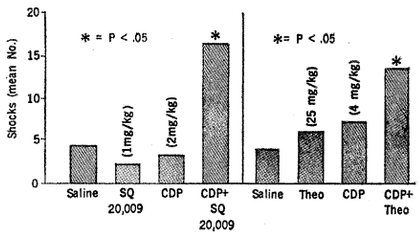

Fig. 3. Mean number of shocks received during the 3-minute test session after intraperitoneal administration of ineffective doses of SQ 20,009, chlordiazepoxide (*CDP*), theophylline (*Theo*), and a combination of the individual doses of chlordiazepoxide and SQ 20,009, and chlordiazepoxide and theophylline.

AMP phosphodiesterase activity in the brain; (ii) dibutyryl cyclic AMP has anxiety-reducing properties, as measured by the conflict test in rats; (iii) the methylxanthines (caffeine, theophylline, and theobromine), known inhibitors of cyclic AMP phosphodiesterase activity, also have significant anxiety-reducing ability in the conflict test; (iv) combinations of theophylline and chlordiazepoxide, or SQ 20,009 and chlordiazepoxide, have at least additive effects in the conflict test; and (v) a significant correlation exists between the activity of a drug in the conflict test and its potency in inhibiting cyclic AMP phosphodiesterase activity in the brain. These results indicate that anxiety-reducing properties of drugs may either involve, or be mediated by, the cyclic AMP system in the brain.

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Avoidance Sessions as Aversive Events

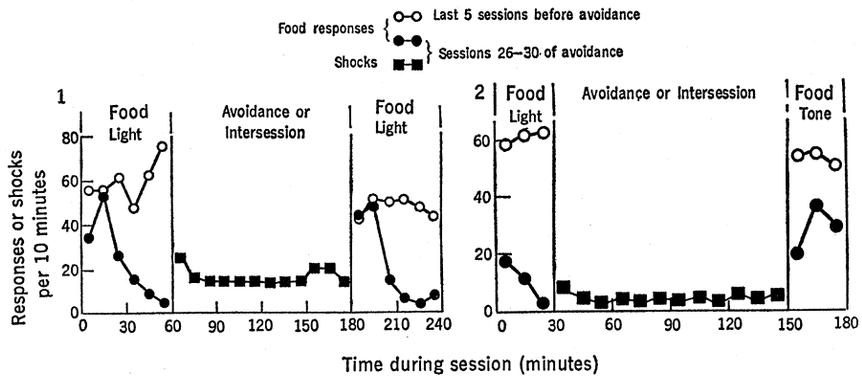
Abstract. *Rats living continuously in conditioning chambers were permitted to work for food before and after their daily avoidance sessions. The avoidance procedure disrupted this responding reinforced by food, a result that indicates conditioned suppression on a time scale much greater than that previously studied in nonhuman animals.*

In their well-known "conditioned anxiety" experiment, Estes and Skinner (*1*) tested animals during training sessions when their responses were being reinforced with food and found that if a 3-minute stimulus terminated with electric shock was presented twice per session in repeated 1-hour sessions, responding was eventually suppressed in the presence of the stimulus. Their procedure is effective with nonhuman animals, and hence is readily used for pharmacological and physiological research on emotion and psychosomatic diseases. The suppression it yields is commonly offered as a laboratory analog of the "fear" or "anxiety" observed in clinical situations with humans. However, the Estes-Skinner procedure uses brief stimuli, seldom more than 5 minutes in duration, followed by brief shocks typically lasting less than a second. Many anxiety-producing situations for humans are not restricted to such brief stimuli and aversive events.

However, the laboratory analog need not be so limited. Laboratory rats respond differentially to different overall shock frequencies, even when brief shocks are distributed over extended periods of time within experimental sessions (*2*). This integration over time may extend beyond the confines of experimental sessions as well as within them. For example, animals in avoidance experiments are usually studied only during the avoidance sessions. Yet, those avoidance sessions may affect behavior in situations that routinely precede or follow them, by periods of minutes or perhaps even hours. That is, extra-session effects of avoidance conditioning may occur on a time scale more like that of anxiety reported from human experience. In the experiments reported here, these effects were examined in rats that lived continuously in conditioning chambers and were permitted to work for food before and after their avoidance sessions.

First, three Long-Evans hooded male rats were housed in identical operant conditioning chambers (Lehigh Valley Electronics), each with the usual response lever, pilot light, grid floor, and dipper. The chambers were modified to include a drinking tube providing free access to water and a ball chain sus-

pended from a microswitch and hanging through a hole in the center of the ceiling. The dipper delivered 0.1 cc of a sweet liquid containing, by weight, 15 percent Sustagen (Mead-Johnson), 0.5 percent NaCl, 14.5 percent sucrose, and 70 percent water. The grid, walls, and lever were wired to deliver brief (0.25-second) shocks of scrambled polarity and of 1.5-ma intensity. The chamber was housed in a sound-resistant cabinet with white noise supplied continuously and with a houselight that could supply dim and diffuse illumination. Control and recording equipment was in a separate room. The subjects were approximately 90 days old when placed in the conditioning chambers. They were weighed daily, several hours after the conditioning sessions, and fed supplementary Purina lab chow as needed to keep them at 80 percent of the weights they had maintained when given free access to food.



