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Memory Reconsolidation after Training of Different Intensities Depends on the Duration of the Reminder Interval

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Two series of experiments were run on formation of a conditioned reflex to context in terrestrial snails using two training protocols with different numbers of unconditioned stimuli. In each experimental series, memory reconsolidation was initiated using a "reminder" of the training context at different times – 3 and 6 days after training – with subsequent blockade of protein synthesis with anisomycin. The training context reminder procedure combined with anisomycin injection on post-training day 3 in both protocols led to derangement of memory reconsolidation (forgetting). However, reminding of the training context with protein synthesis blockade on post-training day 6 was followed by retention of the memory in animals given fewer reinforcements during training, indicating that the memory reconsolidation process was not triggered. At the same time, reminders with protein synthesis blockade on post-training day 6 in animals receiving significantly more reinforcements during training led to forgetting, i.e., derangement of normal memory reconsolidation. Thus, these studies showed that reconsolidation of a contextual memory in terrestrial snails depends on training intensity, which is linked with selection of training protocols with different numbers of unconditioned stimuli. It is suggested that consolidation and reconsolidation processes are mediated by different neural pathways.

Keywords: associative learning, training protocol, reconsolidation of contextual memory, reminder of training context, time window of memory lability, snail.

Introduction. Memory consolidation is the process of gradual stabilization of long-term memory when transferred from the short-term form to the long-term form [McGaugh, 2000]. Newly acquired information is in a labile state for some period of time. However, over time it becomes stable and insensitive to disrupting agents such as electric shock and protein synthesis blockers [Nadel et al., 2012; McGaugh, 2015]. The long-term memory consolidation stage requires gene expression and de novo protein synthesis [Pearce et al., 2017]. The question of how new information interacts with old memory into which it is incorporated has long been asked. Despite the ongoing tendency to regard memory as an exact description of past events, scientific analysis suggest that memories are not fixed objects, but constitute a dynamic process of memory renewal [Alberini, 2011; Lee et al., 2017; Balaban, 2017]. In fact, if memories which have become stable to inhibitors of gene expression are repeatedly extracted, they again become labile over a limited period of time [Alberini, 2011; Zaichenko et al., 2020b; Barense and Sinclair, 2019]. Determination of the nature and temporal evolution of biological changes is key to understanding memory formation [Suzuki et al., 2004; Alberini, 2011; Lee et al., 2017; Kukushkin and Carew, 2017].

Memory consolidation can undergo a process of reorganization or destabilization [Dudai, 2006; McGaugh, 2015; Bessières et al., 2020]. The process by which reactivation of a labile memory stabilizes over time is known as memory reconsolidation [Sara, 2000; Nader and Hardt, 2009; Balaban et al., 2014]. Reconsolidation of contextual memo-

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ry has been demonstrated in invertebrates [Child et al., 2003; Gainutdinova et al., 2005; Kemenes et al., 2006; Lukowiak et al., 2007; Cai et al., 2012; Dodd and Lukowiak, 2015; Balaban et al., 2016; Nikitin et al., 2018]. Consideration of the memory formation process and its reconsolidation in mollusks is also attractive in relation to the opportunity to seek correlations with memory mechanisms at the cellular and molecular levels and at the receptor level [Balaban and Korshunova, 2011; Gainutdinov et al., 2011; Andrianov et al., 2015; Bogodvid et al., 2017; Carhart-Harris and Nutt, 2017; Dyakonova et al., 2019; Bessières et al., 2020; Orlandi et al., 2020].

