

Research report

The balance between approach and avoidance behaviors in a novel object exploration paradigm in mice

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Abstract

Approach and avoidance are critical components of novelty seeking, which plays an important role in susceptibility to drug abuse and aspects of cognition. This experiment was designed to examine whether brief periods of handling or prior exposure to a novel environment affect various measures of novel object exploration in mice. Forty male C57BL/6J mice were handled by the experimenter or received minimal exposure to human contact. In addition to manipulating the degree of familiarity with the experimenter (handling), we also manipulated the degree of familiarity with the object. All mice were tested over a 3-day period. On day 1, all mice were tested in the open field for 60 min. On day 2, there were two, 30-min sessions. In the first 30-min session, there was no object present. In the second 30-min session, half of the mice were exposed to a novel object. On day 3, all mice were placed in the open field for 30 min followed by a 30-min period in which the object was placed in the center of the open field. Handled mice showed a trend toward more object exploration on day 2 compared to non-handled mice. Mice with prior exposure to the novel object showed more object exploration compared to object-naïve mice on day 3. These results are consistent with the hypothesis that a certain degree of familiarity with the object or with the experimenter decreases avoidance and increases exploration of novel stimuli. In combination, these results show that the approach and avoidance dimensions of novelty seeking can be manipulated experimentally and may be used in subsequent studies to examine the effects of drugs of abuse.

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1. Introduction

Attending to novel stimuli is essential for responding to a constantly changing environment [3]. Consequently, novel stimuli create approach–avoidance conflict in the organism by stimulating both the exploration essential to survival (e.g., food-seeking behavior) and avoidance of potentially threatening situations [3,23,32]. Exploration is an essential aspect of behavior and has been well documented in several species (see [3]). For example, rats show a preference for novel environments over familiar environments in a free-choice situation [16,17] and will explore novel aspects of the environment even when they are satiated and the drive for food is presumably low [3]. In a Y-maze, rats will explore the novel arm preferentially over the two familiar arms [10], and hungry rats will choose a new runway in the presence of runways in which they have repeatedly obtained food [3]. This same preference for the novel arm of the Y-maze has also been shown in several mouse strains [9], and mice dis-

play exploratory patterns similar to those of rats in an open field [11]. In addition to showing preferences for novel environments, rats also show an increased preference for discrete novel objects [2,4,14,30]. For example, rats spend more time sniffing a novel object than a familiar object [2,14]. Based on the behavioral response to novelty in many of these paradigms, several investigators have suggested that novelty has incentive (appetitive) motivational properties that may be related to appetitive properties of drugs of abuse [1,5,35]. As with drugs of abuse, rats will demonstrate place conditioning to an environment previously paired with novel objects [5,6].

There has been an increased interest in the concept of novelty seeking in clinical populations based on the link between novelty-seeking traits and the risk of developing substance abuse [20,25,31]. Similarly, the degree of novelty seeking has been implicated as a predictive variable for drug-taking tendencies in animals [18,26]. In contrast to heightened novelty seeking as a component of drug taking behavior, reduced exploration of novel stimuli has been documented in individuals with autism [27] and Alzheimer's disease [8]. Hence, novelty seeking as a personality dimension [7,35,36] may be an important quantitative endophe-

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notype that predicts susceptibility for the development and course of neuropsychiatric disorders.

Approach–avoidance behaviors represent a complex equilibrium that is affected by a number of experimental factors. For example, previous studies have suggested that familiarization with the environment will enhance approach behavior elicited by novelty. Specifically, rats will spend more time exploring a novel object when the environment is familiar [2,6,30]. The aim of the current study was to investigate the effects of (1) familiarity with environment, (2) familiarity with experimenter (handling), and (3) familiarity with the novel object on the exploration of novelty in mice. We have shown previously that an object placed in the center of an open field will elicit approach behavior in mice [12,28]. There were three main hypotheses from this experiment. First, handling will decrease experimenter-induced avoidance behaviors and therefore increase exploration of the novel object. Second, familiarity with the novel environment will decrease avoidance behaviors, particularly in the center of the enclosure and, will increase approach behaviors to a novel object. Third, the increase in exposure to a novel object will have competing effects in that the reduction in novelty will tend to reduce exploration while the reduction in threat will tend to increase exploration. Therefore, the time course of the approach behavior should be altered.

