Physiology & Behavior 228 (2021) 113193

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/physbeh

The impact of varying food availability on health and welfare in mice: Testing the Match-Mismatch hypothesis

Janina Feige-Diller [a,b,*], Rupert Palme [c], Sylvia Kaiser [a], Norbert Sachser [a,b], S. Helene Richter [a,b]

[a] Department of Behavioral Biology, University of Münster, Badestr. 13, 48149 Münster, Germany
[b] DFG RTG EvoPAD, University of Münster, Hüfferstr. 1a, 48149 Münster, Germany
[c] Department of Biomedical Sciences, University of Veterinary Medicine, Veterinärplatz 1, A-1210 Vienna, Austria

ARTICLE INFO

Keywords:
Match
mismatch, Nutrition, Metabolism, Adolescence, HPA axis, behavior

ABSTRACT

During early phases of life, an organism's phenotype can be shaped by the environmental conditions which it experiences. If the conditions change subsequently, the mismatch between the environment in early and later life could have negative effects on the individual's health and welfare. The aim of this study was to systematically test the predictions of this Match-Mismatch hypothesis in laboratory mice. Therefore, female C57BL/6 J mice were exposed to matching or mismatching combinations of low and high food availability in adolescence and early adulthood. A comprehensive analysis of various physiological and behavioral parameters was conducted. No indication of a mismatch effect was found, which might be attributed to the specific ecology of mice. Alternatively, food availability might cause a shaping of the phenotype only during the prenatal or early postnatal development. However, various effects of low vs high food availability were found regarding the individuals' physiology and, to a small extent, their behavior. Low food availability caused higher concentrations of fecal corticosterone metabolites, as well as higher liver and lower spleen weights, suggesting an adaptation of the metabolism to this situation.

1. Introduction

During early phases of life, an organism's phenotype can be shaped in various different ways by the current environmental conditions, a process called developmental plasticity [1,2]. There is increasing evidence that the information gained about the environment throughout this time can be used as a prediction about the future conditions the organism will experience. The trajectory of development could then be adjusted accordingly [3,4]. This would result in a phenotype that is adapted to the current and predicted future environmental conditions as well as possible. However, according to the Match-Mismatch hypothesis, if the environment changes subsequently, a mismatch between the expected and actual environment during adulthood can cause negative consequences for the individual's welfare and health [4–8]. Therefore, predictions of the future environment and a corresponding adjustment of the phenotype are of profound importance, particularly when fundamental needs like nutrition are affected.

A well-known example for this Match-Mismatch hypothesis concerns availability of food in humans. A matching situation of low food availability during early and later life is associated with various adaptations, e.g. a high set point for satiety, arguably rendering affected individuals well-adjusted to an environment of low food availability [4]. In contrast, according to studies of historical events, such as the Dutch potato famine (e.g. Lindeboom et al. [9]; Roseboom et al. [10]; Roseboom [11]), a mismatch effect can be caused by a discrepancy between the maternal nutritional state during pregnancy and the nutrition encountered during later life. For example, a mismatch from low to high food availability increased the risk of a range of health problems, including cardio-metabolic disorders, greater stress responsiveness, poorer mental health, and lower cognitive function [12–15]. Correspondingly, individuals that experienced normal maternal nutrition and later lived in an environment of low food availability (e.g. during war) have been reported to suffer from diseases associated with malnutrition more often [3].

So far, studies regarding the Match-Mismatch hypothesis focused on the very early development of individuals, namely the prenatal and early postnatal phase (see for example Heijmans et al. [16]; Roseboom et al. [10]; Stein et al. [17]). However, more recently, also adolescence

* Corresponding author at: Department of Behavioral Biology, University of Münster, Badestr. 13, 48149 Münster, Germany
E-mail addresses: j.feige-diller@uni-muenster.de (J. Feige-Diller), rupert.palme@vetmeduni.ac.at (R. Palme), kaisesy@uni-muenster.de (S. Kaiser), sachser@uni-muenster.de (N. Sachser), richterh@uni-muenster.de (S.H. Richter).

https://doi.org/10.1016/j.physbeh.2020.113193
Received 10 June 2020; Received in revised form 27 September 2020; Accepted 29 September 2020
Available online 2 October 2020

has come into focus as a developmental phase during which the phenotype of human and non-human individuals can be shaped profoundly by the acute environmental conditions [18,19]. This phase comprises the transition from infancy to adulthood during which individuals now receive information about the environment directly. The information could then allow for an adjustment of the phenotype to the current or predicted environment [18,19]. Evidence suggests that this is made possible for example by significant maturation processes occurring in brain regions important for emotion and cognition [20,21], as well as a significant modulation of the hypothalamic–pituitary–adrenal axis and other neuroendocrine systems (e.g. Romeo [22]; Zimmermann et al. [23]).

The aim of the present study was to systematically test the Match-Mismatch hypothesis using mice as a model species. For this purpose, female C57BL/6 J mice were exposed to matching or mismatching conditions of low and high food availability during adolescence and adulthood. The four groups comprised the matching situations of low to low and high to high food availability, as well as the mismatching situations of low to high food availability and vice versa. Subsequently, a comprehensive analysis of various physiological and behavioral parameters was conducted to test the effects on welfare and health. In line with the effects found in humans, the two mismatch groups were expected to show a greater stress responsiveness as shown in an increase of fecal corticosterone metabolites, poorer emotional state indicated by higher levels of anxiety-like behavior, a lower cognitive function reflected in a decreased learning- and problem-solving ability, as well as impaired social behavior compared to the two matching groups. Additionally, since organ weights can be valuable indicators of general health (see e.g. Marshall et al. [24]; Freymann et al. [25]), the weights of heart, spleen, liver, kidneys and adrenals were measured at the end of the experiment.

2. Material and methods

2.1. Animals and housing conditions

For this study, 64 female C57BL/6 J mice were obtained from Charles River Laboratories (Research Models and Services, Germany GmbH, Sulzfeld). The animals arrived on postnatal day (PND) 21, after they had been weaned from their mothers. All mice were housed in pairs in transparent standard Makrolon type III cages (38 cm × 22 cm × 15 cm). Wood shavings as bedding material (Tierwohl, J. Reckhorn GmbH & Co.KG, Rosenberg, Germany) and a paper towel as nesting material were provided. Additionally, the cages were enriched with a transparent red plastic mouse house (Mouse House™, Tecniplast Deutschland GmbH, Hohenpeißenberg, Germany) as a hiding possibility and a wooden stick for gnawing. All animals had *ad libitum* access to food (Altromin 1324, Altromin GmbH, Lage, Germany) and tap water during the first week of habituation until the start of the experimental phase on PND 28. Individual earmarks were used to identify all animals. Cages were changed weekly and positions of the cages in the housing room were balanced across the treatments. Housing rooms were kept at a reversed dark / light cycle with lights off at 9.00 a.m., a temperature of about 22 °C and a relative air humidity of about 50%.

2.2. Ethics statement

All procedures complied with the regulations covering animal experimentation within Germany (Animal Welfare Act) and the EU (European Communities Council DIRECTIVE 2010/63/EU) and were approved by the local (Gesundheits-und Veterinäramt Münster, Nordrhein-Westfalen) and federal authorities (Landesamt für Natur, Umwelt und Verbraucherschutz Nordrhein-Westfalen 'LANUV NRW," reference number 84–02.04.2018.A067).

2.3. Experimental design

To test the Match-Mismatch hypothesis, female C57BL/6 J mice were assigned to one out of four groups of matching or mismatching conditions during adolescence and adulthood. More specifically, in phase 1, which was conducted during adolescence, (PND 28 – PND 70 ± 1; Fig. 1), two groups were exposed to a situation of low (L) food availability, while two groups were exposed to a situation of high (H) food availability for a period of six weeks. Upon reaching adulthood (PND 71 ± 2), phase 2 started and the food availability was either kept the same ('match') or differed ('mismatch') for another six weeks. This procedure resulted in the following groups: HH ($n = 15$), HL ($n = 15$), LH ($n = 16$) and LL ($n = 16$).

Subsequently, the animals were tested in a battery of tests (see 2.3.2 Measurement of physiological and behavioral parameters) over a duration of five weeks (PND 111 – 142 ± 1) while remaining in the same environment as after the match / mismatch. Additionally, organ weights of 10 randomly selected animals of each group were assessed. A more detailed description of the experimental procedures is given in the following.

2.3.1. Feeding routines

High food availability was simulated by an *ad libitum* diet of a standard laboratory food (Altromin 1324, Altromin GmbH, Lage, Germany). Low food availability was characterized by feeding once per day a reduced amount of food of the same diet.

Upon arrival in our institute, mice were weighed using a digital scale (accuracy: 0.1 g; CM 150–1 N, Kern, Balligen, Germany) and subsequently housed in pairs with a mouse of similar body weight. To ensure that the results were not impacted by initial differences in body weight between the groups, these pairs were assigned to the different combinations of food availability pseudorandomly. For this purpose, an equal number of cages with mouse pairs in similar body weight ranges were assigned to each of the four combinations of food availability.

