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Paradoxical False Memory for Objects After Brain Damage

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Poor memory after brain damage is usually considered to be a result of information being lost or rendered inaccessible. It is assumed that such memory impairment must be due to the incorrect interpretation of previously encountered information as being novel. In object recognition memory experiments with rats, we found that memory impairment can take the opposite form: a tendency to treat novel experiences as familiar. This impairment could be rescued with the use of a visual-restriction procedure that reduces interference. Such a pattern of data can be explained in terms of a recent representational-hierarchical view of cognition.

Although individuals with some types of brain damage—for example, to structures in the medial temporal lobe—are able to remember new information immediately after it is learned, their recall after even a very short interval can be greatly compromised or nonexistent (*1*). It would seem to follow that the experiences of such individuals must be lost rapidly or are inaccessible, such that when a novel object is encountered and later reexperienced, it is as if the object had never before been seen. We explored this assumption with an animal model of object recognition memory that has been widely used as a model of memory impairment (*2*).

The standard object recognition procedure involves exposure to a study object, followed (after a delay) by a test phase in which the study object is again presented, along with a perceptually distinct novel object. The participant's task is to distinguish the novel from the repeated object. Animals and human subjects with damage to the perirhinal cortex are impaired on this task when a sufficiently long delay is interposed between study and test (*2*–*4*); indeed, much work has established that damage to the perirhinal cortex alone is sufficient to cause severe impairments in object recognition (*2*, *5*–*8*). When the standard task procedure is used, the requirement that two items be simultaneously compared precludes determination of whether the novel item is viewed as familiar, or vice versa, because the presence of one item affects how much the other is explored and how it is evaluated.

We therefore devised a method of assessing object recognition that decouples the subjects' evaluation of novel and repeated objects (Fig. 1) (*9*). Consistent with previous studies, intact rats explored in the novel-object condition more than in the repeated-object condition, thus showing intact memory for the repeated object. Also consistent with previous studies, rats with perirhinal cortex damage explored novel and repeated objects equally, indicating an inability to distinguish between them (*2*). Paradoxically, however, this inability to distinguish novel from repeated objects was characterized not by an increase in exploration of the repeated object—which would have indicated that they judged the repeated object as novel—but by a decrease in their exploration of the novel object, indicating that they

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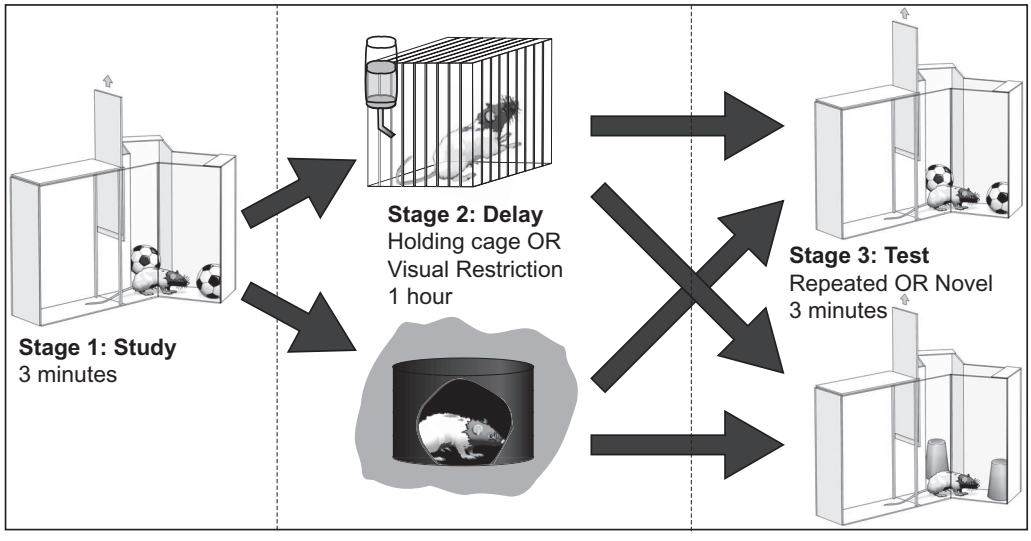

Fig. 1. A modified version of the spontaneous object recognition task, in which exploration of the repeated object is decoupled from exploration of the novel object. In the novel-object condition, an animal received a study exposure to two copies of object A for 3 min. Then the animal was put into an individual holding cage (standard condition) or a visually restricted environment (reduced-interference condition) for a delay of 1 hour. After the delay, the animal received a test exposure of 3 min to two copies of a novel object, object B. In the repeated-object condition, the animal received a study exposure of 3 min to two copies of object A. Then, as before, the animal was put into an individual holding cage or a visually restricted environment for a delay of 1 hour. After the delay, the animal received a test exposure of 3 min to two copies of the familiar object, object A.

