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Reaction Time ("Mental Set") in Control and Chronic Schizophrenic Subjects and in Postaddicts under Placebo, LSD-25, Morphine, Pentobarbital and Amphetamine

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With 4 Figures in the Text

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Introduction

In 1937, HUSTON et al. reported a number of findings in studies on simple auditory-manual reaction time (RT) that significantly differentiated patients with chronic schizophrenia from normal controls: Mean RTs were much longer in the schizophrenic subjects, regardless of the duration of the "warning" or preparatory intervals (0.5, 1, 2, 3, 5, or 10 sec after flash of a light bulb); variability in these subjects was greater; and whereas in normal subjects, mean RTs at each interval used were significantly shorter when, in a given series the interval was held constant ("regular" procedure) than when the duration of the interval was randomized ("irregular" procedure), this difference did not persist in the schizophrenic subjects at intervals of two seconds and longer, indicating that beyond this interval, schizophrenic subjects were unable to profit from regularization of the preparatory intervals.

In general, these findings were confirmed by RODNICK and SHAKOW (1940) in a study on simple visual-manual RT, using intervals of 1, 2, 4, 7.5, 15 and 25 sec after a warning bell. In the normal subjects, mean RTs were shorter on the "regular" than on the "irregular" procedures at all intervals except 25 sec, where no significant difference was found. In the schizophrenic subjects, mean RTs on the two procedures were not significantly different except at the 2 sec ("regular" shorter than "irregular") and the 25 sec ("irregular" shorter than "regular") intervals. On

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the basis of the data obtained in this and in the earlier study, RODNICK and SHAKOW (loc. cit.) concluded that whereas normal subjects can maintain a high preparatory "set" for periods up to between 15 and 25 sec, schizophrenic subjects can do so only for much shorter periods. Furthermore, these investigators found that, in terms of an empirical "set index," their schizophrenic could be differentiated from their normal subjects without any individual overlap. Similar data on chronic schizophrenic and normal subjects have been reported by a number of other investigators (see SHAKOW 1963). However, HUSTON and SENF (1952) found that, although "set" was impaired to the greatest degree in patients with chronic schizophrenia, lesser degrees of impairment could be demonstrated in patients with early schizophrenia or depressive psychoses, and to a smaller extent in psychoneurotic subjects.

HUSTON and SINGER (1945) demonstrated that relative normalization of behavior in schizophrenic subjects proceeds *pari passu* with relative normalization of "mental set". These investigators found that after intravenous injection of a mixture of 250 mg of amobarbital and 10 mg of amphetamine, their patient group (9 subjects with chronic schizophrenia) became ". . . more talkative and seemed to have increased social and self-confidence . . . Their speech content tended to be more relevant, their attention better and their affect warmer" (page 367). Concomitantly, the drug mixture produced a greater difference between "irregular" and "regular" auditory-manual RTs at all preparatory intervals (2, 3.5, 5, 10 and 20 sec after light-flash) than obtained prior to the drug injection, due to slight prolongation of mean RTs on the "irregular" procedure at all intervals and shortening of mean RTs on the "regular" procedure at the longer intervals (5, 10, and 20 sec). In their group of 9 normal control subjects, the effect of the drug mixture was to prolong all mean RTs, without altering significantly the relationships between the "irregular" and "regular" curves. In contrast, WYNNE and KORNETSKY (1960) were unable to demonstrate any significant change in mean RTs or the difference between mean RTs on the "irregular" and "regular" procedures in schizophrenic subjects after treatment with orally administered single or repeated doses of secobarbital or chlorpromazine. However, there is no indication in their report that such treatments produced any clinical improvement in the behavior of the schizophrenic subjects, and therefore the findings of these investigators do not necessarily invalidate those of HUSTON and SINGER (loc. cit.)

Our own investigations of "mental set" stemmed from an interest in the still unresolved question of the relationship of the "model psychosis" produced by LSD-25 to schizophrenia (see discussion in WIKLER 1957). It was thought that the assumption of such a relationship would be strengthened if it could be shown that LSD-25 produces a "schizophrenic-

like" change in "mental set" of non-psychotic subjects when administered in doses sufficient to produce distortions of perception, hallucinations, etc., whereas other drugs (morphine, pentobarbital and amphetamine) which might alter RTs but in the doses used do not produce "psychosis", would fail to alter the relationship between the "irregular" and "regular" RT curves in a "schizophrenic-like" manner. Originally, it was planned to conduct such studies only on non-psychotic "postaddicts", using HUSTON and SINGER's (1945) data on normal and schizophrenic subjects for comparison. That this would not be feasible, however, soon became apparent in pilot studies. Thus, in the studies of HUSTON and SINGER (loc. cit.), the "irregular" procedure was always conducted before the "regular" and completion of both procedures subtended a period of about one and one-half hours; therefore, differential effects of drugs on "irregular" and "regular" RTs might in part be artifacts of their "time-action" courses. To compensate for such a possibility, it was decided to conduct the measurements of RT both in the "irregular" before "regular" and in the "regular" before "irregular" orders (on different days) for each dose of drug (and placebo), and to express the data in terms of "combined" RTs (average of the two "irregulars" and of the two "regulars"). Since no such "combined" data for either normal or schizophrenic subjects had been published, it was therefore necessary to obtain our own. In the present report, our "standard order" data ("irregular" before "regular") under no medication or placebo conditions will be compared with those reported previously in the literature, but our "combined order" data on drug effects in "postaddicts" will be compared with the corresponding data obtained in our normal control and schizophrenic subjects.

Methods

Subjects. These consisted of three groups: "normal" controls, "postaddicts" and chronic schizophrenic patients, all male.

"Normal" control subjects were 10 members of the staff of the Addiction Research Center (physicians, technicians and medical aides), ranging in age from 21 to 38 years (mean, 30.8 years), without known physical or mental disorder.

