

Chapter I

**Intact Environmental Habituation and
Epinephrine-Induced Enhancement of
Memory Consolidation for
a Novel Object Recognition Task in
Pre-Weanling Sprague-Dawley Rats**

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Abstract

Within- and between-session environmental habituation were examined in infant rats on postnatal days 14 and 15 in an open field. Using a computerized animal tracking system, rats showed decreases in the total distance traveled (m) and overall average speed (m/s) across 6 30-sec time blocks each day and from day 1 to day 2 of testing. Although the literature is inconclusive regarding the ontogeny of environmental habituation, these results provide clear evidence of both within-session and between-session habituation. On postnatal day 16, animals were returned to the open field with 2 identical objects for novel object recognition training. Animals were either tested immediately after training or were given a subcutaneous injection of saline or .01 mg/kg of epinephrine, followed by testing 2-hrs later. For testing, animals were placed into the open field with one familiar and one novel object, and the number of object explorations and the time spent exploring each object were recorded by the animal tracking system. From these measures the absolute mean preference for novelty and relative percent preference for novelty were computed. Only the relative percent preference for novelty based on the time spent exploring each object revealed significant differences among the groups. Post-hoc pairwise comparisons indicated that saline animals tested 2-hrs after training performed significantly worse than epinephrine animals and worse than those tested immediately

after training. This indicates a rapid rate of forgetting for object recognition memory which is effectively attenuated with post-training epinephrine.

Introduction

Age-related memory impairments are stereotypically thought of as afflicting the elderly, and are infrequently a concern for children, young adults, or even those of middle-age. However, we have all suffered and continue to suffer from a very significant form of memory loss described by Freud (1914/1938) as infantile amnesia. Research examining the ontogeny of memory encompasses some very important endeavors in behavioral and developmental neuroscience. The goal of the present study was to examine environmental habituation and object recognition memory in preweanling rats and to determine the effect of epinephrine on novel object recognition memory.

Immature mammals commonly exhibit a rapid rate of forgetting (Arnold & Spear, 1997; Campbell & Campbell, 1962; Campbell, Jaynes, & Misanin, 1968; Campbell & Spear, 1972; Hartshorn et al., 1998; Kirby, 1963; Spear & Riccio, 1994; Spear & Rudy, 1991) and an inability to accurately recall events from infancy after reaching adulthood (Freud, 1914/1938; Sheingold & Tenney, 1982; Usher & Neisser, 1993; see Pillemer & White, 1989 for review). While both of these phenomena may be described as infantile amnesia, the present study was interested in the characteristics of the former mnemonic deficit, namely that immature organisms rapidly forget recently learned information. For example, Hill, Borovsky, and Rovee-Collier (1988) used 6-7-month-old human infants and demonstrated that they could acquire and maintain a memory for an operant conditioning procedure for 14 days, but that complete forgetting of the procedure would occur by 21 days post-training.

It is paradoxical that this critical period of development is associated with such poor memory. The cause of infantile amnesia is not known, but Campbell and Spear (1972) and Howe and Courage (1993) reviewed a variety of potential mechanisms for this phenomenon. In humans it was suggested that the development of a cognitive sense of self, along with the personalization of event memory are particularly important. Other proposed mechanisms that are not limited to humans included maturational changes in interference and information-processing and neuroanatomical and/or biochemical changes in the central nervous system. While the cause of infantile amnesia continues to be debated, increased knowledge of biological ontogenetic changes makes this a plausible consideration. For example, it is well-known that both the limbic system, a group of interconnected neuroanatomical structures heavily involved in learning and memory, and the hypothalamic-pituitary-adrenal axis are developmentally immature (Bayer & Altman, 1975; Levine, 1994; Schapiro, Geller, & Eiduson, 1962; Schlessinger, Cowan, & Gottlieb, 1975; Schmidt et al., 2003; Vazquez, 1998).

