

# Mouse twins separated when young: A history of exploration doubles the heritability of boldness and differentially affects the heritability of measures of learning

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## ABSTRACT

Most quantifiable traits exhibit some degree of heritability. The heritability of physical traits is often high, but the heritability of some personality traits and intelligence can also be highly heritable. Importantly, estimates of heritability can change dramatically depending on such variables as the age or the environmental history of the sample from which the estimate is obtained. Interpretation of these changing estimates is complicated in studies of humans, where (based on correlational observations) environmental variables are hard to directly control or specify. Using laboratory mice, here we could control specific environmental variables. We assessed 58 groups of four full sibling male CD-1 genetically heterogeneous mice ( $n = 232$ ). Using a standard full-sibling analysis, physical characteristics (body weight and brain weight) were highly heritable ( $h$  of body weight = 0.66 on a 0–1 scale), while behaviors indicative of a personality trait (exploration/boldness) and learning abilities (in a passive avoidance and egocentric maze task) were weakly-to-moderately heritable. Half of the siblings from each set of four were housed in an “enriched” environment, which provided extensive and varied opportunities for exploration. This enrichment treatment promoted improvements in learning and a shift toward a more bold personality type. Relative to animals in control (“impoverished” environments), the history of enrichment had significant impact on estimates of heritability. In particular, the heritability of behaviors related to the personality trait (exploration/boldness) more than doubled, and a similar increase was observed for learning (in the passive avoidance task). Physical traits (brain and body weight), however, were insensitive to environmental history (where in both environments, animals received the same diet). These results indicate that heritable traits can be responsive to variations in the environment, and moreover, that estimates of heritability of learning and personality traits are strongly influenced by environments that modulate those traits.

## 1. Introduction

Outside of fields related to behavior genetics, it is not always appreciated that estimates of heritability can vary dramatically depending on the environmental conditions and age of the population from which the estimates are obtained. The sensitivity to the environment is most pronounced in estimates of the heritability of cognitive performance. For instance, Turkheimer et al. estimated genetic and environmental effects on IQ in 7-year-old twins in high and low socioeconomic status (SES) families (Turkheimer, Haley, Waldron, D’Onofrio, & Gottesman, 2003). It was reported that among affluent families, most of IQ’s variation was associated with genetic variation, and almost none was associated with shared familial environment (heritability of 0.72, with the rest associated with unique environments). However, among the

poorest families, the reverse was true: most of variation in IQ was associated with the shared familial environment, and little with genetic variation (heritability of 0.10). Similarly, Harden et al. assessed a sample of adolescent twins (Harden, Turkheimer, & Loehlin, 2007). Among those from the lowest SES families, genetic influences accounted for 39% of the variance in cognitive abilities, while among the twins from the wealthiest families, genetic effects accounted for 55% of the variance in cognitive abilities. These patterns reflect a unique property of intelligence, where intelligence can effectively self-organize and select for itself, i.e., similar individuals are disproportionately likely to gravitate to more similar cognitive challenges, ultimately reducing independent environmental sources of variance and increasing estimates of heritability (for discussion and implications, see Sauce & Matzel, 2018). Of course these effects of environment cannot be

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realized in sterile environments in which independent choices cannot be fully realized. For instance, the impact of SES on the heritability of IQ is minimized in populations where educational and health care opportunities are more equitably distributed (for relevant data and discussion, see Bates, Hansell, Martin, & Wright, 2016).

Heritability is an estimate of the degree to which genes are associated with variations in a trait. Estimates of heritability range from 0.0 (meaning that the trait has no genetic component) to 1.0 (meaning that the trait is completely heritable). Among humans, it is recognized that most quantifiable traits are (to varying degrees) heritable. For instance, in infancy, height and body weight are highly heritable physical traits ( $h > 0.90$ ; Mook-Kanamori et al., 2012; van Dommelen, de Gunst, van der Vaart, & Boomsma, 2004). Psychological traits can exhibit similar moderate-to-high degrees of heritability (Bouchard, 2004), such as major depression ( $h = 0.35$ ), alcoholism ( $h = 0.50$ ), and schizophrenia ( $h = 0.80$ ). Strikingly, intelligence is among the most heritable of psychological traits, with estimates (in middle age) sometimes as high as 0.80 (Bouchard Jr., 1997; Plomin, 1999).

Calculations of heritability are commonly obtained by methods which estimate the degree of correlation in a trait between related individuals. A very common approach is to assess the difference in the correlation between fraternal and identical twins. In these cases, environment is assumed to be held constant (i.e., the twins are raised in the same environment). However, this assumption has been the source of much debate. Note that even when twins are raised apart, the degree to which a trait like intelligence determines an individual's choices can result in channeling of both twins into similar cognitive tracks (i.e., they make choices that reflect their similar cognitive dispositions). These complications have led to recurring controversies regarding the interpretation of estimates of heritability (Sauce & Matzel, 2018), in part because the genetic contribution to variations in a trait can be easily over-estimated, while gene-environment interactions (GxE), and particularly correlations (rGE), can be disregarded such that any estimate of heritability is mistakenly attributed solely to genetic influences.

Complications associated with studies of familial relationships could be mitigated were it possible to *manipulate* individual's exposure to particular environments and/or to specify critical environmental variables. While this is difficult to achieve in studies of humans, in laboratory animals the environment can be tightly controlled and environmental history can be precisely defined or measured. Galsworthy et al. (2005) directly calculated (using a classic sibling analysis) in adult mice the heritability of a trait analogous to intelligence (or a general cognitive ability). They tested adult outbred mice on a battery of seven cognitive tasks that were dependent on at least four different motivational states and which required the engagement of a range of sensory and motor systems. A single factor accounted for 36% of the variability in the aggregate performance of individuals across all tasks. The heritability of animals' aggregate performance across all cognitive tasks was estimated at approximately 0.4, suggesting a moderate genetic contribution to the expression of general cognitive performance.

The results of Galsworthy et al. (2005) provide evidence that cognitive abilities in mice are moderately heritable. However, this estimate of heritability is markedly lower than that which is typically reported for intelligence in adult humans (which is commonly estimated to range from 0.7–0.8; Bouchard, 2004; Bouchard Jr., 1997; Haworth et al., 2010). This raises an intriguing possibility: Unlike typical humans, laboratory mice are maintained in a behaviorally sterile (or impoverished) environment that is homogeneous across mice. Thus, these mice cannot select the environments or challenges, or interact with their environment in such a way that might instantiate (or maximize) cognitive differences, i.e., they cannot *select* an environment that is matched to their cognitive ability, the consequence of which might be a reduction in the estimate of heritability relative to what is observed in humans.

