

Spatial Exploration Is Required for the Formation of Contextual Fear Memory

Thomas J. McHugh and Susumu Tonegawa

The Picower Institute for Learning and Memory, RIKEN–MIT Neuroscience Research Center; Howard Hughes Medical Institute; and Massachusetts Institute of Technology

The acquisition of contextual fear in mice is thought to require the formation of a conjunctive representation of the conditioning chamber. This can be achieved during a minimum of 20 to 40 s of exploration immediately prior to the shock or during preexposure to the context at an earlier time. An animal receiving less time in the chamber will show reduced freezing 24 hr later, a condition termed the *immediate shock deficit* (ISD). In this study, the authors have attempted to uncouple the formation of a contextual representation, based on the conjunction of a defined set of cues, from the establishment of a spatial representation, which requires active exploration, by inserting a transparent plastic partition in the center of the chamber. Taking advantage of the ISD and the context preexposure effect, the authors found that animals preexposed to one side of the chamber on Day 1, but shocked on the other side on Day 2, show significantly less fear than animals exposed to and shocked on the same side. Our results indicate that spatial exploration is necessary for mice to benefit from contextual preexposure.

Keywords: fear conditioning, hippocampus, memory, spatial learning, contextual learning

In rodents, learning can be studied using the conditioned fear paradigm, a persistent form of simple associative learning between an aversive foot shock (unconditioned stimulus) and an initially neutral stimulus (conditioned stimulus) (Fanselow, 1984; Rescorla, 1968). Following training, the presentation of the conditioned stimulus elicits the animals' characteristic defensive response, freezing. By employing a multimodal conditioned stimulus made up of a variety of discrete cues, such as the context in which the shocks are delivered, the task can be made dependent on the function of the hippocampal formation (context conditioning; Fanselow, 2000; Kim & Fanselow, 1992; Phillips & LeDoux, 1992; Sutherland, McDonald, Hill, & Rudy, 1989). Given the ability of the hippocampus to rapidly and reliably encode space, it has been hypothesized that the contribution of the structure to this task is in the formation of a representation of the conditioning chamber (Lee & Kesner, 2004; Rudy, Huff, & Matus-Amat, 2004; Sanders, Wiltgen, & Fanselow, 2003). At the level of the hippocampal neurons, this may involve the formation of context-specific place cells in CA1, CA3, and the DG that would then provide the spatial information with which the shock will be associated. In fact, in vivo recordings of place cells in area CA1 of the hippocampus conducted in a chamber before and after condi-

tioning demonstrate that conditioning itself can partially alter the network representation of the environment, revealing an interaction between the spatial code and the learning of the task (Moita, Rosis, Zhou, LeDoux, & Blair, 2003, 2004).

Although most researchers in the field use the term *place cell* when describing the principle excitatory cells of the hippocampus, particularly in area CA1, numerous experiments have demonstrated that the responses of the CA1 pyramidal neurons can be seen to depend not only on place but also on nonspatial attributes such as the shape, color, size, and smell of an environment (Anderson & Jeffery, 2003; Eichenbaum, Dudchenko, Wood, Shapiro, & Tanila, 1999; Jeffery & Anderson, 2003; O'Keefe, 1999; Wiener & Korshunov, 1995; Wills, Lever, Cacucci, Burgess, & O'Keefe, 2005; Wood, Dudchenko, Robitsek, & Eichenbaum, 2000). These findings have been used to argue that the cells of the hippocampus encode more than space and also represent other features of the context. One limitation on the interpretation of those data, however, is that "space" is always present and no single feature can be divorced from the place the animal occupies when perceiving it. Likewise, the behavioral studies using the contextual fear paradigm have defined a context as a unitary representation that encodes the conjunction of the cues present (odor, lighting, shape, and floor texture of the chamber, etc.); however, these experiments do not distinguish the conjunction of cues from the exploration involved in the formation of the representation. Although place-specific fields in the hippocampus form rapidly as an animal explores a novel environment (Wilson & McNaughton, 1993), the formation of fields requires active sampling, suggesting that places that can be seen, but not accessed, remain unrepresented in the hippocampus.