Upon the start of the experiment, each cage with a pair of mice of the low food availability ('L cage') was assigned to a cage with a pair of mice of the high food availability ('H cage') of a similar weight range (< 1.7 g difference in mean body weight). Body weights of all animals were measured daily between 9 am and 10:30 am. In phase 1, during which animals were considered adolescent and in a time at which body growth is not yet completed, mice in the L cages were kept to approximately 90% of the body weight of the animals in the H cages. Despite feeding a reduced amount of food, this procedure still allowed for growth of the L animals [26,27]. After PND 71 ± 2 in phase 2, when mice were considered adult and hence fully grown, the body weight of the animals in L cages was adjusted somewhat differently. Namely, dependent on the respective combination of food availability, either the animal's own maximum body weight (group HL) or that of the mice in the reference cage (group LL) during the last 7 days before the match / mismatch (PND 71 ± 2) was used as the reference body weight for the late phase. Animals were kept to about 90% of that reference body weight for the remaining experiment.

2.3.2. Measurement of physiological and behavioral parameters

To gain a comprehensive picture of the effects of the different combinations of high and low food availability on the animals' physiological health, body weight and fecal corticosterone metabolites (FCMs) were evaluated during six weeks each in adolescence and adulthood. FCMs were monitored non-invasively [28–30] to evaluate the activity of the hypothalamic-pituitary-adrenal axis (for a review see Palme [31]) at the beginning and the end of phase 1 (PND 35; PND 64 ± 2) and 2 (PND 78 ± 1; PND 106 ± 2), as well as directly after the match / mismatch (PND 71 ± 2). Body weights were analyzed before the onset of the different feeding routines (PND 27), at the beginning and the end of phase 1 (PND 35; PND 64 ± 2) and 2 (PND 78 ± 1; PND 106 ± 2), as well as directly before the match / mismatch (PND 70 ± 1).

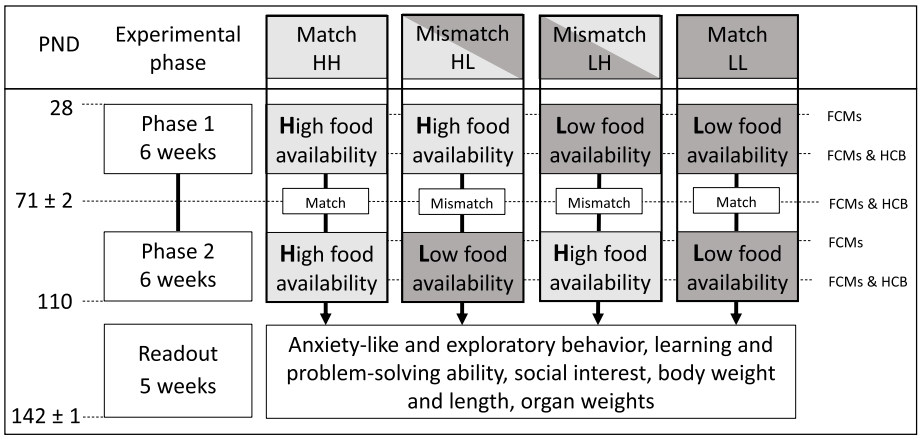

Fig. 1. Experimental design. Mice were provided with either matching or mismatching conditions of high (H) or low (L) food availability during phase 1 and phase 2. Fecal corticosterone metabolites (FCMs) and Home cage behavior (HCB) were assessed during six weeks before and after the match / mismatch. Subsequently, anxiety-like and exploratory behavior, learning and problem-solving ability as well as social interest were evaluated. Afterwards, body weight, body length and organ weights were measured. Age is given in postnatal days (PND).

Additionally, to assess welfare, social behavior and stereotypic behaviors, which are repetitive and invariant behaviors without any obvious goal or function, were measured [32,33] at the end of phase 1 and 2 (PND 64 – 65 ± 2; PND 106 – 107 ± 2) and directly after the match / mismatch (PND 71 – 72 ± 2).

Subsequently, emotional state was assessed in a battery of behavioral tests. The animals were investigated for their state anxiety, i.e. the anxiety at a certain moment in response to certain stimuli [34,35], and their exploratory behavior in several well-established and regularly applied tests, which included the Elevated Plus Maze test (EPM; PND 111 ± 1), the Open Field test (OF; PND 113 ± 1) and the Dark Light test (DL; PND 115 ± 1). Additionally, the Barrier test (B; PND 122 ± 1) was conducted as further assessment of exploratory behavior. In the Free Exploration test (FE; PND 119 ± 2) trait anxiety was measured, i.e. the general tendency of an individual to display anxiety-like behavior [34]. Social interest in same-sex conspecifics was evaluated in the Social Interest test (SI; PND 25 ± 1) and lastly, learning and problem-solving ability were tested in the Puzzle Box test (PB; PND 127 - 137). Afterwards, body length and weights of specific organs (heart, spleen, liver, kidneys and adrenals) were measured to evaluate general health (PND 142 ± 1).

2.3.2.1. Fecal corticosterone metabolites. After weighing, the mice were transferred separately to new Makrolon type III cages ('sample cages") with the standard equipment (see also '2.1 Animals and housing conditions'). After 3 h the animals were moved back to their respective home cages. Fecal samples were collected and frozen at – 20 °C until further preparation. After thawing, fecal samples were dried and homogenized. Aliquots of 0.05 g were extracted with 1 ml of 80% methanol. Subsequently, a 5α-pregnane-3b,11b,21-triol-20-one enzyme immunoassay (established and validated by Touma et al. [30]; Touma et al. [29]) was used to measure the corticosterone metabolites. EIA sensitivity was 1.7 ng/0.05 g and the intra- and inter-assay coefficients of variation were below 10% and 12%, respectively.

2.3.2.2. Home cage behavior. Spontaneous home cage behavior was filmed under red light conditions. At each of the three observation time points (end of phase 1 and 2, after the match / mismatch), videos were recorded for two consecutive days for four hours in the afternoon. The time from 1 pm to 5 pm was chosen because all animals had access to food for about three hours beforehand, resulting in similar satiation levels. To ensure and make individual identification easier, mice were color-marked (edding 3000 Permanentmarker, edding Vertrieb GmbH, Wunstorf, Germany) on the tail prior to the recording. Videos were analyzed by an experienced researcher (JF-D) and social and stereotypic behaviors were recorded using the software Observer XT 7.0 (Noldus Information Technology, Wageningen, The Netherlands). During analysis, the observer was blind to the situation of food availability of the mice as well as to the time point of recording. Definitions of behaviors were based on previous publications (Lewejohann et al. [36]; Gross et al. [37]; Kästner et al. [38], **Table 1**). Stereotypic behaviors were corrected for individual differences in activity. The following social behaviors were defined: approaching, facial/body sniffing, ano-genital sniffing, following, close contact.

2.3.2.3. Battery of behavioral tests. All behavioral tests were conducted between PND 111 and 143. Testing was performed during the animals' active phase when the lights were off in the housing room (between 2 pm and 7 pm). Mice were tested according to a pseudorandomized daily order, which was balanced across the different food availability combinations. Since food trays were either full or empty, depending on the current situation of food availability, blinding was not possible. Barrier test and Social Interest test were executed under red light conditions in the housing room and evaluated by live observations. For the tests on anxiety-like and exploratory behavior (Elevated Plus Maze test, Dark Light test, Open Field test, Free Exploration test) and on learning and problem-solving ability (Puzzle Box test) the animals were transferred to a separate testing room using a darkened transport box. All tests on anxiety-like and exploratory behaviors were recorded by a camera (Logitech Webcam Pro 9000) and automatically analyzed in real time by the video-tracking system ANY-maze (v. 5.33, Stoelting Co., Wood Dale,

Table 1
Definitions of behaviors, based on previous publications [37,38,36].

Behavior	Definition
Active / Inactive (Duration)	The mouse is active when it shows any kind of motion. Tiny whisker, ear or tail movements are excluded. The mouse is inactive when it is not active.
Stereotypies (Duration)	The mouse shows stereotypies when it displays at least one of the following patterns three times or more without interruption: Patterned running: Running on the cage floor along fixed routes; Patterned climbing: Climbing at the cage lid along fixed routes; Circling lid: Climbing in tight circles on the cage lid.
Social behaviors	
Approaching: (Frequency)	The focal mouse moves directly towards the partner mouse until the distance between both is less than one body length.
Facial/body sniffing: (Duration)	The focal mouse contacts the head / body of the partner mouse excluding the ano-genital region.
Ano-genital sniffing: (Duration)	The focal mouse contacts the ano-genital region of the partner mouse.
Following: (Duration)	The focal mouse locomotes after the partner mouse, while its head is directed to the latter's backside. The maximum distance between the animals is one body length.
Close-contact: (Duration)	The focal mouse sits or lies down in direct contact to the partner animal.

USA), while the Puzzle Box test was manually evaluated by live observation. Between subjects, all test equipment was cleaned with 70% ethanol. Mice were given a pause of at least 48 h between individual tests.

2.3.2.4. Elevated Plus Maze test. The light gray apparatus of the Elevated Plus Maze (EPM; Pellow et al., 1985; Lister, 1987, [35]) consisted of a wooden plus-formed apparatus with four arms (30 cm x 5 cm each) and a central square (5 cm x 5 cm), elevated 50 cm above the floor. While two opposing arms were enclosed by a wall of 20 cm height, the open arms only had a small barrier of 0.4 cm to prevent the mice from falling off. The illumination level was set to 25 lux in the center. After transportation to the testing room and one minute in the transportation box, mice were placed on the apparatus with their head facing towards the closed arm of the apparatus pointing away from the experimenter. After starting the tracking software, the mice were allowed to explore the apparatus for 5 min, while the experimenter left the room. The time spent on the open arms compared to the total time spent on open and closed arms and the number of entries to the open arms compared to the total number of entries to open and closed arms were used to assess anxiety-like behavior. Exploratory behavior was assessed by comparing the total number of arm entries.

