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A Single Bout of Torpor in Mice Protects Memory Processes

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Abstract

NOWAKOWSKI, S. G., S. J. SWOAP, AND N. J. SANDSTROM. A single bout of torpor in mice protects memory processes. *PHYSIOL BEHAV* 00(0) 000-000, 2008. – Memory consolidation is the process by which new and labile information is stabilized as long-term memory. Consolidation of spatial memories is thought to involve the transfer of information from the hippocampus to cortical regions. While the hypometabolic and hypothermic state of torpor dramatically changes hippocampal connectivity, little work has considered the functional consequences of these changes. The present study examines the role of a single bout of shallow torpor in the process of memory consolidation in mice. Adult female C57Bl/6NHSd mice were trained on the Morris Water Maze (MWM) task. Immediately following acquisition, the mice were exposed to one of four experimental manipulations for 24 hours: fasted at an ambient temperature of 19°C, fasted at 29°C, allowed free access to food at 19°C, or allowed free access to food at 29°C. Mice fasted at 19°C entered a bout of torpor as assessed by core body temperature while none of the mice in the other conditions did so. Spatial biases were then assessed with a probe trial in the MWM. During the probe trial, mice that had entered torpor and mice that were fed at 29°C spent twice as much time in the prior target platform location than mice that were fed at 19°C and those that were fasted at 29°C. These findings demonstrate that, while food restriction or cool ambient temperature independently disrupt memory processes, together they cause physiological changes including the induction of a state of torpor that results in functional preservation of the memory process.

Keywords

Torpor; Memory; Spatial Learning; Consolidation; Water Maze; Hippocampus; Hibernation

1. Introduction

Many models of memory include the stages of acquisition, consolidation, and retrieval [i.e., 1,2,3]. According to these models, acquisition involves exposure to new information and experiences (e.g., training). During acquisition, new information is particularly vulnerable to decay and interference [4,5]. During consolidation, the newly learned information is stabilized, thereby preserving the information and preventing interference and decay. For several learning paradigms (e.g., contextual fear conditioning and spatial learning), the hippocampus has been shown to play a prominent role in the consolidation process as lesions or inhibition of mRNA

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synthesis performed immediately after training disrupt subsequent performance on a test trial [5,6]. This consolidation process is thought to involve the transfer of information from the hippocampus to cortical sites where it can be accessed during subsequent recall [5,7].

Research in humans has demonstrated that newly formed memories can easily be disrupted by exposure to a stressor after a learning task [4,5,8]. One such stressor is sleep deprivation. Periods of prolonged waking are characterized by an overall decrease in neuronal activity whereby the relevant cortico-cortical synapses are not continually activated as is necessary for memory consolidation [9]. Furthermore, consolidation of new memories may be disrupted by interfering mental activity (the activation of non-relevant synapses) [10]. In contrast, sleep facilitates the consolidation of previously learned information, as the relevant neuronal connections are specifically and synchronously reactivated [10–12].

Like sleep, other changes in physiological state can significantly impact the structure and function of neural systems underlying memory processes. For example, during hibernation, neuronal connections precipitously fall within the hippocampus. Upon waking from hibernation, however, connectivity quickly returns to baseline levels [13,14]. Despite this substantial degree of hippocampal plasticity associated with hibernation, the effects of these changes on learning and memory processes are not well understood and the early evidence is, in fact, somewhat contradictory. Although some studies using European ground squirrels have shown hibernation to negatively affect the retention of conditionally learned information [15], wild-caught arctic ground squirrels demonstrated an enhanced fear conditioned response after experiencing hibernation [16].

While memory is influenced by deep bouts of hibernation in ground squirrels, virtually nothing is known about the influence of shallow, daily torpor bouts on memory. Like hibernation, daily torpor bouts are defined as a hypometabolic and hypothermic state. Unlike hibernation, these bouts of torpor are shorter in duration (hours and not weeks) and shallower in depth (minimum body temperatures of 20°C and not 2°C). In addition, daily torpor differs from hibernation in that the former is a result of an acute food shortage in a thermogenically challenging environment whereas hibernation is often seasonal and photoperiod dependent [17]. When experienced independently, both cool ambient temperature and caloric restriction are stressors that activate the hypothalamic-pituitary-adrenal axis [18,19]. Such sustained activation of the HPA-axis can significantly impact performance on spatial learning tasks [20–23]. Unknown, however, is the degree to which the hypometabolic state of torpor induced by the experience of *both* caloric restriction and cool temperatures influences memory processes. We hypothesized that a shallow torpor bout in mice would exert a protective effect on memory processes. This hypothesis was tested by training mice on a spatial learning task followed by a 24 hr manipulation of the temperature of the home cage and/or food availability. The effect of this manipulation on memory processes was then tested with a single probe trial in the water maze.

