The Effects of Metrazol on Acquisition of an Oddity Task in Squirrel Monkeys

Stephen Wilson

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The Effects of Metrazol on Acquisition of an Oddity Task in Squirrel Monkeys

BY

STEPHEN WILSON

B. S., Eastern Illinois University, 1968

THESIS

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I HEREBY RECOMMEND THIS THESIS BE ACCEPTED AS FULFILLING THIS PART OF THE GRADUATE DEGREE CITED ABOVE

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Abstract

Recent evidence indicates that Metrazol can enhance learning in rodents provided certain variables such as genetic strain, difficulty of problem to be learned, and dosage levels are considered and carefully controlled. The effects of Metrazol on oddity acquisition in four squirrel monkeys was investigated. The apparatus employed was a modified version of the Wisconsin General Testing Apparatus. The dosage level of Metrazol was 15 mg/kg of body weight. The results suggest that Metrazol had no effect on the learning of the oddity task by the squirrel monkeys.
Acknowledgement

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Last but not least, I am grateful to my wife, Julia, whose clerical skills have been a valuable asset in the preparation of this paper.
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The Effects of Metrazol on Acquisition
of an Oddity Task in Squirrel Monkeys

Stephen Wilson
Eastern Illinois University

Drugs have captured the interest of man since the beginning of recorded history. For instance, there exists a historical record of the Chinese physician, Pien Ch'iao, who prepared "narcotic wine" in the fifth century B.C. (Kremers and Urdang, 1951). In time, the discovery and synthesisization of drugs has expanded to a now incredible number. In the growing population of drugs, there is a category which is most properly called central nervous system (CNS) stimulants. The CNS stimulants are so categorized because they possess the property of increasing the activity of various portions of the central nervous system (Goodman and Gilman, 1941).

It has been only in the twentieth century that several of these agents have been found to facilitate learning in animals. This latter finding is probably due in part to the preoccupation of using drugs strictly for medicinal purposes. Now, however, it appears that drugs and their influence on behavior have become a full-time business and recent reports of CNS stimulants and learning have opened a new vista in the attempt at understanding the physiological processes of learning and memory. For instance, several investigators have found facilitative effects on learning with strychnine sulfate (McGaugh, 1961; Petrinovich, 1963), nicotine (Breen and McGaugh, 1961), physostigmine (Strain and Petrinovich, 1963), Metrazol (Pooltliie and Thomson, 1965), 5-7-diphenyl-1-3-diazadaman:an-6-ol (McGaugh, Westbrook,
and Burt, 1961) to name only a few.

McGaugh and his associates have done much to revive the interest of CNS drugs and their effect on learning after a long interim following Lashley's finding in 1917. According to Calhoun (1971), Lashley injected rats intraperitoneally (IP) with either 0.10 or 0.05 mg of strychnine prior to training sessions on a Watson circular maze. Lashley reported that animals which received the highest dose made fewer errors in learning of the maze. In a second experiment with the same doses but heavier rats, no drug effect was noted.

McGaugh and Petrinovich (1959) conducted a study to further clarify the inconsistent results of Lashley's investigation. They divided 76 rats into seven groups, three experimental and four control which were matched for age and weight. A 2% solution of strychnine sulfate which when converted to milligrams of strychnine to body weight was given in 0.33, 0.66, and 1.00 mg/kg to the experimental groups. The four control groups had either a needle inserted, but received no solution, a needle inserted and received quantities of saline equivalent to 0.33 and 1.00 mg/kg, or did not have a needle inserted. The rats were pretrained for acclimation to a food deprivation schedule and straight runway experience. Following this procedure, the animals were injected IP 10 minutes prior to the first maze trial of each day and ran to a learning criterion set at 5 out of 6 errorless trials in a Lashley III maze. The animals were given at least 15 trials. The number of errors (an error was considered to be the extension of the head of a rat into the cul-de-sac a distance of two inches which was marked by a white line on the floor of the maze) and time per trial were recorded. The results showed that the strychnine group made fewer initial and total errors to criterion and had fewer
trials to reach criterion. There was no difference in speed of running.

As a continuation of research in the area of strychnine sulfate and its effect on learning, McGaugh (1961) tested 71 rats in a 14-unit alley maze. Each alley had two doors, one of which was equipped with a micro-switch to record errors and the other door allowed the animals to progress through the maze. The rats were pretrained in a straight alley and were food deprived. A wet mash was used as a reward. After pretraining, the animals were allowed one trial per day for fourteen days and injected IP 10 minutes before the trial. The two experimental groups received either 0.33 mg/kg, designated as the low strychnine group (LS) or 1.00 mg/kg, the high strychnine group (HS). The control group received saline. The LS group made fewer errors than the control and HS groups, while the HS group made more errors than the other two groups indicating a disruptive effect.

Other CNS stimulants have yielded similar results as well as expanding the general knowledge concerning variables important in these drug investigations. McGaugh, Westbrook, and Burt (1961) used a 5-7-diphenyl-1-3-diazamantan-6-ol (1757 T. S.), a newly synthesized compound similar in effect to strychnine sulfate, on three strains of rats, Tryon maze-bright, Tryon maze-dull, and the first generation cross between the two. The rats were pretrained in a straight alley and food deprived. The three strains were divided into experimental and control groups equated for body weight and pretraining running time. Each animal was given 15 trials in a Lashley III maze and given either 1.00 cc/kg of 1757 T. S. dissolved in citric acid (pH 6.5) or 1.0 cc/kg of citric acid IP 10 minutes before each session. The cul-de-sac errors were recorded. The
results indicated significant drug effects, significant strain effects, and significant drug-strain interaction. The mean errors of the maze-dull and crossed strain were significantly lower than their respective controls, but the maze-bright group did not significantly differ from their control counterparts. From this study as well as others to follow, it can be seen that differences in strain appear to be an important variable in psychopharmacological research involving certain CNS stimulants and the learning of particular tasks. It should be noted that Hudspeth and Thomson (1962) found no strain difference (they used the Tryon maze bright and dull genetic strain) using 1757 I. S. and the Lashley III maze; however, a lower dosage (0.67 mg/cc) was employed and the experimental group made significantly fewer errors than the control group.