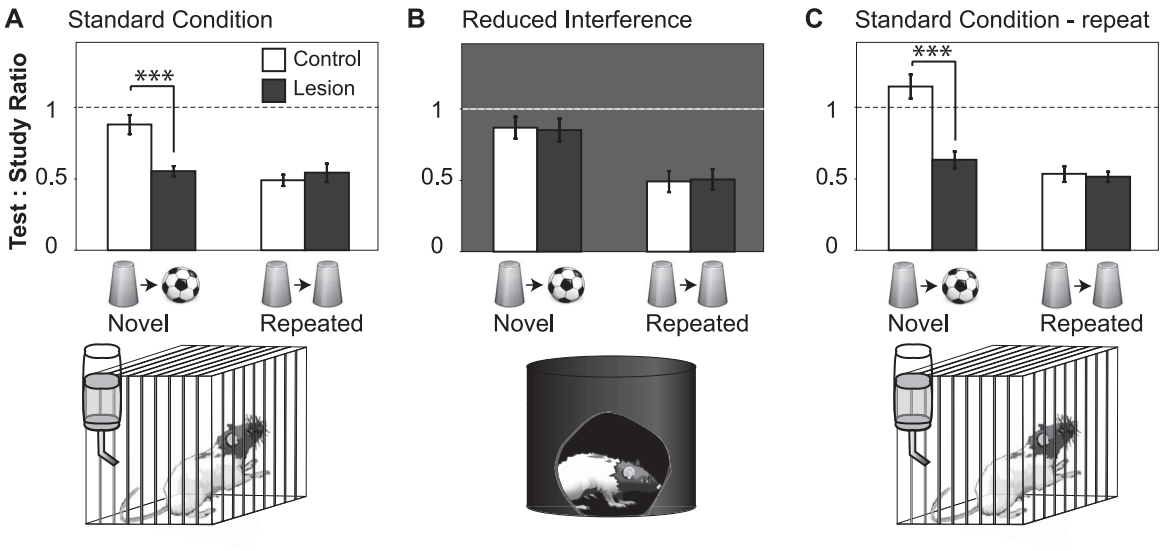

Fig. 2. Performance of rats with perirhinal cortex damage on the object recognition task. (**A**) Standard condition, with normal interference-filled delay. Repeated-measures analysis of variance (ANOVA) showed a significant effect of condition ($F_{1,19}$ = 15.38, P < 0.001), an effect of lesion ($F_{1,19}$ = 5.39, P < 0.05), and a significant interaction ($F_{1,19}$ = 13.58, P < 0.005). Post hoc t tests using Bonferroni correction showed a significant difference in the novel condition (t_{19} = 3.88, P < 0.001) and no difference in the repeated-object condition (t_{19} = 0.76, P > 0.05), indicating that lesioned animals treated the novel object as though it were familiar. (**B**) Reduced-interference condition in which animals were placed into a visually restricted environment during the delay. Repeated-measures ANOVA showed a significant effect of condition ($F_{1,19}$ = 18.33, P < 0.001), no effect of lesion (F < 1), and no interaction (F < 1), indicating that both groups discriminated the objects after visual restriction. (**C**) Repetition of the standard condition. Repeated-measures ANOVA showed a significant effect of condition ($F_{1,18}$ = 33.97, P < 0.001), a significant effect of lesion ($F_{1,18}$ = 14.59, P < 0.005), and a significant interaction ($F_{1,18}$ = 16.17, P < 0.005). Post hoc t tests using Bonferroni correction showed a significant difference in the novel condition (t_{18} = 4.62, P < 0.001) and no difference in the repeated condition (t_{18} = 0.33, P > 0.05), showing that the impairment returned when normal levels of interference were reinstated. ***P < 0.001.

treated the novel object as though it were familiar (Fig. 2A) (*9*).

