Gold, *Adv. Neurol.* **23**, 557 (1979); J. J. Mann, M. Stanley, S. Gershon, M. Rossor, *Science* **210**, 1369 (1980).
15. G. T. A. M. Bots and G. W. Bruyn, *Acta Neuropathol.* **55**, 2122 (1981).
16. E. D. Bird and L. J. Kraus, in *Transmitter Biochemistry of Human Brain Tissue*, P. Riederer and E. Usdin, Eds. (Macmillan, London, 1981), p. 201; P. C. Emson *et al.*, *ibid.*, p. 221; H. Bernheimer and O. Hornykiewicz, in *Huntington's Chorea 1872–1972*, A. Barbeau, T. N. Chase, G. W. Paulson, Eds. (Raven, New York, 1973), p. 525; J.-Y. Wu, E. D. Bird, M. S. Chen, W. M. Huang, *Adv. Neurol.* **23**, 527 (1979); E. G. S. Spokes, N. J. Garrett, M. N. Rossor, L. L. Iversen, *J. Neurol. Sci.* **48**, 303 (1980).
17. J. C. Gillin *et al.*, paper presented at the Annual Meeting of the American Psychiatric Association, New Orleans (1981).
18. T. E. Adrian *et al.*, paper presented at the 13th International Congress of Neuropsychopharmacology, Jerusalem (1982).
19. E. D. Bird *et al.*, *Lancet* **1977-II**, 1157 (1977).
20. T. J. Crow *et al.*, in *Transmitter Biochemistry of Human Brain Tissue*, P. Riederer and E. Usdin, Eds. (Macmillan, London, 1981), p. 85.
21. C. M. Lee, P. C. Emson, L. L. Iversen, *Brain Res.* **220**, 159 (1981).
22. S. H. Buck, P. P. Deshmukh, T. F. Burks, H. I. Yamamura, *Neurobiol. Aging* **2**, 257 (1981).
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Opiate Antagonists Improve Spatial Memory

Abstract. *Rats trained on an eight-arm radial maze were challenged by placing the maze in new spatial environments. Administration of opiate antagonists, either naloxone or diprenorphine, after exposure to the new environments significantly improved subsequent performance. The effect of naloxone on spatial memory was attenuated when drug administration occurred 2 hours after maze exposure.*

Russell and Nathan's clinical description of retrograde amnesia in humans (*1*) was soon followed by reports that treatment after training could impair later retention of a recently learned response in laboratory animals. The effects of treatments such as electroconvulsive shock and protein synthesis inhibition in laboratory animals depend on time—the sooner the agent is administered after training, the greater the amnesic effect (*2*). In the past few years, many studies have reported that opiates and opioid peptides alter time-dependent memory processes in laboratory animals (*3*). In general, administering opiates and opioid peptides at low doses produces amnesia for events before treatment, and this effect can be blocked by concurrent administration of the opiate antagonist naloxone (*4*). The complementary finding is that administering an opiate antagonist (for example, naloxone) by itself enhances retention (*5*).

Almost all the studies that have examined the effects of opiates on memory have used aversive training procedures. Since opioid peptide systems seem to be activated by noxious stimuli (*6*), it has been proposed that perhaps only those memories involving painful or fear-producing events will be influenced by opioids and their antagonists (*7*). We now report, however, that administering opiate antagonists enhances memory of a nonaversive spatial learning task.

Rats can be readily trained to visit each arm of an elevated eight-arm radial maze only once during a session when a food pellet is placed at the end of each arm (*8*). Accurate performance of this task normally depends on information provided by spatial cues in the environment outside the maze (*9*). We studied possible enhancing effects of posttraining opiate antagonist administration on spatial memory using a procedure in which the performance of normal animals on the eight-arm maze was less than optimal. A 6-hour delay was inserted between the fourth and fifth choices; animals were then challenged by placing the maze in new spatial environments. The effects of experimental treatments on the development of criterion performance were assessed.

Male Sprague-Dawley rats (Charles River Laboratories) (*10*) were originally trained on the eight-arm maze until they reached criterion performance by visiting each arm with no more than two errors (that is, an entry into an already-visited arm) on three consecutive days. Subsequently, increasing delays (1 minute, 30 minutes, 6 hours) were introduced between the fourth and fifth choices, and the animals were trained to criterion at each delay. After completing this training, animals were tested on the same maze placed in two novel environments. The two new rooms were comparable in size to the original room used for training; a number of prominent cues outside the maze (lighting fixtures, objects on the walls and floor) differed from room to room. In one of the novel environments, an opiate antagonist was administered; in the other, the same animals were injected with physiological saline. In order to ensure that the results would reflect neither specific differences in the two rooms nor order effects, treatments were counterbalanced. Animals were trained to criterion under the 6-hour delay in each of the novel environments. All injections were administered intraperitoneally immediately after the first four correct choices at the beginning of the delay period on each day of testing until the criterion was reached. Two separate experiments were done: the opiate antagonist used in experiment 1 was naloxone (2 mg/kg), and that in experiment 2 was diprenorphine (1 mg/kg).