Stratton and Petrinovich (1963) used physostigmine, a powerful anticholinesterase, in a maze learning study. Eighty-six rats were drawn from the population of Tryon maze-bright and maze-dull strains. The animals were food deprived and pretrained to a straight runway with wet mash serving as reinforcement. The training in the Lashley III maze consisted of one trial per day after which the animals were injected with either physostigmine or a control solution until they reached a criterion of 4 out of 5 errorless runs. The dosage of physostigmine salicyclate given were 0.25, 0.50, 0.625, 0.75, or 1.00 mg/kg of body weight. Initial errors, repetitive errors, and time in the maze were recorded. There was a difference in control groups between the maze-bright and maze-dull animals with respect to both trials to criterion and initial errors to criterion. The dulls were significantly poorer than the brights. Furthermore, the results indicated that for the
maze-brights, the highest dosage of chrysostamine had a disruptive effect on performance whereas the same level of drug enhanced the performance of the maze-dull animals. Also, the lower dosages given tended to result in better performances for both dull and bright animals with certain levels of dosage (0.50 and 0.625, respectively) being significant for brights and dulls when compared to their respective controls. With regard to repetitive errors and running time, there were no significant differences between any groups.

A study (Breen and McGaugh, 1961) similar to McGaugh's (1961), cited above, in method revealed that another CNS stimulant, nicrotoxin, facilitates learning. Again, the rats were taken from the Tryon maze-bright and maze-dull populations. They were randomly divided into eight groups, six experimental and two control. The six experimental, received either 0.75 mg/kg (low-dose), 1.00 mg/kg (medium-dose), or 1.25 mg/kg (high-dose) per body weight of nicrotoxin. The control animals received a saline solution. All animals were injected TP 30 seconds after the completion of each daily maze trial. The number of errors made in the 14-unit T maze were recorded. The results showed a significant drug-dosage effect, significant strain differences, but no significant drug-strain interaction (See Table 1).

Table 1

Mean Number of Errors (Breen and McGaugh, 1961)

<table>
<thead>
<tr>
<th>Strain</th>
<th>Control Group</th>
<th>Low Dose</th>
<th>Medium Dose</th>
<th>High Dose</th>
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<tbody>
<tr>
<td>Dulls</td>
<td>22.2</td>
<td>16.6</td>
<td>14.5</td>
<td>13.8</td>
</tr>
<tr>
<td>Brights</td>
<td>26.6</td>
<td>26.6</td>
<td>26.9</td>
<td>20.2</td>
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The means of the maze-dull who received medium and high doses were significantly lower than the mean of the maze-dull controls with the low-dose group failing to reach significance when compared to the control group. Comparison of the maze-bright and maze-dull groups showed that the maze-dull had significantly lower means across all dosage levels. The controls of both strains did not differ. The maze-dull high-dose group made significantly fewer errors than all maze-bright groups and the maze-dull medium and low-dose groups averaged significantly fewer errors than the maze-bright control, low, and medium-dose groups. The effects of microtoxin or learning maze tasks appear to be facilitatory provided appropriate dosage levels are employed. Likewise, these findings are similar to other studies using CNS stimulants and maze problems.

All of the studies mentioned have shown some facilitatory effects of CNS stimulants on learning. There are a few studies which have produced negative results using strychnine and/or microtoxin (Prien, Wayner, Jr., and Kahan, 1963; Carlson, 1966; and Louttit, 1965). In the Prien, et. al., (1963) study, they confounded their experiment by enucleating the eyes of the animals (no reason was given for this procedure) and also did not specify the exact genetic strain of rat used. There was a lack of drug effect. Although Carlson (1966) and Louttit (1965) did specify the strain of rat employed, they failed to find a drug effect. Petrinovich (1967), more or less in response to these particular studies, performed a dosage-response study following the exact methodological procedures of the McGaugh and Petrinovich (1959) investigation mentioned above, but used a different strain of rat (Long-Evans hooded rat). Evidently, Petrinovich employed a breed of hooded rat because the other three studies reporting negative findings also employed a type of hooded rat. Petrinovich used the following dose levels of strychnine sulfate: 0.125,
0.25, 0.50, 1.00, 1.50, and 1.75 mg/ko. He obtained significant results for the lowest and highest levels of dosage. The lowest dosage produced fewer initial trials to criterion than the control group and the highest dosage produced more initial trials to criterion. Petrinovich strongly cautioned that dose-response relationships between different genetic strains of animals along with the particular behavioral task are of prime importance in these studies and merit critical consideration.

