Short Title

EFFECTS OF EARLY STRYCHNINE INJECTION ON ADULT BEHAVIOR IN THE RAT - Racine

EFFECTS OF EARLY STRYCHNINE INJECTION ON ADULT BEHAVIOR IN THE RAT

by

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INTRODUCTION

There are a number of studies in the literature which indicate that stimulation in infancy can affect activity, emotionality, and learning in the adult rat (Levine, 1962). The effects are highly dependent upon small differences in treatment (Brookshire, et al, 1961), and not all the studies are in agreement, but there are enough positive results to indicate that the phenomenon is a genuine one.

Early stimulation usually leads to increases in the rate of ontogenetic development (McClelland, 1956; Weininger, 1956). Rats handled from birth showed an adult level of depletion of adrenal ascorbic acid at 12 days of age, whereas non-handled rats showed no depletion until 16 days of age (Levine, 1958). Krech, Rosenzweig, & Bennett have repeatedly shown that early stimulation increases brain weight and enzyme activity (Bennett, et al, 1964). Siamese kittens handled briefly in infancy open their eyes, leave their nesting box, and attain adult pigmentation earlier than unhandled kittens (Meier & Stuart, 1959).

Early drug injections also have effects upon maturation and often result in permanent changes in adult behavior. Guinea pigs injected postnatally with testosterone show early mounting, intromission and ejaculation (Gerall, 1963). Prenatal maternal injections of epinephrine and norepinephrine (Young, 1963; Young, 1964a), and postnatal injections of norepinephrine and chlorpromazine (Young, 1964b) increase the emotionality of the adult rat. Postnatal administration of chlorpromazine results in a decrement in the learning of delayed conditioned avoidance responses in adult rats (Doty & Doty, 1963). It has been suggested that some of these effects of stimulation in infancy are independant of the particular nature of the stimulation (Levine, 1959).

These results are consistant with the possibility that some of the effects of early stimulation are due to an increase in nonspecific neural activity or level of arousal (Henderson, 1964). It has been found that electrical stimulation of the reticular formation in rats produces changes in brain weight and enzyme

activity similar to those found by Krech, Rosenzweig and Bennett (Pryor, et al, 1966).

If diffuse neural activity can serve to alter a developing neural system, at least in some respects, then perhaps early artificial stimulation of neural tissue, electrically or pharmacologically, will also alter the system. Perhaps it is even possible to render the system more efficient, irrespective of any particular cognitive factors in the environment. That is, perhaps some of the effects of enriched environment studies are also partially due to an increase in diffuse neural activity. It is easy to speculate as to how this might take place, but first it is necessary to determine whether it does, in fact, occur.

The question is, then, whether imposing a greater degree of activity on a developing neural system will affect the later activity and efficiency of that system. There is considerable neural development taking place in the newborn rat, including actual cell differentiation, which might be influenced by such activity. Myelination takes place primarily after birth and continues in some

structures for up to 60 days or more (Zeman & Innes, 1963). Also neurogenesis occurs in the hippocampus for up to 8 months after birth in the rat, and most of the microneurons are formed after birth. This neurogenesis also involves the granule cell layers of such structures as the olfactory bulb, cerebellum and cortex (Altman & Das, 1965; Altman, 1966). Many other cells are only partially developed and interconnections between them are still incomplete after birth. The apical dendrites of pyramidal cells, for example, do not attain full development until about 20 days (Ochs, 1965).

Pharmacological stimulation is a convenient approach to a study involving neural activation. There are several neural stimulants which, when injected pre- or post-trial, facilitate learning in the adult rat. Some of these drugs are strychnine (McGaugh et al, 1962), picrotoxin (Breen & McGaugh, 1961), 1757 I.S. (McGaugh et al, 1962; Hudspeth & Thompson, 1962), metrazol (Hunt & Drivanek, 1964), and caffeine (Pare, 1961). Since most of these studies used strychnine as the stimulant, and since more

is known about the physiological consequences of strychnine administration than of any of the other drugs, strychnine was used in the present experiment.

Strychnine affects the spinal cord and brain stem and does not have any direct effects, with intraperitoneal injections, at high levels. The brain stem region appears to be more sensitive to strychnine than higher levels (Gastaut & Williams, 1959; La Grutta & Desmedt, 1964; Andersen et al, 1963). So far, strychnine has been found to reduce all types of inhibitory post-synaptic potentials (IPSP's) in the spinal cord of the cat, and has no effect on excitatory post-synaptic potentials (EPSP's) (Eccles, 1964). Strychnine can reduce cortical inhibition, but only when applied directly to the cortex, rather than IP (Pollen & Marsan, 1965). There are several hypotheses as to the mechanism of the strychnine effect, the currently popular one being that strychnine sterically blocks the action of the inhibitory transmitter at receptor sites (Bradley, et al, 1953). It has also been suggested that strychnine may slightly increase

the membrane permeability caused by an IPSP, allowing a small sodium ion influx, which in some cases is great enough to abolish or reverse the IPSP (Pollen & Marsan, 1965).

This drug, then, seemed well suited for the initial work on the effects of early diffuse stimulation. The following study was a replication and extension of a pilot study in which the drug was used (Racine & Stein, unpublished). Using dose levels initially higher than those used in this study, which were then decreased when some animals began to convulse, adult rats from the strychnine injected group were found to be significantly superior to saline injected control S's in Hebb-Williams maze performance. There was also a non-significant increase in emotionality in the strychnine group, and a significant decrease in weight.

Two learning tests were used in the present investigation: the Hebb-Williams maze and the Thompson discrimination apparatus. These tests were used to determine whether or not the apparent facilitation of learning found in the pilot study was real, and to determine the generality of these effects. Three different

age groups were tested in order to check for differences in rate of maturation of learning ability. Activity measures were taken continuously throughout the injection period, emotionality was tested upon termination of injections, and a lethal dosage measure was made upon termination of testing, in order to test for changes in sensitivity or tolerance.

METHOD

Subjects

S's were 180 Sprague-Dawley albino rats born to 15 mothers obtained pregnant from Carworth Farms, New York.

Apparatus

An open field and a Hebb-Williams maze, both as described by Rabinovitch & Rosvold (1950) were used. A small scale open field was built for infant rats. Its dimensions were 18 in. long X 18 in. wide X 4 in. deep, and its floor was marked off into 36 - 3 in. squares.

