

Brain Weight and Cognitive Abilities of Laboratory Mice

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Received March 15, 2019; revised April 29, 2019; accepted April 29, 2019

Abstract—Differences in brain weight, a morphological trait associated with the level of animal cognition, is usually evaluated via comparison of the respective scores in animals of different taxa. Selection for large and small brain size (in laboratory mice) is a technique that allows this role to be evaluated at the level of intra-species variability. Selection for contrasting values of this trait were stopped at the level of F22, and lines with large and small brain weight were randomly bred inside each line. It was found that brain weight and behavioral differences (the prevalence of large brains in the solution of cognitive tasks) between these lines were maintained without selection. At the same time, selection for high scores of cognitive-task solution resulted in higher brain-weight scores in the selected strain. Therefore, in laboratory mice (widely used by neurobiologists as a model) the brain weight values could be the indicator of cognitive capacities development.

Keywords: relative brain weight, cognitive ability, cognitive tests, selection, laboratory mice

DOI: 10.1134/S2079086420020061

INTRODUCTION

The present review is the complicated issue of relationships between the brain weight and ability to solve the cognitive tasks in laboratory mice. It should be emphasized that learning capacity, the ability to solve elementary logic tasks, reaction to novelty, and the ability to focus attention—they all are based on the plasticity of the central nervous system (CNS). To date, all of these phenomena are referred to as “cognitive abilities,” although this term is used in the present review only to describe the ability to solve simple logic tasks, i.e., tasks for which, according to A.R. Luria, the animal does not have a ready solution to a complex problem (Poletaeva and Zorina, 2014). Our experiments, which are described in detail in this review, were largely focused on the description of tests which evaluate the ability of two pairs of mouse strains to solve the extrapolation task and the puzzle box task. An elementary logic task that assesses the ability for extrapolation of the direction of a stimulus after it disappears from the animal view is a challenge for rodents (see below). The “puzzle-box” test (in which an animal looks for the possibility to hide in the shelter) is simpler in its structure, and its performance depends on the ability of the animal to understand the rule of object permanence (according to J. Piaget). As for their logical structure, these tests do not require preliminary learning and are cognitive tests per se. Since the common scheme of these tests differs from that of traditional learning and memory tasks, the present review contains a brief description of these tests.

Encephalization and the Level of Development of Cognitive Abilities

Brain weight (or brain mass) is a fundamental morphological indicator that, according to comparative research, is associated with the development of the CNS (Tang, 2006) and complex behavior, including cognitive abilities. It is usually compared across animals of different taxa. Traditionally it is regarded as the indicator of the level of evolutionary development of a species. Brain weight in primates, elephants, cetaceans, corvids, and parrots is higher than in many other species; the brain is not only greater in its mass but is also characterized by a higher brain-to-body weight ratio, including the so-called index or quotient of encephalization. The encephalization quotient (EQ) is calculated as follows: $EQ = m \times 0.12M \times 2/3$, where m is the brain mass (g) and M is the body mass (kg). This estimate of the relative brain weight in animals of different species was proposed by Jerisson (1985). The majority of studies measuring the association between cognitive abilities and brain weight were conducted in primates and the role of particular genes in the formation of these association has been studied (McGowen et al., 2011; Villanea et al., 2012). At the same time, studies of the evolution of the brain and its divisions in other species of mammals not only demonstrate the correlation between cognitive capacities and brain size but also show the convergence of a number of indices in animals of different species that occupy similar ecological niches, which is critical for the considered issue (de Winter and Oxnard, 2001). The fundamental role of the index representing the

number of neurons in the determination of cognitive abilities has been demonstrated for different rodent species (Herculano-Houzel, 2007, 2011).

Although the EQ data are sufficiently conclusive to evaluate animal intelligence across evolutionary development, studies of intraspecific variation in brain weight are, first, scarce, and, second, contradictory in their results; therefore, the informative value of these comparisons is less clear (see Kruska, 2005). The relationship between brain weight and cognitive abilities depends on the species type, the population selected for further analysis, and the criteria used to evaluate intelligence. Complex molecular-genetic comparisons may provide a better understanding of these associations (Castillo-Morales et al., 2013). The variability in human brain size is well-known, and its range reaches 800 g (with a mean brain weight of around 1500 g). Nevertheless, extreme variants represent intellectual “norm.” However, this does not apply to pathological mutations that disturb the processes of neural progenitor cell division during prenatal ontogeny, which are currently modeled on mice (genes of microcephaly, megalencephaly, and lissencephaly, Bond et al., 2005; Sugiyama et al., 2009; Yu et al., 2010).

