

Rapid neocortical acquisition of long-term arbitrary associations independent of the hippocampus

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Anterograde amnesia following hippocampal damage involves the loss of the capacity to form new declarative memories but leaves nondeclarative memory processes intact. Current theories of declarative memory suggest the existence of two complementary memory systems: a hippocampal-based system that specializes in rapid acquisition of specific events and a neocortical system that slowly learns through environmental statistical regularities and requires the initial support of the hippocampal system. Contrary to this notion, we demonstrate a neurocognitive mechanism that enables rapid acquisition of novel arbitrary associations independently of the hippocampus. This mechanism has been dubbed “fast mapping” (FM) and is believed to support the rapid acquisition of vocabulary in children as young as 16 mo of age. We used FM to teach novel word-picture associations to four profoundly amnesic patients with hippocampal system damage. Patients were able to acquire arbitrary associations through FM normally, despite profound impairment on a matched standard associative memory task. Most importantly, they retained what they learned through FM after a week’s delay, when they were around chance level on the standard task. By contrast, two patients with unilateral damage to the left polar temporal neocortex were impaired on FM, suggesting that this cortical region is critical for associative learning through FM. Left perirhinal and entorhinal cortices might also play a role in learning through FM. Contrary to current theories, these findings indicate that rapid acquisition of declarative-like (relational) memory can be accomplished independently of the hippocampus and that neocortical plasticity can be induced rapidly to support novel arbitrary associations.

consolidation | medial temporal lobe | neocortex | semantic memory

Memory consolidation is a gradual, time-dependent, reorganization process by which memories become stable. Systems consolidation of declarative memory is thought to occur when memories that are initially supported by both the hippocampus and the neocortex become hippocampus-independent over periods of time that range from weeks to years (1–3). Systems consolidation is thought to be gradual because rapid acquisition of novel information by the neocortex would cause interference with existing knowledge structures [“catastrophic interference” (1)]. Therefore, novel associations always depend initially on the hippocampus, which specializes in rapid representation of novel associations or arbitrary relations. The hippocampus, in turn, supports the gradual changes in neocortical connections that allow for the incorporation of novel information into existing knowledge structures (1–4). We hypothesized that an exception to this rule might be observed in a process called “fast mapping” (FM) (5, 6), which supports the astounding ability of toddlers as young as 16 mo of age (7) to acquire rapidly vast numbers of novel word-referent associations. We predicted that adults with lesions to the hippocampus might be able to learn novel arbitrary association normally by using FM.

Only a few studies have tested FM in adulthood (8–10), with the tacit assumption being that this mechanism is specific to early developmental stages of language acquisition, enabling the prodigious rate of vocabulary expansion. These studies have shown

that adults can learn verbal labels and facts through FM just as well as children (8, 9). Little is known about the neural substrates that mediate FM (11), but the behavioral similarity between adults and children in FM might reflect similar neuroanatomical substrates. FM is implicated in the rapid acquisition of an extensive vocabulary in very young children, in whom episodic memory and the hippocampal system are not yet fully developed (12). We thought it might be mediated by structures outside the medial temporal lobe (MTL), and therefore might support postmorbid learning in adult amnesics with hippocampal system damage and very poor episodic memory.

Six middle-aged patients and 15 matched healthy controls (*Methods*) were administered an FM task adapted for use with adults. FM paradigms differ from standard associative learning procedures in three important ways: (i) Associative links are not given but are discovered actively by participants possibly via disjunctive syllogism (8), as described below; (ii) novel associations are created within a pragmatic communication situation and an existing semantic context; and (iii) learning of associations is not deliberate. Accordingly, in the present study, participants were told that the task was a perceptual task. On each trial (Fig. 1*A*), they were exposed to two pictures (animals, fruits, vegetables, or flowers), one novel and previously unknown to the participants (e.g., numbat) and one previously known (e.g., zebra), and they had to answer a simple perceptual yes/no question that contained the target’s label. By comparing the previously unknown target picture with the previously known lure picture, participants infer that numbat is the name of the previously unknown item. In our task, 16 novel previously unknown associations were presented twice, each time with a different previously known lure and a new sentence. After a 10-min delay, a surprise associative recognition memory test was administered. A previously unknown label was presented with three previously presented unknown items to control for item-based recognition and the correct association had to be selected (Fig. 1*B*). The recognition memory test was administered again after a week to assess long-term retention. A matched standard associative memory task using explicit encoding (EE) was also administered. A single picture appeared on each trial, along with instructions to try to remember the association between the pictures and their labels (Fig. 1*C*). As in the FM task, participants were exposed twice to each stimulus. Identical associative recognition tests were administered at delays of 10 min and 1 wk (Fig. 1*D*).