2.3.2.5. Dark Light test. For the Dark Light test (DL; Crawley and Goodwin [39]) a standard Makrolon type III cage (37 cm x 21 cm x 15 cm) was separated into two compartments by an opaque partition including a sliding door. One third of the cage was painted black and covered by an opaque lid, representing the dark compartment. The light compartment was not modified and illumination was set to 40 lux. For acclimatization, the mice were placed for one minute in the dark compartment. Subsequently, the sliding door was opened, the ANY-maze tracking started and the experimenter left the room. The animals were then allowed to explore the apparatus for 5 min. The latency to the first entry to the light compartment and the time spent in the light compartment were used as assessment of the anxiety-like behavior. The number of entries to the light compartment were used to evaluate the exploratory behavior.

2.3.2.6. Open Field test. The Open Field test (OF; Archer [40,41]) consisted of a white square arena (80 × 80 cm) surrounded by walls (42 cm). The illumination level in the center was set to 35 lux. After one minute in the transport box the mouse was placed into the apparatus with its head facing towards the lower left corner of the apparatus. After starting the ANY-Maze tracking, the experimenter immediately left the room. The mouse was then allowed to freely explore the apparatus for 5 min. Measures for anxiety-like behavior were the duration spent in the center (defined as at least 20 cm distant from the wall) and the number of entries to the center. Exploratory behavior was assessed by the total distance travelled.

2.3.2.7. Barrier test. In the Barrier test (B) mice were individually placed into a standard Makrolon type III cage with a barrier of 3 cm height connecting the long sides of the cage in the middle [42–44]. After placing the animal into the right lower corner, the cage was covered with a transparent Plexiglas. The latency to the first crossing of the barrier within a maximum of 5 min was recorded by live observation.

2.3.2.8. Free Exploration test. In the Free Exploration test (FE; [45,34]), the animal could freely choose to explore a new environment or to stay in the safety of its home cage. The apparatus was a white 60 cm × 60 cm × 35 cm arena surrounded by white walls. The illumination level in the center was set to 40 lux. An opening in one wall (11 cm × 15 cm) connected the apparatus to the animal's home cage via a Plexiglas tunnel. After spending 1 min in the transport box, the mouse was placed back into its home cage and a sliding door was opened, allowing the individual to explore the FE arena for 15 min. After starting the ANY-maze tracking, the experimenter immediately left the room. The entries and time in the arena and the total distance traveled in the arena were analyzed.

2.3.2.9. Puzzle Box test. For the Puzzle Box test (PB; based on O'Connor et al. [46]) a rectangular shaped apparatus of the dimensions 75 cm x 28 cm x 25 cm was divided in a dark (15 cm x 28 cm) and a light (60 cm x 28 cm) compartment enlightened from above (40 lux). The dark compartment served as a goal box and was connected to the light compartment via a small rectangular doorway (4 cm x 4 cm).

Each mouse was tested for five consecutive days with three trials on days one to four and one trial on day five. After the first trial on day one, the doorway was blocked by varying obstructions. These included a u-shaped tunnel (4 cm x 4 cm x 8 cm), 100 ml of bedding material, a balled-up tissue paper and a small Styrofoam plug (4 cm x 4 cm x 3 cm). The animals were always given two consecutive trials with one obstruction to first test the native problem-solving ability and subsequently the ability to reinforce learned behavior. By repeating the same situation during the first trial on the next testing day, retention of the problem-solving was tested. The latency to enter the goal box in the different trials was analyzed.

2.3.2.10. Social Interest test. In the Social Interest test (SI; Lukas et al. [47]; Kästner et al. [48]) subjects were taken out of the home cage and placed in the test arena that consisted of a standard Makrolon type III cage (37 × 21 × 15 cm) containing a thin layer of wood shavings. A transparent plastic cover was placed on the arena to prevent the mice from jumping out. After a habituation phase of 1 min, a cylindrical wire mesh cage (diameter: 10 cm, height: 8 cm) was put in the middle of the arena and the mice could freely explore the set-up for 3 min to become accustomed to it. For the actual test, an unfamiliar female mouse not in estrus was introduced into the wire mesh cage. Subjects could explore the arena for another 3 min and the time the focal mouse investigated (i.e. was sniffing at) the cage containing the stimulus animal was recorded.

2.3.3. Organ weights

On PND 142 ± 1, at least 5 days after the last behavioral test, the body weight and length of 10 mice of each group of the different food availability combinations were measured. Subsequently, the animals were anesthetized using 2.5% isoflurane in oxygen and decapitated. Heart, spleen, liver, kidneys and adrenals were immediately removed and freed from excessive fat tissue. The organs were kept in a moist chamber and weighed using a sensitive digital scale (accuracy: 0.001 g; 510–23, Kern, Balligen, Germany). The whole procedure took about 6 min for each individual animal. Total kidney weight was calculated by adding the weight of the left and right kidneys; this was also done for the adrenals. Relative organ weights were calculated by correcting for final body weight.

2.4. Statistics

Graphs were created and the analysis of this study was conducted using the statistical software R (R Core Team [49], Version 3.5.1) and R Studio (RStudio Team [50], Version 1.1.453). To test for normal distribution, residuals were examined graphically for homoscedasticity and outliers. Additionally, the Kolmogorov-Smirnov test and the Shapiro test were applied. Parametric statistics were applied and, if necessary, data were transformed using logarithmic, square root or inverse transformation (for detailed information, see Supplementary Material, Table 1). Specifically, two different models were established and fitted to the different dependent variables. Both models tested for effects of the four different food availability combinations using either repeated measures ANOVA (Model A) or univariate ANOVA (Model B) and *post hoc* comparisons.

Model (A): Repeated measures ANOVA (RM ANOVA) was used to assess the impact of food availability over a number of repeated tests. For body weight and fecal corticosterone metabolites, the within-subject factor 'week' was included, as these measurements were assessed repeatedly over the duration of the experiment. Regarding learning and problem-solving ability in the Puzzle Box test, 'trial' was included as within-subject factor, as animals had to complete several successive trials. For home cage behavior (stereotypies, social behaviors), 'phase' was included as within-subject factor, representing the measurements during phase 1 and 2, as well as directly after the match / mismatch.

The effects of the respective within-subjects factor 'week / phase / trial' and the fixed between-subject factors 'food availability' as well as the interaction of 'food availability' and 'week / phase / trial' were analyzed.

Model (B): Univariate ANOVA was used to test the impact of food availability on tests that were executed only once. Anxiety-like and exploratory behavior, social interest, final body length and organ weights were analyzed with fixed between-subject factor 'food availability'.

In both models, batches, paired animals and paired cages were included as random factors to control for possible differences not caused by experimental procedures. In case of significant main or interaction effects, Bonferroni-Holm *post hoc* comparisons were conducted. Partial eta squared (η2p) was calculated as a measure of the magnitude of the reported effects (Lakens [51], Supplementary Material, Table 1). Differences were considered to be significant at $p < 0.05$.

3. Results

3.1. Validation of different feeding routines

Animals of the match group of high food availability (HH) gained weight throughout the experiment. In contrast, animals of the match group of low food availability (LL) were successfully kept to ~ 90% of the body weight of animals of the high food availability during phase 1. Afterwards, during phase 2, the LL animals were kept at their maximum body weight of phase 1, with no remarkable further weight gain (Fig. 2).

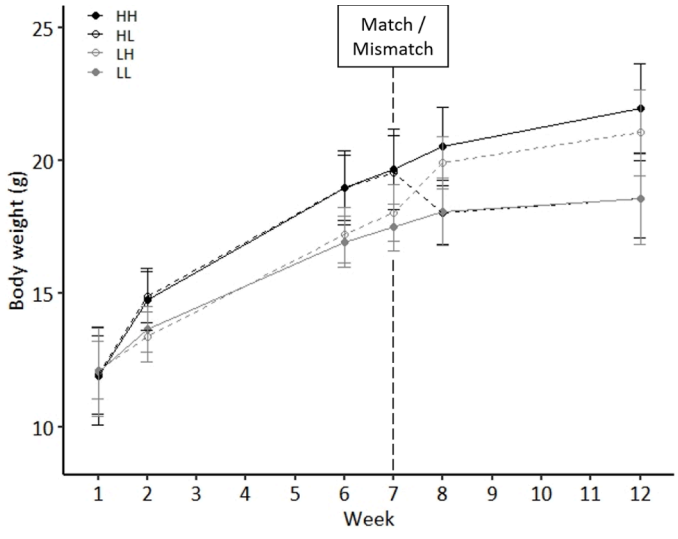

Fig. 2. Body weight development under different combinations of food availability throughout the experiment. Week 1 = *Ad libitum* feeding for all groups, last weight before onset of feeding routines. Groups experienced either high (H) or low (L) food availability before and after the match / mismatch, resulting in four possible food availability combinations (HH, HL, LH, LL). Data are presented as means ± SD. Sample sizes: HH = HL = 15; LH = LL = 16. For details regarding statistical significances, please refer to the text in '3.1 Validation of different feeding routines'.

