

Table 1. Right-key multiple schedules.

Condition	Blue schedule	Green schedule
I	VI 3*	VI 3
II	VI 3	Extinction
III	VI 3	VI 3
IV	Extinction	VI 3
V	VI 3	VI 3
VI	FR 10†	VI 3

* Three-minute variable-interval schedule.

† Fixed-ratio schedule of ten responses.

(records II and IV), demonstrating that the occurrence of conditioned reinforcement was necessary to maintain the behavior. Finally, when the two stimuli were associated with two different schedules of conditioned reinforcement (record VI), both the response rates and the patterns of responding were different in the presence of the different stimuli. Responding in the presence of the green stimulus was similar to that observed in any of the earlier variable-interval conditions, while responding in the presence of the blue stimulus was characteristic of behavior generally obtained on fixed-ratio schedules of primary reinforcement. Responding occurred at high steady rates prior to a conditioned reinforcement and pauses of varying durations occurred immediately after a conditioned reinforcement.

These results are qualitatively similar to those obtained with similar multiple schedules of primary reinforcement (1). The results obtained from the separate components of the multiple schedules are also similar to results obtained by Kelleher (2), who programmed different schedules of conditioned reinforcement during extinction of primary reinforcement.

I have reproduced these results with other subjects in situations that did not utilize multiple schedules but simply examined the various schedules one at a time. I have also demonstrated that these results depend upon the use of stimuli which are paired with primary reinforcement. (The presentation of a set of stimuli which are not associated with primary reinforcement does not maintain behavior).

Stimuli which initially do not influence behavior can acquire the power to reinforce behavior by being associated with primary reinforcement. Since conditioned reinforcement, as a principle, often bears a heavy load in the interpretation of behavioral events, the demonstration and assessment of the conditioned reinforcing function of stimuli is of prime importance to a

scientific analysis of behavior. Much of the prior work in this area, however, has involved the examination of conditioned reinforcement after primary reinforcement has been discontinued. A major disadvantage of this approach is that "the effectiveness of the conditioned reinforcing stimulus is being extinguished while it is being evaluated" (3). In the present study, it was indeed observed that behavior maintained by conditioned reinforcement rapidly became extinguished after the removal of primary reinforcement.

When concurrent schedules of primary and conditioned reinforcement were in operation in the present study, behavior on the conditioned reinforcement key was virtually indefinitely maintained. This result is of significance both for a theoretical analysis of ongoing animal and human behavior and as a potentially powerful laboratory tool for the assessment of the effects of behavioral variables on both the establishment and power of conditioned reinforcers (4).

JOSEPH ZIMMERMAN

*Institute of Psychiatric Research,
Indiana University Medical Center,
Indianapolis 7*

References and Notes

1. C. B. Ferster and B. F. Skinner, *Schedules of Reinforcement* (Appleton-Century-Crofts, New York, 1957).
2. R. T. Kelleher, *J. Exptl. Anal. Behav.* 4, 1 (1961).
3. — and L. R. Gollub, *ibid.* 5, 543 (1962).
4. I thank Ronald Stotts for his help.

9 August 1963

Febrile Convulsions in Infant Rats, and Later Behavior

Abstract. *At 3 days of age, rats were (i) subjected to a febrile convulsion, or (ii) were handled, or (iii) were not handled. Evaluation at 30 days of age revealed that animals in the first group were heaviest and most resistant to audiogenic seizure stimuli. No differences were found in maze-learning ability or activity level.*

Clinical reports (1) of the effects of infantile febrile convulsions on seizure susceptibility and other neurological and behavioral disorders in later life suggest that the experience of a febrile convulsion in infancy or childhood may occasionally result in permanent brain damage and a predisposition to recurrent seizures. Other forms of stimulation in infant animals have demon-

strated a facilitation of subsequent behavioral performance (2). The present investigation was designed to determine the effect of inducing a febrile convulsion in infancy on the later behavior of the rat.

Thirty female albino rats (Sprague-Dawley) were bred in this laboratory and their litters assigned to one of three treatment groups: experimental, control (handled), or reference (not handled). At birth, the pups were removed from the nest (after the mother had first been removed), counted, and either replaced in the nest or discarded, so that there were no more than four males and four females, or a total of eight pups, in each litter.