The present study had two main objectives. First, we intended to estimate the heritability of a range of physical, personality, and

learning traits in genetically heterogeneous laboratory mice. These calculations were based on a classic twin study, i.e., we assessed these traits in a large sample of heterozygous twins, but in our case, the animals' environment was tightly controlled *and* manipulated. A second goal of our study was to assess how estimates of heritability were impacted by environmental manipulation. This was analogous to a human twin adoption study, i.e., twins were maintained in one of two environments, in this instance, one environment could be described as “impoverished” and one was “enriched”. However, unlike a human adoption study, here the animals' nominal exposure to the environments was imposed on the animals (and thus not effected by economic circumstance or the animals' choices or predispositions). With this strategy, it was also possible to manipulate *specific* environmental factors, which of course are beyond experimental control in human adoption studies. In the present study, we intentionally focused on a limited range of cognitive, personality, and physical variables with the intent to establish the degree to which estimates of heritability *can* be malleable in response to environmental history. In a companion analysis (Sauce et al., in press), we will more fully explore the impact of these environmental manipulations on general cognitive ability and its heritability.

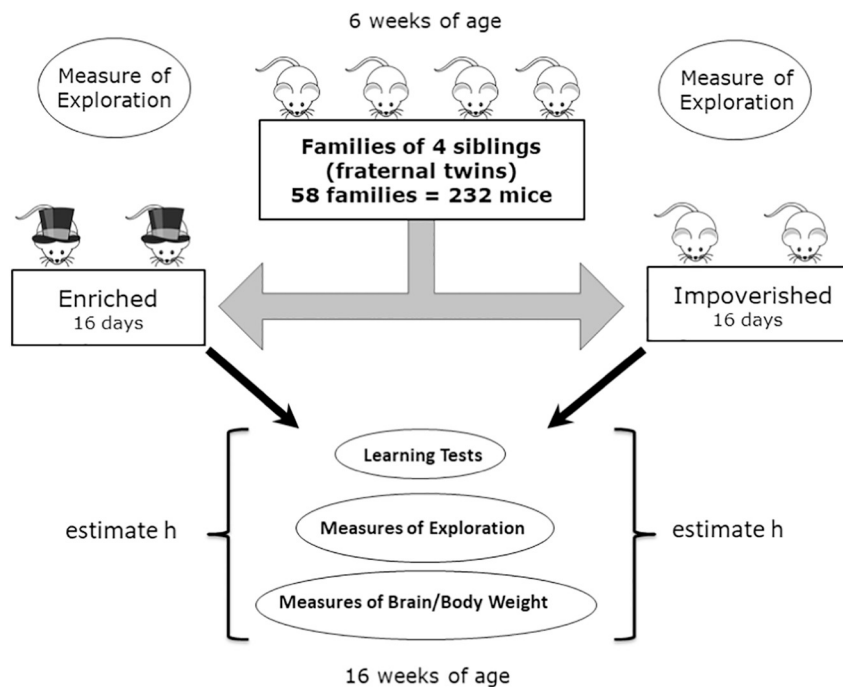
For the present study, we are treating gene-environment interactions and correlations under the umbrella of GE interplay (i.e., we will not attempt to separate their contributions to the expression of a trait). As noted in Rutter and Silberg (2002), these two forms of GE are commonly intertwined in real life, and particularly in studies of humans, are difficult to separate. In addition, it is likely that from an evolutionary perspective, both rGE and  $G \times E$  reflect adaptive effects of G on E as well as of E on G, so we should indeed expect both effects to contribute to individual differences (Rutter & Silberg, 2002). And more to the main argument developed here, rGEs and  $G \times E$ s are together a solution to explain why cognitive abilities (as well as intelligence) can be both highly heritable *and* highly malleable (Sauce & Matzel, 2018).

For the present experiment, we used 58 sets of four twins of genetically heterogeneous CD1 male mice. Half of each set of four twins (two of the twins) were maintained in a typical sterile laboratory environment, i.e., the “impoverished” environment. The remaining two twins from each set were exposed to a series of complex environments that were intended to provide the mice with the opportunity for extensive exploration, i.e., the “enriched” environment. An illustration of the experimental procedure is provided in Fig. 1. Variations in exploratory behaviors are often described as reflective of different personality types related to boldness/shyness or impulsivity (Weiss & Neuringer, 2012; Zampachova, Kaftanova, Simankova, Landova, & Frynta, 2017). Here, a personality trait revealed by exploratory tendencies was characterized prior to the differential treatments. After the differential treatments, personality traits (related to exploratory tendencies/boldness) were again characterized, as were measures of physical traits (body weight and brain weight) and performance on two learning tasks (that were dependent on different information processing, motivational, and motor systems). Using this procedure, we could measure changes in the estimates of heritability of different classes of traits as a function of dramatically different (and controlled) environmental histories. Specifically, exposure to these “enriched” environments might alter estimates of the heritability of learning and exploratory traits, since these traits can reasonably be expected to be influenced by the animals' environmental history.

## 2. Materials and methods

### 2.1. Subjects

We used 232 CD-1 outbred male mice from Harlan Laboratories (Indianapolis, IN). Estimates of genetic variation in this line indicate that, despite over 50 years of laboratory breeding, they are very similar to wild mouse populations (Aldinger, Sokoloff, Rosenberg, Palmer, &



**Fig. 1.** Illustration of the study design. At six weeks of age, sets of four full siblings (fraternal twins) were assessed in an open field (a test of exploration). Subsequently, two mice from each set were exposed for 16 days to a series of complex (enriched) environments or remained in the sterile (impoverished) home cage. Animals were then tested on two learning tasks, as well as additional tests of exploration. At approximately 16 weeks of age, body weight was determined after which animals brains were dissected and weighed. The twins from each group provided independent data points from which to calculate the heritability of the various performance measures.

Millen, 2009). The mice arrived in our laboratory between 4 and 5 weeks of age, and were singly housed in clear shoe box cages inside a temperature-controlled colony room under a 12-h light/dark cycle. In order to minimize any differential stress responses due to experimenter handling, we handled the mice for 90 s a day for a period of seven days prior to the start of the experiment. Handling consisted of removing each mouse from his home cage and holding it while walking throughout the laboratory space. At start of testing, animals were approximately 6 weeks of age (just prior to sexual maturity), and completed the study at approximately 16 weeks of age.

