

Impairing existing declarative memory in humans by disrupting reconsolidation

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During the past decade, a large body of research has shown that memory traces can become labile upon retrieval and must be restabilized. Critically, interrupting this reconsolidation process can abolish a previously stable memory. Although a large number of studies have demonstrated this reconsolidation associated amnesia in nonhuman animals, the evidence for its occurrence in humans is far less compelling, especially with regard to declarative memory. In fact, reactivating a declarative memory often makes it more robust and less susceptible to subsequent disruptions. Here we show that existing declarative memories can be selectively impaired by using a noninvasive retrieval–relearning technique. In six experiments, we show that this reconsolidation-associated amnesia can be achieved 48 h after formation of the original memory, but only if relearning occurred soon after retrieval. Furthermore, the amnesic effect persists for at least 24 h, cannot be attributed solely to source confusion and is attainable only when relearning targets specific existing memories for impairment. These results demonstrate that human declarative memory can be selectively rewritten during reconsolidation.

forgetting | human memory | misinformation effect | testing effect | eyewitness memory

The entrenched view that memory becomes permanent upon consolidation has faced considerable scrutiny based on recent works demonstrating that retrieval can destabilize existing memories, and that the reactivated memories need to be reconsolidated (1, 2). During the past decade, a growing body of evidence has revealed the chemical and molecular nature of reconsolidation and its behavioral consequences (3). Critically, when a consolidated memory (e.g., a conditioned fear response) is retrieved, it becomes labile and requires protein synthesis for restabilization, and later retrieval of that memory can be severely impaired if an amnesic treatment is administered during the reconsolidation process.

Despite the proliferation of research on reconsolidation, few studies have involved human subjects, perhaps because most pharmacological consolidation blockers are unsuitable for human use (3, 4). When reconsolidation associated memory impairments are demonstrated in humans, the effects have been limited to fear conditioning (5–8), motor sequence learning (9), and drug-induced craving (10). To date, we are aware of no study that has shown reconsolidation-associated impairment in declarative memory. Indeed, even when oral administration of propranolol (a systemic pharmacological consolidation blocker approved for human use) reduced the emotional response associated with a fear-inducing experience (6, 7), it left the declarative recollection intact.* Although several studies have examined whether existing declarative memories can be impaired by interference upon reactivation, none has shown memory impairments similar to those regularly exhibited in fear conditioning. Moreover, these studies used a reminder to trigger reactivation of the original memory while prohibiting subjects from actually retrieving that memory (e.g., by briefly mentioning the learning episode without asking about what was learned); thus, it is unclear whether retrieval of the original memory (and thus reconsolidation) actually occurred (11–16). When retrieval of a learned response is ascertained

through a memory test, the results almost unequivocally show that retrieval actually makes the original memory less, not more, susceptible to interference (17–20). In sum, scant evidence exists to support the idea that declarative memory undergoes reconsolidation upon retrieval.

Distinct neural systems subserve the formation and retrieval of fear, motor, and declarative memory (21). Whereas memories acquired via fear conditioning or motor sequence learning can be relatively localized neurologically (22), the encoding and retrieval of declarative memories rely on a more distributed network (23–27). This complexity might be one reason why declarative memory is particularly resistant to treatments designed to disrupt reconsolidation. Here we show that human declarative memory can be selectively impaired in a behavioral paradigm without the administration of harmful pharmacological agents; these results demonstrate that declarative memory, too, is susceptible to reactivation-induced lability.

Results

Experiment 1: Targeting Specific Declarative Memories for Impairment in Humans. In the present study, we used a retrieval–relearning procedure to disrupt reconsolidation of the original memory (Fig. 1). Participants watched a movie about a fictional terrorist attack during the original learning phase. Our key manipulation was whether subjects recalled specific details from the original learning episode (e.g., a terrorist used a hypodermic needle on a flight attendant) before they encountered new information (i.e., misinformation) that replaced the original information (the terrorist used a stun gun). Performance during the reactivation phase indicates moderate retention (Fig. 2). This is important because very strong memories are resistant to postreactivation amnesic treatments (28, 29). Moreover, when recall performance during the reactivation phase was examined based on item type (i.e., whether an item would be represented, omitted, or misinformed during the subsequent relearning phase), no difference emerged across any experiments (all $F < 1.86$, all $P > 0.17$). Therefore, any difference in performance across item type during the final test could not be attributed to base-rate differences.