Four of the patients who participated in this study had severe amnesia, presenting with significant declarative memory impairments and normal intellectual functioning as well as preserved cognitive functioning in domains other than memory (Table S1).

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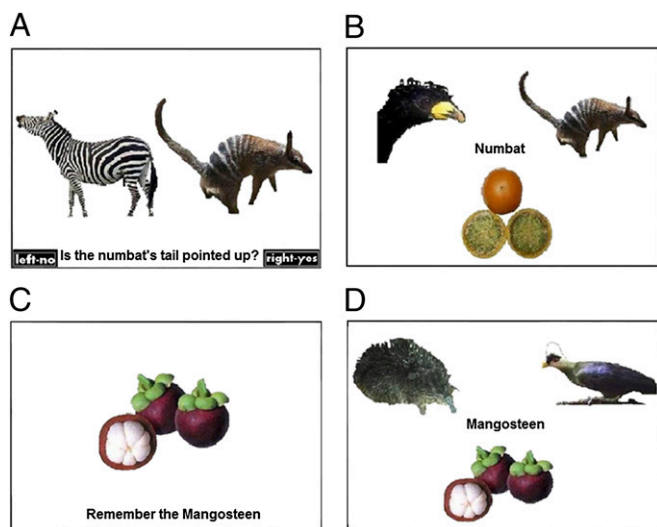


Fig. 1. Examples of stimuli used in the FM and EE experiments. (A) Previously unknown target study phase trial in the FM experiment. (B) Recognition test trial in the FM experiments. (C) Previously unknown target study phase trial in the EE experiment. (D) Recognition test trial in the EE experiment.

All four patients had MRI-confirmed lesions either to the hippocampi bilaterally (N.S., E.C., and Sh.B.) or to the extended hippocampal system through severance of the fornices bilaterally (A.D.) (13, 14), which interferes with hippocampal input and output (Fig. 2, Table 1, Figs. S1–S6, and Table S2). Volumetric analyses were performed on three of these patients (E.C., Sh.B., and A.D.) and revealed significant bilateral (Sh.B. and E.C.) or left (A.D.) hippocampal volume reduction as well as bilateral (E.C.) and left (A.D.) MTL cortex (MTLC) reduction. Note that A.D.'s severe amnesia is the result of his fornix bisection and basal forebrain lesion (Fig. S2). The other two patients were tested because they had lesions that encompassed the polar temporal neocortex (Fig. 2, Table 1, Figs. S5 and S6, and Table S2), which is a critical site for supporting semantic associations (15–17). One of these patients (A.A.) had no tissue in his left temporal pole and also significant reduction to the left hippocampus and MTLC. The right MTL structures were intact, in line with the pattern of his memory deficit, which was more severe for verbal material (Table S1). The second patient (K.S.) was not amnesic and only had mild retention and working memory deficits (Table S1) as well as intact hippocampi. He was included in the study because he had a significant loss of left temporal pole tissue as well as left MTLC (Fig. 2, Table 1, and Fig. S6).

Results

In accordance with the concept of disjunctive syllogism and previous findings in FM (8), we found that controls in our FM task responded more slowly to previously unknown target stimuli [mean (M) = 3,433.56 ms, SD = 738.23 ms] than to previously known target stimuli (M = 2,399.09 ms, SD = 156.91 ms) [$t(14)$ = 12.17, P < 0.001], as did the patients (M = 3,326.09 ms and M = 2,553.14 ms, respectively).

Our recognition test results show that the amnesic patients successfully recognized 68% (range: 58–82%) of the associations between previously unknown labels and previously unknown pictures for which they successfully performed FM (Fig. 3A). This performance was significantly above the chance level of 33% for the patient group as a whole (P = 0.01, binomial test) and also individually for three patients (P = 0.0004 for N.S., P = 0.004 for Sh.B., and P = 0.04 for A.D.; binomial test) and marginally significant for the fourth patient (P = 0.06 for E.C.,