At 3 days of age, when the rat's threshold for febrile convulsions is lowest (3), febrile convulsions were induced in the experimental group by a microwave diathermy generator (Burdick). The method described by Millichap (3) was employed with the diathermy unit, providing a stimulus of 2450-Mcy/sec frequency; the unit was operated at 80-watts power output. The animals' rectal temperature was monitored with an inserted thermistor. The control group was handled in an identical manner (at 3 days of age), except that the diathermy machine was not turned on. Since it required approximately 100 seconds for animals treated with the microwave diathermy to reach the convulsive temperature of 40.3°C (basal temperature 32.5°C), rats in the handled, control group had their temperature monitored for a similar time. Their body temperatures showed a drop from a basal temperature of 32.4° to 30.8°C. Animals from each litter nested in cedar shavings until the entire litter completed the treatment, and all were returned to their home cages. Animals in the reference group received no handling except that received at birth. None of the groups received any further handling until weaning at 30 days of age. Each pup was then weighed and evaluated for either learning ability on a Lashley III water maze, activity-wheel performance, or susceptibility to audiogenic seizures. All behavioral measures started when the animals were 30 days old.

The Lashley III maze was modified for use as a water maze with escape from water as the reinforcement. Total time and errors were recorded for the animals to reach the goal box, where they could escape from the water by climbing a wire ramp. Maximum time

permitted the animals on each trial was 10 minutes. Animals received a maximum of 30 trials, distributed over an 8-day period. The criterion of success was defined as two consecutive errorless trials even if distributed over 2 days.

Activity-wheel performance was recorded for a 5-day period under basal conditions with food and water available ad libitum. Animals lived in the wheels, which had a diameter of 14 inches (36 cm) and were 4 inches (10 cm) wide. Each complete revolution of the wheel covered a distance of 45 inches (114 cm) and activated four counts on an electromagnetic counter. Total counts were recorded daily. Animals received no handling during the 5-day period.

Susceptibility to audiogenic seizures was evaluated under both normal and lowered (with Metrazol) threshold conditions. The apparatus, procedure, and description of convulsive responses have been previously described (4).

The attained mean weight of the 30-day-old animals in the three treatment groups was analyzed by a simple analysis of variance (5). This analysis demonstrated a significant effect ($F = 8.38$, $df = 2/187$, $p < .01$) of the experimental treatment at 3 days of age on the attained weight at 30 days of age. The weight data are presented in Table 1. Differences between individual means were tested for their significance with the t -test. Animals subjected to induced febrile convulsions at 3 days are significantly heavier at 30 days than animals in the handled control or unhandled reference groups ($t = 3.55$ and 3.07 , respectively, $p = .01$ for both). The difference between the control and the reference groups is not statistically significant.

No significant differences between treatment conditions are found in maze-learning ability or activity-wheel performance.

When tested for susceptibility to audiogenic seizure, no animal from the febrile convulsion group ($N = 14$) or from the handled control group ($N = 14$) had an audiogenic seizure under either threshold testing condition. In the unhandled reference group ($N = 17$), seven animals (41.1 percent) manifested some form of a convulsive response in one or the other of the test conditions. This consisted of either the usual audiogenic seizure response (running fit and/or tonic-clonic response) or myoclonic jerking resembling early

Table 1. Body weight, at 30 days, of animals having febrile convulsions in infancy.

No.	Mean body weight (g)	Standard deviation
<i>Febrile convulsion group</i>		
60	66.9	12.2
<i>Handled control group</i>		
57	59.1*	11.1
<i>Unhandled reference group</i>		
73	61.1*	8.8

* Difference between this group and the febrile convulsion group is significant at the 0.01-level of confidence.

stages of a convulsion. The difference between the unhandled reference group and both the febrile convulsion and handled groups is statistically significant ($z = 2.72$, $p < .01$) with the z test for uncorrelated proportions (5).