Our previous work has suggested that impairments in this task may be a result of interference during the delay (*10*) and has shown that the explicit addition of interfering objects during the delay can impair memory in animals with perirhinal cortex damage (*11*). Accordingly, we reduced interference during the delay by putting the animals into a dark environment between the study and test phases (*9*, *12*). This treatment completely rescued the performance of the lesioned animals (Fig. 2B) (*9*). To ensure that the rescue of the impairment was not due to brain reorganization or recovery, we retested the animals under the original experimental conditions, and the impairment returned (Fig. 2C).

The finding that the object recognition memory impairment in this model was characterized by animals judging novel objects as familiar seems counterintuitive. It is difficult to reconcile with the assumption that all information presented during the study phase is lost or inaccessible, because this assumption would suggest that animals should judge repeated objects as novel. An alternative view (*13*–*15*), however, suggests that memory loss after brain damage may be better understood, not in terms of loss of a system dedicated to a specific type of memory—for example, long- versus short-term memory, or memory processes such as encoding, storage/consolidation, or retrieval (*16*)—but in terms of the stimulus representations that the different regions contain (Fig. 3) (*17*). For visual

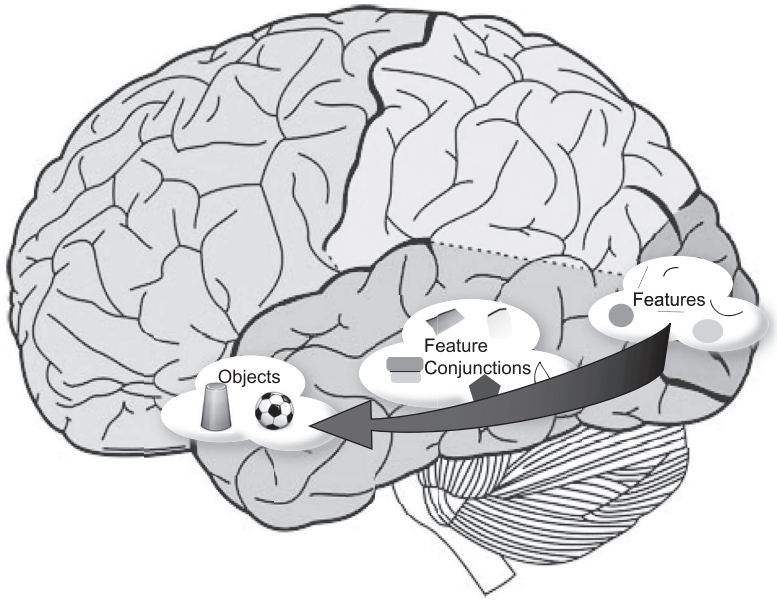

Fig. 3. The representational-hierarchical view. Representations of visual stimulus features are organized hierarchically in increasingly complex conjunctions as information flows from posterior to anterior regions of the ventral visual stream (*18*, *19*). The representation of a particular object is distributed throughout the system, but it is represented differently at different points: as features early in the ventral visual stream, as conjunctions of features in intermediate regions in the ventral visual stream, and as highly complex conjunctions of features—shown here at the level of object wholes—in the perirhinal cortex. The traditional multiple memory systems view suggests that structures within the medial temporal lobe subserve exclusively mnemonic function, whereas structures in the ventral visual stream are important for perceptual functions. In contrast, the representational-hierarchical view suggests that stimulus representations throughout the ventral-visual-perirhinal-hippocampal stream are useful for any cognitive function that requires them.

input, stimulus representations are organized hierarchically, with conjunctive representations of relatively complex stimuli in anterior brain regions, and with representations of relatively simple features in more posterior regions (*18*, *19*). We have suggested that this representational hierarchy may extend into structures within the medial temporal lobe, and that it is the highly complex conjunctive representations of stimuli that are maintained in regions such as the perirhinal cortex (*13*–*15*). According to this view, individuals with damage to such regions should be impaired not just on a particular type of memory function, but also on any cognitive function that requires the complex stimulus representations that are damaged.

