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Michael D. Greenberg
University of Vermont

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Exercise Does Not Affect Context-Dependent Episodic Memory

Michael Greenberg

University of Vermont

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THE EFFECT OF CONTEXT ON EPISODIC MEMORY

Abstract

Memory has been shown to be strongly associated with the context in which it is encoded, suggesting that the context is central to the memory itself. However, the effect of exercise on context dependent object recognition is not fully known. We then set out to investigate the effect of exercise on context dependent object recognition. In Experiment 1 we showed that a context change reduced object recognition memory but did not significantly disrupt object recognition. In Experiment 2 we assessed whether exercise would mitigate the effect of context change. We showed that exercise does not significantly improve object recognition nor did it mitigate the effect of context change on object recognition. These results suggest that a discrete context change can significantly disrupt retrieval of object recognition memory. Our results do not agree with the body of literature related to this topic, so further inquiry into these effects should be undertaken to confirm or refute the impact of exercise on contextual object recognition.

Introduction

Memory is a long-studied concept in humans and animals with the breadth of knowledge increasing each year. Studying memory allows us to get a glimpse into the human experience, the foundational way in which we define ourselves and our existence. Expanding our understanding of how memory works, or what can improve or hinder its function is a worthwhile endeavor to better the human condition.

Human memory is varied and there are several types of memories which are each specific to different types of tasks and functions. Declarative memory, also known as explicit memory, is a type of memory defined as recalling facts or events being consciously recalled or remembered. Implicit memory is a subconscious type of memory that involves priming actions or procedural

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memories. You learn to ride a bicycle through procedural memories, but you can recall the brand of bicycle on which you first learned due to declarative memory. However, each type of memory is not processed the same way in the brain.

Since the early days of neuroscience, the research regarding memory has both expanded in quantity but has focused in on specific structures and circuits. The hippocampus is largely responsible for the acquisition of new declarative memory, first famously elucidated using the epilepsy patient, H.M. (Penfield & Milner, 1958). H.M. underwent surgery to treat his epilepsy which removed portions of his hippocampus. Following the surgery, H.M. could not form new memories; he was continuously trapped in his life before his surgery. Each day he would reintroduce himself to his doctors and the people investigating his case. The work done with H.M. was also the first to show that there are different types of memories, and that memories are distributed widely throughout the brain. Since this time, the hippocampus and the circuits within it have been mapped extensively. The CA3 and CA1 circuits and the function of the NMDA receptor have been shown to be essential in forming new memories (Cherubini & Miles, 2015; Tsien, Huerta, & Tonegawa, 1996). The way in which memories are acquired in the hippocampus can be dependent on different factors such as odor cues, context, or levels of anxiety.

Many aspects of a situation are encoded in memory including odor cues or visual stimuli. Declarative memory acquisition has been shown to be context dependent: the surrounding environment of the subject when the memory is created is central to the ability to recall the memory. This phenomenon has been studied both in humans and in animal models. In 1975, Godden & Baddeley showed that lists of words taught to divers underwater were better recalled underwater than when they were on the beach (Godden & Baddeley, 1975). Smith et al., showed

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that memories were better recalled in the room where they were learned and were less recalled in a different room (Smith & Vela, 2001). The odors of an environment can affect recall; different smells in the same environment can disrupt memory or the same smells can improve recall (Herz, 1997). Even something as small as chewing gum has been shown to impact memory recall (Baker, Bezance, Zellaby, & Aggleton, 2004). These results suggest that memory is context dependent. Studying this context dependence is critical to understanding memory.

Memory in rodents is also context dependent. The paradigm of contextual fear conditioning was first established in 1969 (Blanchard & Blanchard, 1969). They found that they could condition rats to exhibit freezing behavior (crouching and akinesia) in response to the context which was paired with footshock, suggesting the context could be encoded as part of the memory. In 1980, Fanselow repeated a similar experiment and showed similar freezing responses which persisted 24 hours after the original pairing of the stimuli, confirming Blanchard's findings (Fanselow, 1980). More recently, research has shown that the hippocampus is centrally involved in the acquisition of the contextual fear conditioning (Maren, Anagnostaras, & Fanselow, 1998). The role in which the hippocampus plays in contextual fear conditioning in mice and possible parallels in humans has also been reviewed (Rudy, Huff & Matus-Amat, 2004).

