Brief Communication

A brief retraining regulates the persistence and lability of a long-term memory

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An experience extending the persistence of a memory after training *Aplysia californica* with inedible food also allows a consolidated memory to become sensitive to consolidation blockers. Long-term (24 h) memory is initiated by 5 min of training and is dependent on protein synthesis during the first few hours after training. By contrast, a more persistent (48 h) memory is dependent on a longer training session and on a later round of protein synthesis. When presented 24 h after training, a 3-min training that produces no memory alone can cause a memory that would have persisted for only 24 h to persist for 48 h. After a 48 h memory has been consolidated, 3 min of training also makes the memory sensitive to a protein-synthesis inhibitor. These findings suggest that a function of allowing a consolidated memory to become sensitive to blockers of protein synthesis may be to allow the memory to become more persistent.

[Supplemental material is available online at http://www.learnmem.org.]

Long-term memory of an experience is dependent on a consolidation process that follows the experience. Before the memory is consolidated it is labile and can be disrupted (Lechner et al. 1999; Dudai 2004; Alberini and Taubenfeld 2008), particularly by blocking mRNA and protein synthesis (Alberini and Taubenfeld 2008; Klann and Sweatt 2008), which are needed to produce the changes in synaptic structure and function that underlie long-term memory (Sigurdsson et al. 2007; Bailey and Kandel 2008; De Roo et al. 2008). After long-term memory is established by the initial stages of consolidation, later rounds of consolidation may be needed to extend the persistence of the memory (Wittenberg and Tsien 2002; Bekinschtein et al. 2007). Consolidated memories may also be modified when they are retrieved (Dudai 2006; Alberini and Taubenfeld 2008). Retrieving a memory by exposure to the conditioned stimulus, or by re-experiencing aspects of the original training, can destabilize it and initiate an additional protein-synthesis-dependent process of memory stabilization (Nader 2003; Dudai 2006; Alberini and Taubenfeld 2008). The aim of this communication is to explore whether an experience that alone does not cause long-term memory can make a memory more persistent and can also destabilize a consolidated memory and makes it labile.

Training *Aplysia californica* with inedible food until they stop responding to the food initiates long-term memory that can be measured as a reduction in the time to stop responding. Long-term memory is present 1, 2, and 7 d after a single training session (Schwarz et al. 1991). We examined some of the parameters of training that lead to persistence of memory by determining whether shorter training sessions also produce a persistent long-term memory.

As in previous studies (Schwarz et al. 1991; Botzer et al. 1998; Lyons et al. 2005), *Aplysia californica* were trained with inedible food, the seaweed *Ulva* wrapped in plastic net. This food induced biting, leading to food entering the mouth. Animals then attempted to swallow the food. The netted food cannot be swallowed and it became lodged in the buccal cavity, producing repetitive failed swallowing responses. Food eventually left the buccal cavity. The experimenter continued to hold the food against the lips, inducing further biting responses, entries into the mouth, and failed swallows. As training proceeded many bites failed to cause entry of food into the mouth. When food did enter the mouth it stayed within for progressively shorter periods, eliciting fewer attempted swallows. In all animals, food was in the mouth eliciting failed attempts to swallow for at least 100 sec of the initial training, since previous experience showed that such animals almost always show long-term memory. Animals in which food was not in the mouth for 100 sec during training were discarded. A full training session until animals stop responding to food requires 10–25 min of training (Fig. 1). Such a training session caused long-term memory measured after 24 h or after 48 h (Fig. 1A). Memory was measured by comparing the time to stop responding to inedible food during training to the time to stop responding when animals were tested 24 or 48 h later, in a procedure identical to that during training. All tests of memory were performed using a blind procedure in which the experimenter was unaware of the previous training procedure.