Domestication and Brain Weight

The intraspecific variation in brain weight is described in detail for animals that have wild and domestic forms. These comparisons within different species pairs, including mice, rats, chickens, pigs, minks, and other animals, demonstrated that domesticated animals have smaller brain size compared to their wild ancestors (Kruska, 2005). Dieter Kruska, who has extensively studied this problem, suggests that the reduction of brain weight is a result of intraspecific adaptation to a particular ecological niche (i.e., to domestication). Herre and Röhrs (www.primitivism.com/domestic.htm) demonstrated B. Grzhimek’s table of brain morphology indices for wild and domesticated forms in the group of species. The decline of brain weight in domesticated forms was registered for all species analyzed. In mice, rats, cavies, rabbits, pigs, sheep, lamas, ferrets, cats, and dogs, brain weight was lower than in their wild ancestors the difference ranging from 8.1% (rat) to 33.1% (pig). The variation in the volume of neocortex was characterized by a similar pattern. It is evident that in the course of domestication the selection was performed for increased muscle mass and fertility and in some species—against aggression expressed as the fear of humans. Although a reduction of brain weight was the common trait for these species. It should be emphasized that brain size did not increase even when domesticated animals returned to the wild (fertilization, Röhrs and Ebinger, 1999).

The possible role of intraspecific variation in brain size within the population in the context of behavior

associated with the plastic changes in the brain has been far less studied than in the case of domestication.

Cognitive Tests and Behavior of Laboratory Rodents

Before the question whether there is an association between brain size and the animal intelligence (within the range of intraspecific variation) is addressed, the term “cognitive abilities” should be elucidated. According to the general definition, this term comprises all manifestations of behavioral plasticity, including various forms of conditioned reflexes (i.e., learning), as well as attention and habituation. Having in mind the problem introduced earlier we use the term “cognitive ability” in the more narrow sense and define it as the ability to solve elementary logic tasks. These tasks may include the formation of a spatial “map” (Vorhees and Williams, 2014) and the expression of elementary reasoning ability (Krushinskii, 2018). In other words, this definition don’t include the conditioning reaction formation in response to definite environmental signals, but instead includes the reactions, which are based on formation of internal mental representations of events and relationships between them.

According to Krushinskii (2018), the solution of a reasoning task requires animals to be able to “apprehend” empirical laws relating environmental objects and phenomena. This may be observed in experiments (or in real life) in which the animal has to solve an elementary logic task, such as the extrapolation of the direction of the movement of a stimulus after it disappears from the animal’s view (this was one of the tests used in our experiments).

The extrapolation test implies the following. A (hungry) mouse is placed into a plastic chamber and starts to drink milk from a tiny cup via the small aperture in the middle of one of the walls. After that, the bowl of milk is moved to the right or to the left and then disappears from the animal’s view. A control bowl (which is invisible to mouse) is moved in the opposite direction such that the animal could not find food by smelling it (Fig. 1a). If the mouse approaches the opening on the side to which milk was moved, this solution is considered correct, while the solution is considered wrong if the animal approaches the opposite side aperture. To solve this problem, the animal (e.g., mouse or rat) should be able (1) to understand the rule of object permanence (i.e., to comprehend that the object that disappeared from the field of view still exists and therefore can be found); (2) to understand an elementary property of motion, i.e., if the object starts moving, it will keep moving even after it disappears from the field of view; (3) in this experimental situation an animal should be able to keep in recent memory the information on the direction of the movement, in which the food disappeared; (4) it should use adequately the experience (instrumental habit) to find the place where the food could be (in

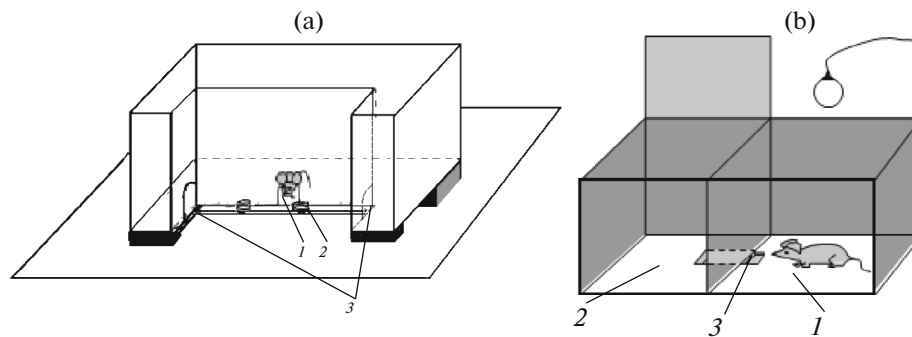


Fig. 1. Cognitive performance tests in mice. (a) Scheme of the experimental apparatus used to test the ability of mice to extrapolate the direction of a food stimulus after it disappears from the field of view (author's figure); 1—central aperture within the opaque front wall of the room; 2—bowl of milk; lateral apertures where drinking bowl can be moved. (b) Scheme of the experimental apparatus used to test the ability of mice to enter the hiding place; 1—illuminated area of the experimental chamber; 2—dark compartment of the chamber; 3—passage dug into the floor.