A few investigators have found that some CNS stimulants facilitate learning of a difficult task (McCaugh, 1961; Coker and Abbott, 1967; and Hudsneth, 1964). Of particular interest is the study conducted by Hudsneth (1964) on the learning of an oddity problem with rats. According to Hudsneth, previous to his study, the white rat had been unable to perform this task successfully unless extended training is permitted. His experiment was divided into three phases: brightness discrimination, reversal, and simple oddity task. All three tasks were performed in an apparatus which consisted of a start box, three doors with attachable coverings, and a goal box. The doors could be arranged so that any door was a means to the goal, but only one door was correct per trial (the doors were randomly chosen as correct). The floor of the apparatus was a grid and shock was given to provide motivation for obtaining access to the goal box. After some preliminary training, the animals were separated into experimental and control groups. In the first stage, half the subjects in each group were required to choose a black-covered door (correct response) as opposed to the other two white-covered doors and the other half learned the opposite discrimination. After 19 out of 20 errorless trials, they were trained to make a reversal discrimination whereby the incorrect brightness stimulus of the initial task now became the correct cue until the same criterion was reached. Finally, in the simple oddity task, only the odd stimulus of the three stimuli on the doors
became correct. Thus, there was no consistent position or brightness to act as the correct cue, but rather only the odd stimulus was consistently rewarded. Twelve trials per day were run until 300 trials were completed. The animals were injected IP 30 seconds after each block of trials with either a 0.20 mg/ml solution of strychnine sulfate per kilogram body weight or an equal volume of saline. The number of errors were recorded. In the first two phases, the rats in the strychnine group made significantly fewer errors. In the oddity problem, the strychnine group made significantly more correct responses.

Some other tasks in which a CNS stimulant (mainly strychnine sulfate) has yielded favorable results of learning are delayed response alternation (Petrinovich, Bradford, and McGaugh, 1965), avoidance learning (Bovet, McGaugh, and Oliverio, 1966), classical conditioning (Renevento and Kandel, 1967), visual discrimination (Petrinovich, 1963), and latent learning of a multiple unit U-maze (Westbrook and McGaugh, 1964).

Therefore, the trend of research would tend to indicate that CNS stimulants can facilitate the learning of various behavioral tasks provided certain variables such as strain of animal, dose level, and time of administration are considered and carefully controlled. Up to this point, the time of administration, that is, post or pretrial perfusion, has received little emphasis. In the next section, a hypothetical-construct is presented and by its very nature will necessitate the restriction of perfusion method to post-trial only.

Consolidation

An underlying theme throughout several of these studies has been the emphasis on the concept of a consolidation theory of memory traces which is generally attributed as Muller and Pilzecker theory according
to Glickman (1961). Basically, consolidation in a neurophysiological sense is the time dependent process involved in the supposed structural or chemical change in the nervous system as a result of some experience. Consolidation, therefore, is deeply rooted in the concept of memory which in itself is intrinsic to certain types of learning. Because consolidation is a hypothetical-construct, it seems necessary to cite evidence supportive of the theory.

There is an extensive amount of research pertinent to the consolidation theory and memory (Glickman, 1961; John, 1967; Weisman, 1963; Deutsch, 1962; Pearlman, et. al., 1961; Madsen and McGaugh, 1961; and McGaugh, 1966). The type of physiological studies or reports which allude to a consolidation theory of memory traces generally falls into one of three main categories: retrograde amnesia in humans as a result of some accidental blow to the head (other causes are cerebral anoxia and carbon monoxide poisoning), drug-induced retrograde amnesia, and electro-convulsive shock (ECS).

Deutsch (1962) in a review of memory from a physiological aspect, described the pattern involved in retrograde amnesia in man of which is conducive to the consolidation of memory traces. Basically, memories of recent events are lost and although several years of memory may be lost, older events (older events in this case refers to chronologically earlier experiences of the individual) may be retained. The events lost may be important to the individual, however, recovery is dependent on the chronological process of events (older events being recalled first), not the importance of the events.

Pearlman, Sharpers, and Jarvik (1961) conducted an interesting study on retrograde amnesia as a function of anesthetic and convulsant
drugs. In that study, 85 Sprague-Dawley rats on water deprivation were initially trained to press a bar on a continuous reinforcement schedule for water reinforcement. After a criterion of stability had been attained (number of presses on final day of preliminary training that did not deviate by more than 10% from the mean of three previous days), formal avoidance training was implemented in which the bar and drinking nozzle were electrified. The animals were divided into groups of five subjects each for treatment. During the avoidance training, three groups were anesthetized with ether at approximately 10 sec, 5 min, or 10 min after the shock. Four groups received 30 mg/kg body weight of sodium pentobarbital intravenously (IV) via an implanted catheter 20 sec, 5 min, 10 min, or 20 min after the shock. In five groups, pentylenetetrazol was injected (20 mg/kg) about 20 sec, 2 hrs, 4 hrs, 8 hrs, or 4 days after the shock. Five groups served as controls with three of these groups receiving no shock but were given the various drugs and the remaining two groups were given shock but no drug. The rate of bar pressing response was recorded and the animals were tested for retention one day or five days (pentylenetetrazol group) later. The loss of memory was represented by expressing each animal's performance as a percentage of its normal rate of pressing. The rats given ether within five minutes and those given pentobarbital within 10 minutes after the shock made significantly fewer avoidance responses than their respective controls. The pentobarbital group showed less avoidance than the ether group indicating that the former had a more powerful effect. Pentylenetetrazol given up to eight hours after shock showed significantly fewer avoidance responses. Remarkably, the animals given pentylenetetrazol four days after shock showed signifi-
cantly fewer avoidance responses. It should be noted that all injections of pentylenetetrazol induced a clonic seizure in the rats who received it. A proponent of consolidation theory can suppose that these agents in some manner interrupted the mechanism involved in the neural change called consolidation and what is more important, there was a time-dependent function involved, an understood factor of consolidation.

Coons and Miller (1960) questioned the consolidation theory of memory traces as an explanation of retrograde amnesia and instead offered a hypothesis about ECS-induced fear of the goal area. In other words, Coons and Miller suggested that an animal developed a fear (which resulted in avoidance) of the goal area as a result of the pain associated with the area.