2. Materials and methods

2.1. Subjects

Forty C57BL/6J male mice were obtained from Jackson Laboratories (Bar Harbor, Maine). Behavioral testing occurred between 8 and 9 weeks of age when the mice weighed approximately 20–40 g. Mice were housed four per cage and kept on a 12 h light/dark cycle (lights off at 9.00 a.m.) with food (Harlan Teklab, Madison, WI) and water available ad libitum, except during behavioral testing. Testing occurred during the dark phase between 11.00 a.m. and 6.00 p.m. Experiments were approved by the local animal care and use committee and were conducted in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23). All efforts were made to minimize the number of animals used and the suffering of animals in these experiments.

2.2. Apparatus

The video-tracker (VT) consisted of four adjacent white Plexiglas enclosures (41 cm × 41 cm × 34 cm) surrounded by a white plastic curtain. Each mouse was tested individually in a separate enclosure. A video camera, mounted 158 cm above the enclosures, provided the signal for the Polytrack digitizer (San Diego Instruments). The signal was processed to obtain the left-uppermost coordinate for each of the four animals simultaneously. The signal was stored in a PC com-

puter for further off-line processing. For this investigation, the (x, y) position (in pixels) of each animal was sampled at a rate of 18.18 Hz and used to generate a (x, y, t) coordinate file consisting of the x -location, the y -location, and the duration of time (t) spent at that location. The spatio-temporal resolution of each event recorded was 0.32 cm, 0.32 cm, and 55 ms, which corresponded to a maximum speed of 25 cm/s. The novel objects in these studies were Mega Bloks[®] structures approximately 5 cm³. They were not perfect cubes, however, because there were some missing pieces in order to provide more complexity to the object. The structures consisted of several different colors and the primary colors were kept consistent between the objects. Objects were glued together with adhesive, soaked in dilute chlorine bleach (~10% solution), rinsed, and stored submerged in bedding for at least 24 h prior to testing. Thus, each mouse was exposed to a clean, pre-soaked Mega Bloks[®] structure.

2.3. Handling procedure

Twenty mice were handled for 5 min per day during the 2 days prior to testing in the VT, and 20 mice were assigned to the non-handled group. For the handling condition, mice were brought to the testing room in their home cages. Handling consisted of picking up two mice at a time and holding them together in the experimenter's hands until they no longer attempted to jump out of the hands. The experimenter allowed the mice to crawl in between his two hands and gently stroked the mice until they were visibly calm. In total, the handling procedure lasted approximately 5 min for a pair of mice.

2.4. Dependent measures

Each mouse was placed in the bottom left hand corner of their respective enclosure at the start of the test session. The movements of the mice were tracked for either 30 or 60 min, with data being stored in 6 or 12, 5-min blocks, respectively. To analyze the locomotor data, an arbitrary maze was created that consisted of a center (20 cm × 20 cm; or 40 × 40 pixels), four corners (10 cm × 10 cm; or 20 × 20 pixels), and four rectangular areas along the walls (20 cm × 10 cm; or 40 × 20 pixels) (Fig. 1). Four dependent measures were calculated. To assess the overall amount of locomotor activity, transitions between the nine regions of the maze were counted. The geometric patterns of locomotor activity were quantified by the spatial scaling exponent, d , as described in detail elsewhere [24]. Briefly, the spatial scaling exponent, d , quantifies the extent to which a sequence of movements are along a straight line ($d = 1$) or within a circumscribed area ($d = 2$). The time spent in the center (min) was also calculated as the primary variable used to quantify response to the novel object. Although center duration does not directly measure interactions with the object, observations of the mice via videotapes indicate that the measure is highly correlated with object exploration (see also Fig. 1). In addi-