binomial test). Furthermore, the amnesic patients' performance was not significantly different from the controls' performance and even numerically higher than it (M = 63%, SD = 12%) (Mann–Whitney U test = 21, not significant). E.C.'s performance also was within the controls' range and not significantly different from it [$t(14)$ = -0.4 , P = 0.35]. After a week's delay, patients and controls retained what they had learned. The patients retained 60% of the associations (range: 50–63%). This performance was still significantly above chance for the patients as a group (P = 0.014, binomial test) and individually for the three patients (P = 0.02 for N.S., P = 0.01 for Sh.B., and P = 0.04 for A.D.; binomial test). E.C.'s performance was not above chance (P = 0.1, binomial test), although he correctly recognized the same items on both occasions, indicating that the items he recognized on the second testing were retained from the first week and were not chosen by chance (P < 0.001, binomial probability). Moreover, the patients' performance remained not significantly different from that of controls (M = 58%, SD = 13%) (Mann–Whitney U test = 24.50, not significant). Again, even E.C.'s performance was within controls' range and not significantly different from it [$t(14)$ = -0.6 , P = 0.28]. Importantly, a closer examination of the pattern of results revealed that, similar to E.C., the associations remembered by patients and controls on the delayed recognition test were the same as the ones they remembered on the first test, confirming that their performance reflected declarative-like learning and was not attributable to chance.

By contrast, patients' performance on the recognition test for the EE task was markedly impaired (Fig. 3B). They correctly recognized an average of only 44% (range: 31–50%) of the associations immediately, which was significantly lower than controls' performance (M = 83%, SD = 12%) (Mann–Whitney U test = 0; P < 0.01, two-tailed probability) and not statistically different from chance performance either as a group (P = 0.25, binomial test) or individually (P = 0.12 for N.S. and E.C., P = 0.56 for Sh.B., and P = 0.25 for A.D.; binomial test). On the other hand, controls showed the opposite pattern, performing significantly better on the EE task than on the FM task [$t(12)$ = 4.51, P < 0.001]. After a week's delay, the patients' recognition performance remained not different from chance as a group (M = 42%; range: 38–56%; P = 0.25, binomial test) and individually for three of four patients (P = 0.44 for N.S., A.D., and Sh.B.; P = 0.05 for E.C.; binomial test), whereas controls still recognized 71% (SD = 19%) of the associations, again performing significantly better on the delayed EE than on the delayed FM test [$t(11)$ = 2.06, P < 0.05]. The patients' performance remained significantly lower than that of the controls (Mann–Whitney U test = 5; P < 0.05, two-tailed probability).

A Bayesian standardized difference test (18) revealed that three of the four patients' pattern of performance fulfilled the criteria for a classic dissociation between FM and EE functions (P = 0.01, P = 0.006, and P = 0.04 for N.S., Sh.B., and A.D., respectively, and P = 0.14 for E.C.; two-tailed probability).

Next, we tested the two patients (A.A. and K.S.) whose lesions incorporated the anterior temporal lobe (ATL) on the FM and EE tasks. Unlike the four amnesic patients, both A.A. and K.S. showed significant impairments on the FM task. They both recognized 36% of the associations between previously unknown pictures and their labels on the immediate recognition test, performing significantly worse than the controls [P < 0.05 for both A.A. and K.S., two-tailed probability, Bayesian test (18)] and scoring around chance levels (P = 0.5 for both A.A. and K.S., binomial test) (Fig. 4). On the delayed recognition test, A.A. recognized 29% of the associations, whereas K.S. correctly recognized 50% of the associations, a performance still not significantly different from chance levels (P = 0.5 for A.A. and P = 0.1 for K.S., binomial test) and still significantly worse than that of the controls for A.A. [P = 0.04, two-tailed probability, Bayesian