Context also plays an important role in the modulation of memory. Bouton (2002) and colleagues have demonstrated a phenomenon known as renewal. Renewal is when an animal is given fear conditioning and then extinction training in a discrete context. When the animal is moved to a new context, the fear is recovered, as if the extinction had never occurred. These data suggest that extinction is context dependent (Bouton, 2002). Perhaps this phenomenon can be extended to context generally, not just when conditioning takes place. Perhaps context is

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important to any memory formation, and a change in context would be significant enough to disrupt that memory. The effect that context has on memory may be limited to certain types of memory, object recognition, perhaps. The influence of outside stimulus is not limited to just context. Exercise and memory have a tightly interwoven relationship.

The effect that exercise has on the human body has been a long researched topic. Aerobic exercise is especially healthy for routine maintenance of the body, and has been shown to have numerous beneficial impacts on human cognition. Exercise has been shown to improve memory in both human and animal subjects (Samorajski, Delaney, & Durham, 1985; for a review see: Smith, Blumenthal, Benson, Hoffman, Cooper, Strauman et al., 2010). Older adults who engage in more regular aerobic exercise demonstrate increased cognitive abilities relative to their more sedentary peers (Hillman, Belopolsky, Snook, Kramer, & McAuley, 2004).

Exercise has also shown to improve memory in mice. Mice who had an enriched environment, including voluntary exercise, showed stronger object recognition than sedentary mice (Bechara & Kelly, 2013). Further research by Griffin et al., found that mice given voluntary exercise had improved spatial and nonspatial memory that coincided with increased BDNF in the hippocampus, dentate gyrus, and perirhinal cortex (Griffin, Bechara, Birch, & Kelly, 2009). Because exercise can have such a significant impact on memory, perhaps it can influence its dependency on context. Falls and colleagues found that exercise can improve context dependent memory with mice exhibiting enhanced responses to conditioned fear (Falls et al., 2010). Their data suggest that exercise can improve context dependent fear conditioning. It is not known whether exercise affects the context dependence of episodic memory. Episodic memory is so central to our everyday function and is often implicated in cognitive decline. As memory has been shown to be central to the context surrounding the memory, perhaps exercise could impact

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that dependency and reduce its relevance. This could present as exercising mice showing less context dependency. This is a result that could be preferable when unpleasant stimuli are paired with a context. However, the connection between exercise and context dependent memory in mice is not well studied. Testing the effect of exercise on contextual object recognition in mice will therefore help bridge the gap between these two subjects, if they exist.

In Experiment 1 we investigated the effect a changing context would have on object recognition in mice. Mice were trained in one specific context and tested in either the same or a different context. The goal of the experiment is to establish the context specificity of object recognition. In Experiment 2 we investigated whether two weeks of voluntary wheel running in mice would improve object recognition and mitigate the effect of a context shift.

The mice were trained in an open field with two novel objects placed diagonally from each other. Novel object recognition was tested 24 hours later when the mice were placed in either the same or a different context with a novel and a familiar object. Object recognition was defined as the mice spending more time investigating a novel object. We hypothesized that the mice would spend more time investigating the novel object in the same context but not in a different context. In Experiment 2, we hypothesized that the exercising mice would show better object recognition in a novel context.

Method

Subjects

Forty-eight 6-week old C57/BL6J mice were purchased from Jackson labs. Mice were housed in a conventional animal facility with a 12-hr light cycle (lights on at 0700) in groups of 4 in standard acrylic cages with food and water available ad libitum. All procedures were approved by the University of Vermont IACUC.

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Apparatus

The mice were trained and tested in either of two acrylic boxes measuring 9 in by 34 in by 18 in located in a dimly lit laboratory room. Context A consisted of a solid floor with two small circles in either corner along with an odor cue of Vick's Vapor Rub. Context B had the same dimensions as Context A, but had wire mesh on the floor, brightly colored stripes on the wall, and dilute anise as the odor cue.

Three objects were used for object recognition training and testing. Objects A, B, and C, consisted of identical plastic vials measuring 2 cm in diameter and 8 cm tall filled with either metal screws, small bits of colored gloves, or pink powder. The objects were placed in the circles in opposing corners of the boxes with a circle drawn around them such that the object was always 2 cm away from the circle. Objects A and B were the novel objects during training. Object C was the novel object during testing and object A was the familiar object during testing.