The second apparatus used to test learning was a Thompson discrimination box. The start box was 6 in. wide by 8 in. long. The runway was 24 in. long, 6 in. wide at the start box end and 16 in. wide at the goal box end. There was a single sliding goal box 8 in. wide by 12 in. long and a blind panel, with a cue card, on either side. The relative positions of the cue cards could be changed by sliding the goal box back and forth. The apparatus was 12 in. deep.

During early infancy, the injections were performed using a microliter syringe and #30 hypodermic needle. When the rats reached a weight of 50 grams, a 1 cc syringe and #27 needle were used. The rats were weighed, until weaned on a triple beam balance and after weaning on a dietetic spring scale .

Treatment

Fifteen rat litters were reduced to 180 animals. These were redistributed so that there were 12 S's per mother rat. One third of each original litter was assigned to one of three groups: a low-dose strychnine group (.10 mg/kg), a high-dose strychnine group (.25 mg/kg),

or a saline group. Solutions were mixed so that the animals were injected with 2 cc of solution per kilogram of body weight. Injections were begun 24 hours after birth. All animals were injected at the same time every day, and care was taken to ensure that all animals received the same amount of handling. Weights were recorded for each animal every day. Throughout the injection period, cages were rotated in the racks to control for differences in temperature or visual experience.

There were 5 experimental groups chosen randomly from this population. Each group consisted of 3 sub-groups, composed of equal numbers of rats, receiving either high-dose strychnine, low-dose strychnine, or saline. The five experimental groups were, 1) S's injected from 1 - 20 days, and then tested on the two learning measures; 2) S's injected from 1 - 40 days and then tested; 3) S's injected from 1 - 60 days and then tested; 4) a group of S's on which activity measures were kept throughout 60 days of injections; and 5) a group tested for differences in emotionality after 60 days of injections. All S's were weaned at 18 days and

placed 4 to a cage.

Testing - 20-day injection group

At 18 days of age 9 animals, 5 males and 4 females, were chosen randomly from each dosage sub-group. All rats were weaned at this age; in the experimental group food was also removed. S's were then fed for ½ hour a day on wet mash. This schedule was continued throughout testing, and the S's were maintained at 85% of body weight on the normal growth curve. Injections were stopped at 20 days of age.

At 21 days of age, pretraining on the Hebb-Williams maze began. The animals were placed in the center of the open field and allowed to run to the goal box; this was repeated 3 times. On day 2 of pretraining the S's were placed one at a time in the start box and allowed to run across the open field to the goal box. In the goal box they were allowed to eat wet mash for 20 seconds; this was repeated for 10 trials. On day 3 of pretraining the S's were run for 10 trials on the first pretraining task as described by Rabinovitch and Rosvold (1950).

Testing proper was begun on the following day using the standard series of 12 problems. Procedure from this point on was similar to that of Rabinovitch and Rosvold, except that 7 trials were run each day instead of 10.

The animals completed this training at age 35 days. On day 36, pretraining was begun on the Thompson Box. The reward was, again, wet mash. Pretraining consisted of running the animal to a randomly alternating open door. On the first trial the door was open 40^{o}. The door was closed by 10^{o} for each following trial until it was closed on the 5^{th} trial. The animal was then run for 5 more trials. Training proper began on the next day. The correct stimulus was horizontal as opposed to vertical striations. S's were run 10 trials per day until they reached a criterion of 9 correct trials out of 10 in one day. Wet mash was placed behind each door to control for olfactory cues.

40-day injection group

At 38 days of age 9 animals, 5 males and 4 females,

were again chosen randomly from each dosage subgroup. The procedure is the same in every way as for group one, except that injections were continued until 40 days of age, deprivation was begun on day 38 and pretraining was begun on day 41.

60-day injection group

At 58 days of age a third group was chosen as before. Injections were continued until 60 days of age, deprivation was begun on day 58 and pretraining was begun on day 61. Otherwise the procedure was identical to that of the 20 and 40 day groups.

Activity measure group

Four males and four females were chosen randomly from each dosage subgroup when S's were 4 days of age. At 5 days of age the animals were placed in the small open-field apparatus and allowed to wander about for 5 minutes each; no measures were kept. This was repeated at 8 and 9 days of age. At 10 days of age, the S's were placed in the apparatus and the number of

squares crossed in a 3 min. period prior to the daily injection was recorded. The S's were injected 15 min. after being taken out of the open field and were placed back in the open field 15 min. after injection. The number of squares crossed in a 3 min. period was again recorded. The S's were tested in this way at 10, 15 & 20 days of age. At 24 days of age, the S's were placed in the large open-field and allowed to explore; no measure was kept. At 25 days of age, the same procedure was followed as on days 10, 15, & 20 except that the large open-field was used. This was repeated on days 35 and 45.

Emotionality

Four males and four females were chosen randomly from the remaining animals at 60 days and were in no other way disturbed. At 80 days of age these S's were placed in the large open-field apparatus for a 3 min. period and the number of squares crossed was recorded. Also, the number of urinations and boluses were recorded.

Lethal dosage

At the termination of the study, 6 males and 6 females were chosen from each drug group for a lethal dose test. The dose level (2.8 mg/kg for males and 2.3 mg/kg for females) which had been found to be the median lethal dose for this strain was injected into all rats and the number which died was recorded.

All tests, except for the lethal dosage test, were run blind.

RESULTS

There were no differences in the growth curves (weight) between the 3 groups (see fig 1). The small differences which are seen are made even smaller by randomly discarding enough extra females in the saline group (days 45-60) to bring the male to female ratio in each group to equality (dotted line - fig. 1). Also, there was no difference in age at which the S's of each group opened their eyes. There was no apparent difference in development of ability to ambulate, and there were no

differences in rate of pigmentation or growth of fur. One thing which was noticed, however, in both the pilot study and in this study, was that the animals began to show effects of strychnine injection at about 10 days. They became tense and hyperreactive to stimuli. This increased until about day 14 or 15 at which time several of the strychnine animals went into convulsions. At day 16 or 17 these convulsions stopped occurring, and by day 18 to 20 the animals no longer showed any behavioral effect of the strychnine.

20-day group

An F test showed the variances between groups on the Hebb-Williams maze data to be significant ($F=3.5$, $p < .05$), so the Kruskal-Wallis rank test for one-way analysis of variance was used in comparisons of all group means. This test showed that there were no significant differences in either total errors in the Hebb-Williams maze or trials to criterion in the Thompson Box. The high-dose strychnine group was, however, superior in both of these tests (see fig. 2).

40-day group

The strychnine groups were, again, not significantly different from each other or from the saline group (fig. 3).

60-day group

Again, there were no apparent differences (fig. 4).