The hippocampus-dependent contextual fear conditioning task has several intriguing properties that make it a useful tool in assessing an animal's ability to form and recall contextual memory. First, if the foot shock is applied immediately after the

Thomas J. McHugh and Susumu Tonegawa, The Picower Institute for Learning and Memory; RIKEN–MIT Neuroscience Research Center; Howard Hughes Medical Institute; and Departments of Brain and Cognitive Sciences and Biology, Massachusetts Institute of Technology.

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Correspondence concerning this article should be addressed to Susumu Tonegawa, MIT / The Picower Institute, 77 Massachusetts Avenue, Building 46 Room 5295, Cambridge, MA 02139-4307. E-mail: tonegawa@mit.edu

delivery of the animal to the context, conditioning is ineffective (termed *immediate shock deficit*, or ISD); a minimum of a 20- to 40-s placement-to-shock interval (PSI) in the context is needed for memory formation (Fanselow, 1986, 1990; Frankland et al., 2004). This finding has led Fanselow, Rudy, and others to suggest that the ISD is a result of the minimum time required for the hippocampus to form a conjunctive representation of the cues that define the conditioning context (Fanselow, 2000; Rudy & O'Reilly, 1999). Although this associative representation can be established quickly, it is not immediate, and as a result, the total amount of exposure to a novel context prior to the delivery of the foot shock is a critical factor in determining the amount of contextual conditioning that mice exhibit 24 hr after training (Wiltgen, Sanders, Behne, & Fanselow, 2001).

A second property of the fear conditioning task is that the ISD can be rescued by preexposure to the conditioning context. Allowing the animal to explore the chamber the day prior to one-trial conditioning facilitates fear learning at short PSIs (Fanselow, 1986, 1990; Kiyama et al., 1998; Wiltgen et al., 2001). This presumably results from the prior storage of a representation of the context and its recall during the short PSI. This hypothesis has been widely supported, and through a series of elegant experiments the context preexposure phenomena have been demonstrated to involve the formation of a conjunctive, hippocampal-dependent memory that can support the process of pattern completion (Rudy & O'Reilly, 2001).

In this study, we utilized the ISD and the context preexposure effect, as well as a small modification of the conditioning chamber, to ask if context can be dissociated from place. To this end we inserted a transparent plastic partition in the center of the conditioning chamber, dividing it into left and right halves, as a means to uncouple a set of cues that define a context from the physical space in which they are experienced. In this preparation the cues available on either side of the barrier are identical, the only distinction between the two sides of the chamber being the animal's physical presence. Using this approach we have asked if spatial exploration is required for the formation of a contextual representation that can support fear conditioning.

Method

Subjects

Ninety-eight experimentally naive, male C57BL/6 mice were obtained from Taconic Farms at 8 weeks of age and housed in the vivarium in our facility for at least 2 weeks prior to the experiments. Animals were housed in groups of two or four and maintained on a 12-hr light–dark cycle with ad-lib access to water and food. All experiments occurred during the light portion of the circadian cycle. Animals were handled for 3 days prior to the experiment to acclimate them to the experimenter and stress of transport.

Conditioning Apparatus

Preexposure, shocking, and testing were all conducted in a dedicated behavioral training room located in the animal facility. The room was brightly lit and contained four conditioning chambers. The chambers, consisting of an acrylic plastic front and back

and aluminum walls on each side, measured 30 × 25 × 21 cm (Med Associates ENV–008, Georgia, VT). The floor of the chamber consisted of 36 stainless steel rods of 3.2 mm diameter and spaced 7.9 mm apart and was connected via a cable harness to a shock generator (Med Associates ENV–414, Georgia, VT). The chambers were cleaned between animals with 70% ethanol, and a solution of 1% acetic acid was placed beneath the chambers during the experiment to provide an olfactory cue. During sessions that required a divided chamber, a single clear acrylic plastic segment was placed between the 16th and 17th bars of the grid floor and spanned the entire distance from the floor to the ceiling of the chamber.