A Go-Pro camera (HERO 7) located approximately 2 ft above the box was used to record interactions with the objects. All trials were recorded in dim lighting.

For Experiment 2, a running wheel (Superpet mini run-a-around, measuring 11.4 cm in diameter) was fixed to the cage top of the home cage. Identical wheels were locked with zip-ties in the sedentary mice cages.

Procedure

Experiment 1

Training

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Mice were transported from the colony and placed into either Context A or Context B in a counterbalanced fashion. Mice were allowed to explore for 5 min. For training, Objects A and B were located in two adjacent corners of the box diagonally from each other.

Testing

Twenty-four hours later, the mice were tested for novel object recognition in either the same or the different context. Both contexts, A and B, had one novel object (object C), and one familiar object (object A). Two groups of mice were tested: one group was tested in the same context in which they were trained and the second group was tested in a different context.

Data analysis

Video files were examined by the experimenter and the time spent exploring each object was measured. Each mouse was considered to be exploring if its front paws were within 2 cm of the object and within the circle. Novel object recognition was defined as greater exploration time with the object the novel than the familiar object.

The training and testing data were analyzed with a repeated measures ANOVA with object (novel, familiar) as a within-subjects factor and testing context (same, different) as a between-subjects factor. Simple effects were examined with t-tests.

Experiment 2

The procedure for Experiment 2 was identical to Experiment 1 except for the addition of Exercise and Sedentary groups. Mice in the exercising groups were allowed free access to a functioning running wheel for two weeks prior to object recognition training. Mice had wheel access throughout the experiment. Mice in the Sedentary group had access to a locked running wheel.

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The training and testing data were analyzed with a repeated measures ANOVA with object (novel, familiar) as a within-subjects factor and Exercise Group (Exercise, Sedentary), Training context (Context A, Context B), and Testing Context (Same, Different) as a between-subjects factors. A paired sample t-test was also used.

Results

Figure 1 shows the exploration time for the two novel objects in training. There were no differences in exploration time between any of the groups ($F(1,7) = 1.531, p=.240$). The physical characteristics of the training box were counterbalanced. There was no effect of the box characteristics on exploration of the two novel objects. ($F(1,7) = .093, p=.766$). However, we found that mice spent more time exploring in box A ($F(1,7) = 11.673, p=.005$), but this effect went away during the testing phase ($F(1,7) = 1.429, p=.255$).

Figure 2 shows that mice spent significantly more time exploring the novel object than the familiar object ($F(1,7) = 55.978, p=.000$). However, this effect was most evident in mice trained and tested in the same context ($p= .000$). Although both groups SAME and DIFFERENT showed object recognition, recognition was stronger in the SAME context. Unlike in training, the physical characteristics of the box did not influence exploration time ($F(1,7) = .020, p=.890$).

Experiment 2

Figure 3 shows the exploration time of the two novel objects on the training day. Mice spent the same amount of time exploring two novel objects, independent of whether they received exercise or not ($F(2,31) = .244, p=.625$). As in Experiment 1, we also counterbalanced the boxes in which the mice were trained, and found that there was a significant difference in exploration time between both objects depending on which box they were trained, with more

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exploration time in context B ($F(2,31) = 5.66, p=.024$). However, this effect disappeared during the testing phase ($F(2,31) = .139, p=.712$).

Figure 4 shows that mice trained and tested in the same context spent more time exploring the novel object than the familiar object, whereas mice trained and tested in the different contexts did not. However, exercise did not influence object recognition ($F(2,31) = .865$) nor did it influence the context dependence of object recognition ($F(2,31) = .06$). We did find a significant interaction between the box in which they were tested in and the amount of time spent exploring the two objects overall ($F(2,31) = 4.332, p=.048$). As in Experiment 1, the amount of time spent investigating the novel object was significantly larger when tested in the same context ($P=.000$) but not in a difference context ($P=.661$).

Discussion

The data suggest that a change in context from training to testing can influence object recognition. Experiment 1 measured the amount of object recognition given a change in context, and the data suggest that a change in context reduces the amount of object recognition. However, both groups (same and different) showed significantly more exploration of the novel object, although, the recognition was greater in the same group. The hypothesis was that changing the context would eliminate object recognition memory. While the context shift reduced memory, it did not eliminate it.