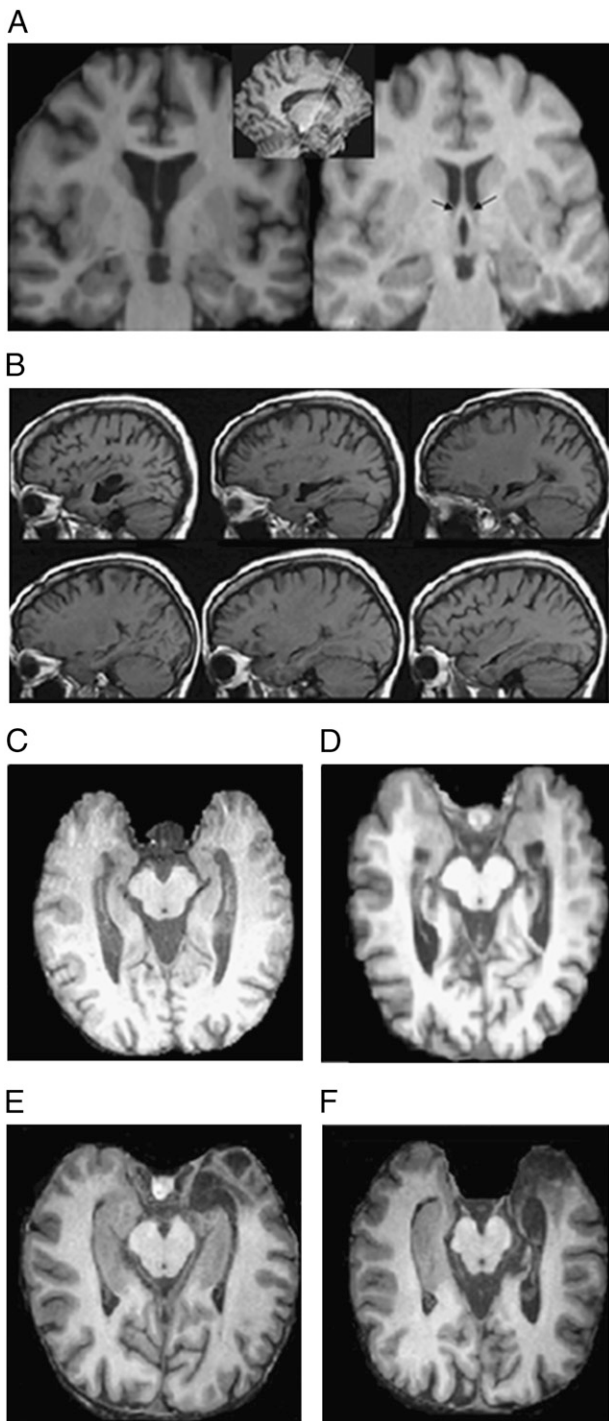


Fig. 2. Neural structures affected in the six patients who participated in the study as revealed in T1-weighted MRI (more details are provided in Figs. S1–S6 and Table S2). (A) A.D. (Left, coronal image) had bilateral fornix transection following removal of a third-ventricle colloid cyst (13, 14). (Right) Matched healthy control's coronal image shows the fornices (black arrows). A.D. had significantly reduced left hippocampus and right perirhinal cortex as determined by volumetric analyses (Table S2), which were not apparent on visual inspection of his clinical MRI scan immediately after surgery in 1999 and may be the result of disuse or degeneration. (B) N.S. (sagittal images) had a bilateral (left > right) anterior cerebral artery (ACA) aneurysm affecting the ACA/posterior cerebral artery (PCA) and corpus callosum. Her lesion included bilateral MTL structures as well as lateral temporal neocortical regions. (C) E.C. (axial image oriented along the hippocampal long axis) experienced the consequences of herpes simplex encephalitis, which extensively affected his MTL structures bilaterally, including significant reduction

test (18)] but not for K.S. [$P = 0.5$, two-tailed probability, Bayesian test (18)].

On the EE task, A.A., who had amnesia comparable to that of the amnesic patients (Table S1), performed at chance level both immediately (25%; $P = 0.4$, binomial test) and after a week (31%; $P = 0.6$, binomial test) and performed significantly below the controls' level on this task immediately [$P < 0.001$, two-tailed probability, Bayesian test (18)]. By contrast, K.S., who does not have significant memory impairments on standard tests of memory, was above chance level on the immediate EE task (69%; $P = 0.004$, binomial test) and performed only marginally statistically differently from controls on this task [$P = 0.06$, two-tailed probability, Bayesian test (18)]. After a week, however, his performance no longer differed from chance (50%; $P = 0.1$, binomial test).

Discussion

Consistent with our predictions, we found that four profoundly amnesic patients with confirmed bilateral lesions to the MTL and/or the extended hippocampal system without ATL damage successfully recognized novel associations incidentally acquired through the FM task. Moreover, they retained the associations after a week's delay, recognizing the same items on both tests, confirming that their performance was not attributable to chance. Their normal performance was all the more remarkable considering their marked impairment in a comparable standard EE associative recognition task even after very short delays. Three of four patients fulfilled the criteria for a classic dissociation between FM and EE functions. The controls' better performance on the EE task argues against the possibility that the FM task might induce deeper encoding, and thus support the patients' performance on this task. In contrast, the patients with lesions to the ATL performed significantly worse than controls on the FM task. On the EE task, A.A., who had amnesia comparable to that of the patients with MTL lesions, performed at chance level; however, K.S., who did not have significant amnesia and had a relatively spared MTL, performed comparably to controls on the immediate test, although performance declined a week later.