Questions linked with reconsolidation mechanisms have been discussed intensely. On the one hand, this addresses the interaction between reconsolidation and forgetting, i.e., the processes of amnesia [Lattal and Wood, 2013; Almeida-Corrêa and Amaral, 2014; Zuzina and Balaban, 2015; Wideman et al., 2018; Nikitin et al., 2020]. An obligate condition for memory reactivation is reminding [Nader et al., 2000; Anokhin et al., 2002; Vorob'eva et al., 2016; Hemstedt et al., 2017]. The reminder can lead to reconsolidation of the initial memory as a result of a series of molecular and cellular processes leading to stabilization of the memory or its extinction [Tronson and Taylor, 2007; Lattal and Wood, 2013; Hu et al., 2018; Borodinova and Balaban, 2020]. Another research direction is associated with the search for time windows in which reminding can lead to reconsolidation and/or forgetting of a memory or be ineffective [Suzuki et al., 2004; Dudai, 2006; Alberini and LeDoux, 2013; Lee et al., 2017; Rodriguez-Ortiz and Bermúdez-Rattoni, 2017; Zaichenko et al., 2020b; Deryabina et al., 2020]. Steps have also been taken to find actions influencing the possibility of reconsolidation at the level of the intracellular signal systems and NMDA receptors [Kemenes et al., 2006; Tronson and Taylor, 2007; Shevchenko et al., 2009; Huang et al., 2017; Nikitin et al., 2018; Zhang et al., 2018]. The dynamics of reconsolidation have been addressed in mollusks with impairments to the serotonin and nitric oxide systems [Balaban et al., 2014, 2016; Bal et al., 2017; Schmidt et al., 2017; Nikitin et al., 2018; Deryabina et al., 2018; Zuzina et al., 2019]. It has also been demonstrated that reconsolidation is disrupted by interaction with the unconditioned signal [Gainutdinova et al., 2005] and on presentation of a stressor signal [Dodd and Lukowiak, 2015].

The time dynamics of memory reconsolidation depend on a number of parameters and there are extensive and contradictory data for this phenomenon [Vorob'eva et al., 2016; Balaban et al., 2016; Travaglia et al., 2018]. Results reported by different authors demonstrate that the more strongly a memory is fixed or the more time has passed between memorization and reminding, the harder it is to destabilize [Nader and Hardt, 2009; Inda et al., 2011; Zuzina and Balaban, 2015]. On the other hand, it has been shown that early aversive contextual memory in rat pups can be restored by a reminder presented later in development [Alberini and Travaglia, 2017; Travaglia et al., 2018]. Another parameter of this type may be post-training "memory strength" [Suzuki et al., 2004; Alberini and LeDoux, 2013]. This leads to the question of which memories, in terms of types of training, are subject to reconsolidation and which remain permanently, and in which cases memory becomes finally consolidated, and in which cases it remains labile.

Thus, analysis of unresolved aspects in the mechanisms of memory reconsolidation led us to pose the task of studying the reconsolidation of long-term contextual memory in the terrestrial snail after acquisition of a conditioned defensive reflex to context using different protocols to form it with different stimulus intensities.

Methods. Experiments were performed using the terrestrial snail *Helix lucorum*. Experiments used animals selected on the basis of weight (20–25 g). Before experiments, mollusks were kept for at least two weeks in the active state in a humid atmosphere a room temperature with an excess of food. A conditioned defensive reflex to context was developed in all animals using the "on the ball" paradigm in a situation in which the animal was firmly attached by the shell. Animals retained the freedom to move across the surface of a ball floating in water, fully retained by the shell. Two days before training sessions and during training (five days), feeding of the experimental animals was stopped, ensuring that the animals were in the active state [Balaban et al., 2016; Deryabina et al., 2018].

Training consisted of presenting electrical stimuli (as the unconditioned stimuli) for five days with the snail in a specific context – on the ball. Animals were presented with electrical stimuli (1–2 mA, 1 sec, 50 Hz, square-wave pulses, 10 msec) by contacting two macroelectrodes to the dorsal area of the anterior and posterior parts of the foot [Gainutdinova et al., 2005; Deryabina et al., 2020]. The time from placing the animals in the context to the first stimulus and the times between successive stimuli were about 15–20 min. Stimulation current intensity was selected to be sufficient to trigger a defensive reaction involving withdrawal of the front half of the body but not damaging the animal's skin [Gainutdinov and Beregovoi, 1994]. Animals of the control group were kept in the same conditions as animals of the experimental groups throughout the experiment.

