the same A system and ELA antigens were grouped together. The formula is described by N. E. Morton, *Am. J. Hum. Genet.* **7**, 277 (1956).
6. G. D. Snell, J. Dausset, S. Nathenson, *Histocompatibility* (Academic Press, New York, 1976), pp. 118 and 216; V. Hruban, M. Simon, J. Hradecký, F. Jílek, *Tissue Antigens* **7**, 267 (1976); J. R. L. Pink, W. Droege, K. Hála, V. C. Miggiano, A. Ziegler, *Immunogenetics* **5**, 203 (1977).
7. A. Trommershausen-Smith, *J. Hered.* **69**, 214 (1978).
8. We thank M. Canon for assistance and D. Bernoco and B. Morris for critically reading the manuscript.

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Retrograde Amnesia for Old (Reactivated) Memory: Some Anomalous Characteristics

Abstract. *Old memory, when reactivated by cue exposure, was disrupted by mild or deep hypothermia treatments. New memory was impaired only by deep cooling. Moreover, old but not new learning showed spontaneous recovery. Old reactivated memory may be qualitatively different from newly acquired memory.*

That old memories are more stable and less susceptible to disruption than recently acquired learning has been a widely accepted proposition since the late 19th century, when Ribot, on the basis of human amnesia findings, formulated his "law of regression" (*1*). Although agreement on Ribot's principle is not universal (*2*), many reports of experimentally induced amnesia in animals have been consonant with the view that memory resists disruption by traumatic events as a function of time (*3*). Several recent studies, however, suggest that the degree of activation of memory may determine its vulnerability to insult more than the age of the information does (*4, 5*). Other evidence suggests not only that new and old (reactivated) memories can produce comparable interference effects (*6*), but also that both classes of memories may be enhanced by strychnine sulfate (*7*). We report here data substantiating several similarities as well as dissimilarities of new and old target memories subjected to amnesic treatment.

Because the induction of amnesia for cue-reactivated older memories has not always been obtained (*8*), we initiated our study in an attempt to replicate and extend the original demonstration (*4, 9*). Hypothermia was chosen as the amnesic agent since, like electroconvulsive shock, it is highly effective in producing retrograde amnesia for new learning (*10, 11*). In our first experiment, 36 adult male Holtzman rats (295 to 380 g) received one-trial training in a black-white passive-avoidance chamber (45.5 by 17.5 by 23.5 cm). When the rats crossed into the black compartment, they received an inescapable 1-second 150-V scrambled footshock.

After the training session, the animals were randomly divided into four groups of nine each; the experimental treatment was given 24 hours later. For three groups, a brief 30-second exposure to the black "fear" compartment was presented to reactivate the memory trace of passive-avoidance training. Immediately after cue exposure, they were subjected to mild or severe hypothermia treatment or no treatment and were then returned to their home cage. Hypothermia was induced by immersing restrained rats to neck level in water at 4°C until body temperatures were reduced to approximately 30.0° or 21.0°C for the mild and severe conditions, respectively. Mild body cooling was intended as a control for the general effects of stress per se (*10, 12*). The third group, which did not receive cold treatment, was used to assess the reactivation or extinction effect of the brief cue exposure. A fourth group of animals, included to establish a retention baseline, did not receive cue exposure or hypothermia treatment, but was simply transported to the experimental room and handled for 30 seconds. Twenty-four hours after experimental treatment all subjects received a passive-avoidance test to assess retention of the original training experience. Latency to enter the compartment previously associated with shock provided the index of memory.

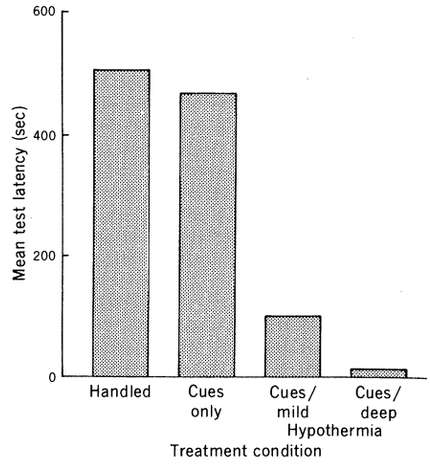

Fig. 1. Mean cross-through latency on a passive avoidance test trial 24 hours after experimental treatments. Considerable loss of retention is indicated by a rapid cross-through response.

Prior to punishment, the groups did not differ in their response latencies ($F < 1.0$). A one-way analysis of variance on the retention-test latencies (*13*) confirmed an effect of the experimental treatments ($P \leq .002$) (Fig. 1). As expected, the brief cue exposure alone had little, if any, effect on the retention normally observed 48 hours after passive-avoidance training. In contrast, the severe-hypothermia group exposed to the cue showed substantial memory loss, as reflected by test scores significantly lower than those of either the cues-only or handled controls ($P \leq .01$). To our surprise, the old reactivated memory was also disrupted by brief cooling ($P \leq .05$) with the resultant decrement indistinguishable from that produced by the more severe treatment. The severity of memory loss is reflected in the finding that the test latencies of both of these groups approached their respective training latencies.