Combined males & combined females in previous two groups

A bimodal pattern was observed in the 40-day group Thompson-box data, with the males tending to cluster toward the upper end of the distribution (fewer trials to criterion), and the females tending toward the lower end. This tendency held up in the 60-day group. Since there was no apparent difference between the age groups on performance of this task, the 40- and 60-day injection test groups were combined and then comparisons were made between males across drug subgroups and between females across drug subgroups. There was a significant ($p < .05$) disruption effect for the female rats. There was also a possible facilitation effect in the males, although this was not significant (p .20, see fig. 5).

Activity measure

The first significant result from the activity data was the post-injection activity of the 10-day-old group (fig.6). The high-dose strychnine animals were more active on the post-injection measure than were the saline animals ($p < .05$). This effect completely disappears on day 15 and the low-dose strychnine group now shows significantly less post-injection activity than either the high-dose strychnine or saline animals ($p < .05$). On day 20, all significant differences disappear on post-injection activity. In no case was there a difference between groups on the pre-injection activity measures.

Emotionality measure

The high-dose strychnine group was slightly more active on this measure (fig. 7) but the difference is not significant.

Lethal dosage

No difference was found in the number of rats in each group which succumbed to the median lethal dose

(2.3 mg/kg for females, 2.8 mg/kg for males - see table 1). The difference was never more than ± 1 rat in any group.

Age differences

All subgroups were combined and age differences, irrespective of treatment variables, were examined (see fig. 8). There were 3 age groups tested on the Hebb-Williams maze (20, 40 & 60 days) and the same 3 groups respectively were tested on the Thompson Box when older (35, 55 & 75 days). The 40-day group scored significantly fewer errors on the Hebb-Williams maze than the 20-day group ($p < .01$), and the 60-day group scored significantly fewer errors than the 40-day group ($p < .01$). The 55-day group took significantly fewer trials to reach criterion in the visual discrimination task than the 35-day-old group ($p < .05$), but the 75-day-old group was not better than the 55-day-old group.

DISCUSSION

Strychnine seems to have an effect on pre-weaning activity. The high-dose animals show significantly more activity after injection at 10 days of age than the saline S's. This effect disappears at 15 days, which is the age at which the animals appear to be most sensitive to strychnine, and the low-dose animals become significantly less active. At 20 days this sensitivity disappears and the post-injection activity goes up again, as can be seen by the comparisons of pre- and post-injection activity (fig. 6). That these activity differences are related to the changes in sensitivity, is supported by the finding that rats become significantly less active with progressively higher doses of strychnine (Calhoun, 1965). This leaves unexplained why there should be a significant increase in post-injection activity in the 10-day-old rat. It may be an adaptive trait of the infant that any kind of disturbance will result in increased motor activity to ensure contact with the mother. More simply,

it may just be a lack of development of the elaborate inhibitory feedback systems and systems of reciprocal innervation present in the adult. At day 25 and after there were no activity differences.

Since the adult animals do not show any activity differences, then a simple increase in diffuse neural activity cannot be said to affect later motor activity. Levine's hypothesis about adrenal activation, in which it is proposed that many of the effects of early stimulation are due to increased maturation of hormonal systems, is perhaps a more adequate one (Levine, 1958). This conclusion also applies to later emotionality. No difference was found in the number of squares crossed in the open field and there were no differences in the number of boluses or urinations.

The increased sensitivity to strychnine at 14 days, which subsequently disappeared, suggested a temporary physiological imbalance in the system occuring during that period in development. This seemed more likely than an increased sensitivity due to the continual injections, because of the fact that the sensitivity

was no longer apparent after about 18 - 20 days. In order to test this hypothesis, forty normal 14-day-old animals were run in a lethal dosage study and the median lethal dosage was found to be between 1.0 and 1.5 mg/kg, half that of adult animals. It was also found that animals at this age will convulse at much lower dosages than this, down to about 0.33 mg/kg which is close to the high dosage used in this study. This sensitivity may be due to the relatively incomplete development of higher motor control centers at this age (Ochs, 1965).

The results show no conclusive facilitation of learning effects. I think it can be said, however, that the results are suggestive. A significant facilitation effect was found in the pilot study. Tendencies toward facilitation have shown up in several of the tests in this study, and facilitation was found in males injected from 25 - 50 days in a related study (Don Stein, personal communication).

All of the comparisons in this study were made using the Kruskal-Wallis rank test. It is of interest to look at these data using other tests. For instance,

with the 20-day group (Hebb-Williams maze - fig. 1), it can be seen that there are two extremely low scores in the high-strychnine group. If the two lowest scores in each group are eliminated then the difference becomes significant ($p < .05$). A sign test also gives a more nearly significant result. This is true also for the 60-day Hebb-Williams maze data (fig. 4) and for the comparison of combined 40- and 60-day males on the Thompson Box (fig. 5). This latter difference also receives support from the fact that it was found in two different test groups. This applies also to the disruption effect found in the females, which was significant and seems to be a real effect (fig. 5).

It is difficult to explain why the females should be disrupted and the males not. Females are more sensitive to strychnine, as was determined by lethal dosage studies (LD_{50} = 2.8 mg/kg for males and 2.3 mg/kg for females). It is perhaps the case that the .25 mg/kg dosage of the high-dose group was too high for females. It is not too surprising that this split between males and females was not found in the Hebb-Williams maze data,

since these two tests appear to be measuring different things, as indicated by the lack of correlation between them.

So, in favor of the notion that early strychnine injections may facilitate later learning are the significant differences found in the pilot study, the fairly consistent but small and non-significant tendencies toward facilitation found in this study, and a significant facilitation effect found for males injected from 25 to 50 days of age and then tested on a Hebb-Williams maze (Don Stein, personal communication). At this point, it is not possible to say with any certainty whether there is a facilitation effect or not; and if there is, what causes it is even less certain. This study has not eliminated some of the possible causes of facilitation. It seems safe to conclude that it is not due to any permanent changes in emotionality or activity, and it also seems that there is no increased rate of maturation in injected animals. The early increases in activity following injection may, however, have something to do with the effect, although it is difficult to see how,

since this occurs very early, before the eyes open, and presumably little relevent information is being picked up from the environment. There are several other possible explanations which have not been covered by this study. Strychnine may increase the animal's ability to attend to cues, as there is evidence that it sharpens sensory acuity (Ruch & Fulton, 1960). Or it may facilitate consolidation of information, as it seems to do in the adult animal when injected post-trial (McGaugh, 1962). Finally, it may increase synaptic efficiency by increasing the rate at which impulses cross given synapses, that is, by increasing the level of diffuse activity. The assumption here, of course, is that learning involves a lowering of synaptic threshold due to increased firing of that synapse. One must be careful about embracing this hypothesis, however, as pointed out by Sharpless (1964), there is considerable evidence to show that some synapses are sensitized by disuse and made less sensitive by excessive stimulation. On the other hand, there is also evidence that, in some

structures, thresholds are lowered upon excess stimulation. It is found, for example, that continuous stimulation of the amygdala produces a long-lasting and rather large lowering of convulsive threshold (Graham Goddard, personal communication).