Before the experiment started and one day after training, animals were tested for the level of the defensive ommatophore withdrawal reaction as a measure of the formation of long-term memory in response to tactile stimulation (Fig. 1). For this purpose, the amplitude of ommatophore withdrawal in response to tactile stimulation – tangential movement of a brush hair along the skin of the dorsal side of the anterior part of the foot at standard speed [Muranova et al., 2019] – was measured. On movement, the fiber touched the animal's skin over a distance of about 1 cm and moved at a speed of about 1 cm/sec. The maximum extent of ommatophore extension was taken as 100%. Behavioral reactions were tested: 1) on the ball; 2) on a strip of the surface

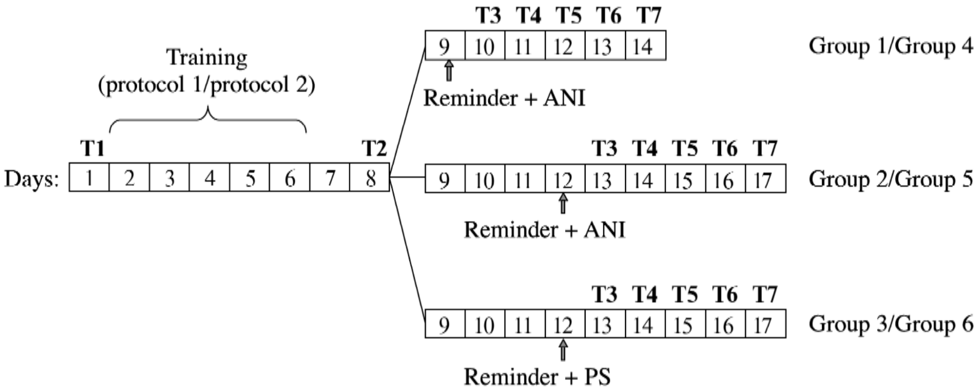

Fig. 1. Experimental scheme. Cells show experimental days. “T1–T7” are testing of the level of the animals’ defensive reactions at different experimental time points on the ball and on a planar surface. “T1” is day 1 – testing of the initial level of the animals’ defensive reactions. “Training (protocol 1/protocol 2)”, days 2–6 – acquisition of a contextual conditioned reflex using two different protocols. “Protocol 1” and “Protocol 2” – presentation of five and three electrical stimuli, respectively, over five days with the animals in a specific context – on a ball. Day 7 – animals’ rest day; day 8 – testing of the level of defensive reactions after the training procedure and rest. “Group 1/Group 4:” “Reminder + ANI,” day 9 – training context reminder followed by injection of ANI; “T3–T7,” days 10–14 – testing of the level of the animals’ defensive behavior. “Group 2/Group 5:” “Reminder + ANI,” day 12 – training context reminder followed by ANI injection, “T3–T7,” days 13–17 – testing of animals’ levels of defensive behavior. “Group 3/Group 6:” “Reminder + PS,” day 12 – training context reminder followed by injection of PS, “T3–T7,” days 13–17 – testing of animals’ levels of defensive behavior. PS – physiological saline.

of the roof of the terrarium (i.e., in conditions different from the training context).

We previously developed a conditioned reflex to context using a single protocol – “five stimuli per day for five days” [Gainutdinova et al., 2004; Deryabina et al., 2018]. The present study used two series of experiments with two training protocols: 1) “five stimuli per day for five days” and 2) “three stimuli per day for five days.” The latter scheme was used to decrease training intensity (the total number of stimuli was 15 instead of 25), thus giving a different “learning strength” [Suzuki et al., 2004].

The experiment started with testing the animal’s level of defensive reactions in response to tactile stimulation in the situations of being on the strip and on the ball – T1 (day 1) (Fig. 1). The training procedure was followed by a rest day, which was followed by test T2, which in these experiments confirmed the successful acquisition of the conditioned defensive reflex to context. Testing of the reflex to context was then continued to 12 days, i.e., tests T3–T7 over five days.