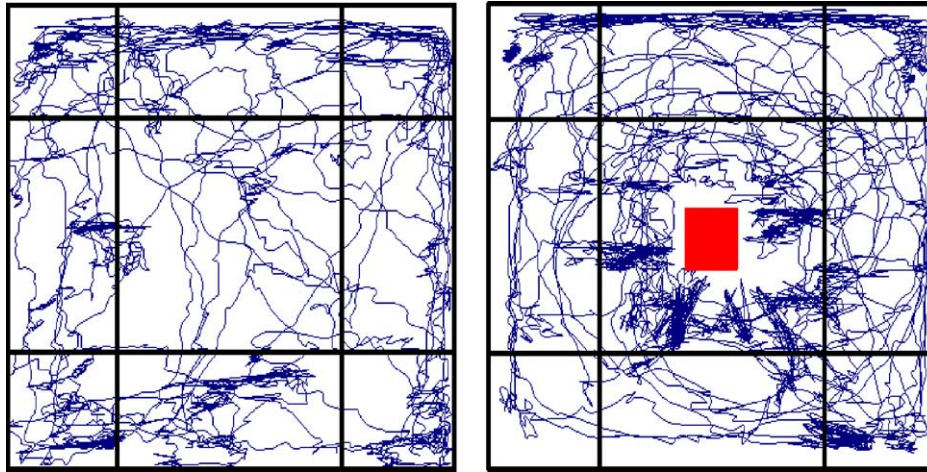


Fig. 1. Locomotor patterns of mice during the first 5 min of habituation (left panel) and object presentation (right panel). Overlay indicates the dimensions of the maze used to calculate center duration. Square in the middle denotes the size and position of the novel object placed in the center of the arena.

tion, the mean duration per response was defined as the average time (s) spent in the center during each entry into the center. In order to validate the ability of the maze to detect differences in the behavior of the mice in response to the novel object, we analyzed the cumulative time spent at various distances (pixels) from the center for the mice exposed to the object on day 2, with the object occupying approximately 7 pixels from center (Fig. 2). These data showed that the presence of the novel object shifts the behavior of the mice towards the center of the open field and indicated that the distance from the center defined by our maze (20–28 pixels) provided a sensitive measure of the behavioral response to the novel object.

2.5. Experimental design

Mice were tested over a 3-day period. On day 1, all mice were exposed to the VT for a 60-min period. On day 2, half of the mice from each treatment group were exposed to the

VT for 30 min, and then a novel Mega Bloks[®] object was placed in the center of each open field and locomotor activity assessed for an additional 30 min (Fig. 1). The other 20 mice were placed in the VT for a 60-min period without an object present. On day 3, all of the mice were placed in the VT for 30 min, and then an object was placed in the middle of the chamber and locomotor activity recorded for an additional 30 min. Thus, mice were exposed to the open field without the object for either two or one, 60-min periods and had the opportunity to explore the novel object in the center of the enclosure once or twice, respectively.

2.6. Data analysis

Since the behavioral experience of the mice differed across day (e.g., exposure to the object), data were analyzed by day. A three-way analysis of variance (ANOVA) with handling condition as a between subjects factor and test (first 30-min versus second 30-min) and block (six, 5-min time bins) as within subject factors were conducted on the four dependent measures. Data from the mice that were exposed to the object and those not exposed to the object were analyzed separately on day 2. On day 3, an additional between subject factor, exposure (whether or not mice had been exposed to the object on day 2), was included in the ANOVA.

3. Results

3.1. Day 1

3.1.1. Center duration

On day 1, the amount of time spent in the center of the arena was not affected by handling, block, or a block by handling interaction (Fig. 3A).

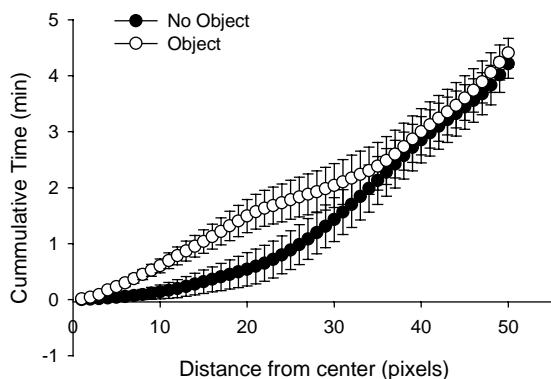


Fig. 2. Cumulative time spent at various distances from the center on day 2 during the first 5 min of the 30-min period during object presentation compared to no object presentation. The Mega Bloks[®] object occupies approximately 7 pixels (center to outer edge).

