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Some Observations Suggesting Preservation of Skilled Motor Acts despite Drug-Induced Stress*

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Summary. Measures of skilled motor performances, both of a task-oriented (tests of eye-hand coordination) and incidental (control of facial and ocular muscles) nature were recorded for a sample of 20 healthy young adults before and after single administrations of perphenazine, opipramol, imipramine and placebo at dose-levels commonly supposed to produce mood or behavioral effects. It was anticipated that such performances would be sensitive even to slight changes in the subjects' physiological and psychological state; the aim was to test the power of tests of subtle skills in providing indices of slight to moderate behavioral effects.

The performance measures remained surprisingly little affected by all drugs, despite their sensitivity to drug-independent improvement in performance throughout the experimental day, and despite evidences of drug-related effects, especially for imipramine and opipramol, in simple objective physiological measures, and for imipramine alone in subjective measures taken concurrently.

There may be a class of skilled sensory-motor acts, particularly those related to well-learned daily activities, which, rather than being vulnerable to adverse effect, remain efficient even in the presence of signs of disturbance of bodily function.

Key-Words: Motion Pictures — Motor Skills — Eye Movements — Psychopharmacology — Psychological Tests.

The normal routine of the day requires skilled sensory-motor coordinations which are at once subtle, numerous, and usually beneath notice. Picking up and putting down, writing, scanning a paper and even communicating by gesture and facial expression are complex performances taken for granted. A high level of efficiency is expected, at least in the adult person. We become annoyed by error in ordinary acts, especially by repetitive mistakes; we may infer some disorder or even motivated

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erring when a person trips over his tongue or upsets a glass. On the one hand, we expect a sustained level of achievement and are intolerant of lapses; on the other hand we implicitly recognize that skilled performance is susceptible to disruption by slight disorder.

The delicacy and speed of performance of many ordinary acts suggests a finely-tuned apparatus which is also fragile and easily upset. SMITH and SMITH (1962) have found that a delay of half a second in visual feedback adversely affects ability to trace geometric patterns manually; similar effects upon speech have been produced by delayed auditory feedback. Perhaps, as is a common conception in pharmacological and psychiatric investigation, minute departures from ordinary levels of performance are useful as signs that subtle disorders are present and as clues to the nature of the disorders. The contrary notion, that well-learned skillful performances are relatively isolated from bodily and psychological distress, has received little attention.

We began the present investigation with the speculation that a sampling of fine sensory-motor coordinations of everyday occurrence could provide a basis for classifying severity of stress. The degree or the order of production of small inefficiencies would, we surmised, permit us to sort various stressors, including behavior-altering drugs, on a common basis (HEIMANN, 1964, 1966; HEIMANN and LUKACS, 1965). At the very outset, the problem arose as to how it would be possible to produce slight, rather than gross stress: the subjects were not to become too ill to proceed or to care. We chose common dose-levels for three drugs purported to affect mood or attention and, as subjects, normal and able young adults. The brief inventories of physiological and subjective states, which were taken concurrently with the performance tasks, showed mixed success in reaching the goal of producing mild distress, as will be seen below. But in the course of the investigation, we observed that, rather than being good candidates for indices of subtle stress, ordinary skilled acts may be relatively immune from disruption. Efficient perceptual and motor performance appears to survive at least minor aberrations in the mechanisms underlying them. That is, the subjective and physiological states of the subject reflect disturbance, but motor efficiency is retained.

Methods

The subjects of the experiment were 20 graduate and medical students of both sexes between the ages of 20 and 25. They were informed that effective psychopharmacological agents would be used, and were paid 120 Swiss francs if they completed four separate days of experiment.

Between two and four subjects underwent the experiments each day. Having breakfasted before arrival, they appeared at the laboratories between 8 and 9 A. M. and the procedures were begun immediately. Each

series of tests took 45 minutes. The subjects were separated by 15-minute intervals. Immediately following completion of the first series of tests, the subject was given a drug or placebo orally. The identity of the substance was unknown both to subject and to the testers. A second series of tests followed for the subject one hour after he had received the substance, three hours after drug-administration (following a light lunch provided in the laboratory) and five hours after taking the drug. The subjects remained in the laboratories between the four test-sessions; they were permitted to read and occasionally to stroll in the courtyard, but were prevented from communicating with each other and other people.

A balanced order of presentation of drugs was used; five subjects received Substance A on their first day, five subjects received Substance B on their first day, five received Substance C and five Substance D. The alphabetic order, however, was maintained: the possible order of administrations were ABCD, BCDA, CDAB and DABC. For a given subject, at least three days intervened between each experimental series, to allow for dissipation of drug effects.