This representational-hierarchical view accounts for the seemingly paradoxical findings of the present study. Indeed, the pattern of results is a central prediction of the model, as illustrated by simulations using a computational model (*9*, *10*). In these simulations, it is assumed that during the delay between study and test, the subject will be exposed to other, non-experimental visual material that occurs naturally in the environment. This material will almost certainly share some features in common with the novel object. This can lead to interference, because as a result of this exposure, features in the novel object will now be familiar. However, because it is very unlikely that the specific complex object presented during the test phase will have been experienced by chance during the delay, the unique, object-level representations in anterior regions of the system will not be familiar and therefore can protect the system from this interference. If these conjunctive representations of complex stimuli are damaged, however, then the subject will have to rely on the simpler, feature-based memory that is highly susceptible to interference. From this theoretical framework, we obtain the perhaps counterintuitive prediction that brain damage can produce impairments in visual recognition memory tasks not because the repeated object looks novel, but because the novel object looks familiar (fig. S3A). The clear corollary of this prediction is that reducing interference in the delay should improve performance in memory-impaired subjects (fig. S3B), which is what we found (Fig. 2B).

These simulations and the current results suggest that object recognition memory impairments may not be due to damage to a dedicated memory system from which all information presented in the study phase is lost or inaccessible. Instead, brain damage that leads to such impairments compromises only a very specific type of complex stimulus representation. Other, simpler feature-level representations of the repeated item remain. Because these remaining, relatively simple stimulus features tend to be repeated across objects and situations, their representations do not provide a unique signal of prior occurrence of an object. As a result, the disruption to the encoding of complex stimulus representations has the knock-on effect of making the system very susceptible to interference. The fact that only a portion of the representation of an object is affected by the lesion is indicated by the lack of impairment when lesioned animals spent the delay in a visually restricted environment. This intact performance must be supported by representations outside the perirhinal cortex, as predicted by the representational-hierarchical view (*9*). This shows that object recognition impairments after perirhinal cortex damage cannot be understood in the usual way—that is, as the result of damage to all or part of a dedicated memory system. The present results also add to a growing body of evidence suggesting that interference may be an important factor in memory impairments after brain damage (*12*, *20*–*26*).

The combination of perirhinal lesions and object recognition used in our study models the disturbances in the recognition of objects and people that are critical components of amnesia. It does not, however, model all forms of memory impairment; for example, it is not a complete model of the dense, global amnesic syndrome observed in people with extensive damage to medial temporal lobe structures including the hippocampus. Nonetheless, these findings raise the possibility that the false memory reported here may be a more general phenomenon. If this turns out to be the case, we may need to reevaluate our current conceptions of memory impairment and amnesia.

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Frequent Mutation of *BAP1* in Metastasizing Uveal Melanomas

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Metastasis is a defining feature of malignant tumors and is the most common cause of cancer-related death, yet the genetics of metastasis are poorly understood. We used exome capture coupled with massively parallel sequencing to search for metastasis-related mutations in highly metastatic uveal melanomas of the eye. Inactivating somatic mutations were identified in the gene encoding BRCA1-associated protein 1 (*BAP1*) on chromosome 3p21.1 in 26 of 31 (84%) metastasizing tumors, including 15 mutations causing premature protein termination and 5 affecting its ubiquitin carboxyl terminal hydrolase domain. One tumor harbored a frameshift mutation that was germline in origin, thus representing a susceptibility allele. These findings implicate loss of BAP1 in uveal melanoma metastasis and suggest that the BAP1 pathway may be a valuable therapeutic target.

Uveal melanoma (UM) is the most common primary cancer of the eye and has a strong propensity for fatal metastasis (*1*). UMs are divided into class 1 (low metastatic risk) and class 2 (high metastatic risk) based on a validated multigene clinical prognostic assay included in the TNM classification system (*2*, *3*). However, the genetic basis of metastasis remains unclear. Oncogenic mutations in the $G\alpha_q$ stimulatory subunit *GNAQ* are common in UM (*4*), but these mutations occur

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Novel or Familiar?

Amnesia is characterized by a number of memory deficits, including the apparent inability to distinguish between novel and familiar stimuli. **McTighe *et al.*** (p. 1408; see the Perspective by **Eichenbaum**) observed that the recognition memory of brain-damaged rats in a standard model of amnesia was impaired not because previously experienced objects seemed to be novel, but because objects not previously experienced seemed to be familiar. Furthermore, simply placing the animal in a visually deprived environment during the delay, reducing visual interference, completely rescued the impairment. This counterintuitive finding contradicts the predominant "multiple memory systems" model in which amnesia is usually considered and forces a reconsideration of fundamental assumptions underlying our understanding of amnesia.