The new learning acquired by the amnesic patients in this study constitutes a first report of rapid acquisition of arbitrary novel associations in amnesic patients using FM. These patients' learning was induced after only two short exposures to the picture-label pairs and occurred despite their marked deficit in explicit learning (on the present EE control task as well as on neuropsychological tests of associative memory). These results show that learning through FM can be achieved independently of

of the hippocampi and perirhinal cortex. Entorhinal cortex volumes were outside controls' range but did not reach statistical significance. (D) Sh.B. (axial image oriented along the hippocampal long axis) had hypoxia associated with ventricular fibrillation. Single-photon emission computed tomography images showed bilateral MTL hypoperfusion. MRI volumetric analyses showed significant bilateral hippocampal volume reduction. All four patients were densely amnesic as revealed by both formal testing (Table S1) and their everyday behavior. The other two patients had anterior temporal damage. (E) K.S. (axial image oriented along the hippocampal long axis) had a left temporal craniotomy for meningioma removal, and MRI showed encephalomalacia in the left ATL cortex, including a significantly reduced left temporal pole as well as significantly reduced left perirhinal and left parahippocampal cortices. Behaviorally, he shows mild memory impairments (Table S1) that are well compensated for by using mnemonic techniques extensively. (F) A.A. (axial image oriented along the hippocampal long axis) had herpes simplex encephalitis, which affected his left ATL, including the temporal pole, hippocampus, and left perirhinal and left entorhinal cortices, and shows severe memory impairment, especially in the verbal domain (Table S1).

Table 1. Percentage of residual tissue for temporal poles, hippocampi, and MTLC of five patients compared with age-matched controls

Patient	Temporal pole		Hippocampus		MTLC	
	Right	Left	Right	Left	Right	Left
A.D.	85	93	88	71*	85	70*
E.C.	80	114	35**	37**	73**	62**
Sh.B.	103	77	58**	64**	96	80
A.A.	103	0**	92	26**	93	15**
K.S.	99	19**	113	92	92	41**

MTLC includes volumes of the perirhinal, entorhinal, and parahippocampal cortices (more detailed information is presented in Table S2). Statistically significant differences between single patient's volumes and the corresponding controls are marked in bold using a modified *t* test for comparing single subjects with small control groups. **P* < 0.05; ***P* < 0.01.

episodic memory and the hippocampus, and indicate that FM may be mediated by extrahippocampal neocortical structures that are implicated in semantic memory, such as the lateral temporal lobe and ATL as well as the inferior prefrontal cortex (PFC) (15–17), and possibly also by anterior parahippocampal structures. In particular, the ATL is hypothesized to serve as an a-modal representational hub for linking together associative semantic knowledge (16, 17) and may be critical for supporting unique semantic associations (15) of the type we taught our subjects. Our findings of severely impaired FM learning in patients with left ATL lesions are consistent with this hypothesis. Both patients, however, also have reduced left MTLC; thus, the possibility that FM learning depends on the combined contribution of ATL and MTLC cannot be ruled out. E.C., with ~40% left MTLC reduction and an intact ATL, was consistently able to learn and retain arbitrary associations through FM, but his performance was not as good as that of the other patients with hippocampal lesions. If MTLC damage impairs FM learning, it may only do so when damage is extensive, because A.D., with ~30% MTLC volume reduction, performed normally on FM.

Our study demonstrates rapid hippocampal-independent acquisition of arbitrary associations in declarative memory. It might be claimed, however, that the performance of our subjects on the FM recognition task is supported by nondeclarative mechanisms, particularly priming, rather than by processes akin to declarative memory. There are at least four features of our paradigm and data that are not compatible with a priming in-

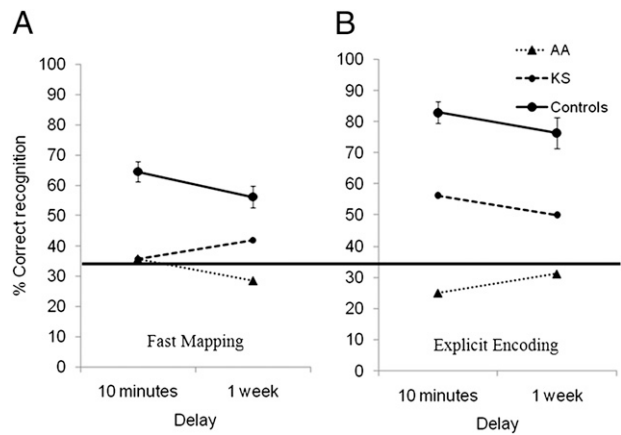


Fig. 4. Associative recognition performance on the FM (A) and EE (B) tasks of the two patients with ATL lesions compared with the healthy controls. The horizontal line represents chance performance. Error bars represent the SEM.