Experiment 2 sought to explore the effect of exercise on object recognition and its context dependence. The hypothesis was that the exercising group would spend more time investigating the novel object during testing, regardless of a change in context. Our results show that exercise did not have a significant impact on object recognition in mice. The data does suggest, however, that object recognition of the mice was decreased in the different context. This

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could suggest that the change in the context alters the memory of the mice such that they do not recognize a familiar object. We did not see this disruption in Experiment 1, maybe because the memory was stronger.

Exercise has been shown to improve memory in rodents, so perhaps the sedentary mice in Experiment 1 were unable to form strong memories that would be impacted by context change. Perhaps because mice rely so heavily on olfaction to interact with their environment, the changing odor context was enough to alter their training from the previous day. Research has shown that odor cues can improve memory recall, so perhaps a significant change in odor produced confusion in the mice. Similarly, the odor cue in the same context might have allowed the mice to be more familiar with their context and exhibit greater object recognition. Odor is just one factor of the context of the box but it likely had a significant impact on their memory.

The literature suggests that the context of a memory is central to the memory itself. Our data support this notion, as we show that the memory is disrupted during a changing context. The idea that memory can be used in dynamic and creative ways in a new situation is called generalization, an idea first considered in 1945 in schoolchildren (Goodwin, Long, & Welch, 1945). Generalization would allow the mice to recognize a similar context and recognize that the objects were something familiar or something novel. A disruption to object recognition in a changed context could represent a disruption to this idea of generalization. Research has shown that when mice are conditioned to associate an odor with a shock, a similar odor can invoke similar freezing behaviors, demonstrating a generalizing memory behavior (Pavesi, Gooch, Lee, & Fletcher, 2013). Perhaps a similar underlying circuitry could explain the results seen here. The ability of the mice to generalize the objects was lost due to disruption in the context, especially

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the changing odor cues. The discrete difference in the two contexts might have been enough to induce anxiety in the mice.

A changing context induces anxiety in mice which could alter their memory as research has shown. In humans, when a traumatic experience occurs, it can become a conditioned stimulus, such that exposure to the same or a similar stimulus evokes feelings of fear and anxiety (Lissek et al., 2010). Similarly, a new context has been shown to induce anxiety-like behavior in mice which could explain the results seen in both experiments. As anxiety can disrupt memory and both experiments demonstrated a significant disruption to memory in a different context, a changing context is enough to disrupt object recognition. Research has shown that induced anxiety can disrupt context-dependent memory (Schwabe, Bohringer, & Wolf, 2009). These researchers drew interesting parallels between the hippocampus and the density of cortisol receptors, suggesting that the hippocampus is particularly responsive to stress. Combining these two ideas together, perhaps the changing context was enough to evoke anxiety in the mice, thus disrupting their ability to recognize the two objects. That could explain why the mice in the different context explore the two objects the same amount of time as if they were novel objects. A similar query into the effects of stress found that cortisol can suppress long-term-potential, a process central to consolidating memories from the hippocampus into more dispersed cortical regions (Diamond, Campbell, Park, Halonen, & Zoladz, 2007). This body of research could be used to support the alternative hypothesis that a changing context induces anxiety in these animals, which disrupts the memory they made during training. This would explain why on test day, both objects were treated like novel objects with similar exploration times.

The data suggest that exercise has no effect on object recognition in mice. The literature suggests that exercise improves memory, but did not seem to have an effect in the current

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experiment However, a significant body of research has shown that exercise does indeed have an effect on memory. In 2011, Erickson et al., showed the aerobic exercise training selectively increases hippocampal volume and hippocampal volume reduction is associated with a decline in memory function (Eickson et al., 2011). They and other researchers posit that an increase in brain derived neurotrophic factor (BDNF) stimulates the increase in hippocampal volume (Erickson et al., 2011; van Praag, Shubert, Zhao, & Gage, 2005; Vaynman, Ying, & Gomez-Pinilla, 2004). Vaynman et al., stipulate that the BDNF binds to the TrkB receptor triggering at least three signaling cascades that ultimately are important for memory acquisition and higher retention rates (Vaynman et al., 2004).

