ing to Trivers, an effective strategy for a male in such circumstances is to sequester a female for a period long enough to determine whether egg laying is imminent. Early egg laying or other evidence that the female has been recently exposed to another male should reduce her attractiveness and be reflected in the male's behavior toward her.

In the ring dove, the amount of parental investment provided by the male is substantial; both sexes construct the nest, incubate the eggs, and feed and care for the young. Ovarian activity, which culminates in ovulation and egg laying, is stimulated by male courtship (*2*); the prominent "nest-soliciting" display of the male appears to be particularly effective in the induction of ovarian activity in the female (*3*). Although the female herself normally exhibits little courtship behavior when first paired with the male, the secretion of ovarian steroid hormones induced by the male stimulates her to engage in the nest-soliciting display with increasing frequency (*4*). This display by the female, coupled with her attachment to the nest site, seems to signal her readiness to construct a nest, an endeavor that the male and female pursue cooperatively (*5*). Thus the female's nest soliciting is important to the social synchrony of nest construction but also indicates that she is rapidly approaching ovulation as a result of recent exposure to a male. According to Trivers' hypothesis, male ring doves should be wary of females that show nest-soliciting behavior too soon after their initial encounter, since such early nest soliciting reflects the fact that the females have been courted and, possibly, inseminated by other males. In our study we compared the courtship and aggressive responses of male ring doves when they were introduced to females that had been either isolated for several weeks or stimulated by other males to the point of active nest soliciting.

All males were hatched in the laboratory and, at the time of the study, were sexually mature. Immediately prior to testing they spent a minimum of 2 weeks in visual (but not auditory) isolation from other animals. Seventeen males were observed, first with a "preexposed" female, then, 4 days later, with an "unexposed" female; 18 males were tested in the reverse order. These tests were conducted between 0900 and 1300 hours in an 89-cm cubical cage supplied with food, water, nesting material, and a glass nest bowl. One group of stimulus females was prepared for testing by giving them six 15-minute exposures to an active male (not a subject male) at 1- or 2-day intervals. These females readily engaged in nest-soliciting displays when introduced to the test males. A second group of stimulus females was given a parallel series of exposures to the empty test cage. None of these showed nest-soliciting behavior when introduced to the test males.

Table 1 shows the differences in male performance on exposure to each kind of stimulus female (*6*). Unexposed females elicited much more nest-soliciting activity from the males than did preexposed females ($t = 97$, $P < .0094$). Conversely, preexposed females provoked more frequent chasing and aggressive pecking ($t = 27.5$, $P < .00006$; and $t = 84$, $P < .0004$, respectively). Typically, the nest-soliciting displays of the male when in the presence of a preexposed female occurred prior to any nest-soliciting performance by the female. In most instances the male terminated his nest soliciting and attacked the female when she began her own nest-soliciting display.

We found no clear relation between the condition of the female and the frequency of male bowing and cooing, a second behavioral display ($t = 251.5$, $P > .94$). However, this behavior is performed most frequently during the first few moments after meeting a female or another male, and its principal function may be to identify the species and sex of the performer (*7*).

The female dove that has been hormonally primed by a male is placed in a difficult position if she loses her mate prior to nest construction and egg laying. Three to 4 days of male courtship are sufficient to induce ovulation and egg laying in a majority of females (*8*). Thus, if the female ring dove loses her mate after such stimulation, she must recruit another before her eggs are laid. If she manages to do so, she still must enlist his aid in nest construction or must attempt to build the nest herself. In either case, the premature emergence of female nest-soliciting displays or nest-building activity after pairing could indicate to a male the likelihood that the female has been recently exposed to another male and, therefore, is to be driven off or avoided. The differences in courtship, chasing, and attack portrayed in our study suggest that, given the opportunity for a direct choice, males prefer those females whose ovaries have not been primed through exposure to other males.

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Stimulant-Related State-Dependent Learning in Hyperactive Children

Abstract. *Hyperactive and nonhyperactive children performed a learning task in two states, while being treated with stimulant medication (methylphenidate) and while taking a placebo, and were tested for retention of each class of learned material in both states. Symmetrical state-dependent learning was demonstrated in the hyperactive group but not in the nonhyperactive group. The state-dependent effect was contingent on the presence of drug-induced facilitation during initial learning. This is apparently the first report on record of state-dependent learning with a drug agent that facilitates rather than impairs performance of human subjects.*

The phenomenon of state-dependent learning has attracted interest with regard to both its underlying mechanism (*1, 2*) and its implication for clinical practice (*3, 4*). In both animals (*1, 5*) and humans (*2, 3, 6*), when a drug affects performance during acquisition of new material, performance at a later time may depend on reinstatement of the drug treatment.