Madsen and McGaugh (1961), in response to Coons and Miller (1960), conducted the following experiment. Madsen and McGaugh took rats from the Tryon strains and divided them into experimental and control groups. The experimental groups was placed on a raised platform located in the center of a small opened box. The platform was adjustable, so it could be lowered and raised with a lever located outside the box. When the platform with animal was lowered, the animal, if it stepped off the platform within 10 seconds, received a shock. Five seconds after the shock, they received ECS via alligator-clip electrodes affixed to their ears. The control group did not receive the ECS. In this one-trial avoidance task, the controls significantly avoided the response of stepping off the platform. Therefore, this method apparently was a step toward the resolution of the fear vs. consolidation controversy of which the latter gained experimental support in this case.

Consolidation becomes an important theoretical variable in studies
involving psychopharmacological facilitation of learning. For example, the question has been raised that CNS agents work in such a manner as to increase visual acuity, reduce locomotor activity allowing a longer decision time, or raise the arousal level of the animal (McGaugh and Petrinovich, 1965). If this was the case, improved learning would be the result of a change in the homeostatic state of the individual and not the result of possible catalytic effects on the formation of the memory trace process. In order to insure that the drug somehow affects learning and facilitates the development of a memory trace, it becomes necessary to instigate certain methodological procedures such as introducing the drug after performance of a task. In this way, any neural excitation generated as a result of some experience which has the potential of becoming a neural trace can be influenced by the agent. This procedure would lend little empirical support to any perceptual, motivational, or arousal hypothesis concerning facilitation of learning. Generally speaking then, studies which use the post-trial perfusion of drugs and results in enhancement of learning are supportive of the consolidation theory.

Post-trial studies and Metrazol

Up to this point, strychnine sulfate, picrotoxin, Metrazol, physostigmine, and 1757 I. S. have been the drugs mentioned as CNS stimulants which can affect learning. The evidence compiled on these agents indicates a differential physiological process exists between these drugs and their locus of interaction with the CNS neuron, however, the overall results produced on learning within limits has been demonstrated to be similar. Strychnine sulfate has been shown to depress post-synaptic inhibition, picrotoxin depresses pre-synaptic inhibition
Metrazol's action is less well known, but is not believed to be specifically related to disinhibition and may directly augment the depolarizing potentials in the cortex. Metrazol (pentylenetetrazol) has become a popular psychopharmacological agent and Calhoun (1971) suggests its popularity is due to its relatively wide range of effective, but sub-convulsive dose levels.

Metrazol has been used in geriatric cases in which some 200 senile women were treated with the agent over a period of two years (Tennent, 1960). The patients were divided into three groups, the first of which were physically helpless and bedridden, the second of which were semi-ambulatory. The third group was comprised of ambulatory patients who were slightly confused whereas the other two groups had individuals who were severely deteriorated mentally. The majority of the patients had an improvement in appetite, but the first two groups described above had little improvement otherwise. The third group gained weight, became more active, their sleep pattern improved, and their appearance became neater. Also, the third group tended to socialize more in the wards and in ground walks around the institution.

Most of the onslaught of psychopharmacological studies employing Metrazol in learning situations have been confined to the 1960's. Hunt and Krivanek (1966) studied the effect of pentylenetetrazol on brightness discrimination, spatial discrimination, and an operant generalization task all of which showed some facilitatory effects. Nonetheless, the injections were given during pre-trial periods and slower running speeds were reported. Therefore, Krivanek and Hunt (1967)
studied the effects of post-trial injections of pentylenetetrazol which conforms more to the consolidation theory earlier advanced. Thirty-six Wistar rats were used. They were divided into four groups and placed on a 23-hour food and water deprivation schedule for one week. The animals were pretrained in a Y-maze in which one arm was black and the other white. The rats were reinforced with wet mash an equal number of times in both arms. During the test however, black was always rewarded for some animals in a group with the rest being rewarded in the white arm (the colored arms were reversible and could be randomly interchanged). The rats were given three massed trials a day with IP injections of either 20 mg/kg of pentylenetetrazol, 0.33 mg/kg of strychnine, 10 mg/kg of mephenesin, or 1 ml/kg of saline immediately after the third trial of each day. The results showed maze learning to be facilitated by strychnine, but more importantly, that post-trial injections of pentylenetetrazol were more effective than strychnine.

Another interesting study was one by Doolittle and Thomson (1966). Prior to their experiment, no attempt had been made in using a topical application of strychnine or Metrazol. Forty-four Tryon maze-bright and maze-dull rats were used and divided into four groups which would receive either potassium chloride, pentylenetetrazol, strychnine, or saline. A 6-unit multiple-U maze was the apparatus used in this experiment. Cannulas were implanted and following surgical recuperation, the rats were placed on a deprivation schedule at approximately 90% of their normal body weight. The training consisted of one trial per day for 10 days in the maze with food reward. Thirty seconds after the animal entered the goal box, the drug was administered. (Administration consisted of cleaning the cannulas and subsequently filling with an appropriate drug solution). The concentration of both pentylenetetrazol
and strychnine was 0.01%. They were returned to the home cage and 10 minutes later the cannulas were flushed. The results showed only the pentylenetetrazol group to differ significantly from the saline in mean total errors. The mean total errors for the pentylenetetrazol were less than the other groups.

Irwin and Benuazizi (1966) found enhancement effects with Metrazol on a one-trial avoidance task using mice. Not only is the behavioral task different from previous studies, but the route of administration of Metrazol was novel (except for human studies). Fourteen mice were randomly placed into treatment groups and food deprived four hours before testing. The training consisted of placing the animals into a smaller compartment with a grid floor separated from a larger compartment by a hurdle 2.5 cm. high. If the animals crossed the hurdle, they were shocked. The route of drug administration was oral. The results showed that Metrazol significantly improved retention (longer latency before crossing) of the task. These results were compared to similar studies using picrotoxin and strychnine. Although memory was improved by strychnine and picrotoxin, it was less markedly so than Metrazol and less consistently reliable.