The design of this study is illustrated in Fig. 1. The sample of 232 mice were comprised of 58 sets of four siblings (fraternal quadruplets), totaling 58 families whose parents were unrelated to each other (as guaranteed by the supplier Envigo). Two siblings of a set, randomly chosen, stayed in the control home environment (Impoverished group) and the two other siblings (Enrichment group) received the environmental “enrichment” treatment consisting of physical exercise and exposure to novel and engaging environments.

All mice had continuous access to both food and water. The only exception was during the food-motivated learning task (Lashley maze), when mice had food access for only 90 min a day, beginning on the day prior to testing and continuing across the days of the test. Although mild, this level of food deprivation was sufficient to maintain stable performance on this task. All experiments were conducted in accordance with protocols approved by the Rutgers University IACUC (Institutional Animal Care and Use Committee).

## 2.2. Environmental enrichment (physical exercise and opportunity to explore)

The environmental-enrichment group received an enrichment manipulation that lasted 16 consecutive days. During this time, those mice were maintained in a separate colony room, and lived in home cages with a running wheel continuously present. All animals (enriched and impoverished) were handled daily in order to perform routine home cage maintenance. In addition, animals in the enriched condition received the handling necessary to undergo the experimental manipulations.

Beginning at about six weeks of age, the mice in the Enrichment

group were also exposed to one novel environment, each with varying degrees of complexity, outside their home cage for 30 min on each of the 16 treatment days. A detailed description of many of these environments is provided elsewhere (Light et al., 2008). In brief, the environments were: 1) A big, black, plastic box with two concave towers on each side and a platform in the center reachable by jumping. 2) A narrow Plexiglas tube with a small box at each end that the mice could reach by traversing the tube. 3) An 8-arm elevated Radial Arm Maze. 4) An acoustic chamber with striped walls and wood chips on the floor that was ventilated by a fan. 5) A black box with white stripe on the walls and the floor covered with soft, 1 cm high plastic spikes that the animals could walk over. 6) A white box with six different small plastic figurines that the animals could manipulate. 7) A social box where there was a second mouse inside a cylindrical cage to interact with. 8) An open rat-sized shoebox cage with 2 cm of bedding material on the floor onto which 15 marbles were distributed across the surface. Mice commonly manipulate and hide the marbles under the bedding. 9) A closed rat-size shoebox cage with bedding material and four pieces of paper towel that the mice would typically shred. 10) A large white box with a fixed “merry-go-round” like structure on the middle of the floor. 11) A closed metal pot with holes on the sides for nose poking. 12) A large white, plastic tub with the two angled cylindrical beams originating on the floor and on which the mice could climb. 13) A closed mouse cage put upside down with 10 strings of rope crossing the top of it creating a net where mice could walk. 14) A white box containing a white PVC tube with a mirror at one of its ends. 15) An acoustic chamber with foam on the wall with a metal plate inside containing jars filled with small metal jingle bells to produce sound whenever the mice rolled the jars. 16) A large black plastic box with an angled ramp that ended at a large metal grid that the animals could climb onto.

Upon completion of the 16 days of enrichment (or control) treatment (at approximately eight weeks of age), the Enrichment group was moved back to standard cages in the same colony room as their Impoverished siblings. To ensure that both groups were receiving similar contact with the experimenters before any subsequent testing, all mice were then handled again for 90 s a day for seven days. Also, these seven days of break would function as “rest” for mice in the Enrichment group to minimize any differences in metabolic levels (that might arise as a consequence of the physical exercise during treatment) in relation

to mice in the Impoverished group. After this seven day period, all mice were tested on learning tasks and tests of exploration, and finally, body weight and brain weight was determined.

### 2.3. Tests of learning

All mice were tested first in a Lashley Maze followed by a Passive Avoidance task. (For an analysis unrelated to the present paper, these animals were also tested on three other brief learning tasks. Those data will not be reported here). These tasks are described in detail elsewhere (Matzel et al., 2003; Matzel et al., 2006; Matzel et al., 2011), and will be described in brief below.

In the Lashley Maze, mice must navigate four interconnected alleys to reach a goal box that contains a food reward. The Lashley maze was constructed of black Plexiglas and consisted of a start box that led to the first of four interconnected alleys, the last of which contained a goal box that held a food reward. The mice were allowed to traverse the maze for five trials in order to obtain the food reward. During each of the five trials, we tracked the two types of errors that could be committed: *backtracking*, which we define as a mouse going from one alley opening to the prior alley opening, and *dead end*, which we define as a mouse walking past an alley opening toward a dead end. For analysis, these two types of errors were combined into a single measure of “errors”. Between each of five learning trials, the mice were placed back in their home cage for 20 min.

In the Passive Avoidance task, a mouse was confined to a “safe” platform for 5 min, after which the exit door was opened. The walls and floor of the “safe” platform were white, and the ceiling was translucent orange. The floor was comprised of plastic rods arranged to form a pattern of square grids. A clear exit door (3 cm square) was flush with the floor of the safe compartment, and the door was able to slide horizontally to open or close the compartment. The bottom of the exit door was located 4 cm above the floor of a second circular chamber. This “unsafe” chamber had a clear ceiling and a floor comprised of aluminum planks that formed a pattern of square grids. When a mouse stepped from the safe platform onto a grid floor it would encounter a 5 s compound aversive stimulus composed of a bright white light and noise (a loud oscillating tone, or “siren”). During the aversive stimulus presentation, the mice retreat onto the safe platform, where they were then confined for a 5 min interval. At the end of this interval, the door from the platform was again opened so that the mouse was again free to exit the platform. Mice should learn that stepping from the platform leads to the aversive stimulus, and we quantified that by comparing the latencies to step from the platform during the first and second periods of access (better learning translates to longer latencies during the second period). This learning ratio normalized for differences between animals in their pre-training step latencies (which might be differentially impacted by environmental history).

### 2.4. Tests of exploratory tendencies

All animals underwent three tests that would allow us to characterize their propensity for exploration and/or impulsivity. The first of these tests (the Open Field) was conducted *prior* to any differential treatment of the groups. This test would then allow us to determine the equivalence of the two groups of animals prior to the environmental enrichment manipulation, and further, to assess changes in exploratory behavior that followed exposure to the enriched environment.

The second test of exploration (the Step Test) was imbedded in the Passive Avoidance learning task, and consisted of the latency with which the animals would step off of an elevated platform after 4 min of confinement on the platform. The third test of exploration (the Elevated Plus Maze) was conducted approximately three weeks after the completion of the two learning tests (and four weeks after the end of the environmental enrichment manipulation). Hence, the third test allowed us to assess the persistence on any effect of environmental enrichment

on exploratory behavior.