2. Materials and Methods

2.1. Animals

Female C57BL/6NHSD mice were obtained from Harlan Sprague-Dawley (Indianapolis, IN). The animals were individually housed with 12:12 hour light/dark cycle at $29 \pm 1^\circ\text{C}$, a temperature that is near or within their thermal neutral zone [24]. Food (AIN93G, Dyets, Inc., Bethlehem, PA) and water were available *ad libitum*. Animals were 2–3 months of age at the onset of experiments. The Williams College IACUC approved all experimental procedures.

2.2. Implantation of Temperature Telemeters

Temperature telemeters (TA10TAF20; Data Sciences International, St. Paul, MN) were implanted into the peritoneal cavity as described previously [25]. Briefly, mice were anesthetized with isoflurane in oxygen. Using aseptic surgical techniques, a 3-cm incision was made through the abdominal skin and muscle wall and the temperature telemeter was implanted in the abdominal cavity. The muscle wall was closed with absorbable sutures and the skin was closed with surgical staples. The mice were housed on a heating pad for 24 hours after surgery, and were allowed to recover for 7 days before water maze training began.

2.3. Morris Water Maze (MWM) & Telemetry

One week following telemeter implantation, mice were trained in the Morris Water Maze [26]. The water maze consisted of a circular pool of water with a diameter of 80 cm. The water was maintained at 24–26°C and was made opaque by the addition of approximately six ounces of non-toxic white paint. The target platform onto which mice were trained to escape was 10 cm in diameter and was submerged 1 cm under the surface of the water. The pool was located in a small, white room with a variety of large, salient patterns attached to the walls to serve as extramaze cues.

Behavioral testing occurred over three consecutive days and consisted of a brief pretraining protocol in which mice were trained to escape to a visible platform, nine hidden platform training trials during which the escape platform was in a fixed pool location but hidden just under the surface of the water, and a probe trial during which the escape platform was removed and the mouse was allowed to swim for 40 sec (Figure 1). An automated tracking system (HVS Image, Hampton, UK) was used to measure the length of the swim path during training trials and the expression of spatial biases during the probe trial.

2.3.1. Pretraining—Naive mice were exposed to the water maze and trained to swim to a visible platform. During pretraining, the target platform was painted black and was raised so that it extended 1 cm out of the water. Each mouse was initially placed on the randomly positioned target platform for 60 sec after which it was removed from the platform, placed in the pool at one of three start locations, and was allowed to swim back to the visible platform. If the mouse did not escape within 60 sec, it was gently guided to the platform by the experimenter. The target platform was repositioned between trials and each mouse performed three consecutive pretraining trials. After the third pretraining trial, each mouse was returned to its cage, which was maintained on a heating pad until the mouse was dry at which point it was returned to the colony.

2.3.2. Hidden Platform MWM Training—Twenty-four hours after pretraining, mice were trained over a course of nine trials using the submerged platform maintained in one of four pool locations. Each mouse performed three blocks of three consecutive trials with an inter-block interval of 20–25 min. During the inter-block interval, mice were individually housed in tub cages maintained on heating pads. For each mouse, the entire session of nine trials was completed in less than two hours. Each mouse was assigned one of four target platform locations, each centered in one of the four pool quadrants and positioned 20 cm away from the edge of the pool. Each trial began by placing the mouse in the water at the edge of the pool facing the wall at one of four starting locations (N, E, S, W). The sequence of starting locations was maintained across all mice. The length of the swim path was recorded for each trial.

2.3.3. Treatment Groups and Telemetry—Immediately following the final training trial, each mouse was individually housed under one of four conditions: fed *ad libitum* at 19°C (Fed-Cool, N = 12), fasted at 19°C (Fasted-Cool, N = 10), fed *ad libitum* at 29°C (Fed-Warm, N = 6) or fasted at 29°C (Fasted-Warm, N = 9). Cage temperature was set individually using a

home-built temperature controller with a precision of $\pm 1^\circ\text{C}$. Core body temperature was sampled via radiotelemetry at 500 Hz for one second every minute for 24 hours using Data Sciences Int. data acquisition software. Mice were not weighed after the manipulation, though prior work in our lab has shown that mice typically lose 3–4 g during an overnight fast [25].

