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 36. Urokinase plasminogen activator (uPA) was expressed from plasmid pDB1519, a derivative of pUC19 containing a 2-kb Xba I–Sma I fragment of cDNA clone pDB15 (25). In this construct, the complete uPA, including its signal sequence, is preceded by part of the α fragment of β -galactosidase. The Δ A-uPA variant was expressed from plasmid pDBM81, a derivative of pDB1519, in which the DNA that codes for the signal sequence and most of the noncatalytic A domain is deleted. The NH₂-terminal 12 amino acids of the α fragment of β -galactosidase is fused to the last 271 amino acids of uPA, which codes for the connecting peptide and the serine protease domain.
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 38. We are greatly indebted to D. Fraenkel, who proposed the selection for active AP in the cytoplasm and provided us with an *fbp*⁻ strain. We thank M. Russel and P. Model for the *trxB::kan* disruption and Δ *trxA* deletion strains and for plasmid pMR20; and K. Johnson Pogliano and J. Pogliano for critically reading the manuscript. Supported by grants from the Swiss National Foundation (to D.B.) and the American Cancer Society (to J.B.). J.B. is an American Cancer Society Research Professor.

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The Learning of Categories: Parallel Brain Systems for Item Memory and Category Knowledge

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A fundamental question about cognition concerns how knowledge about a category is acquired through encounters with examples of the category. Amnesic patients and control subjects performed similarly at classifying novel patterns according to whether they belonged to the same category as a set of training patterns. In contrast, the amnesic patients were impaired at recognizing which dot patterns had been presented for training. Category learning appears to be independent of declarative (explicit) memory for training instances and independent of the brain structures essential for declarative memory that are damaged in amnesia. Knowledge about categories can be acquired implicitly by cumulating information from multiple examples.

Memory is not a single mental faculty but is composed of multiple and separate abilities that are mediated by distinct brain systems (1). The major distinction is between declarative or explicit memory, which depends on limbic and diencephalic structures (2) and provides the basis for conscious recollections of facts and events, and various nonconscious or implicit memory abilities, which support skill and habit

learning, simple conditioning, and the phenomenon of priming (3, 4).

Declarative memory typically refers to memory for recent single encounters and is usually assessed by tests of recall or recognition for specific items. However, when encountering a series of items, a subject not only learns about each item in the series but also accrues information about what all the items have in common. In this way, a subject learns about the category that is defined by the items that are presented. The question of interest is: What kind of memory supports the acquisition of category-

level knowledge (5)? One view holds that category-level knowledge is acquired in the form of information about prototypes (average instances) or information about the statistical properties of the training items, and this knowledge is represented separately from knowledge about the training items themselves (6). Another view is that category-level knowledge has no special status but emerges naturally from item memory (7). Thus, a novel item would be endorsed as belonging to a particular category as a function of the similarity between the new item and the exemplars of that category already stored in memory.

Studies of amnesic patients could illuminate these issues, because these patients have severely impaired declarative (explicit) memory (due to limbic or diencephalic brain damage), but they are fully intact at tasks of nondeclarative (implicit) memory (8). Recently, amnesic patients exhibited normal classification learning (9) when category membership was defined by adherence to the rules of an artificial grammar (10). In the present study, we examined the ability of amnesic patients to learn to classify items on the basis of natural categories, that is, categories such as birds or furniture for which membership is based on family resemblance rather than on adherence of items to fixed rules.

Examples of study items and test items are illustrated in Fig. 1 (11). First, 12 control subjects and 10 amnesic patients (12) were presented with 40 training patterns (13). Then subjects were instructed that these patterns all belonged to a single category of patterns, in the same sense that, if a series of dogs had been presented, every item would belong to the category "dog." Five minutes later, subjects were tested with 84 new patterns and were asked to judge in each case whether the pattern did or did not belong to the same category as the training patterns (14). The two subject groups made category judgments with similar accuracy (Fig. 2A). An analysis of variance (ANOVA) indicated an effect of item type on classification [$F(3, 63) = 33.9$, $P < 0.01$] but no differences between groups and no interaction of group and item type ($P > 0.1$). Figure 2B shows overall performance on the classification task [percent correct; $t(20) = 1.45$, $P > 0.10$] together with the results for a second study-test sequence, scheduled an average of 1 to 2 months later, in which subjects attempted to recognize patterns that had appeared 5 min earlier (15). The subject groups differed in their ability to recognize the particular items that had been presented [$t(20) = 3.3$, $P < 0.01$]. There was also a significant interaction between the performance of the two groups on the classification and recognition tests [$F(1, 20) = 5.5$, $P < 0.05$].

