been some confusion as regards which cue (the reversed vs. the unchanged stimulus cue) should be attended to. It is also possible that there may have been a change, as a function of retention interval duration, in the specific stimulus cues which were controlling initial test performance.

There would seem to be some suggestion of this latter possibility in terms of the test performance of saline-treated mice. After a 1 Day retention interval, saline-treated mice were observed to make more repeated errors on the initial test trial, when the brightness cue rather than the spatial-sequence cue was reversed; after retention intervals of 7 or 21 days, however, saline-treated mice tended to make more repeated errors on the initial test trial, when the spatial-sequence cue was reversed. While these findings might suggest that, after retention intervals of either 7 or 21 days, saline-treated mice were attending more to

the spatial-sequence cue on the initial test trial, these findings would seem to be more indicative of the fact that saline-treated mice were responding more in terms of a brightness preference than the memory of prior discrimination training, since saline-treated mice were observed to exhibit relatively little response impairment, when tested under complete cue reversal conditions after either the 7 or 21 Day retention intervals.

These qualitative differences in initial test performance, which were observed when mice were tested on partial cue reversal conditions, are perhaps one of the most interesting findings of the present studies. While there is a suggestion that the effect of retention interval duration was reflected in terms of a loss or a change in stimulus control, it is difficult to provide a clear interpretation of these findings, since there was an absence of clear differences in initial test performance between the various treatment groups tested at the latter retention intervals. In the face of these difficulties, it should, nevertheless, be realized that the characteristics of these particular retention deficits went largely undetected, when mice were tested on a relearning task. The implications of the present findings, however, go beyond a purely methodological consideration and raise questions for further research.

First, while strychnine was shown to enhance relatively specific attributes of the memory of prior discrimination training, post-training strychnine treatment was not found to demonstrably enhance the retrieval of these memory attributes after a relatively long (21 Day) retention interval. Though this finding may be taken as an initial suggestion that the effects of strychnine may not be reflected in terms

of an enhancement of the organization or "elaboration" of the memory of a learning experience (cf. Lewis, 1976), this issue remains open to question. It is possible, for instance, that while post-training strychnine may not "protect" specific memory attributes from whatever forgetting that may occur as a function of retention interval duration, post-training strychnine may enhance the susceptibility of specific memory attributes to the effects of subsequent "memory reactivation" treatments.

It is also possible, however, that these findings may be indicative of the fact that post-training strychnine treatment may bias the manner in which the memory of a learning event is processed, such that the memory is less accessible for retrieval after extended retention intervals. It may well be the case that both specific and general memory attributes need be organized or "elaborated" into an associative network for efficient memory retrieval. By inducing an enhancement of the processing of specific memory attributes, strychnine may, in this light, have a detrimental effect on the "elaboration" of the memory of a learning event; less time or attention may be afforded to the processing of more general-contextual aspects of a learning event. As a result, a strychnine-enhanced memory may then be more susceptible to interference or be less acceptible at the time of retention testing, when there are pronounced changes in contextual stimuli over temporal intervals.

Second, the present findings also point to the complex changes, which the memory of a learning experience may undergo as a function of retention interval duration. As such, these findings would seem to raise some questions regarding the specificity of the effects of "memory reactivation" treatments. At one level, questions may be raised as to whether

the characteristics of a "reactivated" memory are similar to the characteristics of the memory at the time of original learning (see Gordon, 1977 for an initial treatment of this issue), and whether the characteristics of a "reactivated" memory may vary as a function of the time intervening between original learning and the introduction of the "memory reactivation" treatment. At another level, a question may be raised as to whether different stimuli from a learning situation may bias the retrieval of different memory attributes.

These types of questions are complex and would seem to require a more sophisticated type of behavioral analysis than has typically been afforded by the more conventional behavioral paradigms used in animal memory research. These types of questions do not lend themselves to easy answers. If the present efforts are an example, more questions may be raised than are actually answered. If however, the memory of a learning experience is regarded as a complex entity, represented by various attributes (e.g., Underwood, 1969; Spear, 1971), these and related questions need to be addressed at some level, if further progress is to be made in better understanding the nature of memory processes and the neurobiological correlates of memory processes.

References

Alpern, H. P. Facilitation of learning by implantation of strychnine sulphate in the central nervous system. Dissertation Abstracts International, 1969, 29, 3928.

Alpern, H. P., and Crabbe, J. C. Facilitation of the long term store of memory with strychnine. Science, 1972, 177, 722-724.

Baker, W. W., Kratky, M., and Benedict, F. Electrographic responses to intrahippocampal injections of convulsant drugs. Experimental Neurology, 1965, 12, 136-145

Bauer, R. H. Twenty-four hour facilitation of avoidance and discrimination learning by pentylenetrazol. Psychopharmacologia, 1972, 24, 275-295.

Bauer, R. H., and Duncan, N. C. Twenty-four hour proactive facilitation of avoidance and discrimination by d-amphetamine. Journal of Camparative and Physiological Psychology, 1971, 77, 521-27.

Bovet, D., McGaugh, J. L., and Oliverio, A. Effects of post-trial administration of drugs on avoidance learning in mice. Life Sciences, 1966, 1309-1315.

Breen, R. A., and McGaugh, J. L. Facilitation of maze learning with post-trial injections of picrotoxin. Journal of Comparative and Physiological Psychology, 1961, 54, 498-501.

Brennan, M. J., and Gordon, W. C. Selective facilitation of memory attributes by strychnine. Pharmacology, Biochemistry, and Behavior (in press).

Brennan, M. J., Gordon, W. C., and Komoda, V. L. Cue reversal learning in mice as an index of cue salience. (manuscript in preparation).

Buckholtz, N. S. Shuttle-avoidance learning of mice: Effects of post-trial pentylenetrazol, strain and age. Psychological Reports, 1974, 35, 319-326.