Regardless of the cause of this rapid rate of forgetting, research has clearly indicated that this deficit is the result of a retrieval failure at the time of testing, and not a failure to learn the material during training. This is evidenced by the success of treatments to enhance the retrieval of memories formed during infancy (Anderson, Karash, & Riccio, 2004; Campbell & Jaynes, 1966; Flint, Bunsey, & Riccio, 1999; Flint & Riccio, 1997; Greco, Rovee-Collier,

Hayne, Griesler, & Earley, 1986; Hamberg, & Spear, 1978; Rovee-Collier & Hayne, 1987; Rovee-Collier, Sullivan, Enright, Lucas, & Fagan, 1980; Richardson, Wang, & Campbell, 1993). Spear and Parsons (1976) trained rats at postnatal day 16, postnatal day 23, or as adults and tested them 28 days later. They demonstrated that an unconditioned stimulus (UCS; footshock) reactivation treatment 24-hours prior to testing had differential effects on retention performance based on the age at which training occurred. The reactivation treatment was effective for all groups with the exception of the 16-day-old animals. However, Spear and Parsons did find that the reactivation treatment was effective for subjects at this age if the retention interval was shortened to 7 days instead of 28 days. These results indicate that the training memory was stored, but the effectiveness of the reactivation treatment likely decreases as the retention interval increases. Furthermore, a single exposure to the conditioning reinforcer was sufficient to reactivate the training memory.

The creation and use of new memories involves a complex series of processes including information acquisition, consolidation, storage, and retrieval, with distinct biochemical processes and neuroanatomical substrates which may differ depending upon the nature of the to-be-remembered information. Research indicates that memory consolidation is a time-limited event occurring immediately following acquisition. During this time the memory is in a labile state where manipulations may either enhance or impair the consolidation process, resulting in either enhanced or impaired performance on subsequent tests. For example, some memory enhancing treatments in rats include adrenocorticotrophic hormone (Gold & van Buskirk, 1976), glucose (Flint & Riccio, 1996; 1999; Gold, 1986), vasopressin (Koob et al., 1991), oxytocin (Bohus, Conti, Kovacs, & Versteeg, 1982), gastrointestinal peptides (Morley & Flood, 1991), and epinephrine (Costa-Miserachs, Portell-Cortes, Aldavert-Vera, Torras-Garcia, & Morgado-Bernal, 1994; Gold & van Buskirk, 1975, 1978; Nordby, Torras-Garcia, Portel-Cortes, & Costa-Miserachs, 2006). Of paramount importance to the present study are those experiments demonstrating the memory enhancing effects of epinephrine when administered immediately following training.

Post-training epinephrine has been shown to enhance memory consolidation for a variety of tasks including inhibitory avoidance conditioning (Gold & van Buskirk, 1975, 1978), taste conditioning (Guaza, Borrell, & Borrell, 1986), appetitive conditioning (Sternberg, Isaacs, Gold, & McGaugh, 1985), and novel object recognition memory (Dornelles et al., 2007). Gold, Murphy, and Cooley (1982) trained 16-day-old rats on an inhibitory avoidance conditioning task. They found that these animals demonstrated good retention of the training shortly afterwards (1-hr) but not 24-hrs later, evidence of infantile amnesia. A subcutaneous injection of epinephrine immediately after training enhanced subsequent performance on the retention test 24-hrs later. In a more recent study, Flint, Bunsey, and Riccio (2007) examined the effects of epinephrine on memory retrieval of inhibitory avoidance conditioning in 17-day-old rats. Animals that had received a subcutaneous injection of .01 mg/kg or .1 mg/kg of epinephrine 25 (\pm 5-min) prior to the retention test exhibited significantly better retention scores. Importantly, control groups indicated that these results were not likely due to the effects of epinephrine on vigilance or as an internal contextual reminder cue of training.

In novel object recognition memory, animals are commonly presented with two identical objects in an open field type apparatus. Animals are given a specific amount of time to freely explore these objects. On a subsequent retention test, animals are presented with two objects,

one familiar (from training) and one novel, and are similarly free to explore these objects. Animals with intact object recognition memory will spend more time exploring the novel object, indicating intact retention of the familiar object (Anderson et al., 2004; Ennaceur & Delacour, 1988; Steckler, Drinkenburg, Sahgal, & Aggleton, 1998). Dornelles et al. (2007) utilized the object recognition paradigm with adult rats. Animals exposed to the training objects for 2-min showed intact memory during the recognition test 1.5 or 24 hours later, but not 96 hours following training. Immediate post-training administration of epinephrine attenuated this recognition memory deficit when tested 96 hours after training.

