Schemas and Memory Consolidation
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dissociative electrophilic alkylation of the double bond in IPP by the allylic cations generated from DMAPP or GPP (*23*). By analogy, for biosynthesis of irregular monoterpenes, we suggest that a related dissociative electrophilic alkylation of the double bond in DMAPP by the dimethylallyl cation results in a protonated cyclopropane intermediate. This species can be deprotonated to give CPP or rearrange to a tertiary cation, which can in turn be deprotonated to give LPP. Alternatively, the tertiary cation can cyclize to give a cyclobutylcarbinyl cation that can then be deprotonated to give MPP or LPP. Formation of any specific product would be controlled by the ability of the enzyme to stabilize a specific intermediate along the reaction coordinate through dipolar and electrostatic interactions and to facilitate the selective removal of protons. The stereochemistries of the products result from the conformations of the two bound substrate molecules before the reaction. Only minor changes in the relative positions of the substrates are required to accommodate the formation of the different products.

This scenario provides an attractive mechanism for the evolution of the isoprenoid pathway through gene duplication and random mutagenesis of the duplicate genes to give new proteins, one of which is constrained to retain its original function, whereas the other is free to acquire a new activity. The isoprenoid fold first seen in the *E*-selective chain-elongation enzyme avian FPPase (*12*) has also been found in the cyclopropanation enzyme squalene synthase (*13*) (sterol biosynthesis) and several different terpenoid cyclases (*14*) along with aspartate-rich motifs involved in binding allylic diphosphate substrates, indicating that the enzymes evolved from a common ancestor. Phylogenetic correlations suggest that the cyclopropanation enzyme phytoene synthase (carotenoid biosynthesis) also has an isoprenoid fold. Our discovery that chimeric enzymes from FPPase and CPPase catalyze branching and cyclobutanation reactions suggests that WT enzymes with these activities also share this common ancestor.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/316/5821/73/DC1
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Chemical Ionization (CI) Mass Spectra
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Schemas and Memory Consolidation

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Memory encoding occurs rapidly, but the consolidation of memory in the neocortex has long been held to be a more gradual process. We now report, however, that systems consolidation can occur extremely quickly if an associative "schema" into which new information is incorporated has previously been created. In experiments using a hippocampal-dependent paired-associate task for rats, the memory of flavor-place associations became persistent over time as a putative neocortical schema gradually developed. New traces, trained for only one trial, then became assimilated and rapidly hippocampal-independent. Schemas also played a causal role in the creation of lasting associative memory representations during one-trial learning. The concept of neocortical schemas may unite psychological accounts of knowledge structures with neurobiological theories of systems memory consolidation.

The concepts of "mental schema" and "mental models" as frameworks of knowledge are now well established (*1*, *2*), with implications for story recall, deductive inference, and education (*3*, *4*). For example, the memory of grammatically correct but semantically unusual prose passages is substantially better when subjects have an activated and relevant mental framework with which to understand them (*5*). An everyday experience for working scientists is remembering complex new information in an academic seminar. Our ability to do so depends as much on our possession of an appropriate mental schema as on the communicative skill of the speaker in logically conveying his or her message. In the absence of such mental frameworks, we are unable to follow scientific inferences in a talk and have the phenomenological experience of being functionally amnesic for its content a surprisingly short time later.

Curiously, this fundamental idea about memory has had little impact in neuroscience. Selective activation of a specific region within the posterior parietal cortex occurs in human subjects when, having been given relevant pictorial information earlier, they correctly interpret unusual textual information that would otherwise be incomprehensible (*6*). Animal studies have rarely considered the issue of what the animal itself brings in the way of knowledge to a learning situation, with the exception of studies of spatial and relational memory (*7*–*9*). This is partly because most experiments are conducted with "experimentally naïve" animals, and also because the creation of a mental schema is difficult to map precisely onto concrete neuroscience concepts such as anatomical connectivity or synaptic plasticity. The present experiments test the idea that the schema concept is directly relevant to the neural mechanisms of systems memory consolidation (*10*–*12*).

Experiments on schema learning. We trained rats to learn several flavor-place associations concurrently, using different flavors of food (flavor cues) and sand wells (place cues) located within a familiar testing environment called an "event arena" (*13*). The task was to learn which

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flavor was in which location such that, when cued with a specific flavor in start boxes at the side of the arena, the animals would be rewarded for going to the correct location by receiving more of that same food (i.e., "cued recall"). They should be able to recall that banana-flavored food is at one location, bacon-flavored food at another, and so on (Fig. 1, A and B). Such paired-associate learning is likely to be mediated by the hippocampus initially (*14*–*16*), with long-term storage of paired-associate memory traces eventually consolidated in the neocortex (*17*, *18*). This makes this paradigm ideal for looking at the temporal dynamics of systems memory consolidation (*10*, *12*, *19*, *20*), a process widely held to be quite slow. Additionally, the use of location as one member of each paired associate allowed the animals to learn each association as either an isolated declarative "fact," in which spatial information is generally considered as no different from other kinds of information (*10*), or as some kind of mapping of flavors to arena locations, resulting in the formation of a spatial or relational framework (*7*, *21*).

After habituation, the animals were started from one start box of the arena (at north, south, east, or west) on all six trials of a session. A different start box was used for each session. A trial began when the rat was given a cue flavor in the start box. Upon entering the arena, the animal was confronted by six sand wells (Fig. 1, A and B) of which only one contained flavored food—the same flavor given as a cue in the start box (*22*). The animals visited and sometimes dug at incorrect sand wells, which did not contain food on that particular trial, until they found the correct one. On each trial, the animals would retrieve the first of three buried food pellets, return to the start box to eat it, and then run back to the correct sand well to collect and transport the second and third pellets. One hour later, the second trial began with a different cue flavor in the start box and a different sand well baited. There were six trials per session, with the next session run 48 hours later (*23*).