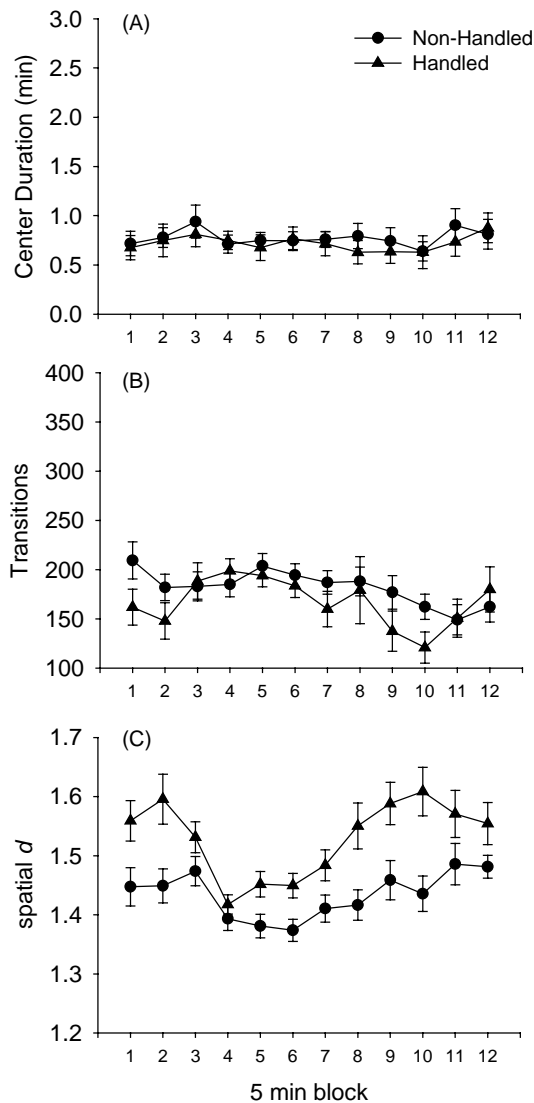


Fig. 3. (A) Center duration, (B) transitions, and (C) spatial d on day 1 in handled and non-handled mice ($n = 20$ per group). Data are presented as mean (\pm S.E.M.).

3.1.2. Locomotor activity

As with center duration, there was no effect of handling on the amount of locomotor activity on day 1, as measured by transitions. There was a main effect of block on transitions [$F(11, 418) = 3.58$, $P < 0.001$], but no block by handling interaction (Fig. 3B).

3.1.3. Spatial d

There was a significant effect of handling on spatial d , with handled mice showing higher spatial d values than non-handled mice [$F(1, 38) = 9.65$, $P < 0.01$] (Fig. 3C). This difference in spatial d indicates that handled mice engaged in more circumscribed locomotor patterns compared to non-handled mice. There was a main effect of block on spatial d [$F(11, 418) = 11.74$, $P < 0.001$], with d values decreasing during the first 30 min and then increasing dur-

ing the last 30 min of the session. This pattern of changes in spatial d was less pronounced in non-handled mice, as indicated by a handling \times block interaction [$F(11, 418) = 2.31$, $P < 0.01$].

3.2. Day 2

3.2.1. Center duration

In the group of animals that was exposed to the object on day 2, there were main effects of test (pre versus post-object exposure) [$F(1, 18) = 7.02$, $P < 0.05$] and block (5 min blocks) [$F(5, 90) = 6.81$, $P < 0.001$] on center duration. Thus, center duration was greater during object presentation than during the habituation period and increased over time during object presentation (Fig. 4A; Fig. 1). There were no main or interactive effects of handling on center duration. In order to capture the interplay between approach and avoidance, which is strongest during the first exposure to the novel object, we analyzed the 5 min blocks before and after the object presentation using a post hoc ANOVA. There was a significant interaction between test and handling [$F(1, 18) = 5.12$, $P < 0.05$]. While handled mice did not initially increase time spent in the center during the 5 min following object presentation compared to the 5 min prior to object presentation, non-handled mice actually decreased their time spent in the center during this initial object presentation [paired t -test, $t(9) = 3.465$, $P < 0.05$; Fig. 4A]. Hence, non-handled mice spent less time in the center during the first 5 min of object presentation than did handled mice [pairwise t -test, $t(18) = -2.44$, $P = 0.025$]. As depicted in Fig. 4A, non-handled mice increased the time spent in the center after this initial avoidance and eventually reached center duration times comparable to those observed in handled mice. The group of mice that did not receive the object showed no effect of handling on center duration. Therefore, the data from these animals were collapsed across handling condition and shown in the graphs for qualitative comparisons only (Fig. 4).

To better quantify the differences between handled and non-handled mice in response to the novel object, the average time spent in the center per entry into the center (mean duration per response; MDPR) during the session on day 2 was calculated (Fig. 5). Handled mice spent more time in the center with each center entry than did non-handled mice, as confirmed by a significant effect of handling on MDPR [$F(1, 14) = 58.21$, $P < 0.05$]. There were also significant effects of test [$F(1, 14) = 5.03$, $P < 0.05$] and block [$F(5, 70) = 2.57$, $P < 0.05$] on MDPR, as well as a significant test \times block interaction [$F(5, 70) = 2.47$, $P < 0.05$], with the average MDPR increasing during the 30-min session following object placement.