"Postaddicts" were 10 patients with previous histories of narcotic drug addiction, ranging in age from 25 to 38 years (mean, 31.9 years), serving sentences at the U.S. Public Health Service Hospital, Lexington, Kentucky, for violation of federal narcotic laws. They had been withdrawn from the drug of addiction three months or more, and had received no drugs of any kind for at least one month before commencement of the study. All were in good physical health and were free from overt manifestations of psychosis. For the group as a whole, Minnesota Multiphasic Personality Inventory (MMPI) profiles were similar to those reported

for a large population of "postaddicts" (HILL et al. 1962), with highest elevations on the "psychopathic deviation" (Pd), "hypomanic" (Ma) and "depression" (D) scales (mean T scores of 68.9, 64.3 and 61.4 respectively).

The chronic schizophrenic subjects were 13 patients without histories of narcotic addiction, who ranged in age from 31 to 54 years (mean, 39.0 years). Seven were classified as paranoid, 1 hebephrenic, and 5 mixed, with durations of hospitalization for mental illness ranging from 4 to 252 months (mean 121.7 months, or 10.14 years). None had received insulin or electroconvulsive therapy for at least two years, or medication of any kind for a least six weeks prior to commencement of the study, and all were in good physical health.

Techniques and apparatus*. For measurement of auditory-manual RT, the subject and experimenter sat at opposite ends of a table about 3 feet (1 m) long, each facing an upright solid wooden panel about 2 feet (60 cm) high, set about 1 foot (30 cm) in front of the experimenter. On the subject's side, the dominant forearm (right, in all subjects) rested comfortably in semipronation (palm of hand down) on the table, with the distal phalanx of the middle finger on the head of a telegraph key, which was so adjusted that the weight of the finger alone closed the contact (45—55 gm required for closure). At eye level on the panel in front of the subject was mounted a small neon light bulb (NE 48), the flash of which served as a "warning" signal (see below). The apparatus for activating the neon bulb and after a slight delay, the auditory stimulus, together with a chronoscope for measuring reaction time, were mounted on the table on the experimenter's side. A mirror, mounted on the wall of the room above and behind the subject, enabled the experimenter to make sure that the subject was complying with instructions (see below).

The apparatus consisted of: a) A contact, which, when closed by the experimenter, produced a single flash of the neon bulb and at the same time activated a delay circuit which could be pre-set by the experimenter for intervals of 2, 3, 3.5, 5, 10 or 20 sec (means and standard deviations for a total of 27 trials on two occasions about three months apart during the course of the study, were 1.967 ± 0.014 sec, 3.476 ± 0.028 sec, 4.930 ± 0.040 sec, 10.164 ± 0.092 sec, and 20.142 ± 0.056 sec, respectively, as measured by a Hunter Chronoscope, Model 120A, "Klockmeter", Hunter Manufacturing Co., Iowa City, Iowa). b) An audiogenerator (Heathkit, Model AG-8, Heath Co., Benton Harbor, Michigan), connected to a speaker through an amplifier, which delivered a loud 480-cycle/sec pure tone beginning at the end of the pre-set delay interval

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and ending when the subject opened the telegraph key contact by lifting his middle finger (see below). Equipment for measuring the intensity of the auditory stimulus was not available when the study was made, but it was subsequently estimated at about 90 db as measured by the Sound Level Meter, Type 1551-B (General Radio Co., Concord, Massachusetts) at about 2 ft. (60 cm) from the listener. And c) a chronoscope (Hunter, see above) which measured RT to 1 msec from the onset to the termination of the auditory stimulus.

Treatments. The "normal" control (personnel) and chronic schizophrenic groups were studied only under "no treatment" conditions. On *two* separate occasions, not more often than one week apart, each of the "postaddicts" received each of the following treatments at the stated time prior to measurement of RT, in random sequence (except as noted below): a) placebo (0.9 percent sodium chloride solution) 1 ml i.m., one hour before; b) *d*-lysergic acid diethylamide tartrate (LSD-25)*, 1.0 and 2.0 mcg/kg in cherry syrup orally, 1.5 hours before; 5 of the "postaddict" subjects were also tested after administration of 3.0 mcg/kg of LSD-25, but because of the severity of the behavioral reactions in 2 of these, this dose was not administered to the other 5 subjects; in those that did received the 3.0 mcg/kg dose, the data on RT were pooled (averaged) with those obtained in the 2.0 mcg/kg dose, and for the whole group of 10 "postaddicts," the dose levels of LSD-25 are hereinafter designated as 1.0 mcg/kg and 2.0—3.0 mcg/kg; c) morphine sulfate, 15 and 30 mg i.m., one hour before; pentobarbital, 250 mg, i.m., 50 min before; d) racemic amphetamine sulfate, 20 mg and 30—50 mg i.m., one hour before (originally it was planned to use only a single dose of amphetamine, 20 mg; because of the paucity of detectable behavioral effects in most of the subjects, however, additional studies were made with 30, 40 or 50 mg, depending on the subject's degree of subjective reaction to the 20 mg dose). All treatments were carried out in a "single blind" manner (i.e., the experimenter knew, but the subjects were not told the nature of the treatment). However, it should be noted that all of the "postaddict" subjects had had previous experience with each of the drugs used (except in some cases, LSD-25), and were able to identify them by their effects on themselves (placebo was invariably reported as a "blank").

Procedures. Both the "irregular" and the "regular" procedures consisted of the presentation of a total of 100 flash-tone signals in five blocks of 20 successive trials, 5—10 sec elapsing between trials, with two-minute rest periods between blocks. In the "irregular" procedure, the sequence of intervals (2, 3.5, 5, 10 and 20 sec) between presentation

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* Supplies of LSD-25 were kindly furnished for this study by the Sandoz Pharmaceutical Company, Hanover, New Jersey, U.S.A.

of flash and tone was randomized within each block, but the total of 100 trials included 20 trials on each of the five intervals. In the "regular" procedure, the interval between flash and tone remained constant within a given 20-trial block, and the sequence of intervals from block to block was 3.5, 10, 5, 2 and 20 sec. In all tests, up to three repeat trials at a given flash-tone interval were given whenever a given RT exceeded 500 msec, and the shortest RT was entered as the datum for that trial.

