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Activation of a remote (1-year old) emotional memory interferes with the retrieval of a newly formed hippocampus-dependent memory in rats

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Abstract
The persistent intrusion of remote traumatic memories in people with post-traumatic stress disorder (PTSD) may contribute to the impairment of their ongoing hippocampal and prefrontal cortical functioning. In the current work, we have developed a rodent analogue of the intrusive memory phenomenon. We studied the influence of the activation of a remote traumatic memory in rats on their ability to retrieve a newly formed hippocampus-dependent memory. Adult male Sprague–Dawley rats were given inhibitory avoidance (IA) training, and then 24 h or 1, 6 or 12 months later, the same rats were trained to learn, and then remember across a 30-min delay period, the location of a hidden escape platform in the radial-arm water maze (RAWM). When IA-trained rats spent the 30-min delay period in the IA apparatus, they exhibited intact remote (1-year old) memory of the shock experience. More importantly, activation of the rats' memory of the shock experience profoundly impaired their ability to retrieve the newly formed spatial memory of the hidden platform location in the RAWM. Our finding that reactivation of a remote emotional memory exerted an intrusive effect on new spatial memory processing in rats provides a novel approach toward understanding how intrusive memories of traumatic experiences interfere with ongoing cognitive processing in people with PTSD.

Keywords: *PTSD, stress, memory, hippocampus, amygdala, amnesia*

Introduction

Traumatic events, such as rape, wartime combat and motor vehicle accidents, can lead to the development of post-traumatic stress disorder (PTSD), a debilitating mental illness characterized by symptoms of persistent anxiety, exaggerated startle, hyperarousal and cognitive impairments (Elzinga and Bremner 2002; Bremner 2006; Nemeroff et al. 2006; Stam 2007). One of the defining features of PTSD is the presence of recurrent and intrusive recollections of the traumatic event (American Psychiatric Association 1994, p. 428). Investigators have described these intrusions as 'unwanted memories that [keep] coming back' (Speckens et al. 2007, p. 251) and 'unbidden occurrence[s] of thoughts, memories and images associated with a personally experienced traumatic event' (Wessel et al. 2002, p. 228). People with PTSD have reported experiencing the sensory stimuli of the original trauma during intrusive memory reactivation and that they feel a sense of 'nowness' during the incidents—that is, the intrusive memory is not merely a recollection of a past event, the patient feels as if the trauma is actually happening in the present (Ehlers et al. 2002, 2004; Hellawell and Brewin 2002, 2004; Berntsen et al. 2003; Hackmann et al. 2004; Holmes et al. 2005; Speckens et al. 2007).

In addition to having powerful, unrelenting memories of the traumatic event, people with PTSD exhibit an impairment of hippocampal and prefrontal cortical

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functioning, as indicated by deficits in declarative and working memory, attention and concentration (Buckley et al. 2000; Gilbertson et al. 2001; Nemeroff et al. 2006). Other studies, however, have reported no evidence of impaired cognitive functioning in people with PTSD (Zalewski et al. 1994; Barrett et al. 1996; Crowell et al. 2002; Neylan et al. 2004). Investigators have explained these inconsistent findings by suggesting that the cognitive impairments observed in some PTSD patients may be the result of idiosyncratic subject characteristics that are associated with, but not necessarily caused by, the disorder, such as comorbid major depressive disorder, a history of substance abuse, less formal education and lower IQ (Gilbertson et al. 2001; Neylan et al. 2004).

An alternative explanation for the basis of the inconsistent findings of cognitive deficits in people with PTSD is that the persistent activation of intrusive memories in these patients transiently interferes with their ability to process new information. Moradi and colleagues addressed this issue with the suggestion that, 'It is not clear why these *(PTSD-related)* memory effects are present. The most obvious candidate is that the presence of the intrusion, avoidance and hyperarousal symptoms of PTSD interferes with everyday memory performance . . . ' (Moradi et al. 1999, p. 360, italicized text added for clarity). McNally offered a similar observation of World War II combat veterans with PTSD, stating that 'their vivid, intrusive memories of combat interfered with their ability to remember things in everyday life' (McNally 2005, p. 820). Thus, clinicians have provided anecdotal observations of people with PTSD which suggest that their re-experiencing of traumatic events interferes with their efficiency in processing new information.

Empirical support for the influence of transient intrusive memories as a causative factor in cognitive deficits in PTSD was provided by Brewin and Smart (2005). These investigators demonstrated that attempts by traumatized people to suppress intrusive memories interfered with their performance in a working memory task. In addition, people with PTSD exhibit an attentional bias to trauma-relevant stimuli (McNally et al. 1993; Bryant and Harvey 1997; Buckley et al. 2000; Golier et al. 2003), and Chemtob et al. (1999) showed that such stimuli significantly interfered with their processing speed for other information. Studies have also reported significant correlations between PTSD patients' intrusive symptoms and their memory performance (Wessel et al. 2002; Golier et al. 2003; Schonfeld et al. 2007).

Overall, there is support for the hypothesis that the persistent activation of intrusive memories contributes to the impairment of cognitive (hippocampal and prefrontal cortical) functioning in traumatized people (Wessel et al. 2002; Clark et al. 2003; Golier et al. 2003; Schonfeld et al. 2007). However, the experimental study of intrusive memories in traumatized people is problematic because of numerous factors, such as elevated levels of baseline anxiety and great individual differences in the expression of intrusive memories in a laboratory setting, which renders the study of intrusive memories and cognition in a clinical population difficult to control (Elzinga et al. 2003; Geracioti et al. 2008; Jelinek et al. 2008). Thus, there are methodological (as well as ethical) obstacles to the study of how the activation of remote traumatic memories affects ongoing cognition in people with PTSD.

Research on fear, stress and memory in rodents has an advantage over clinical experimentation in that the experimenter has a greater degree of control over subject and experimental variables. Animal studies, however, have focused almost exclusively on the use of stimuli which are intrinsically arousing to examine how stress affects brain and behavior. That is, animal studies have shown that unconditioned stress-evoking sensory stimuli, such as restraint, shock or predator exposure, can affect memory and synaptic plasticity in the hippocampus, prefrontal cortex and amygdala (Diamond et al. 1996, 1999, 2007; Kim and Diamond 2002; Maroun and Richter-Levin 2003; Richter-Levin and Akirav 2003; Roozendaal 2003; Jay et al. 2004; Rocher et al. 2004; Roozendaal et al. 2006; Shors 2006; Joels and Krugers 2007). Despite the strengths of the preclinical stress-memory work, to understand how intrusive memories affect ongoing cognition it is necessary to investigate the effects of the activation of the *memory of a fear-provoking experience*, rather than the fear experience, itself, on new memory processing. Thus, the study of the neurobiological basis of intrusive emotional memories in animals must involve a paradigm in which one can show that the reactivation of a remote traumatic memory can impair new memory processing.

In the current series of experiments we have developed a rodent analogue of the intrusive memory phenomenon. We addressed the possibility that activation of an emotional memory in rats would interfere with their retrieval of newly learned, hippocampus-dependent, information. We have found that retrieval of a remote traumatic memory, one that was formed as much as a year before spatial memory testing, exerted a powerful amnestic effect on new memory processing.

Materials and methods

Animals

Adult male Sprague–Dawley rats (250–275 g; Harlan, Indianapolis, IN, USA) were housed on a 12 h/12 h light dark schedule (lights on at 0700 hours) in Plexiglas cages (two per cage) with food and water provided *ad libitum*. All rats were given 1 week to acclimate to the housing room environment before any

experimental manipulations took place. The rats were brought to the laboratory's water maze training room and handled for 2–3 min/day during the last 3 days of the 1-week acclimation period. Behavioral manipulations were conducted between 0800 and 1300 hours and were always preceded by 1 h of acclimation to the testing environment. All experiments were carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals, and the Institutional Animal Care and Use Committee at the University of South Florida approved all procedures.