Accordingly, the repeated measures ANOVA revealed a significant main effect of food availability (Model A, F (3, 169.6) = 4.259, $p = 0.006$) and week on body weight (F (1, 368.0) = 1113.567, $p < 0.001$). The animals of the mismatch groups HL and LH quickly readjusted their weight to the new situation after the mismatch, reflected by a significant interaction of week and food availability (F (3, 368.0) = 23.509, $p < 0.001$).

3.2. Effects of food availability on hormones, behavior and organ weights

3.2.1. Fecal corticosterone metabolites

Concentrations of fecal corticosterone metabolites were assessed at the beginning and the end of the respective phases, as well as directly after the match / mismatch. Mirroring the body weight development in an inversed way, H animals generally showed lower concentrations than L animals. Mice, which experienced a mismatch, showed a rapid change in concentrations when confronted with the new situation.

Accordingly, both a significant main effect of food availability (RM ANOVA, Model A, F (3, 54.900) = 3.418, $p = 0.023$; Fig. 3), as well as a significant interaction of food availability and week was found (F (12, 232.000) = 6.745, $p < 0.001$). Bonferroni-Holm *post hoc* between-group comparisons revealed significant differences in week 8 between HL and LH ($p = 0.020$) and week 12 between HH and HL ($p = 0.034$) and LL ($p = 0.011$).

Overall, the concentrations decreased over the duration of the experiment, reflected by a significant main effect of week (F (4, 232.000) = 59.274, $p < 0.001$).

3.2.2. Home cage behavior

Social and stereotypic behaviors were assessed at the beginning and the end of phase 1 and 2, as well as directly after the match / mismatch. An interaction effect of food availability and time point was found only regarding sociopositive behaviors (sum of following, facial/body sniffing and ano-genital sniffing; RM ANOVA, Model A, F (6, 114.941) = 3.159, $p = 0.007$)) and mice being in close contact to each other (RM ANOVA, Model A, F (6, 147.321) = 6.789, $p < 0.001$). However, in both cases, *post hoc* comparisons revealed no significant differences between groups.

Furthermore, a significant main effect of the combination of food

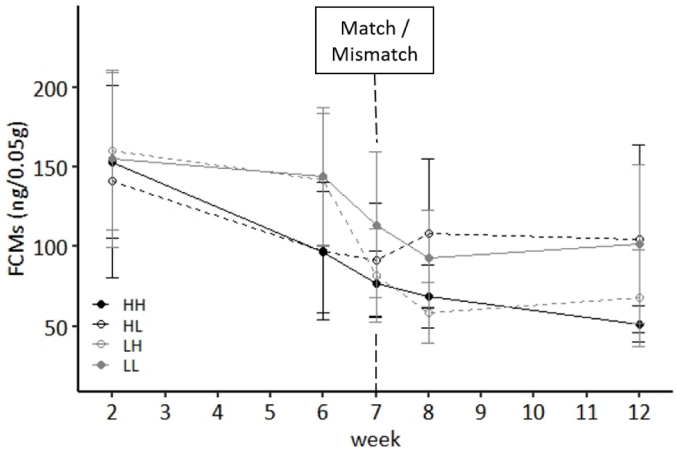

Fig. 3. Levels of fecal corticosterone metabolites (FCMs) throughout the experiment. Groups experienced either high (H) or low (L) food availability before and after the match / mismatch, resulting in four possible food availability combinations (HH, HL, LH, LL). Please note that, although data needed to be transformed for the statistical analysis, graphs are based on untransformed raw data, displaying means ± SD, to facilitate readability and interpretability. Sample sizes: HH = HL = 15; LH = LL = 16. For details regarding significant differences please refer to the text '3.2 Fecal corticosterone metabolites'.

availability was found on stereotypies (RM ANOVA, Model A, F (3, 57.586) = 3.762, $p = 0.016$), with mice of the low food availability condition (LL, LH) performing more stereotypies than mice of the high food availability condition (HH, HL) in phase 1 of the experiment. However, *post hoc* analyses did not reveal any significant differences between the groups.

Lastly, a significant main effect of time point was found for close contact (RM ANOVA, Model A, F (2, 147.462) = 28.995, $p < 0.001$) and approaching (RM ANOVA, Model A, F (2, 147.824) = 7.917, $p < 0.001$) suggesting an effect of aging. *Post hoc* comparisons indicated that animals of groups HL and LL spent more time in close contact to each other during adulthood than directly after the match / mismatch or during adolescence ($p \leq 0.001$). Descriptively, levels of approaching were overall highest during phase 1 and lowest during phase 2. However, *post hoc* comparisons were not significant. Please refer to Supplementary Material, Table 2 regarding means and standard deviations of the respective behavioral parameters.

3.2.3. Behavioral tests

3.2.3.11. Anxiety-like and exploratory behavior. To assess anxiety-like and exploratory behavior, different tests were conducted (EPM, DL, OF, FE, B). Regarding anxiety-like behavior, a significant effect of food availability was found only regarding the time spent in the light compartment of the Dark Light test (Univariate ANOVA, Model B, F (3, 52.172) = 4.671, $p = 0.006$; Fig. 4).

Animals that experienced high food availability during phase 1 (HH, HL) reached higher values than animals that experienced low food availability during this phase (LH, LL). However, *post hoc* analysis revealed no significant between-group differences. No statistically significant effects of food availability were found regarding exploratory behavior in the EPM, DL, OF, FE or B.

3.2.3.12. Social Interest test. Social interest of the animals was assessed by means of an encounter with an unfamiliar female. A significant main effect of food availability (ANOVA, Model B, F (3, 44.165) = 6.663, $p < 0.001$; Fig. 5) was found. *Post hoc* comparisons indicated that animals of the LL group spent significantly more time on sniffing at an unfamiliar female than animals of the HH group, while animals of the HL and the LH group reached intermediate levels.

3.2.3.13. Puzzle Box test. In the Puzzle Box test, the mice had to repeatedly solve different problems over 5 consecutive days. A significant effect of trial (RM ANOVA, Model A, F (12, 692.330) = 95.147, $p < 0.001$) was found, indicating that the time needed to solve the problem was dependent on the kind of obstruction as well as the number of trials. However, no significant effect of food availability was revealed.