Under each treatment condition (no treatment, placebo or drug), two orders of presentation of "irregular" and "regular" procedures were employed (on different days): a) the "standard" order, namely, "irregular" first and "regular" second, and b) the "reverse" order, namely, "regular" first and "irregular" second, with a 5-minute rest period between the two procedures on a given day in either case. Before the need for the "reverse" order became apparent, only the "standard" order was employed. For this reason, all of the control and schizophrenic subjects were tested first on the "standard," and later (up to six months) on the "reverse" order, whereas in the "postaddict" group, the sequence of "standard" and "reverse" orders was randomized.

Instructions to subjects. On the first test day, each subject was instructed as follows, when the "standard" procedure was employed, and with appropriate modifications when the "reverse" procedure was scheduled: (a) "irregular" procedure — "Take this seat and make yourself comfortable. Now place your right hand, palm down, on the table with middle finger on the key, and exert just enough pressure to hold it down steadily, like this (subject's finger is depressed passively). You may place your left hand wherever it's most convenient. Now, when I give the signal, this light bulb will flash. This indicates that you should listen for a tone, which will follow a short time later. The instant you hear the tone, lift your finger off the key completely, then place it back on the key again. Now let's have some practice (present 10 signals with random intervals between flash and tone). That's enough practice; now we're ready to start. Are you all set?" (b) "regular" procedure — "Now, in this part of the test, your part is exactly as before. Place your hand on the table, your middle finger on the key, watch for the light, listen for the tone and as soon as you hear it, lift your finger off the key and put it down on the key again. The difference is on my part; instead of the time interval between the light flash and the tone changing all the time, it will remain the same during any one series, and I will tell you before I change the time interval. Let's have some practice. Now I'm going to set the time at some particular interval and it will remain the same until I let you know. Are you ready? (present three signals with the 5-second interval). Now I'm going to change the time interval; are you ready? (present three signals with the 10-second interval). That's enough practice. Now we're ready to start. I'm going to set the time at a different interval and it will remain the same for this whole series. Are you all set?"

On subsequent test days, the subjects were told that the general procedure was the same as before, mentioning, however, whether in the first part of the test the intervals would "keep changing" or "remain the same". Practice trials were always given as on the first test day, during which

the experimenter made sure that the subject performed properly; if not, the instructions were repeated in detail, with as many additional practice trials as were needed.

Computations. For each subject under each treatment condition, mean RTs were computed for each flash-tone interval on the "irregular" and on the "regular" procedure in the "standard" and "reverse" orders separately, and for the two orders combined—i.e., the average mean RT on the two "irregular" and on the two "regular" procedures ("standard" and "reverse" orders). The "separate-order" data were used for evaluation of "order" effects ("irregular" procedure first, "regular" procedure second, *versus* "regular" procedure first, "irregular" procedure second), while the "combined order" data were used for evaluation of procedure effects ("irregular" *versus* "regular"), for evaluation of treatments (no medication, placebo and drugs with "irregular" and "regular" procedures) and for evaluation of "optimal" flash-tone intervals ("regular" procedure only).

For the purpose of statistical analysis, each RT (in msec) for every subject under each condition was transformed into its logarithm. For computational convenience, the number 2 was subtracted from the characteristic and this value was multiplied by 100. This "simple" transformation sufficed for all analyses restricted to a single group of subjects.

However, the "simple" transformation did not satisfy the criterion of homogeneity of variance between groups (especially between the schizophrenic subjects and the other two groups). For analyses of such data, reaction times were therefore transformed by a "complex" empirical formula,

$$\log\left[\left(\frac{\Sigma \log \mathrm{RT}}{N} - 2.30\right) \times 100\right] 10 + 200$$

where N is the number of trials for a given subject within the smallest cell of the analysis of variance employed. Additional statistical techniques, differing somewhat for various phases of the study, will be described in connection with the particular effects of interactions analyzed.

Other observations. In addition to measurements of reaction time, notes were made of the subject's behavior during the testing procedures, and after each day's testing was completed, a rough estimate was made of changes in pupillary size and kneejerk threshold. In addition, the subject was questioned about his "feelings," and when LSD-25 had been administered, he was required to complete the questionnaire devised by ISBELL et al. (1956), the positive responses on which were further elaborated by the subject in subsequent interrogations. In general, these additional observations yielded data on drug effects that were consistent

with those already described in the literature, and therefore no systematic analysis of them was made. Nor will they be discussed further in this report except to mention that, in the case of LSD-25, the effects ranged from Grades 1 to 3 (ISBELL et al. 1956), depending on the dose, with Grade 4 (hallucinations, delusions, etc. with apparent loss of insight) occurring on two occasions.

Results and Comments

A. Raw data

The raw data are presented in graphic form mainly for the purpose of examining gross trends, the statistical significance of which will be discussed in detail later. Mean RTs under no-medication or placebo conditions for control subjects (personnel), "postaddicts" and schizophrenic subjects, both on the "standard" and on the "reverse" order of procedures, are shown in Figs. 1, 2 and 3. For the control group "standard" order, "irregular" before "regular" procedure (Fig. 1), mean RTs are somewhat shorter than those found for normal control subjects in the study of HUSTON and SINGER (1945), but the shapes of the "irregular" and "regular" curves in the two studies are very similar, and in both the shortest RTs occur at the 2 sec interval on the "regular", and the longest RTs at the same interval on the "irregular" procedure. In the present study, reversal of the order of procedures ("regular" before "irregular", Fig. 1) resulted in some shortening of RTs generally, but the shapes of the curves remained much the same.

On the "standard" order of procedures, the "regular" curve for "postaddicts" (Fig. 2) is quite similar to that of personnel controls, but RTs on the "irregular" procedure were much shorter and the two curves are separated but little at any interval. In these subjects, reversal of the order of procedures resulted in some slowing of RTs on the "irregular" procedure and shortening of RTs on the "regular" procedure, thereby effecting a greater degree of separation of the two curves at all intervals. Curiously, reversal of the order of procedures also resulted in a shift of shortest reaction time from the 2 sec to the 3.5 sec interval.