terpretation. The main one is that knowledge was directly tested using an explicit recognition test, whereas priming is typically revealed through indirect implicit measures of improved performance on tasks that are orthogonal to explicit recognition (e.g., stem completion, category generation, reading times, lexical decisions) and these effects often disappear in patients when knowledge is tested explicitly (19–22). Moreover, the explicit test of knowledge was identical for the FM and EE tasks of our study, and if implicit processes unexpectedly support explicit recognition on the FM task, one would expect them also to do so on the EE recognition task. A second reason is that priming is demonstrated most robustly for single items, whereas the present study tested for formation and retention of novel arbitrary associations. Priming for associations in amnesia is a contentious issue, and some of the effects that have been reported in healthy controls may be ascribed to contamination of explicit memory processing, dependent on the MTL, within an implicit task (19). Even in studies that show performance gains in patients that can be ascribed to associative information, these effects disappear when knowledge is probed explicitly (20–22). Third, the formation and retention of novel associations, as demonstrated by priming or by familiarity in recognition memory, have rarely been reported when items are in different modalities or domains (23), as the picture-label associations were in our study. Finally, insofar as there have been reports of priming of visual objects, and even more so of cross-modal or cross-domain associations between a visual object and a verbal label, the priming effect is sensitive to the specificity of sensory features of the items at encoding and retrieval (19). Items during the recognition phases of our study differed with regard to their size, spatial location, and context of presentation, and for verbal labels, there were also differences in modality (both auditory and visual at encoding and only visual at retrieval). Such associative memory effects, indicative of a certain degree of flexibility of representation, are more characteristic of declarative memory and incompatible with priming.

We also have some preliminary evidence that further supports the flexibility of the arbitrarily formed associations acquired through FM and speaks to another characteristic of declarative memory—conscious awareness (*SI Text*). A.D., the only patient who was available for further testing, was not only able to retain the FM-acquired associations but to classify the individual items he had learned as animals, fruits, flowers, or birds. Moreover, both healthy individuals and A.D. were more confident of their correct responses than of their errors during associative recognition, suggesting that they were consciously aware of the

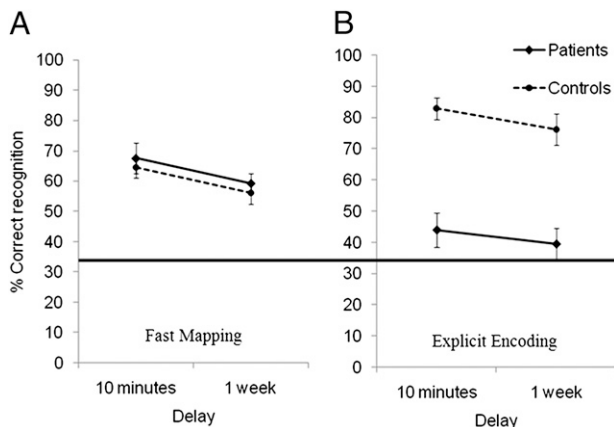


Fig. 3. Associative recognition performance on the FM (A) and EE (B) tasks of amnesic patients and healthy controls. The horizontal line represents chance performance. Error bars represent the SEM.

knowledge they had acquired. Although very preliminary, we believe the current study and the pilot data provide good evidence for declarative-like memory that is formed following FM, independently of the hippocampus. We cannot rule out the possibility that the associative learning we demonstrate might be supported by processes of a type that has not been previously described. Perhaps some hybrid declarative-priming process exists, which is mediated by the temporal poles and allows for long-term adaptation of cell assemblies so that they can sustain long-term representations of arbitrary associations that resemble similar associations in declarative memory. Until evidence favoring this alternative is gathered, the most parsimonious interpretation is that FM allows for the rapid formation of nonepisodic declarative memories independently of the MTL.