mouse experiments - the side aperture); (5) to suppress the innate tendency to move in the direction, opposite to that which had been performed previously (i.e. to inhibit the innate reaction of “spontaneous alternation”). In general, laboratory mice and rats, except for certain genetic groups, solve the extrapolation problem at chance level (the proportion of correct solutions does not usually differ from the 50% level of chance) (Perepelkina et al., 2013). In other words, they do not generally exhibit this cognitive ability (its occurrence may be observed only in certain genetic groups of rats and mice). The most precise indicator of test completion is the proportion of animals that gave a correct solution to this task after the first presentation. When an animal faces the necessity to solve this elementary logic task it has no analogous previous experience and it implements (or not able to implement) the capacity for this task solution. The difficulty of the correct solution to this task by rodents is obvious, since it requires the simultaneous performance of a number of operations that differ in their mechanisms.

Corvids and carnivores are able to complete this task successfully (Krushinsky, 2018).

“**Searching the way to a shelter**” task (further mentioned as puzzle-box, as used in English literature, Galsworthy et al., 2005). Unlike the extrapolation task based on food motivation, the puzzle-box test uses the animal urge to hide in the dark, i.e. is based on aversive motivation (Fig. 1b). In this task, the mouse is placed into the illuminated compartment of a box which is provided by the underpass inserted below the floor surface, and the animal is eager to penetrate the dark part of the box via this underpass. The test includes eight trials. Trials 1 and 2 are the easiest (as a variation of the light–dark box experiment): the entrance through the underpass is unobstructed (as in the common light–dark test). In trials 3 to 5, the passage to the underpass is masked by wood shavings at the floor level, so it is not seen any more. In order to enter the

dark compartment, the mouse has to dig the shavings. In the trials 6 and 7, the passage is blocked by a light plug made of plastic and cardboard that the animal can move with teeth or displace. In trial 8, a 5- to 7-cm-high heap of wood shavings is placed along the lower part of the chamber wall with the underpass. This test is solved successfully if an animal possesses the capacity to understand the rule (or empirical law, by Krushinsky) of “object permanence.” This term was first introduced by J. Piaget, who studied intelligence in children (the results of a study in birds with this test were reported in Zucca et al., 2007). The animal can (or cannot) understand that, though the recently perceived object (in our case, it is the underpass into the dark part of the box) is no longer visible, it still exists and therefore can be found (Fig. 1b shows the scheme of the experiment). Performance is assessed in terms of the time needed for the animal to enter the dark compartment (latency). If the animal performed trials 1–5 and trial 8 within 180 s, the task was considered completed; for trials 6 and 7 (with a plug), the time limit for task completion was 240 s. If the animal did not enter the dark compartment of the chamber within this arbitrary time interval, the trial was counted as unsolved. One more criterion was the proportion of mice that succeeded to solve a given trial.

Selection of Mice for Different Brain Weight and Behavior in Mice of Large Brain and Small Brain Lines

The genetic control of brain weight in laboratory mice using artificial selection was demonstrated for the first time in mice bred for large (LB) and Small (SB) relative brain weight and the variability of this trait was demonstrated in the mouse inbred strains panel as well. It was found that large brain mice were more successful in learning (Fuller, 1979).

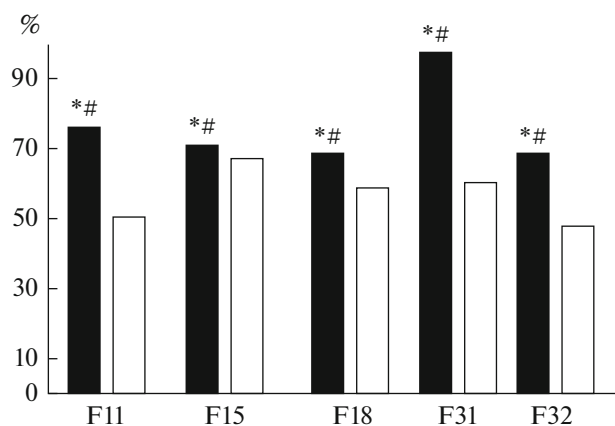


Fig. 2. Solution of the extrapolation task. The percentage (% , ordinate axis) of correct solutions of the first presentation of the extrapolation test by LB and SB mice during (F11–19) and after (F31–32) selection. Designations: black bars—LB, white bars—SB; *—significant difference from SB, $p < 0.05$ and $p < 0.001$ respectively; #—significant difference from the 50% chance level (Fisher's ϕ test).

