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# Effect of Drugs on Visually Controlled Avoidance Behavior in Rhesus Monkeys: a Psychophysical Analysis* **

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The relationship between drug effects and various psychophysical parameters, especially visual, remains one of the less emphasized areas of contemporary behavioral pharmacology. Several years ago, BLOUGH (1956, 1957a, b, 1958) conducted a variety of excellent psychophysical studies with pigeons that involved a number of drugs and visual modalities. In addition, a few other "psychophysical-like" drug experiments have been reported (e.g. CARLSON, 1958; FELDMAN *et al.*, 1959; JARVIK and ADLER, 1961; TERRACE, 1963; and THURMOND, 1965) that, in most instances, were primarily concerned with other than associations between psychophysical and pharmacologic variables.

In the specific instance of intra-stimulus variability, especially scalar relationships, the only visual parameter studied has been intensity. HEARST (1964), KEY (1964) and HANSON and GUTTMAN (1961) have reported drug effects on behavior controlled by fractional intensity scales. However, these reports were concerned with generalization gradients, not scaling *per se*.

In an effort to specifically explore the relationship between a psychophysical scale and drug-effects, the experimentation described in this report utilized performance involving scaled visual size-acuity.

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** In conducting the research reported herein, the investigators adhered to "Principles of Laboratory Animal Care" as established by the National Society for Medical Research and to the "Guiding Principles for the Humane Care and Use of Animals, December 15, 1962" as stated by the American Psychological Association.

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## Method

*Subjects.* A group of 18 one and a half to three years old healthy male rhesus monkeys *(Macaca mulatta)* served as subjects. The animals were individually caged at all times and maintained on a diet of conventional monkey chow, fresh fruit and multi-vitamin supplemented water.

*Apparatus.* Conventional electromechanically automated behavioral analysis equipment was used to control the experimental contingencies and to record the data. Additional data recording involved punching paper tape for computer analysis by the method of Bass (1966).

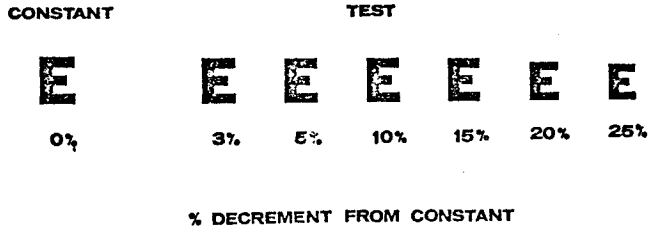


Fig. 1. The stimuli employed in the experimentation. Two constants were presented with one of the test values, all random as to position

The experimental arrangement consisted of portable primate restraining chairs, into which the Ss were placed immediately prior to testing. All experimentation was conducted with the subjects confined in light proof, sound attenuated and ventilated chambers. The seats and foot-rests of the chairs were wired for administration of electric shock (1000 V, 3.0 ma).

The seated Ss faced a $30.5 \times 15.0$ cm one-plane stimulus panel containing three translucent circular response keys (3.2 cm diameter) arranged in a horizontal row 2.5 cm apart from edge to edge. These were at eye level, approximately 16 cm in front of the eyes and easily accessible to both hands. Each of the keys was transilluminated by a random-access film-strip projector.

*Stimuli.* The stimuli were a series of black letters E (Fig. 1) varying only in size of total area. They were centered within the circular key area on a homogeneous white background. Six arbitrarily selected test values, 3.0, 5.0, 10.0, 15.0, 20.0 and 25.0 percent smaller than the constant, were made by calibrated photographic reduction.

*Procedure.* Ss were trained by successive approximations to select the smaller (test) letter from a series of three always consisting of two constants and one of the test values. The procedure was thus a modification of the psychophysical method of constant stimuli. During each hour of experimental session, each stimulus value was presented an equal

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Failure to select the proper value within 30 sec, or an incorrect choice, resulted in a five second shock which could be escaped from by a correct response. A correct response or a full shock period terminated the stimulus presentation. After a 30 sec intertrial period, another stimulus array was presented. Correct and incorrect avoidance and escape responses, and the time from stimulus presentation until a correct response was made (hereafter called Reaction Time) were recorded.