The mean trials to criterion and errors to criterion for each opiate antagonist treatment group, summed over both novel environments, are presented in Table 1 (*11*). In both experiments, administering an opiate antagonist led to acquisition in significantly fewer trials and with fewer errors than were required with saline treatment (*12*). In fact, every animal in experiment 1 required fewer trials to reach criterion with naloxone than with saline.

The spatial nature of the memory in this task was evaluated for both experiments. When the maze was rotated (*13*), accurate performance was based on information provided by spatial cues in the room surrounding the test apparatus. This result indicates that new spatial information was acquired during exposure to each novel environment.

Another experiment was conducted to assess further the reliability of the naloxone effect on spatial memory and to evaluate whether this effect is time-dependent. Ten rats were initially trained

Table 1. Effects of opiate antagonist administration on maze performance (*11*). Values are means ± standard errors.

Treatment	Trials to criterion	Errors to criterion
Experiment 1 (N = *8*)		
Saline	5.38 ± 0.71	12.0 ± 2.89
Naloxone	3.25 ± 0.63*	4.4 ± 2.74*
Experiment 2 (N = *10*)		
Saline	4.90 ± 0.70	12.2 ± 3.03
Diprenorphine	3.60 ± 0.49*	5.8 ± 2.89*

*Significantly different from saline treatment ($P < 0.005$) (*12*).

Table 2. Time-dependent effects of administration on maze performance. Values are means ± standard errors.

Treatment	Trials to criterion	Errors to criterion
Control		
No treatment	4.7 ± 0.64	11.2 ± 3.12
Saline	4.8 ± 0.75	10.6 ± 3.29
Naloxone		
No delay	3.5 ± 0.67*	3.7 ± 1.27*
2-hour delay	4.0 ± 0.89	7.0 ± 2.93

*Significantly different from control treatments ($P < 0.001$) (*14*).

to criterion under a 5-hour delay procedure. These animals were subsequently tested according to a within-subject design in four different novel environments under the following conditions: (i) no-treatment, (ii) saline vehicle injection, (iii) naloxone (2 mg/kg) administered at the beginning of the 5-hour delay immediately after the first four choices on the maze; and (iv) naloxone (2 mg/kg) delayed for 2 hours after the initial four choices. The assignment of animals to treatments in each novel environment (a room) was approximately counterbalanced.

As there was no statistically significant difference between the no-treatment and saline-treatment conditions (Table 2), for each animal, mean trials to criterion and error scores were calculated. These mean control values were used in subsequent statistical analyses. As in the previous experiments, naloxone administered immediately after the first four choices significantly enhanced performance, as reflected in both trials and errors to criterion (*14*). The data from the naloxone-delay condition do not, however, differ significantly from either the control treatments or the naloxone treatment at no delay. These results indicate that naloxone does not produce an effect comparable to that of the no-delay condition when administration is delayed for 2 hours after training. As in the previous experiments, rotation of the maze on a test conducted for each animal after criterion performance indicated that performance was based on extra-maze cues provided in each environment (*13*).

The results indicate that when performance on a spatial learning task is less than optimal, administering an opiate antagonist after training can enhance memory. Thus, the memory-enhancing effect of opiate antagonists seems not to be restricted to memories acquired through aversive training or associated with noxious events. This view of a more general role for opioid peptides in memory is congruent with preliminary clinical studies that have recently indicated that naloxone improves memory functions in patients with Alzheimer's disease (*15*). Further research on the role of opioid peptides in memory may, therefore, have important implications for understanding the biological basis of both normal memory and its disorders.