Early studies on elementary reasoning ability already faced the problem of how to analyze the genetic control of these traits. For this purpose, the performance of the extrapolation task was compared between domesticated (Institute of Cytology and Genetics, Russian Academy of Sciences, Novosibirsk) and wild foxes, as well as between laboratory and wild rats (Krushinsky, 2018). Another approach was to perform the selection of laboratory mice for LB and SB relative weight within a genetically heterogenous population, i.e., F4 hybrids of C57BL6/J, C57BR/J, CBA/Lac-Sto, DBA/2J, BALB/c, and A/He inbred lines. A detailed overview of the data on the selection of mice for LB and SB relative weight was presented in our previous work (Perepelkina et al., 2013). In order to obtain LB and SB strains that significantly differ from each other in both relative and absolute brain weight, we performed three selection experiments. The procedure of selection of mice for LB and SB weight was as follows. First, brain and body weight were determined in half of the animals from a given litter at the age of 1.5 months after they were euthanized. The position of the individual indices of animals from a given litter relative to the regression line that links body and brain weights was used as an indicator of whether the animals of the other half of the litter should be selected for further breeding (the indices had to fall below or above the regression line for SB and LB mice respectively) or not (Perepelkina et al., 2013).

In almost all cases, the selection of mice for brain weight led not only to a rapid (within three to four generations) divergence of strains by a given trait but was also accompanied by the emergence of behavioral differences (Perepelkina et al., 2013; Fuller, 1979). In our first brain weight selection experiment the differences

between LB and SB mice in the ability to solve the extrapolation task and for the success in instrumental learning had been already demonstrated, the LB mice being more successful. As mice, selected for large brain solved the extrapolation task better than SB mice this prevalence was not found in all selection generations. The results also demonstrated differences in cell number and the surface area of the cerebral cortex; LB mice were characterized by 22 and 17% higher surface areas in the neocortex and archicortex, respectively, as compared to SB mice (Popova et al., 1983). The higher scores of instrumental conditioning in large brain mice had been found in both cases—in experiments with food reinforcement (as in J.Fuller work) and in experiments with avoidance (electric shock) learning. In addition, we found differences in exploratory behavior (Salimov et al., 2004), stress reactivity, and anxiety level between LB and SB strains. Moreover, increased stress reactivity and anxiety were characteristic of SB mice (Markina et al., 1999).

After 22 generations were obtained in the third experiment on brain-weight selection (Fig. 2), it was decided to change the experimental procedure and to breed LB and SB mice separately without sustainable selection.

The evaluation of brain weight in subsequent generations of LB and SB mice after the termination of selection procedure demonstrated that the level of inter-strain differences in brain weight remained unchanged. The brain weight scores in LB and SB mice in succeeding generations after the selection stopped demonstrated the same degree of inter line differences for this trait with the lack of differences (in the majority of cases), in the body weight (Table 1).

Next, we assessed whether the behavioral differences between LB and SB strains are preserved in the absence of selection. For example, interstrain differences in exploratory activity after intraperitoneal administration of ethanol (2.4 mg/kg) were examined in the F28 generation (sixth generation without selection). In SB mice, but not LB mice, ethanol administration led to a slower rate of exploration of novel environment (Perepelkina et al., 2013). It should be emphasized that the same experiment was performed on SB and LB mice during the second selection experiment and the differences between the strains were similar (Markina et al., 2001). This could be the evidence that the differences in reaction to ethanol connected with brain weight scores could be rather stable.

LB and SB mice also differed in their performance in finding the entrance to the hiding place, i.e. puzzle-box which was demonstrated both during selection and after it. LB mice demonstrated significantly greater performance in this test compared to SB mice in F37 and F38 (i.e., in the 15th and 16th generations bred without selection) (Fig. 3).

The solution of the puzzle-box test also differed between LB and SB mice. It was demonstrated in both

Table 1. Indices of brain and body weight in mice of several generations in the third selection experiment (selection of mice for large and small relative brain weight)

Generation	Strain	<i>n</i>	Body weight, g	<i>p</i> ≤ #	Brain weight, mg	<i>p</i> ≤ #	Index*	<i>p</i>
F5	LB	54	22.06 ± 0.26	<i>p</i> > 0.05	438 ± 3.86	<i>p</i> > 0.05	19.85	<i>p</i> < 0.05
	SB	30	22.03 ± 0.34		426.4 ± 4.7		19.35	
F10	LB	36	24.68 ± 0.66	<i>p</i> > 0.05	472.9 ± 4.2	<i>p</i> < 0.001	19.14	<i>p</i> < 0.001
	SB	25	25.41 ± 0.82		424.7 ± 5.1		16.72	
F19	LB	44	26.3 ± 0.5	<i>p</i> < 0.001	504.1 ± 5.3	<i>p</i> < 0.001	19.17	<i>p</i> < 0.01
	SB	36	23.2 ± 0.6		409.3 ± 3.6		17.64	
F22	LB	23	21.1 ± 0.5	<i>p</i> < 0.001	481.9 ± 5.8	<i>p</i> < 0.001	22.84	<i>p</i> > 0.05
	SB	22	17.3 ± 0.4		400.5 ± 3.5		23.15	
F25	LB	28	28.4 ± 1.1	<i>p</i> > 0.05	490.2 ± 5.9	<i>p</i> < 0.001	17.26	<i>p</i> < 0.001
	SB	34	28.3 ± 0.8		402.1 ± 3.9		14.21	
F31	LB	27	29.96 ± 0.5	<i>p</i> > 0.05	473.7 ± 5.5	<i>p</i> < 0.001	15.81	<i>p</i> < 0.001
	SB	21	30.6 ± 0.6		420.3 ± 6.2		13.73	
F34	LB	19	27.4 ± 0.4	<i>p</i> > 0.05	461.7 ± 4.3	<i>p</i> < 0.001	17.0	<i>p</i> < 0.001
	SB	26	28.2 ± 0.4		424.4 ± 3.7		15.2	
F36	LB	27	29.4 ± 0.4	<i>p</i> > 0.05	499.5 ± 2.7	<i>p</i> < 0.001	17.32	<i>p</i> < 0.001
	SB	29	29.9 ± 0.4		446.9 ± 2.6		15.30	