The Step Test is described above, and the remaining two tests have been described in detail elsewhere (Grossman, Hale, Light, Kolata, & Matzel, 2007). They will be described in brief below.

The Open Field was used here to assess exploratory behavior prior to any differential treatment of groups. The Open Field is a square field (46 cm × 46 cm) with 13 cm high walls, constructed of white Plexiglas and located in a brightly lit room (300 lx). The field is divided into a 6 × 6 grid comprised of 7.65 cm<sup>2</sup> quadrants, where 20 of the quadrants are next to the outer walls of the field (i.e., “wall” quadrants), and 16 quadrants are located in the center (i.e., “open” quadrants). Mice are placed in the center of the open field, and their behavior monitored for five minutes. Throughout this time, the animals' entries into walled and open quadrants are recorded. An entry is recorded whenever both front paws crossed the border of a quadrant. We recorded the time spent in unwalled (open) quadrants of the field as well as the time spent in walled quadrants. This measure has been previously interpreted to reflect exploratory tendencies, as opposed to non-specific motor activity.

The elevated plus maze was used here to assess the exploratory behaviors of mice approximately four weeks after their group treatments. The maze was constructed of grey Plexiglas in the shape of a “plus.” Each arm of the maze is 28 cm long and 6 cm wide, and the maze is elevated 30 cm above a white floor. Two opposing arms of the maze are enclosed in 8 cm high, grey Plexiglas walls and two of the arms were open. The maze is located in a brightly lit room (300 lx). Mice were placed in the center of the maze facing a closed arm, and their behavior in the maze recorded for 3 min. We recorded the percent time in closed and open arms. Generally, open arms are considered to be stressful to animals, thus measures in the open arms provide indices of exploratory tendencies similar in nature to that of exploration of the open quadrants of the open field.

### 2.5. Physical characteristics

Upon the completion of all testing, we collected measures of animals' body weights. Subsequently, the animals were euthanized and their whole brain (above the brain stem) was dissected and weighed. In addition, animals in the Enrichment group had 16 days of continuous access to running wheels. During that time, we measured the number of wheel revolutions for each mouse daily, allowing us to determine a mouse's propensity for running (potentially an indicator of physical fitness), and its change across days access to the wheels.

### 2.6. Statistical analyses

The mice's rate of learning was determined for each of the learning tasks. In the Lashley maze, animals typically exhibit asymptotic performance within 4–5 training trials, thus performance on Trials 2–4 were averaged for each mouse to provide a sensitive measure of differences in rate of learning. In passive avoidance, 2–3 training trials typically supports asymptotic performance, thus performance after the first trial is typically sub-asymptotic and sensitive to differences in rate of acquisition. The rationale and details about this scoring method are provided elsewhere (Kolata, Light, & Matzel, 2008).

We estimated the heritabilities of all traits studied here from each group (Enrichment and Impoverished) separately, as well as both groups combined. We followed the full-sibling formulas by Falconer to obtain estimates of full-sib heritability (see below; Falconer, 1989). We used a combination of independent sample *t*-tests and one-way analyses of variance in SPSS 24 to test for significance of the treatment effects. (It is often suggested that siblings can be compared with dependent-sample statistical tests. Here we used independent sample methods as these are generally more conservative tests.) We also used a General Linear model in SPSS 24 with treatment condition as the main effect and family as a random effect to test the significance of the heritabilities.

Heritability was estimated using the full-sibling formulas described



by Falconer (Falconer, 1989) to obtain full-sib heritability ( $h_{FS}$ ) and its standard deviation ( $\sigma_{h_{FS}}$ ):

$$h_{FS} = 2\sigma_F^2 / (\sigma_F^2 + \sigma_w^2)$$

$$\sigma_{h_{FS}} = \left\{ \frac{2[1 + (n-1)t]^2}{n(n-1)(N-1)} \right\}^{1/2}$$

Where

$h_{FS}$  is the full-sibling heritability

$\sigma_{h_{FS}}$  is the standard deviation of the full-sibling heritability

$\sigma_F^2$  is the difference between the siblings of different families

$\sigma_w^2$  is the difference between siblings within a family

$n$  is the number of individuals per family

$N$  is the number of families

$t$  is the full-sibling intraclass correlation:  $\frac{1}{2} h_{FS}$

In all cases, qualitative descriptions of heritability magnitude (e.g., “high” or “low”) follow common standards (Knopik, Neiderhiser, Defries, & Plomin, 2017)

Owing to occasional equipment or experimenter error, data was not obtained for every case (a maximum of four data points were lost on any test). Consequently, degrees of freedom will in some instances reflect fewer than the 232 mice (or 116, in the case of treatment groups, or 58 in the case of groups of one sibling) that were scheduled for each analysis.

### 3. Results

Prior to any treatment, fifty-eight sets of four full siblings were first tested in an Open Field. Subsequently, two of each set of siblings were maintained in a sterile home environment (Impoverished) and the remaining two siblings spent 16 days in various complex environments (Enrichment) that allowed the animals to engage in a wide array of exploratory behaviors and physical exercise. All animals then underwent two tests of learning (Lashley Maze and Passive Avoidance), two tests of exploration, and finally, body weights and brain weights were determined. Heritability of each measure was estimated based on comparisons of all siblings, and independently for pairs of siblings in Impoverished or Enrichment groups.

#### 3.1. Exploratory behavior in an Open Field prior to treatments

Prior to any differential treatment, all mice were tested for 4 min in a novel walled Open Field. When placed in a novel walled field, rodents will spend the preponderance of their time moving along the perimeter walls of the field, and will avoid the open center areas of the field. Here, we computed a ratio of time spent in the open center area of the field relative to the walled perimeter area, and this ratio served as an index of each animal's propensity for exploration/impulsivity.

Here, the mice spent an average of 12.3% of their time in the center areas of the Open Field (range = 0–39%; SD = 6.21%). Two siblings from each group of four siblings were then randomly assigned to either the Enrichment or Impoverished treatment condition. The two groups did not differ in the percent of time spent in the open areas of the field,  $t(229) = 0.73$ , ns (Enrichment mean = 12.59%; Impoverished mean = 12.22%). Thus prior to any differential treatment, the two groups were performing similarly on this test of exploration.

#### 3.2. Effects of environment enrichment on exploration/impulsivity

The two treatment groups differed dramatically in their post-treatment patterns of exploration/impulsivity. On the Step Test (obtained ~2 weeks after treatments during the test of Passive Avoidance), the environmental Enrichment treatment promoted faster step latencies relative to the Impoverished treatment,  $t(228) = 13.21$ ,  $p < .0001$ , Cohen's  $d = 1.76$  (large effect size; see Fig. 2A).