Procedure

Mice were randomly assigned to one of four conditioning groups: *all*, *same*, *opposite*, or *none*. Throughout the 3 days of the experiment, all of the mice were transported from the behavioral colony to a holding room adjacent to the behavioral suite containing the fear conditioning chambers, and they sat undisturbed in the holding room for 30 min prior to the experiment. Mice were transported between the holding room and the conditioning room in their home cages. On Day 1 animals in the *all* group were placed in the conditioning chambers and allowed to freely explore them for 5 min. At the conclusion of the session they were returned to their home cages and transported back to the holding room. Prior to preexposing the mice in the *same* and *opposite* groups, we placed a transparent acrylic plastic divider in the center of the grid floor, dividing the chamber evenly into a left and right half. Animals in these groups were pseudorandomly assigned to either the left or right side of the chamber in a balanced manner and placed on that side for 5 min. Following this exploration, the mice were returned to their home cage. Mice in the fourth group, *none*, simply remained in their home cages in the holding room on Day 1 and did not enter the conditioning room.

On Day 2 the animals were transported to the holding room. The chamber was again divided in two by the transparent barrier, this time for all four groups. Animals were transported in their home cages to the conditioning room and placed in either the left or right half of the chamber. Mice in the *all* and *none* groups were pseudorandomly assigned to one side or the other, with equal numbers being shocked on both sides. Mice in the *same* group were returned to the side experienced on Day 1, whereas mice in the *opposite* group were placed on the side opposite the one they were preexposed to. All animals received a foot shock (0.75mA, 2 s) 10 s after placement in the chamber. Following the shock, they remained in the conditioning context for 30 s before being removed and placed back in the home cage. On Day 3 the mice were returned to the undivided context for a 5-min test. During all sessions the animals' activity in the chamber was recorded using FreezeFrame software (Actimetrics, Wilmette, IL). Freezing behavior was assessed from the video image of the mice using FreezeView software, with a minimum bout time of 2 s (Actimetrics).

Results

The mice were divided into four groups according to preexposure and shock protocol (see Figure 1). The first group was

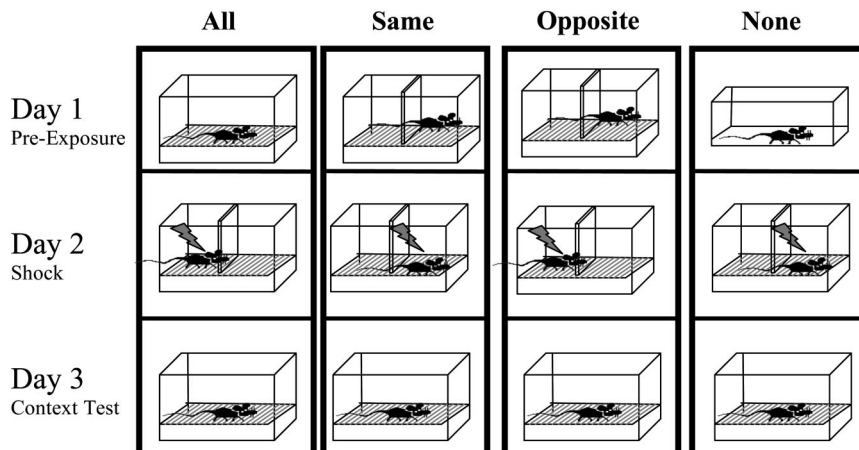


Figure 1. The mice were divided into four groups according to preexposure and shock protocol. Preexposed mice received 5 min in the chamber on Day 1. All mice received a foot shock (0.75mA, 2 s) 10 s after being placed in the chamber on Day 2. On Day 3 the mice were returned to the chamber for a 5-min contextual memory test.

preexposed to the entire chamber then returned the next day to either the left or right half of the divided chamber, determined in a pseudorandom manner, and shocked at a short PSI (see *all* condition in Figure 1). The second group was preexposed to one half of the divided chamber, then 24 hr subsequent shocked on the same side (see *same* condition). The third group was exposed to one side of the divided chamber and the next day shocked on the opposite, unexplored side (see *opposite* condition). Finally, the fourth group received no preexposure, remaining in their home cages during the first day of training. On Day 2 they were returned to either the left or right half of the divided chamber, determined in a pseudorandom manner, and shocked at a short PSI (see *none* condition). Twenty-four hours following the foot shock, the mice were returned to the undivided conditioning chamber and freezing was assessed using an automated method (FreezeView, Actimetrics).