An IBM 620 computer was programmed to perform a three-fold (subject by drug by test) analysis of variance for correlated means for each measure. Main effects of drug and test sessions were tested against the two-fold interaction variance estimates. Significance was set at the 0.01 level but since 50 or so measures were subjected to analysis, the true level of significance is effectively less stringent than 0.01. When it was necessary to interpolate values—for instance when film-recording failed—the interpolated value was set at the mean of the obtained values. In addition to the analyses of variance, chi-square tests were employed for one of the subjective measures, since test scores consisted of category counts (Yes-No, Plus-Minus, for example). It was not apparent that Type 1 errors were more significant than Type 2 or vice versa.

Three kinds of measures were taken at each session: (1) objective measures of physiological function (2) subjective measures and (3) performance measures. In the following account we will use the term "objective" to refer to the first set of measures for the sake of convenience; the performance measures were also objective.

Objective (Physiological) Measures

1. Heart rate (frequency of heart beat).
2. Systolic and diastolic blood pressure.

Subjective Measures

A 32 question inventory of the subjective state of the subject was employed. The content of the questionnaire can be subdivided into the following categories; perception, mood, memory, ability to concentrate,

motor skill and tone, symptoms of the autonomic nervous system, and general change in bodily feeling. Questions and answers were recorded on tape and later response to a question was assigned to one of three categories: zero = no change; plus = positive change or condition (feeling wide-awake, better able to concentrate, increased state of well-being); minus = negative change or condition. A chi-square analysis was performed for each of the four conditions.

Performance Measures

The first two measures listed represent a borderline between performance and objective physiological measures; they were listed in this section because both contain elements of conscious intention, i.e. they are under the voluntary control of the subject.

1. Quantitative analysis of facial movements. 16 mm sound films were taken as the subjects answered a standard set of questions; a telescopic lens provided a close-up view of the face. Motion of the head, unless markedly away from the frontal plane, could be compensated by shifting the coordinate frame, maintaining reference points on the inner canthi. Since the subject was facing the interviewer (and hence the camera lens situated behind the interviewer), no difficulty in meeting this requirement was met. On every 10th frame of the film the following measures were taken: vertical and horizontal position of the inner brow tips and corners of the mouth (measured in relationship to coordinates oriented on the immovable parts of the face so as to eliminate variance due to movement of the head); eight movement quotients derived from change in the foregoing positions; four symmetry coefficients derived from covariant shifts in position. Of each film strip, 40 frames were measured, which corresponds to a total sample of 16.9 seconds of time (Heimann, 1966; Heimann and Lukacs, 1966).

2. Eye movements were recorded in film by amplifying the voltage changes in a photocell whose field covered the margin of iris and sclera of the subject's eyeball (Biosystems Eye Movement Monitor). Horizontal movement of the eye displaced the iris and hence changed the relative amount of light entering the cell. Calibration was based upon the subject's successive fixation on measured positions left and right of center. Evaluation of the film record included: stability of fixation; number of fixations, in unit time; rapidity of movement between fixations; and amplitude of movement during the standard visual task whose description immediately follows.

3. Pattern-recognition. The subject inspected a series of projected slides of square patterns of dots arranged in vertical or horizontal bars. The task was to detect the orientation of the bars formed by the clusters of dots; the difficulty of the task depended upon the relative

density of the dots in adjacent bars. Such visual displays have been proposed to represent the essential visual task in the hidden or embedded figures tests. Ten displays of different difficulty and one with a random distribution of dots were presented at each testing session. The number of correct responses, by difficulty level, and as an overall score, was counted for each trial (REED and POLLACK, 1965).

4. Meili-cancellation test (MEILI, 1951).

5. Word fluency (tested by asking the subject to say in 30 seconds as many words starting with a given letter as he could). The initial letters were not randomized.

6. Digit span. The number of digits successfully repeated after forward and backward presentations (WECHSLER, 1958).

7. Arm-hand steadiness. The subject traced a circular groove with a stylus; number and distribution of contacts with sides of the channel was automatically recorded (FLEISCHMAN, 1954; Factor *V* is the measure used).

8. Overcharge and recovery reaction, measured with stimulus-reaction apparatus of von Mierke. Stochastic sequences of colored light stimuli, sound signals, and left-right white light signals were presented at prescribed rates. The subject activated matching color keys for the color stimuli, specific levers for high and low notes, and right and left footpedals for the right and left white lights. After an adaptation phase, an over-charge was created by sudden increase in the rate of presentation of stimuli. The distress thus produced was followed by presentation at the original rate, in order to measure recovery reaction (HEIMANN and LUKACS, 1965).