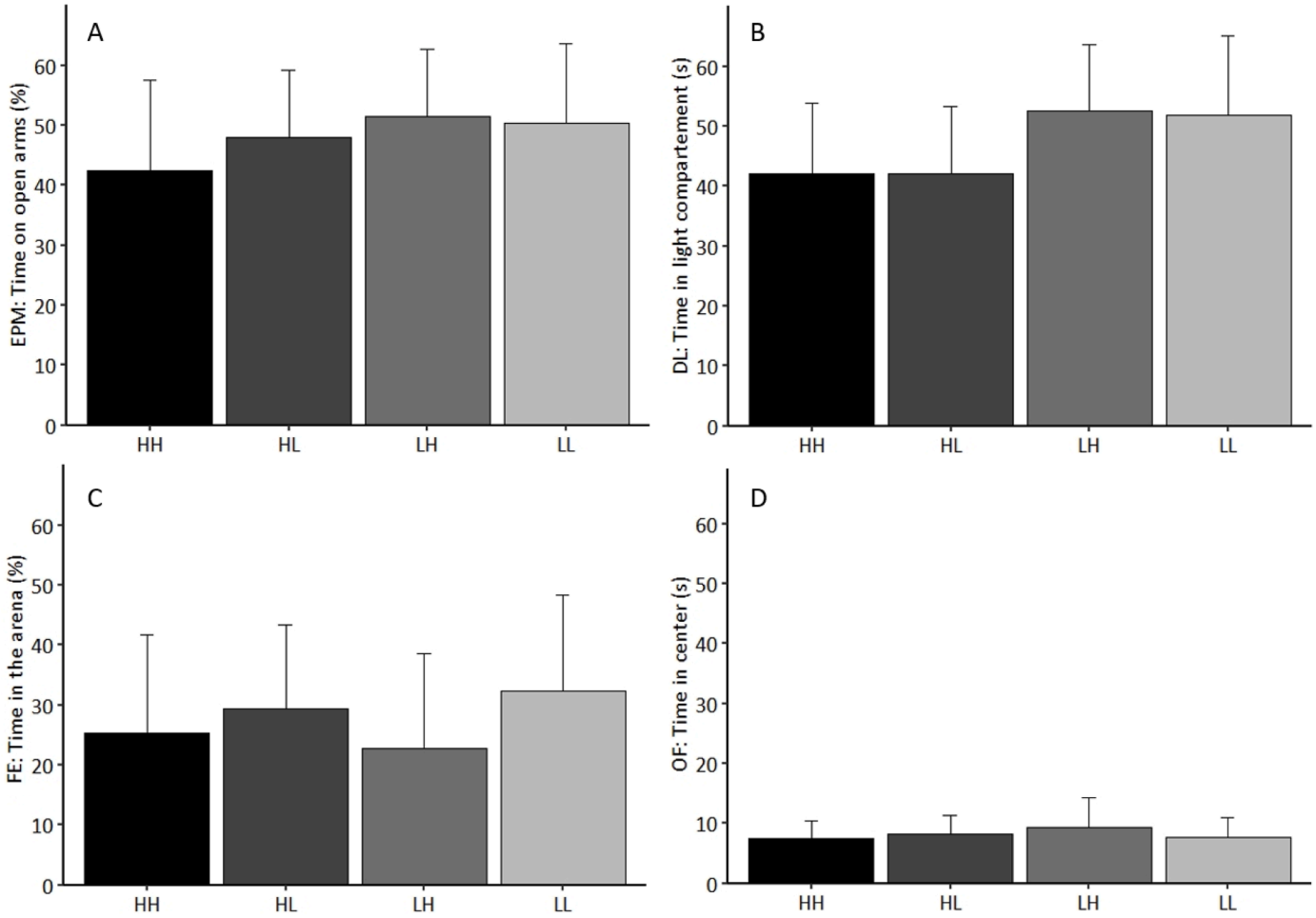

Fig. 4. Behavioral tests on anxiety-like and exploratory behavior. Groups experienced either high (H) or low (L) food availability in phase 1 and 2 of the experiment, resulting in four possible food availability combinations (HH, HL, LH, LL). A) Elevated Plus Maze test (EPM): Relative time on open arms; B) Dark Light test (DL): Time in the light compartment; C) Free Exploration test (FE): Time in the arena; D) Open Field test (OF): Time in the center of the arena. Please note that, although data needed to be transformed for the statistical analysis, graphs are based on untransformed raw data, displaying means ± SD, to facilitate readability and interpretability. Statistics: ANOVA (Model B),*post hoc*: Bonferroni-Holm corrected; sample size: HH = HL = 15; LH = LL = 16. A significant main effect of food availability was found for the time spent in the light compartment of the DL test.

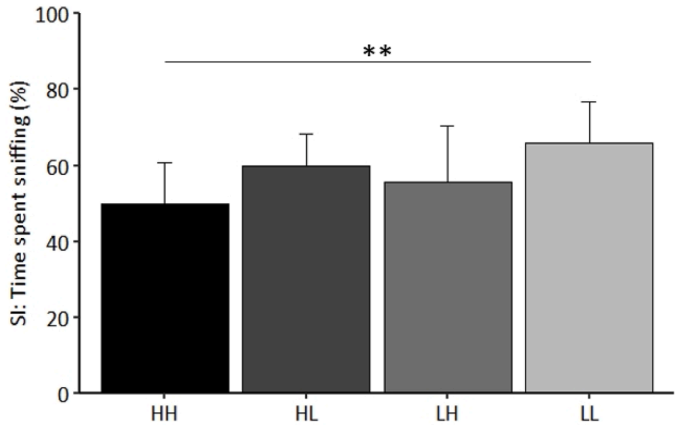

Fig. 5. Social Interest (SI) test. Groups experienced either high (H) or low (L) food availability in phase 1 and 2 of the experiment, resulting in four possible food availability combinations (HH, HL, LH, LL). Data presented as mean ± SD. Statistics: ANOVA (Model B), *post hoc*: Bonferroni-Holm corrected; ** $p < 0.01$; sample size: HH = HL = 15; LH = LL = 16.

3.2.4. Relative organ weights

At the end of the experiment, body length and relative organ weights of 10 randomly selected animals of each group were assessed. A significant main effect of food availability (ANOVA, Model B, F (3, 16.003) = 11.171, $p < 0.001$; Fig. 6) was found for relative spleen weights. *Post hoc* analysis revealed significantly heavier spleens for HH animals than for HL animals ($p = 0.007$) and LL animals ($p = 0.010$). Furthermore, LH animals had significantly heavier spleens than HL animals ($p = 0.014$) and LL animals ($p = 0.018$). Additionally, relative liver weights were significantly influenced by food availability (ANOVA, Model B, F (3, 13.556) = 5.320, $p = 0.012$). *Post hoc* comparisons revealed significantly heavier livers for animals of the LL group than for animals of the HH group ($p = 0.015$), while for HL and LH animals intermediate values were found. No significant differences were found regarding body length and relative weights of kidneys, heart and adrenals.

Regarding total organ weights, results for spleens did not notably differ from the results regarding relative organ weights (ANOVA, Model B, F (3, 30.276) = 26.241, $p < 0.001$). Likewise, a significant main effect of food availability was found concerning total liver weights (ANOVA, Model B, F (3, 15) = 8.333, $p = 0.002$). However, in contrast to relative weights, *post hoc* comparisons indicated significantly lighter livers for HL animals than for animals from the groups HH and LH. Furthermore, food availability significantly influenced total kidney weights (ANOVA, Model B, F (3, 13.096) = 16.502, $p < 0.001$). *Post hoc* comparisons revealed significantly lighter kidneys for animals, which experienced low food availability in adulthood (HL, LL), than for animals, which experienced high food availability during adulthood (HH, LH, p value range: 0.002 – 0.004). Please refer to Supplementary Material, Fig. 1 and Table 3 for more details regarding total organ weights and the respective statistical results.

4. Discussion

In the present study, the Match-Mismatch hypothesis was tested by exposing mice to either a matching or mismatching situation of low or high food availability between adolescence and early adulthood. In contrast to our hypothesis, no effects of a mismatch were found in any of the physiological and behavioral measurements. However, the current food availability situation was reflected in the individuals' physiology and, to a small extent, in their behavior.

4.1. No indication of a mismatch effect

The two mismatch groups were expected to show signs of an impaired welfare or health caused by a suboptimal adaptation of the phenotype to the environment during early adulthood, including higher levels of fecal corticosterone metabolites in response to the mismatch, increased levels of anxiety-like behavior, a decreased learning- and problem-solving ability as well as changes in organ weights. However, in none of the measured parameters did the mismatch groups differ significantly from the match groups.

Concerning its ecology, the mouse is a species that under natural conditions lives in an ever-changing environment, where food availability can vary quickly and often for numerous reasons (reviewed in Latham and Mason [52]). Thus, if the phenotype is permanently adjusted to low or high food availability early in life, it would almost certainly result in a maladaptation at some point during the later life. Instead, a quick adjustment of the physiology and behavior in response to changes in the environment would enable these animals to adjust their metabolism to the currently prevailing situation of food availability, without committing to a permanent change of the phenotype [4]. The absence of any significant differences between the mismatch and the match groups might, thus, be explained by the specific ecology of the mouse.

Furthermore, the focus of match-mismatch studies so far was on the shaping of the phenotype during the very early development of an individual, namely the prenatal and early postnatal phase. However, more recent studies have shown that also during adolescence an individual's phenotype can be shaped profoundly by the acute environmental conditions, thereby adjusting the organism to the current and predicted environment (reviewed in Sachser et al. [19]; Sachser et al. [18]). The influence of the social environment experienced during adolescence on the behavioral and endocrine phenotype of guinea pigs in adulthood is a good example for such a shaping. Namely, males living in mixed-sex colonies during adolescence developed a low-aggressive phenotype in adulthood, enabling them to integrate into large unfamiliar colonies. In contrast, males living in mixed-sex pairs during adolescence developed a highly aggressive phenotype towards strangers, allowing them to defend their mating partners against rivals [53,19,54,23]. Considering a possible similar adjustment of the phenotype in response to varying food availability, the present study tested for a mismatch effect between adolescence and early adulthood in mice. Yet, since no indication of such an effect was found, the shaping caused by food availability might in fact be restricted to the earlier development, on the one hand. On the other hand, the shaping of the phenotype during adolescence might be limited to other environmental factors than nutrition, such as the social environment. Furthermore, negative effects on health and welfare caused by the mismatch situations might become apparent only during later life stages.

Additionally, much evidence stems from situations of large discrepancies between the two mismatching environments, such as the Dutch potato famine, which compares very low food availability to food in abundance (e.g. Heijmans et al. [16]; Lindeboom et al. [9]; Lumey et al. [55]; Roseboom et al. [10]; Roseboom [11]). In contrast, the discrepancies in the present study were caused by the comparison of *ad libitum* feeding and feeding a mildly reduced diet, which lead only to a slight reduction of body weight. Although evidence suggests various effects of such a reduction on the phenotype of rats [56–58], the discrepancy between low and high food availability in this study was possibly too small to bring about a significant mismatch effect on the mice's phenotype.

4.2. Effects of low vs high food availability

Although no mismatch effect was revealed in this study, various effects of low vs high food availability were found regarding physiological and, to some extent, behavioral parameters. A quick adjustment to changes in food availability was found regarding body weight and fecal corticosterone metabolites. Specifically, after the switch from *ad libitum* to a reduced feeding or vice versa, within a week, the body weight of the