2.3.4. Probe Trial—Twenty-four hours following the final training trial, mice were returned to 29°C and were tested with a single 40-sec probe trial during which the target platform was removed from the pool. Swimming patterns during the probe trial were analyzed with respect to a target annulus consisting of a 20-cm diameter circular area centered at the prior target location. The swim path of each mouse was recorded and the percentage of time spent in the target annulus, the latency to cross the target annulus, and the number of times the target annulus was crossed during the probe were recorded for each mouse. In addition, thigmotaxic swimming patterns were assessed by recording the proportion of time that the mouse spent in the outer 13.3 cm of the pool.

2.4. Data Analysis

The length of the swim path for each mouse during acquisition on the hidden platform MWM task was collapsed into 3-trial blocks. These data were analyzed using a mixed model analysis of variance (ANOVA) with Ambient Temperature (Cool ($19\pm 1^\circ\text{C}$) or Warm ($29\pm 1^\circ\text{C}$)) and Nutritional Status (Fast or Fed) as between-subjects factors and Trial Block as a repeated-measure. It should be noted that these experimental manipulations (Ambient Temperature and Nutritional Status) were not performed until *after* the training phase was completed – all mice were maintained at 29°C and under free-feeding conditions prior to MWM training. Maximum and minimum body temperatures during the 24 hours between the end of MWM acquisition and the probe trial were analyzed with a 2-factor (Ambient Temperature and Nutritional Status) ANOVA. If the animals entered a shallow bout of torpor (defined by body temperature below 31°C) [17], the latency to onset and duration of the torpor bout was also assessed. The percentage of time spent in the target annulus, the latency to cross the target annulus, and the total number of target crossings during the 40-second probe trial were analyzed with 2-factor (Ambient Temperature and Nutritional Status) ANOVAs. Additional analyses were conducted as described in the Results section. All statistical analyses were conducted using SPSS (v14.0, SPSS Inc., Chicago, IL) and results are presented as Mean $\pm$ SEM.

3. Results

3.1. Hidden Platform MWM Training

The length of the swim path during acquisition trials was collapsed into 3-trial blocks for each mouse (Figure 2). Analysis of these data yielded a significant main effect of Block, $F(2, 66) = 18.861$, $p < 0.001$. LSD post-hoc tests confirmed that mean pathlength declined significantly between each block of trials ($ps < .05$). As expected, no other main effects or interactions were statistically significant ($ps > .30$). Together, these results indicate that the mice, regardless of subsequent treatment, learned the location of the hidden platform across the acquisition trials.

3.2. Body Temperature and Torpor

After the acquisition phase, mice were placed into one of four groups: fasted at 19°C , fasted at 29°C , fed at 19°C , and fed at 29°C . The maximum and minimum core body temperatures during the 24 hr period between MWM training and probe trial testing were recorded for each animal (Figure 3). These variables were separately analyzed with 2×2 ANOVAs (Figure 4). Two mice were excluded from this analysis due to malfunctioning telemeters (one Fast-Cool and one Fed-Warm). Analysis of the maximum body temperature yielded no significant main effects or interactions ($ps > .69$). In contrast, analysis of the minimum body temperature yielded significant main effects for Nutritional Status, $F(1, 31) = 63.37$, $p < .001$, and Ambient

Temperature, $F(1, 31) = 29.15, p < .001$. The interaction between Nutritional Status and Ambient Temperature was also significant, $F(1, 31) = 47.65, p < .001$, indicating that the effect of nutritional status on minimum body temperature was dependent on the temperature of the housing environment. Analysis of the simple main effects confirmed that, among the fasted mice, those housed in 19°C achieved a lower body temperature than those housed at 29°C ($p < .001$). Similarly, among the mice housed at 19°C, those that were fasted achieved lower body temperatures than those that were fed ($p < .001$). Mice that were fed did not differ in their minimum body temperatures and mice that were housed at 29°C did not differ in their minimum body temperatures ($ps > .05$). All of the mice that were fasted at 19°C entered a bout of torpor, achieving core body temperatures below 31°C. The total duration spent with a core body temperature below 31°C was 202.8 ± 27.9 minutes, and the average time from the fast to the first recorded core body temperature below 31°C was 675.9 ± 62.6 minutes. No mice in any of the other three conditions entered a bout of torpor.

