THE EFFECT OF ELECTROCONVULSIONS, INSULIN COMAS AND CERTAIN CHEMICAL AGENTS ON FIXATIONS IN THE RAT[1]

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Stereotyped patterns of behavior are an important element in most forms of mental illness. It may be that more suitable, more varied patterns cannot occur partly because of the domination of responses which, though maladaptive, have become deeply habitual with the passage of time, with practice, and with a high level of emotional participation.

Stereotyped "maladaptive" habits or "fixations" can be established in the rat. We define fixation in this experiment as an unvarying, maladaptive behavior pattern which is developed in response to a no-solution problem under conditions of stress, and which persists even when the problem is made solvable. This fixation is considered by us to resemble, to some degree, rigid maladaptive behavior in human beings. We hoped to throw some light on this process by studying the effects of various agents on the rat fixation, beginning with those agents whose effects in the human have been more thoroughly studied. Agents used were electroconvulsions (ECT), insulin comas (ICT), alcohol, chlorpromazine, reserpine, and d-lysergic acid-25 (LSD). The work with the latter four drugs, while only exploratory, was felt to be worth including in this report for the use of other investigators.

Assuming that varying intensities of emotion go into the making and maintaining of a habit, and that a fixation is merely an unusually strong habit, treatment could be aimed at mitigating or obliterating the memory component or the emotional component of the behavior pattern. And different agents could operate in different or in overlapping ways to bring about a change. A permanent or temporary breaking up of memory associations might allow new patterns to be formed, providing that the ability to acquire new learning was not disproportionately impaired. A reduction in fear or anxiety could put an animal in a better position to notice the cues which would lead to adaptive decisions at decision-points. The present research was designed to test certain agents as to their ability to impair fixations; their ability to facilitate the acquisition of adaptive behavior was left to later research.

The rationale for the inclusion of ECT, ICT, chlorpromazine, and reserpine in this study needs no special comment. Alcohol was included because of our common knowledge of its effects as a kind of comparison. LSD was included because of the possibility that its dissociating ability might break up well-established patterns and allow new ones to be formed.

METHOD

Thirty-nine male and 21 female Sprague-Dawley rats were run after 24-hour water deprivation in a simple T-maze for 10 trials per day, three days a week. They were allowed Purina Dog Chow ad libitum, and water ad libitum except as stated above. During these trials, rats were randomly rewarded with water or punished with electricity (approximately 50 volts) in the arms of the T so that there could be no solution to the problem, other than removal from the T by hand after the reward or punishment. The trunk of the T was always electrified (approximately 50 volts). The animals were run for 300 trials which was 50 trials after 100 per cent of the animals had become invariable in their choice as to the arm of the T. For the 100 trials just prior to that point, 19 rats made changes; but these were very few as compared with frequency of "correct" (fixated) runs. Thus all rats were eventually fixated, and none discarded. Results during the experiments showed that late fixators were no more likely to lose fixations than early fixators. The problem was not made soluble until the actual experiments with the

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agents were begun. After the fixations were established, the rats were divided into experimental and control groups. The control groups rested while the experimental rats underwent treatment.

The ECT group (17 rats, 3 of which died of broken backs as a result of the treatment) received 18 convulsive treatments on 18 consecutive days and was tested for persistence of fixations along with controls (8 rats) after 3, 6, 12, 15, and 18 convulsions. They were again tested for retention after intervals of 3, 9, 36, and 67 days. ECT was administered with a commonly used apparatus: Medcraft Model B-24, which delivers a sine wave, 60-cycle alternating current. A variac was interposed between source of current and apparatus such that settings as low as 57 volts were utilized. The usual setting was 65 volts for 0.2 or 0.3 seconds.

The ICT group (17 rats, 3 of which died in insulin coma) received 18 insulin comas on 18 consecutive days and was tested along with controls (11 rats) after 4, 8, 12, and 18 comas. Insulin doses were administered subcutaneously and ranged from 4 to 10 units per rat. Rats were fasted for 12 hours prior to insulin injection. Comas were terminated after about 2 hours with multiple subcutaneous injections of 10 per cent dextrose (usually totaling 6 cc.).