The findings of a memory deficit following the combined cue exposure and hypothermia treatment substantiates previous reports (*4, 5*) that retrograde amnesia may be produced for old memories brought back to an active state. Other research indicates that brief cooling, even when administered immediately after acquisition, is not sufficient to produce retrograde amnesia (*10, 12*). Accordingly, as a check on the possibility that there may be some characteristic difference in the susceptibility to disruption of old and new memories, we conducted a direct comparison of the effect of deep and mild hypothermia on both classes of memories.

Fifty-six adult male rats received one-trial passive-avoidance training as in experiment 1. In the new learning condition, two groups of animals ($N = 11$ each) received either deep or mild hypothermia treatment within 30 seconds of the end of footshock. The disruptibility of old memories was assessed with an additional two groups of animals ($N = 11$ each) which were cooled for either a prolonged or a brief period, but only after a 24-hour delay. Both of these latter groups received a brief 30-second exposure to the fear cues of the black chamber prior to cold water immersion to produce reactivation of the target memory. As a control for systemic effects of the cold water treatment, two

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groups of six received the cooling treatments 24 hours after passive-avoidance training, but without a prior reactivation treatment (*14*). Twenty-four hours after their cold water immersion, all animals were tested for retention.

Prior to their experimental treatments, the six groups performed similarly on the cross-through response ($F = 1.1$). A 2 by 2 analysis of variance on the data from the cross-through test latencies (*13*) of the four experimental groups indicated reliable age of memory, immersion treatment, and interaction effects ($P \leq .001$) (Fig. 2). Comparably short test latencies were noted for both deep-cooled groups regardless of the age of the memory, but in the brief cooling condition memory disruption depended on the age of the memory ($P \leq .01$). More specifically, the brief cooling treatment produced forgetting of the old reactivated memory ($P \leq .01$) but had little, if any, behaviorally detectable effect on a recently acquired memory. Furthermore, each of the three groups that experienced "memory failure" displayed test latencies that approached their initial training scores. The remote possibility that the hypothermia treatments act retroactively on 24-hour-old memory is ruled out by the finding that 10 of 12 trained rats showed maximum avoidance (900 seconds) when delayed cooling occurred without the reactivation manipulation. These observations replicated our first experiment and verified that a condition sufficient to produce severe amnesia for a cue-reactivated memory leaves a new memory unscathed. This effect seems specific to the age of the memory, as additional data from our laboratory indicate no significant impairment of retention in the new learning condition when immediate posttraining cue exposure is combined with mild hypothermia treatment.

Although these data point to some important differences in the age-related characteristics of memory, striking evidence of some changing characteristic of a memory trace would be provided by a difference in the permanence of the memory disruption for young as compared with old memories. Accordingly, our next experiment examined the issue of spontaneous recovery. With respect to amnesia for newly acquired responses, it is now well established that memory seldom, if ever, returns spontaneously after electroconvulsive shock or hypothermia treatment (*15*). In contrast, evidence is lacking to answer the parallel question with respect to anmesia for old reactivated memories. Therefore, 1 or 3

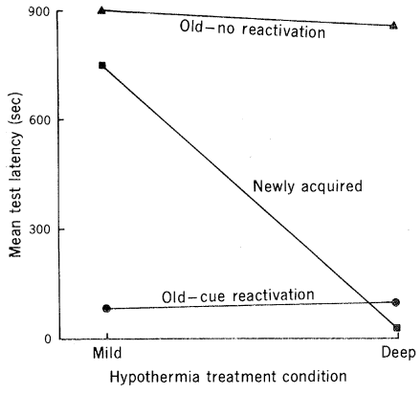

Fig. 2. A new memory was disrupted by deep but not by mild hypothermia when the treatment occurred immediately after the training footshock. An old memory, reactivated 24 hours after training footshock, was susceptible to disruption by either deep or mild hypothermia. Old memory in animals not receiving reactivation exposure was unaffected by mild or deep hypothermia treatment.

days after the initial test we retested the three groups from experiment 2 that had originally displayed amnesia.

Because of the small number of subjects in each of the retest subgroups, the data from the two intervals were pooled. A 3 by 2 repeated-measures analysis of variance (*13*) revealed significant group, test, and interaction effects ($P \leq .003$). The latency scores of both the cue-mild-hypothermia and cue-deep-hypothermia groups increased reliably over the two test sessions (84.6 to 583.9 and 92.5 to 512.7 seconds, respectively; $P \leq .01$), but the training-deep-hypothermia group showed no change (21.6 to 24.6 seconds; $P > .05$). A retest procedure has the drawback that the initial test may provide an implicit reactivation episode (*16*), thus potentially obviating the spontaneous aspect of recovery. However, this confounding was equally applicable to the new-learning-amnesia group, which failed to show a change in latencies across test trials. Thus, the persistence of amnesia is markedly different depending upon whether the treatment affects old or new learning.