Water maze apparatus and multi-day training procedures

Spatial working memory was tested in the radial-arm water maze (RAWM), which has been described at length in previous publications (Diamond et al. 1999, 2006; Woodson et al. 2003; Sandi et al. 2005; Park et al. 2006, 2008; Zoladz et al. 2006; Campbell et al. 2008). Briefly, the RAWM consists of a black, galvanized round tank (168 cm diameter, 56 cm height, 43 cm depth) filled with clear water (22°C). Six V-shaped stainless steel inserts (54 cm height, 56 cm length) were positioned in the tank to produce six swim arms radiating from an open central area. A black, plastic platform (12 cm diameter) was located 1 cm below the surface of the water at the end of one arm (the 'goal arm'). There were visual cues in the room which the rats could use to remember the location of the hidden platform, including different colored walls, book shelves on one wall, an entry door with an exposed window to the hallway and indirect lighting in one corner of the room.

At the start of each trial, rats were released in one arm (the 'start arm') facing the center of the maze. Standardizing the start position to be at the entrance to the center of the maze eliminated any potential relationship between the start position and the goal arm. If a rat did not locate the hidden platform within 60 s it was guided to the platform by the experimenter. Once a rat found, or was guided to, the platform, it was left there undisturbed for 15 s. An arm entry was operationally defined as the rat passing at least halfway down the arm. For each trial, the experimenter recorded the number of arm entry errors that each rat made. An arm entry error consisted of the rat entering an arm that did not contain the hidden platform or, in rare circumstances, entering the goal arm and not climbing on the platform. The goal arm was different across rats within a day to eliminate scent buildup in the vicinity of the hidden platform. Additionally, the start arms varied randomly across trials.

On each day of training, rats were given four acquisition trials (Acquisition Phase; T1–T4) to learn the location of the goal arm, followed 30 min later by four memory test trials (Retention Phase; T5–T8). To illustrate the importance of T5 as the memory test trial, throughout the text and in Figures 2–5, T5 is referred to as the retention trial (RT). For each rat, the hidden platform was always in the same arm within each day and in a different arm across days. The rats, therefore, needed to learn a new goal arm location on each day of training. Rats were trained for 5–6 days per week, for up to 3 weeks, until reaching a performance criterion of committing a total of no more than one error on the RT over three consecutive days of training, as we have described previously (Diamond et al. 1999; Woodson et al. 2003). Once rats met the performance criterion, they were exposed to additional (post-criterion) days of water maze training, and all experimental manipulations occurred during the delay period on post-criterion days of water maze training. In previous work, we have shown that RAWM performance is impaired to chance level of performance in rats with hippocampal damage (Diamond et al. 1999).

Inhibitory avoidance apparatus and training procedures

Step-through inhibitory avoidance (IA) conditioning was performed using IA monitors (Hamilton Kinder, Poway, CA, USA) controlled by a computer. Each avoidance monitor had two white-walled chambers (each 23 × 21.25 × 20.5 cm); one was brightly lit, and the other was left dark. An open doorway connecting the two chambers provided access to either side of the apparatus. The floors consisted of 13 stainless steel rods, spaced 1.25 cm apart, through which scrambled electric shock could be delivered. Photobeam sensors recorded the rat's location throughout the duration of testing.

Avoidance training was conducted by placing the rat in the light side of the IA monitor and then allowing it to explore both sides of the apparatus at its own volition. Upon completely entering the dark side, rats undergoing IA training received a single, uninterrupted 0.6 mA footshock until it returned to the light side (maximum duration = 5 s; mean duration = 4 ± 1 s). Rats in control groups were allowed to explore both sides of the apparatus without receiving footshock. Retrieval sessions were conducted in the same manner, except without shock. The dependent measure of interest during the training and retrieval sessions was initial crossing latency (ICL), or how long it took each rat to cross from the light to the dark side of the apparatus.

Novel environment apparatus

Fear conditioning chambers (Coulbourn Instruments, Allentown, PA, USA) were used as novel environments in 'Experiment 2b'. The chambers (25.5 × 30 × 29 cm; Coulbourn Instruments) were dark with two aluminum sides, an aluminum ceiling, and a Plexiglas front and back. The floor of the chamber

consisted of 18 stainless steel rods, spaced 1.25 cm apart. The rats were *not* exposed to footshock at any time in the fear conditioning chamber. The fear conditioning chambers were not located in the room that contained the IA apparatus.

Statistics

Mixed-model and repeated measures ANOVAs (SPSS, Chicago, IL, USA; Sigmastat) were used to analyze the data. Our prior work indicated that stress impairs performance on the RT of RAWM testing (Diamond et al. 1996, 1999; Woodson et al. 2003). Therefore, we conducted planned comparisons on this trial, as well as on trials 6–8, when there was a memory impairment on the RT. Alpha was set at 0.05 for all analyses. Outlier data points greater than three standard deviations from the exclusive group means were eliminated from analyses (less than 1% of the data were outliers).

Results

The following sections describe findings from three experiments examining the effects of IA training and retrieval on spatial working memory in the RAWM. The general sequence and timing of the events in Experiments 1 and 2 are illustrated in Figure 1.

Experiment 1: Effects of IA training and 24-h retrieval on spatial memory

Experiment 1 first examined the effects of IA (shock) training, itself, on short-term (30 min) spatial memory in the RAWM. Two groups of rats ($n = 10$/group) were trained in the RAWM until reaching the performance criterion. Then, they were given two additional days of water maze training. On day 1 of post-criterion water maze training, one group (IA–no shock) was exposed to the IA apparatus, without footshock, during the 30-min delay period. Another group (IA–shock) was given shock avoidance training in the IA apparatus during the 30-min delay period.

On day 2, the second component of Experiment 1 took place. On this day, we tested the effects of memory reactivation of IA training on short-term (30 min) spatial memory in the RAWM. Both groups were trained to learn a new location of the hidden platform in the RAWM, and then they were re-exposed to the IA apparatus, without footshock, during the 30-min delay period. Re-exposure to the IA apparatus on day 2 thereby served as a shock memory retrieval trial for the IA–shock group.

Analysis of the acquisition phase on day 1 revealed a significant main effect of trials, $F(3,48) = 19.04$, $p < 0.0001$, indicating that both groups learned the task and made significantly fewer errors as the trials progressed. There was no significant main effect of group, $F(1,16) = 1.21$, and the trials × group interaction was not significant, $F(3,48) = 2.75$ ($p > 0.05$). Analysis of the retention phase on day 1 revealed a significant main effect of trials, $F(3,51) = 3.77$, $p < 0.05$, indicating that both groups made significantly fewer errors as the trials progressed. The trials × group interaction was not significant, $F(3,51) = 1.11$, $p > 0.35$. There was a significant main effect of group, $F(1,17) = 13.03$, $p < 0.01$. The IA–shock group made significantly more arm entry errors during the retention phase, and specifically on the RT (Bonferroni-corrected *t*-test; $p < 0.05$), than the IA–no shock group (Figure 2A). Therefore, IA training, interposed in the 30-min period between water maze learning and memory testing, interfered with retrieval of memory of the hidden platform location.

Analysis of the acquisition phase on day 2 revealed a significant main effect of trials, $F(3,51) = 6.16$, $p < 0.01$, indicating that both groups learned the task and made significantly fewer errors as the trials progressed. There was no significant main effect of group, $F(1,17) = 0.10$, and the trials × group interaction was not significant, $F(3,51) = 1.53$ ($p > 0.05$). For the retention phase on day 2, there was no significant main effect of trials, $F(3,48) = 0.89$, and the trials × group interaction was not significant, $F(3,48) = 1.11$ ($p > 0.05$). There was a significant main effect of group, $F(1,16) = 9.33$, $p < 0.01$. The IA–shock group made significantly more arm entry errors during the retention phase, and specifically on the RT (Bonferroni-corrected *t*-test; $p < 0.05$), than the IA–no shock group, indicating that 24-h retrieval of the emotional memory during the delay period impaired short-term (30-min) spatial memory in the RAWM (Figure 2B).