When drugs are used therapeutically (*3, 4*), an important clinical question arises as to whether information acquired by a patient under the influence of

a drug treatment will be retained in the absence of that influence. If learning is state-dependent, retention will be greater when the drug treatment is given both at the time of acquisition and during testing for retention than on only one of those occasions.

Most theories of state-dependent learning are based on data from animal experiments in which the drug treatment substantially impairs performance; such results have caused state-dependent learning to be considered in association with drug-induced impaired brain function (*1, 5*). Research on the effect of two depressant agents (alcohol and marijuana) (*6*) has revealed state-dependent learning in humans in inebriated states, a result consistent with the research on drug-impaired animals. Our research differs from research with depressants. We have investigated the effect of methylphenidate, a stimulant drug agent that improves the learning ability of children who are continuously inattentive and impulsive ("hyperactive").

To the best of our knowledge, state-dependent learning in the context of drug-induced facilitation instead of that of drug impairment has never before been reported. However, since stimulants do improve the learning of children suspected of minimal brain dysfunction (*7*) and those with selective learning disabilities associated with impulsivity and attentional deficits (*8*), the question of state-dependency and drug-induced facilitation deserves further investigation in these clinical groups.

Despite the widespread use of stimulants in the treatment of the heterogeneous clinical population labeled as "hyperactive," the criteria for diagnosing hyperactivity are so ill-defined (*4*) that, in some cases, stimulants have been inappropriately prescribed for nonhyperactive children (*9*). Also, the effectiveness of stimulant treatment of hyperactive children has often been obscured by underdosage (*10*). These problems could be overcome if children manifesting symptoms of hyperactivity were classified into "stimulant-responsive" and "stimulant-unresponsive" subgroups by direct demonstration (*11*) before long-term stimulant treatment was attempted. Working toward this goal, we included in our group of hyperactive children only those who had demonstrated a favorable response to an established therapeutic dose of the stimulant methylphenidate. Thus, we are dealing with a homogeneous group of stimulant-responsive hyperactive children.

The few previous investigations of stimulant-related state-dependent learning do not present a clear picture. With adults as subjects and a large dose of *d*-amphetamine, which slightly impaired performance, Bustamante *et al.* (*12*) obtained large state-dependent effects on learning. However, Hurst *et al.* (*13*), with smaller doses of *d*-amphetamine, which facilitated retention but not initial acquisition, found only an overall drug effect and no state dependency. With hyperactive children as subjects, Aman and Sprague (*14*) found neither an overall nor a state-dependent effect of stimulants on learning. We report here a pattern of stimulant-related state-dependent learning that clarifies these diverse findings.

Table 1. Number of errors (mean ± standard error of the mean) made on tests of retention (day 2) by hyperactive and control children. During the learning and retention phases, the treatment conditions were drug (D) or placebo (P); for example, PD refers to the combination in which the placebo was given during learning and the drug methylphenidate was given during testing for retention.

Treatment combinations (learning-retention)	Errors	
	Hyperactive (N = 32)	Control (N = 16)
PD (different)	12.9 ± 1.6	18.3 ± 4.6
DD (same)	9.1 ± 1.1	17.6 ± 2.8
PD − DD	3.8 ± 1.1	0.7 ± 3.0
DP (different)	20.3 ± 2.3	14.7 ± 2.4
PP (same)	15.9 ± 2.2	11.3 ± 1.5
DP − PP	4.4 ± 1.4	3.4 ± 2.0

Our subjects (mean age, 10.5 years) were 32 hyperactive and 16 nonhyperactive (control) children who were being seen at the learning clinic of the Hospital for Sick Children, Toronto. Ten of the control children were referred to the clinic with questionable hyperactivity that was disconfirmed, and the other six had no symptoms suggestive of hyperactivity. All testing (double-blind) took place on two successive days. On each day, both drug and placebo states were established (one in the morning and the other in the afternoon) by administering 10, 15, or 20 mg of Ritalin (methylphenidate), or Ritalin-placebo (CIBA), 30 minutes before breakfast and 30 minutes before lunch. Testing followed 1 hour after each administration. When taken orally, methylphenidate starts to control hyperactive behavior in about 30 minutes, and its effective duration is about 4 hours. We could thus establish alternate states within an individual in a single day.

