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What Is a "Replication"? Epinephrine Facilitation of Learning under Anesthesia [Correspondence]

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To the Editor:--Replication is the sine qua non of science. Therefore, a reported failure to replicate necessarily raises doubts about the validity of the original findings. Recently, El-Zahaby et al. reported in ANESTHESIOLOGY [1] a failure to replicate the findings of Weinberger et al. [2] that epinephrine facilitates learning under anesthesia. El-Zahaby et al. concluded as follows:

Two reports in the literature have influenced the recent surge of interest in learning during anesthesia and have been cited often. One of them is Weinberger et al.'s work in animals, and the other is Levinson's [citation given] study in humans. . . .It is therefore disturbing [italics added] that we could not replicate the essential aspects of one study [referring to Weinberger et al.] and another group could not replicate the other [citation given].

Two other points are cited to cast doubt on the Weinberger et al. findings. The first questions the validity of the conditioned suppression test that we used to assess learning 10 days after training. The second is their statement that there have been no prior replications of Weinberger et al.

Readers may thus conclude that the Weinberger et al. findings were not genuine. However, none of these points are valid. First, the failure of El-Zahaby et al. to replicate is based on their performing an experiment that differs in so many major respects from Weinberger et al. that it constitutes an attempt to extend the findings to a different situation rather than an attempt to replicate. Second, conditioned fear is known to last for more than 10 days. Third, Weinberger et al. have been replicated using the same paradigm and procedures.

A Comparison of the Experiments.

The El-Zahaby et al. study differed in several major respects from the Weinberger et al. study; species (actually Mammalian order) of the subjects, type of anesthetic, depth of anesthesia, training protocol, behavioral response measured, behavioral testing conditions, and behavioral retention interval. Weinberger et al. studied rats anesthetized with sodium pentobarbital and chloryl hydrate, trained briefly in a single session, and tested for classical fear conditioning by using conditioned suppression of operant behavior 10 days after training. El-Zahaby et al. studied rabbits that were in a subanesthetic state induced by isoflurane, trained extensively in several sessions, and tested for classic conditioning of the nictitating membrane response during acquisition and 2 days later during extinction.

Several of these differences were noted by El-Zahaby et al., and they discussed one, the possibility that the nictitating membrane response is less sensitive than conditioned suppression as an assessment of learning. Given the vast differences between the studies, it is impossible to determine which of the variables is (are) critical. However, it is conceivable that in this situation the nictitating membrane response is less sensitive because subjects learn at least two things: (1) that the conditioned stimulus precedes the unconditioned stimulus (fear conditioning, involving behaviors incompatible with ongoing water licking) followed by (2) learning to make a precisely timed somatic motor response (resulting in the nictitating membrane conditioned response). Fear conditioning, as indexed by conditioned autonomic responses or conditioned suppression, is acquired more rapidly than is the nictitating membrane conditioned response. [3-5].

One major variable was the same for El-Zahaby et al. and Weinberger et al., the doses of epinephrine. Paradoxically, the use of the same doses might help explain the different findings. Weinberger et al. selected these doses based on prior studies in the waking rat that had shown facilitation of fear conditioning and other types of learning. However, apparently there are no published reports of epinephrine facilitation of nictitating membrane conditioning in the rabbit. Thus, the selection of doses by El-Zahaby et al. appear to be based on the rat and on a different aspect of learning. Therefore, one of the many possible reasons for the lack of robust facilitation observed by El-Zahaby et al. is that their doses may not have been optimal for the rabbit in their training situation. It might be helpful to first establish the appropriate facilitating doses for the nictitating membrane conditioned response in the normal rabbit to provide dose-response functions that could be used to guide the study of learning and anesthesia.

Interestingly, El-Zahaby et al. did report a statistically significant facilitation of the 0.01-mg/kg dose of epinephrine on day 6 of acquisition training. However, no effects were found in subsequent extinction training. Of note, the group means of the facilitating dose were greater than for the control and other epinephrine group also on days 4 and 5 (see their Figure 5). These findings suggest that the authors may have obtained a weak effect that might be made stronger if intragroup variability could be reduced, if other doses of epinephrine are used, or both.

Other Attempts to Replicate Weinberger et al.

The second point is that there have been no previous replications of Weinberger et al. that used the same procedures. That is incorrect. In 1985, Gold et al. [6] both replicated and extended the original study by Weinberger et al. That this replication was performed by the same authors as in the original study should not be sufficient reason to discount these findings. More recently, another laboratory has reported a replication of Weinberger et al., also using rats and lick suppression. [7].