We began by examining the impact of neurotoxic hippocampal lesions made before training (experiment 1). After 13 sessions, sham-lesioned animals were digging less frequently at incorrect sand wells before going to the correct one, whereas the hippocampal-lesioned animals did not improve. A single nonrewarded probe trial was then scheduled, which started with the provision of a cue flavor in the start box. The sham-lesioned animals spent significantly more time digging at the cued location than at the other five incorrect sand wells, whereas the hippocampal-lesioned animals were at chance (Fig. 1C; see tables S1 and S2 and figs. S1 to S3 for the lesions and full experimental design). The lesions were extensive, leaving minimal residual tissue throughout the longitudinal axis of the hippocampus (Fig. 1D).

To investigate the properties of paired-associate learning and its consolidation in more detail (experiment 2), we trained normal animals in a similar way. Probe tests, other controls, and novel context training were scheduled at various stages before and after making sham or hippocampal lesions (fig. S4). Using the same paired-associate layout as in experiment 1, we examined acquisition of sand-well choice behavior during training. A "performance index" was calculated, and this index improved monotonically across sessions (Fig. 2A). In nonrewarded probe trials, preferential digging at the correct location rather than the other five locations increased from chance levels at the outset of training to a highly significant preference for the cued location (Fig. 2B). To exclude the possibility that an olfactory cue in the correct sand well guided choice performance on training days, we conducted a single session of six trials in which the daily protocol was unchanged, except that no cue flavors were offered in the start box. Choice performance fell to chance (Fig. 2A, session 18), returning to above chance on the next normal session. The possibility of cryptic olfactory guidance by cues on the arena near the correct sand well was also ruled out in a later session by physically rotating the arena through 90° after the third trial of a session and back to its normal orientation after the third trial of a second session on the next day. The sand wells and intramaze cues were relocated such that their places relative to the distal room cues remained the same. Arena rotation had no effect (fig. S4, A3). With a different start box used in each session, it would appear that the animals can visually perceive their own location relative to the intra- and extramaze landmarks and use allocentric memory representations to identify the correct goal location among the six available sand wells.

If the animals develop a neocortical associative schema for this task, and if this is activated when the animals enter the apparatus, it might aid the encoding of new paired associates and their rapid assimilation into the schema. A single training session of six trials was given (Fig. 2A, session 21) in which paired associates (PAs) 1 and 6 were replaced by two new PAs, 7 and 8, hidden at two nearby locations; PAs 2 to 5 were trained normally. Note that PAs 7 and 8 received only one rewarded trial each. The inset of Fig. 2C shows how the new PAs were located near those of the now-closed sand wells. A nonrewarded probe trial was given 24 hours later to test memory for the new associates. Preferential digging was observed at the correct cued location in the arena relative to the new noncued location (i.e., less digging at location 8 for those animals on a PA7 trial, and vice versa) and to any of the original locations (PAs 2 to 5; Fig. 2D). The rapid acquisition of new PAs in a single trial, and their retention over 24 hours, are indications that the prior learning of an associative schema may aid the encoding, storage, and/or consolidation of new PAs. In contrast, animals trained on a similar one-trial task, but with novel PAs each day, showed consistent forgetting over 90 min (*13*).

Time course of memory consolidation. Hippocampal or sham lesions were then made 24 hours later—a much shorter time after training of the new flavors (48 hours) than is usually thought necessary for systems consolidation to be completed (*24*–*27*), and shorter than the usual time scale of differential changes in the patterns of glucose use or immediate early gene activation between hippocampus and neocortex after learning (*19*, *28*). After recovery from surgery, a series of nonrewarded probe tests (with

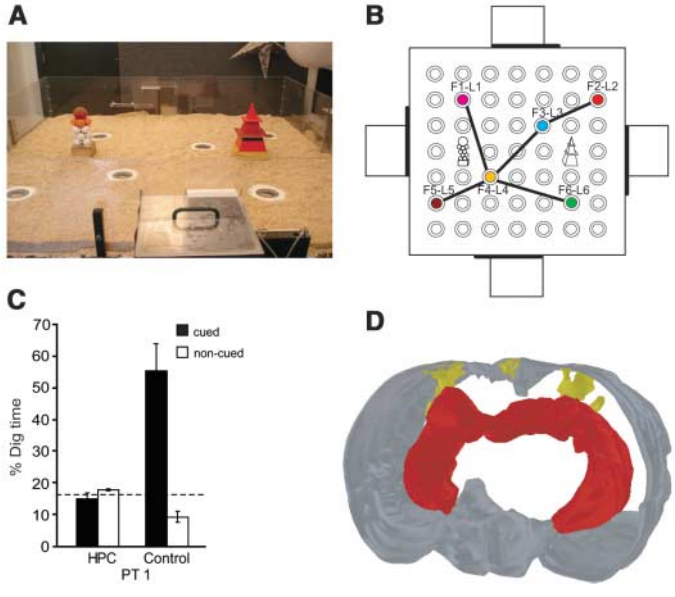

Fig. 1. Paradigm for hippocampal-dependent paired-associate (PA) learning. (**A**) The large event arena (1.6 m by 1.6 m) contains a 7 × 7 grid of locations at which sand wells can be made available and four surrounding start boxes. After being given a cue flavor in a start box, the animals recall the spatial location with which it is associated, and run into the arena to that location to secure more of that flavor of food. (**B**) The spatial arrangement of the six PAs and the "schema" this constitutes (F, flavor; L, location). (**C**) Preferential digging during a nonrewarded probe test [probe trial 1 (PT1)] by sham-lesioned but not hippocampal (HPC)-lesioned animals (*ns* = 6). Groups $t = 5.25$, df = 10, $P < 0.001$; sham versus chance, $t = 5.01$, df = 5, $P < 0.005$; HPC versus chance, not significant (n.s.). (**D**) A three-dimensional reconstruction of the volume of hippocampus lesioned in a representative rat (red), together with typical overlying cortical damage (yellow). The gray region represents the transparent volume of the rat brain.