A mixed-model ANOVA was conducted on the IA data from both groups, with day serving as the within-subjects factor. There was a significant main effect of day, $F(1,18) = 59.11$, and group, $F(1,18) = 58.31$, as well as a significant day × group interaction, $F(1,18) = 63.72$ ($p < 0.0001$). As shown in Figure 2C, both groups displayed very short ICLs on day 1. On day 2, the IA–shock group exhibited significantly greater ICLs than all other groups and time points, indicating that they had developed a powerful avoidance of the dark side of the apparatus ($p < 0.05$).

Experiment 2: General approach

Experiments 2a–c involved the use of 16 experimentally naïve rats that had not been used in Experiment 1. The strategy in this experiment was to implant the memory of the IA shock experience in rats before any water maze training occurred, and then, 1, 6 or 12 months later, the same rats were given RAWM training with memory testing 30 min after they had learned the

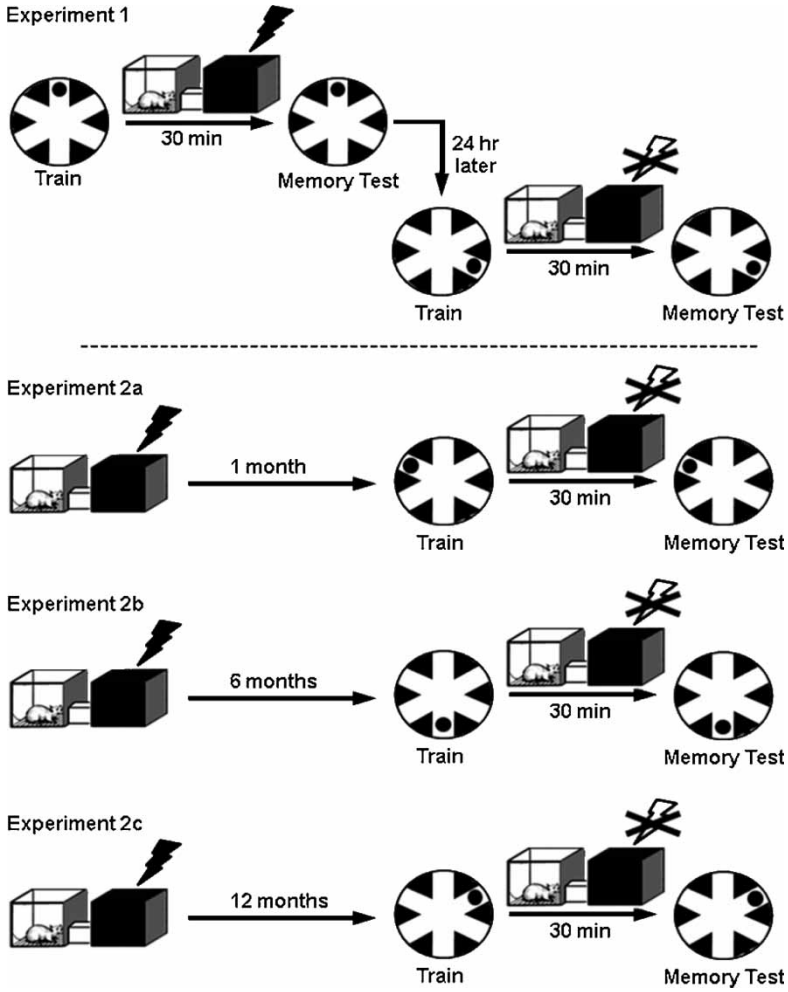

Figure 1. Simplified timeline and procedures for Experiments 1–2. In Experiment 1, rats that were well-trained on the radial-arm water maze (RAWM) learned the within-day location of the hidden platform, which is illustrated by filled circle in the maze diagram (left side; 'train'), followed by a 30-min delay period. Under control conditions, rats spent the 30 min delay in their home cages (not illustrated here), and under stress conditions rats were given inhibitory avoidance (IA) shock training, which is indicated by the dark box and lightning bolt. The 30-min delay period terminated with a memory retention test trial (see 'Methods' for additional details). One day later, the same rats were trained to learn a new location of the hidden platform, and then all rats were exposed to the IA apparatus without shock (as indicated by the X through the open lightning bolt), followed by the memory test. In Experiment 2a, the rats were first given IA training, and then 1 month later they were given RAWM training to learn the within-day location of the hidden platform, as described above. During the 30-min delay period between the RAWM learning and memory test phases, the rats were given an IA retrieval trial, in which they were placed in the IA apparatus, but no shock was delivered. In Experiment 2b, a subset of the rats from Experiment 2a were retested in the RAWM to learn a new hidden platform location, 6 months after IA training, with IA re-exposure during the 30-min delay period. In Experiment 2c, all rats were retested in the RAWM to learn a new hidden platform location, 12 months after IA training, with IA re-exposure during the 30-min delay period. The procedures for Experiment 3, which involved a control study of RAWM memory in unshocked rats placed in the bright side of the IA apparatus, are described in the 'Results' section.

hidden platform location. RAWM testing at 1 month after IA training involved multi-day criterion training (see 'Methods') until rats developed highly accurate within-day spatial memory performance. When the same rats were tested in the RAWM 6 (Experiment 2b) and 12 (Experiment 2c) months later, their within-day learning was highly efficient, indicating savings for the procedures involved in the task. Therefore, multi-day preliminary training was no longer necessary in Experiments 2b and 2c. This series of experiments tested the hypothesis that re-exposure of the rats to the IA apparatus—at 1, 6 and 12 months after IA training—would reactivate the memory of the shock experience, which would interfere with the rats' ability to retrieve the memory of the newly learned location of the hidden platform in the RAWM.

Experiment 2a: Effects of IA retrieval, 1 month after IA training, on 30-min spatial memory

Rats ($n = 16$) were given IA training and then 24-h later they were given an IA memory test. One month later, the same rats were given multi-day water maze training, and after reaching the performance criterion, the rats were given four additional days of water maze training, during which the experimental manipula-