Individual Ss were run daily for four hours until reaching asymptote (defined as two weeks of daily 99% error-free performance), after which they were considered "fully trained". Ss were then tested in once weekly sessions of four hours duration. The first hour served as a pre-injection control period, after which, if the performance during this period was in conformity with asymptotic levels, the test drug or the saline control was administered intravenously. After allowing 15 min pre-treatment time, the Ss were then tested for three hours. Every dose of each drug was tested in six Ss. The doses, including saline treatment, were randomly distributed among the total group. The drugs and doses employed can be seen in the Table. All drugs were administered as saline solutions at a volume of 0.1 cc/kg. In every instance, an attempt was made to select dose ranges between doses having no effect on the maintained behavior and doses that produced overt symptomatology.

## Results

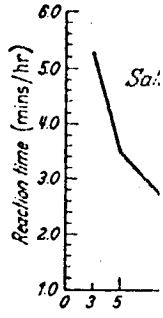
The drug-induced changes in error responding for both Avoidance and Escape are presented in columns one and two of the Table. Because the number of stimulus presentations was dependent upon the performance level of each S, and because the error rate for control sessions was zero (that is, no drug was administered to any S exhibiting less than 100% avoidance during control); it was felt that the most meaningful representation of error responding was by time. An additional consideration here is the fact that this is essentially a "one-response" situation, in that the only type of response that can occur more than once per stimulus presentation is an incorrect escape response. Thus, measures of response rate are difficult to relate to overall performance, and would not be enhanced by statistical analysis.

Figure two presents graphs of mean data for all 18 subjects under conditions of saline (0.9% NaCl) treatment. The first graph shows the total reaction time per hour as a function of stimulus value. The second graph shows the mean change in reaction time for each stimulus value from the one hour pre-treatment sessions. That is, changes in reaction

Table. *Error values and statistical evaluation of changes in reaction time for the effects of various drugs on size-acuity discrimination in rhesus monkeys*