interpolated training days using the original flavor-place pairs) was given to examine memory for the original schema and the two new PAs. These consisted of separate tests of the original PAs 2 to 5 and new PAs 7 and 8, each repeated once across a series of four sessions to enable both PA7 and PA8 to be tested in all animals. The hippocampal-lesioned group not only could successfully recall the original PAs learned over the previous month (Fig. 2D) but also, remarkably, could remember the newly acquired pairs PA7 and PA8. Because the lesions were near-complete (~90%; see Fig. 1D and fig. S2B), these two findings imply that (i) the memory traces for these PAs must be stored outside the hippocampus, probably in the neocortex; and (ii) consolidation of new associates whose acquisition is mediated by the hippocampus takes place within 48 hours.

To be more confident of these claims, it was essential to establish that the learning of further new PAs still required the integrity of the hippocampus in these same animals. Accordingly, immediately after this series of postoperative probe tests, we conducted a single six-trial training session with PAs 2 to 5 of the original schema, but with PAs 7 and 8 now replaced by sand wells containing two new flavors in nearby locations in the arena (PAs 9 and 10; Fig. 2E). The probe test conducted 24 hours later showed that sham-lesioned animals could readily learn and recall these new pairs, whereas the hippocampal-lesioned group could not. Thus, the one-trial acquisition of new PAs in this paradigm in experienced animals was still blocked by hippocampal lesions. Hence, it is unlikely that any relearning took place after the hippocampal lesions during the earlier series of four probe tests that had examined remote memory (the interpolated training was restricted to the well-trained PAs 2 to 5). The effective cued recall of the new PAs 7 and 8 introduced before the lesion must therefore reflect rapid, successful systems consolidation.

Although the animals appear to have acquired an associative schema reflecting the mapping of flavors to places in the arena, an alternative might be a response-based "win-stay, lose-shift" inference strategy in the manner of a learning set (*29*). It is not entirely clear how such a procedural strategy could be applied in this context, with six choice locations and only one trial per day to each cued location. However, as procedural strategies are generally context-independent, this account would predict that the learning of an entirely new set of six PAs in a new context would occur very quickly. In contrast, the schema hypothesis requires that a new schema be gradually learned. The same animals of experiment 2 were first trained on a new set of PAs in the same event arena (fig. S7) and then in a novel event arena in a different room with new intra- and extramaze landmarks, new flavors, and a distinct spatial geometry to the new set of sand wells (Fig. 3, A and B). Acquisition again took