9. Eye-hand coordination in copying a geometric pattern (the pattern is shown in Fig. 1). Subjects were required (after initial practice) to copy

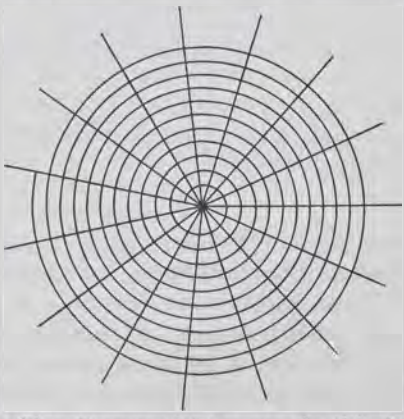

Fig. 1. This figure with a diameter of 17 cm was placed in front of each subject, who was instructed to copy the pattern "as closely as possible" according to certain rules. The first evaluated drawing was always preceded by 2 trials

the pattern as closely as possible, following certain rules of execution (starting position, paper-rotation, etc.) to ensure comparability of product. Computer analysis of selected data-points on the drawing provided comparison of 3 sets of measures (several components in each set): size, shape, and regularity or precision of placement of lines (Reed *et al.*, 1965).

Drugs

In order to sample a wide array of reactions without complex and variable methods for provoking stress, we chose three drugs from those purported to produce behavioral alterations, and administered them in single, standard doses. Three psychopharmacological agents with predominant effects on motor behavior and viligance were selected. Giving a chemical substance at a given time under standard circumstances seemed to us a well-defined way of setting a stress. We selected a level at one third of the usual daily dose.

Perphenazine (Trilafon) is a phenothiazine tranquilizer for which the claim is made that it has a strong antipsychotic effect and minimal sedative properties, in addition to extrapyramidal, hypotensive and strong anti-emetic effects (Bente *et al.*, 1964). The dose used in the experiment was 10 mg per os; clinically it is usually given in a single dose of 5—10 mg intramuscularly.

Imipramine (Tofranil) is a dibenzazepine similar to promazine except for the linkage between the two benzene rings. It is given in the treatment of depression and has strong atropine-like but no euphoriant effects in healthy subjects. It produces orthostatic hypotension and frequently fine tremor. It was given in a dose of 75 mg per os.

Opipramol (Insidon) is a tranquilizer reputed to possess anti-depressant properties, with a chemical structure related to the other drugs in an intermediate fashion. The dose administered was 75 mg per os.

In order to obtain comparable psychological circumstances for the drugs, placebo was administered.

Results

Performance Changes (Subjective and Objective) throughout the Day

Regardless of the substances given the subjects, the analyses of variance yielded main effects to be attributed to time of day. The pulse rate was significantly lower for the second session (one hour after drug-administration a mean of 67) for all conditions as compared to the first session (mean 72). No similar time-related effect was noted in the

subjective reports, but objective measures of performance showed a number of changes:

The total time taken for the Meili-cancellation test dropped significantly between the first (mean 243 sec) and second (mean 220 sec) testings.

Measured by the criterion of number of correct responses, performance on the stimulus reaction test improved significantly from the first session (mean 148.37) to the fourth session (mean 154.34).

Subjects recalled more (a mean of 16.2) words in the word-recall task in the later testing sessions, as compared to 14.6 in the first sessions.

The drawing test took a significantly longer time to perform in each initial morning trial (101 sec) than it did in subsequent trials (93 sec: 2. + 3. + 4. trial).

Two measures of facial expression showed change. The movement quotient for the mouth corners (for vertical directions) became significantly smaller from the first to the third testings (mean of 0.46, 0.43, and 0.41 respectively). The symmetry coefficient of the corners of the mouth decreased significantly from the first session (mean 0.86) to the third session (mean 0.78).

In general, the change in the performance measures can be understood as evidence of increased efficiency or, particularly in the case of the facial measures, as signs of adaptation to the experimental situation (HEIMANN, 1966).

Possible longer term effects, if they occurred, are obscured in this analysis; for a given substance, the data represent the first day's testing for one-fourth of the subjects, the second day's testing for one-fourth, and so on. It is against the background of diurnal change, however, that the particular effects of the drugs have to be assessed.

Changes Particular to the Substance

Placebo Effects. If evaluated against morning-control, no objective changes in performance occurred specific to the placebo. Nor were physiological measures altered.