| Drug | Dose mg/kg | 1 Avoid. errors No./Hr. | 2 Escape errors No./Hr. | 3 Mean latency change min/Hr. | 4 "F" Values Multiple | 5 "F" Values Linear | 6 "F" Values Curvitive | 7 Residual variance |
|---|---|---|---|---|---|---|---|---|
| Critical values | | | | | 9.55 | 10.1 | 10.1 | 0.028 |
| Pento-barbital | 10.0 | 6 | 23 | 0.847*** | 12.40 | 24.44 | 3.02 | 0.385 |
| | 5.0 | 4 | 3 | 0.443*** | 10.30 | 19.64 | 3.96 | 0.0543 |
| | 3.0 | 0 | 1 | 0.181* | 3.46 | 4.28 | 1.21 | 0.0104 |
| | 1.0 | 1 | 1 | 0.196* | 18.51 | 35.94 | 0.15 | 0.0018 |
| Phen-cyclidine | 0.5 | Unable to respond | | | | | | |
| | 0.25 | 23 | 18 | 0.490*** | 1044.34 | 2088.08 | 129.90 | 0.004 |
| | 0.10 | 0 | 1 | 0.233** | 18.00 | 35.54 | 4.23 | 0.0140 |
| | 0.05 | 1 | 1 | 0.113* | 6.70 | 10.98 | 5.22 | 0.0070 |
| *d*-Amphet-amine | 3.0 | 12 | 37 | 1.437*** | 25.92 | 38.57 | 4.40 | 0.0170 |
| | 2.0 | 15 | 23 | −0.530** | 9.69 | 3.05 | 18.80 | 0.0466 |
| | 1.0 | 0 | 2 | −0.548** | 2.65 | 0.00 | 5.00 | 0.0349 |
| | 0.5 | 1 | 0 | −0.310** | 50.46 | 91.43 | 0.59 | 0.0004 |
| | 0.25 | 0 | 3 | 0.005 | 11.75 | 6.46 | 11.71 | 0.0020 |
| Caffeine | 70.0 | 3 | 12 | −0.473*** | 3.95 | 4.56 | 5.18 | 0.0623 |
| | 50.0 | 1 | 1 | −0.193* | 1.80 | 0.75 | 3.39 | 0.1423 |
| | 25.0 | 1 | 1 | −0.342** | 2.18 | 1.26 | 3.90 | 0.2511 |
| | 10.0 | 0 | 0 | −0.522*** | 1.30 | 2.10 | 0.12 | 0.0290 |
| | 5.0 | 0 | 0 | −0.05 | 11.75 | 6.46 | 11.71 | 0.0020 |
| Strych-nine | 0.1 | 0 | 0 | 2.630*** | 1.84 | 2.57 | 0.43 | 0.3480 |
| | 0.03 | 0 | 1 | 0.280** | 0.49 | 0.62 | 0.16 | 0.1881 |
| | 0.01 | 2 | 2 | 0.058 | 0.53 | 0.58 | 0.73 | 0.0444 |
| Chlor-proma-zine | 0.5 | 46 | 33 | 2.998*** | 1.65 | 0.33 | 2.38 | 0.1822 |
| | 0.1 | 2 | 2 | 0.807*** | 0.67 | 0.00 | 1.25 | 0.1154 |
| | 0.05 | 1 | 1 | 0.620*** | 0.04 | 0.02 | 0.08 | 0.2294 |
| | 0.03 | 0 | 1 | −0.185* | 2.40 | 2.39 | 1.32 | 0.0086 |
| Haloperi-dol | 0.1 | 4 | 13 | 2.442*** | 1.82 | 2.84 | 0.229 | 0.0537 |
| | 0.03 | 5 | 4 | 1.535*** | 7.00 | 5.79 | 11.20 | 0.2259 |
| | 0.01 | 1 | 2 | 0.980*** | 25.35 | 48.61 | 0.05 | 0.0288 |
| | 0.003 | 0 | 0 | −0.273** | 17.78 | 33.50 | 0.003 | 0.0020 |
| LSD-25 | 0.1 | 25 | 72 | 0.955*** | 2.72 | 2.26 | 4.35 | 0.0641 |
| | 0.05 | 29 | 66 | 1.197*** | 0.38 | 0.70 | 0.21 | 0.0959 |
| | 0.025 | 12 | 7 | 1.355*** | 0.04 | 0.06 | 0.003 | 0.0962 |
| | 0.01 | 0 | 0 | 0.407*** | 3,12 | 4.79 | 2.83 | 0.0098 |
| | 0.005 | 0 | 3 | 0.307** | 1.97 | 3.23 | 1.54 | 0.0139 |

| Drug | Dose mg/kg | 1 Av err No |
|---|---|---|
| Ditran | 0.3 | 2 |
| | 0.1 | 1 |
| | 0.03 | 0 |
| | 0.01 | 0 |
| | 0.003 | 0 |
| Morphine | 10.0 | 7 |
| | 3.0 | 4 |
| | 1.0 | 0 |
| | 0.3 | 0 |
| Saline | — | 0 |

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| 3.02 | 0.385 |
| 3.96 | 0.0543 |
| 1.21 | 0.0104 |
| 0.15 | 0.0018 |
| 129.90 | 0.004 |
| 4.23 | 0.0140 |
| 5.22 | 0.0070 |
| 4.40 | 0.0170 |
| 18.80 | 0.0466 |
| 5.00 | 0.0349 |
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| 11.71 | 0.0020 |
| 5.18 | 0.0623 |
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| 3.90 | 0.2511 |
| 0.12 | 0.0290 |
| 11.71 | 0.0020 |
| 0.43 | 0.3480 |
| 0.16 | 0.1881 |
| 0.73 | 0.0444 |
| 2.38 | 0.1822 |
| 1.25 | 0.1154 |
| 0.08 | 0.2294 |
| 1.32 | 0.0086 |
| 0.229 | 0.0537 |
| 11.20 | 0.2259 |
| 0.05 | 0.0288 |
| 0.003 | 0.0020 |
| 4.35 | 0.0641 |
| 0.21 | 0.0959 |
| 0.003 | 0.0962 |
| 2.83 | 0.0098 |
| 1.54 | 0.0139 |