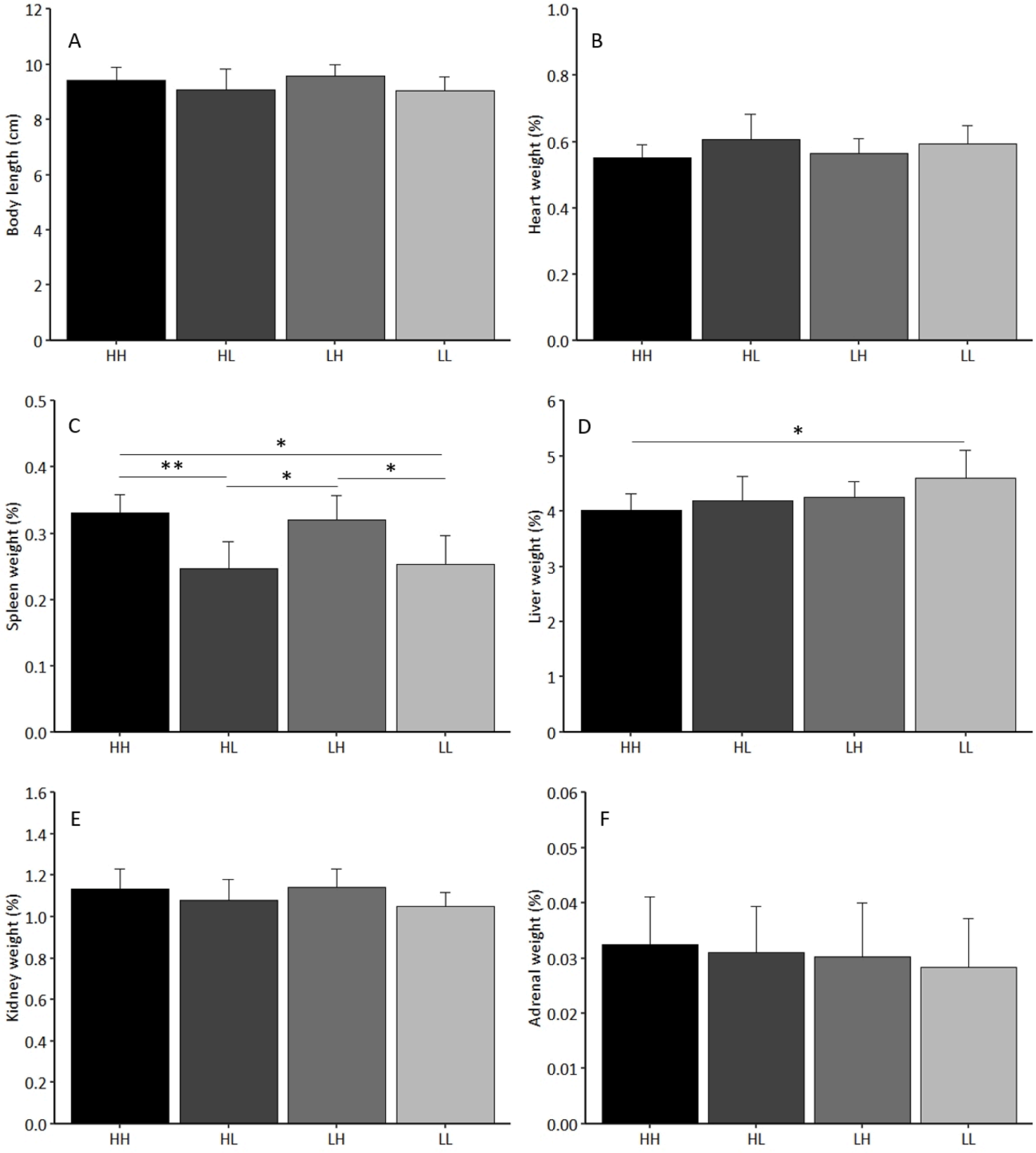

Fig. 6. Final body length and relative organ weights. Groups experienced either high (H) or low (L) food availability in phase 1 and 2 of the experiment, resulting in four possible food availability combinations (HH, HL, LH, LL). A) Body length; B) Heart; C) Spleen; D) Liver; E) Kidneys; F) Adrenals. Please note that, although data needed to be transformed for the statistical analysis, graphs are based on untransformed raw data, displaying means ± SD, to facilitate readability and interpretability. Statistics: ANOVA (Model B), *post hoc*: Bonferroni-Holm corrected; *$p < 0.05$, ** $p < 0.01$; sample size: HH = HL = LH = LL = 10.

animals of the mismatch groups reached similar levels as in the respective match groups. Similarly, concentrations of fecal corticosterone metabolites (FCMs) in the mismatch groups quickly reached the same levels as in the respective match groups. Overall concentrations of FCMs decreased during the course of the experiment, which might be due to an age-related effect or a habituation of the animals to the general housing and handling procedures. Concentrations were generally higher for animals experiencing low food availability than for animals experiencing high food availability at any given time point, thereby inversely mirroring the body weight development. Similar results have been

shown in studies regarding the effects of reduced feeding (e.g. Heiderstadt et al. [59]; Levay et al. [60]; Kenny et al. [61], indicating that low food availability causes an activation of the hypothalamic–pituitary–adrenal (HPA) axis (reviewed in Palme [31]). The primary role of the HPA axis is the regulation of energy acquisition, deposition and mobilization [62]. It affects the feeding behavior as well as the glucose and fat metabolism of an individual [63, 64]. Hence, changes in activity of the HPA axis, as seen here, can lead to a general adjustment of the metabolism in response to a change in food availability. Correspondingly, the liver, which also plays a major role in metabolism, was likewise found to be influenced by food availability. Specifically, low food availability caused increased relative liver weights compared to high food availability, irrespective of whether this situation was experienced during adolescence or adulthood. Furthermore, high food availability during adulthood was found to cause higher relative spleen weights than low food availability. The spleen is the largest secondary immune organ in mammals and an increase in weight likely indicates an activation of the immune system and might be used as an index of chronic inflammation [65]. Different hypotheses exist regarding the origin of such an inflammation, often attributing it to differences in metabolism. For example, an increase of food intake, as indicated by the constant weight gain in animals of the high food availability, could lead to an increased metabolic activity, which in turn would cause the build-up of O_2 radicals. These radicals would then attack the body, causing inflammation (reviewed in Masoro [66] and Gillespie et al. [67]). Correspondingly, improved immunologic parameters (reviewed in Jolly [68]; Nikolich-Žugich and Messaoudi [69]) and improved immunity to infectious agents [70] have been found for mice fed a reduced diet, similar to the situation of low food availability in this study, compared to *ad libitum* fed mice. Thus, the higher fecal corticosterone metabolite levels, increased liver weights and decreased spleen weights likely indicate an adaptation of the metabolic system in response to low food availability, helping the mice to handle periods of poor nutrition.

Regarding the behavioral parameters, only few changes in response to food availability occurred. Namely, low food availability caused slightly lower levels of anxiety-like behavior, which is basically in line with previous studies on rats [59,71,72]. Traditionally, low levels of anxiety-like behavior can be interpreted as a sign of good welfare, as we see such a modification also in mice that experienced for example an enriched environment [44,73,74]. However, slightly higher levels of stereotypies in response to low food availability are in contrast to this interpretation as stereotypies are widely considered to reflect poor welfare [32,33]. Based on these rather contradictory findings, it is difficult to draw any general conclusions about the impact of food availability on welfare. Furthermore, this study concentrated on female mice only. For a comprehensive picture of the effects caused by food availability on behavior and welfare, male mice should also be investigated (e.g. Genn et al. [75]). Considering the ecological background of mice living in low food availability conditions, however, an alternative explanation may arise: A decrease in anxiety-like behavior could also be interpreted as an adequate reaction towards scarce environmental conditions that force the animal to explore its environment and search for food [72].

Author contributions

SK, NS and SHR conceived the study. SK, NS, SHR and JF-D designed experiments. JF-D carried out the experiments. RP determined the hormonal data. JF-D conducted the statistical analysis of the data and wrote the initial draft of the manuscript. All other authors (RP, NS, SK and SHR) revised the manuscript critically for important intellectual content.

Funding

This work was supported by a grant from the German Research Foundation (DFG) to N.S. (281125614/GRK2220, Project B5).

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments

The authors thank Edith Ossendorf, Edith Klobetz-Rassam, Kimberley Kubski and Hanna Sicking for excellent technical assistance. Further thanks to Volker Stefanski for his valuable comments on the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.physbeh.2020.113193.