Bunch, M. E. Transfer of training in the mastery of an antagonistic habit after varying intervals of time. Journal of Comparative Psychology, 1939, 28, 189-200

Bunch, M. E. A comparison of retention and transfer of training from similar material after relatively long intervals of time. Journal of Comparative Psychology, 1941, 32, 217-231 (a).

Bunch, M. E. The measurement of retention by the relearning method. Psychological Review, 1941, 48, 450-456 (b).

Calhoun, W. H. The effect of strychnine sulphate on home cage activity and oxygen consumption in three inbred strains of mice. Psychopharmacologia, 1965, 8, 227-234.

Calhoun, W. H. Effect of level of external stimulation on rate of learning and interaction of this effect with strychnine in mice. Psychological Reports, 1966, 18, 715-722.

Calhoun, W. H. Central nervous system stimulants. In E. Furchgott (Ed.), Pharmacological and biophysical agents and behavior. New York: Academic Press, 1971.

Carlson, K. Lack of facilitation of learning by strychnine sulphate. Psychonomic Science, 1966, 4, 173-174.

Castellano, C. Effects of nicotine on discrimination learning, consolidation, and learned behavior in two inbred strains of mice. Psychopharmacology, 1976, 48, 37-43.

Castellano, C. Effects of pre- and post-trial caffeine administration on simultaneous visual discrimination in three inbred strains of mice. Psychopharmacology, 1977, 51, 255-258.

Chin, T., Donovick, P. J., and Burright, R. G. Septal lesions in rats produce reversal deficits in simultaneous visual discrimination. Journal of Comparative and Physiological Psychology, 1976, 90, 1133-1143.

Chiszar, D. A., and Spear, N. E. Proactive interference in a T-maze brightness discrimination task. Psychonomic Science, 1968, 11, 107-108.

Cooper, R. M., and Krass, M. Strychnine: Duration of the effects on maze learning. Psychopharmacologia, 1963, 4, 472-472.

Coker, D. L., and Abbott, D. W. The effect of strychnine sulphate on maze learning as a function of task difficulty. Psychonomic Science, 1967, 9, 607.

Crabbe, J. C., and Alpern, H. P. A comprehensive analysis of single-trial and criterior maze learning in three inbred strains of mice. Behavioral Biology, 1973, 9, 631-693 (a).

Crabbe, J. C., and Alpern, H. P. Facilitation and disruption of the long-term store of memory with neural excitants. Pharmacology, Biochemistry, and Behavior, 1973, 1, 197-202 (b).

D'Amato, M. R., and Fazzaro, J. Attention and cue-producing behavior in the monkey. The Journal of the Experimental Analysis of Behavior, 1966, 9, 469-473.

Dawson, R. C., and McGaugh, J. L. Drug facilitation of learning and memory. In J. A. Deutsch (Ed.), The physiological basis of memory. New York: Academic Press, 1973.

Doolittle, J. H., and Thomson, C. W. Retroactive effects of topical applications of potassium chloride, penthylenetrazol, and strychnine on the acquisition of a maze habit in rats. Psychonomic Science, 1966, 5, 265-266.

Duncan, D. B. Multiple range and multiple F-tests. Biometrics, 1955, 11, 1-42.

Eccles, J. C., Schmidt, R., and Willis, W. D. Pharmacological studies on presynaptic inhibition. Journal of Physiology (London), 1963, 168, 500-530.

Esplin, D. W., and Zablocka-Esplin, B. Mechanisms of action of convulsants. In H. J. Jasper, A. A. Ward, and A. Pope (Eds.), Basic mechanisms of the epilepsies. Boston: Little, Brown, 1969.

Evangelista, A. M., and Izquierdo, I. The effects of pre- and post-trial amphetamine injections on avoidance responses of rats. Psychopharmacologia, 1971, 20, 42-47.

Eyzaquirre, C., and Lilenthal, J. C., Jr. Vetrinic effects of pentamethylenetetrazon (metrazol) and 2,2 bis (p-chlorophenyl) 1,1,1 trichloroethane (DDT) on mammalian neuromuscular function. Proceedings of the Society of Experimental Biology and Medicine, 1949, 70, 272-275.

Fleming, D. E. Differential effects of convulsive drugs on photically evoked after-discharge parameters. Psychopharmacologia, 1973, 29, 77-84.

Flood, J. F., Jarvik, M. E., Bennett, E. L., Orme, A. E., Rosenzweig, M. R. The effects of stimulants, depressants, and protein synthesis inhibition on retention. Behavioral Biology, 1977, 20, 168-183.

Franchina, J. J., and Moore, M. H. Strychnine and the inhibition of previous performance. Science, 1968, 160, 903-904.

Franz. D. N. Central nervous system stimulants. Strychnine, picrotoxin, pentylenetrazol, and miscellaneous agents (doxapram, ethamivan, nikethamide, flurothyl, methylphenidate). In L. S. Goodman and A. Gilman (Eds.), The pharmacological basis of therapeutics. New York: Macmillan, 1975.

Galindo, A. Gaba-picrotoxin interaction in the mammalian central nervous cystem. Brain Research, 1969, 14, 763-767.

Garg, M. Combined effect of drug and drive on the consolidation process. Psychopharmacologia, 1970, 18, 172-179.

Garg, M., and Holland, H. C. Consolidation and maze learning: A comparison of several posttrial treatments. Life Sciences, 1967, 6 1987-1997.

Gleitman, H. Forgetting of long-term memories in animals. In W. K. Honig and P. H. R. James (Eds.), Animal Memory. New York: Academic Press, 1971.

Gleitman, H., and Jung,L. Retention in rats: The effect of proactive interference. Science, 1963, 142, 1683-1684.

Gold, P. E., and McGaugh, J. L. A single-trace, two process view of memory storage processes. In D. Deutsch and J. A. Deutsch (Eds.) Short-term memory. New York: Academic Press, 1975.