The rats who received drugs and who showed no changes were used again in the ECT and ICT experiments, care being taken to distribute drug rats between treated and controls of the ECT and ICT experiments. Various dosage levels were tried, and the dosage which produced a marked, observable effect was the one finally used. All drugs were given subcutaneously unless otherwise stated. Ethyl alcohol: 2 cc. of a 50% solution were injected subcutaneously plus 4 cc. orally of a 20% solution, totaling 1.8 cc. pure alcohol. These rats were tested $1\frac{1}{2}$ hours later when they had difficulty standing. Chlorpromazine: Average of 3.75 mg. per rat (12.5 mg. kg.). Testing for presence of fixations was done at 1, 3, and 6 hours subsequent to injection, and again 2 days later. Reserpine: average of 0.15 mg. per rat (0.5 mg. kg.). Testing was done 8 hours later. LSD: 4 micrograms per rat (13 micrograms kg.) and on another occasion 12 micrograms per rat (40 micrograms kg.). Testing was done $1\frac{1}{2}$ hours after injections.

In order to determine whether there was any learning deficit due to ECT or ICT, these rats were run in a modified Stone 14 choice-point multiple T-maze until all rats had approached mastery of the maze.

Discussion of Method

Most fixation studies with rats have used the Lashley jumping stand, which is the method pioneered by Maier (11). The stand is placed before two windows in which may be placed appropriate light and dark covers which serve as signals. The rats may become invariable in their choice either of a window with one intensity of light behind it or may establish a right or left position fixation. With this method the rat makes his decision while driven by hunger, thirst, or pain (or combinations) and before he has got into action. His decision involves two alternatives, one of which may lead to relief of drive, and the other to a bump on the head or body and falling into a net.

We had hoped that the T-maze would offer a simpler, quicker method of fixation, but the relative merits of the two methods were not elucidated in this research. One point of difference is that the rat is already in rapid motion down the trunk of the T when he makes his right or left decision—which distance (and action) could allow for some dissipation of fright before the decision point is reached. The work of Obias and Stone (13) suggests that the closer the impingement of a stressful situation on the decision point, the less adaptive the decision is. Another difference is that our rats in the T-maze situation were not so dependent on the cues of vision in developing fixations, whereas with the jumping stand method they are forced to use their eyes. This is a much less natural avenue for the laboratory rat, and consequently might have put the rat under greater stress or another kind of stress than produced by our method. The terminal escape is similar for both methods: after falling into the net the rat is returned by hand to his box; in our method, after he has been shocked or rewarded with water in the arm of the T, he is lifted out and placed in his box.

Another factor which could make for differences in fixation: other methods mass trials, 10 per day every day, whereas we used 10 trials on two or three days a week. Neet

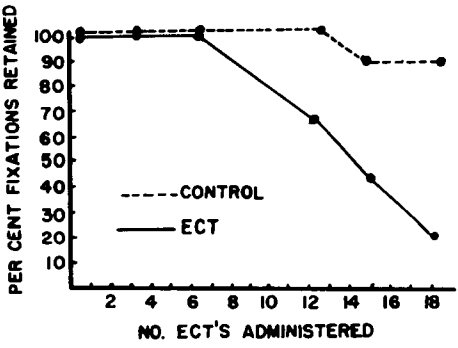

FIG. 1. The reduction of fixations as ECT administrations progress.

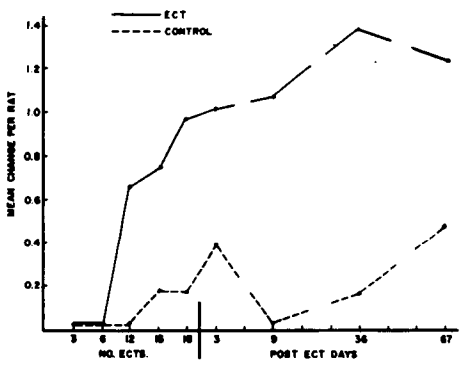

FIG. 2. Variability produced by ECT on fixated rats.

and Feldman (12) eliminated those rats which had not fixated by 160 trials, whereas we carried all rats to the point of fixation.

