Reports

Placebo Effect in the Rat

Abstract. Scopolamine hydrobromide disrupts the learned behavior of rats in a predictable manner. Physiological saline mimics to some extent the effect of the drug when the two substances are alternately administered in a series of injections. This placebo effect appears to be an instance of simple Pavlovian conditioning.

A human patient may react strongly to a drug that is pharmacologically inert. Such reactions, called placebo effects, figure prominently in both therapy and research. Each generation of medical practitioners acknowledges the power of the placebo by rejecting as inert (or worse!) many of the chemical agents believed in by its predecessors. The placebo effect is usually attributed to some kind of "suggestion" that operates, even if temporarily, to fulfill the patient's expectations about a treatment. Viewed as suggestion, the placebo effect derives from the human capacity to react to symbols. The physician, the hypodermic syringe or the tablet, the verbal interchange with the patient—all symbolic of a therapeutic effect—may produce a result that would otherwise have required some specific chemical agent.

The placebo effect can, however, be viewed in a different way. The elicitation of a specific reaction by arbitrary agents, such as the abatement of a symptom after the mere sight of a physician and his medicines, may be nothing more than simple conditioning of the sort originally demonstrated by Pavlov with animals. Pavlov showed that one stimulus may come to elicit responses ordinarily appropriate to a second stimulus after the two stimuli are presented together. Viewed as conditioning, the placebo effect is merely a particular instance of a phylogenetically widespread behavioral phenomenon, and not a manifestation of man's special symbolic capacities. Since we are disposed to speak of nonverbal animals as conditionable rather than suggestible, it may be with animals that the two views are most profitably tested.

Pavlov and others (*1*) have reported the conditioning of some of the effects of morphine on animals. Vomiting and sleep are often caused by morphine and these reactions sometimes occur while the experimeter is preparing an experienced animal for an injection. Presumably, events associated with the administration of morphine become the conditioned stimuli for some of the reactions that are characteristically induced by the drug. The parallel to the placebo effect is clear, but past research has been restricted to morphine, and there have not been enough controls to exclude other interpretations.

The present experiment (*2*) is an attempt to obtain a placebo effect simulating the known effect of scopolamine on the learned behavior of rats (*3*). A rat was placed daily in a chamber that was insulated for light and sound and contained a lever and a feeding device. The rat was hungry and was trained to depress the lever by reinforcement with sweetened condensed milk. After initial training, it was arranged to have the operation of the lever produce milk intermittently according to the following schedule, which constitutes one cycle: (i) 5 minutes: chamber illuminated; no reinforcement; (ii) 2 minutes or less: chamber illuminated; terminated by first response, which is reinforced with 0.3 ml of milk, or, if no response, no reinforcement, and period terminated after 2 minutes; (iii) 5 minutes: chamber dark; no reinforcement; an occasional intraperitoneal injection during this period, after eighth or ninth cycle.

This cycle was repeated 13 or 14 times every day, and preliminary experimentation continued for 4 months to accommodate the rat to this intermittent schedule of reinforcement and also to the accompanying injections of small quantities of physiological saline into the peritoneal cavity. These injections were made at the end of the eighth or ninth cycle during the first 30 seconds of the period of darkness, after which the session continued for five more cycles.

By the end of this preliminary period of 4 months, the schedule of reinforcement had established a characteristic pattern of responding, one whose primary feature is that at the beginning of each cycle there is little or no pressing of the lever, whereas, as the time for reinforcement approaches, the rate of lever-pressing increases continuously but quite gradually. The effect of scopolamine on this behavior is to depress the overall frequency of response and to abolish the orderly progression of rates (*3*). At this time, there was no detectable effect on behavior of the saline administrations.

The scopolamine hydrobromide was administered intraperitoneally 14 times in dosages of 1 mg/kg. Its injection was, like the saline, given at the end of the eighth or ninth cycle and was always followed by five more cycles. These injections were spread over 3 months of daily experimental sessions and were interspersed among an equal number of injections of physiological saline. The two kinds of injections differed in volume by less than 0.03 ml and they followed each other in an irregular order.

The major findings of this experiment are summarized in Fig. 1 with data from a single rat. Entirely analogous results were obtained from a

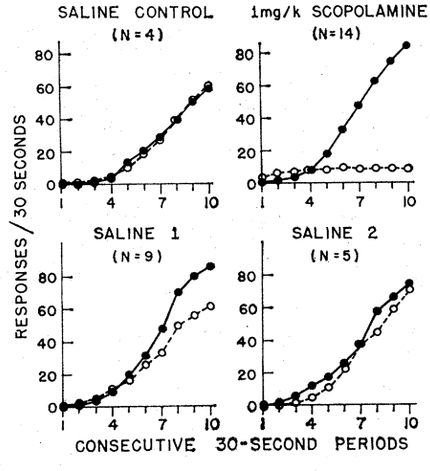

Fig. 1. Rates of lever-pressing during the 5-minute period prior to reinforcement. The filled circles plot average rates during the eight or nine preinjection periods; the open circles, those during the five postinjection periods. The curves labeled "saline control" were obtained before any administrations of scopolamine. Those labeled "saline 1" show the average effect of a saline injection that followed a scopolamine injection. Those labeled "saline 2" show the average effect following a saline injection. *N* refers to the number of injections contributing to these average curves.

second rat with an earlier version of the present procedure. The abscissa in Fig. 1 covers the 5-minute interval prior to the priming of the apparatus for reinforcement, and is broken down into ten consecutive 30-second periods. The ordinate plots the mean rates of responding during these 30-second periods. The increasing rate of responding that typifies behavior on this schedule of reinforcement results in increasing monotonic curves. The curves drawn through filled circles show the preinjection rates; those through open circles, the postinjection rates. Each pair of curves is an average of the data from the indicated number of sessions. The saline-control curves, being for four sessions prior to any administration of scopolamine, demonstrate that saline causes no disruption. The scopolamine curve shows the typical effect of this drug. In it, responding is depressed, having lost the increasing monotonic pattern normal for this schedule of reinforcement. The curves labeled "saline 1" are for the sessions in which saline was administered after a prior injection of scopolamine, whereas the curves labeled "saline 2" are from sessions with saline when the prior injection had been saline.