More work should be done on this topic before anything conclusive can be said. Work is now underway to see if metrazol, a convulsant which works at higher levels of the nervous system than strychnine, will produce facilitation.

One of the more interesting outcomes of this study had little to do with the topic under investigation; that is, the differences between age groups. As can be seen in fig. 8, the 40-day group is superior to the 20-day group, the 60-day group is superior to the 40-day group, and the 55-day group is superior to the 35-day group. Since there is no difference between the 75-day-old group and the 55-day-old group, and since the difference between the 60-day group and the 40-day group is still fairly large, this would indicate that maturation of learning capacity occurs at about 50 days

of age. This seems much more likely than the 30 days and less reported by Stone (1929), and Biel (1940).

SUMMARY

The hypothesis that early stimulation and enriched environment effects may be due, in part to an increase in diffuse neural activity is discussed. The suggestion is made that electrical or pharmacological stimulation in infancy might produce similar effects. Strychnine was chosen as the neural stimulant in the present investigation and was injected daily from birth up to 60 days.

There was no difference found in emotionality between strychnine and saline injected animals. Ten-day old high-dose strychnine animals were significantly more active just after injections, and low-dose strychnine animals were significantly less active just after injection when 15 days old. Combined females from 40- and 60-day injections groups showed a significant disruption of learning. Strychnine animals were superior in several of the learning tests, but the differences were not significant. The evidence for a facilitation effect is discussed.

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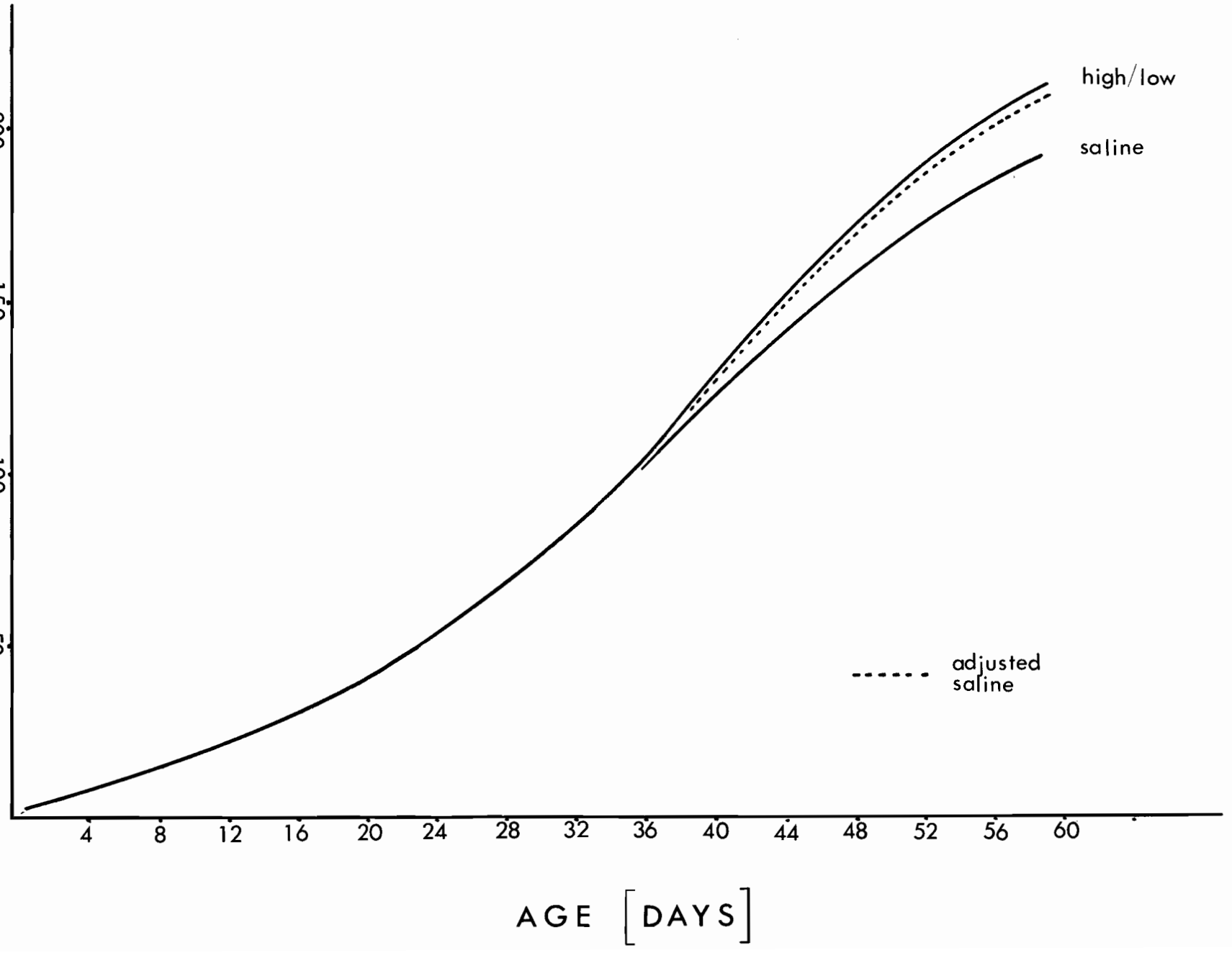
	Hi	Lo	Sal
No. of rats convulsed (over no. injected)	8/12	7/12	8/12
No. of rats also died	6/12	5/12	5/12

LETHAL DOSAGE

TABLE 1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100
50
4
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12
16
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56
60
AGE [DAYS]
high/low
saline
adjusted saline