Gollin, E. S. Reversal learning and conditional discrimination in children. Journal of Comparative and Physiological Psychology, 1964, 58, 441-445.

Gordon, W. C. Susceptibility of a reactivated memory to the effects of strychnine: A time-dependent phenomenon. Physiology and Behavior, 1977, 18, 95-99.

Gordon, W. C., and Brennan, M. J., and Rose, R. C. Facilitation of the long-term memory store with strychnine: A reexamination. Pharmacology, Biochemistry, and Behavior, 1975, 3, 967-972.

Gordon, W. C,, and Spear, N. E. The effects of strychnine on recently acquired and reactivated passive avoidance memories. Physiology and Behavior, 1973, 10, 1071-1075.

Greenough, W. T., and McGaugh, J. L. The effect of strychnine sulphate on learning as a function of time of administration. Psychopharmacologia, 1965, 8, 290-294.

Gross, G. J., and Woodbury, D. M. Effects of pentylenetrazol on ion transport in the isolated toad bladder. Journal of Pharmacological and Experimental Therapeutics, 1972, 181, 257-272.

Grossman, S. P. Facilitation of learning following intracranial injections of pentylenetrazol. Physiology and Behavior, 1969, 4, 625-628.

Hahn, F. Analeptics. Pharmacological Review, 1960, 12, 447-530.

Hall, M. E. Effects of post-trial amphetamine and strychnine on learning as a function of task difficulty. Communications in Behavioral Biology, 1969, 4, 171-175.

Hebb, D. O. The organization of behavior. New York: Wiley, 1949.

Hicks, W. E. Effects of overtraining on acquisition and reversal of place and response learning. Psychological Reports, 1964, 15, 459-462.

Hill, R. G., Simmond, M. A., and Straughan, D. W. Antagonism of GABA by picrotoxin in the feline cerebral cortex. British Journal of Pharmacology, 1972, 44, 807-809.

Hill, W. F., Cotton, J. W., Spear, N. E., and Duncan, C. P. Retention of T-maze learning after varying intervals following partial and continuous reinforcement. Journal of Experimental Psychology, 1969, 79, 584-585.

Hudspeth, W. J. Strychnine: Its facilitating effect on the solution of a simple oddity problem by the rat. Science, 1964, 145, 1331-1333.

Humphrey, G. L. Effects of post-training strychnine on memory of stage I and stage II of sensory preconditioning in rats. Dissertation Abstracts International, 1969, 29, 4400-4401.

Hunt, E. B., and Bauer, R. H. Facilitation of learning by delayed injections of pentylenetetrazol. Psychopharmacologia, 1969, 16, 139-146.

Izquierdo, I., Fernandes, J., Oliveria, R., and Settineri, F. Effect of daily saline, drug, or blank injections on the susceptibility to the convulsant effect of drugs. Pharmacology, Biochemistry, and Behavior, 1975, 3, 721-722.

Keppel, G. Design and analysis: A researcher's handbook. Englewood Cliffs: Prentice-Hall, 1973.

Krauz, V. A. Neurophysiological mechanisms accounting for the action of stimulants on the memory. Farmakol. Tokisol., 1975, 38, 138-141.

Krivanek, J. A. Facilitation of avoidance learning by pentylenetetrazol as a function of task difficulty, deprivation, and shock level. Psychopharmacologia, 1971, 20, 213-229.

Krivanek, J. A., and Hunt, E. The effects of post-trial injections of pentylenetetrazole, strychnine, and mephenisin on discrimination learning. Psychopharmacologia. 1967, 10, 119-195

Krivanek, J. A., and McGaugh, J. L. Effects of pentylenetetrazol on memory storage in mice. Psychopharmacologia, 1968, 12, 303-321.

Landfield, P. M. Computer-determined EEG patterns associated with memory facilitating drugs and with ECS. Brain Research Bulletin, 1976, 1, 9-17.

Lashley, K. S. The effects of strychnine and caffeine upon rate of learning. Psychobiology, 1917, 1, 141-169.

Lewin, J., and Esplin, D. W. Analysis of the spinal excitatory action of pentylenetetrazol. Journal of Pharmacological and Experimental Therapeutics, 1961, 132, 245-250.

Lewis, D. J. A cognitive approach to experimental amnesia. American Journal of Psychology, 1976, 89, 51-80.

Louttit, R. T. Central nervous system stimulants and maze learning in rats. Psychological Record, 1965, 15, 97-101.

MacKintosh, N. J. Overtraining, transfer to proprioceptive control, and position reversal. Quarterly Journal of Experimental Psychology, 1965, 19, 26-36.

Mah, C. J., and Albert, D. J. Electroconvulsive shock-induced retrograde amnesia: Analysis of the variation in the length of the amnesia gradient. Behavioral Biology, 1973, 9, 517-540.

Maier, S. F., and Gleitman, H. Proactive interference in rats. Psychonomic Science, 1967, 7, 25-26.

McGaugh, J. L. Some neurochemical factors in learning. Unpublished doctoral dissertation. University of California, Berkeley, 1959.

McGaugh, J. L. Time-dependent processes in memory storage. Science, 1966, 153, 1351-1358.

McGaugh, J. L. Drug facilitation of learning and memory. Annual Review of Pharmacology, 1973, 13, 229-241.

McGaugh, J. L., and Krivanek, J. A. Strychnine effects on discrimination learning in mice: Effects of dose and time of administration. Physiology and Behavior, 1970, 5, 1437-1442.

McGaugh, J. L., and Petrinovich, L. The effect of strychnine sulphate on maze learning. American Journal of Psychology. 1959, 72, 99-102.

McGaugh, J. L., and Thomson, C. W. Facilitation of simultaneous discrimination learning with strychnine sulphate. Psychopharmacologia, 1962, 3, 166-172.