In the learning task, photographs of 48 animals were stimuli and four familiar city names (Calgary, Montreal, Ottawa, and Vancouver) were responses. Our subjects learned to associate an assigned "zoo location" with each animal by a paired-associate procedure in which, on each trial, a slide of an animal was presented, a verbal response was elicited, and feedback was given.

On the first day, four sets of six items were presented during the morning, when the subject was in one state (drug or placebo), and the other four sets were presented during the afternoon, when the subject was in the other state (*15*). The six items of each set were presented in a random order until two errorless recitations were performed. During each session on day 1, the measure of performance was the sum of the errors that were made while learning the four sets of six items.

The experiment was designed to produce data relevant to state dependency simultaneously within a single test session so that motivational set and other unidentified factors could be held constant. The 48 items learned on day 1 were rearranged into two lists of 24 items each for retention testing on day 2. Each initial list of six items was divided into half, and half of the material learned in the morning of the first day was combined with half of the material learned in the afternoon of the first day. This created two lists of 24 items, each composed of 12 items learned in the drug state and 12 learned in the placebo state. Testing for retention on day 2 with one of these lists in the drug condition and the other in the placebo condition (*15*), we obtained the four combinations of learning and retention states to test for state dependency: drug-drug and placebo-placebo ("same" states) and drug-placebo and placebo-drug ("different" states). In the retention test, we followed the procedure of day 1 (presenting the 24 items as a single long list until the criterion was met). The two measures of performance during each retention session on day 2 were (i) the number of errors made on items learned in the same state as retention, and (ii) the number of errors made on items learned in a different state.

On the first day, we found significant drug-related facilitation of performance for the 32 hyperactive children, in that their scores were significantly better in the drug condition (24.4 errors) than in the placebo condition (33.0 errors) [$t(31) = 3.7$, $P < .01$]. But the performance of the 16 control children did not differ significantly [$t(15) = 1.7$, $P > .05$] between the two conditions of day 1, although the trend toward more errors in the drug condition (36.2) than in the placebo condition (27.9) opposed the drug-related facilitation obtained for the hyperactive group.

To evaluate relearning in terms of the four learning-retention combinations of

the second day (Table 1), three independent statistical comparisons addressed the following questions (*16*): (i) Did overall drug-induced facilitation occur? (ii) Was performance state-dependent during the drug test? (iii) Was performance state-dependent during the placebo test?

In the hyperactive group, overall drug-induced facilitation of performance occurred on day 2 just as on day 1; fewer errors (11.0 versus 18.1) were made in the drug condition than in the placebo condition [$t(31) = 4.4$, $P < .01$]. During relearning in the drug state on day 2, 41.8 percent more errors were made in response to items initially learned in the placebo (different) state on day 1 than to items initially learned in the drug (same) state [$t(31) = 3.4$, $P < .01$]. A similar state-dependent effect was observed in the placebo test condition; 27.8 percent more errors were made in response to items learned in the drug (different) state than to items learned in the placebo (same) state [$t(31) = 3.2$, $P < .01$]. Thus the state dependency is a bidirectional effect (*17*) that goes beyond the overall facilitating effect of the drug treatment.

The performance of the 16 control children on day 2 again showed trends toward impairment of performance resulting from the drug treatment and toward state dependency (Table 1), but neither effect was statistically significant ($P > .05$). Thus, the hyperactive and control subjects produce different patterns of results both with respect to the main drug effect and to the state-dependent effect associated with the drug treatment. This pattern is consistent with a comparison in which an abnormal (alcoholic) group demonstrated greater state-dependent learning than did a normal group (*18*). This suggests that failure to separate normal individuals from special populations, which is likely when hyperactive children are not evaluated for responsivity to drugs (*4, 11*), makes detection of state-dependent learning difficult.

The differences between the two types of subjects, especially with regard to the state-dependent effect, may be explained by an analysis of the drug-placebo differences in performance on day 2 in light of performance on day 1. Among the 32 hyperactive children, the performances of nine were slightly impaired (*19*) in the drug condition on day 1 of testing but were facilitated on the next day (Table 2). The overall drug-related facilitation on day 2 was large (8.9 drug errors versus 20.9 placebo errors), but these nine children did not show state dependency (15.0 same-state errors versus 14.8 different-state errors).