As in the study of HUSTON and SINGER (1945), mean RTs of the schizophrenic group at all intervals were much longer than those of control subjects (or "postaddicts") on the "standard" order of procedures, but in the present study, the "irregular" and "regular" curves were more widely separated, and the shortest RTs occurred at the 3.5, rather than at the 2 sec interval (Fig. 3). In these subjects, reversal of the order of procedures resulted in shortening of RTs, especially in the "regular" procedure at the 3.5, 5 and 10 sec interval, thereby effecting a still wider separation of the two curves and accentuating the "dip" in the "regular" curve at the 3.5 sec interval (Fig. 3). The reasons for these differences in

the two studies are not clear, but they may be related to some differences in method, particularly with regard to the auditory stimuli used (buzzer in the study of HUSTON and SINGER 1945; loud pure tone, perhaps somewhat startling on first series of presentations, with adaptation later, in the present study).

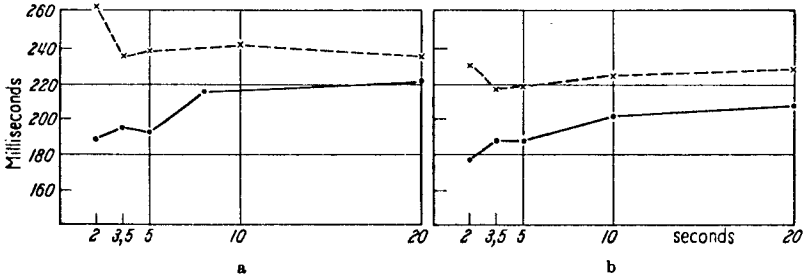

Fig. 1 a and b. Personnel Controls (N = 10); ---- irregular; —— regular. a irregular before regular; b regular before irregular

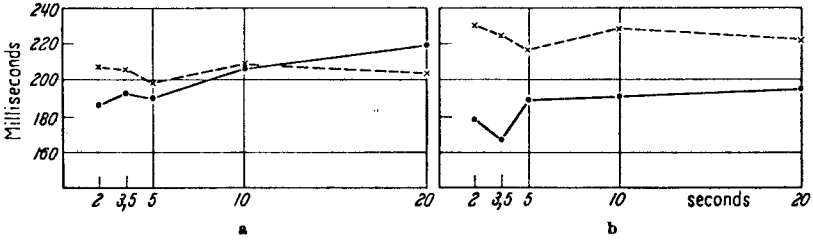

Fig. 2 a and b. Postaddicts (Placebo condition (N = 10); ---- irregular; —— regular. a irregular before regular; b regular before irregular

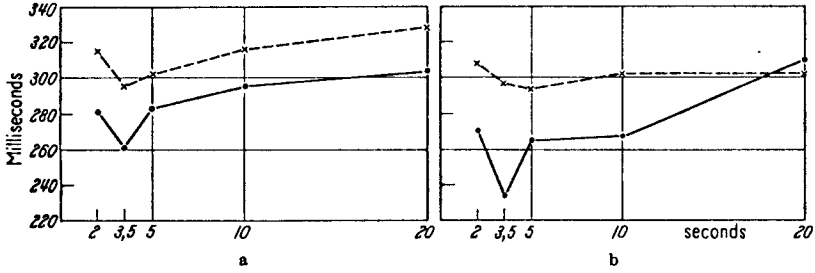

Fig. 3 a and b. Schizophrenic subjects (N = 13); ---- irregular; —— regular. a irregular before regular; b regular before irregular

"Irregular" and "regular" curves on "combined orders" of procedures for all groups under all treatment conditions are shown in Fig. 4. The general features of the "combined order" curves for personnel controls (no medication), "postaddict" (placebo) and schizophrenic subjects (no medication) are quite similar to those mentioned in connection with the

corresponding curves on the "standard" and "reverse" orders (see above). In doses of either 20 mg or 30—50 mg, amphetamine had no gross effect on RTs of "postaddicts" and the shapes of the curves remained much the same as under the placebo condition, except for the apparent "dip" in the "regular" curve at the 3.5 sec interval. At the 1.0 mcg/kg dose level, LSD-25 prolonged RTs moderately at all intervals on the "irregular" and only at some intervals on the "regular" procedure, thereby effecting

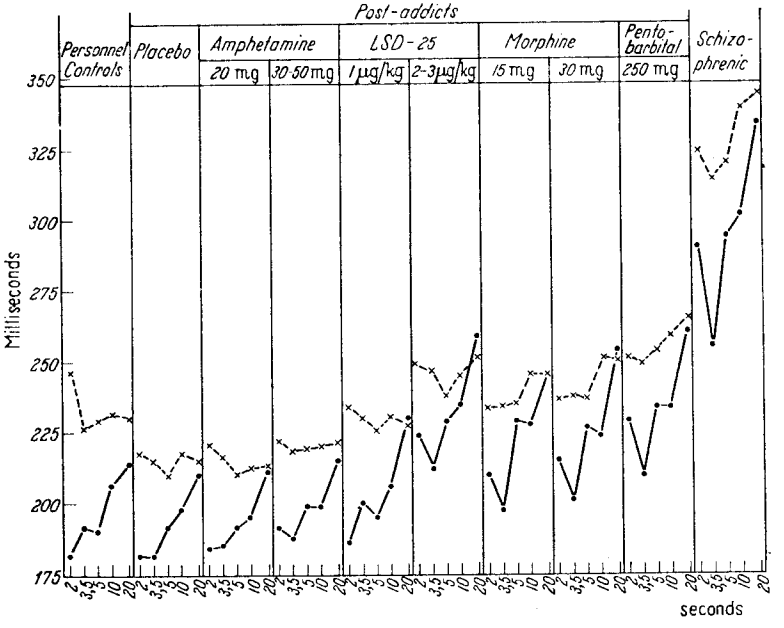

Fig. 4. All groups and conditions. Combined orders of procedure. ---- irregular; ——— regular

a wider separation of the two curves than obtained under the placebo condition, and a greater degree of resemblance to the curves of the personnel controls. At the 2.0—3.0 mcg/kg dose level, however, LSD-25 prolonged RTs markedly on both "irregular" and "regular" procedures, shortest RTs occurring at the 3.5 sec interval on the latter, so that the shapes of the "combined order" curves resemble those of the schizophrenic more than those of the personnel group. Surprisingly, the effects of morphine, 15 and 30 mg, and of pentobarbital, 250 mg, on RTs were at least qualitatively similar to those of LSD-25, 2.0—3.0 mcg/kg.