The phenomenon of reconsolidation of long-term contextual memory formed after training was studied by “reminding” of the training context by placing the animals in the learning context – on the ball – for 20 min. As in training, the animals were firmly attached by the shell with retention of freedom to move across the surface of the ball floating in water. However, the animals received neither tactile nor electrical stimulation. Protein synthesis was then inhibited after the reminding procedure. Protein synthesis was blocked using anisomycin (ANI), 2-(p-methoxybenzyl)-3,4-pyrrolidinediol-3-acetate (Sigma). ANI solutions were used at a dose of 16 mg/kg (0.4 mg/snail) dissolved in 0.2 ml of physiological saline. Testing of the level of the defensive reaction was again tested on the next and subsequent days after the reminder of the training context, as an indicator of retained long-term memory. Significant decreases in the level of the conditioned defensive reaction demonstrated that the process of contextual memory reconsolidation occurred and depended on protein synthesis [Balaban et al., 2016]. Behavioral experiments were run using a double blinded method and a procedure described in detail in our previous work [Gainutdinova et al., 2004; Deryabina et al., 2020].

Results were processed statistically and presented as mean ± SEM. Significant differences were identified using Student’s *t* test and the Mann–Whitney U test. Computations were run in SigmaStat32. Differences were taken as significant at $p < 0.05$.

Results. Testing of post-training defensive ommatophore withdrawal reactions in response to tactile stimulation demonstrated a significant increase in defensive reactions when terrestrial snails were positioned on the ball, both after training using the protocol with stronger reinforcement (Fig. 2, $p < 0.001$) and after training using the protocol with weaker reinforcement (Fig. 3, $p < 0.01$). This result shows that the snails acquired the conditioned reflex to context – significant differences were seen on testing the same experimental group in different contexts (on a plane, i.e., a neutral context, and on the ball, i.e., in the context in which training had taken place). Our previous studies showed that placing animals on a ball, accompanied by presentation of electrical or tactical stimuli, including testing, was not accompanied by reconsolidation [Gainutdinova et al., 2005; Deryabina et al., 2020]. The contextual reflex persisted after reminding with subsequent injection of physiological saline for 12 days (Figs. 2 and 3); this result is analogous to our previous