Falls has shown that voluntary wheel running improves acquisition of fear conditioning (Falls et al., 2010). Many studies have shown that voluntary exercise improves other important memory tests such as the Morris water maze (Marlatt, Potter, Lucassen, & van Praag et al., 2012; Alaei, Moloudi, & Sarkaki, 2006). It is possible that the lack of an effect is because the mice did not receive enough exercise. Marlatt demonstrated positive effects of exercise with running throughout middle-age ((Marlatt et al., 2012). In contrast, the scope of our exercise manipulation was limited to two weeks. However, other research has shown that two weeks of voluntary exercise was sufficient to produce similar positive effects to memory and cognition (Bechara & Kelly, 2013; Falls et al., 2010). Additionally, exercise has even been shown to improve neurogenesis in the hippocampus, a mechanism by which researchers believe exercise positively impacts memory acquisition and consolidation (van Praag et al., 2005). Other factors must be considered in understanding why exercise did not cause an effect.

It is possible that the mice simply weren't exercising. However, infrared imaging has shown that all mice in standard housing with access to a wheel exhibit running behavior in

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approximately equal proportions (Salam et al., 2009). While the amount of exercise in this experiment was not measured, the research confirms mice run at relatively stable levels, suggesting that the mice used in this study were likely active. Further exploration into this topic would clarify this point. Research has shown that mice increase their exercise following stress. Perhaps quantification of the amount of exercise between training and testing could determine if the mice were anxious during the training, a possible source of disruption to their long term potentiation.

We posit that the changing context induces anxiety in the mice which significantly impaired their recall during test day. The exercising mice did not show a recovery to their memory due to the exercising as the literature would suggest. Research has shown that exercising reduces anxiety (Salam, Fox, DeTroy, Guignon, Wohl, and Falls, 2008; Binder, Droste, Ohl, and Reul, 2004). Assuming that this would hold true for our research, the exercising group should have exhibited a decrease in anxiety, and thus a rescue to their object recognition. This was not the observed result, however. Even further, the anxiolytic effects of exercise have been shown to increase hippocampal volume via neurogenesis, a process by which memory would likely be positively affected (Fuss, Abdallah, Vogt, Touma, Pacifini, & Palme et al., 2010; van Praag, Shubert, Zhao, & Gage, 2005). Studies will often choose between voluntary and forced exercise, but use of voluntary exercise has produced enough evidence to support the positive effects of this manipulation (Salam et al, 2008, Binder et al., 2004, Fuss et al., 2010). It is also possible that the test administered wasn't sensitive to changes in behavior due to exercise. Other memory tasks, such as a Morris water maze, or spatial object recognition might show different effects.

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It is also possible that we saw a ceiling effect to the influence of exercise on object recognition. Perhaps the amount of exercising simply wasn't enough to overcome the disruption from the change in context. Although, we didn't see this disruption fully in Experiment 1, a ceiling effect here could explain the results. Perhaps the object recognition in the mice simply wasn't strong enough to persist in the change in context.

Further studies into the effect of context on object recognition are essential at this junction. The results suggest that context is a strong disruptor to object recognition. Further inquisition into the subject could elucidate much more information. Do different odor cues effect object recognition? Is the disruption in memory consistent over a longer or shorter time span? Does an intentional induction of anxiety yield similar results? Would an identical experimental set up measuring anxiety confirm that anxiety is present in these animals? How would other memory tasks such as spatial recognition or temporal recognition be affected by a context change? Of course, further research must be done to explore any of these questions.

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Figures

Figure 1.