The questionnaire yielded two reports which occurred significantly more often with placebo than with any of the three active substances. Bodily feelings were reported "better than usual" for the second and third sessions when the drugs were, by contrast, at the height of their effects. Similarly, placebo was the only substance for which "improved memory" was not claimed by subjects in the second session.

The first of these reports may be interpreted, if the finding is assumed to be reliable, as evidence for a low-level, ineffable discomfort under the

influence of all active substances; subjects who had experienced the active substances would be comparing that experience, unknowingly, with the effect of the placebo. In effect, the placebo may be picked out from the three active substances through the reports alone.

The second report, the claim of "improved memory", is not as readily rationalized as the first, but perhaps it is related to the mild distress which we inferred. This discomfort may have led to heightened attention to bodily feelings, and hence to an illusory impression of improved faculties.

Whatever the validity of these speculations on the findings, the reports taken in concert suggest low order effects for the active substances as far as the experience of the subjects is concerned.

Perphenazine (Trilafon). At the dose administered, no objective changes occurred for this substance.

In addition to the subjective impressions noted in the section on placebo effects (which were the same for all 3 drug days) subjects in significant number reported subjective visual changes in the third testing session of the day. However, no evidence of change could be detected in the eye movement or perceptual measures.

Opipramol (Insidon). A single objective change occurred for this drug, most apparent in session four, the final session of the day. For one of the measures of eye movement the analysis of variance revealed a significant interaction between drug and testing period. The mean amplitude of movement during examination of the random visual display was low for Opipramol (74.10 minutes of arc, SD = 42.31) in the final examination of the day. At that time, mean amplitude of movement for all other conditions was at, or close to, peak levels (placebo: Mean = 251.10, SD = 165.75; Trilafon: Mean = 245.00, SD = 165.75; Trilafon: Mean = 178.15, SD = 133.26) Fig. 2 presents mean data for all sessions and drugs. Variation in this score was large throughout the day, however, a fact which makes it difficult to interpret the results. It was also the case that the photographic record frequently did not allow adequate measurement, and mean values had to be interpolated for missing scores for subjects in some of the sessions. The finding, limited by these two reservations, is that some restriction of movements occurs for opipramol in contrast to the other substances. Much of the contrast in amplitude is due to the increased activity which occurs in the late testing sessions for the placebo and substances other than opipramol.

Despite this significant alteration in the character of movement of the eyes no change in the efficiency of perception appeared in the data; the subjects maintained their usual accuracy in reporting contours in the visual displays. Nor did subjective reports contain, for this drug, any

mention of visual effects. Rather, in common with the other 2 days, the subjects found their state of mind and body "improved". Again we can interpret this report only by the contrast with prior states which it implies.

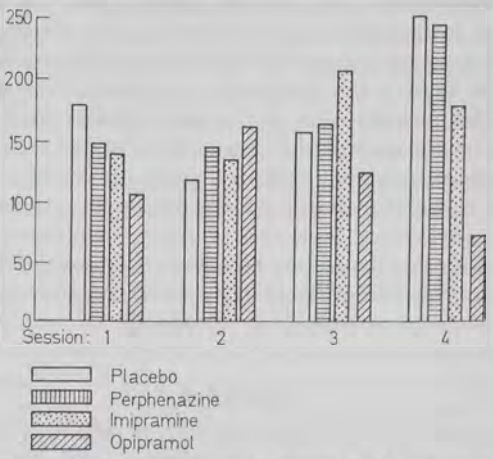

Fig. 2. Mean amplitude of eye movement, in minutes of arc, for drug and placebo conditions during visual examination of the random displays and for each period of testing. While the general effect appears to be an increase in amplitude during the day, eye movement under opipramol progressively declines after the first drug session, until it is significantly below the other substances by the final test, five hours after drug administration

Imipramine (Tofranil). Analyses of variance indicated change in a number of objective indices for this drug.

By the time of the second session, i.e. one hour after drug administration, the blood mean arterial pressure was higher for this drug (120) than for all other substances and placebo (114). This difference remained throughout the day and is significant at the 0.01 level.

Signs of bodily distress were apparent. Some of the subjects became dizzy and nauseated. The questionnaires contained evidences of discomfort throughout the sessions following drug-administration. There were significantly more frequent reports of bodily and mental distress: illness, sleepiness, inability to concentrate.

With regard to performance measures, only the drawing test showed any effect: the length of line traversed by the pencil was significantly greater under the influence of imipramine than for the other substances in all of the post-administration testing periods (4.94 m after imipramine

sessions 2, 3, 4 as compared to 4.6 after placebo 4.7 and 4.6 after other drugs). This measure would seem to be one concerned with style or effort (Reed *et al.*, 1965) rather than precision; all indices of accuracy of the test-pattern remained unaffected by the drug.