3.2.2. Locomotor activity

In the group of animals that was exposed to the object on day 2, there was a main effect of handling on the amount of locomotor activity (transitions; Fig. 4B), with non-handled

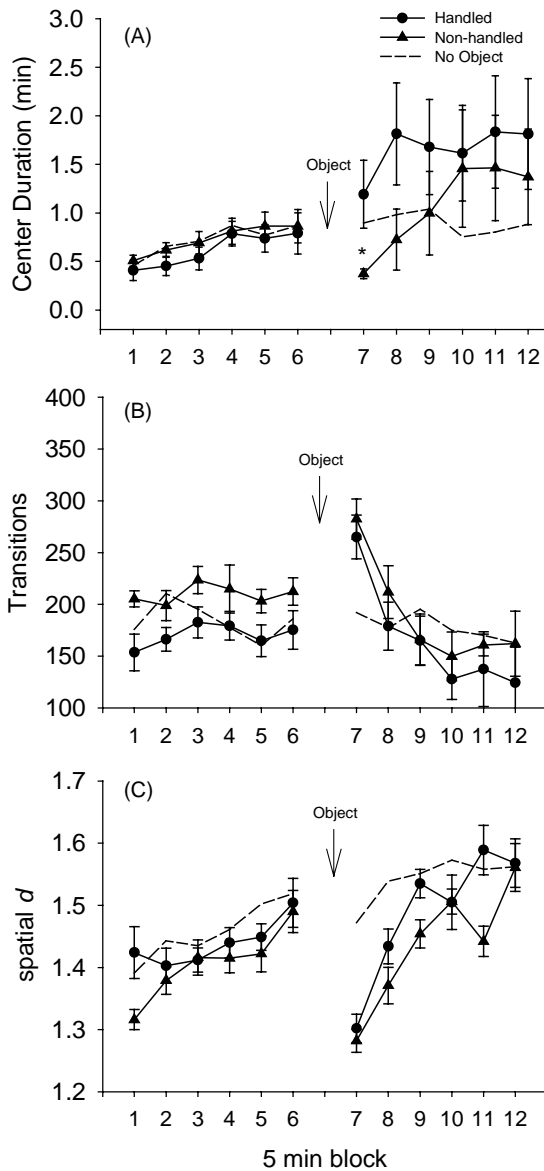


Fig. 4. (A) Center duration, (B) transitions, and (C) spatial d pre- and post-object presentation on day 2 in mice exposed to the object. Mice not exposed to the object are indicated by the dashed line (data collapsed across handling condition). Data are presented as mean (\pm S.E.M.). * $P < 0.05$.

mice showing higher levels of locomotor activity than handled mice [$F(1, 18) = 5.77, P < 0.05$]. There was a significant effect of block [$F(5, 90) = 6.48, P < 0.001$] and a block \times test interaction [$F(5, 90) = 12.78, P < 0.001$] on transitions, with locomotor activity increasing immediately following object presentation and declining to a level below that seen in the habituation period (Fig. 4B).

3.2.3. Spatial d

In the group of animals that was exposed to the object on day 2 there was a significant effect of handling on spatial d with handled mice showing slightly higher values of

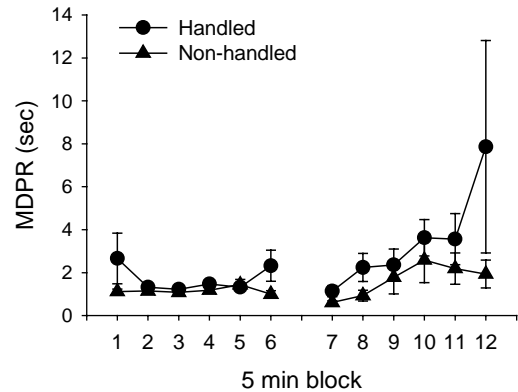


Fig. 5. Mean duration per center entry during day 2 during habituation (left panel) and object presentation (right panel). Data represent the average time spent in the center per entry into the center (mean duration per response). Mice that did not enter into the center in any block were excluded from analyses; handled [$n = 7$]; non-handled [$n = 9$].

spatial d than non-handled mice (Fig. 4C; $F(1, 18) = 5.01, P < 0.05$), i.e., handled mice were engaging in more circumscribed movements relative to non-handled mice. There were significant effects of test [$F(1, 18) = 4.58, P < 0.05$] and block [$F(5, 90) = 105.76, P < 0.001$] on spatial d and a significant test \times block interaction [$F(5, 90) = 24.92, P < 0.001$], with spatial d decreasing during the initial period following object presentation, indicating more straight, linear movements (Fig. 4C).