Table 2. Number of errors (mean ± standard error of the mean) made during retention tests by hyperactive children as a function of the drug effect on initial learning. The notation is the same as that in Table 1.

Treatment combinations (learning-retention)	Errors during retention	
	Facilitated acquisition ($N = 23$)	Impaired acquisition ($N = 9$)
PD (different)	14.3 ± 2.0	9.1 ± 2.3
DD (same)	9.2 ± 1.5	8.8 ± 1.5
PD − DD	5.1 ± 1.3	0.3 ± 1.8
DP (different)	20.3 ± 3.0	20.6 ± 3.5
PP (same)	13.9 ± 2.4	21.2 ± 5.0
DP − PP	6.4 ± 1.2	−0.6 ± 3.3

State dependency, then, is conditional on there being the same drug effect on behavior during acquisition as during retention, which presumably depends on an effective drug treatment. When the drug treatment is initially ineffective in establishing an altered state, as it was for the group of control children and a subset of the hyperactive group, state-dependent effects are not demonstrable (*20*). This explains why two previous attempts (*14, 15*) to demonstrate stimulant-related state-dependent learning failed; in neither was a behavioral (learning) difference in state produced by the initial drug treatment.

Despite this qualification, our basic finding stands: state-dependent learning occurs when a therapeutic dose of stimulant medication is used to treat hyperactivity. Our data confirm and extend the reports of state-dependent learning associated with depressants (*1, 3, 5, 6*), although our drug agent improved rather than impaired performance. Thus the state-dependent learning was not caused by drug-impaired brain function; however, one may consider the hyperactive subjects as having impaired brain function in the placebo state, which is corrected by stimulant medication.

The benefit of stimulant therapy on long-term retention of learned material may occur only when medication is applied consistently over time. The benefit of consistent medication is shown by the superior performance of the hyperactive subjects on the retention test in the drug-drug combinations (Table 2). This finding is consistent with the short-term drug facilitation effect on day 1 during initial learning. But the other two learning-retention combinations involving medication did not produce drug-induced facilitation of performance. When material was learned in the placebo state and later tested for retention in the medicated state (Table 2), there was no difference in performance relative to the placebo-placebo combination. And when medication was given only during initial learning, the long-term effect was to impair performance on the retention test in the placebo state on the following day. Drug impairment occurred in this drug-placebo retention condition even though the immediate effect of the drug treatment had been to facilitate initial learning.

Both of these findings show how the main effect of the stimulant drug treatment is qualified by an interacting state-dependent effect. On these grounds, we advise the constant normalization of hyperactive behavior by stimulants in order to provide full benefit from the therapy.

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16. An alternative partition of the 3 degrees of freedom associated with the four learning-retention conditions may be derived from an analysis of variance incorporating the two main effects, learning state and retention state, and their interaction. For example, in such an analysis (which included a factor to evaluate counterbalancing procedures), the only significant effects were retention state [$F(1,28) = 18.5$] and the interaction of learning state and retention state [$F(1,28) = 15.5$]. The three planned comparisons discussed in the text are preferable because they incorporate a test for bidirectional state dependency, which the regular analysis of variance lacks.
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19. The reasons why these nine hyperactive children failed to show drug facilitation on day 1 but showed a large effect on day 2 are obscure. Hypotheses not testable from our data are (i) for these individuals, drug facilitation will occur in difficult tasks (for example, 24-item lists) but not in easy tasks (6-item lists), (ii) for these individuals, the hyperactive state was normalized on day 1 without medication as a result of the novel situation, the stress experienced, or both. Of these nine children, six received the drug condition the morning of the first day, so perhaps the result was partially due to an effect of practice or of the time of day.
20. Given the trend of our data for the control group, we expect a larger dose of methylphenidate would effectively produce a behavioral difference by imparing performance in the drug state relative to the placebo state, and that under such conditions the group of normal children would show state dependency similar to that reported for adults (*12*).
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Analgesia Mediated by a Direct Spinal Action of Narcotics

Abstract. *Narcotic analgetics administered directly into the spinal subarachnoid space of the rat via a chronically inserted catheter produce a potent analgesia that can be antagonized by naloxone. The narcotics, acting only at the spinal level, changed cord function to block not only spinal reflexes but also the operant response to painful stimuli.*

Morphine, acting within the mesencephalic central gray matter alone, can significantly elevate the nociceptive (pain) threshold (*1*). This observation suggests that narcotic analgesia may be principally mediated by a unique action of the drug upon this supraspinal structure. We now present evidence, however, that the direct injection of narcotics into the spinal subarachnoid space, producing an action limited entirely to the spinal cord, can also produce a well-defined, dose-dependent analgesia in the intact and behaving animal.