In the Elevated Plus Maze (obtained after the completion of tests of

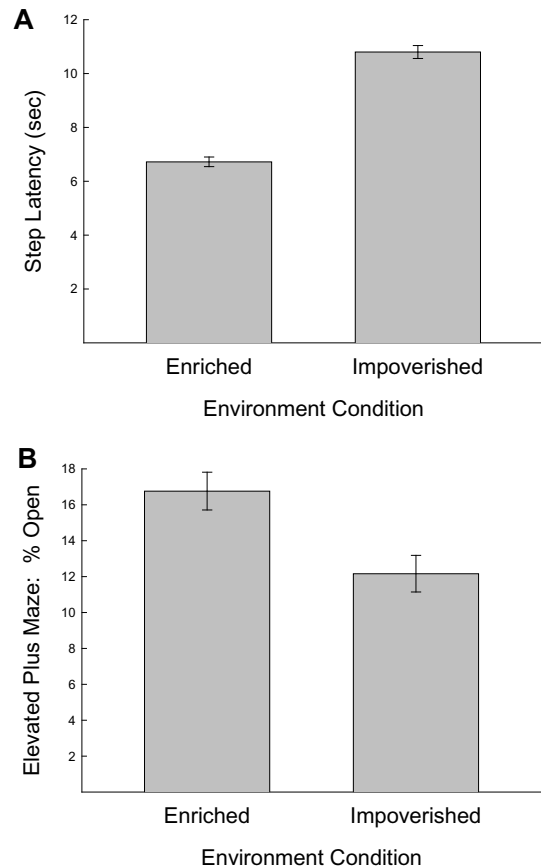
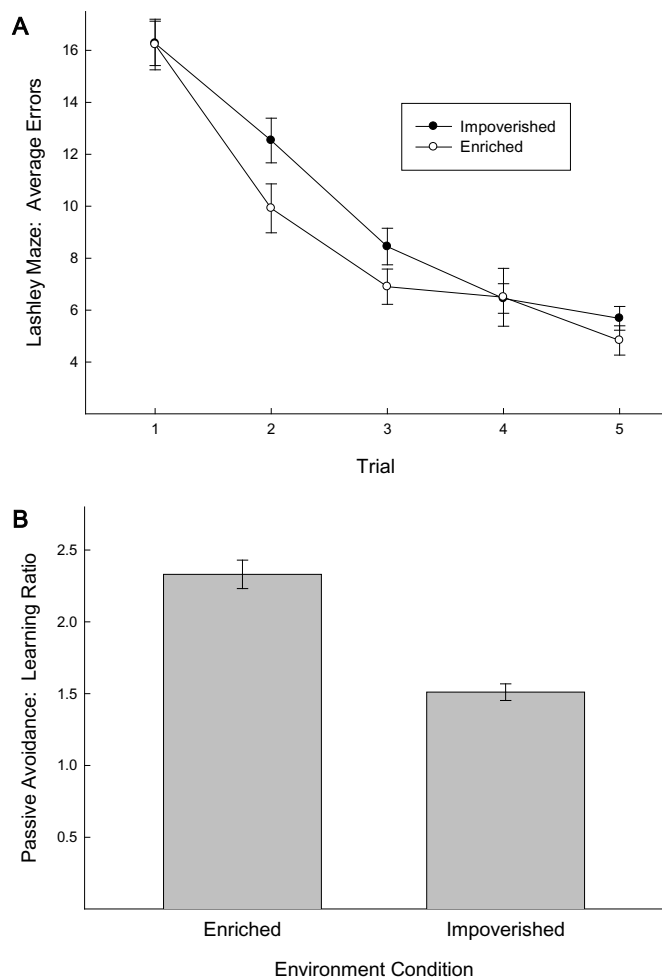


Fig. 2. Both graphs illustrate means and brackets indicate standard errors. A) The latency to step from an elevated platform onto the floor below is illustrated. This response is indicative of the propensity to explore and/or impulsivity or boldness. Prior exposure to novel environments (Enriched) promoted a significant decrease in the step latency. B) The percent of time spent in open relative to closed arms in an elevated plus maze. Like step latencies, this behavior is indicative of traits related to exploration/impulsivity/boldness. Again, a history of exposure to novel environments increased the percent of time spent in the open arms.

learning, ~4 weeks after environmental treatments), the percent of time in the open relative to closed arms was recorded for all mice. Again, the environmental Enrichment treatment increased this measure of exploration/boldness relative to the Impoverished treatment,  $t(229) = 3.12$ ,  $p = .002$ , Cohen's  $d = 0.41$  (small effect size). Thus the 16 days of Enrichment treatment and its associated opportunity to explore induced a long-lasting increase in animals' propensity for exploration/boldness (see Fig. 2B). This lasting increase in exploration relative to Impoverished mice is striking, given that both groups received intervening treatments (i.e., tests of learning) that involved exposure to novel environments.

#### 3.3. Effects of environmental enrichment on tests of learning

After completion of the different environmental treatments, all mice were tested on two learning tasks, the Lashley Maze and passive avoidance. Since the reliability of any measure sets an upper limit on the estimate of heritability, it is worth noting that the Lashley Maze and passive avoidance tasks were used here (in part) because animals' performances on these learning tasks have been found to be among the most reliable of the cognitive tests employed in our laboratory. We have previously reported that test/re-test correlations (obtained with variants of each task) are high on both passive avoidance ( $r = 0.68$ ) and Lashley Maze ( $r = 0.79$ ) tasks (L.D. Matzel et al., 2003).



**Fig. 3.** A) The average number of errors across trials in the Lashley Maze is illustrated for mice that had a history of exposure to Enriched or Impoverished environments. The rate of acquisition (decreasing errors) was facilitated in animals with a history of environmental enrichment. Brackets indicate standard errors. B) The mean learning ratio (post-training step latency/pre-training step latency) in the Passive Avoidance task is illustrated. The higher ratio following environmental Enrichment is indicative of better learning. Brackets indicate standard errors.

In the Lashley Maze, each mouse was assigned a single score that represented its rate of learning across the five training trials (Kolata et al., 2008). The environmental Enrichment treatment facilitated the learning of this egocentric navigation task relative to the Impoverished treatment,  $t(229) = 2.69, p = .008$ , Cohen's  $d = 0.35$  (small effect size; see Fig. 3A). In Passive Avoidance, a single test trial was administered. Upon stepping from a safe platform, the mice encountered loud noise and bright light. The latency to step off the platform was recorded prior to receipt of the aversive stimulation, then again after receipt of the aversive stimulation. The ratio of these two latencies represented the animals' degree of learning. (Notably, this ratio normalized for differences between animals in their pre-training step latencies.) The environmental Enrichment treatment promoted better learning in this task relative to Impoverished treatment,  $t(229) = 7.17, p < .0001$ , Cohen's  $d = 0.94$  (large effect size; see Fig. 3B). In total, based on two learning tasks with different information processing, motivational, and motor requirements, we can conclude that the exposure to the Enrichment environment promoted more rapid learning.