Unlike environmental habituation, object recognition memory requires the animal to establish a memory for a specific environmental stimulus. Since it is common to provide animals with a chance to acclimate to the apparatus prior to training in tasks like novel object recognition (Besheer & Bevins, 2000), the present study took advantage of this opportunity to examine environmental habituation on postnatal days 14 and 15. Prior reports examining the ontogeny of environmental habituation have provided inconsistent results. Ba and Seri (1995) examined head-dip responses on a hole-board test in animals between postnatal day 10 and 45. They did not find any evidence of within-session habituation at postnatal days 10 or 15, but environmental habituation was evident at 20-days-of-age. Similar results have also been reported by Feigley, Parsons, Hamilton, and Spear (1972). In contrast, File (1978) used the head-dip response to examine the ontogeny of habituation and found that 16-day-old animals demonstrated both within- and between-session environmental habituation. Using an open field apparatus, Bronstein, Neiman, Wolkoff, and Levine (1974) recorded the number of grid crossings and the duration of horizontal movement in 15-, 21-, and 100-day-old rats. They found that 21- and 100-day-old animals habituated to the open field, but there was no evidence of within-session habituation in 15-day-old animals.

In the present study we examined the locomotor activity of 14- and 15-day-old animals in an open field for evidence of within- and between-session environmental habituation. On postnatal day 16, animals were returned to the open field for novel object recognition training. Animals were either tested for novel object recognition memory immediately after training, or were given a subcutaneous injection of saline or epinephrine followed by testing 2 hours later. No hypotheses were formulated regarding environmental habituation, given the lack of consensus in the literature. Based upon evidence indicating that epinephrine effectively attenuates infantile amnesia for avoidance conditioning and enhances object recognition memory in adult rats, we hypothesized that immediate posttraining injection of epinephrine would enhance subsequent retention performance.

Methods

Subjects

Fifty-nine (37 male, 22 female) Sprague-Dawley rat pups from 5 litters were used for this study. Animals were bred from Harlan Lab breeding stock at The College of Saint Rose. Litters were culled at 5-6 days-of-age to 11-12 pups per litter and were maintained in large Plexiglas cages with dam, food, and water for the duration of the study. The colony room was

kept at approximately 70° F on a reversed 9:15 hr light:dark cycle. All testing took place during the dark phase of the cycle. The date of birth was counted as day 0 when determining the age of the animals. Animals were handled for 3-min each on postnatal days 12 and 13 and all animals had their eyes open on day 14. Animals were weighed at postnatal day 16 ($M=30.90$ g, $SE=.45$ g) shortly prior to injection to ensure that injection volumes were accurate. All experimental procedures were approved by the Institutional Animal Care and Use Committee prior to the onset of the study.

Materials and Apparatus

The open field apparatus consisted of a round aluminum tub, within which a 54.0 cm diameter 2.0 cm thick board was inserted. Both the board and the aluminum tub were painted with multiple coats of black paint to seal the surfaces as well as provide a background on which animals would be easily visible. The walls of the apparatus were 25.4 cm high and the room was illuminated with overhead fluorescent lighting. A 68 dB white noise was present during all exposures to the apparatus to mask background noises. A total of four objects were used for training and testing on the novel object recognition task (2 identical green plastic bolts and 2 identical purple plastic Mega BloksTM). The green plastic bolt (circular base diameter = 3.5 cm, height = 6.4 cm) and a purple plastic Mega BlokTM (square base width = 3.2, height = 3.5) were selected from a set of objects based on pilot data that indicated equivalent preferences for the two objects. Objects were mounted onto small pieces of black Plexiglas (5.1 x 7.6 cm) with bolts extending from the bottom, that allowed them to be fitted into small pre-drilled holes on the base of the open field. Objects were positioned in the middle of the apparatus 20.3 cm apart on center. The apparatus and objects were thoroughly cleaned with disinfectant after each animal in order to eliminate the potential effect of scent marks left by prior animals.