FIGURE 1

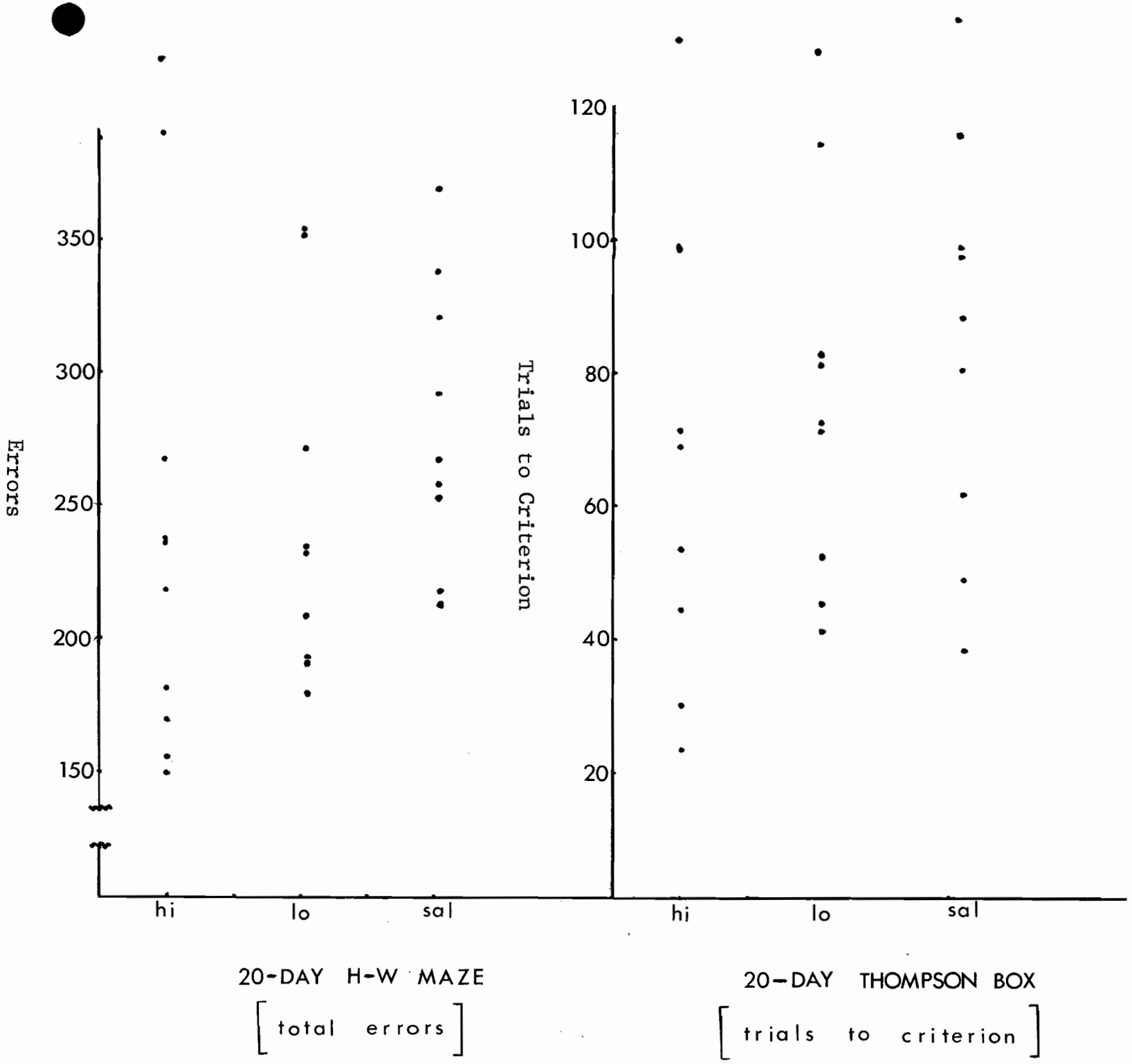

Errors
350
300
250
200
150
hi
lo
sal
20-DAY H-W MAZE
[total errors]
Trials to Criterion
120
100
80
60
40
20
hi
lo
sal
20-DAY THOMPSON BOX
[trials to criterion]