McGaugh, J. L., Thomson, C. W., Westbrook, W. H., and Hudspeth, W. J. A further study of learning facilitation with strychnine sulphate. Psychopharmacologia, 1962, 3, 352-360.

McGaugh, J. L., Westbrook, W. H., and Thomson, C. W. Facilitation of maze learning with post-trial injection of 5-7-diphenyl-1-3-diazadamantan-6-ol (1757 IS). Journal of Comparative and Physiological Psychology, 1962, 55, 710-713.

Oglesby, M. W., and Winter, J. C. Strychnine sulphate and piracetam: Lack of effect on learning in the rat. Psychopharmocologia, 1974, 36, 163-173.

Overton, D. A. Discriminative control of behavior by drug-states. In G. Thompson andR. Pickens (Eds.), Stimulus properties of drugs. New York: Appleton-Century-Crofts, 1971.

Pearl, J., and McKean, D. B. Pentylenetetrazol: Failure to improve memory in mice. Science, 1967, 157, 220.

Petrinovich, L. Facilitation of successive discrimination learning by strychnine sulphate. Psychopharmacologia, 1963, 4, 103-113.

Petrinovich, L. Drug facilitation of learning: Strain differences. Psychopharmacologia, 1967, 10, 375-378.

Postman, L. Transfer, interference, and forgetting. In J. W. Kling and L. A. Riggs (Eds.), Woodworth and Schlosberg's Experimental Psychology (Third Edition). New York: Holt, Rhinehart, and Winston, 1971.

Prien, R. F., Wayner, M. J., Jr., and Kahan, S. A. Lack of facilitation in maze learning by picrotoxin and strychnine sulphate. American Journal of Physiology, 1963, 204, 488-492.

Sara, S. J., and Remacle, J. F. Strychnine-induced passive avoidance facilitation after electroconvulsive shock or undertraining: A retrieval effect. Behavioral Biology, 1977, 19, 465-475

Schaeffer, B. H. Strychnine and maze behavior: Limited effects of varied concentration and injection times. Journal of Comparative and Physiological Psychology, 1968, 66, 188-192.

Schlesinger, K., Boggan, W. O., and Griek, B. J. Pharmacological correlates of pentylenetetrazol and electroconvulsive seizure thresholds in mice. Psychopharmacologia, 1968, 13, 181-188.

Sikorszky, R. D., Donovick, P. J., Burright, R. G., and Chin, T. Experimental effects on acquisition and reversal of sidcrimination tasks by albino rats with septal lesions. Phsiology and Behavior, 1977, 18, 231-236.

Spear, N. E. Forgetting as retrieval failure. In W. K. Honig and P. H. R. James (Eds.), Animal Memory. New York: Academic Press, 1971.

Spear, N. E. Retrieval of memory in animals. Psychological Review, 1973, 80, 163-194.

Spear, N. E., Gordon, W. C., and Martin, P. A. Warm-up decrement as failure in memory retrieval in the rat. Journal of Comparative and Phsiological Psychology, 1973, 85, 601-614.

Squire, L. R. Pharmacology of learning and memory, In S. D. Glick and J. Goldfarb (Eds.), Behavioral pharmacology. St. Louis: C. V. Mosby, 1976.

Stein, D. G., and Kimble, D. P. Effects of hippocampal lesions and post-trial strychnine administration on maze behavior in the rat. Journal of Comparative and Physiological Psychology, 1966, 62, 243-249.

Stevenson, H. W., and Weir, M. W. Response shift as a function of over-training and delay. Journal of Comparative and Physiological Psychology, 1959, 52, 327-329.

Straughan, D. W. Convulsant drugs: Amino acid antagonism and central inhibition. Neuropharmacology, 1974, 13, 495-508.

Synder, S. H., Young, A. B., Bennett, J. P., and Mulder, A. H. Synaptic biochemistry of amino acids. Federation Proceedings, 1973, 32, 2039-2047.

Thiessen, D. D., Schlesinger, K., and Calhoun, W. H. Better learning: Neural enhancement or reduced interference? Psychological Reports, 1961, 9, 493-496.

Underwood, B. J. Attributes of memory. Psychological Review, 1969, 76 559-573.

Westbrook, W. H., and McGaugh, J. L. Drug facilitation of latent learning. Psychopharmacologia, 1964, 5, 440-446.

Wishaw, I. Q., and Cooper, R. M. Strychnine and suppression of exploration. Physiology and Behavior, 1970, 5, 647-649.

Young, A. B., and Synder, S. H. Strychnine binding associated with glycine receptors of the central nervous system. Proceedings of the National Academy of Science (USA), 1973, 70, 2832-2836.

Young, A. B., and Synder, S. H. The glycine synaptic receptor: Evidence that strychnine binding is associated with the Ionic conductance mechanism. Proceedings of the National Academy of Sciences (USA), 1974, 71, 4002-4005.

Appendix A

The effects of strychnine and other "memory-enhancing" agents on CNS activity

While there is evidence that strychnine sulphate and other CNS stimulants may enhance the memory of a learning event, the specific neurobiological mechanism(s), through which these agents exert an effect on memory processing, has not been well defined. One of the principal problems in delineating the physiological basis of the effect of these agents on memory processing has been the fact that these agents affect CNS activity via different mechanisms of action (e.g., Krauz, 1975).

In this regard, consider the effects of strychnine, picrotoxin, and pentylenetetrazol on CNS activity. All three agents have been shown to enhance CNS excitatory activity and, when administered at sufficiently high dose levels, have been shown to induce behavioral convulsions. These agents, however, differ in terms of specific mechanisms of action and also differ in terms of primary sites of effectiveness along the neuroaxis.