B. Statistical evaluations

1. Evaluation of "order" effects ("irregular" procedure first, "regular" second, *versus* "regular" first, "irregular" second). Since certain subject interactions were significantly different for the various groups, analysis

of variance (interval × procedure × order × subjects) were performed separately for each of the three groups (normal personnel, postaddict under placebo treatment, and schizophrenic) as described by LINDQUIST (1956), using the complex transformation of reaction times (see above). With this technique, it was found that the effect of reversing the sequence of presentation of "irregular" and "regular" procedures was statistically significant ($P < .05$) only in the schizophrenic group, though similar trends were noted in two other groups (Table 1, order). The nature of this order effect in all groups was revealed by two sorts of comparison: a) the mean reaction times on all trials in both the "irregular" and "regular" procedures were longer when the "irregular" procedure was presented first rather than second; and b) the mean reaction times on the "regular" (but not on the "irregular") procedure were shorter when the "regular" procedure was presented first rather than second. Again, these effects were significant only in the schizophrenic group (Table 1, order × procedure). The latter effect accounted for the greater separation of the "irregular" and "regular" curves (raw data) in the schizophrenic group when the test was conducted with reversal of the usual order of presentation of the two procedures. The reason for significance of such order effects in the schizophrenic group only was revealed by examination of the interactions, subjects × order, and procedure × order × subjects, the mean squares of which were much smaller in that group than in the normal personnel or postaddict (placebo) groups (Table 1), indicating that, in contrast to the latter two groups, the rank order of performance of the schizophrenic subjects remained relatively constant across procedures and orders.

Interpretation of such "order" effects is difficult because, for the reasons already mentioned, the control and schizophrenic subjects were always tested on the "irregular" first, "regular" second prior to testing on the "regular" first, "irregular" second orders of procedure, whereas in the postaddicts the sequence of orders of procedure was randomized. Therefore, practice effects could have operated in the control and schizophrenic groups. Since the main effect of "order" was non-significant in the control group, it may be inferred that practice effects were negligible in these subjects, but such is not the case for the schizophrenic subjects for whom the "order" effect was significant (Table 1). Possibly, practice effects are more apt to be revealed when RTs are longer (schizophrenic subjects) than when RTs are relatively short (control subjects). On the other hand, "fatigue" may also have operated in the schizophrenic subjects since the "order × procedure" interaction was significant only for that group (Table 1), indicating that in these individuals, RTs on the "regular" procedure in particular are shorter when this is the first procedure given on the test day (cf. Fig. 3).

Table 1. *Analysis of variance of reaction time ("complex" transformation) for personnel, postaddicts (placebo) and schizophrenics*

Source of Variance	Personnel			Postaddicts (Placebo)			Schizophrenics		
	df	MS	F	*df*	MS	F	*df*	MS	F
Order[1]	1	42.32	.49	1	14.58	.26	1	72.19	5.87*
Interval	4	154.22	11.79**	4	56.58	3.26*	4	94.10	6.81**
Procedure	1	3088.98	34.26**	1	890.42	31.69**	1	540.87	14.76**
Order × interval	4	2.68	.32	4	4.88	.41	4	5.74	.84
Order × procedure	1	6.48	.12	1	131.22	2.40	1	140.31	12.99**
Interval × procedure	4	77.74	5.62**	4	23.12	2.06	1	95.41	7.32**
Order × interval × procedure	4	36.27	2.69*	4	16.82	1.61	4	20.20	3.96**
Subjects	9	506.92		9	1006.30		12	544.82	
Order × subjects	9	86.49	6.42**	9	56.84	5.43**	12	12.39	2.41*
Interval × subjects	36	13.08	.97	36	17.34	1.66	48	13.82	2.71*
Procedure × subjects	9	89.90	6.67**	9	28.40	2.69*	12	36.65	7.19**
Order × interval × subjects	36	8.25	.61	36	11.88	1.14	48	6.86	1.34
Order × procedure × subjects	9	55.31	4.10*	9	54.72	5.23*	12	10.82	2.12**
Interval × procedure × subjects	36	13.84	1.03	36	11.24	1.07	48	13.03	2.56*
Order × interval × procedure × subjects	36	13.48		36	10.46		48	5.10	
Total	199	63.42		199	68.28		259	41.44	

[1] "Order" refers to "Irregular" first, "Regular" second *versus* "Regular" first, "Irregular" second. — * $P < .05$. — ** $P < .01$.

2. Evaluation of procedure effects ("irregular" *versus* "regular"). The analysis of variance (intervals × procedure × order × subjects, using the "complex" transformation of reaction times) for each of the three groups separately also revealed that in each group, the procedure effect was significant—i.e., over all intervals combined, mean RTs were longer on the "irregular" than on the "regular" procedure (Table 1, procedure). However, the procedure effect was very much greater in the personnel control than in the schizophrenic group (variance estimates, 3089 and 541, respectively), in agreement with the findings of other investigators who concluded that the schizophrenic patient is less able than normal individuals to improve performance (RT) on regularization of the foreperiods. Surprisingly, however, the procedure effect in the postaddict (placebo) group was only slightly greater (variance estimate, 890) than in the schizophrenic subjects. Possibly, the greater speed of reaction of the postaddict (placebo) group, which in the case of the "irregular" procedure exceeded that of the personnel control group (Fig. 2), set limits on the extent to which reaction times could be facilitated by regularization of the foreperiods.