If retrieval triggers reconsolidation of the original memory, the new information presented during the relearning phase should update the original memory and render it inaccessible. To assess

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*A recent study showed that emotional (but not nonemotional) declarative memory might need to reconsolidate upon retrieval (16). However, this study did not obtain overt recall responses from participants during the memory reactivation phase; thus, like many other human studies, it is not possible to ascertain that retrieval was attempted. Moreover, the amnesic treatment (propranolol) was administered orally 1 h before the memory reactivation phase. Therefore, it is possible that, instead of blocking reconsolidation, propranolol exerted an influence on retrieval and produced a permanent effect on the memory (4).

affected the likelihood that one would demonstrate memory impairment (Table S2). Second, we examined whether reactivation affected the magnitude of memory impairment (Table S3). Third, we examined whether reactivation affected the response latency associated with recognition decisions (Table S4). Details regarding these analyses and the logic behind them are presented in *SI Methods*.

Discussion

Decades of behavioral research in humans has revealed that it is easy to alter people's memory reports and to create false memories (40), but the question surrounding whether it is possible to experimentally erase existing memories in humans has been far more contentious (30). Here, we demonstrate that retrieval can destabilize a declarative memory and render it susceptible to an amnesic treatment by relearning even after a substantial delay (i.e., at least 48 h). Consistent with the known preconditions of reconsolidation, the timing of postretrieval amnesic treatment is critical, such that relearning impairs the original memory only when it occurs within the reconsolidation window. Compared with other studies that have investigated the time course of reconsolidation, our experiments used retention intervals that are at the more extreme ends of the spectrum (e.g., immediate vs. 48 h), whereas some other studies have used more fine-grained comparisons. These studies typically show that the reconsolidation window may last somewhere between 1 and 6 h. We opted for a more extreme comparison because it was not clear whether the time-related parameters found with nonhuman animals (41, 42) and nondeclarative memory in humans (5, 10) are applicable to declarative memory. Future research is needed to better specify the time course of reconsolidation in human declarative memory.

In addition to the time-dependent properties of the effect, we have shown that reactivated memories are vulnerable only to interference that specifically targets existing memories, but are robust to nonspecific interference produced by new learning. Moreover, this effect persists for at least 24 h and cannot be attributed solely to source confusions. When the relearning procedure targeted specific recollections for impairment, considerable amnesia was observed across the four experiments in which we expected reconsolidation disruption. However, when relearning occurred without reactivation of the original memory, it produced no impairments in performance across all six experiments (a nonsignificant increase of 3% in performance).

Although our data suggest that one can target specific existing memories for impairment following their reactivation, we believe specific interference might be necessary, but not sufficient, to disrupt reconsolidation of declarative memory. On a processing level, it is unlikely for people to update an original memory unless they believe that the new learning phase accurately represents the original information. We suspect that a key to impairing the original memory is that relearning does not trigger spontaneous retrieval of the original information. Instead, reactivation of the original memory must occur before, but not concurrently with, relearning. Recalling the original memory while encoding the new one would likely cause people to either discount the new information or to remember both the new and original information, which would likely eliminate the updating effect. In a similar vein, research on eyewitness memory has shown that people are highly resistant to suggestions by misinformation if they detect a conflict between what was originally learned and the misinformation (43, 44). Thus, we believe the expectation under which relearning occurs can determine whether the retrieval–relearning procedure would lead to enhancement or amnesia of the original memory.

One may wonder whether participants who received the initial test were more likely to accept the misinformation as true and thus less likely to recognize the original details during the final test. This could occur if participants, after having their memory tested during the reactivation phase, thought the experimenter

was giving them corrective feedback during the relearning phase. In other words, the retrieval–relearning procedure might have changed participants' belief about what was correct without actually changing memory. If this were the case, we should not have observed time-dependent reconsolidation associated amnesia (in experiments 2 and 3), nor should we have obtained the effect in the source-free recognition test (in experiment 4), in which participants were told to respond based on their memory of the original learning and relearning phases.