Of these three agents, the effects of strychnine have been the most extensively studied. Eccles, Schmidt, and Willis (1963) proposed that strychnine enhances CNS excitatory activity by blocking post-strychnine inhibition.More recent studies (e.g., Straughan, 1974; Synder, Young, Bennett, and Mulder, 1973; Yourng and Synder, 1973; 1974) have attributed the disinhibitory effect of strychnine to a selective antagonism of the inhibitory neurotransmitter, glycine. Strychnine has been shown to have a high affinity for binding on glycine-sensitive receptor sites and is thought to block the inhivitory effects of glycine by means of a competition for receptor sites (e.g., Young and Synder, 1973). The principal

effective sites of strychnine have also been shown to parallel the regional distributions of glycine-sensitive receptor sites, with the principal effective sites of strychnine being in the spinal cord and the lower brain stem (Young and Synder, 1973; Franz, 1975).

Picrotoxin, like strychnine, is thought to enhance CNS excitatory activity via a disinhibitory mechanism; but in contrast to strychnine, the principal mechanism of action of picrotoxin is thought to be a blocking of presynaptic inhibition (Eccles, Schmitt, and Willis, 1963). The disinhibitory effect of picrotoxin has been suggested to be due to an antagonism of another inhibitory neurotransmitter, γ-aminobutyric acid or GABA (e.g., Galendo, 1969; Hill, Simmonds, and Straughan, 1972). While picrotoxin can affect spinal cord activity, the principal effective sites of picrotoxin are thought to be higher (supraspinal) CNS sites (cf., Hahn, 1960; Straughan, 1974).

In contrast to both strychnine and picrotoxin, pentylenetrazol is thought to enhance neural activity by augmenting ongoing CNA excitatory activity (Baker, Katky, and Benedict, 1965; Fleming, 1973; Hahn, 1960). While the specific mechanism of action is unclear, it has been shown that pentylenetrazol can induce repetitive neural firing and shortens the duration of neural refractory periods (e.g., Eyzaquirre and Lilienthal, 1949; Hahn, 1960; Lewin and Esplin, 1961). There is also some suggestion that the enhancement of neural activity by pentylenetrazol may be due to a depolizing action of pentylenetrazol (Gross and Woodbury, 1972). The primary sites of the effects of pentylenetrazol appear to be higher brain (cortical) structures (cf. Esplin and Zablocka-Esplin, 1969; Franz, 1975).

The regional differences in the sites of primary effectiveness of these drugs is also reflected in the findings of the few studies in which these agents were administered directly to different brain structures after training. Doolittle and Thompson (1966) reported that topical (cortical) application of pentylenetrazol (0.01%) facilitated maze learning by rats. Post-trial administration of pentylenetrazol (5-10 mg) directly to the hippocampus has also been demonstrated to enhance brightness discrimination learning by rats (Grossman, 1969). While Doolittle and Thomson failed to observe a facilitory effect of topical strychnine administration, Alpern (1968) has reported that implantation of strychnine crystals in the mesencephalic reticular formation enhanced discrimination learning by rats.

Due to the diverse mechanisms of action of these and other CNS stimulants, shown to enhance the retention of a learned response, recent proposals have tended to suggest that the facilitory effects of these agents on memory processing are expressed via a common (non-specific) mechanism of action (Gold and McGaugh, 1975; McGaugh, 1973; McGaugh and Krivanek, 1970; and Squire, 1976). The principal suggestion along these lines is that strychnine and other CNS stimulants may enhance memory processes by increasing arousal level (e.g., Gold and McGaugh, 1975; Flood, Jarvik, Bennett, Orme, and Rosenzweig, 1977) by way of the effects of these agents on mesencephalic reticular formation activity. While the findings of recent electrophsiological studies (Krauz, 1975; Landfield, 1976), in which a relationship has been observed between the facilitory effects of strychnine on learning and the effects of strychnine on CNS activity, provide some preliminary support for

these suggestions, this issue is far from resolved.

Appendix B

Summary tables for the analyses of variance performed on training and test data from Experiment 1*

* In Appendix B and all subsequent appendices, only the F-ratios and mean square error terms for each analysis of variance are indicated, in order to simplify the presentation of the results of the statistical analyses that were conducted.

Table B1

F-ratios and mean square (MS) error terms for the analyses of variance performed on training data Experiment 1.

		F-ratios and MS error Terms		
Source	df	Choice Error	Repeated Error	Latency
Retention Interval (RI)	3	0.376	0.40	1.629
MS, S/RI	26	(0.229)	(0.316)	(335.80)
Trials (T)	1	0.00	14.00***	20.89***
RI x T	3	1.364	1.50	3.11*
MS, (S/RI) x T	26	(0.223)	(0.178)	(188.494)

* $p<.05$
*** $p<.001$

Table B2

F-ratios and mean square (MS) error terms for the analyses of variance performed on retention test data, Experiment 1.

Source	df	Choice Error	Repeated Error	Latency
Retention Interval (RI)	3	3.623*	1.75	2.96
MS, S/RI	26	(0.336)	(0.067)	(117.81)
Trials (T)	3	7.812***	2.06	11.58***
RI x T	9	0.824	0.77	0.97
MS, (S/RI) x T	78	(0.174)	(0.057)	(52.79)
Discrimination Units (U)	5	1.214	0.94	
RI x U	15	0.932	1.87*	
MS, (S/RI) x U	130	(0.228)	(0.042)	
T x U	15	1.064	0.580	
RI x T x U	45	0.777	0.777	
MS, (S/RI) x T x U	390	(0.220)	(0.051)	

* $p < .05$

*** $p < .001$

Table B3 (a)

F-ratios and mean square (MS) error terms for the analysis of variance performed on repeated error responding in the first three discrimination units during retention testing, Experiment 1.