Pre-training habituation sessions, training, and testing were recorded using the AnyMaze animal tracking system (Stoelting, Inc., Wood Dale, IL). The AnyMaze software was loaded onto a standard IBM office computer to which a digital camera was attached and suspended directly above the open field apparatus. Using the AnyMaze system, the open field was divided into 3 zones, the first zone contained the entire visible area of the open field (2289 cm²), the second zone measured 10.2 cm by 12.7 cm and encompassed the first object, and the third zone with the same dimensions encompassed the second object. The total distance traveled (m), overall average speed (m/s), number of entries into the object zones, and the time spent in the object zones (s) were recorded as dependent measures. Silvers, Harrod, Ferris, Mactutus, and Booze (2006) have demonstrated that the use of automated animal tracking systems produces the same pattern of results for object novelty tasks as coding dependent upon experimenter observation.

Sterile saline (.85% NaCl) or epinephrine (.01 mg/kg; Sigma Chemical Co., St. Louis, MO) were administered subcutaneously in the nape of the neck at a volume of 1 ml/kg. The dose of epinephrine was selected based on extensive literature indicating that this concentration is optimal for enhancing memory consolidation (Costa-Miserachs, Portell-Cortes, Aldavert-Vera, Torras-Garcia, & Morgado-Bernal, 1994; Flint, Bunsey, & Riccio,

2007; Nordby, Torras-Garcia, Portell-Cortes, & Costa-Miserachs, 2006; Williams, Men, Clayton, & Gold, 1998).

Procedure

Animals were handled for 3-min each on postnatal days 12 and 13 in order to acclimate them to being handled. On postnatal days 14 and 15, animals were placed individually into the open field apparatus without any objects present. Animals remained in the apparatus for 3-min during which AnyMaze tracked their behavior. This 2-day pre-training phase was used to acclimate the animals to the apparatus and to specifically examine these animals for within- and between-session environmental habituation. For all pre-training, training, and testing sessions animals were placed onto the center of the open field at the beginning of the session.

On postnatal day 16, animals were pseudorandomly assigned to one of 3 groups, so that 3-4 animals from each litter were represented in each group. Animals in the immediate test group (n=16) were tested immediately after training. Animals in the saline group (n=12) and the epinephrine group (n=17) were administered their respective subcutaneous injection immediately after training, followed by a 2-hr delay before testing was conducted. Training for all animals involved being placed into the center of the open field for 3-min in the presence of 2 identical objects. Designation of the training objects (green bolts or purple Mega Bloks™) was randomly counterbalanced across subjects. Testing for all animals involved being returned to the apparatus with one familiar object (from training) and one novel object (never seen before) for 3-min. The placement of the familiar and novel objects (left/right) was counterbalanced across animals. AnyMaze recorded the behavior of the animals during all phases of the study.

Results

Results were analyzed using parametric tests and were considered significant when p was less than or equal to .05. Partial eta squared (η_p^2) has been reported as an effect-size statistic for all omnibus analysis of variance (ANOVA) tests and Cohen's d (d ; Faul, Erdfelder, Lang, & Buchner, 2007) has been reported for pairwise analyses. Post-hoc power analyses have also been tabulated for all results that failed to reach statistical significance.

Pretraining Locomotor Activity

All animals were given 3-min sessions to explore the apparatus once at 14-days-old and again at 15-days-old during which the distance traveled and overall average speed were determined (see Figures 1 and 2). Each session was divided into 6 30-sec time blocks (epochs). A 2x2x6 (sex x day x epoch) mixed ANOVA for total distance traveled (m) revealed a significant effect of day [$F(1,57)=38.26, p<.001, \eta_p^2=.40$], a significant effect of epoch [Huynh-Feldt Correction $F(4.44,252.91)=45.27, p<.001, \eta_p^2=.44$], and a significant day

by epoch interaction [Huynh-Feldt Correction $F(4.76,271.10)=3.84$, $p<.01$, $\eta_p^2=.06$]. There was no main effect of sex [$F(1,57)=1.25$, $p>.05$, $\eta_p^2=.02$, power=.20]. Analyses of the overall average speed (m/s) revealed the same pattern of results. A $2 \times 2 \times 6$ (sex \times day \times epoch) mixed ANOVA for total distance traveled indicated a main effect of day [$F(1,57)=38.90$, $p<.001$, $\eta_p^2=.41$], a main effect of epoch [Huynh-Feldt Correction $F(4.42,251.70)=45.38$, $p<.001$, $\eta_p^2=.44$], and a significant day by epoch interaction [Huynh-Feldt Correction $F(4.74,270.13)=4.12$, $p=.002$, $\eta_p^2=.07$]. There was no main effect of sex [$F(1,57)=1.26$, $p>.05$, $\eta_p^2=.02$, power=.20].