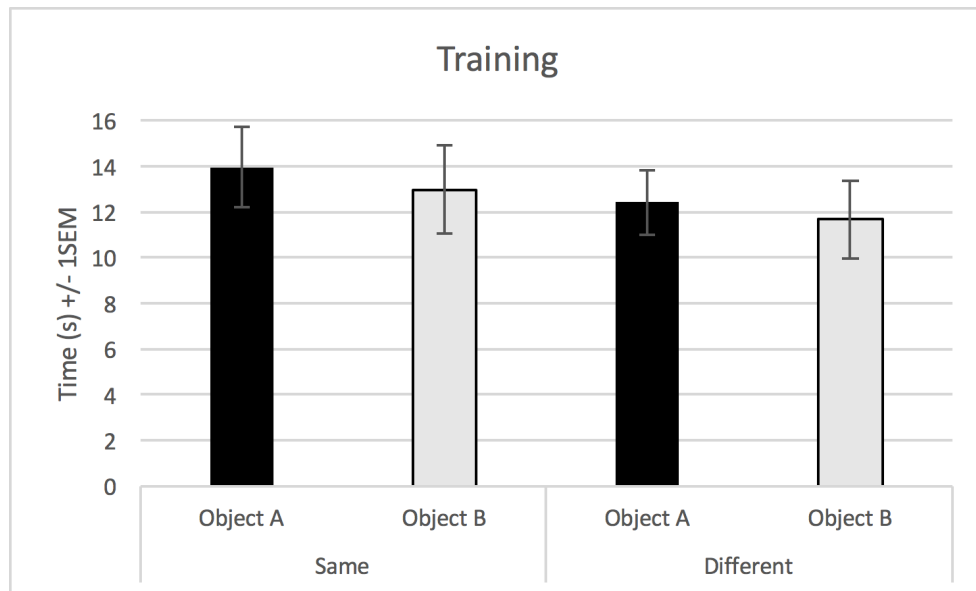


Figure 1 shows the amount of time exploring each object during the trail phase of experiment 1. There was no significant difference in exploration time between the two groups ($P > .05$).

Figure 2.

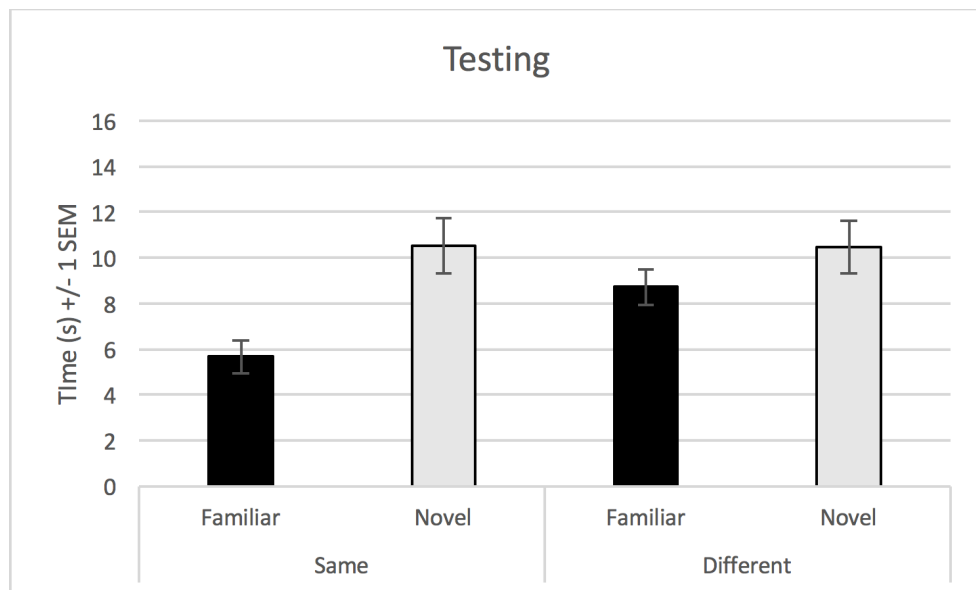


Figure 2 shows the amount of time exploring each object during the test phase of experiment 1. There was a significant difference between Object A and Object C in the same a different context ($P = .000$, $P = .011$).

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Figure 3.