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We next considered the possibility that amnesic patients performed so well on the classification task, in contrast to the recognition task, because of the greater repetition of the information to be remembered in the classification task or because of the smaller amount to be remembered, rather than because different memory systems were used in the two tasks. In the classification task, a single prototype was to be retained after presentation of 40 related patterns, whereas in the recognition task five different items were to be retained and each was presented eight times. To address this issue, subjects were tested for their classification ability after studying only four training examples and were tested for their recognition ability after studying one training example presented four times (16). In this case also, there was an effect of item type on classification performance [Fig. 2C, $F(3, 60) = 38.4$, $P < 0.01$], no difference between groups, and no interaction between group and item type ($P > 0.1$).

Figure 2D shows the overall results for the classification task [percent correct; $t(19) = 1.42$, $P > 0.10$] and shows also that the control subjects performed better than the amnesic patients at recognizing the training pattern [$t(19) = 2.2$, $P < 0.05$].

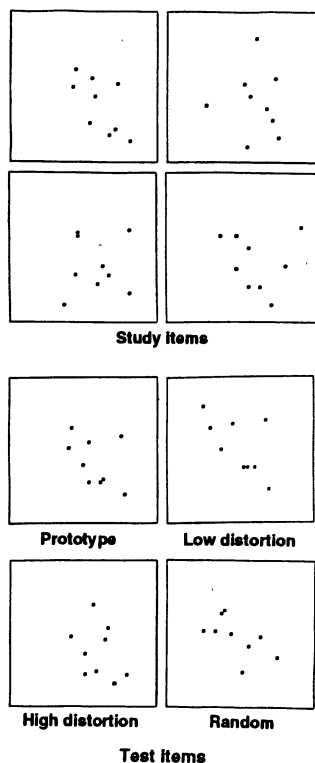


Fig. 1. Examples of study items and test items used to assess classification learning of dot patterns. The study items were high distortions of a prototype dot pattern. The test items consisted of repetitions of the training prototype, high and low distortions of the training prototype, and random dot patterns.

There was a trend for an interaction between subject group and task (classification or recognition) [$F(1, 19) = 3.2$, $P = 0.09$].

In a final test, normal subjects who were not presented any training patterns performed at chance on the classification test ($53.7 \pm 2.1\%$ correct) (17). Thus, classification performance does depend on having experience with the study items.

Performance on the classification task was actually a little better numerically after subjects were shown 4 training patterns than after they were shown 40 training patterns (average score for both groups, 64.4% versus 59.5% correct). However, when there was a 4-week delay between study and test (18), normal subjects performed better after being presented 40 training patterns than after being shown 4 training patterns [66.1% versus 54.5%, $t(23) = 2.2$, $P < 0.05$]. Moreover, after the 4-week delay, subjects who were shown 4 training patterns performed at chance levels ($P > 0.1$). Thus, training with more items does result in more robust, longer lasting category knowledge.