As shown in Figure 2, animals preexposed to the full chamber (*all*), as well as animals receiving the shock on the same side of the chamber they were preexposed to (*same*), demonstrated elevated freezing compared with both the mice shocked on the side opposite their preexposure (*opposite*) and mice receiving no preexposure (*none*). A one-way analysis of variance shows a significant difference between the groups, $F(3, 94) = 5.603$, $p < .002$. Newman-Keuls Multiple Comparison tests were conducted to detect differences between the groups. There was a significant effect of the location of the shock on mice preexposed to only half of the chamber, with mice shocked on the same side ($n = 22$; $41.6 \pm 5.1\%$) freezing significantly more than mice shocked on the opposite side ($n = 26$; $25.4 \pm 3.5\%$, $p < .05$). Mice in the *same* group also showed significantly more freezing than mice receiving no preexposure (*none*; $n = 28$; $22.7 \pm 3.1\%$, $p < .01$). In addition, mice in the *all* group ($n = 22$; $38.7 \pm 4.5\%$) demonstrated significantly more freezing than mice in both the *opposite* ($p < .05$) and *none* ($p < .05$) groups.

Discussion

At the level of *in vivo* physiology, the neurons of the hippocampus are best characterized as “place” cells. This term has been used to define how the cells of CA1, CA3, and the DG rapidly develop stable spatial-receptive fields as the animal explores a novel environment (Muller, Kubie, & Ranck, 1987; O’Keefe & Black, 1977; Rose, Diamond, & Lynch, 1983; Wilson & McNaughton, 1993). Although the responses of the CA1 pyramidal neurons can be seen to depend not only on place but also on nonspatial attributes such as the shape, color, size, and smell of an environment, it is impossible to uncouple physical place from these other variables (Anderson & Jeffery, 2003; Eichenbaum et al., 1999; Jeffery & Anderson, 2003; Wiener & Korshunov, 1995; Wills et al., 2005; Wood et al., 2000). This limitation of the physiological observa-

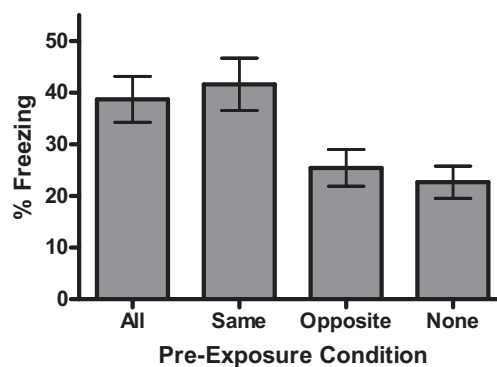


Figure 2. Mean (\pm SEM) percentage of freezing from a 5-min context test conducted on Day 3. Mice were either preexposed to the entire context (*all*), to just the side of the chamber they were shocked on (*same*), or to just the side opposite to the side where they received the shock (*opposite*) or else given no preexposure (*none*). Mice exposed and shocked on the same side demonstrate significantly more freezing than mice either receiving no preexposure or being shocked on the side they had not experienced.

tion has encouraged us to address the question of the equivalence of context and place using the tools of fear conditioning.

The role of the hippocampus in contextual conditioning has been closely examined, and although there still exist some conflicting data, most agree that, when intact, the hippocampus is involved in the acquisition and recall of contextual fear conditioning (Anagnostaras, Gale, & Fanselow, 2001; Bast, Zhang, & Feldon, 2001; Kim & Fanselow, 1992; Phillips & LeDoux, 1992; Wiltgen, Sanders, Anagnostaras, Sage, & Fanselow, 2006). Several studies have provided evidence that the role of the structure is to form a conjunctive, polymodal representation of the cues that define the training environment and can be associated with the unconditioned stimulus (Fanselow, DeCola, & Young, 1993; Maren, Aharonov, & Fanselow, 1997; Rudy & Sutherland, 1995). However, this interpretation makes the assumption that embedded in this contextual representation is the representation of the physical space of the chamber. In the experiment described here we were able to uncouple the formation of a contextual representation, as defined by the collection of cues present, from the formation of a direct spatial representation. The key to the experiment is the fact that the formation of place cells, and the resulting spatial map, requires active exploration. By placing an acrylic plastic divider between the central bars of the grid floor we were able to divide the conditioning chamber evenly into a left and right half. The two halves of the conditioning chamber divided by the acrylic plastic panel could be defined by the identical set of cues, even though the two halves differed in their physical accessibility to the animal.