Our study and findings are also distinct from those of others that demonstrated new learning in hippocampal amnesia following numerous repetitions of novel declarative information (24). Acquisition in such cases is slow, and the representations that are formed resemble nondeclarative knowledge. Normal-rate learning of semantic-like information has recently been reported in a group of four amnesic patients (25). However, the associations formed in that study were self-generated and meaningfully related to their referents (i.e., nonarbitrary), which sets them apart from the arbitrary associations of words with their referents that we showed in our study (e.g., Kerela as the name of a fruit rather than a bird), and learning was considerably slower than in our study (2 vs. 48 trials). Duff and colleagues (25) noted that their patients were unable to learn similar but arbitrary associations despite extensive repetition. They suggest that their patients' performance is compatible with current theories of declarative memory systems because the nonarbitrary associations do not require the creation of novel relationships among items (1–3, 26–28).

One aspect of FM that may make it conducive to rapid neocortical semantic memory acquisition is that novel information appears in the context of old previously known items, possibly supporting the modification of existing semantic schema knowledge (27). A recent report in rats showed that rapid novel learning of associations of spatial locations with odors can be consolidated quickly if the newly learned information is related to existing well-established schema (4). Unlike the present study, however, initial acquisition in that study was still reliant on the hippocampus, such that when the hippocampus was lesioned 2 h after learning, the novel information was lost. In our case, such learning was acquired normally in patients with large MTL lesions and severe amnesia.

An important feature of our findings is the durability of the new associations. When we piloted the task over a year ago using different stimuli, we tested A.D. on it. After completing all testing for the present study, we retested him on the pilot stimuli and were surprised to find out that he still retained six of eight items. This raises the question of why adults with acquired amnesia, who appear to possess the mechanism that enables children to acquire novel vocabulary very efficiently, are only able to learn scant new information (29–31). One possibility is that adults' naturalistic environments do not afford the same opportunities for FM as do children's environments. Another is that there is a critical period in early childhood during which plasticity of regions mediating FM is optimal. In reports of children with very early hippocampal damage and poor episodic memory who nonetheless acquired normal semantic knowledge (32), learning may be partly attributable to normal FM in childhood, which either declines in adulthood or is superseded by a strategy that favors MTL-mediated learning. That our controls performed more poorly on the FM task than on the EE task lends support to this notion.

Our demonstration that declarative-like knowledge can be acquired rapidly and retained for a long time without enlisting

the hippocampus argues against long-held theories that the hippocampus is the gateway for acquisition and retention of all long-term declarative memories. It also speaks against the notion that long-term plasticity in the adult neocortex is limited and does not allow for rapid changes in representations that support declarative memory. It is still unclear whether such plasticity is unique to the ATL because of its role in binding unrelated pieces of semantic information (16, 17) or whether other cortical or subcortical regions contribute to this type of learning. Our findings have important implications not only for neurobiological theories of memory but for the development of treatment for people with memory disorders.

Methods

Participants. Six patients participated in this study. Their demographic characteristics, etiology, and neuropsychological profile are presented in Table S1. A group of 15 healthy control participants matched to the patients with respect to age ($M = 52.81$ y, range: 40–62 y), education ($M = 15.38$ y, range: 11–21 y), and handedness (14 right-handed) was recruited. The control participants were also administered the FM and EE tasks and were tested for recognition at a 10-min delay and after 1 wk.

Stimuli. The stimuli for the tasks were selected from a larger set of 206 previously unknown and previously known pictures of various animals, fruits, vegetables, and flowers collected through searches of the Internet and in nature books. A pilot study was run on a group of 60 first-year psychology students at the University of Haifa (28 and 32 subjects performed the FM and EE tasks, respectively), in which 62 previously unknown and 31 previously known pictures were used as target stimuli. On the FM task, an additional 62 previously known and 31 previously unknown pictures were presented as lures. Twenty additional stimuli were used for practice purposes. Based on the recognition rate, study mistakes, and previous familiarity of the pilot subjects with each of the target stimuli, 16 different previously unknown target stimuli and 8 previously known target stimuli were selected for each task (FM and EE), with 16 previously known stimuli and 8 previously unknown stimuli used as lures during encoding of the FM task. The stimuli selected consisted of those for which there were almost no judgments of previous familiarity ($M = 0.16$, range: 0–2) or response errors made during FM encoding ($M = 0.625$, range: 0–2). The stimuli were randomly assigned to either the FM or EE task with the restriction that tasks would be matched with regard to the following:

1. Representation of semantic categories. On the FM task, there were 6 pictures of animals, 2 of birds, 6 of fruit or vegetables, and 2 of flowers; on the EE task, there were 6 pictures of animals, 2 of birds, 7 of fruit or vegetables, and 1 of a flower. One picture differed in its semantic category between tasks as a result of achieving an optimal match between tasks on the other mentioned parameters.
2. Previous familiarity of pilot study participants [$M = 0.13$ participants per stimulus, range: 0–2 and $M = 0.19$ participants per stimulus, range: 0–2 for the FM and EE tasks, respectively (based on the first 52 participants of the pilot study)].
3. Rate of recognition of pilot study participants ($M = 47\%$ of participants, range: 33–72% and $M = 45\%$ of participants, range: 33–65% for the FM and EE tasks, respectively).