### 3.4. Effects of environmental enrichment on physical characteristics

After the completion of all testing (approximately four weeks after

differential treatments), animals' body weights and brain weights were determined. The mean body weight of the Enrichment mice was 39.24 g (SD = 3.16), while the mean of the Impoverished mice was 39.04 g (SD = 3.46),  $t(228) = 0.45$ , ns. Likewise, brain weight did not differ across groups,  $t(226) = 0.56$ , ns (Enrichment mean = 495.6 mg, SD = 26.26; Impoverished mean = 497.49 mg, SD = 25.35). Thus enrichment had no lasting effect on either body weight or brain weight.

Animals that underwent the Enrichment treatment had 16 days of continuous access to running wheels. This access was associated with an increase in running across the 16 days,  $t(224) = 4.76, p < .0001$ , Cohen's  $d = 0.64$  (medium effect size). Thus similar to its effects on exploration, environmental Enrichment (with its opportunity to run) promoted an increase in running (and potentially, physical fitness).

### 3.5. Estimates of heritability and their sensitivity to environmental history

Heritability could be estimated for three measures of a "personality" trait (Open Field, Step latencies, and Elevated Plus Maze) related to exploration/impulsivity/boldness, two measures of learning (egocentric navigation in the Lashley Maze and Passive Avoidance), and three measures of physical characteristics (body weight, brain weight, and the propensity for running). While performance in the Open Field was only assessed prior to differential treatment and access to running wheels was only available to mice in the Enrichment group, all remaining tests were administered to mice that had received either the Enrichment or Impoverished treatment. Thus in addition to estimating heritability across all mice, we could determine the sensitivity of these estimates of heritability to different environmental histories.

Table 1 provides the heritability estimates for all tests, in descending order indicative of the order of test administration. Most of the tests revealed that the underlying measure was to some degree heritable. Furthermore, the estimates of heritability of many of the traits captured by these tests were sensitive to environmental history. The different categories of tests and the associated estimates of heritability will be described separately below.

#### 3.5.1. The heritability of exploratory behaviors

Prior to their introduction into the Enrichment environment or continued maintenance in the Impoverished environment, all animals were assessed in an open field. Here we focused on a trait that is indicative of exploratory tendencies, and which is sometimes described as sensitive to a personality trait indicative of "boldness" or "impulsivity", specifically, the ratio of time in the center, unwarmed areas of the field. This exploratory/impulsivity/boldness trait was moderately heritable ( $h = 0.40$ ).

After the Open Field test, two of each group of four siblings underwent 16 days of environmental enrichment/opportunity to explore. After this treatment, mice were tested in a Lashley Maze and a Passive avoidance task, the latter of which included a measure of animals' baseline tendency to step down from a safe platform into a novel arena. These step latencies can thus serve as a measure of exploration/impulsivity/boldness. As described above, step latencies were reduced after exposure to the Enrichment environment. Across all mice in this sample, this response was not markedly heritable ( $h = 0.08$ ). However, while the heritability in Impoverished mice was low ( $h = 0.10$ ), this estimate increased dramatically after exposure to the Enrichment environment that provided the animals with an opportunity to explore ( $h = 0.54$ ).

After both learning tests had been completed, all mice underwent a final test of exploration in the Elevated Plus Maze. This test was performed approximately four weeks after the completion of the differential treatments (Enrichment or Impoverished). Here, the percentage of time spent in open arms served as the dependent measure, and as described above, environmental enrichment/opportunity to explore increased animals' time in the open arms of the maze. Across all mice, this exploratory tendency was heritable ( $h = 0.29$ ). However, in

**Table 1**

Heritabilities of measures of physical, learning, and exploratory measures for All, Enriched, or Impoverished mice. The schedule of events (in descending order) in this study is listed in the right column. Note that differential exposure to environmental conditions occurred during the shaded period. Asterisks indicate statistical significance.

TEST CLASS	TEST	GROUP	H	p	SCHEDULE OF EVENTS
EXPLORATION	Open Field	All mice	0.40	0.000*	Prior to treatment
PHYSICAL	Running wheel, Day 1	Enrichment	0.25	0.179	Day 1: begin Enrichment treatment
	Running wheel, Day 16	Enrichment	0.55	0.020*	Day 16: end Enrichment treatment
LEARNING	Lashley Maze	All mice	0.27	0.008*	7 days of rest
		Enrichment	0.12	0.330	Testing begins
		Control	0.59	0.011*	1 day of rest
EXPLORATION	Step latency	All mice	0.08	0.770	
		Enrichment	0.54	0.021*	
		Control	0.10	0.358	
LEARNING	Passive Avoidance	All mice	0.15	0.081	
		Enrichment	0.50	0.026*	
		Control	0.18	0.747	14 days of rest
EXPLORATION	Elevated Plus Maze	All mice	0.29	0.005*	
		Enrichment	0.51	0.025*	
		Control	0.18	0.248	2 days of rest
PHYSICAL	Body weight	All mice	0.55	0.000*	
		Enrichment	0.64	0.008*	
		Control	0.66	0.005*	1 day of rest
PHYSICAL	Brain weight	All mice	0.42	0.000*	
		Enrichment	0.39	0.074	
		Control	0.24	0.187	

Impoverished animals heritability was lower ( $h = 0.18$ ) while it was markedly higher in animals with the history of environmental enrichment ( $h = 0.51$ ). Thus like latencies in the Step Test, the estimate of heritability of exploration in the Elevated Plus Maze was amplified by a history of opportunity to explore.

### 3.5.2. The heritability of physical characteristics

Two of each group of four siblings underwent 16 days of environmental enrichment/opportunity to explore, a treatment that included continuous access to running wheels. Thus the first day of access to the running wheel can be conceived as a baseline measure of the propensity for running. The number of revolutions in the wheel on Day 1 was weakly heritable ( $h = 0.25$ ), but the estimate of heritability increased over days of access such that by Day 16, heritability was high ( $h = 0.55$ ). Thus with increasing experience running, twins became more similar.