Table (Continued)

| Drug | Dose mg/kg | 1 Avoid. errors No./Hr. | 2 Escape errors No./Hr. | 3 Mean latency change Min./Hr. | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|---|
| | | | | | "F" Values | | | Residual variance |
| | | | | | Multiple | Linear | Curvitive | |
| Ditran | 0.3 | 2 | 6 | −1.310*** | 5.39 | 3.72 | 4.55 | 0.0193 |
| | 0.1 | 1 | 0 | −0.642*** | 1.80 | 0.51 | 2.38 | 0.1918 |
| | 0.03 | 0 | 0 | −0.233** | 2.46 | 1.82 | 4.12 | 0.5762 |
| | 0.01 | 0 | 0 | −0.520*** | 1.24 | 1.08 | 0.83 | 0.2797 |
| | 0.003 | 0 | 0 | −0.248** | 1.47 | 1.26 | 1.00 | 0.0555 |
| Morphine | 10.0 | 7 | 6 | −0.685*** | 0.66 | 0.16 | 0.92 | 0.0788 |
| | 3.0 | 4 | 4 | −0.720*** | 2.07 | 1.03 | 3.81 | 0.0736 |
| | 1.0 | 0 | 0 | −1.402*** | 0.41 | 0.23 | 0.40 | 0.2421 |
| | 0.3 | 0 | 1 | 0.127 | 6.26 | 8.89 | 6.48 | 0.0490 |
| Saline | — | 0 | 0 | −0.005 | 0.19 | 0.25 | 0.21 | 0.0024 |

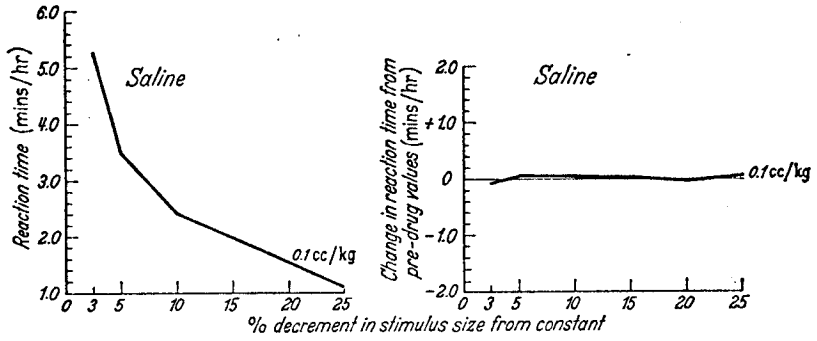



Fig. 2. The left graph shows mean reaction time ($N$ = 18 Ss) as a function of stimulus size. The right graph shows the absence of any significant mean change in reaction time as a function of saline treatment, again for each stimulus value

time post administration of saline were compared to the pre-administration times by plotting the differences at each stimulus value. This latter method of analysis is used to develop the drug data which are presented in figures three through seven, with each plot representing a mean of six Ss.

The best quadratic fit was calculated for each of the above curves, the results of which are presented in the Table under columns three through seven. Column three expresses the mean change in latency for each dose. Figures significant at the 5.0% level are indicated by one asterisk, those at 1.0% level by two asterisks and those at the 0.1% level by three asterisks. Column four, the first column under "F", lists the values indicating a relation between latency and stimulus value.

Columns five and six contain data indicating linearity or curvilinearity in the curves. Significant values are those which are larger than the critical values at the head of each column. Because some drugs seem to indicate a tendency to increase variability, those curves for which variability is significant are indicated in column seven.