One important shortcoming of the rat fixation as a tool is that its persistence depends on certain external stresses to keep it in operation. It is not "built-in", self-propelled as so much human pathological behavior appears to be. And those very external stresses may constantly counteract the mitigating effects of whatever treatment agent is being investigated.

RESULTS

The only agent which decisively affected the fixations was ECT. The per cent of rats changing direction after different numbers of ECTs is shown in figure 1. The retention tests were run on the day after ECT (two or three trials). By the day after the 18th ECT, 11 out of 14 experimental rats and one control had altered direction one or more times. Using Fisher's Exact Test, this difference is reliable at the 1 per cent level of confidence. Three days later a retention test showed that one more experimental rat and one more control had changed. Thirty-six days later two more ECT rats and one more control had shown variability. In the period from the 18th ECT to 67 days later, one experimental rat and three control rats made no changes; one experimental and one control made one change; one experimental and four controls made two changes; four experimentals made four changes; three experimentals made five changes; one experimental made six changes; one experimental made seven changes; and two experimentals made nine changes—out of a total of 16 test trials. As a measure of strength of fixation all trials after the 18th ECT for all rats were totaled: in the experimental group, out of 145 trials 57 were opposite to the fixation (39%); in the control group, out of 82 trials only 6 were opposite to the fixation (7.3%).

Figure 2 shows the mean changes per rat per experimental day. In this graph a change means going opposite to the immediately preceding trial. This shows clearly the greater variability of the experimental as compared with the control groups; that is, once having changed direction the experimental rats tended to continue to change; whereas the controls who changed at all tended to revert to fixation and remain so.

Eighteen insulin comas had no effect on the fixations. No rat of the 14 who successfully completed the 18 treatments changed his fixation, but one control did change once.

Six of 14 rats injected with chlorpromazine changed away from their fixation while under the obvious influence of the drug, and two of their controls changed. When tested two days later, however, all these rats had reverted to their fixated responses. This result suggests that sustained treatments with chlorpromazine should be tried and physical guidance added to see if the drug allows for a giving up of the fixation in favor of the adaptive alternative.

Reserpine and alcohol experiments yielded completely negative results. A very few rats changed while under the influence of the two different doses of LSD, but there was no

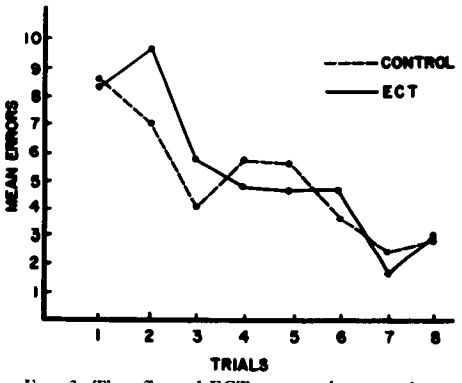

FIG. 3. The effect of ECT on complex maze learning.

significant difference between these and the controls. These few experiments do not negate the possibility that more treatments plus guidance would facilitate the breaking of fixations and learning the adaptive path.

Comparisons of the ECT and ICT groups with their controls on the 14 choice-point maze disclosed no gross decrement in learning proficiency though experimental rats showed a few more errors than their controls.

DISCUSSION

In these experiments ECT was effective in removing a strong, acquired pattern of behavior and so allowed a different pattern to occur. The different pattern was that of random choice of direction. In that the native pattern is that of random alternation, the fixation and the random pattern could be considered as competing, though not in quite the same sense as the competition between an old habit of going right and new one of going left. As compared with the native pattern of random alternation, the fixation was a relatively new, but highly practiced, stressfully developed pattern. If the random pattern had appeared only in the first few days after the last ECT, simple confusion (whatever that is) might account for the results; however, randomness continued for at least nine weeks. This indicates that the fixated pattern was greatly weakened or obliterated. However, the ability of the ECT rats to learn the 14 choice-point maze was only slightly impaired.

Palmer (14) also found that ECT (25 treatments) increased variability of response in rats which had been fixated in a double alternation maze, but that on massed retesting the old fixations tended to return and the rats did not acquire more efficient patterns.