* *n*—Number of animals in the group; *—ratio of brain weight (mg) to body weight (g). The significance of differences was assessed via one-way ANOVA with Fisher's *post hoc* LSD test. #—The significance of the differences was assessed with nonparametric test. Here and in Table 2.

cases—during the selection and after the selection was stopped. In the first two trials (when the underpass was open and the animal could enter the dark compartment of the chamber), mice placed in a box immediately started to explore the environment and found the passage remarkably fast. Notably, the majority of mice (of both strains) exhibit significantly lower aversion to brightly illuminated areas, and they do not immediately escape to the dark part of the box.

However, in trials with the masked underpass, most animals first exhibit a freezing response that usually lasts for a few seconds and is followed by a grooming reaction. This means that mice notices the change in the environment practically instantly After a number of approaches to a blocked passage (sometimes immediately), some animals move shavings aside and enter the dark compartment, whereas other mice spend almost all of the time trying to approach the passage,

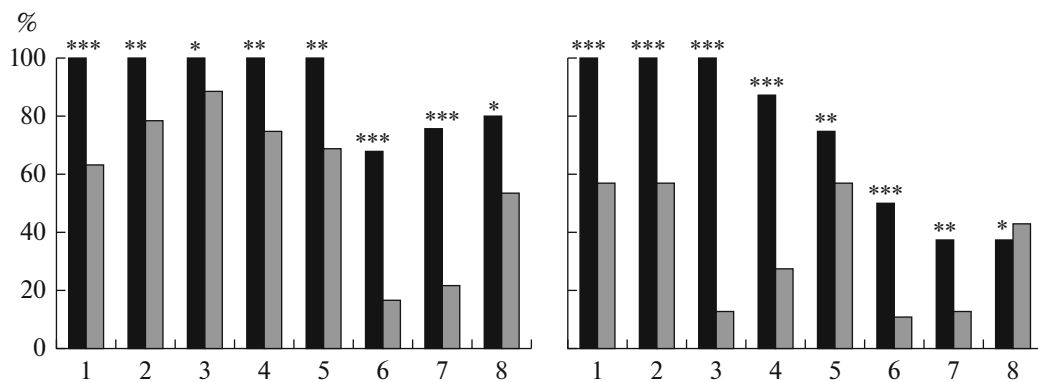


Fig. 3. Solution of the problem of finding the entrance to the hiding place by LB and SB mice. The percentage of LB and SB mice (% , ordinate axis) that solved eight test trials (abscissa axis) in the F37 (left) and F38 (right) generations. For designations, see Fig. 2. *, **, and ***—significant differences from the corresponding percentage of SB mice, *p* < 0.05, *p* < 0.01, and *p* < 0.001 respectively (Fisher's ϕ test).

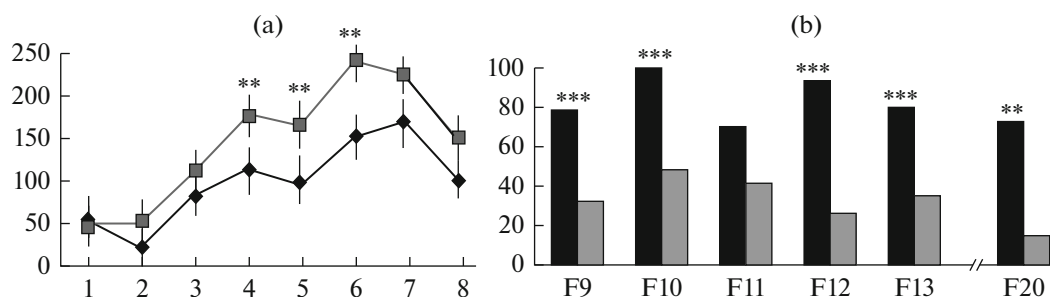


Fig. 4. Solution of the task of finding the entrance to the hiding place by EX and CoEX mice (20th generation of selection). (a) Time spent to solve sequential trials (s, ordinate axis); black rhombus—EX, gray squares—CoEX; **—significant difference from the corresponding CoEX indices, $p < 0.01$ (one-way ANOVA with Fisher's *post hoc* LSD test). (b) The percentage of F20 mice (% , ordinate axis) that solved sequential trials; black bars—EX, gray bars—CoEX; ***—significant difference from the proportion of CoEX mice, $p < 0.001$ (Fisher's ϕ test).

and some animals do not complete the test at all (they do not solve the trial within 180 s). Interestingly, this “recording” of changes in the environment (and the evaluation of the potential opportunity to escape to the dark area) remains in the animal's memory (in an implicit form). When the experimenter tries to take the mouse out from the chamber at the end of the trial by reaching his hand toward the animal, the mouse often escapes rapidly to the dark compartment, moving the shavings that block the passage.