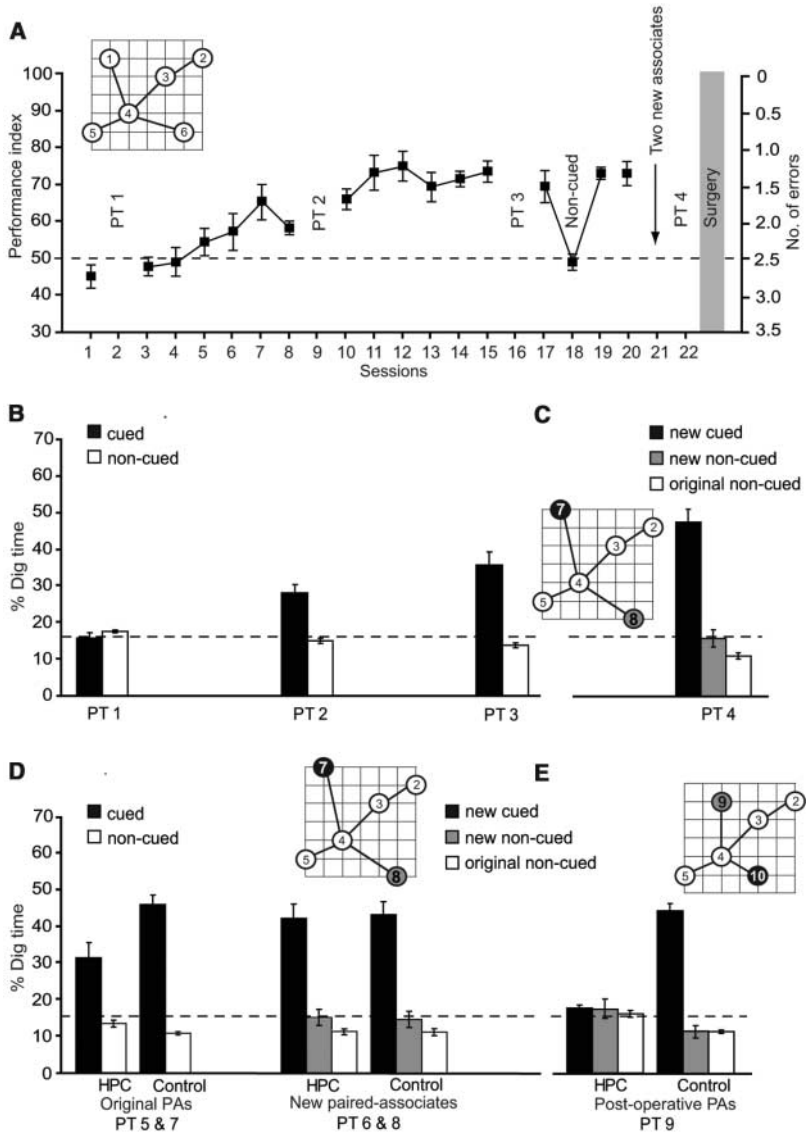

Fig. 2. Acquisition of an associative schema and its role in new learning and consolidation. (**A**) Acquisition of PAs. The animals (n = 18) made fewer choice errors over training (F = 18.24, df = 5.7/97.5, P < 0.001; Greenhouse-Geisser correction, including degrees of freedom) such that the performance index, computed as 100 − [100 × (errors/5)], was significantly above chance from session 10 onward (ts > 5.08, df = 1/17, Ps < 0.001). Removing cue flavors from the start box on session 18 resulted in performance dropping to chance and then returning to 70% correct on a succeeding normal session (session 19). (**B**) Cued-recall probe trials. Nonrewarded probe tests revealed a graded learning of the original PAs (cued flavor = solid bars) across sessions 2, 9, and 16 (F = 16.24, df = 1.54/26.22, P < 0.001; above chance in PTs 2 and 3; ts = 3.94 and 6.17, df = 17, P < 0.005 and P < 0.001, respectively). (**C**) Effective recall in PT4 of the location of the cued new PA (solid bar), coupled with avoidance of the noncued new PA (gray bar) and the remaining original associates (open bar) 24 hours after a single session of training with only one trial of each new PA (repeated-measures F = 65.28, df = 1.7/29.1, P < 0.001; cued location above chance, t = 10.29, df = 17, P < 0.001; noncued versus original, n.s.). (**D**) Postoperative retention. Both sham-lesioned (n = 8) and HPC-lesioned (n = 10) animals could effectively remember both original PAs (PTs 5 and 7) and new PAs introduced for a single trial 2 days before surgery (PTs 6 and 8). Both groups dug at the sand wells of the original associates (flavors 2 to 5) significantly more than chance (HPC t =3.60, df = 9, P < 0.01; sham t = 12.89, df = 7, P < 0.001; sham versus HPC group, t = 2.86, df = 16, P < 0.05). Both groups also dug equally at the cued locations of the new associates relative to the noncued locations (Group × Location F < 1, n.s.), and at these cued locations better than chance (ts > 8.07, df = 9 and 7, P < 0.001). (**E**) Postoperative new training. Hippocampal lesions prevented the learning of new PAs (PAs 9 and 10; Group × Location F = 60.23, df = 1.64/26.17, P < 0.001). Digging at the cued new location in PT9 was significantly above chance only in the sham group (t = 17.07, df = 7, P < 0.001) and significantly lower in the HPC group than in the sham group (t = 13.78, df = 16, P < 0.001).

place gradually, such that the learning curve of the now experienced sham-lesioned animals did not differ from the original rate of learning of the normal animals in the first event arena. The hippocampal-lesioned animals did not learn the new spatial schema despite repeated trials. Probe test performance early in training followed the same gradual pattern in the sham group, resulting in effective probe test performance only by session 67 (Fig. 3C). These findings argue against a response-based strategy, such as a learning set, because learning was no faster in the new room with new flavor-place geometry.

Completion of training in the second room offered the opportunity of returning the animals to the first arena to examine their now remote memory of the original set of PAs first learned 4 to 5 months earlier. Remarkably, the hippocampal-lesioned animals were above chance in cued spatial recall (session 68, Fig. 3D) and even showed a nonsignificant trend toward better performance than did sham-lesioned controls in a probe test as early as session 2. The sham-lesioned animals may have sustained some associative interference arising from their successful training on other sand-well arrangements in this and the other contexts, but after as few as six sessions of retraining, both groups showed effective cued recall of the original PAs (Fig. 3E). Thus, the failure to learn new PAs in a new context after a hippocampal lesion did not affect the ability to remember, after several months, information acquired before the lesion—a pattern exactly like that shown by patient E.P. in his knowledge of current and past hometown topography (*30*).