3.3. Day 3

3.3.1. Center duration

Mice with prior exposure to the novel object spent more time in the center compared to object-naïve mice without previous object exposure (main effect of pre-exposure [$F(1, 36) = 5.16, P < 0.05$]; Fig. 6A). As shown in Fig. 6A, pre-exposed mice spent more time in the center specifically during object presentation as indicated by a test by pre-exposure interaction [$F(1, 36) = 5.42, P < 0.05$]. Subsequent two-way ANOVAs revealed a main effect of exposure on center duration during the second half of the test session (post-object presentation) [$F(1, 36) = 5.74, P < 0.025$], but not during the first half of the test session (pre-object presentation). There was no main effect of test on center duration on day 3, most likely because the non-handled, object naïve mice did not show an increase in the time spent in the center during object presentation. There was a test \times block interaction on center duration [$F(5, 180) = 3.20, P < 0.01$], with center duration increasing slightly over the 30 min prior to object presentation, initially rising (in pre-exposed mice only) and then decreasing slightly over the 30 min following object presentation (Fig. 6A). There was no main effect of handling and no interactions between handling and pre-exposure, test, or block.

The average time spent in the center per entry into the center, MDPR, was also calculated for day 3 (data not shown).

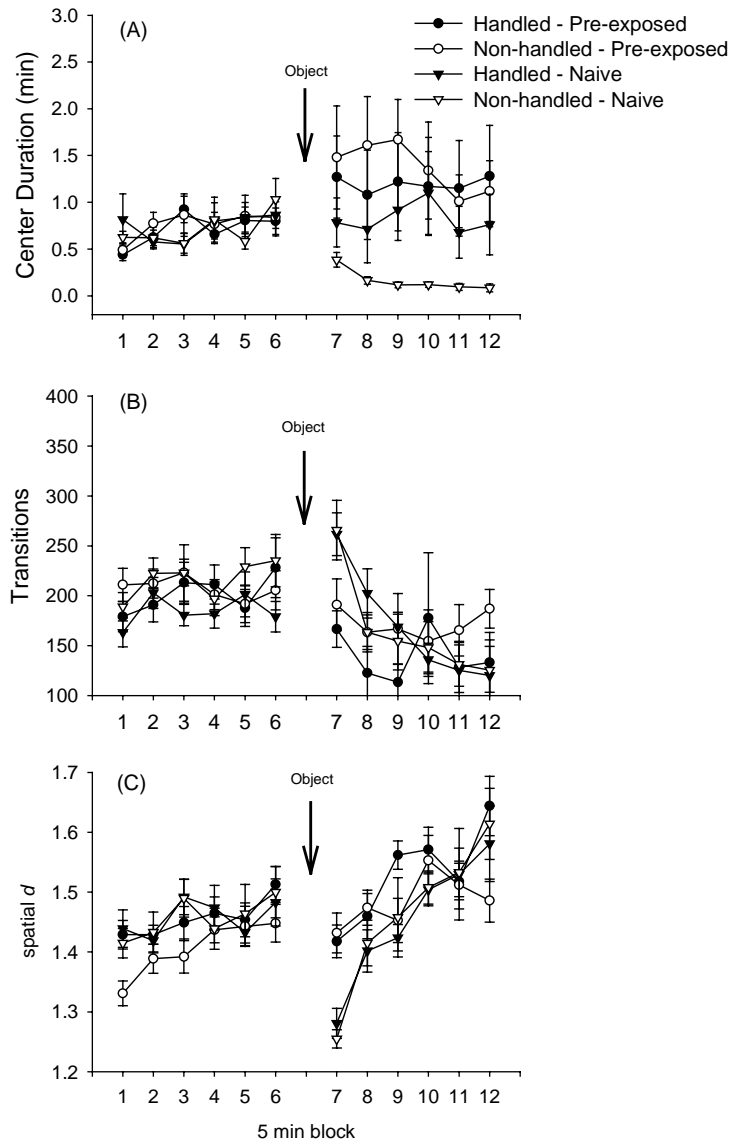


Fig. 6. (A) Center duration, (B) transitions, and (C) spatial *d* pre- and post-object presentation on day 3 in object-naïve (mice not receiving the object on day 2) and pre-exposed (mice receiving the object on day 2) mice. Data are presented as mean (\pm S.E.M.).