Source	df	F-ratios and MS error
Retention Interval (RI)	3	0.82
MS, S/RI	26	(0.166)
Trials	3	1.00
RI x Trials	9	0.99
MS, (S/RI) x Trials	78	(0.147)

Table B3 (b)

F-ratios and mean square error terms (MS) for the analysis of variance performed on repeated error responding in the final three discrimination units during retention testing, Experiment 1.

Source	df	F-ratios and MS error
Retention Interval (RI)	3	4.47 *
MS, S/RI	26	(0.125)
Trials	3	1.95
RI x Trials	9	1.34
MS, (S/RI) X Trials	78	(0.121)

* $p < .05$

Appendix C

Summary tables for the analyses of varianc performed on training and test data from Experiment 2

Table C 1 (a)

F-ratios and mean square (MS) error terms for the analyses of variance performed on training data

Experiment 2

Source	df	Choice Error	Repeated Error	Latency
Drug Treatment (D)	1	0.00	0.270	0.34
Retention Interval (RI)	3	4.14 **	1.40	1.80
D x RI	3	0.48	2.60	1.57
MS, S/D x RI	49	(0.240)	(0.153)	(356.44)
Trials (T)	1	0.58	21.99***	101.94***
D x T	1	0.28	0.08	0.06
RI x T	3	0.85	0.06	0.08
D x RI x T	3	1.20	2.67	1.45
MS, (S/D x RI) x T	49	(0.232)	(0.182)	(239.74)

Table C 1 (b)

F-ratios and mean square (MS) error terms for the analyses of variance performed on Training Trial 2 data, Experiment 2.

Source	df	Choice Error	Repeated Error	Latency
Drug Treatment (D)	1	0.122	0.015	0.81
Retention Interval (RI)	3	3.683 *	0.265	1.20
D x RI	3	0.217	0.142	0.09
MS, S/D x RI	49	(1.4.4)	(0.702)	(135.95)

* $p < .05$
** $p < .01$
*** $p < .001$

Table C2

F-ratios and mean square (MS) error terms for the analyses of variance performed on retention test data, Experiment 2.

Source	df	Choice Error	Repeated Error	Latency
Drug Treatment (D)	1	0.02	0.97	0.69
Retention Interval (RI)	3	5.80**	1.36	1.67
D x RI	3	7.14***	0.90	4.29*
MS, S/D x RI	49	(0.227)	(0.070)	(155.42)
Trials (T)	3	15.20***	0.37	20.95***
D x T	3	1.97	0.68	0.61
RI x T	9	1.10	0.58	1.93*
D x RI x T	9	1.30	0.80	1.88*
MS, (S/D x RI) x T	147	(0.165)	(0.083)	(45.089)
Discrimination Units (U)	5	5.64***	0.66	
D x U	5	1.01	0.46	
RI x U	15	1.94*	0.62	
D x RI x U	15	0.81	0.97	
MS, (S/D x RI) x U	245	(0.219)	(0.083)	
T x U	15	3.95***	0.94	
D x T x U	15	1.08	0.78	
RI x T x U	45	1.71**	0.89	
D x RI x T x U	45	0.81	0.90	
MS, (S/D x RI) x T x U	735	(0.162)	(0.082)	

* $p<.05$
** $p<.01$
*** $p<.001$

Table C3 (a)

F-ratios and mean square (MS) error terms for the analysis of variance performed on choice error responding in the first three discrimination units during retention testing, Experiment 2.

Source	df	F-ratios and MS error
Drug Treatment (D)	1	0.94
Retention Interval (RI)	3	2.89*
D x RI	3	8.48***
MS, S/D x RI	49	(0.504)
Trials (T)	3	8.75***
D x T	3	1.84
RI x T	9	0.62
D x RI x T	9	1.69
MS, (S/D x RI) x T	147	(0.435)

* $p<.05$

** $p<.01$

*** $p<.001$

Table C3 (b)

F-ratios and mean square (MS) error terms for the analysis of variance performed on choice error responding in the final three discrimination units during retention testing, Experiment 2.

Source	df	F-ratios and MS error
Drug Treatment (D)	1	0.50
Retention Interval (RI)	3	4.46**
D x RI	3	3.43*
MS, S/D x RI	49	(0.586)
Trials (T)	3	6.77***
D x T	3	0.44
RI x T	9	1.41
D x RI x T	9	0.47
MS, (S/D x RI) x T	147	(0.591)

* $p<.05$
** $p<.01$
*** $p<.001$

Appendix D

Summary tables for the analyses of variance performed on training and test data from Experiment 3.

Table D1

F-ratios and mean square (MS) error terms for the analyses of variance performed on training data, Experiment 3.

Source	df	Choice Error	Repeated Error	Latency
Drug Treatment (D)	1	0.17	0.02	0.37
Retention Interval (RI)	2	0.01	0.043	3.21*
D x RI	2	0.47	3.31*	0.94
Test Condition (C)	3	2.41	0.51	0.61
D x C	3	1.64	0.74	1.00
RI x C	6	1.48	0.53	0.52
D x RI x C	6	0.43	0.54	0.68
MS, S/D x RI x C	168	(0.210)	(0.335)	(408.80)
Trials (T)	1	0.21	84.41**	291.27***
D x T	1	0.91	0.12	0.00
RI x T	2	0.09	1.97	1.12
D x RI x T	2	0.95	1.39	0.53
C x T	3	0.64	0.74	1.41
D x C x T	3	0.42	1.08	1.02
RI x C x T	6	0.42	0.32	0.42
D x RI x C x T	6	0.68	0.61	0.52
MS,(S/D x RI x C)x T	168	(0.253)	(0.369)	(369.76)

* $p < .05$
*** $p < .001$

Table D2

F-ratios and mean square (MS) error terms for the analyses of variance performed on Training Trial 2 data, Experiment 3.