In a series of experiments, Krivanek and McGaugh (1968) reported on several variables which served to add more information about Metrazol and learning. In the first of six investigations, two strains of mice referred to as poor and bright were tested in a Lashley III maze and the study was so designed as to confirm improvement of learning with post-trial injections of pentylenetetrazol. The mice were water deprived and received preliminary training which consisted of straight runway experience. The formal training consisted of one trial per day for seven
consecutive days in a Lashley III maze. The mice were divided into four groups and received IP injections of either 5, 10, 20 mg/kg of pentylenetetrazol or saline solution. The initial and repetitive errors were recorded. Facilitation of learning was found with both 5 and 10 mg/kg dosages. The facilitation however was a function of the strain of mice. The poorer strain in terms of more errors committed, required 10 mg/kg for maximal facilitation, but the 5 mg/kg group also significantly improved learning. The brighter strain on the other hand was significantly improved by the 5 mg/kg dosage. The authors concluded that the enhancement of maze learning does occur, but depends upon the strain of mice and dosage levels.

In the second experiment, the generality of the facilitating effects of Metrazol was increased to include an aversive motivation task. The behavioral task involved brightness discrimination followed by reversal training in a Y-shaped water maze with escape made available by plastic ladders at the end of the arms. To establish a preference, the first day of preliminary training was composed of three brightness discriminations where only one light at the end of an arm was illuminated (all tasks in this particular study were run in the dark). On the next day, the mice were trained to swim to the non-preferred brightness. From then on, the mice received six massed trials per day until a criterion of six consecutive correct responses were made. Subsequently, the mice were trained to reverse the established brightness preference until six consecutive correct responses were made. The experimental animals received either 10 or 20 mg/kg IP of pentylenetetrazol immediately following the last trial of the day. The errors which consisted of swimming a body length into the wrong arm were recorded for each
segment of the experiment. The results indicated a small but significant effect on the brightness discrimination task when comparing the saline group with the 10 mg/kg dosage group. This was not found with the 20 mg/kg dosage group. In the reversal training however, there was a significant difference between the saline group and the other two drug groups. These results suggest that the degree of facilitation depends on task difficulty as was found with strychnine (Hudspeth, 1964).

The third experiment of the series was concerned with different dosage levels of Metrazol and its effect on Swiss-Webster mice. The mice were food and water deprived (and resulted in a 20% death rate for the males and a 1% death rate for females) and trained on a brightness discrimination task similar to Krivanek and Hunt (1967). A non-correction procedure was used so that an error on trial one resulted in an immediate running of trial two. A correct choice was rewarded with wet mash for 30 seconds. Therefore, the inter-trial interval was dependent on correct performance. The mice were run to a criterion and then 12 more performance trials were run. Following the third daily trial, the mice were injected IP with either saline or 2.5, 5.0, 7.5, 10.0, 12.5, 15.0, or 20 mg/kg dose of Metrazol. Decision time, running time, errors, and trials to criterion were recorded. The results showed that the mean error scores varied with dosage and significantly influenced learning. The 2.5 and 5.0 mg/kg dosage groups did not significantly differ from the controls, but the other dosage levels did. In fact, all dosage levels above 7.5 mg/kg produced fewer errors than the best control animal. Furthermore, the variance about the mean was larger for control and the slightly enhanced groups than the remaining groups. The trials to criterion measure were approximately the same
as the errors analysis. Decision time was thought to significantly af-
fect performance, but once differential experience was taken into ac-
count, it was found that post-trial injections of Metrazol did not ef-
fect the decision time.

In essence, the fourth study was identical in procedure to the
third experiment, but a different time of administration was used and
only one dosage, 15 mg/kg, was employed which was based on the previous
study. The animals received the drug either 60, 30, 15, or 5 minutes
prior to testing or 1, 5, 15, 30, or 60 minutes after testing. The
results showed that the time of administration significantly affects
learning with the 5 minute post-trial interval being the best for en-
hancement. Maximal facilitation occurred within the 15 minute pre-trial
and 15 minute post-trial interval range.

The fifth study was undertaken to determine any difference between
deprived or non-deprived animals and Metrazol. A group of 32 mice were
divided into two smaller groups one of which was placed on a 23-hour
food and water deprivation schedule with free access to dry food and
water only 30 minutes in the day. The other mice had free access to
food and water. Four different dosages of pentylenetetrazol were given
(30, 40, 50, and 60 mg/kg) with one dose per mouse. The animals were
placed in their home cages and observed after receiving the injection.
The convulsions and lethal dosages were lower for the deprived animals.

The final experiment was an exploratory study designed to electro-
physiologically gather information on latency of onset and duration
of the effects of pentylenetetrazol as a function of dosage. Bipolar
electrodes were implanted in six Sprague-Dawley rats. Some of the cites
chosen were the dorsal and ventral hippocampus, the amygdala, median
forebrain bundle, and several thalamic areas. Recordings were taken in an electrically shielded area. Each rat was given a three minute recording session prior to receiving IP either saline or pentylenetetrazol in 2.5, 5.0, 7.5, 10.0, 12.5, 15.0, or 20.0 mg/kg dosages. Recordings were obtained for at least 25 minutes post-injection and sometimes up to 60 minutes was required. The results indicated a small increase in the frequency of the electroencephalograph. There was an occurrence of "spindles", high voltage, slow waves with a frequency of 8/second. The "spindles" were not noticed in any saline animals. Both the onset and duration of the "spindles" varied systematically with the dose level. That is, the higher the dosage level, the faster the onset and the longer the duration of the "spindles".