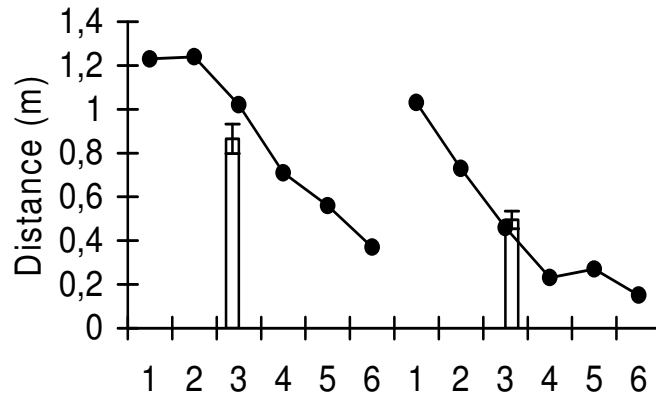


Figure 1. Lines represent the mean total distance traveled (m) during each of the 6 30-sec epochs at 14- and 15-days-of-age. Bars represent the mean total distance traveled on each day. Error bars represent the standard error of the mean.

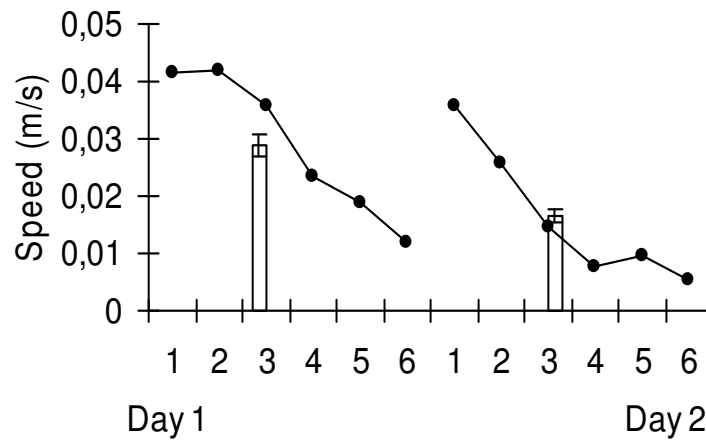


Figure 2. Lines represent the mean overall average speed (m/s) during each of the 6 30-sec epochs at 14- and 15-days-of-age. Bars represent the mean overall average speed on each day. Error bars represent the standard error of the mean.

Object Recognition

The absolute mean preference for novelty (novel minus familiar) and the relative percent preference for novelty [(novel/total) x 100] for the immediate test, saline control, and epinephrine groups were calculated for both the number of object zone entries and the time spent exploring each object. A 2x3 (sex x group) ANOVA on the absolute mean preference for novelty did not reveal any significant effects using the number of explorations [Sex $F(1,39)=1.40$, $p>.05$, power=.21; Group $F(2,39)=1.31$, $p>.05$, power=.27] or the time spent exploring [Sex $F(1,39)=.01$, $p>.05$, power=.05; Group $F(2,39)=1.51$, $p>.05$, power=.30]. ANOVAs for the relative percent preference for novelty, similarly, did not reveal any significant effects using the number of explorations [Sex $F(1,39)=.24$, $p>.05$, power=.08; Group $F(2,39)=1.44$, $p>.05$, power=.29]. However, a significant effect of group for the relative percent preference for novelty on time spent object exploring was revealed [$F(2,39)=5.00$, $p<.05$, $\eta_p^2=.20$] (see Figure 3). Post-hoc Fischer's LSD tests for pairwise comparisons revealed that the saline control tested 2-hrs after training had a significantly lower percent preference score in comparison to both the immediate test group and the epinephrine group tested 2-hrs after training. There was no significant effect of sex for the relative percent preference score [$F(1,39)=.52$, $p>.05$, power=.11].