3.3 Probe Trial Performance

The expression of a spatial bias during the probe trial was assessed by the percentage of time during the probe that was spent in the target annulus (Figure 5). Analysis of this spatial bias revealed no main effect for Nutritional Status or for Ambient Temperature ($ps > .60$). However, the interaction between Nutritional Status and Ambient Temperature was significant, $F(1, 33) = 9.310, p < .01$. Analysis of the simple main effects confirmed that mice in the Fasted-Cool condition exhibited a stronger bias for the target annulus than did mice in either the Fasted-Warm condition or the Fed-Cool condition ($ps < .05$). Mice in the Fed-Warm condition exhibited a marginally weaker bias for the target annulus than mice in either the Fed-Cool condition or the Fasted-Warm condition ($ps < .10$).

Analyses of the latency to cross the target annulus (Figure 5) and the mean number of times mice crossed over the target annulus (data not shown) yielded similar results. While the main effects of Nutritional Status and Ambient Temperature were not significant in either analysis ($ps > .31$), the interaction between Nutritional Status and Ambient Temperature was significant for both the latency to cross the target, $F(1, 33) = 6.46, p < .05$, and the number of target crossings, $F(1, 33) = 6.98, p < .05$. Analysis of the simple main effects confirmed that mice in the Fed-Warm condition crossed earlier and more often than mice in the Fasted-Warm condition ($ps < .05$). Mice in the Fasted-Cool condition crossed marginally earlier and more frequently than mice in the Fasted-Warm condition ($ps < .10$). Likewise, mice in the Fed-Warm condition crossed marginally earlier and more frequently than mice in the Fed-Cool condition ($ps < .10$).

Together, these three variables (percent of time in the target annulus, latency to cross the target annulus, and number of crossings of the target annulus) indicate that either housing at a cool ambient temperature or fasting adversely affects the expression of a spatial bias during the probe trial and that experiencing both cool ambient temperature and fasting prevents this disruption.

The disruptions in probe trial performance evident in mice in the Fed-Cool and Fasted-Warm conditions could be due to a specific impairment in the memory processes underlying spatial aspects of the task while leaving procedural memories unaffected [see 27]. Alternatively, this disruption could be due to a more general disruption in the ability to consolidate *any* aspect of the MWM training. The latter possibility was explored by examining changes in the degree to which mice exhibited thigmotaxic swimming patterns. Naïve rodents typically express a significant bias toward the edge of the pool but this bias declines with training [26,28]. To determine whether Fed-Cool and Fasted-Warm mice exhibited a general disruption in consolidation of this procedural memory, the change in thigmotaxic swimming (i.e., the percentage of time spent in the outer third of the pool) between the first training session and

the probe trial was analyzed with a 3-factor ANOVA with Ambient Temperature (Cool or Warm) and Nutritional Status (Fast or Fed) as between-subjects factors and Block (Session 1 and Probe Trial) as a repeated-measure (Figure 6). This analysis yielded a significant main effect of Block, $F(1, 33) = 25.16, p < .001$. No other main effects or interactions were statistically significant, indicating that, overall, searching strategies changed between initial training trials and the probe trial and the magnitude of this change did not vary as a function of treatment.

4. Discussion

Mice that experienced either fasting or cool ambient temperatures after training exhibited disruptions in probe trial performance when tested 24 h after training. However, experiencing both of these stressors simultaneously caused the induction of a shallow bout of torpor and prevented this disruption. That is, mice maintained under fasted and cool conditions entered a bout of torpor and exhibited the same degree of target bias as those that were maintained under non-stressful conditions during the retention interval. Thus, on a task that has been widely demonstrated to rely on hippocampal function [26,29], the combination of fasting and cool temperature, which induced torpor, prevented the adverse effects of fasting or cool ambient temperatures on memory processes. It is possible that the effects of fasting or cool temperatures on memory are general in nature rather than specific to hippocampally-mediated memories. It is notable, however, that mice in all experimental groups did demonstrate memories for a procedural aspect of the task. Specifically, all groups demonstrated a significant decline in the degree of thigmotaxic swimming between the initial training trials and the probe trial (Figure 5). This type of procedural memory is not dependent on the hippocampus as hippocampally-lesioned rodents are capable of learning alternative search strategies [27]. Together, these findings suggest that the effect of fasting or cool temperature on memory processes is not completely non-specific. Whether only hippocampally-dependent memory processes were affected by the present manipulations or whether some non-hippocampally dependent processes were also affected remains to be determined.