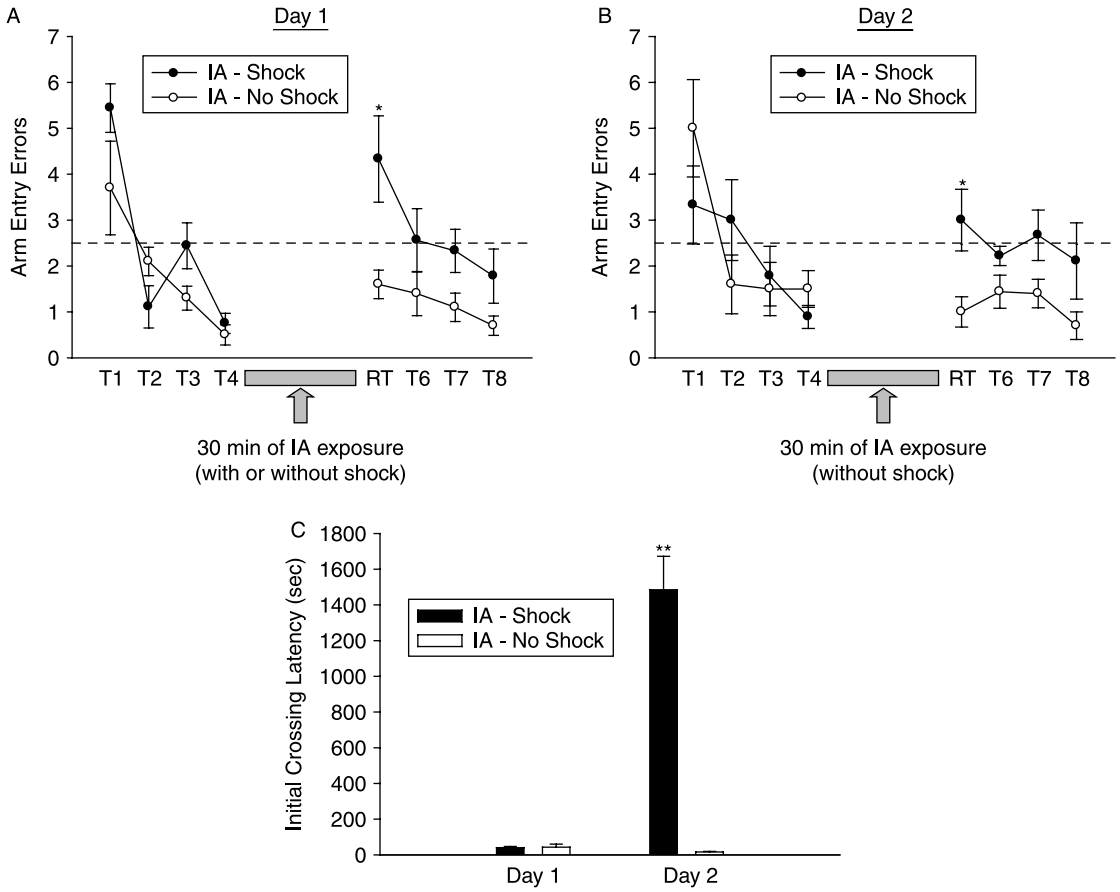

Figure 2. The effects of inhibitory avoidance (IA) training and 24-h IA retrieval on spatial working memory in the radial-arm water maze (RAWM). IA training during the 30-min delay period (A) impaired 30-min memory for the hidden platform location. Twenty-four hours later, re-exposure of the rats to the IA apparatus (without shock) resulted in an increase in arm entry errors on the 30-min retention trial (B). The RAWM data are presented as mean number of arm entry errors (± SEM) committed per trial. As indicated in (C), rats that were exposed to IA training on day 1 exhibited significantly greater mean initial crossing latencies on day 2 than rats that were exposed to the IA apparatus, without footshock, on day 1. This indicates that the trained rats had a powerful avoidance memory for the dark chamber of the IA apparatus. The sample sizes were: IA–shock ($n = 10$) and IA–no shock ($n = 10$). * $p < 0.05$ compared to the IA–no shock group; ** $p < 0.05$ compared to all other groups. In all water maze figures, the dashed line at 2.5 errors indicates chance level of performance (Diamond et al. 1999). The 2.5 error chance level reflects performance by rats following an optimal search behavior in which a rat searches for the platform without re-entering the same (incorrect) arm within a trial. However, when rats perseverated (repeatedly entered incorrect arms), they could perform at levels worst than chance. Perseveration typically occurred only on the first trial of the day, which is why performance was worse than chance on trial 1, but not on other trials. Rats with damage to their hippocampus exhibited chance level of performance on every trial (Diamond et al. 1999).

tions took place. Rats were exposed to their home cage during the delay period on two consecutive days and to the IA apparatus (IA re-exposure) during the delay period on two consecutive days. The order of home cage and IA re-exposure was counterbalanced across rats. There were no significant differences between arm entry errors made on the 2 days of each condition, nor were there any order effects, so we combined the data within each condition and across the order of conditions to increase statistical power. Each rat therefore had two scores from the 4 days of testing, one representing its RAWM memory performance after IA retrieval, and one representing its RAWM memory performance after home cage exposure.

A two-way repeated measures ANOVA was used to analyze the water maze data. Analysis of the acquisition phase revealed a significant main effect of trials, $F(3,45) = 81.48$, $p < 0.0001$, indicating that rats in both conditions made significantly fewer errors as the trials progressed. There was no significant main effect of condition, $F(1,15) = 0.18$, and the condition × trials interaction was not significant, $F(3,45) = 2.37$ ($p > 0.05$). Analysis of the retention phase data revealed a significant main effect of trials, $F(3,45) = 9.60$, $p < 0.0001$, indicating that rats in both conditions made significantly fewer errors as the trials progressed. There was also a significant main effect of condition, $F(1,15) = 38.71$, and a significant condition × trials interaction, $F(3,45) = 8.83$ ($p < 0.0001$). According to *post hoc* tests, rats made significantly more arm entry errors on the RT and T6 when they were exposed to the IA apparatus than when they were exposed to their home cages during the delay period ($p < 0.05$; see Figure 3A).

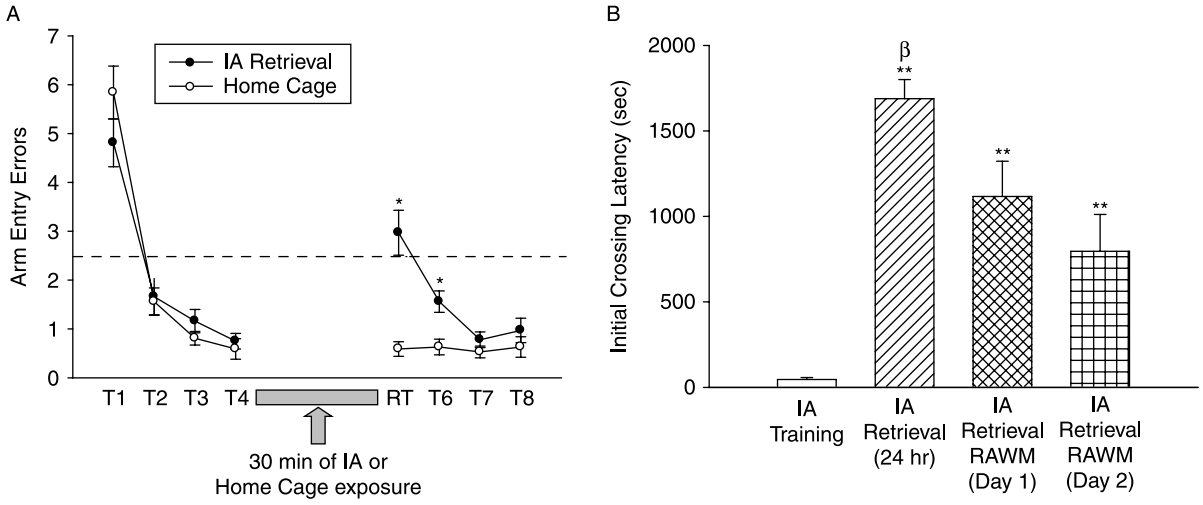

Figure 3. Re-exposure to the inhibitory avoidance (IA) apparatus 1 month after IA training impaired 30-min memory for the hidden platform location (A). Rats exposed to IA retrieval also took longer to relearn the location of the hidden platform after the 30-min delay period, as indicated by significantly more arm entry errors in this group on trial 6 (T6). (B) The mean initial crossing latencies (ICLs) during IA training, 24-h IA retrieval, and the two 1-month IA retrieval sessions during the 30-min delay period in radial-arm water maze (RAWM) training. The mean ICLs during the 24-h and 1-month retrieval trials were significantly greater than those displayed during IA training. The mean ICL on day 2 of water maze training was significantly lower than the ICL during the initial 24-h retrieval trial, 1 month earlier. The sample sizes were: IA retrieval ($n = 16$) and home cage ($n = 16$). * $p < 0.05$ compared to the Home Cage group; ** $p < 0.05$ compared to IA Training, $\beta = p < 0.05$ compared to IA Retrieval RAWM (day 2).

For the IA data, a one-way repeated measures ANOVA indicated that there was a significant main effect of session, $F(3,37) = 24.06$, $p < 0.0001$. Rats demonstrated significantly greater ICLs during the 24-h and 1-month retrieval tests than during IA training (Figure 3B). The mean ICLs declined over the 2 days of RAWM training with IA re-exposure. Thus, the ICL on day 2 of RAWM training was significantly less than the ICL during the 24-h retrieval session 1 month earlier ($p < 0.05$).