General Observations. The subjects showed great variability in performance and in apparent response to drugs. The possibility exists, of course, that there are degrees of sensitivity and differential response to the drugs. To explore this further, one additional test was performed internal to the data for each of the drugs; the number of reports of negative effects was correlated with motility of the corners of the mouth. A significantly negative correlation (−0.73 rank-difference-correlation of Spearman at the 1% level) was found for imipramine, but not for any of the other substances. However, the range of positive and negative response in the other drugs may have been too attenuated to observe a correlation: reports indicative of changed feeling were more prevalent in the imipramine experiment than for any other drug.

Discussion

We may summarize the experimental results by noting first that the questionnaire provided grounds for inferring that mild distress was produced by all of the substances except the placebo. However, only in the case of imipramine were there definite statements of discomfort. The detrimental consequences for the other drugs were inferred only by contrast with the "better" feelings reported in placebo and by interpreting "improved memory" to indicate heightened attention accompanying a mild but otherwise ineffable discomfort. It should also be noted that the yield of significant statements is sparse for a questionnaire of 32 items; in a list of this length, some "significant" results could occur by chance alone. The occurrence of the same result in adjacent sessions or at a similar time of day suggests that the subjective results are not fortuitous.

Objective (i.e. physiological as defined above) indications of change in bodily condition occurred clearly only for the imipramine experiment and for the last session of the opipramol experiment. In the former case, systolic blood pressure altered slightly but significantly, and in the latter one index of eye movement was changed.

The notable finding, however, is the absence of change in performance measure in all conditions, especially in the presence of the subjective and objective evidences of discomfort. The eye movement alterations were not accompanied by decline in perceptual performance, while the distress apparent throughout the imipramine experiment altered performance in only the drawing test. The drawing test finding, whatever

its basis, does not seem to reflect a loss in movement precision; all measures of that nature on the test are unaffected. That the test is sensitive to loss of precision of movement is indicated by earlier results with amphetamine (Reed *et al.*, 1965).

There were performance changes associated with time of testing; these were apparently positive effects of practice in the course of the day and perhaps of the state of alertness or relaxation of the subjects. They were independent of the nature of the drugs.

It could be considered that our battery of tests was simply insensitive to changes which might have occurred, that the dose levels were ineffective in producing any alteration in our sample of normal subjects, or that the drugs were mood-altering substances which should not be expected to affect motor systems.

Apart from previous evidence of sensitivity of some of the measures to central nervous system function (Reed *et al.*, 1965; Heimann, 1966; Reed and Pollack, 1965), the session by session changes which were noted in the experiment suggest that the tasks were responsive to the relative well-being of the subjects throughout a day. The improvement in performance is not, we believe, entirely to be attributed to practice effects, but to some capacity such as attentiveness or wakefulness. By attentiveness, we do not mean vigilance or tension, but a state of readiness to respond based upon relaxation. The tests, therefore, seem justifiably used as indices of greater or lesser efficiency. Secondly, in response to the criticism of sensitivity the comment may be offered that the possibility of effects becoming apparent if only a more sensitive instrument were employed is always an open question until that instrument appears. In the present case, moreover, we wish to stress the discrepancy between the findings for the presumably sensitive recording of subjective experience and those for the performance measures.

The choice of healthy young subjects provided us with a more uniform substrate for investigation than would have been the case with patients, but it is true that this choice may also mean that we dealt with stable organisms less easily affected by chemical interferences than would be ill subjects. The drug-doses used in the experiment are known to be effective in human subjects; but that effectiveness is established in patients and in terms of symptom changes with chronic therapy, not in single-dose administrations. It is the case, however, that we were successful in producing clear changes in at least one of our experiments (imipramine), that is in provoking the mild subjective and objective signs of distress which are consequences of the well-known autonomic effects of this drug. We view our results in this regard as a mixed success; had other choices of dose-level been made, clearer indices of disorder might have been obtained.

Finally, the observed alteration of mood is difficult to define without referring to changes in motor phenomena. Level of activity and facial mobility, for example, are commonly taken as indices of mood. It is this practice which encouraged us first to suppose that particularly delicate motor performances, and the achievements presumably based upon them, could be used to classify the action of mood-altering drugs. Instead, it seems the case that motion of hands, eyes and facial muscles may be particularly immune to deterioration.

Our results are in keeping with the contrary expectation that disorders of intellect and emotion occur without necessarily disrupting the everyday efficiencies of steering through space and performing ordinary actions.

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