Neet and Feldman (12) using a Lashley jumping apparatus for forming fixations, concluded that 25 ECTs were not effective in causing their rats to abandon fixations and learn a solvable problem. They state that a 25-day series of ECT "had no major effect on the stability of the rats fixated responses." Actually 7 out of their 9 rats showed variable behavior, but apparently during the 200 post-shock trials (massed at 10 per day) the fixations reasserted themselves. This may account for the difference in our results in that we avoided massed trials and tested with usually 3 trials at intervals of 1, 3, 9, 36, and 67 days post-shock. The random behavior was decidedly present two months later, whereas the control rats continued at a high level of fixation. Other possible differences could derive from the different methods of fixation used. Moreover our testing days were spaced so far apart that it would be unlikely that even an unfixated rat could develop an adequate response to the problem now made solvable; so that our results show only a loss of fixation and do not indicate whether ECT rats would make an adaptive response in the same situation less well or better than controls.

The present work indicates that ECT impairs memory, a fact which is well known. Recency (5, 18), degree of practice (3), and complexity of task (4, 14, 17) are important determinants of memory which are differentially susceptible to ECT. Previous work of one of us (15), Hunt and Brady (2, 9), Gellhorn (7), and observations on clinical cases (1) suggest that the therapeutic effect of ECT is due more to its action upon the emotional and autonomic correlates of learned behavior than upon the cognitive or symbolic elements. If the latter were the case, the efficacy of ECT would depend very much upon the degree of amnesia produced, and this is not true in clinical work. In most animal work the effect on more or less normal learning and memory has been studied; yet it may be that the pertinent effect is on specific pathological processes of brain functioning rather than

upon normal processes. If such is the case, the studies on relatively normal animals are somewhat off the point.

Fabing (6) has postulated an interesting theory for the effect of ECT on memory. He suggests that nerve nets which are in a state of high excitation are driven to the point of exhaustion by ECTs producing a state of inhibition which is more profound than that of the adjacent nerve nets which had not been previously overworked. He further suggests that this inhibited state may be a Pavlovian ultraparadoxical phase of cortical activity; i.e., that which had been highly excited becomes deeply inhibited and *vice versa*, and that these previously more active nerve nets take longer to recover than less active ones. Therefore, memories carrying a heavy emotional "charge" would be forgotten and trivia more easily remembered.

There is some evidence that ECT selectively impairs the process of inhibition more easily than that of excitation (8, 10), yet how is this process to be separated from recency (5) since generally a process is excitatory before it can be made inhibitory?

It is well known among clinicians that insulin comas have relatively little impairing effect on memory. However, Riess and Berman (16), experimenting upon maze learning in rats, found that one insulin coma (or convulsion) did impair the more recent, the less practiced, and the more complex patterns. Our fixations were "old" by comparison, were highly practiced, and were very simple, which could account for the fact that our fixations were not affected at all by 18 comas. Since Riess gave larger doses of insulin, starved rats for 24 hours, terminated comas with small doses of glucose, and subjected rats to tests "after a recovery period" (length of time not stated), one wonders whether they might not still have been hypoglycemic at the time of testing.

Though ICT and ECT affect memory differently and may bring about results by different machanisms, still both methods have their greatest efficacy in the treatment of acute psychoses and not in the treatment of the deeply habitual processes of chronic psychoses. This supports in some measure the position that studies on learning, memory, and fixations have pertinence to the problem of maladaptive behavior and mental illness. However, it may be that ICT and ECT are therapeutic because of their action upon certain as yet undetermined pathological, neurophysiological or neurochemical processes which are at their height in the acute stage and which happen to share with learning and memory some common laws.

Summary

Albino rats were run in a T-maze with random reward and punishment (no-solution problem) until they became fixated in a left or right direction. ECT and insulin comas were administered to different groups to see if the fixations were altered. ECT decisively reduced the fixations, but insulin comas had no effect. The effects of chlorpromazine, reserpine, d-lysergic acid-25, and ethyl alcohol were studied on an exploratory basis. Chlorpromazine caused a temporary change; the others had no effect. More extensive experimentation on the relative ability of these agents to facilitate adaptive responses is needed.

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