Cool ambient temperature and food restriction can be considered metabolic stressors. That, independently, they adversely affect memory processes in mice is consistent with other observations of acute stress impairing spatial memory processes. For example, 30-min of exposure to an adult female cat either immediately after training on a radial arm water maze or immediately before a delayed test trial disrupts performance of rats on the retention trial [21]. Furthermore, the magnitude of the stress response as measured by corticosterone levels was negatively correlated with performance on the maze task suggesting that, as stress levels increase, spatial learning and memory decrease. Prior work has shown that the separate manipulations used to induce torpor in the present study (fasting and cool ambient temperature) each results in an elevation of corticosterone levels [18,19]. How experiencing them in combination, a manipulation sufficient to induce a bout of torpor, affects corticosterone levels has not yet been determined in the mouse. Among seasonal hibernators like the ground squirrel, corticosterone levels are elevated around the onset of hibernation and are lowest when the animals emerge from hibernation [30,31]. The relationship between corticosterone levels and torpor, however, is not well understood. If either the entrance into torpor or the emergence from it is associated with reduced corticosterone levels, then perhaps this hormonal consequence of torpor may contribute to the preservation of memory processes.

The current study does not address whether the beneficial effect of a torpor bout on memory processes is simply a result of the hypothermia achieved during torpor or the result of a new physiological state induced by fasting at a cool ambient temperature (i.e. circulating hormones, etc.). Forced hypothermia for 6 hours in the gerbil or neonatal rat following a brain ischemic event prevents loss of CA1 neurons in the hippocampus and prevents functional memory

deficits otherwise seen in euthermic conditions following brain ischemia [32,33]. Similarly, neonatal rats that undergo left carotid artery ligation while hypothermic (27 °C) also show improved spatial learning performance in a water maze as compared to rats that were euthermic or hyperthermic [34]. While natural torpor bouts are inherently different from forced hypothermia, it should be noted that both gerbils and neonatal rats can enter shallow bouts of torpor like mice [17,35,36]. Experiments are currently being designed to determine whether the protective effect of a single bout of torpor is related to hypothermia or some other physiological factor associated with caloric restriction in a cool environment.

The present data clearly demonstrate that torpor preserves memory processes in mice as evident by the expression of a bias for the prior target location during the probe trial. What remains unclear, however, is how the memory process is specifically affected by torpor. Experimental manipulations in the present study (i.e., ambient temperature and food availability) occurred after acquisition. Thus, these manipulations could theoretically affect 1) consolidation, 2) long-term storage, or 3) retrieval of information [i.e., 1,2,3]. Several studies have demonstrated a critical period of only a few hours after acquisition during which consolidation processes are vulnerable. For example, infusions of estradiol immediately following water maze training improve consolidation of the new information [37,38]. That consolidation was affected rather than long-term storage or retrieval processes is evidenced by the absence of any effect when the hormone administration was delayed for 2 hours following acquisition [38]. Similarly, inactivation of the dorsal hippocampus by infusion of the AMPA receptor antagonist NBQX immediately after trace fear conditioning disrupts subsequent expression of the conditioned fear; delaying administration for 2 hours, however, fails to affect subsequent performance [39]. In the present study, manipulation of food availability and ambient temperature was initiated immediately following conditioning. However, mice that entered a torpor bout did not do so for approximately 11 hrs following initiation of the manipulations (see Figure 3). This, along with the fact the manipulation was maintained throughout the 24-hr retention period, raises the possibility that the manipulations may have affected any of the post-acquisition memory processes (i.e., consolidation, long-term storage, or retrieval). Experiments altering the timing of the ambient temperature and nutritional manipulations are needed to isolate the specific memory processes influenced by torpor. Clearly, however, the combined experience of cool ambient temperature and food restriction preserves memory processes that are adversely affected by exposure to only one of these conditions.