References

[1] M. Pigliucci, Phenotypic Plasticity: Beyond Nature and Nurture, JHU Press, 2001.
[2] M.J. West-Eberhard, Developmental Plasticity and Evolution, Oxford University Press, 2003.
[3] P. Bateson, Fetal experience and good adult design, Int. J. Epidemiol. 30 (5) (2001) 928–934. https://doi.org/10.1093/ije/30.5.928.
[4] P. Bateson, P. Gluckman, M. Hanson, The biology of developmental plasticity and the predictive adaptive response hypothesis, J. Physiol. (Lond.) 592 (11) (2014) 2357–2368. https://doi.org/10.1113/jphysiol.2014.271460.
[5] P. Bateson, D. Barker, T. Clutton-Brock, D. Deb, B. D'Udine, R.A. Foley, P. Gluckman, K. Godfrey, T. Kirkwood, M.M. Lahr, Developmental plasticity and human health, Nature 430 (6998) (2004) 419–421. https://doi.org/10.1038/nature02725.
[6] P.D. Gluckman, W. Cutfield, P. Hofman, M.A. Hanson, The fetal, neonatal, and infant environments—The long-term consequences for disease risk, Early Hum. Dev. 81 (1) (2005) 51–59. https://doi.org/10.1016/j.earlhumdev.2004.10.003.
[7] P.D. Gluckman, M.A. Hanson, A.S. Beedle, Early life events and their consequences for later disease: a life history and evolutionary perspective, Am. J. Human Biol. 19 (1) (2007) 1–19. https://doi.org/10.1002/ajhb.20590.
[8] P.D. Gluckman, M.A. Hanson, C. Pinal, The developmental origins of adult disease, Matern. Child. Nutr. 1 (3) (2005) 130–141. https://doi.org/10.1111/j.1740-8709.2005.00020.x.
[9] M. Lindeboom, F. Portrait, G.J. van den Berg, Long-run effects on longevity of a nutritional shock early in life: the Dutch Potato famine of 1846–1847, J. Health Econ. 29 (5) (2010) 617–629. https://doi.org/10.1016/j.jhealeco.2010.06.001.
[10] T.J. Roseboom, J.H. Van Der Meulen, A.C. Ravelli, C. Osmond, D.J. Barker, O. P. Bleker, Effects of prenatal exposure to the Dutch famine on adult disease in later life: an overview, Twin Res. Human Genetic. 4 (5) (2001) 293–298. https://doi.org/10.1375/twin.4.5.293.
[11] T.J. Roseboom, Prenatal exposure to famine and ageing, in: A Vaiserman (Ed.), Early Life Origins of Ageing and Longevity. Healthy Ageing and Longevity, 9, Springer, Cham, 2019, pp. 233–244. https://doi.org/10.1007/978-3-030-24958-8_12.
[12] S. Ebrahim, S. Kinra, L. Bowen, E. Andersen, Y. Ben-Shlomo, T. Lyngdoh, L. Ramakrishnan, R.C. Ahuja, P. Joshi, S.M. Das, M. Mohan, G. Davey Smith, D. Prabhakaran, K.S. Reddy, for the Indian Migration Study g, The effect of rural-to-urban migration on obesity and diabetes in India: a cross-sectional study, PLoS Med. 7 (4) (2010), e1000268. https://doi.org/10.1371/journal.pmed.1000268.
[13] J.V. Patel, A. Vyas, J.K. Cruickshank, D. Prabhakaran, E. Hughes, K.S. Reddy, M. I. Mackness, D. Bhatnagar, P.N. Durrington, Impact of migration on coronary heart disease risk factors: comparison of Gujaratis in Britain and their contemporaries in villages of origin in India, Atherosclerosis 185 (2) (2006) 297–306. https://doi.org/10.1016/j.atherosclerosis.2005.06.005.
[14] G.-.P. Ravelli, Z.A. Stein, M.W. Susser, Obesity in young men after famine exposure in utero and early infancy, New England J. Med. 295 (7) (1976) 349–353. https://doi.org/10.1056/NEJM197608122950701.
[15] T.J. Roseboom, R.C. Painter, A.F. van Abeelen, M.V. Veenendaal, S.R. de Rooij, Hungry in the womb: what are the consequences? Lessons from the Dutch famine, Maturitas 70 (2) (2011) 141–145. https://doi.org/10.1016/j.maturitas.2011.06.017.
[16] B.T. Heijmans, E.W. Tobi, A.D. Stein, H. Putter, G.J. Blauw, E.S. Susser, P. E. Slagboom, L.H. Lumey, Persistent epigenetic differences associated with prenatal exposure to famine in humans, Proc. Natl. Acad. Sci. 105 (44) (2008) 17046–17049. https://doi.org/10.1073/pnas.0806560105.

[17] Z. Stein, M. Susser, G. Saenger, F. Marolla, Famine and human development: the Dutch hunger winter of 1944-1945. Famine and Human development: The Dutch Hunger Winter of 1944-1945, Oxford University Press, New York, NY, US, 1975.

[18] N. Sachser, M.B. Hennessy, S. Kaiser, The adaptive shaping of social behavioural phenotypes during adolescence, Biol. Lett. 14 (11) (2018), 20180536. https://doi.org/10.1098/rsbl.2018.0536.

[19] N. Sachser, S. Kaiser, M.B. Hennessy, Behavioural profiles are shaped by social experience: when, how and why, Philos. Trans. R. Soc. B 368 (1618) (2013), 20120344. https://doi.org/10.1098/rstb.2012.0344.

[20] L.P. Spear, The adolescent brain and age-related behavioral manifestations, Neurosci. Biobehav. Rev. 24 (4) (2000) 417–463. https://doi.org/10.1016/S0149-7634(00)00014-2.

[21] L.P. Spear, Adolescent brain development and animal models, Ann. N. Y. Acad. Sci. 1021 (1) (2004) 23–26. https://doi.org/10.1196/annals.1308.002.

[22] R.D. Romeo, Pubertal maturation and programming of hypothalamic–pituitary–adrenal reactivity, Front Neuroendocrinol 31 (2) (2010) 232–240. https://doi.org/10.1016/j.yfrne.2010.02.004.

[23] T.D. Zimmermann, S. Kaiser, M.B. Hennessy, N. Sachser, Adaptive shaping of the behavioural and neuroendocrine phenotype during adolescence, Proc. R. Soc. B 284 (1849) (2017), 20162784. https://doi.org/10.1098/rspb.2016.2784.

[24] N. Marshall, S. Andrus, J. Mayer, Organ weights in three forms of experimental obesity in the mouse, Am. J. Physiol.-Legacy Content 189 (2) (1957) 343–346. https://doi.org/10.1152/ajplegacy.1957.189.2.343.

[25] J. Freymann, P.-.P. Tsai, H. Stelzer, H. Hackbarth, The impact of bedding volumes on laboratory mice, Appl. Anim. Behav. Sci. 186 (2017) 72–79. https://doi.org/10.1016/j.applanim.2016.11.004.

[26] T. Hashimoto, S. Watanabe, Chronic food restriction enhances memory in mice–analysis with matched drive levels, Neuroreport 16 (10) (2005) 1129–1133. https://doi.org/10.1097/00001756-200507130-00019.

[27] K.L. Kliewer, J.-.Y. Ke, H.-.Y. Lee, M.B. Stout, R.M. Cole, V.T. Samuel, G. I. Shulman, M.A. Belury, Short-term food restriction followed by controlled refeeding promotes gorging behavior, enhances fat deposition, and diminishes insulin sensitivity in mice, J. Nutr. Biochem. 26 (7) (2015) 721–728. https://doi.org/10.1016/j.jnutbio.2015.01.010.

[28] M. Lepschy, C. Touma, R. Palme, Faecal glucocorticoid metabolites: how to express yourself – comparison of absolute amounts versus concentrations in samples from a study in laboratory rats, Lab. Anim. 44 (3) (2010) 192–198. https://doi.org/10.1258/la.2009.009082.

[29] C. Touma, R. Palme, N. Sachser, Analyzing corticosterone metabolites in fecal samples of mice: a noninvasive technique to monitor stress hormones, Horm. Behav. 45 (1) (2004) 10–22. https://doi.org/10.1016/j.yhbeh.2003.07.002.

[30] C. Touma, N. Sachser, E. Möstl, R. Palme, Effects of sex and time of day on metabolism and excretion of corticosterone in urine and feces of mice, Gen. Comp. Endocrinol. 130 (3) (2003) 267–278. https://doi.org/10.1016/S0016-6480(02)00620-2.

[31] R. Palme, Non-invasive measurement of glucocorticoids: advances and problems, Physiol. Behav. 199 (2019) 229–243. https://doi.org/10.1016/j.physbeh.2018.11.021.

[32] G.J. Mason, Stereotypies: a critical review, Anim. Behav. 41 (6) (1991) 1015–1037. https://doi.org/10.1016/S0003-3472(05)80640-2.

[33] G.J. Mason, N.R. Latham, Can't stop, won't stop: is stereotypy a reliable animal welfare indicator? Animal Welfare 13 (SUPPL.) (2004) S57–S69.

[34] G. Griebel, C. Belzung, R. Misslin, E. Vogel, The free-exploratory paradigm: an effective method for measuring neophobic behaviour in mice, Behav. Pharmacol. 4 (1993) 637–644.

[35] R.G. Lister, Ethologically-based animal models of anxiety disorders, Pharmacol. Ther. 46 (3) (1990) 321–340. https://doi.org/10.1016/0163-7258(90)90021-S.

[36] L. Lewejohann, V. Kloke, R.S. Heiming, F. Jansen, S. Kaiser, A. Schmitt, K.P. Lesch, N. Sachser, Social status and day-to-day behaviour of male serotonin transporter knockout mice, Behav. Brain Res. 211 (2) (2010) 220–228. https://doi.org/10.1016/j.bbr.2010.03.035.

[37] A.N. Gross, S.H. Richter, A.K.J. Engel, H. Würbel, Cage-induced stereotypies, perseveration and the effects of environmental enrichment in laboratory mice, Behav. Brain Res. 234 (1) (2012) 61–68. https://doi.org/10.1016/j.bbr.2012.06.007.

[38] N. Kästner, S.H. Richter, S. Urbanik, J. Kunert, J. Waider, K.-.P. Lesch, S. Kaiser, N. Sachser, Brain serotonin deficiency affects female aggression, Sci. Rep. 9 (1) (2019) 1366. https://doi.org/10.1038/s41598-018-37613-4.

[39] J. Crawley, F.K. Goodwin, Preliminary report of a simple animal behavior model for the anxiolytic effects of benzodiazepines, Pharmacol. Biochem. Behav. 13 (2) (1980) 167–170. https://doi.org/10.1016/0091-3057(80)90067-2.

[40] J. Archer, Tests for emotionality in rats and mice: a review, Anim. Behav. 21 (2) (1973) 205–235. https://doi.org/10.1016/S0003-3472(73)80065-X.

[41] D. Treit, M. Fundytus, Thigmotaxis as a test for anxiolytic activity in rats, Pharmacol. Biochem. Behav. 31 (4) (1988) 959–962. https://doi.org/10.1016/0091-3057(88)90413-3.