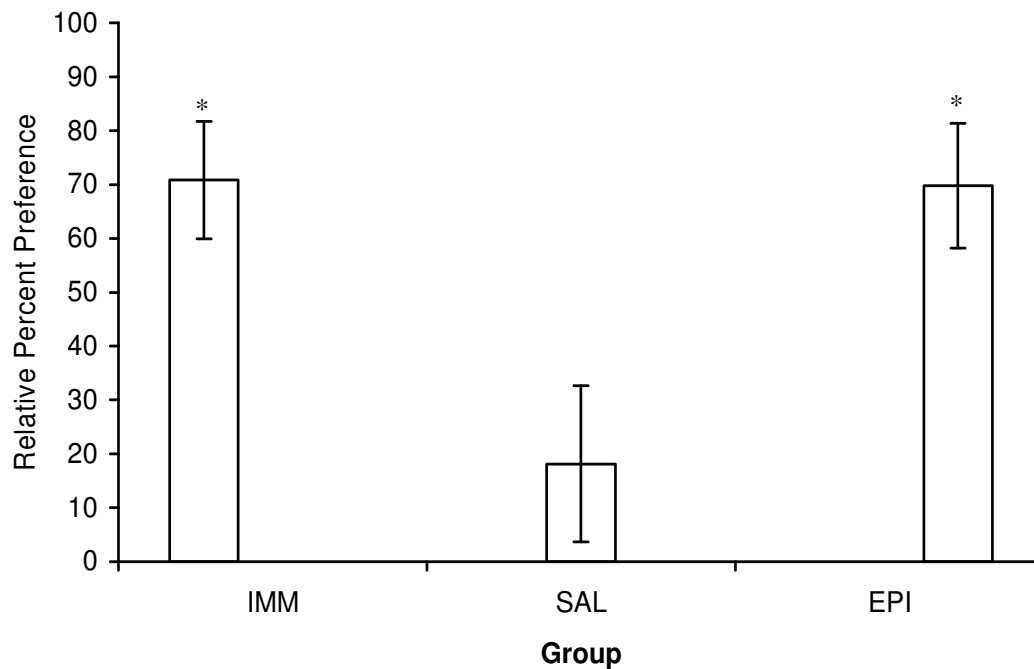


Figure 3. Mean relative percent preference for object exploration time for the immediate test, saline, and epinephrine groups. Error bars represent the standard error of the mean.

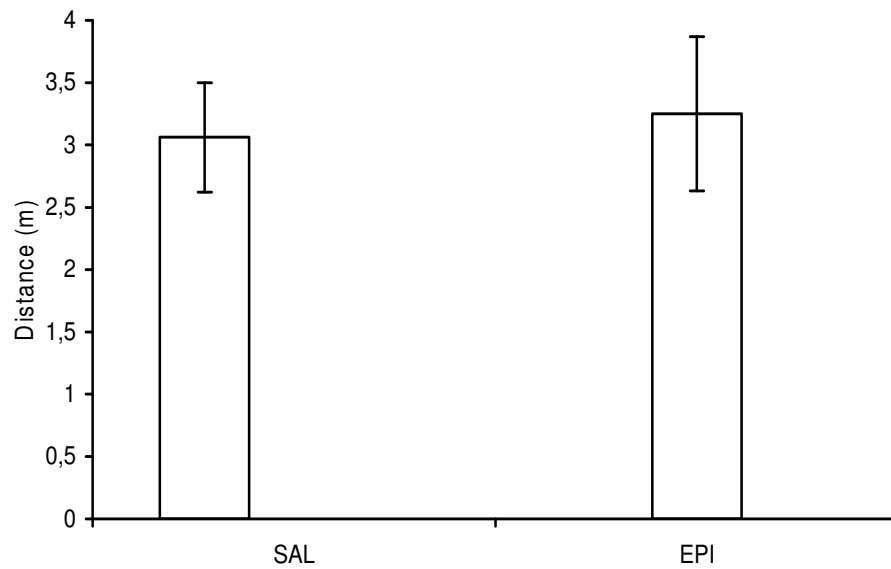


Figure 4. Mean total distance traveled (m) for the saline and epinephrine groups during the novel object recognition test on postnatal day 16. Error bars represent the standard error of the mean.