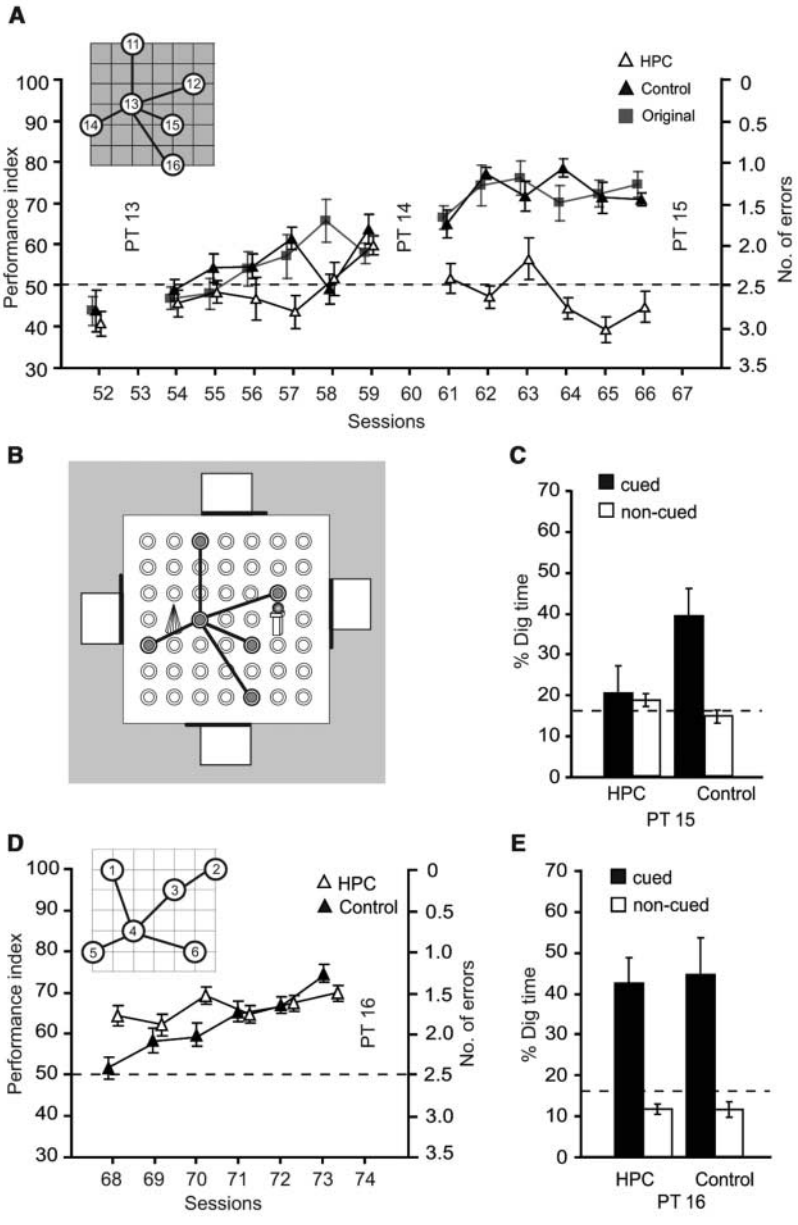

Fig. 3. Gradual acquisition of new PAs in a new context by experienced animals. (**A**) Acquisition of PAs. The now experienced sham group (n = 8) learned a new set of six PAs in the second event arena at a comparable rate to that shown by normal animals in the first event arena (Group × Session F = 1.97, df = 6.9/116.9, 0.10 > P > 0.05, treating Group as a between-subjects factor). Relative to the sham-lesioned group, the HPC-lesioned group (n = 10) failed to learn (Group F = 128.63, df = 1/15, P < 0.001; Group × Session F = 7.42, df = 5.9/89.3, P < 0.001). (**B**) Spatial arrangement of the new PAs (PAs 11 to 16) in the new event arena. (**C**) Cued-recall probe trial. Proportion of digging at the cued location relative to the noncued locations by sham- and HPC-lesioned animals (PT15, session 67). The sham group was above chance (t = 2.38, df = 7, P < 0.05); the HPC group was not (t < 1). However, the difference between groups showed only a trend toward significance (t = 1.83, df = 15, 0.10 > P > 0.05). (**D**) Return to the original event arena and flavors (flavors 1 to 6). Inset indicates transition to the original schema acquired before surgery. The HPC group is above chance at the outset (t = 3.9, P < 0.005; session 68), but neither Group nor Group × Session effects were significant for the performance index (Ps > 0.05). After six sessions of retraining, the sham group caught up, and both groups were well above chance (ts = 8.7 and 8.9, Ps < 0.001). (**E**) Performance in the probe test (PT16) indicated that both HPC and sham groups were consistently above chance in preferentially digging at the cued location (t = 4.37, df = 8, P < 0.005; t = 3.19, df = 7, P < 0.025, respectively) and did not differ from each other (t < 1, n.s.).

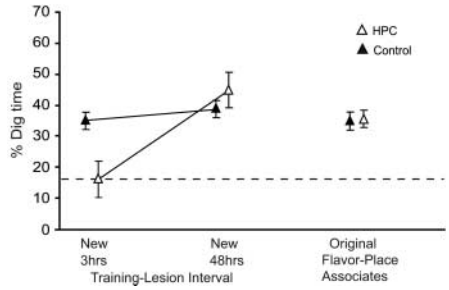

Fig. 4. Identifying the interval between training and hippocampal lesions for consolidation. A striking temporal gradient of retrograde amnesia is observed in this paradigm. HPC lesions made 3 hours after training (n = 7) on the novel flavor tested 14 days later prevented consolidation, whereas consolidation was complete when HPC lesions (n = 6) were made after 48 hours (Group × Delay F = 15.77, df = 1/13, P < 0.005). The HPC and control 48-hour groups did not differ (t < 1). The performance of the HPC 48-hour group was significantly higher than that of the HPC 3-hour group (t = 4.82, df = 11, P < 0.001), but the corresponding two control groups (ns = 9) did not differ (t < 1). The control groups were above chance at both training-lesion intervals (ts > 5.1, df = 8, P < 0.001); the HPC 3-hour group did not differ from chance (t < 1), whereas the HPC 48-hour group was above chance (t = 4.90, df = 5, P < 0.005). Separate analyses of the postsurgery memory for the original PAs learned over 14 sessions showed above-chance performance for both the HPC and sham groups (HPC t = 5.80, df = 12, P < 0.001; sham t = 9.85, df = 17, P < 0.001).