Experiment 2b: Effects of IA retrieval, 6 months after IA training, on 30-min spatial memory

Experiment 2b assessed the effects of IA retrieval, 6 months after IA training, on short-term (30 min)

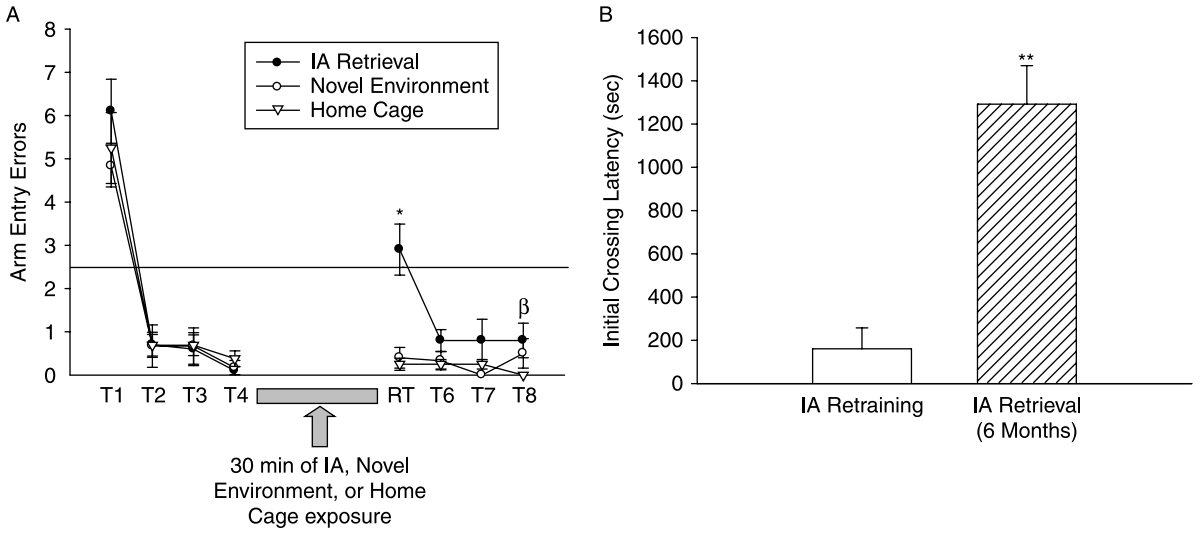

Figure 4. The effects of inhibitory avoidance (IA) retrieval, 6 months following IA training, on 30-min spatial working memory in the radial-arm water maze (RAWM). Re-exposure to the IA apparatus, without shock 6 months after IA training impaired memory for the hidden platform location (A). Exposure to a novel environment during the 30-min delay period had no effect on spatial memory. As illustrated (B), rats given IA 're'-training displayed significantly greater mean initial crossing latencies during the 6-month retrieval trial than those displayed during the retraining session. The sample sizes were: IA retrieval ($n = 8$), novel environment ($n = 8$) and home cage ($n = 16$). For the IA data, the sample sizes were * $p < 0.05$ compared to all other groups; $\beta = p < 0.05$ compared to the home cage group; ** $p < 0.001$ compared to retraining.

spatial memory in the RAWM. The same rats that were used for Experiment 2a were tested in Experiment 2b. Since all rats had been exposed to three IA extinction trials in Experiment 2a, they were given a single IA training session (IA retraining) on the day after the conclusion of Experiment 2a. Six months later, all rats were given a total of 2 days of water maze training. On the first day of training, all rats were placed in their home cages during the 30-min delay period. On the second day of training, half of the rats were exposed to the IA apparatus (without shock) during the 30-min delay period, and the other half were exposed to a novel environment during the delay period. Exposure to the novel environment in previously shocked rats controlled for the potential influence of contextual fear generalization and/or novel environment effects on RAWM spatial working memory.

A mixed-model ANOVA was used to analyze the water maze data. Analysis of the acquisition phase revealed a significant main effect of trials, $F(3,87) = 64.87$, $p < 0.0001$, indicating that rats made significantly fewer arm entry errors as trials progressed. There was no significant main effect of condition, $F(2,29) = 0.24$, and the trials × condition interaction was not significant, $F(6,87) = 0.42$ ($p > 0.05$). Analysis of the retention phase revealed a significant main effect of trials, $F(3,84) = 6.80$, $p < 0.001$, indicating that rats made significantly fewer arm entry errors as trials progressed. There was also a significant main effect of condition, $F(2,28) = 10.52$, and a significant trials × condition interaction, $F(6,84) = 7.03$ ($p < 0.001$). Rats exposed to the IA apparatus during the delay period made significantly more arm entry errors on the RT than when rats were exposed to their home cages or to a novel environment during the delay period (Figure 4A). IA re-exposure also caused the rats to commit significantly more arm entry errors on T8 than when the same rats were exposed to their home cages during the delay period ($p < 0.05$).

A one-way repeated measures ANOVA was used to analyze the IA data from those rats that were trained and then re-exposed to the IA context at 6 months. There was a significant main effect of session, $F(1,9) = 49.26$, $p < 0.0001$, indicating that the rats demonstrated significantly greater ICLs at 6 months than during the retraining session (Figure 4B). The increased ICL at 6 months indicates that the rats exhibited intact memory of the shock experience 6 months after IA training.

Experiment 2c: Effects of IA retrieval, 1 year after IA training, on 30-min spatial memory

Experiment 2c assessed the effects of IA retrieval, 1 year after IA training, on short-term spatial memory in the RAWM. The same rats that were used for Experiment 2b were tested in Experiment 2c. Following the 2 days of water maze training in Experiment 2b, all rats were left undisturbed for 6 months. Then, they were given 2 days of water maze training. The rats were given four acquisition trials, followed 30 min later by a *single* RT. On the first day of training, all rats were placed in their home cages during the 30-min delay period, and on the second day of training, all rats were exposed to an IA retrieval session during the 30-min delay period. Some rats (i.e., those rats that were exposed to the IA retrieval session in Experiment 2b) had experienced an extinction trial of IA training during Experiment 2b, whereas others (i.e., those rats that were exposed to the novel environment in Experiment 2b) had not. We therefore compared these two groups in terms

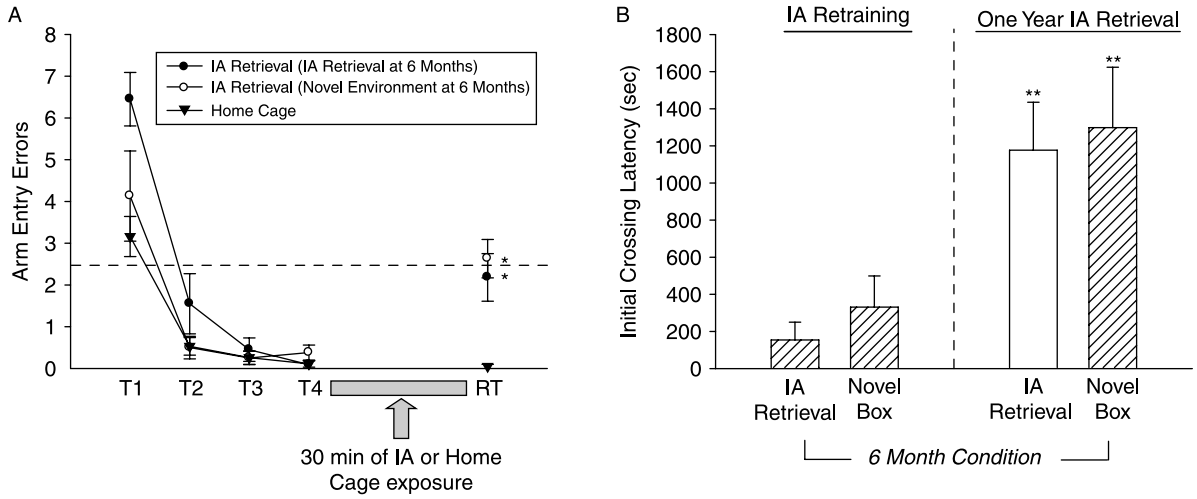

Figure 5. IA retrieval, 1 year following IA training, impaired 30-min spatial memory, independent of the manipulation rats received 6 months earlier (A). The rats demonstrated a significantly greater mean initial crossing latency during the 1-year IA retrieval trial than during IA retraining, independent of whether or not they had been given a retrieval trial 6 months earlier (B). The sample sizes were: IA Retrieval (IA retrieval at 6 months' $n = 8$), IA retrieval (novel environment at 6 months; $n = 8$) and home cage ($n = 16$). ⋆ $p < 0.05$ compared to the home cage group; ⋆⋆ $p < 0.05$ compared to both IA retraining groups.

of potential differences in the strength of their long-term IA memory, as well as the influence of the reactivation of their IA memory on spatial memory tested in the RAWM.