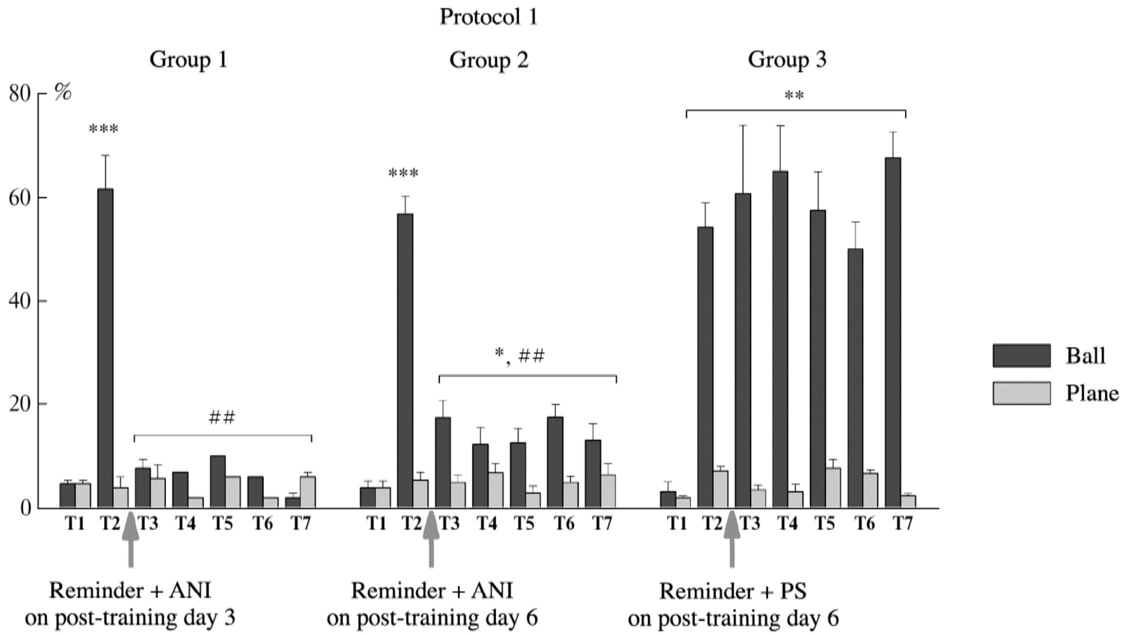

Fig. 2. Levels of defensive reactions (amplitudes of ommatophore withdrawal reactions) in snails in two contexts (on the ball and on a plane) for snails trained using protocol 1 "5 stimuli in 5 days" with ANI injections after the "Reminder" session 3 ($n = 13$) and 6 ($n = 10$) days after training with injection of PS after the "Reminder" session 6 ($n = 10$) days after training. T1 – testing before starting training, T2 – testing one day after training, T3–T7 – testing of animals after substance injections and reminding on days 8–12 after training. Arrows show the moment of reminding and injection of ANI or PS. *Significant differences from T1, $p < 0.05$. **Significant differences from T1, $p < 0.01$. ***Significant differences from T1, $p < 0.001$. ##Significant differences from T2, $p < 0.01$.

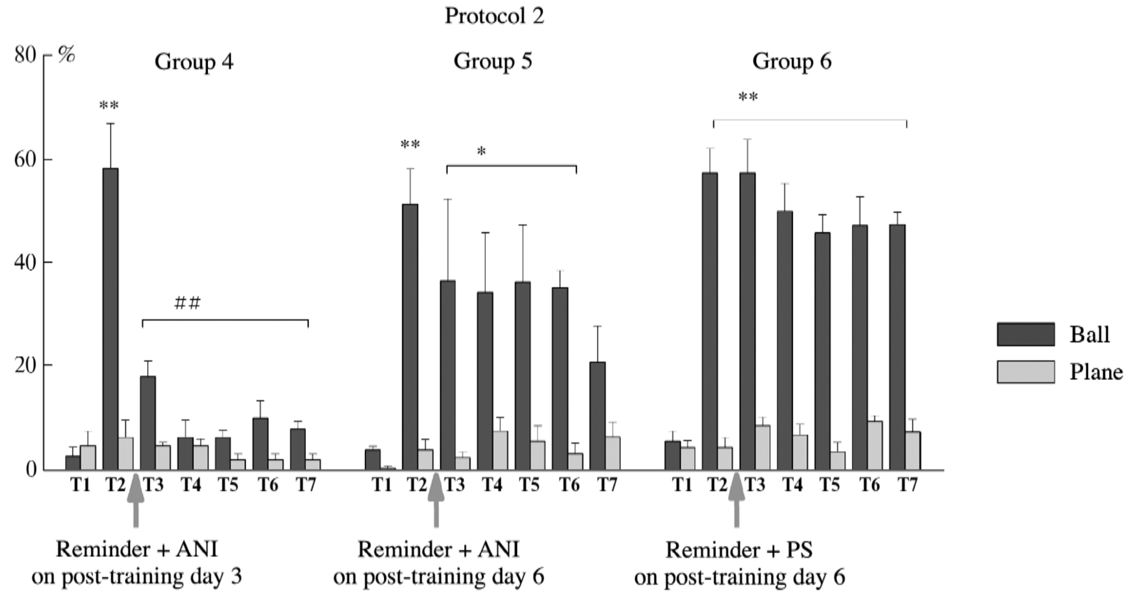

Fig. 3. Levels of defensive reactions (amplitudes of ommatophore withdrawal reactions) in snails in two contexts (on the ball and on a plane) for snails trained using protocol 2 "3 stimuli in 5 days" with ANI injections after the "Reminder" session 3 ($n = 10$) and 6 ($n = 10$) days after training with injection of PS after the "Reminder" session 6 ($n = 10$) days after training. T1 – testing before starting training, T2 – testing one day after training, T3–T7 – testing of animals after substance injections and reminding on days 8–12 after training. Arrows show the moment of reminding and injection of ANI or PS. *Significant differences from T1, $p < 0.05$. *significant differences from T1, $p < 0.05$. **Significant differences from T1, $p < 0.01$. ##Significant differences from T2, $p < 0.01$.

results for conditioned reflex food aversion [Gainutdinova et al., 2003].