FIGURE 2

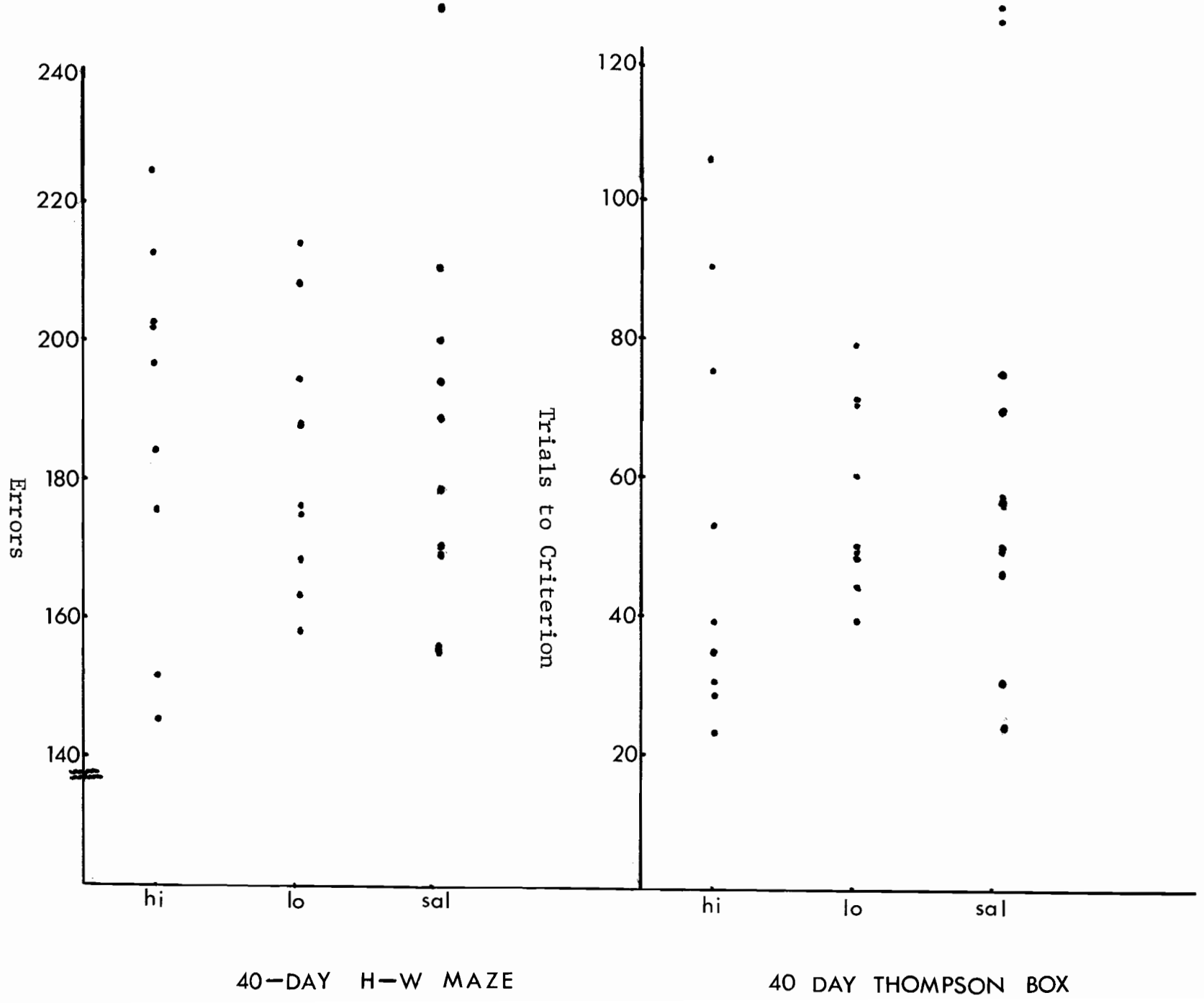

240
220
200
180
160
140
Errors
hi
lo
sal
40—DAY H—W MAZE
120
100
80
60
40
20
Trials to Criterion
hi
lo
sal
40 DAY THOMPSON BOX

FIGURE 3

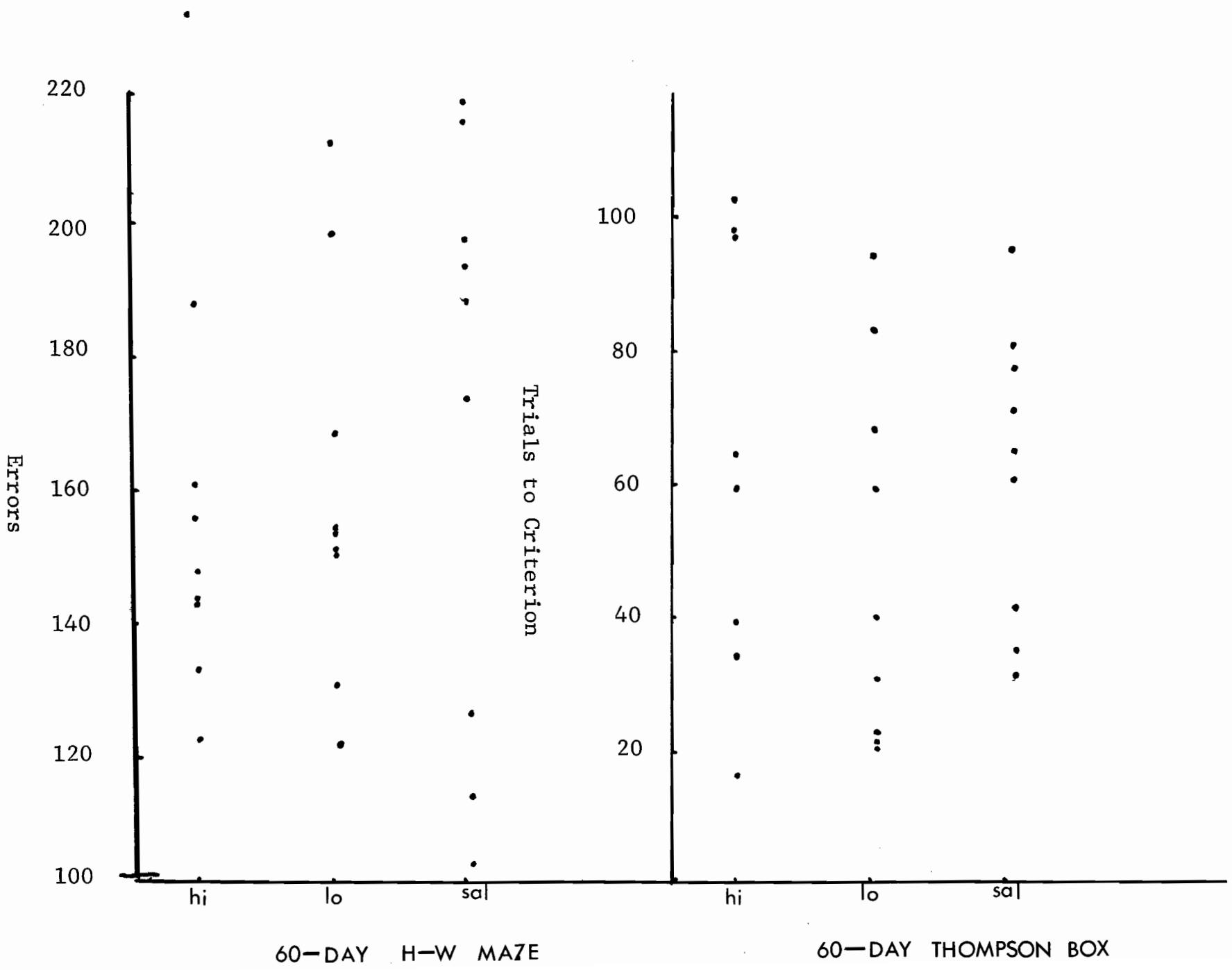

Errors
220
200
180
160
140
120
100
hi
lo
sal
60—DAY H—W MAZE
Trials to Criterion
100
80
60
40
20
hi
lo
sal
60—DAY THOMPSON BOX