The curves show that when saline is administered after scopolamine (saline 1), there is considerable depression of responding, whereas with two consecutive administrations of saline (saline 2) this effect is diminished, although not quite obliterated (*4*). Such a depression of responding by saline may reasonably be termed a placebo effect. This placebo effect does not involve a loss of the monotonic increase in rate during the 5-minute interval. The characteristics of the depression and the manner in which it was brought about suggest, moreover, that it is an example of Pavlovian conditioning. It seems probable that the conditioned stimulus includes the injection of a hypodermic needle into the peritoneal cavity, for mere handling of the animal in several "mock" injections did not result in any noticeable change in responding. The effectiveness of this conditioned stimulus disappeared rapidly (see saline 2 in Fig. 1). In the parlance of classical conditioning, it would be said that extinction of the conditioned response (that is, the depression of responding) was rapid. Conditioning itself appears also to have been rapid in this situation, for the depression of responding by saline was evident after the first administration of scopolamine. Finally, it may be said, further analysis of the data showed that saline depressed responding more after two consecutive scopolamine injections that it did after just one.

It appears, then, that an injection of saline can come to depress the responding of a rat that is occasionally given scopolamine, which is a genuinely suppressive drug. This placebo effect is based on the animal's experience and can be eliminated by withholding the drug, in conformity with the traditional paradigm of simple Pavlovian conditioning. There appears to be no reason to suppose that the placebo effect in human patients differs in any way from that demonstrated here, other than in degree of complexity.

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References and Notes

1. I. P. Pavlov, *Conditioned Reflexes* (Oxford Univ. Press, London, 1927), pp. 35 ff; K. H. Collins and A. L. Tatum, *Am. J. Physiol.* **74**, 14 (1925); N. Kleitman and G. Crisler, *ibid.* **79**, 571 (1927).
2. Supported by grants from the National Science Foundation and by a gift from the Ciba Pharmaceutical Co., Inc., to Harvard University.
3. R. J. Herrnstein, *J. Exptl. Anal. Behavior* **1**, 351 (1958).
4. For the saline-control injections, the average rate of responding was higher during the postinjection than during the preinjection periods in three of the four cases. For the curves "saline 1" (Fig. 1), the postinjection rates were lower than the preinjection rates in all nine cases. For the curves "saline 2," the postinjection rates were lower in four of the five cases. By the sign test for matched pairs (based on the binomial theorem), the results for "saline 1" alone achieve statistical significance (1-percent level of confidence).

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Corticospinal Connections: Postnatal Development in the Rhesus Monkey

Abstract. The spinal distribution of the corticospinal fibers was studied experimentally in infant rhesus monkeys (*Macaca mulatta*) by means of the Nauta-Gygax silver impregnation technique. The findings suggest that the bulk of the direct cortico-motoneuronal connections in the rhesus monkey are established postnatally, during at least the first 8 months of life.

Ablations of the sensorimotor cortex in infant monkeys during the first month of life have little effect on the immediate motor performance by comparison to the motor deficits which result from such ablations in adult monkeys (*1*). The motor deficits resulting from the interruption of the pyramidal tract apparently are likewise less severe in the infant than in the adult (*2*). In addition to these ontogenetic differences, some phylogenetic differences exist. The motor deficits resulting from a hemispherectomy are less severe in cats than in adult monkeys; the former shortly regain normal strength in the affected extremities, whereas the latter never recover completely the normal strength in fingers and toes (*3*). Similar differences seem to exist between the motor deficits which result from interruption of the pyramidal tract in the cat and the monkey, respectively (*2, 4*).

The corticospinal fibers in the cat are distributed primarily to the nucleus proprius of the dorsal horn and the zona intermedia (*5*). The corticospinal fibers in the monkey are distributed to the nucleus proprius of the dorsal horn, the zona intermedia, and the dorsomedial parts of the ventral horn (*6, 7*). However, in the monkey, cortical fibers also are distributed to the motoneuronal cell groups of the ventral horns. These direct corticomotoneuronal connections are lacking in the cat. The differences between the motor deficits which occur in the respective animals might be related to these differences in the spinal distribution of the cortical fibers. Specifically, the long-lasting weakness in the distal musculature of the primates (*3*) might result from the interruption of the direct corticomotoneuronal connections. This is also suggested by the fact that corticomotoneuronal fibers in the rhesus monkey are distributed primarily to the lateral motoneuronal cell groups, innervating the distal musculature which is most severely affected (*7–9*). By contrast, very few cortical fibers are distributed to the medial motoneuronal cell groups innervating the proximal musculature which is far less severely affected. Recently, the corticospinal connections have been studied in the chimpanzee. The motor deficits resulting from the ablation of the sensorimotor cortex are more severe in this animal than in the rhesus monkey (*3*). The direct corti-