Although clinical reports (1) suggest that infantile febrile convulsions may predispose to later neurological or psychiatric disorder, this is likely to occur only if the febrile convulsion is prolonged and associated with electroencephalographic abnormalities indicating cerebral damage. Pathological findings after febrile convulsions in humans (6) and kittens (7) revealed neuronal necrosis of variable distribution and severity in the cerebral cortex, basal ganglia, and cerebellum. However, brain enzyme activity was not altered after a febrile convulsion in mice (8). The fact that our data demonstrated no detrimental effect of the febrile convulsion suggests that it was not so severe an experience as to result in cerebral damage, or that the experimental treatment stimulated other mechanisms that may have been responsible for the observed facilitating effects and overshadowed any deleterious effects which may have occurred.

The literature in the area of early experience is in general agreement that stimulation early in life facilitates a variety of subsequent behavioral performances. However, investigations reporting the effects of intense or noxious chronic stimulation during infancy (before weaning) have yielded equivocal results, with Griffiths and Stringer (9) reporting no significant effects and Spence and Maher (10) demonstrating a facilitating effect on straight-alley maze performance. On the other hand, short-term noxious stimulation in the first few days after birth was found to improve avoidance learning in mice and decrease emotionality in rats (2).

In the present investigation, intense, noxious stimulation (induced febrile

convulsion) was applied only once, at 3 days of age. The fact that the febrile convulsion did not have detrimental effects, but rather enhanced weight gain and increased resistance to audiogenic seizures, supports previous reports, particularly recent ones of Denenberg *et al.* (2), that the newborn is especially sensitive to stimulation. The lack of agreement between the reports previously cited may be due to a most apparent factor, the number of days during infancy, or the duration of time, that the stimulation was applied. The special sensitivity of the very young animal has been further elaborated (11) in physiological terms by the demonstration that animals handled at 2 to 5 days of life exhibited no effect of an electroconvulsive shock treatment on blood sugar concentration, as compared to nonstimulated controls or experimental animals handled later in infancy.

Although a single induced febrile convulsion in animals may not be identical to a febrile convulsion which occurs spontaneously in humans, the data demonstrate that the febrile convulsion in infancy is not deleterious to later behavioral performance in rats. On the contrary, the infantile febrile convulsion appears to be similar to other types of stimulation (noxious and nonnoxious) administered to the very young animal which have a facilitating effect on some aspect of behavior.

JACK WERBOFF*

JOAN HAVLENA†

*Animal Behavior Laboratory,
Lafayette Clinic, and Wayne State
University, Detroit, Michigan*

References and Notes

1. W. G. Lennox, *Pediatrics* **11**, 341 (1953); R. P. Schmidt and A. A. Ward, *Epilepsia* **4**, 41 (1955); J. G. Millichap, J. A. Madsen, L. M. Aledort, *Neurology* **10**, 643 (1960); M. A. Lennox, *Am. J. Diseases Children* **78**, 868 (1949).
2. V. H. Denenberg and R. W. Bell, *Science* **131**, 227 (1960); V. H. Denenberg, P. V. Carlson, M. W. Stephens, *J. Comp. Physiol. Psychol.* **55**, 819 (1962).
3. J. G. Millichap, *Pediatrics* **23**, 76 (1959).
4. J. Werboff, J. Den Broeder, J. Havlena, M. R. Sikov, *Exptl. Neurol.* **4**, 189 (1961).
5. A. L. Edwards, *Experimental Design in Psychological Research* (Rinehart, New York, 1950).
6. M. Fowler, *Arch. Disease Childhood* **32**, 67 (1957).
7. M. A. Lennox, W. A. Sibley, H. M. Zimmerman, *J. Pediatr.* **45**, 179 (1954).
8. J. G. Millichap, *Neurology* **10**, 312 (1960).
9. W. J. Griffiths and W. F. Stringer, *J. Comp. Physiol. Psychol.* **45**, 301 (1952).
10. J. T. Spence and B. A. Maher, *ibid.* **55**, 247, 252 (1962).
11. R. W. Bell, G. Reisner, T. Linn, *Science* **133**, 1428 (1961).

* Present address: Jackson Laboratory, Bar Harbor, Maine.

† Present address: Department of Radiology, Wayne State University, Detroit, Mich.

9 September 1963