Also, to equate the exposure time in the different paradigms, an average of the exposure time to FM items in the pilot study was calculated and served as the exposure time for the EE items (2,380 ms). The practice phase in both tasks consisted of 10 trials: 2 previously unknown and 8 previously known target trials. In the study phase of both tasks, each association was presented twice (each time with a different lure and sentence and on a different side of the screen on the FM task). Altogether, the experiment consisted of 48 trials (32 previously unknown target trials). Memory was tested using a three-choice associative recognition test following the convention in the developmental FM literature (5–11). Previous FM studies [e.g., (8)], as well as our own data, suggest that although FM allows for rapid associative memory formation, both children and adults perform very poorly on recall tests. The stimuli for the recognition test were grouped such that in 2 trials, both lures were of the same category as the target stimulus; in 6 of the FM trials and 7 of the EE trials, only one of the lures was of the same category; and in the rest of the trials, both lures were of a different category than the target-stimulus.

Procedure. Testing was conducted over three consecutive sessions. In the first session, subjects performed the FM task, beginning with a practice phase followed by the study phase. On each study trial, subjects saw and heard a sentence asking for a simple perceptual decision. Two pictures then appeared, and subjects were required to respond with either the left (“yes”) or right (“no”) mouse key (Fig. 1A). Half of the answers were positive and half were negative, and the mapping of keys to responses appeared on the screen. The target stimulus was equally likely to be presented on the right or left side of the screen, and the same stimulus never appeared on the same side on both exposures. Instructions emphasized accuracy over speed, and the task was self-paced. The study phase was followed by a 10-min filler task, which consisted of a forced-choice vocabulary test. Next, recognition memory for the items presented in the study phase was assessed via an associative three-alternative forced choice recognition task. In each step, a previously unknown label appeared in the center of the screen and around it were three pictures: the previously unknown picture to which the label referred and two other previously unknown pictures that appeared as targets in the study phase (Fig. 1B). The lures for the recognition test were chosen to be previously unknown targets and not lure pictures from the study phase so as not to allow a familiarity effect to account for the findings. The subjects had to decide to which of the three objects the label belonged using key presses to indicate their choice. Altogether, this test consisted of 16 trials, 1 for each of the 16 previously unknown associations presented in the study phase. Each previously unknown target picture from the study phase appeared three times in the testing phase, once as the referent for the corresponding label and twice as a lure. The pictures appeared on the upper right and left corners of the screen and in the middle lower part of the screen. The target stimuli were equally likely to be presented at each of these locations. The order of presentation of items both at encoding and at recognition was randomized but was the same for all participants. Next, the participants were presented one by one with all the target and lure pictures from the study phase and were prompted to state whether they had any previous familiarity with these stimuli.

The second testing session, conducted a week after the first, began with the administration of the second long-delay associative recognition test, designed similar to the first. Next, subjects performed the EE task, administered in a similar manner as the FM task. Subjects heard and saw a sentence instructing them to remember a particular item, and the item then appeared (Fig. 1C). Following the encoding stage, subjects were administered a 10-min verbal brainteasers filler task, following which the exact same testing procedure administered on the FM task was given for the EE items (Fig. 1D). Finally, in the third session, which was conducted a week after the second session, subjects were given the delayed EE recognition memory test.

Data Analysis. Previously unknown items identified as previously known ($M = 0.08$, range: 0–1 for FM paradigm; $M = 0.2$, range: 0–1 for EE paradigm for controls; for patients, the previous familiarity was 0 in both the FM and EE paradigms) were excluded from analysis. In addition, items erroneously answered on the FM study phase were excluded from the FM task, regardless of whether recognition was correct or not ($M = 1.83$, range: 0–4). This could be regarded as a removal of trials for which subjects were not attentive, whereas on the EE paradigm, no correction could be made for inattention. For this reason, an additional analysis was performed in which the recognition score on the FM paradigm was calculated without consideration of the study mistakes. The pattern of results remained similar after removal of study mistakes.

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