We examined whether abbreviated training also caused long-term memory. First, we examined long-term memory when training is stopped after 5 min. During the first 5 min of a full training session, food is in the mouth, and animals are attempting to swallow for a mean of 70% of the time in the mouth during a full training session. Attempts to swallow are an integral part of the training (Katzoff et al. 2006). We confirmed an earlier finding (Botzer et al. 1998) that a 5-min training produced long-term memory measured 24 h after the training (Fig. 1B). However, we
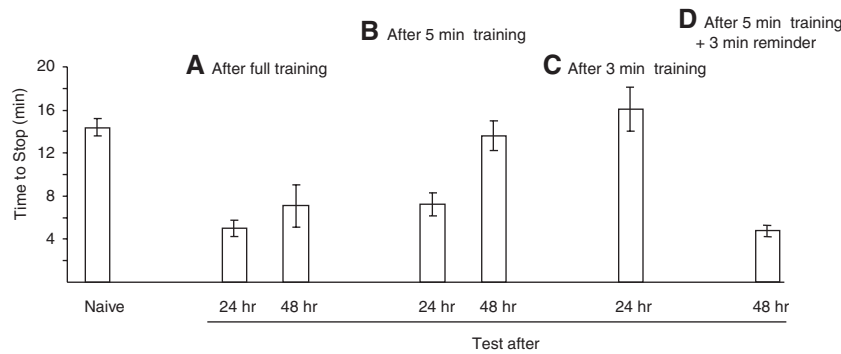
Figure 1. Memory 24 and 48 h after different training procedures. The figure shows the time to stop responding in a group of naïve animals trained with a full training session (training continued until animals stop responding to food), as well as the time to stop responding on memory trials 24 and 48 h later ($N = 38$ naïve animals [naïve animals were run as controls for the various other groups and data from the naïve animals were then combined. There was no significant difference between the various groups of naïve animals: $P = 0.405$, $F_{(5,32)} = 1.053$]); (A) $N = 13$ animals tested 24 h after a full training; $N = 6$ animals tested 48 h after a full training; (B) $N = 9$ animals tested 24 h after a 5-min training; $N = 17$ animals tested 48 h after a 5-min training; (C) $N = 14$ animals tested 24 h after a 3-min training; (D) $N = 7$ animals tested 48 h after a 5-min training, plus an additional 3-min training 24 h later. A one-way analysis of variance showed significant differences between the seven groups shown ($P < 0.001$, $F_{(6,97)} = 11.95$). A post-hoc test (Student-Newman-Keuls, $\alpha = 0.05$) showed that there were no significant differences between the time to stop in naïve animals and in animals tested 48 h after a 5-min training, or in animals tested 24 h after a 3-min training, indicating that these treatments did not cause memory. By contrast, the times to stop in these three groups were significantly different from that in the other four groups, which were not significantly different from one another. These findings indicate significant memory 24 or 48 h after a full training, as well as 24 h after 5 min of training, and 48 h after 5 min of training with 3 min of reminder training, with no differences in memory after these 4 treatments. Standard errors are shown.

have now found that training animals for only 5 min did not cause long-term memory measured 48 h after training (Fig. 1B). A training session that was stopped after 3 min did not give rise to long-term memory measured at 24 h (Fig. 1C), indicating that the last 2 min of a 5-min training are necessary for the production of 24 h memory. These findings allowed us to examine the possible effects of an experience which itself does not cause memory, 3 min of training on memory persistence and memory lability.

A 5-min training session gives rise to memory after 24 h, but not after 48 h, whereas additional training gives rise to 48 h memory. Must the additional training take the form of continuing to train animals during the initial training session, or can an additional 3 min of training that itself does not cause 24 h memory enhance the effect of a 5 min of training? To test the ability of a 3-min training to enhance memory, animals were trained with either a full training session, or with a training session that was abbreviated after 5 min. One group of animals trained for 5 min received an additional 3-min training 24 h after the initial training, whereas another group did not. Memory was tested 24 h later, 48 h after the initial training. Animals receiving a full training, and animals receiving a 5-min training plus a reminder consisting of a 3-min additional training, displayed 48 h memory (Fig. 1D; for a fuller presentation of this experiment, see Supplemental material), whereas animals receiving only a 5-min training, with no additional training, showed no 48 h memory. These data show that a 3-min training, which is itself ineffective in producing memory 24 h later, can lead to significant memory when it follows a 5-min training, which itself would not produce 48 h memory.

In other learning tasks it has been shown that long-term memory is not a unitary process. An earlier round of protein synthesis is necessary for 24 h memory, but a more persistent memory (>24 h), and the synaptic plasticity underlying it, are dependent on later rounds of protein synthesis (Giustetto et al. 2003;

Bekinschtein et al. 2007; Miniaci et al. 2008). We therefore examined whether 24 and 48 h memory differ in their dependence on protein synthesis adjacent to training, or on protein synthesis 6 h after training. The protein-synthesis inhibitor anisomycin was injected into the hemolymph either 10 min before training or 6 h after training. Animals were injected with a 1 cc solution of anisomycin at a concentration that caused a 10 μM concentration within the animals. This concentration blocks protein synthesis in ganglia (Schwartz et al. 1971). Controls were injected with 1 cc of artificial seawater (ASW–NaCl 460 mM, KCl 10 mM, CaCl$_2$ 11 mM, MgCl$_2$ 55 mM, and NaHCO$_3$ 5 mM). Treatment with anisomycin just before training blocked 24 h memory, but anisomycin treatment 6 h after training did not prevent the appearance of 24 h memory, indicating that 24 h memory is consolidated within the first 6 h after training (note that Fig. 2A shows the percent change in time to stop responding during the test of memory, with respect to the time to stop during training). By contrast, 48 h memory was blocked by anisomycin treatment 6 h after training (Fig. 2B), whereas treatment with ASW did not block 48 h memory.