Figure 3 shows that F37 LB mice (16th generation after the termination of selection) moved to the dark compartment significantly faster than SB mice, even in the trials with an open passage. However, in the following trials, they acted much faster only in trial 6, when the passage had to be released by moving or displacing a plug. This behavioral pattern of LB mice that do not dig through the passage and do not move the plug until they see the experimenter's hand (which is assumed to be more threatening for them than brightly lit chamber) explains why the mean latency for entry into the dark compartment was similar in both groups. This assumption is supported by the fact that the proportion of mice completing the test successfully was significantly higher in the LB group, including those in the trials containing a “cognitive” component, i.e., when the animals had to find the entrance to the hiding place with the masked underpas (Fig. 3).

Selection of Mice for the High Scores of Extrapolation Task

Our assumption about the role of brain weight in cognitive task performance was unexpectedly confirmed. In 2008, we started an experiment on the selection of mice for high indices of performance of the extrapolation task. The selection criteria (for formation of pairs for future generations) were as follows: (1) correct solution of the test at its first presentation, (2) five or six correct solutions of six presentations, (3) the absence of fear of the experimental settings. The behavior of mice of the selected line (EX) was

compared with that of mice which belonged to initial heterogeneous population (CoEX) bred without selection and which was used as a control. In the extrapolation test, animal anxiety manifests as the “refusal” to perform the task (the mouse does not approach the central opening) and as “zero” solutions (the mouse does not approach side aperture within 120 s). In the first generations obtained in this experiment (before F8), EX mice were able to solve the extrapolation problem (the proportion of correct solutions was higher than 50%) and were as a whole more successful than nonselected control mice, which in turn demonstrated less stable results (Perepelkina et al., 2011). Selection against anxiety (as one of the criteria used in this selection experiment) in this test resulted in a decrease in anxiety indices according to the results of a specialized anxiety test, the elevated cross maze (Perepelkina et al., 2018).

However, in further generations (after F8–F9), EX mice did not demonstrate the stable superiority of extrapolation scores above the chance level, and their scores practically did not differ from those of control mice (Perepelkina et al., 2015, 2018).

Starting from F9 EX and CoEX mice were tested in the puzzle-box test (Perepelkina et al., 2013). The scores of EX mice in this test were higher than those of control population in the very stable manner. The proportion of mice able to solve the most difficult trials (when the underpass was covered with a plug) was significantly higher in this group than in control animals (Fig. 4).

Therefore, EX mice solve the test more effectively than CoEX mice. This might be explained by a higher level of anxiety, since the differences in this trait in later generations became unstable, and the anxiety level in a number of generations was higher in EX mice than in control animals. However, it then turned out that, after entering the dark compartment of the box, EX mice quickly tried to return to the illuminated part of the chamber (the data are not presented), which is not consistent with the fact of higher anxiety in EX

mice (according to indices of the elevated cross maze) (Perepelkina et al., 2018).

A series of experiments (Fig. 5) comparing the response of EX and CoEX mice to new food (Golobrodo et al., 2014) or a new object (the data are not presented) demonstrate that EX mice exhibit exploratory reaction to, but not fear of, novel objects in the environment (as found in CoEX mice). EX mice also demonstrate a more pronounced response to the experimenter's hand when the mouse is taken out of the chamber, as observed in mice selected for large brain weight (described above).

Since our studies focused on brain weight, this index was also determined in EX and CoEX mice from early selection stages. It turned out that, throughout the entire selection experiment, the brain weight of mice selected for cognitive trait was significantly higher than that in control animals (Table 2).

Therefore, independent selection experiments provided considerable agreement of the data. Selection for LB and SB relative weight led to greater performance by LB mice on the cognitive tests (extrapolation problem and the puzzle-box test). At the same time, selection for cognitive traits (successful for the puzzle-box “aspect,” but not for extrapolation task) resulted in differences in brain weight, such that EX mice were characterized by the greater values of this index. These data suggest the presence of an association between the ability to solve cognitive tests and an increase in brain size in a population of laboratory mice.