Retention of Conditioned Suppression.

El-Zahaby et al. state that there is a lack of evidence that conditioned suppression can be observed as long as 10 days after training. However, fear conditioning is well known to show behavioral evidence of learning and retention in the rat for far longer than 10 days, whether it is assayed by conditioned suppression or by other means. Examples are 25 days (Goldstein [8]), 28 days (Campeau et al. [9]), 30 days (Franchina [10]), 35 days (Hendersen [11]), 42 days (Coulter et al. [12]), 45 days (Neuenschwander-El Massioui et al. [13]), 60 days (Goldstein [14]), and 90 days (Gleitman and Holmes [15]).

Replication versus Extension.

The El-Zahaby et al. paper raises the question of what is meant by a "replication." If this term is to be very helpful to readers, then it should be restricted to circumstances in which either the same experiment is repeated with no more than minor variations or a highly similar experiment is undertaken. Of course, no fixed formula can be applied to the term "highly similar," so that the decision as to whether a study is an attempted replication is likely to remain somewhat subjective unless identical methods are employed. Nonetheless, readers would be better served if authors and editors use a term such as "extension" rather than "replication" whenever the two experiments in question differ greatly. In the present case, it would be clear to readers that El-Zahaby et al. failed to extend epinephrine facilitation of learning under anesthesia to a situation of differences in species of subjects, type of anesthetic, depth of anesthesia, type of training, and nature of the behavioral assay of learning. Moreover, authors would be alerted to the distinction between an attempted replication and an attempted extension and thus be less likely to be concerned by failures to replicate that are more apparent than real. The result would be to reduce or preferably avoid confusion and obviate the need for communications such as this letter. The focus then could be on understanding the phenomenon of learning under anesthesia.

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REFERENCES

1. El-Zahaby HM, Ghoneim MM, Johnson GM, Gormezano I: Effects of subanesthetic concentrations of isoflurane and their interactions with epinephrine on acquisition and retention of the rabbit nictitating membrane response. ANESTHESIOLOGY 81:229-237, 1994.

2. Weinberger NM, Gold PE, Sternberg DB: Epinephrine enables Pavlovian fear conditioning under anesthesia. Science 223:605-607, 1984.

3. Lennartz RC, Weinberger NM: Analysis of response systems in Pavlovian conditioning reveals rapidly versus slowly acquired conditioned responses: Support for two factors, implications for behavior and neurobiology. Psychobiology 20:93-119, 1992.

4. Lennartz RC, Weinberger NM: A comparison of nonspecific and nictitating membrane conditioned responses: Additional support for two-factor theories. Psychobiology 22:5-15, 1994.

5. Kehoe EJ, Macrae M: Classical conditioning of the rabbit nictitating membrane response can be fast or slow: Implications for Lennartz and Weinberger's (1992) two-factor theory. Psychobiology 22:1-4, 1994.

6. Gold PE, Weinberger NM, Sternberg DB: Epinephrine-induced learning under anesthesia: Retention performance at several training-testing intervals. Behav Neurosci 99:1019-1022, 1985.

7. Darolia MK, Yadava A, Malhotra S: Effect of epinephrine on learning under anesthesia. J Indian Acad Appl Psychology 19:47-51, 1993.

8. Goldstein ML: The effect of amygdalectomy on long-term retention of an undertrained classically conditioned fear response. Bull Psychonomic Soc 4:548-550, 1974.

9. Campeau S, Liang KC, Davis M: Long-term retention of fear-pontentiated startle following a short training session. Anim Learn Behav 18:462-468, 1990.

10. Franchina JJ: Retention of fear. Psychonomic Soc 7:323-324, 1967.

11. Hendersen RW: Forgetting of conditioned fear inhibition. Learn Motivation 9:16-30, 1978.

12. Coulter X, Collier AC, Campbell BA: Long-term retention of early Pavlovian fear conditioning in infant rats. J Exper Psychology Anim Behav Processes 2:48-56, 1976.

13. Neuenschwander-El Massioui N, Dutrieux G, Edeline J-M: Conditioned hippocampal cellular response to a behaviorally silent conditioned stimulus. Behav Neurosci 105:313-325, 1991.

14. Goldstein ML: The effect of UCS intensity on the long-term retention of a classically conditioned fear response. Bull Psychonomic Soc 13:357-358, 1979

15. Gleitman H, Holmes PA: Retention of incompletely learned CER in rats. Physchonomic Sci 7:19-20, 1967.