Memory 48 h after training is dependent on protein synthesis 6 h after training. As shown above, 3 min of training can establish 48 h memory after a 5-min training that alone is too brief to establish 48 h memory. Can 3 min of training also establish 48 h memory after it has been blocked by inhibiting protein synthesis at 6 h? To test this possibility, animals were trained with inedible food until they stopped responding, and were then treated with either ASW or anisomycin 6 h later. One group of animals also received 3 min of training with inedible food 24 h after the initial training. When tested 48 h after training, memory was present in animals treated with ASW and in animals that had received the additional 3-min training, but not in animals receiving only the anisomycin treatment (Fig. 2B). This finding indicates that a 3-min training that is effective in causing 48 h memory after 5 min of training can also rescue 48 h memory after it has been blocked by anisomycin.

If 3 min of training saves a blocked 48 h memory, it could also amplify an already-formed 48 h memory. We tested the effect on 48 h memory of a 3-min training 24 h after a full training session, which alone produces 48 h memory. There was no significant difference in memory between animals tested 24 h after training, and animals receiving a 3-min retraining, and then tested 48 h after training, indicating that the 3-min training did not affect the already consolidated 48 h memory (Fig. 3, cf. column 1 and column 3).

The 3-min training does not affect an already-formed 48 h memory, but does cause effects 24 h later if the memory is not fully consolidated. Formation of a long-term memory requires protein synthesis, and recalling a consolidated memory can make a memory sensitive to inhibitors of protein synthesis (Nader et al. 2000). Does a 3-min training 24 h after an initial full training initiate a renewed dependence of 48 h memory on protein synthesis? Animals were trained to criterion and then subjected to either anisomycin, or ASW, 24 h later. Both groups then
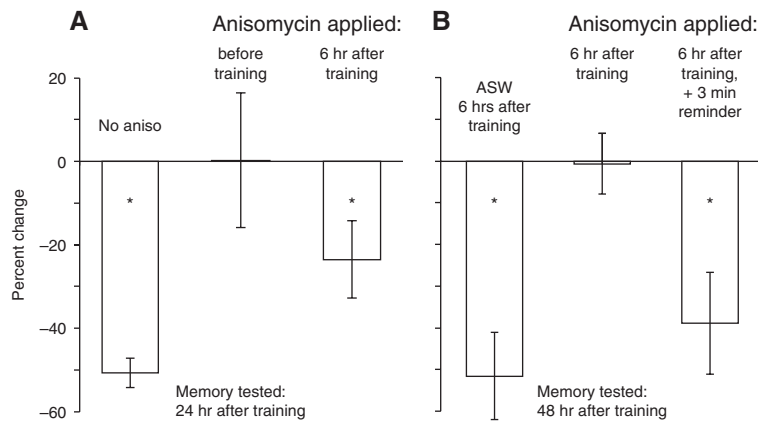
Figure 2. Protein synthesis dependence of 24 and 48 h memory. Data shows the memory test 24 or 48 h after training as a percent change $[-([\text{train-test}]/\text{train}) \times 100]$ from the initial training session. All tests of memory were after a full training session until animals stopped responding to the food. Memory was tested via two-tailed paired t-tests, in which the time to stop responding in a given animal during the initial training was compared with the time to stop responding 24 or 48 h later, when animals were tested. A significant decrease in the time to stop responding was used as an indicator of memory. Treatments showing such a decrease are marked (*). Standard errors are shown. (*A*) Anisomycin treatment blocks 24 h memory when applied just before training, but not when applied 6 h after training. Control animals ($N = 8$) not treated with anisomycin displayed significant 24 h memory ($P < 0.001$, $t_{(7)} = 10.15$). Anisomycin applied 10 min before the training ($N = 9$) blocked memory, as shown by a lack of significant decrease in the time to stop between the initial training and the test after 24 h ($P = 0.96$, $t_{(8)} = 0.05$). By contrast, application of anisomycin 6 h after the initial training ($N = 7$) did not block memory measured 24 h after training, as shown by significant savings after 24 h ($P = 0.05$, $t_{(6)} = 2.45$). (*B*) Forty-eight hour memory is dependent on a later stage of protein synthesis. Anisomycin ($N = 26$), but not ASW ($N = 5$) applied 6 h after training blocks 48 h memory, as shown by significant memory after treatment with ASW ($P = 0.007$, $t_{(4)} = 5.08$) but not with anisomycin ($P = 0.49$, $t_{(25)} = 0.69$). However, a 3-min reminder training 24 h after the training ($N = 12$) rescues 48 h memory after it was blocked by anisomycin treatment 6 h after training ($P = 0.01$, $t_{(11)} = 2.93$).