[42] S. Chourbaji, C. Brandwein, M.A. Vogt, C. Dormann, R. Hellweg, P. Gass, Nature vs. nurture: can enrichment rescue the behavioural phenotype of BDNF heterozygous mice? Behav. Brain Res. 192 (2) (2008) 254–258. https://doi.org/10.1016/j.bbr.2008.04.015.

[43] J. Fuss, S.H. Richter, J. Steinle, G. Deubert, R. Hellweg, P. Gass, Are you real? Visual simulation of social housing by mirror image stimulation in single housed mice, Behav. Brain Res. 243 (2013) 191–198. https://doi.org/10.1016/j.bbr.2013.01.015.

[44] H. Prior, N. Sachser, Effects of enriched housing environment on the behaviour of young male and female mice in four exploratory tasks, J. Exp. Anim. Sci. (Germany) 37 (2) (1995) 57–68.

[45] C. Belzung, F. Berton, Further pharmacological validation of the BALB/c neophobia in the free exploratory paradigm as an animal model of trait anxiety, Behav. Pharmacol. 8 (6–7) (1997) 541–548. https://doi.org/10.1097/00008877-199711000-00012.

[46] A.M. O'Connor, T.J. Burton, C.A. Leamey, A. Sawatari, The use of the puzzle box as a means of assessing the efficacy of environmental enrichment, J. Visual. Exp. (94) (2014) e52225. https://doi.org/10.3791/52225.

[47] M. Lukas, I. Toth, S.O. Reber, D.A. Slattery, A.H. Veenema, I.D. Neumann, The neuropeptide oxytocin facilitates pro-social behavior and prevents social avoidance in rats and mice, Neuropsychopharmacology 36 (11) (2011) 2159. https://doi.org/10.1038/npp.2011.95.

[48] N. Kästner, S.H. Richter, M. Gamer, S. Kaiser, N. Sachser, What a difference a day makes—Female behaviour is less predictable near ovulation, R. Soc. Open Sci. 4 (4) (2017), 160998. https://doi.org/10.1098/rsos.160998.

[49] R Core Team, R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, 2018. URL, https://www.R-project.org/.

[50] RStudio Team, RStudio: Integrated Development for R, RStudio Inc., Boston, MA, 2016. URL, http://www.rstudio.com/.

[51] D. Lakens, Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs, Front. Psychol. 4 (863) (2013). https://doi.org/10.3389/fpsyg.2013.00863.

[52] N. Latham, G. Mason, From house mouse to mouse house: the behavioural biology of free-living Mus musculus and its implications in the laboratory, Appl. Anim. Behav. Sci. 86 (3) (2004) 261–289. https://doi.org/10.1016/j.applanim.2004.02.006.

[53] N. Sachser, M.B. Hennessy, S. Kaiser, Adaptive modulation of behavioural profiles by social stress during early phases of life and adolescence, Neurosci. Biobehav. Rev. 35 (7) (2011) 1518–1533. https://doi.org/10.1016/j.neubiorev.2010.09.002.

[54] N. Sachser, C. Lick, Social experience, behavior, and stress in guinea pigs, Physiol. Behav. 50 (1) (1991) 83–90. https://doi.org/10.1016/0031-9384(91)90502-F.

[55] L.H. Lumey, A.D. Stein, E. Susser, Prenatal famine and adult health, Annu. Rev. Public Health 32 (1) (2011) 237–262. https://doi.org/10.1146/annurev-publhealth-031210-101230.

[56] P. Duffy, J. Seng, S. Lewis, M. Mayhugh, A. Aidoo, D. Hattan, D. Casciano, R. Feuers, The effects of different levels of dietary restriction on aging and survival in the Sprague-Dawley rat: implications for chronic studies, Aging Clin. Exp. Res. 13 (4) (2001) 263–272.

[57] P.H. Duffy, S.M. Lewis, M.A. Mayhugh, R.W. Trotter, J.R. Latendresse, B.T. Thorn, R.J. Feuers, The effects of different levels of dietary restriction on neoplastic pathology in the male Sprague-Dawley rat, Aging Clin. Exp. Res. 16 (6) (2004) 448–456, https://doi.org/10.1007/BF03327400.

[58] P.H. Duffy, S.M. Lewis, M.A. Mayhugh, R.W. Trotter, B.T. Thorn, R.J. Feuers, A. Turturro, The effects of different levels of dietary restriction on non-neoplastic diseases in male Sprague-Dawley rats, Aging Clin. Exp. Res. 16 (1) (2004) 68–78, https://doi.org/10.1007/BF03324535.

[59] K. Heiderstadt, R. McLaughlin, D. Wrighe, S. Walker, C. Gomez-Sanchez, The effect of chronic food and water restriction on open-field behaviour and serum corticosterone levels in rats, Lab. Anim. 34 (1) (2000) 20–28. https://doi.org/10.1258/002367700780578028.

[60] E.A. Levay, A.H. Tammer, J. Penman, S. Kent, A.G. Paolini, Calorie restriction at increasing levels leads to augmented concentrations of corticosterone and decreasing concentrations of testosterone in rats, Nutr. Res. 30 (5) (2010) 366–373. https://doi.org/10.1016/j.nutres.2010.05.001.

[61] R. Kenny, T. Dinan, G. Cai, S.J. Spencer, Effects of mild calorie restriction on anxiety and hypothalamic–pituitary–adrenal axis responses to stress in the male rat, Physiol. Rep. 2 (3) (2014) e00265. https://doi.org/10.1002/phy2.265.

[62] D.S. Busch, L.S. Hayward, Stress in a conservation context: a discussion of glucocorticoid actions and how levels change with conservation-relevant variables, Biol. Conserv. 142 (12) (2009) 2844–2853. https://doi.org/10.1016/j.biocon.2009.08.013.

[63] T. Frodl, V. O'Keane, How does the brain deal with cumulative stress? A review with focus on developmental stress, HPA axis function and hippocampal structure in humans, Neurobiol. Dis. 52 (2013) 24–37. https://doi.org/10.1016/j.nbd.2012.03.012.

[64] M.M. Landys, M. Ramenofsky, J.C. Wingfield, Actions of glucocorticoids at a seasonal baseline as compared to stress-related levels in the regulation of periodic life processes, Gen. Comp. Endocrinol. 148 (2) (2006) 132–149. https://doi.org/10.1016/j.ygcen.2006.02.013.

[65] S. Savastano, C. Di Somma, G. Pizza, A. De Rosa, V. Nedi, A. Rossi, F. Orio, G. Lombardi, A. Colao, G. Tarantino, Liver-spleen axis, insulin-like growth factor-(IGF)-I axis and fat mass in overweight/obese females, J. Transl. Med. 9 (1) (2011) 136, https://doi.org/10.1186/1479-5876-9-136.

[66] E.J. Masoro, Overview of caloric restriction and ageing, Mech. Ageing Dev. 126 (9) (2005) 913–922. https://doi.org/10.1016/j.mad.2005.03.012.

[67] Z.E. Gillespie, J. Pickering, C.H. Eskiw, Better living through chemistry: caloric restriction (CR) and CR mimetics alter genome function to promote increased health and lifespan, Front. Genet. 7 (142) (2016). https://doi.org/10.3389/fgene.2016.00142.

[68] C.A. Jolly, Dietary restriction and immune function, J. Nutr. 134 (8) (2004) 1853–1856. https://doi.org/10.1093/jn/134.8.1853.

[69] J. Nikolich-Žugich, I. Messaoudi, Mice and flies and monkeys too: caloric restriction rejuvenates the aging immune system of non-human primates, Exp. Gerontol. 40 (11) (2005) 884–893. https://doi.org/10.1016/j.exger.2005.06.007.
[70] R.B. Effros, R.L. Walford, R. Weindruch, C. Mitcheltree, Influences of dietary restriction on immunity to influenza in aged mice, J. Gerontol. 46 (4) (1991) B142–B147. https://doi.org/10.1093/geronj/46.4.B142.
[71] K. Inoue, E.P. Zorrilla, A. Tabarin, G.R. Valdez, S. Iwasaki, N. Kiriike, G.F. Koob, Reduction of anxiety after restricted feeding in the rat: implication for eating disorders, Biol. Psychiatry 55 (11) (2004) 1075–1081. https://doi.org/10.1016/j.biopsych.2004.01.026.
[72] E.A. Levay, A. Govic, J. Penman, A.G. Paolini, S. Kent, Effects of adult-onset calorie restriction on anxiety-like behavior in rats, Physiol. Behav. 92 (5) (2007) 889–896. https://doi.org/10.1016/j.physbeh.2007.06.018.
[73] P. Chapillon, C. Manneché, C. Belzung, J. Caston, Rearing environmental enrichment in two inbred strains of mice: 1. Effects on emotional reactivity, Behav. Genetics 29 (1) (1999) 41–46. https://doi.org/10.1023/a:1021437905913.
[74] V. Roy, C. Belzung, C. Delarue, P. Chapillon, Environmental enrichment in BALB/c mice: effects in classical tests of anxiety and exposure to a predatory odor, Physiol. Behav. 74 (3) (2001) 313–320. https://doi.org/10.1016/S0031-9384(01)00561-3.
[75] R.F. Genn, S.A. Tucci, A. Thomas, J.E. Edwards, S.E. File, Age-associated sex differences in response to food deprivation in two animal tests of anxiety, Neurosci. Biobehav. Rev. 27 (1–2) (2003) 155–161.