3. Evaluation of treatments, procedures, intervals and groups (combined order data). A "global" analysis of variance (treatment × procedure × interval × subjects) on the data ("simple" transformation of RTs) obtained in the postaddict group alone, revealed that all the sources of variance were significant except for the treatment × procedure interaction (Table 2). To delineate these sources of variation more clearly, and to relate the changes in RT produced by drugs in postaddicts to the values found in the normal personnel and schizophrenic subjects, similar analyses of variance were applied to the data ("simple" transformation of RT) obtained in the normal personnel and also in the schizophrenic group, and "*t*" tests were made on certain of the differences of the means which were found between postaddicts under various drug treatments and those of the normal personnel and schizophrenic groups, using the estimation test developed by LINDQUIST (loc. cit.) with employment of separate error terms for replicated and independent samples. These analyses revealed the following:

a) The main effect of procedure was significant in each group (Table 1)—i.e., mean RTs on the "irregular" procedure at all intervals combined and under all treatments combined ("postaddicts," Table 2) were always longer than on the "regular" procedure.

b) The main effect of interval was significant in personnel controls, in "postaddicts" under all treatment conditions combined, and in the schizophrenic subjects—i.e., mean RTs (*"irregular" and "regular" combined*) were shortest at the 3.5 sec interval and longest at the 20 sec interval; (Tables 1 and 2, interval; cf. also Fig. 4).

Table 2. *Analysis of variance for the postaddict group*[1] (combined order data, "simple" transformation)

Source of Variance	*df*	SS	MS	F
Treatment	7	5956.16	850.88	9.24**
Interval	4	1661.97	415.49	19.63**
Procedure	1	3486.13	3486.13	46.52**
Treatment × interval	28	311.43	11.12	2.50**
Treatment × procedure	7	158.27	22.61	1.23
Interval × procedure	4	1033.93	258.48	15.40**
Treatment × interval × procedure	28	201.27	7.19	1.76*
Subjects	9	26402.91	2933.66	
Treatment × subjects	63	5799.69	92.06	22.56**
Interval × subjects	36	762.13	21.17	5.19**
Procedure × subjects	9	674.37	74.93	18.36**
Treatment × interval × subjects	252	1120.47	4.45	1.09
Treatment × procedure × subjects	63	1161.83	18.44	4.52**
Interval × procedure × subjects	36	604.07	16.78	4.11**
Treatment × interval × procedure × subjects	252	1027.13	4.08	
Total	799	50361.76		

[1] All treatment conditions combined. — * $P < .05$. — ** $P < .01$.

c) The interval × procedure interaction was significant in personnel controls, "postaddicts" under all treatment conditions combined, and in the schizophrenic subjects—i.e., relative to RTs on the "irregular" procedure, RTs on the "regular" procedure were shortest at the 3.5 sec, and longest at the 20 sec interval (Tables 1 and 2; cf. also Fig. 4). Such, however, was not the case to a significant degree in "postaddicts" under the placebo condition alone (Table 1, interval × procedure), probably because of their "supernormally" short RTs (Table 3) even on the "irregular" procedure (Fig. 2).

d) Over-all RTs ("irregular" and "regular" at all intervals combined) were longest in the schizophrenic group, and shortest in the postaddict group under amphetamine, 20 mg (Table 3). Mean RTs of schizophrenic patients were significantly longer than those of "normal" subjects and of postaddicts under placebo, amphetamine, morphine and LSD-25, 1.0 mcg/kg, but not under pentobarbital or LSD-25, 2.0—3.0 mcg/kg. Mean RTs of normal personnel did not differ from those of postaddicts under any treatment. In postaddicts, mean RTs were prolonged significantly by morphine (15 and 30 mg), pentobarbital (250 mg) and LSD-25 (1.0 and 2.0—3.0 mcg/kg) as compared with RTs under placebo or amphetamine (20 and 30—50 mg) treatments.

e) Though all drugs except amphetamine prolonged RTs, there was no evidence of differential effects on the "irregular" and "regular" procedures (Table 2, treatment × procedure). However, "*t*" tests revealed that for all intervals combined, the index, I-R (difference of mean RT on the two procedures), of postaddicts treated with LSD-25, 1.0 mcg/kg could not be differentiated from the index of normal personnel, which, in turn, could otherwise be differentiated from the index of all other groups under all other treatments (Table 4). This finding is consonant with the impression gathered from the raw data, indicating that, with respect to this index, the smallest dose of LSD-25 used (but not the higher doses) "normalized" the postaddict subjects. The high significance of the difference in the index, "I-R" between personnel control and schizophrenic subjects is in accord with the findings of previous investigators (see SHAKOW 1963).

f) "*t*" Tests on the index, I-R, at the 2 sec interval alone revealed (Table 5) that the LSD-25, 1.0 mcg/kg condition could be clearly differentiated from the morphine (30 mg), pentobarbital (250 mg), and LSD-25 (2.0—3.0 mcg/kg) conditions, whereas under the latter three conditions, postaddicts could not be differentiated from the schizophrenic subjects. Furthermore, under the LSD-25, 1.0 mcg/kg condition, postaddicts could not be differentiated from normal personnel, while the latter could be differentiated from all other groups and treatment conditions. The lack of statistical significance of the differences in index I-R, between the schizophrenic and postaddict subjects under any treatment condition appears to be due, at least in part, to the much greater variability of reaction times in the former group. Inspection of the actual differences in I-R between the schizophrenic subjects and postaddict treatment conditions reveals that for postaddicts under LSD-25, 1.0 mcg/kg, the difference (−4.2) was at least as large as several of the differences with postaddicts under other treatment conditions that were statistically significant.