The laboratory tests, performed by EX and CoEX mice after such strong challenge as the “environmental enrichment,” revealed the general activation of behavior, the increased reaction to novelty and the increase in brain weight, which were clearly marked in EX in comparison to CoEX (Tarasova et al., 2018). A similar experiment on “enrichment” of the environment performed earlier with LB and SB mice (during second selection) demonstrated more profound changes in the behavior of LB mice, although an enriched environment was not observed to affect brain weight (Perepelkina et al., 2006). It was found (Kempermann et al., 2010) that “movement exercises,” i.e., wheel running, are the most essential component of activation effect of enriched environment on neurogenesis in an adult brain. Brain MRI data demonstrate that wheel running is a key factor associated with greater gray matter volume in the CA3 region of the hippocampus in animals fed a high-calorie diet (Sack et al., 2017). This may indicate that the increase in brain volume that occurred as a result of selection (both for brain weight and expressivity of cognitive traits) is associated with the realization of more active behavior during the performance of cognitive tasks. In other words, the activation of certain cognitive phenomena, such as attention (during exploration of environment) and the ability to inhibit behavioral caution

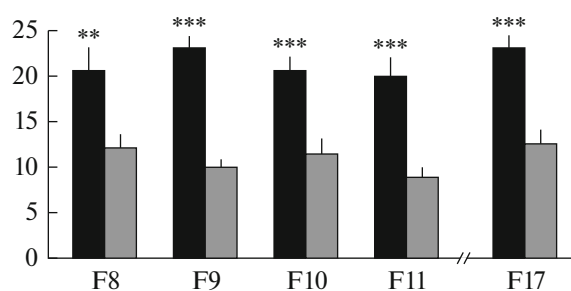


Fig. 5. Solution of the novelty-detection task (new food in the new environment) by EX and CoEX mice. The number of approaches to new food (ordinate axis) in mice of several selection generations. For designations, see Fig. 2. **, ***—significant difference from the CoEX indices, $p < 0.01$ and $p < 0.001$ respectively (one-way ANOVA with Fisher's *post hoc* LSD test, Golobrodo et al., 2014).

that arises during the examination of new objects (and, probably, their joint manifestation) may underlie the ability to solve elementary logic tasks, including the ability to perform actions that are appropriate to a given environment, i.e. which are actions that the animal did not previously perform due to the absence of relevant experience.

To date, genetic research on differences in brain weight use the method of quantitative trait loci (QTL), which links the expression of the quantitative trait and molecular markers with a known location on a chromosome. QTL studies found that mouse brain weight is controlled by genes located on chromosomes 11, 15, 16, and 19 (Peirce et al., 2003). On the other hand, there are ample data demonstrating the influence of particular components of intracellular signaling pathways and the intercellular medium of the brain on cognitive behavior. One of these studies shows the role of the TNF (tumor necrosis factor) signaling system in the realization of cognitive behavior (Morgan et al., 2018). However, it should be emphasized that the determination of the role of particular genetic elements in the realization of behavior does not indicate the importance of the corresponding signaling pathways for behavioral response (and its cognitive components in particular). To date, many studies underestimate the role of possible disturbances in general behavior, including, for example, increased anxiety. The changes in functional brain activity caused by genetic engineering interventions may decrease the general capacity of the organism for adaptation, and the changes in behavioral responses may be considered nonspecific (Edgar et al., 2011; Ng et al., 2016; Kaitsuka et al., 2018), since they are not associated with the realization of cognitive response.

The physiological analysis of behavior started to use the notion the concept of “executive functions” derived from psychological sciences. This concept is associated with the ability to utilize existing knowledge

Table 2. Body weight, brain weight, and the ratio of brain weight (mg) to body weight (g) in EX and CoEX mice of several generations of the selection experiment