## Discussion

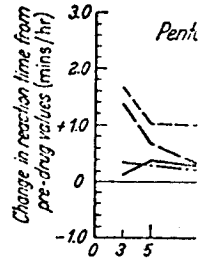
It is apparent from these data that Rhesus monkeys are capable of scalar size acuity discriminations, and that such discriminations are differentially sensitive to drug effects. The range of stimulus values employed is, on the basis of number of errors, apparently well above the absolute threshold, however, the reaction time curve for saline-treated Ss, by its marked upward trend at the smaller decrements, suggests that the acuity threshold is being approached. In view of the small differentiation involved (3.0%), it would be interesting to determine the absolute threshold for this discrimination.

The drugs tested can be readily distinguished by the level changes in the reaction time curves, thus, offering respectively a definition of stimulant and depressant. In addition, the shapes of the curves appear to afford even greater specification—a fact which is presently under more thorough investigation.

Error responding, where it was exhibited, occurred in a dose-dependent manner (columns one and two, Table) but was not differentially graded to a sufficient degree to lend itself to the overall analysis of drug effects.

The anesthetics pentobarbital and phencyclidine (Fig. 3) exhibited dose-dependent effects on response latency, The pentobarbital data are not compatible with those reported by Blough (1956, 1957b) or Dews (1955) for pigeons in that there was a decrease rather than an increase in response rate. Error responding, however, was increased at the higher dose levels. It is interesting to note that phencyclidine, reported to be psychotomimetic (Domino, 1963), manifested its effects similar to pentobarbital, with regard to latency, response rate and error responding; showing no resemblance to other psychotomimetics (Fig. 6). A significant linear relationship is evident for three doses of pentobarbital and all doses of phencyclidine. It could be postulated that the non-linearity exhibited by the 3.0 mg/kg dose of pentobarbital reflects the excitatory-depressant action sometimes seen with pentobarbital in many species, including humans (Sharpless, 1965).

The CNS stimulant drugs, *d*-amphetamine and caffeine (Fig. 4), decreased reaction time except at the highest dose of *d*-amphetamine. Error responding was exhibited to a moderate degree with *d*-amphetamine at the two highest doses, however, the next lower dose showed

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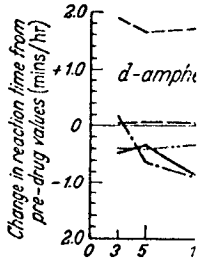


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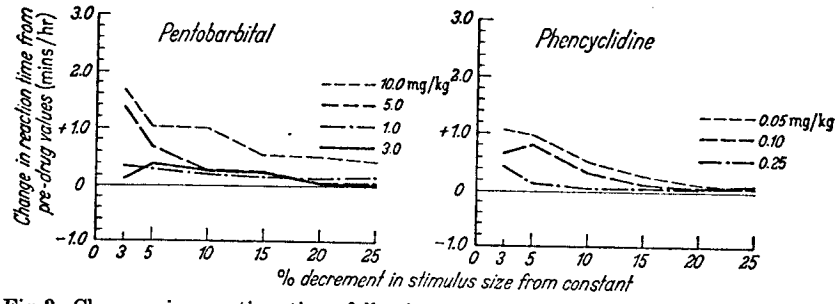


Fig. 3. Changes in reaction time following treatment with the anesthetic agents pentobarbital and phencyclidine

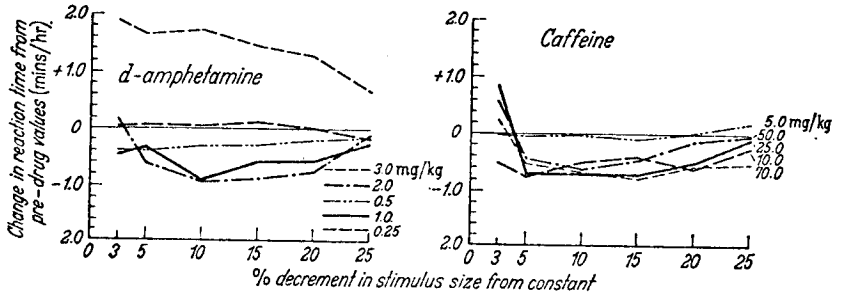


Fig. 4. Changes in reaction time following treatment with the CNS stimulants, *d*-amphetamine and caffeine