4. Evaluation of "optimal" foreperiod (interval). To isolate further the significance of the results of the higher order interaction analyses (group × interval × procedure), some comparisons were made of mean RTs at the 2 and 3.5 sec intervals on the "regular" procedure. These revealed that when data for postaddicts under LSD-25, 2.0—3.0 mcg/kg and for schizophrenic subjects are combined, the mean reaction time at the 3.5 sec interval is significantly shorter than at the 2 sec interval ($F = 4.48$, $df = 1/21$, $P < .05$). Using the error term for the interval × group interaction established between postaddicts on the LSD-25, 2.0 to 3.0 mcg/kg condition and schizophrenic subjects, this difference between reaction times at the 2 and 3.5 sec interval is also significant for postaddicts under morphine (15 and 30 mg) and under pentobarbital treat-

Table 3. *Mean reaction times ("simple" transformation), differences and "t" values*

Groups or Treatments	Mean	Pe[1]	Sc	Pl	M15	M30	Pb	L1	L2—3	A20	A30—50
Personnel-no medication (Pe)	20.79		3.79*	.98	.79	.88	1.61	.28	1.43	1.19	.73
Schizophrenics -no medication (Sc)	28.90	−8.11		4.18*	2.35*	2.25*	1.50	2.88*	1.69	4.40*	3.92*
Postaddicts-placebo (Pl)	18.19	2.60	10.71		4.81*	5.06*	7.04*	3.43*	6.54*	.57	.69
Postaddicts-morphine 15 mg (M15)	22.88	−2.09	6.02	−4.69		.26	2.23	1.37	1.73	5.38*	4.12*
Postaddicts-morphine 30 mg (M30)	23.13	−2.34	5.77	−4.94	− .25		1.98	1.63	1.48	5.64*	4.38*
Postaddicts-pentobarbital 250 mg (Pb)	25.06	−4.27	3.84	−6.87	−2.18	−1.93		3.61*	.50	7.61*	6.35*
Postaddicts-LSD-25, 1.0 mcg/kg (L1)	21.54	− .75	7.36	−3.35	1.34	1.59	3.52		3.10*	4.01*	2.75*
Postaddicts-LSD-25, 2.0—3.0 mcg/kg (L2—3)	24.57	−3.78	4.33	−6.38	−1.69	−1.44	.49	−3.03		7.11*	5.85*
Postaddicts-Amphetamine, 20 mg (A20)	17.63	3.16	11.27	.56	5.25	5.50	7.43	3.91	6.94		1.26
Postaddicts-Amphetamine 30, 40, 50 mg (A30—50)	18.86	1.93	10.04	− .67	4.02	4.27	6.20	2.68	5.71	−1.23	

Differences

"t" Values

[1] Differences refer to column headings minus row headings — e.g., Personnel (column) minus schizophrenics (row) is −8.11, indicates that mean reaction time for personnel is shorter than for schizophrenics (20.79 *versus* 28.90).

* $P < .05$.

Table 4. *Differences in mean reaction time ("simple" transformation), "Irregular" minus "Regular" for all intervals combined (I—R): Means of I—R, differences in I—R between groups and treatments, and "t" values*

Groups or Treatments	Mean	Pe[1]	Sc	Pl	M 15	M 30	Pb	L 1	L 2—3	A 20	A 30—50
Personnel-no medication (Pe)	8.94		3.55*	2.76*	2.51*	2.74*	3.04*	1.58	3.38*	2.15*	2.40*
Schizophrenia-no medication (Sc)	2.97	5.97		.77	1.13	.80	.37	2.47*	.12	.93	1.29
Postaddicts-placebo (Pl)	3.94	5.00	— .97		.54	.05	.58	2.49*	1.30	.23	.77
Postaddicts-morphine, 15 mg (M15)	4.40	4.54	—1.43	— .46		.49	1.12	1.96	1.84	.30	.23
Postaddicts-morphine, 30 mg (M30)	3.98	4.96	—1.01	— .04	.42		.63	2.45*	1.35	.19	.72
Postaddicts-pentobarbital, 250 mg (Pb)	3.44	5.50	— .47	.50	.96	.54		3.08*	.72	.82	1.35
Postaddicts-LSD-25, 1.0 mcg/kg (L1)	6.08	2.86	—3.11	—2.14	—1.68	—2.10	—2.64		3.80*	2.26*	1.72
Postaddicts-LSD-25, 2.0—3.0 mcg/kg (L2—3)	2.82	6.12	.15	1.12	1.58	1.16	.62	3.26		1.54	2.07
Postaddicts-Amphetamine, 20mg (A20)	4.14	4.80	—1.17	—.20	.26	— .16	— .70	1.94	—1.32		.54
Postaddicts-Amphetamine, 30, 40, 50 mg (A30—50)	4.60	4.34	7.63	—.66	— .20	— .62	—1.16	1.48	—1.78	— .46	

"t" Values

Differences

[1] Differences in I—R refer to column headings minus row headings — e.g., Personnel (column) minus Schizophrenia (row) is 5.97 indicating that mean I—R for Personnel is greater than for Schizophrenics (8.94 *versus* 2.97).

* $P < .05$.

Table 5. *Differences in mean reaction time ("simple" transformation), "Irregular" minus "Regular" for the 2-second interval only (I—R): Means of I—R, differences in I—R between groups and treatments, and "t" values*

Groups or Treatments	Mean	Pe[1]	Sc	Pl	M 15	M 30	Pb	L 1	L 2—3	A 20	A 30—50
Personnel-no medication (Pc)	14.2		3.78*	3.03*	2.99*	3.93*	3.97*	1.97	3.52*	2.58*	3.07*
Schizophrenia-no medication (Sc)	5.2	9.0		.74	.79	.28	.32	1.94	.18	1.25	.69
Postaddicts-placebo (Pl)	6.8	7.4	−1.60		.08	1.82	1.91	2.15	.99	.91	.08
Postaddicts-morphine, 15 mg (M 15)	6.9	7.3	−1.70	−0.10		1.90	1.99	2.07	1.08	.83	.17
Postaddicts-morphine, 30 mg (M 30)	4.6	9.6	.60	2.20	2.30		.08	3.98*	.83	2.73*	1.74
Postaddicts-pentobarbital, 250 mg (Pb)	4.5	9.7	.70	2.30	2.40	.10		4.06*	.91	2.82*	1.82
Postaddicts-LSD-25, 1.0 mcg/kg (L 1)	9.4	4.8	−4.20	−2.60	−2.50	−4.80	−4.90		3.14*	1.24	2.24
Postaddicts-LSD-25, 2.0—3.0 mcg/kg (L 2—3)	5.6	8.6	− .40	1.20	1.30	−1.00	−1.10	3.80		1.91	.91
Postaddicts-amphetamine, 20 mg (A 20)	7.9	6.3	−2.70	−1.10	−1.00	−3.30	−3.40	1.50	−2.30		.99
Postaddicts-amphetamine, 30, 40, 50 mg (A 30—50)	6.7	7.5	−1.50	.10	.20	−2.10	−2.20	2.70	−1.10	1.20	

Differences

"t" values

[1] Differences in I—R refer to column headings minus row headings — e.g., Personnel (column) minus Schizophrenics (row) is 9.0, indicating that mean I—R for Personnel is greater than for Schizophrenics (14.2 *versus* 5.2).