The authors concluded by indicating that Metrazol enhances learning by affecting, in some manner, processes involved in memory storage. This series of studies is of tantamount importance in giving some insight into the wide range of experimental variables which require some attention in psychopharmacological studies.

Another investigation was constructed around recent evidence implicating the hippocampal area of the brain in memory functions and consolidation (Grossman, 1969). Forty-two rats of the Holtzmann Sprague-Dawley strain were subjected to a bilateral implantation of cannulas into the hippocampal area. The cannulas were insulated to permit electrophysiological tests to be conducted from the same region as that of the drug placement. Although some animals died from the operation, four groups were formed which were comprised of the operated-drug group, operated-saline group, sham-operated, and unoperated group. Following recovery, the animals were placed on a 22-hour food deprivation schedule. They were subjected to a brightness discrimination task in a T-maze.
On the first day, a record was made as to the choice of the arm entered for each animal. From that point on, the animals were trained to chose brightness opposite that selected on the first day's trial. They were run on six trials a day for 14 days. Five minutes before and immediately after the last trial of the day, the cannulas were removed, cleaned, replaced, filled with from 5 to 10 µg. of pentylenetetrazol, or left empty. In this manner, certain groups received the drug on pre-trial runs while others had post-trial injections. The start latency, running speed, and choice time were recorded. The results indicated that the implanted animals had a small deficit on the correct choice measure. The latency data showed the operated animals to be significantly slower than the unoperated animals. The results give support to the notion of enhancement of learning with pentylenetetrazol and also substantiate recent data on the hippocampus as being involved in memory processes because the post-trial groups performed significantly better than all other groups. The animals receiving pre-trial injections differed significantly from the sham-operated group, but not from the unoperated group.

One other experiment investigated the facilitatory effects of pentylenetetrazol given in delayed injections on learning (Hunt and Bauer, 1969). Actually, this study is similar to an earlier mentioned study (Krivanek and McGaugh, 1968), but here different dosages were used along with different delayed task-injection intervals. Sixty Wistar rats were equally divided into four groups. Each group, in turn, either were injected with saline or 7.5, 10.0, or 15.0 mg/kg of pentylenetetrazol. Within each dose level, the animals were randomly separated in order to permit the IP injections to be given either immediately following the last trial or 15 minutes later. The animals were food deprived and
pretrained in a Y-maze for brightness discrimination. Formal training consisted of food reinforcement when the animals entered the white arm (previous studies indicated that this strain preferred the dark arm), and subsequent injections. The rats were retested 24 hours later and the number of errors on the last day was a measure of retention of the previous day's performance. The results indicated that on the average, drug groups performed better than controls, but the drug group did not differ amongst themselves. The most reliable facilitation was obtained with a 7.5 mg/kg dose given immediately after training and the 10 mg/kg dose given in a delayed injection. As a sequel to this study, the experimenters changed the task to a position discrimination test. Basically, the same type of pretraining as was used in the first study was employed, but after formal training the rats were injected IP with either saline or 10 mg/kg of Metrazol at either 0, 5, or 10 minutes after the last trial. The results demonstrated that the group injected immediately did not differ from the saline group whereas the other two delay-injected groups did significantly differ. These studies indicate that at intermediate dose levels, a delayed injection of Metrazol produces the best facilitation of learning.

As indicated by the above studies, Metrazol can affect the central nervous system so as to enhance learning of a task provided that important variables are recognized and adequately controlled. A factor that may or may not appear obvious at this point is the restriction of animals to only two species, namely rats and mice (excluding the work with geriatric patients and the study performed by Benevento and Kandel, 1967 in which cats were used). Since the strain of these animals has been demonstrated to be a factor in these studies, it would be of
interest to expand the number of species to see whether the enhancement appears across species or if it is limited to only those animals thus far mentioned. If the data of well controlled experiments do indicate some consistency across species, then possible practical situations may arise where enhancement of learning by pharmacological agents are advantageous. Also, as pointed out by Lockard (1968) and Beach (1950), there appears to exist a heavy bias on the use of one animal in psychological research which in turn prevents any generality of findings.

Squirrel monkeys (Saimiri sciureus) according to Hansen (1968) are satisfactory human "models" in pharmacological studies. This conjecture appears to be based on a drug study using squirrel monkeys as subjects and later comparing results of a human study in a clinical situation using the same drug. Even more interesting is the fact that the number of squirrel monkeys, and other monkeys as well, used in pharmacological experiments is very minimal when compared to other animals, particularly the white rat. Because of the small number of pharmacological studies with squirrel monkeys, the possibilities of experimentation are many.

It should be noted that the squirrel monkeys are not without their disadvantages. They are relatively expensive which probably contributes a great deal to the small number of monkey studies, often highly infected with parasites, and become ill or lethargic when subjected to prolonged experimentation, high drug dosages, experimental stress, or frequent electric shocks (Kelleher, Gill, Riddle, and Cook, 1963). These factors do not necessarily outweigh the advantages of employing this animal as a subject in research.
A task which was suggested to be a study on abstraction was an oddity problem with a primate (Robinson, 1933). She reasoned that in an oddity problem, the animal is required to discriminate and further, to form a relationship between stimuli simultaneously presented in order to solve the problem. In that study, a cynomologus monkey was required to pull in one of three boxes depending on which one was odd in color for food reinforcement. On the last of 424 trials, the monkey was performing near the 90% level of correct choices, although on two days prior to the termination of the study, performance hit the 100% level. Since then, other monkeys have been known to learn oddity tasks, including squirrel monkeys (Martin, 1966; Noble and Thomas, 1970; and Thomas and Boyd, 1973).