There was no effect of handling or pre-exposure [$F(1, 24) = 2.47$, $P = 0.13$] or a handling \times pre-exposure interaction. There was a marginal effect of test [$F(1, 24) = 2.98$, $P = 0.097$] and a test \times pre-exposure interaction [$F(1, 24) = 2.90$, $P = 0.10$], but no test \times handling interaction. There was also no effect of block or any interactions with block on MDPR.

When data from mice receiving the object on day 2 (Fig. 4A) are compared with mice receiving the object on day 3 for the first time (Fig. 6A, object-naïve group), there was an overall effect of object exposure [$F(1, 36) = 8.10$, $P < 0.01$]. Mice that spent less time in the open field prior to object exposure (day 2 exposure; 90 min total time in VT) showed more novel object exploration compared to mice that spent more time in the arena prior to object exploration (day 3 exposure; 150 min total time in VT). In

this comparison, there was also a main effect of handling [$F(1, 36) = 4.27$, $P < 0.05$] with handled mice spending more time in the center than non-handled mice.

3.3.2. Locomotor activity

There were main effects of test [$F(1, 36) = 21.10$, $P < 0.001$] and block [$F(5, 180) = 3.26$, $P < 0.01$] on transitions and a significant test \times block interaction [$F(5, 180) = 9.35$, $P < 0.001$], indicating that transitions increased immediately after object exposure but declined to below baseline levels at the end of the 30-min session with the object (Fig. 6B). There was no main effect of handling or exposure on transitions, and no handling by exposure interaction. There was, however, a block \times exposure interaction [$F(5, 180) = 3.21$, $P < 0.01$] and a test \times block \times exposure interaction [$F(5, 180) = 4.41$, $P < 0.01$], with object-naïve mice

showing higher levels of locomotor activity immediately after object presentation compared to pre-exposed mice, but declining to levels below pre-exposed mice by the end of the session.

3.3.3. Spatial *d*

Similar to day 2, there were significant effects of test [$F(1, 36) = 9.17, P < 0.01$] and block [$F(5, 180) = 32.71, P < 0.0001$] on spatial *d*, as well as a test \times block interaction ([$F(5, 180) = 9.29, P < 0.001$]; Fig. 6C). There was no significant effect of handling or exposure and no handling \times exposure interaction. There was a significant test \times block \times exposure interaction [$F(5, 180) = 5.56, P < 0.001$] with spatial *d* decreasing during the initial 5–10 min period following object presentation in both handled and non-handled object-naïve mice, similar to the initial decrease in spatial *d* seen in mice exposed to the object on day 2 (Fig. 6C).

4. Discussion

This investigation yielded two main results. First, handling significantly increased approach to the novel object, but only in the first 5 min. Moreover, handled mice spent more time in the center per center entry than did non-handled mice. Second, mice with prior exposure to the novel object spent more time in the center compared to object-naïve mice without previous object exposure. In combination, these results are consistent with the hypothesis that novel object exploration as a behavioral paradigm to assess novelty seeking is not invariable, but is affected by context (handling-experimenter) and stimulus-related (pre-exposure-object) factors.

Placing a novel object in the center of the testing environment elicited a complex set of responses in mice that can best be described as an equilibrium between approach and avoidance. Moreover, this equilibrium is affected by handling, pre-exposure, and familiarity. Specifically, approach behaviors (defined as an increased time spent in the center of the open field in response to the object), similar to those observed by Dulawa et al. [12] and Powell et al. [28] were observed during the first exposure of the mice to the object on day 2 (Fig. 1). It should be noted, however, that the mice not exposed to the object were not disturbed in the same manner as the object exposed mice (e.g., a hand placing the object in the center of the arena). Future experiments should address this issue by disturbing the non-object-exposed mice in a manner similar to that of the object-exposed mice.

During the initial object presentation, handled mice increased their time spent in the center; whereas, non-handled mice showed an initial avoidance of the center. These data support previous studies in rats showing that pre-test handling increased time spent in the center of the open field and the number of object approaches [29]. While handling did not affect locomotor activity or time spent in the center on day 1, handled mice actually showed less locomotor ac-

tivity on day 2 compared to non-handled mice. These data appear to contrast with reports of an increase in locomotion in rats exposed to early infantile handling [34]; however, the brief, pre-test handling conducted in the current experiment is drastically different in timing and duration from early infantile handling, as has been well documented in the literature [21,22].