Generation	Group	<i>n</i>	Body weight	<i>p</i> #	Brain weight	<i>p</i> #	Index*	<i>p</i>
F2	EX	54	29.7 ± 0.6	<i>p</i> > 0.05	499.4 ± 2.4	<i>p</i> < 0.001	17.1	<i>p</i> > 0.05
	CoEx	23	30.2 ± 0.9		476.2 ± 6.01		16.2	
F4	EX	36	31.1 ± 0.8	<i>p</i> > 0.05	513.2 ± 5.2	<i>p</i> > 0.05	16.4	<i>p</i> > 0.05
	CoEx	24	31.7 ± 0.6		499.9 ± 6.2		16	
F6	EX	16	36.9 ± 0.5	<i>p</i> > 0.05	518.6 ± 4.8	<i>p</i> < 0.001	14.1	<i>p</i> < 0.01
	CoEx	17	32.1 ± 0.5		491.9 ± 5.9		13.0	
F9	EX	39	32.1	<i>p</i> < 0.01	492.3 ± 4.0	<i>p</i> > 0.05	15.6	<i>p</i> < 0.001
	CoEx	35	38.1		503 ± 9.0		13.7	
F10	EX	21	30.7 ± 0.8	<i>p</i> > 0.05	498.7 ± 6.6	<i>p</i> < 0.001	16.24	<i>p</i> < 0.001
	CoEx	40	30.5 ± 0.5		526.6 ± 4.4		12.3	
F11	EX	29	30.4 ± 0.5	<i>p</i> < 0.01	482.7 ± 5.3	<i>p</i> < 0.001	16.3	<i>p</i> > 0.05
	CoEx	26	32.6 ± 0.6		512.3 ± 5.6		15	
F12	EX	94	29.3 ± 0.3	<i>p</i> < 0.001	485.8 ± 3.1	<i>p</i> < 0.001	16.7	<i>p</i> < 0.01
	CoEx	81	33.1 ± 0.34		543.9 ± 3.4		16.4	
F14	EX	119	31.1 ± 0.28	<i>p</i> < 0.001	500.6 ± 2.8	<i>p</i> < 0.001	16.3	<i>p</i> < 0.001
	CoEx	80	34.8 ± 0.37		535.8 ± 3.7		15.0	
F15	EX	65	31.7 ± 0.35	<i>p</i> < 0.001	507.0 ± 3.1	<i>p</i> < 0.01	16.3	<i>p</i> < 0.001
	CoEx	50	33.6 ± 0.45		521.5 ± 4.0		14.9	
F16	EX	68	33.8 ± 0.34	<i>p</i> > 0.05	513.8 ± 3.4	<i>p</i> > 0.05	15.5	<i>p</i> > 0.05
	CoEx	42	34.7 ± 0.48		518.5 ± 4.6		14.5	
F17	EX	81	30.95 ± 0.29	<i>p</i> > 0.05	507.5 ± 2.6	<i>p</i> > 0.05	16.7	<i>p</i> > 0.05
	CoEx	76	32.79 ± 0.3		514.1 ± 2.7		15.9	
F19	EX	69	32.3 ± 0.6	<i>p</i> < 0.001	516.1 ± 2.64	<i>p</i> < 0.001	16.24	<i>p</i> > 0.05
	CoEx	59	32.3 ± 0.6		532.9 ± 2.8		15.45	

and skills in order to achieve an adaptive result (Ben Abdallah et al., 2011; Marquardt et al., 2014).

To date, there is a large database containing information on the role of particular genetic elements in the realization of cognitive capacities in mice, including their capacity for spatial orientation in the Morris water maze. These studies were mostly carried out on genetically engineered animals (including gene knock-out) (Wolfer and Lipp, 1996; Malleret et al., 1999; Gerlai, 2001; Kirchner et al., 2004; Curzon et al., 2006; Ren et al., 2007; etc.) and studied behavioral differences in inbred mouse strains (Holmes et al., 2002; Wahlsten et al., 2005; Moy et al., 2007). To date, despite neuroscientists' strong interest in the genetic basis of cognition, no artificial selection for high and low performance indices in the Morris maze or radial arm maze tests has been performed. At the same time, research has been conducted on correlations for the

performance of tasks, including cognitive ability assessments (Bushnell et al., 1995; Plusnina et al., 2008), but these studies do not evaluate a number of indices, including brain weight and the ability to solve elementary logical tasks.

CONCLUSIONS

Overall, it can be concluded that the population of laboratory mice contains a certain number of animals that are able to solve the extrapolation problem (the ability to anticipate the position of a stimulus after it has changed its location) and the test based on the principle of object permanence (an understanding of this principle is also required to solve the extrapolation problem). In general, artificial selection for the ability to solve the extrapolation task was ultimately unsuccessful and did not result in a greater proportion of

mice that were able to solve this task. At the same time, this selection was effective in that the selected strain contained a greater number of object animals that were able to understand the principle of permanence. The selection of mice for LB and SB weight demonstrated that LB mice have better cognitive abilities as indicated by their better performance in the test that utilized the rule of object permanence. We suggest that this influence of selection on both cognitive and morphological indicators (brain weight) is correlated.

The association between brain weight and better performance in adaptive tasks is found in other species. For example, the selection of guppy (*Poecilia reticulata*) for LB and SB relative weight was accompanied by the occurrence of behavioral differences. Fishes selected for LB weight were characterized by a greater mobility and increased exploratory activity, the speed of conditioning and further discrimination learning (Kotrschal et al., 2013). A study of this association in different species of mammals demonstrated that adaptation to a new environment was more successful in species with a greater brain-to-body weight ratio index (Sol et al., 2008). Comparison of the values of this index inside the order of Passeriformes in the context of their ability to adapt to life in urban environments led to similar results (Maklakov et al., 2011).

Therefore, the literature data and the results of our experiments indicate that increased brain weight is a factor that positively affects the expression of adaptive capacity of animals, especially in terms of cognitive behavior.

FUNDING

This study was supported by the Russian Foundation for Basic Research, project no. 16-04-01169, and State Program AAA-A16-11602166005-1.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest. The authors declare that they have no conflict of interest.

Statement on animal welfare. All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

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Translated by I. Matiulko