The malleability of human declarative memory has been a major topic of research for decades (40, 45). Recently, the instability of memory following reactivation has been suggested to play a key role in the production and implantation of erroneous memories (46). Although the unreliability of declarative memory is typically considered a disadvantage, our results show that it is possible to leverage the lability of reactivated engrams for targeted impairment, thus providing a noninvasive method to weaken the impact of unwanted memories. Aside from its noninvasive nature, this technique is particularly powerful because one can target specific recollections for impairment while sparing others. Humans are notoriously inept at suppressing unwanted thoughts (47). In fact, attempting to block unwanted thoughts from consciousness often leads to the opposite effect (48). Remarkably, when treating posttraumatic stress disorders, therapeutic techniques that require patients to recall their traumatic memories (e.g., exposure, acceptance, and paradoxical approaches) are typically far more successful than suppression (49–51). For example, a form of acceptance therapy requires patients to recall their intrusive thoughts and reinterpret them in a safe context (e.g., imagine the thought as a band of marching soldiers emerging from the ears). Existing explanations have ascribed the efficacy of these approaches to the acceptance of the unwanted events as belonging to the past and to detaching oneself from the negative feelings associated with the experience (52). Based on the present findings, it is possible that these techniques are successful because they are, at some level, exploiting the postretrieval updating characteristics of memory.

A note of caution is in order here. Similar to many existing experiments demonstrating reconsolidation-like effects, it is not possible to know whether our reactivation–relearning manipulation impaired memory performance by weakening the original memory (i.e., a storage deficit) or by impairing its retrieval. It is also unknown whether different retrieval environments or subject factors [e.g., differences in overall suggestibility (53), differences in executive functioning (54)] can protect one from the present forgetting effect. Thus, further research is needed to clarify the boundary conditions of our findings. However, these data represent an important step toward a fuller understanding of the mechanisms responsible for the plasticity of declarative memory in humans. Knowing the limits and operating characteristics of reconsolidation blockage in declarative memory can have a profound impact on how memory is conceived theoretically. These data also further bolster the idea that reconsolidation plays a fundamental role in the formation and maintenance of memory in humans. All experiments were approved by the institutional review board at Iowa State University. Informed consent was obtained from all participants.

Methods

Subjects. All subjects were recruited from the Iowa State University community and they received either partial course credit or a payment of \$15 for their participation. All participants were native English speakers.

Materials and Procedure. In all experiments, subjects viewed a ~40-min movie about a terrorist attack (the original learning phase). The movie was the pilot episode of the television program 24 (55). Subjects were given intentional learning instructions before watching the movie. Reactivation of the original memory was then manipulated by having participants complete a cued recall test of the movie (the reactivation condition) or play the video game Tetris (56) (the no-reactivation condition). During the recall test,

subjects were asked 24 questions about the video (e.g., “What does the terrorist use on the flight attendant?”) and they had 25 s to answer each question. No feedback was provided during this reactivation phase. After a filled delay during which subjects completed a working memory task (Fig. 1 shows the exact delay implemented in each experiment), participants listened to an 8-min audio narrative that purportedly recapped the movie (the relearning phase). However, among the 24 details queried during the reactivation phase, eight were presented incorrectly, and these details (misinformed items) replaced the original information (e.g., in the movie, a terrorist knocked a flight attendant unconscious with a hypodermic syringe, but the narrative described the weapon as a stun gun). Eight other details that were queried during the reactivation phase were not mentioned during the narrative (neutral items), and the remaining eight details were represented correctly during the narrative (represented items). Fig. S1 shows data regarding the represented items. Participants were not informed about any inaccuracies, and all information in the narrative was presented as fact. After a retention interval (which was 5 min in experiments 1–5 and 24 h in

experiment 6), memory of the movie was assessed in a final test. We devised a special true/false recognition test to estimate the accessibility of the original memory (57, 58). Recall tests are not suitable for our purpose because participants can withhold responses based on various metacognitive control processes (31, 59), making assessment of the true strength of a memory difficult. In the recognition test, participants encountered one statement during each trial and indicated whether the statement was true (e.g., the terrorist used a hypodermic syringe on the flight attendant) or false (e.g., the terrorist used a chloroform rag on the flight attendant). Critically, the misinformation (e.g., the stun gun) was never presented during this recognition test so that performance would not be influenced by non-memory-based factors (e.g., demand characteristics). In experiment 4, instead of this true/false recognition test, a source-free recognition test was administered. Here, participants were told to make an old judgment if they remembered the event detail from the original learning or the relearning phase; otherwise, they were to make a new judgment.

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