In addition to manipulating the degree of familiarity with the experimenter (handling), we also manipulated the degree of familiarity with the object. Prior familiarity with the object resulted in increased approach behavior, i.e., on day 3, mice with prior exposure to the novel object showed more object exploration compared to mice having had no previous object exposure. Pre-exposure and handling resulted in a complex interaction. While non-handled, pre-exposed mice showed slightly more object exploration on day 3 (compared to first exposure), handled mice showed slightly less object exploration on day 3. It appears that the main effect of pre-exposure is explained by the object-naïve mice not increasing center time during object presentation on day 3. In fact, non-handled mice appeared to avoid the object.

These results are consistent with the hypothesis that a certain degree of familiarity with either the object (pre-exposure) or the experimenter (handling) decreases avoidance and increases exploration of novel stimuli. In a similar set of experiments using an object recognition paradigm, Besheer and Bevins [4] found that rats displayed a preference for a novel over a familiar object only when they had been familiarized to the environment. In our study, however, repeated exposure to the open field without the object resulted in less exploration of the object. Thus, our findings did not support the observation of Besheer and Bevins [4] that familiarization solely with the environment (open field) increased exploration of the novel object. In our study, it appeared that too much exposure to the open field without the object reduced novel object exploration.

One possible explanation for this finding could be that exploration of a novel object is a function of the “relative” novelty difference between the object and the environment. Thus, in a novel environment, a novel object shows relatively little additional novelty effect and therefore elicits relatively little additional exploration. In contrast, in a highly familiar environment, a novel object may elicit an avoidance response due to the large difference between the environment and the object. Thus, one would expect to observe the largest increase in novel exploration when the environment and novel object novelty difference is at an intermediate level. Along these lines, File [15] has argued that the elevated plus maze requires a certain degree of novelty to elicit exploration of the open arms. Specifically, mice with prior exposure to the testing apparatus show reduced activity on the elevated plus maze [15]. It should be noted, however, that the comparison between mice exposed to the object on day 2 and mice exposed to the object for the first time on day 3 is confounded by concomitant differences in other variables, such as number of exposures to the arena,

degree of handling, and transport to the test room. Thus, the behavioral difference between the two groups may not be due only to the amount of time spent in the arena (i.e., familiarization). Future studies should address these issues in more complete parametric designs comparing responses to novelty in conditions of familiarity and no familiarity with the open field prior to object placement.

One of the benefits of the current novel object paradigm is that we can distinguish between diversive vs. inspective exploration by examining the change in the amount of time spent in the center upon each center entry (MDPR) over the course of the 30-min object exposure. For example, on day 2, the MDPR starts low and progressively increases during object exposure (Fig. 5). The first half of the object presentation session (first 15 min) could be considered diversive exploration and the second half of the session could be considered inspective exploration based on the assumption that initially the mice sample the environment with the addition of the new stimulus and subsequently explore the novel stimulus in greater detail. This notion is supported by the observation that upon initial exposure to the novel object, spatial d was low, indicating more straight, distance-covering movements. Spatial d then increased throughout the 30-min object presentation, indicating the transition to more of the local, circumscribed movements characteristic of object investigation. Similarly, on both days when mice were exposed to the object for the first time, transitions initially increased and then subsequently declined over the 30-min session. A more detailed analysis of the spatio-temporal organization of locomotor behavior (e.g., stops, darting behavior) in response to novel objects may be warranted [13,19].

The data from these studies suggest that alterations in the avoidance properties of the open field may be manipulated in order to facilitate approach behavior (to a certain extent exposure to the experimenter and to a greater extent exposure to the object). Whimbey and Denenberg [33] argue that the level of exploration and “emotional reactivity” are two independent factors and not inversely related aspects of the same behavioral continuum [33]. While we agree that the factors are not part of the same continuum, we and others have conceptualized approach and avoidance (or exploration and “fear”) as competing factors determining the resultant behavior [34]. To better understand the relative contributions of approach and avoidance factors to exploratory behavior, future studies could further assess the effects of modulation of approach and avoidance components of the paradigm. For example, manipulating factors contributing to levels of avoidance (e.g., increase/decrease lighting conditions) and assessing the behavioral response to anxiolytic and anxiogenic compounds in this paradigm may be warranted.

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