FIGURE 4

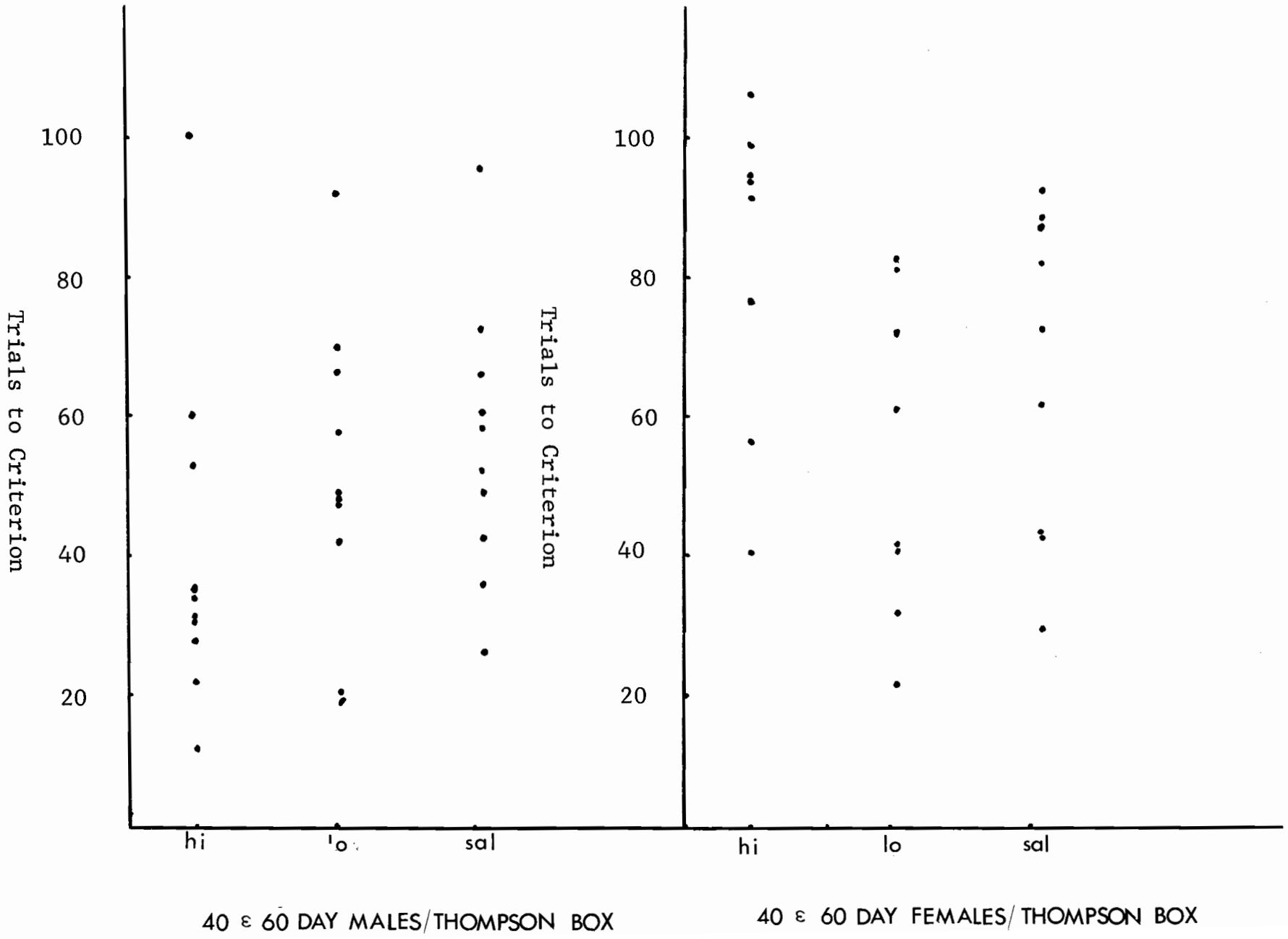
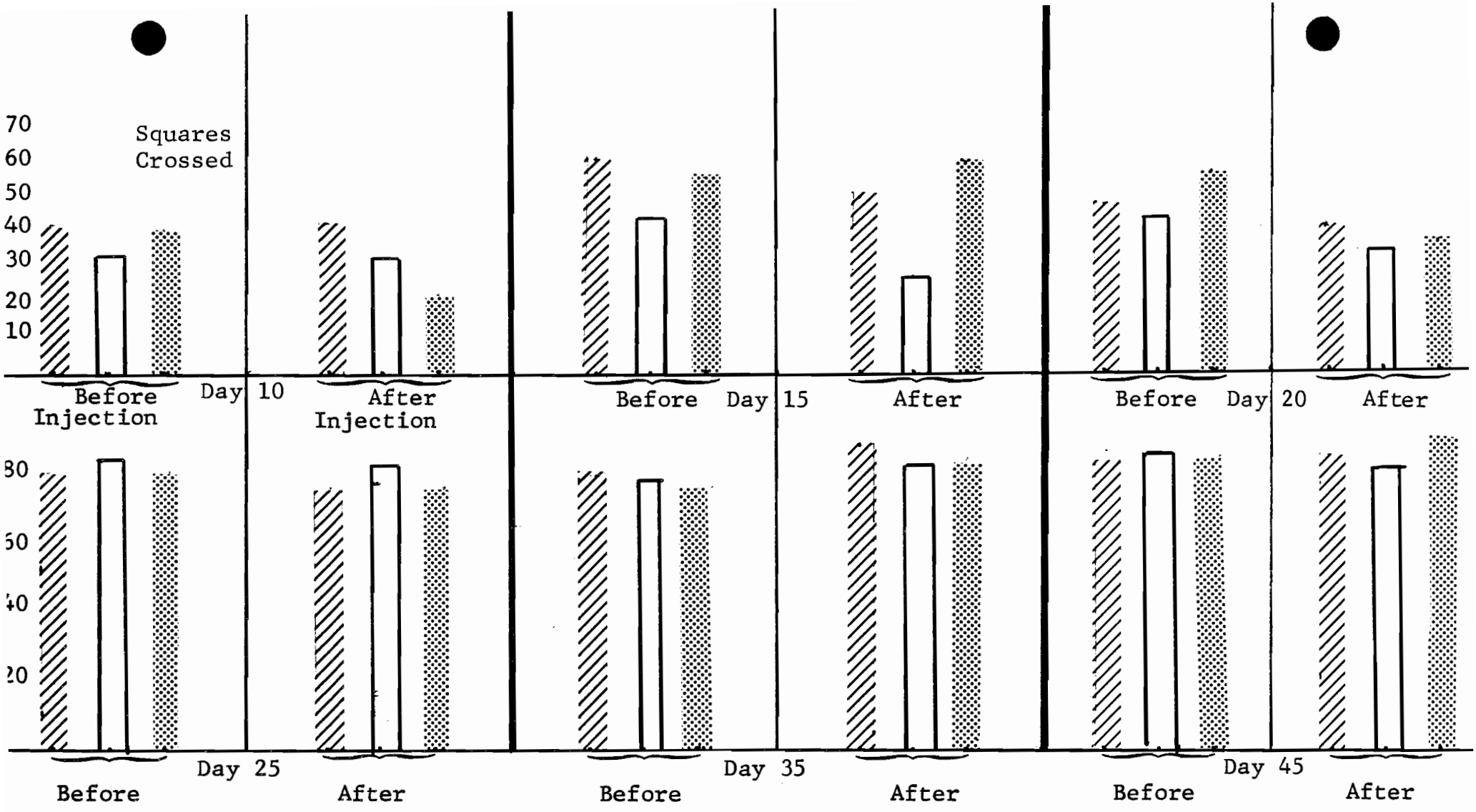