To permit the long-term administration of drugs into the spinal subarachnoid space, polyethylene catheters (*2*) were inserted through a slit made in the cisternal membrane of the anesthetized rat. The catheter was cut to extend to the level of the lumbar enlargement and was affixed to the back of the skull with stainless steel screws and dental acrylic. After a 2-week recovery period, 5 μl of drug solution (*3*) was injected by a gear-driven pump (5 μl of vehicle was given immediately to wash the catheter). We assessed the pain threshold with both a spinally mediated response, the tail flick (*4*), and responses that have a supraspinal component, namely, the hot-plate response (*5*) and the squeak-escape response (*6*).

Narcotics administered into the subarachnoid space of the spinal cord elevated the analgetic thresholds (Fig. 1). All elevated thresholds produced by these narcotics could be antagonized by naloxone injected either intraperitoneally (0.5 to 2.0 mg per kilogram of body weight), or directly into the spinal catheter (0.1 to 3.0 μg). The time of onset of the analgesia varied with the drug; fentanyl produced marked changes within 2 to 3 minutes, but morphine, codeine, and ethylmorphine required about twice as long. Similarly, the duration of action was drug- and dose-dependent, with the effects of fentanyl lasting 20 to 30 minutes and those of morphine lasting as long as 2 hours.

The withdrawal-squeak response to hindpaw pinch was attenuated with the same time course as that observed in the hot-plate test. In contrast, the forelimbs and, particularly, the face remained normally sensitive to pinch. After 40 to 60 minutes, however, with the higher dose of morphine, the forepaws would also begin to lose their responsiveness. The face, however, never became insensitive.

To further verify that the change in the thresholds represented a change in the animal's perception of stimulus intensity, we performed experiments using the operant shock titration procedure (*7*). In these experiments, fentanyl (5 μg) and morphine (15 μg) produced a uniform elevation in the level of tolerated shock to between two and three times the threshold in the absence of drugs.

We were concerned that the intrathecally injected narcotics were moving rostrally to supraspinal structures either by diffusing through the subarachnoid

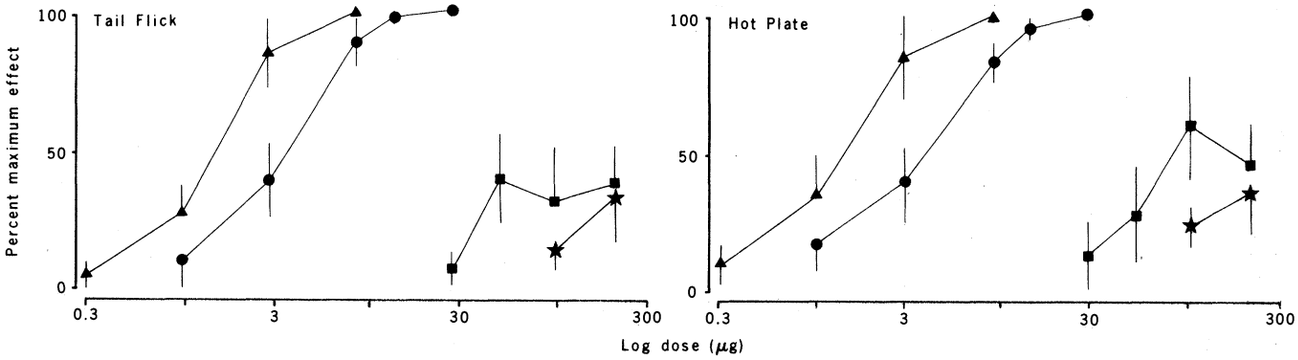

Fig. 1. Log dose–response curves for fentanyl citrate (▲), morphine sulfate (●), codeine alkaloid (■), and ethylmorphine hydrochloride (★) obtained on the tail-flick and hot-plate tests. The vertical bars are standard errors of the mean. Each point is the mean response of at least four animals, plotted in terms of the percentage of maximum effect (*15*).