regulating memory persistence has not been examined. Indeed, many of the previous studies on reconsolidation used a conditioned stimulus (CS) alone as a reminder, and thereby caused extinction along with reconsolidation (Eisenberg et al. 2003; Pedreira and Maldonado 2003), rather than causing a strengthening of memory. Previous studies have indicated that after memory is initially consolidated, its persistence is dependent on successive waves of protein synthesis (Giustetto et al. 2003; Bekinschtein et al. 2007; Miniaci et al. 2008) and that reactivation of a memory improves its persistence (Spear 1973). Later waves of protein synthesis affecting persistent memories could be modulated or modified by retrieving a memory.

We have taken advantage of a memory task affecting *Aplysia* feeding to examine the possibility that memory retrieval via a brief additional training affects later waves of protein synthesis, and thereby affects the persistence of a memory. We found that pairing a brief additional training with block of protein synthesis blocks memory (Fig. 3). We also found that a more persistent memory measured at 48 h is dependent on a longer training session (Fig. 1), and a later wave of protein synthesis (Fig. 2) than is 24 h memory. Retrieval of memory by a 3-min retraining can establish 48 h memory even when the latter portion of training is absent (Fig. 1), or when the later wave of protein synthesis is blocked (Fig. 2). This finding suggests that the initial experience required to establish 48 h memory, as well as the wave of protein synthesis elicited by this experience, can be deferred. A later experience, and a later wave of protein synthesis, can substitute for the absence of experience in the initial training, or for the blocked wave of protein synthesis. In addition to creating a more persistent memory, a 3-min retraining also makes a consolidated memory sensitive to blocking by inhibitors of protein synthesis (Fig. 3). Thus, a function of experiences that permit reconsolidation may also be to extend the persistence of a memory.

In our study we cannot exclude the possibility that the 3-min retraining does more than just retrieve memory, and thereby make it labile. The increased persistence of memory could be caused by processes initiated by the 3-min training, such as increased consolidation, that are not related to the ability of the added training to make the memory labile. Indeed, previous studies have suggested that memory consolidation and reconsolidation may utilize different molecular mechanisms (Taubenfeld et al. 2001; Lee et al. 2004; Alberini 2005). The different molecular mechanisms activated by consolidation or reconsolidation have been used to classify the process by which retrieval affects memory, although use of the molecular markers to classify a behavioral process is controversial (Nader et al. 2005). Such studies have shown that changing a memory when it is retrieved sometimes utilizes a molecular mechanism for consolidation (Tronel et al. 2005), and sometimes for reconsolidation (Lee 2008). In the learning task utilized we have not examined separate molecular markers for consolidation and reconsolidation, raising the possibility that a 3-min retraining affects persistence by

received a 3-min reminder training 10 min later. Memory was then assessed 24 h later (48 h after initial training). There was significant memory 48 h after the training after treatment with ASW, but not after treatment with anisomycin, indicating that the 3-min reminder training restored the ability of anisomycin to block memory (Fig. 3).