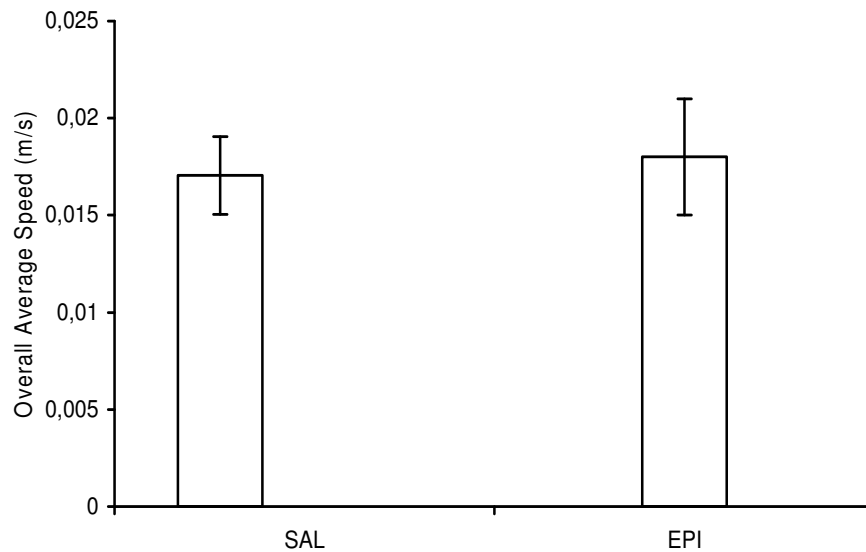


Figure 5. Mean overall average speed (m/s) for the saline and epinephrine groups during the novel object recognition test on postnatal day 16. Error bars represent the standard error of the mean.

Locomotor Activity during Testing

Since testing was conducted two hours following training in the saline and epinephrine groups, it is possible that residual effects of epinephrine might have elevated activity levels confounding the results. In order to examine this potential confound, the test data for male and female animals were combined, as prior analyses did not reveal any sex differences.

Independent samples t-tests for the total distance traveled [$t(38)=.25$, $p>.05$, $d=.45$, power=.28] and overall average speed [$t(38)=.23$, $p>.05$, $d=.00001$, power=.05] did not reveal any differences between the saline and the epinephrine groups (see Figures 4 and 5).

Conclusions

Early studies of environmental habituation depended upon manual coding, frequently involving counting the number of times animals crossed lines on the grid floor of an apparatus. With the advent of computerized animal tracking systems we are now able to obtain detailed measurements such as the exact distance traveled and the average speed providing a more accurate measure of exploratory behavior and activity level. In the present study, open field activity measures in animals at postnatal days 14 and 15 showed significant within- and between-session environmental habituation. The total distance traveled and the overall average speed declined across the 6 30-sec epochs within the test sessions on each day, and there was a significant reduction in these measures from day 1 to day 2. These changes in behavior indicate that at postnatal day 14, animals are capable of forming a memory of their environment and maintaining it for at least 24-hrs. Similar within- and between-session habituation results have been reported using head-dipping as a dependent measure in 16-day-old rats (File, 1978) and Goodwin and Barr (1997) have reported environmental habituation of locomotor activity at postnatal day 10. However, our results are in contrast to those reported by Bronstein, Neiman, Wolkoff, and Levine (1974) in a study of the ontogeny of environmental habituation (see also Feigley, Parsons, Hamilton, & Spear, 1972). The reason for this difference is not clear, but our study differs on many levels including the method of data collection, the size of the groups, and behavioral protocol.