very little error responding, yet an equally high degree of stimulation as reflected by decreased latency. The highest dose of caffeine, which produced an equivalent degree of stimulation, produced even less error responding. Thus, it can be seen that error responding is not necessarily correlated to degree of stimulation. These findings are in general agreement with the widely reported effects of such drugs on human behavior (Weiss and Laties, 1963). However, the *d*-amphetamine results are not similar to Dews (1955) finding with pigeons, nor to Thurmond's (1965) and Brown's (1966) monkey data. Dews' and Brown's studies involved complex color discriminations, Thurmond's work was with white light intensity. In all these instances, performance was decrementally affected. The depressant action of the high dose of *d*-amphetamine is an experimentally defined phenomenon (Owen, 1960; Brown, 1963, 1965) and, thus not unusual. The graphic plots for both drugs, with the exception of the high dose of *d*-amphetamine, were dose-dependent, but were not uniformly linear or curvilinear with relation to each other (Fig. 4). Reaction time for the middle range of stimulus values appeared to be more affected than for those at either end of the scale.

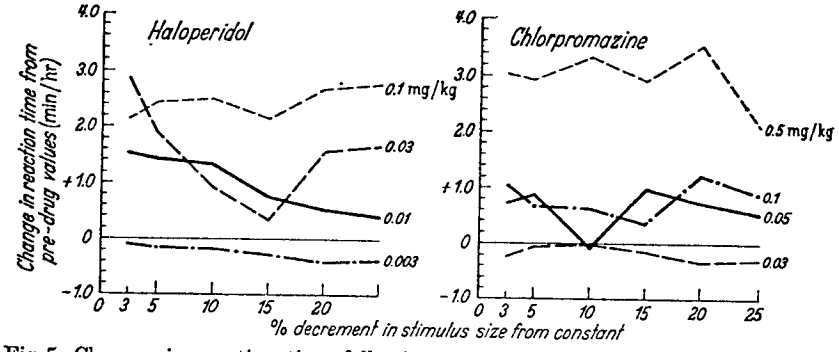


Fig. 5. Changes in reaction time following treatment with the tranquilizers haloperidol and chlorpromazine

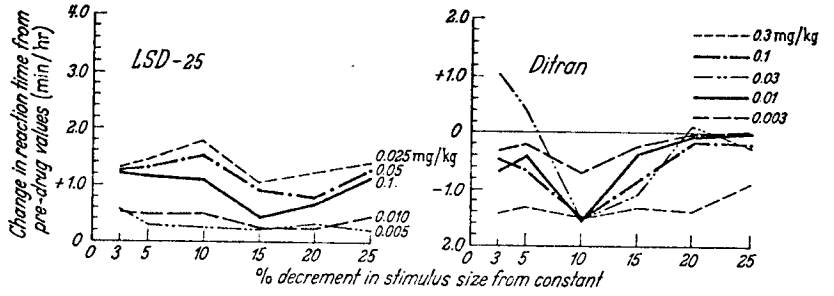


Fig. 6. Changes in reaction time following treatment with the psychotomimetic agents LSD-25 and Ditran

The "tranquilizers" chlorpromazine and haloperidol show significant level changes in the reaction time curves, but have non-specific qualitative effects. That is, the curves are devoid of any characteristic shape (Fig. 5), but rather, are marked by extreme variability. In his study of intensity generalization, HEARST (1964) also reported marked response variability following chlorpromazine dosage. Error responding was again exhibited only at the higher doses.