After the completion of all behavioral testing and approximately four weeks after the completion of differential treatments (Enrichment or Impoverished), body weight was determined, and then two days later, brains (above the brain stem) were extracted and weighed. Body weight was strongly heritable ( $h = 0.55$ ), and the estimate of heritability was comparable in animals with the history of environmental Enrichment ( $h = 0.64$ ) or Impoverished treatment ( $h = 0.66$ ). Brain weight was also heritable ( $h = 0.42$ ), and was similar in both groups of animals (Enrichment,  $h = 0.39$ ; Impoverished,  $h = 0.24$ ).

### 3.5.3. The heritability of learning performance

After the Enriched or Impoverished treatments, mice were first tested in the Lashley Maze, a task that is dependent on egocentric navigation abilities. As described above, the environmental Enrichment treatment (which involved opportunities for exploration) promoted a decrease in errors in the Lashley maze (i.e., improvement in learning). Across all mice, performance in the Lashley Maze was heritable,  $h = 0.27$ . However, unlike exploratory behaviors (where estimates of heritability increased following a history of opportunity to explore), the estimate of heritability following the Enrichment treatment was markedly lower ( $h = 0.12$ ), while the estimate obtained for Impoverished animals was higher ( $h = 0.59$ ). Thus the history of opportunity to explore made twins *less* similar on this test of learning (performance on which was at least in part dependent on exploration).

After completion of the Lashley Maze, mice were trained and tested on a Passive Avoidance task. This task requires that animals inhibit their tendency to leave a safe platform (i.e., to step into an arena that was associated with aversive stimulation). Across all mice, performance in this task was weakly (non-significantly) heritable ( $h = 0.15$ ). However, following Enrichment treatment (with its opportunity for exploration), the estimate of heritability of Passive Avoidance performance was high ( $h = 0.50$ ), while it was lower in animals that experienced the Impoverished environment ( $h = 0.18$ ). Thus like both measures of exploration (Step Test and Elevated Plus Maze), a history of exploration was necessary to reveal the high heritability of the Passive Avoidance response.

## 4. Discussion

Using a standard “twin” method and groups of four siblings of genetically heterogeneous CD-1 mice, here we were able to estimate the heritability of a number of physical, exploratory/personality, and learning abilities. Furthermore (and analogous to a “twin adoption” study), two of the siblings from each group of four received extensive exposure to an enriched environment (that provided the animals with an opportunity for exploration and exercise) while the remaining two siblings were simply maintained in their control environment (analogous to “impoverishment”). With this procedure it was then possible to assess changes in the estimate of heritability as a consequence of different environmental histories. In addition to assessing the heritability in mice of a wide range of characteristics, this procedure provides an advantage relative to analogous studies of humans, i.e., we could specifically control the environments into which the twins were assigned and could specify the features of the different environments. In this regard, we could assess predictions and assumptions that are sometimes difficult to interpret in human twin studies that rely solely on correlational methods.

Across all animals, physical traits were at least moderately heritable. The propensity for running was initially moderately heritable ( $h = 0.25$ ), but this estimate increased over 16 days of access to running wheels ( $h = 0.55$ ). Body weight was highly heritable ( $h = 0.55$ ), but did not respond to environmental history. The heritability of body weight in humans is also high when measured at an early age, but the estimate tends to decline across the lifespan (Silventoinen & Kaprio, 2009; Stunkard, 1991). This decrease in the estimate of heritability is commonly interpreted as the increasing role of environment (and independent choices) to the determination of body weight across the lifespan (an interpretation that is widely applied to similar observations for many physical traits). We would not anticipate a similar change in the estimate of heritability here, as diet choices were not available and diet was not manipulated. This indicates that absent the accumulation of life choices, the heritability of body weight can be quite stable. Brain weight was also heritable ( $h = 0.42$ ), an effect that has previously been reported in humans (Weise et al., 2017) and mice (Zhou & Williams, 1999). Although the brain weight of rodents has previously been reported to respond to environmental enrichment (Fares et al., 2013;

Lewis, 2004), the treatment here was likely not sufficiently intensive, or not administered early enough in development, to induce such an effect. Given no effect of our treatment on brain weight, it is not surprising that the estimate of heritability of brain weight did not change appreciably as a result of the enrichment treatment. Notably though, despite no change in brain weight, the enrichment treatment did support increases in performance on at least two tests of learning. This indicates that the beneficial effects of environmental enrichment needn't necessarily be dependent on increases in brain weight (for relevant discussion, see Matzel & Sauce, 2017).

Variations in exploratory behaviors are often described as reflective of different personality types related to boldness/shyness or impulsivity (Weiss & Neuringer, 2012; Zampachova et al., 2017). Variations in behavior indicative of exploration/personality type was moderately heritable ( $h = 0.40$ ) when assessed in the Open Field (before any differential treatment). Furthermore, behaviors indicative of exploration in the Step Test and Elevated Plus maze increased following the exposure to enriched environments (that was accompanied by the opportunity to explore novel environments). In line with that result, we had previously found that a similar set of novel environments (though not paired with physical exercise) dramatically increased behaviors indicative of exploration/impulsivity in CD-1 mice (Light et al., 2008). Interestingly, the increase in exploration (or change in personality) seen in the current study was accompanied by increases in the estimates of heritability. Following environmental enrichment, the heritability of behavior in the Step Test was high ( $h = 0.54$ ) but was low after Impoverished treatment ( $h = 0.10$ ). A similar pattern was observed in the Elevated Plus Maze (Enrichment,  $h = 0.51$ ; Impoverished,  $h = 0.18$ ). Thus while the heritability of these exploratory/personality traits is moderate, a higher expression of heritability is dependent on a history that includes the opportunity to explore.

Among humans, the heritability of general cognitive ability (c.f., IQ) is among the highest of any psychological trait (Plomin & Spinath, 2002), with estimates commonly reaching levels of  $h = 0.80$  in middle age. However, it is recognized that at very young ages, estimates of heritability of intelligence are much lower (Bouchard, 2004). Unlike physical traits (where estimates of heritability typically decrease as divergent choices accumulate with age), the increase in the heritability of estimates of intelligence are sometimes said to reflect a “channeling” of cognitive abilities, such that environmental influences and the choices that they provoke tend to make genetically similar individuals disproportionately more alike over time (for discussion and implications, see Sauce & Matzel, 2018). Similarly, estimates of heritability of general intelligence tend to be high in high SES environments, while they are typically lower among families of low SES (Kendler, Turkheimer, Ohlsson, Sundquist, & Sundquist, 2015; Turkheimer et al., 2003). Both these aging and SES effects on heritability suggest that given the wide range of opportunities afforded by some environments, genetically similar individuals may gravitate to similar cognitive choices, ultimately increasing their cognitive similarity. This effect (among many others) highlights the important role of gene-environment interactions and correlations in the shaping of estimates of heritability. Given this foundation, here we were particularly interested in the estimate of heritability of cognitive behaviors, as well as the influence of environmental history on these estimates.