A mixed-model ANOVA was used to analyze the water maze data. Rats that were exposed to the IA apparatus or the novel environment in Experiment 2b were analyzed as separate groups. Analysis of the acquisition phase revealed a significant main effect of trials, $F(3,87) = 59.74$, $p < 0.0001$, indicating that the rats made significantly fewer arm entry errors as trials progressed. There was also a significant main effect of condition, $F(2,29) = 6.20$, and a significant trials × condition interaction, $F(6,87) = 4.96$ ($p < 0.01$). Rats that were exposed to IA retrieval at 6 months post-training made significantly more arm entry errors on T1 of day 2 water maze training than both of the other groups ($p < 0.05$). Analysis of the RT data revealed a significant main effect of condition, $F(2,29) = 13.08$, $p < 0.0001$. Rats made significantly more arm entry errors when they were re-exposed to the IA apparatus during the delay period than when they were exposed to their home cages during the delay period, independent of which experimental manipulation they had received 6 months earlier ($p < 0.05$; Figure 5A).

A mixed-model ANOVA was used to analyze the IA data, with session (retraining, 1-year retrieval) serving as the within-subjects factor and 6-month exposure (IA retrieval or novel environment) serving as the between-subjects factor. The analysis revealed a significant main effect of session, $F(1,14) = 24.85$, $p < 0.001$, indicating that both 6-month exposure groups demonstrated significantly greater ICLs during the 1-year retrieval session than during training (Figure 5B). There was no significant main effect of 6-month exposure, $F(1,14) = 0.33$, and the session × 6-month exposure interaction was not significant, $F(1,14) = 0.02$ ($p > 0.05$). These findings indicate that the groups given extinction versus no extinction trials at 6 months post-IA training were equivalent in terms of their ICLs at 1 year post-IA training. Moreover, these findings indicate that the rats exhibited intact fear memory of the dark side of the box 1 year after experiencing IA training.

Experiment 3: influence of restriction of rats to the light side of the IA apparatus on spatial memory

When IA-trained rats were re-exposed to the IA apparatus in Experiments 1 and 2, they spent a significantly greater amount of time on the light side of the apparatus than did the control (i.e., untrained) rats. It was possible that IA-trained rats exhibited water maze memory impairments following re-exposure to the IA apparatus only because spending more time in the light side of the apparatus had an adverse effect on their RAWM performance. To address this potential confound, we trained two additional groups of rats ($n = 8$ rats/group). One of the two groups was given IA (shock) training, and a day later, both groups were given water maze training. As in the previous experiments, the IA-trained group was re-exposed to the IA apparatus during a 30-min delay period after the acquisition phase and before a single memory test trial in the RAWM. These rats could choose to remain in the light side of the IA box or to step into the dark side. Conversely, the control group spent the entire 30-min delay period confined to the light side of the IA apparatus.

The IA-trained group made significantly more arm entry errors than the control (light side confined) group (2.5 ± 0.50 versus 1.0 ± 0.33 errors; $t(14) = 2.50$, $p < 0.05$) on the memory test trial. Therefore, light side exposure, alone, did not adversely affect water maze performance. This finding indicates that it was the activation of the memory of the IA shock experience in Experiments 1 and 2, and not just the rat's presence in the light side of the IA apparatus, that interfered with their retrieval of the memory of the platform location.

Discussion

This series of experiments generated two primary findings. First, we found that IA training, occurring immediately after spatial water maze training, impaired short-term (30 min) retrieval of a rat's memory of the location of the hidden escape platform. This finding replicates previous work from our laboratory (Diamond et al. 2004), as well as similar findings from other groups (de Quervain et al. 1998; Sandi et al. 2003; Costanzi et al. 2008), in which training involving shock has been used to impair spatial memory. Our second and entirely novel observation is that activation of a rat's *memory* of the IA training experience, alone, impaired retrieval of the memory of the location of the hidden escape platform. The spatial memory impairment was produced when IA memory reactivation occurred 24 h, as well as 1, 6 and even 12 months, after IA training took place. These observations are potentially relevant to well-described findings in people in which activation of one memory interferes with the retrieval of another memory (Anderson et al. 1994; Anderson et al. 2000a; Forcato et al. 2007; Garcia-Bajos et al. 2008), as well as the influence of traumatic memory reactivation on cognition in people with PTSD (Wessel et al. 2002; Golier et al. 2003; Schonfeld et al. 2007).

Why does reactivation of the memory of IA training impair spatial memory?

The basis of the impairment of spatial memory produced by IA memory reactivation cannot be attributed to a general impairment of learning and

memory in IA-trained rats, as they exhibited intact spatial memory performance under control (home cage) conditions. Moreover, IA-trained rats exhibited intact spatial memory performance when they were exposed to another chamber, which had features in common with the IA apparatus, such as a metal floor grid. This finding indicates that spatial memory was resistant to impairment by exposure of the rats to a novel environment. IA-trained rats exhibited impaired spatial memory only when their memory of the shock experience was activated (as indicated by their avoidance of the dark side of the chamber) in response to their return to the original shock environment.

The memory impairment produced by IA-re-exposure cannot be attributed to a global cognitive impairment in IA-trained rats. Therefore, we will speculate on factors specific to the IA re-exposure experience, such as the influence of distraction and arousal on spatial memory retrieval, and cognitive factors, such as retroactive interference and retrieval-induced forgetting (RIF), to explain why IA re-exposure impaired the retrieval of their new spatial memory. First, in the control condition rats were placed in their home cages, an environment which provided minimal sources of distraction, during the 30 min period between water maze learning and spatial memory testing. It was possible that IA memory reactivation impaired spatial memory only because the IA chamber served as a potent distraction. However, extensive research indicates that rodent spatial memory is highly resistant to being impaired by distracting stimuli. As mentioned above, IA-trained rats exhibited intact memory when they were placed in a conventional fear-conditioning chamber (where they had not been shocked) during the delay period. Thus, the ability of the IA-trained rats to exhibit intact memory following placement in the novel chamber helps illustrate the resistance of their spatial memory to being impaired by distraction. This finding is consistent with other work which demonstrated that distracting stimuli, including a novel environment (Diamond et al. 1999), strong sensory cues (flashing lights, odors) (Maki et al. 1979) and even exposure of a male rat to an estrus female rat (Woodson et al. 2003), were all ineffective at impairing rodent spatial memory. Thus, distraction, *per se*, is an insufficient explanation for why IA chamber re-exposure impaired spatial memory retrieval.

Second, when people re-experience traumatic memories they commonly react with increased anxiety (Halligan et al. 2006) which may be accompanied by elevated levels of stress hormones, e.g., cortisol (Elzinga et al. 2003). Although we did not measure emotional responses of the rats in this study, it is likely that IA re-exposure increased arousal in IA-trained rats, and the increase in arousal, itself, may have impaired their spatial memory. However, just as with distracting stimuli, studies have shown that rat spatial memory is resistant to being impaired by arousing stimuli. For example, in the study mentioned above, male rats exposed to a female rat exhibited elevated levels of corticosterone in response to female rat exposure, but the male rats did not exhibit an impairment of spatial memory (Woodson et al. 2003). In other work, Diamond et al. (1996) reported that spatial memory for food location was unaffected when water-acclimated rats were given an arousing experience (immersion in cold water). Therefore, elevated arousal may have contributed to the spatial memory impairment described here, but the presumed increase in arousal, alone, does not fully explain why IA re-exposure impaired spatial memory.

Third, cognitive (memory reactivation) components of IA re-exposure may have interfered with spatial memory retrieval. For example, activation of the IA training memory may have produced a form of retrograde interference, which then interfered with spatial memory retrieval. Retrograde interference is a well-described phenomenon in the human and rodent literature (Osgood 1948; Mehler and Miller 1964; Jarrard and Elmes 1981; Jarrard and Elmes 1982; Elmes and Svalina 1986; Izquierdo and Pereira 1989) in which the learning of new information interferes with the retrieval of previously learned information. Work showing that rat spatial memory is resistant to being impaired by new learning experiences is relevant to this issue. For example, in a study by Diamond et al. (1996), rats were trained to learn the within-day location of food in a 14-arm maze, and then they were given water maze training to find a hidden platform, followed 4 h later by a memory test of food location in the 14-arm maze. Importantly, spatial learning of the new platform location in the water maze did not affect retrieval of spatial memory for food location in the 14-arm maze. Indeed, after rats learned the within-day location of food they were then able to repeatedly learn new locations of the hidden platform in the water maze on a daily basis, without the water maze learning affecting their memory of food location in the other maze. These findings illustrate the great resistance of rat spatial memory to be impaired by incidental learning experiences, and therefore suggest that retrograde interference, alone, does not explain the IA re-exposure-induced amnesia.