Our data show that animals preexposed to the full cue set—but denied, during this preexposure period, the opportunity to physically explore the space in which they were subsequently conditioned—experienced decreased levels of freezing 24 hr later, as compared with animals that were allowed to explore the entire space during the preexposure period. Furthermore, the freezing deficit displayed by the animals without prior access to the space in which the shock was delivered was as pronounced as that in animals receiving no preexposure to the context. This finding argues not only that spatial experience is required for the formation of contextual fear conditioning but that preexposure to the full cue set, in the absence of spatial experience, provides little benefit to the animal. Previously, using the Morris Water Maze paradigm (Morris, 1984; Sutherland, Chew, Baker, & Linggard, 1987) reported that visual access to space, in the absence of exploration, did not provide the spatial information necessary for efficient navigation. Although we employed only transparent partitions in our study to ensure full access to the available cues, in the water maze these authors found transparent barriers to be as effective as opaque barriers in causing spatial learning deficits. Taken together these results suggest that in both tasks experiencing space is crucial in the formation of a usable hippocampal representation.

The work detailed here can be viewed as an extension of the work of Rudy and O'Reilly (1999) supporting the conjunctive representation view of hippocampal function. These authors reported that, in contrast to exposure to the entire context, preexposure of rats to individual features of a conditioning context did not facilitate subsequent fear learning. On the basis of these data they concluded that preexposure to the conjunction of the cues that define a context is required for the formation of a representation robust enough to support contextual fear conditioning. The results of our experiments can be used to extend their notion to include,

in addition to preexposure to the full conjunctive cues set, the requirement of spatial sampling and the resulting formation of place cells to support contextual conditioning.

Although there is a great deal of agreement between the two sets of results, Rudy and O'Reilly (1999) reported a finding that appears at odds with ours. They demonstrated that preexposure to a context very similar, but not identical, to the conditioning context does facilitate later learning. They suggested that this benefit is a result of "context generalization." In addition, in a later study they provided evidence that the conjunctive contextual representation formed during the preexposure session can support the process of pattern completion, that is, the recall of the stored representation based on exposure to a partial cue set (Rudy, Barrientos, & O'Reilly, 2002; Rudy et al., 2004; Rudy & O'Reilly, 2001). From these data it can be suggested that in our experiment animals in the *opposite* group should demonstrate a conditioned fear response based on the same mechanisms of pattern completion. We believe that the failure of these animals to demonstrate fear based on the recall of the preexposed context is a result of their ability to recognize the shock context as novel and distinct from the preexposure context. The process of pattern completion works in constant opposition to a second hippocampal computation: the process of pattern separation. Previous experience has allowed the mice not only to form a representation of the portion of the chamber they explored but to recognize the unexplored region as novel when returned to the context. This process would leave them without a sufficient "online" contextual representation in the hippocampus at the time of shock delivery to form a contextual fear memory. This result suggests that future experiments using this protocol to better understand the interplay between these opposing phenomena would prove valuable.

In conclusion, these experiments provide the first evidence that exploratory behavior is required for the formation of a contextual representation adequate to support fear conditioning. It has been suggested that exploration is required for the formation of contextual representation; however, the divided chamber approach allows the explicit dissociation of space from context (Wilson & McNaughton, 1993). It has been almost 30 years since O'Keefe and Nadel first proposed the cognitive map hypothesis of hippocampal function (O'Keefe & Nadel, 1978). Our results support this idea and suggest that although nonspatial factors can and do influence the activity of the neurons of the hippocampus, it is only when active exploration triggers the formation of place-responsive fields that a hippocampal representation of a context is formed.

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