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Effect of Reserpine on Learning and Performance

Reserpine, an alkaloid extract of *Rauwolfia serpentina*, is now widely used in clinical psychiatry. It has been shown that it depresses well-established performance patterns of rhesus monkeys—for example, pressing a bar to avoid shock or to obtain food (*1*). The present study shows that reserpine can depress "discriminated" or "conditioned" responses, as well as "operant" responses, and suggests that reserpine depresses learning as well as performance.

The technique employed was the establishment and extinction of a conditioned emotional response to a signal (white noise) that preceded a noxious stimulus (electric shock). We observed the caged animal from an adjoining room through a one-way window, and independently rated responses to the noise and shock on a four-point scale. A rating of "zero" indicated no response, "one" a questionable response, "two" a fairly definite response, and "three" a very definite response. Response was defined as any recognizable change in ongoing behavior. The various responses to the sound included running, crouching, climbing, and lying prone. The pattern of response most commonly conditioned to the sound was a period of running, followed by crouching.

Eight rhesus monkeys, approximately 2 years of age, served as subjects. They were first given eight preconditioning trials consisting of the noise alone. The noise was approximately 25 decibels sensation level (human) and was sounded for 20 seconds on each occasion. The intervals between successive presentations of the noise were randomized, with an average interval of 2 minutes. The following day the monkeys were divided into two groups of four members each, a reserpine-conditioning group and a saline-conditioning group, and given the appropriate injection. A dosage of reserpine was selected (0.75 mg/kg) that is within the range of previous studies in which monkeys were employed and that typically depresses the general behavior of the animal significantly (*1*, *2*). The saline dosage chosen (0.3 ml/kg) was the same in volume as the reserpine solution.

Conditioning was begun 3 hours after injection for the reserpine group. The interval between injection and conditioning for the saline group was of the same order, but it was not carefully controlled. In the conditioning procedure, each presentation of the noise was followed by five short, strong pulses of electric shock (one per second) delivered by a method described elsewhere (*1*, *3*). The injections and conditioning procedures were repeated 2 days later. All animals received ten trials on each of the 2 days.

Three days after the second conditioning day, all animals were tested (without further injections) for "retention" of the conditioning experience. Conditioning trials were presented to a given animal at the rate of ten per day on alternate days, until a series of five successive noise responses was obtained, such that both investigators gave ratings of "two" or "three" to any four of the five responses.

In the study of extinction, the eight animals were again divided into reserpine and saline groups of four members each. The reserpine-extinction group consisted of two members from the reserpine-conditioning group plus two members from the saline-conditioning group, while the saline-extinction group consisted of the remaining two members of each of the two conditioning groups. Injections were given before each session. In the extinction procedure, electric shock was not presented. The trials were given in two sessions of ten each and were separated by 2 days. Three days later, the animals were tested for "extinction retention" by presenting further extinction trials (without injections), ten per day on alternate days, until a series of five successive noise responses was obtained, such that both investigators gave ratings of "zero" or "one" to any four of the five responses.

The following results were obtained. During conditioning, the reserpine group showed only slight deviations from "zero" values in their responses to the noise, although they definitely responded to the electric shock. The saline group showed a definite increase in noise response values. The following figures are the averages of both our ratings for each group of animals during the first ten and the second ten conditioning trials (the numbers in parentheses represent the range of the average ratings for each trial): reserpine group—0.03 (0 to 0.2), 0.17 (0 to 0.4); saline group—1.70 (0.9 to 2.6), 2.40 (1.9 to 2.8).

Table 1. Conditioning

Conditioning retention		Conditioning Saline (3)
Reserpine (1)	Saline (2)	
18	0	9
13	0	7
7	0	7
2	0	3

In Table 1 is listed the number of trials (not including the criterion trials) required for each animal to reach the retention criterion. All saline animals had perfect retention (column 2), while all reserpine animals required additional training (column 1) (this difference is significant at the 0.05 level by the Mann-Whitney test). Column 3 lists the number of trials in which the saline animals achieved criterion performance, if computations are made from the beginning of the conditioning period. This is a measure of how long it took control animals to learn this particular habit. By comparing the reserpine retention scores with the scores in column 3, one can determine whether the reserpine animals benefited from their experience under the drug. It can be seen that the difference between column-1 and column-3 scores is not significant, although the reserpine mean (and variance) is slightly larger.

In extinction, the reserpine group again showed considerably lower noise-response values than the saline group, regardless of which drug had been used during conditioning. The average ratings and ranges for the first ten and second ten extinction trials were as follows: reserpine extinction-reserpine conditioning group—0 (0 to 0), 0.05 (0 to 0.5); reserpine extinction-saline conditioning group—0.05 (0 to 0.5), 0.20 (0 to 0.5); saline extinction-reserpine conditioning group—1.75 (1.0 to 2.0), 1.70 (1.0 to 2.0); saline extinction-saline conditioning group—2.15 (1.8 to 2.5), 1.71 (1.0 to 2.5).

The first two columns of Table 2 give retention scores. The response of the animals that had had conditioning with sal-

Table 2. Extinction

Extinction drug	Extinction retention				Extinction Saline (3)	
	Reserpine (1)		Saline (2)			
Conditioning drug	Reserpine	Saline	Reserpine	Saline	Reserpine	Saline
Trials	12	40	0	14	20	34
Trials	10	13	0	2	19	22

ine was extinguished more slowly than the response of the animals that had had reserpine conditioning, regardless of *which extinction drug was employed* — this is presumably further evidence that the *saline animals* had learned more during the conditioning period. The reserpine extinction animals required more trials, on the average, to reach criterion than did the saline animals. Indeed, there is almost no overlap between the extinction subgroups. The reserpine group required slightly fewer trials, on the average, for extinction during the retention period than the total number of trials that the saline animals required *during* both the *extinction* and *extinction* retention periods (column 3).

On the present evidence, the most parsimonious interpretation is in favor of reserpine's depressing temporarily both performance and learning—that is, that the drugged animals were functionally impervious to conditioning and extinction events, had to "start from scratch" *once the drug had worn off, but subsequently responded normally to such events.* Insofar as the reserpine groups, when tested after the gross effects of the drug had dissipated, differed from the controls in their rate of conditioning or extinction, they required more conditioning trials and fewer extinction trials, although these differences are far from being statistically significant. If, with a larger *N* or more refined technique, such differences were to become significant, explanation might follow one of several courses.

Examples of such possible explanations include the following: slight amounts of reserpine (or a metabolic product) might be active in the organism long after its gross effects had disappeared; in extinction, the reserpine animals have a longer time to "forget" the conditioned response, if they are impervious to *the extinction events; the "baseline level of anxiety" might remain lower even* after the drug has been completely metabolized.

LAWRENCE WEISKRANTZ*
WILLIAM A. WILSON, JR.
Department of Neurophysiology,
Institute of Living,
Hartford, Connecticut

References and Notes

1. L. Weiskrantz and W. A. Wilson, Jr., *Ann. N.Y. Acad. Sci.* 61, 36 (1955).
2. A. E. Earl and R. C. Dibble, *The Effect of Reserpine (Serpasil) on Monkeys*, a film narration (Ciba, Summit, N.J., 1953); A. J. Plummer *et al.*, *Ann. N.Y. Acad. Sci.* 59, 8 (1954).
3. The shock intensity used was the strongest value in the listed series.

* Present address: University Laboratory of Physiology, Oxford, England.

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