If systems consolidation within the neocortex can take place in as little as 48 hours, it becomes of interest to find out the minimal time required for it to occur. Some theoretical models suppose that a memory trace stored in the hippocampus, serving as an "index" or "pointer" to cortically encoded information, must last sufficiently long to guide the slower systems-level consolidation process that is thought to take place in sleep, requires sharp-wave activity, and has previously been shown to involve hippocampal-neocortical interactions over time (*31*–*35*). The prediction is that hippocampal lesions made 3 hours after training to animals that do not sleep during this short training-surgery interval should prevent neocortical consolidation. In experiment 3 (using a new set of 18 rats that acquired the basic schema of PAs 1 to 6 over 14 sessions as before), we compared the impact of hippocampal lesions given 3 or 48 hours after the training of two new PAs in single trials (PAs 7 and 8). This experiment used a "reverse" day-night cycle (with all testing during the animal's night) to minimize, in the case of the 3-hour interval, the likelihood of sleep episodes between the end of training and the time of the lesion. A partial within-subjects design was also used (fig. S8), with some animals having hippocampal lesions at appropriate time points soon after novel PAs 7 and 8, and others that were only anesthetized in this first phase given hippocampal or sham lesions after the later introduction of PAs 9 and 10. Cued recall was examined for the new associates shortly before surgery and was found to be effective for all animals. After surgery, cued recall for the new one-trial PAs was at chance for those animals subject to hippocampal lesions 3 hours after acquisition, but—replicating the results of experiment 2—it was effective when lesions were made 48 hours after training (Fig. 4). This is a strikingly steep upward temporal gradient of remote memory.

Causal role for schemas in learning. The final issue to consider is whether an activated schema is causally necessary for rapid memory consolidation (*5*). An alternative account of these experiments could be that the animals find it increasingly easier over the course of training to encode, store, and/or consolidate individual PAs as a result of increasing familiarity with the context of learning, with the "schema" concept being superfluous. To contrast these alternatives, we trained normal animals in two event arenas concurrently (experiment 4). In one room, they were trained on a "consistent" schema in which flavors 1 to 6 were always placed consistently at locations 1 to 6, respectively (schema 1 = PAs 1 to 6; Fig. 5B). In the other room, the animals were trained on "inconsistent" schema in which a single set of six locations (locations 11 to 16) and a set of six flavors (flavors 11 to 16) were used, but the mapping of flavors to locations was changed every two sessions (Fig. 5B). The scheduled inconsistency was therefore in the relational pairing of the items rather than the identity of the flavors or the locations of the sand wells. Moreover, a change only every two sessions did not preclude the animals attempting to learn these PAs across sessions, but would have precluded the creation of a context-specific schema. Choice performance gradually improved in the consistent schema room but not in the inconsistent room (Fig. 5A); nonrewarded probe tests also established that the animals dug preferentially in the cued location in the arena of a start-box flavor in the consistent but not the inconsistent context (Fig. 5C). This difference between the two contexts is not in itself surprising and would occur even if the animals were still trying to learn individual PAs in the inconsistent room. However, this differential rate of learning sets the stage for a last and crucial test of the schema concept.

This test involved the learning of new PAs. If animals learn PAs as isolated "facts," and if they do so ever more quickly because of context familiarity as training in this protocol proceeds, the rate of learning in the two contexts should be the same. However, if the animals bring something like "activated schema" to bear on the process of learning, a difference between the two contexts might be observed. The "consistent schema" would only be activated in its appropriate context. Procedurally, the comparison in the rate of