* $P < .05$.

ment, when the data for these treatments are combined with those of the schizophrenic subjects. On the other hand, such an interval effect was not found in analyses in which normal personnel and postaddict (placebo) subjects were combined into one group, indicating that no such trend appeared in these two groups. In contrast, mean RT at the 3.5 second interval was significantly shorter than at the 2 sec interval for the schizophrenic group when compared with the combined normal personnel and postaddict groups.

Discussion

The answer to the question that originally prompted these studies—"Does LSD-25 specifically produce a 'schizophrenic-like' change in the 'mental set' of non-psychotic subjects?"—is rather complex. On the basis of our "combined order" data, patients with chronic schizophrenia could be distinguished from personnel control subjects and from "post-addicts" (placebo condition) in three ways: a) slowest RTs (both "irregular" and "regular"); b) shortest RTs at the 3.5 sec interval ("regular" procedure) and c) smallest difference between mean RTs on the "irregular" and the "regular" procedures (all intervals combined). Compared with the values obtained under the placebo condition, over-all mean RTs were significantly prolonged, and shortest RTs tended to occur at the 3.5 second interval in "postaddicts" after administration of LSD-25, 2.0—3.0 mcg/kg. However, evaluation of the "I-R" criterion of "schizophrenic-like" change is difficult because under the placebo condition, this source of variance (main effect of procedure) in "postaddicts" was much smaller than in personnel control subjects and only slightly greater than in the schizophrenic subjects, and it could hardly be expected that any drug would reduce the variance ascribable to the difference in procedure still further. Nevertheless, it can be argued that the failure of LSD-25, 2.0—3.0 mcg/kg to *increase* the value of "I-R" in spite of significant slowing of RTs, constitutes indirect evidence of impairment of the ability to profit from regularization of preparatory intervals, since the small value of "I-R" in "postaddicts" under the placebo condition is clearly due, not to impairment of "mental set", but to "supernormally" short RTs on the "irregular" procedure. In support of this contention is the finding that by a predominant effect (slowing) on mean RTs on the "irregular" procedure, the lower dose of LSD-25 (1.0 mcg/kg) "normalized" the relationship between the "irregular" and "regular" curves in "postaddicts". It may be concluded, therefore, that in the higher dosage (2.0—3.0 mcg/kg), LSD-25 does produce "schizophrenic-like" change in "mental set" by all three criteria.

On the other hand, very similar changes in "mental set" (all three criteria) were also produced by the non-psychotomimetic drugs, morphine

and pentobarbital. From these findings, it may be concluded that the disturbance in "mental set" characterizing chronic schizophrenia can be produced, at least to some degree, by diverse etiological factors which, operating alone, are not necessarily "psychotogenic". Among these may be considered alteration of perception, bodily feelings, motivation and motor efficiency—effects common to all the drugs used in this study in varying kinds and degrees (HILL et al. 1963). Such relative etiological non-specificity is suggested also by the evidence for impairment of "mental set" in psychoneurotic and depressive patients as well as in early schizophrenia, reported by HUSTON and SENF (1952). What appears to distinguish chronic schizophrenia from all the other conditions discussed is the degree of impairment of "mental set," rather than its quality.

In contrast to LSD-25, morphine and pentobarbital, even relatively high doses of amphetamine did not impair "mental set"; indeed, this drug had little action except to shorten RTs to some extent. This finding suggests that whatever the changes in "internal" conditions produced by amphetamine may be, they are not of the sort produced by the other drugs investigated, or shared by the patients in the psychiatric classifications mentioned.

Summary

1. Auditory-manual reaction times, 2, 3.5, 5, 10 and 20 sec after flashing of a "warning" light, both on "irregular" and "regular" schedules of preparatory intervals, were measured under "no medication" conditions in 10 personnel control and 13 chronic schizophrenic subjects, as well as in "postaddicts" after administration of placebo, LSD-25, morphine, pentobarbital or amphetamine.

2. Each subject was tested twice under each condition (no medication, placebo or drug) on different days, once with the "irregular" procedure preceding the "regular," and again in the reverse order. Comparisons of the effects of treatment (placebo or drugs) on mean reaction times of "postaddicts" with mean reaction times of personnel controls and schizophrenic subjects were based on the "combined order" data (average of the two "irregular" and the two "regular" data under each condition).

3. Compared with personnel controls, mean reaction times of chronic schizophrenic subjects were significantly longer, variance due to difference in procedure ("irregular" or "regular") was significantly smaller, and shortest reaction times tended to occur at the 3.5 sec interval (rather than at the 2 sec interval).

4. In the "postaddict" group under the placebo condition, mean reaction times on the "irregular" procedure were shorter than in the personnel control group, with consequent reduction of variance due to difference in procedure. At a dose level of 1.0 mcg/kg, LSD-25 prolonged

reaction times on the "irregular" procedure, thereby "normalizing" the relationships between the "irregular" and "regular" curves.

5. LSD-25 at the dose level of 2.0—3.0 mcg/kg, morphine (15 and 30 mg), and pentobarbital (250 mg) all prolonged reaction times significantly and produced a trend for occurrence of shortest reaction times at the 3.5 sec interval on the "regular" procedure. While these treatments did not affect reaction times on the "irregular" and "regular" procedures differentially, indirect evidence suggests that they did impair the ability of "postaddicts" to profit from regularization of the presentation of preparatory intervals. Amphetamine had no effect except to shorten reaction times to some extent.

6. It is concluded that LSD-25 (2.0—3.0 mcg/kg), morphine and pentobarbital produce changes in "mental set" qualitatively similar to that which characterizes patients with schizophrenia, but that the nature of such impairment is not specific for schizophrenia, except possibly in degree.

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