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References and Notes

1. W. P. Russell and P. W. Nathan, *Brain* **69**, 280 (1946).
2. C. P. Duncan, *J. Comp. Physiol. Psychol.* **42**, 32 (1949); J. L. McGaugh, *Science* **153**, 1351 (1966).
3. I. Izquierdo *et al.*, in *Endogenous Peptides and Learning and Memory Processes*, J. L. Martinez, Jr., *et al.*, Eds. (Academic Press, New York, 1981), pp. 269–290; R. B. Messing *et al.*, *ibid.*, pp. 431–443.
4. C. Castellano, *Psychopharmacologia* **42**, 235 (1975); I. Izquierdo, *Psychopharmacology (Berlin)* **66**, 199 (1979); ——— and R. D. Diaz, *Neurosci. Lett.* **22**, 189 (1981); J. L. Martinez, Jr., and H. Rigter, *ibid.* **19**, 197 (1980).
5. M. Gallagher and B. S. Kapp, *Life Sci.* **23**, 1973 (1978); R. B. Messing *et al.*, *Behav. Neural Biol.* **27**, 266 (1979); M. Gallagher, *ibid.* **35**, 375 (1982); I. Izquierdo and M. Graudenz, *Psychopharmacology (Berlin)* **67**, 265 (1980).
6. J. Rossier, E. D. French, C. Rivier, N. Ling, R. Guillemin, F. Bloom, *Nature (London)* **270**, 618 (1977); H. Akil, S. J. Watson, J. D. Barchas, C. H. Li, *Life Sci.* **24**, 1659 (1979); I. Izquierdo *et al.*, *Psychopharmacology (Berlin)* **70**, 173 (1980).
7. M. Gallagher and B. S. Kapp, in *Endogenous Peptides and Learning and Memory Processes*, J. L. Martinez, Jr., *et al.*, Eds. (Academic Press, New York, 1981), pp. 445–461.
8. D. S. Olton and R. J. Samuelson, *J. Exp. Psychol.: Animal Behav. Process* **2**, 97 (1976).
9. J. O'Keefe and D. H. Conway, *Exp. Brain Res.* **31**, 573 (1978); S. Suzuki, G. Augerinos, A. H. Black, *Learn. Motiv.* **11**, 1 (1980).
10. Rats weighed approximately 250 g at the beginning of each experiment. All animals were maintained at 80 percent of free-feeding body weight by being fed a measured amount of laboratory chow each day after behavioral testing. Rats were housed on a 12-hour light-dark cycle (lights on between 0700 and 1900), and water was available at all times.
11. On each day of training and testing, animals were run on the maze until they had visited each arm once. Since an animal was free to re-enter arms already visited, it could accumulate many errors on a trial. Thus, because of a relatively large number of errors on early test trials, there can be more errors than trials to criterion.
12. Multivariate analysis of variance applied to trials and errors to criterion indicated a significant overall difference between treatment conditions [$F(2, 6) = 29.43$, $P < 0.001$]. Univariate analysis of variance revealed that naloxone treatment resulted in significantly fewer trials to criterion, [$F(1, 7) = 51.87$, $P < 0.0002$] and errors to criterion [$F(1, 7) = 21.44$, $P < 0.005$]. Multivariate analysis of variance revealed a significant overall difference between the saline and diprenorphine treatment conditions [$F(2, 8) = 7.36$, $P < 0.015$]. Diprenorphine treatment significantly reduced trials to criterion [$F(1, 9) = 15.06$, $P < 0.005$] and errors to criterion [$F(1, 9) = 14.49$, $P < 0.005$].
13. After four choices had been made, the maze was rotated 180° during the delay interval. The remaining food rewards were placed on arms that conformed to the correct location in the testing room. After maze rotation, the choice of arms during retention testing exhibited reliable accuracy based on food location in the extra maze environment.
14. Multivariate analysis of variance conducted on the control values and the combined data from the naloxone and naloxone-delay treatments revealed a significant treatment effect [$F(4, 5) = 11.44$, $P < 0.006$]. Subsequent specific statistical analyses indicated that, compared to the control conditions, naloxone administration immediately after the first four choices on the maze significantly decreased trials and errors to criterion from control values [$F(1, 9) = 22.96$, $P < 0.001$ and $F(1, 9) = 46.96$, $P < 0.0001$, respectively]; however, no significant differences were obtained between the control and the naloxone-delay condition.
15. B. Reisberg *et al.*, *Psychopharmacol. Bull.* **19**, 45 (1983); *N. Engl. J. Med.* **308**, 721 (1983).
16. Supported by NIMH grant MH35554, an Institutional Development Foundation Award, and NIMH research scientist development award K02 MH00406 to M.G. We thank Endo Pharmaceutical for their gift of naloxone and NIDA Research Technology Branch for providing diprenorphine.

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Optimization: A Result or a Mechanism?

Mazur reported "evidence against optimization as the basic mechanism underlying choice behavior" (*1*, p. 823). But in so doing, he missed an important point: optimality accounts are explanations in terms of final causes, not descriptions of a mechanism. It is a fundamental error to identify optimization theory with any particular mechanism by which optimal results are achieved (*2, 3*). Consequently, an experiment ruling out a particular optimizing mechanism has little bearing on the general usefulness of optimality accounts.

Mazur described a possible optimizing mechanism that involves variation (properties unspecified) in the distribution of responses between two choices and comparison (across unspecified time periods) of the overall payoff rates so obtained. His results rule out such a process. However, many other processes, sufficient to yield maximizing under the usual conditions that yield matching of response and reinforcement ratios, are not ruled out. For example, if the animal always chooses the alternative with highest probability of payoff (hill-climbing), where the probabilities are based on its past history of choices, results similar to Mazur's are to be expected (*4*). Hence his experiment shows only that overall payoff rate (averaged over periods of an hour or so) is not used by pigeons as a guide to choice proportion. Few optimality theorists, however, assume either that overall reward rate is directly assessed by animals or that pigeons are capable of selecting a particular choice proportion, as opposed to simply making one or the other choice.

Optimality theory in general is not testable, since any experimental result can be expressed as the optimal solution to some problem; what is testable is constrained optimization, the idea that animals behave optimally subject to specified constraints (*5*). Mazur wrote, "One might argue that the pigeons in this study failed to optimize because they did not 'understand' the complex contingencies in effect. An animal's 'understanding' is not relevant to optimization theory, however" (*1*, p. 825). Actually, though, the animal's "understanding" defines the constraints within which it