Trials to Criterion
100
80
60
40
20
hi
lo
sal
40 ε 60 DAY MALES/THOMPSON BOX
Trials to Criterion
100
80
60
40
20
hi
lo
sal
40 ε 60 DAY FEMALES/ THOMPSON BOX

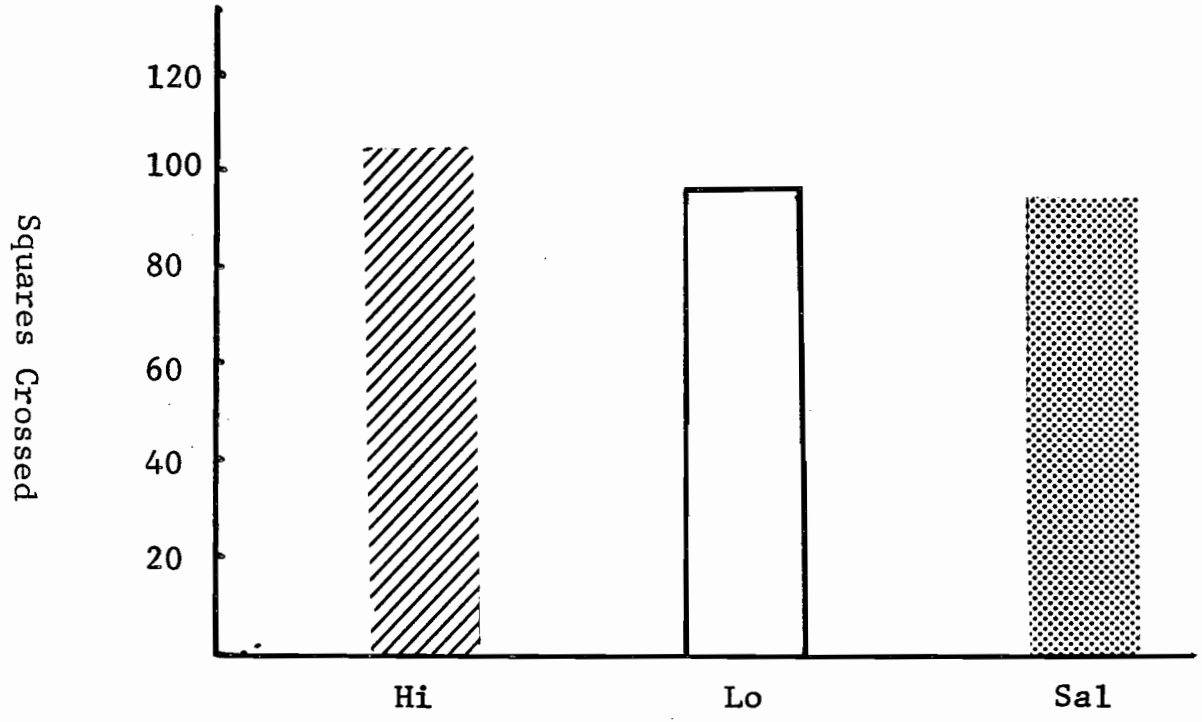
FIGURE 5



ACTIVITY

Mean number of squares crossed

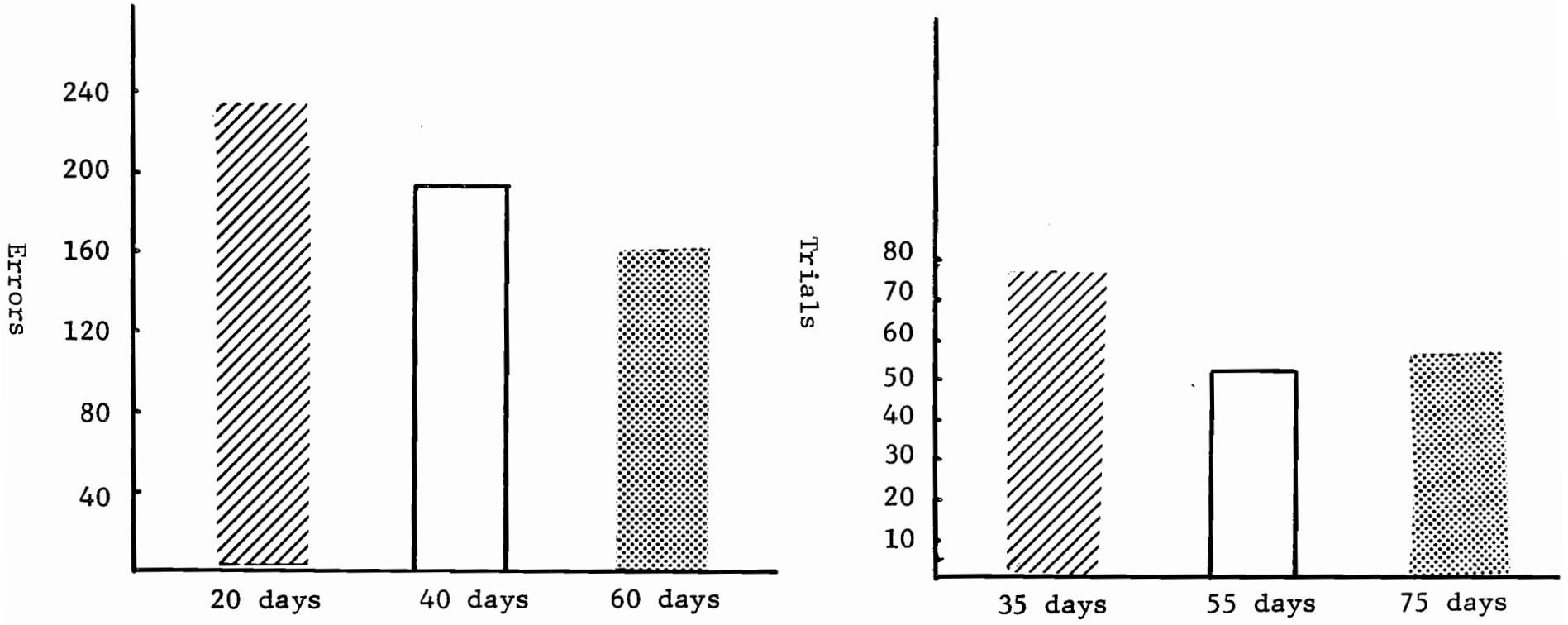
FIGURE 6



EMOTIONALITY

Mean number of squares crossed

FIGURE 7



AGE DIFFERENCES

FIGURE 8