Based, in part, upon earlier studies failing to show sufficient environmental habituation in immature animals, some researchers have suggested that this apparent behavioral deficit may be a result of an immature hippocampal system (Bronstein et al., 1974) or underdeveloped cholinergic inhibitory mechanism (Feigley et al., 1972). Carman and Mactutus (2001) used the water maze to investigate the ontogeny of spatial navigation in rats. A critical manipulation they made was to adjust the size of the apparatus to that of the developmental size of the animal. Using this technique, they were able to demonstrate that 17-day-old preweanling animals show evidence of learning in a water maze 1/3 the size of that used for adults. Based upon these data, Carman and Mactutus suggested that the developmentally immature state of the hippocampus in 17-day-old preweanling rats did not preclude its ability to integrate visual-spatial information. This hypothesis is important to the present study, as environmental habituation and novel object recognition memory are hippocampal-dependent tasks. If Carman and Mactutus are correct, it is logical to expect that the developmental state of the hippocampus between 14 and 16 days may similarly be sufficient to allow for visual-spatial learning. More importantly, it appears as though environmental habituation may be retained for at least 24-hours, similar to those reported by Carman and Mactutus using the water maze.

Results of the object recognition memory task indicate that epinephrine administered immediately following training attenuated the memory deficit seen in these infant animals

according to relative percent preference scores for the time spent exploring the objects. It is important to note that overall average speed and distance traveled during the object recognition memory test did not differ between groups, suggesting that there were no residual effects of epinephrine present. Additional support for this comes from the finding that absolute novelty preference scores, known to be sensitive to differences in activity levels, did not reflect any group differences. Epinephrine has a very short half-life and reaches peak plasma levels following stress in less than 1 minute (Berne & Levy, 1993; Dimsdale & Moss, 1980; Steptoe, 1987) in humans, so if plasma levels are similar in rats it is unlikely that epinephrine would have influenced locomotor activity 2-hrs following administration.

Although considerable evidence indicates that epinephrine enhances memory consolidation (Introini-Collison & McGaugh, 1991; McGaugh, 1983; McGaugh & Roozendaal, 2002), two studies by Izquierdo and colleagues have suggested that epinephrine may sometimes prevent the disruptive effects of retroactive interference (Izquierdo, Barcik, & Brioni, 1989; Izquierdo & Pereira, 1989). In their studies, the disruptive effects of post-training (conditioned emotional responding or inhibitory avoidance conditioning) exposure to an open field or extinction session were prevented with epinephrine administration. However, Izquierdo and Pereira did report that the retroactive interference produced by a series of tones presented following inhibitory avoidance conditioning was not attenuated by post-training epinephrine administration. It is therefore possible that post-training epinephrine effects on subsequent memory performance may, in part, be due to increased resistance to retroactive interference.

One potential mechanism of epinephrine-induced memory modulation involves the subsequent elevation in blood glucose level. Epinephrine does not easily cross the blood brain barrier (Axelrod, Weil-Malherbe, & Tomchick, 1959), but glucose does. Epinephrine affects the liver which in turn may then affect the pancreas, both leading to an elevation in blood glucose level (Flint, 2002). It is not clear whether or not this potential mechanism is intact and functional in 16-day-old rats. The development of the pancreas is ongoing following birth (Bourassa et al, 1999; Hill, Hogg, Petrik, Arany, & Han, 1999; Lu, Lebenthal, & Lee, 1987) and these immature animals are primarily utilizing ketones for energy at this age as opposed to glucose (Vannucci & Simpson, 2003). The later developmental switch from ketones to glucose is accompanied by elevations in glucose transporters in the brain (Vannucci, 1994; Vannucci et al., 1998; Vannucci, Seaman, Brucklacher, & Vannucci, 1994; Vannucci, Willing, & Vannucci, 1993) which recent evidence suggests may be important for memory (Choeiri, Staines, Miki, Seino, and Messier, 2005). Other mechanisms of epinephrine-induced memory modulation may include indirect effects on the nucleus tractus solitarius, basolateral nucleus of the amygdala, locus coeruleus, and the hippocampus (Clayton & Williams, 2000ab; Ferry, Roozendaal, & McGaugh, 1993; Liang, McGaugh, & Yao, 1990; Miyashita & Williams, 2004; Williams & McGaugh, 1993; Williams, Men, & Clayton, 2000). Future research may help to elucidate the mechanisms of epinephrine-induced memory modulation.

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