Related research has characterized a phenomenon which is referred to as RIF (Anderson et al. 1994; Anderson et al. 2000a,b; Forcato et al. 2007; Garcia-Bajos et al. 2008). This approach, which has been performed entirely on people, may provide the most relevant explanation for why IA memory reactivation impaired spatial memory. These studies have shown that the act of remembering information strengthens the processes involved in retrieval of that information, but simultaneously inhibits retrieval of other, unrelated, information; essentially, 'remembering can cause forgetting' (Anderson et al. 1994). In the

case of RIF applied to PTSD, one may hypothesize that repeated intrusive recollections will enhance the vividness and strength of the memory of the traumatic experience (Ferree and Cahill 2009), at the cost of impairing the ability of traumatized people to store new information.

Our findings describe the first evidence of RIF in non-human subjects, in that the retrieval of the IA shock memory caused the rats to forget the hidden platform location in the water maze. A commonality between the RIF research in people and the current work is that the work on people involved declarative (hippocampus-dependent) memory (word lists), which was forgotten by memory retrieval, and in the current study, spatial (hippocampus-dependent) memory was forgotten by IA re-exposure. Whether RIF is exclusively a hippocampal sensitive phenomenon in humans and rats remains to be determined.

Another feature of RIF which is relevant to the current findings is the idea that the combination of memory retrieval and response inhibition impairs subsequent memory processing. Specifically, Levy and Anderson (2002, 2008) hypothesized that inhibitory mechanisms suppress competing traces, which will then impair the later recall of competing memories. These authors speculated that inhibitory processes involving the prefrontal cortex (PFC) are involved in the suppression of motor-override tasks and RIF. Support for the role of the PFC in RIF is provided from imaging studies in people (Anderson et al. 2004) and brain (PFC) manipulations in rodents given IA training (Liang et al. 1996; Mello e Souza et al. 2000; Quirk and Gehlert 2003; Costanzi et al. 2008). In the current work, the rats exhibited RIF, as well as active response inhibition, and the combination of the two factors were likely to contribute to IA re-exposure-induced spatial memory deficit. Understanding how emotional memory reactivation and a suppression of motor activity affect ongoing memory processing is an area of research which may provide insight into cognitive and neural mechanisms adversely affected in traumatized people.

Taken together, our finding of IA-induced retrograde amnesia does not appear to be explained merely as a result of the vulnerability of rat spatial memory to be impaired by incidental influences, such as interference produced by shifts of attention and arousal, or even by new learning. Rather, IA-induced retrograde amnesia may be considered to be a form of RIF activated by the retrieval of the remote memory of IA training. A potentially important factor in the expression of IA-induced RIA is the involvement of memory-evoked activation of the PFC to suppress the rat's innate drive to approach the dark side of the IA chamber. Subsequent work, therefore, will address the involvement of the PFC, as well as the approach-avoidance component, in the impairment of spatial memory produced by IA-memory reactivation.

In related findings, Holahan and White (2002, 2004) showed that exposure of rats to an environment where they had received shock 15 or 30 min after appetitive conditioning (conditioned place preference for food) improved their 24 h memory for food preference. Their work contrasts with the findings of the current study at multiple levels. In our work, strong, distraction-resistant, short-term (30 min) spatial memory was impaired by post-training exposure of rats to an IA apparatus where they had been shocked as much as 12 months before. Holahan and White (2002, 2004) demonstrated that long-term (24 h) appetitive memory for food location was enhanced by post-training exposure of the rats to a shuttle box where they had been shocked 24 h before. There are too many methodological factors that differed between the studies to determine why memory was impaired in our study and enhanced in the studies by Holahan and White. One issue to consider is the idea, discussed above, that response inhibition, with its great taxing of PFC functioning, exerts a powerful adverse effect on cognitive processing. In our case, rats inhibited their innate preference for the dark side of the chamber as a result of their experience with shock in that side. In contrast, the rats in Holahan and White's studies were given the opportunity to choose between two physically equivalent sides of the shuttle box, so as to avoid the side that had been previously paired with shock. Thus, response inhibition (current work) versus response preference (Holahan and White) may engage brain memory systems differently, which will have different consequences on the retrieval-induced forgetting versus enhancement of memory.

It is important to note that Holahan and White (2002, 2004) confirmed the critical role of the amygdala in the re-exposure-induced enhancement of 24 h memory. This finding is consistent with our suggestion (discussed below) that the amygdala may be involved in the retrieval-induced impairment of spatial memory reported here.

Relation to studies on stress, memory and hippocampal function

The present findings are consistent with a substantial literature demonstrating adverse effects of stress on hippocampus-dependent memory in humans and rodents (Kirschbaum et al. 1996; Kim and Diamond 2002; Payne et al. 2002; Diamond et al. 2004, 2005, 2007; Kim et al. 2006; Payne et al. 2006; Sandi and Pinelo-Nava 2007). Extensive work has also demonstrated that stress impairs the induction of hippocampal synaptic plasticity (long-term potentiation, LTP; Foy et al. 1987; Garcia 2001; Kim and Diamond 2002; Diamond et al. 2004, 2005, 2007; Huang et al. 2005; Kim et al. 2006; Joels and Krugers 2007). It is notable that fear conditioning (Sacchetti et al. 2002;

Li et al. 2005) or the re-exposure of rats to a fear-conditioned environment, alone, (Garcia et al. 1998; Li et al. 2005) has been shown to impair the induction of hippocampal LTP. Therefore, the reactivation of either a fear-provoking memory or a sensory-evoked (unconditioned) stress response can produce inhibitory effects on hippocampal plasticity. Thus, our strategy of using re-exposure of rats to a fear-provoking environment provides a means with which to study memory-evoked activation of hippocampal plasticity mechanisms, as well as to evaluate how the reactivation of an emotional memory interacts with the processing of newly formed memories.

We have speculated that the basis of the stress-induced impairment of hippocampal functioning is that the stressful experience generates a new emotional memory, and it is the formation of the new emotional memory that interferes with the capacity for the hippocampus to retrieve other memories (Diamond et al. 1999, 2004, 2005, 2007). We suggest that the stress-induced impairment of hippocampal functioning, expressed as stress-induced retrograde amnesia, is adaptive because the processing of information with great survival value, such as shock avoidance, predator exposure or the reactivation of a traumatic memory, takes priority over the retrieval of other, less salient, memories (de Kloet et al. 1999; Joels et al. 2006; Sandi and Pinelo-Nava 2007), such as the location of food (Diamond et al. 1996) or the hidden platform in the water maze (Diamond et al. 1999, 2004; Sandi et al. 2005; Campbell et al. 2008).

We have also theorized that a stressful experience induces an endogenous form of hippocampal synaptic plasticity (Diamond et al. 1990, 2004, 2005), which 'overwrites,' or prevents access to, recently stored information (see also de Kloet et al. 1999; Joels et al. 2006; Sandi and Pinelo-Nava 2007). However, in all of our previous work on stress and memory, as well as in work from other laboratories, the stress was induced by sensory stimulation that evoked unconditioned arousal. That is, rats are routinely stressed with stimuli that produce unconditioned arousal, such as shock, restraint or predator exposure (Diamond et al. 1996, 1999, 2004, 2005, 2007; Packard and Cahill 2001; Kim and Diamond 2002; Richter-Levin and Akirav 2003; Roozendaal 2003; Phelps and LeDoux 2005; Roozendaal et al. 2006; Shors 2006; Joels and Krugers 2007; Campbell et al. 2008). The findings of the present series of experiments have extended research on how stress affects memory by demonstrating that the retrieval of a rat's emotional memory, alone, can be so powerful and intrusive that it can interfere with ongoing hippocampus-dependent memory-related functioning.