The next stage consisted of presentation of the reminder of the training context at different times: on post-training day 3 and post-training day 6 with subsequent injection of ANI or physiological saline. Snails given injections of physiological saline after reminding demonstrated retention of the memory (the level of the defensive reaction) after training using both protocols (Figs. 2 and 3). This results demonstrates on the one hand the prolonged retention of the training result and, on the other, that injection of physiological saline after reminding of the conditioned signal (context) did not prevent reconsolidation. Testing five days after reminding and injection of ANI given on post-training day 3 showed a significant – mean six-fold – decrease in defensive reactions on testing on the ball for snails trained using both protocols (n = 13 and n = 10) (Figs. 2 and 3). This result demonstrates complete and significant loss of the acquired contextual memory in both experimental series.

Testing five days after reminding and ANI injection given on post-training day 6 yielded different results. In this case, snails trained using the protocol with stronger reinforcement (n = 10) also showed a significant – by a mean factor of 3–4 – decrease in defensive reactions on testing on the ball (Fig. 2). At the same time, animals trained using the protocol with weaker reinforcement (n = 10) showed no significant reduction in defensive reactions on testing on the ball (Fig. 3). The level of defensive reactions in these snails was significantly different from the initial level of defensive reactions on the ball before training.

Thus, these studies show that snails trained using the protocol with stronger reinforcement led to retention of the ability to reconsolidate contextual memory for longer periods than when the protocol with weaker reinforcement was used.

Discussion. It has now been established that reactivation of a stored memory in the brain as a result of reminding can make it temporarily labile [Nader and Hardt, 2009; Balaban et al., 2014; Zhang et al., 2018]. As a result, the time required for recovery of the memory can differ using different training types and protocols [Suzuki et al., 2004; Alberini, 2011; Lee et al., 2011]. Experiments have shown that reactivation and reconsolidation are not synonymous, i.e., processes triggered after reminding can occur differently depending on the specific experimental conditions [Elsey and Kindt, 2015]. Reminding can lead to processes resulting in memory stabilization (reconsolidation) or extinction [Lattal and Wood, 2013; Zuzina and Balaban, 2015]. Changes in the extent of memory are linked with changes in the brain, which are correlates of long-term memory. A number of authors have suggested that this search-driven plasticity is ideally suitable for updating memory with new information [Lee et al., 2017; Barense and Sinclair, 2019]. Memories are easily distorted. This raises the question: in which conditions can this occur?

Studies of reconsolidation have used partial reminders with the aim of detecting prediction errors and updating and fixing memories. Evidence has been reported showing that partial reminding controls memory updating in humans, from classical conditioning to naturalistic episodes [Barense and Sinclair, 2019]. This is consistent with the view that memory reconsolidation and memory updating are two sides of the same coin [Bermúdez-Rattoni and McGaugh, 2017]. It was suggested that reconsolidation is consolidation without the endless process of schema modification [McKenzie and Eichenbaum, 2011].

The parameters of the processes leading to memory reconsolidation have received insufficient study and are the subject of intense research. In particular, memory extraction is regarded as a necessary condition for initiation of repeat consolidation. This suggestion makes sense, as only relevant signals will evoke reconsolidation of a particular memory [Rodriguez-Ortiz and Bermúdez-Rattoni, 2017]. Thus, the possibility that an initially acquired operant skill (the “old” memory) will be degraded after reactivation, by mechanisms including the formation of a “new” memory, has been demonstrated [Zaichenko et al., 2018, 2020a]. Two hypotheses have been proposed to explain the function of reconsolidation, these not being mutually exclusive. One holds that memory becomes labile because repeat consolidation involves integration of new information onto the background of the past, allowing the memory to be updated. The other suggests that memory is stronger after recovery and more resistant to failure [Sara, 2000, Dudai, 2004; Alberini, 2011; Bavassi et al., 2020].