Figs. 1 and 2. Performances in successive 10-minute segments of food sessions and avoidance sessions. Open circles indicate responding during the last 5 days of food reinforcement before exposure to the avoidance procedure; food sessions were separated by 120-minute intersessions. Solid circles describe food-reinforced responding immediately before and after avoidance sessions 26 through 30. Performance in the 120-minute avoidance sessions is indicated by squares representing shock rates. Each point represents pooled data for three animals. In Fig. 1 (left), a light was on during all sessions of food reinforcement. In Fig. 2 (right), a light was on during food sessions that preceded the 120-minute intersessions or avoidance sessions, and a tone was on during food sessions that followed the intersessions or avoidance sessions.

The response of chain-pulling was established with food reinforcement and then maintained on the following second-order schedule. Each response that occurred at least 4 seconds after the preceding response produced a click, and every *N*th click was accompanied by food. For each rat the value of *N* was adjusted (between 3 and 7) to produce stable responding throughout four daily 1-hour sessions. These sessions of reinforcement by food were accompanied by the dim houselight and were separated by intervals of 2, 4, and 2 hours. When responding became stable, two daily 2-hour avoidance sessions were introduced, with the use of Sidman's conditioning procedure (interval between shocks, 2 seconds; interval between response and shock, 20 seconds) (*3*). During the avoidance sessions, the pilot light flashed once per second. These avoidance sessions were placed so that each was immediately preceded and immediately followed by a 1-hour food session, with a 4-hour rest interval still separating the second and third food sessions.

The daily sessions can be divided into two groups, each containing an avoidance session with its preceding and following food sessions, the two groups separated by 4 hours. Although they were preceded by different periods of rest (4 compared with 12 hours), the two groups of sessions produced nearly identical results, so data of the two groups of sessions have been combined. Effects of the daily avoidance sessions on chain-pulling reinforced by food can be assessed by inspecting Fig. 1, where data for the food sessions before and after avoidance sessions on days 26 to 30 of avoidance conditioning are given, along with data for the food sessions before avoidance conditioning was begun. The avoidance conditioning had little effect on responding in the early minutes of food sessions but produced suppression later, whether the food sessions preceded or followed the avoidance sessions. While the suppression pattern (Fig. 1) was similar in all animals after several weeks of avoidance conditioning, the onset of this suppression, during the first few days when avoidance conditioning was given, was not consistent in different animals. In two of the animals it developed gradually; in the third, the introduction of avoidance eliminated all responding for food, with only gradual recovery to the final, stable pattern.

The suppression of responding just before each avoidance session resembles the conditioned suppression of the procedure of Estes and Skinner, but on a greatly expanded scale. The present food sessions serve in place of preshock stimuli, and the sessions of avoidance serve as unitary noxious events that replace the single shocks. However, Estes and Skinner noted a compensatory increase in responding after the stimulus was removed and the shock had occurred. In the postavoidance periods described here (minute 180 to 200 in Fig. 1), responding recovered but not to compensatory levels, and was again suppressed late in these food sessions even though the next avoidance session was at least 5 hours away. Hence, the suppression observed in food sessions that followed avoidance sessions is not directly analogous to the within-session suppression reported by Estes and Skinner. Still, this postavoidance suppression may reflect the Estes-Skinner effect, and stimulus generalization of postavoidance with preavoidance sessions may have occurred, since the same exteroceptive stimuli were supplied in all food sessions. The possibility of such generalization was examined by a second experiment with differing preavoidance and postavoidance stimuli.

A second interpretation of the results in Fig. 1 would be that the avoidance conditioning produced a pervading loss of appetite and that satiation effects were seen late in each food session. This possibility was made less likely in the next experiment by reducing the length of the food sessions.

Four rats, different from those used in the first experiment, were submitted to procedures the same as before, with two exceptions. The four daily food sessions were 30 minutes in length (still separated by 2, 4, and 2 hours), and the houselight was on only during the first and third sessions. During the second and fourth daily food sessions, a 600-hz tone was presented. Again, after responding had become stable, avoidance conditioning was in-

troduced during the 2-hour periods between the first and second and between the third and fourth sessions of food reinforcement. Hence, sessions of food reinforcement immediately preceding avoidance sessions were accompanied by the houselight; those immediately following avoidance sessions were accompanied by the tone.