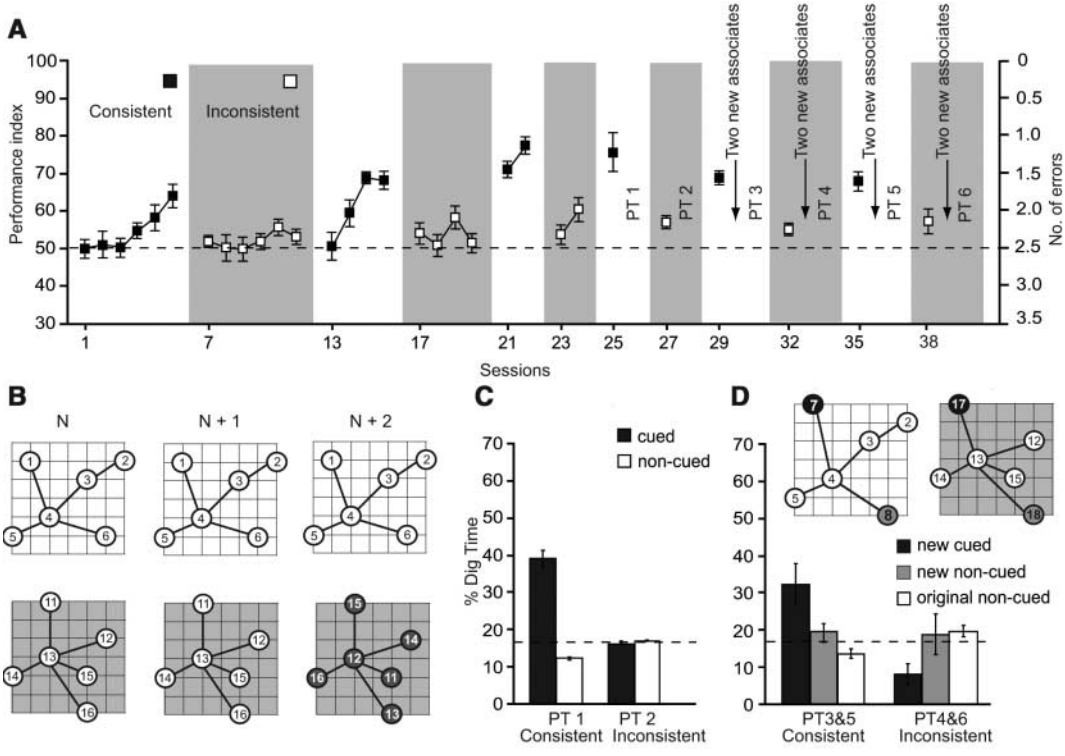

Fig. 5. A consistent activated schema promotes effective memory. (**A**) Differential acquisition of consistent and inconsistent schemata. Effective acquisition by normal rats (n = 9) occurred when mapping of flavors to places remained consistent, with six, four, two, and then single sessions (sessions 1 to 40; white background). Above-chance performance was consistent from session 15 onward ($P < 0.025$ for each comparison with chance). The same animals failed to learn a series of inconsistent schemas in the second event arena (selected days are above chance, e.g., session 27, but performance never rose above 60% correct; gray background). (**B**) With the consistent schema, the mapping of flavors to places is consistent across sessions; inconsistent schema used a common set of six flavors and locations that were associated for two sessions but then changed every third session (see N + 2, shaded gray). (**C**) Preferential digging in the probe trials at the cued locations for the consistent schema (PT1: $t = 10.9$, df = 8, $P < 0.001$) but not for the inconsistent schema (PT2: $t < 1$). (**D**) New PA probes. Performance 24 hours after exposure to the two new cue flavors and their locations when the animals would be encoding information using a consistent activated schema (PTs 3 and 5) was consistently good to the cued new location, whereas performance after use of an inconsistent schema was not (PTs 4 and 6; Group × Location $F = 13.92$, df = 1.64/26.30, $P < 0.001$). Approach latencies from the start box to the correct sand well during these probe trials were equivalent in the consistent (20.9 ± 1.9 s) and inconsistent (20.0 ± 2.5 s) contexts, indicating comparable motivation to perform each task.

learning new information had to be done in a manner that ensured an identical behavioral protocol in the consistent and inconsistent rooms. In this phase, beginning at session 29, the animals were therefore trained on four successive sequences of three training sessions beginning as follows: session 29, further consistent-context training of flavors 1 to 6; session 30, two new PAs trained in a session consisting of only two trials (PAs 7 and 8); session 31, a nonrewarded probe test for these novel associates. This three-session sequence was then repeated in the inconsistent context (sessions 32 to 34) using flavors 11 to 16, then PAs 17 and 18 followed by a nonrewarded probe test; and again in the consistent and then the inconsistent context with PAs 9 and 10 and PAs 19 and 20, respectively. The sequence ended with PT6 on session 40 (Fig. 5). The use of only two rewarded trials instead of the usual six trials per day on session 2 of this three-session sequence ensured that both the behavioral procedure and the memory-encoding demands on the animals were identical in the two training contexts on session 2. Figure 5D shows successful acquisition and 24-hour retention of these new PAs only when encoding occurred in the consistent-schema context. The apparent motivation of the animals to perform these two learning tasks was equivalent, as indexed by equivalent approach latencies to the target sand well in both the consistent and inconsistent contexts (Fig. 5D).

These findings indicate that animals—no less than people—can bring activated mental schemas to bear in a PA learning task and thereby encode, assimilate, and rapidly consolidate relevant new information after a single trial. The capacity of animals to make deductive inferences on the basis of their "mental models" of the world is, of course, far more limited than that of humans (*4*), but the principle that associative schemas can be useful in memory is not unique to humans.

In experiment 1, animals used hippocampal-dependent learning to acquire several PAs concurrently, of which one member of each pair was a spatial location in a familiar environment. This enabled the animals to treat these several associates as a connected spatial set, rather than as individual "facts," and so build up a framework in which similar new information could be stored. The construction of this "schema" took about a month—approximately the same period that several studies of retrograde amnesia have suggested is always required after learning for effective systems consolidation to occur. We observed, however, that if the several weeks of schema building was completed before new learning, the assimilation and consolidation of novel information within these neocortical schemata could be very rapid (experiments 2 and 3). We also established that the possession of an activated schema is causally important in the acquisition of new information (experiment 4). The use of rigorous control protocols (e.g., the noncued memory test, arena rotation) established that performance is mediated by PA memory rather than by cryptic uncontrolled olfactory cues. Similarly, the use of two new PAs exploring associative assimilation into a schema, rather than a single PA, ensured that the effective recall in probe trials was not an artifact of stimulus novelty.

Discussion. These findings have implications for a number of key issues in the neurobiology of learning and memory. First, they indicate that the rate at which systems consolidation occurs in the neocortex can be influenced by what is already known. In contrast, in the complementary learning systems approach (*36*, *37*), the hippocampus is said to be "specialized for rapidly memorizing specific events" (*37*) and the neocortex for "slowly learning the statistical regularities of the environment." Consolidation of memory traces in the neocortex is held to be a largely time-dependent process determined by the specific patterns of information representation, anatomical connectivity, and synaptic plasticity expression rules that it can support. Broadly speaking, this is a fair characterization of a large body of data (*27*), but it does not quite capture the potential that the neocortex has for rapid consolidation when newly acquired information is compatible with previously acquired knowledge. Given our observation that the neocortex can sometimes consolidate very rapidly, it follows that it must also be able to encode associative memory traces very rapidly—perhaps even "on-line" within sensory-perceptual systems. The widely held supposition that the neocortex is a slow learner therefore needs to be reappraised. The distinct temporal dynamics of these memory processes may contribute to the usual finding that the cortex does learn more slowly than subcortical structures—a generality that extends to conditional-associative motor learning (*38*)—but that this may not always occur.