Sleep has been well documented as a facilitator of memory processes likely due to the lack of interference that exists during sleep, particularly non-REM sleep [7,10,11,40–42]. The disruptive effect of either cool ambient temperature or food restriction on subsequent memory for the target location may be due to stress-induced disruptions in sleep. Recent studies have shown that exposure to physical stressors affects the sleeping patterns of rats, resulting in decreased amounts of REM sleep, non-REM sleep and total sleep episodes [43,44]. Specific reactivation of the neuronal circuits relevant to recently learned information, along with a decreased ability to create new synaptic connections during non-REM sleep reduces interference that could disrupt memory consolidation in an awake animal [10]. While the inactive state of torpor may limit the degree to which interactions with the environment interfere with memory consolidation, the improved performance on the MWM memory task in the mice that entered torpor may be unrelated to sleep. Deep bouts of torpor as seen in hibernators are associated with significant synaptic restructuring within the CA3 region of the hippocampus, which include decreases in dendritic branching, dendritic spine density, and the number of post-synaptic connections [13,16,45]. Within several hours of arousal from deep torpor, these synaptic parameters quickly re-grow to form functional synapses [16]. Taken together with the present data, these findings suggest that torpor may be associated with synaptic remodeling that maintains the substrates of consolidation processes. The functional protection of memory processes demonstrated by mice that experienced torpor may, therefore, be attributable to a

lack of degradation of recently learned information as opposed to the facilitation of its consolidation.

The present data suggest that a single bout of torpor in mice protects against disruptions in memory processes resulting from either cool ambient temperature or fasting. Given the dramatic changes in synaptic organization associated with torpor, these findings highlight the value in studying this naturally occurring physiological state with regard to learning and memory processes. The torpor model may prove extremely valuable in studies exploring the disorders of memory.

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Figure 1.

Diagram of the experimental timeline. Prior to the acquisition phase, the mice were fed and housed at 29°C. After pretraining, the acquisition phase consisted of nine training trials in a Morris Water Maze over a period of 2.5 hours. Immediately following acquisition, the mice were divided into one of four groups: 1) Fasted at an ambient temperature of 19°C, 2) Fed at 19°C, 3) Fasted at 29°C, and 4) Fed at 29°C. After exposure to those conditions for 24 hr, memory for the platform location was tested using a single probe trial.

Figure 2.

Path length of trials during hidden platform training. Mice are grouped according to the condition to which they were assigned after training was completed. Prior to these trials, all mice were free-fed and housed at 29°C. All mice exhibited significant decreases in path length over the course of training, regardless of subsequent treatment group assignment. Data are presented as mean $\pm$ SEM. * $p < 0.05$.

Figure 3.

Representative body temperature functions for one mouse from each of the four conditions during the 24 hours between acquisition training and probe testing. The criterion for a torpor bout is 31°C and is represented by the dashed line. Note that the mouse that was fasted at 19°C entered a shallow bout of torpor while mice in the other three conditions did not.

Figure 4.

Body temperatures during the 24 hr between acquisition and probe testing. Mice that were fasted at 19°C exhibited a significant decrease in minimum core body temperature (left). Maximum core body temperature (right) did not differ across groups. Data are expressed as mean $\pm$ SEM. $*p < .05$.

Figure 5.

(Top) Spatial biases exhibited toward the target (% time spent in target annulus) by mice in each of the four conditions during the probe test. The target annulus (dotted circle) is an area centered over the prior platform location that is twice the diameter of the platform. When experienced separately, fasting and housing at a cool temperature (19°C) resulted in a decrease in time spent in the target annulus. Experiencing both fasting and cool ambient temperature did not affect the expression of the target bias. (Bottom) Latency to cross the target annulus on the probe test. Separately, fasting and cool temperature adversely affected latency. When experienced together, performance did not differ from Fed-Warm mice. Data are expressed as mean $\pm$ SEM. * $p < .05$, # $p < .10$.

Figure 6.

Percentage of time engaged in thigmotaxic swimming (swimming in the outer 13.3 cm of the pool) during the first block of training trials and during the probe test. The boundary of the outer zone is indicated by the larger dotted circle and the prior platform location is indicated by the smaller dotted circle. Mice spent less time in the peripheral zone during the probe than during the initial training trials. Data are expressed as mean $\pm$ SEM. * $p < 0.05$.