As before, similar results for the two groups of daily sessions permitted pooled data as for Fig. 1. Again, responding reinforced by food during days 26 to 30 of avoidance conditioning was suppressed relative to that before avoidance conditioning (Fig. 2). In the 30-minute food sessions preceding avoidance sessions, the pattern of suppression was comparable to that in the 30-minute periods before avoidance sessions in the first experiment. In Fig. 2, less suppression is shown in the postavoidance food sessions than in preavoidance sessions, a result suggesting that the postavoidance suppression of the first experiment constituted at least partial stimulus generalization with sessions preceding avoidance sessions. Whether postavoidance suppression is entirely explained as generalization with preavoidance sessions is an open question, for the continuing partial suppression may have resulted from stimulation provided by the food-reinforcement schedules themselves as well as by static stimuli present in all conditioning sessions.

The slightly reduced suppression in this second experiment, compared to the first, accompanied more effective avoidance behavior, as revealed by lower shock rates. However, in neither experiment did an analysis of within-subject data reveal any simple relation between amounts of suppression in the food sessions and the animals' performances in the adjacent avoidance sessions.

The present experiments extend research on "conditioned anxiety" and suggest a redefinition of aversive events, even within the context of laboratory studies. They also present a technique for evaluating variables that affect not only behavior in aversive situations but behavior that is outside those sessions but is still affected by them. In addition, these studies raise questions regarding experiments where endocrine changes or other physiological variables are studied in subjects that are under the influence of avoidance conditioning or other stressful procedures. In most experiments each animal is tested at a given time each day and is exposed to the cyclical activities of laboratory routine. This could result in conditioned suppression on a grand scale, in the presence of whatever stimuli characteristically preceed the avoidance sessions, perhaps of a magnitude that dwarfs the within-session events that are usually observed.

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Independence of Short- and Long-Term Memory: A Neural System Analysis

Abstract. *Rats were given electrical stimulation to the midbrain reticular formation or to the hippocampus 4 seconds after they received shocks contingent on the animals' bar-press responses. They were retested for memory of the shocks 64 seconds or 24 hours after the shocks. The animals that received stimulation to the midbrain reticular formation showed amnesia at the 64-second retest and memory at the 24-hour retest. In contrast, animals that received stimulation to the hippocampus showed memory at the 64-second retest and amnesia at the 24-hour retest. The data support a dual, parallel-processing model of memory.*

A major issue in the study of memory is the number of memory systems necessary to process newly acquired information, and the interrelations among these systems. There are probably at least two processes, one for short-term memory (STM) and one for long-term memory (LTM) (*1–3*). If STM and LTM constitute different processes, then different neural systems should be involved. In order to identify the neural systems that subserve the two processes, relatively localized brain stimulation of subseizure intensity should be used to disrupt ongoing neural activity. Low-intensity electrical stimulation of either the hippocampus, amygdala, or centre median in cats or of the caudate in rats disrupts LTM of aversive information (*4, 5*). However, the effect of electrical brain stimulation on STM has not been elucidated. The purpose of the present study was to stimulate various neural structures of animals after they had an aversive experience and to test for retention at short and long intervals.

In the first experiment, 41 male Long-Evans rats, 230 to 270 g at the start of the experiment, were subjects. The animals were divided into three groups—two for brain stimulation, either to the midbrain reticular formation (MRF) ($N = 13$) or to the hippocampus ($N = 12$), and a nonstimulation control group ($N = 16$). All animals were anesthetized with Nembutal, 35 mg/kg, and had bilateral implants of bipolar electrodes, into the MRF (coordinates: 6.5 mm posterior Bregma, 1.5 mm lateral, 6.4 mm vertical), into the hippocampus (coordinates: 40 mm posterior Bregma, 2.0 mm lateral, 4.3 mm vertical), or into the skull for the control group. The electrode assembly was fixed to the skull with acrylic cement. After recovery from surgery all animals were reduced to 80 percent of their initial weights and maintained at these weights. They were then tested, by an ascending method of limits, for the intensity of current required to produce a behavioral withdrawal response for subjects with MRF implants or a behavioral seizure response for subjects with hippocampus implants.

The electrical stimulation was delivered bilaterally via two Nuclear-Chicago constant-current stimulators and consisted of a 5-second train of biphasic symmetrical pulses. Pulses lasted 0.1 msec and were at 100 hz for animals with MRF implants and at 30 hz for the animals with hippocampus implants. For the critical treatment, the current intensity for each animal was half the observed threshold intensity. Current intensity for treatments fell between 20 and 45 μa for the MRF group and between 15 and 32 μa for the hippocampus group.

Each rat was trained to press a bar in a Skinner box on a continuous reinforcement schedule for 15 minutes daily. The Skinner box was equipped