Therefore, oddity appears to be a task on which to test whether Metrazol has any effect on learning using squirrel monkeys. According to McCaugh (personal communication, July 1973) and to the best of this author's knowledge, the effects of Metrazol on learning have never been determined using primates barring research currently in progress at the Wisconsin Primate Center under the direction of Bowman and Harlow. If a Metrazol facilitatory effect on learning can be demonstrated in squirrel monkeys, then such a study would provide more generality of the effectiveness of the drug.

The hypothesis of this investigation is that Metrazol will facilitate the learning of an oddity task in squirrel monkeys.
Method

Subjects:

The subjects (Ss) were four female naive Peruvian squirrel monkeys (Saimiri sciuereus) which were obtained through a commercial dealer. The Ss were housed two per cage and the ambient room temperature was approximately 80 to 85°F. The monkeys were maintained on Purina Monkey Chow.

Apparatus:

The apparatus consisted of a modified version of the Wisconsin General Testing Apparatus (Harlow and Bromer, 1938). The Wisconsin General Testing Apparatus (WGTA) was comprised of two joinable frames. One frame supported the monkey testing cage. The other frame supported the sliding test tray, the purpose of which was to advance the stimuli and any underlying food reinforcement to within the monkey's reach (See Appendix 1).

The stimuli consisted of four pairs of differently shaped pieces of plywood which covered the foodwells on the sliding test tray. The shapes of the stimuli were a star, circle, square, and triangle. All of the stimuli were sprayed with white glossy paint (See Appendix 2).

Procedure:

The Ss were randomly divided into drug and control groups with two monkeys per group. For the first four days, the animals were given food and water ad libitum. On the fourth day, the Ss were weighed, deprived of food for 22 hours, and maintained between 90 and 95% of their free feeding weight throughout the study.

On the first of four days of preliminary training, each monkey was
shaped to displace the stimulus from over the foodwell and take the reinforcer. Shaping consisted of placing the reinforcer on top of the sliding tray and in front of one of the foodwells. The reinforcer was gradually moved toward the hole and placed into the foodwell by the fifth trial. On the sixth trial, a stimulus was placed to the back of a foodwell and on each subsequent trial, was gradually moved to cover more of the foodwell opening. By the tenth trial, all monkeys had learned to displace the stimulus from over the foodwell and take the reinforcer. The reinforcer was half of a white miniature marshmallow (Kraft).

The three subsequent preliminary sessions was composed of 20 trials per session. On each trial, S was presented one stimulus which covered one of the three foodwells and was allowed the opportunity of displacing the stimulus and take the reinforcer. The position on the sliding tray and the shape of the stimulus was randomly determined on each trial, but each differently shaped stimulus was equally presented five times per session.

Formal training was comprised of 20 trials per session (day) for 45 consecutive sessions or until one group reached a criterion of 75% correct responses on two consecutive sessions, whichever occurred first. On each trial three stimuli were presented to the S. Two of the stimuli were identical in shape with the third being odd in shape. The stimulus configuration on each trial was randomly selected from the pool of 36 possible combinations of stimuli. If the monkey selected the odd stimulus, he was reinforced. An incorrect choice resulted in no reinforcement and withdrawal of the tray. A non-correction procedure was used. The inter-trial interval was approximately 30 seconds. The number of correct responses were recorded.
Immediately after the end of the session, the animal was taken from the testing cage and given either 15 mg/kg of Metrazol or saline intramuscularly in accordance to their assigned group and returned to their home area. At approximately two weeks into the experiment, the method of injecting the animal was changed. This change in procedure became necessary because an assistant who aided in the holding of the animal during injection was not always present. The new method involved the drawing of the animal to the front of the cage, holding it immobile against the front bars of the cage by a moveable squeeze-bar partition located within the cage, and then injecting the monkey with the solution.

On the second and third sessions of the formal training, an animal in the saline group (S2) would displace the stimulus, but did not take the reinforcer. After eight trials, S2 failed to displace the stimulus. For the next four days, S2 was given sessions identical to the preliminary training, but again the animal would only respond for about five trials without taking the reinforcer and then failed to respond on subsequent trials. On the next four sessions, the reinforcer was changed to bits of Purina Monkey Chow and S2 responded and took the reinforcer on all 20 trials of each session.

At approximately 20 sessions into the experiment, one monkey in the drug group (D1) developed a series of movements which were incompatible to task acquisition. These movements consisted of climbing to the front and top of the testing cage and looking toward a nearby bookcase and then rapidly dropping to the floor of the cage and selecting the closest stimulus when the tray was advanced. These movements persisted for several sessions and finally an attempt was made by the author to induce a more compatible response to the stimuli by eliminating the above described movements. The new procedure was essentially the rapid fanning
of the door which separated the animal's testing cage from the sliding tray area before the tray was advanced. This procedure was used whenever the monkey climbed to the top of the cage and resulted in extinction of the climbing response.

Results

There appeared to be no significant difference between the drug and saline groups. The drug animals averaged 48.3% correct responses and the saline animals averaged 45.9% correct responses over sessions. Table 1 gives a summary of the total number of correct responses, number of sessions, and the per cent of correct responses for the drug and saline groups. The number of correct responses is shown cumulatively over sessions for each animal in Figure 1.

Individually, D1 and D2 averaged 43.4% and 53.1% correct responses over sessions, respectively. S1 and S2 averaged 47.5% and 43.7% correct responses over sessions, respectively. Table 2 gives a summary of the total number of correct responses, number of sessions, and the per cent of the correct responses for each animal. Figures 2-5 shows the per cent of correct responses over sessions for the individual animals.