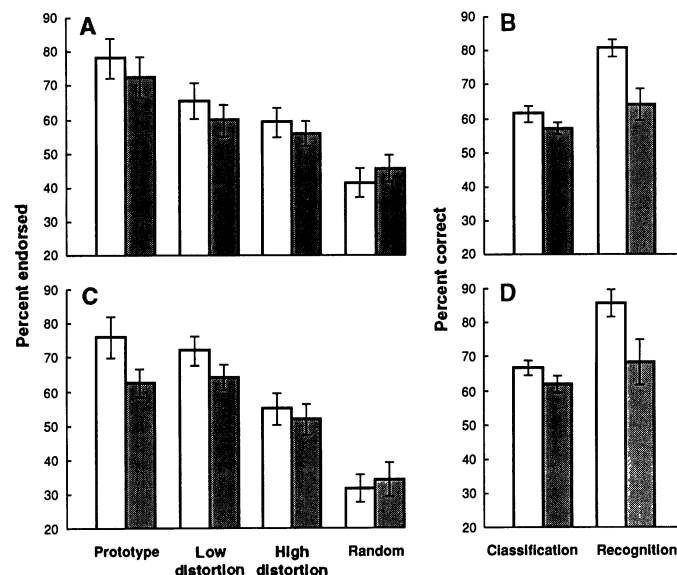
The results suggest that category-level knowledge can develop independently of and in the absence of normal declarative memory for the items presented during learning (19). Thus, experience with a succession of items appears to lead to two parallel consequences. First, information can be retained about each training item, which depends on the limbic and diencephalic structures that are damaged in amnesia and that are essential for declarative memory. Second, repeated experience leads to category-level knowledge in the form of information about the category to which the training items belong. Category-level

knowledge may be acquired by abstracting information across encounters with examples. Alternatively, classification learning could depend on specific-item information stored in a distributed fashion, as commonly proposed in theoretical models (5, 7). However, in the latter case, the information supporting classification learning must be distinct from declarative information about the separate items. Single-factor models in which classification judgments derive from, or in any way depend on, long-term declarative memory do not account for the finding that the amnesic patients performed well on the classification tasks.

The possibility must be considered that classification learning is dependent on declarative knowledge, such that even a little declarative memory for the training patterns could support substantial classification ability. Although the difference in classification performance between amnesic patients and control subjects in our tests never approached statistical significance, the amnesic patients did perform numerically worse than the control subjects (Fig. 2). Is it possible that residual declarative knowledge available to the amnesic patients translates into nearly normal classification performance? Although this possibility is difficult to address definitively, it is worth noting that amnesic patients have scored numerically better than normal subjects on a classification task for artificial grammar (9).

If classification does not depend on the limbic or diencephalic structures damaged in amnesia, which brain systems could be involved? One clue comes from the parallel between classification learning and the learning of skills and habits; namely,

Fig. 2. (A) Classification by subject group of novel dot patterns after studying 40 exemplar patterns. Control subjects (open bars); amnesic patients (closed bars). Performance varied similarly in each group as a function of how closely the test items resembled the study items. (B) Overall classification performance together with recognition memory performance for specific items that had been studied. (C) Classification of novel dot patterns after the study of four exemplar patterns. (D) Overall classification performance together with recognition performance for specific study items. Brackets show standard error of the mean.



knowledge of a specific trial is not crucial. Rather, subjects detect invariance in the stimulus environment across many trials (20), independently of declarative memory. It is therefore possible that corticostriatal systems are involved in category learning, as has been suggested for habit learning (21). Alternatively, the learning could reflect gradual changes intrinsic to neocortex by which the neocortex can gradually accrue knowledge independently of the hippocampus and related structures.