Source	df	Choice Error	Repeated Error	Latency
Drug Treatment (D)	1	0.808	0.325	0.47
Retention Interval (RI)	2	0.208	1.900	1.23
Test Condition (C)	3	0.425	1.846	0.15
D x RI	2	1.177	1.853	0.29
D x C	3	0.379	0.568	1.27
RI x C	6	0.251	0.805	0.27
D x RI x C	6	0.432	0.514	0.96
MS, S/D x RI x C	168	(1.650)	(1.207)	(173.73)

Table D3

F-ratios and mean square (MS) error terms for the analyses of variance performed on retention test data, Experiment 3.

Source	df	Choice Error	Repeated Error	Latency
Drug Treatment (D)	1	0.29	0.16	0.07
Retention Interval (RI)	2	2.18	0.35	0.24
D x RI	2	0.72	0.80	0.01
Test Condition (C)	3	6.78***	13.41***	6.67***
D x C	3	1.12	0.29	1.05
RI x C	6	1.17	0.79	1.03
D x RI x C	6	0.72	1.54	0.67
MS, S/D x RI x C	168	(0.328)	(0.194)	(173.39)
Trials (T)	3	43.21***	11.59***	39.50***
D x T	3	0.14	0.61	1.20
RI x T	6	0.31	0.70	1.18
D x RI x T	6	1.06	1.23	0.69
C x T	9	2.39**	1.21	1.62
D x C x T	9	0.16	1.25	0.89
RI x C x T	18	0.79	1.21	0.92
D x RI x C x T	18	1.12	0.44	0.98
MS,(S/D x RI x C)x T	504	(0.197)	(0.169)	(125.26)
Discrimination Units (U)	5	4.47*	1.33	
D x U	5	0.96	0.47	
RI x U	10	1.44	0.83	
D x RI x U	10	2.72**	0.81	
C x U	15	5.06***	1.96*	
D x C x U	15	1.44	1.78*	
RI x C x U	30	0.71	0.71	
D x RI x C x U	30	1.70	0.86	
MS,(S/D x RI x C)x U	840	(0.242)	(0.164)	
Trials x Units (T x U)	15	1.90**	1.75*	
D x T x U	15	1.63*	1.25	
RI x T x U	30	1.04	1.39	
D x RI x T x U	30	0.84	0.67	
C x T x U	45	1.08	1.66**	
D x C x T x U	45	1.61**	1.86**	
RI x C x T x U	90	1.25	1.04	
D x RI x C x T x U	90	0.85	0.74	
MS,(S/D x RI x C)xTxU	2520	(0.197)	(0.171)	

* $p < .05$ ** $p < .01$ *** $p < .001$

Table D4

F-ratios and mean square (MS) error terms for each of the analyses of variance performed on choice error responding in the first three discrimination units at each test trial, Experiment 3.

Source	df	Test Trial 1	Test Trial 2
Drug Treatment (D)	1	1.951	0.083
Retention Interval (RI)	2	0.567	3.329*
Test Condition (C)	3	1.285	6.453***
D x RI	2	2.052	0.360
D x C	3	0.583	0.526
RI x C	6	0.468	0.513
D x RI x C	6	0.441	1.061
MS,S/D x RI x C	168	(0.772)	(0.562)

Source	df	Trial 3	Trial 4
Drug Treatment (D)	1	0.759	0.367
Retention Interval (RI)	2	0.590	1.235
Test Condition (C)	3	1.659	0.558
D x RI	2	0.197	1.316
D x C	3	1.559	1.048
RI x C	6	1.565	0.650
D x RI x C	6	0.772	0.813
MS,S/D x RI x C	168	(0.556)	(0.510)

* $p < .05$
*** $p < .001$

Table D5

F-ratios and mean square (MS) error terms for each of the analyses of variance performed on choice error responding in the final three discrimination units at each test trial, Experiment 3.

Source	df	Test Trial 1	Test Trial 2
Drug Treatment (D)	1	0.267	0.293
Retention Interval (RI)	2	0.823	1.978
Test Condition (C)	3	1.592	6.685***
D x RI	2	3.493*	2.271
D x C	3	1.275	0.467
RI x C	6	2.237*	1.663
D x RI x C	6	1.209	1.566
MS,S/D x RI x C	168	(0.702)	(0.640)

Source	df	Test Trial 3	Test Trial 4
Drug Treatment (D)	1	0.837	0.294
Retention Interval (RI)	2	1.080	1.428
Test Condition (C)	3	4.175**	0.936
D x RI	2	1.917	0.073
D x C	3	0.547	1.664
RI x C	6	0.768	1.123
D x RI x C	6	0.421	1.379
MS,S/D x RI x C	168	(0.622)	(0.638)

* $p < .05$
** $p < .01$
*** $p < .001$

Table D6

F-ratios and mean square (MS) error terms for each of the analyses of variance performed on repeated error responding in the first three discrimination units at each test trial, Experiment 1.

Source	df	Test Trial 1	Test Trial 2
Drug Treatment (D)	1	1.893	3.111
Retention Interval (RI)	2	1.924	1.835
Test Condition (C)	3	4.745**	1.394
D x RI	2	0.634	1.835
D x C	3	4.829**	2.819*
RI x C	6	1.484	0.652
D x RI x C	6	0.110	0.425
MS,S/D x RI x C	168	(0.993)	(0.429)

Source	df	Test Trial 3	Test Trial 4
Drug Treatment (D)	1	0.441	0.891
Retention Interval (RI)	2	0.193	0.564
Test Condition (C)	3	0.792	1.958
D x RI	2	2.278	0.939
D x C	3	0.965	0.903
RI x C	6	0.652	0.612
MS,S/D x RI x C	168	(0.189)	(0.286)

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

Table D7

F-ratios and mean square (MS) error terms for each of the analyses of variance performed on repeated error responding in the final three discrimination units at each test trial, Experiment 3.