These data are consistent with a growing body of evidence that old reactivated memories share some of the characteristics of new memories (*4–7*). As such, our findings indicate a boundary condition on Ribot's concept of memory disruptability: Although early memories may be more resistant to disruption than new ones, an old reactivated memory appears to be highly vulnerable. Moreover, after cue reactivation, the susceptibility of memory to disruption by either mild or deep hypothermia decreases over time (*17*), an outcome parallel to that with recently acquired memory. Thus, time since original learning does not appear to be the only determinant of the "fragility" of a trace (*18*). Whether the cue exposure induces memory activation (*4, 5*) or reinitiates either rehearsal (*19*) or a motivational state akin to that of training (*20*) is not yet clear. But it should be noted that dormant memories of comparable age remained impervious to disruption. Although the similarities between reactivated and new memories are impressive, some intriguing differences remain. That memories of different ages may differ in qualitative as well as quantitative characteristics warrants further consideration.

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References and Notes

1. T. A. Ribot, *The Disease of Memory* (Humboldt Library, New York, 1883).
2. P. Rozin, in *The Neurosciences*, F. O. Schmidt and F. T. Worden, Eds. (MIT Press, Cambridge, Mass., 1974), vol. 3.
3. S. E. Glickman, *Psychol. Bull.* **58**, 218 (1961); J. L. McGaugh, *Science* **153**, 1351 (1966).
4. J. R. Misanin, R. R. Miller, D. J. Lewis, *Science* **160**, 554 (1968).
5. D. J. Lewis, *Am. J. Psychol.* **89**, 51 (1976).
6. W. C. Gordon, *ibid.* **90**, 231 (1977); ——— and N. E. Spear, *J. Exp. Psychol.* **99**, 349 (1973).
7. J. L. McGaugh and R. G. Dawson, in *Animal Memory*, W. K. Honig and P. H. R. James, Eds. (Academic Press, New York, 1971), pp. 215–242; W. C. Gordon and N. E. Spear, *Physiol. Behav.* **10**, 1071 (1973); W. C. Gordon, *ibid.* **18**, 95 (1977).
8. R. G. Dawson and J. L. McGaugh, *Science* **166**, 525 (1969); G. Banker, E. Hunt, R. Pagano, *Physiol. Behav.* **4**, 895 (1969); P. E. Gold and R. A. King, *ibid.* **8**, 797 (1972); T. A. Weaver and J. G. Magnus, *Psychonom. Sci.* **16**, 265 (1969); J. L. Jamieson and D. J. Albert, *ibid.* **18**, 14 (1970); L. R. Squire *et al.*, *Behav. Biol.* **18**, 335 (1976).
9. A. M. Schneider and W. Sherman, *Science* **159**, 219 (1968).
10. D. C. Riccio, L. A. Hodges, P. K. Randall, *J. Comp. Physiol. Psychol.* **66**, 618 (1968).
11. R. E. Beitel and P. B. Porter, *ibid.*, p. 53.
12. G. S. Grosser and H. E. Percy, *ibid.* **76**, 119 (1971); N. A. Marlin, C. Greco, R. R. Miller, *Bull. Psychonom. Soc.* **11**, 295 (1978).
13. Not only did parametric and nonparametric analyses lead to the same interpretation of the latency data, but analyses of a second measure, amount of time spent in the white "safe" compartment during the 15-minute test session, were similar in pattern to the latency data.
14. To minimize implicit reactivation when these rats were moved for the cooling treatment, they were carried in a gloved hand rather than in the transport cage used earlier to bring them to the training apparatus.
15. D. J. Lewis, *Psychol. Rev.* **76**, 461 (1969); R. R. Miller and A. D. Springer, *ibid.* **80**, 69 (1973); D. C. Riccio and E. R. Stikes, *Physiol. Behav.* **4**, 649 (1969); C. F. Hinderliter, T. Webster, D. C. Riccio, *Anim. Learn. Behav.* **3**, 257 (1975).
16. N. E. Spear, *Psychol. Rev.* **80**, 163 (1973).
17. C. F. Mactutus, thesis, Kent State University, in preparation.
18. W. A. Wickelgren, *Mem. Cognit.* **2**, 775 (1974).
19. A. R. Wagner, J. W. Rudy, J. W. Whitlow, Jr., *J. Exp. Psychol. Monogr.* **97**, 407 (1973).
20. D. R. Meyer, *Am. Psychol.* **27**, 124 (1972).
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