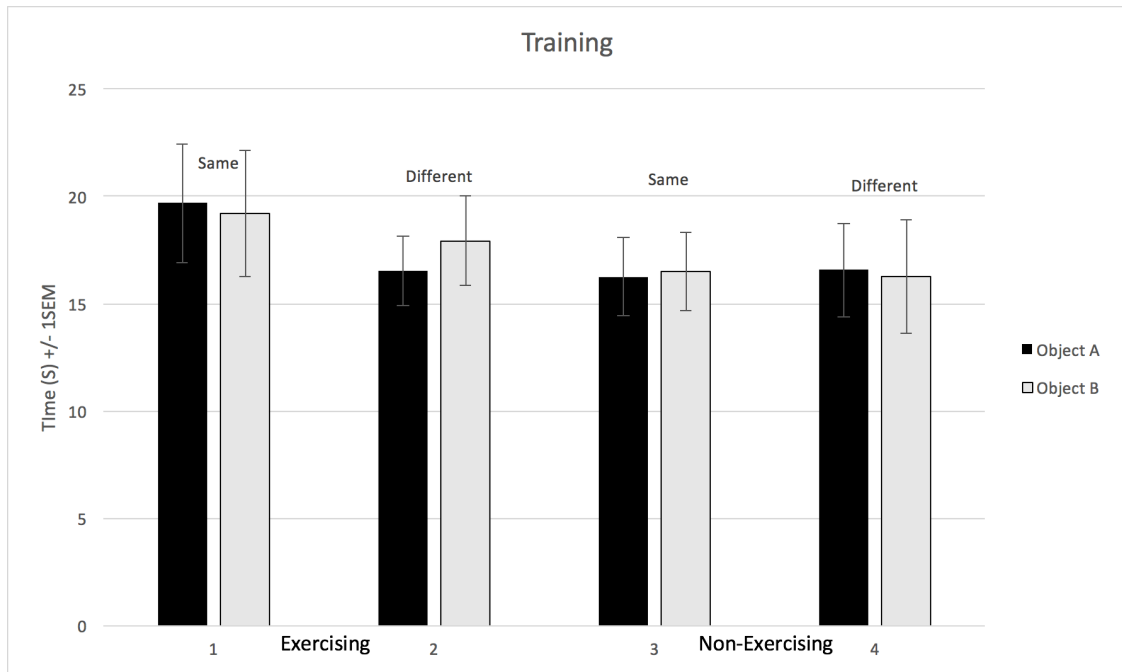


Figure 3 shows the amount of time exploring each object during the trial phase of experiment 2. There was no significant difference between exploration time and the two groups ($P > .05$).

Figure 4.

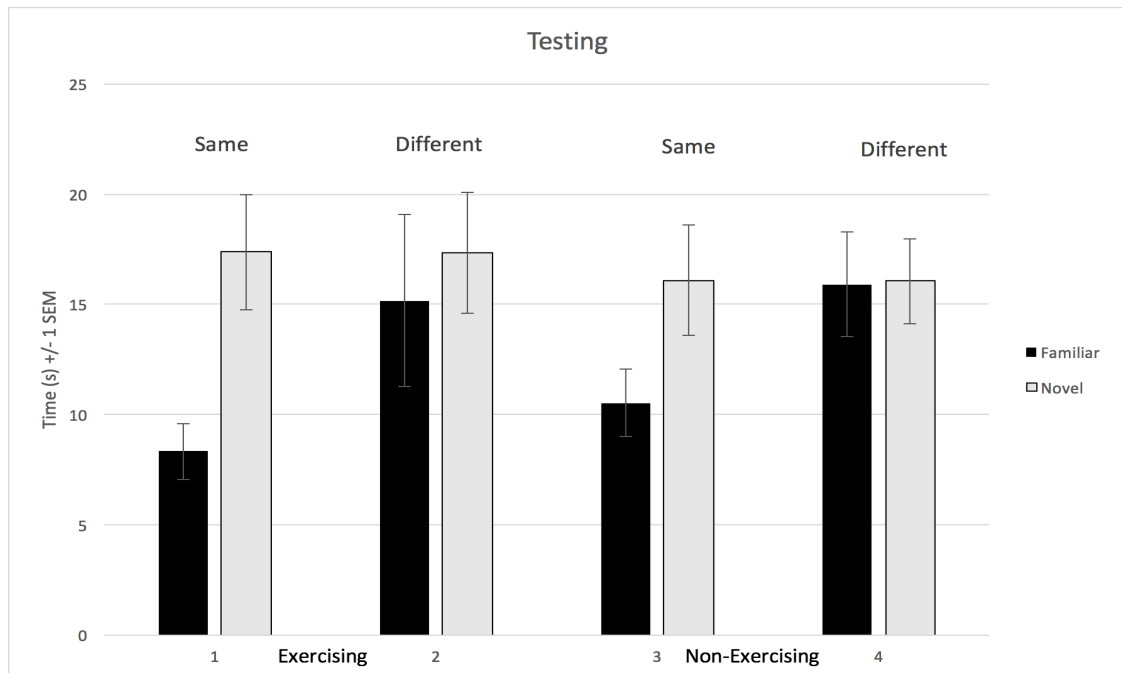


Figure 4 shows the amount of time spent exploring each object during the testing phase of experiment 2. Exercising mice showed no significant difference in exploration time of the novel object compared to the sedentary mice ($P > .05$). Time spent exploring the novel object in the same context was significantly higher than in the different context ($P = .000$, $P = .661$).