Across all mice in our sample, the heritability of performance in the Lashley Maze (a test dependent on egocentric navigational skills) was moderate ( $h = 0.27$ ), although in the Passive Avoidance task (a test that requires the animals to inhibit their natural tendency to leave an elevated platform), we observed only a nonsignificant tendency for heritability ( $h = 0.15$ ). It is not surprising that performance on learning tests is heritable in CD-1 mice, given that we have reported differences in patterns of gene expression (and dopaminergic signaling) between mice characterized as having high or low cognitive abilities (Kolata et al., 2010; Wass et al., 2013; Wass, Sauce, Pizzo, & Matzel, 2018).

After the environmental enrichment procedure (and its opportunity

to explore novel environments), the heritability of the Passive Avoidance response increased dramatically ( $h = 0.50$ ) relative to Impoverished animals ( $h = 0.18$ ). This increase in heritability is similar to that which occurs in estimates of human intelligence, where similar individuals become disproportionately *more* similar as environmental experiences accumulate with age. Surprisingly though, the *opposite* pattern was observed for estimates of heritability of performance in the Lashley Maze. Following Impoverished treatment, the estimate of heritability was  $h = 0.59$ , while after environmental Enrichment, that estimate *decreased* to 0.12. The most plausible interpretation of this result is that the enriched environment did not only create direct cognitive opportunities (which, like in humans for intelligence, should have made siblings more similar, increase the heritability of both Lashley Maze and Passive Avoidance performance). Instead, we believe that the enriched environment also created personality opportunities related to exploration/boldness/impulsivity (in other words, the new environments changed/stimulated personality traits of the mice over the 16 days). These changes in personality could be expected to have dramatically different effects on performance between the Lashley maze and Passive Avoidance tasks. In the Passive Avoidance task, the learning ratio (post-training relative to pre-training step latencies) would be expected to normalize differences in traits like “boldness” or “impulsivity”, while in the Lashley Maze, no normalization is inherent to the performance measure (errors). Thus, in the Lashley Maze, differences in exploration count as a further source of environment-induced variance. Hence the heritability for the Lashley Maze would be expected to decrease in the Enrichment group. In contrast, in Passive Avoidance environmental variance is not related to differences in exploration (as they were normalized), so we might expect no change in heritability in the Enrichment group compared with the Impoverished group of mice. Note, however, that since the estimate of heritability *did* increase for Passive Avoidance following environmental enrichment, then it stands to reason that the source of environmental variance is not only of the exploration/personality type, but might also be of the “cognitive” type. In short, the 16 days of opportunity to explore novel environments added environmental variance of both personality and cognitive types. In the Lashley Maze, most of the variance was of the exploration type, which resulted in a decrease in heritability of learning performance (i.e., it made siblings less similar). For Passive Avoidance (having normalized for exploratory differences between animals), most of the source of variability (after normalizing for differences in exploration) was only of the cognitive type, resulting in an increase in the heritability of cognitive performance (i.e., it made siblings more similar, like in humans for intelligence). Regardless of the validity of this interpretation, it is clear that estimates of the heritability of learning are highly sensitive to animals' environmental history and cannot be reduced to the isolated contribution of genes.

Based on two distinctly different tests of learning, here we found that the cognitive performance of mice can be promoted by a regimen of exposure to an “enriched” environment that provided the animals with the opportunity to explore novel environments and to engage in physical exercise. While cognitive performance on these tasks was weakly-to-moderately heritable, these estimates of heritability changed in response to environmental history. In at least one case (Passive Avoidance), the increase in heritability that accompanied environmental enrichment is similar to what is seen in humans across socioeconomic status (Harden et al., 2007; Turkheimer et al., 2003).

Estimates of IQ's heritability in humans are usually described as “high,” but studies across SES reveal quite low heritability in impoverished populations (Turkheimer et al., 2003). That discrepancy, we believe, is (at least in part) due to the environments in which these samples are drawn. Most studies of intelligence are in fact obtained from high SES samples, i.e., the participants are drawn from middle class and above, who reside in wealthy countries. In these populations, an abundance of opportunities and favorable conditions can amplify small genetic differences in intelligence via gene-environment interplay



(interactions and correlations). The same is not true of estimates obtained from low SES samples, where environments are necessarily more restricted. In the case of high SES samples, the favorable environment can inflate estimates of the heritability of IQ (leaving the impression that genes underlie the high estimates). With this in mind, recall that Galsworthy et al. (Galsworthy et al., 2005) observed that the heritability of general cognitive ability in mice ( $h = 0.4$ ) is low relative to that observed in humans, an estimate that was recently confirmed in a study by Sauce et al. (Sauce et al., in press). But “typical” estimates of heritability in (wealthy) humans are made in favorable environments in which individuals can “self-select” the conditions appropriate for their cognitive abilities, and are freer to meet a vast array of experiences, leading to more opportunities for gene-environment interplay (more opportunities, for example, for a genetically gifted student to go to pursue advanced education, an experience that will increase her IQ more than it will her less gifted classmate).

Recall that Galsworthy et al.'s mice were raised and maintained in a standard (sterile) laboratory environment. The cognitive opportunities for these mice were necessarily restricted and homogeneous, analogous to the low SES environment of humans from which estimates of the heritability of IQ are correspondingly low. Indeed, in our current study the “enriched” environment used here is only enriched relative to the typical, sterile environment of laboratory mice. This “complex” environment is surely impoverished relative to a mouse' natural environment. At the same time, it should be noted that while the more complex environment of a mouse in the wild may benefit cognitive abilities, those benefits might be outweighed by irregular/inadequate food sources, the stress that accompanies life in the wild, including threats of predation, climate irregularities, dominance hierarchies, etc. All we can say is that under controlled conditions, animals with varying environmental history (more or less complexity) behave differently. The pattern in our results and in Galsworthy et al. presents the intriguing possibility that like humans, in a more favorable environment, mice might encounter cognitive challenges appropriate for their genotype, and estimates of heritability might increase. This represents one of the great virtues of animal research. While this possibility, although consistent with interpretations based on correlational data, are hard to directly test in humans (owing to ethical considerations), environmental manipulations can easily be administered to laboratory mice, and such an experiment could help resolve the role of gene-environment interplay in the determination of the heritability of intelligence.

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