Our data have shown that 3 min of training with inedible food alone does not produce long-term memory (Fig. 1), and does not amplify an already established 48 h memory (Fig. 3). Nonetheless, 3 min of training induces a protein-synthesis-dependent state in which memory can be modified (Figs. 2, 3). After a previous training leading to only 24 h memory (Fig. 1), or after a treatment blocking 48 h memory, the 3-min training makes the memory more persistent (Fig. 2). In addition, after a 48 h memory has already been consolidated, 3 min of training makes the memory labile, so that it can be blocked by inhibitors of protein synthesis (Fig. 3).
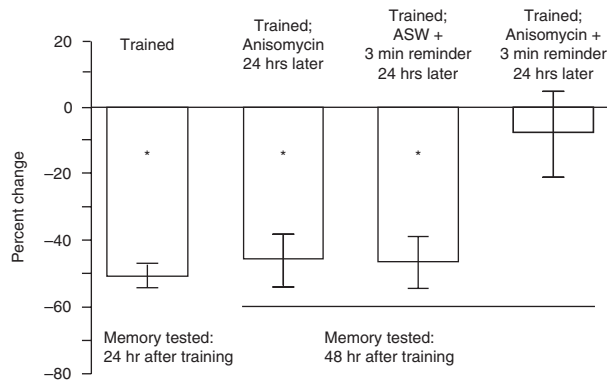
Reconsolidation is a process by which a consolidated memory returns to a protein-synthesis-dependent labile state by retrieving the memory (e.g., Nader et al. 2000; Sangha et al. 2003; Kemenes et al. 2006). In learning that food is inedible 3 min of training makes the memory labile. There has been much speculation on the possible function of memory reconsolidation. It has been suggested that the destabilization of memory by retrieval could function as a means to update and modify the magnitude and the persistence of the original memory trace (Dudai 2002, 2006). There is good evidence that reconsolidation can update (Rodriguez-Ortiz et al. 2005; Morris et al. 2006), strengthen (Frenkel et al. 2005; Tronson et al. 2006; Lee 2008), or modify (Rossato et al. 2006) memories, as well as block them (Nader et al. 2000), but the possible role of reconsolidation in

Figure 3. Brief training makes memory labile. Twenty-four hours after training with inedible food, animals were treated with anisomycin, or with ASW. The animals treated with ASW ($N = 9$), as well as one of the two groups treated with anisomycin ($N = 9$), were also given a 3-min training session 10 min later. Memory was then tested again 24 h later, 48 h after the training, by comparing the time to stop measured 48 h after training with the time to stop measured during the original training session, using a two-tailed paired t-test. A significant decrease in the time to stop responding was used as an indicator of memory. Data are also shown for 24 h memory after a full training session, to allow a test of whether a 3-min retraining at 24 h improves memory tested at 48 h. Treatment with anisomycin alone ($N = 8$) did not block 48 h memory ($P = 0.002$, $t_{(7)} = 4.66$). The 3-min reminder training plus treatment with ASW also did not block 48 h memory ($P = 0.001$, $t_{(8)} = 5.02$). By contrast, when the 3-min reminder training was preceded by anisomycin treatment, there was no significant difference between training and the 48 h test ($P = 0.27$, $t_{(8)} = 1.18$), indicating that the 3-min reminder allowed the anisomycin to block 48 h memory. Note that there is also no significant difference in savings after the 3-min training following ASW treatment and 24 h memory following training ($P = 0.13$, $t_{(10)} = 1.63$), indicating that the 3-min training on day 2 alone did not affect memory.

activating molecular mechanisms that are specifically associated with a separate round of consolidation, rather than activating reconsolidation.

Memory reconsolidation also affects a number of other molluscan learning paradigms (Sekiguchi et al. 1997; Sangha et al. 2003; Gainutdinova et al. 2005; Kemenes et al. 2006). In some, the memory becomes labile when animals are exposed to a CS alone, which does not itself create memory, whereas in others the memory becomes labile only when the CS is paired with an unconditioned stimulus (US), as in the original training (see Eisenhardt and Stollhoff 2008). In our experiments, memory was made labile by a second training session, which was shorter than that needed to itself create memory. It will be of interest to determine whether components of the experience alone in which animals learn that food is inedible do not give rise to memory, such as lip stimulation alone (Schwarz et al. 1988), can also give rise to reconsolidation, although they would not cause a more persistent memory.

Where in the *Aplysia* nervous system are molecular changes related to reconsolidation and the persistence of memory localized? The earliest molecular changes leading to long-term memory that a food is inedible (e.g., increased expression of C/EBP and sensorin), are localized to the buccal ganglia, specifically to a population of mechanoafferents (Levitan et al. 2008a,b). It is possible that the later molecular changes leading to a persistent memory are also localized to these neurons, similar to the localization to the same sensory neurons of earlier and later molecular events leading to long-term facilitation underlying sensitization in *Aplysia* (Miniaci et al. 2008). However, it is also possible that

the later phases of consolidation, and reconsolidation, may arise by molecular changes localized to other sites with the *Aplysia* nervous system, similar to the movement of earlier and later phases on long-term declarative memories from the hippocampus to the neocortex (Squire and Kandel 1999). Future studies will need to examine these points.

Acknowledgments

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