Source	df	Test Trial 1	Test Trial 2
Drug Treatment (D)	1	0.008	0.887
Retention Interval (RI)	2	2.350	0.820
Test Condition (C)	3	1.381	1.684
D x RI	2	1.154	1.128
D x C	3	1.470	0.312
RI x C	6	0.601	0.310
D x RI x C	6	0.490	1.637
MS,S/D x RI x C	168	(0.627)	(0.845)

Source	df	Test Trial 3	Test Trial 4
Drug Treatment (D)	1	0.028	0.474
Retention Interval (RI)	2	0.790	0.053
Test Condition (C)	3	4.724**	2.298
D x RI	2	0.500	2.053
D x C	3	0.503	2.579
RI x C	6	0.790	0.614
D x RI x C	6	0.638	0.368
MS,S/D x RI x C	168	(0.732)	(0.099)

** $p < .01$

Table D8

F-ratios and mean square (MS) error terms for analyses of variance comparisons of the test performance of control (non-trained) and experimental subjects (1 day Retention Interval), Experiment 3.

Source	df	Choice Error	Repeated Error	Latency
Exp. vs. Control (EC)	1	0.84	0.90	8.91**
Drug Treatment (D)	1	0.260	0.15	0.75
EC x D	1	0.030	1.76	1.59
Test Condition (C)	3	7.64***	2.16	1.44
EC x C	3	26.31***	7.37***	11.92***
D x C	3	0.90	1.44	1.21
EC x D x C	3	1.74	1.22	0.030
MS,S/EC x D x C	100	(0.306)	(0.174)	(211.24)
Trials (T)	3	28.890***	16.40***	112.76***
EC x T	3	1.36	0.54	19.94***
D x T	3	0.15	0.59	0.23
EC x D x T	3	0.39	0.42	0.93
C x T	9	0.46	0.27	1.68
EC x C x T	9	1.53	2.37*	2.60**
D x C x T	9	1.30	0.98	1.52
EC x D x C x T	9	0.76	0.55	0.84
MS,S/EC x D x C)x T	300	(0.215)	(0.167)	(115.634)
Discrimination Units (U)	5	5.03***	2.26*	
EC x U	5	0.85	0.58	
D x U	5	7.57***	0.54	
EC x D x U	5	0.68	0.45	
C x U	15	2.87**	1.35	
EC x C x U	15	1.59	1.52	
D x C x U	15	0.667	0.93	
EC x D x C x U	15	2.87**	1.20	
MS,(S/EC x D x C)x U	500	(0.207)	(0.155)	
Trials x Units (T x U)	15	1.89*	2.81***	
EC x T x U	15	2.02*	0.78	
D x T x U	15	2.06**	0.65	
EC x T x U	15	0.85	0.92	
C x T x U	45	1.08	0.99	
EC x C x T x U	45	1.37	1.50*	
D x C x T x U	45	1.37	1.01	
EC x D x C x T x U	45	0.85	1.19	
MS,(S/EC x D x C)x T x U	1500	(0.188)	(0.164)	

* $p < .05$ ** $p < .01$ *** $p < .001$

Table D9

F-ratios and mean square error (MS) terms for the analyses of variance comparisons of the first test trial choice error responding of control (non-trained) and experimental subjects (1 day retention interval), Experiment 3.

Source	df	F-ratios and MS error terms Choice Error Responding First 3 Units	Final 3 Units
Exp. vs. Control (EC)	1	0.473	0.250
Drug Treatment (D)	1	3.692	10.319 **
EC x D	1	1.293	0.000
Test Condition (C)	3	2.023	1.232
EC x C	3	1.387	3.092 *
D x C	3	0.417	2.164
EC x D x C	3	0.111	1.438
MS, S/EC x D x C	100	(0.708)	(0.611)

* $p < .05$

** $p < .05$

Table D10

F-ratios and mean square (MS) terms for the analyses of variance comparisons of the first test trial repeated error responding of control (non-trained) and experimental subjects (1 day retention interval), Experiment 3.

		F-ratios and MS error terms Repeated Error Responding	
Source	df	First 3 Units	Final 3 Units
Exp. vs. Control (EC)	1	0.097	1.342
Drug Treatment (D)	1	0.002	0.919
EC x D	1	2.637	1.340
Test Condition (C)	3	1.304	1.951
EC x C	3	5.660 ***	2.587 *
D x C	3	1.765	0.302
EC x D x C	3	1.428	2.514
MS, S/EC x D x C	100	(1.147)	(0.471)

* $p < .05$

*** $p < .001$

Table D11

F-ratios and mean square (MS) error terms for the analyses of variance performed on the test data of control (non-trained) subjects, Experiment 3.

Source	df	Choice Error	Repeated Error	Latency
Drug Treatment (D)	1	0.05	0.62	2.00
Test Condition (C)	3	25.93 ***	1.20	7.29 **
D x C	3	1.46	0.98	0.71
MS, S/D x C	44	(0.330)	(0.114)	(215.21)
Test Trials (T)	3	17.04 ***	17.45 ***	118.04 ***
D x T	3	0.41	0.39	0.55
C x T	9	0.65	1.119	2.55 **
D x C x T	9	1.03	1.21	1.17
MS,(S/D x C) x T	132	(0.227)	(0.095)	(99.08)
Maze Units (U)	5	2.07	2.53 *	
D x U	5	2.95 *	0.37	
C x U	15	2.80 ***	1.74 *	
D x C x U	15	1.72 *	1.86 *	
MS,(S/D x C) x U	220	(0.156)	(0.081)	
Trials x Units (T x U)	15	1.93 *	2.11 **	
D x T x U	15	1.30	1.06	
C x T x U	45	1.31	1.32	
D x C x T x U	45	1.07	1.68 **	
MS,(S/D x C) x T x U	660	(0.179)	(0.092)	

* $p < .05$
** $p < .01$
*** $p < .001$