We also tried to approach the question of which memories – resulting from different types of training – will be labile and which will be permanent, i.e., finally consolidated. To answer these two questions, we selected a model of training in which the conditioned stimulus is a reminder of the context [Gainutdinova et al., 2004; Balaban et al., 2014, 2016; Deryabina et al., 2020]. Models in which the context is used as the conditioned signal in training the animals and for subsequent reminding are used in many experiments, and in some cases the initial memorization of the context and its subsequent association with the unconditioned stimulus can be spread over longer intervals of time [Vorob’eva et al., 2016]. We have shown that training using a lower intensity narrows the window of memory lability in which the reconsolidation process can be initiated, the memory entering the stable consolidated state earlier. One explanation for this phenomenon may be the suggestion advanced by Alberini [2011] that when memory reaches an asymptotic level it becomes resistant to degradation in postreactivation amnesia. It is possible that after lower-intensity training the memory reaches this level more quickly and is therefore less subject to reconsolidation. Another cause may be a difference in the rate of amnesia after reactivation, and the effects of protein synthesis blockade with anisomycin may differ in different experiments depending on the internal physiological state [Lee et al., 2017]. Tools for acting on reconsolidation processes include actions on transmitters: serotonin, nitric oxide, and glutamate [Balaban et al., 2014, 2016; Bal et al., 2017; Nikitin et al., 2018; Palikhova, 2020; Deryabina et al., 2020]. These tools also include actions on the intracellular signal system such as propranolol [Huang et al., 2017]. Comparison of our results with our previous data on the effects of blockade of serotonin synthesis on memory reconsolidation [Deryabina et al., 2018, 2020] and data obtained in Balaban's laboratory on the effects of a neurotoxic serotonin analog and its precursor on memory reconsolidation [Balaban et al., 2016; Zuzina et al., 2019] led to the suggestion that there are different neural pathways for consolidation and reconsolidation processes. This suggestion is also supported by results reported by Bavassi et al. [2020]. Using functional magnetic resonance imaging (fMRI), they studied activity in defined areas activated during seeking and analyzed the functional connectivity of different parts of the brain. They found that memory after reconsolidation was stronger than memory without reconsolidation and suggested that the process of reconsolidation allows more effective (complete) recruitment of a local network, with better exchange of information as compared with memories not subjected to this action [Bavassi et al., 2020]. Application of fMRI methods have also led other authors to the suggestion that there are different pathways for consolidation and reconsolidation processes [Liu et al., 2016].

Reminding was suggested not to be a unitary process but to consist of two different components, one leading to expression of a memory and the other to reconsolidation [Rodriguez-Ortiz and Bermúdez-Rattoni et al., 2017]. Existing data emphasize that not only the processes underlying memory formation and extinction, but also the processes of memory reconsolidation, are dynamic [Suzuki et al., 2004; Alberini, 2011]. The present works shows that the possibility of triggering reconsolidation of contextual memory depends on the period between training and reminding, as well as the intensity of the training.

The relevance of our data is consistent with the significant number of studies of the mechanisms and temporal dynamics of reconsolidation and the wide discussion of this problem. Our results, along with published data [Sorg, 2012; Lattal and Wood, 2013], led us to the conclusion that the possibility of triggering reconsolidation of long-term memory depends on training intensity or "the strength of the memory" [Suzuki et al., 2004; Alberini, 2011]. Thus, reconsolidation of contextual memory in terrestrial snails has been shown to depend on training intensity, which depends on the choice of training protocol with different numbers of unconditioned stimuli.

Conclusions. The possibility of triggering reconsolidation of contextual memory depends on the time passing between training and reminding and on the intensity of the training used. Snails trained using a protocol with stronger reinforcement were found to retain the possibility of reconsolidation of contextual memory for a longer period than those trained using a protocol with weaker reinforcement.

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