The psychotomimetic, LSD-25, significantly increased reaction time in all instances. However, the effects are unusual in that the level of reaction time is not dose-dependent, but rather varies widely. The shape of the curves at effective dose levels is not significantly linear or curvilinear, rather appearing to be somewhat sinusoidal. Error responding was exhibited to a marked degree with LSD-25, and unlike the reaction time curves, appears to be dose-dependent. These effects are unlike the facilitating effects of LSD-25 reported by BLOUGH (1957b) for pigeons. FUSTER (1959) also found increased reaction time effects with LSD-25 in monkeys responding to tachistoscopically presented objects, but he

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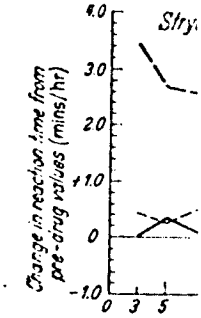

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did not obtain the variability with regard to dose-dependence. ABRAMSON *et al.* (1955) reported a decrease in the reaction time of LSD-25 treated humans.

Conversely the anticholinergic psychotomimetic, Ditran (ABOOD and BIEL, 1962; DEVITO and FRANK, 1964) had effects totally unlike those just described. As can be seen in Fig. 6, the drug was stimulating in that it decreased reaction time. The dose-response relationship was, like LSD-25, somewhat variable, but roughly directly dependent. The shape of the curves is again not significantly classifiable between the various

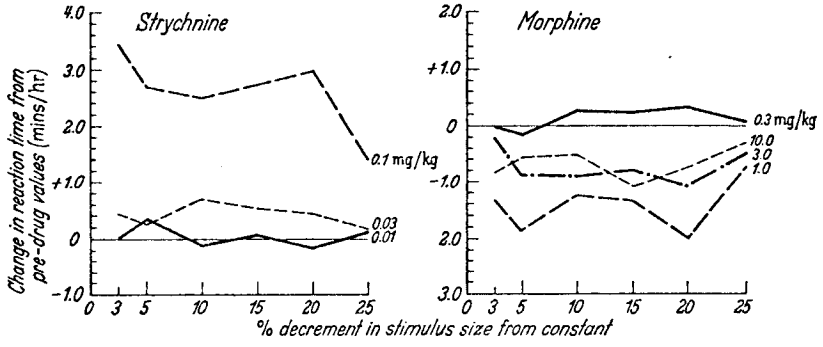


Fig. 7. Changes in reaction time following treatment with strychnine and morphine

doses. It is interesting to note, however, that the maximal effect of Ditran for every effective dose was seen at the ten percent stimulus value. The stimulating effect of Ditran is similar to that reported for rats (LIPMAN *et al.*, 1963).

The above described data for the CNS stimulants and depressants on the basis of increases or decreases in reaction time, tends to conform to expectations. CNS stimulants decrease reaction time, CNS depressants increase reaction time. However, as Fig. 7 shows, the CNS stimulant, strychnine, effected a marked increase in reaction time (thus, by this procedure, is a depressant) while the CNS depressant, morphine, decerased reaction time (hence, a stimulant). It can be seen that the stimulant or depressant effects of these drugs occurred at all doses between non-effective and near lethal; that is, they are not biphasic. The finding for morphine is not surprising since the species specificity of the drug in this regard is well known; indeed, it is a stimulant in many non-human organisms (JAFFE, 1965). In the instance of strychnine, the only related report is OSKARSSON's (1962) study of the effects of the drug on visual acuity of human subjects. He found no changes at doses of 4.0 mg, i.m.

Thus, the present experimentation clearly indicates that drug effects are quantitatively stimulus dependent in that the magnitude of the drug effect varies as a function of the stimulus magnitude, although not always in a linear manner. The direction of the drug-induced changes is also a significant indicator of effect—allowing a classification of drugs in terms of stimulatory or depressant effects. It now remains to specify the factors relevant to the interaction of psychophysical scales and drug effects as well as the generality of the effects in regard to both drug classes and stimulus modalities.

## Summary

Rhesus monkeys, conditioned to respond to a scaled series of different sized letters E by a shock-reinforced psychophysical method of constant stimuli, were tested following treatment with several drugs. The primary measure employed was change in reaction time—a variable which proved sensitive to magnitude and overall direction of change. These data were plotted as a function of stimulus values for each dose of drug. The resulting curves were analyzed to determine significant relationships between various classes of drugs.

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