A second finding is that the storage and recall of allocentric spatial memory can occur outside the hippocampus in the rat, even for information that has been acquired in a single trial as a consequence of hippocampal-dependent processing. This conflicts with both the cognitive-map theory and the multiple-trace theory of memory consolidation (*7*, *39*, *40*). Spatial memory has been shown previously in rats with hippocampal lesions, but the information was either acquired postoperatively and inflexibly over very extended training (*41*, *42*) or "semanticized" over many months before the lesion (*43*). The long-sought upward gradient of remote spatial memory in rats when varying intervals of time are systematically scheduled before making hippocampal lesions (*44*–*47*) is now definitively shown using a cued-recall protocol for information acquired in one trial. The temporal gradient is much steeper than might have been expected on the basis of prior work using a within-subjects design for contextual fear conditioning (*26*). Moreover, the effective remote spatial memory in hippocampal-lesioned animals upon their return to the first event arena, learned as young animals, is strikingly similar to that displayed by patient E.P. (*30*). It is unclear why effective remote spatial memory is found here but not in the water maze (*48*). One possibility is that the water maze is more "recall-like" in character (*10*), requiring an animal to generate its own reminder cues. The PA paradigm used here could allow apparent cued recall to be mediated in part by cued recognition based on proximal intramaze cues.

Third, the failure of animals with near-complete hippocampal lesions to acquire PAs over many trials of training (experiments 1 and 2) calls into question the capacity for effective "semantic-like" learning in the absence of functional hippocampal tissue. This idea emerged particularly in studies of developmental amnesia (*49*), but it has proved difficult to distinguish whether the intriguing dissociations between impaired episodic and intact semantic memory in such patients are due to intact neocortical learning of semantic information (*50*), to functional reorganization in the developing brain, or to islands of residual hippocampal function in these amnesic patients. When the medial temporal lesions are large, as in patient E.P., essentially no declarative fact learning occurs (*51*). Our findings suggest that, in animals in which it is possible to make selective 90% lesions of the hippocampus as adults, the acquisition of new flavor-place PAs is also consistently blocked and not rescued by multiple training trials. The generality of this observation beyond the spatial domain should be followed up in young animals, including primates, in order to model the situation in developmental amnesia more closely.

That the acquisition of a schema took about a month points to the possibility of it involving some kind of neuroanatomical growth process in the neocortex that creates an associative "space" in which new PAs can be rapidly stored without interference—analogous to "phase sequences" (*52*). Intercortical synaptic connections may be created or unmasked within a functional network that has only silent or baseline synaptic strengths. These could then be rapidly potentiated by relevant information when the network is in an "active" state (an activated schema). The initial growth process would necessarily take a period of days or weeks—the very time period that has hitherto been thought to mediate systems consolidation and to occur only after learning (*20*). Thus, an intriguing speculation to emerge from the present data, with conceptual similarities to the principles of synaptic tagging and capture (*53*, *54*), is that an associative space into which new information can be assimilated can be constructed before the exposure to that information. However, this construction of associative interconnections can be noncommittal or "experience-expectant" in character (*55*).

The findings bring to neuroscience a set of ideas hitherto largely discussed in the context of psychological studies of human memory. The concept of "activated schemas" has been discussed only in relation to humans (*3*), as it implies a conscious awareness that rats are unlikely

to possess. However, even if they are implicit, schemas are an economical way to characterize the gradual acquisition of an organized framework of associative "semantic-like" information from "episodic-like" events that, once acquired, allows relevant new information to be assimilated and stored rapidly. Given that animals have daily activities such as finding food and water, it is important for them to retain an organized body of knowledge about where these may be found and to be able to update such a framework rapidly, within one trial. This inferential flexibility of rodent cognition is now established in several domains (*9*).

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Supporting Online Material

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REPORTS

Nonstoichiometric Dislocation Cores in α-Alumina

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Little is known about dislocation core structures in oxides, despite their central importance in controlling electrical, optical, and mechanical properties. It has often been assumed, on the basis of charge considerations, that a nonstoichiometric core structure could not exist. We report atomic-resolution images that directly resolve the cation and anion sublattices in alumina (α-Al_2O_3). A dissociated basal edge dislocation is seen to consist of two cores; an aluminum column terminates one partial, and an oxygen column terminates the second partial. Each partial core is locally nonstoichiometric due to the excess of aluminum or oxygen at the core. The implication for mechanical properties is that the mobile high-temperature dislocation core structure consists of two closely spaced partial dislocations. For basal slip to occur, synchronized motion of the partials on adjacent planes is required.

The core structures of dislocations are critical to the electronic, optical, and mechanical properties of a wide range of materials. For most simple monometallic crystals, dislocation core termination can be determined; however, in complex crystals such as oxides, either cation or anion columns (or both) can be the terminating atomic columns even with the same dislocation character (i.e., characteristic displacement vectors called Burgers vectors, **b**). The possibility of nonstoichiometric cores also arises but has usually been rejected because it suggests the possibility of charged dislocations (*1*, *2*) and the presence of long-range Coulomb fields with a high associated electrostatic energy. This has been suggested to be the reason why the close-packed {111} crystal plane in alkali halides cannot be an easy slip system (*2*, *3*). Detailed knowledge of dislocation core structures and compositions is critical to understand dislocations in ionic crystals.

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