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11. We constructed a dot pattern (the prototype) by placing nine dots randomly within a 12 cm by 12 cm area in the center of a computer screen. The study items consisted of "high" distortions of this prototype constructed with the method of M. I. Posner, R. Goldsmith, and K. E. Welton [*J. Exp. Psychol.* **73**, 28 (1967)]. "Low" distortions of the prototype pattern, which served among the test items, were also constructed. Finally, we constructed random items for the test using high distortions of new prototypes.
12. The amnesic patients (seven men, three women) consisted of five patients with diencephalic amnesia and five with medial temporal lobe amnesia. For eight of the patients, their bilateral diencephalic or hippocampal lesions had been confirmed by quantitative neuroimaging [A. P. Shimamura, T. L. Jernigan, L. R. Squire, *J. Neurosci.* **8**, 4400 (1988); L. R. Squire, D. G. Amaral, G. A. Press, *ibid.* **10**, 3106 (1990)]. Two of the patients were suspected of having hippocampal damage on the basis of etiology. The patients averaged 65.3 years of age (range, 55 to 76), had an average of 13.8 years of education, attained an average score of 106.3 on the Wechsler Adult Intelligence Scale-Revised (WAIS-R), and attained average scores of 102.6, 74.1, 76.9, 69.1, and 57.4 on the five indices of the Wechsler Memory Scale-Revised (Attention-Concentration, Verbal Memory, Nonverbal Memory, General Memory, and Delayed Memory). These scores have a mean of 100 in the normal population (SD = 15). A control group of six men and six women (average age, 63.8; range, 53 to 74; average education, 14.6 years) was also tested.
13. Forty study items (40 different high distortions of the prototype) were presented for 5 s each on a computer screen, and the subject was instructed to point to the dot closest to the center of the pattern.
14. The 84 test items were a mixed order of 4 instances of the prototype, 20 high distortions of the prototype, 20 low distortions of the prototype, and 40 random dot patterns. No more than three test items of the same type occurred consecutively. We tested subjects twice, using different stimuli, with at least 1 week between sessions. The order of presentation of the two sets of stimuli was balanced across subjects.
15. The training procedure for the recognition memory task was the same as for the classification task except that the 40 study items consisted of five high distortions made from five different prototypes and presented a total of eight times each. After a 5-min delay, subjects decided for each of 10 dot patterns whether it was or was not "exactly the same" as one just presented. The 10 test patterns consisted of the five items that had been presented earlier and five new, similarly constructed items.
16. New prototypes were used to construct two classification tasks (minimum 1-week interval between tests) and four recognition tasks (minimum 4-day interval between tests). These were given to the same subjects, excluding one amnesic patient. For classification, four study items were presented, each a high distortion of a prototype pattern. Testing occurred 5 min later with 84 dot patterns (14). Beginning about 6 months later, we tested recognition by presenting one study item (a high distortion of a prototype) four times in succession, followed after 5 min by a two-item, yes-no recognition test. One item was the one that had just been presented, and the other item was a similarly constructed new item. Across the subjects in each group, the new and old item appeared first equally often.
17. Thirty-six subjects (18 men and 18 women, average age, 64.3 years; average education, 14.2 years) were instructed to imagine that they had seen a series of dot patterns and then were given classification instructions and tested with 84 test items (14). The same four test forms were used (nine subjects received each form) that had been given to the groups that saw 4 or 40 training patterns. The 36 subjects endorsed 46.5% of the prototypes, 49.3% of the low distortions, 37.4% of the high distortions, and 35.0% of the random items. To compare this no-training group to the two trained groups, we calculated an average percent correct score for each amnesic patient and control subject across all four tests (two sessions each with 4 or 40 patterns). The amnesic patients and control subjects performed similarly [$59.9 \pm 1.3\%$ versus $63.9 \pm 2.1\%$ respectively; $t(19) = 1.65$, $P > 0.1$], and both groups performed better than the group that received no training ($t > 2.4$, $P < 0.02$). Within 5 test trials, the overall scores for the two trained groups were within 3% of their value after all 84 test trials. The no-training group was averaging 47.2% correct after the first 5 test trials. The amnesic patients and control subjects also performed better overall than the no-training group for each trial type in the trained category: prototypes and high distortions, $P < 0.02$; low distortions, $P < 0.06$. Finally, we obtained a difference score for each subject by subtracting the false-alarm rate (the endorsement rate for random patterns) from the hit rate (the endorsement rate for the other three trial types). The amnesic patients and control subjects performed similarly [$27.8 \pm 4.2\%$ versus $20.0 \pm 2.7\%$, respectively; $t(19) = 1.45$, $P > 0.10$] and better than the no-training group ($9.5 \pm 4.1\%$, $t > 2.1$, $P < 0.04$).
18. One group (four men and nine women; average age, 62.8 years; average education, 14.8 years) studied 40 items and were tested after a 4-week delay, and a second group (four men and eight women; average age, 62.8 years; average education, 15.3 years) studied four items and were tested after a 4-week delay.
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