Theoretically, in the present experiments, reactivation of the memory of the shock experience initiated a reconsolidation process (Duvarci and Nader 2004; Tronson and Taylor 2007) which could have contributed to the impaired retrieval of the memory of the hidden platform in the RAWM. The reconsolidation of an established memory involves some of the same processes that have been implicated in the original consolidation process, such as protein synthesis, activation of the mitogen-activated protein kinase pathway and activation of specific transcription factors, such as cAMP response element binding protein and zif268 (Alberini 2005). How reconsolidation may be involved in the intrusive memory process is a matter of speculation. We have suggested previously that, in response to stress, the hippocampus is powerfully activated by neuromodulators, including glutamate, acetylcholine, norepinephrine and corticosterone, and indirectly by afferent stimulation from the amygdala (Diamond et al. 2007). In theory, it is this rapid and dramatic emotion-induced activation of endogenous forms of hippocampal plasticity that underlies the formation of flashbulb memories (Akirav and Richter-Levin 2002; Joels et al. 2006; see also Richter-Levin and Akirav 2000; Richter-Levin and Akirav 2003; Sandi and Pinelo-Nava 2007). We therefore speculate that retrieval of the shock avoidance memory activated endogenous mechanisms of neuroplasticity in the hippocampus which are involved in flashbulb memory and reconsolidation processes.

Amygdala-hippocampus interactions underlying the IA memory retrieval-induced impairment of spatial memory

It is likely that an amygdala-mediated modulation of hippocampal function played a role in the adverse effects of IA memory reactivation on spatial memory retrieval. The amygdala plays a crucial role in fear conditioning (LeDoux 2003; Rudy et al. 2004; Sigurdsson et al. 2006; Quirk and Mueller 2008) and in trauma-induced psychopathology (Quirk and Gehlert 2003; Shekhar et al. 2003; Shin et al. 2006). Studies have shown that synaptic plasticity in the amygdala, unlike the hippocampus, is enhanced by fear conditioning or stress (McKernan and Shinnick-Gallagher 1997; Rogan et al. 1997; Vouimba et al. 2004, 2006; Schroeder and Shinnick-Gallagher 2005; Rodriguez Manzanares et al. 2005; Diamond et al. 2007), that lesions or inactivation of the amygdala blocks the stress-induced impairment of hippocampal function (Kim et al. 2001; Almaguer-Melian et al. 2003; Kim et al. 2005; Korz and Frey 2005; Park et al. 2005), and that activation of the amygdala can impair hippocampal synaptic plasticity (Akirav and Richter-Levin 1999, 2002; Abe 2001). Also germane to the current findings is the demonstration that the amygdala is activated in response to the representation of a fear-provoking experience, alone (Phelps et al. 2001; Phelps 2004), which suggests that memory activation in the IA-trained rats in the current study increased activity in their amygdala, thereby contributing to the

impairment of hippocampal functioning. This hypothesis has been supported by recent work by Elliott and Packard (2008) who found that activation of the amygdala prior to memory retrieval prevented rats from utilizing a hippocampus-dependent learning strategy.

This perspective on an amygdala-mediated inhibition of hippocampal functioning is consistent with, and extends, the work of McDonald and White (1993), who provided the first evidence of a competitive interaction between the hippocampus and amygdala in memory processing. Their work indicated that hippocampal and amygdala memory systems compete with, and inhibit, one another. We would hypothesize that in the current work, the reactivation of the IA memory, with its presumed emotional (i.e., amygdala-activating) component, resulted in the dominance of the amygdala over the hippocampus. The control exerted by the amygdala over the hippocampus during the 30-min period after spatial learning would have contributed to the impairment in spatial memory retrieval.

Potential relevance to intrusive memories in PTSD

Studies have shown that people with PTSD are impaired at storing and retrieving new information (Yehuda et al. 1995; Bremner et al. 2004; Van Praag 2004). Some investigators have proposed that the cognitive impairments are caused by subject characteristics other than the core symptoms of PTSD itself, such as major depressive disorder, substance abuse, less education and lower IQ (Gilbertson et al. 2001; Neylan et al. 2004). It is possible, though, that the cognitive impairments are to some extent, a state, rather than trait, characteristic of people with PTSD. That is, a cardinal feature of this disorder is that PTSD patients experience extreme psychological distress by repeatedly reliving their trauma through intrusive, flashback memories (Brewin et al. 1998; Reynolds and Brewin 1998, 1999; Ehlers et al. 2002; Berntsen et al. 2003; Hackmann et al. 2004; Holmes et al. 2005; Speckens et al. 2007). Since these intrusions are defined by their spontaneity, they could have a powerful, yet fleeting, influence on cognition in people with PTSD. Studies have also reported significant relationships between intrusive symptoms and memory impairments in PTSD patients (Wessel et al. 2002; Golier et al. 2003). Here, we have shown in an analogous condition that the retrieval of a remote, emotionally charged memory (IA retrieval), can impair a rat's retrieval of a newly acquired spatial memory.

One potential limitation of the current study is that IA-trained rats were returned to the same environment where their trauma occurred, but people with PTSD would be unlikely to experience the identical environment where they were traumatized. Indeed, a common symptom of PTSD is the great effort these individuals expend to avoid cues associated with the traumatic experience (Norman et al. 2007; Williams and Moulds 2007). Moreover, intrusive memories seem to occur spontaneously, in the absence of explicit cues that remind the patient of the traumatic experience. According to Michael and Ehlers (2007, p. 342), 'Frequently, trauma survivors are not aware which stimuli trigger their intrusive memories and thus experience them as coming out of the blue.' However, a closer examination of the intrusive memory phenomenon reveals commonalities between intrusive memories in people and IA-re-exposure in rats. There is evidence that intrusive memories are not evoked 'out of the blue', but are actually triggered by environmental cues that were associated with the original traumatic event (Hackmann et al. 2004; Michael and Ehlers 2007). Ehlers and Clark (2008) noted that the link between intrusive memory reactivation to environmental stimuli 'is often of a sensory, rather than a meaningful, nature, ... (which) makes it hard for patients to spot the triggers'. They further noted that 'Associative learning and perceptual priming make it likely that involuntary memories are triggered by matching cues.'.

These observations of the cue-driven nature of intrusive memories are supported by evidence of enhanced perceptual priming for trauma-related cues (Michael and Ehlers 2007). In addition, the increased excitability of the amygdala in people with PTSD (Rauch et al. 2006; Bremner et al. 2008) may contribute to enhanced sensitivity of these patients to attend to salient, and perhaps implicit, emotion-laden cues (Anderson and Phelps 2001). Overall, there is strong support for Michael and Ehler's (2007) assertion that 'the triggering of intrusive memories appears to be mainly cue-driven'.

In addition to cue-evoked activation of intrusive memories, people with PTSD report that during intrusive memory activation they feel a sense of 'nowness' during the incidents—that the sensory experiences are actually happening in the present and are not merely a recollection of a past event (Ehlers et al. 2002; Hellawell and Brewin 2002; Berntsen et al. 2003; Ehlers et al. 2004; Hackmann et al. 2004; Hellawell and Brewin 2004; Holmes et al. 2005; Speckens et al. 2007). Thus, the sense that the patients are actually reliving their original traumatic experience during an intrusive memory is analogous to the re-exposure of rats to the IA apparatus. This perspective on the abnormal nature of intrusive memories, as a cue-driven process in which the patient seems to re-experience the sensory features of the original trauma, supports the view that IA-re-exposure in rats can serve as a model for intrusive memory reactivation in people.

In summary, our approach provides a novel paradigm with which to examine how strong emotionality produces powerful and durable memories, and

more importantly, how the reactivation of a remote emotional memory interacts with newly formed memories. Since intrusive, traumatic memories are such a critical component of PTSD symptomatology, our approach provides a strategy with which to study the neural mechanisms, and develop treatment strategies, for the detrimental effects of intrusive memories on cognitive processing in traumatized people.

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