D1 and S2 encountered difficulties in the experiment, as was mentioned in the method section under procedure, therefore, Figure 6 represents the cumulative correct responses over sessions for D2 and S1. D2 averaged 53.1% correct responses and S1 averaged 47.5% correct responses over sessions. During the last 14 sessions, D2 averaged 64.9% correct responses and S1 averaged 50.4% correct responses. Figure 7 represents the per cent of correct responses over the last 16 sessions of the experiment for D2 and S1. D2 was the only monkey to make the criterion of 75% correct responses on two consecutive days. D2 reached criterion on trial 840.
### TABLE 2

**Summary of Drug and Saline Groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>Sessions</th>
<th>Total number of correct responses</th>
<th>Per cent correct responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>90</td>
<td>869</td>
<td>48.28</td>
</tr>
<tr>
<td>Saline</td>
<td>81</td>
<td>743</td>
<td>45.86</td>
</tr>
</tbody>
</table>
Fig. 1. Cumulative correct responses for drug and saline animals over sessions.
<table>
<thead>
<tr>
<th>Group</th>
<th>Sessions</th>
<th>Total number of correct responses</th>
<th>Per cent correct responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>D₁</td>
<td>45</td>
<td>391</td>
<td>43.44</td>
</tr>
<tr>
<td>D₂</td>
<td>45</td>
<td>478</td>
<td>53.11</td>
</tr>
<tr>
<td>S₁</td>
<td>45</td>
<td>428</td>
<td>47.55</td>
</tr>
<tr>
<td>S₂</td>
<td>36</td>
<td>315</td>
<td>43.75</td>
</tr>
</tbody>
</table>
Fig. 2. The percentage of correct responses per session for D1.
Fig. 3. The percentage of correct responses per session for D₂.
Fig. 4. The percentage of correct responses per session for S1.
Fig. 5. The percentage of correct responses per session for $S_2$. 
Fig. 6. Cumulative correct responses for "best" drug and saline animal over sessions.
Fig. 7. The percentage of correct responses per session for D2 and S1.
Discussion

The results indicated that Metrazol had no significant effect on the acquisition of an oddity task with squirrel monkeys in this experiment. Although the results did not support the hypothesis of this investigation, there were some trends which suggest that the drug may have had an effect provided the number of sessions had been extended.

For instance, D2 reached criterion after 840 trials and D1 reached a 75% correct responding level after 240 trials, but failed to make the 75% correct responding level on the next session which was necessary to reach criterion. D1 began to develop the interfering responses cited above shortly after reaching the 75% correct responding level. Once the interfering response was extinguished, then D1 began to respond comparably to the other animals. If one refers to Figures 2 and 4, there can be seen that D1 made slightly more correct responses during the last ten sessions than S1. D1 averaged 54% correct responding and S1 averaged 53% correct responding.

The average percents of correct responses of the first 10 sessions were 37.5% and 43% for D1 and D2, respectively, and 44% and 42% for S1 and S2, respectively. The last 10 sessions for each animal resulted in 54% and 67% correct responding for D1 and D2, respectively, and 53% and 46.5% for S1 and S2, respectively. Both drug animals had the largest increase in terms of the average percent of correct responses in comparing the first 10 sessions with the last 10 sessions. Such trends indicate that Metrazol may have facilitated the oddity learning if the experiment was extended in sessions.

Noble and Thomas (1970) reported that three of four squirrel monkeys reached a 90% (36 correct in 40 successive trials) criterion on a four
problem two-odd form oddity task. The range of trial to criterion for
the three monkeys was from 714 to 827 trials. The fourth monkey only
approached an 80% correct responding level after 1200 trials when the
experiment was terminated. The present study used a 12 problem two-odd
form oddity task and only the drug animals reached the criterion level
of 79% correct responding. The results of this study and the Noble and
Thomas (1970) investigation appear to be comparable if one considers
that the monkeys in their study had some prior experience with
one-odd form oddity and brightness discrimination in pretraining phases.
The fact that more problems were used in the present study may have con­
tributed to the slower acquisition of oddity responding as with more
problems there will be more reversals encountered in the oddity situation.
A reversal in oddity learning means that on one trial the correct stimulus
may be the incorrect stimulus on the next trial (AAB followed by BBA, for
example). One author (Saravo and Collin, 1969) has suggested that ir­
relevant response tendencies such as perseveration to object cues in
reversal situations may produce intermittent reinforcement and thereby
strengthen such response tendencies which will not produce a solution
to the oddity problem.

In comparing the present study with one performed by Strong
and Hedges (1966), the results of both experiments are similar. On
trial 768, three rhesus monkeys in the Strong and Hedges study had a
mean of approximately 56% correct responding on an oddity task in
which six problems were employed in a concurrent series. The three
squirrel monkeys (D1, D2, and S1) in this study had a mean of 59% correct
responding on trial 760. In an unpublished study, Martin (1966) succeeded
in training three squirrel monkeys who were known to be superior in learn-
ing set performance. The monkeys reached an oddity achievement level of about 70% on a series of one trial oddity problems. The results of the present study do not appear to be atypical of squirrel monkeys learning oddity considering the number of trials attempted. It should be noted that most studies usually involve a few thousand trials.

Several investigators have suggested that dose response relationships should be established for different genetic strains of rodents (Petrinovich, 1967; Krivanek and McGaugh, 1968; and Hunt and Bauer, 1969). The results of this study suggest that the dosage level of 15 mg/kg of Metrazol had no effect on oddity learning, but there was a small number of subjects used and it is possible that another dosage level would have facilitated oddity acquisition. Further investigations involving dose response curves is warranted to determine if Metrazol has an enhancement effect on oddity learning in Peruvian squirrel monkeys. If such investigations produce negative results, then one may speculate that Metrazol enhancement is possible only with specific tasks, with specific species and/or strains of animals, or with some combination of these variables.
References


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Appendices
Appendix 1

Wisconsin General Testing Apparatus